Development of the neural correlates of self- and other-referential processing across adolescence

Mariët van Buuren*, Hester Sijtsma, Nicky Lute, Rebecca van Rijn, Miriam Hollarek, Reubs J. Walsh, Nikki C. Lee, Lydia Krabbendam

Department of Clinical, Neuro and Developmental Psychology, Faculty of Behavioral and Movement Sciences, Institute for Brain and Behavior Amsterdam, Vrije Universiteit Amsterdam, Van der Boechorststraat 7, Amsterdam 1081 BT, the Netherlands

ARTICLE INFO

Keywords: Adolescence fMRI Self Development Functional connectivity Social cognition

ABSTRACT

During adolescence, major changes in brain mechanisms take place and differentiated representations of both the self and of others are developed. Although studies have investigated the neural mechanisms of self- and other-referential processing in adolescents, the development of these mechanisms remain largely unaddressed. Here, we report a three-year longitudinal study with annual measurements, and investigate the developmental trajectories of activity and connectivity underlying self- and other-referential processes in 34 participants from early to mid-adolescence (mean age timepoints 1, 2, 3 = 12.9, 13.9, 15.0 years). Moreover, we probe whether these correlates continue to develop from mid-adolescence to young adulthood by comparing neural correlates of the adolescents at the last measurement to an independent group of 42 young adults (mean age 22 years). Participants underwent functional MRI while performing a trait judgement task in which they indicated whether an adjective described themselves, a similar or a dissimilar peer. Brain activity within the dorsal medial prefrontal cortex (dMPFC) and right temporal parietal junction (TPJ) showed a quadratic change from early to mid-adolescence, with a peak in activity at the second measurement when evaluating the self, the similar and dissimilar peer. No differential activity was observed when comparing the adolescents to young adults. Functional connectivity did not change from early to mid-adolescence, however, connectivity of the dMPFC with a posterior midline region during self- and other-referential processing relative to the control condition reduced from mid-adolescence to young adulthood. Together, these findings provide insight in the developmental trajectories of brain activity and connectivity underlying the development of the self-concept and representations of peers in adolescence.

1. Introduction

During adolescence, major changes in social cognitive processes and underlying brain mechanisms take place, possibly triggering the development of differentiated representations of both the self and of others (Crone and Dahl, 2012; Kilford et al., 2016; Pfeifer and Peake, 2012). Self-concept becomes more abstract and complex (Labouvie-Vief et al., 1995), and increasingly sensitive to the opinion of peers (Steinberg and Morris, 2001). That is, adolescents become more interested in the opinions of others (Vartanian, 2000) and evaluations of peers become more salient and of relevance to their self-concept (Jankowski et al., 2014; Sebastian et al., 2008). At the same time, adolescents spend more time with their peers, and less with their family members (Güroğlu, 2020; Pfeifer and Peake, 2012). Moreover, social surroundings change profoundly as young adolescents transit from primary to secondary education where they experience daily interactions with peers that may shape their self-concept and representations about others. Although recent neuroimaging studies have started to investigate the neural mechanisms of self- and other-representations (or referential processing) in adolescents, the development of these mechanisms remains largely unaddressed. Moreover, despite the importance of peers in adolescence, it is unclear how the developmental changes in these neural correlates differ during referential processing about the self or peers.

Prior neuroimaging studies of self- and other-referential processing in adults have consistently reported involvement of the ventral medial prefrontal cortex (vMPFC), the dorsal MPFC (dMPFC), posterior midline regions, including the posterior cingulate cortex (PCC) and precuneus, and the bilateral temporal parietal junction (TPJ), extending into the angular gyrus (meta-analyses of studies in adults (Denny et al., 2012; Murray et al., 2012; Northoff et al., 2006)). While the vMPFC is preferentially engaged in evaluating the self, the dMPFC, TPJ and PCC appear to be more strongly involved when evaluating other people (Denny et al., 2012; Murray et al., 2012). Moreover, in adults, the ventral and dorsal MPFC show differential activity when evaluating others, depending on the perceived closeness of the other person. Specifically, the vMPFC...
has been implicated in processing of close others such as the mother or close friend (Benoit et al., 2010; Krienen et al., 2010; Moore et al., 2014), while the dMPFC is more engaged when evaluating socially distant others (Mitchell et al., 2006).

The vMPFC, dMPFC, PCC and bilateral TPJ have also been implicated in self- and other-referential processing in adolescents, however differences in activity have been observed. That is, studies in adolescents have reported no differential activity within the dMPFC during self-referential compared to other-referential processing (van Buuren et al., 2020), or even increased activity within the dMPFC during self-compared to other-referential processing (Romund et al., 2017). Although these studies did not compare activity in adolescents to adults or probe age-related changes directly, these findings may suggest that dMPFC activity during self- and other-referential processing changes with development. Further support for developmental changes in activity is provided by a limited number of studies directly comparing adolescents and adults or investigating age-related changes in a cross-sectional sample (Barendse et al., 2020; Jankowski et al., 2014; Pfeifer et al., 2007, 2009, 2013; van der Crujsen et al., 2018). These studies mainly focused on self-referential processing, either in comparison to non-referential control processing or to other-referential processing, and thus do not provide insight into developmental changes in differences between evaluating close and more distant others. When comparing adolescents to adults, increased recruitment of the dMPFC (Pfeifer et al., 2009, 2007) and left TPJ (Pfeifer et al., 2009), as well as reduced activity within the ventral striatum (Jankowski et al., 2014) was reported. Furthermore, a recent cross-sectional study showed a positive association between age and activity within a region encompassing the vMPFC and dMPFC across adolescence (age 12–21 years) (van der Crujsen et al., 2018), while another study in young adolescents (age 10–13 years) failed to observe an association between age and neural activity during self-referential processing (Barendse et al., 2020). To date, only one study has probed developmental changes in early adolescents in a longitudinal fashion (Pfeifer et al., 2013). This study measured brain activity twice, with a three-year interval, and showed an increase in vMPFC activity during self-compared to other-evaluations with age (10 to 13 years). Together, these studies provide initial, but mixed, evidence for developmental changes underlying self-evaluations, with most support for increased engagement of the vMPFC during self-evaluations across adolescence. However, the developmental trajectories within other regions involved in self-evaluations remain unclear, as well as the trajectories underlying evaluations of close and distant others.

Aside from brain activity, connectivity between brain regions supports self- and other-referential processing. Such connectivity is expected to show developmental changes, as development of connectivity between and within brain networks has been observed during rest-state across adolescence (Grayson and Fair, 2017; Gu et al., 2015; Marek et al., 2015; Stevens, 2016; Váša et al., 2020). These developmental changes in connectivity have been related to the integration and specialization of intrinsic brain networks and are believed to facilitate maturation of cognitive processes (Luna et al., 2015; Marek et al., 2015). In line with these findings, development of task-based connectivity has also been associated with cognitive development (Smith et al., 2018; Wang et al., 2020) and may be associated to the development of self- and other-referential processing. To date, only a few studies have investigated connectivity during self- and other-referential processing in adults (Davey et al., 2016; de Brigard et al., 2015; Lombardo et al., 2010; Schmitz and Johnson, 2006; Van Buuren et al., 2010) or adolescents (Davey et al., 2016; van Buuren et al., 2020). Davey and colleagues (Davey et al., 2016) showed positive effects of PCC activity on the vMPFC and left TPJ, but a negative influence of vMPFC activity on PCC activity during self-evaluations in participants aged between 15 and 25 years. In our recent study in young adolescents, we investigated functional connectivity of the vMPFC underlying self-evaluations and evaluations of both a similar and dissimilar peer (van Buuren et al., 2020). While we did not observe connectivity differences during self-referential processing relative to the control condition, we did report widespread connectivity patterns during other-referential processing that appeared to depend on the similarity of the other. That is, evaluating a peer perceived as similar resulted in increased connectivity of the vMPFC with the right striatum, insula and left dorsolateral frontal cortex, while evaluating a peer perceived as dissimilar was accompanied by increased connectivity with more widespread fronto-parietal regions, and, when compared to self-referential processing, with the angular gyrus. Although these findings improve our knowledge on the connectivity patterns underlying self- and other-referential processing in adolescents, they do not provide insight into the developmental trajectory of these connectivity patterns during adolescence.

