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The Role of Puberty in the Developing Adolescent Brain

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Abstract: Adolescence refers to the period of physical and psychological development between childhood and adulthood. The beginning of adolescence is loosely anchored to the onset of puberty, which brings dramatic alterations in hormone levels and a number of consequent physical changes. Puberty onset is also associated with profound changes in drives, motivations, psychology, and social life; these changes continue throughout adolescence. There is an increasing number of neuroimaging studies looking at the development of the brain, both structurally and functionally, during adolescence. Almost all of these studies have defined development by chronological age, which shows a strong—but not unitary—correlation with pubertal stage. Very few neuroimaging studies have associated brain development with pubertal stage, and yet there is tentative evidence to suggest that puberty might play an important role in some aspects of brain and cognitive development. In this paper we describe this research, and we suggest that, in the future, developmental neuroimaging studies of adolescence should consider the role of puberty. *Hum Brain Mapp 31:926–933, 2010.*

Key words: puberty; adolescence; development; hormones; prefrontal cortex

INTRODUCTION

Adolescence is the period of physical, cognitive, and social maturation between childhood and adulthood [Lerner and Steinberg, 2004; Sisk and Foster, 2004]. The beginning of adolescence occurs around the onset of puberty and is therefore marked by dramatic changes in hormone levels and in physical appearance (including rapid physical growth, changes in facial structure, and the appearance of secondary sexual characteristics). Over the same interval, adolescents experience numerous changes in social, academic, and other environmental influences, and typically enter a stage of profound psychological transition. The end of adolescence is said to occur when an individual has attained a stable adult role, by which time the majority of pubertal transitions will have reached completion, at least in industrialized nations [Choudhury, 2010; Lerner and Steinberg, 2004]. Throughout adolescence, there are changes in the structure and function of the brain. Sexual dimorphisms in many of these changes suggest possible relationships to puberty.

Relatively little is known about the relationship between puberty and neural development in humans. However, a wealth of evidence from nonhuman animal studies indicates that the hormonal events of puberty exert profound effects on brain maturation and behavior [Cahill, 2006; Sisk and Foster, 2004; Spear, 2000]. These changes mould the perceptions, motivations, and behavioral repertoire of an individual, enabling reproductive behavior and independence [Sato et al., 2008]. In recent years, a small but

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growing number of human behavioral and neuroimaging studies, including in populations with endocrine disruptions, have provided tentative evidence that pubertal hormones might influence the structure and function of the developing human brain.

PUBERTY: THE BEGINNING OF ADOLESCENCE

Early adolescence is characterized by changes to the body as a result of puberty, which comprises three endocrine events: adrenarche, gonadarche, and activation of the growth axis [Dorn, 2006; Spear, 2000]. Gonadarche, which is often taken to constitute puberty per se, is a biological process beginning with activation of the hypothalamic-pituitary-gonadal axis and ending with the attainment of reproductive competence. This process usually begins between ages 8 and 14 years in females (mean age 11), and between ages 9 and 15 in males (mean age 12), in response to pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which stimulates pituitary production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH activate maturational changes in the gonads (ovaries or testes), which respond by attaining reproductive capacity (producing gametes). The maturing ovaries and testes also secrete the gonadal steroids estrogen and testosterone, respectively. These increases in gonadal steroids in turn trigger additional changes in the reproductive organs, and the appearance of secondary sexual characteristics [Susman and Rogol, 2004].

Adrenache, or activation of the hypothalamic-pituitary-adrenal axis, often begins earlier than gonadarche, typically between ages six and nine in females, and a year later in males [Dorn, 2006; Grumbach and Styne, 2003]. Adrenal androgens (weaker forms of gonadal testosterone) begin to rise at the start of adrenarche and continue to increase until they reach a peak in the early 20s [Worthman and Stallings, 1997]. These increases in adrenal androgens contribute to the development of secondary sexual characteristics such as axillary and pubic hair and changes in sweat glands/body odor. It is possible that adrenarche also gives rise to maturational effects that begin prior to the period usually considered as adolescence; however, these effects are not well understood [Dorn, 2006].

