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Facing puberty: associations between pubertal development and neural responses to affective facial displays

William E. Moore III,[1] Jennifer H. Pfeifer,[1] Carrie L. Masten,[2] John C. Mazziotta,[3] Marco Iacoboni,[3,4] and Mirella Dapretto[3,4]

[1]Department of Psychology, University of Oregon, [2]Center for Mind and Brain, University of California, Davis, [3]Ahmanson-Lovelace Brain Mapping Center, University of California, Los Angeles and [4]UCLA-FPR Center for Culture, Brain, and Development

Adolescence is marked by profound psychosocial and physiological changes. Although investigations into the interactions between these forces have begun to shed light on the neural correlates of affective processing during the transition to adolescence, relatively little is known about the relationship between pubertal development and emotion perception at the neural level. In the current longitudinal study, 45 neurotypical participants were shown affective facial displays while undergoing fMRI, at ages 10 and 13. Neural responses to emotional expressions at both time points were then correlated with a self-report measure of pubertal development, revealing positive associations with activity in amygdala, thalamus and visual cortical areas at age 10 that increased in magnitude and extent by age 13. At the latter time point, pubertal development was additionally correlated with enhanced responses to faces in temporal pole, ventrolateral prefrontal cortex (PFC) and dorsomedial PFC. Longitudinal comparisons revealed that the relationships between pubertal development and activity in the amygdala, hippocampus and temporal pole were significantly stronger during early adolescence than late childhood. These results suggest that pubertal development per se is linked to neural processing of socioemotional stimuli, particularly with respect to the integration of complex perceptual input and higher order cortical processing of affective content.

Keywords: adolescence; puberty; emotion; fMRI; amygdala; longitudinal

Folk wisdom suggests that teenagers are ruled by their emotions, in part due to their 'raging hormones'. Teens also have to cope with considerable interpersonal changes, as relationships with peers take on a new level of importance (Larson and Richards, 1991; Brown, 2004). Together, these facts raise questions concerning not only the adolescent emotional experience, but also how teens perceive emotional states in others (Dahl and Gunnar, 2009). In light of the 'social reorientation of adolescence' (Nelson *et al.*, 2005), reacting appropriately to the feelings of peers is an important skill for the developing brain to hone. Of course, in addition to shifting social and emotional contexts, adolescence is also a period of significant physiological change. While outward manifestations that signal the end of childhood are often plain to see (e.g. increased height), the effects of puberty on brain function are by nature more elusive. It is important to determine how neural responses to key socioemotional stimuli, such as affective facial displays, are affected by pubertal development—distinct from chronological age.

Although it has been said that the science of adolescent brain development is itself at an age often associated with pubescent growing pains (Steinberg, 2010), the field is in many ways still in its infancy. The neural networks associated with perceiving and reacting to emotional expressions have been targets of neuroimaging research for more than a decade (Adolphs, 2002; Haxby *et al.*, 2002), and patterns of structural and functional development in the regions comprising these networks (e.g. amygdala, prefrontal and extrastriate visual cortex) are garnering increasing scientific attention. Yet the relationships between pubertal and neural development have rarely been assessed directly in human adolescents (for exceptions see Silk *et al.*, 2009; Blakemore *et al.*, 2010; Forbes *et al.*, 2010, 2011).

Much of what *is* known about physiological changes in the brain during the transition from childhood to adulthood comes from research in animal populations, because adolescent behavior and neural function can be conserved across mammalian species (e.g. with respect to risk-taking; Sisk and Foster, 2004; Spear, 2004). Such homology is convenient to the extent that it allows for an enhanced degree of precision in generating hypotheses about pubertal contributions to

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Correspondence should be addressed to Jennifer H. Pfeifer, Department of Psychology, 1227 University of Oregon, Eugene, OR 97403-1227, USA. E-mail: jpfeifer@uoregon.edu

development. Approaches informed by empirical findings at the cellular and molecular levels are particularly relevant to the study of adolescence because they provide an appropriate analytic framework from which to consider the organizational and activational effects of hormones on the brain. For example, sex steroid hormones associated with typical development have been causally linked to changes in the hippocampus for social memory (Hebbard *et al.*, 2003) and reorganization of the visual cortex (Spear, 2009).