Here, we report a three-year longitudinal follow-up of our prior study (van Buuren et al., 2020) and investigate the developmental trajectories of activity and connectivity underlying self- and other-referential processes from early to mid-adolescence (mean age timepoints 1, 2, 3 = 12.9, 13.9, 15.0 years). Moreover, we probe in a cross-sectional setup whether these neural correlates remain stable or show further development from mid-adolescence to young adulthood, by comparing neural activity and connectivity of the adolescents at the last measurement to an independent group of young adults. Young adolescents underwent functional MRI at three timepoints, with one-year intervals, while performing a trait judgment task. During this task, participants had to indicate whether an adjective described their personality, that of a peer they regarded as similar, that of a peer they regarded as dissimilar, or whether the adjective contained the letter A (control condition). The same task was employed once during functional MRI in young adults. Brain activity was investigated using a region-of-interest (ROI) approach and was further explored using whole-brain analyses. A priori defined regions-of-interest were the vMPFC, dMPFC, PCC and the left and right TPJ. Moreover, connectivity of the vMPFC and dMPFC during the task was examined using generalized psycho-physiological interaction (gPPI) analyses. Based on initial evidence, we hypothesize increased involvement of the vMPFC with age in self-referential processing during adolescence, that continues to increase towards young adulthood. In the other regions-of-interest as well as in connectivity of the vMPFC and dMPFC, we expect developmental changes during self- and other-referential processing, but given the absence of consistent prior evidence, we do not have clear expectations regarding the shape of these developmental trajectories.

2. Material and methods

2.1. Participants

This study is part of a longitudinal study, the #SO CONNeCT project, examining development of social cognition, social networks, and behavior from early to mid-adolescence. The current study is a follow-up of our previous study (van Buuren et al., 2020), investigating the neural correlates of self- and other-referential processing at baseline. Details of recruitment of the adolescent participants are described in that study. For the longitudinal study, functional MRI data was acquired for 84 participants at the first measurement, 60 participants at the second measurement one year later, and 48 participants at the third measurement, again one year later (see Supplementary Materials - Methods - Participants total sample adolescents, for a description of this sample). In total, 46 adolescents participated in all three waves. Of these participants, 9 were excluded because of motion (total displacement > 3 mm), 2 participants because of the loss of data due to a technical failure, and 1 because of incorrect task performance (wrong button presses). This left 34 participants for data analyses (mean age ± SD wave 1: 12.9 ± 0.50 years; mean age ± SD wave 2: 13.9 ± 0.50 years; mean age ± SD wave 3: 15.0 ± 0.55 years, 15 females, 19 males). For the cross-sectional analyses, 45 young adults were recruited from the university campus in Amsterdam. Of these young adults, one was excluded based on excessive motion (total displacement > 3 mm) and two because of poor coverage
of the vMPFC, resulting in 42 adult participants for data analyses (aged 20–26 years, mean age 22.0 ± 1.56 years; 22 females, 20 males). All participants and, in case of the adolescents, their parents gave written informed consent before participating, and none had contraindications for MRI, or a self-reported current or past neurological disorder.

All participants received monetary compensation for participation and (at the first measurement) a picture of their brain. The experimental protocol was reviewed, and ethical approval was provided by the institutional review board (VCWE, Faculty of Behavioral and Movement Sciences, VU Amsterdam, The Netherlands).

2.2. General procedure

Data acquisition was performed for three years with one-year intervals for the adolescents. Data acquisition of the first and second wave was performed over the course of four months, however due to Covid-19, data acquisition of the third wave was temporarily stopped for 2.5 months and was therefore spread over a six-month-period. The adult participants were scanned in a period of three months, starting two months prior to the start of the third wave.

All participants were screened for MRI contraindications when arriving at the research center. After this, participants were asked to fill in a questionnaire about two of their peers within their class, or within the same study year in case of the young adults (see for details (van Buuren et al., 2020). In this questionnaire, participants were asked for the name of a peer they regarded as being similar to them and a name of a peer perceived as dissimilar. These names served as cues for the similar and dissimilar condition of the trait judgement task. The peers both had to be well-known and liked by the participant to reduce effects of differences in liking and familiarity, and participants rated the peers on similarity, familiarity and liking on a scale from 0 to 10. After the questionnaire, participants received instructions about the MRI scanner procedure and the trait judgement task was explained. The adolescents then entered a mock scanner at every wave to familiarize them with the MRI environment, before they were placed in the MRI scanner. The adult participants were placed in the MRI scanner immediately after the instructions.

2.3. Experimental task

The trait judgement task is detailed in our previous study (van Buuren et al., 2020) and depicted in that study as well as in the Supplementary Materials (see Supplementary Fig. 1). In brief, participants had to indicate whether a trait adjective described themselves (self condition), a peer regarded as similar (similar other condition), a peer regarded as dissimilar (dissimilar other condition), or whether the trait contained the letter “a” (control condition), by pressing a button. A total of 160 adjectives were presented, 80 positive and 80 negative, and were pseudorandomly distributed to each condition and presented in blocks of five traits per condition. In total, 8 blocks per condition were presented. Each block started with a cue (1 s) indicating the condition. After this, five adjectives were presented sequentially for 3 s each or until a response after which a fixation cross appeared for the remaining trial duration.

2.4. Peer ratings and behavioral analyses

To test for longitudinal differences in similarity, familiarity and liking ratings of the peers, these ratings were submitted into a repeated-measures ANOVA with wave (1, 2, 3) and peer (similar, dissimilar) as factors. Additionally, the ratings of the adolescents at wave three were compared to the ratings of the young adults using a mixed ANOVA with peer and group (adolescents, adults) as factors, for each of the three dimensions (similarity, familiarity and liking). Peer ratings and results of these analyses are detailed in the Supplementary Materials (see Supplementary Results - Peer ratings and Supplementary Tables 1 and 2).

To examine longitudinal changes in behavioral responses during the trait judgement task, endorsement of the traits (i.e., ‘yes’ responses to positive and negative traits) and reaction time were included as dependent variables in two repeated measures ANOVAs with wave (1, 2, 3), reference condition (self, similar and dissimilar) and valence (positive, negative) as factors. Analyses were each followed by post hoc ANOVAs, as well as post hoc pairwise comparisons when indicated by significant effects.

Group differences in endorsement and reaction time between adolescents (at wave three) and young adults were tested with two mixed ANOVAs with reference condition (self, similar and dissimilar), valence (positive, negative) and group (adolescents, adults) as factors. Motion during scanning as measured with framewise displacement (FD) differed significantly between the adolescents (FD: mean 0.17 ± 0.04 mm) and adults (FD: mean 0.15 ± 0.03 mm) (t (74) = 2.94, p = .004) and was therefore included as covariate (mean-centered) in the analyses. As the aim of these behavioral analyses was to test group differences, only interaction effects of group by valence or by condition were followed by post hoc ANOVAs, as well as pairwise comparisons. No follow-up tests were performed to elucidate main effects of valence or reference condition.

In all analyses a Greenhouse-Geisser correction was applied when the assumption of sphericity was violated and all post hoc pairwise comparisons were corrected for multiple comparisons using a Bonferroni-corrected threshold of p = .016 (α = .05 / 3 (reference conditions, self, similar, dissimilar) or waves (1, 2, 3)).

2.5. MRI data acquisition

All MRI data were acquired on a 3.0 Tesla Philips Ingenia CX MRI scanner, with a 32-channel phased array head coil (Spinco Center for Neuroimaging; Philips Medical Systems, Best, The Netherlands). A total of 326 functional images were acquired during the task using a two-dimensional echo planar imaging-sensitivity encoding sequence, with a 3 mm isotropic voxel size and the following parameters; repetition time (TR): 2000 ms; echo time (TE): 27.63 ms; flip angle = 76.1°; matrix 80 × 80; field of view 240 × 240; 37-slice volume with a 0.3 mm gap. A structural image was acquired using a three-dimensional fast field echo sequence (voxel size: 1 mm isotropic, TR = 8.2 ms; TE = 3.7 ms; flip angle = 8°; matrix 240 × 188; field of view 240 × 188; 220 slices).

2.6. MRI data preprocessing

Preprocessing steps of the MRI data are detailed in our previous study (van Buuren et al., 2020). In brief, all images were preprocessed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Functional images were re-aligned and the structural image was co-registered to the mean functional image obtained after realignment. Unified segmentation was applied by segmenting the co-registered structural image and estimating the normalization parameters using tissue probability maps matched for the age and gender of our full adolescent subject sample (Cerebromatic toolbox (Wilke et al., 2017)). Next, the functional and structural image were transformed into Montreal Neurological Institute (MNI) space using the estimated normalizing parameters, and normalized functional images were smoothed using a 3D Gaussian filter (6 mm full width at half maximum).

