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Molecular and Cellular Endocrinology 254–255 (2006) 154–162

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Molecular and Cellular Endocrinology

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Puberty-related influences on brain development

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Abstract

Puberty is a time of striking changes in cognition and behavior. To indirectly assess the effects of puberty-related influences on the underlying neuroanatomy of these behavioral changes we will review and synthesize neuroimaging data from typically developing children and adolescents and from those with anomalous hormone or sex chromosome profiles. The trajectories (size by age) of brain morphometry differ between boys and girls, with girls generally reaching peak gray matter thickness 1–2 years earlier than boys. Both boys and girls with congenital adrenal hyperplasia (characterized by high levels of intrauterine testosterone), have smaller amygdala volume but the brain morphometry of girls with CAH did not otherwise significantly differ from controls. Subjects with XXY have gray matter reductions in the insula, temporal gyri, amygdala, hippocampus, and cingulate—areas consistent with the language-based learning difficulties common in this group.
Published by Elsevier Ireland Ltd.

Keywords: Puberty; Magnetic resonance imaging; Brain; Congenital adrenal hyperplasia; Sex chromosome aneuploidy; Children and adolescents

Adolescence, in addition to being a time of substantial physical changes, is also characterized by changes in cognition, emotion, and behavior. Despite these obvious changes in brain-based phenomena, few direct links between the behaviors and the underlying maturational neuroanatomical changes have been revealed. Also elusive has been knowledge of whether the changes are related to maturational events relatively independent of the hormonal changes of puberty or whether a dynamic interplay between hormones and the brain drive the behavioral changes.

In this manuscript we will attempt to address part of this issue by reviewing data from an ongoing longitudinal brain imaging project being conducted at the Child Psychiatry Branch or the National Institute of Mental Health. The project is founded in the belief that greater understanding of the neurobiology of brain development, and the parameters that influence it, may lead to improved interventions for neuropsychiatric disorders and/or to the optimization of normal maturation. Our approach to pursuing this greater understanding has been to combine longitudinal brain imaging, neuropsychological, and genetic data to map and discern the influences on brain development in health and disease. The data set currently consists of approximately 4000 scans from 2000 subjects, about half of whom are typically developing healthy children or adolescents.

This paper will begin with a description of the trajectories of brain morphometry during typical child and adolescence development, with an emphasis on the male/female differences in these trajectories. Because our study design determined pubertal status only by self report on the Tanner scale and has not included quantification of hormone levels at the time of scan, we can only address the question of the relationship between changes in puberty/hormones and changes in brain/behavior indirectly. Insight into the neurobiology of these sex differences may be gained from studies of populations with anomalous numbers of sex chromosomes and from populations with anomalous hormone profiles. To this end we will examine brain morphometric differences in subjects with congenital adrenal hyperplasia (characterized by high levels of intrauterine testosterone) and in subjects with XXY (Klinefelter Syndrome).

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0303-7207/$ – see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.mce.2006.04.016

1. Trajectories of anatomical brain development during typical development

Healthy control subjects for the NIMH Pediatric Neuroimaging Project are recruited from the community and undergo physical and neurological exams, clinical interviews, family history assessment, and an extensive neuropsychological testing battery. All subjects are scanned on the same MRI machine using a sequence designed to be less than 10 min long and optimized to discriminate between gray matter, white matter and cerebrospinal fluid. The images are analyzed using a variety of automated and manual techniques through collaboration with several imaging centers throughout the world. Results will be presented for total cerebral volume and various white matter (consisting mostly of myelinated axons) and gray matter (consisting mostly of cell bodies and dendrites) subcomponents of the brain. Further details of the testing and screening of this sample and the methods of image analysis are published elsewhere (Giedd et al., 1996a,b, 1999; Zijdenbos et al., 1994; Chung et al., 2001).

1.1. Total cerebral volume

Total cerebral volume peaks on average at 14.5 years in males and 11.5 years in females (Giedd et al., 1999), having reached 95% of this peak by age 6 years (see Fig. 1a). Because of the different trajectories the size relationship between male and female brains varies with age but averages approximately 9% larger in males across this age span. In pediatric populations this difference is not likely accounted for by height differences as average height for girls is larger from ages 10 to 13.5 and cumulative mean height across the first 15 years of life for boys and girls are within 1% of each other (Kuczmarski et al., 2002). Decreasing brain volume and increasing height during adolescence further suggest a decoupling of brain and body size.