Although translational inference cannot speak directly to the role of hormones in human neural development, such findings can inform neuroimaging investigations in the selection and construction of homologous anatomical regions of interest (ROIs), for instance based on the distribution of endocrine receptors in the brains of other species (Goldstein *et al.*, 2001). Two such regions that have received considerable attention in developmental research are the prefrontal cortex (PFC) and the amygdala (Romeo, 2003; Sanz *et al.*, 2008; Schulz *et al.*, 2009). As it has been hypothesized that one of the principle consequences of pubertal increases in hormone levels is to reorganize motivational tendencies, specifically with respect to social targets (Forbes and Dahl, 2010), it seems likely that the PFC and amygala might be critical targets of the endocrine system during the transition to adolescence in humans as well. It is important to note, however, that the extension of conclusions derived from animal models to human adolescents must be undertaken with great care, as there are important differences between humans and other animals at levels of analysis ranging from the molecular (e.g. discrepancies in genetic makeup and expression) to the psychosocial (e.g. media influences on social behavior). Fortunately, advances in neuroimaging technology can help to bridge the gap between research in animal models and investigations of the living human brain.

Human neural development has been studied with both structural and functional magnetic resonance imaging (sMRI, fMRI) for years, but the literature is still relatively limited in scope. Here we briefly summarize known developmental trajectories that are relevant to the core network for processing affective facial displays, which includes both cortical (fusiform gyrus, superior temporal gyrus, post-central gyrus, temporal pole, anterior cingulate gyrus, insula, orbitofrontal cortex, PFC) and subcortical (brainstem, superior colliculus, lateral geniculate and pulvinar nuclei of the thalamus, hypothalamus, corpus striatum, amygdala, hippocampus) regions (Adolphs, 2002). Although total cerebral volume is nearly fully realized by the age of six, the proportions of different tissue types and relative size and composition of various anatomical structures undergo considerable change during the transition from childhood to adulthood (Lenroot and Giedd, 2010). White matter (WM) increases in a linear fashion throughout adolescence, and such increases imply enhanced connectivity between spatially remote areas of the cortex as well as between cortical and subcortical regions. The development of WM is most protracted in the PFC, a region which is crucial not only to response inhibition, planning and executive control (Behrens *et al.*, 2009), but also in computing the value of affective stimuli and determining appropriate behavior in social contexts (Sowell *et al.*, 2002; Rushworth *et al.*, 2007). Gray matter (GM), on the other hand, follows an inverted U-shaped developmental trajectory, with the inflection point occurring earliest in primary sensory cortex and latest in higher-order association cortices like lateral PFC and temporal pole (Giedd and Rapoport, 2010). Situated directly adjacent to the amygdala and orbitofrontal cortex, the temporal pole has been regarded as association cortex for affective perception, integrating sensory information about complex stimuli (e.g. facial expressions) with limbic signals indexing motivational salience and emotional content (Olson *et al.*, 2007). Along with PFC, GM reduction begins latest in the temporal poles, which are not fully mature until well into adulthood (Gogtay *et al.*, 2004).

This U-shaped developmental trajectory is common to a number of anatomical structures, but the exact point in time at which GM volume 'peaks' varies both across neural structures and across individuals (Lenroot and Giedd 2010). For example, the ventral striatum (vS) achieves maximal GM density during late childhood or early adolescence and subsequently undergoes a linear course of volumetric reduction (Sowell *et al.*, 2002). Central components of the limbic system like the amygdala and hippocampus exhibit slight increases in GM density into adulthood, but the rate of change plateaus in early adolescence, suggesting that the vast majority of their macroscopic development is complete shortly after a period of rapid expansion in late childhood (Ostby *et al.*, 2009).

In terms of neural function, there appears to be a similar U-shaped developmental trajectory of amygdalar response to emotional expressions, in which adolescents exhibit stronger amygdala reactivity upon perceiving emotional expressions than either children or adults (Guyer *et al.*, 2008). This has been explained in terms of a temporal mismatch: the subcortical structures are said to reach adult-like levels of functioning during early adolescence, while the relatively immature PFC has yet to achieve the ability to optimally regulate appetitive or aversive emotional signals (Casey *et al.*, 2010; Somerville *et al.*, 2010). For example, early reports posited that immature reward-value computation in the striatum was responsible for increases in adolescent risk-taking (Galvan *et al.*, 2006; Steinberg, 2008).

Recent longitudinal work has also demonstrated that striatal reactivity to emotional displays increases during the transition to adolescence, such that children exhibited increases in vS response from age 10 to 13 (as well as in vmPFC and temporal pole; Pfeifer *et al.*, 2011). Critically, this increase in vS activity was negatively correlated with susceptibility to peer influence and risky behavior, suggesting that the role of the vS in governing behavior is perhaps more complex than simply promoting impulsive approach motivation.

