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Discovery of key whole-brain transitions and dynamics during human wakefulness and non-REM sleep

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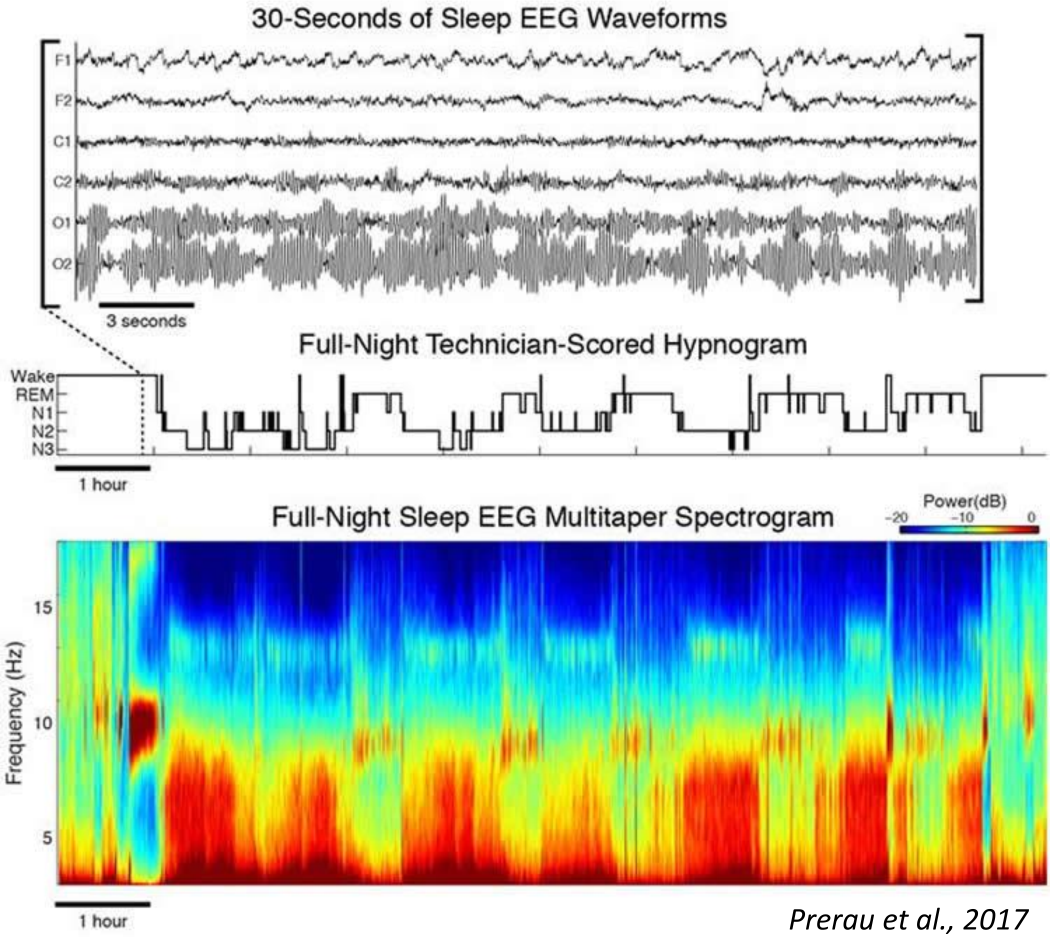
Background: sleep

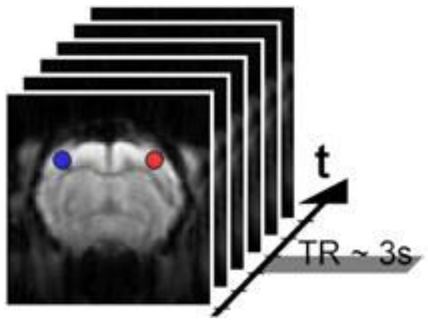
- Current understanding of sleep is based on sleep stage classification of EEG signatures
  - Underlying brain dynamics remain unclear!
- The latest guidelines subdivide sleep into 5 classes
  - Wake, N1, N2, N3 and REM
- In this paper, a data-driven analysis is carried out solely on wake/sleep fMRI-data and with subsequent comparisons with the sleep profile (scored EEG).

