Multivariate Analysis of *in vivo* PET data using Partial Least Squares

Martin Nørgaard

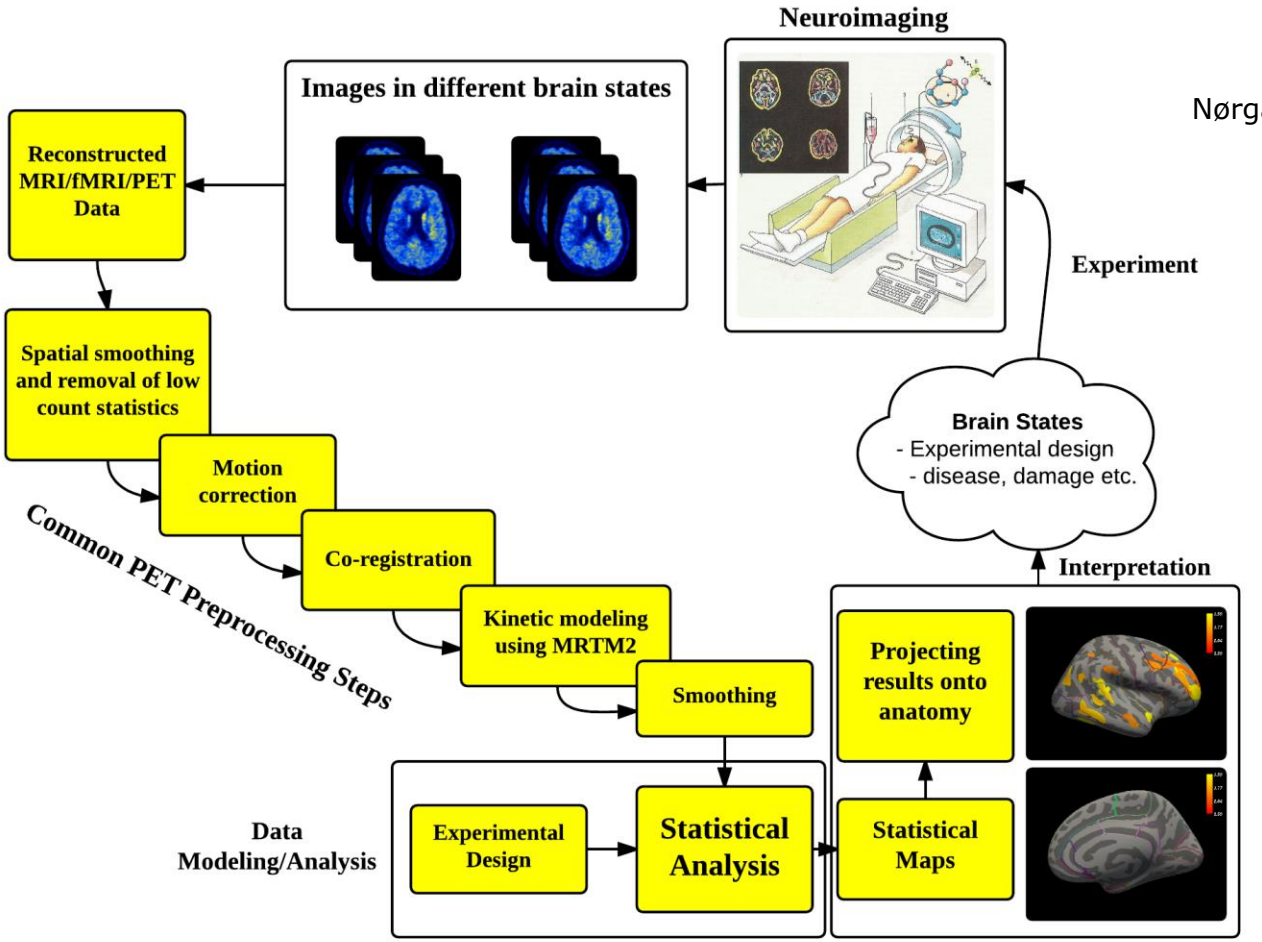
Neurobiology Research Unit
Copenhagen University Hospital, Rigshospitalet

5-HTT Brain Network Response to Seasonal Affective Disorder in Females with the Short 5-HTTLPR Genotype: A Partial Least Squares Approach

Martin Nørgaard

Neurobiology Research Unit
Copenhagen University Hospital, Rigshospitalet

Neuroimaging Workflow



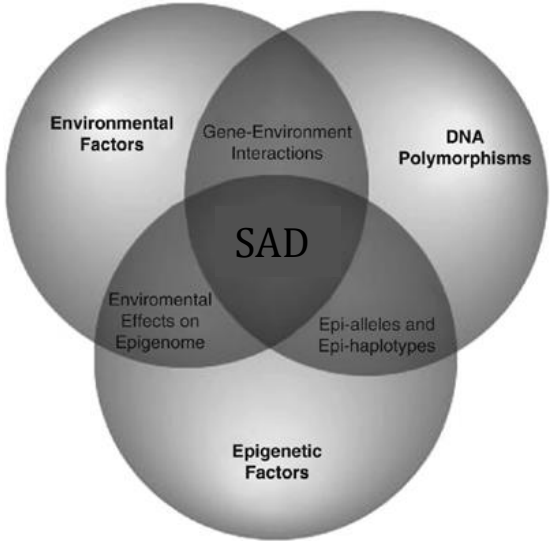
Nørgaard et al. 2015

[Tabachnick and Fidell, 2001] – "Do not expect garbage in, roses out"

Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Biological sources of individual variability in Seasonal Affective Disorder (SAD)

- Characterized by season triggered depression and encompasses feelings of **hopelessness** and **blameworthiness**, **loss of energy**, **impaired concentration** and **hypersomnia**.
- Is estimated to affect **5%** of the Northern inhabitants (mostly due to long and dark winters).
- Seasonal Affective Disorder is, in part, hypothesized to be triggered by a **seasonal dysregulation** of **the serotonin transporter**, the mechanism in which serotonin is taken up by the presynaptic neuron and recycled.



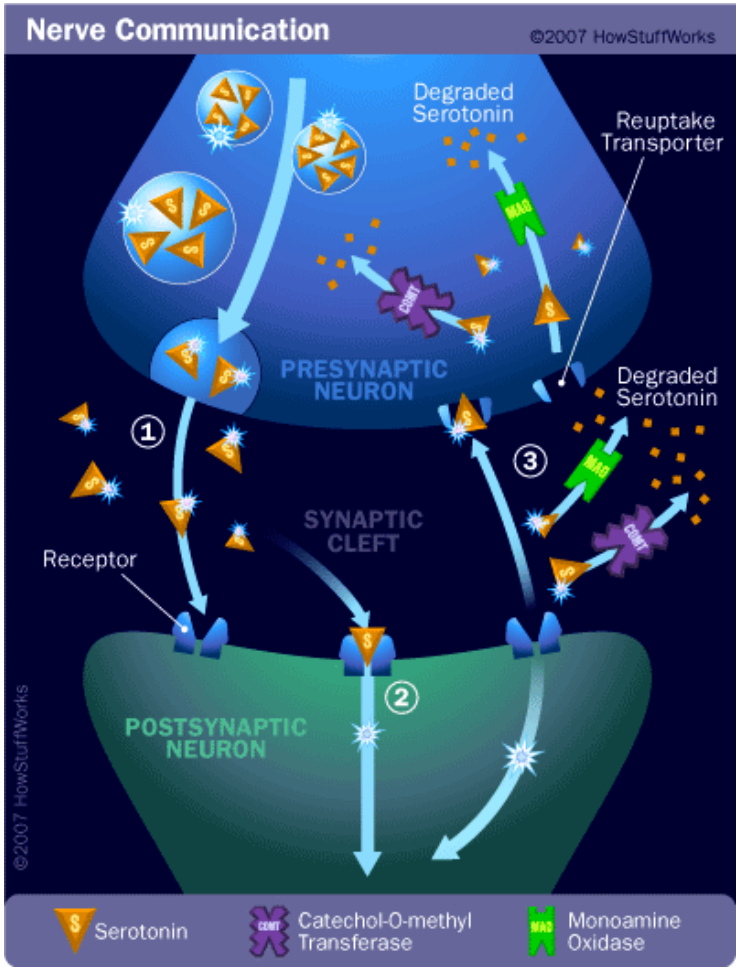
Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Biological sources of individual variability in Seasonal Affective Disorder (SAD)

