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Neurodevelopmental Changes in Social Reinforcement Processing: A Functional Magnetic Resonance Imaging Study

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Objective: In the current study we investigated neurodevelopmental changes in response to social and non-social reinforcement.
Methods: Fifty-three healthy participants including 16 early adolescents (age, 10-15 years), 16 late adolescents (age, 15-18 years), and 21 young adults (age, 21-25 years) completed a social/non-social reward learning task while undergoing functional magnetic resonance imaging. Participants responded to fractal image stimuli and received social or non-social reward/non-rewards according to their accuracy. ANOVAs were conducted on both the blood oxygen level dependent response data and the product of a context-dependent psychophysiological interaction (gPPI) analysis involving ventromedial prefrontal cortex (vmPFC) and bilateral insula cortices as seed regions.
Results: Early adolescents showed significantly increased activation in the amygdala and anterior insula cortex in response to non-social monetary rewards relative to both social reward/non-reward and monetary non-rewards compared to late adolescents and young adults. In addition, early adolescents showed significantly more positive connectivity between the vmPFC/bilateral insula cortices seeds and other regions implicated in reinforcement processing (the amygdala, posterior cingulate cortex, insula cortex, and lentiform nucleus) in response to non-reward and especially social non-reward, compared to late adolescents and young adults.
Conclusion: It appears that early adolescence may be marked by: (i) a selective increase in responsiveness to non-social, relative to social, rewards; and (ii) enhanced, integrated functioning of reinforcement circuitry for non-reward, and in particular, with respect to posterior cingulate and insula cortices, for social non-reward.

KEY WORDS: Functional magnetic resonance imaging; Social reward; Ventro-medial prefrontal cortex; Amygdala; Anterior insula; Context-dependent psychophysiological interaction.

INTRODUCTION

Regions implicated in the response to reward include ventromedial prefrontal cortex (vmPFC), dorsomedial frontal cortex, ventral striatum (VST), anterior insula cortex (AIC) and posterior cingulate cortex (PCC) for a review.[1-3] Moreover, these regions have been shown to be responsive to reward in adolescents (including the amygdala which has been reported to show responses to reward outcomes; for a review, see the article of Silverman *et al*.[4] in 2015. Regions such as vmPFC, VST, and PCC typically show greater responsiveness to reward relative to punishment across tasks, reward modalities and stages of the decision-making process.[2] AIC shows responsiveness both in anticipation,[3] and receipt of, rewards for a meta-analysis[4] and may be particularly important for the organization of avoidance responses.[5]

Adolescence potentially represents a period of heightened sensitivity to reward and increased reward-seeking behavior.[4,6-10] In this regard, many previous studies have investigated the neuro-developmental trajectory of reward processing in this period for a comprehensive review.[11] The findings have been somewhat inconsistent. Many, but by no means all, studies have reported heightened reward sensitivity in adolescence[11-14] and a recent meta-analytic review concluded that adolescents showed greater re-

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sponses relative to adults to reward within regions including bilateral ventral and dorsal striatum, insula, dorsomedial frontal cortex and right amygdala.[4] However, there are also other studies showing decreased responses in adolescents relative to adults in response to reward, depending on task design and neural areas involved.[11]

One variable that has received surprisingly little attention, particularly given the importance of social development in this period,[15] is the response to social reward. Social reinforcement and punishment are critical for healthy development of social skills in adolescence, thus it is worthwhile to investigate the developmental trajectory of neural areas responsible for social reward and punishment processing.[11] Regions responsive to non-social rewards also appear responsive to social rewards[16-19] though additional regions, such as the amygdala, may be particularly important with respect to social reward processing.[20] However, it remains unknown whether there are developmental differences in the responses of these regions to social relative to non-social reward in adolescents.

There is also very little work considering the developmental trajectory in the connectivity of the neural systems engaged in reward processing.[11] One study, using the monetary incentive delay task, reported no changes in connectivity between regions involved in reinforcement processing from the ages of 10 to 48.[21] Alternatively, several studies examining resting-state functional connectivity studies have reported that adolescents show weaker connectivity between structures involved in reward processing than adults.[22-24] It should also be noted that there is relatively little data regarding developmental changes in connectivity between structures involved in processing social reinforcements, though there are indications of a progressive increase in negative amygdala-medial prefrontal cortex connectivity from the ages of 10 to 22 years in response to emotional expressions.[25]

The goal of the current paper was to use the social/non-social reinforced learning task of Scott-Van Zeeland *et al*.[16] to examine developmental differences in decision-making as a function of both non-social (money loss/gain) and social (happy/sad facial expressions) reinforcements. Given previous work indicating heightened reward responsiveness in adolescents within VST, ventromedial frontal cortex and amygdala to reinforcement,[2,4] we predicted increased responsiveness within these regions in adolescents relative to adults and that this would be seen for social *and* non-social rewards relative to social and non-social non-rewards. Based on previous studies, we also expected that areas related to emotional processing (i.e., amygdala and vmPFC) will show increased responses to social rewards in adolescents relative to adults.[26,27] Given the findings of the developmental resting-state functional connectivity studies,[28,29] we also predicted that decreased connectivity between VST and ventromedial frontal cortex seeds and other regions implicated in emotional/reinforcement processing (PCC, AIC and amygdala) for adolescents relative to adults, in response to reward relative to non-reward.