To ensure sufficient quality of the images, signal-to-noise ratio (SNR) was calculated using normalized, unsmoothed functional images. Next, average SNR was calculated for each participant and wave, by extracting the average SNR signal within individual, normalized and resliced gray matter masks obtained with segmentation. These average SNR values were then submitted into a repeated-measures ANOVA with wave (1, 2, 3) as factor to test for differences in SNR with wave. Additionally, an independent sample t-test was performed, comparing SNR levels of the adolescents at wave three with the SNR levels of the young adult
The results of these analyses are described in the Supplementary Materials (see Supplementary Results – signal-to-noise).

2.7. Definition of regions-of-interest

Regions-of-interest (ROIs) were created by 10-mm radius spheres centered on following coordinates (based on Denny et al., 2012): vMPFC: x, y, z = -6, 56, 10, dMPFC: x, y, z = -6, 54, 32, PCC: x, y, z = -4, -56, 30, left TPJ: x, y, z = -50, -62, 22, and right TPJ: x, y, z = 50, -62, 22 (see van Buuren et al., 2020 for a detailed description).

2.8. MRI data analyses

2.8.1. MRI first-level analyses – activity and connectivity

The first-level analyses are similar to the analyses described in our previous study (van Buuren et al., 2020). For each subject and each wave, the smoothed functional images were submitted into a general linear model regression analysis, consisting of four regressors of interest: modeling the self, similar, dissimilar and control condition (onset at first trial of each block, duration 15 s). Additionally, the cue periods were included in a regressor of no-interest (duration 1 s) as well as the six realignment parameters and a high-pass filter was applied to remove low-frequency fluctuations (<128 s). Contrast images were created by comparing the self, similar and dissimilar condition to the control condition. Also, an average reference condition contrast was created by taking the three reference conditions together relative to the control condition ((self, similar, dissimilar) > control).

To examine functional connectivity of the vMPFC and dMPFC during self- and other-referential processing, the generalized form of context-dependent psycho-physiological interaction analyses was performed (gPPI, McLaren et al., 2012) using the gPPI toolbox (version 13.1, https://www.nitrc.org/projects/gppi/). For each subject and each wave, the time course of both seed regions were extracted and adjusted for task-related activity. Next, for each subject, wave and seed region, a first-level gPPI model was created consisting of the task conditions, the time course of the seed regions (vMPFC or dMPFC), interactions between this time course and the task conditions as well as the realignment parameters. Contrast images were again created by comparing connectivity during the self, similar and dissimilar condition to the control condition. Also, an average reference condition contrast relative to the control condition was created.

2.8.2. MRI group-level analyses: longitudinal

To longitudinally examine developmental changes in activity and connectivity, three types of analyses were performed. First, ROI analyses were conducted to target developmental changes in activity within a priori defined regions. Second, to explore developmental changes in activity outside these ROIs, whole-brain analyses were conducted. Third, to investigate developmental changes in connectivity of the vMPFC and dMPFC, gPPI analyses were performed. These three types of analyses are detailed below. To facilitate integration of the findings of these MRI group-level analyses as well as of the behavioral findings, all analyses were performed on the same sample of participants (N = 34) of whom complete data on all three waves was available. Complete datasets are a requirement for the whole-brain activity and connectivity analyses, since these analyses cannot handle missing data. However, to test the robustness of the findings of the ROI analyses and to probe for additional effects within the ROIs, ROI analyses were repeated using a multilevel regression approach allowing for missing data in a sample of 78 adolescents. This sample comprised the 34 participants included in the repeated-measures ANOVAs, as well as 44 adolescent participants who were included in only one (N = 20) or two waves (N = 24). These analyses are detailed in the Supplementary Materials (see Supplementary Material and Methods - Region-of-interest analyses - longitudinal total sample adolescents).

We did not investigate effects of gender on the development of activity or connectivity, given the sample size and the absence of hypotheses related to gender.

2.8.2.1. MRI group-level analyses: longitudinal – regions-of-interest

ROI analyses were performed by extracting the average contrast estimate (self, similar, dissimilar all relative to control) within a ROI for each subject and each wave (MarsBar toolbox, version 0.44, http://marsbar.sourceforge.net/). First, to examine possible effects that are present within all regions, these average signal changes were submitted into a repeated-measures ANOVA with ROI (vMPFC, dMPFC, PCC, left TPJ, right TPJ), wave (1, 2, 3) and reference condition (self, similar, dissimilar) as factors. In line with our previous study (van Buuren et al., 2020), this analysis was followed by repeated-measures ANOVAs per ROI with wave (1, 2, 3) and reference condition (self, similar, dissimilar) as factors, to test effects of reference condition and wave per ROI. When indicated by significant effects, these repeated-measures ANOVAs were each followed by tests of within-subject contrasts (linear, quadratic) and post hoc pairwise comparisons. In all analyses, a Greenhouse-Geisser correction was applied when the assumption of sphericity was violated, and all post hoc pairwise comparisons were corrected for multiple comparisons using a Bonferroni-corrected p-value of $p = .016$.

2.8.2.2. MRI group-level analyses: longitudinal – whole-brain activity

Next, to explore brain activity outside our ROIs, whole-brain analyses were performed. A flexible factorial repeated-measures ANOVA with wave (1, 2, 3) and reference condition (self, similar, dissimilar, all relative to the control condition) as factors was conducted. We examined the interaction between wave and condition and the main effect of wave and condition. In case of a main effect of wave, both a linear change and a quadratic change in activity was tested. Also, when indicated by significant effects, post hoc pairwise comparisons were performed using paired sample-tests. The whole-brain results were tested for significance using cluster-inference with a cluster-defining threshold of $p < .001$, and a cluster-probability of $p < .05$ family-wise error corrected (FWE).

2.8.2.3. MRI group-level analyses: longitudinal – connectivity

Developmental trajectories of connectivity of the vMPFC and dMPFC during self- and other-referential processing were examined by submitting the contrast images of the first-level gPPI models into a flexible factorial ANOVA with wave (1, 2, 3) and reference condition (self, similar, dissimilar, all relative to the control condition) as factors for the vMPFC and dMPFC separately. Again, the results were thresholded with a cluster-defining threshold of $p < .001$, and a cluster-probability of $p < .05$ family-wise error corrected (FWE).

2.8.3. MRI group-level analyses: adolescents wave 3 versus young adults

2.8.3.1. MRI group-level analyses: adolescents wave 3 versus young adults – Regions-of-interest

First, to examine if possible group differences in activity were present in all ROIs, a mixed ANOVA with ROI (vMPFC, dMPFC, PCC, left TPJ, right TPJ), reference condition (self, similar, dissimilar) and group (adolescents, adults) as factors, and mean-centered FD as covariate was conducted. Next, group differences in activity within the ROIs were examined by a mixed ANOVA per ROI with reference condition (self, similar, dissimilar) and group (adolescents, adults) as factors, and mean-centered FD as covariate.

2.8.3.2. MRI group-level analyses: adolescents wave 3 versus young adults – whole-brain activity

To explore brain activity outside the ROIs, whole-brain analyses were performed. First, to test for an interaction between reference condition and group, a flexible factorial mixed ANOVA was performed with reference condition (self, similar, dissimilar) and group (adolescents, adults) as factors. As SPM does not properly partition the error terms of between and within-subject factors, the main effect of group could not be explored in this analysis (Chen et al., 2014). Therefore, a two-sample t-test on the average reference condition contrast
was performed to test for overall differences, irrespective of reference condition, between the groups, with FD as covariate. The whole-brain results were tested for significance using cluster-inference with a cluster-defining threshold of $p < .001$, and a cluster-probability of $p < .05$ FWE-corrected.

### 2.8.3.3. MRI group-level analyses: adolescents wave 3 versus young adults – connectivity.

Group differences in connectivity were examined following a similar procedure to the whole-brain analyses. First, for each seed region, the contrast images of the first-level pGPI models were submitted into a flexible factorial (mixed) ANOVA with reference condition (self, similar, dissimilar) and group (adolescents, adults) as factors to test for an interaction effect of reference condition by group. Also, a two-sample t-test for each seed region was performed on the average reference condition contrast to test for overall group differences in connectivity, with FD as covariate. Results were tested for significance using cluster-inference with a cluster-defining threshold of $p < .001$, and a cluster-probability of $p < .05$ FWE-corrected.

