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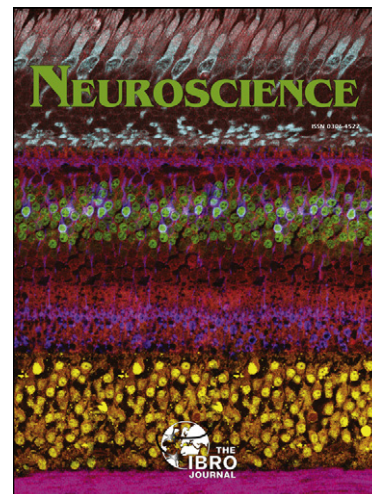
### Pubertal Stage and Brain Anatomy in Girls

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PII: S0306-4522(12)00421-6  
DOI: <http://dx.doi.org/10.1016/j.neuroscience.2012.04.059>  
Reference: NSC 13743

To appear in: *Neuroscience*

Accepted Date: 23 April 2012



Please cite this article as: R.E. Blanton, R.E. Cooney, J. Joormann, F. Eugène, G.H. Glover, I.H. Gotlib, Pubertal Stage and Brain Anatomy in Girls, *Neuroscience* (2012), doi: <http://dx.doi.org/10.1016/j.neuroscience.2012.04.059>

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## Pubertal Stage and Brain Anatomy in Girls

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Running Head: Pubertal Stage and Brain Anatomy

Keywords: Puberty, Brain Development, Girls

## 1. Introduction

The onset of puberty is often delineated by changes in physical body characteristics; there are several neuroendocrine-related developments, however, that occur prior to observable changes in physical characteristics. For example, the release of gonadotropin releasing hormone (GnRH) is signaled by the hypothalamus in a pulsatile fashion and initiates the cascade of events that have been postulated to characterize the onset of puberty (Sizonenko, 1978). Following the release of GnRH, the pituitary responds by releasing luteinizing and follicular stimulating hormones that cause the release of estrogen and testosterone by the ovaries and lead to the development of secondary sexual characteristics (Apter, 1980). Importantly, these dramatic changes in hormonal physiology and in bodily characteristics during puberty coincide, particularly in girls, with an increased vulnerability to behavioral problems and dysregulation of emotional behaviors, such as depression, anxiety, and addictive behaviors (e.g., Angold & Costello, 2006; Chambers *et al.*, 2003; Costello *et al.*, 2007; Reardon *et al.*, 2009). More specifically, an increase in the prevalence of changes in mood has been linked to reproduction in females (Parry & Haynes, 2000). This increase in vulnerability to change in mood in girls during and after puberty has been hypothesized to involve changes in neuroanatomy of limbic structures, such as the hippocampus and amygdala, and underscores the importance of gaining a comprehensive understanding of this stage of development and its relation to these neuroanatomic structures (Chen *et al.*, 2010; Caetano *et al.*, 2007; MacMillans *et al.*, 2003; Rosso *et al.*, 2005).

In this context, it is possible that this vulnerability is associated with the

simultaneous (and possibly interrelated) changes in brain morphology that mirror puberty. For example, investigators have reported changes in cortical complexity, global and region-specific decreases in cortical gray matter, and increases in white matter with chronological age during childhood and adolescence (Blanton *et al.*, 2001; Giedd *et al.*, 1999; Toga *et al.*, 2006). Moreover, girls show decreases in cortical gray matter earlier than do boys, paralleling the sex difference in the timing of puberty (Giedd *et al.*, 2004; Papadimitriou, 2001). It is important to note, however, that there are few direct *in vivo* investigations of the relation between puberty and brain maturation. Using a dichotomous Tanner staging variable in girls, Bramen *et al.* (2010) examined pubertal changes in mesial temporal lobe structures as well as cortical gray matter and reported significant decreases in amygdala volume with increasing pubertal stage. Peper *et al.* (2009) also examined relations between brain morphometry and puberty in girls and found significant decreases in gray matter in the temporal lobe with increasing estradiol levels. Interestingly, however, no puberty-associated effects were found in the hippocampus for either study even though the hippocampus is known to have sex steroid hormone receptors and is influenced by the release of sex steroid hormones (Beyenburg *et al.*, 2000; Gould *et al.*, 2000).

***There is considerable variation in chronological age regarding the onset, transition, and completion of puberty. For example, dramatic changes in skeletal and height physiology can occur at a young chronological age in one child and much later in another child, indicating that chronological age may not be a sensitive index.*** Indeed, pubertal stage is a better predictor of such physiological changes than is chronological age (Baccetti *et al.*, 2006; ***Dorn et al., 2006***).

This finding raises the important question of whether pubertal stage is also a stronger predictor than is chronological age in brain morphology.

The present study was designed to examine associations of pubertal stage, as assessed by Tanner Staging *as a measurement of gonadarche (Dorn et al., 2006)*, and brain anatomy in a sample of girls, ages 9 to 15 years. Given the abundance of sex steroid hormone receptors in the hippocampus and amygdala and the onset of sex steroid hormone release with puberty, we hypothesized that pubertal stage would be a stronger predictor than would age of changes in volumes of the hippocampus and amygdala.

