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Increased functional connectivity with puberty in the mentalising network involved in social emotion processing

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Abstract

There is increasing evidence that puberty plays an important role in the structural and functional brain development seen in adolescence, but little is known of the pubertal influence on changes in functional connectivity. We explored how pubertal indicators (salivary concentrations of testosterone, oestradiol and DHEA; pubertal stage; menarcheal status) relate to functional connectivity between components of a mentalising network identified to be engaged in social emotion processing by our prior work, using psychophysiological interaction (PPI) analysis. Female adolescents aged 11 to 13 years were scanned whilst silently reading scenarios designed to evoke either social emotions (guilt and embarrassment) or basic emotions (disgust and fear), of which only social compared to basic emotions require the representation of another person's mental states. Pubertal stage and menarcheal status were used to assign participants to pre/early or mid/late puberty groups. We found increased functional connectivity between the dorsomedial prefrontal cortex (DMPFC) and the right posterior superior temporal sulcus (pSTS) and right temporo-parietal junction (TPJ) during social relative to basic emotion processing. Moreover, increasing oestradiol concentrations were associated with increased functional connectivity between the DMPFC and the right TPJ during social relative to basic emotion processing, independent of age. Our analysis of the PPI data by phenotypic pubertal status showed that more advanced puberty stage was associated with enhanced functional connectivity between the DMPFC and the left anterior temporal cortex (ATC) during social relative to basic emotion processing, also independent of age. Our results suggest increased functional maturation of the social brain network with the advancement of puberty in girls.

Keywords

Puberty; Hormones; Social brain; fMRI; Functional connectivity; Psychophysiological interaction

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Introduction

During adolescence, major changes in social and cognitive behaviours take place (Spear, 2000). Changes in social behaviours include increased focus on peer relationships and development of social skills required for more complex social relations (Steinberg and Morris, 2001). It has been proposed that many of these changes are partly due to the effects of puberty – and associated increased hormone levels – on the human brain (Blakemore et al., 2010; Forbes and Dahl, 2010). Puberty, the biological process of increased gonadal steroid hormone secretion resulting in reproductive competence, occurs between the ages of 8 and 14 years in females, and 9 and 15 years in males (Tanner, 1962). The steroid hormones involved in puberty, particularly testosterone and oestradiol, have been shown to influence brain maturation in animal models (Sisk and Zehr, 2005). Recently, studies in humans have shown effects of puberty, independent of the effects of age, on neural responses in reward-related tasks (e.g., Forbes et al., 2010), emotion processing (Moore et al., 2012) and social emotion processing (Goddings et al., 2012). The aim of the current study was to examine the effects of puberty on *functional connectivity* within a mentalising network identified to be engaged in social emotion processing by our prior work (Burnett and Blakemore, 2009).

In a previous functional magnetic resonance imaging (fMRI) study (Goddings et al., 2012), we investigated the effects of puberty on the blood oxygenation-level dependent (BOLD) signal within a particular social brain component, the ‘mentalising network’, comprising the dorsomedial prefrontal cortex (DMPFC), the posterior superior temporal sulcus (pSTS) at the temporo-parietal junction (TPJ) and the anterior temporal cortex (ATC) (Frith and Frith, 2003). Mentalising – the ability to understand another person’s intentions, emotions, desires and beliefs – is a crucial capacity for a range of social behaviours and depends on important components of the social brain network (Olsson and Ochsner, 2008). In our previous study, 42 girls within a narrow age range in early adolescence (11.1–13.7 years) were divided into two groups according to stage of puberty (pre/early vs. mid/late) and also provided salivary sex hormone assays (testosterone, oestradiol, and dehydroepiandrosterone (DHEA)). BOLD signal was recorded whilst participants silently read scenarios designed to evoke either social emotions (guilt and embarrassment) or basic emotions (disgust and fear). Across the entire group, the social brain network was activated when social emotion processing was contrasted with basic emotion processing. In addition, there were functionally dissociable effects of pubertal hormones and chronological age on the mentalising network. Increasing sex hormone levels (independent of chronological age) were associated with increasing BOLD signal in the left ATC during social emotion processing. Increasing age (independent of hormone levels) was associated with decreasing DMPFC activity during social emotion processing (Goddings et al., 2012).

Several neuroimaging studies of mentalising have found a similar *age-related* decrease in DMPFC activity during adolescence into adulthood (e.g., Burnett et al., 2009; Gunther Moor et al., 2011; Pfeifer et al., 2009; Wang et al., 2006). These studies often report age-related increases in activity in other parts of the mentalising network (pSTS/TPJ and ATC) during this period. In addition to functional changes during mentalising tasks in adolescence, there are also structural changes in the social brain network during this period of life (Mills et al.,

2012). In terms of behavioural development, a previous study demonstrated pubertal development in the appreciation of mixed emotions for social compared with basic emotion processing (Burnett et al., 2011). Furthermore, speed of mentalising has been found to increase with age during adolescence (Keulers et al., 2010) and the same study found that pubertal phase in boys aged 12–15 contributed independently to mentalising speed after controlling for age. Finally, the ability to take into account another person's perspective in order to guide appropriate decisions and actions is still improving during mid-late adolescence (Dumontheil et al., 2010).

Whilst several studies have investigated mentalising in adolescence, and the effect of puberty on mentalising, no previous studies have investigated how puberty influences connectivity between brain regions within the social brain network. In the current study, we investigated the effect of puberty on functional connectivity between brain regions within a mentalising network identified to be engaged in social emotion processing by our prior work (Burnett and Blakemore, 2009) during the social emotion paradigm.

