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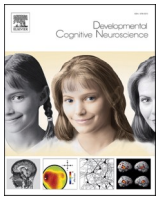

Exogenous testosterone administration is associated with differential neural response to unfamiliar peer's and own caregiver's voice in transgender adolescents

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ABSTRACT

Changes in gonadal hormones during puberty are thought to potentiate adolescents' social re-orientation away from caregivers and towards peers. This study investigated the effect of testosterone on neural processing of emotional (vocal) stimuli by unfamiliar peers vs. parents, in transgender boys receiving exogenous testosterone as a gender-affirming hormone (GAH+) or not (GAH-). During fMRI, youth heard angry and happy vocal expressions spoken by their caregiver and an unfamiliar teenager. Youth also self-reported on closeness with friends and parents. Whole-brain analyses (controlling for age) revealed that GAH+ youth showed blunted neural response to caregivers' angry voices—and heightened response to unfamiliar teenage angry voices—in the anterior cingulate cortex. This pattern was reversed in GAH- youth, who also showed greater response to happy unfamiliar teenager vs. happy caregiver voices in this region. Blunted ACC response to angry caregiver voices—a pattern characteristic of GAH+ youth—was associated with greater relative closeness with friends over parents, which could index more "advanced" social re-orientation. Consistent with models of adolescent neurodevelopment, increases in testosterone during adolescence may shift the valuation of caregiver vs. peer emotional cues in a brain region associated with processing affective information.

1. Introduction

Across the teenage years, youth spend less time with their caregivers and are more motivated to interact with peers (Forbes and Dahl, 2010; Larson et al., 1996; Steinberg and Morris, 2001), a phenomenon referred to as social re-orientation (Nelson et al., 2016, 2005). This process is a critical developmental step towards integrating with peer groups and forming stable social networks outside of the family. These changes in social behaviour are accompanied by shifts in the motivational salience of social information at this age (Spear, 2000; Steinberg and Morris, 2001), whereby cues from peers (e.g., emotional expressions, signs of acceptance or rejection) provoke heightened neural and emotional responses in adolescents (Blakemore and Mills, 2014; Casey, Jones, et al., 2010; Crone and Dahl, 2012; Guyer et al., 2009; Somerville, 2013). Differential neural responses to peer stimuli are particularly evident in brain regions associated with emotional processing, such as the ventral

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striatum, amygdala, and prefrontal cortex (Galvan, 2010; Guyer et al., 2008; Hare et al., 2008; Somerville et al., 2010). The large-scale changes in social affiliative behaviour that occur during adolescence are thus hypothesized to be at least partially mediated by altered responses to different types of social stimuli in emotion- and salience-related brain regions (Nelson et al., 2016).

This adolescent-emergent phenomenon (which can vary in its timing across chronological age) is thought to be related to increases in gonadal hormones at puberty (Peper and Dahl, 2013; Silk et al., 2014; Sisk and Zehr, 2005; Steinberg, 2008; Vijayakumar et al., 2018). Gonadal hormones sensitize subcortical regions to salient emotional information (Blakemore et al., 2010; Nelson et al., 2005). For instance, more advanced (self-reported or physician-assessed) pubertal stage and higher testosterone levels have been linked to heightened response to emotional faces in the amygdala and hippocampus (with less known about the effect of estradiol on face processing; Dai and Scherf, 2019; Moore et al., 2012; Vijayakumar et al., 2019). Pubertal maturation is also thought to fine-tune the organization and function of broader networks involved in complex social behaviour (Blakemore et al., 2010; Sisk and Zehr, 2005), such as the "social brain" or mentalizing network. Engagement of these systems—including regions like the anterior medial prefrontal cortex (PFC), dorsolateral prefrontal cortex (dlPFC), and temporo-parietal junction (TPJ)—during social cognitive tasks varies as a function of pubertal status for both girls and boys (see reviews by Crone and Dahl, 2012; Dai and Scherf, 2019; Goddings et al., 2019; Peper and Dahl, 2013). However, much of the available research to date has inferred the effect of pubertal hormones by correlating endogenous hormone levels with neural responses to emotional stimuli. The current study extends this work by examining how changes in testosterone, in particular, may impact teenagers' neural response to socio-affective stimuli from peers and caregivers, in transgender boys who were either receiving gender-affirming exogenous testosterone or not.

1.1. Salience of peers vs. caregivers

Changes in pubertal hormones have been associated with enhanced responses to emotional stimuli. However, less is known about whether these hormonal changes impact neural responses to different types of social stimuli, thereby encouraging a *shift* in salience and motivational engagement from caregivers to peers in adolescence (Nelson et al., 2016; Spear, 2000). Although parents remain important sources of support for adolescents (Suleiman and Dahl, 2019; Telzer et al., 2018), their functional role begins to change at this developmental stage. For example, youth's dependency on their parents decreases by early adolescence (Lieberman et al., 1999) and teenagers increasingly seek support and emotional intimacy with their friends over their parents with age (De Goede et al., 2009; Furman and Buhrmester, 1992; Hunter and Youniss, 1982; Rice and Mulkeen, 1995). Caregivers, who provide a buffering effect against stress in childhood, may have a diminished impact on stress response in adolescence (Gee et al., 2014; Hostinar et al., 2015); however, they continue to play an important role in scaffolding teenagers' decision-making, cognitive control, and emotion regulation at both a behavioural and neural level (Guassi Moreira and Telzer, 2018; Rogers et al., 2020; Telzer et al., 2015). Moreover, pubertal maturation has been linked to changes in neural response to caregivers. For example, cisgender boys' neural response to their mother's smiling face in the anterior PFC (measured via EEG) varied with pubertal development: response shifted from the inferior PFC in pre-pubertal boys, to the superior PFC in mid-pubertal boys, to a lack of PFC response to their mother's smile in post-pubertal boys (Takamura et al., 2015).