## 2. Experimental Procedures

### 2.1. Participants

Participants in this study were 54 girls (mean age 12.602 years; SD: 1.632; minimum and maximum: 9.32 and 15.58 years; (*Frequency histogram presented in Figure 1*) who were recruited with their mothers through advertisements posted in numerous locations within the local community (e.g., internet bulletin boards, university kiosks, supermarkets). Sixty-seven percent were Caucasian-American, 15% Bi-racial-American, 7% Asian-American, 6% Hispanic-American, and 6% African-American. Institutional Review Board approval was obtained for this project. At least one parent of each participant gave written informed consent for the child's participation, and each child gave written assent. To eliminate possible effects of psychiatric disorders on brain morphology, all girls were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL; Kaufman *et al.*, 2000) to assess current and past psychiatric diagnoses. The K-SADS-PL

generates reliable and valid child psychiatric diagnoses (Kaufman *et al.*, 1997). Girls with a current or past episode of a psychiatric Axis I disorder were excluded from the study.

### *2.2. Pubertal Assessment*

Tanner Staging (Tanner & Whitehouse, 1976) was used to examine pubertal status, with Tanner stage 1 representing an absence of secondary sexual characteristics and Tanner stage 5 indicating physiological sexual maturity. Tanner Breast and Tanner Hair assessments were included separately in the analyses. Whereas stages of Tanner Hair are postulated to reflect increases in testosterone, Tanner Breast is associated more strongly with increases in estrogen during puberty (Penfold *et al.*, 1981; Shirtcliff *et al.*, 2009). Mean ages and standard deviations for Tanner Breast and Hair Stages are presented in Table 1.

### *2.3. Menarche*

Twenty-one of the 49 participants in the sample who provided menarche status had started menarche. The mean age of girls who had not started menarche was 11.59 years (SD = 1.09) and of girls who had started menarche was 13.78 years (SD = 1.29;  $t(47) = 6.43, p < .001$ ).

### *2.4. Socioeconomic status variables*

***Socioeconomic status (SES) data included total household income and the school education of the mother and father. To examine the effects of SES on menarche status, an ordinal logistic regression was conducted using SES variables as independent measures and menarche status as the dependent variable.***

### *2.5. Brain Assessment*

Sagittal T1-weighted 3D IR-prep SPGR magnetic resonance imaging (MRI) scans were collected from all subjects using an image acquisition matrix with  $0.86 \times 0.86 \times 1.5 \text{ mm}^3$  voxels (TI/FA 400ms/15 deg.) *and acquired utilizing a 1.5T MRI scanner*. Each scan was interpolated to  $1 \text{ mm}^3$  voxels and normalized to the CCHMC female pediatric brain template (<http://www.irc.cchmc.org>) using a rigid body registration based on mutual information, as implemented in SPM2 to correct for possible head tilt differences. Total intracranial volume (ICV) and ICV gray, white, and CSF tissue types were automatically measured after the removal of extra-cerebral tissue voxels using BrainSuite2 (<http://www.loni.ucla.edu/software>). The hippocampus and amygdala were manually traced in successive 1 mm slices in the coronal viewing plane (*an example tracing of the amygdala is presented in Figure 2*). Both the axial and sagittal viewing planes were utilized to corroborate anatomy (for details on the anatomic guidelines see Levitt *et al.*, 2001). Prior to manual tracings of all MRI scans, both intra- and inter-rater reliability were conducted. Intra-rater reliability had a coefficient of variation of 3%. The intra-class correlation coefficient for inter-rater reliability was .93 for the hippocampus and .89 for the amygdala. All morphometric analyses for the study were conducted by one rater blind to age and pubertal stage.

## 2.6. Statistical Analyses

A stepwise linear regression analyses was conducted using total ICV, chronological age, and puberty as independent variables and volumes of the hippocampus and amygdala as dependent variables. First, total ICV was entered into the model, followed by pubertal stage (Tanner-H and Tanner-B, independently), followed by age to examine associations with hippocampus and amygdala volumes. To

compare the relative strengths of the effects of age and puberty, a second analysis was conducted, first entering total ICV into the model, followed by age, followed by pubertal status (Tanner-H and Tanner-B, independently) to predict hippocampus and amygdala volumes. Finally, one-way (by menarche status) analyses of covariance (ANCOVAs) were conducted on hippocampus and amygdala volumes, with total ICV and age as covariates.

### 3. Results

#### 3.1. Menarche

There were no significant differences between girls who had started their menses and girls who had not started menses in total ICV gray or white matter or in volumes of the right or left hippocampus or amygdala (see Table 2). ***There were also no significant effects of SES variables on menarche status.***

#### 3.2. Hippocampus and amygdala

Means and standard deviations for volumes of the hippocampus and amygdala at each Tanner stage are presented in Table 3. In all regression models, ICV was found to be a significant predictor of volumes of both the right and left hippocampus after controlling for age and pubertal stage ( $\beta=.291$ ,  $t=2.203$ ,  $p=.032$ ;  $\beta=.291$ ,  $t=2.24$ ,  $p=.030$ ). Even after controlling for ICV, however, Tanner-H was a significant predictor of right hippocampal volume ( $\beta =-.295$ ,  $t=-2.297$ ,  $p = .026$ ) (**Figure 3**). Age was not found to be a significant predictor of either left or right hippocampal volume before or after controlling for ICV. Controlling for ICV, Tanner-B was found to be significantly associated with right amygdala volume ( $\beta =-.292$ ,  $t=-2.211$ ,  $p = .031$ ) (**Figure 4**). In addition, controlling for ICV and age, Tanner-B was found to predict left amygdala



volume ( $\beta = -.408$ ,  $t = -2.406$ ,  $p = .020$ ) (**Figure 5**). Age was not found to predict left or right amygdala volumes before or after controlling for ICV.