Previous studies investigating the serotonin transporter in SAD

- Neumeister et al., 2000 *(n=12)* ↓
- Buchert et al., 2006 *(n = 29)* ↑
- Koskela et al., 2008 *(n = 24)* -
- Praschak-Rieder et al., 2008 *(n = 88)* ↑
- Kalbitzer et al., 2010 *(n = 57)* ↑
- Murthy et al., 2010 *(n = 63)* -
- Matheson et al., 2015 *(n = 40)* -
- Mc Mahon et al., 2016 (n = 40) ↓↑
- Tyrer et al., 2016 (n = 40) ↓↑

What is going on in SAD?



Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

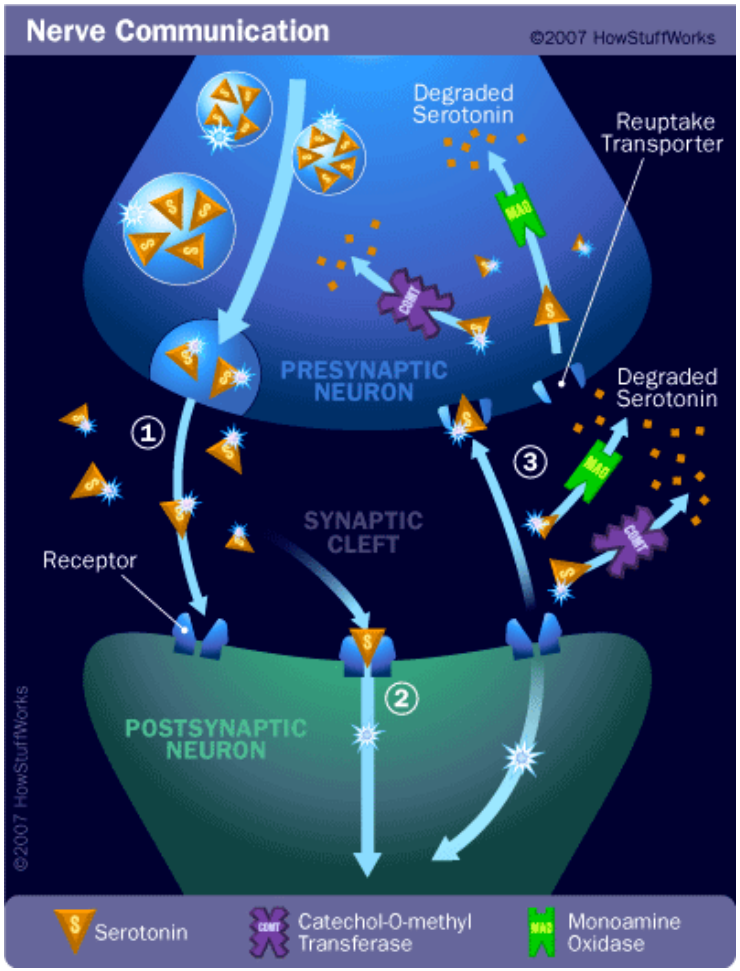
Biological sources of individual variability in Seasonal Affective Disorder (SAD)

Previous studies investigating the serotonin transporter in SAD

- Neumeister et al., 2000 *(n=12)* ↓
- Buchert et al., 2006 *(n = 29)* ↑
- Koskela et al., 2008 *(n = 24)* -
- Praschak-Rieder et al., 2008 *(n = 88)* ↑
- Kalbitzer et al., 2010 *(n = 57)* ↑
- Murthy et al., 2010 *(n = 63)* -
- Matheson et al., 2015 *(n = 40)* -
- Mc Mahon et al., 2016 (n = 40) ↓↑
- Tyrer et al., 2016 (n = 40) ↓↑

So why do we want to investigate females with the short 5-HTTLPR variant?

What is going on in SAD?



Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Biological sources of individual variability in Seasonal Affective Disorder (SAD)

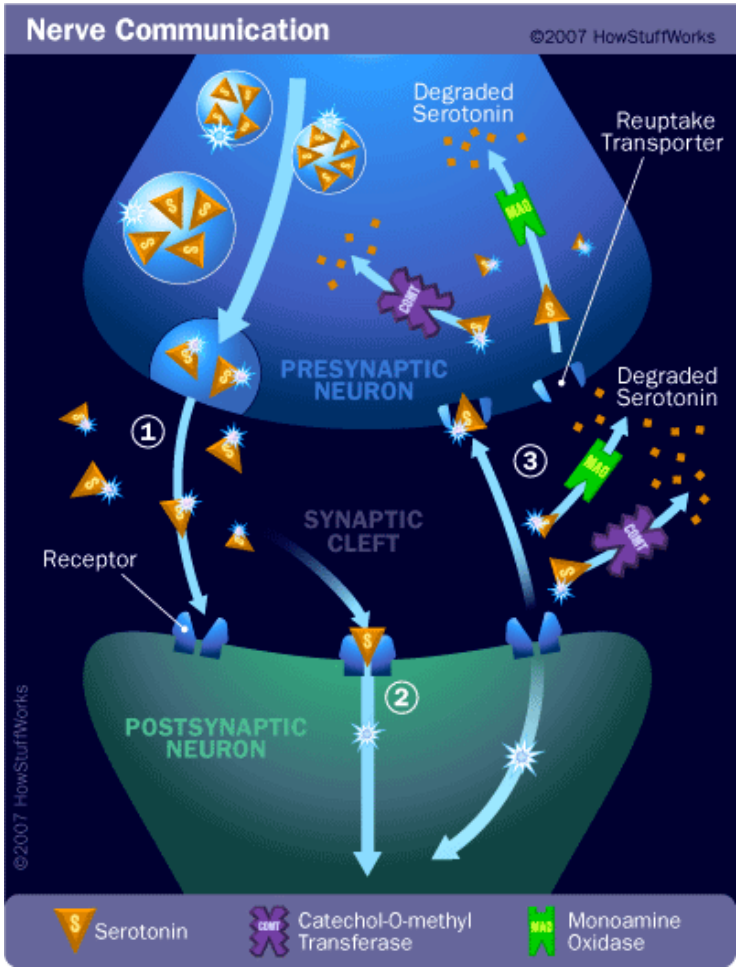
Previous studies investigating the serotonin transporter in SAD

- Neumeister et al., 2000 *(n=12)* ↓
- Buchert et al., 2006 *(n = 29)* ↑
- Koskela et al., 2008 *(n = 24)* -
- Praschak-Rieder et al., 2008 *(n = 88)* ↑
- Kalbitzer et al., 2010 *(n = 57)* ↑
- Murthy et al., 2010 *(n = 63)* -
- Matheson et al., 2015 *(n = 40)* -
- Mc Mahon et al., 2016 (n = 40) ↓↑
- Tyrer et al., 2016 (n = 40) ↓↑

So why do we want to investigate females with the short 5-HTTLPR variant?

1. Females have a 4-fold increase in developing SAD compared to men [1]
2. S'-carriers of the 5-HTTLPR genotype are thought to be more susceptible to developing depression [2].

