

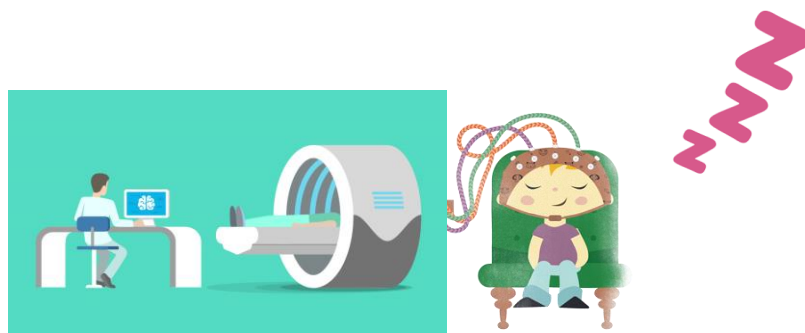


# Hidden Markov Models and Sleep

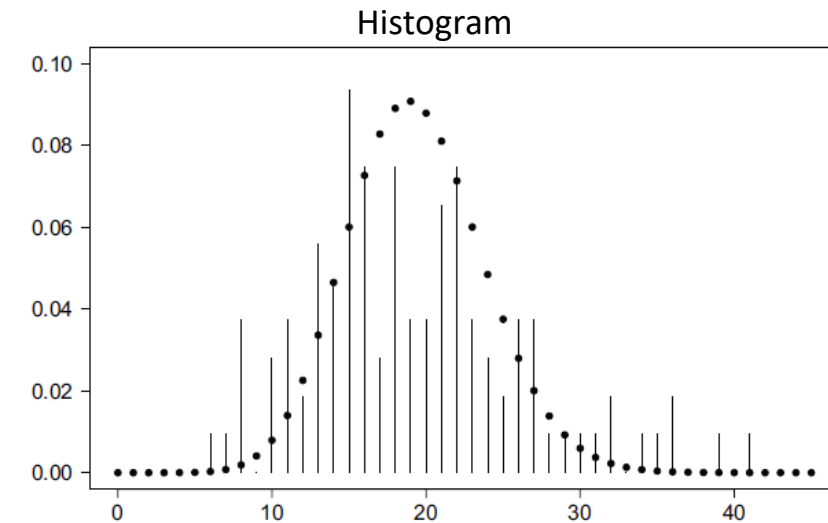
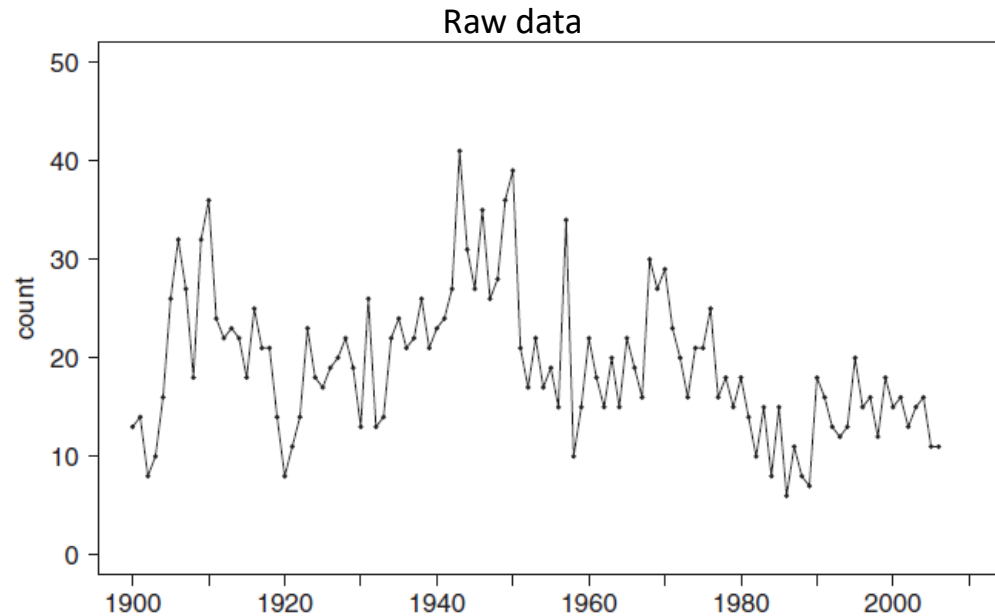
An introduction to the Master's thesis project

Quantification of sleep states using dynamical modeling of functional neuroimaging data

*Anders S. Olsen, thesis student*

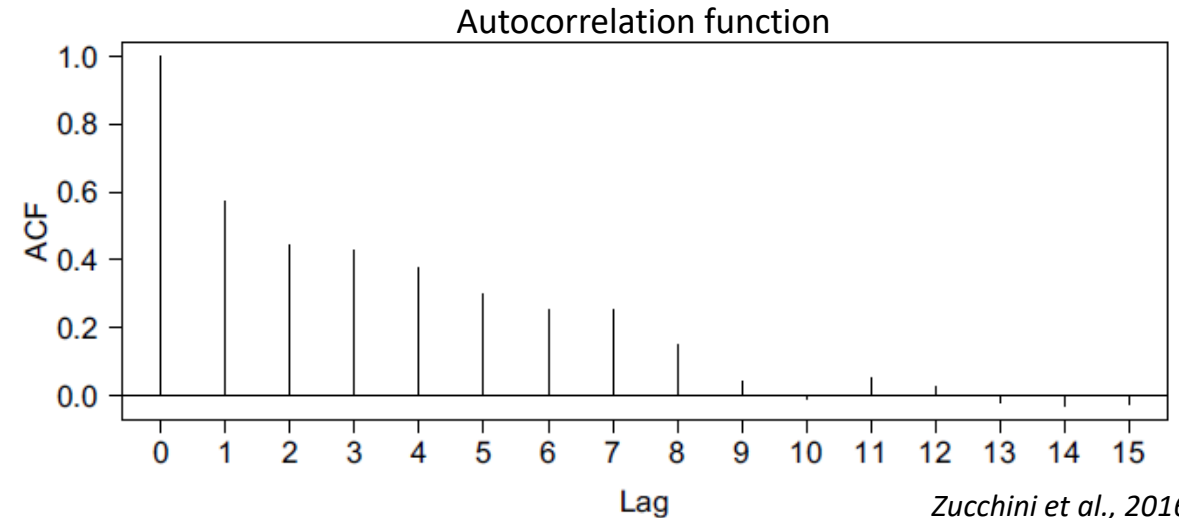


# Example: US major earthquakes count



The usual distribution assumption for an unbounded count is the Poisson distribution.

- However, there is considerable overdispersion:  
 $E(X) = 19.36 \neq Var(X) = 51.57$
  - Also, there is serial dependence (samples are not IID)
- Hidden Markov Models can account for this!