As much of brain maturation takes place by selective elimination and gross size differences are insensitive to a myriad of possible differences in neuronal connectivity and receptor density, differences in total brain size should not be interpreted as imparting any sort of functional advantage or disadvantage. However, differences in trajectories of brain size may be relevant to understanding some cognitive or behavioral differences.

1.2. Gray matter

1.2.1. Cortical gray matter

Cortical gray matter (GM) volume tends to follow an "inverted U" developmental trajectory (see Fig. 1c–f). Initial studies examined cortical GM volumes at the lobar level and found that the maximum GM volume occurs at different times in different lobes. Frontal lobe gray matter reaches its maximal volume at 11.0 years in girls and 12.1 years in boys; temporal lobe cortical gray matter peaks at 16.7 years in girls and 16.2 years in boys; parietal lobe cortical gray matter peaks at 10.2 years in girls and 11.8 years in boys (Giedd et al., 1999). Occipital GM volumes increased throughout this age span in both boys and girls.

Subsequent studies applying image analysis methods to model a one-to-one correspondence between surface voxels of different brains (across different individuals or the same individuals over time) have allowed quantification of cortical GM changes at a spatial resolution of about 1.3 cm^3. Using this approach to track GM changes in a group of 13 subjects scanned 4 times at approximately 2-year intervals we created a time-lapse movie of cortical GM changes across the ages of 4–22 years (Gogtay et al., 2004) (see Fig. 2) (the movie can be viewed at: http://www.loni.ucla.edu/SVG/index.php). The dorsolateral prefrontal cortex (DLPFC), involved in circuitry subserving control of impulses, judgment, and decision making, is notably late to reach adult levels of cortical thickness. Although at an individual level no direct behavioral implications have been established the possible implications of late maturation of this area have entered educational, social, political, and judicial realms.

1.2.2. Subcortical gray matter

Basal ganglia. The basal ganglia, consisting of the caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra, have long been known to play a role in the control of movement and muscle tone but more recently have been shown to be involved in circuits mediating higher cognitive functions, attention, and affective states. The caudate nucleus is the only basal ganglia structure we have been able to reliably quantify. Similar to cortical GM the caudate nucleus follows an inverted U shape developmental trajectory. Caudate size peaks at age 7.5 years in girls and 10.0 years in boys.

Amygdala and hippocampus. The amygdala and hippocampus are of particular interest in studies of puberty or sexual dimorphism as they are rich in hormone receptors with non-human primate studies indicating a relatively high number of androgen receptors in the amygdala (Clark et al., 1988) and a relatively higher number of estrogen receptors in the hippocampus (Morse et al., 1986). In a previous cross-sectional study of a subset of this longitudinal data, amygdala volume increased with age significantly only in males and hippocampal volume increased significantly with age only in females (Giedd et al., 1996a,b) (see Fig. 3).

1.3. White matter

1.3.1. Lobar white matter volumes

White matter (WM) volumes at the lobar level, in contrast to the inverted U shape of GM developmental curves, increase throughout childhood and adolescence (see Fig. 1b). Also unlike the GM trajectories, although the rate of WM increase varies with age the trajectories are similar for the frontal, temporal, and parietal lobes.

These differences between GM and WM developmental trajectories are intriguing given that the neurons, glial cells, and myelin that comprise the GM and WM voxels are parts of the same brain circuitry and have a lifelong reciprocal relationship (Fields and Stevens-Graham, 2002). Neuronal activity influences myelin production and the proliferation and survival of oligodendrocytes (Barres and Barde, 2000; Fields et al., 2001),