#### 4. Discussion

Given the importance of the role of the amygdala and hippocampus in changes in behaviors that develop with the onset of puberty, such as depression and anxiety, we examined the associations of pubertal stage and age with amygdala and hippocampus volumes in young girls. We found that, after controlling for ICV, increasing Tanner-Hair stage was associated with lower volume in the right hippocampus and increasing Tanner-Breast stage was associated with lower volume of the right and left amygdala. Age was not a significant predictor of hippocampus or amygdala volumes.

***Our finding that puberty, rather than chronological age, predicted changes in the hippocampus and amygdala could be due to chronobiology. Adolescents show greater phase delay and increased sleep/wake cycles in their sleep patterns than do children (Carskadon et al., 1993), possibly as a result of the stronger relation of melatonin secretion with puberty than with chronological age (Salti et al., 2000). This well-known pubertal shift in sleep patterns in adolescents, leading them to want to stay up later, may decouple the synchronicity or entrainment of daily circadian rhythms and angle the timing of the biological clock towards other endogenous rhythms rather than the ~24-hour sleep/wake cycle, such as the release of hormones and, in effect, alter brain morphology in a non-chronological age-dependent manner. Gonadal hormones have “activational effects” on circadian rhythms and the circadian pacemaker (Hagenauer et al., 2009). This, in theory, could alter the sleep/wake patterns (or biological clock) to align with***

***gonadal pubertal changes rather than with daily circadian rhythms and influence brain chronobiology. Brain chronobiology includes the hippocampus and amygdala, two brain networks that have been characterized to be influenced by the circadian system (Vandewalle et al., 2009).***

Our finding of decreasing volume of the right hippocampus with increasing Tanner-Hair pubertal stage in healthy girls suggests that testosterone plays a role in the maturation of this region. Indeed androgen sensitivity is found to occur in the hippocampus and could be the cause of the association between pubertal status and change in volume of the hippocampus (Beyenburg et al., 2000). The association of hippocampal volume with pubertal stage may also reflect an important change in autobiographical memories during this developmental stage (Cabeza et al., 2004). For example older children and adolescents are able to provide more retrospective autobiographical as well as future narratives. ***In a meta-analysis, Van Patten (2004) describes that the relation of mesial temporal lobe volumes and cognition, and in particular, memory, is affected by age of the participants. Thus, whereas in older individuals memory is positively related to volume, in younger individuals memory and volume are negatively related. This suggests that smaller volumes in children and adolescents are an indicator of an increase in cognitive performance. Furthermore, in a recent study of parental nurturance and hippocampal volumes, Rao et al. (2010) found that increased parental nurturance is related to decreased hippocampal volumes in children and adolescents. A decrease in hippocampal volumes may be one positive indicator of outcomes in children and adolescents.*** Describing autobiographical memories is related to the ability

to regulate emotions (Habermas *et al.*, 2009; McLean, 2005). Overgeneralized autobiographical memories have been conceptualized as a risk factor for depression (Rice & Rawal, 2011). In this context, the adaptive use of autobiographical memories may be impaired in Major Depression (Conway & Pleydell-Pearce, 2000; Habermas *et al.*, 2009). Given that depressive symptoms develop in girls during puberty, this formulation is consistent with both a difficulty in emotion regulation and reductions in the volume of the right hippocampus (Joormann & Gotlib, 2010; Maller *et al.*, 2007).

We also found a significant relation between the amygdala and pubertal stage. Our finding that Tanner-Breast stage is associated with amygdala volume is consistent with studies in humans that describe the expression of  $\alpha$ -estrogen receptors in the amygdala nuclei (Osterlund & Hurd, 2001). Correctly extracting socially and emotionally salient information from faces is thought to involve amygdala function (Adolphs *et al.*, 1998; Adolphs, 2003; 2010; Sergerie *et al.*, 2006); indeed, the amygdala may aid in the social construction of one's self through automatic feedback of social responses from others, especially during teen years when peers take on special significance in the development of the self (Spear, 2000). Plus, investigators implicate the right amygdala in self-relatedness to facial stimuli, suggesting a close link between the self and evaluation of emotions (Northoff *et al.*, 2007). Our finding of an association of pubertal stage and the left amygdala is consistent with these findings. The left amygdala is proposed to involve the retrieval of emotional memories (Sergerie *et al.*, 2006). Such retrieval of emotional memories is influenced by mood, which affects accessing both negative and positive memories (Haas & Canli, 2008). Interestingly, healthy adolescents are characterized by fluctuations in mood that are not related to negative symptoms

(Larson *et al.*, 1980), which could explain, in part, changes in the left amygdala that relate to the release of estrogen that occurs during puberty as  $\alpha$ , yet not  $\beta$ , estrogen receptors are implicated in ***brain regions involved*** in emotions (***Osterlund & Hurd, 2001***).