# Example: US major earthquakes count

## - Dealing with overdispersion

In independent mixture models, we have  $m$  distributions  
Each distribution is selected by the random variable  $C$ :

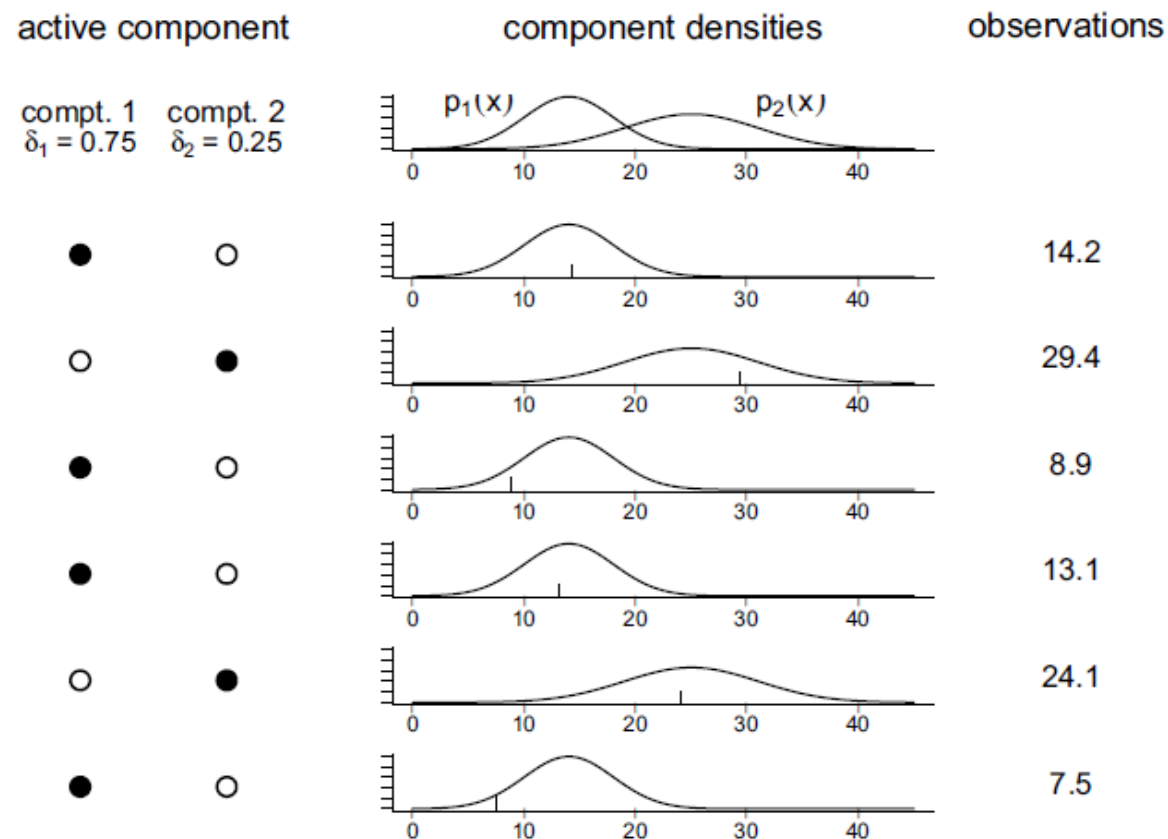
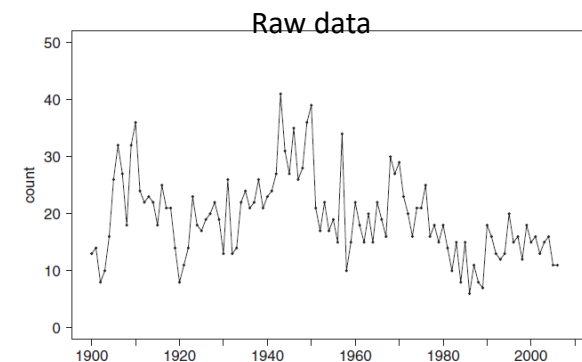
$$C = \begin{cases} 1 & \text{with probability } \delta_1 \\ \vdots & \vdots \\ i & \text{with probability } \delta_i \\ \vdots & \vdots \\ m & \text{with probability } \delta_m = 1 - \sum_{i=1}^{m-1} \delta_i \end{cases}$$

With  $m = 2$  and mixing probabilities  $\delta_1 = 0.75$ ,  $\delta_2 = 0.25$ , this means that the transition probability matrix is

$$\mathbf{\Gamma} = \begin{pmatrix} \gamma_{11} & \gamma_{12} \\ \gamma_{21} & \gamma_{22} \end{pmatrix} = \begin{pmatrix} 0.75 & 0.25 \\ 0.75 & 0.25 \end{pmatrix}$$

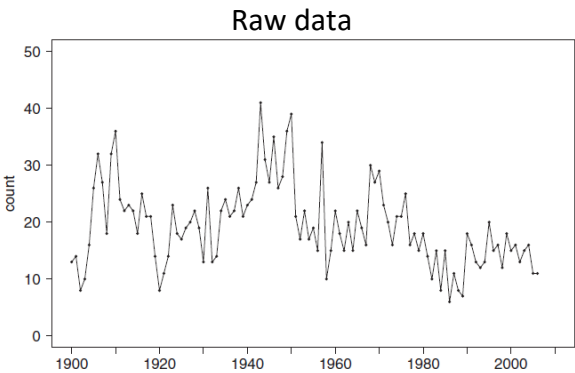
Parameter estimation by ML:

$$L(\theta_1, \dots, \theta_m, \delta_1, \dots, \delta_m | x_1, \dots, x_n) = \prod_{j=1}^n \sum_{i=1}^m \delta_i p_i(x_j, \theta_i)$$

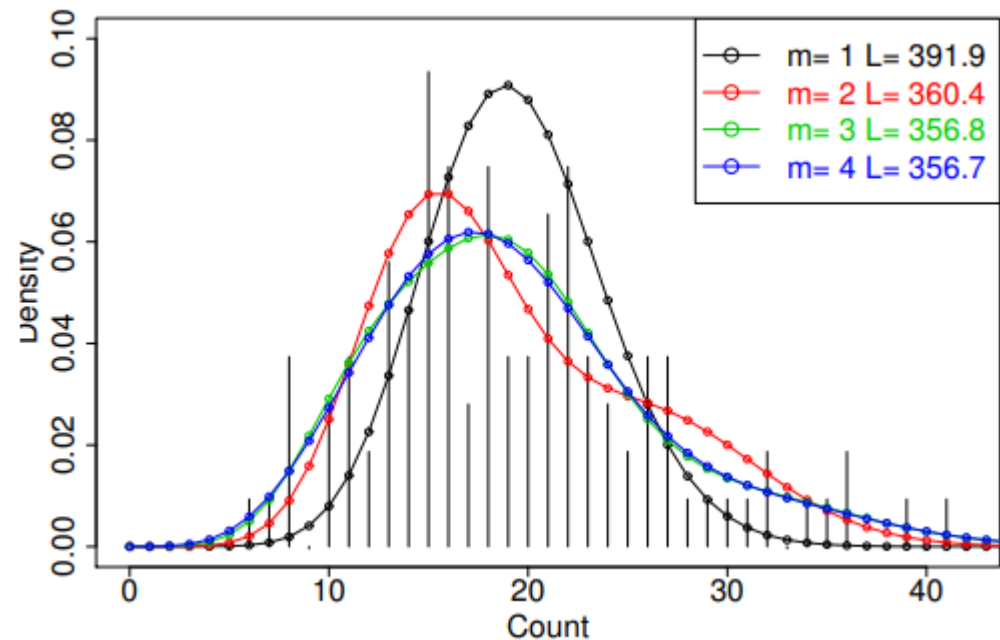


# Example: US major earthquakes count

- Dealing with overdispersion



If we fit independent mixtures of Poisson models to the data:

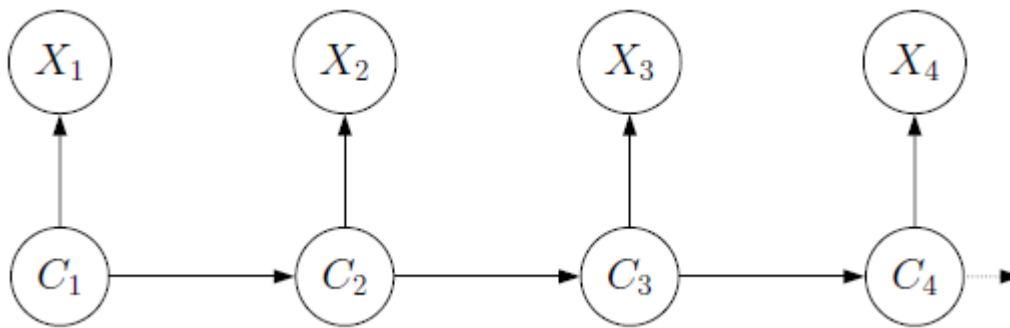


model	$i$	$\delta_i$	$\lambda_i$	$-\log L$	mean	variance
$m = 1$	1	1.000	19.364	391.9189	19.364	19.364
$m = 2$	1	0.676	15.777	360.3690	19.364	46.182
	2	0.324	26.840			
$m = 3$	1	0.278	12.736	356.8489	19.364	51.170
	2	0.593	19.785			
	3	0.130	31.629			
$m = 4$	1	0.093	10.584	356.7337	19.364	51.638
	2	0.354	15.528			
	3	0.437	20.969			
	4	0.116	32.079			
observations					19.364	51.573

