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Volumetric analysis of medial temporal lobe structures in brain development from childhood to adolescence

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ABSTRACT

Puberty is an important stage of development as a child's sexual and physical characteristics mature because of hormonal changes. To better understand puberty-related effects on brain development, we investigated the magnetic resonance imaging (MRI) data of 306 subjects from 4 to 18 years of age. Subjects were grouped into before and during puberty groups according to their sexual maturity levels measured by the puberty scores. An appearance model-based automatic segmentation method with patch-based local refinement was employed to segment the MRI data and extract the volumes of medial temporal lobe (MTL) structures including the amygdala (AG), the hippocampus (HC), the entorhinal/perirhinal cortex (EPC), and the parahippocampal cortex (PHC). Our analysis showed age-related volumetric changes for the AG, HC, right EPC, and left PHC but only before puberty. After onset of puberty, these volumetric changes then correlate more with sexual maturity level, as measured by the puberty score. When normalized for brain volume, the volumes of the right HC decrease for boys; the volumes of the left HC increase for girls; and the volumes of the left and right PHC decrease for boys. These findings suggest that the rising levels of testosterone in boys and estrogen in girls might have opposite effects, especially for the HC and the PHC. Our findings on sex-specific and sexual maturity-related volumes may be useful in better understanding the MTL developmental differences and related learning, memory, and emotion differences between boys and girls during puberty.

Introduction

Recent studies have shown that the human brain tends to develop in waves with different parts of the brain developing at different times rather than the entire brain growing at an even pace (Gogtay et al., 2004; Thompson et al., 2000). In particular, at birth, the human brain has developed more than 100 billion neurons, and has reached 25% of the adult brain size. In the first 6 years after birth, the brain grows very quickly, reaching 80% of the adult size at the age of two, 90% by the age of four, and almost 100% around the age of six (Dekaban, 1978; Pfefferbaum et al., 1994). After that, the overall brain size does not increase significantly but the connections or synapses between neurons are continuously developing to form a complex network of neuronal pathways (Paus et al., 1999). Because of such continuous development, the tissues and structures inside the brain, such as the gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), demonstrate gradual volumetric changes. These changes can be analyzed and characterized on magnetic resonance (MR) images. As an illustration, Fig. 1 shows MR images of the brains of four subjects aged 4, 8, 12, and 18, from which we can see that as age increases, the T1-weighted (T1w) contrast between the gray matter and white matter increases. Age-related changes in the gray matter and white matter have been reported by many researchers (e.g., Filipek et al., 1994; Jernigan et al., 1991). Furthermore, recent studies have suggested that brain development is regionally specific and that some regions may demonstrate sex-specific development patterns (Blanton et al., 2004; De Bellis et al., 2011; Sowell et al., 1999, 2004b; Witte et al., 2010). In addition, several large scale longitudinal studies have focused on characterizing the growth pattern of cortical areas in children (Giedd et al., 1999; Sowell et al., 2004a). Thus, it is of interest to characterize brain development at a local structure level.

Of human brain structures, medial temporal lobes are an important part of the limbic system responsible for learning, memory, and emotion (Barense et al., 2005; Baxter, 2009). Located at the mesial wall of the temporal lobe, they consist of several inter-connected structures that include the temporal pole, the hippocampus (HC), the amygdala (AG), and three surrounding cortical areas, namely the entorhinal cortex (ERC), the perirhinal cortex (PRC), and the parahippocampal cortex

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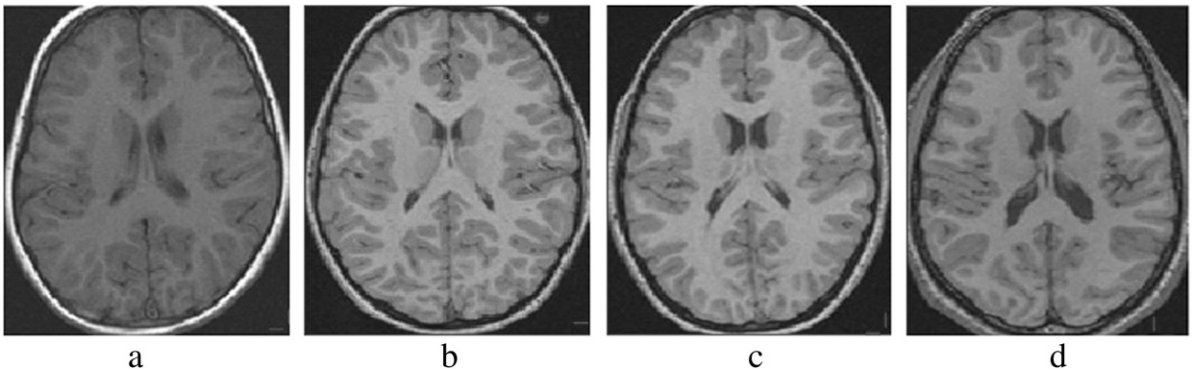

Fig. 1. MR images of children brains from 4 to 18 years old. (a) 4 years old, (b) 8 years old, (c) 12 years old, and (d) 18 years old.