Previous developmental functional and effective connectivity studies

Developmental changes in functional connectivity – that is, correlated activity between brain regions during "resting state", or during one psychological task relative to another – have been reported in a growing number of studies. Time perception, spelling and scene retrieval studies show age-related increases between childhood and adulthood in functional connectivity between regions focally associated with task performance (Booth et al., 2008; Ofen et al., 2012; Smith et al., 2011). Successful response inhibition, as assessed using the Go/No-go task, shows patterns of both increasing and decreasing functional connectivity with age in adolescence, depending on the particular region and the functional network examined (Keulers et al., 2012; Stevens et al., 2007). In a study that employed a probabilistic learning task, increasing age during adolescence was associated with increased functional connectivity between the striatum and medial prefrontal cortex during positive relative to negative performance feedback (Van den Bos et al., 2011).

In "resting-state" functional connectivity studies, which often examine large-scale connectivity patterns across the brain, a consistent finding is that functional connectivity between spatially distant, functionally-related brain regions increases between childhood and adulthood, whilst connectivity between more spatially proximal regions decreases (e.g., Dosenbach et al., 2010; Fair et al., 2008; Fair et al., 2009; Qin et al., 2012; for a review see Vogel et al., 2010). Resting-state functional connectivity is modulated by serotonin transporter genotype (Wiggins et al., 2012), stress-induced activation of the hypothalamic–pituitary–adrenal axis (Thomason et al., 2011) and oestrogen level in adult females (Ottowitz et al., 2008a, 2008b).

Relatively few developmental studies have examined functional connectivity during social cognition tasks. Studies investigating face processing show evidence for age-related increases in functional connectivity in the core face processing network between childhood and adulthood (Cohen Kadosh et al., 2011), and in networks mediating the impact of prior expectations on the processing of emotional faces between adolescence and adulthood (Barbalat et al., 2012). A longitudinal fMRI study showed adolescent age-related increases

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in functional connectivity between action observation and social brain regions during observation of angry versus neutral hand gestures, in males but not in females (Shaw et al., 2011). Previously, we have shown an age-related *decrease* between adolescence and adulthood in task-dependent functional connectivity between the DMPFC and the pSTS/TPJ (Burnett and Blakemore, 2009). To the best of our knowledge, previous developmental studies have not explored potential relationships between puberty measures and functional connectivity during social cognitive tasks. In our previous developmental functional connectivity study (Burnett and Blakemore, 2009) no pubertal measures were acquired; thus it is unknown whether functional connectivity between regions within this mentalising network is influenced by pubertal development. However, it is increasingly recognised that pubertal hormones organise structural brain connectivity in humans (Peper et al., 2011a). Given the evidence for gender-specific patterns of adolescent functional connectivity during social cognition (Shaw et al., 2011), and evidence for an impact of female gonadal hormones on functional connectivity in adults, investigating this relationship could be fruitful.

The current study

In the current study, we performed a psycho-physiological interaction (PPI) analysis to explore functional connectivity between the DMPFC and the other regions of a mentalising network identified to be engaged in social emotion processing by our prior work (Burnett and Blakemore, 2009), using data from a previously reported sample (Goddings et al., 2012). PPI analysis examines the association between BOLD signals in particular brain regions in one psychological context (experimental condition) compared with another (Friston et al., 1997; O'Reilly et al., 2012). We chose the DMPFC as a source region in accordance with our previous PPI analysis of the same task in another sample (Burnett and Blakemore, 2009) and its general role in mentalising (Amodio and Frith, 2006). In the current study, three independent measures of puberty were obtained from female participants aged 11.1–13.7 years: salivary hormone assays for testosterone, oestradiol and DHEA; visual clinician assessment of Tanner stage (Marshall and Tanner, 1969); and a self-report measure of menarcheal status. We explored how functional connectivity within a mentalising network identified to be engaged in social emotion processing by our prior work relates to these measures of puberty.

Methods

Participants

42 female adolescents aged 11.1 to 13.7 years (mean 12.5; SD 0.7) participated in this study. Here, we report data from N = 35 participants in the PPI analysis (mean age: 12.6; SD 0.7), after exclusion of 7 participants who showed no significant activation cluster in the DMPFC (*Analysis of functional connectivity (PPI)*). Furthermore, missing data from the saliva samples provided the following numbers for the PPI analyses with puberty hormone levels: N = 34 for testosterone, N = 32 for oestradiol and N = 33 for DHEA. Within the narrow age band of our sample, adolescent girls undergoing normal development can be at all stages of puberty from Tanner stage 1 to stage 5 (Marshall and Tanner, 1969), thereby providing maximal pubertal variability whilst minimising variance in age. Potential participants were excluded if they had a history of previous neurosurgery, premature birth (<34 weeks

gestation), a diagnosis of epilepsy, autistic spectrum disorder or dyslexia, known psychiatric disorder, or a known endocrine disorder. All participants had normal or corrected to normal vision and spoke English as their native language. Each participant assented to the study, and informed written consent was obtained from a parent/guardian. Participants received £10/h for their participation, and data collection took up to 2 h per participant. The study was approved by the UCL National Hospital for Neurology and Neurosurgery Ethics Committee.

Verbal IQ (vIQ) was measured using the British Picture Vocabulary Scale II (Dunn et al., 1997). Since our task involved reading verbal cues, differences in vIQ between groups could potentially impact on performance in the behavioural task. Behavioural measures were administered individually to participants in a quiet testing room. Body Mass Index (BMI) was calculated for each participant except one whose height was not measured (see Table 1). Puberty incorporates changes in height, weight and body fat distribution, and therefore may lead to changes in BMI, which can increase or decrease with relative changes in height and weight. We did not find any group differences or correlations with hormones for vIQ or BMI in our sample. See Tables 1 and 2 for more details about participant characteristics.

