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Adolescent risk taking : the influence of pubertal development, neural responses to rewards and social context

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Chapter 5

Longitudinal Changes in Social Brain Development: Processing Outcomes for Friend and Self

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Adolescence is an important time for social development, during which friendships become more intimate and more complex. In this study we tested how outcomes for self and friends are processed on the neural level across adolescent development. For this purpose, we used a longitudinal design in which participants between 8 and 27 years of age were tested twice with a two year difference between the first (N=299) and second (N=254) time point. Participants played a gambling game in the scanner in which they could win and lose money for themselves and their best friend. Results showed robust activity in the social brain network including temporal-parietal junction (TPJ), precuneus and ventral medial prefrontal cortex (mPFC) when receiving outcomes for friend, and in dorsal mPFC when receiving outcomes for self. Mixed linear models revealed a linear decrease in activity for Friend > Self over development in TPJ, precuneus and ventral mPFC. In contrast, dorsal mPFC showed a non-linear effect with a peak in mid-adolescence when processing outcomes for self. Activity patterns in these regions were modulated by self-reported perspective taking and whether participants believed their friend deserved to win. Taken together, the results confirm linear and non-linear changes in the social brain network across age, and show that individual changes in self-reported perspective taking further moderate these neural changes.

5.1 Introduction

Understanding others and inferring mental states of others is critical for forming close social bonds, which is often considered a fundamental human need (Williams, 2007). Prior studies based on self-report questionnaires (Sumter, Bokhorst, Steinberg, & Westenberg, 2009), sociometric analyses (Cillessen, 2007) and laboratory tasks (Dumontheil, Apperly, & Blakemore, 2010) have reported that adolescence is an important transition period for social development, specifically for the ability to understand the intentions of others and consequences of actions for others (for a review, see Blakemore, 2008). Although there is much research on *thinking about* self and others (such as traits or intentions of others), it is currently not well understood how adolescents process *outcomes* for self and others. Yet, these outcomes, which are defined as the consequences of our own actions for others, are of great importance in many types of social interactions (Crone, 2013). Furthermore, despite the important changes in friendships during adolescence (Rubin, Fredstrom, & Bowker, 2008), research to date has often focused mainly on thinking about distant others. How adolescents process friend relevant outcomes is largely unknown (but see Braams, Peters, Peper, Güroğlu, & Crone, 2014; Fareri, Niznikiewicz, Lee, & Delgado, 2012;

Pfeifer, Masten, Borofsky, Dapretto, Fuligni, & Lieberman, 2009). The current study aimed to unravel these questions by testing neural responses to outcomes for self and friends, and investigate changes in these neural responses during adolescence by testing whether these patterns are linear or adolescent-specific (i.e., quadratic).

Neuroscience studies on social information processing in adults have revealed a network of brain areas related to thinking about self and others (Van Overwalle, 2009). These studies have pointed out that this network of brain regions, also referred to as the social brain, includes the temporo-parietal junction (TPJ), superior temporal sulcus (STS) and midline structures including the precuneus and medial prefrontal cortex (mPFC). Even though these regions work in close concert, prior studies have related TPJ activity to perspective taking (Carter & Huettel, 2013; Young, Dodell-Feder, & Saxe, 2010), whereas midline regions such as the precuneus and mPFC are more strongly related to self and other referential processing (Amodio & Frith, 2006; D'Argembeau & Salmon, 2012; Denny, Kober, Wager, & Ochsner, 2012). Within mPFC, ventral parts are often related to affective components of self-referential processing, whereas more dorsal parts are often related to cognitive self-evaluation or perspective taking (for a meta-analysis, see Van Overwalle, 2009), although this conceptualization is thought to change during adolescence (Blakemore, 2008; Pfeifer & Blakemore, 2012).

Developmental neuroscience studies have compared thinking about self and others in a variety of paradigms. These studies showed that activity in all regions of the social brain network changes considerably during adolescence (for a review, see Blakemore, 2008). These findings fit well with reports that show that regions in the social brain network also develop structurally during adolescence (Mills, Lalonde, Clasen, Giedd, & Blakemore, 2014). Pfeifer et al. (2007; 2009) reported that thinking about traits of self versus traits of others resulted in activation in the dorsal mPFC, which was more pronounced in adolescents than in adults (see also Burnett, Sebastian, Kadosh, & Blakemore, 2011; van den Bos, van Dijk, Westenberg, Rombouts, & Crone, 2011). The reverse contrast, thinking about traits of others versus traits of self, resulted in activation in the TPJ, precuneus, and ventral mPFC (Pfeifer, Kahn, Merchant, Peake, Veroude, Masten, Lieberman, Mazziotta, & Dapretto, 2013). Intriguingly, when following the same adolescents across two time points, it was found that the ventral mPFC was increasingly engaged when thinking about self relative to friend over time (Pfeifer, et al., 2013).

Taken together, most studies in adults have reported robust activity in the social brain network (TPJ, precuneus, ventral mPFC) when thinking about others (Van Overwalle, 2009) and it was previously found that this network is more engaged

when thinking about close friends (Güroğlu, Haselager, van Lieshout, Takashima, Rijpkema, & Fernandez, 2008). Although, developmental studies have shown changes during adolescence in this network when thinking about self and others (Blakemore, 2008; Burnett, et al., 2011), these prior studies have not yet addressed two important questions: 1) how does the social brain network process *outcomes* for self and others and 2) how does activation in the social brain network change over development when processing outcomes for self and *friends*, rather than for unknown others?

The current study set out to test these questions by making two important modifications to the design in comparison to prior studies. Firstly, in the current study, participants played a gambling task in which the *outcomes*, i.e. winning or losing money, could be for different beneficiaries (Braams, Güroğlu, de Water, Meuwese, Koolschijn, Peper, & Crone, 2013; Braams, et al., 2014). Secondly, the outcomes in the gambling task could be for a best *friend* instead of an unknown other. Developmental changes for outcomes for *friends* specifically are not yet well understood (Braams, et al., 2013). Participants in a continuous age range between 8 and 27 years of age were tested twice with a two-year interval. We previously found using the same task in a cross-sectional sample that social brain regions, including TPJ, precuneus and mPFC, were most strongly engaged when processing outcomes for friend relative to self (Braams, et al., 2013). In the current study, we addressed the question of stability versus change in activity in this network of the brain by making use of a longitudinal, rather than a cross-sectional design.

An important advantage of the longitudinal design is that this type of design allows us to relate changes in neural activity to changes in self-reported behavioral changes. Therefore, in addition to the fMRI task, friendship quality, ratings of how much the participant felt their friend deserved to win, and general perspective taking tendencies, were assessed at each time point. These reports were chosen because prior studies have reported links between friendship relation and ventral MPFC recruitment (Güroğlu, et al., 2008) and perspective taking and TPJ recruitment (Carter & Huettel, 2013; van den Bos, et al., 2011). We tested whether changes in these self-report measures showed a relationship with changes in neural activation during the task. The potential differential sensitivities to individual differences in friendship quality, the rating of how much the friend deserves to win, and perspective taking, speak to the question which brain region is most important for which aspect of social reasoning.

A longitudinal design is optimized for the possibility to assess developmental trends over time. In line with major changes in social development during adolescence and structural changes in the social brain (Mills, et al., 2014), we expect to find

developmental changes in TPJ, precuneus and mPFC. As directionality of the effect is difficult to hypothesize based on previous work, we tested whether neural activation in these regions increases, decreases or shows a quadratic response over development. Prior developmental studies led us to predict that especially the mPFC is a brain region sensitive to non-linear changes, with heightened activation in mid-adolescence (Somerville, Jones, Ruberry, Dyke, Glover, & Casey, 2013; van den Bos, et al., 2011). Based on these studies, we hypothesized that mPFC would show age-related decreases (Blakemore, den Ouden, Choudhury, & Frith, 2007) or non-linear change (Somerville, et al., 2013).

