



Developmental influences on the neural bases of responses to social rejection: Implications of social neuroscience for education

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ABSTRACT

Relational aggression such as social rejection is common within school peer groups. Converging evidence suggests that adolescent females are particularly sensitive to social rejection. We used a novel fMRI adaptation of the Cyberball social rejection paradigm to investigate the neural response to social rejection in 19 mid-adolescent (aged 14–16) and 16 adult female participants. Across all participants, social exclusion (relative to inclusion) elicited a response in bilateral medial prefrontal cortex (mPFC) extending into ventral and subgenual anterior cingulate cortex and medial orbitofrontal cortex; and the left ventrolateral PFC (vlPFC); regions that have been associated in previous studies with social evaluation, negative affective processing, and affect regulation respectively. However, the exclusion-related response in right vlPFC, a region associated in previous studies with the regulation of rejection-related distress, was attenuated in adolescents. Within mPFC, greater activation during exclusion vs. inclusion was associated with greater self-reported susceptibility to peer influence in adolescents but not in adults. This suggests that the brain's response to experimentally-induced social rejection relates to adolescent behaviour in real-world social interactions. We speculate about the potential implications of these findings for educational settings. In particular, functional development of affective circuitry during adolescence may influence social interaction within the school peer group.

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Introduction

In exploring the contributions that neuroscience can make to educational practice, it is important to consider the pastoral role that schools must fill, particularly at secondary level. Adolescence is a time of opportunity for learning new skills and forging an adult identity. However, it is also a time of vulnerability, as adolescents begin to face adult challenges while still developing physically, socially and cognitively (Steinberg, 2005). Understanding the brain basis of social development and functioning during adolescence is crucial for the fostering of social competence and psychological wellbeing inside and outside the classroom (Blakemore, 2010).

Managing social relationships is a significant challenge for adolescents. Relational or social forms of bullying are common within school peer groups, particularly among adolescent girls. One recent study (Wang et al., 2009) found that 27.4% of adolescent girls (mean age

14.3 years) reported being excluded or ignored by a group of peers while at school. Being bullied (including relational aggression) is associated with decreased school achievement and psychological wellbeing (Hawker and Boulton, 2000; Boulton et al., 2008); thus, a greater understanding of adolescent responses to phenomena such as social rejection may contribute to greater understanding of the factors contributing to schooling success and failure (Blakemore, 2010). Recently, several influential fMRI studies have investigated the neural bases of responses to social rejection. However, responses in adolescents and adults have not been directly compared. Given evidence showing continuing structural and functional development in social brain regions during adolescence (Blakemore, 2008) the current study investigated whether adolescents differ from adults in the neural processing of social rejection.

One of the difficulties in investigating social rejection with fMRI is the choice of an appropriate rejection paradigm. This must aim to preserve some of the ecological validity of social rejection, while maintaining sufficient experimental control. The paradigm most commonly used with fMRI is the Cyberball game (Williams et al., 2000). Participants believe they are playing a game of 'catch' over an internet connection with two other players, whereas the actions of these players are actually pre-programmed to include or exclude the

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participant. In adults, a positive relationship has been found between self-reported distress during social exclusion and blood-oxygen-level-dependent (BOLD) responses in brain regions associated with affective and pain processing, including the dorsal anterior cingulate cortex (dACC), amygdala, periaqueductal grey and anterior insula (Eisenberger et al., 2003; Eisenberger et al., 2007a; Eisenberger et al., 2007b). A negative relationship between social distress and BOLD response has also been found in right ventrolateral prefrontal cortex (vlPFC), a region associated with top-down regulatory control (Eisenberger et al., 2003).

The key advantage of the Cyberball paradigm is its ecological validity. However, it has been criticised in terms of experimental control. For example, Somerville et al. (2006) argued that the task confounds social distress with expectation violation, i.e. participants expect to be thrown the ball, but during the exclusion condition they are not. To address this issue, Somerville et al. (2006) designed a task in which social expectation and social distress served as separate factors within a social evaluation task. As predicted, dACC responses were elicited when participants' expectations differed from the feedback they received. In contrast, responses in ventral ACC (vACC)/medial PFC (mPFC), regions associated with social and self-relevant evaluation, were associated with the difference between positive and negative feedback. This finding was replicated in a similar study by Somerville et al. (2010). The current study sought to address these conflicting findings with a novel adaptation of the Cyberball task, which improved experimental control while preserving the idea of an online interaction.

Using this framework, the current study aimed to explore brain regions responding to social rejection across all participants, as well as those in which BOLD response may differ between adolescents and adults. Behavioural studies have shown that adolescent females report lower mood and greater anxiety in response to social rejection, relative to both younger children (O'Brien and Bierman, 1988) and adult females (Kloep, 1999; Sebastian et al., 2010a). However, the neurocognitive processes underlying these age differences remain unclear. Increased emotional reactivity measured behaviourally may result from greater activity in regions associated with an affective response, reduced activity in regulatory regions, or a combination of the two (Eisenberger, 2006).

One recent fMRI study from our laboratory (Sebastian et al., 2010b) found attenuated right vlPFC responses in adolescents relative to adults during the processing of rejection-related words. As mentioned above, previous studies have suggested that right vlPFC may regulate the affective consequences of social rejection (Eisenberger et al., 2003; Masten et al., 2009). This finding was therefore consistent with models of adolescent cognition such as the Social Information Processing Network model (Nelson et al., 2005), which suggest that prefrontal regulatory regions such as vlPFC regulate affective states less effectively in adolescents than in adults, resulting in a more acute subjective experience of social rejection. There is also some indirect evidence that the response to social rejection in affective brain regions may be increased in adolescents. One previous study to use the Cyberball paradigm with fMRI in adolescents (Masten et al., 2009) reported a positive correlation between subgenual ACC (sgACC) responses and exclusion-related distress in adolescents. A response in this region had not been found in previous studies with adults (e.g. Eisenberger et al., 2003), although adolescents and adults were not directly compared in the same study. Therefore in the current study we tested whether adolescents engage this region to a greater extent than do adults in the processing of social rejection, in addition to exploring possible group differences in regulatory regions such as vlPFC.