Conversely, social cues from peers become highly salient during adolescence (Crone and Dahl, 2012; Somerville, 2013). Compared to adults, youth aged 10–12 years showed heightened response in the subgenual anterior cingulate cortex (ACC) to rejection from peers (Gunther Moor et al., 2012). Moreover, neural responses to negative cues from peers vary as a function of puberty. In 11- to 17-year-old youth, those who were more advanced in self-reported pubertal maturation showed greater response in the amygdala, parahippocampal gyrus, and subgenual ACC when rejected by peer-aged confederates, compared to less mature youth (Silk et al., 2014). More advanced pubertal development from age 10–13 was also associated with greater response to witnessing another teenager be rejected in the dorsomedial PFC, precuneus, TPJ, and temporal pole (Masten et al., 2013). Although this has not yet been investigated using neuroimaging methods, sensitivity to negative peer cues could be even higher in transgender youth, since they experience peer rejection and harassment at school at disproportionally high rates (Clark et al., 2014; Johns et al., 2019; McGuire et al., 2010).

Although the above studies have demonstrated changes in neural response to either peers *or* to caregivers during adolescence, few studies have examined within-person responses to peer-aged *vs.* caregiver emotional cues. One such study found that 15- to 18-year-old adolescents showed greater response in the mentalizing network and subcortical regions when viewing videos of unfamiliar teenagers, compared to videos of their parents (Saxbe et al., 2015). However, little is known about the role of pubertal hormones in potential differential processing of these two classes of stimuli. Understanding how testosterone affects the processing of emotional cues from caregivers vs. peers will help specify the mechanisms underlying social re-orientation in adolescence—and thus refine related theories of adolescent neurodevelopment (e.g., the social information processing network model; Nelson et al., 2016, 2005) for both cis- and transgender youth.

1.2. Current study's goals and hypotheses

The current study investigated the effect of testosterone changes on neural processing of emotional cues by peer-aged teens vs. caregivers in a sample of adolescent transgender boys, who were either receiving exogenous testosterone as a gender-affirming hormone (GAH) or not. Specifically, we examined youth's responses to emotional (happy and angry) *voices* produced by their own caregiver and by an unfamiliar teenager. We focused on the processing of emotional voices, given that the ability to recognize emotions in prosody and its accompanying neural correlates is undergoing active maturation that extends throughout adolescence and into adulthood (Morningstar, Ly, et al., 2018; Morningstar, Nelson, et al., 2018), at a more protracted rate than the processing of emotional faces (Morningstar et al., 2020; Zupan, 2015). Recent evidence suggests that neural response to mothers' voices vs. those of unfamiliar adults also shifts with age during adolescence (Abrams et al., 2022). Our hypotheses were guided by the theoretical predictions of the social information processing network model (Nelson et al., 2016, 2005), which posits that gonadal maturation leads to tuning of neural response to developmentally relevant social cues (i.e., peers). Given behavioural shifts towards peers during this developmental stage, this may manifest as enhanced neural response to peers *over* caregivers—although this hypothesis is primarily based on theoretical models rather than direct empirical evidence. We also investigated whether differences in neural processing of such cues related to behavioural indices of social re-orientation, as indexed by self-reported closeness with peers over caregivers.

The receipt of GAH is not a true proxy for advanced pubertal maturation, since youth in the GAH- group are also experiencing changes in gonadal hormones as part of puberty. However, the repeated administration of testosterone may mirror the increases in testosterone levels that are typically noted in mid-adolescence (in both cisgender girls and boys, although the increase is steeper in cisgender boys; Braams et al., 2015). Testosterone in particular has been linked to approach-related behaviours in social contexts (Eisenegger et al., 2011; Peper and Dahl, 2013) and is thought to influence the motivational appraisal of socially relevant threats and rewards (Crone and Dahl, 2012). However, work with teenagers has typically been limited to indirect measures of the effects of testosterone, whereby sex differences in

neural structure or function are inferred to be due to differential exposure to sex steroid hormones during puberty (see Goddings et al., 2019). Research on testosterone's relationship to social behaviour often cannot disentangle the directionality of effects in teenagers: changes in response to socio-emotional stimuli may be facilitated by increases in gonadal hormones and accompanying pubertal maturation, but it is also possible that changes in hormones are potentiated by the experience of novel social stimuli in expanding peer contexts. Research designs involving exogenous doses of testosterone can help establish its functional role, but much of this research has been conducted in adult men and women (e.g., Bos et al., 2013; Goetz et al., 2014; Radke et al., 2015) and does not capture the effect of increasing hormones in the developing brain. The current study assesses these effects in adolescents receiving testosterone as part of gender-affirming care.