There was also a longitudinal increase in negative coupling between vS and amygdala while viewing happy and sad facial expressions, relative to neutral ones. However, these findings did not address the influence of puberty on the development of adolescent neural functioning, in vS or elsewhere.

Therefore, an important next step is to simultaneously consider the coordinated activity of neural and endocrine systems in determining behavioral, emotional and psychosocial outcomes for teens (Dahl, 2011). The current investigation sought to address the influence of pubertal development on the neural correlates of affective processing during the transition to adolescence, rather than using age as a proxy for puberty. The ages of 10 and 13 are particularly relevant for addressing such questions, as they allow investigation of late childhood, when relatively few children have experienced significant pubertal development, and early adolescence, when most children have already progressed through the first several stages of puberty (Shirtcliff *et al.*, 2009). Furthermore, these ages represent important developmental epochs from a socioemotional perspective, including the end of elementary school and the end of middle school, respectively. Because data were collected during a tightly constrained window of chronological age during both late childhood and early adolescence, this sample provides a unique opportunity to study pubertal development in a continuous manner within a single timepoint, as well as to consider whether puberty exerts distinct effects in late childhood and early adolescence on the neural correlates of emotion reactivity. Our primary regions of interest, derived from the above literature review, included amygdala, PFC (both medial and lateral aspects), vS and temporal pole.

METHODS

Participants

Typically developing children ($N = 45$, 26 girls) completed data collection at two visits (separated by 36 ± 10 months), and provided high-quality fMRI and behavioral data at both timepoints (M's = 10.1 and 13.1 years, SDs = 0.30 and 0.31 years, at T1 and T2, respectively). Participants and their parents provided written informed assent/consent according to guidelines specified by the Institutional Review Board at UCLA. Participants had no history of significant medical, psychiatric, or neurological disorders.

The Pubertal Development Scale (PDS; Petersen *et al.*, 1988) was completed by participants at both timepoints. On this measure, participants self-report visible development of secondary sexual characteristics. The PDS was always administered with a researcher nearby to answer any questions participants had about the meaning of items. Parents were notified several days in advance of the session that a form assessing pubertal development would be part of the assessment, which gave parents the opportunity to talk with their children about this topic in advance if they so desired. We utilized the scoring guidelines provided by Crockett and colleagues (Petersen *et al.*, 1988), and we omitted the social comparison question (about development relative to the pace of peers). Across all participants, Cronbach's test indicated that the PDS was reliable (five items, $\alpha = 0.80$). There was a highly significant increase from T1 to T2 on the PDS (M's = 1.60 and 2.60, SDs = 0.37 and 0.62 at T1 and T2, respectively; $t(1,44) = 11.36$, $P \sim 0$). At T1, there was no relationship between chronological age and pubertal development [$r(43) = 0.11$, $P = 0.47$]. However, at T2, PDS scores and chronological age were moderately correlated [$r(43) = 0.34$, $P < 0.05$]. See Figure 1 for visualization of raw PDS data at both timepoints. Because there was no significant difference in mean PDS scores for male and female subjects at T1 [$t(1,43) = 0.25$, $P = 0.8$] or T2 [$t(1,43) = 1.55$, $P = 0.13$], fMRI analyses collapsed across gender to increase statistical power.

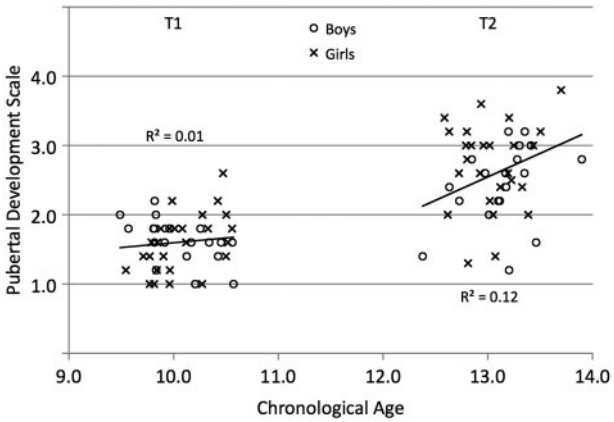

Fig. 1 Correlations between pubertal development and chronological age. Figure 1 depicts the relationship between pubertal development and chronological age at T1 [$r(43) = 0.11$, $P = 0.47$] and at T2 [$r(43) = 0.34$, $P < 0.05$].