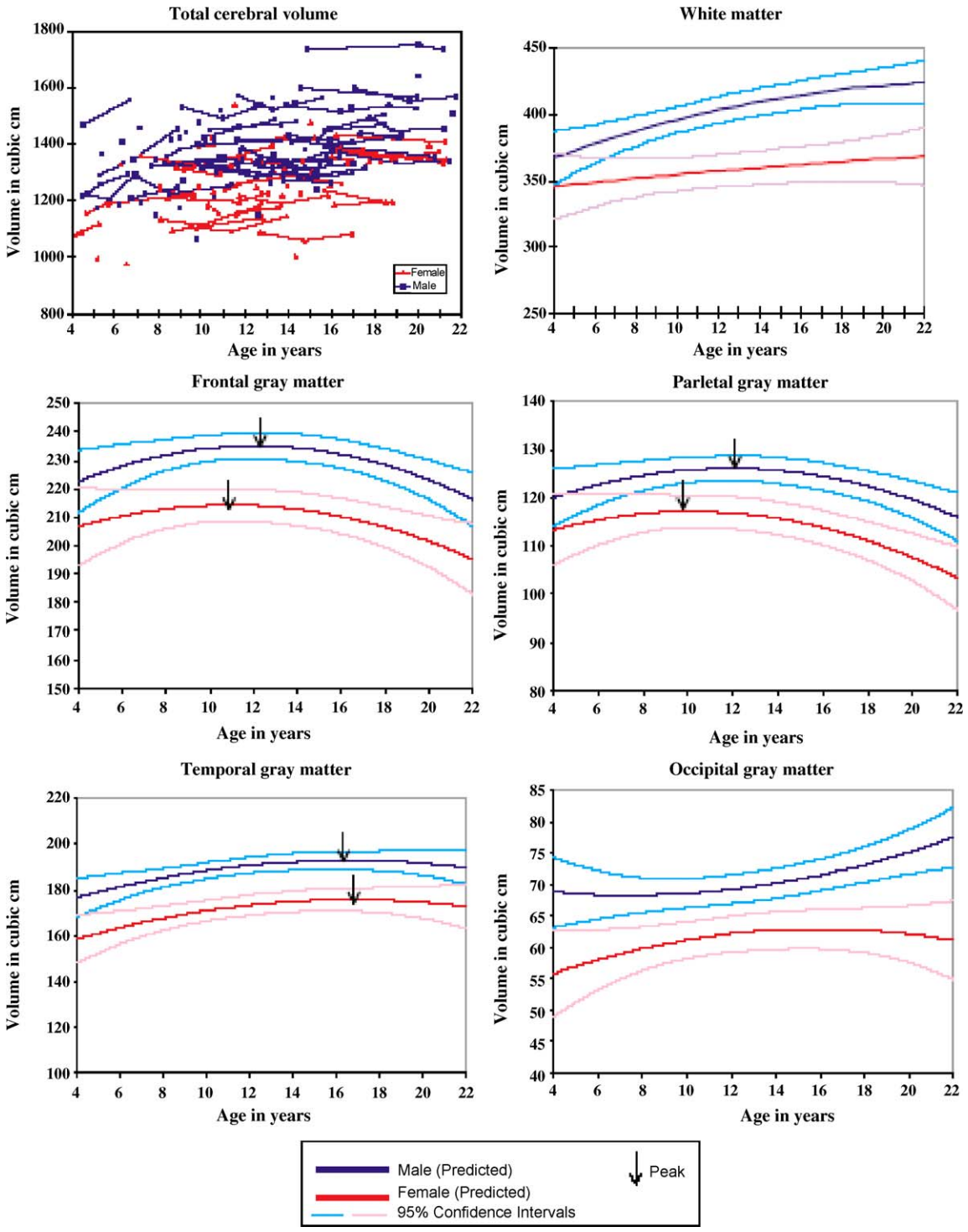

Fig. 1. Predicted size with 95% confidence intervals for cortical gray matter in frontal, parietal, temporal, and occipital lobes for 243 scans from 89 males and 56 females, ages 4–22 years. The arrows indicate peaks of the curves. From Giedd et al. (1999).

while oligodendrocytes via secretion of neuronal growth factors influence axonal growth and clustering of ion channels (Du and Dreyfus, 2002).

1.3.2. Corpus callosum

The corpus callosum (CC) is the most prominent WM structure consisting of approximately 200 million myelinated fibers, most of which connect homologous areas of the left and right cortex. The CC is generally thought to subserve functions integrating activities of the left and right cerebral hemispheres such as the unification of sensory fields (Berlucchi, 1981; Shanks et al., 1975), memory storage and retrieval (Zaidel and Sperry, 1974), attention and arousal (Levy, 1985), and enhancing language and auditory functions (Cook, 1986). Sexual dimorphism of the CC is a widely debated topic with some authors reporting male/female differences (De Lacoste et al., 1986; Holloway

