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Development and sexual dimorphism of the pituitary gland☆

Frank P. MacMaster [a], Matcheri Keshavan [a], Yousha Mirza [a], Normand Carrey [b], Ameet R. Upadhyaya [a], Rhonda El-Sheikh [a], Christian J. Buhagiar [a], S. Preeya Taormina [a], Courtney Boyd [a], Michelle Lynch [a], Michelle Rose, Jennifer Ivey [a], Gregory J. Moore [c], David R. Rosenberg [a,*]

[a] *Department of Psychiatry & Behavioral Neurosciences, Wayne State University, and Children's Hospital of Michigan, Detroit, MI 48201, USA*
[b] *Department of Psychiatry, Dalhousie University, Halifax, NS, Canada B3H 2E2*
[c] *Departments of Psychiatry and Radiology Pennsylvania State University College of Medicine, Hershey, PA 17033, USA*

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Abstract

The pituitary gland plays a central role in sexual development and brain function. Therefore, we examined the effect of age and gender on pituitary volume in a large sample of healthy children and adults. Volumetric magnetic resonance imaging (MRI) was conducted in one hundred and fifty four (77 males and 77 females) healthy participants. Males were between the ages of 7 to 35 years (16.91±5.89 years) and females were 7 to 35 years of age (16.75±5.75 years). Subjects were divided into subgroups of age (7 to 9, 10 to 13, 14 to 17, 18 to 21, 22 and older) and sex (male/female). Pituitary gland volume differed between sexes when comparing the age groups ($F=3.55$, $df=2$, 143, $p=0.03$). Females demonstrated larger pituitary glands than males in the age 14 to 17 year old groups ($p=0.04$). Young (19 years and under) and old (20 years and older) females demonstrated a correlation between pituitary volume and age. Males did not show this relationship. These findings provide additional evidence for gender differences in the normative anatomy of the pituitary and may have relevance for the study of various childhood onset neuropsychiatric disorders in which pituitary dysfunction has been implicated.

Keywords: Child; Magnetic Resonance Imaging; Neurodevelopment; Pituitary

Introduction

Males and females can react differently to the same stimuli. Whether this is due to environmental or biological influences is a matter of much debate. It is known that during development, the brain does change in a sexually dimorphic manner Giedd et al. (1997). For example, in the limbic system, the amygdala develops at a faster pace in males and the hippocampus in females Giedd et al. (1996). Interestingly, the amygdala is rich in androgen receptors (Clark et al., 1988) while the hippocampus is rich in estrogen receptors (Morse et al., 1986). These differences in limbic system development may be reflected in sex differences in stress reactivity. Another stress related region thought to develop in a sexually dimorphic manner is the pituitary gland.

Early in vivo studies of the pituitary gland were conducted using computed tomography (CT) imaging. Although typically of a lower resolution than MRI, CT evaluations of the pituitary gland have been shown to be roughly equivalent to MRI for gross measures of the gland (Wiener et al., 1985). Using coronal CT scans, Peyster et al. (1983) examined the volume of the pituitary gland in 27 youths (8 – 21 years of age; 11 males and 16 females) and 27 adults (24 – 91 years of age; 11 males and

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* Corresponding author. Wayne State University, Psychiatry 9B, 4201 St. Antoine Boulevard, Detroit, MI 48201. Tel.: +1 313 577 9000; fax: +1 313 577 5900.
E-mail address: drosen@med.wayne.edu (D.R. Rosenberg).

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16 females). They found that the pituitary gland was larger in the adolescent subjects when compared to both the younger and older subjects. Peyster et al. (1983) also noted that females had larger average pituitary gland volumes than males. In axial CT scans from 184 subjects (9 – 84 years of age; 98 males, 86 females), Peyster et al. (1984) did not note any age or sex differences with regard to pituitary length. In a coronal CT study of pituitary gland height, Peyster et al. (1986) examined 251 subjects (7 – 91 years of age; 92 males and 124 females). Females demonstrated a larger pituitary gland height than males. Pituitary gland height also demonstrated a decline with age.