The third hormonal event that occurs during puberty is activation of the growth axis, resulting in a linear growth spurt at around age 12 in girls and age 14 in boys, as well as changes in body size and composition [Marshall and Tanner, 1969, 1970].

HORMONAL EFFECTS ON BRAIN AND BEHAVIOR

The gonadal steroid hormones estrogen and testosterone, as well as their weaker adrenal counterparts, influence the physical appearance of the body. They also affect the brain and behavior. These effects are hypothesized to occur via two relatively distinct processes: organization and activation [Schulz et al., 2009; Sisk and Foster, 2004]. Organizational effects occur pre- and perinatally, with waves of testosterone masculinizing and defeminizing neural circuits in males, and the absence of testosterone resulting in a female neural phenotype. Activational effects occur at puberty, as gonadal steroid hormones act on dormant neural circuits to elicit adult reproductive behaviors in context; a recent modernization of this dichotomy suggests that the hormonal events of puberty also organize neural circuits for adult social and reproductive behaviors [Schulz et al., 2009; Sisk and Foster, 2004]. Indeed, based on findings from nonhuman animal studies, it is suggested that the hormonal events of puberty trigger a second period of structural reorganization and plasticity in the brain [Sisk and Foster, 2004]. In humans, however, there is very little understanding of the specific relationships between puberty and adolescent brain development.

Animal studies indicate that sex steroid hormones exert three main effects on behavior at puberty, via specific brain structures. The first effect is the facilitation of directly reproductive behaviors, which occurs mainly via the hypothalamus. The second effect is via the reorganization of sensory and association regions of the brain, including visual cortex [Nunez et al., 2002], amygdala, and hippocampus [Hebbard et al., 2003; Romeo and Sisk, 2001; see also Shen et al., 2010]. This results in altered sensory associations, e.g. to the smell or sight of potential sexual partners or competitors [Sisk and Foster, 2004], which may facilitate some attentional and motivational changes at puberty. The third effect of puberty hormones occurs via reward-related brain structures such as the nucleus accumbens, and dopaminergic pathways to the prefrontal cortex. These effects are necessary for establishing strong motivation to seek out reproductive opportunities. For example, in the rodent nucleus accumbens, pubertal increases in testosterone remodel neural circuits influencing motivation toward reward-seeking behaviors, including sexual behavior [Sato et al., 2008]. It is possible that adrenarchel hormones (DHEA and DHEAS) begin to exert similar effects on brain and behavior prior to the onset of gonadarche, but these effects are poorly understood. There is clearly a need for more research focusing on the earliest stages of puberty/adrenarche to advance understanding of these aspects of puberty and adolescent brain development and behavior [see Dorn, 2006; for discussion].

MEASURING PUBERTY IN STUDIES OF ADOLESCENT BRAIN DEVELOPMENT

Relatively little is known about puberty-specific changes in human brain development. Advancing understanding

in these areas will require careful attention at two levels: conceptually and methodologically. Conceptually, this will require the development and refinement of models of adolescent brain development that address specific aspects of pubertal maturation (e.g. specific hormones) that are causally linked to specific aspects of brain and behavioral changes. Methodologically, it will require studies that are designed with the selection of samples and measures of puberty that permit testing of these specific hypotheses. Because age and pubertal maturation are often correlated (and age is easily measured with great precision and validity, while puberty is often estimated with rough categorical measures that are not easily validated), there is a need for studies with designs that explicitly disentangle puberty and age effects (e.g. recruiting samples that are the same age and grade level but differ on pubertal maturation, and then restudying longitudinally).

These goals raise a number of issues regarding how to measure specific aspects of pubertal maturation in human studies. For a start, puberty is neither a brief event nor a unitary phenomenon, but instead, comprises several distinct but temporally-overlapping processes that extend over several years [Dorn, 2006]. As described earlier, these processes include activation of adrenal, gonadal, and growth hormone systems, and in addition a variety of direct and indirect effects, from growth spurts to changing self-image. The most appropriate measure of puberty will therefore depend in part on the specific research question in each study.