As mentioned previously, the prevalence of a change in mood and anxiety behaviors in girls increases during the transition through puberty (Hankin *et al.*, 1998). Changes in neural morphology at this time may predispose increased variation in neurodevelopment and could exacerbate the normal changes in autobiographical memories, mood, and social behaviors that accompany maturation. For example, puberty is associated with symptoms of anxiety, depression, and stress during adolescence (Huerta & Brizuela-Gamiño, 2002). More specifically, major depression is reported to involve dysfunction of the amygdala and hippocampus (Gotlib & Hamilton, 2008; Hamilton & Gotlib, 2008), anatomic structures found in the present study to differ volumetrically with pubertal stage. Hormone replacement therapy has neuroprotective effects on both mood and brain anatomy, suggesting that sex-steroid mechanisms play a role in mood (Ha *et al.*, 2007; Stephens *et al.*, 2006).

### *Conclusions*

In closing, we should note three limitations of this study. First, we used Tanner staging to assess pubertal status rather than assessing sex steroid hormones such as estrogen, progesterone, and testosterone, which could provide more detailed information regarding the relation between brain morphology and pubertal development (***see Dorn et al., 2006***). However, strong correlations between Tanner staging and levels of these hormones have been documented in prior studies (Shirtcliff *et al.*, 2009).

Second, we did not assess the phase of menstrual cycle during which the girls were scanned; this should be examined in future studies. Finally, we had relatively small sample sizes, particularly in Tanner Stages 1 and 5. ***These sample sizes precluded an examination of the effects of ethnicity on the relation between puberty and brain morphology. This is an important area for future research.***

Despite these limitations, however, the present findings highlight the significance of pubertal status as an important developmental milestone associated with volumes of the right hippocampus and amygdala. Future research should examine more explicitly the mechanisms underlying the associations between pubertal status and neuroanatomical development and begin to explore the nature of the relations among brain physiology, socio-cognitive functioning, onset of emotional disorders, and puberty.

### Acknowledgements

***We would like to thank Melissa L. Henry, Yamanda Wright, and Hannah Burley for their contributions to this scientific manuscript.*** This research was supported by National Institute of Mental Health Grant MH74849 awarded to Ian H. Gotlib.

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Figure Legends

**Figure 1. Frequency histogram of the age distribution of individuals.**

**Figure 2. Example tracings of the left and right amygdala using structural MRI.**

Figure 3. After controlling for ICV, Tanner-H was a predictor of right hippocampal volume.

Figure 4 After controlling for ICV, Tanner-B was found to predict right amygdala volume.

Figure 5. After controlling for ICV and age, Tanner-B was found to predict left amygdala volume.

### Highlights

- Little is known regarding the relation of puberty and brain development
- Puberty was found to be a significant predictor of changes in the hippocampus and amygdala
- This highlights the importance of the developmental stage of puberty

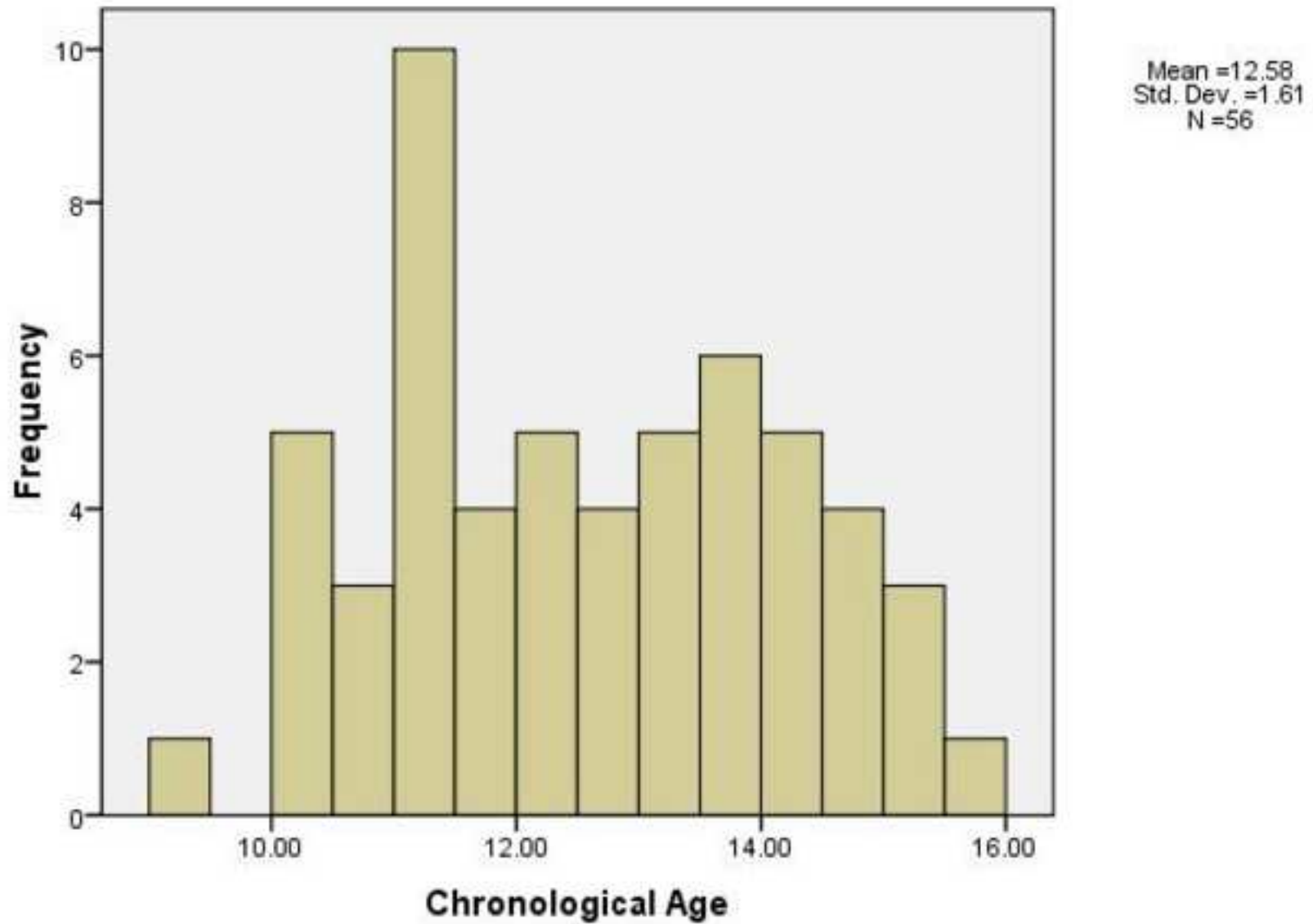
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**Abstract**