Endocrine assessments

Three independent measures of pubertal development were taken from each participant on the day of the MRI scan acquisition:

1. Salivary hormone assays for the puberty hormones testosterone, oestradiol and DHEA. These are the principal hormones that drive the physical and behavioural changes of puberty. Salivary hormone assays were used to minimise invasive testing. Upon waking on the morning of their scan, before 9 am, each participant collected 2 ml passive drool (unstimulated) samples of saliva after rinsing their mouths with water, and before brushing their teeth, eating or drinking anything (except water). We verified that these instructions had been followed by parental report. The samples were transported on the day of collection to the functional imaging laboratory on ice in an insulated box. Samples were stored at −80 °C and later analysed simultaneously by Salimetrics Europe Ltd (www.salimetrics.com).
2. A visual assessment of breast and pubic hair stage using established Tanner stages (Marshall and Tanner, 1969) by a trained paediatric physician (ALG). If a participant chose not to be examined (N = 2), they were asked to rate their own stage of breast and pubic hair development using Tanner stage diagrams (Taylor et al., 2001).
3. Self-report of menarcheal status. Whilst menarche most frequently occurs when a girl is at Tanner stage 4, it can occur when she is phenotypically at Tanner stage 3 (Marshall and Tanner, 1969).

On the basis of the Tanner staging (2) and menarcheal status (3), participants were dichotomised into pre/early puberty (referred to as Early) and mid/late puberty (referred to as Late) puberty groups. Participants were characterised as Early puberty if both breast and pubic hair Tanner stages were 1, 2 or 3 and if they were pre-menarcheal. Participants were

characterised as Late puberty if either breast or pubic hair stage was 4 or 5 or they were postmenarcheal (Dorn, 2006). Since menarche indicates gonadal maturation and reproductive competence, we felt that it would be inappropriate to incorporate individuals who had commenced menarche in an early puberty group, and that they should be considered more appropriately in terms of their physiology in the late puberty group. Early and Late puberty groups differed significantly on age (see Table 1); therefore, we included age as a covariate of no interest in the model.

Emotion task

Whilst being scanned with fMRI, participants read scenarios designed to evoke one of four emotions: two social emotions (embarrassment and guilt) and two basic emotions (disgust and fear; see Burnett et al., 2009, for detailed Methods). Examples of social emotion scenarios are “You were quietly picking your nose but your friend saw you” (embarrassment) and “You laughed at a quiet girl you know and it made her sad” (guilt). Examples of basic emotion scenarios are “Your dad told you that the fridge was infested with maggots” (disgust) and “Your friend screamed that there was a wasp inside your jumper” (fear). Both social and basic scenarios featured the protagonist (‘you’) plus one other person. Hence, the difference between the social and basic emotion conditions was the need to take into account another person’s mental state in the social emotion condition, not the mere presence of another person in the scenario (Abraham et al., 2008). Participants had 9 s to read each scenario silently and imagine their response. Next, participants rated their emotional response to the scenario on a rating scale from 1 (not at all) to 4 (very much). There were 72 emotion scenarios in total, which were presented in blocks of three. In each block, all three scenarios featured the same emotion (disgust, embarrassment, fear or guilt). At the start of each block, a 1 s cue screen informed participants which emotion the subsequent three sentences would feature. The fMRI experiment was split into two 7 min sessions. Each session contained 12 emotion blocks, each lasting 28 s. Condition order was fully randomised. In addition there were four 7 s visual fixation blocks per session, occurring at regular intervals through each of the two sessions. Stimulus presentation was programmed in Cogent (www.vislab.ucl.ac.uk/Cogent/index.html) running in Matlab 7.3.0, which recorded participant responses.

Data acquisition

A 1.5 T Siemens Sonata head MRI scanner with 8-channel phased-array coil was used to acquire multi-slice T2*-weighted echo-planar volumes with BOLD contrast. Each functional brain volume was composed of 45 3 mm axial slices with a 1.5 mm gap and in-plane resolution of $3 * 3$ mm, with $-30°$ slice tilt, zero z-shim and negative (down) phase-encoding (PE) direction to minimise signal dropout in the orbital/rostral prefrontal and anterior temporal cortices. Repetition time was 4.05 s (90 ms per slice $*$ 45 slices). Functional data were acquired in two scanning sessions of 7 min each, during which a total of 218 volumes were acquired, or 104/114 scans per session. Prior to functional scanning we acquired individual field maps to correct for distortions in functional images (Weiskopf et al., 2006). Field map acquisition time was 2 min. After functional scanning we acquired a 10 min T1-weighted anatomical image for each participant using a 3D modified driven equilibrium Fourier transform (MDEFT) sequence and an isotropic resolution of 1 mm with

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the following parameters: echo time: 3.6 ms; repetition time: 12 ms; flip angle: 23°; acquisition matrix: 256 × 176; field of view: 25 cm; and 176 slices. The total duration of scanning was approximately 30 min per participant.

Hormonal data analysis

Duplicate assays for testosterone, oestradiol and DHEA were performed for each participant, and the mean values were used for all analyses. Samples were tested in duplicates. No samples varied by more than 6%. The oestradiol range of sensitivity was from 1 to 32 pg/mL. The average intra-assay coefficient of variation was 1.8%. The testosterone range of sensitivity was from 1 to 600 pg/mL. The average intra-assay coefficient of variation was 1.4%. The DHEA range of sensitivity was from 5 to 1000 pg/mL. The average intra-assay coefficient of variation was 1.6%. All measured ranges for the three hormones fell within the range of sensitivity for all participants.

