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*Chapter 4*

**THE ROLE OF STEROID HORMONES IN  
BRAIN DEVELOPMENT AND VISUOSPATIAL  
PROCESSING ON ADOLESCENCE**

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**ABSTRACT**

One of the central aims in developmental cognitive neuroscience, is to relate changes in cognition to maturational changes in the brain. Research with animals has been helpful in understanding links between brain changes during development as they relate to cognition. A good example comes from studies of spatial memory in relation to the development of the hippocampus. Before 19 days of age, rats pups are unable to solve the hidden platform version of the Morris water maze task. By 21 days of age, however, rats can typically solve the Morris water maze (Purves et al., 2008). In this structure were found a high density of steroid receptors, suggesting there must be some relationship between steroid receptors and development of hippocampus (Simerly et al., 1990).

Adolescence is now recognized as a major and dynamic period of neural development during which behavioral circuits are remodeled and refined. Although the human brain of a 5-year old child is already 90% of its adult size (Dekaban, 1978), significant remodeling is still to come.

This concept was kindled by research in both humans and animals documenting that many of the basic developmental processes occurring during perinatal brain development are recapitulated during adolescence. Compared with activation of neural circuits by steroid hormones, it is relatively little known about steroid-dependent organization during adolescence. Presumably, there are many similarities to the processes involved in steroid-dependent sexual differentiation during early neural development, such as regulation of cell death and survival, and synaptic density and connectivity.

During the adolescent phase of organization, steroid-dependent refinement of neural circuits results in long-lasting structural changes in brain, which determine adult behavioral responses to hormones or sensory stimuli and improve the cognitive abilities such as attention, learning and memory, reasoning and visuospatial processing as adaptive response to environment and social interaction.

The organizational changes in the adolescent brain under steroid hormones could evolve in a progressive manner, in order to respond from simple to complex stimuli and thus, the trajectory of cognitive development follow the developmental course of brain neuromaturation, from visual perception and spatial memory to visuospatial processing and semantic association between visual informations and abstract categories.

### **ADOLESCENCE AS A BRAIN SENSITIVE PERIOD FOR STEROID HORMONES**

Adolescence is an important developmental period in which major physical, psychological, cognitive, and social transformations occur (Blakemore and Choudhury, 2006; Galvan et al., 2007; Markham et al., 2007) and gender differences emerge and manifest themselves (Lenroot et al., 2007; Schmithorst et al., 2007). Behavioral transformations are closely related to cerebral development, encompassing dramatic and widespread changes in brain morphology under gonadal steroid hormones.

Although basic developmental processes are comparable between boys and girls, such as linear increases in white matter volume and nonlinear inverted u-shaped development of regional gray matter, sexual dimorphisms have been reported for global and regional brain volumes and the time course of brain development (Giedd et al., 1997, 1999).

Whereas peaks in gray matter volume typically occur 1 year earlier in girls than in boys, the rates of global volume changes follow a steeper slope in boys

than in girls with respect to both increase of white matter and decrease in gray matter volumes.

Likewise, volumes of subcortical structures like the striatum, the hippocampal, and the amygdala change during adolescence in a sex-dependent manner, with amygdala volume increasing significantly more in males than in females and hippocampal and striatal volume increasing more in females (Caviness et al., 1996; Giedd et al., 1997; Lange et al., 1997). Although it has recently been demonstrated that sexual dimorphism in total cerebral and subcortical gray matter and white matter volumes are already present in the neonatal brain (Gilmore et al., 2007), many sex differences in brain structures seem to occur after the age of 9 or 10 (Goldstein et al., 1999; Giedd et al., 2006). Recently, De Bellis et al. (2001) demonstrated that brain maturation is not only affected by significant interaction effects between sex and age but also by interactions between sex and measures of physical maturation (De Bellis et al., 2001) as assessed by Tanner stages (TS, Tanner and Davies, 1985).