# Example: US major earthquakes count

## - Dealing with serial dependence

The basic directed graph of an HMM:

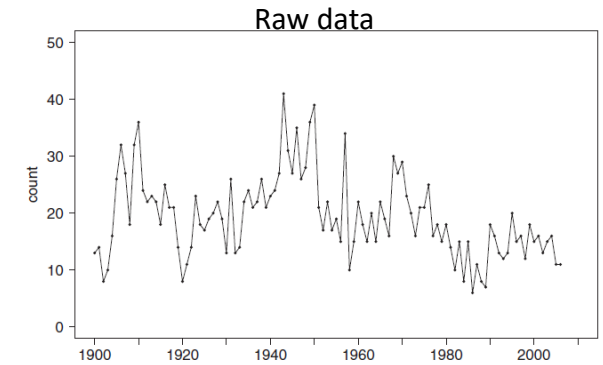


$$\text{Or, } \Pr(C_{t+1} | C_t, \dots, C_1) = \Pr(C_{t+1} | C_t)$$

We still have stationary mixing probabilities  $\delta_1 = 0.75$  and  $\delta_2 = 0.25$ .

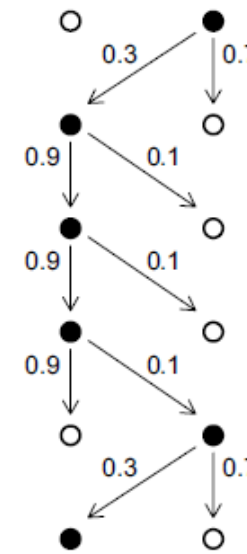
The transition probability matrix is now

$$\Gamma = \begin{pmatrix} \gamma_{11} & \gamma_{12} \\ \gamma_{21} & \gamma_{22} \end{pmatrix} = \begin{pmatrix} 0.9 & 0.1 \\ 0.3 & 0.7 \end{pmatrix}$$

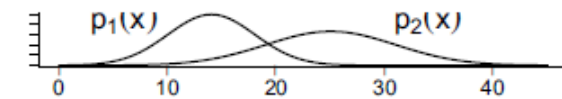


Markov chain

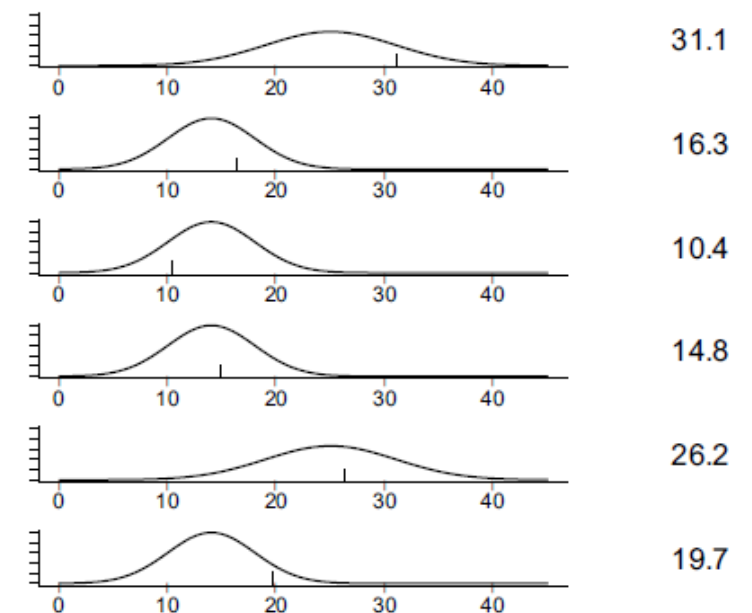
state 1  $\delta_1 = 0.75$  state 2  $\delta_2 = 0.25$



