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PUBERTY IN THE CORPUS CALLOSUM

M. C. CHAVARRIA,[a] F. J. SÁNCHEZ,[b] Y.-Y. CHOU,[c] P. M. THOMPSON[a,d,e,f,g,h,i,j] AND E. LUDERS[a]*

[a] *Department of Neurology, UCLA School of Medicine, Los Angeles, CA, United States*

[b] *Department of Counseling Psychology, University of Wisconsin, Madison, WI, United States*

[c] *Image Processing Core, Center for Neuroscience and Regenerative Medicine, Bethesda, MD, United States*

[d] *Imaging Genetics Center, Institute for Neuroimaging and Informatics, USC Keck School of Medicine, Los Angeles, CA, United States*

[e] *Department of Neurology, USC Keck School of Medicine, Los Angeles, CA, United States*

[f] *Department of Psychiatry, USC Keck School of Medicine, Los Angeles, CA, United States*

[g] *Department of Radiology, USC Keck School of Medicine, Los Angeles, CA, United States*

[h] *Department of Engineering, USC Keck School of Medicine, Los Angeles, CA, United States*

[i] *Department of Ophthalmology, USC Keck School of Medicine, Los Angeles, CA, United States*

[j] *Department of Psychiatry & Biobehavioral Sciences, Semel Institute for Neuroscience & Human Behavior, UCLA, Los Angeles, CA, United States*

Abstract—Adolescence is an important period for brain development. White matter growth is influenced by sex hormones such as testosterone, and the corpus callosum—the largest white matter structure in the human brain—may change structurally during the hormone-laden period of adolescence. Little is known about puberty's relationship to structural brain development, even though pubertal stage may better predict cognitive and behavioral maturity than chronological age. We therefore aimed to establish the presence and direction of pubertal effects on callosal anatomy. For this purpose, we applied advanced surface-based mesh-modeling to map correlations between callosal thickness and pubertal stage in a large and well-matched sample of 124 children and adolescents (62 female and 62 male) aged 5–18 years from a normative database. When linking callosal anatomy to pubertal status, only positive correlations reached statistical significance, indicating that callosal growth advances with puberty. In tests of differences in callosal anatomy at different stages of puberty, callosal growth was concentrated in different locations depending on the pubertal stage. Changing levels of circulating sex hormones during different phases of puberty likely contributed to the observed effects, and further research is clearly needed. Direct quantification of sex hormone levels and regional fiber connectivity—ideally using fiber tractography—will reveal whether hormones are the main drivers of callosal change during puberty. These callosal findings may lead to hypotheses regarding cortical changes during puberty, which may promote or result from changes in inter-hemispheric connectivity.

Key words: corpus callosum, development, gender, pubertal status, sex.

INTRODUCTION

Adolescence is a critical period for human brain development, and much research has been devoted to the anatomical study of teenage brains. Hu et al., for example, linked pubertal status to volumetric changes in medial temporal lobe structures (Hu et al., 2013). Bramen et al. addressed puberty effects on medial temporal lobe, thalamic, caudate, and cortical gray matter volumes as well as on cortical thickness (Bramen et al., 2011, 2012). These brain measures were related to measures of physical sexual maturity and also to measures of testosterone. Similarly, Perrin et al. (2008) and Paus et al. (2010) obtained actual testosterone measures from the adolescent brain while also genotyping a functional polymorphism in the androgen receptor gene to see if it moderated the effect of testosterone on different tissue types (Perrin et al., 2008; Paus et al., 2010). The latter two studies revealed that characteristics of the androgen receptor gene moderated the impact of testosterone not only on gray matter, but also on white matter. Thus, it stands to reason that the corpus callosum—the largest white matter structure in the human brain (Lebel et al., 2010)—may display morphological changes during the hormone-laden period of adolescence.

The corpus callosum connects the cerebral hemispheres through over 200 million fibers of varying diameter and degree of myelination (Aboitiz et al., 1992). Numerous studies have found that dramatic changes occur in callosal micro- and macro-anatomy throughout childhood and adolescence (Allen et al., 1991; Giedd et al., 1996, 1997, 1999; Rajapakse et al., 1996; Thompson et al., 2000; Chung et al., 2001; DeBellis et al., 2001; Lenroot et al., 2007; Hasan et al., 2008, 2009; Muetzel et al., 2008; Lebel et al., 2010, 2012;

*Corresponding author. Address: Department of Neurology, UCLA School of Medicine, 635 Charles Young Drive South, Suite 225M, Los Angeles, CA 90095-7334, United States. Tel: 1-310-267-5121; fax: 1-310-206-5518.
E-mail address: eileen.luders@ucla.edu (E. Luders).

Abbreviations: DTI, diffusion tensor imaging; FDR, False Discovery Rate; GE, General Electric.

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Luders et al., 2010; Dennis and Thompson, 2013). Rather than uniformly changing over time and/or across the entire structure, the corpus callosum seems to display both temporally and spatially distinct changes. These region-specific growth patterns may reflect a permanent adjustment and fine-tuning of fibers (Luders et al., 2010), perhaps due to hormonal surges during adolescence. Recently, Blakemore et al. advocated more extensive research on puberty's relationship to structural brain development (Blakemore et al., 2010), suggesting that pubertal stage may better account for changes in cognition and behavior than simple chronological age.