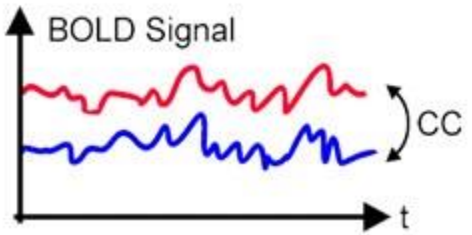


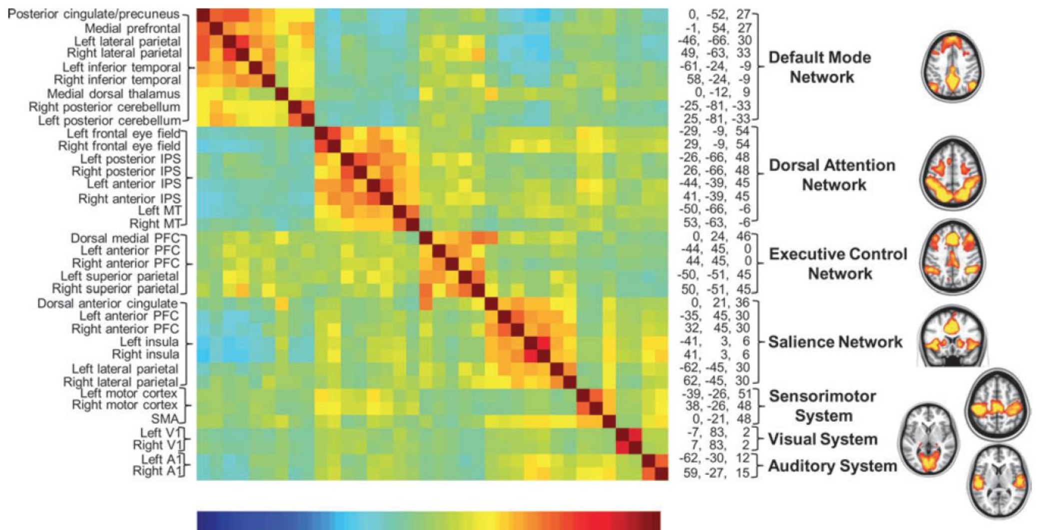
Prerau et al., 2017

Background: functional connectivity

- In the fMRI community, functional connectivity is used to quantify the relation between brain areas during resting state or task fMRI.
    - Along with independent component analysis (ICA), this method has established a number of resting state networks (RSNs)
- In recent years, the connectivity community within fMRI research has begun to explore dynamic functional connectivity (dFC) with the idea that brain connectivity can change over time.



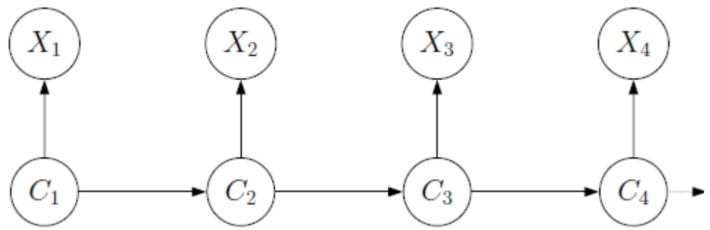


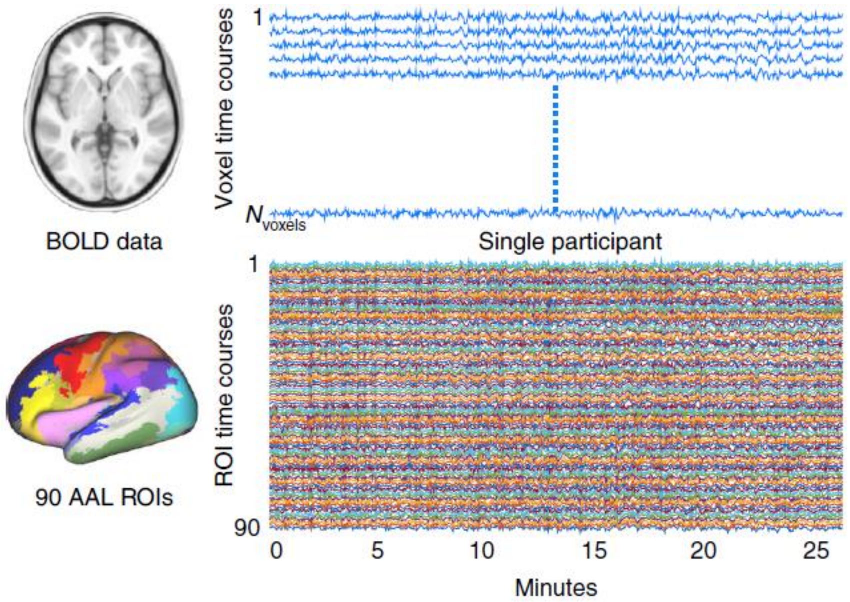


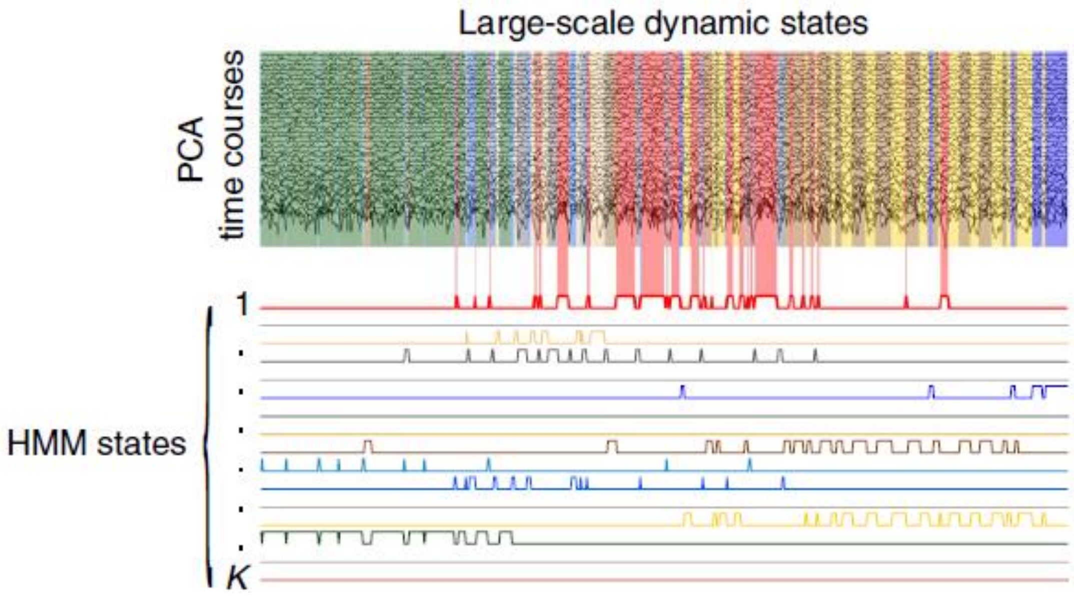
Marcus Raichle 2011

Background: Hidden Markov Models

- A Hidden Markov Model (HMM) is a generative model that can segment a multivariate time-series into K *states* that are fully characterized by their mean and covariance matrix.
    - Imagine a discrete set of latent states (potentially the RSNs) that, for each time point is responsible for generating a multivariate realization from a probability distribution