Conventional imaging data analysis

Analysis was conducted using SPM5 (statistical parametric mapping; www.fil.ion.ucl.ac.uk/spm). The first six functional image volumes from each run were discarded to allow for T1 equilibrium effects, leaving 206 image volumes per participant. Pre-processing included rigid-body transformation (realignment), unwarping with field maps and slice timing to correct for head movement and slice acquisition delays. The images were stereotactically normalised into the standard space defined by the Montreal Neurological Institute (MNI) template using the mean of the functional volumes, and smoothed with a Gaussian filter of 6 mm full-width at half maximum. The time series for each participant were high-pass filtered at 128 s to remove low-frequency drifts.

The analysis of the functional imaging data entailed the creation of statistical parametric maps representing a statistical assessment of hypothesised condition-specific effects (Friston et al., 1994), which were estimated with the General Linear Model. The effects of interest were the two scenario block types: social emotion and basic emotion and the visual fixation blocks. We modelled the six realignment parameters as effects of no interest, in order to account for possible group differences in head movement. Each component of the model then served as a regressor in a multiple regression analysis for each participant. The resulting parameter estimates for each regressor at each voxel were then entered into a second level analysis where ‘participant’ served as a random effect in a within-subjects analysis of variance (for further details, see the Methods section of Goddings et al., 2012).

Analysis of functional connectivity (PPI)

Functional connectivity analyses are based on the principal that, if BOLD signal in one region (area A) correlates with BOLD signal in another region (area B), then the strength of the regression reflects functional coherence between the two areas. If the strength of the regression varies with the psychological context in which the physiological activity is measured then this is evidence for a psychophysiological interaction (PPI) (Friston et al., 1997). In PPI analysis, a brain region of interest is defined as the physiological source. We used PPI analysis to estimate functional connectivity within a mentalising network identified to be engaged in social emotion processing by our prior work (Burnett and Blakemore,

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2009) between the DMPFC (source region) and other social brain regions (pSTS, TPJ and ATC), during Social vs. Basic emotion. Consequently, activity within the DMPFC served as the physiological regressor in the PPI analysis, whilst emotion condition (Social vs. Basic) was the psychological regressor. A third regressor in the analysis represented the interaction between the first and second regressors.

We defined our DMPFC source region based on our previous study (Burnett and Blakemore, 2009; see also Gilbert et al., 2006) and in order to include data from as many participants as possible in the analysis we increased the size of the source region according to the DMPFC definition used in meta-analysis by Amodio and Frith (2006). This resulted in the following DMPFC source region: −20 to +20 on the x-axis, +35 to +65 on the y-axis, and −10 to +40 on the z-axis. This source region also falls within the range of MPFC activity observed in meta-analysis of mentalising regions by Van Overwalle and Baetens (2009). In each single-subject t-contrast map for the emotion contrast (Social > Basic), thresholded at $P < 0.005$ uncorrected, we located the nearest local maximum to the centre of this volume. We created a spherical volume of interest (VOI) of radius 8 mm centred on the single-subject peak. If there was no significantly active cluster within the DMPFC at this threshold (N = 10), we lowered the threshold to $P < 0.01$ uncorrected. Seven datasets that did not contain a peak within our defined DMPFC volume at this significance level were excluded (four Early puberty, three Late puberty participants), leaving 17 Early puberty and 18 Late puberty participants (see Table 1 for details) in subsequent PPI analyses. Individual participant peaks were distributed evenly around the centre of the DMPFC source region and no differences in x, y, and z coordinates were observed between Early and Late puberty groups ($t < 1$). Finally, we extracted the BOLD signal time series from each participant's VOI in the DMPFC.

Voxel-wise PPI analysis was conducted at the combined group level (N = 35), in order to identify target social brain regions of interest (pSTS/TPJ and ATC) that showed a significant increase in functional coupling with the DMPFC during Social relative to Basic emotion. We conducted small volume corrections (SVCs) on spheres with radius 12 mm centred on peaks in the pSTS/TPJ and ATC, as reported in our previous PPI study of social emotion processing (Burnett and Blakemore, 2009). We then ran a partial correlation between puberty hormone levels and the PPI between DMPFC activity and social > basic emotion, covarying out participant age (N = 32). We compared PPIs for Social vs. Basic emotions between the two puberty groups, controlling for participant age. Finally, we analysed age related changes in PPI with puberty status as a covariate of no interest (N = 35).

Control analysis: head motion

Since head motion can result in spurious activation patterns in (resting state) functional connectivity studies (Power et al., 2012), we analysed whether motion was related to puberty grouping, hormone levels and age. In our PPI analysis, we are only interested in the difference between social versus basis conditions, therefore we investigated whether there were any interactions between condition and the participant characteristics in terms of head movement. There was no significant difference between mean movement during the social and basic elements of the task for either translational or rotational movement (Translation: t

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= 0.09, P > 0.9; Rotation: t = 0.19, P > 0.8). In addition, there was no significant correlation between Social–Basic mean movement and age (For translation, r = 0.22, P > 0.2; for rotation, r = 0.20, P > 0.2). We repeated this for hormones and found no effect of hormones on movement in social versus basic emotions (For translation: Testosterone, r = 0.03, P > 0.8; Oestradiol, r = 0.14, P > 0.4; DHEA, r = −0.09, P > 0.6. For rotation: Testosterone, r = −0.04, P > 0.8; Oestradiol, r = 0.10, P > 0.5; DHEA, r = −0.06, P > 0.7). There was also no interaction between puberty group and movement in social versus basic emotions (Translation: t = 0.09, P > 0.6; Rotation t = −0.02, P > 0.9).