### 2.9. Data and code availability

The participants and their parents did not provide explicit consent for public archiving of the research data, therefore the data is not stored in a public repository. Anonymized data will be made available to individual researchers upon request, when compatible with the General Data Protection Regulation. Additionally, researchers that request the data will be required to have obtained ethics approval from their host institution and are not allowed to share the data. Matlab code that was written to preprocess and analyze the fMRI data has been made publicly available on Github.

(https://github.com/marietybuuren/self_other_longitudinal).

### 3. Results

#### 3.1. Behavioral findings

##### 3.1.1. Longitudinal development

Developmental changes in endorsement of positive and negative traits in the self, similar and dissimilar other reference condition were examined (see Table 1). We found a main effect of wave ($F(2,66)=3.46$, $p = .037$, partial $\eta^2 = 0.095$), with an overall higher level of endorsement across positive and negative traits in the last compared to the first wave ($p = .012$). No interaction effect of wave by reference condition ($p = .082$) or by valence ($p = .373$) was observed, nor an interaction effect of wave by reference by valence ($p = .545$). Additionally, we found an interaction effect of reference condition by valence ($F(1,58,52.20)=15.52, p < .0005$, partial $\eta^2 = 0.230$) and main effects of reference condition ($F(2,66)=9.97, p < .0005$, partial $\eta^2 = 0.232$) and valence ($F(1,33)=259.31, p < .0005$, partial $\eta^2 = 0.887$). Follow-up one-way ANOVAs were performed with endorsement averaged over wave and detailed in the Supplementary Materials (see Supplementary Results - Behavioral findings - task effects adolescents). Next, developmental changes in reaction time were analyzed (see Table 1). A repeated-measures ANOVA revealed a main effect of wave ($F(2,66)=17.24, p < .0005$, partial $\eta^2 = 0.343$), with slower responses in the first wave compared to the second ($p = .002$) and to the third wave ($p < .0005$). No interaction effect of wave by reference condition ($p = .303$), wave by valence ($p = .465$) or wave by valence by reference condition ($p = .844$) was observed. No main effect of valence ($p = .224$) was observed, but we did find an interaction effect of reference by valence ($F(2,66)=4.17, p = .020$, partial $\eta^2 = 0.112$), and a main effect of reference ($F(2,66)=11.84, p < .0005$, partial $\eta^2 = 0.264$). Follow-up one-way ANOVAs are again detailed in the Supplementary Materials.

##### 3.1.2. Adolescents compared to young adults

A mixed ANOVA testing group differences in endorsement of the positive and negative traits in the three reference conditions revealed no three-way interaction between group, reference condition and valence ($p = .620$), no group by reference condition ($p = .493$), or by valence interaction effect ($p = .352$), nor a main effect of group ($p = .592$). Similar to the longitudinal findings, a significant interaction effect of reference condition by valence was found ($F(1,8,128.5)=19.27, p < .0005$, partial $\eta^2 = 0.209$), as well as main effects of reference condition ($F(2,146)=27.69, p < .0005$, partial $\eta^2 = 0.275$) and of valence ($F(1,73)=580.15, p < .0005$, partial $\eta^2 = 0.888$) (See Table 2 for endorsement and reaction time of the adults). No main effect of motion (FD) was found ($p = .102$).

Next, group differences in reaction time were investigated. Again, no interaction effect was observed of group by reference condition by valence ($p = .095$), nor of group by reference condition ($p = .659$), or group by valence ($p = .947$). However, a main effect of group was found, with overall slower responses for the adult participants compared to the

---

**Table 1**

Average endorsement and reaction time in response to positive and negative traits during the self, similar other and dissimilar other condition in the three waves. Endorsement is measured as the average number of ‘yes’ responses and reaction time as the average response time in ms. SD= standard deviation.

| Trait         | Self Mean (SD) Wave | Similar Other Mean (SD) Wave | Dissimilar Other Mean (SD) Wave |
|---------------|---------------------|-----------------------------|--------------------------------|
|               | 1                   | 2                           | 3                             | 1                   | 2                           | 3                             |
| **Endorsement**|                      |                              |                               | **Endorsement**|                      |                              |                               |
| Positive       | 14.1                | 13.6                        | 14.8                          | 14.3                | 15.4                        | 15.6                          | 11.5                          | 10.9                        | 12.3                          |
| Negative       | 4.7                 | 5.7                         | 6.3                           | 3.9                 | 4.4                         | 3.9                           | 5.7                           | 6.4                         | 5.7                           |
| Reaction Time  | 1224                | 1142                        | 1041                          | 1217                | 1160                        | 1052                          | 1277                          | 1181                        | 1129                          |
| Positive       | 1279                | 1153                        | 1077                          | 1236                | 1122                        | 1068                          | 1274                          | 1154                        | 1126                          |
| Negative       | 160                 | 203                         | 156                           | (173)               | (189)                       | (186)                         | (177)                         | (198)                       | (203)                         |

**Table 2**

Average endorsement in number of adjectives and reaction time in ms of responses to the positive and negative adjectives in the three reference conditions in the adult participants. SD= standard deviation.

| Trait         | Self Mean (SD) | Similar Other Mean (SD) | Dissimilar Other Mean (SD) |
|---------------|---------------|-------------------------|---------------------------|
|               | Wave          | Wave                    | Wave                      |
| **Endorsement**|               |                         |                           | **Endorsement**|               |                         |                           |
| Positive       | 15.9          | 16.6                    | 12.3                      | 2.6               | 2.7                 | 4.3                       |
| Negative       | 6.3           | 3.3                     | 5.8                       | (3.6)             | (2.3)               | (3.8)                     |
| Reaction Time  | 1120          | 1147                    | 1260                      | 183               | 233                 | 242                       |
| Negative       | 1216          | 1155                    | 1230                      | (222)             | (206)               | (261)                     |

---
adolescents ($F(1,73)=4.57$, $p = .036$, partial $\eta^2 = 0.059$). Additionally, a main effect of reference condition ($F(1,81,132.5)=18.4$, $p < .0005$, partial $\eta^2 = 0.202$), a main effect of valence ($F(1,73)=4.32$, $p = .041$, partial $\eta^2 = 0.056$) and an interaction effect of reference condition by valence ($F(2,146)=9.79$, $p < .0005$, partial $\eta^2 = 0.118$) were observed. No main effect of motion was found ($p = .347$).

In sum, behavioral findings show no changes in endorsement of positive or negative traits with wave, nor between the adolescents at wave three and the young adults. Responses to the traits did become faster over waves, and the adolescents at wave three responded faster than the young adults.

3.2. Brain activity – regions-of-interest

3.2.1. Longitudinal development

First, to examine possible developmental changes or effects of reference condition that are present within all ROIs (vMPFC, dMPFC, PCC, left and right TPJ), a repeated-measures ANOVA was performed with ROI, wave and reference condition as factors. A main effect of wave was observed ($F(2,66)=3.83$, $p = .027$, partial $\eta^2 = 0.104$), with higher activity in the second wave compared to the first wave ($p = .008$), but compared to the third wave ($p = .275$). Activity did not differ between the first and third wave ($p = .101$). Additionally, a main effect of ROI was observed ($F(5,165.22)=27.48$, $p < .0005$, partial $\eta^2 = 0.454$), and an interaction effect of ROI by reference condition ($F(4,132)=60.70$, $p < .0005$, partial $\eta^2 = 0.648$), indicating differences in activity between the ROIs. No main effect of reference condition ($p = .230$), or interaction effects of ROI by wave ($p = .443$), reference condition by wave ($p = .667$), or ROI by wave by reference condition ($p = .771$) were observed. Next, to investigate developmental changes in brain activity within each of the ROIs, repeated-measures ANOVAs were performed per ROI with wave and reference condition as factors. No interaction effect of wave by reference condition was observed in any of the ROIs (vMPFC, $p = .382$; dMPFC, $p = .670$; PCC, $p = .738$; left TPJ, $p = .714$; right TPJ, $p = .885$) (see Fig. 1 and Supplementary Table 3). All main effects and post hoc comparisons are listed per ROI below.

