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Letter

ON NEURODEVELOPMENTAL DISORDERS: RELEVANCE OF SEX STEROID HORMONES

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The interesting article by Eirís-Puñal and Monteagudo-Saavedra[1] stands out for offering an in-depth and rigorous review of the genetic and epigenetic basis of neurodevelopmental disorders, particularly attention-deficit/hyperactivity disorder and autism spectrum disorders[1]. This valuable contribution helps update and consolidate knowledge about the hereditary factors involved in these disorders. To complement what is presented in this article, we wish to highlight a relevant aspect of neurodevelopment that is not addressed in sufficient depth in this work or the rest of the supplement: the role of sex steroid hormones in the structural and functional organisation of the child and adolescent brain. Therefore, this Letter to the Editor aims to highlight the importance of considering the organisational and activational effects of sex steroid hormones as a key modulating variable in brain maturation and the emergence of sex-differentiated behaviours during adolescence.

Adolescent brain development is influenced by intense neuroendocrine reorganisation, triggered by the activation of the hypothalamic-pituitary-gonadal axis. This process stimulates the production of sex hormones such as androgens, oestrogens, and progestogens, which modulate neuroplasticity mechanisms, affecting processes such as: myelination and dendritic spine remodelling, representing forms of structural and functional neuroplasticity, which improve the efficiency of neuronal conduction and modify synaptic connectivity, respectively; synaptic pruning, a form of structural plasticity that optimises neuronal networks by eliminating redundant synapses; and epigenetic programming, which corresponds to molecular plasticity, and regulates gene expression without altering the DNA sequence, allowing for lasting environmental adaptations[2,3]. These transformations are essential for consolidating executive and emotional functions, especially in areas such as the prefrontal cortex and the limbic system[4].

The organisational-activational hypothesis, proposed by Phoenix *et al.*[5], argues that sex hormones have permanent structural (*i.e.*, organisational) effects when they act during critical stages such as the prenatal period and reversible (*i.e.*, activational) effects when they act on previously organised circuits. Adolescence constitutes a second sensitive window for brain organisation[6], with early childhood being the first. This idea has growing support in the literature, although the exact boundaries between the two types of hormonal effects are still debated (Table 1).

From a sex-differentiated perspective, recent neuroimaging studies have shown statistically significant, albeit modest, distinct patterns of brain connectivity between adolescent males and females, influenced by testosterone and oestradiol levels[7,8]. Although these differences exhibit a high degree of interindividual variability, they provide valuable insights into understanding neurodevelopmental trajectories from a sex-specific perspective.

Likewise, research on hormonal contraceptives in animal models and adult women has

Table 1 | Hormonal influences on brain development across stages and conditions: organisational and activational effects

Developmental stage	Hormones involved	Type of effect	Main observed evidence
Prenatal	Testosterone, oestradiol (via aromatization)	Organisational (irreversible)	Differentiation of limbic structures, sexual orientation, organisation of neural circuits (CAH, CAIS)
Adolescence (puberty)	Testosterone, oestrogens, progesterone	Organisational and activational	Synaptic remodelling, myelination, maturation of the prefrontal cortex and limbic system
Exogenous exposure (COCs)	Ethinyloestradiol, progestins	Activational (reversible)	Changes in brain activation patterns involving regions such as the amygdala and hippocampus in adult women; preliminary evidence in adolescents
Clinical conditions (*e.g.*, CAH, PCOS, CAIS)	Elevated androgens or androgen insensitivity	Organisational (case-dependent)	Variable behavioural phenotypes; increased risk of ASD in specific conditions such as CAH; female-typical gender identity in CAIS; effects dependent on timing and degree of androgen exposure

ASD: autism spectrum disorder; CAH: congenital adrenal hyperplasia; CAIS: complete androgen insensitivity syndrome; COCs: combined oral contraceptives; PCOS: polycystic ovary syndrome
Source: Based on the revised literature

demonstrated changes in regions such as the hippocampus, amygdala, and prefrontal cortex, associated with variations in emotional memory, social processing, and brain structure[9]. However, the evidence is still preliminary in the human adolescent population and requires further longitudinal validation before definitive conclusions about its potential neurobiological implications can be obtained.

Swift-Gallant et al.[10] recently reinforced this line of argument, analysing conditions such as congenital adrenal hyperplasia, androgen insensitivity syndrome, and polycystic ovary syndrome. These clinical models have collectively demonstrated that prenatal androgen levels can modulate sexual differentiation in the human brain through organisational mechanisms, which aligns with what has been observed in animal models. However, it is also necessary to consider the interaction of these hormonal factors with the psychosocial, environmental, and genetic context.

Based on the aforementioned facts, integrating the hormonal component into etiopathogenic models of neurodevelopmental disorders would allow for a more comprehensive and up-to-date view of human neurodevelopment. The dialogue between genetics, epigenetics, and developmental endocrinology would enrich biomedical research and have relevant clinical implications for prevention and treatment, which are differentiated by sex and developmental stage.

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