I see you: insights into the neural and affective signatures of connectedness between parents and adolescents

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Chapter 4

Neural and affective responses to prolonged eye contact with parents and unfamiliar others in depressed and non-depressed adolescents

Under review:
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Link to preregistration prior to data analyses: https://osf.io/p6r28/?view_only=77a2cc7485ae41a2888a8d2301dd943c

ABSTRACT

Eye contact improves mood, facilitates feelings of connectedness, and is assumed to strengthen the parent-child bond. Adolescent depression is linked to general difficulties in social interactions, including the parent-child relationship. We aim to elucidate adolescents' affective and neural responses to prolonged eye contact with one's parent and how these responses are affected by adolescent depression. While in the MRI scanner, 59 non-depressed (healthy controls; HC) and 19 depressed adolescents were asked to make eye contact with their parent, an unfamiliar peer, an unfamiliar adult, and themselves using videos of prolonged (16-38 s) direct and averted gaze. After each trial, adolescents reported on their mood and feelings of connectedness, and we measured their eye movements and BOLD-responses during the videos. Eye contact boosted adolescents' mood and feelings of connectedness and increased activity in inferior frontal gyrus (IFG), temporal pole and superior frontal gyrus. Unlike HCs, eye contact did not boost the mood of depressed adolescents. While HCs reported increased mood and feelings of connectedness with their parent relative to others, depressed adolescents did not. Depressed adolescents exhibited blunted activity in IFG, potentially reflecting a blunted response to the prolonged presentation of faces. This study indicates that eye contact with others is less rewarding for depressed adolescents, including with their parents, whereas the blunted IFG may reflect a lack of social engagement characteristic for (adolescent) depression.

Keywords: Prolonged eye contact; MDD; Parent-child bonding; Non-verbal social cues; fMRI; Eye tracking

INTRODUCTION

Eye contact facilitates feelings of connectedness with others (Emery, 2000; Hietanen, 2018) and particularly *prolonged* eye contact has been associated with stronger positive affect (Kuzmanovic et al., 2009; Wever et al., 2022). Within the parent-child context, eye contact constitutes one of the first acts of reciprocity between a parent and child after birth and is considered an important facilitator of the parent-child bond (Robson, 1967). Being able to draw the attention of one's parent by making eye contact enables infants to signal their physical and emotional needs to their parent. At the same time, the rewarding nature of positive affect through eye contact with a child is thought to reinforce sensitive caregiving behavior in parents (Robson, 1967). In a prior study we showed that eye contact between a parent and child is still relevant during adolescence, since parents reported a better mood and feel more connected in response to eye contact with their adolescent child compared to unfamiliar others (Wever et al., 2022). However, *adolescents'* neural and affective responses to eye contact with their parent have not been studied, yet.

Adolescence is characterized by substantial transitions in the socio-emotional domain (Crone & Dahl, 2012). This is also reflected in the fact that adolescents start to become more independent from their parents and focus more on peers, although parental support remains positively associated with adolescents' wellbeing and mental health (Baumrind, 1991; Yap et al., 2014). Adolescents show enhanced sensitivity to social evaluation, with negative social experiences (e.g., rejection) particularly inducing negative feelings (Vijayakumar et al., 2017; Will et al., 2016). Moreover, the increased sensitivity to social evaluation combined with exposure to social adversity has been linked to the onset of depression in adolescence (Crone & Dahl, 2012; Dahl, 2004; Giedd & Rapoport, 2010; Hankin & Abramson, 2001; Wilson et al., 2015). Common characteristics of adolescent depression are difficulties in the social domain, including social isolation and dysfunctional interpersonal relationships (Hammen, 2009; Hammen et al., 2008), putting a strain on their relationships with both parents and peers (Babore et al., 2016; Branje et al., 2010; Heaven et al., 2004; Sheeber et al., 2001). Moreover, depressed adolescents tend to perceive their parents as less warm and more critical and report a lower parent-child relationship quality compared to non-depressed adolescents (Branje et al., 2010; Sheeber & Sorensen, 1998; Yap et al., 2010). One hypothesis is that, similar to adults with a depression (Suffel et al., 2020), depressed adolescents have more difficulties to attune to others during social interactions and may show altered neural responses in networks supporting social cognition. As such, examining how adolescents respond to eye contact with their parents and unknown others, and whether these responses differ between depressed and non-depressed adolescents in terms of their neural and affective responses might elucidate processes regarding difficulties in interpersonal functioning in depressed adolescents and whether this concerns interactions in general or is specifically relevant to the parent-child context.

This study therefore examined adolescents' general neural responses to prolonged eye contact with their parent in healthy adolescents (aim 1). In addition, we examined whether these responses differ between depressed and non-depressed adolescents (aim 2). To examine whether adolescents' responses are unique to the parent-child relationship, we compared these responses to adolescents' responses to eye contact in other social contexts, i.e., with an unfamiliar peer and adult. We used a novel eye contact task (validated in adults (Wever et al., 2022)) in which adolescents are presented with personalized videos of prolonged direct and averted gaze. All study measures, hypotheses and analyses were preregistered prior to data analyses (https://osf.io/p6r28/). Non-depressed adolescents were hypothesized to have a better mood and feel more connected after making prolonged eye contact with others. Moreover, based on prior neuroimaging findings in parents of adolescents (Wever et al., 2022), we expect them to show differential neural responses when looking at their parent versus unfamiliar others in brain regions associated with mentalizing (i.e., dmPFC, TPJ) and familiarity (i.e., IFG, fusiform gyrus) (Laurita et al., 2019a). We expected that depressed adolescents report a lower mood and feel less connected in response to eye contact, independent of target identity. Lastly, we explored whether depressed and non-depressed adolescents differ in their neural and gaze responses to eye contact with their parents and unfamiliar others.

METHOD

Participants

Adolescents and their parents participated in the context of the RE-PAIR study: "Relations and Emotions in Parent-Adolescent Interaction Research". This study compared families with an adolescent with major depressive disorder (MDD) or dysthymia to families with an adolescent without psychopathology. Families included in the study were Dutch speaking, adolescents were aged between 11 and 17 years at study inclusion, and lived with at least one of their parents/caregivers. Families with an adolescent without psychopathology (healthy controls; HC) were included if the adolescent was not diagnosed with a (neuro)psychiatric disorder in the two years leading up to the study and had no lifetime diagnosis of MDD/dysthymia. Families with an adolescent with MDD/dysthymia (DEP) were included if the adolescent met criteria for one of these primary diagnoses, verified with the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS; Kaufman et al. (1996)). They could not participate if the adolescent met criteria for a primary diagnosis of a current (neuro)psychiatric disorder other than MDD or dysthymia, a comorbid psychosis, substance use disorder, or mental retardation. Exclusion criteria for the functional magnetic resonance imaging (fMRI) part of the study were incompatibilities with MRI scanning (e.g., metal implants, pregnancy).

Sixty-three HC and 22 DEP adolescents participated in the fMRI part of the study. Four HCs were excluded; $n = 3$ due to scanner artefacts and $n = 1$ due to an (a posteriori discovered) depression score in the clinical range according to the Patient Health Questionnaire (i.e., PHQ-score of 18), which was preregistered as an exclusion criterion. Three DEP adolescents were excluded; $n = 1$ due to scanner artefacts, $n = 1$ due to claustrophobia, and $n = 1$ due to distress related to exposure to participants' own videos. This resulted in a final sample of $n = 59$ HC and $n = 19$ DEP adolescents performing the eye contact task in the MRI scanner (see Table 4.1 for demographics and clinical characteristics). Details on the full study procedure can be found in Supplement S4.1.

The study was approved by the medical ethical committee of the Leiden University Medical Centre (LUMC; P17.241) and was performed in accordance with the declaration of Helsinki and the Dutch Medical Research Involving Human Subjects Act (WMO).

Eye contact task

To assess neural and affective responses to prolonged eye contact, adolescents performed the "eye contact task" (see Wever et al. (2022) and Figure 4.1 for an overview of the task). During this task adolescents were shown pre-recorded videos of their parent, an unfamiliar peer, an unfamiliar adult, and themselves; all facing the camera. Each video contained a single target who looked straight into the camera (direct gaze) or averted their gaze to the left side of the camera (averted gaze), resulting in eight distinct conditions: Gaze direction (2 levels: Direct gaze, averted gaze) × target (4 levels: Parent, unfamiliar child, unfamiliar adult, self). See Supplement S4.2 for details about preparation and presentation of the videos. We simultaneously recorded eye movements during the task using an eye-tracker.