Results

Behavioural data

Emotion rating data from three participants were not recorded by the stimulus computer, leaving N = 32. Table 3 shows emotion ratings by scenario and puberty group. Correlations between emotion ratings, pubertal measures and participant demographics can be found in Table 2. After co-varying out age, there was a main effect of group: the Early puberty group gave higher emotion ratings than the Late puberty group (F(1,28) = 6.02, P = 0.007). There was a significant main effect of emotion, where basic emotion scenarios were given higher emotion ratings than social emotion scenarios (F(1,31) = 9.60, P = 0.004). There was no interaction between puberty group and emotion (F(1,30) <1).

PPI data

Psychophysiological interaction data across participants (N = 35)—Across the entire group of participants, PPI analysis revealed that the right pSTS and the right TPJ showed greater functional connectivity with the DMPFC during Social compared with Basic emotion (Table 4a and Fig. 1). Whole brain analyses with family wise error correction thresholded at P < .05 revealed one significant cluster outside our regions of interest in the left superior occipital gyrus (see Table 4a).

PPI between hormones and emotion—There was increasing connectivity between the DMPFC and the right TPJ for Social vs. Basic emotions with increasing levels of oestradiol (see Table 4b and Fig. 2). We also conducted the analysis without the two participants with the highest oestradiol levels, which did not change the significance of the results.

PPI between puberty group and emotion—There was a significant interaction between puberty group (Late vs. Early puberty) and the PPI between the DMPFC and the left ATC in Social vs. Basic emotion (Table 4c and Fig. 3). The Late puberty group showed increased functional connectivity between the DMPFC and the left ATC compared with the Early puberty group, independent of age (see Table 4c). For the reverse contrast (Early vs. Late puberty), we found no significant interaction in the pSTS/TPJ or ATC.

For all PPI analyses, the results did not change after controlling for vIQ, except for one minor change in the size and position of the left ATC cluster in the Late vs. Early puberty analysis (6 voxels centred around [−50, 12, −28], instead of 4 voxels at [−50, 14, −28]).

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PPI between age and emotion—No interactions between age and connectivity between the DMPFC and the other regions of a mentalising network identified to be engaged in social emotion processing by our prior work, nor any other brain regions, were observed at FWE corrected thresholds.

Discussion

In the current study, we investigated how functional connectivity between regions within a mentalising network identified to be engaged in social emotion processing by our prior work (Burnett and Blakemore, 2009) is influenced by pubertal stage and puberty hormone levels in girls. We found that increasing oestradiol concentrations were associated with enhanced functional connectivity between the DMPFC and the right TPJ during social relative to basic emotion processing, independent of age. When the PPI data were analysed by phenotypic pubertal status, more advanced puberty stage was associated with enhanced functional connectivity between the DMPFC and the left ATC during social relative to basic emotion processing, also independent of age. Below, we interpret these findings as reflecting maturation of functional interactions within the mentalising system across adolescent pubertal development. Behaviourally, the pre/early puberty group gave higher emotion ratings for both Social and Basic emotion conditions than did the mid/late puberty group. We previously found that girls in late puberty report a wider combination (‘mixedness’) of emotions in response to social emotion scenarios than do girls in early puberty (Burnett et al., 2011), implicating an increasingly complex handling and understanding of emotions during puberty. As in our previous study (Burnett et al., 2009), across participants, basic emotion scenarios were given higher ratings than social emotion scenarios, possibly reflecting the higher intensity of basic emotions. There was no interaction between group and emotion for ratings, meaning that puberty stage did not have a greater influence over one type of emotion than the other.

Pubertal effects on functional connectivity within the mentalising network

In the current study as well as in the previous one, we found evidence for functional connectivity between the DMPFC and parts of the mentalising network during social emotion processing (Burnett and Blakemore, 2009). Specifically, we found increased functional connectivity between DMPFC and the right pSTS and right TPJ during social relative to basic emotion processing. Furthermore, the current PPI analysis revealed that, with increasing phenotypic puberty stage and levels of oestradiol (independent of age), connectivity between the DMPFC and the left ATC and right TPJ, respectively, increased during social versus basic emotion processing. The mechanism by which this increase in connectivity might emerge is not yet clear. In case of the social brain network, direct anatomical connections between brain regions might account for the observed functional connectivity. In the macaque brain, direct connections exist between DMPFC and both STS/TPJ and ATC (Bachevalier et al., 1997; Barbas et al., 1999). In human adolescence, fronto-temporal white matter integrity has been found to be associated with self-reported puberty stage (Asato et al., 2010), and the relationship between functional and structural (i.e. anatomical) connectivity increases from childhood into adolescence (Hagmann et al., 2010). Therefore, the pubertal and puberty hormone-related increases in functional connectivity

observed in the current study might result from hormonal effects on white matter structure and function (cf., Peper et al., 2011a).