Given enhanced sensitivity to emotional information in subcortical structures (e.g., amygdala, hippocampus; Blakemore et al., 2010; Nelson et al., 2005) and regions of the social brain (e.g., medial PFC, dlPFC, TPJ; Goddings et al., 2019) with pubertal maturation, we hypothesized that youth receiving exogenous testosterone would show heightened response to peers over caregivers in these brain regions—but that those not receiving testosterone may not. We also expected that heightened responses to peers over caregivers across GAH groups would be related to behavioural correlates of social re-orientation, such as closeness to peers over parents. Lastly, we expected that response to socio-affective cues may vary as a function of emotional valence (e.g., happy vs. angry prosody), but did not make a priori hypotheses about the directionality of emotion-specific effects.

2. Methods

2.1. Participants

A sample of 44 transgender boys was recruited from a multidisciplinary gender development clinic at an academic pediatric center in the Midwest (U.S.A.). (An additional 9 participants were excluded from analyses due to the receipt of puberty-blocking medication ($n = 4$), diagnosis of Turner's syndrome ($n = 1$), brain resection after a tumor ($n = 1$), unavailability of a caregiver to provide stimuli (see below; $n = 1$), or failure to complete the scan portion of the study ($n = 2$)). Of the final sample, 19 were receiving gender-affirming hormones (GAH+; exogenous testosterone) and 25 were not receiving exogenous hormones (GAH-). No participant had a history of puberty-blocking medication. Doses of testosterone in the GAH+ group ranged from 12.5 to 60 mg/week, with a mode of 25 mg/week. On average, GAH+ youth had been receiving testosterone for 1.1 year (range: 1 month to 2.8 years), with doses starting at age 15.8 years (range: age 13–18). Two-thirds of our sample (63 %) had been receiving GAH for over 6 months, with an additional 16 % receiving testosterone for over 5 months; although this was not assessed in our study, previous research suggests that serum testosterone levels are significantly elevated from baseline after 6 + months of GAH in transgender adolescents (Laurenzano et al., 2021), even for youth who received relatively low initial doses of testosterone (e.g., < 160 mg/month). The GAH+ group was 14–18 years old (M age = 16.21, SD = 1.13); the GAH- group was 12–18 years old (M age = 15.32, SD = 1.49). Given the age difference in groups, $t(42) = 2.17$, $p = .04$, all analyses presented below controlled for age in years.[1] Across groups, 68 % of youth self-reported as White, 5 % as Black or African American, 5 % as Hispanic or Latino, 2 % as Native American or American Indian, and 16 % reported being bi/multiracial (with 4 % preferring not to self-report on race or ethnicity). GAH groups did not differ in racial/ethnic distribution ($p = .51$). Geolocation IDs derived from participant addresses were cross-referenced to the Area Deprivation Index (Kind and Buckingham, 2018; University of Wisconsin, 2015; missing for 7 participants): GAH+ youth (M national rank = 59.65, SD = 23.04) and GAH- youth (M = 53.55, SD = 19.94) did not differ in national SES rank, $t(35) = -0.86$, $p = .39$. Given the common occurrence of autism spectrum traits among transgender populations (Warrier et al., 2020) and the importance of determining whether differences in autism-related traits might be driving neural differences between the groups, we verified that GAH groups did not differ in autism symptom scores on the Social Responsiveness Scale 2 (SRS-2; Constantino and Gruber, 2012), $p = .18$; as such, SRS-2 scores were not controlled for in analyses.

2.2. Procedure

All procedures were approved by the institutional review board. The tasks presented here are part of a larger study on the receipt of exogenous gonadal hormones during adolescence. Written parental and participant consent/assent was obtained. Participants completed questionnaires prior to the scanner session. Youth were given the option of visiting a mock scanner prior to the task scan.

2.3. Materials

2.3.1. Auditory perception task

While undergoing functional magnetic resonance imaging (fMRI), participants were presented with recordings of vocal expressions of anger and happiness produced by their caregiver and by an unknown teenage speaker (see Section 2.3.1.1). Stimuli were presented through pneumatic earbuds, separated by a jittered intertrial interval of 1–6 s (mean 3.83 s). A fixation cross was presented on screen during the intertrial intervals, visible to participants via a mirror mounted on the head-coil. To promote attention during this passive listening task, participants were asked to press a button when they heard the sound of a bicycle bell (6 per run). Responses were recorded on a handheld Cedrus Lumina button box in the scanner. The task comprised 174 recordings: 39 spoken words x 2 speakers [caregiver and teenager] x 2 emotion types [happy and angry], and 18 instances of the bell. Stimuli were split evenly between 3 runs (pseudorandomly to ensure an equal amount of each stimulus type per run) and presented randomly within each run. Runs (each ≈ 6 min) were presented in random order.

2.3.1.1. Stimuli. Stimuli were created prior to the scanning session. Recordings of the unfamiliar teenager were used as the peer voice for all participants, whereas caregiver recordings were individualized to each participant. The recordings of caregivers were produced by the participant's parental figure while participants completed questionnaires in another room. The majority of recordings were completed by participants' mothers (n = 34); 3 were produced by step-mothers, 2 by grandmothers, and 5 by fathers. GAH groups did not differ in the identity of the caregiver who provided recordings, χ^2 (2, $N = 44$) = 3.12, $p = .21$. The unfamiliar teenager recordings were produced by a 16-year-old cisgender girl.[2] All speakers produced 39 words of either positive, negative, or neutral valence (e.g., "stop", "great", "here"; see Appendix for list and Supplemental materials for additional information about the valence and arousal of the selected words) in both angry and happy tones of voice. (Neutral versions of these words were also recorded for

[1] Tanner staging at the time of scanning was not consistently available for youth in the current study. All but 1 participant (who was in the GAH- group) had experienced the onset of menarche prior to the study (average age of menarche = 11.5 years; no difference between GAH groups in age of onset, $p = .33$; data missing for 3 participants), suggesting that most participants were in later stages of endogenous pubertal maturation.