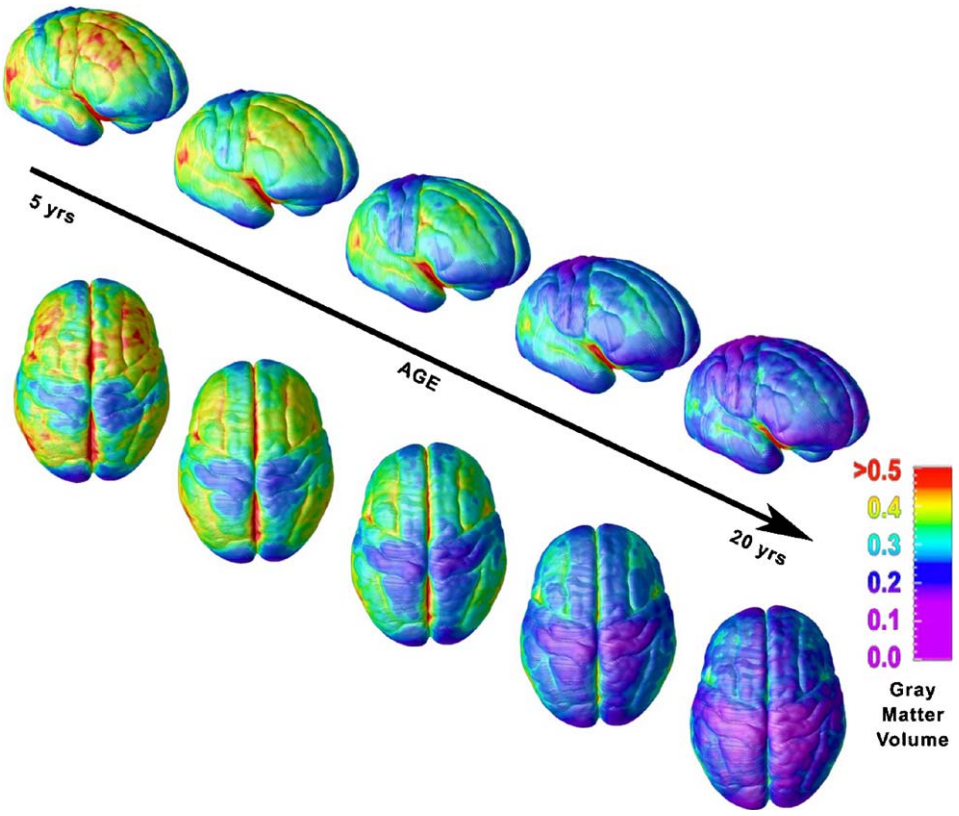

Fig. 2. Right lateral and top views of the dynamic sequence of GM maturation over the cortical surface. The side bar shows a color representation in units of GM volume. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

and De Lacoste, 1986; Clarke et al., 1989; Cowell et al., 1992) while many have not (Bell and Variend, 1985; Witelson, 1985; Oppenheim et al., 1987; Weis et al., 1988, 1989; Byne et al., 1988). In our sample total midsagittal corpus callosum area increased from ages 4 to 22 years, but whether it was sexually dimorphic or not depended on the age.

1.4. Summary of brain morphometric changes during typical development

Total brain size peaks at age 11.5 in females and 14.5 years in males, reaching 95% of this maximum size by age 6 years. Both cortical and subcortical GM volumes follow region specific inverted U shape developmental curves whereas WM volume changes tend to be more linear and less variant across regions. Developmental trajectories of brain morphometry are different between boys and girls but age 12, an approximate time of the observable physical changes of puberty, does not appear to be a point of particular divergence.

To examine the potential role of anomalous hormone levels on the developing brain we will next review brain imaging data from subjects with congenital adrenal hyperplasia (CAH).

2. Congenital adrenal hyperplasia

Classic CAH stems from a deficiency of the hormone 21-hydroxylase, which helps convert progesterone to cortisol. This creates a buildup of progesterone which is also a precursor to testosterone, resulting in low levels of intrauterine cortisol and high levels of intrauterine testosterone. There is some behavioral evidence that this high level of intrauterine testosterone may result in "masculinization" of the female fetal CAH brain (Berenbaum, 2001), but the issue remains unresolved and is complicated by the myriad of other endocrinologic differences such as an excess of exogenous glucocorticoids, which is a frequent complication of therapy (Cutler and Laue, 1990; Merke et al., 2002).