Paradigm

During the fMRI scan, participants passively observed full-color, whole-face emotional displays (angry, fearful, happy, sad and neutral) from the NimStim set (Tottenham *et al.*, 2009). Events lasted 2 s, with an interstimulus interval of variable (jittered) length ranging from 0.5 to 1.5 s ($M = 1$ s), and were presented in counterbalanced orders optimized for efficient detection of contrasts between emotions using a genetic algorithm (Wager and Nichols, 2003). A total of 96 whole-brain volumes were acquired on a Siemens Allegra 3.0 Tesla MRI scanner at each time point, including the 80 stimuli described above and an additional 16 null events (fixation crosses at eye-level).

fMRI acquisition and analysis

Data were acquired using a Siemens Allegra 3.0 Tesla MRI scanner. A 2D spin-echo scout (TR = 4000 ms, TE = 40 ms, matrix size 256 by 256, 4-mm thick, 1-mm gap) was acquired in the sagittal plane to allow prescription of the slices to be obtained in the remaining scans.

The scan lasted 4 min and 54 s (gradient-echo, TR = 3000 ms, TE = 25 ms, flip angle = 90°, matrix size 64 by 64, FOV = 20 cm, 36 slices, 3.125-mm in-plane resolution, 3-mm thick). For each participant, a high-resolution structural T2-weighted echo-planar imaging volume (spin-echo, TR = 5000 ms, TE = 33 ms, matrix size 128 by 128, FOV = 20 cm, 36 slices, 1.56-mm in-plane resolution, 3-mm thick) was also acquired coplanar with the functional scan. Stimuli were presented to participants through high-resolution magnet-compatible goggles (Resonance Technology, Inc.).

Using Automated Image Registration (Woods *et al.*, 1999) implemented in the LONI Pipeline Processing Environment (http://www.pipeline.loni.ucla.edu; Rex *et al.*, 2003), all functional images were (i) realigned to correct for head motion and co-registered to their respective high-resolution structural images using a six-parameter rigid body transformation model, (ii) spatially normalized into a Talairach-compatible MR atlas using polynomial non-linear warping and (iii) smoothed using a 6-mm FWHM isotropic Gaussian kernel. No participant averaged >2.0 mm of motion at either time point (*M*'s = 0.317 and 0.413 mm, SDs = 0.262 and 0.365, at T1 and T2, respectively), and no participant moved >2.0 mm between any image. All coordinates are reported in Talairach space.

Statistical analyses were implemented in SPM8 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). For each subject, condition effects were estimated according to the general linear model, using a canonical hemodynamic response function, high-pass filtering (128 s), AR(1) and no global scaling. At the fixed effects (single subject) level, linear contrasts were constructed to assess comparisons of interest within individual participants at each timepoint (each of the expressions *vs* null events as well as the average of all expressions *vs* null events). In other words, activity for each emotional expression was contrasted against a resting baseline rather than a low-level control. Because neutral facial expressions are socially meaningful and often elicit considerable activity in regions associated with processing affective salience and uncertainty, results comparing emotional expressions to neutral ones may be difficult to interpret (Kober *et al.*, 2008; Pfeifer *et al.*, 2011). An ideal control is one that possesses the visual complexity of facial expressions with no social or affective content (e.g. scrambled faces; Rahko *et al.*, 2010). Unfortunately, scrambled faces were not included in this paradigm at the outset of the longitudinal investigation. However, comparisons between each facial expression and null events allowed us to identify where neural responses to affective displays were more or less associated with pubertal development (a continuous predictor) across subjects, independent of mean levels of activity. Furthermore, in the group level analyses we could then contrast any of the five facial expressions versus rest, as well as the four emotional expressions versus neutral.

