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Brain Networks involved in Seasonal Affective Disorder: A Neuroimaging PET Study of 5-HTT Expression

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Introduction:

Seasonal Affective Disorder (SAD) is a subtype of Major Depressive Disorder characterized by seasonally occurring depressions that often are associated with excessive sleepiness and carbohydrate craving (Rosenthal et al., 1984). It has recently been shown that unlike healthy people, patients with SAD fail to globally downregulate their cerebral serotonin transporter (5-HTT), and that seemed to be particularly pronounced in female S-carriers of the 5-HTTLPR genotype (Mc Mahon et al., 2016). The purpose of this study was to identify a reproducible and unique 5-HTT brain network that accounts for the adaption to the environmental stressor of winter in females with the short 5-HTTLPR genotype, a specific subgroup previously reported to be at increased risk for developing SAD.

Methods:

Nineteen females, either S' carriers (LG- and S-carriers) resilient to SAD (N=13, mean age 23.6±3.2 y, range 19-28) or S' carriers with SAD (N=6, mean age 23.7±2.4, range 21-26) were PET-scanned with [11C]-DASB during both summer and winter seasons (asymptomatic and symptomatic phase, 38 scans in total) in randomized order, defined as a 12-week interval centered on summer or winter solstice (Mc Mahon et al., 2016; King et al., 2016; Kim et al., 2006). We used a data-driven Partial Least Squares (PLS) approach with NPAIRS split-half cross-validation on an optimized PC-subspace and with a 1,000 splits, to identify a stable and generalizable whole-brain network of 5-HTT expression that distinguishes the brains of resilient females from females suffering from SAD (Grady et al., 2013; Churchill et al., 2013; McIntosh et al., 1996; Strother et al., 2002). By running the PLS analysis in the NPAIRS split-half cross-validation framework, the validity of the reported results can directly be compared to a test-retest validation study, a criterion that is necessary for strong scientific inference.

Results:

We identified a robust pattern of 5-HTT expression, distinguishing resilient females from those with SAD; it included the right superior frontal gyrus, brainstem, globus pallidus and the hippocampus. Across seasons, resilient female S' carriers showed nominally higher 5-HTT levels in these regions compared to female S' carriers with SAD, but the group difference was only significantly different in the winter (Figure 1).

By contrast, female S' carriers with SAD displayed lower 5-HTT levels in these regions compared to resilient female S' carriers, but in turn showed robustly increased 5-HTT levels in the ventral striatum, orbitofrontal cortex, middle frontal gyrus, extending to the supramarginal gyrus, precentral gyrus and postcentral gyrus during winter compared to resilient female S' carriers (Figure 2).

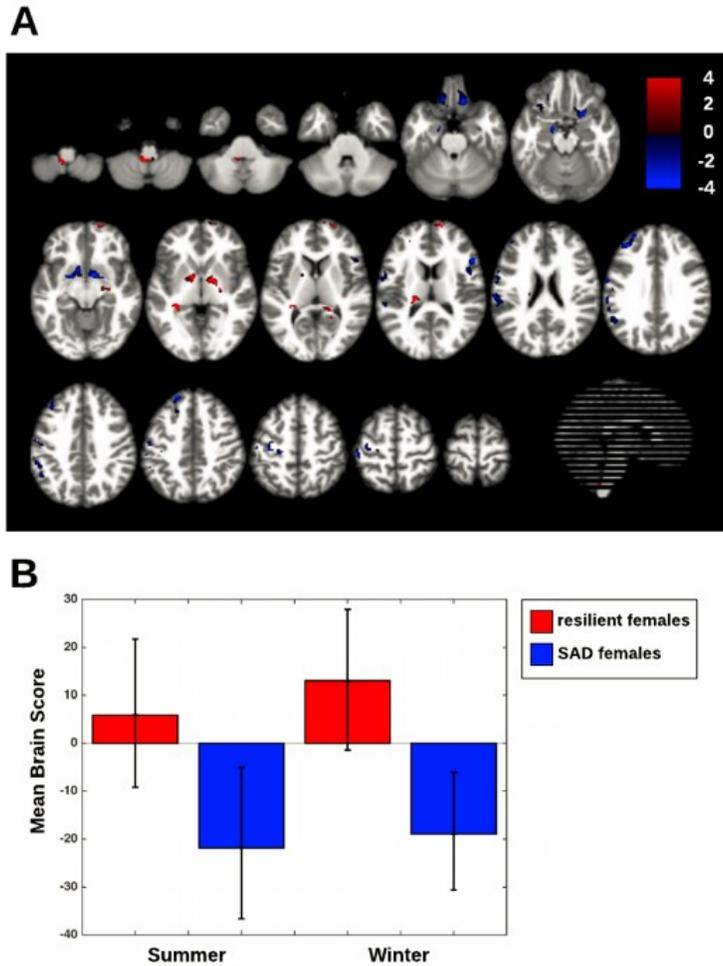


Figure 1: (A) Brain network predicted by the PLS analysis. The image is thresholded at $|Z\text{-score}_{\text{split}}| > 2.8$ ($P \leq 0.005$) and with cluster extent threshold $> 640 \text{ mm}^3$. Red colors represent areas with higher 5-HTT binding in resilient female S' carriers compared to female S' carriers with SAD. Blue colors represent higher 5-HTT binding in female S' carriers with SAD compared to resilient female S' carriers. Scale reflects $Z\text{-score}_{\text{split}}$ units. Slices are in MNI coordinates. **(B)** Mean brain scores for seasonal conditions by either resilient female S' carriers or female S' carriers with SAD. Error bars indicate 95% confidence interval for the brain scores. Non-overlapping confidence intervals correspond to significant differences between groups or conditions.