The effects of the multiple hormonal imbalances associated with CAH on pediatric brain morphometry were explored in a study of 27 children with classic CAH (11 females, ages 4–11 years; 16 males, ages 6–16 years) and 47 sex- and age-matched controls (Merke et al., 2002). At the level of this analysis females with CAH did not have brains more similar to males than their age-matched controls. Amygdala volume, however, was significantly decreased in both males and females with CAH (see Fig. 4). The hormones responsible for decreased amygdala size may include excess androgens, estrogens, progestins, endogenous deficiency or exogenous excess of glucocorticoids or some combination of these.

The hippocampus, an *a priori* structure of interest in this study because of its abundance of estrogenic and glucocorticoid receptors, was not significantly different between groups. Nonsignificant differences between groups in small sample studies should be interpreted in light of statistical power. Given the

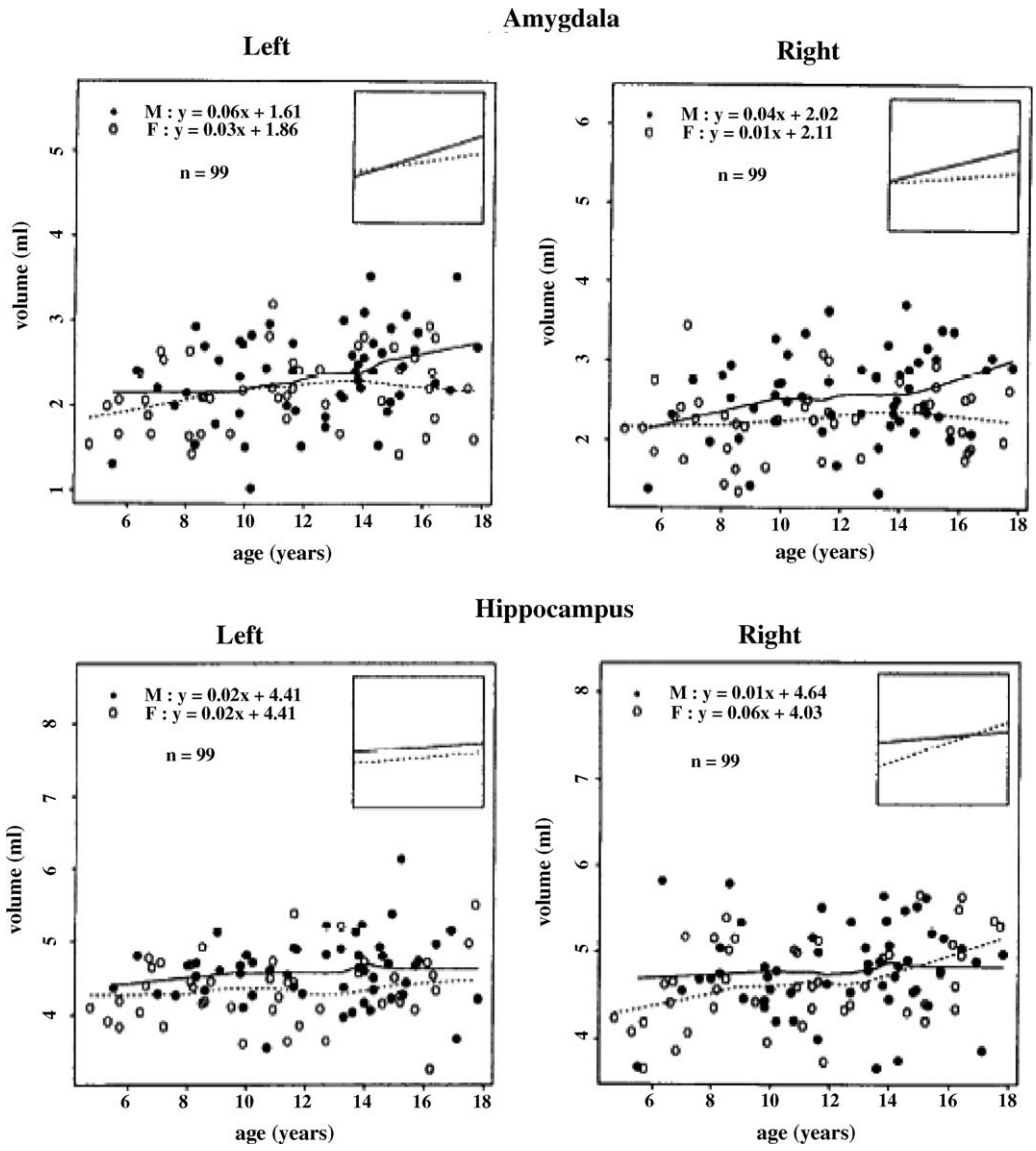

Fig. 3. Scatterplots by age and gender of left and right amygdala and hippocampus volume for children and adolescents (aged 4–18 years; $n = 99$). Nonlinear, local regression curve fitting is displayed. The boxes in each upper right corner show linear regression models for males (solid lines) and females (dashed lines).

sample size and the coefficient of variation of the hippocampal measures there was a 64% chance to detect a 10% hippocampal volume difference in the girls and an 81% chance to detect a 10% hippocampal volume difference in the boys.