It is also useful to consider whether the brain's response to social rejection relates to behaviour in the real world. Eisenberger et al. (2007a) found that individuals with the highest ratings of perceived social distress during real-world interactions also showed greater responses in dACC and amygdala during Cyberball. Behavioural

studies in adults have shown that social exclusion not only causes distress, but also increases the extent to which individuals conform to group norms, possibly because excluded individuals seek to increase their sense of 'belonging' within the group (Williams et al., 2000). Adolescence is a time when peer approval is of particular salience (Steinberg, 2008) and when ability to resist peer influence is still developing (Steinberg and Monahan, 2007). Therefore, we additionally investigated whether the neural response to rejection relates to self-reported ability to resist peer influence, and whether this relationship differs between adolescence and adulthood.

The current study employed a modified version of the Cyberball paradigm in order to explore neural responses to social rejection on a task with increased experimental control relative to previous studies. We predicted that social exclusion would activate a network of regions involved in the generation of negative affect (ACC, amygdala, and insula), affect regulation (vlPFC), and social evaluation (mPFC). We aimed to address conflicting findings across previous studies, such as the role of dACC in social rejection. We also compared adolescents and adults within the same study. Based on previous studies, we specifically investigated the possibility of group differences in the sgACC (Masten et al., 2009) and vlPFC (Sebastian et al., 2010b). Finally, it was predicted that haemodynamic responses in rejection-sensitive brain regions would correlate with real-world measures of social behaviour, and with self-reported distress during Cyberball (cf. Eisenberger et al., 2003, 2007a).

Methods

Participants

The study included 19 adolescent and 16 adult native-English speaking female participants. Age and full IQ data (measured with the two-subscale version of the WASI (1999)) are displayed in Table 1. IQ did not differ between the groups. Adolescents' mean Tanner stage based on a puberty questionnaire adapted from Carskadon and Acebo (1993) was 3.49 (SD = .038; mid-late puberty). Participants had no history of psychiatric, neurological or neurodevelopmental disorder, based on parent report (adolescents) or self-report (adults). Procedures were approved by the local ethics committee. Only females were included as previous studies have found sex differences in brain development trajectory during adolescence (Giedd et al., 1999). Averaging across males and females might therefore yield an inaccurate picture and reduce statistical power. Females were chosen as they have been reported to be more sensitive to social rejection than males (Crick et al., 2002), and adolescent girls are more likely than boys to use or to be subjected to social isolation as a bullying technique (Wang et al., 2009).

Experimental task

An fMRI-adapted version of the original Cyberball game was used. To improve experimental control, the task was reprogrammed from the original html into Matlab 6.5 using the Cogent toolbox (<http://www.>

Table 1
Participant variables for each Age group.

		Adolescents	Adults
Age	Mean	15.44	28.70
	Range	14.00–16.97	23.87–38.84
	SD	.81	3.91
WASI IQ ^a	Mean	114.00	120.56
	Range	91–130	99–133
	SD	11.96	9.24
Tanner Stage	Mean	3.49	–
	Range	2.63–4.00	–
	SD	.38	–

^a No significant Age group difference in IQ scores: $t(33) = 1.79$, $p = .083$.

vislab.ucl.ac.uk/cogent.php). Compared with previous studies using this paradigm with fMRI, the game was modified in the following ways. The use of a fixed condition order (inclusion followed by exclusion) was replaced with short blocks of each condition in a pseudorandom order. This reduced the possibility of expectation violation, and order effects including neural adaptation. Blocks were also shortened to increase design efficiency, in line with a recent Cyberball fMRI study (Kumar et al., 2009). Additionally, motor responses were matched between conditions by requiring participants to 'mark' with a key press whenever one of the other players caught the ball: this ensured that participants made motor responses during both inclusion and exclusion blocks. This also removed any differences in inhibitory requirements between conditions, as otherwise during exclusion blocks, participants may be preparing movements that they never execute. It also ensured that participants were paying attention to the game equally in both conditions.

As in previous Cyberball studies, participants were told prior to scanning that we were interested in 'mental visualisation' ability (to avoid the topic of social interaction), and that they would play a game of catch over the internet with two other players. As part of the 'mental visualisation' exercise, we instructed participants to imagine the experience was as real as possible. However, unlike previous Cyberball studies, we did not explicitly state whether the other players were real people or not because our more controlled experimental design rendered an elaborate cover story much less believable. This decision was taken on the basis of evidence showing that participants report feeling equally distressed by rejection when they know they are playing against a computer as when they believe the other players are real (Zadro et al., 2004). This is in line with theories suggesting that the immediate distress caused by social exclusion is an automatic and reflexive response (Williams, 2007).

Each block began with an instruction screen telling participants to "Get ready to throw the ball". Participants chose which of the other players to throw the ball to using a right index or middle finger key press response. Participants also marked each time one of the other players received the ball with a key press response. Participants had to press this 'mark' key before the game could continue. To heighten the sense that the other players were deciding to whom to throw the ball, a random interval between .5 and 1 s was introduced after the participant had pressed the mark key before the ball was thrown again. In the inclusion condition, the other players threw the ball to the participant with an 80% probability, i.e. the participant was over-included (a 50% probability would have yielded equal inclusion of the two other players). This figure of 80% was chosen on the basis of task piloting. This showed that, in the short blocks suitable for fMRI, participants needed to be over-included in inclusion blocks in order for them to register systematic differences between the inclusion and exclusion conditions.