It is believed that the development of gray matter volume in particular more or less coincides with the onset of puberty (De Bellis et al., 2001; Sowell et al., 2002; Gogtay et al., 2004). The increase of gray matter volume at the onset of puberty might reflect a coincident wave of synaptic proliferation and the gradual decrease in gray matter density that takes place after puberty might be attributed to postpubescent synaptic pruning (Bourgeois et al., 1994).

The remodeling of the adolescent brain is accomplished through a variety of mechanisms, including neurogenesis (Eckenhoff and Rakic, 1988; He and Crews, 2007; Pinos et al., 2001; Rankin et al., 2003), programmed cell death (Nunez et al., 2001, 2002), elaboration and pruning of dendritic arborizations and synapses (Andersen et al., 1997; Huttenlocher and Dabholkar, 1997; Lenroot and Giedd, 2006; Sowell et al., 2004), myelination (Benes et al., 1994; Paus et al., 2001; Sowell et al., 2001), and sexual differentiation (Chung et al., 2002; Davis et al., 1996; Nunez et al., 2001). These processes are known to be influenced by both androgens (MacLusky et al., 2006) and estrogens (Galea et al., 2006).

The effects of sex steroids on brain morphology are classically described as operating through two distinct mechanisms (Cooke et al., 1998). One mechanism, called „organization”, is defined as a developmental mechanism in which steroids act during critical periods to mediate permanent sexually dimorphic differentiation of brain morphology that gives rise to male and female sexual behavior and physiology in adulthood. The other mechanism, called „activation”, is mediated through the acute effects of gonadal hormones

on the fully developed nervous system and is responsible for maintaining sex-specific behaviors in adulthood (Breedlove and Hampson, 2002).

Although the organization-activation framework for steroid control of reproductive behavior originally presumed 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 organize neural circuits during adolescence (Romeo et al., 2002). The sequence of events during steroid-dependent adolescent maturation of reproductive behavior may be an initial reorganization of circuits that further sensitizes them to hormone activation (Sisk and Foster, 2004).

Obviously, the adolescent brain maturation under steroid hormones involves the development of other cognitive abilities which improve the social interaction, communication, competition and complex behaviors than innate reproductive behavior.

Identifying the structural correlates of behavioral maturation and determining which structural features are related to steroid hormonal changes is an important area for further research.

## **BRAIN DEVELOPMENT ON ADOLESCENCE**

During adolescence cortical gray matter volume tends to follow an „inverted U” developmental course with volumes peaking at different times in different lobes (Lenroot and Giedd, 2006). For instance, 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; and parietal lobe cortical gray matter peaks at 10.2 years in girls and 11.8 years in boys (Giedd et al. 1999b).

The developmental trajectory of cortical gray matter followed a regionally specific pattern with areas subserving primary functions, such as motor and sensory systems, maturing earliest and higher order association areas, which integrate those primary functions, maturing later. For example, in the temporal lobes the latest part to reach adult levels is the superior temporal gyrus/sulcus which integrates memory, audio-visual input, and object recognition functions, along with prefrontal and inferior parietal cortices (Mesulam, 1998; Calvert, 2001; Martin and Chao, 2001). Notably, late to reach adult levels of cortical thickness is the dorsolateral prefrontal cortex, involved in circuitry subserving control of impulses, judgment, decision making and visual processing

