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Review article

Puberty and structural brain development in humans

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ABSTRACT

Adolescence is a transitional period of physical and behavioral development between childhood and adulthood. Puberty is a distinct period of sexual maturation that occurs during adolescence. Since the advent of magnetic resonance imaging (MRI), human studies have largely examined neurodevelopment in the context of age. A breadth of animal findings suggest that sex hormones continue to influence the brain beyond the prenatal period, with both organizational and activational effects occurring during puberty. Given the animal evidence, human MRI research has also set out to determine how puberty may influence otherwise known patterns of age-related neurodevelopment. Here we review structural-based MRI studies and show that pubertal maturation is a key variable to consider in elucidating sex- and individual- based differences in patterns of human brain development. We also highlight the continuing challenges faced, as well as future considerations, for this vital avenue of research.

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1. Introduction

Puberty is an important period of development that occurs during adolescence. However, only recently has the notion been accepted that hormonal changes during puberty may continue to remodel and facilitate sexual differentiation of the brain. As outlined in a recent review (Juraska et al., 2013), sexual differentiation in mammals was originally thought to occur during a relative finite period of prenatal and early postnatal development, with sex-specific increases in testosterone leading to masculinization along with defeminization of the male brain. In recent years, however, animal studies on the impact of pubertal hormones have revealed that the brain continues to be remodeled and is even further sexually differentiated by sex steroids during pubertal development (see Juraska et al. (2013) for extensive review of the animal literature). Similarly, the field of neuroimaging has also begun to explore the role of puberty in human brain development. Here, we review the most up to date findings regarding pubertal maturation and typical brain development using magnetic resonance imaging (MRI). While it is important to note there are a number of physical growth and endocrine disorders that lead to early onset or delayed patterns of pubertal maturation (e.g. precocious puberty, Turner's Syndrome, Klinefelter Syndrome, etc.) (Bramswig and Dubbers, 2009), these conditions are not reported on below as the current review aims to highlight the role puberty may have on brain maturation, above and beyond age, in typically developing adolescents.

2. Puberty

Puberty is a complex set of neuroendocrine processes that occur between childhood and adulthood to produce internal and external physical changes to primary and secondary sexual characteristics allowing for sexual reproduction. Puberty is initiated by reactivation of the hypothalamic-pituitary-gonadal (HPG) axis. During prenatal and early postnatal development, the HPG axis is responsible for sexual differentiation and organization of the central nervous system through its production of high levels of gonadal steroids, including testosterone and estradiol. After the first year of postnatal life, the HPG-axis lays dormant until resurgence of gonadotropin releasing hormone (GnRH) is secreted from neurons in the median eminence of the hypothalamus to facilitate pubertal onset (Knobil, 1988; Grumbach and Styne, 2003). Pulsatile GnRH release stimulates the pituitary gland to produce gonadotropins (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)) into the circulatory system. While early production of LH and FSH occur during sleep (Boyar et al., 1972), the amplitude of LH and FSH release increase over time and eventually act on the ovaries and testes to produce gonadal sex steroids of estradiol and testosterone, respectively. The gonadal sex steroids result in breast and uterine tissue development as well as testes and penile size and structure. These processes, from the reactivation of GnRH release to the first signs of physical maturation, are thought to take up to a year for pubertal onset to be put in motion and are together referred to as "gonadarche" (Grumbach and Styne, 2003).

A separate endocrine function, known as "adrenarche", is the maturation of the adrenal glands, and is complementary to gonadarche in terms of its contribution to additional notable physical changes that occur during puberty. As the adrenal glands mature from approximately ages 6–8 years in girls and 7–9 years in boys, they produce an increase in adrenal androgens, including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione (Cutler and Loriaux, 1980; Parker, 1991; Grumbach and Styne, 2003). Increases in these androgens continue during gonadarche as well as into young adulthood (Saenger and Dimartino-Nardi, 2001), and are responsible for the development of under-arm and pubic hair.

While separate processes that lead to different external physical characteristics, both gonadarche and adrenarche are relevant in our quest to measure puberty and to further our understanding of how puberty may contribute to brain and behavioral development.

2.1. Measuring puberty in humans

2.1.1. Physical markers

Physical measurements may be used to estimate stages of gonadarche and adrenarche. Physical changes to secondary sexual characteristics are often captured by non-invasive techniques including self-report or clinical inspection by a trained medical expert. The most well recognized system for physical staging of pubertal development is based on Tanner (Marshall and Tanner, 1969, 1970). Breast (in females) or genital development (in males) (gonadarche) as well as pubic hair (adrenarche) are given ratings, including Stage 1 – prepubertal; Stage 2 – breast and genital development have begun; and up to Stage 5 – full maturity. The gold standard for Tanner staging continues to be physical examination by a trained medical expert using these criteria. However, alternative methods of self-report have become widely popular and also use Tanner staging to benchmark physical stages of pubertal development. For example, Tanner stage pictorial representations (Dorn et al., 1990) or line schematic drawings (Morris and Udry, 1980; Taylor et al., 2001) have been created for each of the 5 stages of breast development and pubic hair for females and testis growth and pubic hair for males. In addition, the Pubertal Development Scale (PDS) is a self-report verbal questionnaire that has been shown to be reliable and valid in assessing physical stages of pubertal maturation (Petersen et al., 1988). The PDS asks 5 questions for each individual, with items 1 thru 3 relating to growth in height, growth in body hair, and changes in skin (i.e. pimples), whereas items 4 and 5 include deepening of voice and facial hair growth for males or breast growth and menstruation (yes/no; age of menstruation) for females. PDS scores range from 1 to 4 ("not yet started" to "seems complete"), with the ability to calculate 1 of 5 Puberty Category Scores ("Prepubertal", "Early puberty", "Midpubertal", Late pubertal", "Postpubertal") (Carskadon and Acebo, 1993). A more recent advancement is a new automated audio computer-assisted self-interview (ACASI) to help aid children and adolescents in completing a self-report of sexual maturation (Lamb et al., 2011); although note the ACASI version is not widely accepted for use (Dorn and Susman, 2011).

2.1.2. Hormonal markers

Hormone levels can be assessed to allow for an objective measure to estimate pubertal development. Testosterone and estradiol levels increase in both males and females during puberty, but the magnitude is greater for testosterone in boys and estradiol in girls. Testosterone has been shown to be 45 times higher in adult males as compared to prepubertal boys (Biro et al., 1995), whereas estradiol levels have been shown to be 4–9 times higher in later adolescence as compared to childhood in girls (Ikegami et al., 2001). Adrenal and gonadal sex steroids, such as DHEA, DHEA-S, testosterone, and estradiol, may be obtained from various biological samples, including urine, saliva, and blood; although the latter two methods are more common in the literature. The total amount of testosterone and estradiol circulating in the bloodstream is either "bound" or "unbound". The majority of the bound testosterone or estradiol is attached during transport to sex hormone binding globulin (SHBG) (Selby, 1990). Only a very small amount (~1–2%) of the total is actually unbound, or "free", meaning it is biologically active and able to enter a cell and bind to a receptor.