A commonly used measure of puberty is Tanner Stage. Tanner staging categorizes individuals along an ordinal puberty scale from 1 to 5, on the basis of pubic hair and breast development in females, and pubic hair and genital development in males [Tanner, 1971; Tanner and Whitehouse, 1976]. Tanner staging by physical exam should be carried out by a trained clinician. There are several limitations to Tanner staging. The scale was developed with reference to a single ethnic group (there may be cross-ethnic differences) and in a relatively small sample of 200 children. Overweight girls will tend to be inaccurately staged, due to the reliance of the staging on breast development, which can be erroneously over-estimated in a purely visual examination. Despite these limitations, Tanner staging has historically been considered the gold standard for puberty measurement [Dorn, 2006].

In light of the above-mentioned concerns, it might be expected that Tanner staging by physical examination could be usefully supplemented by hormonal assays, since these measure adrenal and gonadal (or adrenal/gonadal-releasing) hormones upstream from their external physical effects. Hormone assays may be increasingly useful for measuring pubertal stage in the future; however, at the present time it is unclear how hormone measurements should be combined with (or used in conjunction with) other measures such as Tanner stages [see Shirtcliffe et al., 2009]. There are also other practical issues regarding hormonal measures, including cost, subject burden, and the fact that levels of different puberty hormones fluctuate in monthly and circadian cycles. Little research has been done comparing hormone levels in different biological samples (saliva, blood, urine) with clinician-assessed Tanner stages [see Dorn, 2006; Shirtcliffe et al., 2009], so it is unclear how much weight should be given to hormone levels. At a conceptual level, for example, some neurobehavioral changes at puberty may be the direct result of increasing hormone levels on specific neural systems during adolescent brain development (and thus best quantified by hormone measures) while other neurobehavioral changes may reflect more complex influences (e.g. changes in social experience that are more directly tied to the physical changes and social roles, and better linked to Tanner stages than any specific hormone change).

Tanner staging by physical examination by a qualified clinician can raise practical issues regarding appropriateness and convenience. Often this is best accomplished in the context of doing a brief "health" exam. That is, Tanner staging can be part of a normal physical health exam and therefore should not be associated with any stigma or ethical concerns (beyond a normal physical health check). However, the cost (clinician time, special room and equipment for a physical exam, and explaining the procedures to the adolescent and family) can make this impractical for many research studies. Therefore, it is valuable to consider alternative ways to quantify pubertal maturation, such as assessments by self-report questionnaire. A relatively large number of studies have assessed self-rated (or parent-rated) Tanner stage using the Petersen Development Scale [PDS; Petersen et al., 1988]. This is a questionnaire that includes items assessing hair growth, skin changes, and growth spurt, with sex-specific items i.e. menarche and breast development in females, and genital growth and facial hair in males. As such, the PDS measures a composite puberty score that includes the effects of adrenal and growth hormones, as well as gonadal hormones. Correlations with clinician-assessed Tanner stage are not especially high: one study found correlations between 0.61 and 0.67 in 11- to 13-year-old girls for the self-report PDS [Brooks-Gunn et al., 1987; correlations are even lower for parent-report PDS; see Shirtcliffe et al. 2009]. The extent to which these relatively low correlations are due to inaccurate self-rating, or to distinct constructs, such as the distinct effects of adrenal/growth versus gonadal hormones, needs to be evaluated. The PDS can be used with caution to estimate Tanner stage when a physical examination is not possible. However, if the research question does not concern hormone levels and Tanner stage, but instead relates to self-image and self-consciousness, or to puberty stage relative to peers, it can be argued that the PDS is the most relevant measure [see Dorn, 2006 for discussion]. In summary, researchers should give ample consideration to which aspect of puberty is most relevant to their research question and select their measures of puberty (and overall design of the study) accordingly.

PUBERTY AND STRUCTURAL BRAIN DEVELOPMENT AS MEASURED BY MRI

The advent of noninvasive brain imaging techniques, in particular magnetic resonance imaging (MRI), has enabled investigation of the development of the living human brain. Developmental changes that have been delineated using MRI include alterations in the amount of gray and white matter, and changes in white matter microstructure.