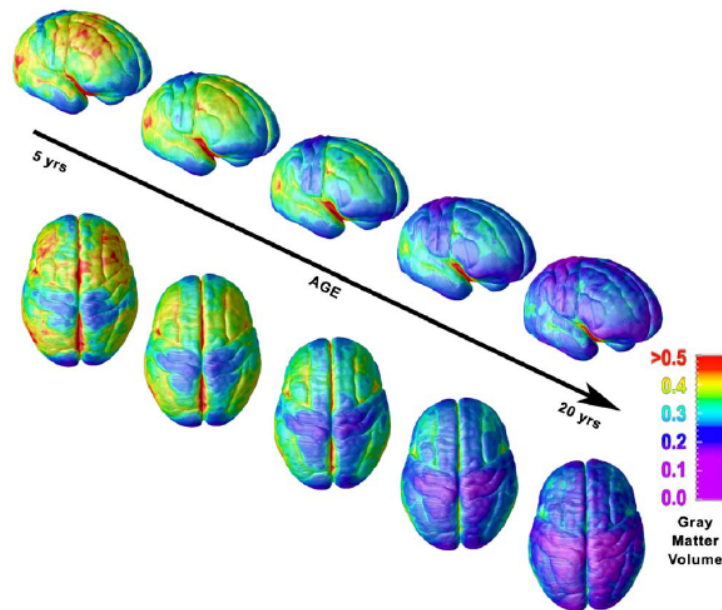
(Lenroot and Giedd, 2006; Nieder et al., 2002; Fuster 1989; Miller and Cohen, 2001).

In contrast to the inverted U shape of gray matter developmental curves, the amount of white matter in the brain generally increases throughout childhood and adolescence.

Unlike the lobar differences seen in gray matter trajectories, the white matter slopes are similar in frontal, temporal, and parietal lobes (Lenroot and Giedd, 2006).

The differences in gray matter and white matter developmental trajectories belie the inseparable connection among neurons, glial cells, and myelin, which are components of the same neural circuits and share lifelong reciprocal relationships (Fields and Stevens-Graham, 2002).

Neuron activity influences myelin production and the proliferation and survival of oligodendrocytes (Barres and Barde, 2000; Fields et al., 2001) while oligodendrocytes influence neurons via secretion of neuronal growth factors and influence axonal growth and clustering of ion channels (Du and Dreyfus, 2002). Proximal pathways tend to be myelinated before distal, sensory before motor, and projection before association (Volpe, 2000).



Right lateral and top views of the dynamic sequence of gray matter maturation over the cortical surface (Lenroot and Giedd, 2006).

Later-maturing myelin sheaths, such as those in association tracts and intracortical regions, tend to be thinner with greater axonal load per oligodendrocyte (Yakovlev and Lecours, 1967; Kinney et al., 1994), which may render them more vulnerable to environmental or aging-related factors (Bartzokis, 2004).

It shows that the cortical ribbon is actually thicker in some brain regions in females, despite the fact that females tend to have smaller bodies, and smaller brains, including smaller overall gray and white matter volumes than do men. The regions in which cortices are most prominently thicker in females than in males are in the right hemisphere association cortices, particularly the temporal and parietal lobes. In these regions, the cortex is up to 0.45 mm thicker in women; permutation analyses confirmed that these effects were not attributable to chance. The nonsignificant age-by-sex interactions in these regions suggest that the sex differences in temporoparietal cortices are stable across the life span (Sowell et al. 2007).

Regional cortical thickening in women may also be consistent with the profile of cognitive differences observed between the sexes, particularly the female advantage on language tasks that may be attributable to their thicker cortices in posterior perisylvian language regions. Gur and others (1999) have suggested that more cortical gray matter in women may provide a computational advantage, compared with possible differences in white matter, which would affect speed of information transfer.

A thicker cortex, however, may not necessarily be better than a thinner one. Studies of normal development, for example, have consistently shown cortical thinning to occur with age as part of normal brain maturation (Jernigan et al., 1991; Giedd et al., 1999; Sowell et al., 2004).

Thinning of frontal and parietal cortices in normally developing children, moreover, is associated with improvements in performance on language tasks (Sowell et al., 2001; Sowell et al., 2004). Cortical thinning during childhood and adolescence is thought to derive both from progressive changes in myelination (Yakovlev and Lecours, 1967; Benes et al., 1994) and from regressive changes, such as synaptic pruning (Huttenlocher and de Courten, 1987). Both of these cellular changes are thought to improve computational speed and efficiency as redundant synapses are eliminated and oft-used cortical circuits are insulated with myelin.

