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Me, My Friends, and I : a neuro-ecological perspective on adolescent prosocial development

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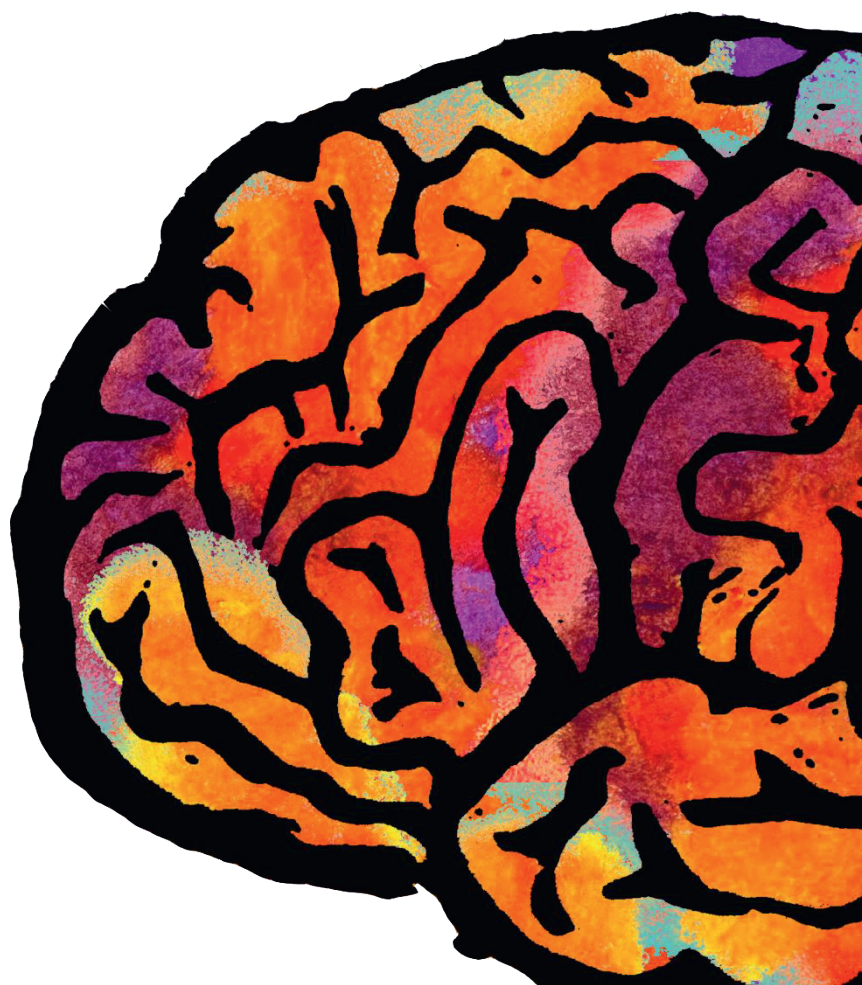


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CHAPTER 3

A longitudinal structural brain imaging study
on adolescent development of social brain regions:
Testing the relation with changes in friendship
quality

Rosa Meuwese, Kathryn L. Mills, Anna van Duijvenvoorde, Sarah-Jayne Blakemore, Eveline A. Crone, Berna Güroğlu

ABSTRACT

Numerous studies have provided support for prolonged trajectories of structural brain development, particularly in the prefrontal and temporal brain regions, from childhood through young adulthood. One recent longitudinal study showed that a specific network of cortical regions involved in social cognition and mentalizing (the 'social brain network') continues to develop structurally throughout adolescence (Mills et al., 2014). However, relatively little is known about how these brain developmental trajectories relate to the social changes occurring during this period of life. In the current study, we tested how the structural development of the social brain network relates to friendship quality in a longitudinal sample of 211 participants who were scanned twice between ages 8-26 years. Our results replicated and extended the cortical developmental patterns previously found by Mills et al., with gray matter volume, cortical thickness and surface area in mBA10, TPJ, pSTS and precuneus decreasing from childhood into the early twenties. Furthermore, we found evidence for an association between increases in friendship quality and accelerated longitudinal changes in mBA10 (older males only) and pSTS surface area and in TPJ cortical thickness (females only). As such, these findings are relevant for our understanding of the biological mechanisms underlying developmental changes in social relationships across adolescence.

3.1 INTRODUCTION

Adolescence is an important developmental period between childhood and adulthood during which individuals develop autonomy and independence (Crone & Dahl, 2012). In recent years, there has been an accumulating body of research showing prolonged development in cortical brain structure across adolescence (Aubert-Broche et al., 2013; Lebel & Beaulieu, 2011; Raznahan et al., 2011; Tamnes et al., 2013; Wierenga, Langen, Oranje, & Durston, 2014; see the review by Mills & Tamnes, 2014). Specifically, large structural changes take place in a network of prefrontal and temporal-parietal regions that are consistently recruited in tasks that involve understanding the mental states of others (Mills et al., 2014). Adolescence is also a phase when peer experiences become more important (Nelson, Jarcho, & Guyer, 2016). Moreover, the quality of peer relations has been shown to have long-lasting effects on social development (Berndt, 2002; Buhrmester, 1990). This suggests that changes in social functioning may relate to changes in structural brain changes in this 'social brain network' (Blakemore & Mills, 2014; Blakemore, 2008).

Prior studies have reported several insights into how social interactions with parents in early childhood and adolescence may be related to cortical development. For example, one study showed that adult attachment style, taken as a representation of early parent-child attachment, was related to decreased gray matter volume in the anterior temporal pole and increased volume in the orbitofrontal cortex in adulthood (Benetti et al., 2010). Furthermore, in two longitudinal studies, social experiences with parents were related to later brain structure: early parental sensitivity was related to greater whole brain gray matter volume in middle childhood (Kok et al., 2015) and warm and supportive parenting in adolescence was related to accelerated cortical thinning in the right anterior cingulate (males only) and in bilateral orbitofrontal cortices (Whittle et al., 2014).

The studies above provide evidence of the association between social interactions with parents and structural brain development. In recent years, an increasing number of studies have examined longitudinal links between adolescent peer experiences and neural activity (Masten, Telzer, Fuligni, Lieberman, & Eisenberger, 2012; Telzer, Fuligni, Lieberman, Miernicki, & Galván, 2013; Will, Crone, Van Lier, & Güroğlu, 2016; Will, Van Lier, Crone, & Güroğlu, 2016). However, the association between social experiences with peers across adolescence and cortical structural development remains relatively understudied.

The current study had two main aims. First, we investigated the development of the social brain network across adolescence using a longitudinal design, using similar procedures as in Mills and colleagues (2014). The social brain network refers to the brain regions activated when individuals think about mental states of others ('mentalizing'; Van Overwalle & Baetens, 2009). This network comprises the dorsomedial prefrontal cortex (DMPFC), temporal parietal junction (TPJ), posterior superior temporal sulcus (pSTS), and anterior temporal cortex (ATC). Several studies have reported developmental differences across adolescence in the functional activity within this network during social cognition tasks (Blakemore & Mills, 2014). Mills and colleagues (2014) have shown that this social brain network shows structural development across adolescence. This finding was based on structural brain scans of 288 participants aged between 7-30 years, who were scanned between two and seven times. Specifically, the results showed linear changes in cortical thickness, and non-linear (cubic) changes in gray matter volume and surface area in each of the four social brain regions.