Brain activity within the vMPFC showed no main effect of wave ($p = .400$), however did show a main effect of reference condition ($F(2,66)=12.00$, $p < .0005$, partial $\eta^2 = 0.266$), with higher activity in the self condition as compared to the similar ($p < .0005$) and dissimilar other condition ($p = .001$). No differences in activity were found when comparing the two other reference conditions ($p = .272$). Within the dMPFC, a main effect of wave on activity was observed ($F(2,66)=5.09$, $p = .009$, partial $\eta^2 = 0.134$), showing a quadratic effect over waves ($F(1,33)=8.47$, $p = .006$, partial $\eta^2 = 0.204$). Pairwise comparisons showed significantly increased activity during the second wave when compared to the first wave ($p = .004$), but not when compared to the third wave ($p = .053$). No difference in activity were found between the first and third wave ($p = .248$). Also, a main effect of reference condition was found ($F(2,66)=9.24$, $p < .0005$, partial $\eta^2 = 0.219$), with decreased dMPFC activity during the similar other reference condition relative to the self condition ($p = .001$) and to the dissimilar condition ($p < .0005$). No difference in dMPFC activity was found when comparing the self and dissimilar other condition ($p = .573$). Within the PCC, no main effect of wave ($p = .181$) was observed, but a main effect of reference condition was revealed ($F(1,7,55.8)=16.10$, $p < .0005$, partial $\eta^2 = 0.328$). Pairwise comparisons showed decreased activity during the self condition compared to the similar ($p < .0005$) and dissimilar condition ($p < .0005$), with no differences between the two other conditions ($p = .831$). Within the left TPJ, no main effects of wave ($p = .081$) or reference condition ($p = .212$) on activity were found. Within the right TPJ, a main effect of wave on activity was observed ($F(2,66)=4.92$, $p = .010$, partial $\eta^2 = 0.130$), showing a quadratic effect over waves ($F(1,33)=6.88$, $p = .013$, partial $\eta^2 = 0.172$). Also, a main effect of reference condition was found ($F(1,6,53.5)=7.0$, $p = .004$, partial $\eta^2 = 0.175$). Post hoc pairwise comparisons showed increased activity within the right TPJ in the second wave compared to the first wave ($p = .006$), but not compared to the third wave ($p = .098$), or when comparing activity in the first wave to the third wave ($p = .138$). Regarding the effect of reference condition, decreased activity within the right TPJ was shown during the self condition compared to both the similar ($p = .008$) and the dissimilar condition ($p = .005$). No differences were found between the two other conditions ($p = .457$).
To test whether these age-related developmental changes were also present in participants who participated at least once ($N = 78$), multilevel regression analyses were performed with wave and reference condition as predictors, and activity within each ROI as the dependent variable (see Supplementary Material and Methods - Region-of-interest analyses - longitudinal total sample adolescents). All findings were in line with the findings of the ROI analyses on the participants with complete data on all the three waves ($N = 34$), with exception of a linear effect of reference condition on activity within the left TPJ.

As before, no effect of wave was observed within the vMPFC (linear, $p = .712$; quadratic, $p = .068$), but vMPFC activity did exhibit an effect of reference condition (linear; $t(336) = -5.31, p < .0005$, quadratic; $t(336) = 4.96, p < .0005$). Importantly, a negative quadratic effect of wave was observed within the dMPFC ($t(336) = -3.38, p < .0005$), with a peak of activity at the second wave (see Supplementary Fig. 2). No linear effect of wave was found ($p = .147$). Also, a positive quadratic effect of reference condition was observed on activity within the dMPFC ($t(336) = 5.62, p < .0005$, linear effect; $p = .483$), with decreased activity during the similar condition relative to the self and dissimilar other condition. Activity within the PCC also showed an effect of reference condition (linear; $t(336) = 7.51, p < .0005$, quadratic; $t(336) = -3.12, p < .002$), but not of wave (linear, $p = .067$; quadratic, $p = .578$). Again, no effect of wave was observed within the left TPJ (linear, $p = .528$; quadratic, $p = .176$), however, activity did show a linear increase over reference condition (self to dissimilar other; $t(336) = 2.88, p < .004$, no quadratic effect; $p = .229$). Last, comparable to the ROI findings of the smaller sample ($N = 34$), the right TPJ showed a negative quadratic effect of wave on activity ($t(336) = -2.60, p = .016$; no linear effect; $p = .136$), with a peak of activity at the second wave (see Supplementary Fig. 2). Furthermore, a linear effect of reference condition was found on activity within the right TPJ ($t(336) = 6.42, p < .0005$).

In sum, an overall effect of wave was observed for activity within the ROIs, with increased activity at wave two. This effect appeared to be driven by activity within the dMPFC and right TPJ. Both regions showed a quadratic effect of wave with increased activity at wave two, compared to wave one, but not when compared to wave three. No interaction effect of wave by reference condition was observed for any of the ROIs. Findings were comparable when analyses were conducted on the sample with complete data ($N = 34$) and on the sample with data of at least one wave ($N = 78$).

3.2.2. Adolescents compared to young adults

Mixed ANOVA over ROIs did not show a main effect of group ($p = .097$), nor an interaction effect of group by ROI ($p = .217$), nor an interaction effect of group by reference condition ($p = .375$), or of ROI by reference condition by group ($p = .129$). A main effect of ROI ($F(3,27,238.63) = 110.85, p < .0005$, partial $\eta^2 = 0.603$) and an interaction effect of ROI by reference condition was observed ($F(6,14,448.48) = 39.84, p < .0005$, partial $\eta^2 = 0.353$). Next, mixed ANOVAs per ROI showed no main effect of group, nor an interaction effect of group by reference condition for any of the ROIs (main effect group: vMPFC, $p = .097$; dMPFC, $p = .162$; PCC, $p = .977$; left TPJ, $p = .799$; right TPJ, $p = .709$; interaction effect: vMPFC, $p = .560$; dMPFC, $p = .490$; PCC, $p = .079$; left TPJ, $p = .418$; right TPJ, $p = .966$). Similar to the findings of the longitudinal analyses, a main effect of reference condition was observed within the vMPFC ($F(2,146) = 19.11, p < .0005$, partial $\eta^2 = 0.208$), dMPFC ($F(2,146) = 11.62, p < .0005$, partial $\eta^2 = 0.137$), PCC ($F(2,146) = 26.92, p < .0005$, partial $\eta^2 = 0.269$) and right TPJ ($F(1,8,133.4) = 9.05, p < .0005$, partial $\eta^2 = 0.110$), but not within the left TPJ ($p = .092$). No main effect of motion was found within the vMPFC ($p = .812$), dMPFC ($p = .361$), PCC ($p = .724$) or right TPJ ($p = .398$), but was significant within the left TPJ ($F(1,73) = 5.02, p = .028$, partial $\eta^2 = 0.064$). See Supplementary Table 4 for average signal changes within each of the ROIs for the adult sample.

In sum, no group differences were observed in activity within the ROIs between the adolescents at wave three and the young adults.

### Table 3

| Brain region and contrast | MNI Coordinates | Z score | voxels |
|---------------------------|-----------------|---------|--------|
| **Main effect of wave**    |                 |         |        |
| R angular gyrus           | 57.2             | .63     | 4.63   | 68    |
| **Quadratic effect of wave** |                 |         |        |
| R angular gyrus           | 54.2              | -3.36   | 4.61   | 118   |
| R middle temporal gyrus   | 57.2              | -2.05   | 4.42   | 91    |
| R precenental gyrus       | 45.2              | 2.03    | 4.37   | 179   |
| R middle frontal gyrus    | 36.2              | 1.17    | 3.90   | 95    |
| R precuneus               | 3.2               | 1.17    | 3.82   | 70    |
| **Main effect of reference condition** |                 |         |        |
| R precuneus               | 3.2               | 1.17    | 3.82   | 70    |
| L superior frontal gyrus  | 0.2              | 1.17    | 3.13   | 122   |
| R middle frontal gyrus    | 21.2              | 1.17    | 5.40   | 122   |
| L lateral orbitofrontal gyrus | 33.2           | 1.17    | 5.40   | 122   |
| L angular gyrus           | -36.2             | -1.17   | 5.40   | 122   |
| R angular gyrus           | 42.2              | 1.17    | 5.40   | 122   |
| R lateral orbitofrontal gyrus | 42.2           | 1.17    | 5.13   | 95    |
| R fusiform gyrus          | 39.2              | 1.17    | 4.70   | 257   |

**Fig. 2.** Whole-brain longitudinal activity changes during self- and other-referential processing. A negative quadratic change in activity over waves during the reference conditions, with a peak in activity in the second wave. Results are shown at a cluster-defining threshold of $p < .001$ and a $p < .05$ FWE-corrected cluster threshold. Brain activity is overlaid on an average anatomical brain obtained with Cerebralomatic toolbox. Numbers represent z-coordinates, left= left. Color bars represent t-values.