5.2 Methods

Participants

On the first time point (T1) 299 participants participated in the study ($Mean_{age} = 14.15$ years; $SD_{age} = 3.56$; $Range_{age} = 8.01-25.95$ years; 143 males). Approximately two years later ($Mean_{time\ difference} = 1.99$ years; $SD_{time\ difference} = 0.10$; $Range_{time\ difference} = 1.66 - 2.47$ years) all participants were invited to participate again for data collection for the second time point (T2). Thirteen participants indicated that they could not or did not want to participate again. Therefore, data at T2 were collected from 286 participants ($Mean_{age} = 15.80$ years; $SD_{age} = 3.54$; $Range_{age} = 9.92 - 26.62$ years; 135 males). Of the 286 participants who participated at T2, 32 participants were unable to participate in the MRI session due to braces. Written informed consent for the study (parental consent and participant assent for children and adolescents) was provided by all participants at both time points. All participants were right-handed, reported normal or corrected-to-normal vision and an absence of neurological or psychiatric impairments.

Estimated intelligence scores were obtained using four subscales of the Wechsler Adult Intelligence Scale (WAIS) for participants aged 17 and older or the Wechsler Intelligence Scale for Children (WISC) for participants aged 16 and younger. At T1 the subtests similarities and block design of the WISC/WAIS were administered, at T2 the subtests picture completion and vocabulary were administered. Different subtests were used at both measurements to avoid carry-over or learning effects from the first measurement. IQ scores and age were not correlated on both time points (T1 $r(294) = -.041$, $p = .49$; T2 $r(256) = .045$, $p = .48$).

Participants received an endowment for participation in the larger study. Adult participants received 60 euro on each time point, participants aged 12-17 received 30 euro and participants younger than 12 received 20 euro on each time point. In addition

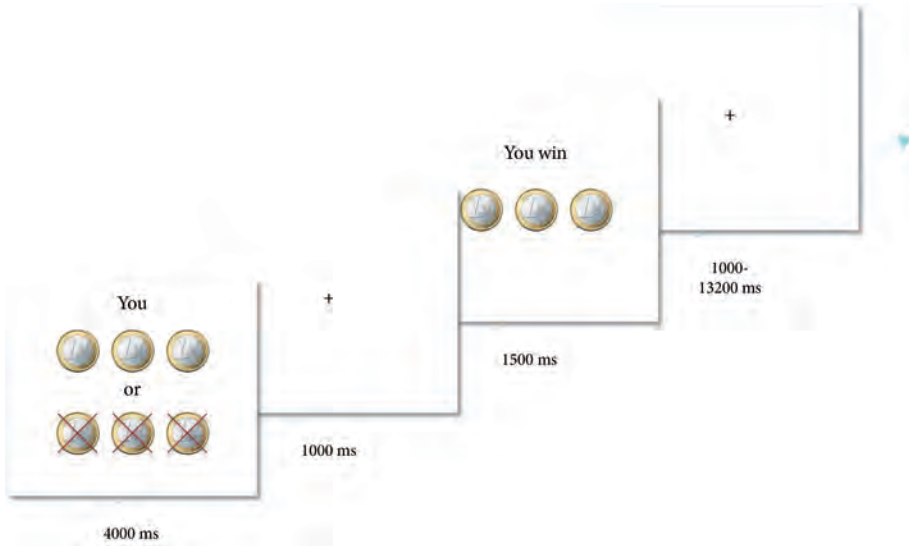


Figure 5.1. Example of a trial. On trial onset, participants were presented with a screen for 4000 ms indicating how many coins could be won or lost. During this time, participants chose to play heads or tails by pressing the corresponding button. After a 1000 ms delay, trial outcome was presented for 1500 ms. Participants won when the computer randomly selected the same side of the coin as chosen by the participant, see also (Braams et al., 2013).

to this endowment participants could win 4, 5 or 6 euros in the fMRI task (see fMRI task description). All procedures were approved by local institutional review boards.

Data for the current study were collected at Leiden University, The Netherlands as part of a large longitudinal study named Braintime. The procedure and task design has been described in detail previously in Braams et al. (2015). Results from the first measurements have previously been published in Braams et al. (2014), and a separate longitudinal report in Braams et al. (2015).

Procedure

Participants were prepared for the testing session in a quiet room. They were familiarized with the MRI scanner with a mock scanner and by listening to recordings of the scanner sounds. Next, participants received instructions for the fMRI task and performed six practice trials of the task. Procedures were similar for the two sessions.

Experimental Design and Self-Report Measures

fMRI task

Participants played a heads or tails gambling game in which they could win or lose money (Braams et al., 2013; Braams et al., 2014; Braams et al., 2015). On each trial

participants guessed whether the computer would pick heads or tails and they won when the computer selected the chosen side of the coin. Each trial started with a trial onset screen (4000 ms) during which the participant made their choice to play for heads or tails. On the trial onset screen the participants saw how much they could win or lose on that trial. Probabilities for winning were 50%. Three different distributions of coins were included; trials on which 2 coins could be won and 5 lost, trials on which 3 coins could be won or 3 lost and finally trials on which 5 coins could be won or 2 could be lost. These different distributions of coins were included to keep participants engaged in the task, but were not analyzed separately (see also Braams, et al., 2013; Braams et al., 2014). Participants were informed about the different distributions of coins and were familiarized with them during the practice task. The trial onset screen was followed by a fixation screen (1000 ms) and a feedback screen, which showed whether participants won or lost on that trial (1500 ms). Trials ended with a variable jitter (1000-13200 ms), see Figure 5.1. Trial sequence and timing was optimized using OptSeq (Dale, 1999); see also (<http://surfer.nmr.mgh.harvard.edu/optseq/>). Participants were explained that the coins won during the experiment translated to real money at the end of the experiment. Participants received 4, 5 or 6 euros at the end of the task. Unbeknownst to the participants, the total earnings on the task did not relate to the amount won during the task.

Participants played 30 trials in the gambling game for themselves, 30 trials for their best friend and 30 trials for another person. The other person was a disliked other on the first time point, and their mother (or another primary caregiver for participants who were unable to play for their mother) on the second time point. Only the trials in which participants played for themselves and their best friend were administered at both time points and therefore only those trials are the focus of the current study.

Self-report Measures

Friendship quality

Friendship quality was assessed by an adapted version of the Friendship Quality Scale (FQS; Bukowski, Hoza, & Boivin, 1994). Participants filled out the FQS about their best friend, at home before the scanning session. The adapted FQS is comprised of 20 questions and assesses both positive and negative friendship quality. An example item for the positive scale is 'I can trust and rely upon my friend' and an example item for the negative scale is 'My friend can bug or annoy me even though I ask him not to'. Participants indicated on a 5-point scale how true this item is with (1) 'not true at all', to (5) 'very true'. Separate scores were calculated for both the positive and negative friendship quality subscales. The positive subscale consists of 13 items, therefore total

scores for the positive subscale can range between 13 and 65. Higher scores on the positive friendship subscale indicate more positive friendship quality. Mean score for the positive subscale was 55.45 (SD = 6.3; range = 37-65) at T1 and 55.97 (SD = 6.0; range = 36-65) at T2. The negative subscale consists of 7 items, total scores for the negative subscale can range between 7 and 35. Higher scores on the negative subscale indicate more negative friendship quality. Mean score for the negative subscale was 11.5 (SD = 3.9; range = 7-26) at T1 and 12.0 (SD = 3.9; range = 7-25) at T2. In total friendship quality scores were available for 277 participants at T1 and 286 participants at T2. In total, combined fMRI and FQS ratings were available for 234 participants at T1 and 236 participants at T2.