Using precisely the same social brain regions of interest (ROIs) and analysis, here we aimed to replicate these findings in a different cohort. The current sample consisted of 211 participants aged between 8-26 years who were tested twice (with a 2 year lag) in an accelerated longitudinal design. The measures of interest were volume, cortical thickness and surface areas in mBA10, pSTS, TPJ and precuneus (PC). We added the PC in our study as part of the social brain network because of its role in the mentalizing system (Van Overwalle & Baetens, 2009), for example in thinking about intentions (Blakemore, Den Ouden, Choudhury, & Frith, 2007; den Ouden, Frith, Frith, & Blakemore, 2005) and violations of social expectations (Petrini, Piwek, Crabbe, Pollick, & Garrod, 2014). We expected to find similar developmental patterns in the PC as in the other ROIs.

The second aim was to detect how changes in friendship quality are related to changes in brain structure across adolescence. Friendship quality is an important dimension of social competence in adolescence (Hartup, 1996). One of the most distinct changes in adolescence concerns social relations and networks, with a more pronounced focus on intimate friendships (Bukowski, Hoza, & Boivin, 1993). Friendship quality is a strong indicator of social functioning and related to positive social development (Berndt, 2002). High quality friendships are typically characterized by high levels of positive features, such as prosocial behavior, intimacy and support, and are found to be an indicator of success in the social world of peers (Berndt, 2004). Findings also indicate the important role of prosocial behavior and empathic skills

in high levels of friendship quality (Cillessen, Jiang, West, & Laszkowski, 2005; Meuwese, Cillessen, & Güroğlu, 2016). As such, social skills, such as mentalizing, play a significant role in forming and maintaining friendships of high quality.

The current study investigated how changes in friendship quality relate to changes in the structure of the social brain regions. We predicted that friendship quality changes would be related to more mature brain structure in the social brain network, given previous findings showing a relationship between positive social parent interactions and cortical thinning (Whittle et al., 2014) and the inverse relationship between cortical thickness in social brain regions and empathy and mentalizing in adults (Banissy et al., 2012; Rice & Redcay, 2015). We explored whether the association between longitudinal friendship quality and structural brain development was different for females and males, since previous studies report sex differences in friendship characteristics and in the differential impact of friendship quality on development between sexes (Bagwell & Schmidt, 2011).

3.2 METHOD

Participants

Within a large longitudinal study, a total of 299 typically developing individuals from 8 to 24 years old ($M = 13.96$; $SD = 3.65$) underwent a high-resolution structural MRI-scan at time point 1 (t1) and 254 of them (ages 9-26; $M = 13.96$; $SD = 3.65$) at time point 2 (t2). Of the 299 participants at t1, 33 could not be scanned at t2 due to metal dental braces, and 12 decided to cease participation or had moved abroad. Quality control (see below for details) of all scans resulted in 211 participants (112 females, 99 males) with good quality scans at both time points. The two scans of each of these participants were obtained with an average of 1.99 years in between them ($SD = 0.10$, $Min = 1.66$, $Max = 2.47$). Participants were only included at t1 after a telephone screening for right-handedness and absence of neurological and psychiatric disorders or use of medication known to affect nervous system functioning.

Of the 211 participants, 49 were siblings (6 of them with two siblings participating). Intelligence was approximated using block design and similarities (t1) and arithmetic and vocabulary (t2) of the WISC-III for children up to 16 years of age and of the WAIS-IV for 16 years and older. All participants had normal intelligence (t1: $M = 110.43$, $SD = 9.59$; t2: $M = 108.94$, $SD = 10.27$). One participant had a measurement error when administrating the tests at t1, but had an estimated IQ score of 108 at t2, therefore we included this participant in the analyses but left out their t1 IQ-

score in Table 1. For descriptive purposes, pubertal development of participants under age 18 was assessed with the PDS; a self-report questionnaire which contains questions about secondary sexual characteristics (Petersen, Crockett, Richards, & Boxer, 1988). Of all participants, 90.1% were either Caucasian (i.e. no non-Caucasian parents or grandparents) or had one non-Caucasian grandparent. The remaining 9.9% of non-Caucasian participants were from diverse cultural/ethnic backgrounds.

Participants were recruited through local schools and advertisements. Primary caregivers (for all minors) and all participants from age 12 and up gave informed consent. Adults were paid for their participation and minors and their parents received gifts and travel reimbursement. The internal review board from the Leiden University Medical Center approved the study.

Table 1
Sample characteristics

	t1				t2			
	M	SD	Min	Max	M	SD	Min	Max
Age	14.74	3.64	8.01	24.55	16.72	3.67	9.92	26.62
% Female	53.1							
IQ ¹	110.43	9.59	85	138	108.94	10.27	80	147.50
Puberty ² (% in stage 4 ³)	2.53 (18.7)	0.88	1.00	4.00	2.82 (36.8)	0.78	1.00	4.00
% Caucasian ⁴ (one non-Caucasian grand- parent)	83.3 (6.9)							
Positive friendship quality (same friend T1-T2)	55.54 (56.09)	6.43 (6.08)	38 (40)	65 (65)	56.03 (57.28)	6.10 (4.72)	37 (43)	65 (65)
Negative friendship quality (same friend T1-T2)	30.49 (30.66)	3.77 (3.72)	16 (19)	35 (35)	29.95 (30.77)	3.93 (3.60)	17 (21)	35 (35)

Note. ¹One participant's t1 IQ-score had a measurement error and was therefore excluded from these statistics; ²PDS-score for participants < 18 years; ³For all ages; ⁴At least two generations back

MRI measurements

All participants were scanned on a 3-Tesla whole body Philips Achieva MRI system, Best, Netherlands. High-resolution T1-weighted anatomical scans were obtained: 3D-T1-weighted scan: TR = 9.717 msec; TE = 4.59 msec, flip angle = 8°, 140 slices, .875 x .875 x 1.2 mm, FOV = 224.000 x 168.000 x 177.333). All anatomical scans were reviewed and cleared for gross abnormalities by a radiologist. Cortical reconstruction was performed with the Freesurfer 5.3 image analysis suite, which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). To extract reliable volume and thickness estimates, images were automatically processed with the longitudinal stream (Reuter, Schmansky, Rosas, & Fischl, 2012). This process includes the creation of an unbiased within-subject template space and image using robust, inverse consistent registration (Reuter, Rosas, & Fischl, 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter et al., 2012). One anatomical scan was acquired at each time point.

The technical details of cortical reconstruction procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002; Fischl et al., 1999a; Fischl et al., 1999b). Briefly, this processing includes motion correction (Reuter et al. 2010), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, intensity normalization (Sled et al., 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl et al., 2001; Segonne, Pacheco, & Fischl, 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000). The quality of cortical reconstruction was visually inspected by the first author and a trained assistant; unsuccessful reconstructions (n=43) were identified and these participants were excluded from analyses.

Each cortical model was registered to a spherical atlas using individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999b). Measurements of mean cortical thickness (mm), white matter surface area (mm²) and gray matter volume (mm³) were extracted for each region of interest in both hemispheres. Total bilateral surface area and volume were calculated; cortical thickness was averaged across left and right hemisphere.

Selection of social brain ROIs and control region

The ROIs for the mBA10, the pSTS, and the TPJ regions were defined based on Brodmann's areas, the Desikan-Killiany atlas (Desikan et al., 2006) and functional coordinates (see Figure 1). See Mills et al. (2014) for a detailed description. The ROIs from the Mills (2014) paper can be downloaded from the website figshare (Mills, 2013). The precuneus (PC) was defined in the Desikan-Killiany atlas. We selected the primary visual cortex (V1) as defined in the Desikan-Killiany atlas to examine the specificity of developmental patterns of the social brain regions (Rice & Redcay, 2015). Unfortunately, changes of the ATC could not be analyzed, due to poor scan quality of the temporal pole region for the majority (>50%) of our scans.