Studies of puberty have focused primarily on changes in hormones and on observable physical bodily characteristics. Little is known, however, about the nature of the relation between pubertal status and brain physiology. This is particularly important given findings that have linked the onset of puberty with both changes in cognitive functioning and increases in the incidence of depression and anxiety. The present study examined relations between pubertal stage, as assessed by Tanner Staging, and brain anatomy in a sample of 54 girls aged 9 - 15 years. Brain morphometric analysis was conducted using high-resolution magnetic resonance imaging (MRI). The hippocampus and amygdala were manually traced on MRI scans in all participants. Stepwise regression analyses were conducted with total intracranial volume (ICV), age, and pubertal status as the predictor variables and hippocampus and amygdala volumes as outcome variables. Pubertal status was significantly associated with left amygdala volume, after controlling for both age and intracranial volume (ICV). In addition, puberty was related to right hippocampus and amygdala volumes, after controlling for ICV. In contrast, no significant associations were found between age and hippocampal and amygdala volumes after controlling for pubertal status and ICV. These findings highlight the importance of the relation between pubertal status and morphometry of the hippocampus and amygdala, and of limbic and subcortical structures that have been implicated in emotional and social behavior.



Histogram



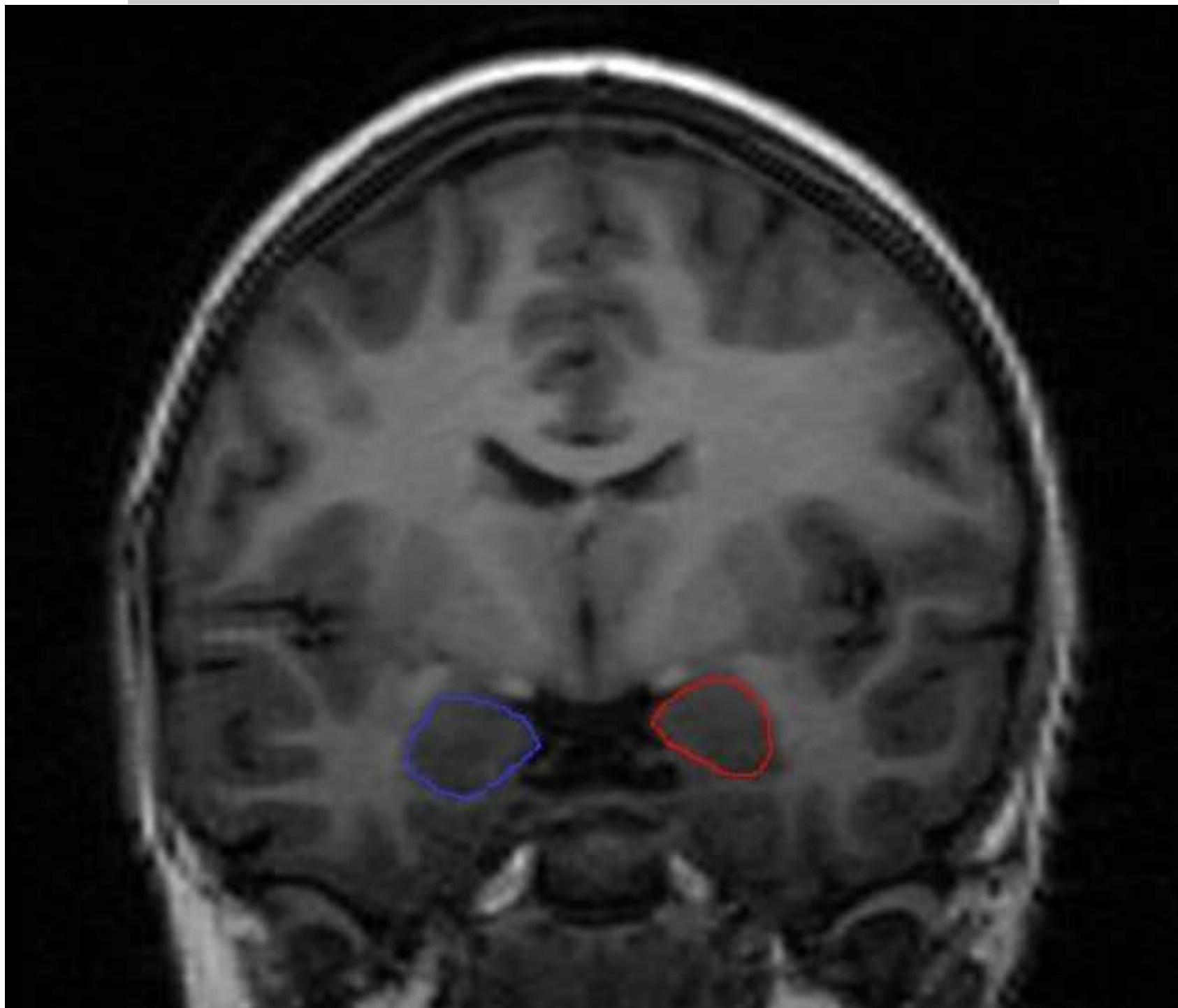


Figure 1.