The parietal cortex subserves visuospatial functions, and thus, thinner cortices in men within temporoparietal regions, if it indeed arises from greater pruning and myelination during development and more efficient computational processing, may contribute to the superior visuospatial skills of men.

Differences in the rates of cortical maturation between males and females, and relationships between cortical maturation and changes in cognitive function, could be assessed across the cerebrum.

### **STEROID HORMONE AND DEVELOPING OF COGNITIVE ABILITIES**

Studies have identified weak but significant differences between the overlapping distributions of male and female abilities, with women reported to perform better as a group than men on verbal, perceptual, and fine motor tasks, but poorer than men on spatial and quantitative measures (Sherwin, 1994).

As suggested by studies in other species, differences in brain structure established during development by the presence or absence of androgen probably account for performance differences between the sexes (Nass and Baker, 1991; Naghdi et al., 2001; Gurzu et al., 2008). Based on evidence from studies of adults, it has been suggested that androgen levels correlate negatively with performance on verbal tasks, but positively with performance on spatial tasks. Endogenous testosterone levels determined from plasma or saliva samples have been positively correlated with the performance of men on spatial measures (Christiansen and Knussmann, 1987; Christiansen, 1993, Errico et al., 1992) and testosterone supplementation selectively improved spatial performance in elderly men and female-to-male transsexuals (Janovsky, 1994; van Goozen et al., 1995). There also is evidence that endogenous and supplemental testosterone impaired performance on some verbal measures (Christiansen and Knussmann, 1987; Christiansen, 1993; Phillips and Sherwin, 1992a; van Goozen et al., 1995), but improved the object location (Postma et al., 2000).

Available data indicate that endogenous or exogenous estrogen enhances performance on tasks that depend primarily on working memory, but usually fails to alter or even impairs, performance of reference-memory tasks (Daniel et al., 1997; Chesler and Juraska, 2000).

Both androgens and estrogens support the maintenance of synapses in hippocampus and prefrontal cortex in animal models. For instance, gonadectomy or ovariectomy causes a profound loss of synapse density in hippocampus of male and female rats (Leranth et al., 2003; Wooley and McEwen, 1994) and monkeys (Leranth et al., 2004).

During adolescence and this time of active neural maturation, many cognitive processes are also developing. One such process is working memory. Working memory refers to the ability to actively store and manipulate information online over brief periods of time (Baddeley, 1986). This ability is fundamental to intact performance in a variety of other cognitive domains, including language comprehension, abstract reasoning, learning and memory and visuospatial processing (Baddeley, 1992; Gathercole, 1999; Vuontela, 2003).

Verbal and spatial working memory abilities improve throughout childhood and adolescence (Gathercole et al., 2004; Luna et al., 2004), with accuracy and reaction times increasing and decreasing respectively during spatial n-back (Kwon et al., 2002; Vuontela et al., 2003) and spatial delayed response tasks (Zald and Iacono, 1998). It is likely that these behavioral improvements in working memory are the result of the described neuromaturation processes that are occurring during the child and adolescent years.

In a recent morphometric study, the most pronounced gray matter loss was found in the parietal lobes in normally developing children for both sexes (Wilke et al., 2007). Thus, the negative correlations between parietal structures and testosterone in boys and girls might be considered within the context of the general decrease in parietal gray matter volumes during normal development.

The development of gray matter in the parietal cortex might also be associated with its increasing specialization for visuospatial and attentional functions (Casey et al., 2005).

## **VISUOSPATIAL PROCESSING ON ADOLESCENCE**

In the past several years, there has been an explosive growth in the field of human brain imaging. Much of this work has demonstrated that information processing in the human brain involves the concerted activity of multiple, spatially distributed cortical regions.

Major goals for those engaged in human brain mapping of cognitive function include identifying the regions that participate in various information processing operations, characterizing the functional role played by each region, and modeling the interactions among regions. Vision and visual

memory have been especially fruitful domains for studies of distributed neural systems in the human brain (Ungerleider et al. 1998).