Assessment of friendship quality

We asked participants to report on the quality of their same sex best friendship using a Dutch adaptation of the Friendship Qualities Scale (FQS; Bukowski, Hoza, & Boivin, 1994). At t2 participants were asked to indicate their current best friend again, independent of their choice at t1; 43.9% still had the same best friend after two years. Of all the participants who had good quality scans at t1 and t2 ($N = 211$), 13 decided not to participate in this part of the study. Therefore, $n = 198$ for all analyses that included the friendship quality measures.

The FQS consisted of two subscales; one measuring positive friendship quality (13 items; Cronbach's $\alpha = .90$), such as closeness, companionship and security; and one measuring negative friendship quality (7 items; Cronbach's $\alpha = .78$), such as conflict and imbalance. Items were scored on a 5-point scale. Sum scores were cal-

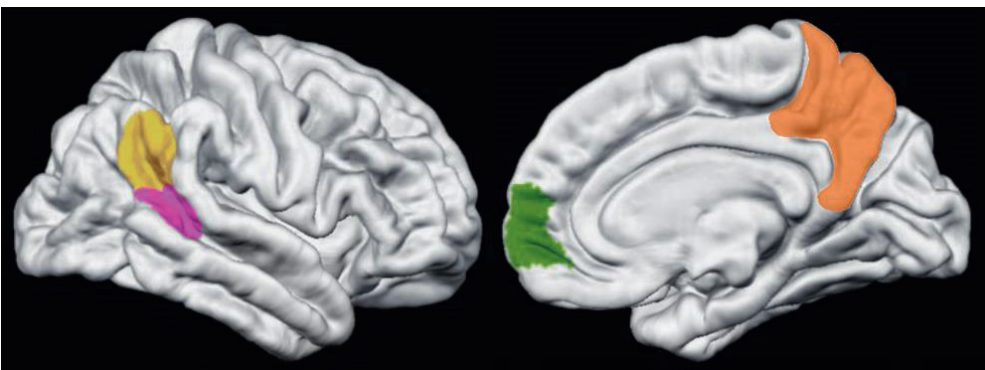


Figure 1. Social brain regions of interest. Medial Brodmann Area 10 (mBA10; green), temporoparietal junction (TPJ; yellow), posterior superior temporal sulcus (pSTS; pink) and precuneus (PC; orange).

culated for each subscale; higher scores imply higher levels of positive friendship quality and lower levels of negative friendship quality.

Statistical analyses

In order to test for age effects in anatomical features of the social brain we used linear mixed modeling to predict development of gray matter volume, cortical thickness and surface area for each ROI separately. This method is suited for longitudinal data because it controls for dependency on measures within individuals and takes into account individual differences in intercepts. We used these models 1) to examine the developmental trajectory for each ROI; and 2) to test whether friendship quality could explain additional variance above age within these regions.

We performed mixed analyses with the NLME package in R (Pinheiro et al., 2013) version 3.1-117. This package enabled us to examine both fixed effects and random effects. The intercept-only model included a fixed intercept and a random intercept, with the latter capturing individual differences in overall brain structure to account for the repeated nature of the data. We tested for linear, quadratic and cubic effects of age, by adding three polynomial functions for age to the base-model. We compared model fit of the null model with linear, quadratic and cubic slopes and the lowest AIC (Akaike Information Criterion; Akaike, 1974) determined best model fit. For example, an equation for a model using cubic gray matter volume (vol) growth for i th individual's j th timepoint is:

$$\text{vol}_{ij} = \text{Intercept} + d_i + \beta_1(\text{age}) + \beta_2(\text{age}^2) + \beta_3(\text{age}^3) + \varepsilon_{ij}.$$

In our initial analyses we used bilateral brain measures to examine the developmental patterns. Sex ($F = 0$; $M = 1$) differences were examined by comparing best age model, best age model with sex added as a main effect and a model with all previous terms and an interaction term for sex and age (linear, quadratic or cubic term) using the AIC. For example, given a cubic best age model, an equation with a sex interaction term included, predicting cortical thickness (ct), is:

$$\text{ct}_{ij} = \text{Intercept} + d_i + \beta_1(\text{age}) + \beta_2(\text{age}^2) + \beta_3(\text{age}^3) + \beta_4(\text{sex}) + \beta_5(\text{age} * \text{sex}) + \beta_6(\text{age}^2 * \text{sex}) + \beta_7(\text{age}^3 * \text{sex}) + \varepsilon_{ij}.$$

A similar procedure was used to test for effects of friendship quality on structural development in the social brain. First, if there was an effect of sex on brain development in the ROI, the main and/or interaction term of sex and age was added to the best age model. Second, friendship quality was added; main effects and interaction effects were tested. For example, given a quadratic best age model with a sex

interaction effect, an equation for positive friendship quality, predicting surface area (sa), is:

$$sa_{ij} = \text{Intercept} + d_i + \beta_1(\text{age}) + \beta_2(\text{age}^2) + \beta_3(\text{sex}) + \beta_4(\text{FQS.pos}) + \beta_5(\text{age}*\text{sex}) + \beta_6(\text{age}^2*\text{sex}) + \beta_7(\text{age}*\text{FQS.pos}) + \beta_8(\text{age}^2*\text{FQS.pos}) + \beta_9(\text{sex}*\text{FQS.pos}) + \beta_{10}(\text{age}*\text{sex}*\text{FQS.pos}) + \beta_{11}(\text{age}^2*\text{sex}*\text{FQS.pos}) + \varepsilon_{ij}.$$

Third, if there was a three-way interaction, the effect of friendship quality on brain development was tested for the two sexes separately. For example, given a linear best age model, an equation for negative friendship quality, predicting gray matter volume, is:

$$vol_{ij} = \text{Intercept} + d_i + \beta_1(\text{age}) + \beta_2(\text{FQS.neg}) + \beta_3(\text{age}*\text{FQS.neg}) + \varepsilon_{ij}.$$

We reported likelihood ratio test statistics of best fitting model vs. the previous nested model and unstandardized beta values for sex effects.

In addition to the statistical analyses, for each ROI and each measure we divided the participants into three groups: participants showing a decrease ($\geq 2\%$), no change, or increase ($\geq 2\%$) in volume/cortical thickness/surface area between time points. This was done for visualization purposes: graphs were created to show the proportions of “decrease”, “no change”, and “increase” of the structural measures over age groups consisting of two years (8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20 and up).

3.3 RESULTS

We first examined the developmental trajectories of gray matter volume, cortical thickness and surface area in the mBA10, pSTS, TPJ, and PC. Figures 2B through 5B show the raw individual developmental trajectories for the social brain ROIs. Figures 2C through 5C show the proportion of participants in whom volume, cortical thickness, and surface area decreased, did not change, or increased between time points, divided over age groups. Next, for the second goal of the study, we tested effects of friendship quality on social brain structure development, adjusting for age and sex effects.