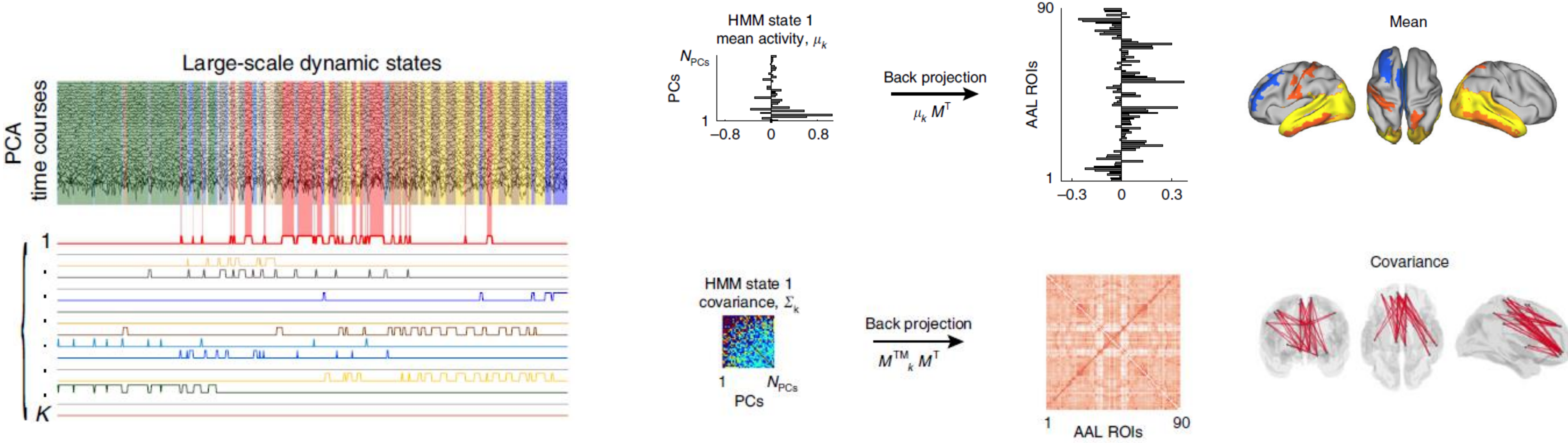






Spatial activation and FC maps

- An HMM state is fully characterized by its mean and covariance matrix
  - Mean: Average activation of state X in each ROI
  - Covariance: The coactivation of ROI A with ROI B (functional connectivity)

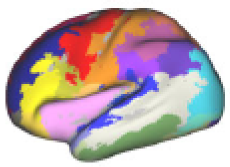


Methods

- 57 participants underwent 52 minutes simultaneous EEG-fMRI acquisition
  - fMRI: 3T EPI with TR 2.08s (1505 volumes). Data was normalized into MNI152 space using SPM8. Cardiac- and respiratory-induced noise were regressed out and the data was temporally filtered in the range 0.01-0.1Hz
  - PSG (including ECG, EMG, EOG, EEG, pulse oximetry and respiration) were recorded simultaneously. Pulse and gradient artifacts were removed using Vision Analyzer2

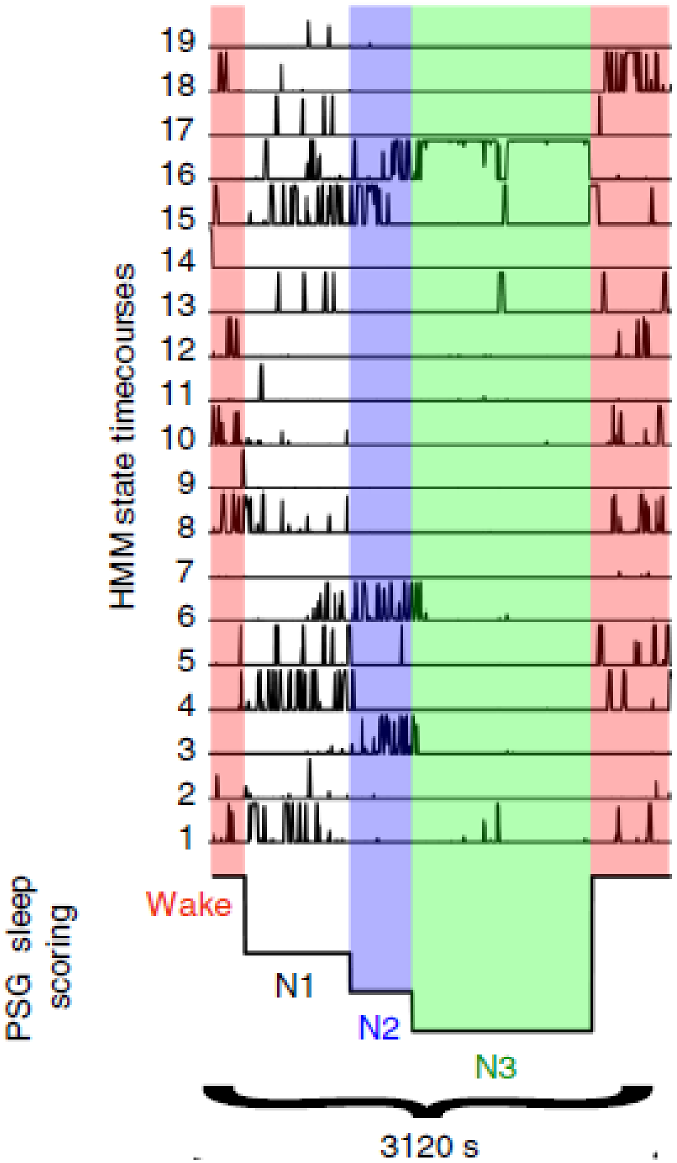
- The participants were instructed to lie still in the scanner with closed eyes and relax.
  - EEG was scored by an expert (excluding REM sleep)
  - 18 participants reached all four stages of sleep
  - 31 participants woke up after having reached consolidated (N2) sleep (WASO)

- Time courses from the normalized fMRI were extracted using the AAL-90 atlas
- PCA was performed, keeping 90% explained variance
- HMM was implemented using the HMM-MAR toolbox in MATLAB on the PCA time courses
  - The number of states is a free parameter. They chose 19.