While in the scanner, adolescents were instructed to make eye contact with the targets in the videos. Each trial started with a fixation cross (2-5 s), after which they were presented with a video of one of the targets in one of the gaze directions for 16-38 s. The gender of the unfamiliar peer was matched to adolescents' own gender and the gender of the unfamiliar adult was matched to the gender of their parent in the task. After watching a video of their parent, an unfamiliar peer, and an unfamiliar adult, adolescents were asked to answer three questions; (1) "How connected do you feel with this person at this moment?", (2) "How do you feel about this person at this moment?", and (3) "How do you feel at this moment?". After the videos of themselves, adolescents only reported on their mood (question 3). Adolescents answered the questions on a Likert scale ranging from 1 (*not at all/very negative*) to 7 (*very much/very positive*) and were instructed to answer and confirm the question within 8 s. The questions were self-paced and participants could press any button to display a box around the middle option, and then press the button corresponding to their right index (to go left) and right middle finger (to go right) to move the box to their preferred answer. They could confirm their answer by pressing the button corresponding to their left index finger. Prior to the task, adolescents answered all abovementioned questions in response to pictures of each target with a direct gaze. We included this baseline measure to ascertain whether increases in affect could be attributed to making prolonged eye contact relative to baseline. Stimulus presentation and simultaneous eye movement recordings were conducted using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, United States) and the screen resolution was 1024×768 pixels. The videos were presented on the screen in 960×540 pixels.

Table 4.1 Demographics and clinical characteristics of depressed (DEP) and non-depressed (HC) adolescents.

	HC	**DEP**	**HC vs. DEP[1]**	
Mean (SD) / *n* (%)	**(*n* = 59)**	**(*n* = 19)**	***t* / χ^2**	***p***
Age adolescents, years	16.20 (1.21)	16.04 (1.50)	0.45	.650
Age parents, years	49.90 (5.17)	50.82 (4.81)	-0.69	.495
Gender adolescents				
Girls, n (%)	39 (66.1)	15 (79.0)	1.11	.291
Current educational level			2.00	.788
Lower vocational	7 (11.86)	3 (15.79)	-	-
Higher vocational	17 (28.81)	3 (15.79)	-	-
Pre-university	28 (47.46)	9 (47.37)	-	-
Secondary vocational	5 (8.48)	3 (15.79)	-	-
Higher professional	2 (3.39)	1 (5.26)	-	-
Handedness (EHI)				
Right-handed, n (%)	54 (91.53)	18 (94.74)	0.21	1.00
Pubertal development (PDS)	3.26 (0.63)	3.47 (0.62)	-1.27	.209
Depression severity (PHQ-9)	4.32 (2.54)	17.90 (4.05)	-17.32	<.001
Anxiety severity (SCARED)	12.32 (7.27)	34.21 (9.21)	-10.67	<.001
Parental-child bonding (PBI)				
Care	30.90 (5.12)	26.47 (5.99)	3.13	.003
Overprotection	3.41 (2.24)	7.26 (4.07)	-5.22	<.001
Lack of autonomy support	3.52 (2.57)	5.05 (4.55)	-1.84	.070

Note. DEP, Depressed adolescents; EHI, Edinburgh Handedness Inventory (Oldfield, 1971); HC, Healthy control or non-depressed adolescents; PBI, Parental Bonding Instrument (Parker et al., 1979); PDS, Pubertal Development Scale (Petersen et al., 1988); PHQ-9; Patient Health Questionnaire (Kroenke et al., 2001); SCARED, Screen for Child Anxiety Related Emotional Disorders (Simon & Bögels, 2009); SD, Standard deviation. [1] *p*-values were obtained using independent samples t-tests or Chi-square comparisons between depressed and non-depressed adolescents.

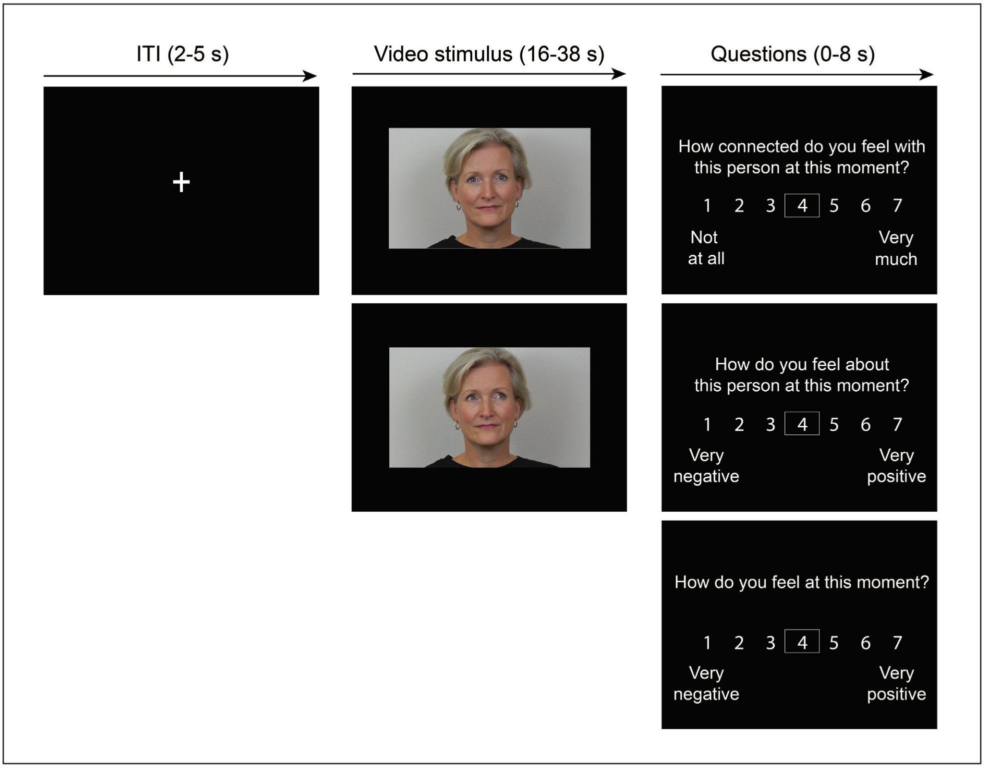


Figure 4.1 *Displays and timings of video stimuli of an unfamiliar adult with a direct and averted gaze in the eye contact task. Videos of adolescents' parent were contrasted with videos of an unfamiliar same-sex parent, an unfamiliar peer (same-sex adolescent), and videos of the self.*

Data preprocessing and analyses

Affective and gaze responses

Adolescents' affective and gaze responses were analyzed in R (R Core Team (2013), version 3.6.1) with the following packages: Lme4 for mixed model analyses, psych for descriptive statistics, and ggplot2 for data visualization (Bates et al., 2012; Revelle, 2012; Wickham et al., 2016). Questions that were not answered and/or confirmed were excluded from all affective response analyses, which resulted in 0.5% missing responses (11/ 2360 trials) in HC adolescents and 0.3% (2/760 trials) in DEP adolescents.

Eye tracking analyses

Eye movements were recorded with a tower mounted monocular EyeLink 1000Hz MRI-compatible eye tracker (SR Research Ltd., Mississauga, Ontario, Canada), placed inside the scanner bore. We used a customized MATLAB (MathWorks, Inc., Natick, MA, version 9.5) script to preprocess raw eye movement data into information on gaze position and duration. Using an established algorithm for face and facial feature detection (Viola & Jones, 2001) we created rectangular areas of interest (AOIs) around the left and right eye of the targets in all videos that were combined into a single AOI of the eye region for further analyses. The primary gaze measure was the percentage of dwell time within the eye region per video relative to the total video duration, in which dwell time is defined as the time spent looking within an AOI. The eye tracker was calibrated and validated using a nine-point calibration grid from EyeLink's calibration protocol. Collection of gaze data of 25 adolescents (HC: $n = 17$, DEP: $n = 8$) was unsuccessful due to technical problems or a failed calibration procedure (e.g., due to sight deficiencies, participants wearing glasses, or participants having light-colored eyes). In addition, 19 trials of nine adolescents (HC: $n= 6$, DEP: $n=3$) were excluded due to $>$30% missing gaze data. This resulted in a final set of gaze data of 53 (out of 78) adolescents (HC: $n = 42$; DEP: $n = 11$), including 829 trials (out of 848; 2.2% missing).

fMRI data acquisition and neuroimaging analyses

MR images were acquired using a Philips 3.0T Achieva MRI scanner equipped with a SENSE-32 channel head coil. For the eye contact task, T2*-weighted echo planar imaging was used and a structural 3D T1 scan was acquired (see Supplement S4.3 for details on scan parameters). MRI data were preprocessed and analyzed using SPM12 (Wellcome Trust Centre for Neuroimaging, University College London). Functional MR images were slice-time corrected, corrected for field-strength inhomogeneity's using b0 field maps, unwarped and realigned, co-registered to subject-specific structural images, normalized to MNI space using the DARTEL toolbox (Ashburner, 2007), and smoothed using an 8-mm full width at half maximum isotropic Gaussian kernel. Raw and preprocessed data were checked for quality, registration, and movement. Average head movement per adolescent did not exceed 1 voxel (i.e., 3 mm) (M = 0.075 mm, SD = 0.083 mm, range: 0.038-0.252 mm). We corrected for serial autocorrelations using a first order autoregressive model (AR(1)). Low-frequency signals were removed using a high-pass filter (cutoff = 128 s) and we included nuisance covariates to remove effects of run.