Whilst changes in white matter interregional connections could contribute to changes in functional connectivity, previous studies have shown that this direct mechanism is unlikely to account for the complete picture (Hagmann et al., 2010). Indeed, neurochemical modulation and changes in synaptic physiology may also play a significant role (Uhlhaas et al., 2009). Oestrogens and other steroid hormones have been shown to exhibit neuromodulatory properties (Saldanha et al., 2011; Srivastava and Penzes, 2011; Zehr et al., 2008), influencing synaptic plasticity and connectivity in cortical and subcortical brain regions. Changes in circulating oestradiol, as measured in our study, might therefore affect functional connectivity via changes in synaptic physiology. Consistent with this account, a previous study revealed an inverse relationship between circulating oestradiol and prefrontal, parietal and middle temporal grey matter volume in adolescent females (Peper et al., 2009). Besides the influence of pubertal changes in grey and white matter on the observed increases in functional connectivity within the mentalising network, the connectivity in the current study may have been mediated by other regions beyond this network (Friston et al., 1997). Since we restricted our analysis to the mentalising network, we might have missed such a common input to the DMPFC, the TPJ and the ATC. Furthermore, we stress that the results of the PPI analysis differ fundamentally from both structural connectivity analysis and conventional task-related fMRI analysis. PPI analysis provides information regarding task-dependent changes in the relationship between two brain regions (Friston et al., 1997; O'Reilly et al., 2012). This relationship does not have to correspond to structural connections between these regions or be restricted to regions found active in conventional task-related analysis.

In this study we found no relationship between levels of circulating testosterone or DHEA and functional connectivity during our social emotion task. Whilst increases in sex hormones during puberty are correlated, they have demonstrably different effects throughout the body depending on the location and role of specific hormone receptors. A recent review (Peper et al., 2011b) highlighted the differential effects of steroid hormones on connectivity in the brain, which may relate to receptor distribution, enzyme location or differences in hormone properties.

Our results show differential correlations between oestradiol and phenotypic puberty status and functional connectivity. Whilst both hormone level and puberty status are measures of pubertal development, they focus on different aspects of the developmental process. Phenotypic puberty stage (Tanner stage) provides an estimation of the time since the activation of the hypothalamic–pituitary–gonadal (HPG) axis in an individual (Bordini and Rosenfield, 2011), and therefore the cumulative exposure to sex steroid hormone levels above the pre-pubertal baseline. In contrast, salivary hormonal measurements provide an accurate indication of systemic concentrations at the time of sampling and therefore salivary hormones give an indication of current exposure. Our contrasting results emphasise the need to consider differing views of pubertal development, since absolute and relative hormone exposure may have differing, and perhaps complementary effects on brain development.

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Limitations

Several limitations of the study should be noted. First, not all participants from the original sample could be included in the PPI analyses, due to the lack of a significant activation cluster in the DMPFC or missing hormonal data. We lowered the initial threshold for the individual DMPFC activations and increased the search space, which resulted in the maximum number of eligible PPI participants in our sample. Although all reported analyses included a minimum of 32 participants, using a larger sample size might reveal relationships between levels of testosterone or DHEA and functional connectivity during the social emotion task that were not observed in the current study. The comparison of the two puberty groups in particular needs replication with larger sample sizes, given the small size of the cluster observed in the ATC. Furthermore, the absence of significant activation in the DMPFC in some of the participants suggests that tasks with more robust activation patterns should be considered for future studies using task-related connectivity analyses.

Second, our study investigated pubertal effects on functional connectivity in the social brain in girls. We included female participants only since sex differences are observed in pubertal timing (Spear, 2000) in neural maturation of grey matter in early adolescence (Giedd et al., 1999), including in the social brain (Mills et al., 2012), and in activation during social and emotional tasks (Schulte-Rüther et al., 2008; Whittle et al., 2011). It would be interesting for future studies to investigate the effect of puberty stage and puberty hormones on functional connectivity during social emotion processing in boys.

Third, we did not control for variations in menstrual cycle phase in the current study. Our current design was not able to disentangle effects of menstrual cycle phase and pubertal growth since participants would still have an irregular cycle before and for up to two years after menarche, with many cycles being anovulatory (Bordini and Rosenfield, 2011; World Health Organization Task Force on Adolescent Reproductive Health, 1986). This precluded us controlling for cycling of hormone levels in our participants in our cross-sectional design.

Finally, in this study we specially focused on functional connectivity within a mentalising network identified to be engaged in social emotion processing by our prior work. Future studies are needed to see whether similar increases in functional connectivity with puberty are also observed during other (non-emotional) mentalising tasks or during tasks designed to study basic instead of social emotion processing.

Conclusion

We found that with increasing pubertal stage (independent of age), connectivity between the DMPFC and the left ATC increased during social versus basic emotion processing, and that with increasing oestradiol concentrations (also independent of age) connectivity increased between the DMPFC and the right TPJ during social versus basic emotion processing. Together, these results can be interpreted to show increasing long distance connectivity between regions of a mentalising network identified to be engaged in social emotion processing by our prior work with advancing puberty in girls.

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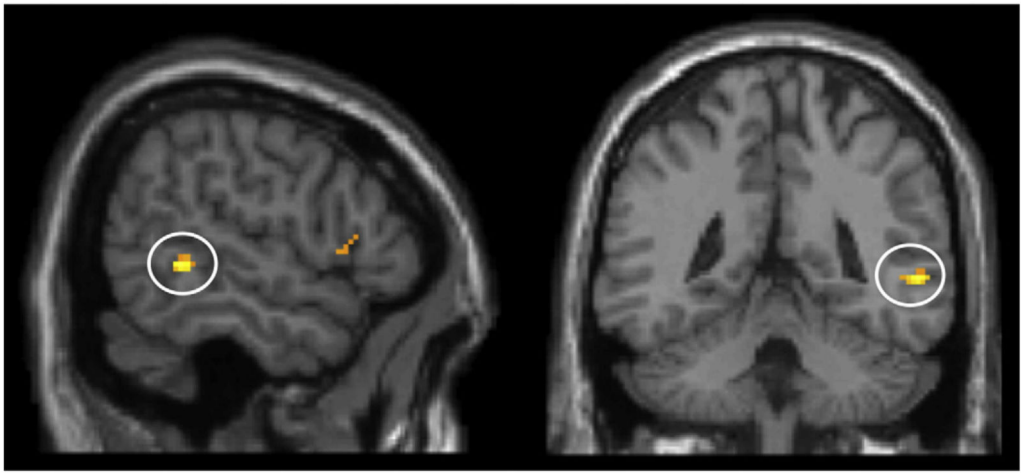

Fig. 1.