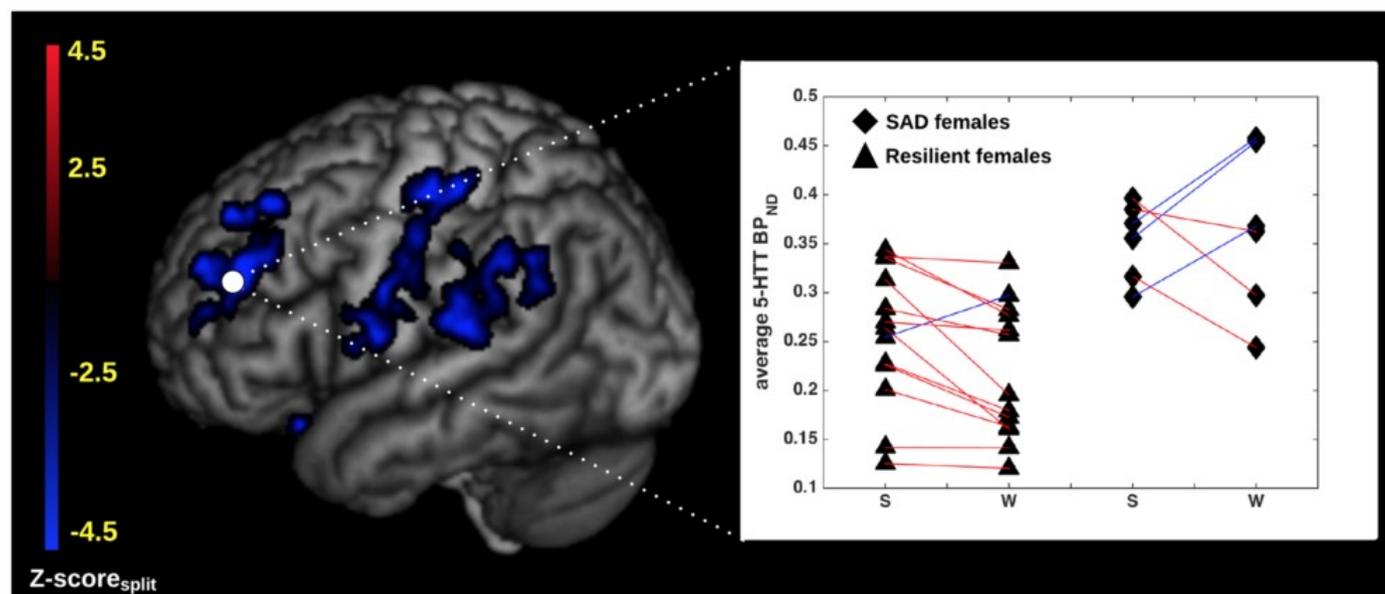


Figure 2: (A) Cortical rendering of the 5-HTT brain network predicted by the PLS analysis. The image is thresholded at $|Z\text{-score}_{\text{split}}| > 2.8$ ($P \leq 0.005$) and with cluster extent threshold $> 640 \text{ mm}^3$. Blue areas represent a higher 5-HTT binding in female S' carriers with SAD compared to resilient female S' carriers. The plot shows the average 5-HTT BP_{ND} for group and season within a cluster located in the right middle frontal gyrus. S is summer, W is winter.

Conclusions:

These findings provide novel evidence for a wintertime state-dependent difference in 5-HTT expression that may leave SAD females with the short 5-HTTLPR genotype more vulnerable to persistent stressors like winter. The affected brain regions comprise a distributed set of areas responsive to emotion, voluntary and planning of movement, executive function and memory. The findings provide additional insight into the neurobiological components through which the anatomical distribution of serotonergic discrepancies between individuals genetically predisposed to SAD, but with different phenotypic presentations during the environmental stressor of winter, may affect the related risk for developing SAD.

Disorders of the Nervous System:

Depressive Disorders ¹

Emotion and Motivation:

Emotion and Motivation Other

Imaging Methods:

Multi-Modal Imaging
PET

Modeling and Analysis Methods:

Multivariate modeling ²

Poster Session:

Poster Session - Monday

Keywords:

Other - 5-HTTLPR; Seasonal Affective Disorder; Partial Least Squares; Serotonin; PET; [11-C]-DASB; Neuroplasticity; Kinetic Modeling; Reproducibility; Prediction

¹²Indicates the priority used for review

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Please indicate which methods were used in your research:

PET

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Neuropsychological testing

Computational modeling

For human MRI, what field strength scanner do you use?

3.0T

Which processing packages did you use for your study?

SPM

Free Surfer

Provide references in author date format

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