The Role of Puberty in Human Adolescent Brain Development

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Abstract Many of the physical, social and behavioural changes associated with adolescence are linked with puberty, the physiological process resulting in reproductive competence. Recent research has demonstrated that the human brain undergoes significant change during adolescence, but little is known about the role of puberty in this process. This review summarises findings from current human imaging studies regarding the relationship between both structural and functional brain development and pubertal maturation, and it explores how these occur in the context of changing chronological age and pubertal status. The findings across these structural and functional MRI studies are consistent with the hypothesis that pubertal hormones interact with the neuroanatomical and neurocognitive changes seen during puberty (Blakemore et al., Hum Brain Map 31:926–933, 2010; Sisk and Foster, Nat Neurosci 7:1040–1047, 2004) and that some aspects of brain development in adolescence might be more closely linked to the physical and hormonal changes of puberty than to chronological age.

Introduction

Adolescence is a key stage in human development, incorporating physical, social, and psychological changes and culminating in the attainment of a stable adult role. During adolescence, new behaviours are laid down, educational, socioeconomic and relationship trajectories are canalized, and a new epidemiology of disease burden emerges (Patton and Viner 2007). Many of these changes have been linked with puberty, the biological process that culminates in reproductive competence and a defining event of adolescence (Sisk and Foster 2004). Research has demonstrated that the human brain undergoes significant change during adolescence, as determined by age, but little is known about how puberty influences the development of the human brain.

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Since there is a normal variation of four to five years in the timing of onset of puberty in healthy humans (Parent et al. 2003), pubertal development is partially dissociable from chronological age. Nevertheless, puberty and age are inevitably highly correlated when considered over the whole age range of adolescence. Most developmental studies have not tried to dissect these two differing developmental variables, either inferring pubertal effects using age-based studies (e.g. Giedd et al. 1999) or focussing on puberty effects in a wide age range (e.g., Peper et al. 2009). Where studies have attempted to dissociate age from pubertal development, different techniques have been employed. One method involves limiting the age range studied to a sufficiently narrow range that puberty is no longer correlated with age (e.g., Forbes et al. 2010). An alternative approach is to statistically incorporate age as a confounding variable within an analysis looking at pubertal stage (e.g., Op de Macks et al. 2011). Different methods may be best suited to different types of study, e.g., size of sample and cross-sectional vs. longitudinal.

This review summarises the findings from current human imaging studies regarding the relationship between both structural and functional brain development and pubertal maturation, and it explores how these occur in the context of changing chronological age and pubertal status.

Structural Brain Development and Puberty

The past 20 years have seen a major expansion in research on the structural development of the human adolescent brain, based largely on the results of cross-sectional and longitudinal magnetic resonance imaging (MRI) studies (Brain Development Cooperative Group 2012; Raznahan et al. 2011; Sowell et al. 2002). To date, studies of brain growth trajectories over adolescence have predominantly considered growth in relation to chronological age, with few exceptions (Paus et al. 2010; Raznahan et al. 2010). It has been hypothesised that the brain restructuring and development seen in adolescence might be specifically related to the hormonal influences that control the onset of and progression through puberty (Giedd et al. 1999; Lenroot et al. 2007; Peper et al. 2011; Sowell et al. 2002). Sex steroids such as testosterone (an androgen) and oestradiol (an oestrogen) have been shown to be capable of inducing both synaptogenesis and synaptic pruning in rats and non-human primates (Ahmed et al. 2008; Hajszan et al. 2008; Sato et al. 2008), with differential effects of androgens and oestrogens on different brain areas, which might be related to hormone receptor distribution (Clark et al. 1988; Sholl and Kim 1989). These differential effects across brain areas might provide an explanation for the diverging growth trajectories of particular brain structures between males and females that has been documented across studies and the resultant increasing sexual dimorphism in adolescence reported in some regions (Brain Development Cooperative Group 2012; Lenroot et al. 2007; Neufang et al. 2009; Sowell et al. 2002).

