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HORMONAL CONTRACEPTIVES AS SYSTEMIC NEUROENDOCRINE MODULATORS

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Hormonal contraceptives (HCs) are extensively used worldwide, primarily exerting their contraceptive effect by suppressing the hypothalamic-pituitary-gonadal axis, which leads to inhibition of ovulation (Horvath et al., 2000). Beyond their role in contraception, an increasing body of evidence indicates that HCs may function as systemic neuroendocrine modulators, influencing brain physiology, mood, and cognitive processes (Song et al., 2022). Neuroimaging and translational research have identified potential links between HC use and alterations in neurotransmitter systems, regional brain morphology, and functional connectivity, particularly within networks associated with emotional and cognitive regulation (Gravelsins et al., 2023; Haase et al., 2025). Notably, these neurobiological effects appear to differ depending on hormonal formulation, age at initiation, and individual variability (Gravelsins et al., 2023).

The present review aims to examine the current literature on HCs as systemic neuroendocrine modulators and to evaluate their potential influence on brain function, affective states, cognition, as well as selected systemic risks.

HCs may affect the central nervous system through their interaction with steroid-sensitive pathways that contribute to the regulation of affect and cognition. Experimental findings suggest potential impacts on neuroplasticity mechanisms, including modulation of brain-derived neurotrophic factor and neurogenesis; however, these results are inconsistent and appear to vary with specific formulations (Concas et al., 2022). Neuroimaging studies have further suggested that HC use may correspond with altered connectivity in structures such as the amygdala and within broader functional networks implicated in attentional control and default-mode processing (Haase et al., 2025).

Clinical data regarding mood and cognitive outcomes associated with HC use are heterogeneous. Certain studies report that formulations containing ethinyl estradiol combined with specific synthetic progestins may produce adverse mood effects in susceptible individuals, whereas more recent formulations could exhibit a reduced psychiatric impact (Mussawar et al., 2025). Moreover, evidence indicates that adolescents and young adults might exhibit increased sensitivity to neuroendocrine effects, potentially due to ongoing brain maturation during early adulthood (Gravelsins et al., 2023). The variability in findings likely reflects differences in hormonal composition, duration of exposure, psychiatric background, and individual biological responsiveness.

In addition to neuropsychological considerations, some HCs have been linked to systemic adverse events, including venous thromboembolism and other vascular complications (Mussawar et al., 2025). Emerging data also suggest substantial differences in risk profiles across formulations, underscoring the importance of personalized evaluation of risks and benefits (Haase et al., 2025; Roland et al., 2025).

In summary, HCs should be regarded not only as contraceptive agents but also as modulators of systemic neuroendocrine function. Their influence on brain function, mood, and cognition is multifaceted, variable, and dependent on formulation specifics. Further investigation is warranted to elucidate underlying mechanisms, identify vulnerable populations, and guide a more tailored approach to contraceptive selection and clinical counseling.