### 3.3. Brain activity – whole-brain

To explore development in activity outside the ROIs, whole-brain analyses were performed. In line with the ROI-analyses, no interaction effect of wave by reference condition was found. However, a main effect of wave was observed within the right angular gyrus (See Table 3). To further examine this main effect, both linear effects and quadratic effects were tested. Results showed no linear increases or decreases with wave, however, did show a negative quadratic effect, with a peak in activity at the second wave, within the right angular gyrus (overlapping with the cluster obtained in the main effect of wave), right middle temporal gyrus, right precenental gyrus, right middle and superior frontal gyrus and precuneus (see Table 3 and Fig. 2). Of note, overlap was limited between regions showing an effect of wave and regions showing increased activity during the reference conditions (relative to the control condition) when averaged over waves (see Supplementary Fig. 3). Also, with the exception of the right angular gyrus cluster, these regions did not show a significant main effect of wave. To gain insight in the activity...
changes with wave within the regions showing a quadratic effect, the contrast values of each reference condition relative to the control condition were extracted within these clusters for each subject and each wave. Next, for each cluster, these values were averaged over the reference conditions and subjects per wave and visualized, no statistical tests were performed. As depicted in Supplementary Fig. 4, all regions, except for the middle frontal gyrus cluster, showed a change in deactivation over waves, indicating more activity in the control condition compared to the reference conditions. This limits the relevance of the whole-brain findings for understanding developmental changes in activity underlying self- and other-referential activity.

Last, a main effect of reference condition was found (see Table 3). This was followed by paired sample t-tests to examine differences in activity between the reference conditions and one-sample t-tests to show task effects averaged over waves. As the current study focuses on longitudinal changes, these findings are detailed in the Supplementary Materials (See Supplementary Tables 5 and 6).

In sum, whole-brain analyses revealed a main effect of wave in the right angular gyrus. Follow up analyses showed a quadratic effect of wave within this region, as well as four other regions that were not shown in the main effect. Of these regions, only a cluster with a peak in the middle frontal cortex showed changes with wave in activity. The other regions, including the right angular gyrus, showed changes in deactivation instead of activity.

3.3.2. Adolescents compared to young adults

No interaction effect of group by reference condition was observed, nor any differences in activity when comparing overall activity during the reference conditions (relative to control condition) between the two groups.

3.4. Brain connectivity

3.4.1. Longitudinal development

To examine developmental changes in connectivity of the vMPFC and the dMPFC, an ANOVA was performed with wave and reference condition as factors for each seed region. Connectivity of the vMPFC and of the dMPFC showed no main effect of wave and no interaction effect of wave by reference condition. Also, no main effect of reference condition was found. To show task-related connectivity changes of both the vMPFC and dMPFC, one-sample t-tests on average contrast images over waves were performed for each reference condition relative to the control condition (see Supplementary Tables 7 and 8).

3.4.2. Adolescents compared to young adults

A mixed ANOVA with reference condition and group as factors did not show an interaction effect of reference condition by group for the vMPFC or dMPFC. When testing group differences in overall connectivity during the reference conditions (relative to the control condition) using two-sample t-tests, no group differences were observed in connectivity of the vMPFC. However, increased connectivity between the dMPFC and the superior parietal gyrus, extending into the precuneus, was observed when comparing the adolescents with the young adults (peak voxel: x, y, z = -12, -63, 27; k = 129, Z = 4.37) (see Fig. 3A). For visualization purposes, the contrast values were extracted from this posterior midline cluster for each subject and averaged per group (see Fig. 3B). This shows that the tested group difference resulted from increased connectivity between the dMPFC and the posterior midline region in the adolescents, compared to decreased connectivity between these regions in the young adults.

To summarize, increased connectivity between the dMPFC and the superior parietal gyrus, extending into the precuneus, was observed when comparing the adolescents with the young adults.

4. Discussion

4.1. Summary

In this study, we examined the developmental trajectories of brain activity and connectivity underlying self- and other-referential processing in adolescence. To this end, we extended our previous study (van Buuren et al., 2020) by measuring these neural correlates annually from early to mid-adolescence during a three-year period. Second, we examined whether these correlates developed further from mid-adolescence to young adulthood, by comparing neural activity and connectivity of the adolescents at the last (third) measurement to an independent group of young adults. Behaviorally, no developmental changes were observed in the endorsement of traits, suggesting that the behavioral responses when evaluating the self, similar peer and dissimilar peer do not change with age. Adolescents did become faster when responding on the task over timepoints and were faster compared to the young adults, which may be due to learning effects. On a neural level, brain activity showed a quadratic change from early to mid-adolescence within regions of interest. This effect appeared to be driven by activity within the dMPFC and right TPJ that showed a quadratic change, with a peak in activity at the second measurement around the age of 14 years when evaluating the self, the similar and dissimilar peer. No interaction effect between reference condition and wave was observed, and we did not find the expected developmental increase in activity within the vMPFC during self-referential processing. On whole-brain level, we did not observe a developmental change in activity within the right angular gyrus with a peak at the second measurement. However, this was driven by a change in activity during the control condition, thus a change in deactivation during self- and other-referential processing, limiting the relevance of the whole-brain findings for understanding development of the neural correlates underlying self- and other-referential processing. No changes in activity were observed when comparing the adolescents to young adults in any of the regions of interest, nor at whole-brain level. When investigating brain connectivity, we found increased connectivity between the dMPFC and the superior parietal gyrus, extending into the precuneus, during self- and other-referential processing relative to the control condition in the adolescents when compared to young adults. Again, no interaction effect between group and reference condition was observed. In contrast to the activity findings, no longitudinal changes in connectivity of the dMPFC were observed from early to mid-adolescence, nor any developmental changes in connectivity of the vMPFC.

4.2. Self- and other-referential processing across time

Across timepoints, the vMPFC was more engaged during self- compared to other-referential processing, while the right TPJ and PCC.
showed the opposite pattern. These findings were already evident in the analyses of the first, baseline measurement (van Buuren et al., 2020) and are in line with prior research in adolescents (Pfeifer et al., 2013, 2007; Schneider et al., 2012). The dMPFC showed increased activity when evaluating the self and the dissimilar peer compared to evaluating the similar peer. This increased activity during self-referential processing is in contrast to studies in adults, showing more engagement of the dMPFC during evaluation of socially distant others compared to the self (Mitchell et al., 2006; Murray et al., 2012). However, this pattern is in line with a previous study in mid-adolescents showing increased dMPFC activity when making trait judgements about oneself or teachers, compared to friends (Romund et al., 2017). Also, studies investigating mentalizing processes have reported more engagement of the MPFC in adolescents compared to adults (Andrews et al., 2021; Blakemore et al., 2007; Gunther Moor et al., 2012). Together, these findings may tentatively indicate that adolescents rely on the opinions of others when making trait judgements about themselves and are engaged in more mentalizing processes when evaluating oneself as well as when evaluating (distant) others (Crone and Fuligni, 2020).