There was a total of 12 blocks (six each of inclusion and exclusion). The order of inclusion and exclusion blocks was pseudorandomised,

with the constraint that the same block type was never presented more than twice in a row. Block length was approximately 24 s. This balanced optimal signal-to-noise ratio with blocks long enough for participants to be able to notice that they were being included or excluded. Exact block length varied slightly with each block due to a number of factors designed to increase ecological validity. The game was self-paced, and the onset of the block was defined as the onset of the participant's first throw. The offset of the block was defined as the end of the last video preceding the onset of the fixation cross. Mean (SD) block length across all participants and conditions was 24.35 (1.27) s. After each block, a fixation cross was displayed. Mean (SD) fixation time was 16.68 (1.11) s. The timing and structure of each block is shown in Fig. 1.

Questionnaire measures

Prior to scanning, participants completed the State/Trait Anxiety Inventory (Spielberger, 1983). Following scanning, participants completed a measure of social distress comprising four need threat scales taken from Williams et al. (2000). The four needs comprise self-esteem, belonging, meaningful existence and control, and combined ratings have been used as a measure of social distress in previous studies (Eisenberger et al., 2003, 2007a,b; Masten et al., 2009). As inclusion and exclusion conditions were pseudorandomised throughout the scanning session, participants completed two sets of questionnaires following scanning, in which they were asked to think back to the times for which either 'the other players were throwing the ball to you' or 'the other players were not throwing the ball to you'. After each social distress questionnaire, participants also rated their current mood using a scale taken from Williams et al. (2000). The order in which participants completed these two questionnaires was counterbalanced across participants.

Participants also completed the Resistance to Peer Influence questionnaire (RPI; Steinberg and Monahan, 2007). This asks participants to rate on a 4 point scale the extent to which 10 statements pertaining to peer influence apply to them, e.g. 'Some people go along with their friends just to keep their friends happy.' The questionnaire has been validated as addressing susceptibility to peer influence as distinct from willingness to engage in anti-social behaviour. At the very end of the session, participants completed a manipulation check measure from Williams et al. (2000) which asked participants whether they noticed that they had been included and excluded in different conditions during the scan, and asked them to estimate percentage ball possession for inclusion and exclusion conditions.

fMRI data acquisition

A 1.5 T Siemens Sonata MRI scanner was used to acquire 12 min 3D T1-weighted structural images, and multislice T2*-weighted echo planar volumes with BOLD contrast. The T2* EPI sequence was optimised to

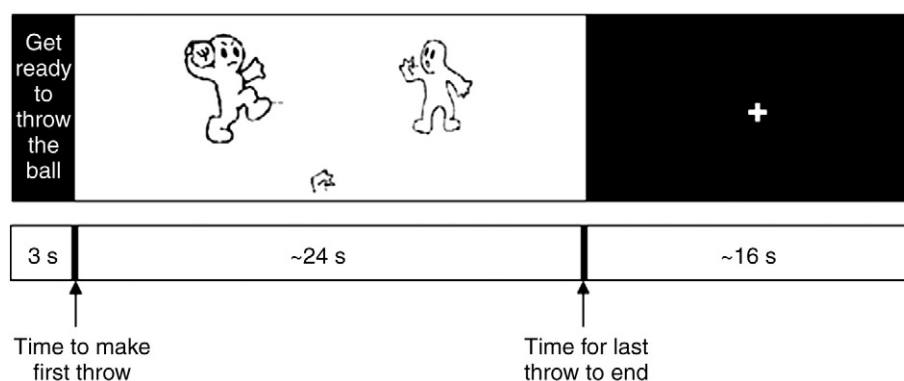


Fig. 1. Timeline showing one block (of 12) of the Cyberball paradigm. The time of the participant's first throw defined the onset of each game. Following this throw, participants were included or excluded by the other players with equal probability. Each game lasted approximately 24 s.

reduce dropout in the orbitofrontal cortex (Weiskopf et al., 2006), and used the following acquisition parameters: 33 2 mm slices acquired in a descending trajectory with a 1 mm gap, TE = 50 ms; TR = 90 ms; slice tilt = -30° ($T > C$); flip angle = 90° ; field of view = 192 mm; matrix size = 64×72 . Functional data were acquired in a single scanning session of approximately 9.5 min, in which 191 volumes were acquired.

fMRI data analysis

Imaging data were analysed using SPM5 (www.fil.ion.ucl.ac.uk/spm). The first five functional image volumes from each run were discarded to allow for T1 equilibrium effects, leaving 186 image volumes per participant. Pre-processing included rigid-body transformation (realignment) and normalisation into the standard space defined by the Montreal Neurological Institute (MNI) template with a voxel size of $3 \times 3 \times 3$ mm, and smoothing with a Gaussian filter of 8 mm full width at half maximum.

A block analysis was conducted in order to compare neural activity associated with inclusion and exclusion conditions. The time series of 186 image volumes was deconstructed into 5 block types, each of which was included as a separate regressor in the design matrix. These consisted of inclusion, exclusion, baseline fixation, times during which the instruction screen was displayed, and times during which the start of the game was displayed but before the participant had thrown the first ball (which defined block onset). These latter two block types were included as regressors of no interest. These 5 regressors were modelled as boxcar functions convolved with a canonical haemodynamic response function. The six realignment parameters were modelled as effects of no interest, in order to account for any variance due to head movement. For three participants (1 adult, 2 adolescents) extra regressors were included to model a small number of corrupted images resulting from excessive motion. These images (amounting to 1–1.6% of those 3 participants' data) were removed and the adjacent images interpolated in order to prevent distortion of the between-subjects mask. Data were high-pass filtered at 128 s to remove low-frequency drifts.