Self-report ratings

After the scanning session participants indicated how much they felt that their friend deserved to win. Ratings were made on 10-point scale ranging from (0) 'not at all' to (10) 'very much'. The mean score for this rating was 8.12 at T1 (SD = 1.8; range = 0 - 10) and 8.0 (SD = 1.8; range = 0 - 10) at T2. Ratings were available for 291 participants at T1 and 251 participants at T2. In total, combined fMRI and ratings were available for 243 participants at T1 and 233 participants at T2.

Perspective taking

Perspective taking was measured by the perspective taking subscale of the Interpersonal Reactivity Index (IRI; Davis, 1983). The perspective taking subscale constitutes of a total of 6 items. Each item was rated on a five point Likert scale ranging from 0 'does not describe me well' to 4 'describes me very well'. The total score was calculated by adding up scores for all individual items. Higher scores indicate better perspective taking skills. The IRI perspective taking subscale was only assessed at T2. The mean score was 15.9 (SD = 3.9; range 2 - 24). IRI scores were available for 286 participants at T2. In total, combined fMRI and IRI scores were available for 236 participants at T2.

MRI Data Acquisition

Scanning was performed on a 3 Tesla Philips scanner, with a standard whole-head coil. The functional scans were acquired using a T2*-weighted echo-planar imaging (EPI) (TR= 2.2 sec, TE= 30 ms, sequential acquisition, 38 slices of 2.75 mm, field of view 220 mm, 80x80 matrix, in-plane resolution 2.75 mm). The first two volumes were discarded to allow for equilibration of T1 saturation effects. After the functional runs, a high-resolution 3D T1-weighted anatomical image was collected (TR= 9.751 ms, TE=4.59 ms, flip angle= 8°, 140 slices, 0.875mm x 0.875mm x 1.2mm, and FOV= 224.000x168.000x177.333). Visual stimuli were displayed on a screen in the magnet

bore. A mirror attached to the head coil allowed participants to view the screen. Foam inserts inside the coil were used to limit head movement. MRI data acquisition was performed at the same scanner and all procedures were comparable at the two time points (see also Braams et al., 2014).

fMRI Preprocessing and Statistical Analyses

At T1 299 participants were included in the MRI session and at T2 254 participants. For fMRI-analyses, 36 participants on T1 and 10 participants on T2 were excluded for moving more than 1 voxel. An additional 14 participants on T1, and six participants on T2, were excluded for not finishing the task, technical problems and/or artifacts during data collection. The final sample for fMRI analyses was therefore 249 participants on T1 and 238 participants on T2.

All data were analyzed with SPM8 (Wellcome Department of Cognitive Neurology, London). Images were corrected for slice timing acquisition and differences in rigid body motion. Structural and functional volumes were spatially normalized to T1 templates. Translational movement parameters of the included sample never exceeded 1 voxel (<3 mm) in any direction for any participant or scan. The normalization algorithm used a 12-parameter affine transform together with a nonlinear transformation involving cosine basis functions and resampled the volumes to 3mm cubic voxels. Templates were based on the MNI305 stereotaxic space. Functional volumes were spatially smoothed with a 6 mm FWHM isotropic Gaussian kernel. Statistical analyses were performed on individual subjects data using the general linear model in SPM8. The fMRI time series were modeled as a series of zero duration events convolved with the hemodynamic response function (HRF). On trial onset events were modeled separately for playing for self, friend and other. On feedback onset winning and losing for self, friend and other were modeled. This resulted in three conditions at trial onset (self, friend, other) and six conditions at feedback onset (self win, self lose, friend win, friend lose, other win, other lose). Trials on which the participants failed to respond were modeled separately as covariate of no interest and were excluded from further analyses. The modeled events were used as regressors in a general linear model, along with a basic set of cosine functions that high-pass filtered the data, and a covariate for session effects. The least-squares parameter estimates of height of the best-fitting canonical HRF for each condition were used in pair-wise contrasts. The resulting contrast images, computed on a subject-by-subject basis, were submitted to random-effects group analyses.

The whole brain contrasts of interest were Friend > Self and Self > Friend. As we were specifically interested in effects related to processing outcomes for friend and for self, we combined winning and losing for friend and winning and losing for self

for these whole brain analyses. To test whether the activation patterns were related to winning or losing specifically, we performed whole brain analyses for winning for Friend > winning for Self and losing for Friend > losing for Self. These whole brain analyses resulted in highly similar clusters of activation as the whole brain contrast for Friend (win & lose combined) > Self (win & lose combined). Furthermore, the whole brain Person x Outcome interaction did not result in any above threshold activation in the social brain network, also not when the threshold was lowered to $p < .001$, uncorrected for multiple comparisons. Therefore, the subsequent analyses focused on the combined outcomes of winning and losing.

Region of Interest Analysis

We used the MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002) (<http://marsbar.sourceforge.net/>) for SPM8 to perform region of interest (ROI) analyses to extract patterns of activation in clusters active on both the first time point and the second time point. The ROIs were defined based on clusters of functional activity for Friend > Self and Self > Friend on the first time point because this allows us to test for change relative to a baseline time point. This procedure was also used in other studies (Koolschijn, Schel, de Rooij, Rombouts, & Crone, 2011). The regions of interest concerned the bilateral TPJ, precuneus, and mPFC (ventral and dorsal).

Mixed Model Building Procedure

Analyses on ROI values were performed using a mixed models approach in R (R Core Team, 2014) and package *nlme* (Pinheiro, Bates, DebRoy, & Sarkar, 2013). Mixed models (also known as hierarchical linear modeling, multilevel modeling or random effects modeling) allow for data hierarchies as observed in longitudinal datasets. Time points within a longitudinal dataset are nested within participants and a mixed models approach recognizes this type of data dependency. Mixed models were used to determine general patterns, i.e. grand mean trajectories, of age-related change (linear or quadratic) and within these general patterns, assess individual variation in intercepts (i.e. starting points) and slopes (i.e. pattern of change over time). These goals concur with (i) the inclusion of fixed effects that account for a grand-mean trajectory thereby capturing the mean developmental pathway of the full sample and (ii) random effects that can test for individual variation in intercepts and slopes.

To test developmental effects, all mixed-models followed a formal model-fitting procedure. That is, we started with a null model that included a fixed and a random intercept, to allow for individual differences in starting points and account for the repeated nature of the data. The null model with random intercept was compared against two additional models that tested the grand mean trajectory of age. These models were

created by adding two polynomial terms (linear and quadratic; mean-centered) for age to the null model. Linear effects of age indicate a monotonic change over age, quadratic effects of age indicate an adolescent-specific effect, in which adolescent responses differ from those of children and adults (Somerville et al., 2013). Akaike Information Criterion (AIC; Akaike, 1974) values as well as Bayesian Information Criterion (BIC; Schwarz, 1978) values were compared between the null model and each of the models with a polynomial term for age to test whether a null model, linear or quadratic model best explained the relationship between the dependent measure and age. AIC and BIC are standardized model-fit metrics that allow for comparison of models. Preferred models have lower AIC and BIC values. To formally compare whether models with lower AIC and BIC values were significantly better, we compared models differing one degree of freedom (i.e. null and linear, and linear and quadratic) using a log likelihood ratio test. Level of significance used for the log likelihood test was $p < .05$.