The differential visual impairments produced by focal lesions in clinical cases suggest that human visual cortex, like that of the monkey, may be similarly organized into two anatomically distinct and functionally specialized ventral and dorsal processing pathways, occupying about one-half of the total cortex (Desimone and Ungerleider, 1989; Felleman and Van Essen, 1991).

These areas are organized into two functionally specialized processing pathways, each having the primary visual cortex (V1) as its source and each being composed of multiple areas beyond V1.

The occipitotemporal pathway, or “ventral stream”, is crucial for the identification of objects, whereas the occipitoparietal pathway, or “dorsal stream”, is crucial for spatial perception (Ungerleider and Mishkin, 1982; Ungerleider and Haxby, 1994) and for the visual guidance of movements toward objects in space (Goodale and Milner, 1992; Jeannerod and Rossetti, 1993). A simple way to conceptualize the functions of the two processing streams is “what” versus “where”.

The ventral stream in the human brain is located almost entirely on the ventral surface of the temporal lobe; in addition, it does not extend as far anteriorly in the human compared with the monkey. The dorsal stream in the human brain has a more superior location in parietal cortex than in the monkey. Such differences suggest that these regions of cortex were displaced in the course of human brain evolution.

The inferior displacement of ventral stream areas and the superior displacement of dorsal stream areas both may be related to the emergence of phylogenetically newer areas specialized for language in the posterior perisylvian cortex. Similarly, the posterior displacement of ventral stream areas away from the temporal pole may be related to the role the latter cortex plays in semantic and lexical knowledge about objects (Damasio et al., 1996; Nobre et al., 1994).

The current version of the visual hierarchy includes 10 levels of cortical processing. Altogether, it contains 14 levels if one includes the retina and lateral geniculate nucleus at the bottom as well as the entorhinal cortex and hippocampus at the top. Within this hierarchy, there are multiple, intertwined processing streams, which, at a low level, are related to the compartmental organization of areas V1 and V2 and, at a high level, are related to the distinction between processing centers in the temporal and parietal lobes (Felleman and Van Essen, 1991).

Sex differences in processing and performance within the visuospatial domain have been of great interest. Generally, tasks involving spatial transformations (i.e., mental rotation) produce the most robust sex-based differences, with males outperforming females; however, differences have also been reported on spatial perception/visualization tasks (Voyer et al., 1995). Most studies have typically addressed the issue of identifying and understanding the neurobiology of sexbased differences using mental rotation tasks as these tend to produce robust results (Butler et al., 2006; Halari et al., 2006; Hugdahl et al., 2006; Jordan et al., 2002; Kucian et al., 2007; Thomsen et al., 2000; Weiss et al., 2003). Additionally, a limited number of studies have utilized more basic perceptual tasks, such as spatial line orientation tasks, to assess whether differences are evident at a more basic level of processing and not only during greater cognitive demands (Clements et al., 2006; Gur et al., 1991, 2000).

A limited number of studies have investigated the neurobiology of sex differences as related to development in visuospatial processing in younger populations. Kucian and colleagues (2007) conducted a study comparing activation associated with a mental rotation task in children and adults. Both groups had activation in right fusiform gyrus and bilateral parietal lobe—superior parietal for the child group ( $R > L$ ) and inferior parietal for the adult group; adults had additional activation in bilateral extrastriate cortex. The child group showed additional activation when compared to adults, in bilateral posterior cingulate and precuneus while adults had greater activation than children did in left intraparietal sulcus. There were no sex differences in the child group while adult females showed stronger activation in right middle temporal gyrus, right inferior frontal gyrus, and left primary motor. Thus, this study shows that there is a developmental shift in the intraparietal sulcus from stronger right lateralization in younger groups to a bilateral representation in adults.