state-dependent distribution

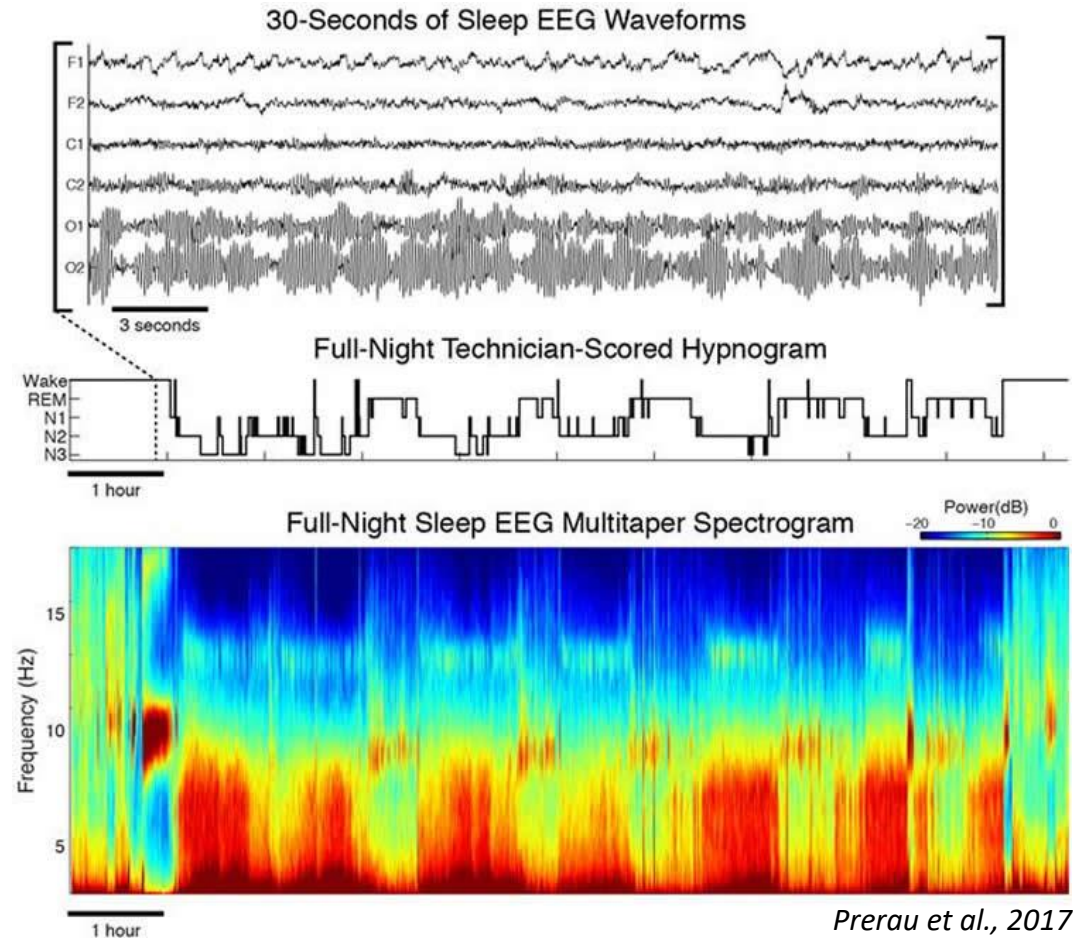


observations



# Sleep

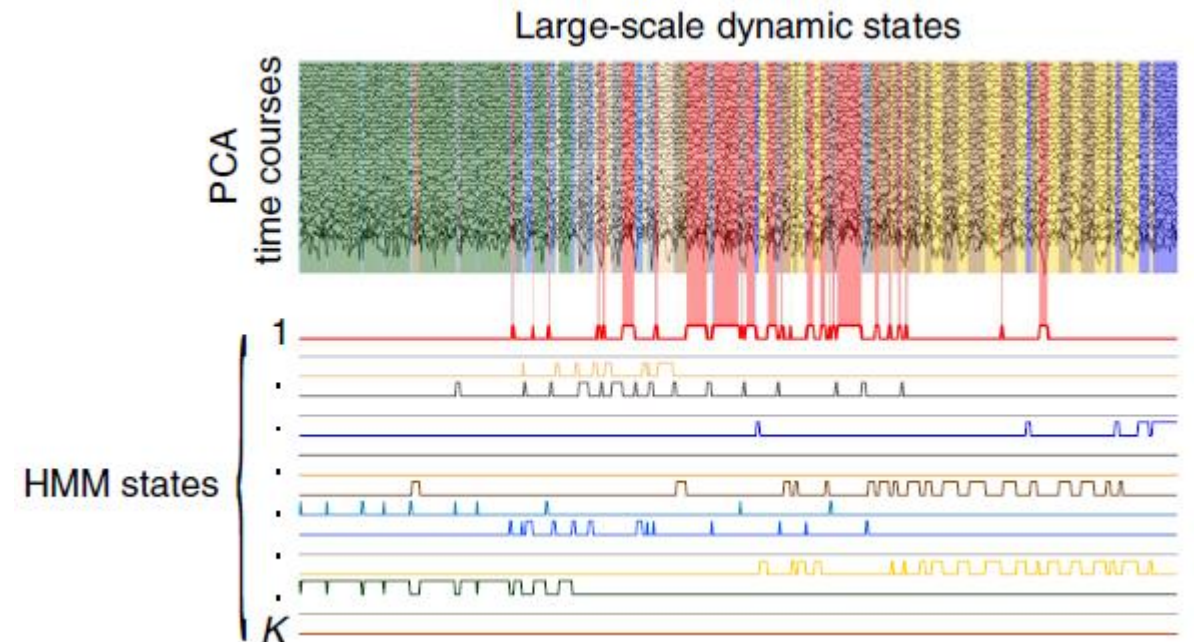
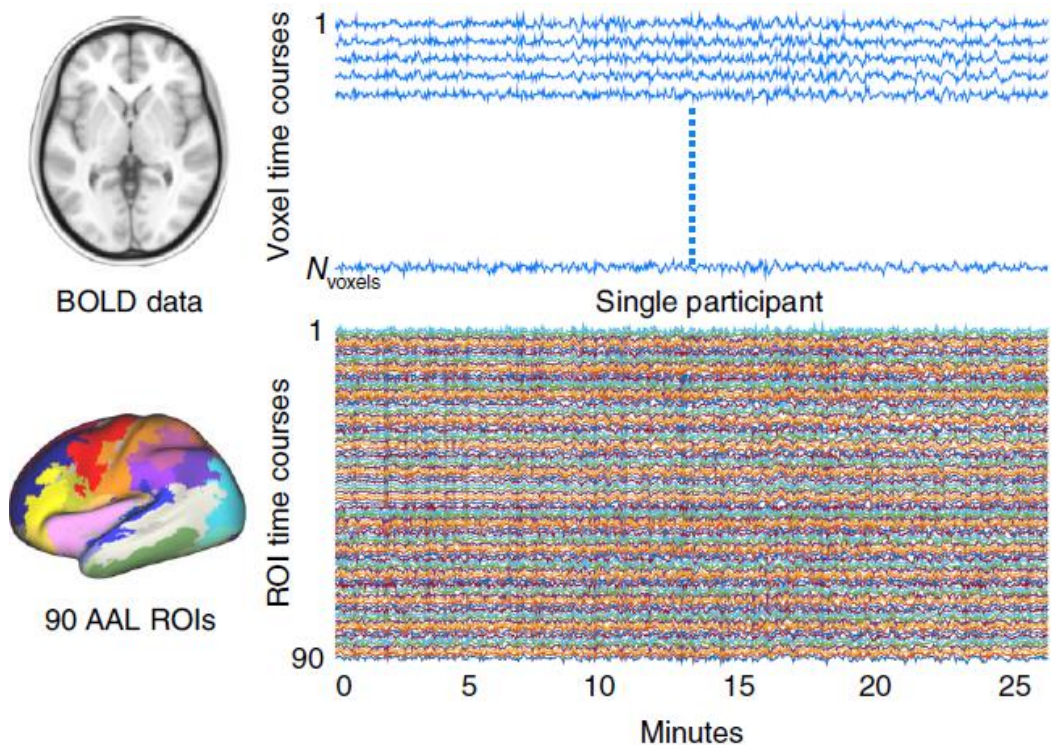
- Historically, sleep has been characterized by polysomnography
- Currently, we work with 5 stages:
  - Wakefulness
  - REM-sleep
  - Non-REM 1-3
- Maybe these stages can be captured by HMM trained on sleep fMRI?





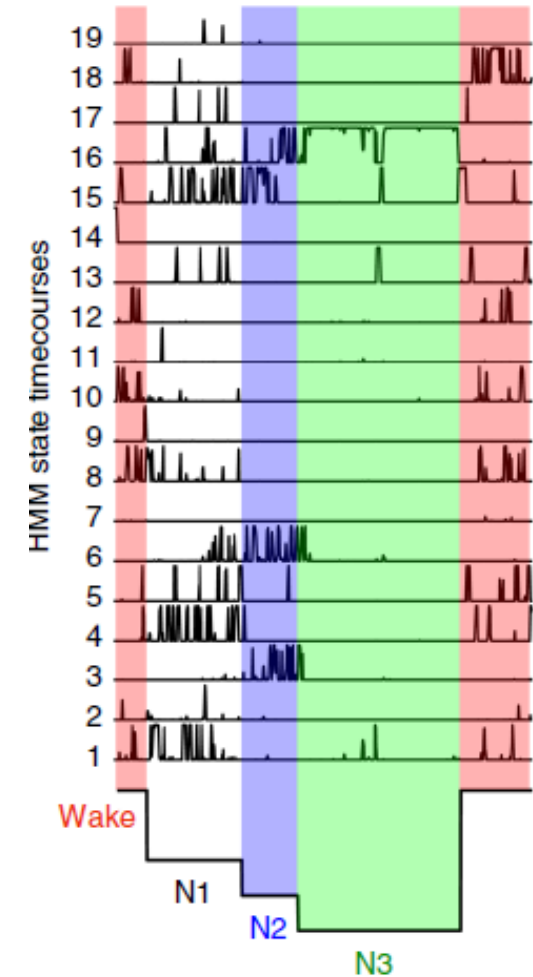
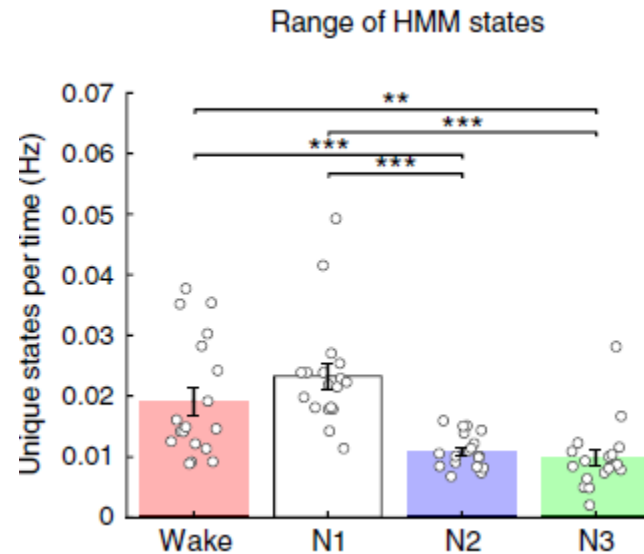
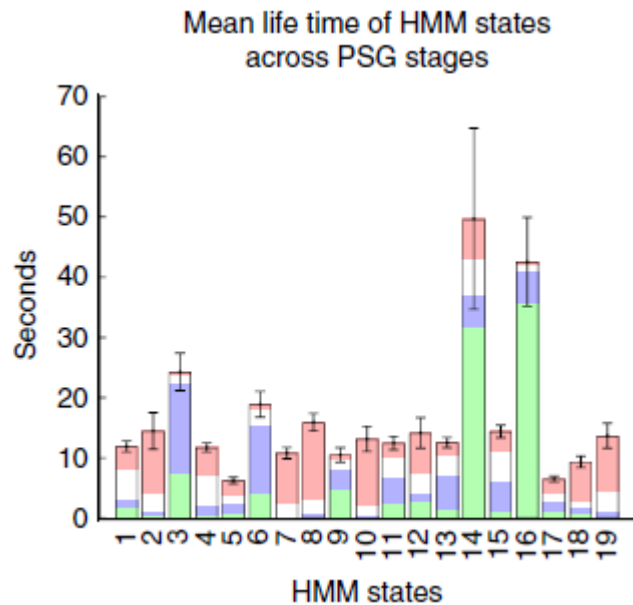
# Stevner et al., 2019