First, to examine neural responses to gaze direction, target, and their interaction within the sample of HC adolescents, we constructed a generalized linear model with 8 regressors indicating cue onset for each condition and one regressor for onsets of subjective ratings. Cue onset regressors were defined from the onset of the video and modeled for its duration (16-38 s). The subjective rating regressor was defined from the onset of each question and modeled for the duration the question was displayed on the screen, including 1000 ms during which a "Too late!" screen was shown in case adolescents did not answer within the set time period of 8000 ms (self-paced; M = 2946 ms; SD = 1259 ms; range = 749-9002 ms). Six motion parameters (based on the realignment parameters) were included to correct for head motion.

Eight first-level SPM T-contrasts were specified, one for each condition (i.e., direct and averted gaze of parent, unfamiliar peer, unfamiliar adult, self). These T-contrast images were entered in a 2 × 4 full factorial ANOVA design with two within-subject factors (i.e., gaze direction and target). SPM F-maps were computed to assess main effects of gaze direction and target, and their interaction, followed up by post-hoc analyses between all conditions. Second, to examine group differences between DEP and HC adolescents, we entered previously described t-contrasts in a 2 × 2 × 4 full factorial ANOVA design with one between-subject factor (group) and two within-subject factors (gaze direction and target). SPM F-maps were computed to assess main effects of group, gaze direction and target, and their interactions (i.e., group × gaze direction, group × target, group × gaze direction × target), followed up by post-hoc analyses between all conditions.

At the second-level, we first performed region of interest (ROI) analyses using independently defined functional ROIs (8-mm spheres MNI space) surrounding peak voxels of brain region based on previously found regions using the eye contact task in a sample of adults Wever et al. (2022) and Supplement S4.4). We used the MarsBar toolbox (Brett et al., 2002) to extract activity from five ROIs, i.e., left temporoparietal junction (TPJ), dorsomedial prefrontal cortex (dmPFC), bilateral inferior frontal gyrus (IFG), and right fusiform gyrus (FG). To assess the effects of group, gaze direction, target, and their interactions, we performed generalized linear mixed regression analyses and post-hoc tests in R. All ROI analyses were Bonferroni corrected for the number of tests ($p < .05/5$). Thereafter, to explore blood oxygenation level-dependent (BOLD)-responses in brain regions outside the ROIs, we performed complementary whole-brain analyses that were corrected for multiple comparisons with family-wise error cluster (FWE) correction at $p < .05$ (with a cluster-forming threshold of $p < .001$).

To check whether results were not driven by differences in age, gender, handedness, and pubertal status of adolescents, we performed additional analyses to control for these variables (see Supplement S4.5 for details on associated questionnaires).

RESULTS

Adolescents' general responses to prolonged eye contact in HC adolescents (aim 1)

Affective responses

To examine adolescents' affective responses to eye contact in HC adolescents and how this may vary as a function of target, we performed a generalized linear mixed regression model with gaze direction and target, and their interaction on adolescents' affect ratings (i.e., mood, connectedness, feelings about the targets).

Mood. Adolescents reported a better mood in response to direct versus averted gaze videos (B = -0.16, SE = 0.04, t(880) = -4.21, p <.001, d = 0.27, Figure 4.2-A left panel). In addition, adolescents' mood was dependent on the target in the videos ($\chi^2(3)$ = 42.77, p <.001). Bonferroni corrected post-hoc analyses revealed that they reported a better mood after videos of their parent versus an unfamiliar peer (p <.001, d = 0.47), unfamiliar adult (p <.001, d = 0.56), or themselves (p <.001, d = 0.40). Adolescents did not significantly differ in their mood after videos of an unfamiliar peer, unfamiliar adult, and themselves (all ≥ p = .597). There was no significant interaction between gaze direction and target on adolescents' self-reported mood (p = .204).

Connectedness. Adolescents reported enhanced feelings of connectedness in response to direct versus averted gaze videos (B = -0.55, SE = 0.08, t(640) = -6.72, p <.001, d = 0.51, Figure 4.2-B left panel). In addition, adolescents' feelings of connectedness were dependent on the target in the videos ($\chi^2(2)$ = 1406.24, p <.001), with adolescents feeling more connected with their parent versus an unfamiliar peer (p <.001, d = 2.95) or adult (p <.001, d = 3.06), but they did not differ in how connected they felt with an unfamiliar peer versus adult (p = .665, all Bonferroni corrected). There was no significant interaction between gaze direction and target on adolescents' feelings of connectedness with others (p = .940).

To test whether prolonged eye contact boosted adolescents' mood and feelings of connectedness relative to baseline, we examined adolescents' self-reported affect in response to static pictures with direct gaze prior to the task with their averaged ratings after prolonged direct gaze videos of the targets during the task. These analyses indicated significant interactions between target and time point (i.e., pre-task versus task) on adolescents mood ($\chi^2(3)$ = 10.31, p = .016) and feelings of connectedness ($\chi^2(2)$ = 70.50, p <.001). Adolescents did not report a mood-boosting effect in response to prolonged videos of others (versus static pictures), but reported a lower mood after being confronted with a prolonged video of their own direct gaze. In addition, adolescents reported enhanced feelings of connectedness in response to prolonged eye contact (versus static pictures), which was most pronounced in response to direct gaze videos of unfamiliar others compared to their parent (Supplement S4.6).

Responses to the question "How do you feel *about this person* at this moment?" were highly correlated with adolescents' feelings of connectedness (r = 0.72, p <.001) and showed similar effects (see Supplement S4.7).

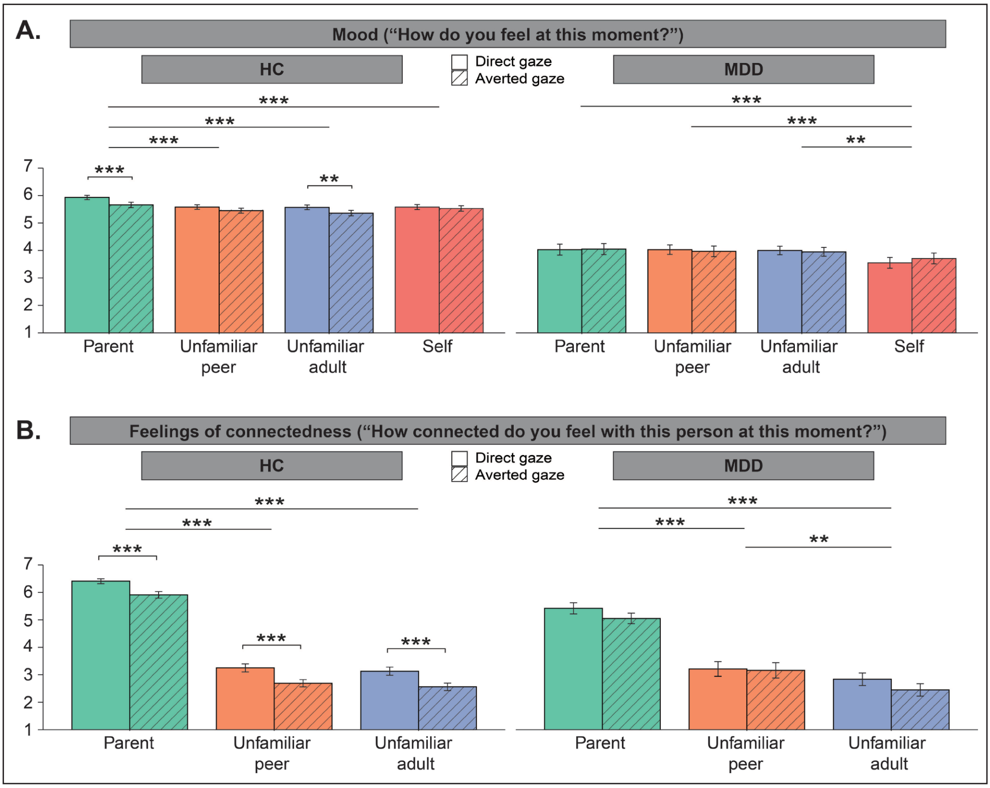


Figure 4.2 *Mean levels of self-reported mood (A) and feelings of connectedness (B) after the videos of each target (i.e., parent, unfamiliar peer, unfamiliar adult, self) in either gaze direction (i.e., direct and averted) in HC (n = 59) and DEP adolescents (n = 19). Eye contact boosted the mood and feelings of connectedness in HCs. Eye contact did not boost the mood of depressed adolescents and they reported lower feelings of connectedness after seeing their parent relative to seeing unfamiliar others compared to HC adolescents. Error bars represent standard error of the mean. Significant p-values <.05 are indicated by *, p <.01 by **, and p <.001 by ***.*

Gaze responses

HC adolescents gazed more towards the eye region of targets during videos of direct versus averted gaze (B = 3.09, SE = 1.22, t(611) = 2.54, p = .011, d = 0.20, see Figure 4.3-B left panel). Our analyses did not reveal a main effect of target (p = .143), nor an interaction between gaze direction and target on adolescents' gaze responses to the eye region of targets (p = .557).