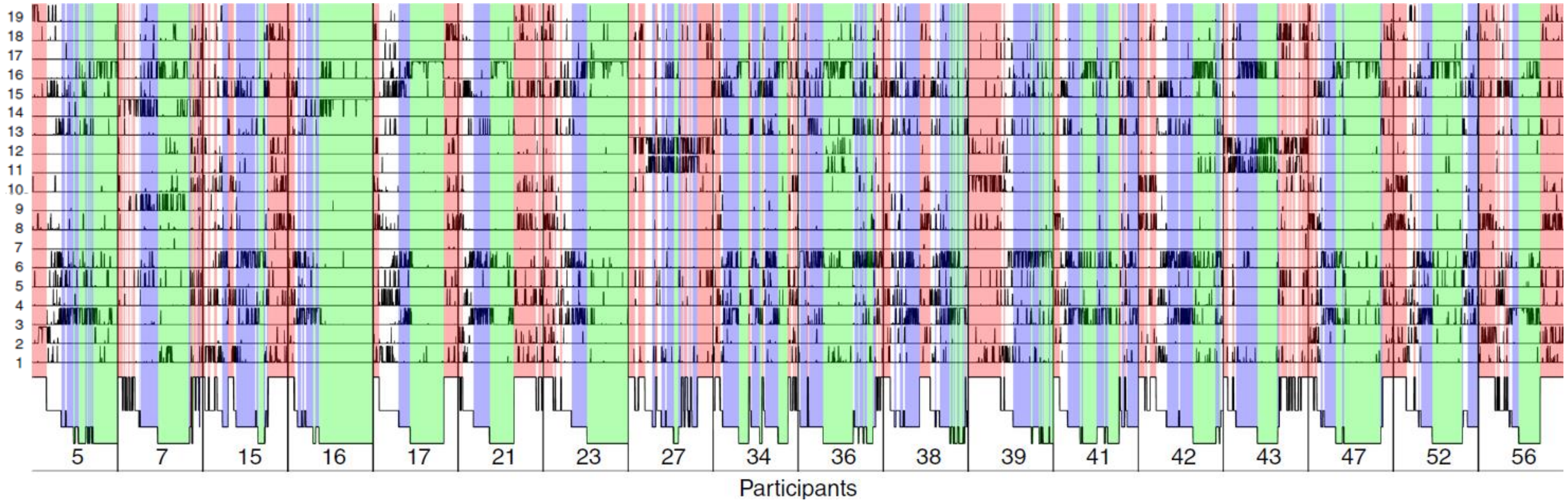


90 AAL ROIs

Some states are more active during specific sleep stages



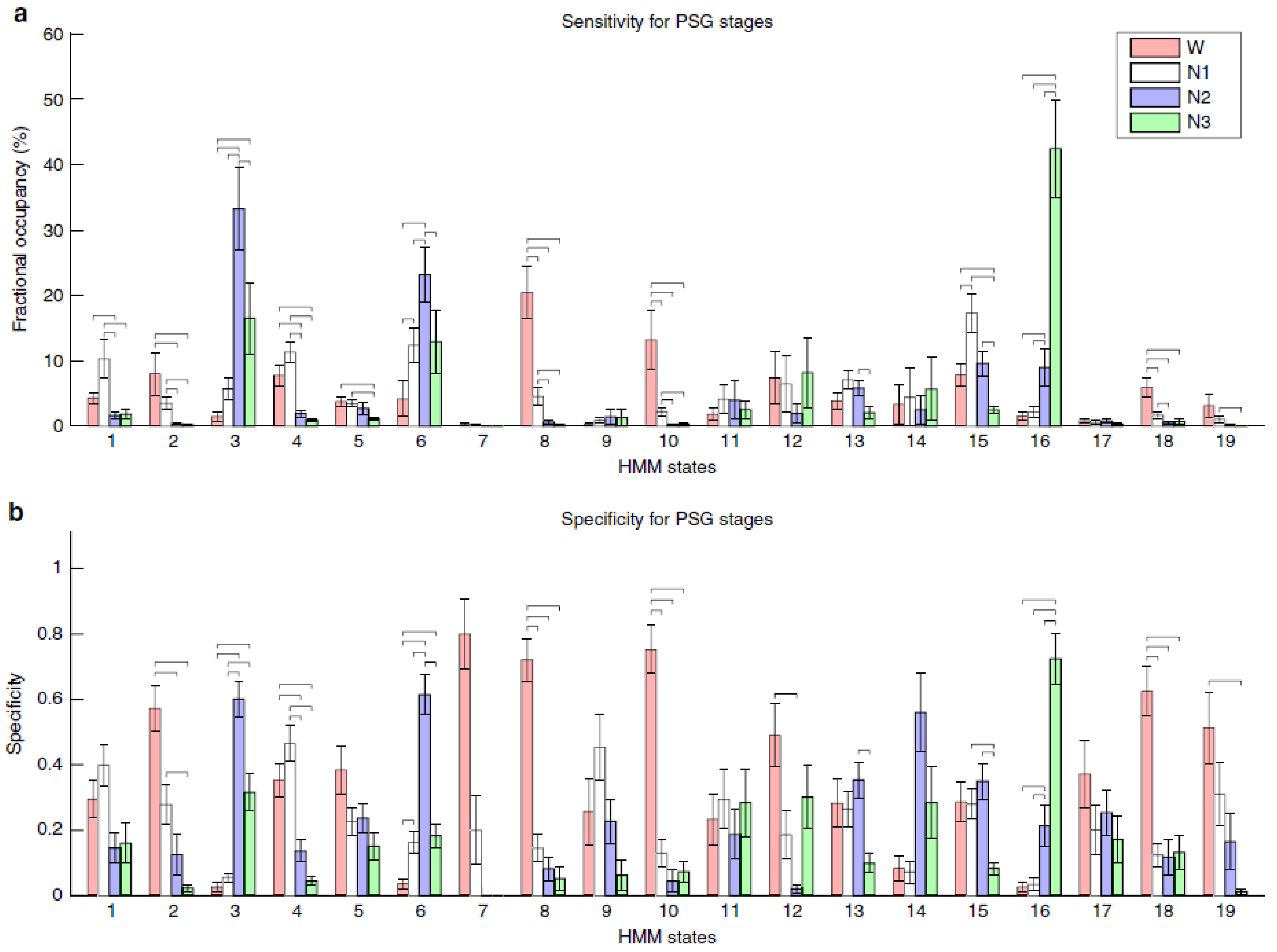
- Results are analyzed for the 18 participants that reached all four stages of sleep. From visual inspection:
  - HMM state 8 occurred mostly during wakefulness
  - HMM state 3 occurred during N2 sleep
  - HMM state 16 occurred during N3 sleep
  - Some states are subject-specific



