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Why do some get depressed and others don't? Clues from the "winter blues"

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What's the story? Some people can adjust to environmental stressors to avoid depression. Women need to do this more than men to avoid getting depressed.

Why is this important? The researchers used 'winter blues' (SAD) as a model for depression, and were able to show that some people – in spite of being genetically predisposed to depression - are more resilient in resisting it. This will help us understand which factors might prevent depression.

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Depression is notoriously hard to study, but what if you could switch depression on and off and look at the biological differences between when people are depressed and when they are not? Now a study of seasonal depression, SAD (Seasonal Affective Disorder), suggests that some people, and especially women, can avoid depression by maintaining or even increasing levels of the neurotransmitter serotonin throughout the year, even though they carry a gene which would normally cause winter blues. This work is published (in press) in the peer-reviewed journal *European Neuropsychopharmacology*.*

SAD is a condition caused by lack of daylight, leading to an increase in clinical depression in the winter, especially in areas further from the equator. Studies have shown that around 90% of people living in Copenhagen are affected in some way, such as sleeping or eating disturbance, with around 5% showing clinical depression in the winter. Copenhagen is at roughly the same latitude as major population centres such as Glasgow and Edinburgh, Moscow, Novosibirsk, and Sitka, Alaska. With the coming of spring, these clinical symptoms generally disappear.

As lead researcher, Dr Brenda McMahon (Rigshospitalet, Copenhagen) said "*Daylight is effectively a natural antidepressant. It acts like an SSRI, and more daylight prevents serotonin being removed from the brain".*

Scientists had previously found that SAD is more common in women, and in people carrying the 5-HTTLPR gene. This gene determines the efficacy of the serotonin transporter which regulates how the neurotransmitter serotonin is removed from the brain: most modern anti-depressive medicines (such as Prozac) work by slowing the clearance of serotonin between the brain cells.

The team of scientists from Copenhagen studied 23 young volunteers who had the HTTLPR genetic predisposition to depression, but who were amongst the 10% of Danes who are unaffected by the change of season. The volunteers were given two brain scans (PET scans, Positron Emission Tomography) in summer, with two follow-up scan in winter, with the aim of measuring both the serotonin transporter and serotonin levels in the brain.

According to Brenda McMahon

"*Daylight deprivation is a potent trigger of depressive symptoms. This is the first time anyone has used PET scans to look at resistance to winter depression. We found that the level of serotonin*

transporter protein dropped by an average of around 10% from summer to winter, with the drop being noticeably greater in women.

We found that some people who you would expect to have SAD because of their genetic disposition were nevertheless able to control how much serotonin transporter was produced, which means that they were able to regulate how much serotonin was removed from their brain: in this way they become more resilient to depression. SAD resilient women down-regulate their brain serotonin transporter more in the winter than men do, meaning that the levels of serotonin did remained unaltered between seasons. In general SAD resilient people maintained the same level of serotonin across seasons.

Senior author, Professor Gitte Knudsen (Rigshospitalet, Copenhagen) said: *"We need to note that this is a small study, and we measured serotonin levels indirectly. Nevertheless, our findings offer good grounds for treatment of SAD with SSRIs".*

Commenting, Professor Eduard Vieta (Institute of Neuroscience, University of Barcelona) said:

"Psychiatry has traditionally focused on risk factors and illness outcomes. This is one of those rare studies that focuses on protective factors, something called "positive psychiatry". By selecting and studying people who did not develop seasonal depression, the authors provide further knowledge on the neurobiology of resilience, which may translate, in the future, on better ways to prevent depression."

Professor Vieta was not involved in this work, this is an independent comment.

*See paper at: https://www.europeanneuropsychopharmacology.com/article/S0924-977X(18)30164-0/fulltext

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Seasonality-resilient individuals downregulate their cerebral 5-HT transporter binding in winter – A longitudinal combined ^{11}C-DASB and ^{11}C-SB207145 PET study

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Abstract

We have recently shown that the emergence and severity of seasonal affective disorder (SAD) symptoms in the winter is associated with an increase in cerebral serotonin (5-HT) transporter (SERT) binding. Intriguingly, we also found that individuals *resilient* to SAD downregulate their cerebral SERT binding in the winter. In the present paper, we provide an analysis of the SERT- and 5-HT dynamics as indexed by 5-HT$_4$ receptor (5-HT4R) binding related to successful stress coping. We included 46 ^{11}C-DASB positron emission tomography (PET) scans (N = 23, 13 women, age: 26 ± 6 years) and 14 ^{11}C-SB207145 PET scans (7 participants, 3 women, age: 25 ± 3 years) from 23 SAD-resilient Danes. Data was collected longitudinally in summer and winter. We found that compared to the summer, raphe nuclei and global brain SERT binding decreased significantly in the winter

(p_{raphe} = 0.003 and p_{global} = 0.003) and the two measures were positively correlated across seasons (summer: R^2 = 0.33, p = .004, winter: R^2 = 0.24, p = .018). A voxel-based analysis revealed prominent changes in SERT in clusters covering both angular gyri (0.0005 < $p_{corrected}$ < 0.0016), prefrontal cortices (0.00087 < $p_{corrected}$ < 0.0039) and the posterior temporal and adjacent occipital cortices (0.0001 < $p_{corrected}$ < 0.0066). We did not observe changes in 5-HT4R binding, suggesting that 5-HT levels remained stable across seasons. We conclude that resilience to SAD is associated with a global downregulation of SERT levels in winter which serves to keep 5-HT levels across seasons.