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WOMEN ARE UNDER-REPRESENTED IN PSYCHIATRIC RESEARCH, SAY NEUROSCIENTISTS

Basic research into psychiatric disorders must include females, neuroscientists said today at the FENS Virtual Forum of Neuroscience today (Saturday 11 July). Women suffer twice as much from depression, anxiety and PTSD and still the vast majority of preclinical testing of drugs is conducted in male animals. Yet there are potentially important differences between the male and female response to medicines to treat depression, anxiety and PTSD.

"We believe that this mismatch has contributed to the failure of discovering new antidepressants for women and men," said **Professor Christina Dalla from the National and Kapodistrian University of Athens**. "If you don't design experiments to study the effects of drugs on the brains of female animals and women, then you don't get the right results."

Neuropsychiatric disorders are overall more prevalent in women than in men. The way women metabolise drugs that treat these conditions and how they act on the brain differs in women and men. Therefore, in some cases doctors may prescribe doses that are correct for men but not for women or vice-versa. Professor Dalla's group has been investigating sex differences in depression and stress and the effects of antidepressants in male and female rats, including their effects on the HPA axis. The HPA axis is a complex chain of hormonal activity by the hypothalamus, pituitary and adrenal glands in a stressful situation.

They have found sex differences in behaviour and that the stress hormone corticosterone may not be a valuable biomarker – or indication - for depression in female rodents. Their findings suggest that using models and biomarkers, which do not correspond to the emotional characteristics of both sexes might drive research to an impasse.

This work has led to their general observations that in the search for new antidepressants based on the HPA axis, compounds tested in male rodents that were then tested mostly in women in clinical trials did not control for potential sex differences. Thus, these compounds failed to reach the market.

Some differences can be very subtle, found in the biological mechanisms of a disorder. "Even when symptoms for disorders look the same in men and women, the underlying processes may be different," explained **Dr Debra Bangasser from Temple University, Philadelphia, USA**.

Stress can be a trigger for episodes of schizophrenia and ADHD, disorders with disrupted attention. Dr Bangasser is investigating how stress affects attention. In a recent study of male and female rats exposed to stress, she found that stress disrupts their ability to sustain attention. Stress also changes the shape of neurons in the cholinergic system in the brain, which is involved in the regulation of attention. Even though stress altered the shape of neurons

in both males and females, the gene altered by stress were very different between the sexes. This result suggests that the biological processes underlying how stress impairs attention are different in males and females.

"This demonstrates a good reason to study the basic mechanisms in the brain, so that even if outwardly the response looks the same, the mechanisms driving the response are likely to be specific to the sexes. The standard practice has been to use male animals in drug development. Given that molecular processes can be sex-specific, there is no guarantee that drugs designed for males will work well in females," she said.

The regulation of sex differences by sex hormones is significant. Female hormones, in particular a type of oestrogen called oestradial plays an important role in the variation in response between men and women. High levels of oestradial appear to help inhibit or extinguish fear.

Professor Mohammed Milad at New York University Grossman School of Medicine is interested in how the brain learns fear and how not to fear, and what makes each of us different. If we cannot shake that fear, it can lead to mental illness. "Most of us are frightened after a traumatic event, such as a road accident, but with time we recover. In some people, however, their fear persists and they cannot find the courage to drive a car again," he said. Anxiety and PTSD is twice as likely to occur in women than in men.

In his clinic, Professor Milad has conducted tests on healthy men and women aged 20-40 years old, showing them a blue flashing light then administering a low-level electric shock so they became conditioned to be fearful of the blue light. Then they were shown the blue light again, 20-30 times but received no shock, gradually extinguishing their fear of the blue light. (This test is similar to exposure therapy.) While both men and women showed comparable levels of fear expression, there was little variance in men's response to the blue light. In women, however, the variance was substantial.

"In our research setting, if women go through extinction learning when their natural oestrogen levels are high, the next day their fear is low. But when their oestrogen levels are low, they are much more fearful," he said.

It is not known yet whether the correlation between fear and oestrogen levels is age-dependent, and what the effects on post-menopausal women might be. Women's responses to fearful situations are likely to vary according to their menstrual cycle and could further be affected by the contraceptive pill, which lowers their oestrogen. More research is needed to understand how age and reproductive state can affect sex-specific outcomes.

Conversely, however, the response to conditional stimuli is not the same in men who always have low levels of oestrogen. They were able to extinguish fear more effectively in the morning when their levels of testosterone were higher.

The under-representation of females in research is gaining attention, and Professor Dalla is one of the leaders calling for a change in research strategies in support of recent policies and recommendations from the USA and Europe on incorporating sex in research. Addressing the topic in a special issue of the *European Journal of Neuroscience* published this month, Professor Dalla, who is one of the editors says: "If you end up making drugs that are suitable for only half the population and you do not even know about it, that is unethical. It's a waste of money and resources."

END

Symposia S12: Sex differences and estrogen effects: implications for neuropsychiatric disorders
Abstracts: *Christina Dalla* **-** Sex differences in animal models of depression: from behaviour to neuroplasticity
Debra Bangasser - Sex differences in risk and resilience to stress regulation of cognition
Mohammed Milad - Impact of estradiol on threat conditioning and its extinction: implications to psychopathology

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Further Reading (Dalla)

Sex differences in the hypothalamic–pituitary–adrenal axis: An obstacle to antidepressant drug development? Kokras, Hodes, Bangasser, Dalla. *Br J Pharmacology* 2019;1-17, **DOI: 10.1111/bph.14710**

Sex differences in neuroscience and neuropsychopharmacology. Special issue- guest editors C Dalla et al. *European Journal of Neuroscience* July 2020

The 12th FENS Virtual Forum of Neuroscience
As a consequence of the COVID-19 pandemic, the FENS Forum 2020 will be held entirely virtually.

The FENS Forum of Neuroscience is the largest basic neuroscience meeting in Europe, organised by the Federation of European Neuroscience Societies and hosted by the British Neuroscience Association. It will attract around 5,000 international delegates. FENS was founded in 1998. With 44 neuroscience member societies across 33 European countries, FENS as an organisation represents 20,000 European neuroscientists with a mission to advance European neuroscience education and research.