### 4.3. Developmental changes in activity

Longitudinally, we expected, but did not find, a linear increase in activity within the vMPFC during self-evaluations. Such an increase was reported in previous studies either comparing young adolescents or children to adults (Pfeifer et al., 2009, 2007), or by testing this increase longitudinally (Pfeifer et al., 2013). However, a recent study in young female adolescents aged between 10 and 13 years (Barendse et al., 2020) also failed to observe age-related changes in activity. We did observe developmental activity changes within the dMPFC and right TPJ during self- and other-referential processing. This pattern was present in the sample of adolescents who were included in all measurements (N = 54), as well as in the sample of adolescents who participated at least once (N = 78). No interaction effect was observed between measurement and reference condition, suggesting that the developmental changes in activity did not differ between evaluating the self, a similar and dissimilar peer. The change in activity within the dMPFC and right TPJ showed a quadratic shape, with a peak of activity at the second timepoint, around the age of 14 years. This appeared to be predominantly driven by an increase in activity from the first to the second timepoint, after which no change in activity to the third timepoint was found. In line with this finding, no differential activity was observed when comparing the adolescents at the last measurement to young adults. Based on the mixed findings of prior research, we did not have specific hypotheses regarding the shape of the developmental change in activity within the dMPFC and right TPJ. That is, age-related increases in activity were observed in a cross-sectional study within a region comprising both the ventral and dorsal MPFC in adolescents and young adults (age 12–21 years) (van der Cruijsen et al., 2018), while other studies reported age-related decreases in dMPFC activity (Davey et al., 2019; Pfeifer et al., 2009, 2007) as well as left, but not right, TPJ activity (Pfeifer et al., 2009) during self-evaluations. To our knowledge, no study has yet observed developmental activity changes within the right TPJ. While we did not expect a quadratic age-related change in activity within the dMPFC and right TPJ, such a pattern is in line with recent findings of quadratic age-related activity changes within the dorsal lateral prefrontal cortex, supplementary motor area and a striatal region during self-evaluations depending on the valence of the traits (van der Cruijsen et al., 2018) albeit over a broader age-range. Additionally, similar developmental activity changes have been related to other cognitive processes, including within the striatum during a gambling task in participants aged between 8 and 27 years (Braams et al., 2015) and within the MPFC during a social-evaluation task in participants aged between 8 and 22 years (Somerville et al., 2013). Although these changes have been reported over a broader age range, they may suggest that various regions may show a peak in activity in (mid) adolescence during different types of (social) cognitive processing. Tentatively, we suggest that dMPFC and right TPJ activity during self- and peer-evaluations first increases from the age of 13 to the age of 14 years, before potentially stabilizing towards young adulthood. We speculate that such a peak in activity at the age of 14 years may possibly indicate that a consistent self-concept is being established as well as stable representations of close and more distant peers. Support for this tentative notion is provided by limited studies linking self-esteem (van der Aar et al., 2019), and certainty about, as well as the importance of, self-views with activity within the MPFC during self-evaluations (D’Argembeau et al., 2012). These studies showed that self-esteem and self-view are positively related to activity within the MPFC. However, future longitudinal research is required to further investigate the developmental trajectories of self- and other-referential processing across adolescence and to relate this to the development of self-concept and representations of others. Of note, small but significant differences in signal-to-noise ratio (SNR) values within gray matter were observed, with higher values at the second timepoint when compared to the first timepoint in the adolescent sample. However, we believe it is unlikely that this has affected the findings regarding the dMPFC and right TPJ. That is, the SNR values were calculated over the course of the entire task, including all reference conditions, the control condition and baseline, while these (ROI) findings were based on contrast estimates of each reference condition relative to the control condition. Therefore, overall differences in SNR values between timepoints should have been averaged out when calculating the contrasts estimates by comparing a reference condition to the control condition. Additionally, if differences in SNR would have driven the reported ROI findings, these SNR differences would likely have resulted in widespread longitudinal changes in task-based activation (reference conditions relative to control condition) on whole-brain level, which we did not observe.

### 4.4. Developmental changes in connectivity

Functional connectivity of the vMPFC and dMPFC during self- and other-referential processing did not show longitudinal changes from early to mid-adolescence, and no differences in connectivity of the vMPFC were found when comparing the adolescents to the young adults. However, connectivity of the dMPFC with a region of the superior parietal gyrus, extending into the precuneus, was increased in the adolescents compared to the young adults. This connectivity difference was not specific to self- or other-referential processing but was present across reference conditions relative to the control condition. Interestingly, while the adolescents showed increased connectivity between the dMPFC and the posterior midline region, the young adults showed reduced connectivity. This reduced connectivity in the adult group is in line with a previous finding of reduced connectivity between the dMPFC and a posterior midline region in young adults (mean age 21.5 years) during self-referential processing (Van Buuren et al., 2010). Moreover, a recent study reported an age-related decrease in connectivity during self-evaluations from adolescence to adulthood (15–25 years) between an anterior and posterior subnetwork of the default-mode network comprising regions including the dMPFC (anterior subnetwork) and midline parietal cortex (posterior subnetwork) (Davey et al., 2019). The default-mode network, largely overlapping with the ‘mentalizing network’, has been associated to self-relevant processes as well as social cognitive processes (Buckner et al., 2008; Fox et al., 2005; Greicius et al., 2003; Gusnard and Raichle, 2001). We speculate that the observed decreased connectivity in adulthood may indicate functional segregation or specialization within the network (Davey et al., 2019; Van Buuren et al., 2010), possibly related to maturation of the self-concept and distinction between reflecting or thinking about oneself and others.

### 4.5. Limitations and future directions

To our knowledge, this is the first study to target development of neural correlates of self- and peer-evaluations in a longitudinal setup with...
three timepoints. Due to motion and participants unable to join in all measurements over three years, a total of 34 adolescents were included in analyses of all timepoints. While the region-of-interest analyses could be replicated in the sample of 78 adolescents who participated at least once (after exclusion because of motion or incorrect task performance), connectivity analyses were conducted on whole-brain level and could only be performed on the participants with complete data on all three measurements. Although our sample size is modest, particularly for the connectivity analyses, we believe that our study provides a starting point for future studies investigating development of brain connectivity and activity across adolescents. Furthermore, the focus of the study was primarily on developmental changes in neural correlates of both self- and other-referential processing. To this aim, we followed-up our previous study (van Buuren et al., 2020) by including two additional measurements, as well as comparing the last measurement to an independent group of young adults. As in our prior study, we used a block-design with negative and positive traits within one block, that elicited robust activity as well as connectivity patterns. However, this design did not allow us to probe effects of valence, as the traits in the blocks followed each other without (jittered) intervals. Also, the traits were only selected based on valence and not based on type of trait such as belonging to the social or academic domain. Therefore, we could not test effects of various types of traits (for example social, academic) on activity underlying self- referential processing, as has been suggested by other studies (Pfeifer et al., 2013; van der Aar et al., 2019; van der Cruijsen et al., 2018, 2017). Future studies incorporating event-related study designs may investigate the differential effects of valence and type of traits on the development of neural correlates of both self- and other-referential processing.

5. Conclusions

This study probed the developmental trajectories of brain activity and connectivity underlying self- and other-referential processing in adolescents and examined whether these correlates further developed from mid-adolescence to young adulthood. Brain activity within the dMPFC and right TPJ showed a quadratic change from early to mid-adolescence, with a peak in activity at the second measurement when evaluating the self, the similar and dissimilar peer. Activity did not differ from the second to the third measurement, and no differential activity was observed when comparing the adolescents to young adults. Functional connectivity did not change from early to mid-adolescence, however, connectivity of the dMPFC with a posterior midline region reduced from mid-adolescence to young adulthood. We tentatively suggest that brain activity may peak at the age of 14, possibly related to the development of a consistent self-concept and representations of peers. At the same time, connectivity between brain regions underlying these processes may continue to refine into young adulthood, possibly facilitating functional specialization that may support further maturation of the self-concept and representations of others.

Data and code availability

The participants and their parents did not provide explicit consent for public archiving of the research data, therefore the data is not stored in a public repository. Anonymized data will be made available to individual researchers upon request, when compatible with the General Data Protection Regulation. Additionally, researchers that request the data will be required to have obtained ethics approval from their host institution and are not allowed to share the data. Matlab code that was written to preprocess and analyze the fMRI data has been made publicly available on Github. (https://github.com/marietvburen/self_other_longitudinal).

Funding

This work was supported by the European Research Council (ERC Consolidator grant, grant number 648082, to L.K.) and by an Institute for Brain and Behavior Amsterdam (IBBA) research support fund (to M.v.B and L.K).

Declaration of Competing Interest

None.

Credit authorship contribution statement

Mariët van Buuren: Conceptualization, Investigation, Methodology, Software, Formal analysis, Writing – original draft, Project administration, Supervision. Hester Sijtsma: Project administration, Resources, Methodology, Writing – review & editing. Nicky Lute: Investigation, Project administration, Writing – review & editing. Rebecca van Rijn: Investigation, Project administration, Writing – review & editing. Miriam Hollarek: Project administration, Resources, Writing – review & editing. Reubs J. Walsh: Investigation, Project administration, Resources, Writing – review & editing. Lydia Krabbensd: Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Acknowledgments

The authors thank Sanne Riemmans and Annika Wirsching for their assistance with data acquisition.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119032.