To our knowledge, research linking callosal morphology to pubertal maturation status (rather than chronological age) is currently lacking. This study, therefore, was designed to explore the degree to which pubertal status was associated with changes in callosal anatomy. For this purpose, we applied advanced surface-based mesh-modeling methods and mapped correlations between callosal thickness and pubertal stage in a large and well-matched sample of 124 children and adolescents (62 female and 62 male) aged 5–18 years from a normative participant database (Evans, 2006). As sex differences in brain development have been found in white matter in general (Reiss et al., 1996; DeBellis et al., 2001; Wilke et al., 2007; Perrin et al., 2008; Paus et al., 2010) and callosal measures in particular (DeBellis et al., 2001; Lenroot et al., 2007; Luders et al., 2010), we also set out to assess the degree to which sex moderates the link between pubertal status and callosal thickness.

EXPERIMENTAL PROCEDURES

Participants

Scans were selected from "The NIH MRI Study of Normal Brain Development" database (Evans, 2006), which excluded participants who met criteria "established or highly suspected to adversely impact healthy brain development" (see Evans, 2006). Informed consent was obtained from parents and adolescents; and assent was obtained from child participants. All protocols and procedures were approved by the relevant Institutional Review Board at each evaluation site and at each coordinating center (Evans, 2006).

Given the aims of the study, only scans that included existing callosal contours (Luders et al., 2010, 2011; Kurth et al., 2013), data on sexual development (Hu et al., 2013), and puberty scores of less than 4—as measured by the Pubertal Development Scale (Petersen et al., 1988)—were included. The Pubertal Developmental Scale has been found to be both valid and reliable in discerning subjects' pubertal status (Petersen et al., 1988). It is a non-invasive, self-reported measure of the physical presentations of puberty that develop concomitantly with underlying changes in circulating sex hormones. As previously described (Hu et al., 2013), the Pubertal Development Scale is based on five categories for each sex (male/female), ranked 1 through 4, with 1 = "not started," 2 = "barely started," 3 = "definitely under way," 4 = "completed." For girls, the categories include height growth spurt, body hair growth, skin changes, breast growth, and menstruation started (1 = no; 4 = yes). For boys, the categories include height growth spurt, body hair growth, skin changes, voice deepening, and facial hair. Averaging the values across all categories results in the puberty score (i.e., a continuous variable between 1 and 4). For the purpose of this study, we excluded individuals with an average score of 4 because having "completed" puberty, they were outside our scope of interest. Consequently, the final sample consisted of 124 participants (62 males; 62 females) between ages 5 and 18 (mean ± SD: 11.8 ± 3.2 years).

We subsequently devised three subgroups based on puberty score: Group 1 (G1) included 62 participants with puberty scores of less than 2 (puberty score < 2), Group 2 (G2) contained 30 participants with puberty scores including 2 but less than 3 ($2 \leqslant$ puberty score < 3), and Group 3 (G3) included 32 participants scoring 3 and above but less than 4 ($3 \leqslant$ puberty score < 4). Within each group (G1; G2; G3), we balanced the number of boys and girls (31:31; 15:15; 16:16) while matching them closely for the proportion of non-right-handed participants (3:2; 1:2; 4:3), as summarized in Table 1. As previously described (Kurth et al., 2013), to determine handedness, subjects were asked to perform eight different activities, modified from the Edinburgh Handedness Inventory (Oldfield, 1971). The use of the right hand for each activity was scored as 1; the use of the left hand was scored as 0. Participants with a total score of < 7 were classified as non-right-handed. There were no significant differences between the three groups with respect to parental education (using six distinct categories for the mother and the father separately) or the combined annual household income (using ten distinct categories). In contrast, as expected, there were significant differences with respect to chronological age between the three groups (Table 1), with the mean age being smallest in the groups with the lowest maturation status, and largest in the groups with the highest maturation status (G1 < G2 < G3).

Image acquisition

Images were obtained on 1.5 T systems from General Electric (GE) or Siemens Medical Systems (Siemens) using a 3D T1-weighted spoiled gradient recalled (SPGR) echo sequence with the following parameters: repetition time (TR) = 22–25 ms, echo time (TE) = 10–11 ms, excitation pulse = 30°, refocusing pulse = 180°, orientation: sagittal; field of view: anterior-posterior (AP) = 256 mm; left-right (LR) = 160–180 mm (whole-head coverage). The voxel size was set to 1 mm^3, except on GE scanners, where the maximum number of slices was 124, and hence the slice thickness was increased to 1.5 mm in the sagittal plane (Evans, 2006). Importantly, the three groups were comparable with respect to the systems used to acquire the scans. More specifically, 17 out of the 62 subjects (Group 1), 8 out of the 30 subjects (Group 2), and 10 out of the 32 subjects (Group 3) received a Siemens scan. Scanner-specific information for four subjects (all in Group 1) was not