Statistical connection between HMM states and sleep stages

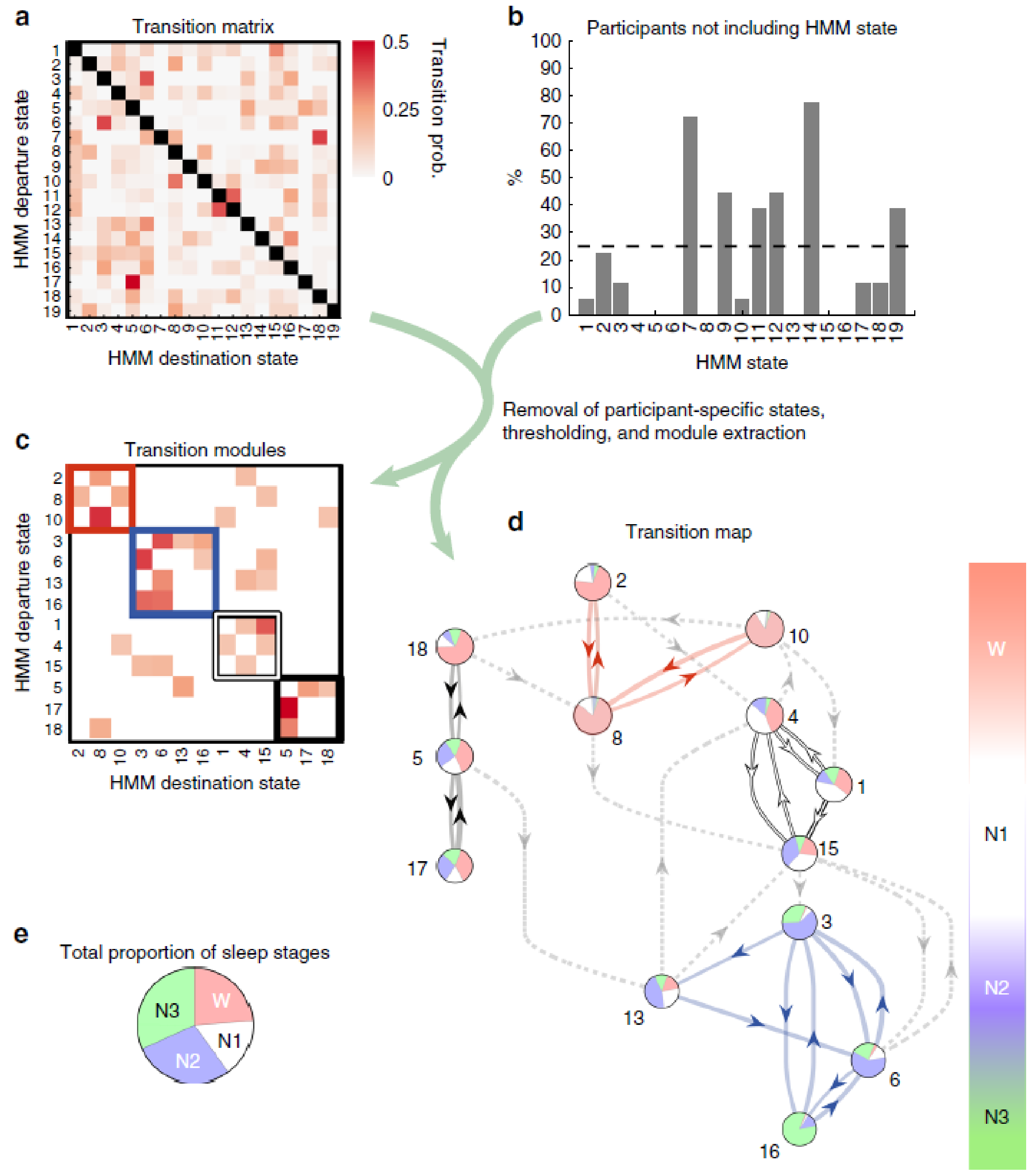
- The sensitivity is the proportion of N2 sleep, say, allocated to each HMM state

- The specificity is the proportion of HMM state 3, say, allocated to each sleep stage