An early cross-sectional study by De Bellis and colleagues (2001) found significant correlations between Tanner stage (Marshall and Tanner 1969, 1970), a marker of physical pubertal development, and changes in grey matter (GM) volume, white matter (WM) volume and corpus callosum (CC) area in a sample of 118 children and adolescents aged 6.9–17 years. They reported a Tanner stage by age interaction in development and hypothesised that this might relate to differential hormone exposure in males and females in puberty (De Bellis et al. 2001). Subsequent cross-sectional studies have investigated pubertal development by considering both the physical changes of puberty and by measuring sex steroid hormone levels. A study looking at cortical GM and pubertal measures found region-specific correlations between GM density and both pubertal stage and oestradiol concentration in girls (Peper et al. 2009). Neufang and colleagues (2009) studied a sample of 46 healthy participants aged between 8 and 15 years of age, focussing on the association between brain volumes and both pubertal stage ($n = 46$) and testosterone concentration ($n = 30$). They found that males and females in later stages of puberty, and with higher circulating testosterone concentration, had larger amygdala volumes and smaller hippocampal volumes than their less well-developed peers (Neufang et al. 2009). A second study ($n = 80$; 10.75–13.48 years) investigating puberty and pubertal hormone correlations with GM volume again showed larger amygdala volumes in more pubertally mature males than in their less mature counterparts but showed the opposite trend in females, with decreasing amygdala volume with increasing testosterone levels (Bramen et al. 2011). They also studied other brain regions, including the hippocampus, thalamus, caudate and cortex, and reported significant decreases in volume in the right hippocampus and cerebral cortex in females, but no significant changes in males. The discrepant findings between these two latter papers could result from the relatively small sample sizes or the differing age ranges of the two studies, which also used different methods to extract the volumes of interest (Neufang et al. 2009: voxel-based morphometry; Bramen et al. 2011: surface-based reconstruction). This final study conducted multiple regression analyses incorporating both age and puberty measurements to study the relative contributions of both variables to the changing brain structure seen (Bramen et al. 2011). Puberty and age are highly correlated when considering adolescence as a whole, since puberty is a progressive process that usually begins during early-mid adolescence and develops over time. However, since there is a four- to five-year normal variation in the timing of onset of puberty (Parent et al. 2003), careful study design, appropriate age ranges of participants, and suitable analytical tools can allow puberty and age to be teased apart so that the differing contributions of each variable to development can be studied.

These studies have limited power due to relatively small sample sizes, which constrain our ability to attribute causality to this association or to investigate the effect of sex steroids on brain developmental trajectories during adolescence. Longitudinal analysis allows comparison of brain volumes both between participants and also within each participant over time and, therefore, can provide a measure not just of brain volume at a particular time point but also of

developmental trajectories for each of these subcortical regions by following what happens to each participant. This approach is particularly advantageous when looking at brain volumes, which vary substantially between individuals (Brain Development Cooperative Group 2012; Lenroot et al. 2007; Tamnes et al. 2013).

We recently conducted a study using longitudinal data to address some of these issues and to further explore the relationship between structural brain development and the correlated but physiologically distinct variables of chronological age and pubertal stage. This study included 275 individuals aged between 7 and 20 years, each of whom was scanned at least twice, with a total of 711 scans used in the study (Goddings et al. 2013). We focussed on the developmental trajectories of subcortical regions across adolescence, and we used multi-level modelling analyses to tease apart the effects of pubertal status (measured by Tanner stage) and chronological age. In this study, we found that the development of all regions examined was associated with pubertal maturation (Fig. 1; Goddings et al. 2013), and for many structures (females: amygdala, hippocampus, caudate, putamen; males: amygdala, putamen), models including both Tanner stage and age best described volume change over adolescence. Despite the close proximity of the subcortical structures explored, there were clear differences in their structural development during adolescence. These results might reflect the different mechanisms that influence macroscopic volume changes between structures, with varying influences