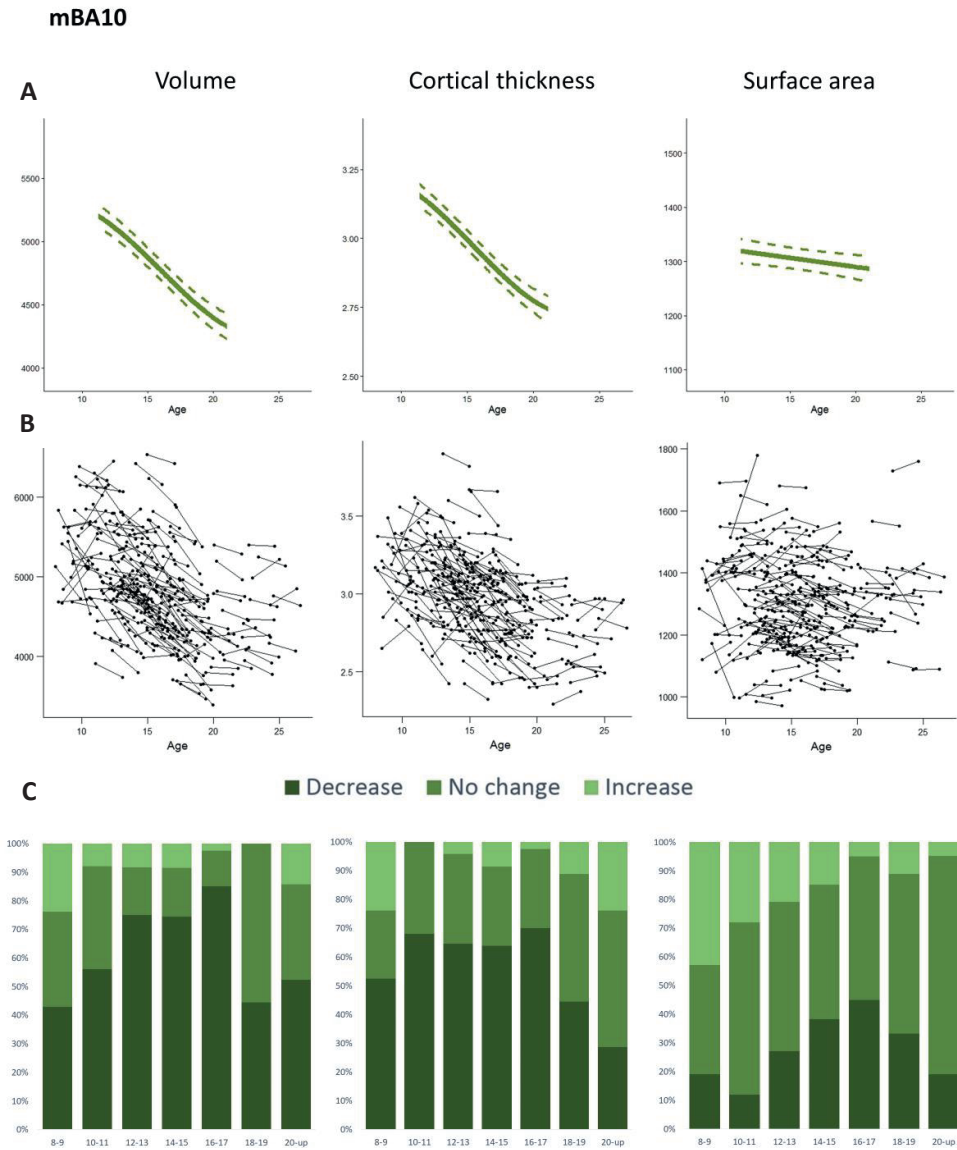


Figure 2. A. Predicted curves for bilateral mBA10 gray matter volume, cortical thickness and surface area. Graphs show the middle 80% of the age range in our sample; B. Raw individual developmental changes for bilateral mBA10 gray matter volume, cortical thickness and surface area; C. Distribution of proportion of participants that show a decrease ($>2\%$), no change ($-2\% \leq x \leq 2\%$) or an increase ($>2\%$) in bilateral mBA10 gray matter volume, cortical thickness and surface area.

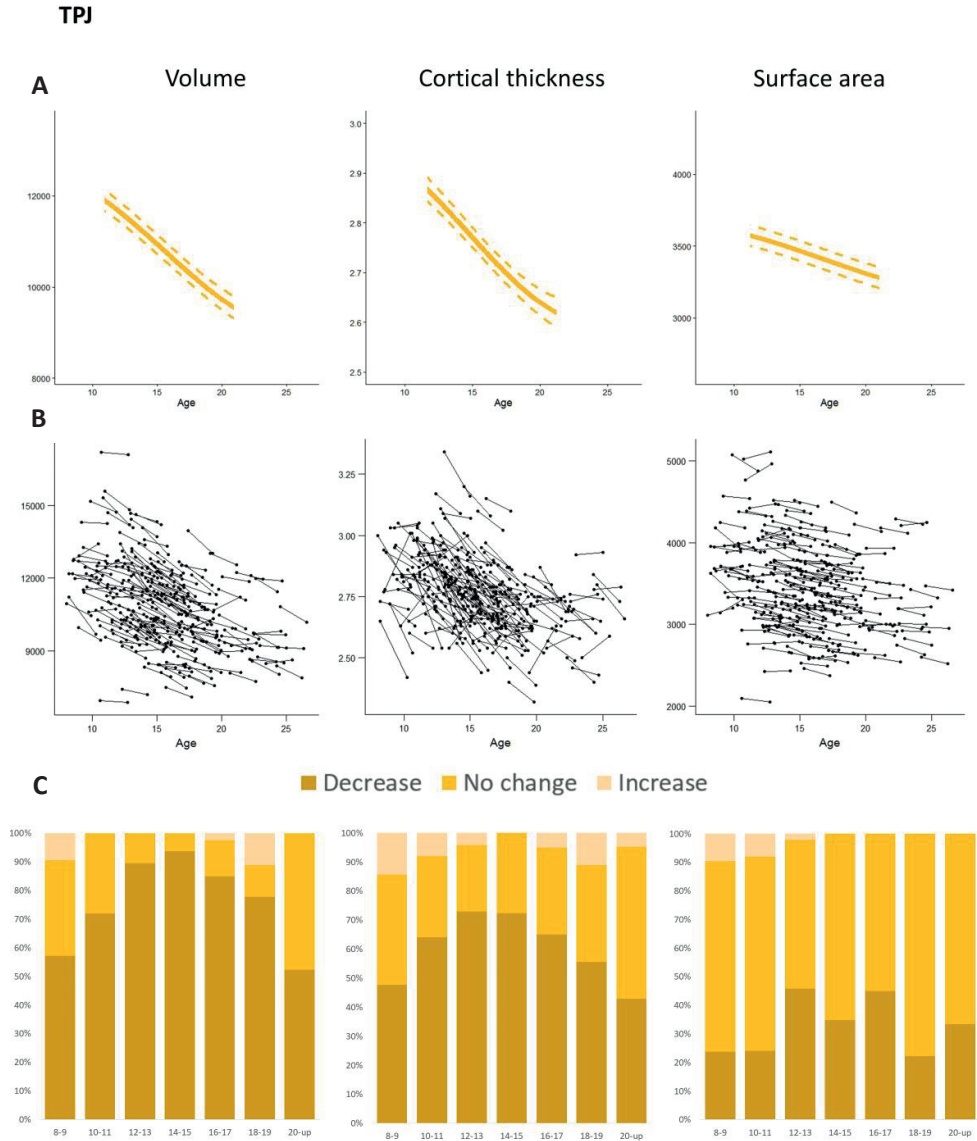


Figure 3. A. Predicted curves for bilateral TPJ gray matter volume, cortical thickness and surface area. Graphs show the middle 80% of the age range in our sample; B. Raw individual developmental changes for bilateral TPJ gray matter volume, cortical thickness and surface area; C. Distribution of proportion of participants that show a decrease ($>-2\%$), no change ($-2\% \leq x \leq 2\%$) or an increase ($>2\%$) in bilateral TPJ gray matter volume, cortical thickness and surface area.