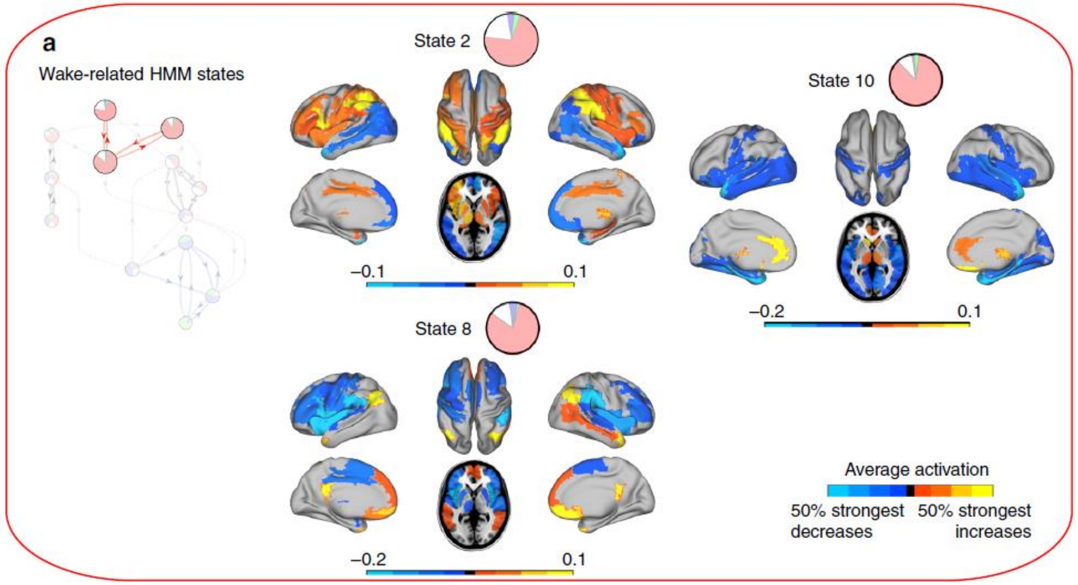
Modules of transitions

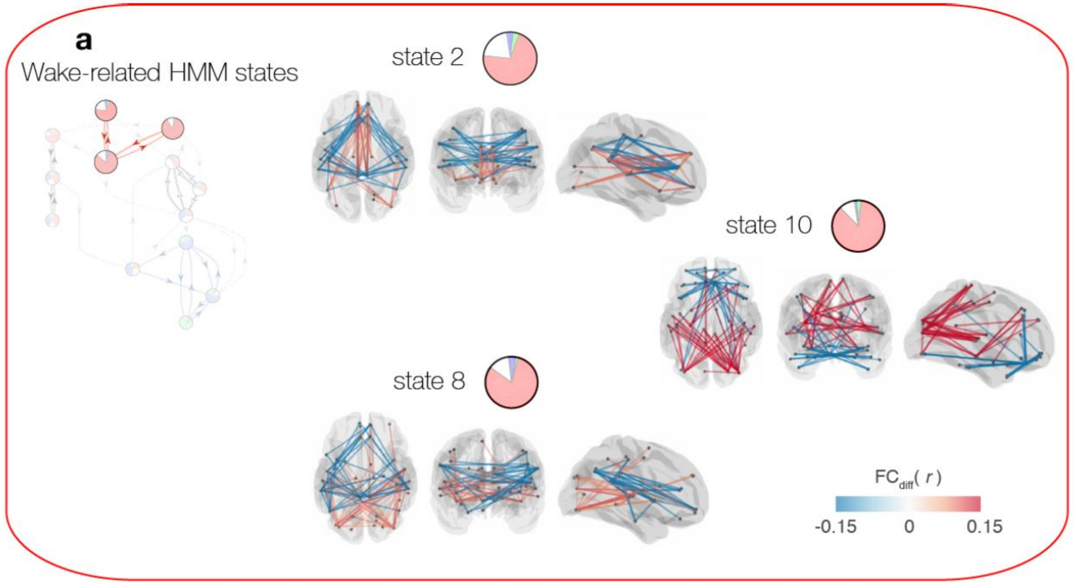
- The transition probability matrix contains the probability of switching to other states.
  - If HMM states are subject-specific, they don't generalize to sleep stages!
- A modularity analysis can group states in the transition probability matrix into modules, where switching between module states occurs more frequently
  - Such modules can be represented with a nice map
- An analysis of this sort can help us make reverse inference:
  - Is N2 sleep really a combination of three whole-brain states represented by HMM states 3, 13 and 6?



Spatial activation of wakefulness

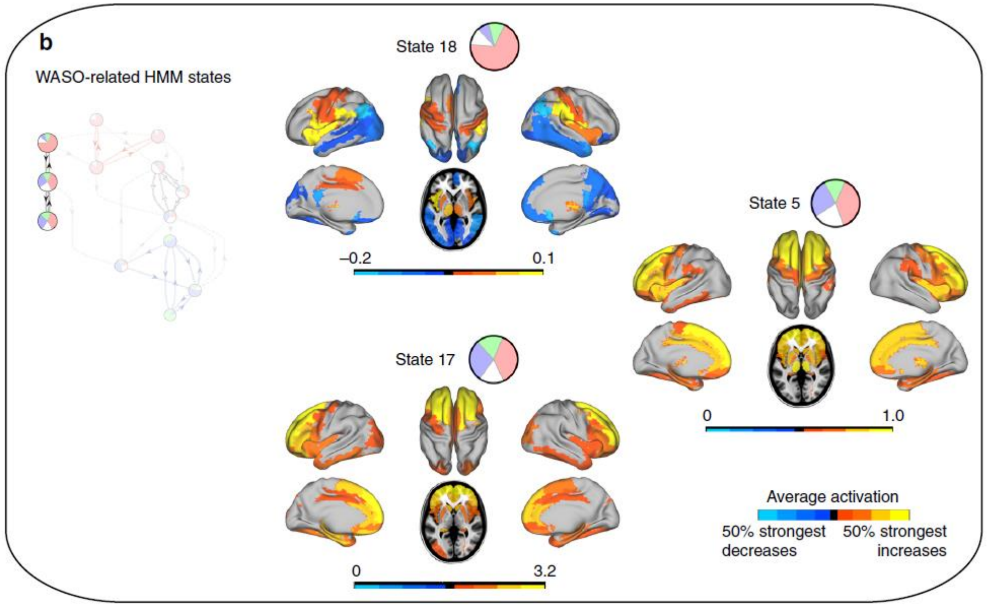
- State 8: DMN-like increases, decreases in the anti-correlated network (ACN)
- State 2: Increases in ACN
  - The inverse relationship between DMN and ACN is a well established trait within RSNs!