Adolescent Gray Matter Development

The amount of cortical gray matter (its density, volume, and thickness) changes during childhood and adolescence in a region-specific and predominantly nonlinear manner [Giedd et al., 1999; Shaw et al., 2008; Sowell et al., 1999; Tamnes et al., 2009; see e.g. Blakemore, 2008 for review]. Across much of the cortical surface, gray matter development conforms to an inverted-U shaped developmental trajectory, initially increasing in volume during childhood, reaching a peak in adolescence, and declining steadily into adulthood. Gray matter is composed of the cell bodies, dendrites and nonmyelinated axons of neurons, as well as glial cells and capillaries. Therefore, and based on evidence from histological samples [e.g. Huttenlocher, 1979], it has been suggested that the inverted-U shaped developmental trajectory of gray matter volume seen in human MR scans is due to dendritic outgrowth and synaptogenesis, followed by synaptic pruning [e.g. Giedd et al., 1999]. An early paper by Giedd et al. [1999] showed this inverted-U shaped pattern of gray matter development across the frontal, temporal, and parietal cortical lobes, although not all subsequent studies have provided clear replication of this pattern (e.g. Shaw et al., 2008; Tamnes et al., 2009). In Giedd et al., the frontal and parietal lobes attained peak gray matter volume at age 11 in girls and 12 in boys, before undergoing an extended sequence of thinning into adulthood. The ages at which these peaks in gray matter volume were observed correspond to the sexually dimorphic ages of gonadarche onset, which suggests possible interactions between puberty hormones and grey matter development. Other MRI studies have shown the gradual emergence of sexual dimorphisms across puberty, with increases in amygdala volume during puberty in males only, and increases in hippocampus volume in females only [Lenroot et al., 2007; Neufang et al., 2009]. Thus, it is possible that neuroanatomical development in certain brain regions is more tightly linked to puberty than it is in other brain regions. However, no direct measures of puberty were acquired in these studies.

The Role of Puberty in Gray Matter Development

In recent years, a number of adolescent MRI studies have investigated in more detail the relationships among structural brain development, gender, and puberty. An adolescent structural MRI study by Peper et al. [2009b] showed evidence for a positive association between testosterone levels and global gray matter density in males (and not in females), while females showed a negative association between estradiol levels and both global and regional gray matter density. Whether these gender differences can be replicated, and whether they are indeed region-specific, remains to be seen. Elsewhere, evidence has been shown for region- and gender-specific effects of pubertal measures on structural brain measures. For example, Neufang et al. [2009] investigated relationships between gray matter volume, gender and pubertal measures in participants aged 8–15. The pubertal measures were physician-assessed Tanner stage and plasma concentrations of gonadotropic (LH, FSH) and gonadal (testosterone, oestrogen) hormones. Irrespective of gender, there was a positive relationship between pubertal measures (Tanner stage and testosterone) and gray matter volume in the amygdala, and a negative relationship between these measures and hippocampal volume. In addition, there were gender-specific effects: females showed a positive relationship between estrogen levels and limbic gray matter, and males showed a negative relationship between testosterone and parietal cortex gray matter. All of these findings are preliminary and require replication, but they represent an important first step in this new area of research.

Adolescent White Matter Development

Many MRI studies show a steady linear increase in global white matter volume between childhood and adolescence, with this increase slowing and stabilizing into adulthood [Giedd et al., 1999; Tamnes et al., 2009]. This increase differs between the sexes across adolescence, with males showing considerably steeper age-related increases in white matter volume than do females [e.g. Perrin et al., 2008, 2009]. The increase in white matter volume has been attributed to progressive age-related axonal myelination observed in histological samples [Benes et al., 1994; Yakovlev and Lecours, 1967], or alternatively, to increasing axonal calibre [Paus et al., 2008].