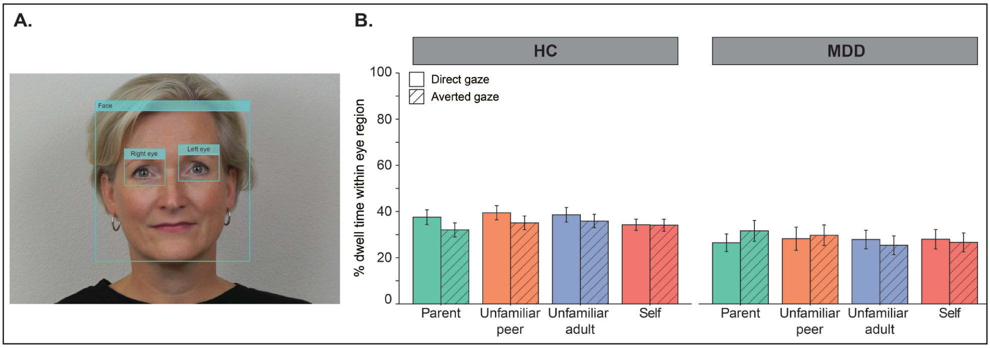


Figure 4.3 *Average levels of gaze toward the eye region of targets (i.e., parent, unfamiliar peer, unfamiliar adult, self) in either gaze direction (i.e., direct and averted gaze) in HC (n = 42) and DEP adolescents (n = 11). Gaze was operationalized as the percentage of dwell time within the eye region of targets relative to the total video duration per video. The right and left eye AOIs were combined into a single AOI of the eye region (A). HC adolescents gazed more toward the eye region of targets during direct versus averted gaze videos (B=3.09, SE=1.22, t(611)=2.54, p=.011, d=0.20). Gaze responses of HC adolescents were independent of the identity of the targets in the videos. DEP and HC adolescents did not differ in their eye gaze patterns, indicating that they made equivalent eye contact with the targets (B).*

Neuroimaging findings

For all ROIs we extracted BOLD-responses to direct and averted gaze of the targets. We examined the effects of gaze direction, target, and their interaction, while controlling for multiple comparisons ($p < .05/5$) in five separate generalized linear mixed regression model analyses.

Our analyses in HC adolescents revealed a significant main effect of target in left TPJ ($\chi^2(3) = 36.99$, $p < .001$), right IFG ($\chi^2(3) = 43.48$, $p < .001$), and right FG ($\chi^2(3) = 121.54$, $p < .001$). Post-hoc (Bonferroni corrected) pairwise comparisons revealed decreased deactivation in BOLD-response in left TPJ (parent: $p < .001$, $d = 0.56$; unfamiliar peer: $p < .001$, $d = 0.60$; unfamiliar adult: $p < .001$, $d = 0.73$) and decreased activation in BOLD-response in right IFG (parent: $p < .001$, $d = 0.68$; unfamiliar peer: $p < .001$, $d = 0.76$; unfamiliar adult: $p < .001$, $d = 0.65$), and in right FG (parent: $p < .001$, $d = 1.11$; unfamiliar peer: $p < .001$, $d = 1.20$; unfamiliar adult: $p < .001$, $d = 1.20$) in response to 'others' versus the self (Figure 4.4, left panels). There were significant main effects of target ($\chi^2(3) = 8.40$, $p = .038$) and gaze direction ($\chi^2(3) = 6.22$, $p = .013$) in dmPFC, but these effects did not survive correction for multiple comparisons ($p < .05/5$). Analyses in other ROIs did not reveal additional main effects of gaze direction, nor there were significant interactions between gaze direction and target on adolescents' neural responses in the eye contact task.

To test whether task-related BOLD-activation in brain regions outside the ROIs was found in HC adolescents in response to direct and averted gaze of all targets, we performed a complementary whole-brain analysis. These analyses revealed a main effect of gaze direction in left superior frontal gyrus (SFG), right IFG, and left temporal pole and a main effect of target in right FG, right precentral gyrus, bilateral angular gyrus/TPJ, left middle occipital gyrus, right cuneus, right middle frontal gyrus, left middle temporal gyrus, left superior temporal gyrus. See Supplement S4.8 and S4.9 for details and post-hoc analyses on the directions of the whole-brain effects.

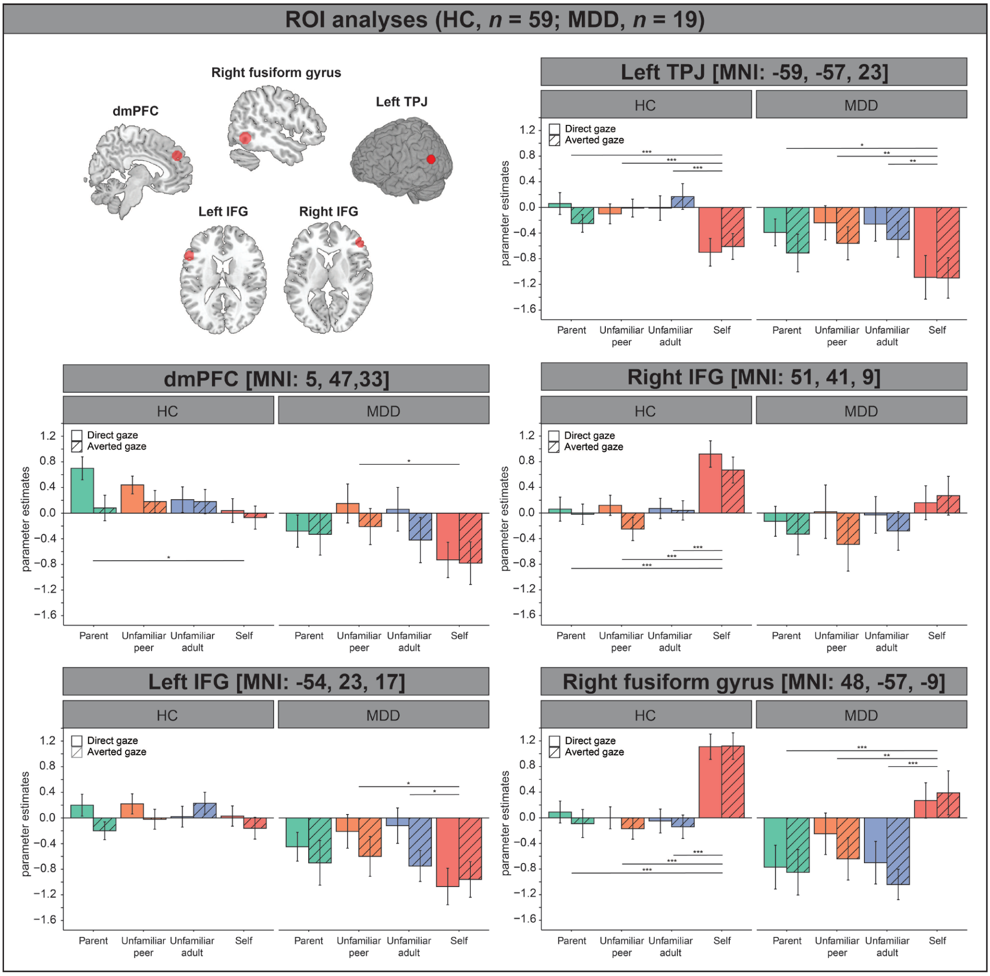


Figure 4.4 *Overview of regions of interest (ROIs) in brain regions previously found to be involved in prolonged eye contact in adults and results showing how gaze direction and target modulated BOLD-responses to prolonged eye contact with one's parent, an unfamiliar peer or adult and the self in HC (n = 19) and DEP adolescents (n = 19). All ROIs were Bonferroni corrected for the number of tests (p <.05/5). Error bars represent standard error of the mean. Significant p-values <.05 were indicated by *, p <.01 by **, and p <.001 by ***.*

Responses of DEP (versus HC) adolescents to prolonged eye contact (aim 2)

Affective responses

To examine differences in affective responses to eye contact between DEP and HC adolescents, we performed a generalized linear mixed regression analysis on the main effect of group (i.e., DEP versus HC), and its interactions with gaze direction and target on adolescents' affect ratings.

Mood. Overall, DEP adolescents reported a significantly lower mood after the videos compared to HCs (main effect group: $\chi^2(1) = 55.17$, $p < .001$, Figure 4.2-A). In addition, we found a significant interaction between group × target ($\chi^2(3) = 19.82$, $p < .001$). Whereas HCs reported a higher mood after videos of their parent versus an unfamiliar peer or adult, or themselves (all $p < .001$), DEP adolescents reported a lower mood after videos of themselves versus their parent ($p < .001$), an unfamiliar peer ($p = .001$), and an unfamiliar adult ($p = .003$). DEP adolescents did not show differences in self-reported mood in responses to videos of their parent versus an unfamiliar peer or adult. There was also a significant interaction between group × gaze direction ($\chi^2(1) = 5.07$, $p = .024$). Whereas HCs reported a better mood after videos with direct versus averted gaze ($p < .001$), gaze direction did not influence the mood of DEP adolescents ($p = .777$). There was no significant interaction between group × gaze direction × target on adolescents' mood ($p = .829$).