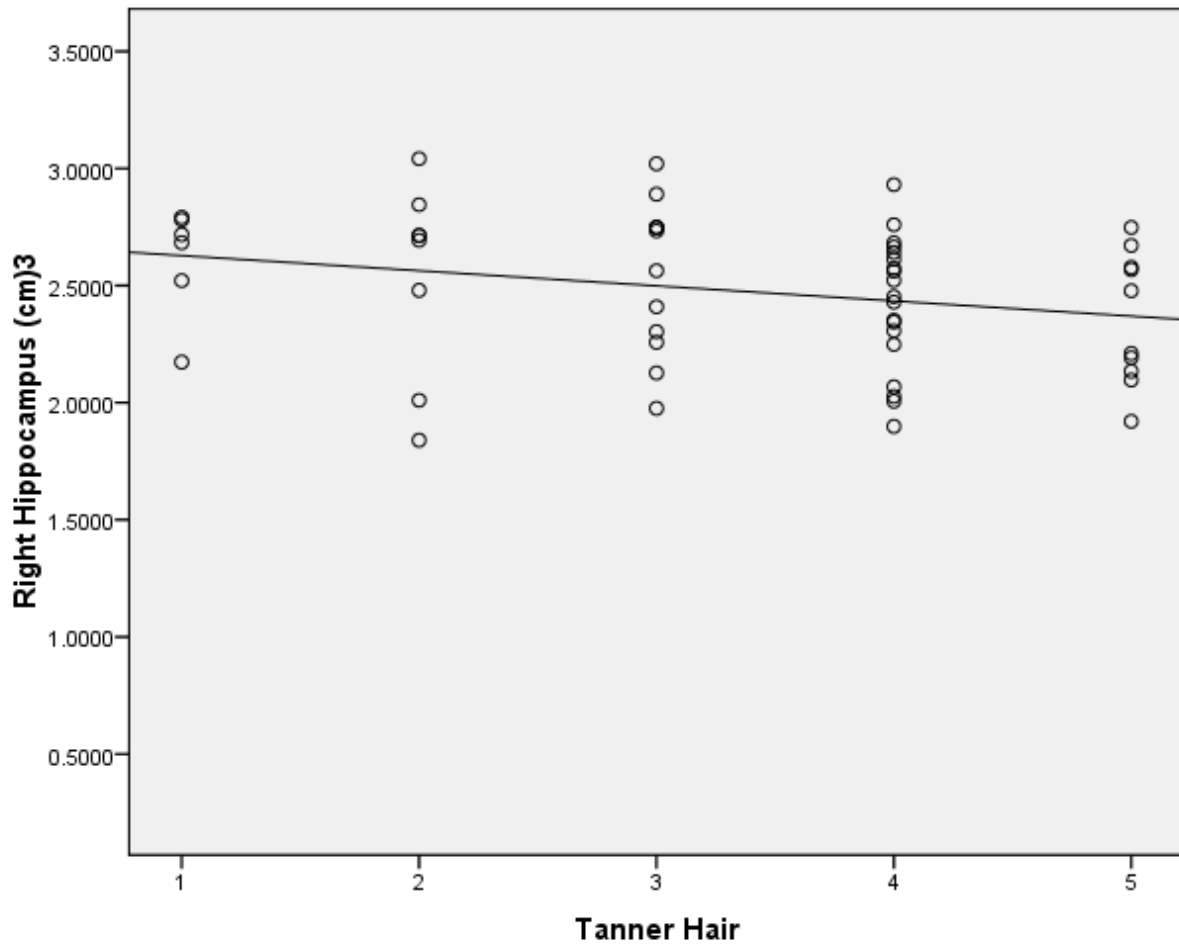
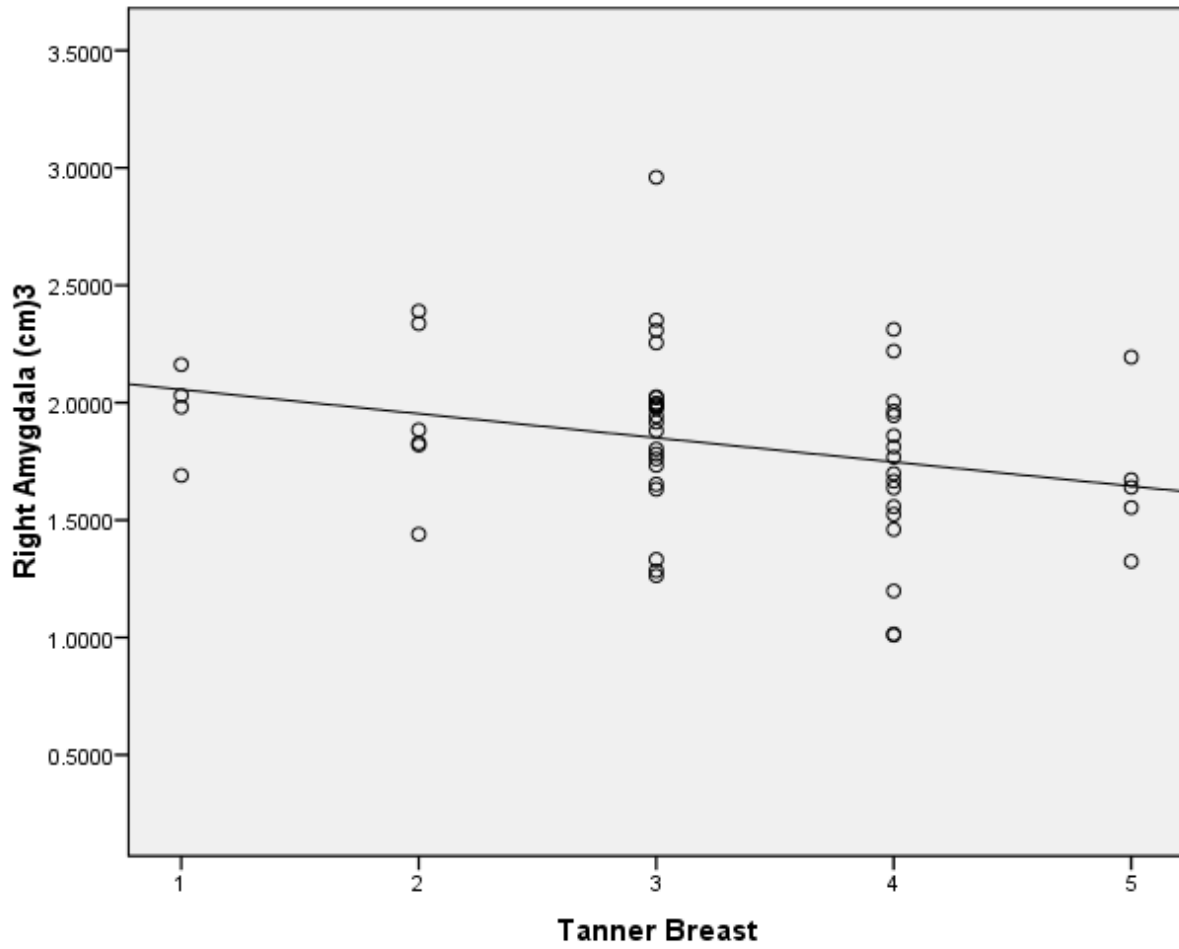