References

Andrews, J.L., Ahmed, S.P., Blakemore, S.J., 2021. Navigating the social environment in adolescence: the role of social brain development. Biol. Psychiatry 89, 109–118. doi:10.1016/j.biopsych.2020.09.012.
Barendse, M.E.A., Cosme, D., Flourny, J.C., Vijayakumar, N., Cheng, T.W., Allen, N.B., Pfeifer, J.H., 2020. Neural correlates of self-evaluation in relation to age and pupertal development in early adolescent girls. Dev. Cogn. Neurosci. 44, 100799. doi:10.1016/j.dcn.2020.100799.
Benot, R.G., Gilbert, S.J., Volle, E., Burgess, P.W., 2010. When I think about me and simulate you: medial rostral prefrontal cortex and self-referential processes. Neuroimage 51, 1340–1349. doi:10.1016/j.neuroimage.2009.12.092.
Blakemore, S.J., den Ouden, H., Choudhury, S., Frith, C., 2007. Adolescent development of the neural circuitry for thinking about intentions. Soc. Cogn. Affect. Neurosci. 2, 130–139. doi:10.1093/socne/2n009.
Bramb, R.K., van Duivenvoorde, A.C.K., Peper, J.S., Crone, E.A., 2015. Longitudinal changes in adolescent risk-taking: a comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. J. Neurosci. 35, 7226–7238. doi:10.1523/JNEUROSCI.4764-14.2015.
Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain’s default network: anatomy, function, and relevance to disease. Annu. N. Y. Acad. Sci. 1124, 1–38. doi:10.1196/annals.1440.011.
Chen, G., Adleman, N.E., Saad, Z.S., Leibenuh, E., Cox, R.W., 2014. Applications of multivariate modeling to neuroimaging group analysis: a comprehensive alternative to univariate general linear model. Neuroimage 99, 571–588. doi:10.1016/j.neuroimage.2014.06.027.
Crone, E.A., Dahl, R.E., 2012. Understanding adolescence as a period of social affective engagement and goal flexibility. Nat. Rev. Neurosci. 13, 656–660. doi:10.1038/nrn3313.
Crone, E.A., Fuligini, A.J., 2020. Self and others in adolescence. Annu. Rev. Psychol. 71, 447–469. doi:10.1146/annurev-psych-010419-050927.
D’Argembeau, A., Jédidi, H., Balteau, E., Bahr, M., Phillips, C., Salmon, E., 2012. Valuing one’s self: medial prefrontal involvement in epistemic and emotive investments in self-views. Cereb. Cortex 22, 659–667. doi:10.1093/cercor/bhr144.
Davey, C.G., Fornito, A., Pujol, J., Breakspear, M., Schmaal, L., Harrison, B.J., 2019. Neurodevelopmental correlates of the emerging adult self. Dev. Cogn. Neurosci. 36. doi:10.1016/j.dcn.2019.100628.
Davey, C.G., Pujol, J., Harrison, B.J., 2016. Mapping the self in the brain’s default mode network. Neuroimage 132, 390–397. doi:10.1016/j.neuroimage.2016.02.022.
de Brigard, F., Spreng, N.R., Mitchell, J.P., Schacter, D.L., 2015. Neural activity associated with self, other, and object-based counterfactual thinking. NeuroImage 109, 12–26. doi:10.1016/j.neuroimage.2014.12.075.

Denny, B.T., Koher, H., Wager, T.D., Ochsner, K.N., 2012. A meta-analysis of functional neuroimaging studies of self and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. J. Cogn. Neurosci. 24, 1742–1752. doi:10.1162/jocn.a_00233.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102, 9673–9678. doi:10.1073/pnas.0504136102.

Grayson, D.S., Fair, D.A., 2017. Development of large-scale functional networks from birth to adulthood: a guide to the neuroimaging literature. NeuroImage 160, 15–31. doi:10.1016/j.neuroimage.2017.01.079.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U. S. A. 100, 253–258. doi:10.1073/pnas.0335081100.

Gu, S., Satterthwaite, T.D., Medaglia, J.D., Yang, M., Gur, R.E., Gur, R.C., 2015. Emergence of system roles in normative neurodevelopment. Proc. Natl. Acad. Sci. U. S. A. 112, 13681–13686. doi:10.1073/pnas.1502829112.

Gunther Moor, B., op de Macks, Z., Gurrolu, B., Rombouts, S.A.R.B., van der Molen, M.W., Crone, E.A., 2012. Neurodevelopmental changes of reading in the eyes. Soc. Cogn. Affect. Neurosci. 44–52. doi:10.1093SCAN/nrt020.

Gürrolu, B., 2020. Adolescent brain in a social world: unravelling the positive power of peers from a neurobehavioral perspective. Eur. J. Dev. Psychol. 00, 1–23. doi:10.1080/17405629.2018.1413101.

Gusnard, D.A., Raichle, M.E., 2001. Searching for a baseline: functional imaging and the resting human brain. Nat. Rev. Neurosci. 2, 685–694. doi:10.1038/35045400.

Jankowski, K.F., Moore, W.E., Merchant, J.S., Kahn, L.E., Pfeifer, J.H., 2014. But do you think I’m cool?: developmental differences in striatal recruitment during direct and reflected self-social evaluations. Dev. Cogn. Neurosci. 8, 40–54. doi:10.1016/j.dcn.2014.01.003.

Kilford, E.J., Garrett, E., Blakemore, S.J., 2016. The development of social cognition in adolescence: an integrated perspective. Neurosci. Biobehav. Rev. 70, 106–120. doi:10.1016/j.neubiorev.2016.08.016.

Krienen, F.M., Tu, P.C., Buckner, R.L., 2010. Clan mentality: evidence that the medial prefrontal cortex responds to close others. J. Neurosci. 30, 13906–13915. doi:10.1523/JNEUROSCI.2180-10.2010.

Labourie-Vieuf, G., Chiolo, L.M., Gougon, L.A., Diehl, M., Orwell, L., 1995. Representations of self across the life span. Psychol. Aging 10, 404–415.

Lombard, M.V., Chakrabarti, B., Bullmore, E.T., Wheelwright, S.J., Sadek, S.A., Sackin, J., Baron-Cohen, S., MRC AIMS Consortium, 2010. Shared neural circuits for mentalizing about the self and others. J. Cogn. Neurosci. 22, 1623–1635. doi:10.1162/jocn.2009.21297.

Luna, B., Marek, S., Larsen, B., Tervo-Clemmens, B., Chahal, R., 2015. An integrative model of the maturation of cognitive control. Annu. Rev. Neurosci. 38, 151–170. doi:10.1146/annurev-neuro-071714-034054.

Marek, S., Hwang, K., Foran, W., Hallquist, M.N., Luna, B., 2015. The contribution of network organization and integration to the development of cognitive control. PLoS Biol. 1–25. doi:10.1371/journal.pbio.1002528.

McLaren, D.G., Ries, M.J., Johnson, S.C., 2012. A generalized form of context-dependent psychophysiological interactions (pPI): a comparison to standard approaches. NeuroImage 61, 1277–1286. doi:10.1016/j.neuroimage.2012.03.068.

Mitchell, J.P., Macre, C.N., Banaji, M.R., 2006. Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. NeuroImage 30, 655–663. doi:10.1016/j.neuroimage.2006.03.040.

Moore, W.E., Merchant, J.S., Kahn, L.E., Pfeifer, J.H., 2014. Like me?: ventromedial prefrontal cortex is sensitive to both personal relevance and self-similarity during social comparisons. Soc. Cogn. Affect. Neurosci. 9, 421–426. doi:10.1093/scan/nst007.

Murray, R.J., Schaer, M., Debnath, M., 2012. Degrees of separation: a quantitative neuroimaging meta-analysis investigating self-specificity and shared neural activation between self- and other-reflection. Neurosci. Biobehav. Rev. 36, 1043–1059. doi:10.1016/j.neubiorev.2011.12.013.

Northoff, G., Heinzel, A., de Greck, M., Brempolh, F., Dobrovonly, H., Panksepp, J., 2006. Self-referential processing in our brain—a meta-analysis of imaging studies on the self. NeuroImage 31, 440–457. doi:10.1016/j.neuroimage.2005.12.002.

Pfeifer, J.H., Kahn, L.E., Merchant, J.S., Peake, S.J., Veroude, K., Masten, C.L., Lieberman, M.D., Mazzotta, J.C., Dapretto, M., 2013. Longitudinal change in the neural bases of adolescent self-evaluations: effects of age and pubertal development. J. Neurosci. 33, 7415–7419. doi:10.1523/JNEUROSCI.4074–12.2013.