Connectedness. We found a significant interaction between group × target ($\chi^2(2) = 31.04$, $p < .001$), indicating that DEP (versus HC) adolescents reported to feel less connected with their parent ($p = .021$), whereas they did not differ in feelings of connectedness in response to videos of an unfamiliar peer or adult ($p = 1.000$, for both). There was no main effect of group on adolescents' feelings of connectedness ($p = .234$), nor a significant interaction between group × gaze direction ($p = .103$), indicating that DEP adolescents did not differ from HCs in how connected they felt in response to direct versus averted gaze videos. There was also no significant interaction between group × gaze direction × target on adolescents' feelings of connectedness ($p = .642$).

Gaze responses

To examine differences in gaze responses between DEP versus HC adolescents, we performed a generalized linear mixed regression model on the main effect of group, and its interactions with gaze direction and target on adolescents' percentage of gaze to the eye region of targets relative to the total video durations. We did not find a significant main effect of group ($p = .278$), indicating that DEP and HC adolescents did not differ in eye gaze behavior towards the eye region, irrespective of gaze direction or target. Also, there was no significant interaction between group × target (p = .491), group × gaze direction (p = .154), or between group × target × gaze direction (p = .441).

Neuroimaging findings

To examine differences in neural responses in DEP versus HC adolescents within the ROIs, we examined the main effect of group and their interactions with gaze direction and target on adolescents' neural responses, while controlling for multiple comparisons (p <.05/5) in five separate mixed regression model analyses in *R*. These analyses revealed a main effect of group in left IFG (B = 0.65, SE = 0.24, $t(76)$ = 2.68, p = .009, d = 0.73), showing diminished BOLD-activation in this brain region in DEP versus HC adolescents, irrespective of gaze direction or target. There was also a main effect of group in dmPFC (p = .026) and right FG (p = .017), but these effects did not survive corrections for multiple comparisons. There were no significant interactions between group × target (all ≥ p = .207) or between group × gaze direction (all ≥ p = .204), nor a significant interaction between group × gaze direction × target (all ≥ p = .069) on adolescents' neural responses in the ROIs.

4

To test for differences in task-related BOLD-activation in brain regions outside the ROIs between DEP and HC adolescents in response to direct and averted gaze of the targets, we conducted complementary whole brain analyses. The analyses revealed an overall hypoactivation in left secondary visual cortex in DEP versus HC adolescents when performing the eye contact task (main effect of group: MNI peak-coordinate [-8, -87, -9], Z = 5.23, $p_{\text{cluster-level}}$ <.001, k = 4746). There were no significant interactions between group × gaze direction, group × target, or group × gaze direction × target.

Neural responses to prolonged eye contact over time

As preregistered, we tested whether we could replicate a finding in adults who exhibited increased activation within the dmPFC with increasing duration of eye contact (MNI peak-coordinate: [2, 38, 47] (Wever et al., 2022). We performed a ROI analysis using an 8-mm spherical ROI around the peak-coordinate on the contrast of direct minus averted gaze videos pooled over all 'other' conditions (i.e., parent, unfamiliar peer, unfamiliar adult) for HC adolescents. We split each trial into three epochs of equal length and subsequently tested for parametric increases and decreases with presentation duration [-1 0 1]. We did not find a significant increase in BOLD-activation over the course of prolonged eye contact duration in this region of the dmPFC in HC adolescents.

Between-group differences in parametric increases and decreases of neural responses with increasing durations of eye contact were tested with an independent t-test between DEP and HC adolescents, using a whole-brain approach. We found a parametric decrease over time in left SFG in DEP adolescents, while activation in this region was not associated with eye contact duration over time in HCs (Figure 4.5).

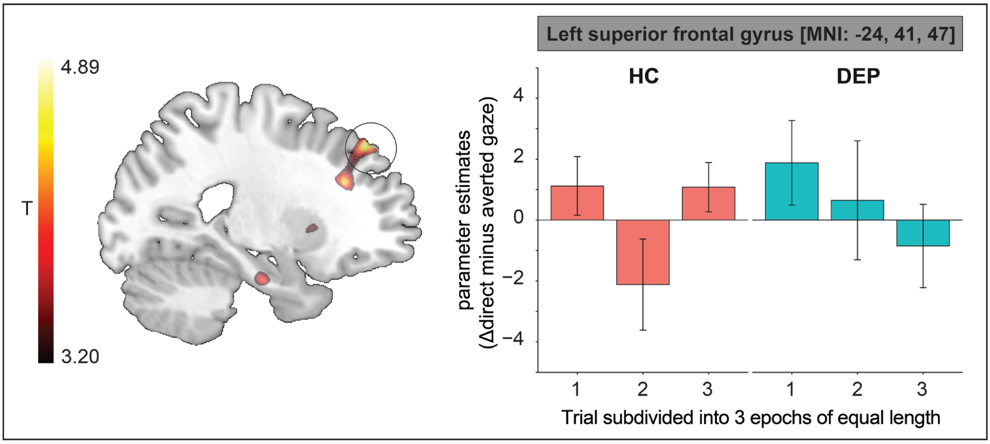


Figure 4.5 *Prolonged eye contact was associated with parametric decreases over time in left superior frontal gyrus in DEP adolescents, while activation in this region was not associated with eye contact duration over time in HCs. We performed a parametric analysis testing for differences in linear increases and decreases in neural responses associated with presentation duration of eye contact (Δdirect–averted gaze) between DEP and HC adolescents using a whole-brain approach. To visualize the parametric effect, we subdivide each video in 3 epochs of equal length and plotted average BOLD-responses in left superior frontal gyrus for each epoch.*

Confound analyses

All outcomes remained significant after controlling for age, gender, and pubertal status of the adolescents. In addition, all outcomes at the neural level remained significant after controlling for handedness. These findings indicate that results were not driven by one of these variables.

DISCUSSION

This study examined adolescents' affective and neural responses to prolonged eye contact with their parent and whether these responses differed in depressed adolescents. In response to eye contact, HC adolescents reported enhanced affective responses, made more eye contact, and showed enhanced neural responses in right IFG, left temporal pole, and left SFG, regardless of the target. Interestingly, they reported a better mood and felt more connected after the sight of their parent versus unfamiliar others. In contrast to HCs, eye contact did not induce a mood-boosting effect in depressed adolescents. While HCs reported increased mood and feelings of connectedness with their parent relative to the other targets, this effect was less strong in depressed adolescents. Furthermore, regardless of the target, depressed adolescents showed diminished neural activation in left IFG and left secondary visual cortex compared to HCs, suggesting blunted neural responses in these regions that may indicate a lack of social engagement. Lastly, depressed adolescents showed decreased neural activation over time in left SFG, while this region was not associated with eye contact duration in HCs.

Consistent with findings in adults (Wever et al., 2022), prolonged eye contact (versus averted gaze) induced a better mood and feelings of connectedness in adolescents and substantial overlap in brain regions related to the processing of eye contact with others versus the self (i.e., left TPJ, right IFG, right FG, precentral gyrus, and left MOG). These are all brain regions that have been consistently found in socio-emotional processing and mentalizing (Herlin et al., 2021; Senju & Johnson, 2009), and have been linked to the communicative intent of eye contact (Cavallo et al., 2015). In addition, adolescents' affective responses were strongest when they were presented with their own parent versus unfamiliar others, while they did not distinguish between the sight of an unfamiliar peer or adult. This aligns with research showing that parents are still subjectively *perceived* by the child as important advisors and continue to be important for their mental health and well-being (Baumrind, 1991; Steinberg & Silk, 2002; Yap et al., 2014). Remarkably, we did not find evidence for the engagement of a specific neural network in adolescents when presented with videos of their own parent versus others, indicating that this enhanced sensitivity to their parent was not reflected in their neural responses. Although the reason for this discrepancy is unclear, this is in contrast to what we found in parents who showed enhanced affective responses *and* decreased deactivation in left middle/inferior occipital gyrus and right IFG to the sight of their own child versus others (Wever et al., 2022).

The finding that depressed adolescents (versus HCs) reported a lower mood and diminished feelings of connectedness in response to the sight of their parent versus unknown others point towards a less positive perception of the parent in depressed adolescents. This is in line with numerous studies indicating that adolescent depression is associated with a lower parent-child relationship quality, (Branje et al., 2010; Restifo & Bögels, 2009; Sheeber et al., 2001; Yap et al., 2014) and with a lower level of self-reported parental care in depressed versus non-depressed adolescents in this study (see Table 4.1). Several studies suggest that the directionality of this effect may go in both ways: Negative parenting behaviors, such as a lack of warmth and more critical parenting, are associated with increased depressive symptoms in adolescents over time, but adolescent' depressive symptoms are also related to a lower *perceived* relationship quality with their parents (Branje et al., 2010; Heaven et al., 2004; Pavlidis & McCauley, 2001; Sheeber et al., 1997). As such, this emphasizes the importance of also considering how adolescents *perceive* the relationship with their parents, especially when developing interventions to improve the parent-child relationship in families with a depressed adolescent.