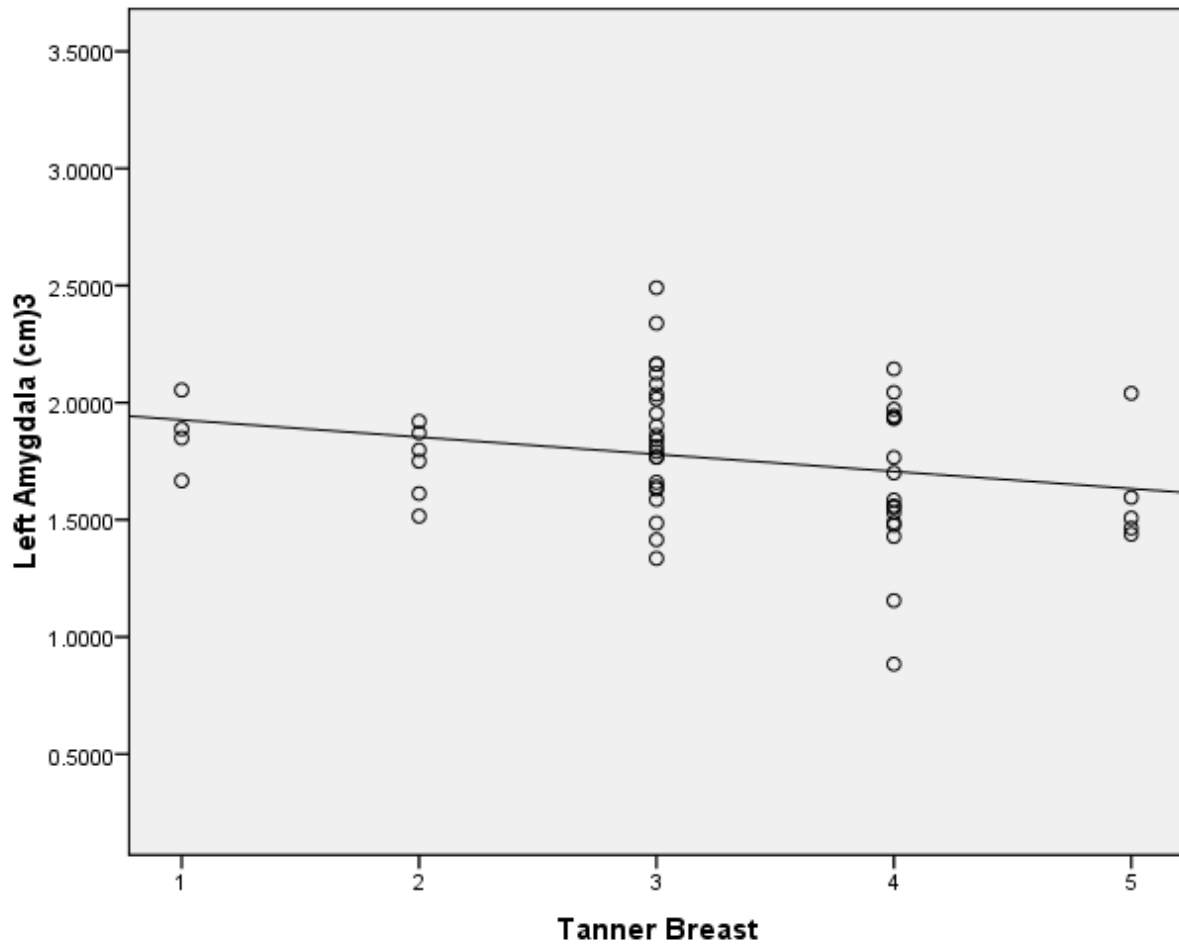