It is possible that sex differences in the brain are not mediated solely through hormones but may involve gene or gene dosage differences related to the X- or Y-chromosomes. We will next discuss the effects of having an extra X-chromosome on developmental brain morphometry.

3. Klinefelter's Syndrome

47,XXY, or Klinefelter Syndrome (KS), the occurrence of an additional X-chromosome in males, is the most common sex chromosome aneuploidy, found in between 1/600 (Linden et al., 2002; Patwardhan et al., 2000) and 1/1000 (Nussbaum et al., 2004) live male births. Supernumerary X-chromosomes typically arise from nondisjunction during either maternal or paternal meiotic cell division (Thomas and Hassold, 2003) and can affect development of central nervous, endocrine, reproductive, skeletal, and cardiac systems.

The original phenotype, described by Klinefelter in 1942 (Klinefelter et al., 1942) consisted of hypogonadism, gynecomastia, sparse body hair, eunuchoid body habitus, above average height, and infertility. Other physical characteristics subsequently identified include long legs and arm span, decreased bone mineral density, taurodontism (Varrela and Alvesalo, 1988), and low testosterone levels. Except for hypogonadism, which is present in nearly all XXY individuals, the physical phenotype may be quite variable.

Similarly to the physical phenotype, XXY males have characteristic but highly variable cognitive and behavioral features. Language-based learning disorders are the most frequently reported impairment, occurring in up to 80% of those with XXY

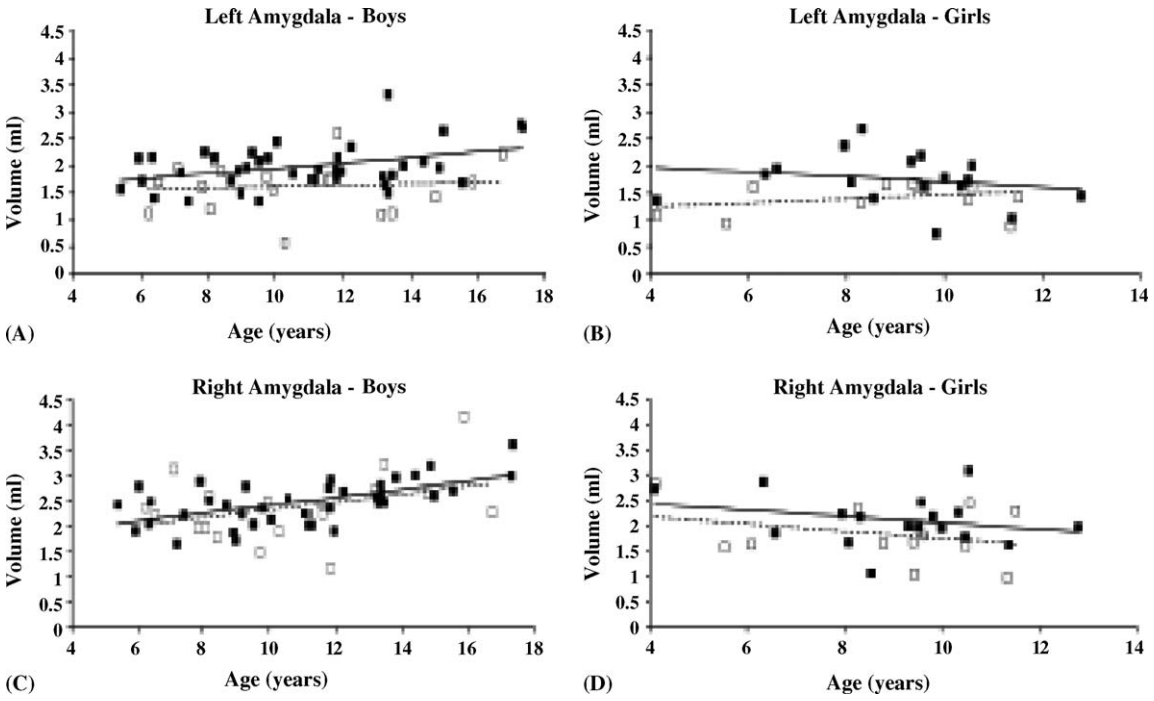

Fig. 4. Left and right amygdala volumes for children with CAH (□) and age-matched controls (■) in relation to age and gender. Linear regression curves are displayed for children with CAH (dashed lines) and age-matched controls (solid lines). A maturational increase in the volume of the amygdala was observed in boys (A and C).

