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Unraveling age, puberty and testosterone effects on subcortical brain development across adolescence

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ABSTRACT

The onset of adolescence in humans is marked by hormonal changes that give rise to secondary sexual characteristics, noted as puberty. It has, however, proven challenging to unravel to what extent pubertal changes may have organizing effects on the brain beyond chronological age, as reported in animal studies. The present longitudinal study aimed to characterize the unique effects of age and puberty on subcortical brain volumes and included three waves of data collection at two-year intervals and 680 T1-weighted MRI scans of 271 participants (54% females) aged between 8 and 29 years old. Generalized additive mixed model procedures were used to assess the effects of age, self-report pubertal status and testosterone level on basal ganglia, thalamus, hippocampus, amygdala and cerebellum gray matter volumes. We observed age-related increases in putamen and pallidum volumes, and decreases in accumbens and thalamus volumes, all show larger volumes in boys than girls. Only the cerebellum showed an interaction effect of age by sex, such that males showed prolonged increases in cerebellar volume than females. Next, we showed that changes in self-report puberty status better described developmental change than chronological age for most structures in males, and for caudate, pallidum and hippocampal volumes in females. Furthermore, changes in testosterone level were related to development of pallidum, accumbens, hippocampus and amygdala volumes in males and caudate and hippocampal volumes in females. The modeling approach of the present study allowed us to characterize the complex interactions between chronological age and pubertal maturational changes, and the findings indicate puberty unique changes in brain structure that are sex specific.

1. Introduction

Adolescence, the transitional period between childhood and adulthood, is characterized by substantial changes in brain structure and activity, particularly in regions that have been indicated to play key roles in adolescent specific behaviors (Mills et al., 2016; Braams et al., 2015). The onset of adolescence is delineated by puberty, characterized by hormonal changes that give rise to secondary sexual characteristics (Shirtcliff et al., 2009). Several studies showed associations between subcortical brain development and pubertal characteristics (Herting et al., 2015; Bramen et al., 2011; Blanton et al., 2012; Satterthwaite et al., 2014; Goddings et al., 2014, but see Koolschijn et al. (2014)). Additionally, animal studies suggest that testosterone has modulating effects on brain development that are puberty specific (Schulz and Sisk, 2016), it remains an open question to what extent puberty in humans may be another period during which gonadal hormones may affect human brain development. The present longitudinal study aimed to address this issue by characterizing the specific role of age-related and puberty-related development on change in subcortical brain volumes in a community sample of adolescents and young adults.

Several lines of research suggest that puberty may represent a (second) reorganizational period in the brain (Juraska and Willing, 2017). Animal research has provided initial direct evidence that puberty represents a critical period during which hormones may promote organizing effects on brain structure. For example, experienced deprivation of testosterone in pubertal hamsters resulted in structural alterations in amygdala volume in adulthood, independent of adult levels of testosterone (De Lorme et al., 2012). Furthermore, Zehr et al. (2006) showed that synaptic pruning in the medial amygdala was associated with pubertal status in male Syrian hamsters. Moreover, pubertal exposure to androgens in male rates was related to increases in spine density of amygdala and hippocampal structures (Cunningham et al.,

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2007). In addition, it was observed that exposure of gondal hormones during puberty was critical for the sensitivity of limbic regions to steroid hormones in adulthood: androgen receptor density was increased following prepubertal (but not postpubertal) castration in male Syrian hamsters (Romeo et al., 2000). Also in female species, puberty specific effects on brain development were observed. For example, prepubertal ovariectomy in female rats resulted in neural overproduction in the frontal cortex (Koss et al., 2015), while adult ovariectomy did not (Chisholm et al., 2012). These studies support a causal role for puberty on developmental brain changes.

Although causal relations between puberty and brain development can not be exerted in humans, there are several lines of evidence that indicate that puberty may mark a sensitive period in brain development in humans (Peper et al., 2011). First, several subcortical structures showed volume changes that emerge or peak in the pubertal age range (e.g. Ostby et al., 2009; Koolschijn and Crone, 2013; Wierenga et al., 2014), however, there are inconsistencies regarding the timing and directionality of these developmental trajectories (Herting et al., 2018). This highlights the importance of studying these effects in a large single cohort, covering a wide age range and including more than 2 time points. Second, studies have reported that males show a delay in peak volume compared to females (Lenroot et al., 2007), which has been suggested to correspond to sexual dimorphic trajectories in pubertal maturation. Third, a puberty related peak in functional activity (e.g nucleus accumbens) has been related to adolescent characteristic behaviors (e.g. heightened reward sensitivity) (Galvan et al., 2006; Braams et al., 2014). These peaks in functional activity showed to be related to testosterone (Braams et al., 2015).