The next step in the model-building procedure was to determine whether there were significant individual differences in the effects of age by adding a random-slope of age to each of the best-fitting models. A random-slope of age allows the inclusion of different beta-coefficients for each subject. A significant random-slope term would indicate significant individual differences for the effect of age. The significance of the random terms was determined via AIC and BIC evaluation for improvement in model fit, as well as a log likelihood test. For none of the fitted models, a random slope was significant and random slopes are therefore not discussed further in the results section.

All models were fit with full information maximum likelihood estimates. A fitted mixed-model with only a, mean-centered, linear term of age (referred to as Age Linear) reads in formal notation:

Level 1:

$$Y_{ti} = \pi_{0i} + \pi_{1i} \cdot (\text{Age Linear})_{ti} + e_{ti}$$

Level 2:

$$\pi_{0i} = \gamma_{00} + r_{0i}$$

$$\pi_{1i} = \gamma_{10} + r_{1i}$$

In which Y_{ti} represents, for instance, neural activation in a region of interest at the t 'th timepoint for the i 'th individual. Substitution of the second level model into the first level model gives the integrated model that was fitted to the data. As age is mean-centered, the fixed intercept γ_{00} represents grand mean neural activation level at the mean age of the sample. γ_{10} represents the grand mean slope (main effect) of age (linear). The random intercept (r_{0i}) captures between-participant variance in the intercept

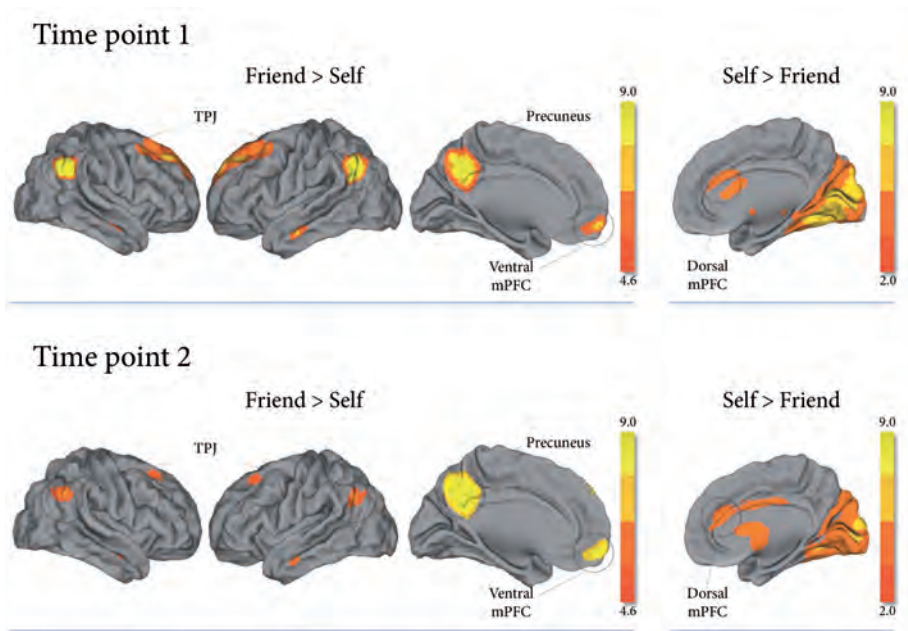


Figure 5.2. Whole brain activation for the contrasts Friend > Self and Self > Friend at time point 1 and time point 2. Whole brain results are corrected at FWE $p < .05$ at the voxel level. Note that for the Self > Friend contrast the threshold was lowered for display purposes only.

(e.g., individual differences in the mean neural activation level at the mean age of the sample), and individual differences in the slope (r_{ii}) (i.e., the change in neural activation level over age). Finally, the variance of e_{ii} denotes within-participant variance. We fitted separate models for each region of interest and describe the best fitting model for each region in the results section.

5.3 Results

Whole Brain Analysis

We performed a whole brain analysis on the moment of feedback onset to test which regions were significantly more activated when processing outcomes for a friend compared to processing outcomes for self. As expected, the whole brain contrast Friend > Self resulted in significant activation in a wide network of regions including the right and left TPJ, the precuneus and the ventral mPFC on both time points, see Figure 5.2. Table 5.1 shows an overview of the full list of regions and coordinates. The reversed contrast, Self > Friend resulted in activation in the dorsal mPFC on both time points, see Figure 5.2. Table 5.2 shows an overview of all activation on both time points.

Table 5.1. Whole brain table for neural activation for the contrast Friend > Self for time point 1 and time point 2.

Region	R/L	x	MNI		T(1488)	Voxels
			y	z		
Time point 1						
Paracentral Lobule	R	3	-28	61	5.41	13
Precuneus	L	-3	-58	34	12.59	601
Temporo Parietal Junction	L	-48	-64	31	11.09	506
Medial Prefrontal Cortex	R	0	53	-8	9.91	212
Temporo Parietal Junction	R	57	-64	31	9.53	326
Temporal Gyrus	L	-63	-16	-14	8.96	184
Superior Frontal Gyrus	L	-21	38	49	8.18	702
Middle Occipital Gyrus	L	-42	56	-2	6.08	33
Middle Temporal Gyrus	R	63	-10	-20	6.07	35
Precentral Gyrus	L	-39	-22	61	5.65	57
Time point 2					T(1422)	
Precuneus	L	-3	-55	34	9.57	365
Temporo Parietal Junction	L	-51	-70	34	8.58	423
Medial Prefrontal Cortex	L	-3	53	-8	7.65	93
Middle Temporal Gyrus	L	-60	-10	-20	7.30	113
Temporo Parietal Junction	R	60	-67	25	6.74	153
Superior Frontal Gyrus	L	-15	29	52	6.24	115
Precentral Gyrus	L	-24	-16	58	5.64	25
Postcentral Gyrus	L	-36	-28	52	5.25	37

Table 5.2. Whole brain table for neural activation for the contrast Self > Friend for time point 1 and time point 2.

Region	R/L	MNI			T(1488)	Voxels
		x	y	z		
Time point 1						
Lingual Gyrus	R	27	-52	-8	10.20	3262
Medial Prefrontal Cortex	R	6	35	19	6.99	72
Inferior Frontal Gyrus	R	42	29	4	6.79	304
Precentral Gyrus	R	42	5	28	6.71	140
Superior Temporal Gyrus	R	48	-25	-2	6.14	38
Cerebellum	R	3	-34	-2	5.51	11
Superior Parietal Lobule	L	-24	-64	49	5.06	13
Time point 2					T(1422)	
Superior Occipital Gyrus	L	-9	-97	4	8.59	1603
Inferior Frontal Gyrus	R	48	29	22	8.01	398
Medial Prefrontal Cortex	R	9	35	25	6.83	136
Middle Frontal Gyrus	R	48	-4	64	6.63	87
Insula	R	33	17	-5	6.54	113
Inferior Frontal Gyrus	L	-42	5	28	5.97	39
Thalamus	R	3	-31	1	5.53	19
Calcarine Gyrus	L	-12	-73	10	5.49	34
Inferior Parietal Lobe	L	-24	-67	43	5.10	13
Cerebellum	L	-36	-64	-23	5.01	13
Precentral Gyrus	L	-57	-4	52	5.69	11

Table 5.3. Intra Class Correlations for contrast values for regions of interest identified in the Friend > Self and Self > Friend contrasts.