PPI results for all subjects: Significant interaction between emotion (social vs. basic) and DMPFC BOLD signal in the right pSTS (56, −44, 0), shown at $P < 0.001$ projected onto sagittal and coronal T1 images (at x = 56 and y = −44).

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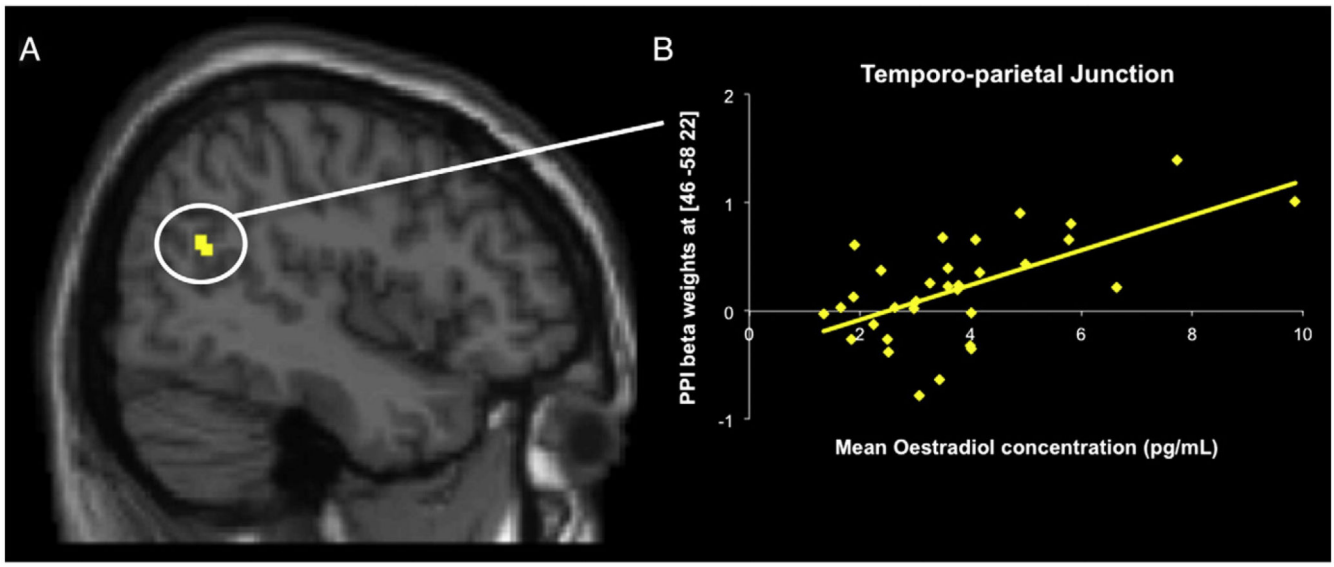

Fig. 2.

Interaction between oestradiol levels, emotion and DMPFC BOLD signal in the right TPJ (MNI 46, −58, 22), with age partialled out: (A) shown at $P < 0.001$ projected onto sagittal T1 image at x = 46 and (B) graph showing PPI beta weights in this region (based on the DMPFC time series × Social > Basic emotion) as a function of oestradiol levels. Graphs are plotted from peak voxel for illustration.

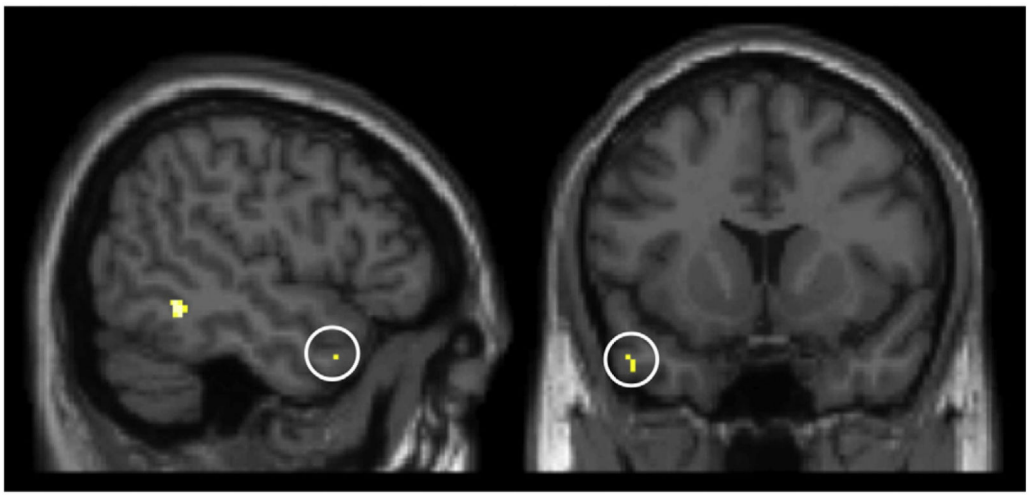

Fig. 3.