Most studies investigating pubertal effects on subcortical brain development in humans have been cross-sectional. In one study, pubertal maturation was associated with grey matter volumes in the medial temporal lobe (MTL), yet differently for boys and girls: more advanced pubertal maturation was associated with larger hippocampal volume in boys, but with smaller hippocampal volume in girls (Bramen et al., 2011). Cross-sectional studies also demonstrate a relation between pubertal maturation and hippocampal volume, yet the direction of the effect remains inconclusive (Hu et al., 2013; Neufang et al., 2009; Satterthwaite et al., 2014). Cross-sectional studies that focused on effects of testosterone on subcortical brain development have also shown mixed results. Both positive as well as negative associations between amygdala volume and testosterone were observed (Bramen et al., 2011; Neufang et al., 2009). In addition, caudate volume and thalamus volume did not show significant relations with pubertal measures (Bramen et al., 2011). However, these cross-sectional studies evaluated only a limited number of subcortical structures and do not take into account the inter individual variation in brain and pubertal development, for which longitudinal studies designs are crucial.

To date, there are only a few longitudinal studies available in humans that assessed puberty-related associations on subcortical brain development (for a review, see Herting and Sowell (2017)). Goddings et al. (2014) showed that increase in pubertal stage was related to subcortical brain development; a positive relation with hippocampus and amygdala volume and a negative relation with caudate, putamen and nucleus accumbens volume. Another longitudinal study only found this longitudinal relation between pubertal stage and caudate volume (Herting et al., 2015). The latter study also observed that decreases in amygdala and caudate volumes were associated with increases in testosterone levels. These findings suggest that pubertal development may accelerate typical developmental trajectories. One difficulty with these prior studies concerns the collinearity between predictors (age, self-report puberty and sex hormones all increase over time). Our study aimed to overcome these challenges by assessing the effect of individual differences in the onset and change in pubertal measures on subcortical brain development. The inclusion of 3-wave longitudinal assessments of structural brain indices (N = 680 scans), participants in a wide age range (8–29-years) and individual assessment of age, pubertal stage and testosterone levels allowed us to do so.

The goals of this study were to i) delineate chronological age effects on development of subcortical brain volumes, and ii) test effects of pubertal measures, self-report pubertal stage and testosterone level, above and beyond chronological age, and iii) test whether the influence of testosterone is puberty specific. In addition to subcortical regions, we also included cerebellum gray matter in our analyses, given that – in our previous study partly based on the same sample- it was observed to be associated with testosterone (Schutter et al., 2017). Based on the literature we expected to observe regional effects of puberty. We aimed to elucidate the inconsistent findings of pubertal effects on amygdala and hippocampal volumes (Bramen et al., 2011; Herting et al., 2015; Hu et al., 2013; Goddings et al., 2014; Neufang et al., 2009; Peper et al., 2009; Satterthwaite et al., 2014). Furthermore, we hypothesized no effect of puberty on thalamus volume, as no significant effects have been reported (Bramen et al., 2011; Herting et al., 2015). For caudate, putamen, pallidum and accumbens volumes we hypothesized a negative association with pubertal measures (Goddings et al., 2014). We had no hypothesis related to the effect of puberty on cerebellar cortical development, as this has not been investigated previously.

2. Methods

2.1. Participants

The data in the present study are part of a large accelerated longitudinal research project, BrainTime (Braams et al., 2015; Achterberg et al., 2016; Peters and Peper, 2016; van Duijvenvoorde et al., 2016). A total number of 299 participants were enrolled in the study. Magnetic Resonance Imaging (MRI) scans of 271 participants (53% females) aged between 8 and 26 years old at enrollment were included in the present study for further analysis (see Table 1 for demographics). These scans passed the MRI quality control (QC) procedure, which is described in more detail below. Of these participants, 241 had two or more scans (60% females), and 168 participants had three scans (56% females) that passed QC. There was no significant sex difference in age (p-value = 0.103), and the distribution of males and females was similar across the age range (see Fig. A1). Self-report questionnaires were assessed to confirm the absence of neurological, endocrinological, mental health problems or use of psychotropic medication at T1. Written informed consent was obtained from all participants at each time point. For participants younger than 18 years old, additional consent from their parents was acquired. An independent clinical neuroradiologist evaluated all MRI- scans. No gross abnormalities were reported for any of the participants. The study was approved by the Institutional Review Board at Leiden University Medical Center. A financial reimbursement was granted for participation in the study.

Table 1
Subject characteristics.

	Males		Females	
N	127		144	
Age (min-max)	8.01	−28.72	8.01	−26.83
Total number of scans	315		365	
scannr	*N* mean age	(SD)	*N* mean age	(SD)
1	127 14.86	(3.79)	144 14.11	(3.31)
2	114 14.86	(3.77)	127 14.11	(3.24)
3	74 14.86	(4.11)	94 14.11	(3.37)
Height, *mean* (SD)	176.45	(12.23)	167.37	(7.6)
Weight, *mean* (SD)	66.94	(16.78)	61.51	(12.2)
IQ, *mean* (SD)	109.32	(10.96)	109.29	(9.44)
Testosterone, *mean* (SD)	272.58	(167.91)	21.42	(13.81)
PDS, *mean* (SD)	2.53	(0.84)	2.92	(0.79)

N = number of subjects, SD = standard deviation.