Another remarkable finding in depressed versus non-depressed adolescents is the overall blunted BOLD-activity in left IFG and secondary visual cortex in response to all task conditions. The IFG has been consistently linked to human's capacity to build and maintain attachment and the perception of shared internal states with others (Feldman, 2017), and suggests that depressed adolescents might feel more alienated from others and themselves. The secondary visual cortex has been found in relation to experiences of social exclusion in 7-10 year old children in a meta-analysis of three distinct samples (van der Meulen et al., 2017). Together, this might reflect a lack of social engagement characteristic of adolescent depression, and even a feeling of being excluded whilst making eye contact (Arce et al., 2009; Jankowski et al., 2018; Joiner et al., 2002). It is of note to emphasize that depressed and non-depressed adolescents did not differ in their eye gaze patterns, indicating that they made equivalent eye contact with the targets. Hence, the blunted neural responses of depressed adolescents did not reflect a greater avoidance of eye contact in depressed versus non-depressed adolescents.

This study contributes to our understanding of adolescents' responses to making eye contact with their parent and unknown others and how this may differ between depressed and non-depressed adolescents. We used personally tailored stimuli including adolescents' own parent and assessed a combination of subjective, gaze, and fMRI data. Nevertheless, this study is not without limitations. The task did not include a familiar peer or adult condition and therefore we cannot rule out novelty effects introduced by the unfamiliar peer and adult conditions. However, presenting videos of a familiar peer might have introduced new complexities, such as variations in friendship quality. Lastly, our sample size of depressed adolescents was relatively small ($n = 19$) due to difficulties persuading depressed adolescents and their parents to participate in an extensive fMRI study and the recruitment period coinciding with COVID-19. Future studies including larger sample sizes are necessary to replicate our findings.

Our findings indicate that depressed adolescents do not benefit as much from the mood-boosting and connectedness-inducing effects of eye contact and have a less positive perception of the relationship with their parents compared to HCs. Moreover, they reported a lower mood and diminished neural responses in brain regions related to attachment and social exclusion compared to HCs, suggesting a sense of alienation from others and self in depressed adolescents. Together these results contribute to our understanding of interpersonal difficulties in adolescents with depression, especially towards their parents, and highlight the importance of including adolescents' perception (among other perspectives) in interventions focusing on improvement of the parent-child bond in families with a depressed adolescent.

SUPPLEMENTARY MATERIALS

SUPPLEMENT S4.1

Study procedure

Families with an HC adolescent were recruited via public advertisements and (online) social media, including Facebook and advertisement in the monthly magazine of the Royal Dutch Touring Club (ANWB). Families with a depressed adolescent were recruited via mental health facilities. Parents and adolescents were briefed about the study and underwent a comprehensive telephone screening during which family circumstances and informed consent were discussed and adolescents were pre-screened for (a history of) psychiatric disorders. Families were invited for two appointments: An assessment day in the lab and an MRI session on a separate day. Prior to the first appointment adolescents were asked to fill out an online questionnaire battery including demographics and clinical and cognitive measures (see Supplement S4.5 for details). During the first appointment, families performed parent-adolescent interaction tasks and filled out additional questionnaires. During the second appointment, adolescents underwent an MRI scan at the LUMC in Leiden, the Netherlands. Prior to and after the scan, adolescents filled out a set of questionnaires, received instructions about the MRI tasks, and performed some practice trials. Adolescents performed four tasks in the MRI scanner: The eye contact task as described below, the parental social feedback task (van Houtum et al., 2022), a peer evaluation task (van Houtum, wever, et al., 2023), and an autobiographical memory task (van Houtum, van Schie, et al., 2023). Upon completion of the MRI scans, adolescents were fully debriefed about the goals of the study and received a monetary compensation and travel allowance. All participants provided written informed consent for each individual testing day. The median of days between the first and second appointment was 42 days (range: 7-265 days) and did not significantly differ between depressed and non-depressed adolescents ($t(76) = -0.77$, $p = .444$).

SUPPLEMENT S4.2

Details concerning the preparation of the video stimuli

For the preparation of the video fragments, videos of adolescents and one of their parents were recorded during the lab visit. The videos had a minimal duration of 45 s and were recorded in front of a white wall. Adolescents and parents wore a black t-shirt during the recordings to avoid distraction due to their clothing. We asked them to look in the camera with a friendly, but neutral, facial expression and to imagine looking into the eyes of their parent/child. They were also instructed not to stare, but to gaze as natural as possible and blinking was allowed. The individuals featured as the male and female unfamiliar peer and adult were selected based on age (between 11-17 years for the unfamiliar child and between 45-55 years for the unfamiliar adults) and gender. Videos were recorded under similar circumstances as videos of adolescents and parents who participated in the study and written informed consent was taken to confirm their approval to use the videos in the task.

All videos were presented twice in two separate runs ($2 \times 8 = 16$ trials in total). During the first run, all targets were presented in a random order. For each target, adolescents were presented with two successive videos of the same target, but with gaze direction randomized (i.e., either starting with direct gaze or averted gaze, followed by the other direction). During the second run, the order of targets was randomized again, but the order of the presentation of the gaze direction was counterbalanced to the first run. The durations of the videos were based on a randomly chosen interval between 16-38 s from prerecorded videos of 45 s. The first and last 3s of each prerecorded video were discarded due to movement in the video recording. Stimuli of each condition were presented for a total duration of 54 s across two repeats, meaning that duration of a stimulus in a specific condition in run 2 was 54 s minus stimulus duration in run 1 with a minimum of 16 s (range: 16-38 s).

SUPPLEMENT S4.3

fMRI data acquisition

MR images were acquired at the LUMC using a Philips 3.0T Achieva MRI scanner equipped with a SENSE-32 channel head coil. For the eye contact task, T2*-weighted echo planar imaging was used with the following parameters: TR = 2200 ms, TE = 30 ms, flip angle = 80°, FOV 220 × 220 × 114.7 mm, matrix size = 80 × 80, voxel size = 2.75 mm^3, slice gap = 0.275 mm, 38 transverse slices in descending order. As subjective response ratings were self-paced, number of volumes varied between participants (run 1: *M* = 146.6, SD = 8.2, range = – 126 165; run 2: *M* = 147.7, SD = 8.7, range = 172 – 129). A structural 3D T1 scan was acquired with the following parameters: TR = 7.9 ms, TE = 3.5 ms, TI = 820 ms, flip angle: 8°, voxel size = 1 mm^3, 155 transverse slices FOV 195.8 × 250 × 170.5 mm, matrix size = 228 × 177, duration: 4:11 min. The first five volumes were discarded to allow for equilibration of T1 saturation effects. A b0 field map was acquired with the following parameters: TR = 200 ms, TE = 3.2, matrix size = 80 × 80, with 38 slices, voxel size = 2.75 mm^3. The task was programmed and presented electronically using E-prime 2.0 (Tools Psychology Software, 2012) and participants could see the task through a mirror attached to the head coil. Foam inserts were used to restrict head motion if necessary.

SUPPLEMENT S4.4

MNI-coordinates of centers of mass of regions of interest

Brain regions of interest (ROIs)	MNI-coordinates		
	x	y	z
Left temporoparietal junction (TPJ)	-59	-57	23
Dorsomedial prefrontal cortex (dmPFC)	5	47	33
Left inferior frontal gyrus (IFG)	-54	23	17
Right inferior frontal gyrus (IFG)	51	41	9
R fusiform gyrus (FG)	48	-57	-9

Note. The MNI-coordinates used in this study were selected based on previously found regions using the same eye contact task in adults (Wever et al., 2022).

SUPPLEMENT S4.5

Questionnaire details

Patient Health Questionnaire (PHQ-9)

Adolescents' severity of depressive symptoms was assessed with the Patient Health Questionnaire (PHQ-9) after the scan session (62). The questionnaire includes nine items corresponding with the nine symptoms of a major depressive disorder in DSM-IV. Adolescents were asked to assess how much they were bothered by the symptoms over the past two weeks. Answers were given on a Likert scale ranging from 0 (*not at all*) to 3 (*nearly every day*). The sum score could range from 0-27, with higher scores representing a higher depression severity. The PHQ-9 has been validated and internal consistency and test-retest reliability are excellent and criterion, construct and external validity were established (62). PHQ-9 scores of ≥ 15 were indicated as within the clinical range. The internal consistency in the current sample was $\alpha = 0.92$. Sum scores were log-transformed to account for skewness.

Screen for Child Anxiety Related to Emotional Disorders (SCARED)

Adolescents' severity of anxiety symptoms was assessed with an adapted version of the Screen for Child Anxiety Related Emotional Disorders for (SCARED) prior to the first assessment day (Birmaher et al., 1997; Muris et al., 2007). This version was based on the original 71-item version of the SCARED (Bodden et al., 2009), and includes 31 items from the subscales panic disorder, generalized anxiety disorder, and social anxiety. Adolescents were asked to assess to what extent the sentences were reflecting their current situation. Answers were given on a Likert-scale from 0 (*Not true or hardly even true*) to 2 (*very true or often true*). The total score is computed by summing up all items and could range from 0-62, with higher scores representing a higher anxiety severity. A total score of ≥ 20 was indicated as within the clinical range. The internal validity and reliability have been established (Birmaher et al., 1997). The internal consistency in the current sample was $\alpha = 0.94$.