METHODS

Subjects

Sixty-six healthy participants from the Washington D.C. metropolitan area volunteered for the study and were paid for their participation. Participants were recruited from the community through newspaper ads, fliers, and referrals from area mental health practitioners. Thirteen subjects were excluded from the final data analysis due to performance artifacts (for example, too much movement—over 15% of participants' repetition times [TRs] were censored due to movement [>1 mm within the TR]—or falling asleep). As such, 53 participants were included in the final analyses (aged 10-25 years, average age=17.69 [4.65]; 25 females, 28 males; 51 right handed and 2 left handed). Sixteen participants were in early adolescence ($10 \leq$ age < 15, average age=12.81 [1.17]; 8 females and 8 males; 1 left handed), sixteen in late adolescence ($15 \leq$ age < 18, average age=15.94 [0.85]; 7 females and 9 males; 1 left handed), and twenty one young adults ($18 \leq$ age ≤ 25, average age=23.00 [2.03]; 10 females and 11 males; 0 left handed). There were no significant group difference in gender ($\chi^2=1.364$, $p=0.506$) or intelligence quotient (IQ) as indexed by the Wechsler Abbreviated Scale of Intelligence two-subtest form[30] ($F=2.868$, $p > 0.05$). There was no significant correlation between age and IQ ($r=0.195$, $p > 0.05$; IQ for participants in early adolescence=108.31 [12.35], IQ for participants in late adolescence=111.19 [12.94], IQ for young adults=116.70 [12.29]).

All subjects, or their legal guardians in the case of minors, gave written informed consent and assent to participate in the study, which was approved by the National Institute of Mental Health Institutional Review Board. Ethics approval for this study was granted by the NIH Combined Neuroscience Institutional Review Board under protocol number 05-M-0105. Subjects were assessed and examined by an expert psychologist and physicians, and were included if they were in good health with no his-

tory of medical, psychiatric, or neurological disease.

Exclusion criteria were pervasive developmental disorder, Tourette's syndrome, lifetime history of psychosis, depression, bipolar disorder, generalized, social or separation anxiety disorder, post-traumatic stress disorder, neurologic disorder, history of head trauma, history of substance abuse, and IQ <70. All children/adolescents and parents completed Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS)[31] assessments conducted by a doctoral-level clinician as part of a comprehensive psychiatric assessment. The KSADS has demonstrated good validity and inter-rater reliability (kappa >0.75 for all diagnoses).[31]

Experimental Design

We used an adapted version of the social and non-social (monetary) reinforcement-learning task.[16] On each trial of a run (Fig. 1), participants saw a fractal image for 2,000 ms and were asked to classify it into one of two groups via button press. There was then an inter-stimulus interval of randomly jittered length (500-1,500 ms) during which a blank screen was presented. Following this, the participants received feedback for 1,250 ms. There was then an inter-stimulus interval of randomly jittered length (1,250-2,500 ms) during which a blank screen was presented before the next trial began.

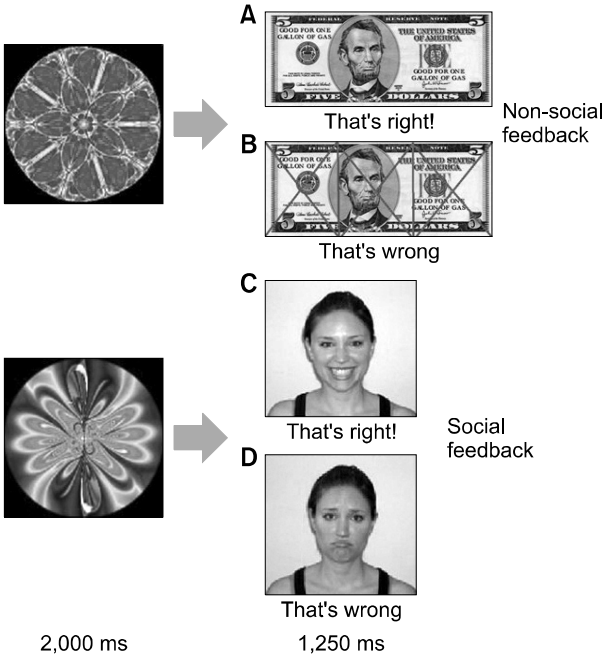

Fig. 1. Example trial sequences. (A) Non-social reward, (B) non-social non-reward, (C) social reward, (D) social non-reward.

The task consisted of two social and two non-social (monetary) reinforcement runs. During non-social (monetary) runs, correct responses were reinforced with the image of a 5-dollar bill and the words "That's right!" (monetary reward) and incorrect responses with the image of a 5-dollar bill struck through with red lines and the words "That's wrong" (monetary non-reward). On neutral trials, feedback consisted only of the words "That's right", or "That's wrong", depending on the accuracy of the participants' response (monetary neutral). During social runs, correct responses were reinforced with a happy face and the words "That's right!" (social reward) and incorrect responses with the image of a sad face and the words "That's wrong" (social non-reward). On neutral trials, feedback consisted of a neutral face and the words "That's right", or "That's wrong" depending on the accuracy of the participant's response (social neutral). The same individual was used for the happy and sad expressions (Fig. 1).

Each run (social or non-social [monetary]) contained six fractal images. Social runs involved a different set of fractal images from those used in non-social runs. Four of the 6 fractals always provided information with respect to whether the participant's response was correct or incorrect with 100% probability. However, for 67% of responses to these trials, feedback was social or non-social (depending on the run) while for the other 33% of responses to these trials feedback was neutral. The other 2 of the six fractals were reinforced at chance level, i.e. these fractals were randomly rewarded in 50% of the trials, irrespective of the participants' response. Participants completed four runs in total and the presentation order of the runs was counterbalanced across the participants (social-monetary-social-monetary or monetary-social-monetary-social). Two runs involved social reinforcement and two runs involved non-social (monetary) reinforcement. Each run involved 54 trials (9 presentations of each of the 6 fractal images).