Using sagittal MRI scans Hayakawa et al. (1989) examined the pituitary gland in 150 subjects (newborn to 60 years of age; 87 males and 63 females). A growth spurt was noted in the 10 – 15 year olds and decline in volume in the 51 – 60 year olds. Otherwise the relationship with age was linear. Elster et al. (1990) studied 169 subjects (1 – 30 years of age; 84 males and 85 females) and noted that adolescents and adults had larger pituitary gland volumes than children. Lurie et al. (1990) used sagittal and coronal MRI scans to examine 35 subjects (26 – 79 years of age; 16 males and 19 females). Subjects over 59 years of age demonstrated smaller pituitary height, volume and cross-sectional area. A reduction in pituitary gland volume with age was noted. No sex differences were seen in this study. Doraiswamy et al. (1992) studied pituitary gland height and cross-sectional area in 71 adults (21 – 82 years of age; 31 males and 40 females). Height and area reduced with age. Maximum height was seen in female subjects in the 20 – 40 year old age range.

Similar to Peyster et al. (1986), Suzuki et al. (1990) found greater pituitary gland height in females as compared to males (213 subjects, 117 males, 96 females; newborn to 70 years). Maximum height was shown in both males and females in the 10 – 19 year olds. Argyropoulou et al. (1991) studied 60 youths (8 days to 21 years of age; 30 males and 30 females) using sagittal MRI scans to examine pituitary gland height. A linear growth pattern was noted from 1 year of age to puberty followed by a plateau. In the largest study to date, using sagittal MRI scans Tsunoda et al. (1997) examined pituitary height in 1020 subjects (10 – 78 years of age; 533 males, 487 females). Pituitary height was greater in females than males. Pituitary height increased till age 29 years then declined. In females aged 50 to 59 years, an increase in pituitary height was noted. It was thought that this reflected changes in gonadotropin releasing hormone that occurs in women during this period. Finally, Takano et al. (1999) studied pituitary gland volume in 199 subjects (newborn to 19 years of age; 90 males and 109 females). A strong growth spurt was noted during puberty, and was especially prominent in females. Posterior pituitary gland volume did not change with age. In the 5 – 9 year old age range, the posterior pituitary gland was larger in males than females. In very young subjects (3 days to 4 years of age), Tien et al. (1992) did not note any sex differences with regard to pituitary gland volume. Cox and Elster (1991) studied 48 neonates and infants and found an increase in length and a decrease in area over the first year of life. As these two studies did not include adolescent subjects, this may be why no sex differences were noted.

One of the core problems with many of the previous studies of pituitary development is that they did not use purely healthy controls, instead they used patients referred for scanning for medical reasons (for example Peyster et al. (1983, 1984, 1986), Argyropoulou et al. (1991), Tsunoda et al. (1997)). The medical conditions did not have pituitary pathology as a primary concern. However, it is difficult to envision given the central role of the pituitary gland in body function, that the various disease and injury states would not affect pituitary gland function in even a small way. Secondary to sample composition, many of the previous studies relied on simple area, length and/or height measures rather than volume of the gland (see Peyster et al., 1986; Suzuki et al., 1990; Argyropoulou et al., 1991; Doraiswamy et al., 1992; Tsunoda et al., 1997). Given those concerns, data on pituitary gland volume are presented here that utilize medically and psychiatrically healthy controls from a wide age range. Based on the previously presented studies, it was hypothesized that (1) older subjects would have a larger pituitary gland volume than younger subjects, (2) females will have larger pituitary volumes than males and (3) pituitary volume will correlate with age, although less so in older subjects.

Materials and methods

Subjects

One hundred and fifty four (77 males and 77 females) healthy subjects participated in this study. Data was gathered at three sites: (1) Wayne State University, (2) Dalhousie University and (3) University of Pittsburgh (see Table 1). Subjects were pairwise age and sex matched within each data set. Males were between the ages of 7 to 35 years (16.91±5.89 years) and females between the ages of 7 to 35 years of age (16.75±5.75 years). Subjects had no current or previous history of an Axis I psychiatric disorder, no prior exposure to any psychotropic medication within 6 months of their baseline assessment, no history of any neurological or other medical disorders which could affect neurologic function, IQ>75 and no reported history of psychiatric illness in first degree relatives. Subjects (or their guardians) provided informed consent for their participation in the research study. Subjects younger than 18 years also provided written assent prior to participating in the study.