Figure 2.



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Figure 3.



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Table 1. Mean age, standard deviations (in years), and frequencies for Tanner breast and hair stages.

TANNER STAGE	TANNER BREAST (MEAN AGE $\pm$ SD; FREQUENCY)	TANNER HAIR (MEAN AGE $\pm$ SD; FREQUENCY)
1	10.278 $\pm$ .851 4	10.403 $\pm$ .883 6
2	11.182 $\pm$ .842 6	11.295 $\pm$ .633 8
3	12.424 $\pm$ 1.442 23	12.670 $\pm$ 1.441 11
4	13.505 $\pm$ 1.414 16	12.883 $\pm$ 1.286 19
5	14.090 $\pm$ .530 5	14.357 $\pm$ .991 10

Table 2. Means and standard deviations (in cm<sup>3</sup>) of hippocampus and amygdala volumes by menarche status.

MENARCHE	RIGHT HIPPOCAMPUS	LEFT HIPPOCAMPUS	RIGHT AMYGDALA	LEFT AMYGDALA
No	2.541 ± .329	2.241 ± .278	1.933 ± .339	1.781 ± .299
Yes	2.453 ± .274	2.170 ± .222	1.792 ± .346	1.766 ± .277

Table 3. Means and standard deviations (in cm<sup>3</sup>) for hippocampus and amygdala volumes by Tanner breast and hair stages.

TANNER STAGE	RIGHT HIPPOCAMPUS	LEFT HIPPOCAMPUS	RIGHT AMYGDALA	LEFT AMYGDALA
Tanner-breast 1	2.377 ± .450	2.123 ± .217	1.966 ± .199	1.864 ± .159
Tanner-breast 2	2.703 ± .171	2.341 ± .145	1.950 ± .358	1.744 ± .155
Tanner-breast 3	2.546 ± .313	2.278 ± .274	1.906 ± .369	1.864 ± .290
Tanner-breast 4	2.372 ± .253	2.094 ± .210	1.674 ± .382	1.701 ± .272
Tanner-breast 5	2.371 ± .350	2.157 ± .254	1.677 ± .320	1.609 ± .248
Tanner-hair 1	2.611 ± .236	2.340 ± .228	1.918 ± .146	1.750 ± .164
Tanner-hair 2	2.542 ± .415	2.200 ± .239	1.864 ± .389	1.783 ± .188
Tanner-hair 3	2.582 ± .312	2.230 ± .269	1.915 ± .385	1.932 ± .326
Tanner-hair 4	2.425 ± .281	2.200 ± .273	1.745 ± .443	1.754 ± .289
Tanner-hair 5	2.360 ± .282	2.127 ± .207	1.794 ± .279	1.671 ± .237