Image Acquisition and Analysis

Whole brain blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) data were acquired using a 3-T General Motors MRI scanner (USA). Following sagittal localization, functional T2*-weighted images were acquired using an echo-planar single-shot gradient echo pulse sequence with a matrix of 64×64 mm, TR of 3,000 ms, echo time (TE) of 30 ms, field of view (FOV) of 240 mm, and voxels of 3.75×3.75×4 mm. Images were acquired in 30 continuous 4mm axial slices per brain volume across four runs. The duration of each run was 6 minutes 40 seconds. In the same session, a high-resolution

T1-weighed anatomical image was acquired to aid with spatial normalization (three-dimensional spoiled GRASS; TR=8.1 ms; TE=3.2 ms, flip angle 20°; FOV=240 mm, 128 axial slices, thickness=1.0 mm; 256×256 acquisition matrix).

fMRI Analysis

Data were analyzed within the framework of a random effects general linear model using Analysis of Functional Neuroimages (AFNI). Both individual and group-level analyses were conducted. The participants' anatomical scans were individually registered to the Talairach and Tournoux atlas.[32] The first 5 volumes in each echo-planar imaging (EPI) dataset, collected before equilibrium magnetization was reached, were discarded. Motion correction was performed by registering all volumes in each EPI dataset to a volume that was collected shortly before acquisition of the high-resolution anatomical dataset. The individuals' functional EPI data were then registered to their Talairach anatomical scan within AFNI. The EPI datasets for each subject were spatially smoothed (using an isotropic 6 mm Gaussian kernel) to reduce the influence of anatomical variability among the individual maps in generating group maps. Next, the time series data were normalized by dividing the signal intensity of a voxel at each time point by the mean signal intensity of that voxel for each run and multiplying the result by 100. This means that resultant regression coefficients represented a percent signal change from the mean.

The model involved six motion regressors, four regressors for stimulus onset (onset of fractal images for non-social reinforcement with 100% probability, social reinforcement with 100% probability, non-social reinforcement with 50% probability, social reinforcement with 50% probability), and the following task regressors: non-social reward, non-social non-reward, non-social neutral, social reward, social non-reward, and social neutral. A regressor modeling incorrect responses was also included. All regressors were convolved with a canonical hemodynamic response function to account for the slow hemodynamic response (with time point commencing at time of first image onset). There was no significant regressor collinearity. Linear regression modeling was performed using the 11 regressors described earlier, plus regressors to model a first-order baseline drift function. This produced β coefficients and associated *t* statistics for each voxel and regressor.

The BOLD data were analyzed via a 3 (group: early adolescents, late adolescents, young adults) by 2 (reinforcement: reward, non-reward) by 2 (sociality of feedback: non-social, social) ANOVA. With respect to multiple comparison correction, it is worth considering recent suggestions that a more conservative approach that strictly controls for type I error should be adopted.[33] This approach contrasts with arguments that such a strict approach fails to account for theory-driven hypotheses and introduces an unacceptable amount of type II error Cox *et al*.,[34] under review. The disadvantage of the conservative approach is that there are no post-publication remedies for type II error. Data is simply not available for later consideration. In contrast, results that are type I errors will fail to replicate and/or will not survive meta-analysis. Given this, we considered statistical maps for each main effect and interaction by thresh-holding at a single-voxel $p < 0.005$. With these maps, a result was considered significant if it was both predicted *a priori* and had an extent threshold greater than 10 voxels.[35] A priori regions were selected from the previous studies on neural areas of emotional/reinforcement processing, including anterior insular cortex, amygdala, and VST.[1-3,36] In addition to this, regions that were not predicted *a priori* but which survived the new ClustSim multiple comparison results for a minimum cluster size (33 voxels) are reported as well.[34] Furthermore, in order to facilitate future meta-analytic work, effect sizes for all clusters/ follow-up *t*-tests (partial eta [η] square) are reported.

Context-dependent Psychophysiological Interaction (gPPI) Analysis

Context-dependent gPPI analyses were conducted to examine group differences in functional connectivity following the method described by McLaren *et al*.[37] Our main goal was to examine group differences in functional connectivity within the reinforcement processing network. As such, we took three seed region identified from the BOLD response ANOVA (main effect of reinforcement): left vmPFC (coordinates: −10.5, 46.5, 2.5; 35 voxels) and bilateral insula cortices (coordinates: 43.5, 13.5, 11.5 and −28.5, 22.5, 2.5; 41 voxels and 52 voxels, respectively) (Supplemental Fig. 1). These regions met our two criteria for ROI selection. First, it was revealed via the main effect of reinforcement in the main BOLD response ANOVA. As such, it was a region specifically sensitive to *reinforcement across* age groups (ROIs identified through a group-by-reinforcement interaction might have revealed differences via PPI that simply reflected reduced signal in the region in one of the groups). Second, they were regions identified to be *reinforcement* sensitive within the pre-

vious literature.[4,11)]