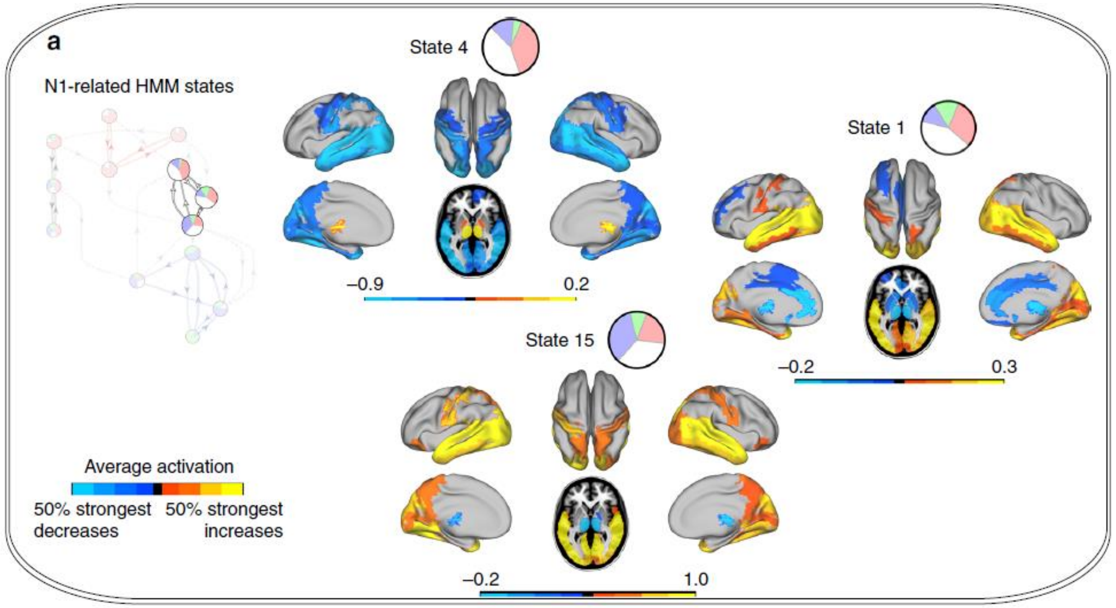




Spatial activation of WASO and N1

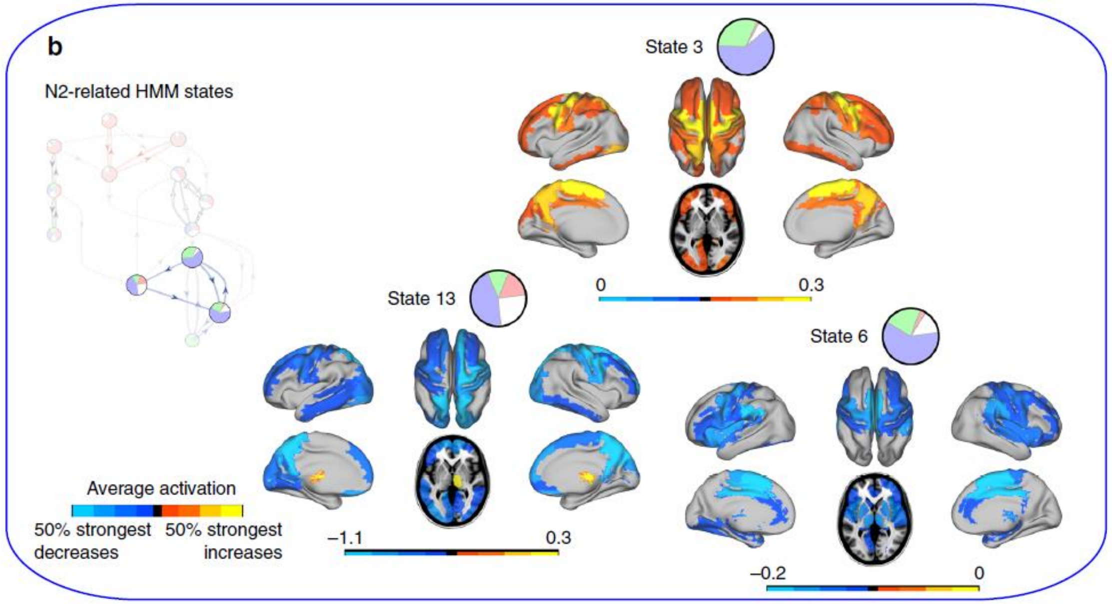
- WASO:
  - State 18 shows the same DMN/ACN configuration as in state 8, but with opposite signs.
  - States 5 and 17 mainly show activation in the frontal cortex.
- N1:
  - Inverse relationship between subcortical areas and primary sensory cortical areas.

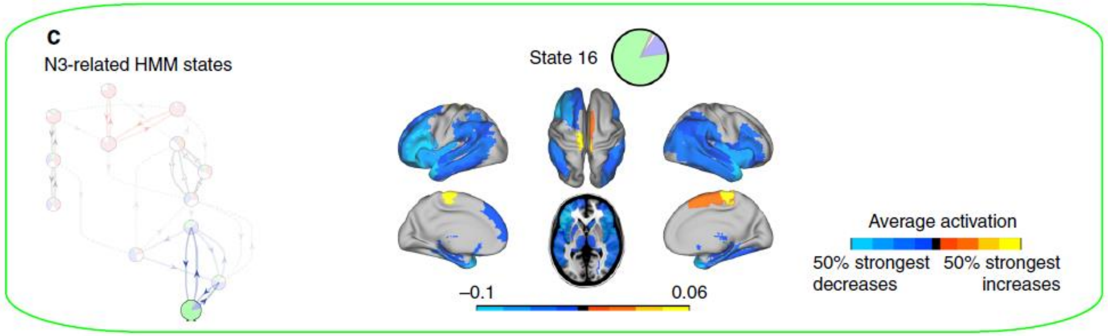




Spatial activation of N2 and N3

- N2:
  - Supplementary motor area involved in states 3 and 6. Previous studies have shown a connection between sleep spindles (a defining feature of N2 sleep) with the supplementary motor area.
- N3:
  - Activation mainly characterized by decreases, except for the supplementary motor area.