Region of Interest	ICC
<i>Friend > Self</i>	
Ventral mPFC	0.125
Precuneus	0.078
TPJ Left	0.090
TPJ Right	0.106
<i>Self > Friend</i>	
Dorsal mPFC	0.033

ROI selection

In subsequent analyses we made use of regions of interest (ROIs) to test for time-related stability vs change, developmental trajectories, and self-report relations. We extracted parameter estimates from the clusters identified in the whole brain analysis for Friend > Self and Self > Friend at time point 1 (FWE corrected, $p < .05$). This resulted in a total of 5 a priori hypothesized ROIs: left TPJ (MNI: -48 -64 31), right TPJ (MNI: 57 -64 31), precuneus (MNI: -3 -58 34) and ventral mPFC (MNI: 0 53 -8) (Friend > Self); and dorsal mPFC (MNI: 6 35 19) (Self > Friend). These regions were based on the whole brain contrast across all participants and were therefore not biased towards a specific age group.

Intra Class Correlations

Intra Class Correlations (ICC) over time were calculated to investigate stability of neural activity across time points. ICC values were calculated using SPSS with a two-way mixed effects model with absolute agreement. ICC values were low, ranging between 0.033 and 0.125. Values below .4 are considered low in test-retest stability as described by Cicchetti (1981). Thus, these values indicate considerable change across time points in neural activity. All ICC values are reported in Table 5.3.

Developmental Effects

We used a linear mixed modeling approach to test for grand mean trajectories of age for each ROI. We tested linear and quadratic effects of age for each of the ROIs separately. AIC and BIC values were used to guide model selection and a formal model comparison using a log likelihood ratio test was used to determine which model showed the best fit.

Friend > Self

The developmental trajectories for all ROIs identified in the whole brain analysis Friend > Self: left and right TPJ, precuneus and ventral mPFC were all best described

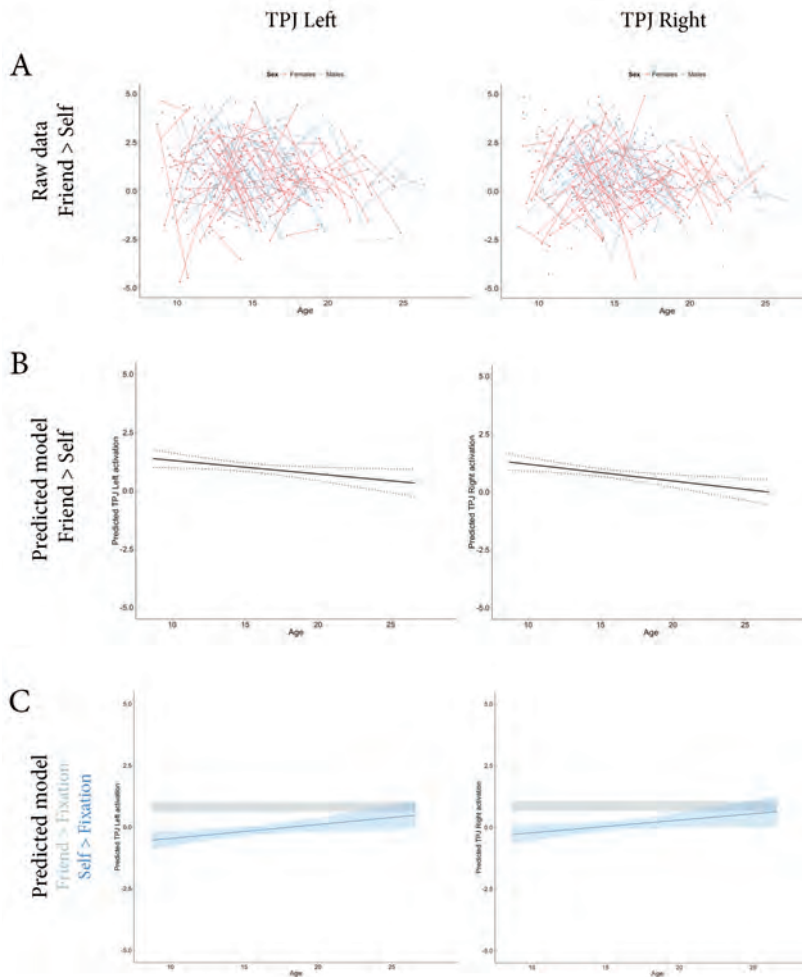


Figure 5.3. A -Longitudinal representation of raw data for the contrast value for Friend > Self for TPJ left, TPJ right. Raw data is plotted for males in blue and females in red.

B - The predicted values for the best fitting model for each region of interest. Dotted lines represent 95% confidence interval.

C - Predicted values for the best fitting model for Friend > Fixation (grey line) and Self > Fixation (blue line) for each region of interest. Shaded areas represent 95% confidence interval.

by a negative linear relationship with age (see Figure 5.3 and 5.4 for raw and predicted model for each of the clusters, see Table 5.4 for an overview of AIC and BIC values and Table 5.5 for a description of the fitted models). This indicates that the difference in activation in these areas when processing outcomes for Friend versus Self decreases over age. To test if these changes were accounted for by Friend or Self changes, follow up

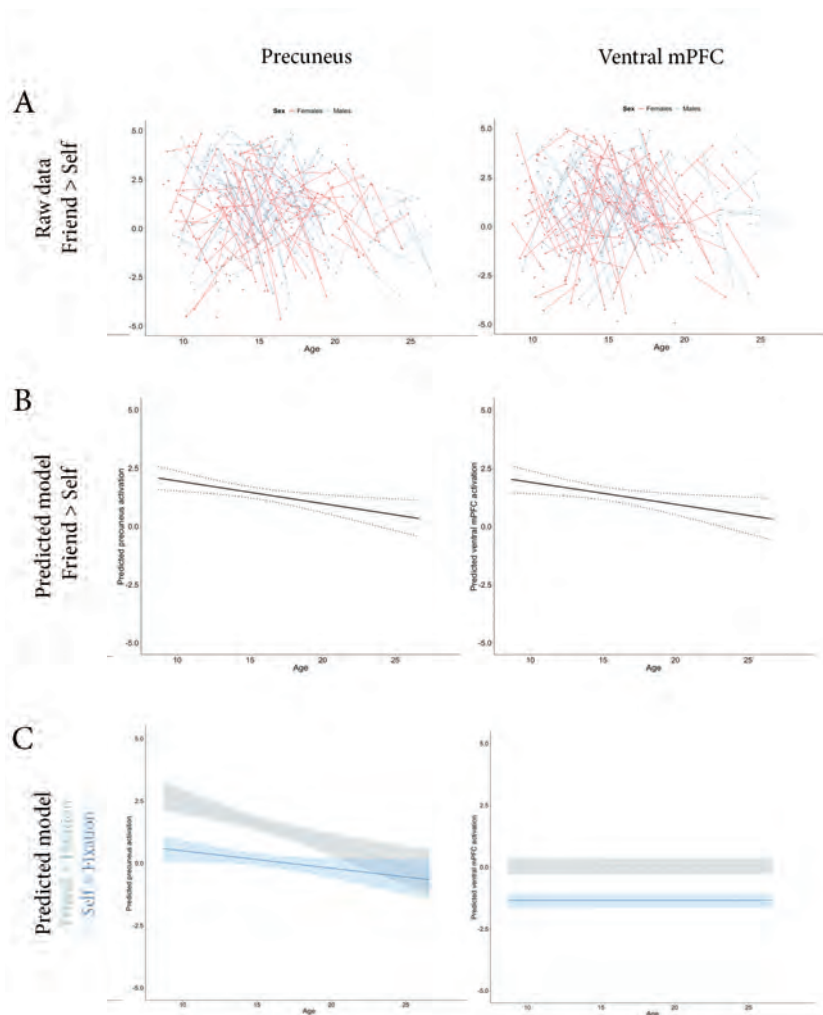


Figure 5.4. A -Longitudinal representation of raw data for the contrast value for Friend > Self for precuneus and ventral mPFC. Raw data is plotted for males in blue and females in red. B - The predicted values for the best fitting model for each region of interest. Dotted lines represent 95% confidence interval. C - Predicted values for the best fitting model for Friend > Fixation (grey line) and Self > Fixation (blue line) for each region of interest. Shaded areas represent 95% confidence interval.