In addition to changes in white matter volume, studies have shown concurrent changes in white matter microstructure. Fractional anisotropy (FA) is an MRI measure describing the extent to which the diffusion of water molecules in the brain is anisotropic (not equal in all directions). High FA values shown in diffusion tensor imaging (DTI)-MRI studies are thought to reflect increasing organization of white matter tracts, due to processes including myelination. Studies consistently show an increase in FA during adolescence, for example, in the frontal lobes [Barnea-Goraly et al., 2005]. To date, studies have not shown evidence for sexually dimorphic developmental trajectories of FA.

Another MRI measure that has been used developmentally is the myelin-transfer ratio [MTR: Perrin et al., 2008,

2009]. MTR provides information on the macromolecular content (e.g. myelin content) of white matter tissue. Unlike for FA, there is evidence for sexually-dimorphic developmental trajectories of MTR. Specifically, MTR has been shown to decrease with age across adolescence in males only [Perrin et al., 2008, 2009]. It has been suggested that this decrease in MTR reflects increasing axonal caliber, since the larger the caliber, the fewer axons will fit into the same unit of imaged volume and this will result in a relative decrease in the amount of myelin [Paus et al., 2008]. Questions remain regarding these intriguing findings using MTR: for example, whether these sex differences emerge prior to, or exclusively during, adolescence.

The Role of Puberty in White Matter Development

Developmental white matter trajectories differ as a function of pubertal measures. One study reported a positive relationship between LH concentration and white matter density at age nine; this relationship did not differ between the sexes [Peper et al., 2009a]. However, it has been shown that during adolescence, developmental trajectories of white matter volume, as well as the MTR, differ between the sexes. Recent studies by Perrin et al. [2008, 2009] have investigated whether this difference may be due to puberty hormones downstream from LH. Perrin et al. [2008] investigated the relationship between expression levels of a gene encoding the androgen (testosterone) receptor, and white matter development, in males. The results showed that variance in trajectories of white matter development in males was indeed related to gene expression levels, suggesting that effects of testosterone may be responsible for the sexually dimorphic relationship between age and white matter volume. In Perrin et al. [2009], evidence was presented for sexual dimorphism in the mechanism underlying adolescent increases in white matter volume.

In summary, a number of studies have shown evidence that gonadotropic and gonadal puberty hormones influence structural brain development. Further work is needed to investigate mechanisms underlying region-specificity and sexual dimorphism in the relationship between puberty hormones and brain development. Finally, studies thus far have not investigated possible interactions between the timing of pubertal events and structural brain development; this is an area for future investigation.

THE ROLE OF PUBERTY IN COGNITIVE DEVELOPMENT

Only a small number of empirical behavioral studies have focused on the effect of puberty on a particular cognitive process. Some of the earliest studies focused on face processing. A study by Carey et al. [1980] showed that, while performance in a facial identity recognition task improved steadily during the first decade of life, this was followed by a decline in performance at approximately age 12. This decline may be due to puberty, rather than to age per se, as a later study showed that females at mid-puberty performed worse those at pre- or postpuberty, when these groups were matched for age. More recently, evidence for a pubertal "dip" in facial emotion processing was shown [McGivern et al., 2002]. In this study, male and female participants aged 10–17 performed a match-to-sample task in which faces showing emotional expressions were matched with emotion words. An increase in reaction time of around 10–20% was shown at an age corresponding roughly to puberty onset (age 10–11 years in females, 11–12 in males), which then declined during adolescence to reach prepuberty levels at age 16–17. However, this study did not assess puberty stage. These results should now be replicated, for example with more accurate hormonal measures of puberty, and using longitudinally assessed cohorts. Further studies should also investigate whether these results are specific to face processing, or are a more domain-general effect of adolescent cognitive development.

The Effect of Sex Hormones on Cognitive Function

There is evidence that hormones can have different influences on behavior during puberty than in adulthood. For example, the challenge model of testosterone-aggression associations suggests that while testosterone levels increase during puberty, aggressive behavior does not show any simple relationship with testosterone during adolescence [Archer, 2006]. Rather, there is emerging evidence from both human and nonhuman primate studies that testosterone increases motivation to attain higher status, but the specific effects on behavior are dependent on the social and developmental context. It is important to emphasize the complexity of these issues-that is, we are at a very early point in integrating animal research (where experiments can be designed to elucidate specific hormonal effects on specific neural systems) and human studies, to address the important but complex issues regarding cognitive, emotional, and motivational changes directly linked to puberty [see Dahl and Gunnar, 2009, for further discussion of some of the clinical and public health implications].