[2] We anticipated that most caregivers would likely identify as women based on typical parent participation rates in research; we thus opted to include only a female-presenting voice for the 'peer' condition to reduce variability that may have been induced by speaker gender.

speech analysis, but were not included in the auditory perception task.) Recordings were edited in Audacity (Audacity Team, 2017) to reduce background noise and echo, and inserted into an E-Prime protocol for use in the scanner. Ratings by 5 independent judges suggest that the resulting recordings were well-recognized as the intended valence: happy recordings were recognized with 87.7 % accuracy, and angry recordings with 87.8 % accuracy (no difference in accuracy between emotion types, $p = .89$, or between GAH groups, $p = .30$). Speech analysis also confirmed that the happy and angry recordings reflected expected patterns of acoustic cues for each type of emotion (see Supplemental materials).

2.3.2. NRI questionnaire

Participants completed a modified version of the Network of Relationships Inventory—Relationship Qualities (NRI) questionnaire (Furman and Buhrmester, 2009). The NRI comprises 30 questions about the features of different relationships, on a 5-point scale (from "never or hardly at all" to "always or extremely"). Although the original measure asks about same- and opposite-sex friends/parents, we collapsed across these categories to assess participants' relationship with 4 people: their best friend, their boy/girlfriend, a sibling, and a parent (without specifying the target's sex). For their parent, youth were instructed to report about the caregiver they think of as their primary parental figure. Youth reported about their biological/adoptive mother ($n = 30$), step-mother/parent's significant other ($n = 2$), their biological/adoptive father ($n = 8$), or a grand-parent ($n = 2$); 2 participants did not complete the NRI. For their best friend, youth reported about relationships ranging in length from a few weeks to 16 years (with average length of friendship = 3.6 years). GAH groups did not differ in the length of reported friendships, $t(39) = 0.42$, $p = .68$, nor on the type of parental relationships they reported on in the NRI, χ^2 (3, $N = 42$) = 3.07, $p = .38$). As recommended by the NRI manual, scores for the companionship, emotional support, satisfaction, intimate disclosure, and approval subscales were averaged to create a "closeness score" for each relationship (Furman and Buhrmester, 2009). To obtain an index of social re-orientation towards peers over caregivers (as in Morningstar et al., 2019), we computed a 'Relative Closeness' to peers (RC) score by subtracting 'parent' closeness scores (Cronbach's alpha = 0.957) from 'best friend' closeness scores (Cronbach's alpha = 0.939). A higher RC score indicates greater relative closeness to peers over parents.

2.4. Image acquisition and processing

MRI data were acquired on a Siemens 3T Prisma scanner with a 64-channel head coil. The imaging sequence included a T1-weighted anatomical scan of the whole brain (MPRAGE), with 1 mm isotropic pixels, 160 sagittal slices, repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, and field of view (FOV) = 248 × 256 mm. Functional MRI data were acquired with echo planar imaging (EPI) sequences, with 36 slices, a voxel size of 2.55 × 2.55 × 4 mm, TR = 1500 ms, TE = 30 ms, and FOV = 240 × 240 mm.

EPI images were preprocessed and analyzed using AFNI, version 20.3.01 (Cox, 1996). Functional images were slice-timing corrected to the first volume, realigned to the AC/PC line, co-registered to the T1 MPRAGE, and masked for voxels that had valid data at every TR. Resulting images were then non-linearly normalized to the MNI152 template (Fonov et al., 2009) and spatially smoothed with a Gaussian filter (FWHM, 6 mm kernel). Voxel-wise signal was scaled to a mean value of 100 within each run, with a maximum scaled value of 200. Volumes in which at least 10 % of the voxels were signal outliers or contained movement greater than 1 mm between volumes were regressed out as nuisance in subject-level models (2 % of volumes were above this threshold). No participant was removed for excessive motion (mean percentage of censored volumes during stimulus presentation = 0.02 %, ranging from 0 % to 15 %). GAH groups did not differ in the percentage of censored volumes, $t(42) = -0.433$, $p = .67$.

2.5. Analyses

Event-related response amplitudes were estimated at the subject level. We convolved the hemodynamic response function with a base function that included regressors for each type of stimulus (angry caregiver, happy caregiver, angry teenager, happy teenager, and bell) contrasted to the implicit baseline (non-stimuli periods). Nuisance regressors for motion (6 affine directions and their first-order derivatives) and scanner drift (within each run) were also included at the subject level. Individual contrast images were then fit to a group-level multivariate model (3dMVM; Chen et al., 2014) testing the effect of GAH group (between-subjects variable, 2 levels: GAH+, GAH-), Emotion type (within-subjects variable, 2 levels: happy, angry), and Speaker type (within-subjects variable, 2 levels: caregiver, teenager) on neural activation to the vocal stimuli, controlling for age (mean-centered; in years). Within this model, we computed *F*-statistics for effects relating to the between-subjects variable of GAH group: the main effect of GAH group, the interactions of GAH group × Emotion and of GAH group × Speaker, and the 3-way interaction of GAH group × Emotion × Speaker.[3] The standard false discovery rate correction factor was employed by combining a cluster-forming threshold ($p < .001$) with a cluster-size correction. Cluster-size correction thresholds were estimated using 3dFWHMx with spatial autocorrelation (-acf), based on participants' first level blur statistics (Cox et al., 2016), which addresses the correction issue raised in Eklund et al. (2016). This threshold estimation applied Monte Carlo simulations with study-specific smoothing estimates, two-sided thresholding, and second-nearest neighbour clustering. Clusters larger than the calculated threshold of 32 contiguous voxels and comprising > 50 % grey matter (based on the Eickhoff-Zilles macro labels for MNI space in AFNI) are reported below. Mean activation in voxels within resulting clusters was extracted for post-hoc comparisons and for analyses relating neural activation to RC scores on the NRI.