For the gPPI analysis, the average BOLD response across the vmPFC was extracted from the preprocessed time-series as used in the main analysis, but before the spatial smoothing had been applied. The seed time-series was first detrended and deconvolved. Eleven interaction terms were created by multiplying the detrended and deconvolved seed time-series with eleven indicator regressors, which indicated the onset of the four stimulus onset, six feedback types (one for each reinforcement and sociality condition), and one incorrect responses. Finally, these eleven interaction terms were convolved with the hemodynamic response function to create eleven gPPI regressors. Linear regression modeling was performed using the task regressors from the main analysis, six motion regressors, a regressor reflecting the seed time-series, the eleven gPPI regressors and regressors to model a first-order baseline drift function. This produced a β coefficient and associated *t* statistic for each voxel and regressor. A 3 (group: early adolescents, late adolescents, young adults) by 2 (reinforcement: reward, non-reward) by 2 (sociality of feedback: non-social, social) ANOVA was then applied to the data. We considered statistical maps for each main effect and interaction by thresh-holding at a single-voxel $p < 0.005$.

RESULTS

Behavioral Data

Two 3 (group: early adolescents, late adolescents, young adults) by 2 (sociality of feedback: non-social, social) by 2 (first phase (first two runs), second phase (last two runs)) ANOVAs were applied to the accuracy and reaction time (RT) data respectively (Table 1 and Supplementary Fig. 2). With respect to accuracy data, there was a significant main effect of phase ($F(2,50)=13.82$, $p=0.000$), as well as significant group by sociality, and group by phase interactions ($F(2,50)=4.28$, $p=0.046$ and $F(2,50)=8.25$, $p=0.001$, respectively). Specifically, accuracy was significantly better in the last two runs relative to the first two runs ($t(35)=3.02$, $p=0.005$). Moreover, young adults showed significantly greater accuracy than early adolescents in the second phase ($t(35)=3.48$, $p=0.001$), but not the first ($t(35)=0.48$, $p=0.64$) while early and late adolescents did not significantly differ in performance for either phase ($t(35)=0.69$, $p=0.50$ and $t(35)=0.23$, $p=0.82$, respectively). In addition to this, early adolescents showed significantly better accuracy in monetary reward runs compared to late adolescents ($t(35)=2.40$, $p=0.02$). No other main effects or interactions were significant.

With respect to RT data, there was a significant main effect of phase ($F(2,50)=4.60$, $p=0.037$) and a group by sociality by phase interaction ($F(2,50)=14.93$, $p=0.000$). Specifically, RTs were significantly shorter in the last two runs relative to the first two runs ($t(35)=4.63$, $p=0.000$). Moreover young adults had significantly shorter RTs than early adolescents in the second phase ($t(35)=3.14$, $p=0.03$), but not the first ($t(35)=1.51$, $p=0.14$) while early and late adolescents did not significantly differ in performance for either phase ($t(35)=0.26$, $p=0.79$ and $t(35)=0.58$, $p=0.57$, respectively). No other main effects or interactions were significant.

fMRI Data

Whole brain analysis

A whole-brain 3 (group: early adolescents, late adolescents, young adults) by 2 (reinforcement: reward, non-reward) by 2 (sociality: non-social feedback, social feedback) ANOVA was applied to the BOLD data. This revealed regions showing significant main effects of reinforcement and sociality and significant reinforcement-by-sociality, and group-by-reinforcement-by-sociality interactions. Core results for our hypotheses are presented below (regions showing significant group-by-reinforce-

Table 1. Behavioral data

	Early adolescent		Late adolescent		Young adult	
	First phase	Second phase	First phase	Second phase	First phase	Second phase
RT (ms)						
Non-social	1,005.23 (141.23)	916.90 (94.73)	940.05 (197.06)	892.35 (237.61)	926.33 (114.18)	826.33 (114.18)
Social	960.37 (130.20)	956.68 (49.68)[a]	959.33 (190.46)	844.65 (190.94)	943.46 (104.92)	811.25 (48.35)[b]
Accuracy (%)						
Non-social	69.5 (1.7)	74.1 (1.9)	67.1 (1.2)	75.3 (1.5)	72.1 (1.2)	86.3 (1.3)
Social	66.3 (1.4)	75.7 (1.6)	79.7 (1.4)	77.3 (1.8)	73.4 (1.2)	83.5 (1.9)
Total accuracy*	67.9 (1.8)	74.9 (1.8)[a]	73.4 (1.8)	76.3 (1.4)	72.8 (1.8)	84.9 (1.7)[b]

Values are presented as mean (standard deviation).
*$p<0.05$ (difference between a and b).

Table 2. Brain regions showing significant main effects/interaction from whole brain analysis

Region*	Coordinates of peak activation					F	Voxels	Partial η^2
	Left/right	BA	x	y	z			
Main effect of reinforcement								
Superior frontal gyrus	Right	6	10.5	7.5	56.5	48.79	281	0.41
Middle frontal gyrus	Right	9	40.5	4.5	38.5	23.70	50	0.41
Ventromedial prefrontal cortex†	Left	10	−10.5	46.5	2.5	13.68	35	0.74
Insula	Right	44	43.5	13.5	11.5	30.88	173	0.42
Insula	Left	13	−28.5	22.5	2.5	29.79	78	0.52
Superior temporal gyrus	Right	22	46.5	−28.5	−0.5	28.67	39	0.51
Supramarginal gyrus	Right	39	40.5	−52.5	29.5	23.42	34	0.40
Main effect of sociality								
Fusiform gyrus	Right	36	28.5	−40.5	−9.5	16.75	75	0.17
Reinforcement by sociality								
Anterior Insula cortex	Left	13	−40.5	4.5	2.5	18.47	33	0.38
Superior temporal gyrus	Left	38	−37.5	4.5	−27.5	15.07	34	0.28
Caudate	Right		7.5	4.5	8.5	12.08	39	0.24
Lentiform nucleus	Right		19.5	−1.5	−0.5	17.63	41	0.29
Lentiform nucleus	Left		−25.5	1.5	2.5	17.00	93	0.28
Group by reinforcement by sociality								
Amygdala	Right		16.5	−7.5	−9.5	8.77	36	0.68
Anterior insula cortex‡	Left	13	−34.5	13.5	−9.5	9.86	23	0.42
Superior parietal lobule	Right	7	25.5	−58.5	53.5	8.32	40	0.39