(Bender et al., 1993; Geschwind et al., 1998, 2000; Mandoki et al., 1991; Samango-Sprouse and Rogol, 2002; Visootsak et al., 2001; Simpson et al., 2003). Disorders of executive function (Boone et al., 2001; Samango-Sprouse and Law, 2001) and social impairments are also common.

To explore the possible neurobiological substrates of the observed cognitive and behavioral phenotypes during development we compared brain MRI scans from 34 XXY males ranging in age from 5.3 to 19.2 years to 62 age-matched controls (Shen et al., 2004). A whole-brain automated image analysis technique was used to create density maps of the GM, WM, and CSF for the brains in each group. The technique used a procedure called HAMMER (Hierarchical Attribute Matching Mechanism for Elastic Registration) (Shen and Davatzikos, 2002; Shen and Davatzikos, 2003) to put the brains into a standard stereotaxic space and a mass-preserving function to ensure the total amount of tissue in any structure was the same before and after spatial normalization. Because the resulting GM, WM, and CSF density maps are spatially co-registered, voxel-based statistics can be used to examine regional differences.

Total brain volume was smaller in the XXY group with total GM volume about 8.5% smaller and total WM volume about 8.1% smaller. Ventricular CSF volume was 42.7% larger in the XXY group. The regional differences in GM volume reductions were predominantly in the left cerebral hemisphere and localized to the insula, temporal gyri, amygdala, hippocampus, cingulate, and occipital gyri (see Fig. 5).

The difference in brain morphometry between the groups is largely consistent with the observed cognitive and behavioral differences between the groups. Specifically, the insula and temporal gyri regions are linked to verbal and language abilities. Also, the amygdala, hippocampus, and cingulate are all parts of the medial limbic system which subserve functions related to memory and emotional regulation (Mandoki et al., 1991; Bender et al., 1995; Walzer et al., 1990).

4. Discussion

Although direct evidence of the hormonal effects of puberty on the anatomy of the developing human brain is lacking, evidence from clinical populations is beginning to suggest specific effects of hormones and/or sex chromosome anomalies on this process. Studies of typical development highlight the importance of considering not just the final destination of brain morphometry, but the path, or developmental trajectories, that lead to the later findings.

It is an obvious goal of developmental neuroimaging studies to link the neuroanatomical trajectories to trajectories of behavioral or cognitive change. However, the concept that most brain functions arise from distributed neural networks and that within any given region lies a daunting complexity of connections, neurotransmitter systems, and synaptic functions makes straightforward relationships between brain size and function the exception rather than the rule.

Another challenge in discerning the effects of puberty on brain development is the brain's inherent plasticity and the dynamic interplay between the brain and its environment. Environmental stressors may result in increased cortisol which may in turn have effects on brain physiology and eventually structure that may confound effects due more directly to sex hormones