What is going on in SAD?



[1] Melrose S et al., 2015
[2] Kalbitzer J et al, 2010

Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Dataset

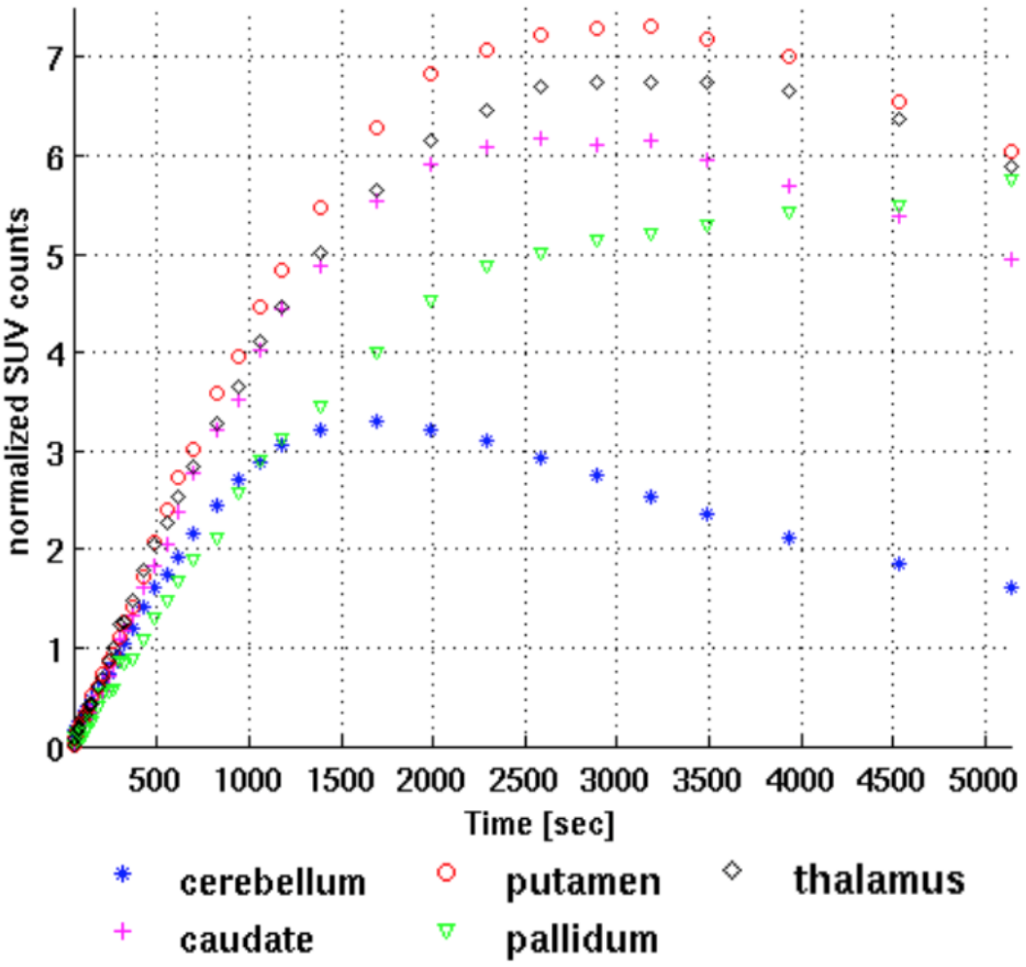
	Resilient females	SAD females	P-value
N	12	6	
Age (Mean±SD)	23.6±3.16	23.74±2.36	0.925
BMI (Mean±SD)	22.79±2.26	20.87±1.74	0.088
MDI (s/w)	5.08/5.25	6/23.33	0.64/0.0001
PSQI global score (s/w)	3/3.38	4.83/6.16	0.083/0.013
Neuroticism (s/w)	81.83/81.58	84.33/86.16	0.86/0.595
GSS	4.33±2.15	14.5±2.07	< 0.0001
Daylight minutes (s/w)	1009/438	1043/475	0.045/0.02

Table I: Demographic information. * One resilient female was omitted because in an initial analysis, this person's neuroticism-score exceeded 3 S.D.'s from the mean (neuroticism-score = 139).

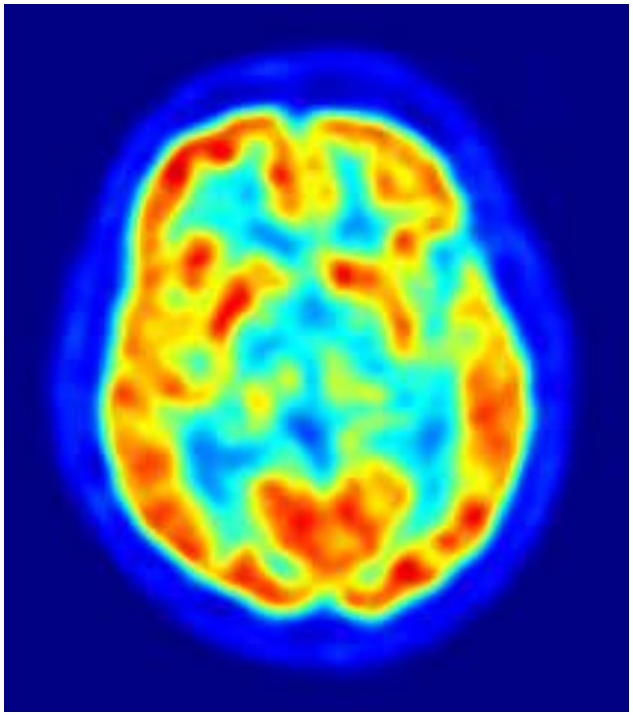
Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Positron Emission Tomography (PET)

Time Activity Curve (TAC)

