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INVITED REVIEW

Sex steroids and connectivity in the human brain: A review of neuroimaging studies

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Summary Our brain operates by the way of interconnected networks. Connections between brain regions have been extensively studied at a functional and structural level, and impaired connectivity has been postulated as an important pathophysiological mechanism underlying several neuropsychiatric disorders. Yet the neurobiological mechanisms contributing to the development of functional and structural brain connections remain to be poorly understood. Interestingly, animal research has convincingly shown that sex steroid hormones (estrogens, progesterone and testosterone) are critically involved in myelination, forming the basis of white matter connectivity in the central nervous system. To get insights, we reviewed studies into the relation between sex steroid hormones, white matter and functional connectivity in the human brain, measured with neuroimaging. Results suggest that sex hormones organize structural connections, and activate the brain areas they connect. These processes could underlie a better integration of structural and functional communication between brain regions with age. Specifically, ovarian hormones (estradiol and progesterone) may enhance both cortico-cortical and subcortico-cortical functional connectivity, whereas androgens (testosterone) may decrease subcortico-cortical functional connectivity but increase functional connectivity between subcortical brain areas. Therefore, when examining healthy brain development and aging or when investigating possible biological mechanisms of 'brain connectivity' diseases, the contribution of sex steroids should not be ignored.

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Conditions in which patients suffer from gonadal abnormalities such as — but not limited to — hypogonadal gonadism, Klinefelter syndrome (low levels of testosterone, Steinman et al., 2009) or polycystic ovary syndrome (high levels of testosterone) and receive hormonal replacement therapies could also shed light on the effects of sex steroid administration on brain circuitries. However, to the best of our knowledge, studies directly focussing on sex steroid treatment on white matter (lesions) or functional connectivity in these conditions are currently lacking.

6. Methodological considerations and future directions

When interpreting the findings discussed in this review, several methodological issues need to be taken into account. We provided an overview of studies on endogenous hormonal levels as well as exogenous manipulations. Although both ways offer unique insight into the relation between sex steroids and brain connections, they differ obviously in interpretation of results and both approaches have their own advantages and disadvantage. For instance, exogenous manipulations have shown to be able to directly affect brain networks, whereas studying endogenous levels of sex steroids only provides an indirect measure (correlational research) and no causal inferences can be drawn. When applying an elegant within subject-placebo controlled design, participants form their own controls and the effects of sex hormones can be directly compared within the same individual. On the other hand, (long-term) administration of gonadal hormones to healthy developing individuals might pose ethical constraints.

Pertaining to the direction of causation, it should be noted that the relation between sex steroids and white matter is bidirectional. Sex hormones are able to increase white matter parameters (e.g. axons, myelination, or supporting glial cells), and, conversely, sex steroids can also be produced from white matter (glial steroidogenesis) as shown by animal studies (Garcia-Segura and Melcangi, 2006) and by human post-mortem work (Steckelbroeck et al., 1999).

With respect to processing of MRI data, different types of brain analyses could introduce dissimilar findings across studies. For example, by employing a region-of-interest (ROI) approach, functional connections between possibly relevant brain areas might stay undetected, whereas these areas might have been observed using a (model-free) whole brain type of analysis. Studies employing ROIs have carefully chosen their targets based on for example a high density of sex steroid receptors, or on earlier reported associations with sex steroids. This could have introduced a bias towards certain brain regions to be reported more often (e.g. the amygdala and hippocampus) than others, such as the cerebellum. Indeed the cerebellum is a brain structure known for its high density of sex steroids (Dean and McCarthy, 2008) and the involvement in motor, cognitive and affective processes (Schutter and van Honk, 2005).

Thus, ovarian hormones (estradiol and progesterone) seem to enhance both cortico-cortical and subcortico-cortical functional connectivity, whereas androgens (testosterone) may increase functional connectivity between subcortical brain areas but decrease subcortico-cortical functional connectivity. Further research is needed to establish the anatomical basis of these functional connections in the human brain. Diffusion tensor imaging could be a method of choice, since this technique enables the examination complete white matter tracts (and microstructural properties of these tracts) of connecting brain areas (Jones, 2008). However, to date no human studies have been carried out that employed DTI and measured sex hormonal levels, leaving the specific white matter tracts on which sex steroids exert their effects unexplored.

7. Concluding remarks

Studying the role of sex steroid hormones in human brain function and organization is an exciting and important new field of research. Despite a wide variety of methods being applied to approximate their effects, evidence is accumulating that androgens, estrogens and progestins are critically involved in establishing proper communication in the human brain network. Therefore, when examining healthy brain development and aging or when investigating possible biological mechanisms of 'brain connectivity' diseases, such as depression, ADHD, autism and schizophrenia, the contribution of sex steroids should not be ignored.

Conflict of interest

The authors declare no competing financial interests.

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