Image acquisition and analysis

Data has been gathered from five MRI scanners. All data was provided stripped of any identifying information. At Dalhousie University, MRI scans were conducted on a 1.5 Tesla Siemens Vision system (Erlingen, Germany) at the Queen Elizabeth II

Table 1
Sample breakdown across sites

Measure	Wayne State	UPMC	Dalhousie A	Dalhousie B
Age	14.59±2.53	21.39±4.96	11.31±2.72	11.81±3.93
Sex (M/F)	23/23	34/34	6/6	24/24
Pituitary volume (cc)	0.63±0.17	0.66±0.15	0.53±0.19	0.51±0.19

Health Sciences Centre and the 1.5 Tesla General Electric Scanner (Horizon LX software, General Electric Medical Systems, Milwaukee, WI) at the IWK Health Centre. At Wayne State University, MRI studies were conducted at the Children's Hospital of Michigan Imaging Center on a 1.5 Tesla scanner (Horizon LX software, General Electric medical Systems, Milwaukee, WI). On the Dalhousie and Wayne State University GE MRI scanners, a 3 dimensional spoiled gradient echo pulse (SPGR) sequence was utilized to obtain high-resolution images for volumetric analysis (parameters: 124 slices, 1.5 mm thick coronal contiguous slices through the entire brain, perpendicular to the anterior commissure–posterior commissure line, echo time=5 ms, repetition time=25 ms, acquisition matrix=256×256, field of view=24 cm, flip angle=10°). On the Dalhousie Siemens MR scanner, a high-resolution anatomical coronal fast low angle shot (FLASH) sequence was used. Parameters were as follows: TR=25 ms, TE=5.40 ms, Flip=40°, Slice thickness=1.45 mm, 124 slices, matrix=256×256 pixels. On the University of Pittsburgh MR scanner a three dimensional SPGR acquisition in the steady state pulse sequence was utilized to obtain 1.5 mm coronal images (TE=20 ms, TR=40 ms, acquisition matrix=256×192, FOV=20 cm, flip angle=10°). Image acquisition has been described in detail in our previous reports (Gilbert et al., 2000; MacMaster and Kusumakar, 2004a,b; MacMaster et al., 2006; Nolan et al., 2002; Rosenberg et al., 1997; Szeszko et al., 2004a,b). All MRI scans were reviewed to rule out any clinically significant abnormalities. Hence the acquisition parameters were nearly identical in the Dalhousie and Wayne State University samples. The University of Pittsburgh sample was very close with regard to TE and TR and identical with regard to resolution. As this analysis does not rely on grey/white matter segmentation, the TE/TR/Flip is not as critical. Again, the resolution was nearly identical (~ 1×1×1.5 mm) for all scanners in this study. The pituitary, by nature of its anatomical placement, is quite separate and easy to distinguish from surrounding structures. Indeed, in a recent multi-site high field feasibility study using very different acquisition methods, anatomical measures were very comparable among the subjects scanned at three sites (MacMaster et al., unpublished observation).