BA, Brodmann area.
*According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon).
p=0.005 for the entire table, except for the main effect of reinforcement (p=0.001); †p=0.005, uncorrected/for the rest of the regions showing main effect of reinforcement, p=0.001.
‡*a priori* region.

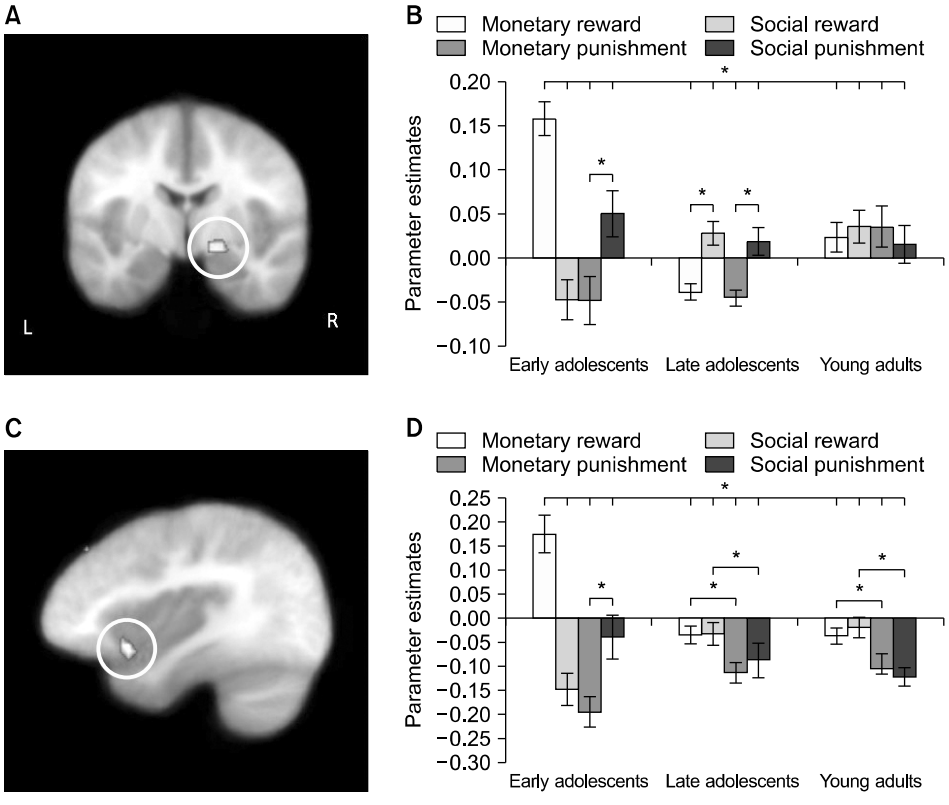

Fig. 2. The ANOVA on the blood oxygen level dependent response data revealed that (A) right amygdala (coordinates: 16.5, −7.5, −9.5) and (C) left anterior insula cortex (AIC) (coordinates: −34.5, 13.5, −9.5) showed a significant group-by-reinforcement-by-sociality interaction corrected for multiple comparisons; (B) Parameter estimates for right amygdala, which reflect percent signal change for monetary and social rewards and non-rewards per group; (D) Parameter estimates for left AIC, which reflect percent signal change for monetary and social rewards and non-rewards per group.
*Statistically significant.

ment-by-sociality interactions and those showing main effects of reinforcement). No regions showed significant group-by-reinforcement or group-by-sociality interaction.

Group-by-Reinforcement-by-Sociality interaction

Three regions showed significant group-by-reinforcement-by-sociality interactions. Two of these (right amygdala and right superior parietal lobe) met statistical criteria for multiple comparisons (extent threshold >33 voxels). The third, left anterior insular cortex, did not met the criteria for multiple comparisons (voxel size=23). However, this was an *a priori* region of interest (Table 2). Within all three regions, early adolescents showed significantly greater responses to monetary rewards relative to both social reward/non-reward and monetary non-rewards compared to older adolescents and young adults ($F(1,30)=11.61$, $p<0.001$; $F(1,30)=4.19$, $p<0.001$, $F(1,30)=3.90$, $p<0.06$, respectively). Late adolescents and young adults did not significantly differ in responsiveness within these regions (Fig. 2).

Main effect of reinforcement

Regions showing a significant main effect of reinforcement included bilateral insula cortices and vmPFC (Table 2). Within the bilateral insula cortices BOLD responses were significantly greater to non-reward than reward. For left vmPFC, BOLD responses were significantly greater to reward than non-reward.

gPPI results

One 3 (group: early adolescents, late adolescents, young adults)-by-2 (reinforcement: reward, non-reward)-by-2 (sociality: social, non-social) ANOVA was conducted on the gPPI data using a seed identified via the main effect of reinforcement (left vmPFC).

