



HORMONES AND THE TEEN BRAIN

THEY DO MORE
THAN FOSTER
ADOLESCENT ANGST

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Slamming doors, week-long sulks, reckless driving: Welcome to a world steered by hormones in the teen brain. Although these sex steroids that burst onto the scene during puberty are known for disrupting emotions along with fostering the development of sexual organs, recent research suggests they also help put the final finishing organizational touches on a teen's brain. This research reveals that hormones, including ovarian hormones, sculpt brain anatomy and wire key neurocircuits such as those that govern impulse control, certain cognitive abilities, and motivation and reward-seeking behaviors.

"There's been an explosion of studies done in just the last few years that correlate hormone levels with brain development during adolescence," noted pharmacologist Cynthia Kuhn, Ph.D., of Duke University.

The growing appreciation for sex hormones' important role in adolescent brain development has unleashed research aimed at uncovering whether it can explain sex differences in brain anatomy and functioning, as well as susceptibility to various mental disorders, including schizophrenia, eating disorders, and drug addiction. In a follow-up to the January cover feature in *Endocrine News* on the same topic, this article focuses on concerns that hormone supplements, endocrine disruptors, and other factors that can affect hormonal exposure during puberty might significantly and permanently alter behavior, mood, and cognitive ability.

Fine-Tuning Brain Anatomy

Based on animal research done prior to the 1980s, scientists have long assumed that the amount of androgens during the prenatal and perinatal period triggered development of the neurocircuits that determined male- and female-typical behavior, especially sexual behavior. Researchers postulated that sexual behavior doesn't come into play until years later, when these neurocircuits are jolted into action by the surge of hormones released during puberty.

Recent studies have revealed that the burst of hormonal activity during puberty does more than just wake up these neurocircuits. "Converging evidence from studies of rodents, primates, and now humans has made it clear that hormones in puberty don't just activate neurocircuits in the brain, but organize them," said Jay Giedd, M.D., a neuropsychiatrist at the National Institute of Mental Health.

How strongly hormones organize brain anatomy in ways that permanently affect behavior was revealed in rodent studies by Cheryl Sisk, Ph.D., of the Neuroscience Program at Michigan State University.¹ These studies found that the window of sensitivity to the brain-sculpting actions of steroid hormones opens prenatally and closes tightly at the end of adolescence. This period of sensitivity is bookended by two dramatic bursts of elevated hormone secretion during which heightened brain development occurs. What's remarkable is the immunity of the rodent brain to hormonal ripening once this window of sensitivity closes at the end of adolescence.

Dr. Sisk discovered that castrated hamsters given testosterone during the equivalent of childhood or adolescence behaved normally once they became adults. In comparison, those not given the hormones until after reaching adulthood did not show proper mating behavior; nor were their levels of aggression and territorial marking up to snuff. Their adult brains were no longer sensitive to the developmental effects of the hormones. Other researchers found that male rats castrated before puberty lacked the typical wary behavior seen in adult males traversing open environments, and that testosterone replacement during puberty, but not in adulthood, restored the behavior.

Role for Female Hormones

Recent findings have also overturned previous assumptions that only androgens produced prenatally or shortly after birth determine sex-typical behavior, with the female brain being the default condition when androgen levels are low. Instead, rodent studies find that ovarian hormones affect brain development and subsequent behavior during adolescence. For example, when researchers remove their ovaries before puberty, they show the food-guarding and -ingesting behavior typical of males, whereas those whose ovaries were removed after puberty show typical female behavior. Female rodents whose ovaries were removed prior to puberty do not experience the typical shrinkage in their visual cortices that occurs in normal females during puberty.

Female hormones may also influence susceptibility to addiction. Studies of rodents by Dr. Kuhn and others suggest the dopamine-producing reward neurocircuits in the brain

mature during the teen years, in part due to the influence of hormones.² During adolescence, dopamine-producing cells in the base of the brain sprout numerous connections to more cerebral controlling regions higher up in the brain. At the same time, a large number of dopamine-producing neurons dramatically die off, perhaps due to a lack of growth factors coaxing them to the upper reaches of the brain. Estrogen's growth-promoting effects help stem the loss of dopamine-producing neurons, but androgens tend to boost such cell loss. These hormonal differences might help explain why men are more prone to drug addiction than women, Dr. Kuhn speculates. This sex difference emerges late in adolescence in humans.

Human Hormonal Sculpting and Sex Differences

Evidence for hormonal sculpting of the brain during adolescence is also seen in human studies, and might help explain why the sexes, on average, tend to differ in their ability to visualize objects in space and mentally manipulate them. Decades ago, researchers showed that men with a condition that makes them produce little to no testosterone during their teen years show subpar spatial visualization abilities compared to normal men. This hormonal effect on spatial visualization is also seen in women with a condition that makes them produce more than normal androgens during childhood and early puberty. These women perform better on a maze test than their normal peers.