- Stevner and colleagues employed HMM on fMRI-data from 57 participants, of which 18 reached all three non-REM stages.
- The output from HMM may be interpreted from state probabilities or Viterbi decoding



# Stevner et al., 2019

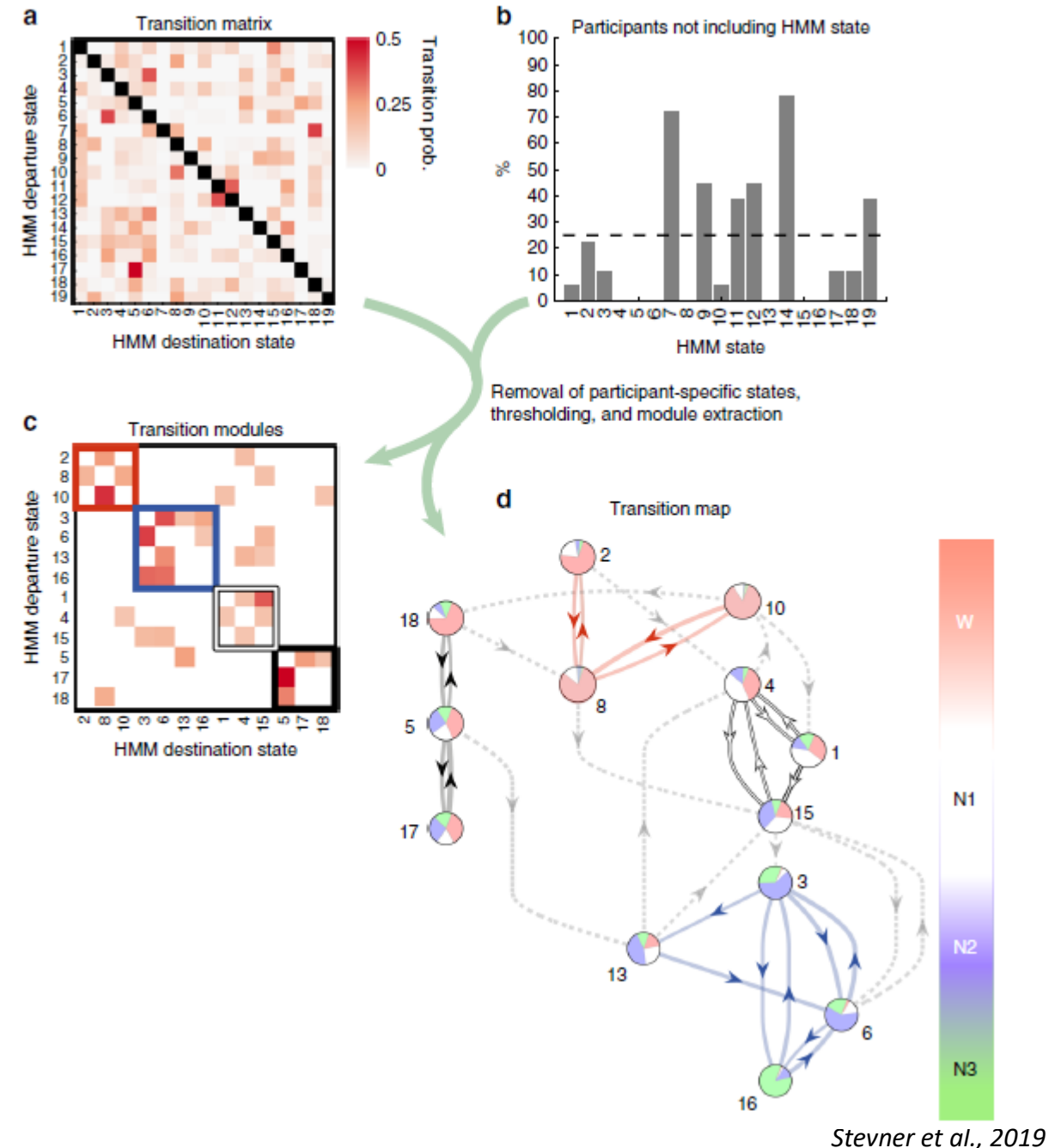
- State probabilities compared with scored PSG-stages may reveal spatial brain characteristics of sleep and wakefulness





