Hormonal contraceptives and cognition – time to refocus on women!

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Hormonal contraceptives shape women's brains in ways we still barely understand, and it's time to study their effects on the cognitive functions that really matter, not just "male-like" performance, says Belinda Pletzer, Professor of Neuroendocrinology, Centre for Cognitive Neuroscience – Paris Lodron University of Salzburg

Psychological studies of cognitive changes during female hormonal transition periods have yielded inconsistent – and often non-significant – findings. Even for the strongest hormonal transitions, such as pregnancy and menopause, laboratory findings regarding cognitive changes don't necessarily align with patients' subjective reports, suggesting that laboratory tasks may not fully capture women's experiences in daily life. (1)

Importantly, for less substantial hormonal transitions like the menstrual cycle or hormonal contraception, women generally don't report subjective changes in their cognitive functions. In line with this, most studies have found no changes in cognitive functions throughout the menstrual cycle. (2)

Most findings on hormonal contraception and cognition were obtained from cross-sectional studies, comparing women using certain hormonal contraceptives to women not using them. (3) Thus, these studies face an inherent chicken-and-egg problem, as differences may either be a result of hormonal contraceptive use or a prerequisite for tolerating it. Hence, longitudinal studies are required to investigate the effects of hormonal contraceptives on female cognition.

Simultaneously, we propose expanding the focus from the gendered cognition tasks traditionally used to cognitive functions relevant for women's mental health.

It is quite popular in cognitive psychology to address hormonal questions via a gender shift lens. Given that there are some cognitive functions for which sex/gender differences are robustly reported, research questions are generally framed from the perspective of whether hormonal transitions make someone more "male-like" or "female-like".

However, by borrowing research questions from the field of sex/gender differences, we not only inherit biases regarding women's cognitive functions. We also focus on specific endocrinological mechanisms that may not necessarily be the most relevant to women. So, it's time to expand this focus!

Why are women's cognitive functions a matter of opinion?

Sex/gender differences in cognition are probably the most controversial field of science, yet they are probably also the one many people have vigorous – sometimes opposing – opinions on

Biopsychosocial interactions regarding gender expressions in cognition are well established; however, it remains a matter of opinion rather than scientific evidence whether there are sex/gender differences in certain cognitive tasks and whether these differences are related to genes, hormones, or learning experiences.

By focusing on tasks showing sex/ gender differences in women's health research, we inherit those opinions. But whether cognitive functions change along the menstrual cycle or with hormonal contraceptive use shouldn't be a matter of opinion.

Sex/gender differences in cognition depend on numerous factors, varying from task to task, from situation to situation, and most importantly, depending on the individuals being studied. Sex/gender difference research typically utilizes a cross-sectional, population-based approach. But this is not what we need in hormonal contraceptive research.

We know by now that hormonal contraceptive effects on women's mental health are highly individualized – the same may well apply to cognitive changes. In women's health research, and specifically with regard to hormonal contraceptive use, we need personalized longitudinal approaches! [4] If we view hormonal contraceptives' association with cognition not from a cross-sectional but from an individualized perspective, we automatically expand our focus in multiple steps.

It matters when differences occur!

First, expand the timescales! Sex differences – where hormonally mediated – are likely to arise from organizational actions of sex hormones during sensitive periods of brain development. Such organizational effects are long-lasting. With hormonal contraceptive use, however, we need to understand short-lived activation effects before we can ask if some effects might accumulate over time and become long-lasting.

Distinguishing between short-lived and long-term changes can only be achieved by tracking individual cognitive trajectories over time. This is particularly relevant since mood changes occur within a very short timeframe after initiating hormonal contraceptive use. [5,6] Addressing the timescale of potential hormonal contraceptive effects on cognition may further the prevention and treatment of adverse mood effects of hormonal contraceptives.

Why is it so important how "male" we are?

Second, expand the hormones investigated! Sex differences – where hormonally mediated – are often linked to androgenic effects of testosterone. Androgenic actions during sensitive periods of development will result in a male phenotype; otherwise,

development defaults to a female phenotype. While alterations in androgenic activity during hormonal transitions are relevant, it is more likely that changes can be attributed to estrogens and gestagens. Both are classes of hormones with strong neuroplastic effects that constantly balance different brain networks in women [7], allowing for remarkable neuronal flexibility. [8] So why is it so important how “male-like” we are? Maleness is neither the default nor some ideal to be achieved.

Which functions are most important for women’s mental health?

Third, expand the choice of tasks! The tasks sensitive to sex hormone actions during sensitive periods of development may not be sensitive to sex hormones in adults. The tasks sensitive to testosterone may not be as sensitive to estrogens and gestagens. And the tasks showing sex differences may not be most relevant for women’s mental health.

For instance, the task that most consistently elicits sex differences in favor of men is the mental rotation task. The brain networks supporting this task are probably sensitive to organizational effects of testosterone during brain development. But are they also sensitive to estrogens and gestagens in adult women? And do they contribute to women’s mental health?

Neuroscience links adverse mood effects during hormonal contraceptive use to changes in brain networks relevant to attention and executive function. (9) Thus, it is not surprising that some women report troubles concentrating and brain fog associated with these adverse mood effects.

However, neuroimaging evidence demonstrates the strongest link to adverse mood effects for connections between different brain networks. Thus, it is likely not an improvement or impairment in one specific cognitive function that supports mental health but a balance between those functions. So, let us focus on this balance rather than on male-like performance in mental rotation tasks.

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