3. Results

3.1. Neural responses to caregivers vs. peers

There was no effect of GAH group on neural activation during the auditory perception task.[4] There were no interactions of GAH group x Speaker nor of GAH group x Emotion, but there was a three-way interaction of GAH group × Emotion × Speaker in two clusters in the rostral anterior cingulate cortex (ACC) at midline (Fig. 1 and Table 1). Coefficient values for these clusters were entered into a multivariate general linear model (identical to that performed in AFNI) in SPSS to obtain post-hoc (least-significant difference) comparisons. These revealed that GAH+ youth showed less ACC response to their caregiver's angry voices than to the teenager's angry voice ($p = .03$); however, this pattern was reversed in GAH- youth ($p = .03$). In contrast, GAH- youth showed greater ACC response to the teenager's happy voice than to their caregiver's happy voice ($p < .01$). The primary 3-way interaction and all significant post-hoc comparisons are depicted in Fig. 1.

3.2. Association between neural response and relative closeness to peers vs. parents

Independent-samples *t*-tests revealed that GAH groups did not differ in relative closeness to peers over parents, $p = .25$ (nor in closeness to peers, $p = .88$, or to parents, $p = .11$). We examined whether patterns of

[3] Effects related to within-subject factors and their interactions can be found in Supplemental materials.

[4] There was no main effect of Age on neural activation, nor interactions of Age × Speaker or Age × Emotion × Speaker. Small clusters emerged for the Age × Emotion interaction (see Supplemental materials).

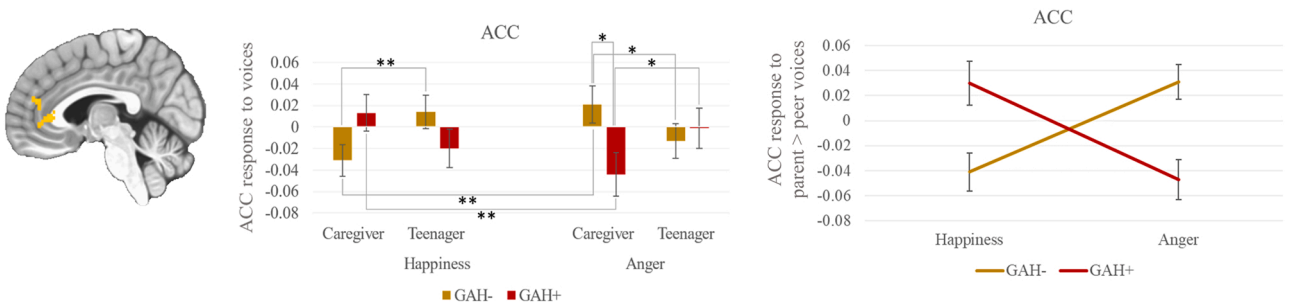

Fig. 1. ***Interaction of GAH group, emotion, and speaker on neural activation.*** *Note.* ACC = anterior cingulate cortex. GAH = gender-affirming hormone group. The *y*-axis on graphs represents mean activation to emotional voices (vs. the implicit baseline) within the specified clusters. The brain image in the first column was rendered in the MNI template space. Clusters were formed using 3dclustsim at $p < .001$ (corrected, with a cluster size threshold of 32 voxels). Refer to Table 1 for description of regions of activation. The graph in the second column represents the 3-way interaction of GAH group, emotion, and speaker type on activation within these clusters of the ACC. *: $p < .05$, **: $p < .01$. The graph in the third column is a simplified depiction of the main comparison of interest in the 3-way interaction, for ease of interpretation: values on the *y*-axis here represent a difference score between activation to caregiver vs. teenage voices, such that negative values represent lesser response to caregivers than to the teenage voice in the ACC clusters.

Table 1
Interactions of GAH group, speaker, and emotion type on neural activation to voices.

Structure	*F*	*k*	*x*	*y*	*z*	Generalized η^2	Brodmann area
ACC & mid-orbital gyrus [bottom]	14.37	32	6	37	2	0.03	24
ACC & superior medial gyrus [middle]	21.50	35	7	45	19	0.03	9

Note. Clusters listed here represent areas in which there was an interaction of GAH (gender-affirming hormone) group with Speaker and Emotion type on activation during stimulus presentation, controlling for Age in the model. Clusters were formed using 3dclustsim at $p < .001$. Clusters of activation greater than the cluster size threshold of 32 voxels are presented here. R = right, L = left. ACC = anterior cingulate cortex. Due to their proximity, ACC clusters were grouped for further analyses; notations in square brackets represent the location of the cluster in Fig. 1 (i.e., bottom or middle ACC cluster). *k* = cluster size in voxels. *xyz* coordinates represent the cluster's center of mass, in MNI space. η^2 = eta squared.

neural response to different stimuli (caregiver angry voice, caregiver happy voice, teenage angry voice, teenage happy voice) were related to youth's self-reported relative closeness to peers over parents. To account for the multicollinearity between estimates of neural response for each type of stimulus, we first conducted a partial least squares regression (Tobias, 1995) to identify uncorrelated latent factors for ACC response. Estimates of neural response for all four stimulus types were entered in the model as predictors, and RC scores on the NRI were entered as the outcome variable. X-scores generated for the latent variables were then entered as uncorrelated predictors into a linear regression model predicting RC scores. Factor loadings were interpreted as meaningful if predictors loaded onto latent factors at |.7| or above (Henseler et al., 2012).