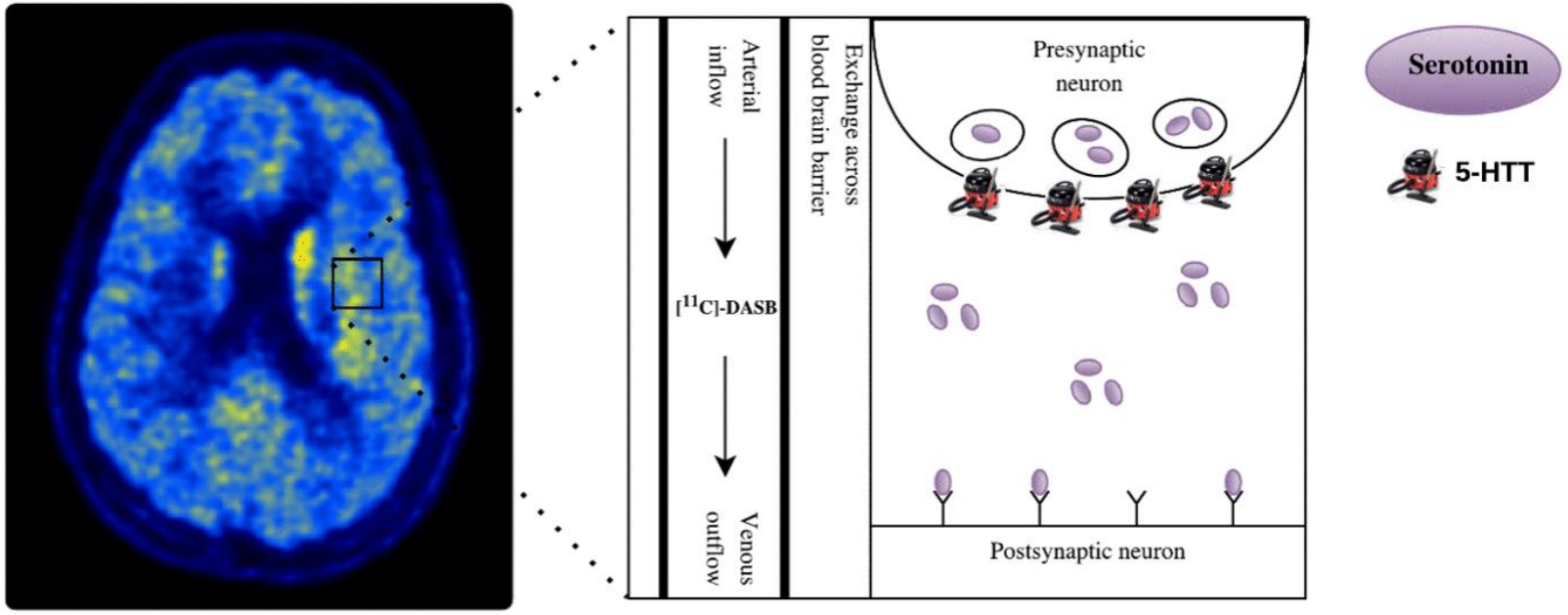


[^{11}C]-DASB uptake in the brain



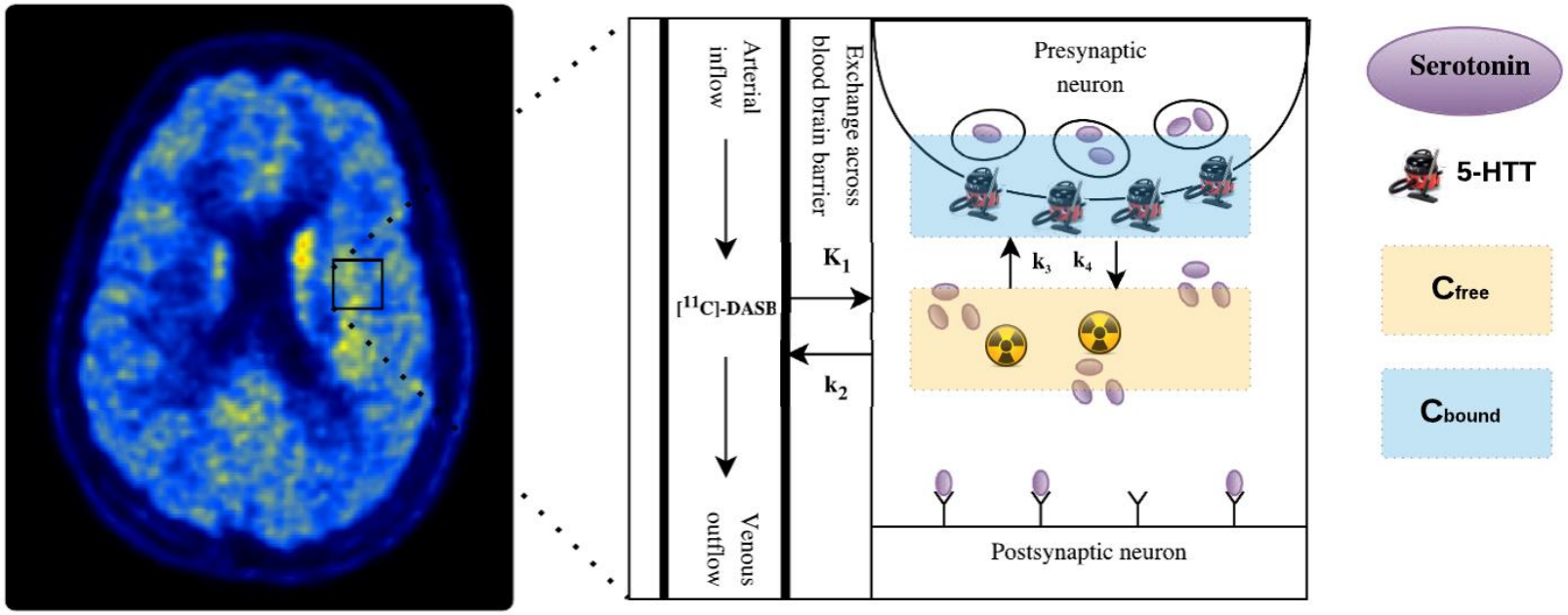
Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Kinetic Modeling in [^{11}C]-DASB for generating parametric images of serotonin transporter binding



Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Kinetic Modeling in [^{11}C]-DASB for generating parametric images of serotonin transporter binding



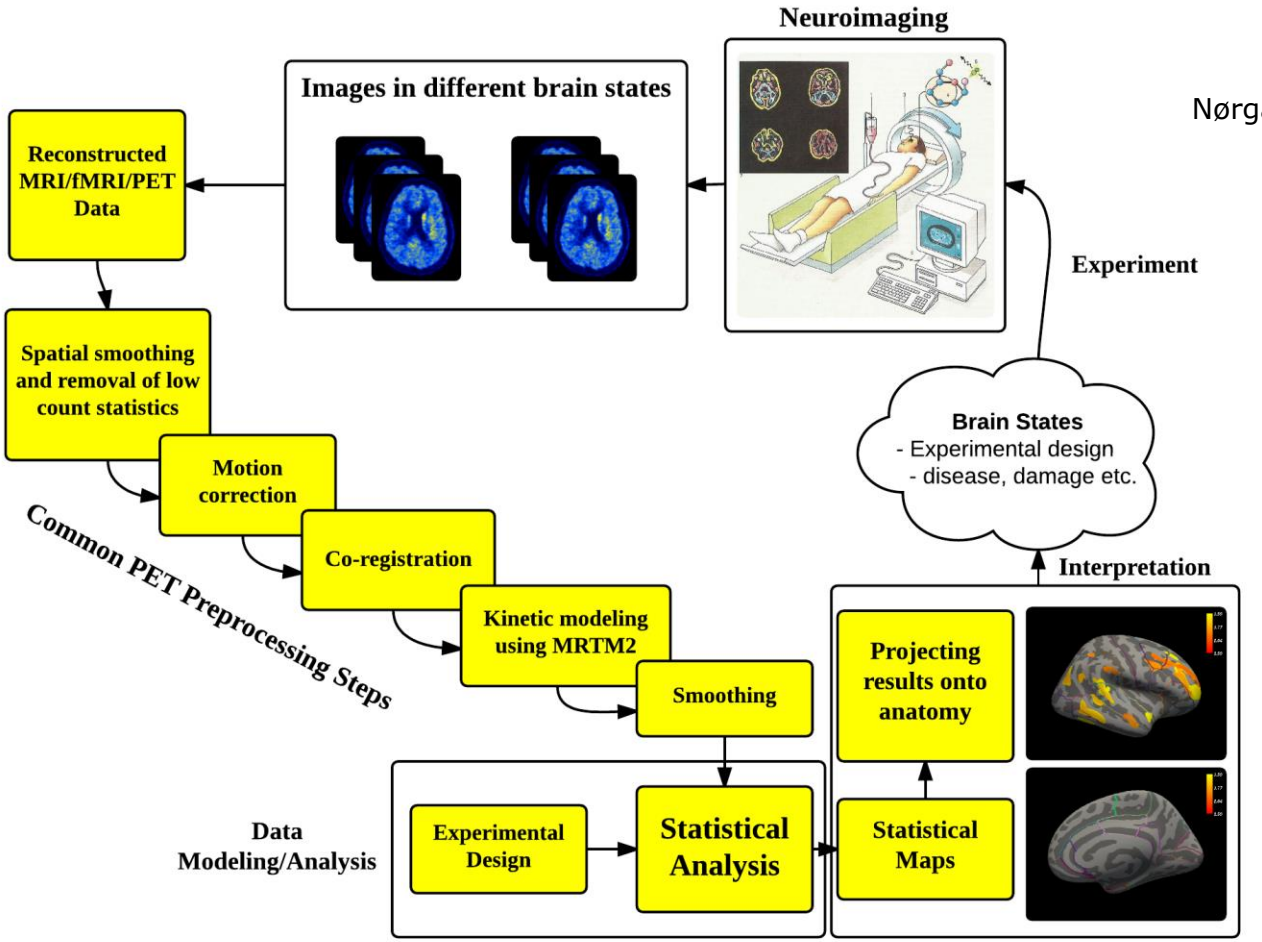
(1) $$\frac{dC_{free}(t)}{dt} = K_1 C_p(t) - (k_2 + k_3) C_{free}(t) + k_4 C_{bound}(t)$$