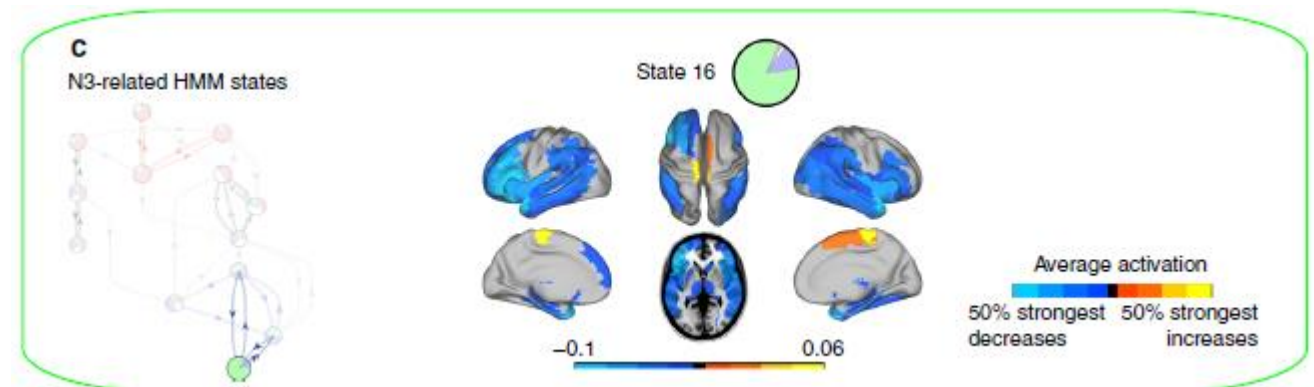
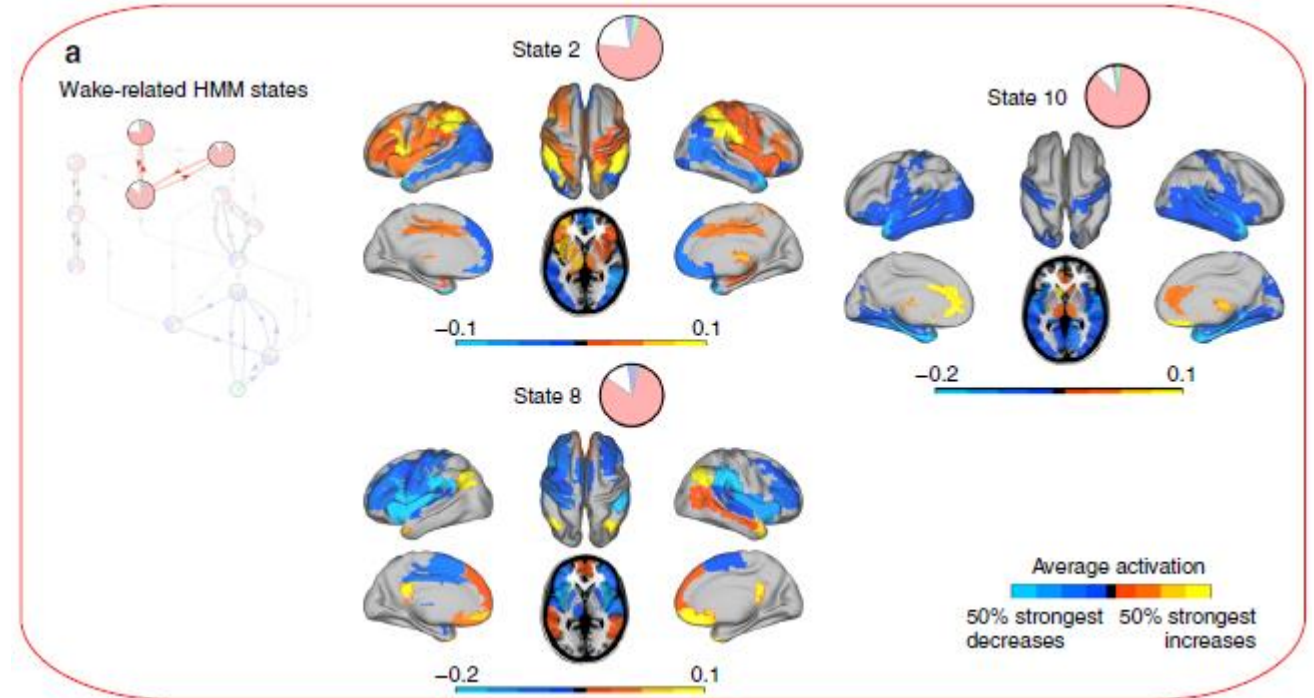
# Stevner et al., 2019

- Investigating modules of transitions between whole-brain network states may reveal a transition map that correlates well with our modern-day understanding of sleep stages.

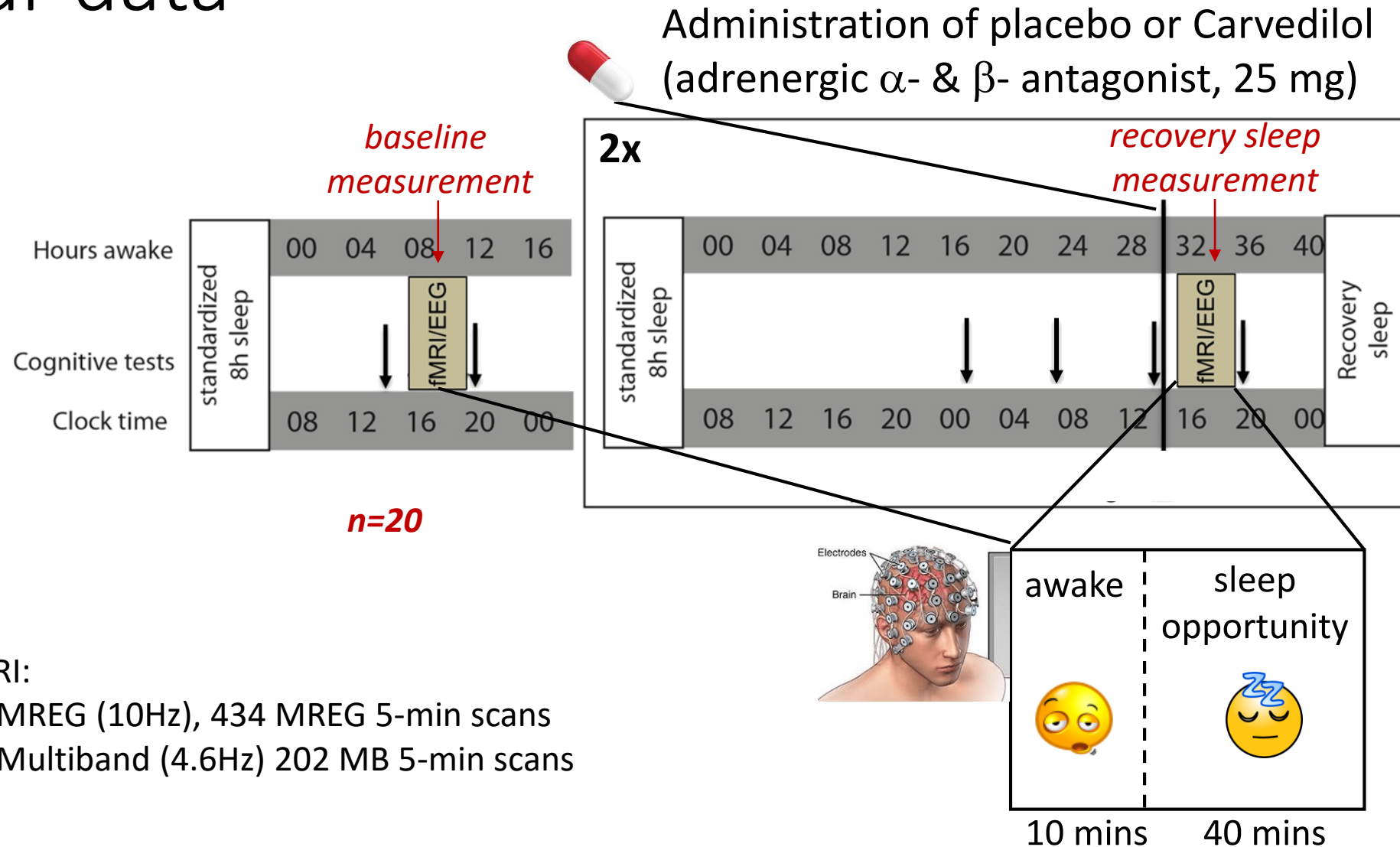


# Stevner et al., 2019

- Mean activation distributions can be interpreted and potentially lead to new hypotheses



# Our data



fMRI:

- MREG (10Hz), 434 MREG 5-min scans
- Multiband (4.6Hz) 202 MB 5-min scans

# Our data

- Each subject has appeared in three trials: Baseline, sleep deprived with Carvedilol and sleep deprived with placebo.
- For each session we have 40-60 minutes of wake-(sleep)-wake
- Two experts have scored the PSG data as follows:

30s epochs total	BL 2000		Carv 2280		Plac 2210	
Agreement	1521	(76%)	1175	(52%)	1162	(53%)
2-min agreement	1410	(71%)	944	(41%)	943	(43%)
"Artifact"	97	(5%)	167	(7%)	177	(8%)
"Wake"	1286	(64%)	310	(14%)	303	(14%)
"N1"	8	(0.4%)	20	(0.9%)	22	(1%)
"N2"	19	(1%)	242	(11%)	230	(10%)
"N3"	0	(0%)	205	(9%)	211	(9%)

# Thesis research questions

1. With data from ultra-fast fMRI sequences of wakefulness and sleep, can we reveal vigilance states using dynamical modeling, and what do we gain from having a high temporal resolution?
  - An approach to Stevner et al., 2019



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2. At the group analysis level, what are differences between the three conditions of which the data originate (Baseline, sleep deprivation + Carvedilol, sleep deprivation + Placebo)
  - Statistical comparisons of state occupancy, dwell time and transition matrices
3. What are the advantages of modeling state transitions, and do Gaussian mixture models provide as much information as HMM?
  - What do we see when modeling samples as IID?



