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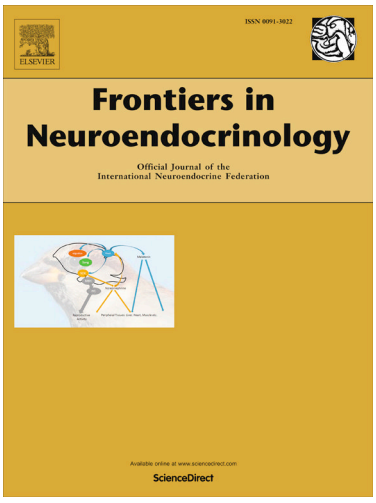

Editorial

Beyond 'bikini medicine' –the need of a gender and sex sensitive approach for brain and mental diseases

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"Drug development for brain disorders: why sex matters"

Editorial:
Beyond 'bikini medicine' –the need of a gender and sex sensitive approach for brain and mental diseases

Sex- and gender-specific medicine is so much more than 'bikini medicine' – it does not deal exclusively with conditions *unique* to women, such as uro-genital or breast pathologies, but extends to a wide array of conditions, including atrial fibrillation, autism, obstructive pulmonary disease, burns, kidney cancer, and pain. As highlighted in this special issue, biological sex is a crucial driver of disease susceptibility in a number of brain and mental diseases, including Parkinson's Disease (Jurado-Coronel et al.), Alzheimer's Disease (Hampel *et al*.), traumatic brain injury (Spaeni *et al.*), stroke (Liberale *et al.*), multiple sclerosis (Houtchens and Bove), depression (Rainville *et al*., Williams and Trainor), and brain tumors (Recouvreux *et al.*). Until now, however, the implications of sex differences in drug development remain relatively unexplored.

Neglecting sex differences in drug development can have dire consequences for patients. Decades of preclinical studies using mostly, or exclusively, one-sex (male) rodents [1] has created a knowledge void that unfortunately migrated into clinical studies. In doing so, drugs have reached the market with safety and efficacy profiles optimized for men only. For instance, pharmacovigilance revealed that severe side effects of zolpidem (Ambien®) were more frequent in women than men, due to lower excretion of the drug. Indeed, zolpidem was the first drug the US Food and Drug Administration recommended to have a different dosing regimen in men versus women ((http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm). However in our opinion this is just the start of recommendations for treatment efficacy differing in men versus women. In the case of aspirin, systematic analysis revealed that, while effective in primary prevention of myocardial infarction in men, it was not protective in women, where instead it can prevent stroke [2]. The characterization of sex differences in prevalence, presentation, prognosis of diseases and drug response is therefore not a 'niche' interest for a small number of scientists; it is an issue of broad impact for drug development and for better health and treatment for all of society.

Sex and gender differences in brain and mental diseases, in particular, deserve special attention. Psychiatric and neurological conditions are non-communicable diseases with a devastating impact on global health [3] and a huge unmet need, with several clinical trials that have failed in the past years. Clinical heterogeneity across patients and lack of predictive preclinical models, are two of the crucial factors hindering drug development in this field. In both cases, neglecting the effects of sex as a factor has likely played a crucial role. Sex is indeed an important driver of phenotypic variability in patient populations, affecting biomarkers and modulating the response to drugs and as such any