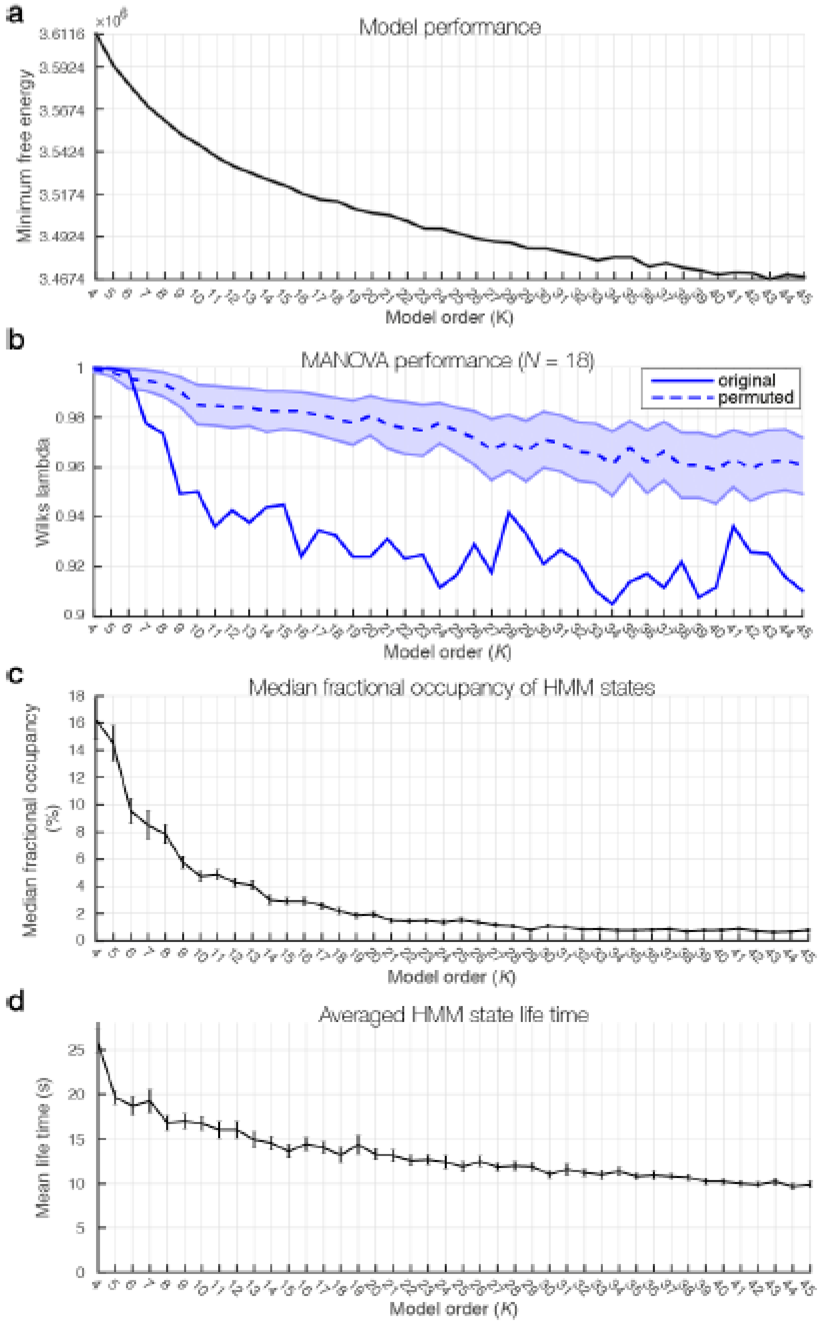




Discussion: Why 19 states?

- The selection of the number of states is a very difficult, but important problem.
  - The free energy is the statistical metric that the HMM tries to minimize.
  - The MANOVA describes how well the HMM state time courses can be grouped by the PSG stages.
  - The fractional occupancy is the temporal fraction of a recording where an HMM is active. For higher than 19 states, the new states modeled participant-specific subparts of the data.
  - The average state life-time also stabilizes around 19.

- Sensitivity/specificity and transition maps are reproduced in the supplementary material for 15,17,21,23 states and show splitting/clumping of HMM states but otherwise consistent results.



Discussion

- Interesting explorative analyses:
  - Until now, only static FC studies of sleep have been conducted. The use of HMMs brings us closer to a dynamical description of activities in the brain both during specific periods of sleep and in the transitions between them.
  - The transition from wakefulness to N1 sleep is shown to include a decrease in the DMN activation.
  - N1 is poorly defined by the HMM. However, this corresponds to the general acceptance of N1 sleep being the most vaguely defined stage and also the hardest one to classify with machine learning techniques. The transitions defined from wakefulness to N2 sleep travelling through a multiple of HMM states that include the decoupling of subcortical and cortical areas may suggest that a new categorization of early sleep could be within reach?
- Stability:
  - The HMM is a randomly initialized model! Several studies have shown that there may be poor relation between different initializations of the model (SFV Nielsen et al., 2018). This study only computes 5 HMMs.
- Number of states
- Is HMM a biological model?
  - The brain is continuously active, and we cannot assume that a discrete set of whole-brain states are sequentially generating activation in the brain. But utilizing HMMs may bring us closer to understanding sleep.,

Statistical connection between HMM states and sleep stages (2)