VmPFC seed

Several regions showed significant group-by-reinforcement and group-by-reinforcement-by-sociality interactions in their connectivity with the left vmPFC seed (Table 3). The areas showing significant group-by-reinforcement interactions included left lingual gyrus and left amygdala

Table 3. Brain regions showing differential connectivity with vmPFC as a function of group, reinforcement and or sociality

Region*	Coordinates of peak activation					F	Voxel	Partial η^2
	Left/right	BA	x	y	z			
(A) Left ventromedial prefrontal cortex seed (at p=0.005, 35 voxels)								
Main effect of reinforcement								
Middle temporal gyrus	Right	21	46.5	4.5	−30.5	23.70	89	0.31
Group by reinforcement								
Lingual gyrus	Left	18	−13.5	−76.5	−6.5	8.73	41	0.54
Amygdala	Left		−28.5	1.5	−12.5	8.73	14	0.53
Group by sociality								
Precuneus	Left	7	−1.5	−67.5	35.5	14.02	236	0.59
Posterior cingulate cortex	Right	29	7.5	−43.5	17.5	10.37	91	0.16
Middle temporal gyrus	Left	22	−61.5	−31.5	5.5	8.72	44	0.21
Thalamus	Right		4.5	−22.5	2.5	10.89	75	0.22
Group by reinforcement by sociality								
Posterior cingulate cortex	Left	31	−1.5	−55.5	23.5	9.03	71	0.48
Insula	Left	13	−40.5	−19.5	17.5	9.30	25	0.35
(B) Right insula seed (p=0.00005, 41 voxels)								
Group by reinforcement								
Precuneus	Right	7	13.5	−76.5	41.5	9.41	40	0.51
Posterior cingulate cortex	Left	24	−10.5	−4.5	32.5	13.46	23	0.30
Group by sociality								
Posterior cingulate cortex	Right	24	4.5	−1.5	32.5	8.66	27	0.18
Posterior cingulate cortex	Left	31	−10.5	−37.5	41.5	8.94	26	0.15
(C) Left insula seed (p=0.00005, 52 voxels)								
Group by reinforcement								
Lentiform nucleus	Left		−25.5	−16.5	−6.5	9.09	38	0.78
Group by sociality								
Inferior parietal lobule	Left	40	−28.5	−40.5	56.5	8.92	35	0.19
Posterior cingulate cortex	Right	31	13.5	−34.5	41.5	9.75	32	0.43

BA, Brodmann area.
*According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon).
p=0.005 for the entire table.

(Table 3). The connectivity between the vmPFC seed and left lingual gyrus/left amygdala was significantly more positive in response to non-reward relative to reward in early adolescents, compared to late adolescents and young adults (t=2.379 and 4.240; p=0.023 and $<$0.001; effect size=0.53 and 0.54, respectively) (except between early adolescents and young adults in lingual gyrus, where there was a trend [t=1.790, p=0.082]) (Fig. 3). The late adolescents and young adults groups did not significantly differ (t=1.031 and 1.745, p=0.31 and 0.09, respectively).

The areas showing significant group-by-reinforcement-by-sociality interactions included left PCC and left insula (Table 3). There was significantly more positive connectivity between the vmPFC seed and left PCC/left insula for social non-reward relative to social reward feedback in the early adolescents, compared to late adolescents and young adults (t=3.312 and 2.327; p=0.002 and 0.027; effect size=0.48 and 0.35, respectively) who did not significantly differ (Fig. 3). There were no group differences in connectivity with vmPFC for non-social reward and non-reward feedback.

Right insula seed

Several regions showed significant group-by-reinforcement and group-by-sociality interactions in their connectivity with right insula seed (Table 3). With respect to the group-by-reinforcement interaction, these included right precuneus and left PCC. Within both regions, early adolescents and late adolescents showed significantly more positive connectivity with the right insula seed in response to non-reward, compared to young adults (t= 2.429-3.767; p=0.001-0.020; effect size=0.51 and 0.30, respectively). This difference was not observed between early adolescents and late adolescents (t=0.048-1.618; p=0.015-0.962) or in response to reward (t=0.027-0.666, p=0.510-0.999).

The areas showing significant group-by-sociality interaction included bilateral posterior cingulate cortices (Table 3). For both areas, early adolescents showed significantly more positive connectivity with the right insula seed in response to social feedback, compared to late adolescents (t=3.203 and 2.858; p=0.003 and 0.008; effect size=0.18 and 0.15, respectively) and, albeit at trend levels, young adults (t=1.754 and 1.980; p=0.088 and 0.056, respectively). This difference was not observed between late adolescents and young adults (t=1.532 and 1,468, p=0.134 and 0.151, respectively) or in response to non-social feedback.