At the group level, we used two complementary analysis strategies. First, in order to specifically examine the effects of puberty on reactivity to all affective displays as well as specific facial expressions at T1 and T2, separate random effects analyses were based on the contrast images from each expression, using each participant's PDS score as the sole predictor. Second, a repeated measures mixed design was employed in order to quantify longitudinal change in neural activity to facial expressions that was associated with pubertal development. In order to assess the influence of puberty independently from that of chronological age, linear regression was conducted to obtain unstandardized residual values of pubertal development, indexing variability in PDS scores that could not be explained by age (in other words, age was used as a covariate in the regression computed to obtain the residualized PDS scores). Including the residualized PDS scores as regressors in this design, with time and emotion as factors, replicated previous reports of longitudinal increases in vS activity for all expressions compared to rest (see Pfeifer *et al.*, 2011, Table 1), despite slight changes in the sample to achieve greater gender balance (increasing proportion of boys and decreasing proportion of girls). Correlations between the BOLD signal elicited by the task and behavioral measures of social, affective and interpersonal functioning used in prior studies conducted on overlapping subsets of participants (Interpersonal Reactivity Index, Davis, 1983; Interpersonal Competence Scale, Cairns *et al.*, 1996; Resistance to Peer Influence, Steinberg and Monahan, 2007; and Indicators of Risk Behavior and Delinquency, Gestsdóttir and Lerner, 2007) did not reveal any significant relationships beyond those reported previously (Pfeifer *et al.*, 2008, 2011). For all whole-brain analyses, results were reported at an alpha threshold of $p < 0.05$ for magnitude at peak voxels, corrected for multiple comparisons using False Discovery Rate (Genovese *et al.*, 2002), and an additional extent threshold of $p < 0.05$ at the cluster level, derived using a Monte Carlo simulation (3dClustSim, the successor to AlphaSim in the AFNI software package; Cox, 1996).

RESULTS

Based on the suite of regression analyses, positive correlations with pubertal development at age 10 were constrained to extrastriate cortex, thalamus and amygdala, while by age 13, level of pubertal development was further correlated with increased activity in the left temporal pole, ventrolateral PFC and ventromedial PFC for the combination of all affective facial displays (see Figure 2; for comprehensive reports of additional activity correlated with pubertal development at each timepoint, see Tables 1 and 2).

Similar patterns were observed when each expression was queried individually, although there were some notable differences. At age 10, pubertal development was correlated with greater activity in extrastriate cortex and thalamus in response to angry, fearful, happy and neutral facial

Table 1 Positive correlations between pubertal development and neural response to affective facial displays at Time 1

Time 1	Region		*k*	*t*	*r*	*x*	*y*	*z*
All expressions	Extrastriate cortex	BA 18	7011	10.26	0.71	2	−84	2
	Extrastriate cortex	BA 18		9.26	0.66	−14	−94	12
	Thalamus		116	6.29	0.47	18	−32	4
	Thalamus			5.50	0.41	−22	−32	2
	Amygdala		108	4.59	0.32	−22	−12	−12
Anger	Extrastriate cortex	BA 18	4160	6.80	0.51	−20	−80	−8
Fear	Extrastriate cortex	BA 18	6513	11.12	0.74	0	−80	4
	Thalamus		160	5.98	0.45	18	−30	4
	Thalamus		117	5.24	0.38	−20	−32	2
Happy	Extrastriate cortex	BA 18	6302	10.98	0.86	6	−90	12
	Extrastriate cortex	BA 18		10.94	0.86	−18	−76	−6
	Thalamus		99	5.61	0.65	16	−32	4
	Thalamus		146	5.57	0.64	−24	−32	2
Sad	Striate cortex	BA 17	6052	12.81	0.89	8	−88	2
Neutral	Extrastriate cortex	BA 18	6057	11.07	0.86	−14	−94	12
	Extrastriate cortex	BA 18		9.89	0.83	4	−92	16
	Thalamus		107	6.06	0.67	18	−30	4
	Amygdala		113	3.61	0.48	26	−4	−12

Table 1 describes neural responses that are significantly correlated with pubertal development at T1. *k* corresponds to the spatial extent of significant clusters (2 mm^3 voxels). *t* represents the *t*-statistic at the peak voxel. *r* indexes the correlation between PDS score and activity at the peak voxel. *x*, *y* and *z* refer to the Talairach coordinates corresponding to the left-right, anterior-posterior and inferior-superior axes, respectively. All activity is reported at a peak threshold of $P < 0.05$ (FDR corrected) and a cluster threshold of $P < 0.05$.