(2) $$\frac{dC_{Bound}(t)}{dt} = k_3 C_{free}(t) - k_4 C_{bound}(t)$$

(3) $$BP_{ND} = \frac{k_3}{k_4}$$

Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Neuroimaging Workflow



Nørgaard et al. 2015

[Tabachnick and Fidell, 2001] – "Do not expect garbage in, roses out"

Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Good references on Partial Least Squares

Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review

Anjali Krishnan [a], Lynne J. Williams [b], Anthony Randal McIntosh [c,d,*], Hervé Abdi [a,*]

NeuroImage 56 (2011) 455–475

Spatial Pattern Analysis of Functional Brain Images Using Partial Least Squares

A. R. McIntosh,* F. L. Bookstein,† J. V. Haxby,‡ and C. L. Grady*,§

NEUROIMAGE 3, 143–157 (1996)

Partial least squares analysis of neuroimaging data: applications and advances

Anthony Randal McIntosh[a,*] and Nancy J. Lobaugh[b]

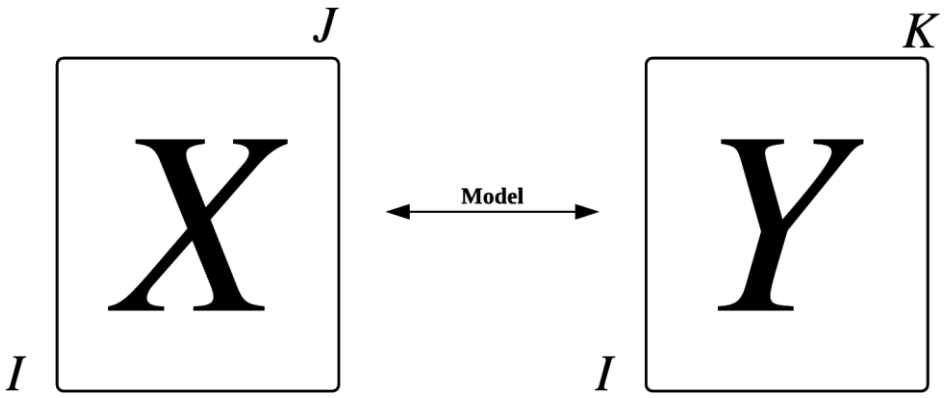
NeuroImage 23 (2004) S250–S263

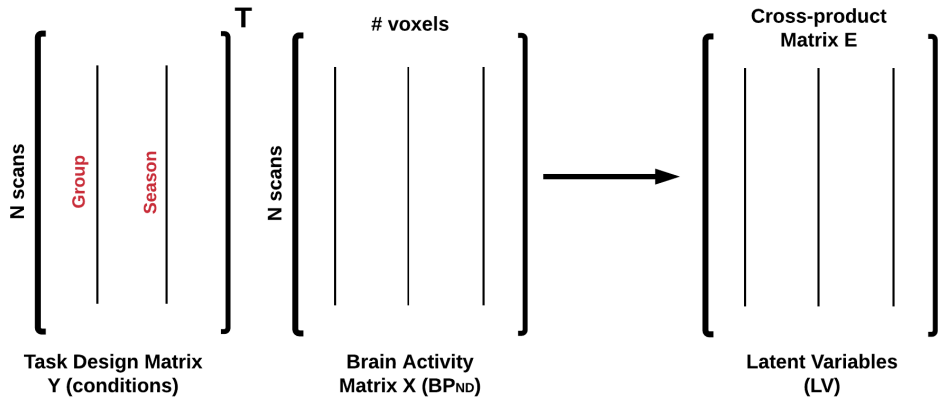
Partial Least Squares (PLS)

- An acronym: **P**artial **L**east **S**quares
- Correlational technique that analyzes associations between two sets of data
  - For example: behavior & brain activity
- "A multivariate approach that robustly identifies spatiotemporal patterns that covary with tasks or experimental conditions"
  - Grady et al., ENPP (2013)
- Similar to a PCA in maximizing covariance explained but with respect to additional "condition" information
  - Behavioral measure(s)
  - Group status
- PLS evaluates data from all voxels, all time points and all people simultaneously
  - Brain function is a "network" of areas not individual regions
  - No need to correct for multiple comparisons

Courtesy of Patrick M. Fisher

Partial Least Squares (PLS)





OUTPUT

- **Layer 1: "The Forest"/Latent variables**
  - Latent variables are constructs
  - Magnitude of latent variable is positively related to how much covariance it explains
  - Need to determine which LVs are unlikely to occur by chance (permutations)

$$Y^T X = E = U\Sigma V^T$$

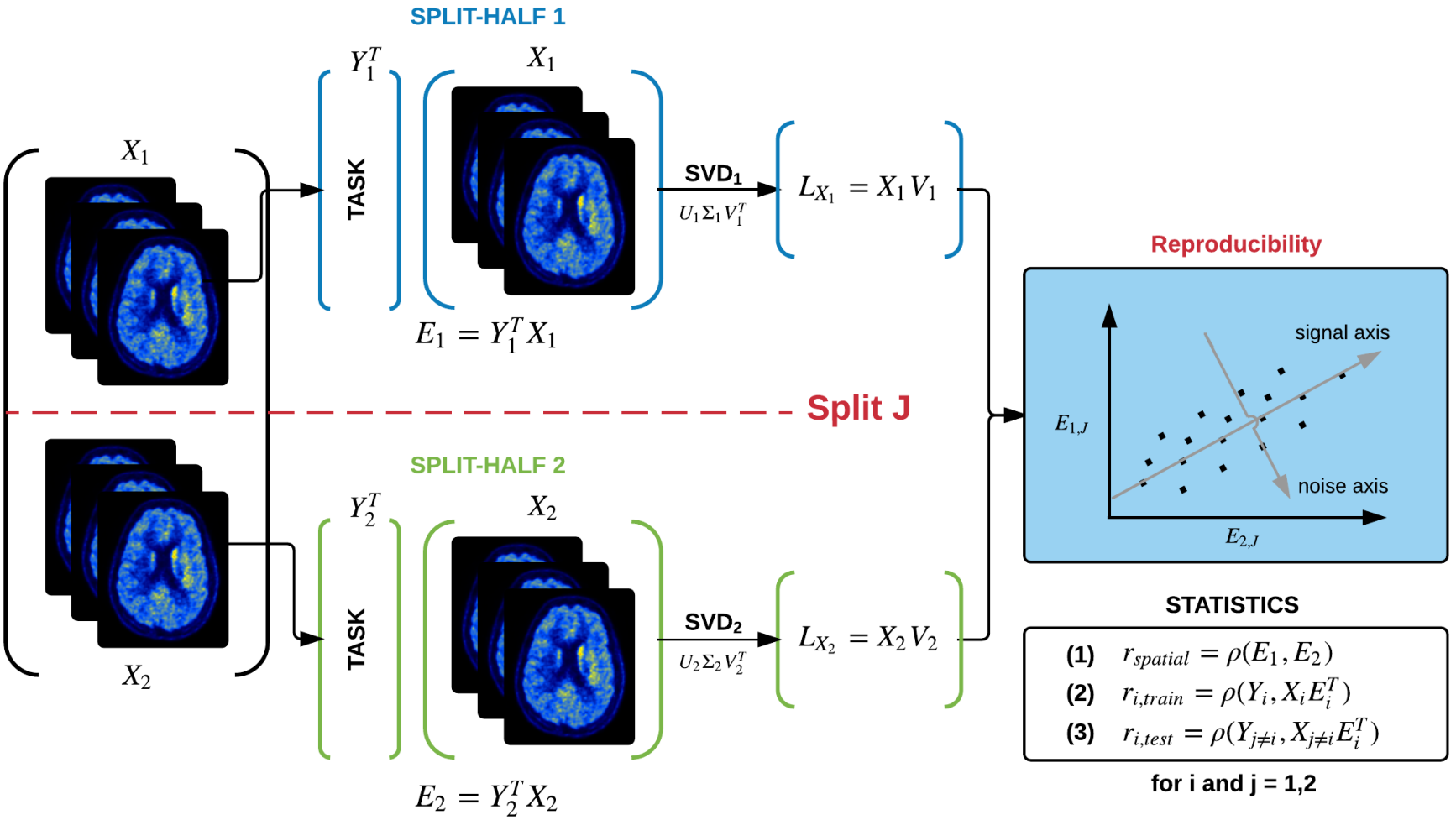
- **Layer 2: "The Trees"/Brain Scores**
  - Describes relation between PET task conditions and behavior/group measure being evaluated
  - How does a given LV capture differences in task-condition responses