(PHC) (e.g., Pruessner et al., 2000, 2002; Squire et al., 2004). Among them, the HC is the most studied component of the MTL memory system and is a main contributor to the memory-related information acquisition and spatial navigation; the AG is heavily involved in emotional and social processing, such as feeling of fear and anxiety; the ERC is the main interface between the HC and the neocortex and contributes to the formation and optimization of spatial memories; the PRC participates in visual perception and memory, while the PHC is engaged in scene recognition and social context. Neurodegenerative changes in MTL structures have been closely associated with specific brain disorders (Mori et al., 1997). Volumetric changes in the HC and ERC are important markers of early stages of Alzheimer's disease, and temporal lobe epilepsy (Coupé et al., 2012; Düzel et al., 2006; Wang et al., 2005). Larger AG volumes are associated with depression (Zetzche et al., 2006), and have been found in anxiety disorders as well.

Such findings have intrigued and motivated researchers to quantitatively analyze, using magnetic resonance imaging (MRI) and structure segmentation techniques, the MTL structures from imaging data to characterize shape and volumetric changes, ultimately to help early diagnosis of neurological diseases, locate the pathological changes for brain disorders, monitor disease progression, and evaluate efficacy of drug treatments. Studies have further revealed that volumetric changes of MTL structures may have different characteristics before and during puberty, due to the rapid pace of inter-neuron connection and synapse development as a child's sexual and physical characteristics mature because of hormonal changes (Bramen et al., 2011; Giedd et al., 1997, 2006). Certain hormones are believed to induce the formation of new synapses (Kretz et al., 2004; McEwen et al., 2001). One example is estrogen, whose concentrations increase dramatically with the onset of puberty, and which has been shown to be linked with increased dendritic branching of neurons rich in estrogen receptors (Liu et al., 2008; Woolley et al., 1990). Due to the high densities of estrogen/androgen steroid hormone receptors especially in the HC and AG, we hypothesized to find puberty-related changes particularly in these MTL structures (Loy et al., 1988). In the meantime, the rapid maturation process of MTL structures also faces increasing risks to developmental disorders during adolescence when there are dramatic physical, emotional, and social changes, associated with the potential onset of many neurological diseases and psychiatric disorders such as depression, physical abuse, and schizophrenia (Harrop and Trower, 2001; Lewinsohn et al., 1994; Pelcovitz et al., 2000). In this context, analysis of brain structure volumetric changes before and during puberty may help understand part of the complex development of MTL structures.

There has been much research work on studying the volumetric changes of MTL structures of children. In particular, Giedd et al. (1997, 1999, 2006) found a linear increase of white matter over age and an inverted "u" shape for the developmental trajectory of cortical gray matter for children from 4 to 18 years old. In addition, they also documented the volumetric changes for certain MTL structures. Specifically, the AG and HC volumes were found increased with age for both boys and girls, but the AG volume increased faster for boys than girls while the HC volume increased faster for girls than boys. Age-related increase of the hippocampus and amygdala volumes from young children to young adults were also reported by Sowell and Jernigan (1998), and Suzuki et al. (2005). Apart from age-related differences, the sex-specific differences on volumes of temporal–limbic and frontal regions in young healthy adults were observed by Gur et al. (2002). A recent study (Neufang et al., 2009) indicated that the gray matter development in certain brain regions coupled with sexual maturation and puberty hormones might have organizational effects on brain development. Sex differences were also found associated with medial temporal lobes and cortical gray matter, a region that has high sex steroid hormone receptor densities (Simerly et al., 1990), based on a study of 80 adolescent boys and girls from Bramen et al. (2011). They further reported that the puberty-related maturation of three structures: the HC, the AG, and cortical gray matter were different for boys and girls and the volumetric changes of these three structures for sexually mature adolescents demonstrated a sex-specific difference: larger volumes for more sexually mature boys as compared with smaller volumes for sexually mature girls. Another study from Witte et al. (2010) showed that in young adulthood, sex hormones had organizational effects on regional gray matter, resulting in functional diversities and congruence between female and male brains. It has been found that sex-specific hormonal changes may further moderate the redistribution of cerebral functions. For example, a functional MRI study on the redistribution of cerebral functions from Killgore et al. (2001) with 19 children and adolescents found there was a sex-specific difference in the patterns of amygdala and prefrontal activation during adolescent maturation when stimulated with photographs of faces expressing fear. Apart from the studies on healthy young adults, there are also studies on young patient populations. For example, Jacobsen et al. (1998) studied ten adolescent patients and reported volume reductions of medial temporal lobe structures correlated with ongoing illness in childhood-onset schizophrenia. Mattai et al. (2011) found significant volumetric or trajectory differences in hippocampus between childhood-onset schizophrenia patients and healthy subjects. However, to the best of our knowledge, while many studies have focused on the HC and AG, no studies have analyzed the developmental changes of these structures together with the ERC, PRC, and PHC, before and after puberty.

In this paper, we investigated the volumetric changes of individual structures of medial temporal lobes before and during puberty. The motivation for our study was to analyze the effect of physical and sexual maturity on the development of medial temporal lobes. Unfortunately, research evidence on structures other than the HC and AG is sparse possibly because of the complexity and time required to