Parental Bonding Instrument (PBI)

Adolescents' perspective on the parent-child bond was assessed with the Parental Bonding Instrument (PBI) prior to the first assessment day (Parker et al., 1979). Adolescents were asked to report on perceived parenting styles of the parent of whom videos were shown in the eye contact task. The instrument consists of three subscales: Parental care (12 items), parental overprotection (6 items), and autonomy support (6 items) of parents. One item of the autonomy support scale ("my mother/father don't want me to grow up") was left out due to a programming issue in the questionnaire. A total score and a score per subscale were computed for all adolescents by summing all items. The internal validity and reliability have been established (Arrindell et al., 1998; Enns et al., 2002). The internal consistency of the PBI in the current sample was α = 0.68 for the total score, α = 0.87 for parental care, α = 0.66 for overprotection, and α = 0.78 for autonomy support.

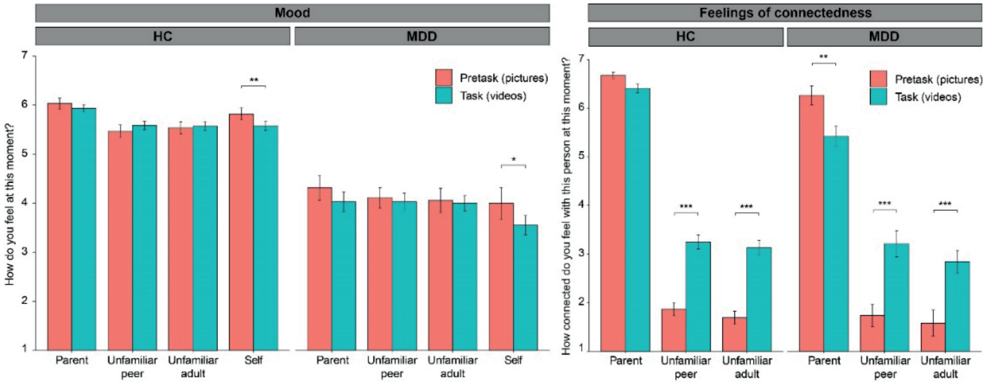
Edinburgh Handedness Inventory (EHI)

Handedness was assessed by a modified 10-item version of the Edinburgh Handedness Inventory (EHI) developed by Oldfield (1971). The self-report questionnaire consists of ten questions about which hand is used during specific actions and answer categories were always left (−100), most times left (-50), both (0), most times right (50), and always right (100). Sum scores were calculated by the following formula for the laterality quotient (LQ): $[R-L]/[R + L] \times 100$ and ranged from −100 (left-handedness in all tasks) to +100 (right-handedness in all tasks). To convert the continuous laterality quotient into a dichotomous variable of left- and right-handedness that was used to control for in analyses we used the cut-off score of zero with quotients > 0 indicating right-handedness and < 0 indicating left-handedness. In the current sample, 72 adolescents (n = 18 DEP, n = 54 HC) were right-handed (92.3%) and 6 adolescents (n = 1 DEP, n = 5 HC) were left handed (7.7%).

Pubertal Development Scale (PDS)

Pubertal status was assessed by the Pubertal Development Scale (PDS), prior to the first assessment day (Petersen et al., 1988). This self-report measure consists of five questions about secondary sexual characteristics, including growth spurt, body hair, changes in the skin, for boys a question about changes in voice and facial hair, and for girls a question about breast development and menarche. Answers were given on a four-point scale: (1) Had not yet started to develop, (2) was showing the first signs of development, (3) was showing clear development, or (4) had already finished developing. Scores were averaged to create a composite pubertal status score.

SUPPLEMENT S4.6



*Self-reported affective responses of adolescents about their mood and feelings of connectedness after seeing a static picture of each target prior to the task (pre-task) and in response to the direct gaze videos in the scanner. Dynamic videos of prolonged eye contact, in contrast to static pictures, enhanced adolescents' feelings of connectedness, but did not enhance adolescents' mood. Error bars represent standard error of the mean. Significant p-values <.05 were indicated by *, p <.01 by **, and p <.001 by ***.*

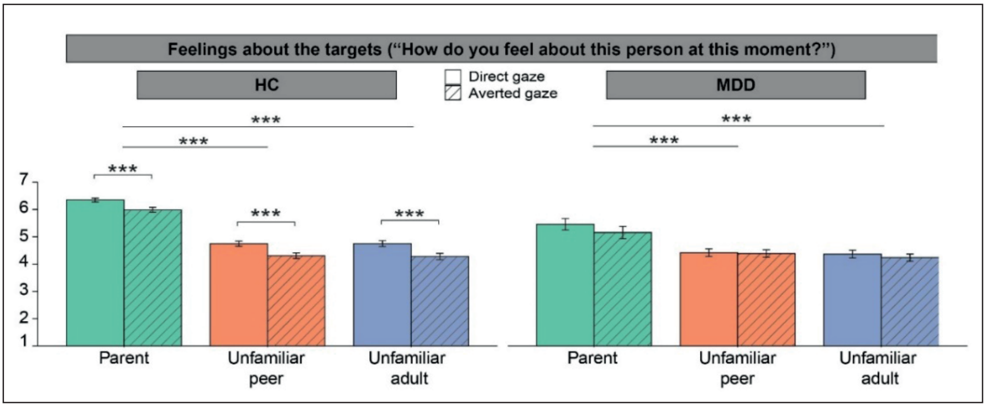
SUPPLEMENT S4.7

Adolescents' feelings about the targets

After watching each video, adolescents were asked to answer three questions: (1) "How connected do you feel with this person at this moment?", (2) "How do you feel about this person at this moment?", and (3) "How do you feel at this moment?". Responses to the question "How do you feel about this person at this moment?" were highly correlated with adolescents' feelings of connectedness ($r = .72$, $p < .001$) and showed similar effects, which are presented here in this supplement. We performed a generalized linear mixed regression model with gaze direction and target on adolescents' affect ratings to the question "how do you feel about this person at this moment?".

HCs reported more positive feelings about the targets ($B = -0.42$, $SE = 0.06$, $t(642) = -7.44$, $p < .001$, $d = 0.56$) in response to direct versus averted gaze videos. In addition, adolescents' feelings about the targets were dependent on the target in the videos ($\chi^2(2) = 750.18$, $p < .001$). Bonferroni corrected post hoc analyses revealed that they felt more positive about their parent versus an unfamiliar peer ($p < .001$, $d = 2.17$) or adult ($p < .001$, $d = 2.20$), but did not significantly differ in how they felt about an unfamiliar peer versus adult ($p = 1.000$). There was no significant interaction between gaze direction × target on adolescents' feelings about the targets with the others ($p = .689$).

Regarding differences in adolescents' feelings about the targets between DEP and HC adolescents, we found a significant interaction between group × target ($\chi^2(2) = 29.98$, $p < .001$). DEP adolescents reported to feel less positive about their parent compared to HC adolescents ($p = .002$), while no differences were found in how positive they felt about an unfamiliar peer or adult in response to their videos ($p = 1.000$, for both). In addition, we found a significant interaction between group × gaze direction ($\chi^2(1) = 4.62$, $p = .032$), showing that DEP adolescents did not significantly differ in how positive they felt about the targets after direct versus averted gaze videos ($p = .172$), while HC adolescents did feel more positive about the targets after direct versus averted gaze videos ($p < .001$). Lastly, DEP adolescents reported to feel less positive about the targets in general compared to HC adolescents ($\chi^2(1) = 4.18$, $p = .041$). There was no significant three-way interaction between group × gaze direction × target on adolescents' feelings about the targets ($p = .437$).