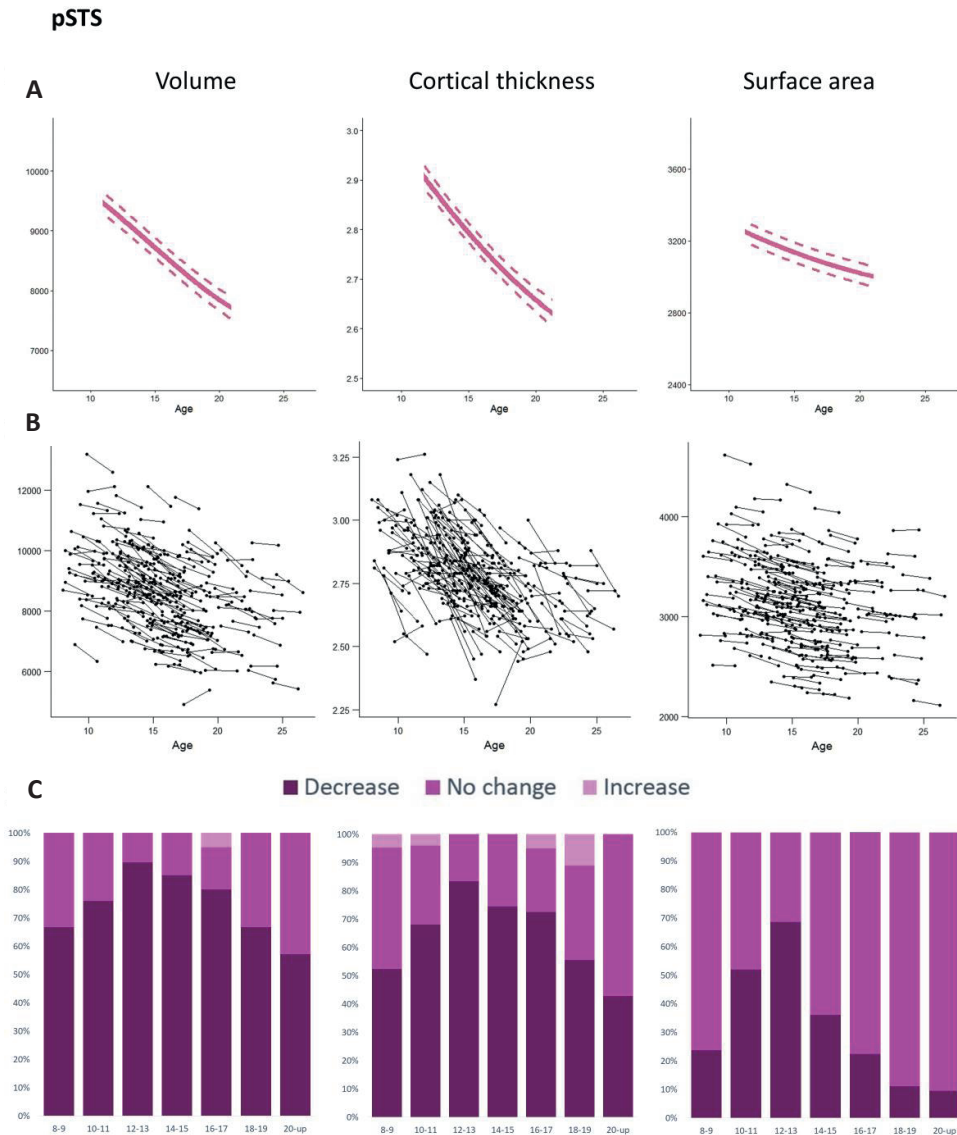


Figure 4. A. Predicted curves for bilateral pSTS gray matter volume, cortical thickness and surface area. Graphs show the middle 80% of the age range in our sample; B. Raw individual developmental changes for bilateral pSTS gray matter volume, cortical thickness and surface area; C. Distribution of proportion of participants that show a decrease ($>-2\%$), no change ($-2\% \leq x \leq 2\%$) or an increase ($>2\%$) in bilateral pSTS gray matter volume, cortical thickness and surface area.

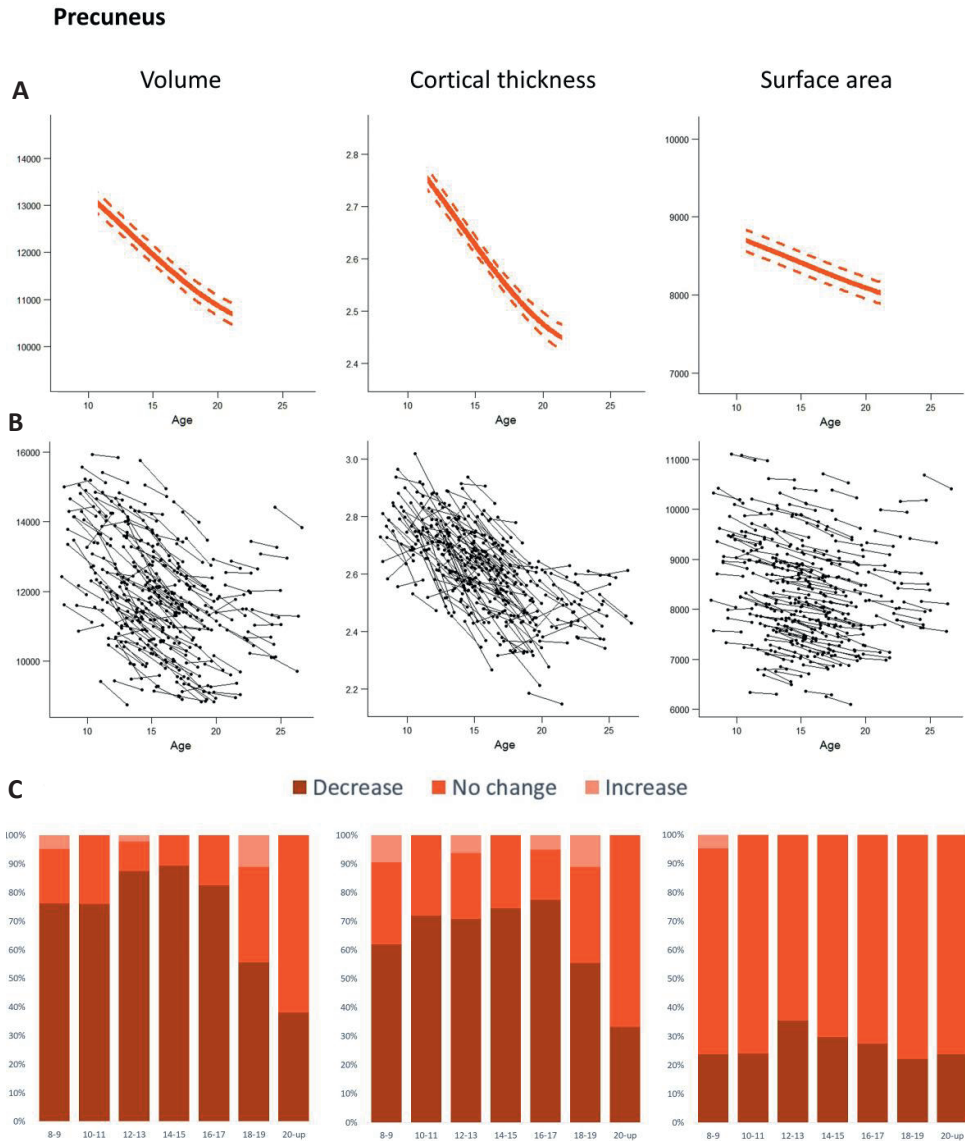


Figure 5. A. Predicted curves for bilateral precuneus gray matter volume, cortical thickness and surface area. Graphs show the middle 80% of the age range in our sample; B. Raw individual developmental changes for bilateral precuneus gray matter volume, cortical thickness and surface area; C. Distribution of proportion of participants that show a decrease ($>2\%$), no change ($-2\% \leq x \leq 2\%$) or an increase ($>2\%$) in bilateral precuneus gray matter volume, cortical thickness and surface area.