At the first level, the main contrast of interest, exclusion > inclusion (as well as inclusion > exclusion), was conducted for each participant. Random effects analyses were performed by entering the resulting contrast images into a second-level analysis, where Age group served as a between-subjects variable. T-statistics were calculated at the whole brain level for the main effects of Condition across all participants (exclusion > inclusion and inclusion > exclusion), and for the interaction between Condition and Age group.

For the main effects of exclusion > inclusion and inclusion > exclusion, regions reaching cluster-level significance at $p < .05$, FWE-corrected (following initial thresholding at $p < .001$, uncorrected), are reported. Where peaks fell in predicted regions, post-hoc analyses were conducted on contrast estimates from the peak voxel to investigate relationships with self-report measures. Peak voxel data are a weighted average of the surrounding voxels due to smoothing. A peak voxel approach was chosen because using peak voxels for correlation analyses avoids having to arbitrarily choose a shape or statistical threshold to define a cluster of interest.

For the Condition by Age group interaction analysis, the SPM was initially thresholded at $p < .001$, uncorrected. Small volume correction (SVC) was performed using spheres of 8 mm radius in two regions where the prediction of an Age group effect was strongest based on previous studies: right vIPFC (adult > adolescent) and right sgACC (adolescent > adult). The coordinate for right vIPFC (MNI [45 30 –6]) was taken from Sebastian et al. (2010b). In this previous study, which used a rejection-themed emotional Stroop task, this coordinate was associated with significantly greater activity in adults compared with adolescents in response to rejection words relative to acceptance words. The coordinate for sgACC (MNI [8 22 –4]) was taken from the main effect peak (exclusion > inclusion) from Masten et al. (2009). A

significance threshold of $p < .05$ FWE was used. Interactions were interrogated using t-tests. Covariate analyses including participant age and self-report measures were also conducted in a similar manner.

Results

Questionnaire data collected after scanning

State and trait anxiety

There were no group differences in trait anxiety: $t(33) = -1.40$, $p = .17$, or state anxiety: $t(33) = -.63$, $p = .54$. Across all participants, trait anxiety $M = 37.80$, $SD = 9.81$; and state anxiety $M = 33.31$, $SD = 7.53$.

Resistance to peer influence

Adults reported significantly greater resistance to peer influence (RPI) ($M = 3.11$, $SD = .25$) than did adolescents ($M = 2.91$, $SD = .28$; $t(33) = 2.15$, $p = .039$).

Manipulation check

One participant did not give an estimate of ball possession. For the remaining 34 participants, a Condition (inclusion, exclusion) by Age group (adult, adolescent) mixed model ANOVA showed a main effect of Condition: $F(1,32) = 63.75$, $p < .001$, $\eta_p^2 = .67$, with a higher percentage estimated in inclusion ($M = 43.34\%$, $SD = 18.34$) than in exclusion blocks ($M = 12.09\%$, $SD = 9.82\%$). There was no main effect of Age group, or Condition by Age group interaction ($ps > .05$). These estimates also did not differ from actual ball possession in inclusion (possession $M = 42.01\%$, $SD = 2.63\%$, $t(34) = .43$, $p = .67$) and exclusion (possession $M = 13.31\%$, $SD = .68\%$, $t(33) = -.73$, $p = .47$) blocks.

Participants also rated how much they agreed with the statements “I was ignored” and “I was excluded” during inclusion and exclusion conditions. In a Condition by Age group ANOVA, there was a main effect of Condition: $F(1,33) = 147.63$, $p < .001$, $\eta_p^2 = .82$, with greater feelings of exclusion in the exclusion condition ($M = 3.94$, $SD = 1.04$) than in the inclusion condition ($M = 1.40$, $SD = .71$). There was no main effect of Age group. However, there was a Condition by Age group interaction: $F(1,33) = 10.82$, $p = .002$, $\eta_p^2 = .25$. Both groups felt significantly more excluded in the exclusion condition than in inclusion ($ps < .001$), but adolescents reported feeling more excluded during the exclusion condition ($p = .011$), and included during the inclusion condition ($p = .047$) than did adults.

Social distress

Across all four needs, greater need threat was reported during exclusion than inclusion across all participants ($ps < .001$). Therefore, scores were averaged to create one overall ‘social distress’ variable, with higher scores indicating greater distress (scale from 1 to 5). This allowed comparison with previous Cyberball fMRI studies, which have also used this aggregate measure of distress. Mean distress across the whole sample was 1.86 ($SD = .45$) for inclusion, and 3.70 ($SD = .87$) for exclusion. In a Condition by Age group ANOVA, there was a main effect of Condition: $F(1,33) = 125.05$, $p < .001$, $\eta_p^2 = .79$, with greater distress after exclusion than inclusion. There was also a crossover interaction between Condition and Age group: $F(1,33) = 13.45$, $p = .001$, $\eta_p^2 = .29$, with lower distress during inclusion and higher distress during exclusion in adolescents compared with adults ($ps < .001$). There was no correlation between age and distress following exclusion, or the difference score for distress following exclusion relative to inclusion, within each Age group ($ps > .20$).