$$L_X = XV \qquad L_Y = YU$$

- **Layer 3: "The Leaves"/Brain Saliences**
  - Magnitude (*i.e.*, distance from 0) of salience reflects "stronger" association between that voxel and a given LV
  - Describes what set of brain areas (*network*) map onto a given LV
  - Brain areas with reliably non-zero salience estimates are identified using split-half resampling (*validity?*) Z-score$_{split}$

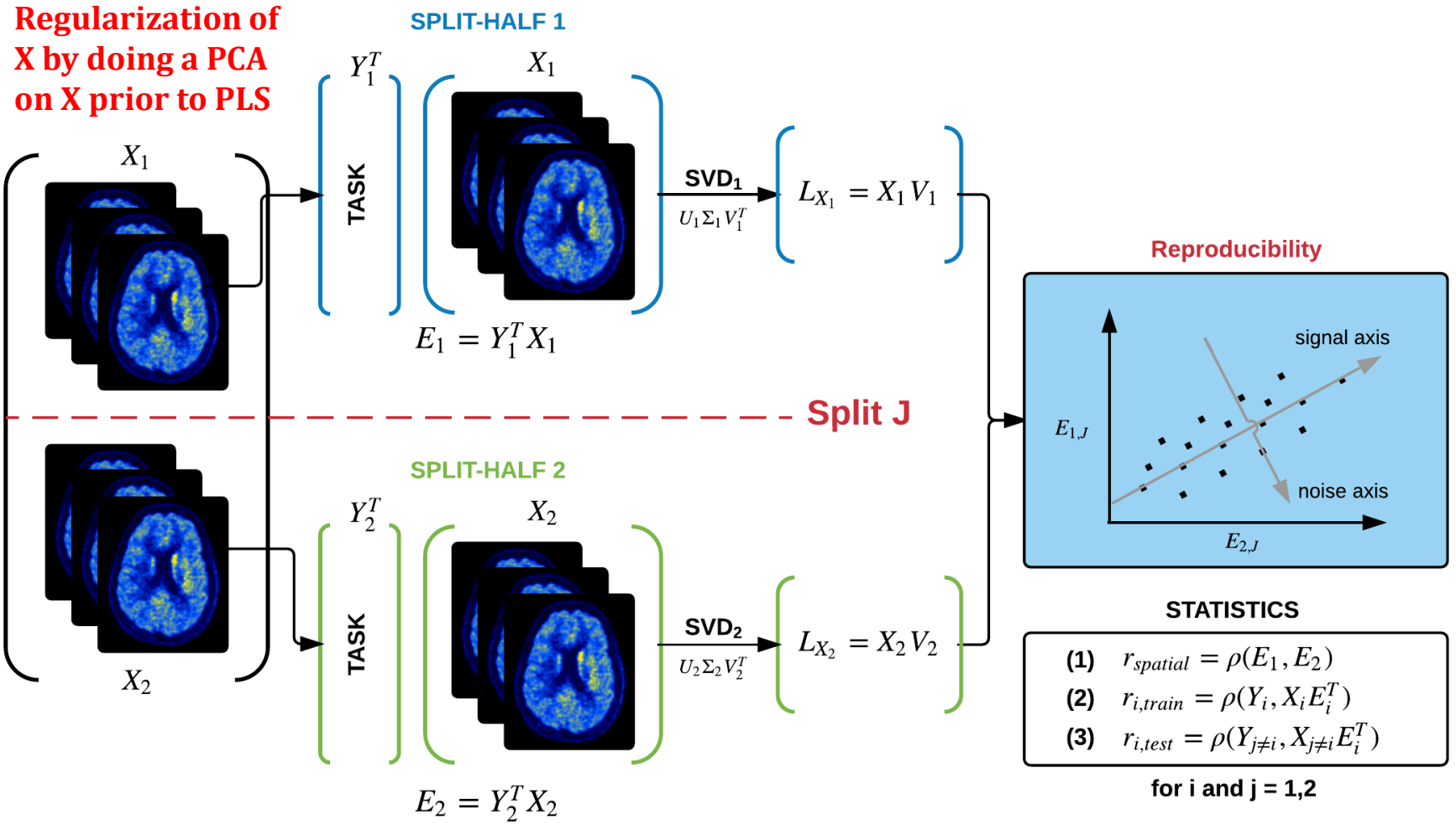
Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Partial Least Squares (PLS) – stabilizing the results using split-half resampling



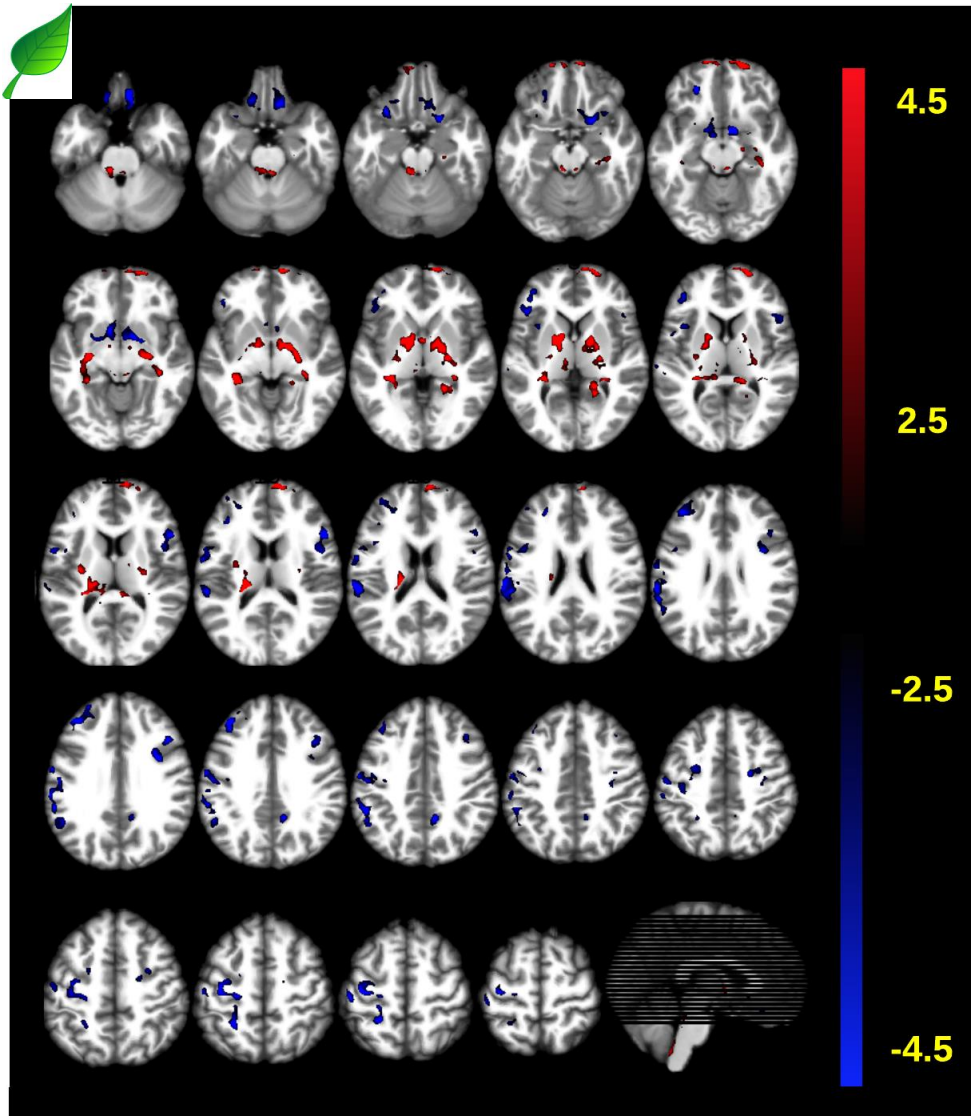
Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