Age and sex effects on social brain development

mBA10

Analyses revealed that best fitting model for bilateral gray matter volume of the mBA10 was a cubic trajectory ($LR = 18.23$; $p < .001$); cortical thickness decreased in a cubic fashion ($LR = 14.57$; $p < .001$) and surface area decreased linearly ($LR = 5.97$; $p = .015$). Figure 2A shows the predicted curves for the mBA10. Between the 10th (11.04 years old) and 90th percentile (21.08 years old) of the age range in our sample, predicted values showed a decrease of 17.0% in volume, 13.4% in cortical thickness and 2.5% in surface area (Table 2). There was a main effect of sex on volume ($LR = 26.22$; $p < .001$, $\beta = 285.19$; $p < .001$), and an interaction between sex and age on surface area ($LR = 3.54$; $p = .060$, $\beta = 332.01$; $p = .062$): males had overall more volume and slower decreasing surface area in the mBA10 than did females. There were no sex differences for cortical thickness.

TPJ

Analyses revealed a cubic decrease in volume ($LR = 14.92$; $p < .001$), cortical thickness ($LR = 6.46$; $p = .011$) and surface area ($LR = 5.35$; $p = .021$). Figure 3A shows the predicted curve for all measures of the bilateral TPJ. The predicted decrease in volume between the 10th and 90th percentile of our age range was 19.8%, for cortical thickness this was 9.1% and for surface area 8.3% (Table 2). There was a main sex effect on volume ($LR = 26.22$; $\beta = 285.19$; $p < .001$) and cortical thickness ($LR = 3.061$; $\beta = 0.028$; $p = .080$), indicating that males of all ages had more volume and thicker cortices. There was no effect of sex on surface area.

Table 2

Predicted developmental decrease between ages ~11 and ~21

	Gray matter volume	Cortical thickness	Surface area
mBA10	-17.0%	-13.4%	-2.5%
TPJ	-19.8%	-9.1%	-8.3%
pSTS	-18.6%	-10.1%	-7.9%
precuneus	-17.5%	-11.3%	-7.5%
V1	-2.5%	-	-5.7%

Note. Developmental change in the middle 80% of the age range in our sample. Age at 10th percentile was 11.04 and at 90th percentile was 21.08.

pSTS

Gray matter volume showed a cubic decrease ($LR = 7.48$; $p = .006$). Both cortical thickness ($LR = 8.03$; $p = .005$) and surface area ($LR = 27.60$; $p < .001$) of the pSTS showed a quadratic decrease. Predicted values at the 10th and 90th percentile of age decreased 18.6% for volume, 10.1% for cortical thickness, and 7.9% for surface area (see Figure 4A and Table 2). There was an interaction between sex and the quadratic age term and the cubic age term on volume ($LR = 13.52$; $p = .004$), indicating different trajectories between females and males. There was no effect of sex on cortical thickness or surface area.

Precuneus

The best fitting model for bilateral gray matter volume of the PC was a cubic age trajectory ($LR = 7.52$; $p = .006$). Cortical thickness also showed a cubic decrease ($LR = 8.43$; $p = .004$), as did surface area ($LR = 4.82$; $p = .028$). Figure 5A shows the predicted curves for the PC. The predicted decrease in volume between the 10th and 90th percentile of our age range was 17.5%, for cortical thickness this was 11.3% and for surface area 7.5% (Table 2). There was a main effect of sex on cortical thickness ($LR = 6.15$; $\beta = 0.03$; $p = .013$) and surface area ($LR = 8.93$; $\beta = 93.09$; $p = .003$): males had a thicker cortex and larger surface area in the bilateral PC. There was an interaction between the sex term and the quadratic age term on volume, indicating different trajectories between males and females in gray matter volume decrease ($LR = 14.42$; $p = .002$).

V1 - control ROI

Similar to the social brain areas, gray matter volume in the primary visual cortex decreased over age ($LR = 4.72$; $p = .030$), but in a linear matter. This was a 2.5% change over the course of adolescence (10th to 90th percentile of ages; see Table 2). Furthermore, this effect was only driven by a linear decrease in surface area ($LR = 38.53$; $p < .001$; 5.7% predicted change; see Table 2), since there was no effect of age on cortical thickness. There was an interaction of sex on volume ($LR = 8.68$; $\beta = 3834.95$; $p = .003$): males of all ages had more gray matter volume in the V1. There were no effects of sex on surface area or cortical thickness.

Best friendship quality and structural social brain development

After testing the developmental patterns of our sample, we aimed to examine the links between changes in friendship quality as a measure of social functioning and changes in brain structure. In order to do this, we first examined developmental

changes of friendship quality and then tested for relations between the structural brain development of the social brain and friendship quality changes. For the latter analysis, all analyses reported above were performed with the addition of friendship quality as a predictor above the best age model or best age and sex model.

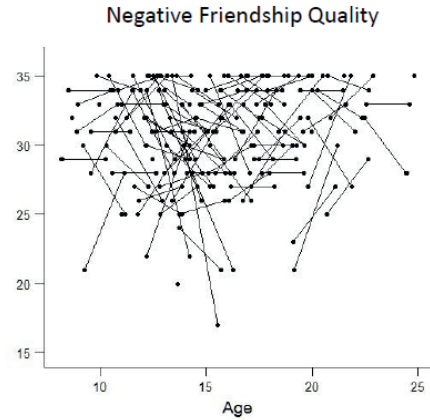
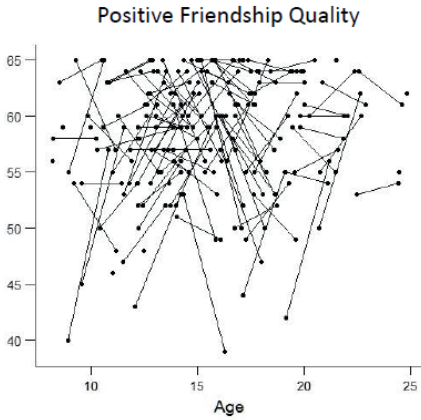
There was no age effect on negative or positive friendship quality. Girls reported higher levels of positive ($LR = 53.02$; $p < .001$, $\beta = -5.15$; $p < .001$) and lower levels of negative friendship quality ($LR = 6.35$; $p = .0117$, $\beta = 1.09$; $p = .012$). Adding the sex term before the age term(s) and as an interaction with age did not result in different developmental patterns for males and females. See Figure 6 for spaghetti plots of the friendship quality measures against age, separately for the two sexes.