However, there are a few areas of convergence emerging from research in this area that highlight promising areas of progress. For example, there is increasing evidence that adolescent changes in sensation-seeking may include some puberty-specific changes, and may provide new insights into adolescent risk taking. Sensation-seeking is one of the developmental contributors to risk behaviors and is more likely to emerge during adolescence than any other time period [e.g. Arnett and Balle-Jensen, 1993]. Sensation-seeking tendencies appear to be more strongly linked to

puberty than to age [Spear, 2000]. One of the first studies to demonstrate the specific link between sensation-seeking and puberty focused on adolescents within the narrow age range of 11–14 years. Boys and girls with more advanced pubertal development had higher ratings of sensation seeking and greater drug use [Martin et al., 2002]. More recently, Steinberg and Monahan [2007] have found evidence that parsing sensation-seeking from the broader construct of impulsivity (which is sometimes experimentally confounded with sensation-seeking) shows an inverted U-shaped developmental trajectory, peaking at the time of pubertal maturation, and significantly linked to measures of puberty in boys. Dahl and Gunnar [2009, for further discussion] have reported a broader range of affective changes linked to puberty, for example emotions in response to social situations.

In summary, few studies as yet have investigated the link between puberty and cognitive development, and this area will be an interesting focus for future research.

THE ROLE OF PUBERTY IN FUNCTIONAL BRAIN DEVELOPMENT AS MEASURED BY FMRI

A very small number of functional neuroimaging studies conducted thus far have included measures of puberty. However, a number of adult and adolescent functional MRI (fMRI) studies show gender differences in neural activity in a range of cognitive paradigms (a full review of these findings it is beyond the scope of this article). Some gender differences may be due to prenatal sex hormone effects, to puberty-independent effects of genes encoded on the sex chromosomes, or to gender-specific environmental effects across the lifetime. However, certain of these effects may be attributable to puberty. These effects could be mediated by effects on neural-to-hemodynamic coupling, via organizational or activational effects on neural responsiveness, influences on cognitive processing, or via indirect influences of pubertal transitions on cognitive processing via stereotypes and identity. Further studies are needed to elucidate these possible relationships.

Several fMRI studies have been conducted in populations with endocrine disruptions. Although the results are difficult to interpret with regards typical puberty and adolescence (these populations are hormonally abnormal prior to puberty onset), they provide converging evidence that determinants or correlates of puberty influence functional brain activity. For example, an fMRI study by Mueller et al. [2009] compared brain activity during a facial emotion-processing task between adolescent males with familial hyperandrogenism (causing excess testosterone from an early age). Relative to controls, the group with excess testosterone showed elevated hippocampal activity during fear processing, as well as faster behavioral responses to faces showing fearful expressions. In an fMRI study by Ernst et al. [2007], seven male and seven female adolescents with congenital adrenal hyperplasia (resulting in excess testosterone *in utero*) were compared with age- and gender-matched controls in a similar facial emotion-processing task. In contrast to the study by Mueller et al., no group differences were reported in the hippocampus. However, in the female clinical group, there was enhanced amygdala activity during fear and anger processing, relative to female controls. The enhanced amygdala activity in the female clinical group was similar to that in male controls, which suggests a mediating effect of testosterone.

CONCLUSION

Puberty represents a period of profound transition in terms of drives, emotions, motivations, psychology and social life. Recent preliminary evidence from developmental MRI studies has suggested that stage of puberty might play an important role in adolescent brain development, perhaps more so than chronological age. Further behavioral and neuroimaging studies are needed in which accurate and reliable measures of puberty are taken, to shed light on how puberty hormones influence the development of brain structure and function. Clearly, there is great value in achieving a better understanding of the relationships between the brain, cognition, behavior, and puberty. However, these goals will require conceptual and methodological advances focusing on how best to integrate different pubertal measures within developmental studies of adolescent brain and behavioral maturation.

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