Mood

Mood ratings were averaged to produce an overall mood score (from 1 to 7), with higher scores indicating better mood. A Condition by Age group ANOVA showed a main effect of Condition: $F(1,33) = 11.11$, $p = .002$, $\eta_p^2 = .25$, with lower mood reported after participants had

thought about exclusion blocks ($M = 5.44$, $SD = 1.21$) than inclusion blocks ($M = 5.89$, $SD = 1.08$). There was no main effect of Age group: $F(1,33) = .002$, $p = .97$, or Condition by Age group interaction: $F(1,33) = .23$, $p = .64$.

Behavioural responses during scanning

As the games were self-paced, the number of button presses (combining throws and mark responses) made in inclusion and exclusion conditions were compared in a mixed model Condition by Age group ANOVA. There was a main effect of Condition: $F(1,33) = 162.88$, $p < .001$, $\eta_p^2 = .83$, due to a higher mean number of throws per block in the inclusion condition ($M = 8.71$, $SD = .61$) than in the exclusion condition ($M = 7.53$, $SD = .37$). This was likely because the videos in which the other characters passed the ball to each other were slightly longer than those involving the participant, as RTs were actually slightly faster in the exclusion condition ($M = 500$ ms, $SD = 160$) than in inclusion, ($M = 555$ ms, $SD = 192$; though this difference was not significant ($p = .094$)). There was no main effect of Age group or Condition by Age group interaction for either the mean number of throws per game, or mean RTs to make/mark each throw. The choice of which player to throw to on each trial also did not vary between Age groups ($p > .40$). Across inclusion and exclusion (in which the first throw was made by the participant) 52.04% of throws were made to the player on the left, and 47.96% to the player on the right.

fMRI data

Results surviving cluster-level correction at $p < .05$ for the contrasts exclusion > inclusion and inclusion > exclusion are presented in Table 2.

Main effect of condition

Significantly increased BOLD responses to exclusion relative to inclusion falling in predicted regions were seen in the left vIPFC (BA 47), and in a large bilateral cluster with its peak in mPFC (Fig. 2). As this midline cluster was so extensive, Brodmann area masks were systematically applied using WFU PickAtlas (Maldjian et al., 2003) in order to determine which specific brain regions it comprised. Regions surviving cluster-level FWE correction were identified in each of Brodmann areas 10, 11, 25 and 24/32 (medial PFC, medial OFC, subgenual ACC, ventral ACC, respectively). Significant clusters in non-predicted regions were seen in the bilateral occipital cortex, left fusiform gyrus, right anterior temporal cortex, and caudate. For the reverse

contrast (inclusion > exclusion), significant clusters fell in the bilateral occipital cortex, right superior temporal sulcus, and left dorsolateral PFC.

Effects of age and self-report variables in predicted main effect peaks

Post-hoc analyses were conducted on contrast estimates in the two peak voxels from clusters in predicted regions: left mPFC ($[-12\ 42\ -9]$) and left vIPFC ($[-48\ 33\ -15]$). Resistance to Peer Influence (RPI) score and social distress were used as continuous self-report variables. There was an interaction between Age group and RPI score in the left mPFC peak: $F(1,31) = 5.72$, $p = .023$. This was driven by a negative correlation between BOLD response and RPI score in the adolescents: $r = -.51$, $p = .025$, but not in the adults: $r = .27$, $p = .31$ (Fig. 3). No other relationships between self-report variables and BOLD signal reached significance in either peak.

Condition by Age group interaction

Small volume correction (SVC) performed in the right vIPFC revealed a significant interaction in the predicted direction (adult > adolescent) (MNI peak coordinate $[45\ 27\ -3]$, $k = 2$, $t = 3.46$, $z = 3.17$, voxel-level FWE-corrected $p = .048$). Post-hoc t-tests showed greater activation during exclusion than inclusion in adults: $t(15) = 3.00$, $p = .005$, uncorrected; and greater activation during inclusion than exclusion in adolescents: $t(18) = -2.35$, $p = .015$, uncorrected (Fig. 4). No interaction was found between Condition and Age group in the sgACC.

Whole brain regression analyses

There were no significant correlations between BOLD signal and age within the adolescent group in predicted regions, potentially due to the small age range within this group. Controlling for significant Age group differences in distress ratings and RPI scores, there were no significant relationships between BOLD signal and either of these self-report measures in predicted regions.

Discussion

The present study investigated neural responses to social rejection in healthy adolescent and adult females using an adapted version of the Cyberball social exclusion paradigm. Self-report data collected outside the scanner replicated previous studies (Sebastian et al., 2010a), with adolescents finding social exclusion more distressing than adults. Neural responses to social exclusion (relative to inclusion) across all participants were seen in a large cortical midline cluster and in left

Table 2
Main effects for exclusion > inclusion and inclusion > exclusion surviving FWE correction at the cluster level. BA = Brodmann area; L/R = Left/Right; Peak voxel = xyz voxel coordinates in MNI space; k = cluster size in $3 \times 3 \times 3$ mm voxels; z = z-score; * result in predicted region.