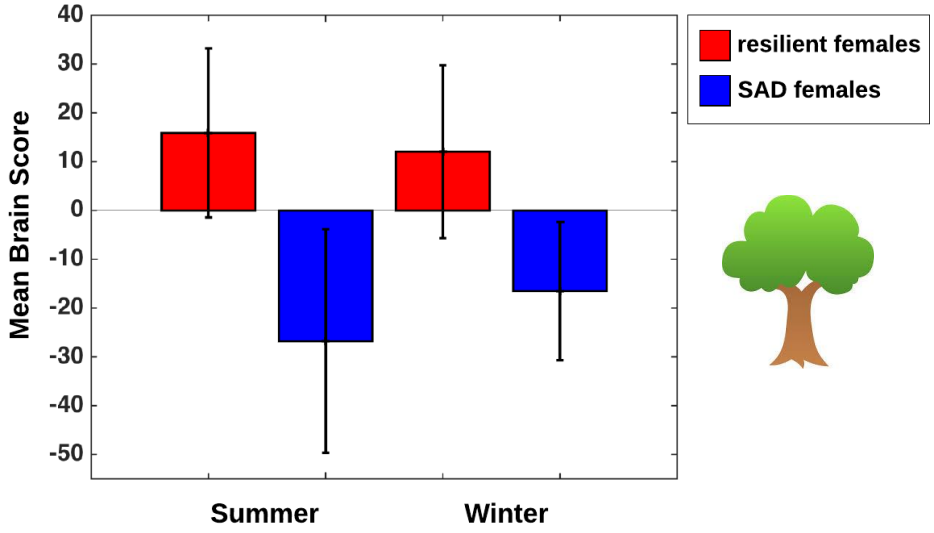
Partial Least Squares (PLS) – stabilizing the results using split-half resampling

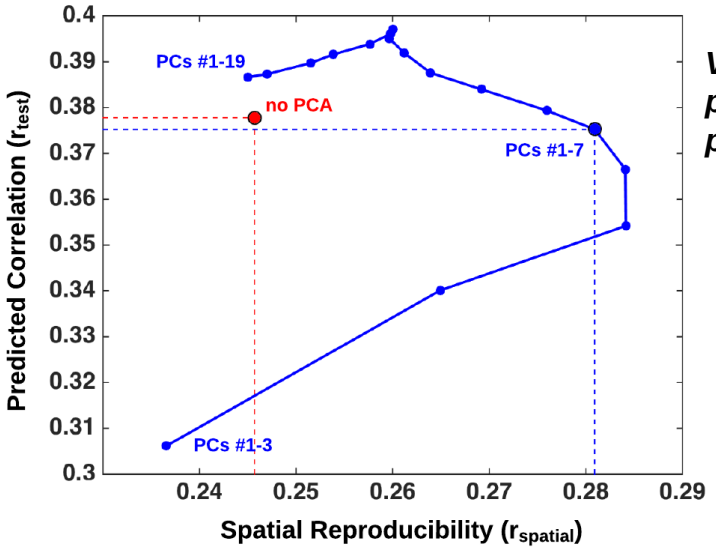


Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

5-HTT Brain network of LV1-associated brain regions





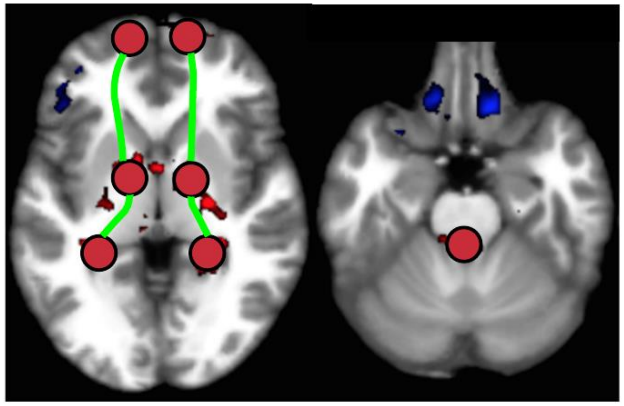


Var_{exp} = 75%
p_{test} = 0.011
$p_{spatial}$ = 0.016

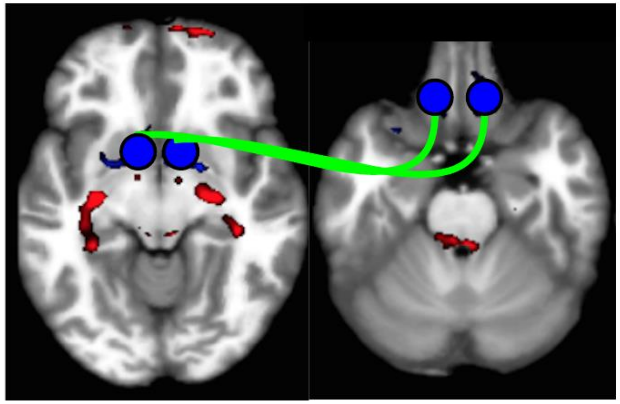
Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

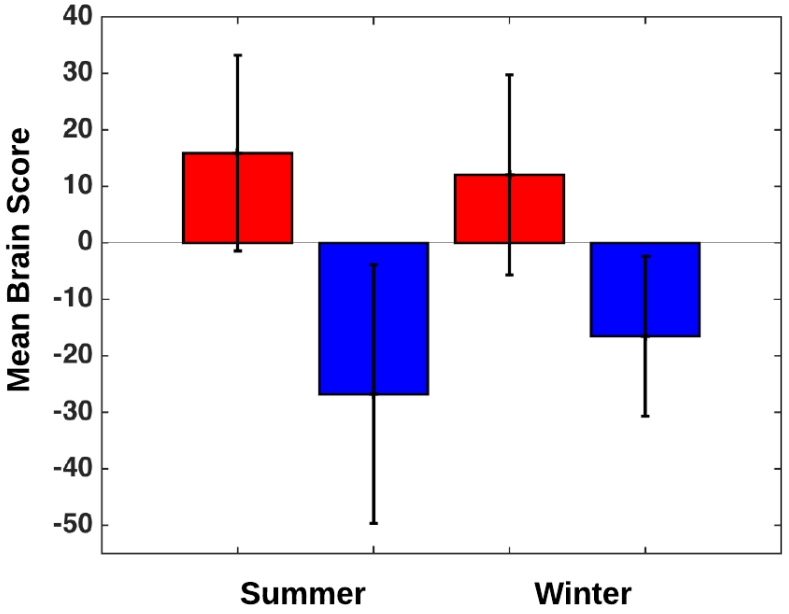
The Leaves: Network of LV1-associated brain regions