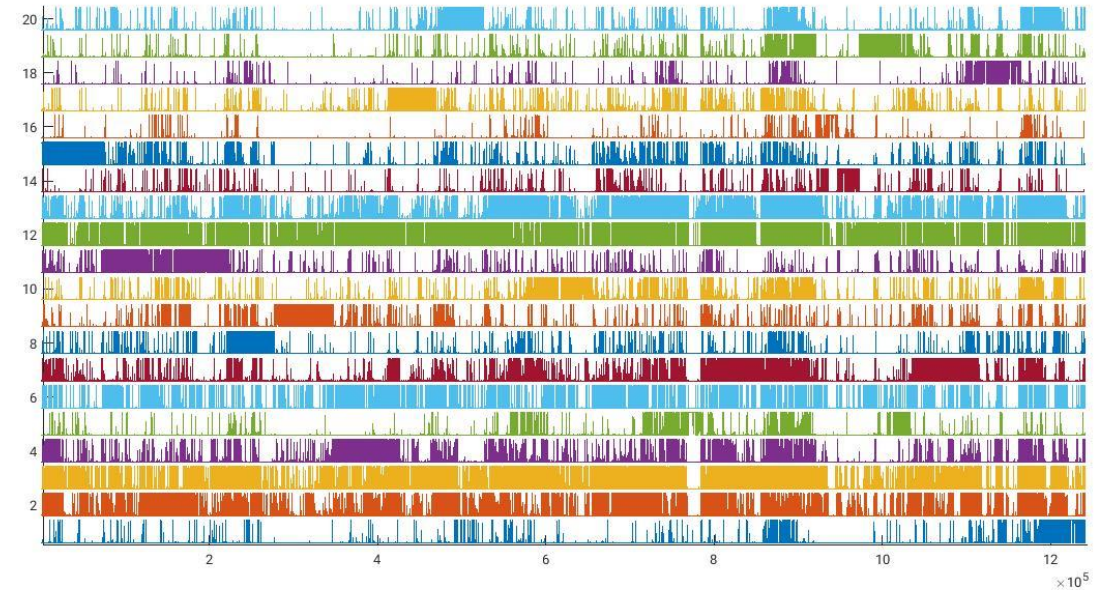
# Current stage of project

- fMRI preprocessing completed (awaiting quality check)
- Data extraction completed (using the AAL atlas as in Stevner, 2019)
- Data selection scheme created
- First implementation of HMM-toolbox completed



Immediate next steps:

- Filter physiological artifacts using RETROICOR
- Perform analyses as in Stevner (2019)



# Thank you for the attention!

## References:

- Damaraju et al., 2020. Connectivity dynamics from wakefulness to sleep. Neuroimage.
- Prerau et al., 2017. Sleep Neurophysiological Dynamics Through the Lens of Multitaper Spectral Analysis. Physiology.
- Stevner et al., 2019. Discovery of key whole-brain transitions and dynamics during human wakefulness and sleep. Nature communications.
- Zucchini et al., 2016. Hidden Markov Models for time series analysis.

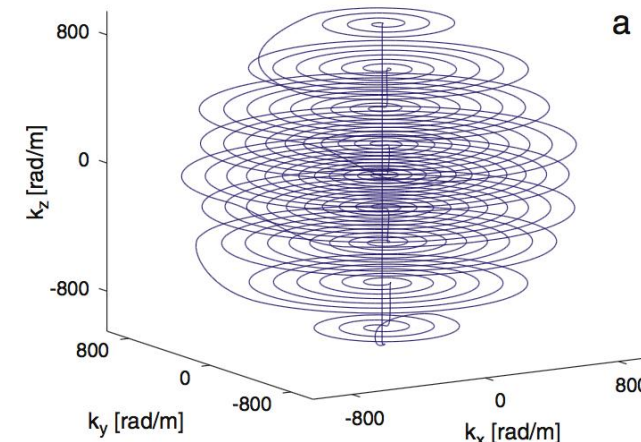
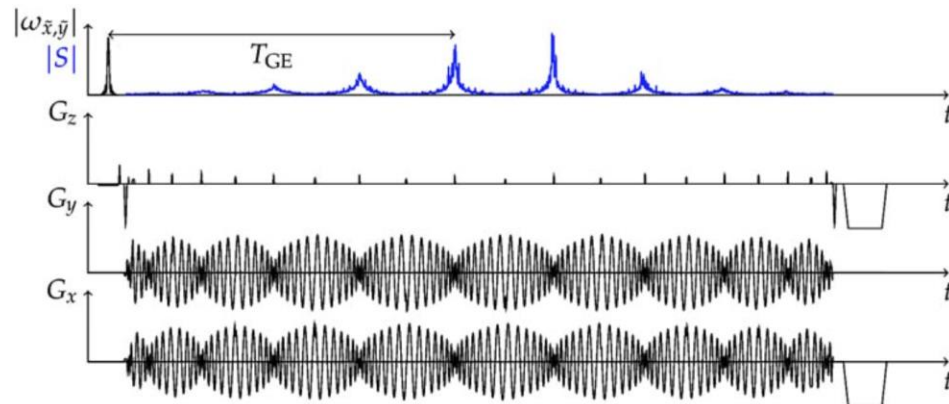


# Introduction

## ***Ultra fast MR – Magnetic resonance encephalography (MREG)***

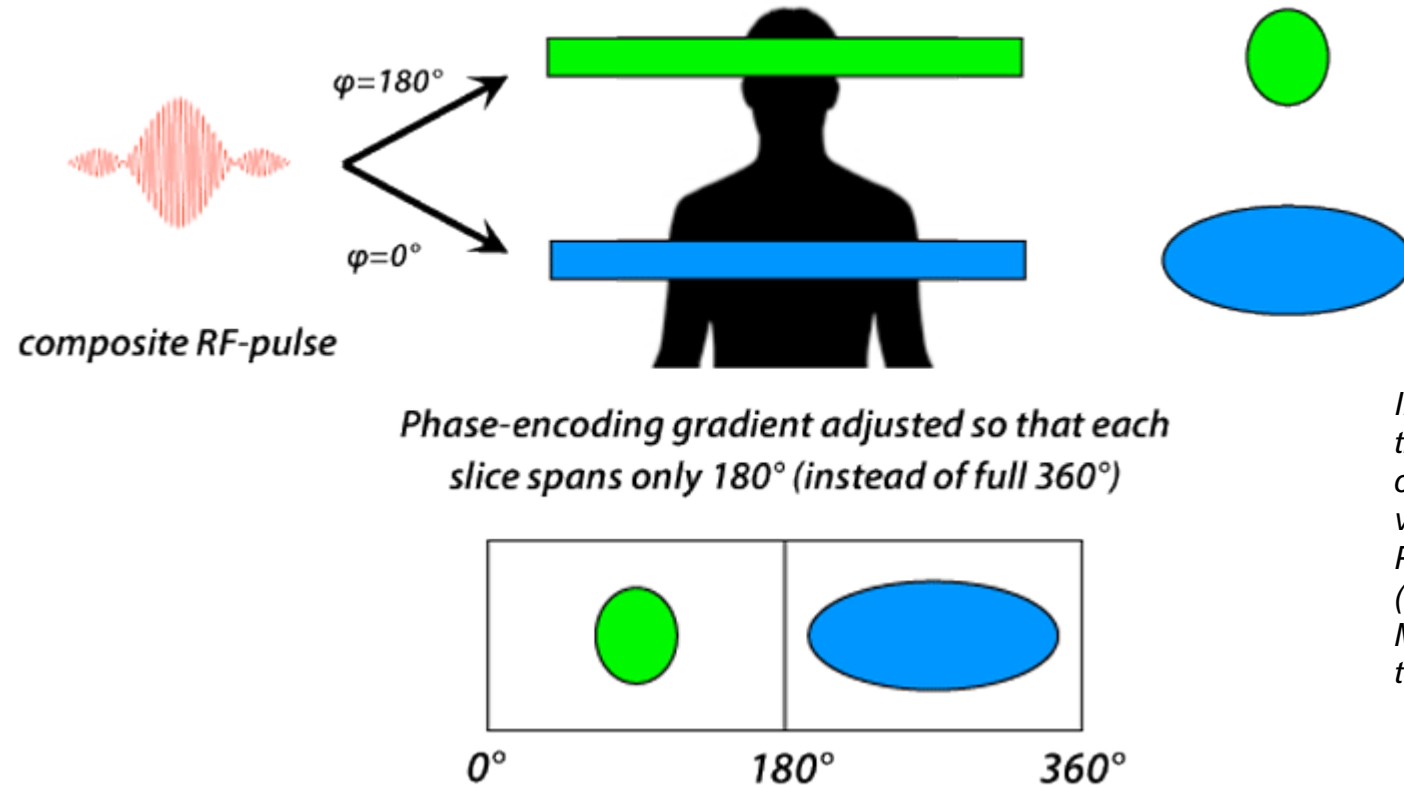
- Images represent part “BOLD” and part “soft tissue movements”