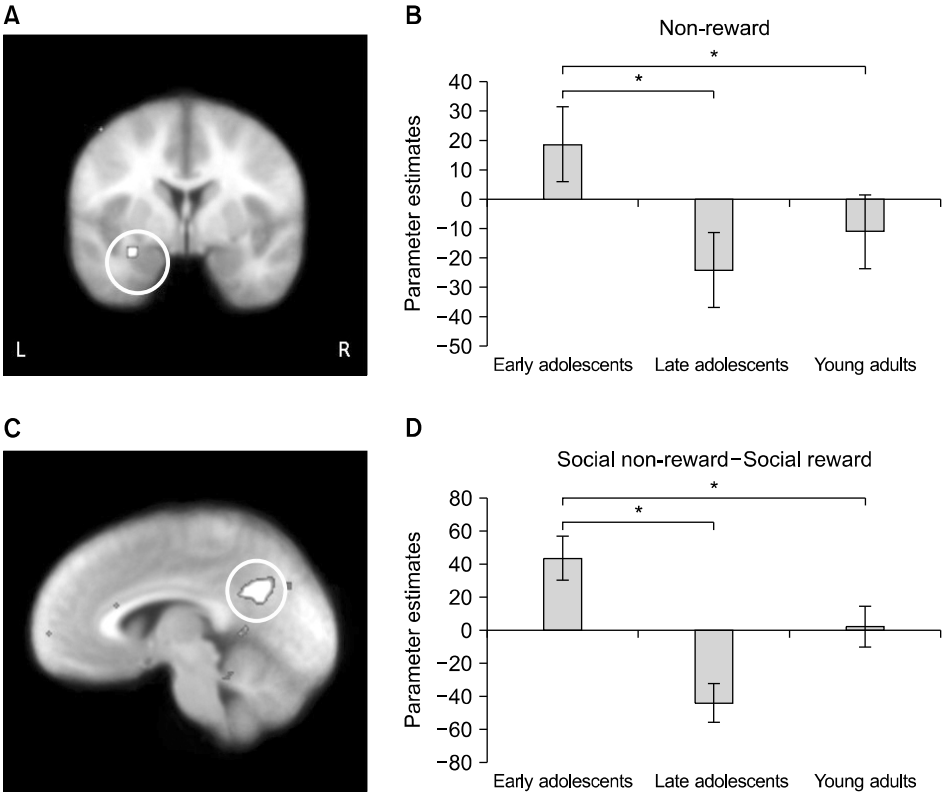

Fig. 3. (A) Left amygdala (coordinates: −28.5, 1.5, −12.5) showing significant group-by-reinforcement interaction on connectivity with ventromedial prefrontal cortex (vmPFC) seed; (B) Parameter estimates for this region, which reflect connectivity between vmPFC and this region during non-reward feedback; (C) Left posterior cingulate cortex (coordinates: −1.5, −55.5, 23.5) showing significant group-by-reinforcement-by-sociality interaction on connectivity with vmPFC seed; (D) Parameter estimates for this region, which reflect connectivity between vmPFC and this region during social non-reward feedback−social reward feedback. *Statistically significant.

Left insula seed

Several regions showed significant group-by-reinforcement and group-by-sociality interactions (Table 3). Specifically, a significant group-by-reinforcement interaction was observed within left lentiform nucleus (Table 3). In this area, early adolescents showed significantly more positive connectivity with left insula seed in response to reward, compared to late adolescents and young adults (t=3.348; p=0.002; effect size=0.78). This difference was not observed between late adolescents and young adults (t=1.376, p=0.178).

The areas showing significant group-by-sociality interaction included left inferior parietal lobule and right PCC (Table 3). In both regions, early adolescents showed significantly more positive connectivity with the left insula seed in response to social feedback, compared to late adolescents and young adults (t=2.448-2.574; p=0.014-0.020; effect size=0.19 and 0.43, respectively). This was not observed between last adolescents and young adults (t= 0.196-1.506, p=0.141-0.846).

DISCUSSION

The current study investigated developmental changes in neural responses and connectivity in individuals aged 10-25 years in response to social and non-social reinforcement. There were two main results. First, early adolescents showed a significantly greater response to non-social relative to other reinforcements reward (money won vs. happy facial expressions, sad facial expressions, or money lost) compared to late adolescents and young adults within right amygdala and left AIC. Second, early adolescents showed greater positive connectivity between the vmPFC seed/bilateral insula cortices seed and other regions implicated in processing reinforcement information (including amygdala, PCC, insula cortex, and lentiform nucleus) following the receipt of non-reward (particularly social non-reward for PCC and insula cortex) relative to reward when compared to late adolescents and young adults.

Previous studies have demonstrated that adolescents, relative to adults, show heightened reward responses in a number of regions including bilateral ventral and dorsal striatum, insula, dorsomedial frontal cortex and right amygdala.[4] However, previous work has not differentiated social and non-social reward. In the current study early adolescents showed greater responses to non-social reward compared to older adolescents and young adults within both the insula and amygdala (indeed the peak activations for insular cortex were notably similar for the current study [coordinates: −36, 16, −17 MNI] and the meta-analytic review [coordinates: −38, 18, −8]). Notably, and partly in line with this, early adolescents, in their behavioral data, showed significantly better accuracy in non-social (monetary) reward runs compared to late adolescents. The amygdala has been long-recognized as a core node within the meso-limbo-cortical dopamine system, and serves to modulate ventral striatal activity.[38] The region of anterior insula has been implicated in attending to task set features.[39-41] The insular cortex is related to refocusing attention and evaluation.[39,41] Also it is related to maintaining attention during task performance.[40] Thus potentially in this study, anterior insula is implicated in increasing the representational strength of stimulus features associated with reward. The current study replicates previous work showing that in early adolescence these areas are engaged more intensely by reward relative to later adolescence and young adulthood. Importantly, the current study extends this earlier work by indicating that the increased salience of reward for young adolescents is particularly marked for non-social rewards (or at least money) but not shown for social rewards. Yet social rewards generally engage regions implicated in non-social rewards[2] though not in patients with autism.[16] This might be related to the increased dopaminergic activity in early adolescents,[9,42,43] and its relation to non-social (mostly monetary) reward processing.[44,45] However, why there was no significant difference in *social* reward processing in those neural areas is not clear, although there are differences in the *connectivity* of reward processing areas between early adolescents and the other age groups in response to social non-reward (see below for further discussion). This warrants future study. It is noteworthy that also in the behavioral data, early adolescents showed significantly better accuracy in non-social (monetary) reward runs compared to late adolescents (see Result section), thus is in line with the BOLD response results.