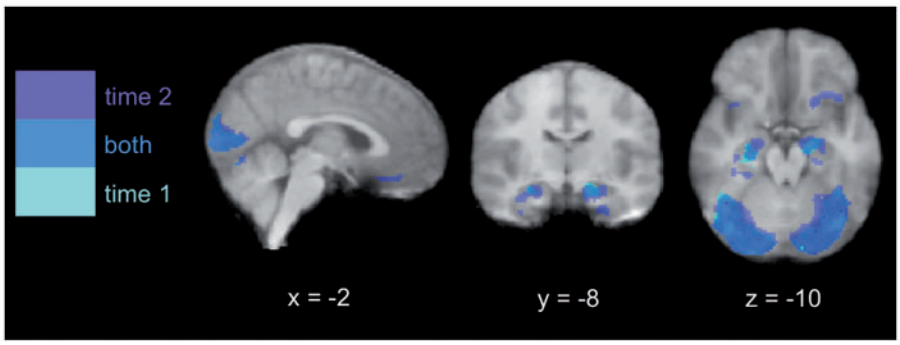

Fig. 2 Correlations between neural activity and pubertal development. Figure 2 depicts activity in extrastriate cortex, amygdala, and hippocampus that correlates with pubertal development at T1 and T2. x, y and z refer to the Talairach coordinates corresponding to the left-right, anterior-posterior and inferior-superior axes, respectively. All activity is displayed at a peak threshold of $P < .05$ (FDR corrected) and a cluster threshold of $P < 0.05$.

expressions. This pattern was even more robust at age 13, and also included the neural response to sad expressions. At 10 years of age, activation in the amygdala was only modulated by pubertal development while viewing neutral facial expressions. However, at age 13, level of pubertal development was associated with significantly greater activation in the amygdala for all five expressions examined, although whether the response was lateralized to the left or right hemispheres, or bilateral, varied by emotion. Furthermore, at age 10 there were no correlations in the temporal pole between pubertal development and neural response to affective facial displays, but by age 13 pubertal development was significantly linked to enhanced activity in temporal pole for happy, sad, fearful and neutral expressions. Positive correlations between pubertal development and ventrolateral PFC response for fearful, neutral and happy expressions were also evident at age 13 but not age 10. Finally, this pattern was replicated in dorsomedial PFC responses, but only for happy facial expressions.

Although there were no statistically significant differences in PDS scores between male and female participants, confirmatory fMRI analyses were carried out to ensure that gender was not a confound. Direct statistical comparisons including gender as a factor revealed no significant differences in the relationship between pubertal development and neural response to facial expressions. However, conducting separate linear regression analyses by gender revealed slight differences in cluster sizes, stereotactic locations and *t*-values. For example, for the average of all expressions compared to rest at T2, activity in ventrolateral PFC was bilateral for girls,

Table 2 Positive correlations between pubertal development and neural response to affective facial displays at Time 2

Time 2	Region		*k*	*t*	*r*	*x*	*y*	*z*
All expressions	Extrastriate cortex	BA 18	9713	10.62	0.72	8	−82	−2
	Fusiform gyrus	BA 37		9.52	0.67	36	−48	−14
	Thalamus			6.72	0.51	−24	−30	2
	Thalamus			6.38	0.48	18	−30	4
	Amygdala		691	4.82	0.35	−24	−12	−12
	Amygdala	BA 28	667	4.70	0.33	14	−4	−12
	Temporal pole	BA 38		4.37	0.30	−38	14	−22
	vlPFC	BA 47	119	3.93	0.26	−40	20	−12
	vlPFC	BA 47	94	3.84	0.25	28	28	−12
	vmPFC	BA 11		4.25	0.29	20	24	−10
Anger	Extrastriate cortex	BA 18	7821	10.53	0.72	8	−82	0
	Cuneus	BA 17		9.89	0.69	−14	−90	4
	Thalamus		121	6.24	0.47	−24	−32	2
	Thalamus		137	5.64	0.42	18	−30	4
	Amygdala		117	5.41	0.40	16	−6	−10
Fear	Extrastriate cortex	BA 18	8830	10.65	0.72	8	−80	0
	Extrastriate cortex	BA 18	241	10.48	0.71	−10	−80	0
	Thalamus		313	5.38	0.40	20	−28	2
	Amygdala		69	3.72	0.24	24	−4	−14
	Amygdala		416	4.40	0.31	−24	−2	−12
	Fusiform gyrus	BA 20		4.39	0.30	−38	−12	−22
	Temporal pole	BA 38		4.55	0.32	−36	14	−22
	vlPFC	BA 47	53	3.94	0.26	−40	22	−12
	vlPFC	BA 47	47	3.68	0.24	40	28	−8
Happy	Extrastriate cortex	BA 18	9062	10.39	0.84	8	−78	−2
	Thalamus		244	5.49	0.64	18	−30	2
	Thalamus		134	4.41	0.55	−22	−30	0
	Temporal pole	BA 38	140	5.45	0.63	−40	16	−24
	Temporal pole	BA 38	402	4.69	0.58	32	10	−30
	Amygdala			4.30	0.54	26	−6	−14
	Amygdala		203	4.77	0.58	−20	−8	−14
	dmPFC	BA 10	104	3.74	0.49	4	56	18
	vlPFC	BA 47		3.85	0.50	−40	20	−12
Sad	Extrastriate cortex	BA 18	9748	12.41	0.88	6	−80	0
	Thalamus		262	5.85	0.66	−24	−30	0
	Thalamus		802	6.98	0.72	24	−32	4
	Temporal pole	BA 38		5.56	0.64	30	12	−30
	Temporal pole	BA 38	76	4.31	0.54	−40	16	−20
	Amygdala		198	4.01	0.52	−24	−10	−10
	Amygdala			3.67	0.48	−32	−8	−14
Neutral	Extrastriate cortex	BA 18	9252	11.70	0.87	6	−82	0
	Striate cortex	BA 17		10.32	0.84	−20	−90	4
	Thalamus		260	5.33	0.63	−26	−30	0
	Thalamus		118	4.45	0.56	20	−30	2
	Temporal pole	BA 38	119	4.83	0.59	−38	14	−24
	vlPFC	BA 47		3.99	0.52	−42	20	−14
	Hippocampus		132	4.11	0.53	−24	−14	−12
	Amygdala			4.07	0.52	−28	−6	−16
	Amygdala		94	3.26	0.44	26	−8	−12