Pituitary measurement has been described previously by MacMaster and Kusumakar (2004b), MacMaster et al. (2006). Pituitary volume was measured with National Institute of Health image software (version 1.62) at Wayne State University. A semi-automated segmentation algorithm for obtaining reliable quantitative neuroanatomical measurements was used for the University of Pittsburgh sample (Keshavan et al., 1995). Validation of this method by a point-counting stereological approach based on Cavalieri's theorem of systematic sampling has been achieved with both methods having documented validity and sensitivity (Keshavan et al., 1995). The University of Pittsburgh sample neuroanatomical measurements were conducted using the BRAINS2 image analysis software (Magnotta et al., 2002). Neuroanatomical boundaries of the pituitary gland were determined by reference to standard neuroanatomical atlases (Daniels et al., 1987; Talairach and Tournoux, 1988) with specific definitions adapted from previously published neuroimaging studies of the pituitary (Doraiswamy et al., 1990, 1991a,b; Krishnan et al., 1991; MacMaster and Kusumakar, 2004b; MacMaster et al., 2006; Sassi et al., 2001; Thomas and De Bellis, 2004; Tien et al., 1992). The superior border of the pituitary was identified as the optic chiasm and infundibular recess of the third ventricle. The sphenoid sinus was used to mark the inferior border of the pituitary. Serial coronal slices (each slice 1.45 mm thick) were used for measuring the pituitary. The serial measures of pituitary area were summed and multiplied by the slice thickness. The number of coronal slices used to quantify the pituitary gland ranged from 5–9 slices, with an average (±SD) of 6.77±1.21 slices. As the volume was acquired in a 3D mode, sagittal views were also used to guide and enhance precision of measurement. Three raters made all measurements, blind to any identifying subject or clinical information. Previously reported inter-rater reliabilities were high for pituitary measurements (intraclass r=0.83 to 0.98; intrarater=0.92) (MacMaster and Kusumakar, 2004b).

Statistical methods

Analysis of covariance (ANCOVA) was used to compare ten groups based on subgroups of age (7 to 9, 10 to 13, 14 to 17, 18 to 21, 22 to 35) and sex (male/female) using Statistica (StatSoft, Inc., Tulsa, OK, USA). Planned comparisons included males=−1 with females=1. Age was used as a covariate as age had demonstrated a strong relationship with pituitary gland volume previously and within this dataset (MacMaster and Kusumakar, 2004b; MacMaster et al., 2006; Takano et al., 1999). Pearson correlations were used to examine the relationship between age and pituitary volume using SPSS (SPSS Inc, Chicago, IL, USA). For the correlations, groups were limited to 19 years of age and younger and 20 years of age and older. This was done to improve the statistical power for the correlations by keeping the sample sizes large. Comparison of correlation coefficients was done using MedCalc software (MedCalc software, Mariakerke, Belgium).

Results

Groups comparisons

Pituitary gland volume differed between sex/age groups (F=3.55, df=2, 143, p=0.03, see Table 2, Fig. 1). Females demonstrated larger pituitary glands than males in the age 14 to

Table 2
Mean and STD (standard deviation) for age groups by sex

	Males			Females		
Age group	*N*	Mean	STD	*N*	Mean	STD
7 to 9	8	0.51	0.21	11	0.39	0.11
10 to 13	17	0.54	0.21	14	0.54	0.13
14 to 17	25	0.62	0.15	23	0.72	0.13
18 to 21	12	0.64	0.10	14	0.65	0.12
22 to 35	15	0.68	0.18	15	0.72	0.18

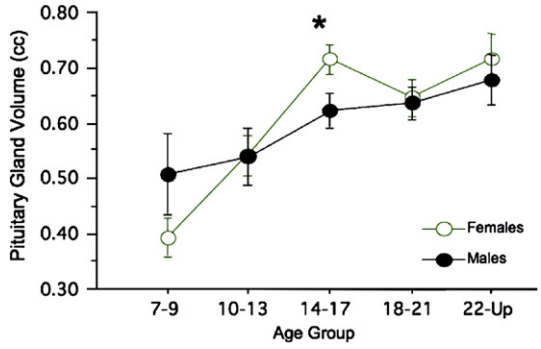

Fig. 1. Mean (standard error) of pituitary volume (*y*-axis) by sex for each age group (*x*-axis). *Significantly different.

17 year old groups ($p=0.04$). No other differences were noted between the sexes for the remaining age groups. Within the males, pituitary gland volume was smaller in the 7 to 9 year old ($p=0.01$) and 10 to 13 year old ($p=0.01$) when compared to the 22 to 35 year old males. No other differences within the males were noted. Within the females, the youngest group (7 to 9 years of age) was smaller than all other female age groups (10 to 13: $p=0.02$, 14 to 17: $p<0.0001$, 18 to 21: $p=0.0001$, 22 to 35: $p<0.00001$). Additionally, the 10 to 13 year old females were smaller than 14 to 17 year olds ($p=0.001$) and 22 to 35 year olds ($p=0.003$). No other differences within the females were noted.