Brain region	BA	L/R	Peak voxel	k	z	Cluster corrected p-value
<i>Main effect of Condition (exclusion > inclusion)</i>						
Occipital cortex (middle occipital gyrus)	18	R	24 – 87 – 9	225	5.43	<.001
	17	R	15 – 90 – 9		5.23	
	17	R	9 – 93 – 3		4.36	
Medial PFC (medial frontal gyrus) (Ext. ventral/subgenual ACC) (Ext. medial OFC)	10	L	– 12 42 – 9	193	4.97	<.001*
	24/32	R	3 24 – 9		4.62	
	11	L	– 3 39 – 15		4.41	
Occipital cortex (cuneus)	18	L	– 24 – 99 – 6	79	4.58	<.001
Inferior temporal cortex (fusiform gyrus)	20	L	– 42 – 15 – 24	83	4.40	<.001
Ventrolateral PFC (inferior frontal gyrus)	47	L	– 48 33 – 15	32	4.39	.042*
	47	L	– 39 33 – 12		3.12	
Caudate tail	–	L	– 18 – 42 18	40	4.23	.016
Anterior temporal cortex (middle temporal gyrus)	21	R	48 9 – 33	71	4.15	.001
<i>Main effect of Condition (inclusion > exclusion)</i>						
Occipital cortex (cuneus, ext. bilaterally)	30	–	0 – 69 3	328	5.71	<.001
	–	R	3 – 66 – 15		4.33	
Superior temporal sulcus	39	R	48 – 51 15	35	4.30	.029
Dorsolateral PFC (middle frontal gyrus)	10	L	– 36 51 18	35	3.92	.029
	46	L	– 42 45 12		3.80	
	10	L	– 27 51 15		3.44	

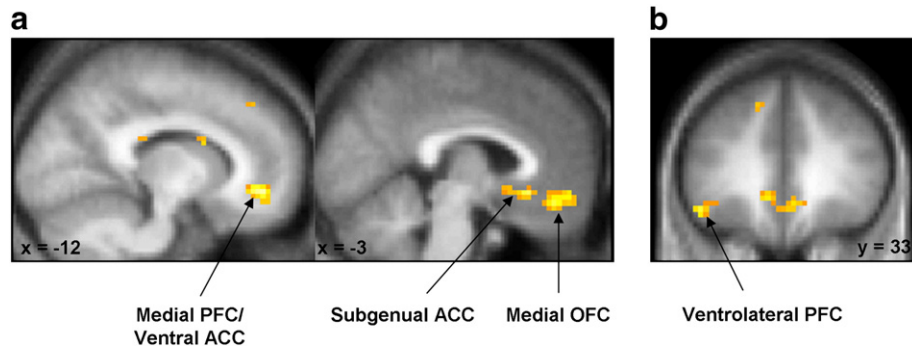


Fig. 2. Main effects for the contrast exclusion > inclusion. Elevated BOLD response to exclusion relative to inclusion was seen in the following predicted regions: a) a cluster in medial PFC extending into subgenual/ventral ACC and medial OFC bilaterally; and b) left ventrolateral PFC. Results are shown at a threshold of $p < .001$, overlaid on an average structural scan from all 35 participants.

vlPFC. In the mPFC peak, there was a negative relationship between BOLD response and RPI score in the adolescents, but not in the adult group. Comparing age groups directly revealed that adults activated right vlPFC in response to exclusion (relative to inclusion), more than did adolescents. This is in line with previous studies suggesting functional development between adolescence and adulthood in this regulatory region, and suggests that increased sensitivity to rejection in adolescence may result from reduced regulation of social distress.

Effects of Cyberball task adaptations

One aim of this study was to explore whether brain regions involved in social and affective processing would respond to social exclusion (relative to inclusion) in a version of the Cyberball paradigm with improved experimental control. The task was indeed capable of eliciting robust effects, largely in predicted regions.

Across all participants, a response was seen in the left vlPFC (inferior frontal gyrus, orbital part). Effects of exclusion in this region in previous Cyberball studies have been right lateralised (Eisenberger et al., 2003,

Masten et al., 2009), in line with lesion evidence suggesting that right vlPFC is crucial for inhibitory control (Aron et al., 2004). However, recent work suggests that this region is recruited bilaterally during inhibitory control (Hampshire et al., 2010), and a left vlPFC response in a very similar region to that reported here has been shown to correlate with emotion reappraisal success (Wager et al., 2008). One additional possibility is that the Condition by Age group crossover interaction found in right vlPFC (discussed below), may have obscured a main effect in this region. Previous studies have found activity in vlPFC to correlate negatively with reported distress (Eisenberger et al., 2003; Masten et al., 2009), suggesting that this region is involved in the regulation of negative affect caused by exclusion. The inclusion of the 'mark' key press response during exclusion blocks in the current study additionally reduced the possibility that vlPFC activity may reflect inhibition of a prepared motor response, and thus increases the specificity of the finding to social rejection.

The other significant cluster had its peak in left mPFC, but extended into vACC, sgACC and mOFC bilaterally. This result provides a partial replication of previous studies. Responses in the current study were