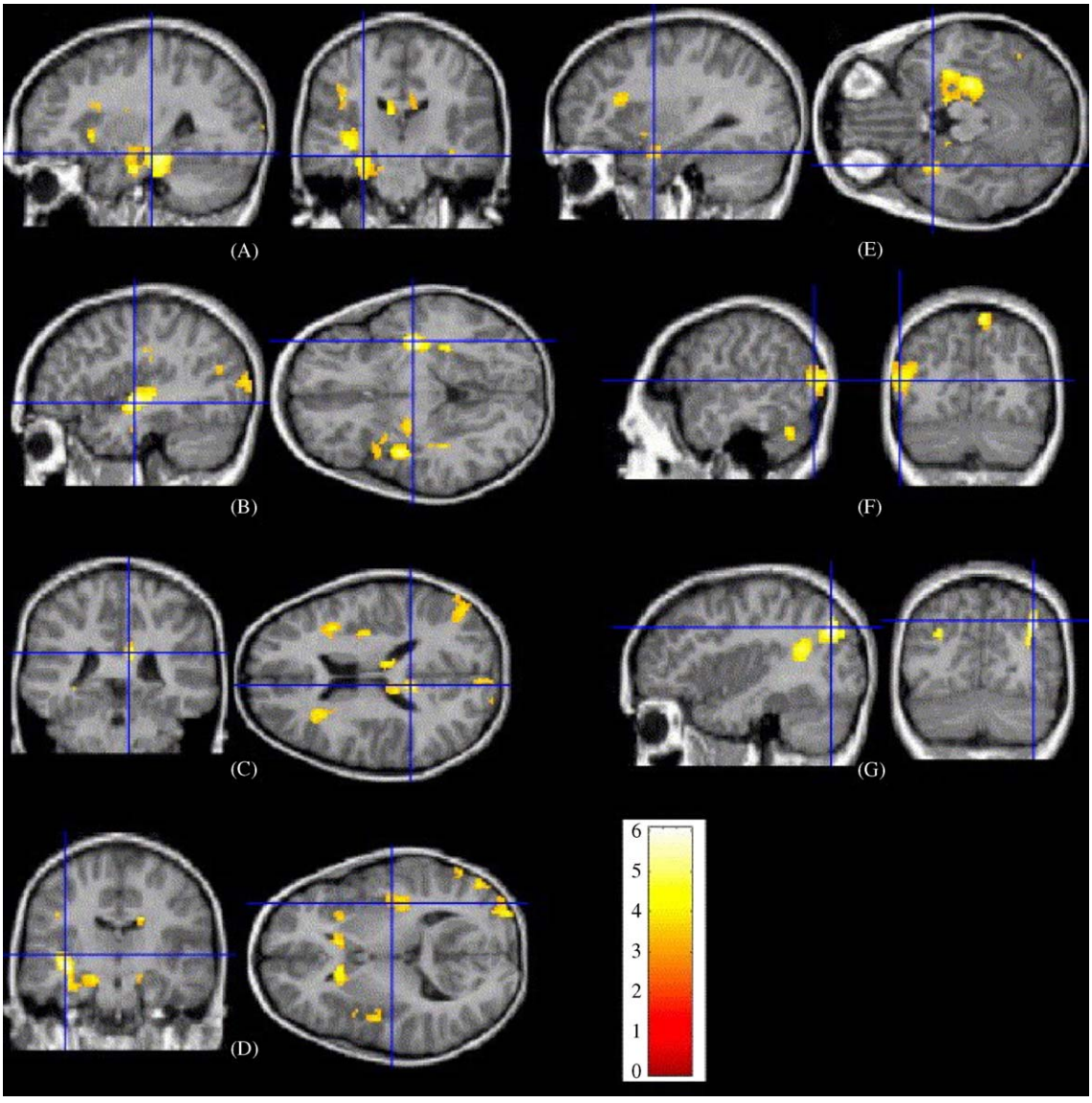

Fig. 5. Visual summary of several detected regions with significant group differences between XXY brains and normal control brains. The underlying image is the template that we used to normalize individual brains. Color-coding was based on the value of the *t*-statistic. Only the voxels with significant group differences, i.e. the corrected *P* values exceeding a significance threshold of 0.005, are shown. (A) Left hippocampal formation; (B) left superior temporal gyrus; (C) cingulate region; (D) left insula; (E) right amygdala; (F) left middle temporal gyri; (G) right parietal lobe WM. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

or sex chromosomes. Compensatory brain changes may be difficult to discern from causal brain differences without carefully designed longitudinal studies.

Future directions exploring the effects of puberty on brain anatomy will include the quantification of finer and finer subdivisions of neuroanatomy, characterizing different aspects of tissue composition, combining data from multiple sites to increase sample sizes, employing novel image acquisition techniques, and applying increasingly sophisticated image analysis and statistical modeling methods. Expanding studies to other clinical populations with anomalous sex chromosome (e.g., 45,X, XXX, XYY, and XXXXY) or hormone profiles (e.g., Familial Male Precocious Puberty, Androgen Insensitivity Syndrome) may further elucidate the influence of puberty-related factors on typical and atypical brain development.

Acknowledgments

We would like to thank the families who participated in this research and *The American Association for Klinefelter Syndrome Information and Support* (*AAKSIS*) and *Klinefelter Syndrome and Associates* (*KS&A*) for assisting us in the recruitment of participants.

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