In contrast to predictions based on the previous literature,[4] we observed no group differences in the striatal response to reward. This may reflect Type II error perhaps due to idiosyncrasies of this particular cohort. Indeed, it is notable that striatum was only weakly seen as a main effect of reward in the current study (p=0.02, 17 voxels; coordinates: 10.5, 7.5, −3.5). Yet, in a parallel study focusing on children/adolescents with disruptive behavior disorders from our lab (Hwang *et al*., manuscript in preparation) using the same neuropsychological task,[16] strong striatal activity was seen to reward relative to non-reward.

It is possible that the weak striatal responsiveness to reward shown by the present sample prevented the revelation of developmental changes in activity within this region in the current study.

In contrast to our hypothesis, we did not observe increased response in early adolescents in amygdala or vmPFC in response to social reward/non-reward. Rather, early adolescents showed the strongest positive connectivity between our vmPFC seed/bilateral insulae seeds and other regions responsible for reinforcement processing in response to non-reward, and especially to social non-reward (sad facial expression). A few previous studies suggested potential developmental changes in the *network* of reward/reinforcement processing areas as a future direction of study.[4,11,25] VmPFC has been implicated in reward processing by encoding values related to the reward information,[2,46] especially during reward outcome processing.[47] Early adolescents showed the strongest connectivity of this area with areas implicated in visual processing of reward/reinforcement information lingual gyrus[48] and the generation of emotion-provoking signals in reward/reinforcement processing amygdala,[4,49] especially in response to non-reward. Two previous studies have reported a "developmental shift" with respect to vmPFC-amygdala connectivity whereby this is positive in early adolescents but is negative in later adolescents.[25,50] This was seen both when participants were reappraising negative stimuli[50] and responding to fearful expressions.[25] This is highly compatible with our results during the response to non-reward (including sad facial expression[25]). This developmental shift in connectivity relationship may reflect the development of the individuals' capacity for emotional regulation. This also might be reflected on the behavioral data, in that early adolescents showed longer RT and less accuracy especially in the second phase compared to young adult, in that early adolescents have stronger connectivity in response to social-emotional values of the feedback, which might in turn compromise cognitive capacity of responding.

It is also noteworthy that vmPFC showed the most positive connectivity with areas implicated in salience of reinforcement (e.g., AIC[51,52]) and attention to and awareness of reinforcement (e.g., PCC[53]) in response to *social* non-reward in early adolescents compared to the other groups. Previous anatomical and resting state functional MRI studies have shown connectivity between vmPFC and insula.[28,29] Positive connectivity between regions involved in reward processing (vmPFC) and reinforcement processing/attention (PCC) in response to social non-reward in early adolescents implicates the importance of social reinforcement (especially non-reward/punishment) in this age group.[1,15] This is also further supported by increased connectivity between bilateral insulae seeds that are involved in refocusing attention and maintaining attention to reward, and other reinforcement processing areas (especially PCC) in response to non-reward and social reward.[39-41]

All groups, as indexed by their behavioral performance, showed significant learning on the task. But it is noteworthy that while early adolescents showed significantly poorer behavioral performance than young adults, they showed greater: (i) responsiveness to non-social rewards; and (ii) positive connectivity between regions involved in reinforcement processing (vmPFC seed/bilateral insula, amygdala, PCC, insula cortex, and lentiform nucleus) in response to non-reward. Whether this greater responsiveness and connectivity reflects compensatory recruitment in an attempt to achieve or comparable behavioral performance or, perhaps more likely, reflects the relative lack of developmental progression of the early adolescents (i.e., greater recruitment that interferes with behavioral performance) will need to be clarified in future work.

There are two limitations of the current study: First, we did not assess the physical developmental changes in the adolescent participants. Given previous findings of the impact of puberty on relevant brain structures especially amygdala,[54-56] it would be useful to know to what extent puberty status may have contributed to the current results. Future work might focus on this. Second, the reward value of different monetary amounts may differ as a function of age. It could be plausibly argued that 5 dollar only has significant reward value for early adolescents and not, for example, young adults because of the different economic circumstances of these groups. As such activation differences between groups might reflect the differing economic realities of the participants rather than heightened reward responsiveness within the amygdala/anterior insular cortex. Of course, attempts to match participants' subjective values of different monetary amounts would be difficult and the current approach has been adopted extensively in the previous literature.[4,8,42] Moreover, it is important to remember that several regions, most notably vmPFC, a region classically implicated in the representation of subjective value,[46,57,58] did not show group-by-reinforcement and group-by-reinforcement-by sociality interactions. As such, the current results are more consistent with an explanation based on differential responsiveness to reward as a function of neural region and age rather than

global differences in the subjective value of different monetary amounts.

In this study, we investigated developmental changes in the neural systems engaged by social and non-social reinforcement. Early adolescents showed increased response within amygdala and AIC to non-social reward, and more positive connectivity between vmPFC and regions engaged in reinforcement processing including AIC, and PCC in response to non-reward (especially social non-reward). We suggest that these data indicate that the sociality of the reinforcement is an important factor when considering developmental changes in reinforcement processing.

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