In spatial line orientation task for children between 7 and 15 years of age, further differences in the development of processing visuospatial information are confirmed through the correlation data. With increasing age, males shift from traditional right hemisphere network (including IPL) to engagement of the left hemisphere; this is consistent with previous literature (Clements et al., 2006; Gur et al., 1991, 2000). These findings suggest that an efficient right hemisphere network is developed at an early age for males and that with increasing age the left hemisphere is recruited and both hemispheres are utilized in a parallel fashion.

Furthermore, these results could indicate that regions within the left hemisphere, for males, are part of an efficient visuospatial and/or visuomotor network. However, a different developmental pattern is seen in females. With increasing age, females shift from the engagement of bilateral medial frontal and posterior regions (e.g., medial frontal gyrus and cingulate) to more traditional areas seen in visuospatial processing (e.g., rIPL, rITG, rDLPFC, bilateral SPL) (Butler et al., 2006; Weiss et al., 2003). Findings suggest that younger females recruit regions typically seen in decision-making and possibly verbal strategy use and as females get older, greater activation is seen in right hemisphere regions. Specifically, activation in females is seen in more traditional areas associated with visuospatial processing, in particular, spatial attention and working memory.

The few studies examining fMRI response during verbal and spatial working memory in children and adolescents suggest that, overall, children and adolescents demonstrate similar frontal and parietal patterns of response as adults (Casey et al., 1995; Thomas et al., 1999), but show greater (Klingsberg et al., 2002; Kwon et al., 2002) and more widespread (Kwon et al., 2002) activation in these regions with increasing age. Schweinsburg et al. (2005) conducted a study investigating the impact of age and sex on spatial working memory. They showed that there was a significant positive correlation with age in a left prefrontal region and bilateral inferior posterior parietal lobe; a significant negative correlation with age was seen in bilateral superior parietal cortex. Moreover, females demonstrated a diminished response in anterior cingulate activation while males demonstrated a greater response in frontopolar cortex compared to females. Schweinsburg et al. concluded that frontal and parietal neural networks that are involved in spatial working memory change during adolescences, influenced by sex, which possibly reflects the development of sex-specific strategies used for task completion.

These neurocognitive studies suggested that brain regions activation during visuospatial processing in adolescence could be correlated with the developmental trajectory of brain neuromaturation processes and also demonstrate the gradual developing of dorsal and ventral visual processing pathways on the brain during adolescence. Also, the sex difference in visuospatial processing could be correlated with the difference in development of brain regions involved in visuospatial abilities under gonadal steroid hormones, testosterone and estrogens, during adolescence.

## CONCLUSION

Studying of the human adolescent brain has sparked scientific interest in studying adolescence from a neurobiological perspective, and it has captured the neuroscientist's fascination with the profound neuronal rewiring that takes place during this period of development.

This review highlights the organizational and activational role of steroid hormones, which become elevated during puberty, in development and remodeling the adolescent brain and cognitive abilities.

The influences of steroid hormones during adolescence occur in both females and males, occur across a wide range of species including humans, and impact many behaviors and cognitive abilities such as visuospatial processing.

Examining sex-based differences in visuospatial processing in younger populations could provide further insights into the maturation of important regions involved in visuospatial processing as well as to identify potential differences in strategies used, and the development of these strategies under organizational and activational effects of steroid hormones.

One research purpose for developmental cognitive neuroscientists could be the neurobiology of cognitive abilities on younger population in visual processing and semantic association between visual information and abstract categories as assessing the neuromaturation of "high level" pathways during adolescence. Direct observations on my young students between 10 and 17 old, revealed differences between sexes, age and their education. It is possible that gonadal steroid hormones could play an important role in brain regions development involved in visuospatial processing, spatial memory and semantic association during adolescence.

Also, understanding the nature of visuospatial abilities and their relationships to general intelligence or to general-purpose executive functions should contribute strongly to more fair and comprehensive tests of intelligence (Miyake et al. 2001).

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