Feelings about the targets ("How do you feel about this person at this moment?")
HC
MDD
Direct gaze
Averted gaze
***
7
6
5
4
3
2
1
Parent
Unfamiliar peer
Unfamiliar adult

SUPPLEMENT S4.8

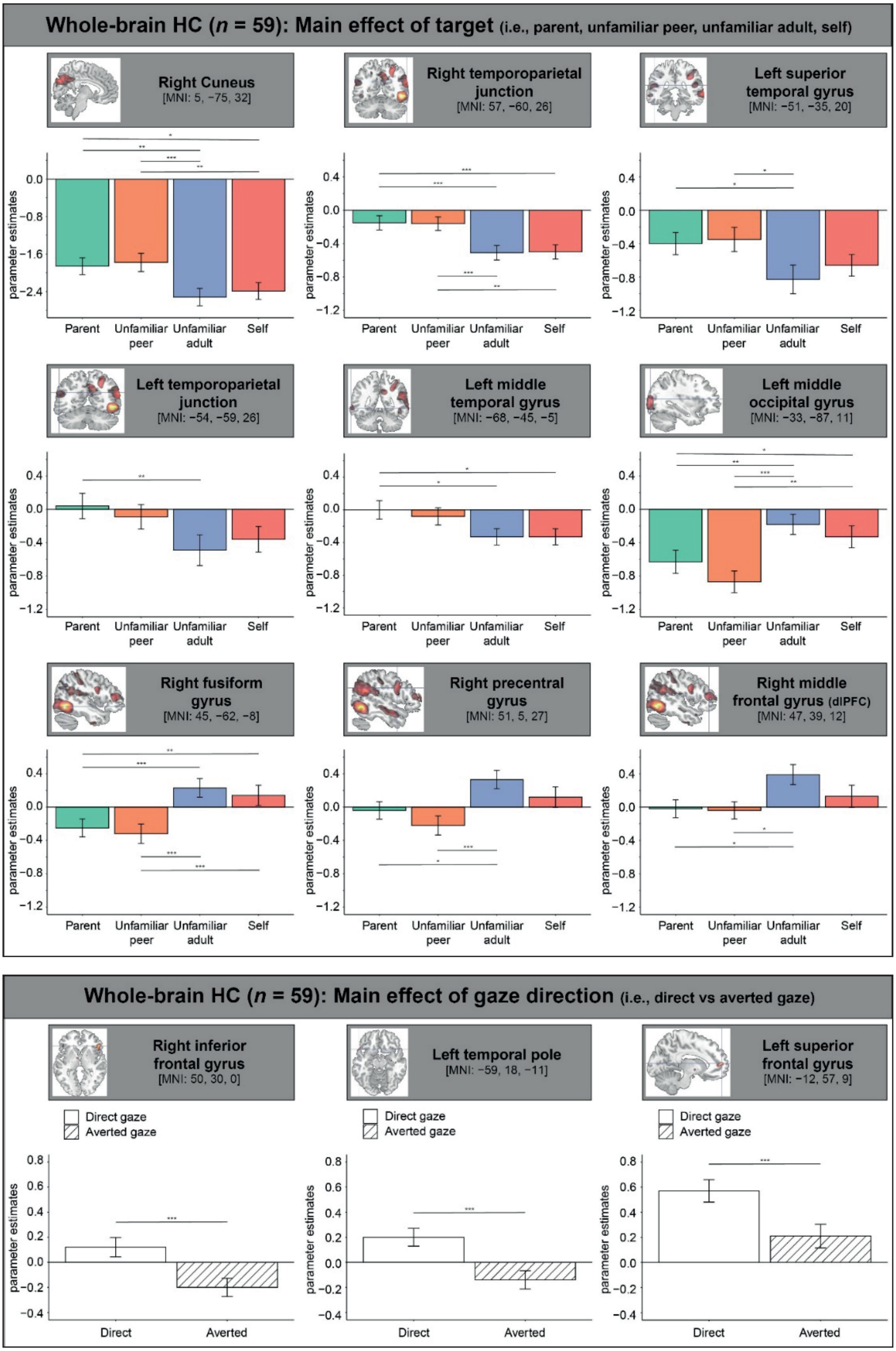
Neuroimaging findings: Whole-brain results in HC adolescents

To test whether task-related BOLD-activation in brain regions outside the ROIs was found in HC adolescents in response to direct and averted gaze of all targets, we performed a complementary whole-brain analysis. This analysis revealed a significant main effect of gaze direction in left superior frontal gyrus (extending into dmPFC), right inferior frontal gyrus (extending into dlPFC), and left temporal pole, indicating enhanced BOLD-responses to direct versus averted gaze videos.

In addition, there was a main effect of target in right fusiform gyrus (overlap with right fusiform gyrus ROI), right precentral gyrus, bilateral TPJ (overlap with left TPJ ROI), left middle occipital gyrus, right cuneus, right middle frontal gyrus/dlPFC (overlap with right IFG ROI), left middle temporal gyrus, left superior temporal gyrus. Post-hoc pairwise (Bonferroni corrected) comparisons indicated decreased deactivation to videos of their parent versus an unfamiliar adult in right cuneus ($p = .003$), right TPJ ($p < .001$), left TPJ ($p = .006$), right superior temporal gyrus ($p = .033$), and left middle temporal gyrus ($p = .018$). In addition, we found enhanced activation to videos of an unfamiliar adult versus their parent in left middle occipital gyrus ($p = .003$), right fusiform gyrus ($p < .001$), right precentral gyrus ($p = .030$), and right middle frontal gyrus/dlPFC ($p = .023$). Regarding adolescents' neural responses to videos of an unfamiliar peer versus an unfamiliar adult, we found decreased deactivation in right cuneus ($p < .001$), right TPJ ($p < .001$), and left superior temporal gyrus ($p = .011$) and enhanced activation to an unfamiliar adult versus unfamiliar peer in left middle occipital gyrus ($p < .001$), right fusiform gyrus ($p < .001$), right precentral gyrus ($p < .001$), and right middle frontal gyrus/dlPFC ($p = .014$). Adolescents did not show any significant differences in BOLD-responses between parents and unfamiliar peers.

Regarding the self, adolescents showed diminished activation to videos of the self versus their parent in right cuneus ($p = .026$), right TPJ ($p = .001$), and right middle temporal gyrus ($p = .020$) and enhanced activation in right fusiform gyrus ($p = .008$). In addition, adolescents showed diminished activation to videos of the self versus an unfamiliar peer in right cuneus ($p = .006$) and right TPJ ($p = .001$) and showed enhanced activation in left middle occipital gyrus ($p < .001$) and right fusiform gyrus ($p < .001$). Adolescents did not significantly show altered BOLD-responses to videos of an unfamiliar adult versus the self.

There was no significant interaction between gaze direction × target on adolescents' neural responses to eye contact at whole brain level.


Whole-brain HC (n = 59): Main effect of target (i.e., parent, unfamiliar peer, unfamiliar adult, self)
Right Cuneus
[MNI: 5, −75, 32]
Right temporoparietal junction
[MNI: 57, −60, 26]
Left superior temporal gyrus
[MNI: −51, −35, 20]
Left temporoparietal junction
[MNI: −54, −59, 26]
Left middle temporal gyrus
[MNI: −68, −45, −5]
Left middle occipital gyrus
[MNI: −33, −87, 11]
Right fusiform gyrus
[MNI: 45, −62, −8]
Right precentral gyrus
[MNI: 51, 5, 27]
Right middle frontal gyrus (dlPFC)
[MNI: 47, 39, 12]
parameter estimates
Parent
Unfamiliar peer
Unfamiliar adult
Self
Whole-brain HC (n = 59): Main effect of gaze direction (i.e., direct vs averted gaze)
Right inferior frontal gyrus
[MNI: 50, 30, 0]
Left temporal pole
[MNI: −59, 18, −11]
Left superior frontal gyrus
[MNI: −12, 57, 9]
Direct gaze
Averted gaze
parameter estimates
Direct
Averted

4

SUPPLEMENT S4.9

Peak activation coordinates of healthy control adolescents (n = 59) at whole-brain level for main effects of target and gaze direction

Brain regions	MNI-coordinates			Voxel test value	Cluster p-value	Cluster size
	x	y	z	Z		
Target						
R Fusiform gyrus	45	-62	-8	≥8	<.001	12900
R Middle occipital gyrus	36	-81	6	7.55		
R Superior parietal gyrus	24	-63	50	5.93		
R Precentral gyrus	51	5	27	6.09	.003	1053
R Angular gyrus (TPJ)	57	-60	26	6.00	<.001	10283
R Middle temporal gyrus	69	-33	0	5.87		
R Superior temporal gyrus	53	-50	23	5.86		
L Middle occipital gyrus	-33	-87	11	5.89	<.001	3338
L Fusiform gyrus	-47	-69	-9	5.18		
R Cuneus	5	-75	32	5.79	<.001	5873
R Posterior cingulate cortex, ventral part	14	-53	32	5.41		
L Cuneus	-8	-78	27	4.25		
R Middle frontal gyrus (dlPFC)	47	39	12	5.47	.001	1185
R Middle frontal gyrus	44	59	8	3.22		
L Middle temporal gyrus	-68	-45	-5	4.56	.013	768
L Middle temporal gyrus	-65	-38	-6	4.09		
L Middle temporal gyrus	-57	-32	-6	3.56		
L Superior temporal gyrus	-51	-35	20	4.23	.004	1005
L Superior temporal gyrus	-63	-26	11	3.58		
L Angular gyrus (TPJ)	-54	-59	26	4.17	.005	962
Gaze direction						
L Superior frontal gyrus, medial part	-12	57	9	4.46	.006	1100
L Superior frontal gyrus, medial part	-3	57	17	3.98		
L Superior frontal gyrus (dmPFC)	-6	54	26	3.62		
R Inferior frontal gyrus, triangular part	50	30	0	4.27	.005	1135
R Inferior frontal gyrus, opercular part	48	18	8	3.99		
R Inferior frontal gyrus (dlPFC)	51	24	18	3.56		
L Temporal pole	-59	18	-11	4.03	<.001	1873
L Temporal pole	-41	23	-24	3.97		
L Temporal pole	-50	14	-39	3.84		

Note. The Automated Anatomical Labeling atlas (AAL3) by Rolls et al. (2019) was used to label the peak-coordinates

4