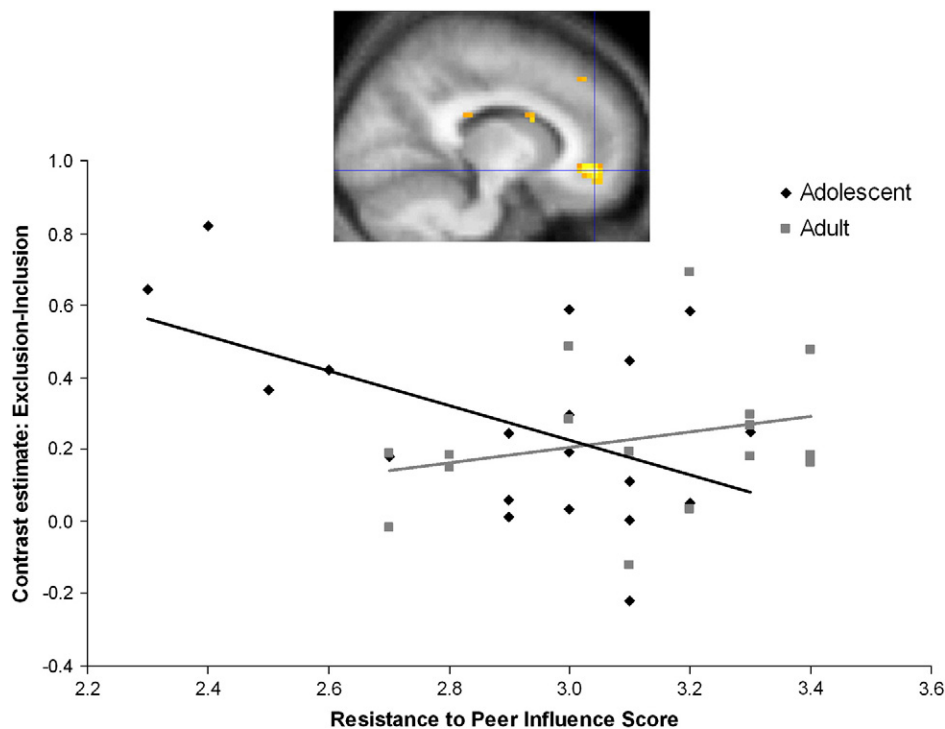


Fig. 3. In the medial PFC peak voxel for the contrast exclusion > inclusion ($[-12\ 42\ -9]$), there was an inverse relationship between BOLD response and Resistance to Peer Influence (RPI) score in the adolescents (in black) but not in the adults (in grey). The interaction between Age group and RPI score was significant.

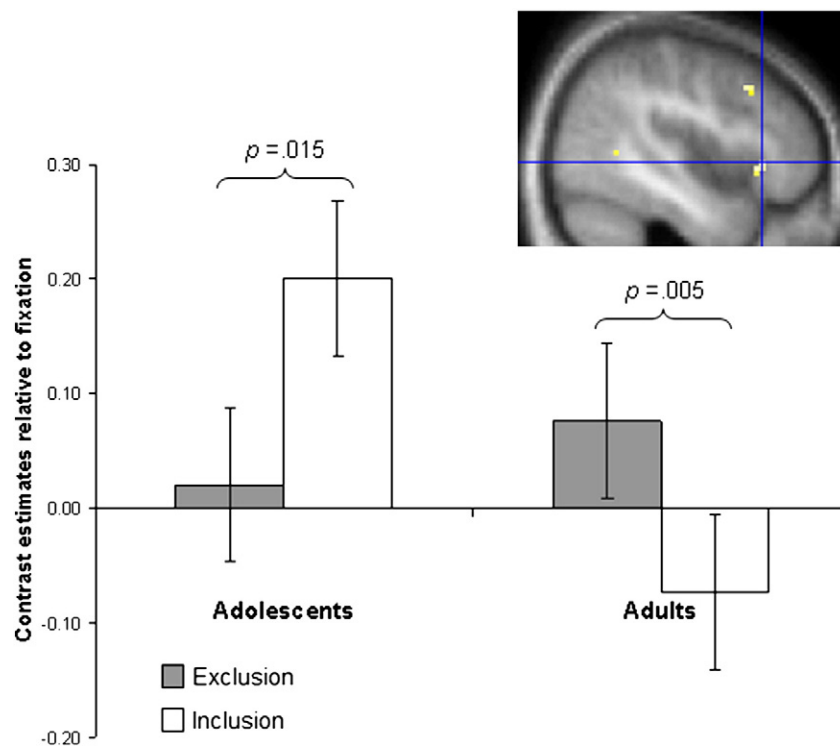


Fig. 4. Condition by Age group interaction in the right ventrolateral PFC ([45 27 –31]) (shown inset, at a threshold of $p < .005$, overlaid on an average structural scan from all 35 participants). Adults activated this region more in response to exclusion than inclusion, while adolescents exhibited the reverse pattern. Bars indicate the pooled standard error of the difference for exclusion–inclusion.

confined to the ventral portion of the PFC, and did not include the dorsal ACC (dACC), a region activated during rejection in previous studies (Eisenberger et al., 2003, 2007a,b). The lack of a dACC response may have been due to methodological differences between this and previous Cyberball studies. In particular, motor responses were matched between conditions in the current study. In addition, the current study used multiple and randomised blocks, which aimed to reduce the possibility of expectation violation during the exclusion condition (Somerville et al., 2006).

In a study of adolescents aged 12–13, Masten et al. (2009) also failed to find a dACC response to rejection, but instead found a positive association between sgACC response and self-reported distress. In the current study, sgACC responded to exclusion relative to inclusion across the entire sample. This is in line with previous studies showing sgACC activation to negatively valenced stimuli in healthy adults (George et al., 1995; Haas et al., 2007), and with evidence showing a relationship between activity in this region and symptom severity in major depression (Keedwell et al., 2009). The sgACC has autonomic connections with the central nucleus of the amygdala and periaqueductal grey (Neafsey et al., 1993), both of which are involved in the perception of affect, including social pain (Eisenberger, 2006). It has been suggested that sgACC integrates autonomic information and is preferentially activated by personally relevant emotional experience as opposed to simple nociception (Vogt, 2005). The current data are in line with this account, suggesting a role for sgACC in the affective experience of social pain.

