Press Release

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Dynamic expression of brain serotonin receptors across the menstrual cycle provides clues about premenstrual dysphoric disorder

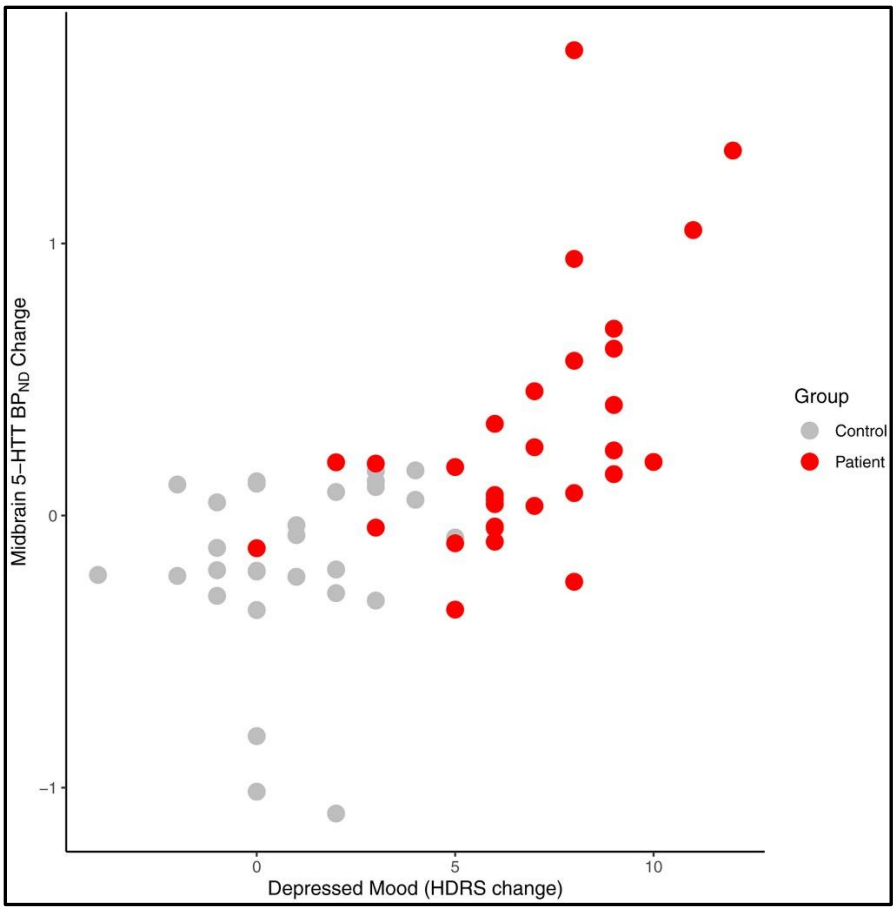
Philadelphia, February 23, 2023 – A new study in *Biological Psychiatry*, published by Elsevier, explores the interplay between the serotonin system and estradiol in the brain, showing that the central nervous system in patients with premenstrual dysphoric disorder (PMDD) seems to increase serotonin transporter density from the periovulatory phase (when estradiol levels are high) to premenstrual cycle phase (when both estradiol and progesterone are decreasing). The findings have the potential to advance the clinical treatment of PMDD.

Premenstrual syndrome (PMS), which can include physical symptoms as well as depression and anxiety, affects about half of menstruating individuals a few days before the onset of menstruation. About 3 to 8% of people who menstruate experience PMDD, a far less recognized diagnosis. PMDD is also associated with mood swings, depression, and anxiety, but its symptoms are more severe and can last for up to two weeks at a time. The lifetime toll of PMDD is comparable to that for people with major depressive disorder.

Previous studies that compared fluctuations in ovarian hormones between women with PMDD and healthy women interestingly found no substantial differences, suggesting that dysregulated hormones in the periphery are not the underlying cause of the disorder. An alternative idea is that the brain's response to normal endogenous hormonal changes differs in patients with PMDD, although how that happens remains unclear. Treatment of PMDD with selective serotonin reuptake inhibitors, or SSRIs, results in remarkably rapid alleviation of symptoms – on the order of hours or days, rather than weeks as in treatment for depression.

In the current study, led by Julia Sacher, MD, PhD, from the Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, examined 30 patients with PMDD and 29 unaffected control women over the course of two menstrual cycles. The researchers used positron emission tomography (PET) imaging to visualize availability of the serotonin transporter protein in the brain throughout the cycle, reflecting short-term changes in its expression.

"We found a significant increase of serotonin transporter from periovulatory to premenstrual phase in patients with PMDD – an 18% change in the midbrain, a brain region with the richest serotonin transporter expression. This increase was associated with the severity of depressed mood premenstrually," said Dr. Sacher.



Caption: Serotonin transporter binding (5-HTT BP_{ND}) in midbrain across the menstrual cycle correlates with the severity of depressed mood in patients with PMDD (red circles) (Credit: *Biological Psychiatry*).

Unexpectedly, Dr. Sacher and colleagues also found a decrease in midbrain serotonin transporter density in healthy women, which could point to a protective mechanism of the healthy female brain in the midst of a changing hormonal environment.

“Typically, it is assumed that serotonin transporter density is an individual trait, with only an approximately 10% change over a decade as the human brain ages, rather than a state that changes within shorter periods of time. However, studies in patients with seasonal affective disorder (SAD) show seasonal changes of serotonin transporter,” Dr. Sacher explained. “Although the reports of serotonin transporter availability in depression have been mixed, this may be due to the heterogeneity of that disease. In more homogenous types of affective disorders, such PMDD or SAD, relatively rapid dynamics of serotonin transporter availability seem to play an important role.”

John Krystal, MD, editor of *Biological Psychiatry*, said of the work, “This technically demanding study identifies a new potential mechanism contributing to negative premenstrual mood states in some women. It also supports the use of SSRIs to treat premenstrual dysphoric mood.”

The findings provide evidence that individuals with PMDD experience short-term changes in serotonin transporter density throughout the menstrual cycle, which suggests that patients might benefit from taking SSRIs at specific times during the cycle to best target these changes.

Notes for editors
The article is "Increase in serotonin transporter binding in patients with premenstrual dysphoric disorder across the menstrual cycle: a case-control longitudinal neuroreceptor ligand PET imaging study," by Julia Sacher, Rachel G. Zsido, Claudia Barth, Franziska Zientek, Michael Rullmann, Julia Luthardt, Marianne Patt, Georg A. Becker, Pablo Rusjan, A. Veronica Witte, Ralf Regenthal, Abhay Koushik, Juergen Kratzsch, Beate Decker, Petra Jogschies, Arno Villringer, Swen Hesse, and Osama Sabri (https://doi.org/10.1016/j.biopsych.2022.12.023). It appears as an Article in Press in *Biological Psychiatry*, published by Elsevier.

Copies of this paper are available to credentialed journalists upon request; please contact Rhiannon Bugno at +1 254 522 9700 or Biol.Psych@sobp.org. Journalists wishing to interview the authors may contact Julia Sacher at sacher@cbs.mpg.de.

The authors' affiliations and disclosures of financial and conflicts of interests are available in the article.

John H. Krystal, MD, is Chairman of the Department of Psychiatry at the Yale University School of Medicine, Chief of Psychiatry at Yale-New Haven Hospital, and a research psychiatrist at the VA Connecticut Healthcare System. His disclosures of financial and conflicts of interests are available here.

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