A Biological Blind Spot in Addiction Research:

Hormonal Contraceptives and Adolescent Reward Seeking

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Many women do not experience their natural hormonal cycles uninterrupted throughout their lives. In the U.S., about 88% of reproductively-aged women who have had sexual intercourse with a male partner report having used hormonal contraceptives, with 82% having used oral contraceptive pills[1]. Oral contraceptive pills are particularly popular among adolescents, with one in five females aged 15-19 reporting current use of oral contraceptives[2]. Because oral contraceptive pills are commonly used throughout the lifespan and have the potential to disrupt the female hormonal milieu, we propose the need for an updated framework for understanding female developmental biology that incorporates this reality, particularly as it applies to substance use research. The importance of an updated biological framework is increasingly necessary given the rising rates of substance use among women and increasing rates of binge drinking among girls.

A major push has been made to understand female vulnerability to substance use, with a priority placed on elucidating the role of endogenous sex hormone fluctuations. Significant strides are being made, with recent exciting work identifying estrogen-sensitive drinking behaviors in mice which are further modulated by estrogen-targeting interventions[3]. While these questions are fundamental to our understanding of female biology, efforts to effectively translate these findings to humans may be hampered by the reality of widely used hormonal interventions by girls and women. This is particularly likely to impact adolescents due to the popularity of oral contraceptives among this demographic.

Formulations for oral contraceptive pills can vary, with popular variants containing both a progestin (a synthetic agonist at progesterone receptors) and ethinyl estradiol (a synthetic estrogen)[4]. These synthetic hormones have distinct interactions and off-target effects from their endogenous analogues, creating a unique hormonal landscape. Oral contraceptive pills mainly act to disrupt hypothalamic and pituitary control of ovarian function – making their entry into and influence over the brain necessary for their mechanism of action. Over time, exposure to these hormones can change functional connections in the brain related to reward seeking[5]. There are also reports of adolescents being uniquely sensitive to some persistent depression-related side effects of oral contraceptives[6]. Clearly, oral contraceptive pills have the potential to shape mental health in adolescents, and this warrants careful and thorough consideration.

It is crucial that preclinical research develops appropriate models incorporating common human hormonal interventions. Given the immense demand for oral contraceptive pills among adolescents, and the wider popularity of hormonal contraceptives among all women worldwide, it is both necessary and prudent to expand our definition of a typical hormonal milieu and reframe our approach to understanding female sex hormones and behavior to be inclusive of the actual physiological and developmental experiences of most women. Incorporating emerging work on hormonal contraception as a biological variable is essential for a more accurate understanding of the development of risk and resilience in female adolescents.

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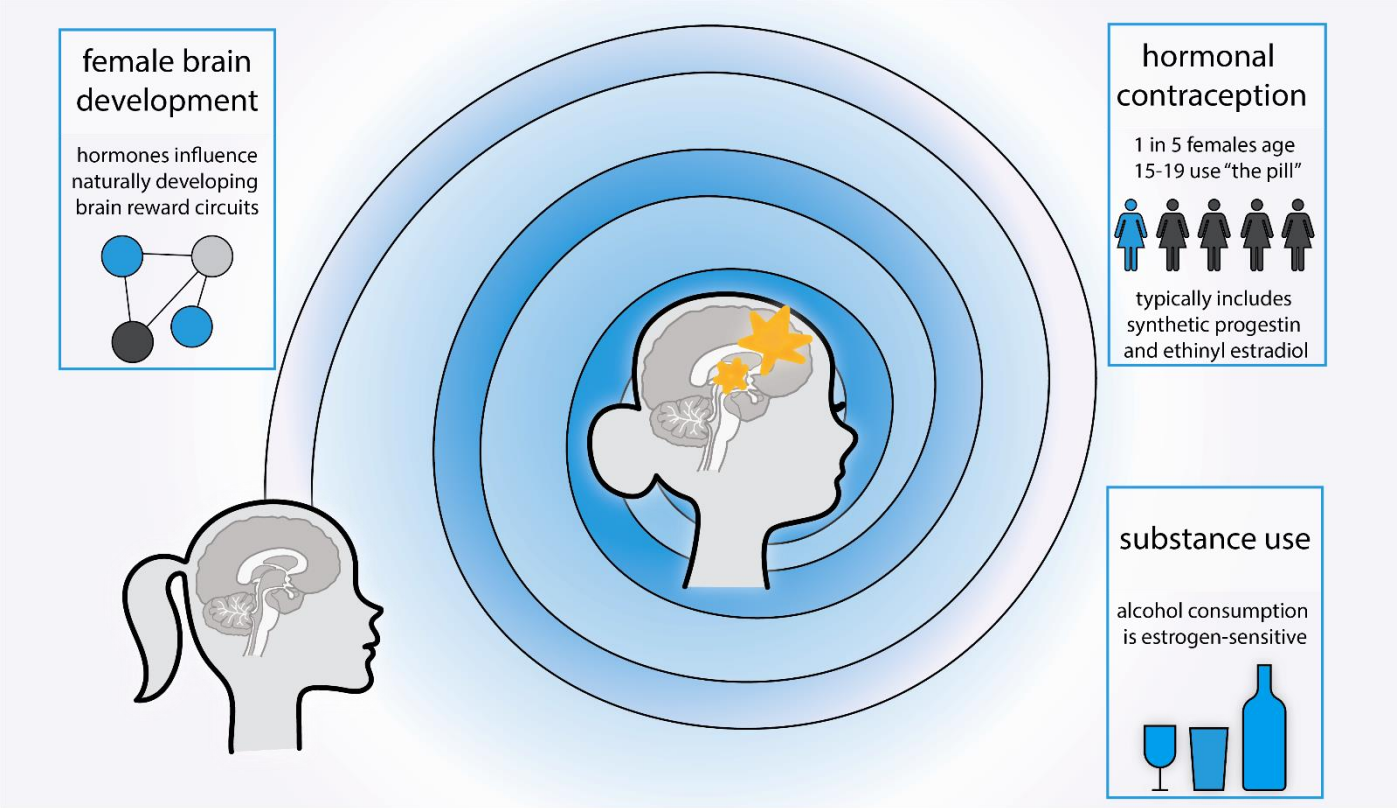

Figure 1. The adolescent female brain is sensitive to perturbations. Such disturbances include endogenously circulating hormones, which naturally increase during puberty and continue to fluctuate throughout the lifespan, as well as voluntary use of substances of abuse like alcohol. However, very little work has been conducted to understand how these variables interact to influence brain development, particularly in reward-related neurocircuits, which could lead to lifelong shifts in brain function in adult women. Preclinical and animal models must consider synthetic hormone exposure through hormonal contraception such as "the pill". Incorporating contraceptive exposure paradigms into addiction and reward models will more accurately reflect the biological milieu of girls and women and will provide greater translational insights.

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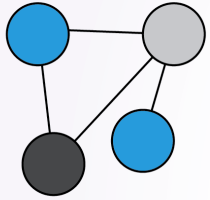
female brain development

hormones influence naturally developing brain reward circuits



hormonal contraception

1 in 5 females age 15-19 use “the pill”

typically includes synthetic progestin and ethinyl estradiol

substance use

alcohol consumption is estrogen-sensitive