The loadings of each original predictor onto the latent factors are provided in Table 2. The first latent factor for the ACC clusters was

Table 2
Loading of stimulus-specific estimates onto latent factors in partial least-squares (PLS) regression.

		Latent factors			
Structure	Stimulus estimate	1	2	3	4
ACC	Caregiver anger	-0.85	0.55	-0.42	0.38
	Teenage anger	0.54	0.60	-0.44	0.59
	Caregiver happiness	-0.11	0.91	-0.19	-0.61
	Teenage happiness	0.18	0.04	-0.77	-0.36

Note: The PLS regression generated 4 latent factors. ACC = anterior cingulate cortex.

significantly predictive of RC scores, $t(38) = 2.55$, $p = .02$. This factor was primarily represented by low response to caregivers' angry voices. As such, low response to caregivers' angry voices in the ACC clusters was related to higher RC scores, indexing higher closeness with peers than with parents.[5]

4. Discussion

In addition to the benefits of gender-affirming care on physical and mental health outcomes for transgender youth (Call et al., 2021; Lopez et al., 2017), the exogenous administration of gonadal hormones can also provide insight into the effect of hormonal changes on brain function during adolescence. The current study examined the relative neural response to socio-emotional cues conveyed by caregivers vs. an unfamiliar peer, in transgender boys receiving or not receiving exogenous testosterone. Our findings suggest that the administration of exogenous testosterone—above and beyond the effect of age—may be associated with shifts in neural response to emotional vocal cues from caregivers vs. unfamiliar peer-aged speakers in the rostral ACC. Consistent with our hypotheses, youth receiving testosterone (GAH+) showed blunted responses to caregivers' angry voices—but heightened responses to unfamiliar teenage angry voices—in this region; conversely, youth not receiving exogenous testosterone (GAH-) showed the opposite pattern. Interestingly, GAH- youth showed heightened responses to unfamiliar

[5] Partial least squares (PLS) regressions were conducted due to concerns about multicollinearity in the estimates for neural response to each type of stimuli in each cluster (correlations among estimates for ACC *r*s = 0.36–0.52, *p*s ≤ 0.05; variance inflation factor > 1, ranging from 1.32 to 1.42, in least squares regressions). Results of least squares regressions (in which all estimates were entered simultaneously into the model) were consistent with the PLS analyses: response to angry caregiver voices in the ACC was negatively associated with RC scores, $t(38) = -2.31$, $p = .03$.

teenage vs. caregivers' happy voices. Across groups, a pattern of reduced ACC response to angry caregiver voices was linked to greater closeness with peers relative to caregivers, which could index more "advanced" social re-orientation. Although preliminary, our findings suggest that rising levels of testosterone during adolescence may play a role in the expected recalibration of the salience of various sources of socio-emotional information (Spear, 2000) and in the normative social re-orientation from caregivers to peers (e.g., Nelson et al., 2005) in teenagers.

4.1. Neural response to caregivers vs. peers

In the current study, youth receiving testosterone vs. those not receiving testosterone showed different relative patterns of neural response to caregiver and unfamiliar peer-aged voices in two sections of the rostral ACC. Although we did not find effects in traditional mentalizing network regions like the TPJ or mPFC (which could be related to age or driven by changes in sex hormones more generally rather than by testosterone specifically), the ACC has also been involved in the processing of social and affective information.

Embedded in attentional and emotional networks, the ACC can be considered a part of the rostral limbic system (Bush et al., 2000; Devinsky et al., 1995). Like the subcortical structures it is connected to (e.g., hippocampus, amygdala, nucleus accumbens, insula, orbitofrontal cortex; Behrens et al., 2007; Devinsky et al., 1995), the rostral ACC is thought to contribute to the assessment of the salience or value of socio-emotional cues (Bush et al., 2000; Devinsky et al., 1995; Vogt et al., 1992). Whereas the dorsal ACC has primarily been implicated in cognitive functions like error monitoring and conflict detection (review by Botvinick et al., 2004), the rostral part of the ACC—which showed differential response to caregivers vs. an unfamiliar peer in both groups of youth in the current study—has been primarily implicated in affective processing of emotional stimuli (Bush et al., 2000; Gunther Moor et al., 2010) and reward (Kennedy and Adolphs, 2012). Perhaps relatedly, the rostral ACC has been involved in up- and down-regulating emotional responses (Devinsky et al., 1995; Li et al., 2018). Given this, it is possible that the patterns of neural response that we noted across GAH+ and GAH- youth are related to emotion regulation processes. Although this is speculative, surges in testosterone during adolescence (e.g., as in the GAH+ group) may reduce the need for ACC-mediated regulation of response to parental angry voices—but not of teenagers' angry voices, which could be more socially consequential. Although conflict with parents is more common than conflict with friends during adolescence (Collins et al., 1997; Furman and Buhrmester, 1992), teenagers may view their relationships with friends as more vulnerable to ruptures after conflicts (Laursen and Collins, 2009; Scholte and van Aken, 2006) and may be more motivated to mitigate disputes with peers to maintain amity (Collins et al., 1997). Given their additional vulnerability to peer rejection (Clark et al., 2014; McGuire et al., 2010), it is possible that transgender youth would be particularly motivated to maintain positive social relationships. As such, angry cues by unfamiliar peers may elicit heightened neural responses in regions involved in regulating internal emotional responses.