There was a three-way interaction for age, sex and positive friendship quality on surface area change in the mBA10 ($LR = 10.21$; $p = .017$; $\beta = -52.25$; $p = .005$). Additional analyses for females and males separately showed that the best model for males included a negative interaction effect between age and friendship quality ($LR = 2.69$; $p = .101$, $\beta = -16.05$; $p = .106$). There was no such effect for females ($\beta = 9.18$; $p = .381$). This indicates that the association between higher friendship quality and a decrease in surface area is stronger for older males than for younger males.

Friendship quality change was also differentially related to a decrease in TPJ cortical thickness for females and males: there was an interaction of sex and positive friendship quality ($LR = 4.61$; $p = .032$, $\beta = 0.00$; $p = .033$). In follow-up analyses only females showed a negative effect of friendship quality on cortical thickness ($LR = 2.85$; $p = .091$, $\beta = 0.00$; $p = .096$), males did not ($LR = 1.06$; $p = 0.3031$, $\beta = 0.00$, $p = 0.308$).

Finally, increase in positive friendship quality was related to a decrease in surface area in the pSTS over time ($LR = 5.46$; $p = .019$, $\beta = -0.95$; $p = .021$), equally for both sexes. Adding sex as a control variable before positive friendship quality did not change this result. There were no effects of negative friendship quality on structural development of the social brain network.

Females



Males

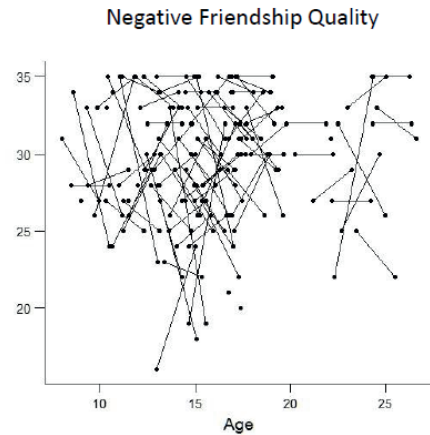
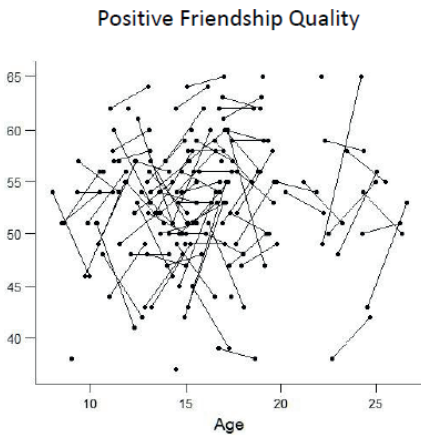


Figure 6. Spaghetti plots for friendship quality plotted against age.

3.4 DISCUSSION

In the current study we aimed to examine links between social functioning across adolescence and structural changes in four regions of the social brain network, namely mPFC, TPJ, pSTS, and the precuneus, in a large longitudinal study

between 8-26 years, including two measurements with two years in between. We first demonstrated that gray matter volume, cortical thickness and surface area within the social brain regions decrease from pre-adolescence onwards and that this development extends into early adulthood. Across adolescence, cortical volume of all four social brain regions reduced by 17-20% in size, within a time frame of 10 years. Importantly, we were able to replicate the prior findings of Mills et al. (2014) to a large extent. The second goal of the current study was to investigate whether developmental changes in brain structure are related to changes in friendship quality, an indicator of social functioning in adolescence. We showed that higher levels of friendship quality are related to accelerated cortical maturation of regions in the social brain network.

General developmental patterns of the social brain network

We examined age-related changes in three indices of brain structure: cortical thickness, surface area and gray matter volume. For gray matter *volume*, we showed a general pattern of decreasing volume in all four social brain regions that we examined in the current study. This finding is in line with prior studies showing whole brain gray matter decreases across adolescence (Aubert-Broche et al., 2013; Tamnes et al., 2013; Wierenga et al., 2014), and within the social brain network specifically (Mills et al., 2014). Between approximately 11 and 21 years of age, the predicted decrease over time is between 17-20%. In comparison, volume in the control region V1 decreased by only 2.5%. Our results provide evidence for non-linear decreasing trajectories of volume across 8-26 years, yet the graphs with the predicted curves, depicting only the middle 80% of the age range (11-21 years) reveal a more constant decrease of volume from early adolescence to early adulthood. This display of the middle 80% of the age range provides a more reliable representation of population brain structure development and therefore we cautiously interpret the non-linear volume decreases.

Similarly, we found that cortical thickness within the social brain network also decreases in a quadratic or cubic pattern and shows an accelerated decrease from pre- to mid-adolescence, before continuing onto a slower pace of decrease. Previous research shows that this moderate decrease in cortical thickness continues after early adulthood (whole brain) (Hogstrom, Westlye, Walhovd, & Fjell, 2013). Between approximately 11 and 21 years of age, the predicted decrease over time is around 10%. In the Mills study, cortical thickness in the mBA10, TPJ and pSTS also decreased, yet in a linear pattern. We discuss differences in findings between our study and the study by Mills and colleagues below. Change in cortical thickness in

our control region V1 could not be predicted with statistical models; hence there was no statistical evidence for change in this region across adolescence.

Of the three structural measures, surface area was most stable over time, consistent with previous studies (Brown et al., 2012; Mills et al., 2014; Raznahan et al., 2011; Wierenga et al., 2014). The initiation of a developmental decrease in childhood lies outside the age range in our study, and this decrease continues well into early adulthood for some individuals. Although non-linear trajectories best predicted surface area development in most regions, the decrease in surface area in the middle 80% of the age range is mainly linear.

In the study by Mills and colleagues (2014), instead of cortical thickness, surface area was found to drive the non-linear patterns in volume changes. Overall, surface area in the Mills study decreased non-linearly whereas this decrease in our study is mainly linear. On the other hand, cortical thickness in the Mills study decreased in a linear pattern, whereas this decrease was mainly cubic in our study. Three methodological differences could explain the seemingly divergent results for surface area: first, we used the longitudinal pipeline of Freesurfer, a procedure that was not yet available at the time of data processing of the Mills study. It is possible that the longitudinal pipeline of Freesurfer increases stability between time points, especially in the cortical measure that is most sensitive to error in reconstruction, which would be surface area. More variation in individual developmental trajectories in the data of Mills and colleagues allows for more deviation from a strictly linear decrease. Therefore, although the longitudinal pipeline is more accurate (Reuter et al., 2012) this could be at the cost of variance that is of interest.

Second, whereas Mills and colleagues' area measure consisted of average surface area between white matter surface area and pial surface area, for convenience purposes we used the white matter surface area that was automatically extracted by Freesurfer. Future studies on structural brain development should compare within-person changes over time in longitudinal white matter surface area with within-person changes in pial surface area, and relate this to the degree of cortical gyrification. Greater concordance in developmental changes would be expected between the two area measures in flatter areas. This could explain some of the differences in findings between the Mills study and the current study.

Third, the age range in our study was slightly narrower (Mills study: 7-30; current study: 8-26). Our age range could have been too narrow to include a sufficient number of individuals with increasing surface area prior to adolescence and stable or increasing surface area post-adolescence to fit a nonlinear model. On the other hand, following this line of reasoning, one would not expect to find more cubic patterns predicting cortical thickness in our study and only linear patterns in the

Mills study. A related statistical vulnerability, which is inevitable when fitting non-linear models, could account for the difference in thickness development. The model fit of quadratic and cubic effects in mixed models is considerably dependent on individual measurements at each end of the independent variable range and a small number of deviating measurements could alter the best model fit. As a consequence, not finding differences in best fitting models across different samples would actually be more exceptional than the differences that we observe across the two studies here. Therefore, in order to be able to investigate timing of peaks in gray matter development, it is crucial to include younger children in future studies.

