The Impact of Steroid Hormones on the Developing Human Brain and Sex Differences

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Received: 02-May-2022, Manuscript No. JSHS-22-17307; **Editor assigned:** 16-May-2022, **PreQC No.** JSHS-22-17307(PQ); **Reviewed:** 24-May-2022, **QC No.** JSHS-22-17307(Q); **Revised:** 27-May-2022, Manuscript No. JSHS-22-17307(R); **Published:** 29-May-2022, **DOI No.** 10.35248/ 2471-7536-22.13(3).236

Abstract

Puberty's hormonal effects on the anatomy of the developing human brain are poorly understood. Sex-related differences in Grey Matter (GM) volume were investigated in 46 subjects aged 8 to 15 years in a voxel-based morphometry study. Males had larger GM volumes in the left amygdala, while females had larger GM volumes in the right striatum and bilateral hippocampal. A subsample of 30 subjects had sexually dimorphic areas linked to Tanner Stages (TS) of pubertal development and circulating levels of steroid hormones. Regardless of gender, amygdala and hippocampal volumes changed with TS and were linked to circulating testosterone (TEST) levels. Contrary to pubertal development and circulating steroid hormones, striatal GM volumes were unrelated. TEST levels and diencephalic brain structures were found to have positive associations with circulating oestrogen levels and parahippocampal GM volumes in whole-brain regression analyses. Furthermore, a negative relationship was discovered between circulating TEST and left parietal GM volumes. These findings imply that GM development in specific brain regions is linked to sexual maturation and that pubertal hormones may have organizational effects on the developing human brain.

Key Words: Brain morphometry • Sex differences • Sexual maturation • Steroid hormones

Introduction

Adolescence is a critical developmental stage during which major physical, psychological, cognitive, and social transformations occur and gender differences emerge and manifest. Behavioral transformations are closely related to cerebral development, encompassing dramatic and widespread changes in brain morphology. Although basic developmental processes, such as linear increases in White Matter (WM) volume and nonlinear inverted u-shaped development of regional Grey Matter (GM), are comparable between boys and girls, sexual dimorphisms in global and regional brain volumes, as well as the time course of brain development, have been reported. Whereas peaks in GM volume occur one year earlier in girls than in boys, the rates of global volume changes in boys follow a steeper slope in terms of both WM increase and GM volume decrease.

Although sexual dimorphism in total cerebral and subcortical GM and WM volumes has recently been demonstrated in the neonatal brain, many sex differences in brain structures appear to occur after the age of 9 or 10 recently demonstrated that brain maturation is affected not only by significant interaction effects between sex and age, but also by interactions between sex and physical maturation measures. The development of GM volume, in particular, is thought to coincide with the onset of puberty. The increase in GM volume at the onset of puberty could be attributed to a coincidental wave of synaptic proliferation, while the gradual decrease in GM density after puberty could be attributed to postpubescent synaptic pruning.

The adolescent brain remodels through a variety of mechanisms, including both progressive events like cell number increases, dendritic elaboration, and axonal sprouting and regressive events like apoptosis and synaptic pruning. These processes are known to be influenced by both androgens and estrogens (EST). The effects of sex steroids on brain morphology are traditionally described as operating through two distinct mechanisms. One mechanism, known as "organisation," is defined as a developmental mechanism in which steroids act during critical periods to mediate permanent sexually dimorphic differentiation of brain morphology, giving rise to male and female sexual behaviour and physiology in adulthood. The other mechanism, known as "activation," is mediated by the acute effects of gonadal hormones on the fully developed nervous system and is responsible for maintaining sex-specific behaviours in adulthood. Although the organization—activation framework for steroid control of reproductive behaviour originally assumed a strictly activating role for gonadal steroids during adolescence, a recent modernization of this thinking incorporates dual roles for steroid hormones, proposing that they not only activate but also organise neural circuits during adolescence. The sequence of events during steroid-dependent adolescent reproductive behaviour maturation may be an initial reorganisation of circuits that further sensitises them to hormone activation.

However, no empirical studies in humans have been conducted to date that directly link sex-specific changes in brain development to the general status of pubertal development and the effects of pubertal hormones in particular. The majority of the available evidence comes from animal studies, studies of sex hormone changes during the menstrual cycle, or studies on abnormal brain development in people with abnormal hormone or sex chromosome profiles.

Thus, one challenge for developmental neuroscience is to determine which aspects of adolescent brain development are related to hormone levels and which are not, as well as to comprehend the behavioural consequences of steroid-dependent adolescent brain organisation and activation. Importantly, understanding the mechanisms underlying sexual differentiation in the brain may lead to a better understanding of the brain's susceptibility to neuropsychiatric disorders such as Attention Deficit Hyperactivity Disorder (ADHD), tics, eating disorders, depression, or schizophrenia, all of which have sex-specific prevalence rates, times of onset, and courses. Animal research suggest that derived sex differences in behaviour are established during development by the actions of gonadal steroid hormones. Odor preferences, behavioural responses to sensory stimuli, and social affiliations, for example, all change during adolescent development. Furthermore, androgen deprivation causes a 40% decrease in synaptic density in the hippocampus of both rats and monkeys, whereas testosterone (TEST) replacement in male animals normalises synaptic density. Behaviorally, androgen deprivation via gonadectomy in male rodents impairs performance on hippocampus-dependent tasks such as maze learning and fear conditioning. In contrast, synapse number and dendritic spine density in the hippocampus of female rats appear to vary throughout the estrous cycle, with low levels of estradiol associated with lower synapse density and high levels of estradiol associated with a higher density of synapses. However, hormonal mechanisms do not fully explain some sexual dimorphisms. It has been shown, for example, that adolescent remodelling of cortical and subcortical regions involves changes in synaptic organisation at both the pre- and postsynaptic levels, which may contribute to regional differences in GM development. Researchers demonstrated that pre puberty is characterised by a high level of dopamine receptor expression in the rat striatum, in contrast to receptor pruning during the postpubertal stage. This pattern is more pronounced in males than in females, but it persists even when the gonads are removed before puberty, indicating that neither overexpression nor pruning of dopaminergic receptors in the striatum is dependent on pubertal hormones.

Identifying the structural correlates of behavioural maturation and determining which structural features are associated with steroid hormonal changes is an important area of future research. As a result, the goals of this study were to 1) investigate sex differences in brain development during childhood and adolescence using fully automated Voxel-Based Morphometry (VBM) and to determine which of these differences are

influenced by sexual maturation and which are associated with the circulating level of steroid hormones, and 2) identify brain regions affected by circulating steroid levels using a whole-brain approach. Based on previous research, we predicted that males would have a larger amygdala and females would have larger hippocampal and striatal GM volumes. Furthermore, we hypothesised that amygdala and hippocampal volumes would be associated with sexual maturation as well as TEST and EST levels, whereas striatal volumes would be unaffected by circulating steroid hormones. We hope to gain a better understanding of sexual dimorphisms in brain development during childhood and adolescence by combining direct (circulating hormonal levels) and indirect (TS) measures of puberty.

Cite this article: Hirpa D. The Impact of Steroid Hormones on the Developing Human Brain and Sex Differences. J Steroids Horm Sci. 2022, 13 (3), 001-002.