In addition, the ACC has been implicated in Bayesian learning and mapping outcomes to predictions about future events (review by Behrens et al., 2007). Thus, an alternative interpretation of our findings is that increases in testosterone are associated with differential coding of the predictive value of caregiver and peer-aged angry voices in the rostral ACC. The ACC has been linked to the approach and avoidance of different socio-affective stimuli (Aupperle et al., 2015; Güroğlu et al., 2008; Stevens et al., 2011). The valuation of negative emotional outputs from various actors in youth's lives could be expected to shift as a function of the target's salience across adolescence. With age, a parent's displeasure may be less tied to perceived consequences and outcomes; conversely, as peers gain increasing significance as the "social judges" of adolescents' behaviour, angry signals from other teenagers may index potential social consequences. Differential ACC response to angry emotional cues from various sources in the social environment may thus reflect testosterone-mediated changes in the assessment of stimuli's functional relevance for social behaviour.

Increased exposure to testosterone may have a specific impact on the valuation of aggressive (angry) cues: GAH+ youth did not show differential ACC response to happy voices by different speakers, although GAH- youth showed greater responses to the unfamiliar teenager's happy voice than to their caregiver's happy voice. Cues of acceptance from peers have been found to be attentionally salient (e.g., Silk et al., 2011) and to elicit ACC response (e.g., de Water et al., 2017; Guyer et al., 2012); as such, we would expect youth in both GAH groups to show enhanced processing of this type of voice. It is possible that marked increases in testosterone during adolescence (as in the GAH+ group, but to a lesser extent in the GAH- group) rebalance the processing of *aggressive* cues from peers and caregivers—but not necessarily of positive cues. Indeed, there is some evidence that testosterone may have emotion-specific effects on processing of social information. In rhesus monkeys, for example, the receipt of exogenous testosterone resulted in increased attentional engagement to videos of fights between conspecifics, but had no effect on attention to positive or neutral social scenes (Lacreuse et al., 2010). In a social approach-avoidance task, greater levels of endogenous testosterone in 14-year-old cisgender teenagers were associated with greater prefrontal (and lower amygdala) activation in trials in which youth had to approach angry or avoid happy adult faces, compared to the opposite (approaching happy and avoiding angry faces; Tyborowska et al., 2016). Although replication of our findings with other experimental paradigms will be important to support this interpretation, our results point to the possibility that testosterone differentially impacts the relative neural processing of affiliative (happy) and aggressive (angry) cues from peers and caregivers.

Generally, our findings are in line with theoretical hypotheses that limbic systems are "learning" about what is important in the environment during the teenage years (Casey, Duhoux, et al., 2010), and suggest that testosterone specifically may play a role in this process. We did not find differential responses to emotional voices in the amygdala, which was somewhat surprising given its role in coding the salience of social and affective cues (Kennedy and Adolphs, 2012; Redcay and Warnell, 2018) and its differential response to emotional stimuli following testosterone administration in adults (e.g., Goetz et al., 2014; Radke et al., 2015). It is possible that our vocal stimuli were not intensely emotional in nature, given the mixed valence of linguistic content and the fact that stimuli were produced by community members rather than trained actors. Although our stimuli were characterized by expected patterns of acoustic characteristics that are associated with the expression of happiness and anger (Johnstone and Scherer, 2000; see Supplemental materials) and well-recognized by independent raters, they were generated by untrained speakers who naturally vary in their ability to convey emotional intent. This is a limitation inherent to the use of individualized emotional stimuli. Nonetheless, regions involved in coding salience of social and affective cues in the environment showed differential response to the various types of stimuli as a function of GAH group, suggesting that the receipt of testosterone may bias how caregiver vs. unfamiliar peer-aged stimuli are processed regardless of their emotional intensity.

4.2. Association between neural response patterns and social behaviour

We did not find GAH group differences in relative closeness with peers over parents. Across all youth, higher RC scores were associated with blunted response to caregivers' anger in the ACC. This pattern of neural response was more characteristic of GAH+ youth than of GAH-. It is important to note the potential implications of having a transgender identity in understanding these patterns: for instance, it is plausible that youth receiving GAH are more affirmed in their gender, and thus perhaps more comfortable socializing with peers, than the GAH- group.

Although reasons for not receiving GAH were not assessed, it is also possible that the groups differed in parental support of/affirmation of their child's trans identity—which could influence youth's perception of their parents. Although a longitudinal follow-up study would be needed to make claims about the directionality of effects, our findings suggest that this process of social re-orientation may be potentiated by increases in testosterone during adolescence (which occurs in all sexes at puberty). Indeed, puberty has been conceptualized as a "neurobehavioural nudge" towards exploration of novel social contexts (Peper and Dahl, 2013). These changing responses to caregivers vs. peers may thus be part of a larger recalibration process that encourages motivational engagement with peers over family in the pursuit of independence (Casey, Duhoux, et al., 2010; Nelson et al., 2016).