- Whole brain imaging with repetition times  $T_R \leq 100$  ms ( $T_E = 36$  ms,  $25^\circ$  flip angle, approx. 10 images per second) with a spatial resolution of  $\sim 3 \times 3 \times 3$  mm using a  $> 32$ -channel head coil and “*stack of spirals*” sampling in K-space.
- Generates a large amount of data :  $\sim 35$  GB data for 10 min recording
- Data is “K-space under sampled”, which is associated with complex non-linear image reconstruction



J. Assländer et al., NeuroImage, 2013  
Hollingsworth, *Phys Med Biol*, 2015

# Multiband method



*Illustration of the oldest commercial version is GE's POMP ("Phase-Offset MultiPlanar") technique,*

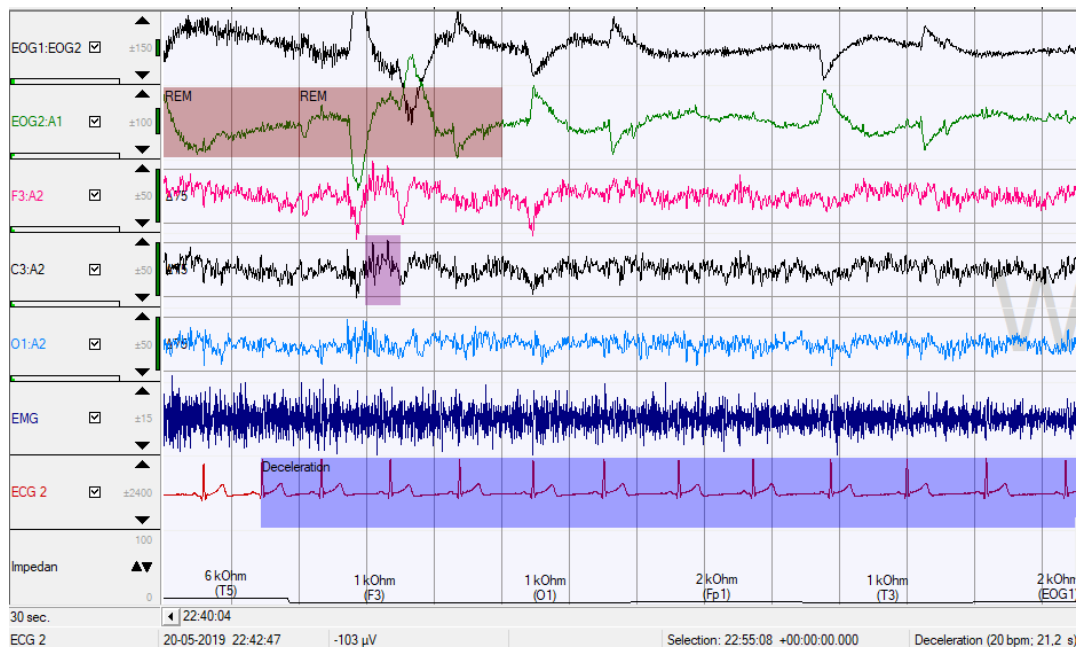
Multiband: An initial complex RF-pulse simultaneously stimulate two or more slices that are encoded using a binary (Hadamard) scheme or view-dependent phase modulation.

The RF- pulse is a multiplex of the individual RF-pulses needed to stimulate each of the two slices, phase shifted from each other so that the resulting images do not overlap

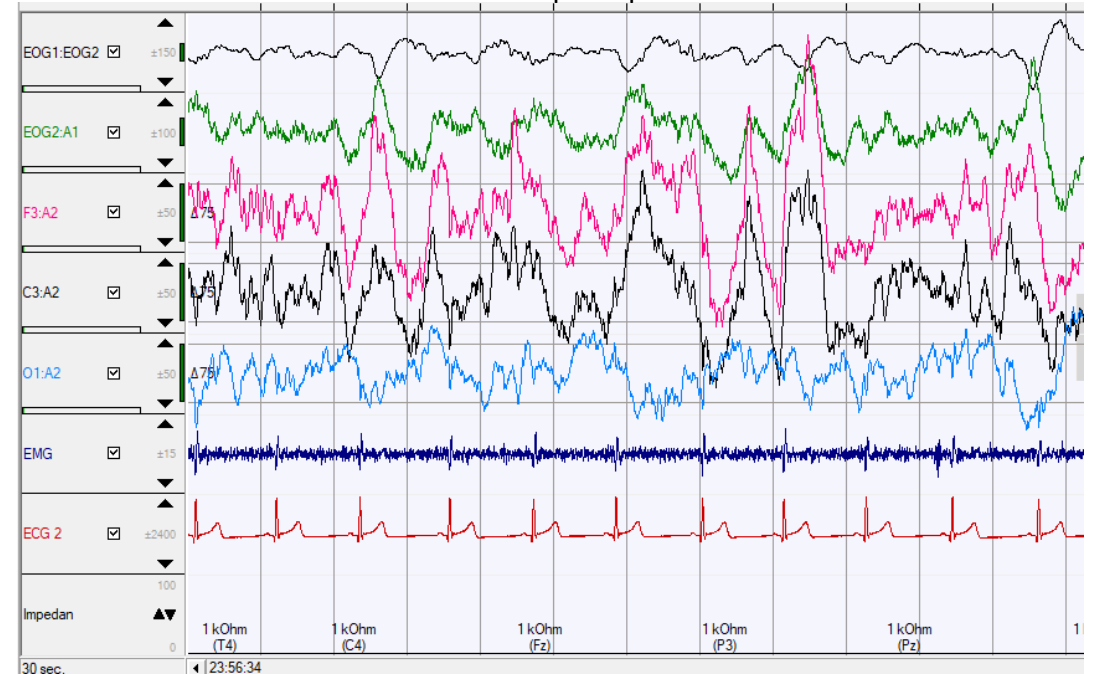
# Sleep 2

- Sleep dynamic function connectivity (dFC) has previously been examined using a sliding windows correlation approach.

PSG: wakefulness



PSG: deep sleep





# Indhold

- Forside: HMM and sleep
- Et par slides om HMM (Markov chains + mixture modeling)
  - Earthquake example
- Et par slides om Sleep (billede af EEG), AASM inddeling
  - Hvor sejt kunne det ikke være at kunne forudsige søvn fra fMRI
  - Referencer fra BOLD correlates study
- Stevner study – mange slides
- Vores data – inkludér MREG studies
- Problemstillinger inklusiv deres drawbacks
- I morgen:
  - Billede af EEG + egne resultater
  - referencer