The response in mPFC (BA10) and vACC (BA24/32) is partially in line with predictions. The ventral portion of mPFC commonly responds during self-evaluation (Kelley et al., 2002; Macrae et al., 2004), and self-evaluation processes are automatically triggered by social exclusion (Leary et al., 1995; Williams, 2007). This region may also regulate negative affect via connections with rostral ACC and amygdala (Buckholz et al., 2008). However, Somerville et al. (2006, 2010) found that activity in a region of the mPFC encompassing both regions (termed vACC/mPFC) responded preferentially to positive social

feedback relative to negative, in contrast to the present study. Since the cluster in the present study includes the peak reported by Somerville et al. ([–6 49 –13]), task differences may explain the discrepancy. Both tasks involved social evaluation; however, there may be similarities between the rejection condition in the present study, and the acceptance condition in the studies by Somerville et al. For example, Somerville et al. (2010) found activity in this region was enhanced to positive feedback specifically in individuals with low self-esteem. In these participants, positive feedback may have triggered a re-evaluation of the self, while rejection feedback did not. In contrast, previous Cyberball studies have shown that it is only the exclusion condition (and not inclusion) that causes a shift in affective ratings and self-esteem relative to baseline measurement (Sebastian et al., 2010a). As such, it is exclusion, rather than inclusion, that would be more likely to trigger self-evaluation processes mediated by mPFC.

Finally, the medial cluster also extended into medial OFC (BA 11). This region has not previously been reported in studies of social rejection, possibly because this is a region commonly affected by susceptibility artefact. The present study used an EPI sequence that had been optimised to detect signal within the orbitofrontal cortex and compensates for susceptibility artefact (Weiskopf et al., 2006). Medial OFC predicts reward and punishment outcomes in order to guide flexible behaviour (Schoenbaum et al., 2009), a role which may extend to encoding the value associated with a particular person in a social encounter (Behrens et al., 2009). Over the course of an exclusion block, this value might need to be updated.

Although the new task aimed to preserve some of the ecological validity of the original, some compromises were inevitable. For example, the short, randomised blocks made the task less realistic, and so we decided not to explicitly deceive participants into believing that the other players were real people. However, since Zadrozny et al. (2004) has shown that participants are equally distressed by rejection when they know they are playing Cyberball with a computer as with 'real' people, it was decided that this was an acceptable compromise. One further difference between this and previous Cyberball fMRI

studies, is that no relationships were found between BOLD responses and self-reported distress. The short blocks and randomised condition order meant that it was difficult to assess online subjective distress during inclusion and exclusion conditions. Instead, participants completed a single questionnaire after the scanning session. The questionnaire may therefore have lacked specificity to capture a particular affective response at a particular time. Overall, however, the new task was able to demonstrate that social, affective and regulatory brain regions respond to social exclusion, relative to inclusion, in a relatively minimal online social rejection paradigm which aimed to optimise experimental control.

Developmental differences

A further aim of this study was to investigate the neural bases of behavioural evidence suggesting that adolescent females report heightened negative affect relative to adults following social rejection (Sebastian et al., 2010a). Social rejection is experienced by a significant minority of adolescents on a regular basis (Wang et al., 2009). It is therefore important to understand how an experience like social rejection impacts on the developing brain as compared with adults.

An interaction between Condition and Age group was found in a small cluster in right vIPFC, with a greater response in this region in adults than in adolescents. This was driven by a greater response to exclusion than inclusion in the adults, and the reverse pattern in the adolescents. This finding is in agreement with previous studies showing a reduced or reversed response in right vIPFC in adolescents compared with adults during affective and behavioural control tasks (Sebastian et al., 2010b; Eshel et al., 2007). As discussed above, vIPFC has been characterised in terms of its role in inhibitory aspects of cognitive control (Aron et al., 2004), including the regulation of negative affect (Eisenberger et al., 2003; Masten et al., 2009), potentially via connections with subcortical structures such as the amygdala (Wager et al., 2008; Ochsner and Gross, 2005). It may be that the atypical adolescent response seen in this region underlies increased levels of self-reported distress following rejection in this group relative to adults. Understanding that adolescents may not have the same regulatory resources to bring to bear on an experience of social rejection may inform strategies for helping victims of social bullying to overcome their responses to it.

Correlational analyses revealed a further developmental effect. In the mPFC peak, an interaction was found between age and RPI score (accounting for the overall difference between Age groups). In adolescents, but not in adults, mPFC activity was negatively correlated with RPI score, i.e. the less this region responded to social rejection, the more adolescents reported being resistant to peer influence. The specificity of the effect for the adolescent group suggests that the relationship may be driven by a developmental process in this region. Behavioural data suggests that the ability to resist peer influence develops in a linear fashion between the ages of 14 and 18 (a range which includes the adolescent group), and plateaus thereafter (Steinberg and Monahan, 2007). The mPFC is known to mediate self-evaluative processes (Kelley et al., 2002; Macrae et al., 2004), and adolescents may rely on others' appraisals of them during self-evaluation more than do adults (Pfeifer et al., 2009). Although speculative, the observed reduction in mPFC response with increasing RPI score may reflect a similar reduction in the extent to which external cues (such as social rejection) trigger a self-evaluative response in the adolescents. It was noted that RPI scores showed relatively small variance in adults compared to adolescents. This may be one reason for the absence of neural association in adults. An alternative explanation is that the larger variance in adolescents is mediated by developmental processes in regions such as the mPFC, with inter-individual variance on this trait decreasing in adulthood.

In sum, this study demonstrated that social brain regions respond to rejection in a version of the Cyberball game optimised for experimental control. This may be of use in future investigations into the neural bases of responses to social rejection. Differences between adolescents and adults in regions including right vIPFC and left mPFC suggest continuing maturation of regions subserving emotional control and self-evaluative processing during social rejection. Future studies could investigate the extent to which individual differences in the experience of rejection in everyday life might mediate these effects. Future work could also build on the current findings to increase applicability to the educational setting, for example by exploring whether emotion regulation training might mitigate some of the negative affective consequences of social bullying. As we learn more about the extent to which social cognitive abilities continue to develop during adolescence, it is possible that the development of skills such as self-awareness and emotion regulation will be factored into the school curriculum.

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