Positive network



Negative network



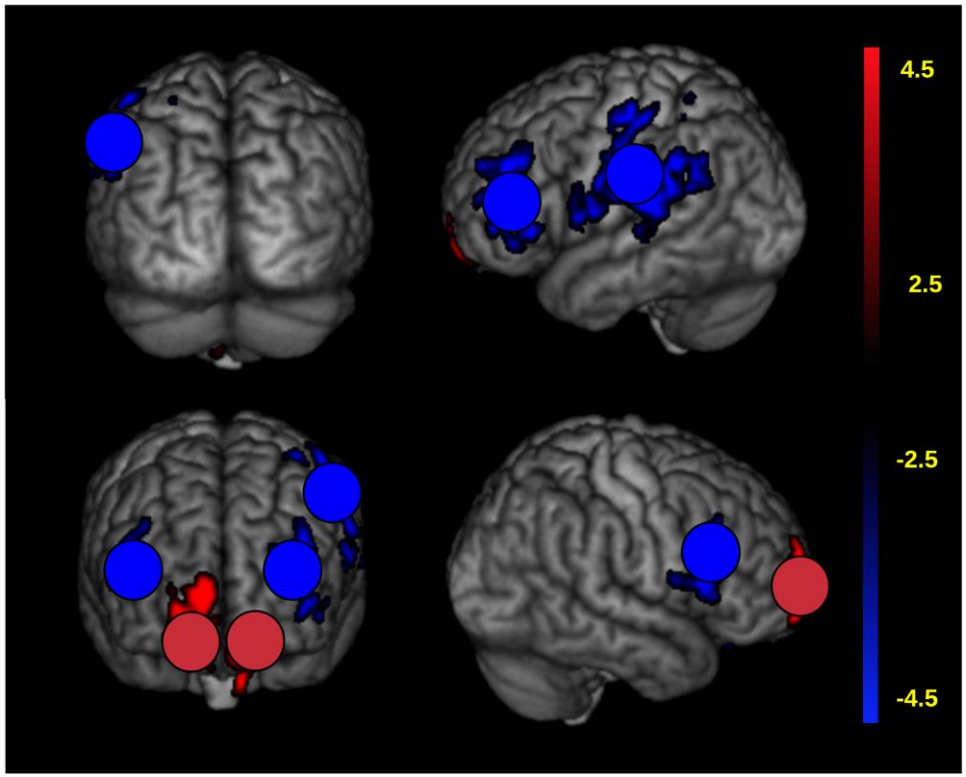


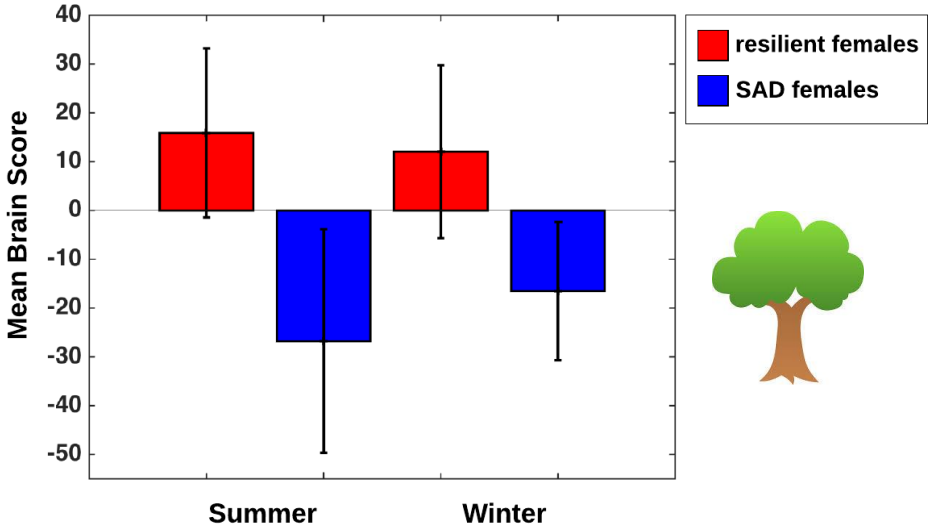
Error bars reflect 95% CI from bootstrap

Threshold: brain regions with Z-score$_{split}$ > ± 2.6 and volume > 640 mm^3

Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

The Leaves: Network of LV1-associated brain regions





Error bars reflect 95% CI from bootstrap

Threshold: brain regions with Z-score$_{split}$ > ± 2.6 and volume > 640 mm^3

Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Summary – females with the short 5-HTTLPR genotype

- Evidence for a latent variable that significantly distinguished condition responses across groups
  - LV “positive” network: hippocampus, thalamus, pallidum, mPFC, and median raphe.
  - LV “negative” network: ventral striatum (nucleus accumbens), omPFC, dlPFC, supramarginal gyrus.

- Adaptation of a 5-HTT network to the environmental stressor of winter
  - resilient: higher 5-HTT in a subcortical network in the summer compared to females with SAD.
  - SAD: higher 5-HTT in parts of a cortical network and ventral striatum.

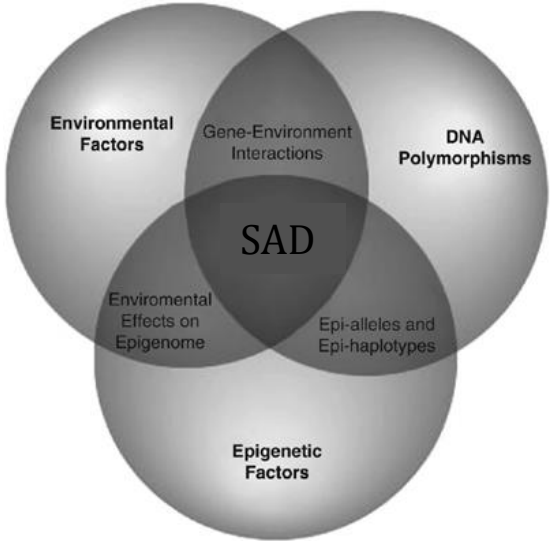
  - PLS analysis suggests a network of brain areas that respond to the environmental stressor of winter in a serotonin-dependent fashion. But we only observe a significant difference in the network between groups in the summertime?

Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Biological sources of individual variability in Seasonal Affective Disorder (SAD)

- **Future perspectives**
  1. Optimizing the preprocessing pipeline to lower variability within subject and between subjects.
  2. Investigate functional connectivity using fMRI within the identified network and using the same cohort.
  3. Individual evaluation of brain response -> a biomarker for personalized treatment in SAD?

- **Questions still to be answered:**
  1. Different networks/mechanisms for males vs. females in SAD?
  2. More data? Split-half resampling represents a powerful procedure for providing unbiased measures of brain behavior and spatial reproducibility. Therefore current results can be "trusted"!
  3. Neurobiological interpretation?



Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Thank you for your attention!

- Collaborators
  - Melanie Ganz
  - Nathan Churchill
  - Brenda Mc Mahon
  - Patrick Fisher
  - Vincent Beliveau
  - Peter S. Jensen
  - Claus Svarer
  - Gitte Moos Knudsen
  - Stephen C. Strother

Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet

Questions?

Martin Nørgaard
NRU, Copenhagen University Hospital, Rigshospitalet