comparisons for Friend > Fixation and Self > Fixation were performed. These analyses showed that separate developmental patterns were observed for these brain regions. First, for the precuneus, age related decreases were found for both Friend > Fixation and for Self > Fixation, but the developmental pattern was more pronounced for Friend > Fixation. Second, for both left and right TPJ, Friend > Fixation remained stable across age, but Self > Fixation activation increased across development. Thus, young

Table 5.4. AIC and BIC values for null, linear and quadratic models. Preferred models, based on AIC values, BIC values and a log likelihood ratio test, are highlighted in bold.

	Null		Model Linear		Quadratic	
	AIC	BIC	AIC	BIC	AIC	BIC
Precuneus						
Friend > Self	2316	2329	2310	2326	2309	2330
Friend > Fix	2424	2436	2406	2423	2408	2429
Self > Fix	2303	2315	2301	2317	2302	2323
TPJ L						
Friend > Self	2047	2059	2043	2060	2045	2066
Friend > Fix	2090	2102	2092	2108	2093	2114
Self > Fix	2005	2018	2002	2019	2004	2025
TPJ R						
Friend > Self	1959	1972	1952	1968	1953	1974
Friend > Fix	2075	2087	2076	2093	2077	2098
Self > Fix	2000	2012	1998	2015	1999	2020
Ventral mPFC						
Friend > Self	2430	2443	2426	2443	2427	2448
Friend > Fix	2477	2490	2478	2494	2478	2499
Self > Fix	2405	2417	2406	2422	2407	2428
Dorsal mPFC						
Self > Friend	2258	2270	2260	2276	2261	2282
Self > Fix	2313	2325	2309	2326	2307	2328
Friend > Fix	2268	2281	2264	2281	2263	2284

adolescents recruited TPJ more for outcomes for Friend, whereas adults recruited TPJ both for outcomes for Friend and for Self. For ventral mPFC the best model for Friend > Fixation and Self > Fixation was a null model, indicating no change in activation over development in these post hoc analyses. Thus, for ventral mPFC the negative developmental pattern was only found in the Friend>Self contrast. See Figure 5.3 and 5.4 for predicted model plots for all areas.

Self > Friend

The dorsal mPFC cluster identified in the whole brain analysis Self > Friend did not show a significant relationship with age. However, when the analyses were performed for Friend > Fixation and Self > Fixation separately, it was found that Friend > Fixation decreased linearly with age, whereas Self> Fixation showed a quadratic pattern, peaking in mid-adolescence, see Figure 5.5.

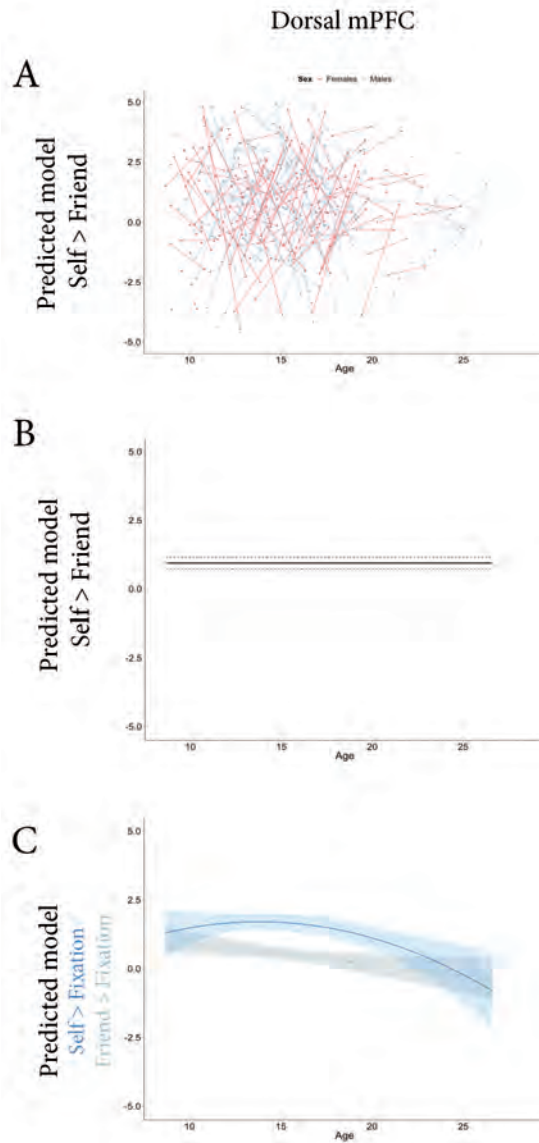


Figure 5.5. A - Longitudinal representation of raw data for the contrast value Self > Friend for the dorsal mPFC. Raw data is plotted for males in blue and females in red.
 B - The predicted values for the best fitting model for dorsal mPFC. Dotted lines represent 95% confidence interval.
 C - Predicted values for the best fitting model for Friend > Fixation and Self > Fixation for dorsal mPFC. Shaded areas represent 95% confidence interval.

Correlations with Self-Report Measures

The final question that was addressed was whether neural activity patterns were modulated by self-report measures. Firstly, we tested whether there was a relationship with age for self-report friendship quality as measured with the Friendship Quality Scale, the self-report ratings in which participants indicated how much they felt their friend deserved to win, and the self-report measures for perspective taking as measured with the IRI perspective taking subscale. Secondly, we used linear mixed models to test which variables showed a linear relationship with neural activation in left and right TPJ, precuneus and ventral mPFC (tested contrast Friend > Self), and dorsal mPFC (tested contrast Self > Friend). To correct for developmental effects each of these models was fitted with a linear term for age included, also when age effects were not significant.

Friendship quality

No relationships were found between the friendship quality scale, positive and negative, and age and neural activation in any of the clusters.

Self-report rating

The rating for how much a friend deserved to win did not show a relationship with age ($\beta = 3.48$, $t_{(244)} = 1.80$, $p = \text{n.s.}$). This rating showed a positive linear relationship with the TPJ left ($\beta = 4.48$, $t_{(195)} = 2.7$, $p = .007$), TPJ right ($\beta = 3.94$, $t_{(195)} = 2.0$, $p = .018$), the precuneus ($\beta = 4.73$, $t_{(195)} = 2.88$, $p = .004$) and the dorsal mPFC ($\beta = -5.01$, $t_{(195)} = 3.12$, $p = .002$). In other words, those participants who indicated that they felt that their friend deserved to win most, also showed the highest activation when receiving outcomes for a friend compared to outcomes for self. Note that the beta value for the dorsal mPFC cluster is negative. This is the result of testing the contrast Self > Friend in this cluster. For ventral mPFC the relationship between the rating and neural activation was not significant.