Friendship quality and the developing social brain

Our analyses testing for associations between changes in friendship quality and development of the social brain network showed that including changes in friendship quality improved our models fits of structural change in the mBA10, TPJ and pSTS beyond age. We found that higher levels of positive friendship quality are related to accelerated surface area development for both sexes in the pSTS and only for older male participants in the mBA10. In cortical thickness of the TPJ, this accelerated developmental pattern was present in females of all ages. These findings are in line with our expectations that more positive relationship features as indicated by higher friendship quality are related to more accelerated maturing of the cortex in social brain regions.

Possible mechanisms

There are two possible mechanisms by which the link between positive friendship quality and development of social brain regions can be explained: a conditional mechanism that addresses the social circumstances under which social cognition skills are more likable to be trained and a motivational mechanism directed at the amount of social experiences that adolescents chose to expose themselves to. Considering the conditional mechanism: since social cognition requires effortful attention and cognitive control (Lin, Keysar, & Epley, 2010; Mills, Dumontheil, Speekenbrink, & Blakemore, 2015), and stress can impair cognitive functions (Sandi, 2013), an environment that is low in social stress would provide the necessary conditions for using higher-order social skills such as mentalizing. Therefore, it is perhaps surprising that there was a lack of significant relationship between negative friendship quality and social brain development. It is possible that in our sample of typically developing adolescents, the levels of best friendship conflict were within a normal range of friend conflict. Also, to a certain extent, mild conflict is an oppor-

tunity to practice social skills, for example by being able to make amends after putting effort into seeing the conflict through the eyes of the friend (i.e., perspective-taking). Having the opportunities to practice social skills during conflict resolution could cancel out possible limiting effects of conflict on social skills practice and social brain development.

The motivation to seek out social experiences could be dependent upon prior social experiences. It is highly likely that friendships with higher levels of positive interactions are very rewarding to the individual. This might encourage individuals to spend more time with the friend, thereby exposing them to more social interactions with this friend. In addition, exposure to best friendship positive social experiences can accumulate into internal working models of social interactions in general. This can increase the motivation to seek out more interactions with others outside the friendship. More social exposure provides increased opportunities for using social cognitive skills. Future research should focus on the role of exposure to social experiences during adolescence in social brain maturation.

These proposed mechanisms do not necessarily imply changes in skillfulness in social cognition but address how positive social interactions can increase the daily recruitment of functions that rely on the social brain network. Yet, these mechanisms do assume a relationship between experience-dependent long-term regional recruitment and cortical changes in these regions over time. Neurobiological theories of human development point out that specific changes in the brain are dependent upon experience (Greenough, Black & Wallace, 1987), and animal studies show that experience influences synaptic pruning (Bloodgood, Sharma, Browne, Trepman, & Greenberg, 2013; Yu et al., 2013). In turn, this experience-dependent pruning may be reflected in the links that we found between friendship quality changes and indices of social brain maturation. Although we do not discuss changes in social cognition skills here, it should be noted that cortical thinning in the social brain network was related to better mentalizing skills in an adult sample: less cortical thickness in the medial prefrontal cortex and right inferior frontal gyrus was associated with more spontaneous mentalizing, and thinner cortex in the right pSTS was associated with less autistic personality traits (Rice & Redcay, 2015).

It is important to highlight that the association between changes in relationship quality as an indicator of social functioning and cortical brain maturation does not imply causality, it identifies co-variation of two important factors in human development. More mature cortex in the social brain network might influence relationship quality, and conversely relationship quality might influence brain maturation, and the two explanations are not exclusive: mutual influence through brain-environment interactions may also occur (see also: Rice & Redcay, 2015).

Social environmental effects on cortical development

Comparing our results with previous studies on the relation between the social environment and the brain in development, results of positive social interactions seem to have an accelerating effect on development. Whole brain gray matter, cortical thickness and surface area increase dramatically during the first 1-2 years of life (Dobbing & Sands, 1979; Gilmore et al., 2012; Stiles & Jernigan, 2010) and continue to show region-dependent increases during early to mid-childhood, after which overall decreases characterize development of the cortex (Walhovd, Tamnes, & Fjell, 2014). The studies that are aimed at effects of more positive or less negative social experiences that take place during infancy find relations with increases in measures of cortical development, in other words: possibly indicating a beneficial (or lack of limiting) effect on brain development (Benetti et al., 2010; Kok et al., 2015). Similarly, but in the opposite direction, in the study by Whittle and colleagues (2014) and in our study, a relation between adolescent social experiences and accelerated brain development was also found: here, more positive experiences relate to *less* gray matter, thinner cortices and smaller surface area.

A possible explanation would be that the impact of these experiences in the social environment imply a certain developmental benefit of relatively more advanced brain structure, with the experience-dependent molecular processes that are underlying cortical changes being dependent on developmental stage (early childhood vs. adolescence). Because the effects of social experiences on brain development that have been found in early childhood and in adolescence are in opposite directions, they may be driven by different underlying neurobiological processes. The earliest prenatal and postnatal brain development is marked by synapse overproduction and this process of synaptogenesis is not only dependent on genetic signaling but also on experiences and these early changes have long-lasting effects (Black & Greenough, 1986). In contrast, changes in grey matter volume or cortical thickness during adolescence are often discussed in terms of synaptic pruning and increased myelination (for example see: Stiles & Jernigan, 2010). Therefore, instead of conflicting, results from studies with different developmental stages as its brain development construction site could be complementary. In support of shaping a comprehensive theory of (social) environmental influences on brain development, future hypotheses on social environment-brain relations should incorporate underlying neurodevelopmental processes appropriate for the phase in development.

Considering the detrimental effects of the lack of positive social experiences such as parental neglect during early childhood on the human brain (for a review, see: Belsky & De Haan, 2011), it is likely that the human cortex is expectant of sufficient beneficial social interactions, at least during early childhood. In adolescence,

social adjustment is of such great importance in multiple aspects of psychosocial functioning (e.g. academic achievement, self-esteem, emotional well-being and even psychopathology) and it has been proposed that adolescence is a sensitive period for social development (Blakemore & Mills, 2014; Fuhrmann, Knoll, & Blakemore, 2015). From a biological perspective, shifting the focus away from parents to the extended social environment is essential for healthy human reproductive behavior (Nelson et al., 2016; Seyfarth & Cheney, 2012) and therefore even serves a basic purpose of survival through genetic transmission and variation. This suggests that sufficient exposure to social experiences with peers during adolescence could be essential for (social) brain maturation. The extent to which these peer interactions are important for normal brain development could be tested by focusing on the impact of social deprivation during adolescence. More specifically, examining the longitudinal associations between social exclusion and psychopathology and the mediating role of adolescent brain maturation in regions of the social brain network is a fruitful avenue for future research.

Conclusion

In this study, we confirm that the social brain network undergoes major changes in gray matter volume, cortical thickness and surface area during adolescence and that this development is related to adolescent-salient social experiences. Using a longitudinal design we analyzed changes at the individual level and related these to changes in the quality of the relationship with the best friend. Positive relationship qualities are related to accelerated cortical maturation in the social brain network. This development in brain structure emerges in a life phase typical for major social changes and this study adds to the framework of how adolescent brain development emerges within their social context.