4.3. Implications for care of transgender youth

The current results suggest that the administration of testosterone may be associated with alterations in neural response to peers relative to parents in transgender youth. These patterns are aligned with expected neurodevelopment in adolescence, as they are akin to effects of gonadal hormones observed in studies with cisgender youth. As such, these results should not be interpreted as contraindicators of testosterone administration as part of gender-affirming care. Rather, we interpret these results as furthering our understanding of neuroendocrine mechanisms that drive behavioural change across adolescence, in both cis- and transgender populations.

4.4. Strengths and limitations

The current study used a novel paradigm to examine how the consistent receipt of exogenous testosterone—similar to the sharp increases in testosterone that are characteristic of pubertal maturation—influenced neural responses to individualized stimuli by caregivers and an unfamiliar teenager. Moving beyond inferences about the influence of testosterone based on sex differences in neural response to various tasks in adolescents (see Goddings et al., 2019), and extending designs involving exogenous testosterone administration in adults (e.g., Bos et al., 2013; Hermans et al., 2008) to a sample of transgender adolescents receiving gender-affirming hormones, our approach allowed us to probe how the neural coding of familiar others compared to novel others may change with increases in testosterone levels during adolescence.

This approach comes with some limitations. First, the current study grouped youth into two groups based on receipt of GAH, which obscures differences in endogenous hormone levels and exogenous hormone doses. The lack of information about serum testosterone levels at the time of study and our modest sample size precluded us from conducting "dose-response" analyses. Because variations in dose and duration of GAH administration were highly skewed (with over half of adolescents receiving no testosterone—i.e., a 0 mg/week dose for 0 months), we could neither assess dose/duration as continuous predictors of neural response nor control for these variables in our analyses. As such, our conclusions are not specific to precise variations in testosterone levels, but rather to broad differences between groups of youth with varied levels of exposure to exogenous testosterone. However, there may be a wide variety of reasons why GAH- teenagers may not be receiving exogenous hormones (e.g., family support for GAH, youth's desire or comfort with GAH; not recorded in the current study), which introduces heterogeneity into the groups. Nonetheless, we view this study as a preliminary first step towards understanding how increasing levels of testosterone may impact the developing brain's response to salient social cues. Larger studies that can more precisely assess and control for the timing (relative to pubertal stage), duration, and dosage of testosterone would be beneficial in specifying how changes in this hormone at varying points in development lead to changes in neural function.

Second, we cannot disentangle whether effects of caregiver vs. unfamiliar teenage speakers are due to the salience of these actors for adolescents, or to differences in familiarity or novelty. Although confounds related to familiarity are arguably inherent to all studies comparing peers to parents, there is evidence that exposure to facial expressions of loved ones elicits emotional reactions over and above the effect of familiarity and arousal (Guerra et al., 2012)—suggesting that neural responses to caregiver voices may be driven by more than familiarity. Moreover, as teenagers mature, they encounter novel social stimuli which may be processed differently than the more familiar social signals of their family members; as such, we believe that it is indeed likely that our results are at least partially driven by the novelty of peer cues compared to those of caregivers.

Last, since no behavioural responses were logged during the processing of auditory recordings to avoid interfering with youth's processing of these stimuli, it is difficult to disentangle the many possible functions of the rostral ACC during this task. Given that our task paradigm required only minimal response, we think it likely that differential responses to voices in these areas of the brain reflect differences in the processing of the affective qualities of the stimuli, rather than functions like error monitoring in the ACC. Nonetheless, the use of approach/avoidance tasks (e.g., using joysticks) would help further disentangle the potential functional role of these areas in processing various aspects of caregiver vs. peer stimuli.

5. Conclusion

In addition to its gender-affirming benefits for transgender youth's mental and physical well-being, the administration of gonadal hormones can provide some insight into the effect of puberty-related hormonal changes on neural response to socio-emotional cues during adolescence. Consistent with expected changes related to endogenous puberty, transgender boys who received exogenous testosterone demonstrated blunted response to caregivers' angry voices—but heightened response to unfamiliar teenage angry voices—in the rostral ACC. In contrast, youth not receiving testosterone showed the opposite pattern. Moreover, youth not receiving testosterone showed enhanced ACC response to the unfamiliar teenage happy voices relative to caregiver happy voices. Blunted response to angry caregiver voices was related to increased self-reported closeness with peers over caregivers. Although preliminary, our results point to the possibility that changes in testosterone levels in adolescence result in modified processing of social cues in the ACC, a brain region associated with the evaluation of socio-affective information. Longitudinal work with larger samples will be necessary to elucidate how changes in testosterone contribute to youth's social re-orientation towards peers and increasing independence from the family environment.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Ethical approval

All procedures were in accordance with the 1964 Declaration of Helsinki and its later amendments.

Competing interests

No author has any competing interests to declare.

Appendix A. List of spoken words

Stop
Great
Don't
Here
Really
Why
Hi
Hungry
Tired
Please
Come on
Ready
Let's go
Beautiful
Awesome
Happy
Hurry
Look
No
Eat
Don't spill
Careful
Comfortable
Quietly
Unbelievable
No way
Wait
Time's up
Fine
Get it
Sure
Yes
Yours
For real
Definitely
Later
Bye
Wow
Never

Appendix B. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2022.101194.

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