Perspective taking

For the IRI perspective taking subscale there was a positive relationship with age ($\beta = 19.73$, $t_{(284)} = 5.22$, $p < .001$), indicating that over development participants improved in perspective taking. On the neural level, the perspective taking scale showed a positive linear relationship with the precuneus ($\beta = 7.96$, $t_{(233)} = 2.09$, $p = .038$). This means that, corrected for age, participants who scored higher on the perspective taking scale, differentiated more in neural activation between playing for a friend and playing for self. For the TPJ, left and right, and the ventral and dorsal mPFC there was no relationship between neural activation and the perspective taking scale.

Table 5.5. Variances, beta's, p values and 95% confidence intervals (CI) for best fitting models for the relationship between age and the regions of interest identified in the Friend > Self contrast, i.e. precuneus, mpfc, TPJ left and TPJ right, and the Self > Friend contrast, i.e. mpfc. Linear age terms are represented by Age¹, quadratic terms are represented by Age².

		variance	β	p value	95% CI lower	upper
Precuneus						
<i>Friend > Self</i>						
Random effect	Intercept	0.82			0.39	1.71
Fixed effects	Intercept		1.43	.000	1.18	1.67
	Age ¹		-7.82	.004	-13.13	-2.50
<i>Friend > Fix</i>						
Random effect	Intercept	1.41			1.04	1.92
Fixed effects	Intercept		1.55	.000	1.26	1.83
	Age ¹		-13.84	.000	-20.0	-7.70
<i>Self > Fix</i>						
Random effect	Intercept	1.23			0.89	1.70
Fixed effects	Intercept		0.12	.345	-0.13	0.37
	Age ¹		-5.64	.044	-11.1	-0.16
TPJ L						
<i>Friend > Self</i>						
Random effect	Intercept	0.53			0.21	1.37
Fixed effects	Intercept		0.99	.000	0.80	1.17
	Age ¹		-4.71	.022	-8.71	-0.70
<i>Friend > Fix</i>						
Random effect	Intercept	1.10			0.84	1.44
Fixed effects	Intercept		0.82	.000	0.61	1.03
<i>Self > Fix</i>						
Random effect	Intercept	0.85			0.59	1.21
Fixed effects	Intercept		-0.16	.092	-0.34	0.03
	Age ¹		4.58	.025	0.59	8.58
TPJ R						
<i>Friend > Self</i>						
Random effect	Intercept	0.69			0.41	1.15
Fixed effects	Intercept		0.81	.000	0.63	0.98
	Age ¹		-5.84	.002	-9.57	-2.11
<i>Friend > Fix</i>						
Random effect	Intercept	1.24			1.00	1.53
Fixed effects	Intercept		0.86	.000	0.65	1.08
<i>Self > Fix</i>						
Random effect	Intercept	1.16			0.94	1.43
Fixed effects	Intercept		0.06	.584	-0.14	0.25
	Age ¹		4.12	.050	-0.02	8.35
Ventral mPFC						
<i>Friend > Self</i>						
Random effect	Intercept	1.25			0.84	1.87
Fixed effects	Intercept		1.39	.000	1.11	1.68
	Age ¹		-7.66	.015	-13.81	-1.50

Table 5.5. Continued

		variance	β	<i>p</i> value	95% CI lower	upper
<i>Friend > Fix</i>						
Random effect	Intercept	1.77			1.40	2.24
Fixed effects	Intercept		0.04	.812	-0.28	0.36
<i>Self > Fix</i>						
Random effect	Intercept	1.25			0.80	1.96
Fixed effects	Intercept		-1.35	.000	-1.63	-1.07
Dorsal mPFC						
<i>Self > Friend</i>						
Random effect	Intercept	0.33			0.00	24.3
Fixed effects	Intercept		0.94	.000	0.71	1.16
<i>Self > Fix</i>						
Random effect	Intercept	1.25			0.91	1.71
Fixed effects	Intercept		1.46	.000	1.20	1.71
	Age ¹		-6.81	.016	-12.3	-1.29
	Age ²		-5.96	.032	-11.4	-0.55
<i>Friend > Fix</i>						
Random effect	Intercept	0.85			0.41	1.77
Fixed effects	Intercept		0.51	.000	0.28	0.75
	Age ¹		-6.31	.016	-11.4	-1.21

5.4 Discussion

In this study we tested developmental patterns of brain responses to processing outcomes for friends and self. Consistent with prior studies that tested neural patterns when thinking about traits and intentions of others, processing outcomes for friend resulted in more activation in the bilateral TPJ, precuneus and ventral mPFC (Blakemore, 2008; Van Overwalle, 2009). In contrast, processing outcomes for self resulted in more activation in the dorsal mPFC, which is consistent with prior studies showing that this region is active when monitoring self-relevant outcomes (van den Bos, et al., 2011). The mPFC cluster identified for processing outcomes for friends was more ventral than the cluster for processing outcomes for self. These findings fit well with several meta-analyses studies showing a functional gradient along the prefrontal midline structures for self versus other processing (Amodio & Frith, 2006; Denny, et al., 2012). Although self-referential processing is often related to more ventral, rather than dorsal mPFC activation (Denny, et al., 2012), prior developmental studies also reported self-related activation in dorsal mPFC (Pfeifer, et al., 2007; van den Bos, et al., 2011). These findings set the stage for examining developmental trajectories of these social brain regions.

Developmental patterns

Although behavioral changes in social reasoning have been well documented in the past decades (Cillessen, 2007; Steinberg & Morris, 2001), only recently have studies reported extensive changes in neural activity of social brain areas during adolescence (Blakemore, 2008; Pfeifer & Peake, 2012). The current study provides a novel contribution to this growing literature by (1) investigating how adolescents process outcomes for others, (2) by focusing specifically on outcomes for best friends rather than distant or unknown others, and (3) by using a longitudinal design in a large study with age samples across the whole range of adolescence.

It is important to note that even though the regions of interest in the social brain network (TPJ, precuneus, ventral and dorsal mPFC) were robustly activated across two time points, there was high variability in the extent to which these regions were recruited. That is to say, test-retest stability was considered low, and this stands in sharp contrast with studies using cognitive control paradigms which have reported fair to good test-retest across periods of months (Bennett & Miller, 2013) and years (Koolschijn, et al., 2011). To our knowledge, this is the first study reporting test-retest stability in a longitudinal study on social brain regions, and therefore an important question concerned the extent to which these changes over time were related to age and to self-report changes in how participants felt about their friends. Future studies should test reliability and stability of social brain activity also across shorter time intervals to assess how variable these activities are over time.

The question to which variability in neural activity over time was attributed to age related changes was addressed using linear mixed models that tested for linear and non-linear trajectories of age (see also Braams, et al., 2015). Results show that in regions identified in the Friend > Self contrast, which were TPJ, precuneus and ventral mPFC, neural responses to outcomes for friends became more aligned with, or more similar to neural responses to outcomes for self with increasing age. In other words, in early adolescence there was a relatively large differentiation between outcomes for self and friend, which became smaller in late adolescence and early adulthood. These findings suggest that when adolescents are developing their self-concept and identity (Crocetti, Rubini, Branje, Koot, & Meeus, 2015; Pfeifer & Peake, 2012), possibly they distinguish more between consequences for self and others, whereas in adulthood best friends are possibly experienced as more similar to self. These findings fit well with prior research in which we showed that activity in the ventral striatum, often referred to as the reward center of the brain (Delgado, 2007), was more similar when winning for self and friends in adulthood (Braams, et al., 2014).