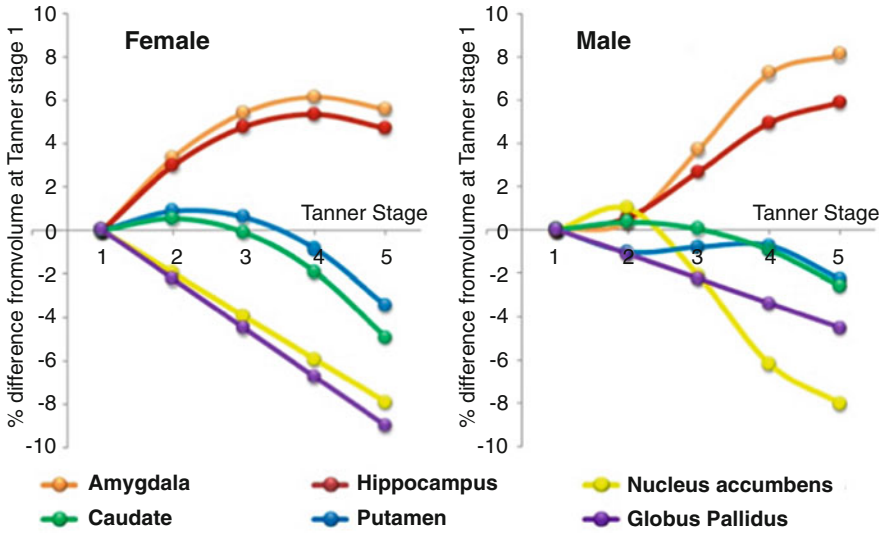

Fig. 1 Growth trajectories (in terms of % volume change) for subcortical regions in females and males across puberty. For each structure, the percentage volume was calculated for each pubertal stage as a proportion of prepubertal volume (at Tanner stage 1). This allows comparison between structures for relative changes in volume across puberty. For both sexes, the amygdala and hippocampus increased in volume over puberty, while the nucleus accumbens, caudate, putamen and globus pallidus decreased in volume (From Goddings et al. 2013)

of age and puberty between regions. Alternatively, the regions might undergo similar growth patterns but do so at different chronological time points.

These studies provide evidence for a role for puberty in the development of the human adolescent brain. Further large longitudinal studies incorporating both hormonal and physical indicators of puberty are needed to further explore this relationship and to tease apart puberty and age effects on structural brain maturation.

Functional Brain Development in Puberty

In addition to assisting in the investigation of changing brain structure over adolescence, MRI techniques can be used to assess changing brain function with development. Functional MRI (fMRI) techniques have allowed researchers to investigate the patterns of neural activation in subjects, as measured by recording blood-oxygen-level dependent (BOLD) signal changes while they perform specific tasks within the scanner, and to establish how these patterns develop from childhood to adulthood. Only a small number of functional neuroimaging studies of the adolescent brain have included puberty measures. These studies have focussed on a range of different behavioural tasks pertinent to adolescent development.

Two fMRI studies have been published assessing changes in face processing with puberty. Reading emotions from faces is an important skill for perceiving emotional states in others and is, therefore, likely to be of particular importance during adolescence (Dahl and Gunnar 2009). Both studies showed differential patterns of neural activation across puberty within the network of regions known to be involved in perception and reaction to emotional expressions. One study showed evidence of increased BOLD signal in the amygdala and ventrolateral prefrontal cortex to threatening faces in a pre/early puberty group compared with a mid/late puberty group (aged 11–13; Forbes et al. 2011). In a different study, with 10 and 13 year olds, Moore and colleagues (2012) found that participants in later stages of pubertal development showed increased signal in face processing regions when looking at affective facial expressions.. These studies reported some discrepant findings, which might reflect the use of different methods of assessing pubertal development or the administration of different tasks (Moore et al. 2012; Op de Macks et al. 2011).

A further aspect of emotional development that is likely to be important during adolescence is the ability to process social emotions. Social emotions require an individual to understand that other people have different mental states to their own and to be able to represent those mental states, a process known as mentalising. Examples of social emotions include ‘guilt’ and ‘embarrassment’. In contrast, basic emotions, e.g., ‘disgust’ and ‘fear,’ do not require this mentalising ability (Burnett et al. 2009). A network of regions involved in mentalising has been robustly demonstrated across a range of fMRI studies (see Blakemore 2012, for review), and the ongoing structural and functional development of this mentalising network

has been shown to continue across adolescence, as determined by chronological age (Mills et al. 2014). We conducted an fMRI study to explore whether the processing of social emotions by this mentalising network changes with puberty in adolescence. The study showed that girls (aged 11 to 13 years) with higher levels of pubertal hormones had increased activation of the anterior temporal cortex - one of the regions of the mentalising network - than their age-matched peers with lower levels of pubertal hormones (Fig. 2; Goddings et al. 2012). In contrast, activation in the prefrontal cortex, which is also involved in mentalising, showed no correlation with pubertal status but showed decreasing activation with increasing chronological age (Goddings et al. 2012), a finding that has been replicated in a number of studies (e.g., Burnett et al. 2009; see Blakemore 2012 for review).