Table 2 describes neural responses that are significantly correlated with pubertal development at T2. *k* corresponds to the spatial extent of significant clusters (2 mm^3 voxels). *t* represents the *t*-statistic at the peak voxel. *r* indexes the correlation between PDS score and activity at the peak voxel. *x*, *y* and *z* refer to the Talairach coordinates corresponding to the left-right, anterior-posterior, and inferior-superior axes, respectively. All activity is reported at a peak threshold of $P < 0.05$ (FDR corrected) and a cluster threshold of $P < 0.05$.

but left lateralized for boys. Such minor differences may have resulted from slight variability between groups in sample size.

Looking to the repeated measures mixed design, no significant relationship between pubertal development (independent of age) and BOLD response to emotional expressions versus neutral ones was apparent at T1. However, at T2 pubertal development (independent of age) was correlated with activity in visual cortex, right amygdala, bilateral hippocampus and temporal pole. These patterns, identified by querying each timepoint individually,

were statistically different from each other: the positive correlations between pubertal development (independent of age) in visual cortex ([−14, −94, 12], $t = 9.81$), bilateral hippocampus (left: [−24, −32, 4], $t = 4.22$, right: [20, −30, 4], $t = 5.37$), bilateral amygdala (left: [−24, −12, −12], $t = 3.22$, right: [18, −6, −10], $t = 4.47$) and bilateral temporal pole (left: [−42, 16, −12], $t = 3.55$, right: [32, −8, 26], $t = 3.61$) were significantly greater at T2 than T1, as demonstrated by direct comparison of the two timepoints within a repeated measures mixed design. These results imply an interaction between time and pubertal development, insofar as the effects of pubertal development are significantly different between the two waves of data collection. It should be reiterated that this statistical approach used residualized PDS values in order to examine the unique effect of pubertal development, independent from that of age.

DISCUSSION

These results provide evidence of changing relations between pubertal development and neural responses to affective facial displays across the transition from late childhood to early adolescence. Recent longitudinal work focusing on this specific period (Pfeifer *et al.*, 2011) demonstrated age-related increases in a number of key regions of interest, particularly the vS. Here, a different subset of regions exhibited longitudinal increases with respect to pubertal development, including the amygdala and lateral PFC. This is consistent with the idea that puberty per se, and not just age, is associated with enhanced reactivity to socioemotional stimuli, as would be expected in the 'social reorientation of adolescence' (Nelson *et al.*, 2005). Here, neural activity in the amygdala, hippocampus and temporal pole elicited by the affective content of facial displays was significantly correlated with an age-independent measure of pubertal development by age 13, accompanied by significant longitudinal increases in the strength of this coupling.