PPI results for Late compared to Early puberty groups: the left ATC (−50, 14, −28) showing significant interaction between group (Early vs. Late puberty), emotion (social vs. basic) and BOLD signal in the DMPFC (with age partialled out), shown at $P < 0.001$ projected onto sagittal and coronal T1 images (at $x = -50$ and $y = 14$).

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Table 1

Demographics showing mean, standard deviation and range of participants for age (in years), BMI, vIQ, pubertal hormone levels (in pg/mL) and Tanner stage for the whole group (N = 35) and for the Early and Late puberty groups separately. Significant differences (P < 0.05) between puberty groups in bold. Age was covaried out of subsequent analyses.

	Whole group (n = 35) Mean (SD) Range	Puberty groups Early (n = 17) Mean (SD) Range	Late (n = 18) Mean (SD) Range	Difference between group means
Age	12.6 (0.7)	**12.3 (0.7)**	**12.8 (0.6)**	**t_{34} = 2.57; P = 0.015**
	11.1–13.7	**11.1–13.5**	**11.9–13.7**	
BMI[a] (N = 34)	19.3 (3.0)	19.7 (3.6)	19.0 (2.3)	t_{33} = 0.687; P = 0.497
	13.5–27.3	15.4–27.3	13.5–23.9	
vIQ	120.4 (11.9)	117.4 (14.2)	123.3 (8.7)	t_{34} = 1.49; P = 0.147
	89–143	89–139	107–143	
Testosterone[b] (N = 34)	61.2 (23.7)	54.1 (12.5)	67.5 (29.3)	t_{33} = 1.77; P = 0.090
	28.1–148.3	30.9–78.3	28.0–148.3	
Oestradiol[b] (N = 32)	3.78 (1.84)	3.37 (0.81)	4.13 (2.38)	t_{31} = 1.25; P = 0.224
	1.34–9.86	2.24–4.98	1.34–9.86	
DHEA[b] (N = 33)	172.4 (96.7)	155.4 (63.0)	188.4 (120.1)	t_{32} = 1.00; P = 0.329
	56.5–521.1	56.5–304.3	69.4–521.1	
Tanner stage breast	3.4 (1.1)	**2.5 (0.5)**	**4.2 (0.6)**	**t_{34} = 8.83; P < 0.001**
	2–5	**2–3**	**3–5**	
Tanner stage pubic hair	3.2 (1.1)	**2.3 (0.8)**	**4.1 (0.6)**	**t_{34} = 7.37; P < 0.001**
	1–5	**1–3**	**3–5**	

[a] One girl in the Early puberty group was not measured for height, leaving N = 34 for BMI for the whole group and N = 16 for the Early puberty group.

[b] One subject did not produce a saliva sample. There was insufficient sample collected for one subject for analysis of either DHEA or oestradiol, and insufficient in a second participant for oestradiol only.

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Table 2

Correlations between pubertal measures, participant demographics and behavioural ratings showing Pearson r coefficients for the PPI sample (N = 35). Significant correlations (P < 0.05) are shown in bold.

	Tanner stage pubic hair	Tanner stage breast	Oestradiol	Testosterone	DHEA	Age	BMI	vIQ
Tanner stage breast	**0.87** **							
Oestradiol	0.21	**0.38** *						
Testosterone	**0.43** *	**0.42** *	**0.52** **					
DHEA	0.23	0.25	**0.61** **	**0.62** **				
Age	**0.68** **	**0.52** **	0.15	0.15	0.12			
BMI	0.01	0.03	0.07	−0.14	0.01	0.08		
vIQ	0.13	0.27	−0.08	0.04	−0.04	0.01	0.28	
Mean Basic rating	−0.32	**−0.42** *	−0.02	0.07	0.14	−0.25	−0.11	−0.37
Mean Social rating	−0.28	**−0.44** *	−0.14	0.00	0.04	−0.26	−0.11	−0.38

** P < 0.005.

* P < 0.05.

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Table 3

Mean emotion ratings by participants in Early and Late puberty groups. There was a main effect of group: the Early puberty group gave higher ratings than the Late puberty group, which remained significant after age was partialled out ($F(1,28) = 6.02$, $P = 0.007$). There was no interaction between puberty group and emotion ($F(1,30) = 0.014$; $P = 0.907$).

Emotion	Puberty group	Emotion rating Mean (SD)
Basic	Early puberty (N = 15)	3.36 (0.27)
	Late puberty (N = 17)	3.02 (0.38)
Social	Early puberty (N = 15)	3.24 (0.34)
	Late puberty (N = 17)	2.91 (0.35)

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Table 4

MNI coordinates, Z-values and cluster size for brain regions expressing a psychophysiological interaction between:

a. Activity within MPFC and emotion condition (Social vs. Basic) across subjects (n = 35), thresholded at P < 0.001.

b. Activity within MPFC, emotion condition (Social vs. Basic) and oestradiol, with age partialled out, thresholded at P < 0.001.

c. Activity within MPFC, emotion condition (Social vs. Basic) and group (Late puberty vs. Early puberty) with age partialled out, thresholded at P < 0.001. All reported regions survive small volume (12 mm sphere) correction, except (*) survives whole-brain family-wise error correction thresholded at P < .05.

Interaction	Region	MNI coords	Z	Size in voxels at P < 0.001
a. Whole group				
Across all participants	R pSTS	56 −44 0	4.75	55
		48 −40 0	3.88	(part of above)
	R TPJ	44 −52 22	3.25	2
	L superior occipital gyrus*	−12 −94 8	5.48	9
b. Hormonal regression				
Oestradiol	R TPJ	46 −58 22	3.51	16
c. Puberty groups				
Late puberty > Early puberty	L ATC	−50 14 −28	3.25	4