More recently, a series of brain images of adolescents and young adults, done by Dr. Giedd, has also found distinctive male and female patterns of brain maturation linked to hormone activity. His scans reveal that girls' brains, on average, mature before boys, especially the regions involved in impulse control, planning, and decision making.³

Dr. Giedd has shown that brain maturation patterns are linked to androgen receptor activity. Male teens with the most active androgen receptors had the most masculine pattern of brain maturity, including accelerated maturity in the portions of the brain that govern spatial visualization tasks. Girls with more active androgen receptors showed a more delayed brain maturation pattern in regions responsible for language and impulse control, as typically seen in males. These findings reinforce the stereotype that thanks to the influence of hormones on adolescent brain development, teen girls are more likely to underestimate the spatial dimensions of the car they are driving and bang into something while backing out. Teen boys are probably more capable in this, but less likely than girls to control their impulse to drive fast, let alone to brag about it.

"Our study unveils a map of how the brains of boys and girls grow differently as they negotiate the sensitive developmental transition into adulthood, and suggests that androgen receptor activation plays a role in the drafting of this map," wrote Dr. Giedd and his colleagues in a recent journal article.³ He stressed to *Endocrine News*, however, that "there is great individual variation *and* a huge amount of overlap between the sexes—girls' and boys' brains are overwhelmingly more alike than different."

Dr. Kuhn added, "Biology is not destiny. We can strengthen some of these subtle underlying differences by the way we socialize people."

Dr. Giedd agreed, noting that prior to taking a math aptitude test, if women are told men perform better on the test than women, they score much lower than a control group of women who were not told this stereotype prior to testing.

Hormones and Mental Illness

The recent findings on hormones and brain development during adolescence suggest that abnormal hormone levels are likely to not just affect a teen's moods at the moment, but may disrupt brain development and mental health and abilities, because they occur when the brain is laying down permanent pathways that will determine future capabilities. This may be especially true given that pediatric neuroimaging studies indicate "the journey of brain development is often as important as the destination," as Dr. Giedd put it. For example, the path and pace of cortical thickness development is linked to IQ predictions more than final adult cortical thickness measurements.

Dr. Sisk stressed that delayed puberty, such as what occurs in female athletes, or due to other conditions, might also be hazardous to normal brain development. "If kids have hypogonadism, you might want to get them on hormonal replacement therapy earlier rather than later because you don't want to bypass that window of brain development sensitivity," she said. Children who undergo unusually precocious puberty might also be susceptible to altered brain development, she added.

Dr. Giedd and his colleague Tomás Paus, Ph.D., of the Montreal Neurological Institute at McGill University, suggest that the reason adolescence is linked to the onset and increasing incidence of many mental disorders, such as schizophrenia, depression, and addiction, is because "moving parts get broken." They point out that the brain is extremely malleable and rapidly changing during adolescence. Many of the cognitive abilities shaped during this time, including control of emotions and risk taking, may be changed by faulty timing of brain development, resulting in mental disorders. Boys may be especially vulnerable to such aberrations because their brains take longer to mature than girls', thus broadening the window of potential harm, according to Dr. Giedd.

Girls may be especially vulnerable to certain mental disorders, such as depression, eating disorders, and anxiety, because of the influence of female hormones on their brain development. It is only after puberty that girls become much more likely to develop these disorders than boys, with pubertal status or estradiol levels linked to such vulnerability more than age. The role of female hormones in fostering anxiety in some people is suggested by a study in mice, which found that a steroid derived from progesterone (tetrahydroprogesterone) can increase anxiety when it binds to a certain subtype of receptor found in brain cells. After puberty, the number of these receptors dramatically increases in the brains of mice genetically

prone to develop this receptor subtype. Such increases are tied to heightened anxiety in the mice.⁴

Support for female hormones fostering susceptibility to eating disorders comes from twin studies, which have found that genetic differences in eating disorder susceptibility in girls do not manifest themselves until puberty—with its surge of ovarian hormones. In contrast, the genetic risk for eating disorders for boys remains the same before, during and after puberty.⁵

Environmental Hormones

Some alterations in brain development may stem from environmental hormonal exposures. Of special concern is the increasing use of anabolic steroids by teen athletes, given that adolescent hamsters exposed to such steroids showed more aggressive behavior ("roid rage") than those exposed as adults. A steep rise of testosterone in male adolescents with a particular variant of the androgen receptor gene was linked to increased likelihood of depression as well. Other studies have linked anabolic steroid use to depression in both female and male teens.

Female hormones also probably play a role in heightening susceptibility to certain mental illnesses, raising concern about environmental estrogens. Although one study showed that prenatal exposure to the endocrine disruptor bisphenol A spurred the development of dopamine-producing neurons in rodents, researchers are just beginning to look at whether these environmental chemicals affect adolescent brain development.

"We don't know much about this yet, but endocrine disruptors certainly could be interfering with or adding to the effects of hormones during adolescence. Some people have suggested they help explain why girls are entering puberty earlier than they used to," Dr. Sisk said.

Dr. Kuhn pointed out that environmental estrogens are weak estrogens. "You'd almost have to eat a plastic bottle to have enough bisphenol A exposure to have it really disturb hormonal levels in teens," she said.

All researchers agree, however, that more attention should be paid to the role of hormones in teen brain development. "Sex hormones definitely affect brain development. The more research we do, the more we're finding hormonal factors affect just about everything," said Dr. Kuhn. ■

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