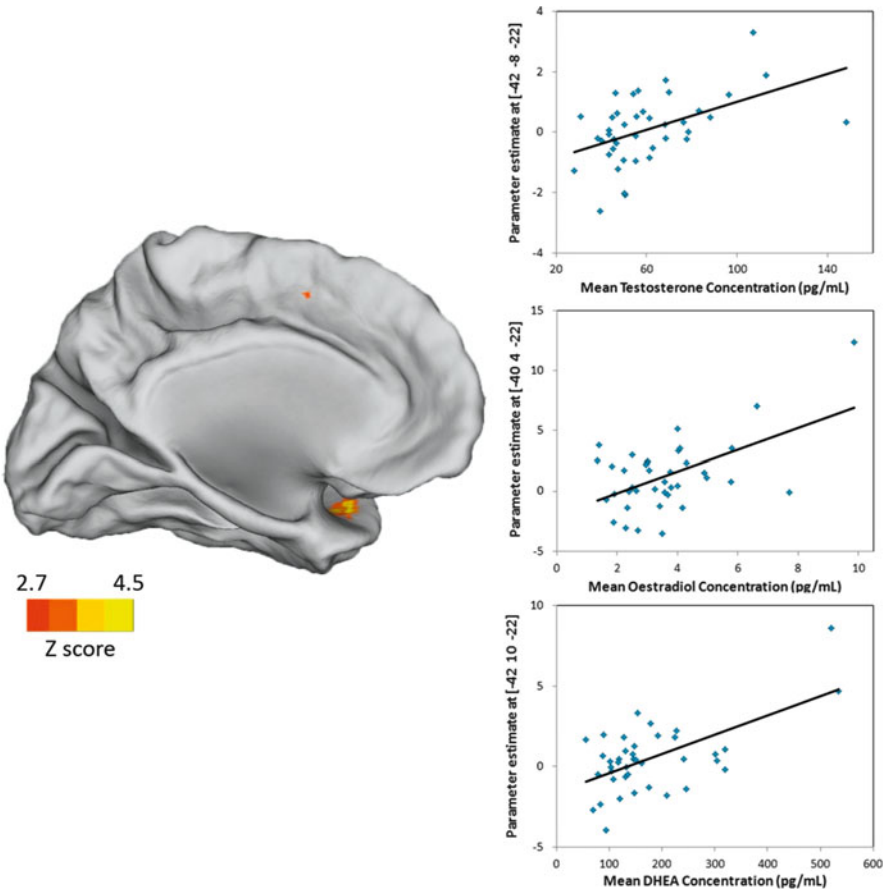

Fig. 2 There was a positive association between level of puberty hormones and BOLD signal in the anterior temporal cortex during a Social>Basic emotion condition of an emotion task (From Goddings et al. 2012) The graphs on the right show the positive correlation at the peak voxel between each puberty hormone and adjusted BOLD signal in the Social>Basic contrast in the left anterior temporal cortex

A different aspect of adolescent cognitive development that has been studied from the perspective of pubertal changes is that of reward processing. Two studies have tackled this topic, with both showing significant differences in patterns of neural activation with advancing puberty. One fMRI study demonstrated differences in caudate and rostral medial prefrontal BOLD signal between early and late puberty groups (aged 11-13) when processing reward outcome in a gambling task, and a correlation between testosterone level and caudate BOLD signal (Forbes et al. 2010). A second fMRI study investigating reward and pubertal hormonal concentration showed a significant correlation between testosterone level and activation in the ventral striatum (caudate in girls and putamen in both genders; Op de Macks et al. 2011). Both of these studies focussed on risk-taking tasks with a binary choice (risky option vs. safer option) and found significant patterns of activation and change with puberty, adding to the evidence for an underlying role of puberty in functional brain development.

Summary

The findings across these structural and functional MRI studies are consistent with the hypothesis that pubertal hormones interact with the neuroanatomical and neurocognitive changes seen during puberty (Blakemore et al. 2010; Sisk and Foster 2004) and that aspects of brain development in adolescence might be more closely linked to the physical and hormonal changes of puberty than to chronological age. Further work is needed to understand these complex relationships. The current set of findings suggests that changes during adolescence in brain structure and activity are not under the control of a single system. Instead, these changes may be differentially related to the effects of age and puberty and could have multiply-specified biological and environmental drivers. Sex hormone receptors are found throughout the brain, with differing concentrations across regions. Thus, the increase in sex hormones at puberty might have direct effects on structural development and on activation of specific brain regions during cognitive tasks. A second potential mechanism to explain differing patterns of neural activation could be that increases in pubertal hormones cause a developmental shift in cognitive strategy, which is then measured as changing patterns of BOLD signals during the task. Ongoing work testing these theories using different methods and paradigms will help to further ascertain the precise role of puberty in ongoing brain development during adolescence.

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