Our prior longitudinal fMRI study (Pfeifer *et al.*, 2011) observed that, unlike vS reactivity to emotional expressions, the amygdala does not exhibit a significantly greater response at age 13 than at age 10 (except to sad faces). However, we now show that pubertal development enhances amygdala responses to emotions in late childhood, and this link appears to strengthen in early adolescence such that the two are correlated across all expressions individually at this time (happy, neutral, sad, fearful and angry). Activity in the thalamus and extrastriate cortex, structures that work in tandem with the amygdala to process the affective salience of social signals (Adolphs, 2008), shows a similar pattern (although visual cortical regions also exhibit increase over time in the absence of pubertal predictors). These data begin to elucidate the neural foundations of how puberty may 'reorient' adolescents toward social stimuli, such that complex communicative signals like emotional facial expressions begin to take increased relevance as children transition into their teenage years.

Recent findings on social threat and pubertal development have indicated that activity in amygdala and ventrolateral PFC while viewing fearful or neutral faces is stronger during early stages of pubertal development than later stages (Forbes *et al.*, 2011), suggesting that a reduction in threat-related response may be adaptive for adolescents insofar as promoting social approach. The opposite patterns elucidated in the present study may be attributable to differences in fMRI data analysis (e.g. whole brain regression as opposed to ROI analysis), or differences in manner of calculating pubertal development using the PDS. These differences may also be due to the fact that our design employed both longitudinal and cross sectional approaches, or the fact that we also used non-threatening facial expressions such as happiness and sadness.

We discerned another interesting pattern in the responses of several regions that are not significantly related to puberty at age 10, but tightly linked to it at age 13, including the medial PFC, lateral PFC and temporal pole. By early adolescence, the neural response to emotional expressions in these regions is positively correlated with pubertal development. This suggests puberty may affect frontal and temporal association cortices in a way that allows for increasingly mature integration of perceptual and affective information. These higher order cortical areas will continue to develop well into adulthood, and while their functional profile differs for adolescents (Casey *et al.*, 2005; Burnett and Blakemore, 2009; Pfeifer *et al.*, 2009), it is difficult to draw clear boundaries for what constitutes 'mature activity' in any isolated region (Poldrack, 2010). Because adult brain activity is the product of a large number of regions and systems working in concert, the 'maturity' of a functional neural response cannot be fully assessed independently from that of other regions. Thus it may be helpful to frame adolescent neural development in terms of network-wide changes including not only higher-order association cortices, but also their interactions with subcortical regions of interest.

Our findings also demonstrate that different anatomical structures have different developmental profiles. For example, the relationship between puberty and change in amygdala activity appears relatively continuous, as it correlates with pubertal development at both timepoints. The transition from late childhood to early adolescence, however, cannot be explained purely in linear terms. Several important discrete events are also likely to take place within this age range, such as entry into middle school, the start of early romantic relationships, and a shift in self-concept from regarding oneself as a child to internally adopting the mantle of teenager (Pfeifer *et al.*, 2009). However, the relationship between pubertal development and activity in ventrolateral PFC, medial PFC and temporal pole is likely driven by both developmental stage and puberty. The relationship between puberty and responses to emotional stimuli in temporal pole (longitudinal increases which also correlated with increases in resistance to peer influence;

Pfeifer *et al.*, 2011) in particular speaks to a pattern by which the successful integration of perceptual input from complex social stimuli is gradually incorporated with online emotional processing and inhibitory control. This process is more complex than a simple dichotomy between the roles of subcortical and cortical structures is suited to explain, especially in light of the neural consequences of puberty.

While this work is an important step toward studying adolescence in a more comprehensive manner, it is only a preliminary one. Relationships established in the current work between pubertal development and changes in neural activity of key regions like the amygdala and temporal pole may help lay the foundation for more comprehensive study of the way that the adolescent endocrine system influences the roles of these and other structures in perceiving and experiencing emotion. An ideal advancement would be to simultaneously investigate pubertal changes at multiple levels of analysis (Cacioppo and Berntson, 1992), such as by measuring hormones and administering physical exams in addition to self-report measures and neuroimaging techniques. Also much needed in the field of adolescent neuroscience is the application of methods that allow for data driven, model testing approaches, which will allow investigators to more robustly account for the large number of variables at work. As our understanding of the biological mechanisms underlying adolescent emotion processing grows, we will be better equipped to address the mental health problems, risk-taking behavior and profound social changes that often accompany this developmental epoch. By mapping out the dynamic systems involved in the transition from childhood through adolescence to adulthood, we will be able to better understand how social context, pubertal hormones and neural function simultaneously affect adolescent motivational tendencies and emotional experiences, bringing us closer to unlocking the mysteries of the teenage brain.

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