Correlation with age

Overall, age was strongly correlated with pituitary gland volume ($r=0.40$, $p<0.0001$). Under age 19 years, the correlation remained ($r=0.46$, $p<0.0001$), while in older subjects it was a considerably weaker relationship ($r=0.30$, $p=0.03$). These two correlation coefficients were not significantly different however (z statistic $=1.07$, $p=0.28$). There was no correlation between age and pituitary gland volume in young males ($r=0.20$, $p=0.17$) and older males ($r=0.06$, $p=0.76$). These two correlation coefficients were not significantly different (z statistic $=0.56$, $p=0.57$). In females, younger subjects demonstrated the correlation between age and pituitary volume ($r=0.72$, $p<0.0001$) while the older females showed a weaker relationship ($r=0.55$, $p=0.005$). These two correlation coefficients did not differ (z statistic $=1.14$, $p=0.26$). The correlation between age and pituitary volume did differ between young males and young females (z statistic $=0.72$, $p=0.0005$) while older males vs. older females demonstrated a trend (z statistic $=1.86$, $p=0.06$).

Discussion

In this study, we report that younger females had significantly larger pituitary gland volume than young males (14 to 17 years of age). In the other age groups, no sex difference was observed. Within each of the sex groups, younger subjects had significantly smaller pituitary glands than older subjects and this was more robust in the females. Both young and old females demonstrated a correlation between pituitary volume and age. Males did not show this relationship. These findings are consonant with previous reports of sex differences in pituitary volume, with females being larger than males (Peyster et al., 1983, 1986; Suzuki et al., 1990; Doraiswamy et al., 1992; Tsunoda et al., 1997). However, these findings are not consonant with Lurie et al. (1990) who did not note any sex differences with regard to pituitary volume. The subjects used in that report (Lurie et al., 1990) were older, and no adolescent subjects included so they may have missed the primary effect noted here.

The fundamental question arising from these findings is why does the volume differ between the sexes? The terms puberty and adolescence are sometimes confused (Sisk and Foster, 2004). Puberty is the activation of the hypothalamic–pituitary–gonadal (HPG) axis that results in gonadal maturation. Adolescence, on the other hand, refers more commonly to the maturation of social and cognitive behaviors to the adult levels. The two are inextricably linked to each other however. Given the hormonal changes that occur as a result of puberty during adolescence (and development in general), changes in both pituitary cell volume and number are distinct possibilities. In central precocious puberty, a larger pituitary gland has been noted (Kao et al., 1992; Sharafuddin et al., 1994). In female mice, the number of somatotrophs and lactotrophs increased with age as well (Sasaki, 1988). It may be the different hormonal changes in males and females in childhood and adolescence are reflected as a difference in gland volume during this period. The earlier onset of puberty in girls, as compared to boys, may be at the root of the sex difference in pituitary volume noted here. Indeed, growth spurts have been noted in previous reports that may result form pubertal changes (Hayakawa et al., 1989; Elster et al., 1990; Argyropoulou et al., 1991; Takano et al., 1999). This spurt, by occurring in females prior to males, may lead to a temporary difference in volume between the sexes. This conjecture is further supported by our exploratory analysis, which found that the sex difference was most prominent between the ages of 14 and 17 years of age.

The main strength of this study is its large sample comprised of healthy subjects across a wide age range. Secondary to that, the quantification of pituitary volume using 3 dimensional high-resolution MR images is a strength as well. The main limitation of this study is the lack of direct endocrine measures of the pituitary hormones. Another limitation is the cross-sectional nature of the study. A longitudinal study would offer robust information on pituitary development. A lack of Tanner stage data on all the subjects is also a limitation given that this is most commonly accepted method for assessing pubertal stages. Finally, a lack of a robust analysis of the relationship between body size and pituitary volume is a limitation. Of course, the multi-site nature of the study is both a strength and a limitation. The sequences were not perfectly identical and we did not have direct data assessing reliability across sites either in vivo or in phantoms. However, the resolution of the tissue was very similar across sequences. In conclusion, we have noted significant sex and age effects in the pituitary gland in healthy subjects. This study provides fresh evidence of sex differences in developmental morphology.

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