Intriguingly, when tested against fixation baseline, different developmental patterns for TPJ, precuneus and mPFC were revealed. These analyses allowed us to test specific age-related changes for processing outcomes for friends and for self. In the precuneus neural activation for both self and friend decreased during adolescence, with a stronger decrease for friend compared to self. In a study by Saxbe et al. (2015) short video clips of parents and unknown peers were shown, more precuneus activation was found for the peer videos. The precuneus activation in this study was interpreted in light of the social reorientation of adolescents in which peers become more important. The decrease found in precuneus activation over age in this study would fit with this interpretation.

In the bilateral TPJ, activation for friend remained stable across age, whereas activation for self increased with age. The age-related decrease for TPJ for Friend>Self seems inconsistent with prior research, which generally shows an increase in TPJ activity with increasing age (for a meta-analysis, see Crone & Dahl, 2012). However, the post hoc analysis shows that the results are consistent with these prior findings, but the increase is observed specifically for the self-condition. Possibly, all participants engaged in perspective taking when processing outcomes for friends, a function purportedly regulated by TPJ (Carter & Huettel, 2013; Mars, Sallet, Schuffelgen, Jbabdi, Toni, & Rushworth, 2012), which resulted in the absence of age differences in the friend condition. The age-related increase in TPJ activity in the self condition may indicate that during adolescence, participants engage in thinking about others when processing outcomes for self. Similar findings were previously reported in a Trust Game. In this study, when participants received trust from another player (a self-relevant outcome), TPJ was more active for adults compared to adolescents, and the extent of activation increased during adolescence (van den Bos, et al., 2011).

In the dorsal mPFC we observed no change in activity for Self > Friend over age. However, when both conditions were tested against a fixation baseline we found a quadratic peak for Self > Fixation and a linear decrease for Friend > Fixation. Thus, the pattern for Self>Friend was probably more complicated than a simple linear or quadratic function, and could only be detected in these follow up analyses. The region where the peak in activation was found, was comparable to the dorsal mPFC which was found to be more active for 12-14-year-olds in a Trust Game (van den Bos, et al., 2011) and which was revealed as peak activity in a meta-analysis (Blakemore & Robbins, 2012). Even though several studies reported more activity in dorsal mPFC in mid-adolescence, few studies tested if this pattern is linearly decreasing or showing an adolescent peak. One prior study confirmed peak activity (Somerville, et al., 2013). In this study participants were told that a camera would record them and that peers would watch them via a monitor while they

were lying in the scanner. The mPFC was the only region that showed a peak in neural activation during adolescence. The current findings are consistent with this prior study and confirm that mid-adolescence is a time of heightened self-referential processing.

Finally, ventral MPFC also showed a linear age related decrease for Friend > Self, although this was no longer significant when testing the conditions relative to fixation baseline. Nonetheless, the pattern matches results previously reported in a longitudinal study by Pfeifer et al. (2013). In this study, participants were tested in a self-other attributes task at ages 10 and 13 years. This longitudinal design showed an increase in ventral mPFC for Self>Friend, which is the same pattern as the decrease for Friend>Self in the current study. The finding that the follow up comparisons were not significant, and the absence of brain-behavioral relations (see below) makes interpretation still challenging, but future studies should test the role of this region in more detail.

Relationship with self-report measures

Changes in neural activation are difficult to interpret per se, i.e. when they are not related to a specific type of behavioral change. To better understand these changes, we tested the relationship between self-report measures and neural activation, and the longitudinal design provided an excellent opportunity to test these brain-behavior relations. For this purpose, we assessed friend relation information (friendship quality, and self-report ratings of how much participants felt that their friend deserved to win), and general perspective taking by self-report.

Firstly, friendship quality was not related to age or neural activation in any of the clusters. Participants were all asked to play for their best friend, meaning that friendship quality was relatively high for all participants. Possibly, friendship quality is an interesting factor to take into account when playing for beneficiaries who vary in level of friendship quality.

Secondly, how much participants felt that their friend deserved to win was positively related to neural activation in the bilateral TPJ, and precuneus. A study by Aue (2014) found more precuneus activation, when a desirable outcome was predicted compared to when an undesirable outcome was predicted. If participants think that their friend deserves more to win, this might reflect a more desired outcome and subsequently explains precuneus activation. The TPJ has previously been interpreted as an important region for perspective taking, and therefore this result may indicate social relevance (Schurz, Aichhorn, Martin, & Perner, 2013).

Finally, it was found that perspective taking increased significantly with advancing age, consistent with prior studies (Hawk, Keijsers, Branje, Van der Graaff, de Wied, & Meeus, 2013). Furthermore, we found that those participants who showed higher scores on perspective taking showed larger precuneus activation, above the age changes that were observed. Research on the role of the precuneus in social interactions, including perspective taking, has yielded mixed results. Some studies find more activation for self compared to other (Cavanna & Trimble, 2006), whereas other studies find the reverse (Farrer & Frith, 2002). A study by Güroğlu et al (2008) showed more robust activation in the precuneus in relation to peers compared to celebrities, confirming the role of precuneus in social interactions. The exact role of the precuneus in social interaction remains unclear and it has been suggested that different parts of the precuneus may serve different goals (Petrini, Piwek, Crabbe, Pollick, & Garrod, 2014). This relation should be investigated in more detail in future studies, relating behavior to neural activity.

Limitations and future directions

A limitation of the current paradigm is that we did not include a formal, non-social baseline condition. A suitable baseline condition for future studies could be for instance receiving outcomes for a computer (Delgado, Frank, & Phelps, 2005). To describe the developmental trajectories in more detail, we tested patterns of change against a fixation baseline. Although these analyses provide important information on developmental change per condition, in a formal non-social baseline condition effects of receiving an outcome can be compared between social and non-social conditions. Future studies should test whether the developmental patterns as observed in the current study are also observed when tested against a non-social baseline condition.

Furthermore, future studies could focus on changing friendships in adolescence. As friendships and best friends change often in (Bowker, 2004), future work could test whether social processing is more related to friendship duration or friendship quality. In the current sample not all participants report that they have the same friend two years later. In such an experiment adolescents could be measured more often, to better capture the changing nature of their social environment. The current paradigm is a relatively simple task in which more automatic processing of social information is measured compared to the more deliberate processes on which other social tasks focus. As such it might be used to measure these automatic processes and compare those to more deliberate social processes.

Conclusions

Taken together, the current results confirm continuous changes in the social brain network across age, and show that social relations and perspective taking skills further moderate these changes. In other words, those participants who showed better perspective taking skills also showed higher differentiation in neural responses to outcomes for a friend compared to outcomes for themselves. The rating for how much a friend deserved to win showed a positive linear relationship with activation in left and right TPJ, and the precuneus. This means that those participants who indicated that they felt that their friend deserved to win most, also showed the highest activation when playing for a friend compared to playing for self.

Future studies should test how these patterns are related to daily life experiences of adolescents by using multiple sampling procedures. The current findings show first evidence in the direction that unraveling brain change-behavioral change relationships are important for understanding the dynamics of the social brain. In the long run, these longitudinal studies will prove to be important for understanding how neural development is influenced by positive and negative social experiences, such as having positive peer relations (Will, van Lier, Crone, & Guroglu, 2015), or experiencing positive parental affect (Tan, Lee, Dahl, Nelson, Stroud, Siegle, Morgan, & Silk, 2014).

