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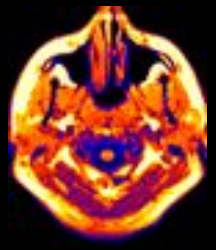
Mount Sinai
MEDICAL CENTER

15th ANNUAL MCI SYMPOSIUM
Session 3: Sleep Disorders and MCI

# Poor Sleep Before Dementia:
## A Risk Factor for Cognitive Decline and Clinical Conversion?



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*University of California, Berkeley*

# Conflict of Interest Disclosures

## Presenter: Bryce Mander

[X] 1. The authors do not have any potential conflicts of interest to disclose, **OR**

[ ] 2. The authors wish to disclose the following potential conflicts of interest:

| Type of Potential Conflict | Details of Potential Conflict |
|---|---|
| Grant/Research Support | |
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| Speakers' Bureaus | |
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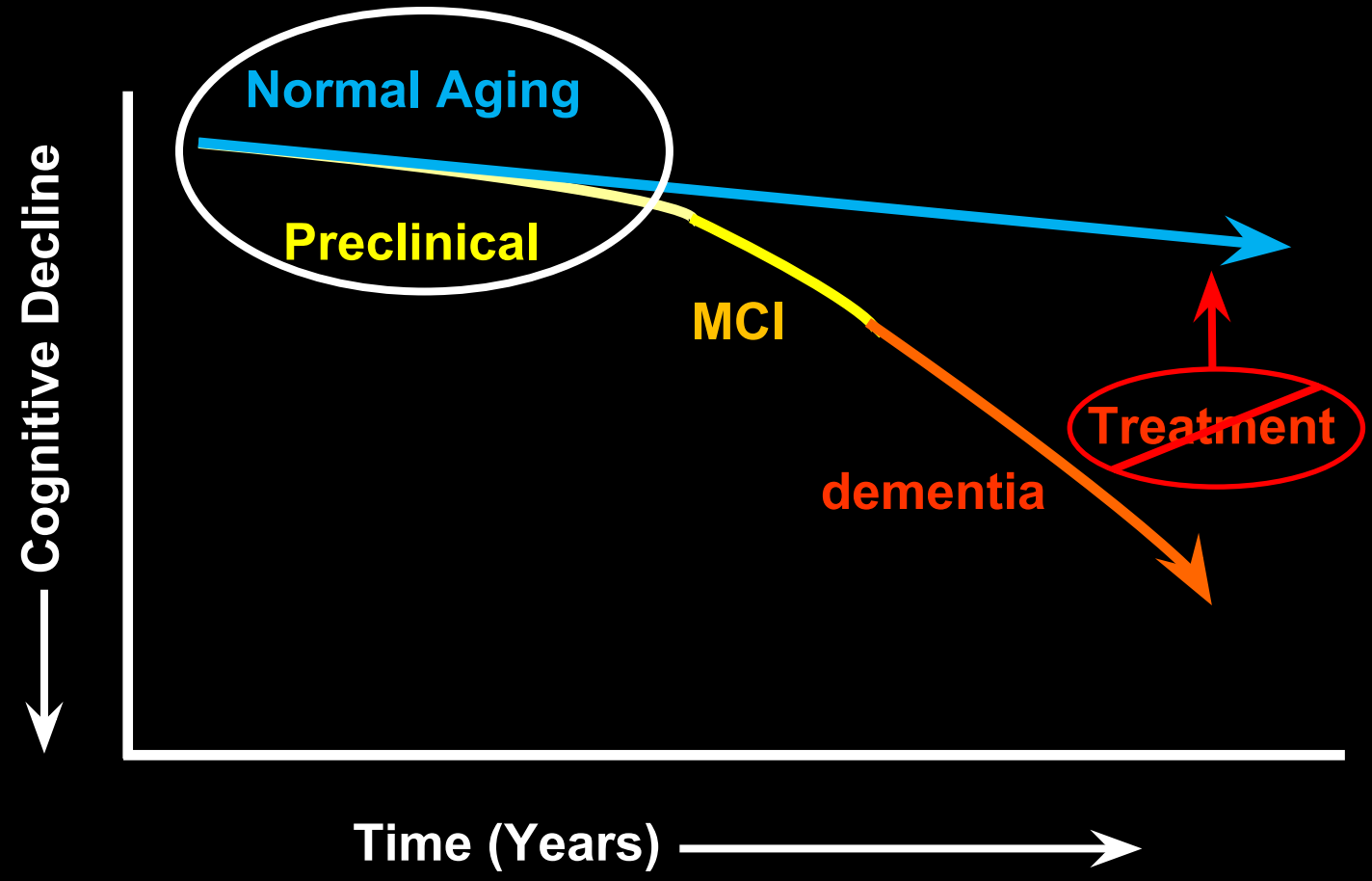
[ ] 3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**

[ ] 4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

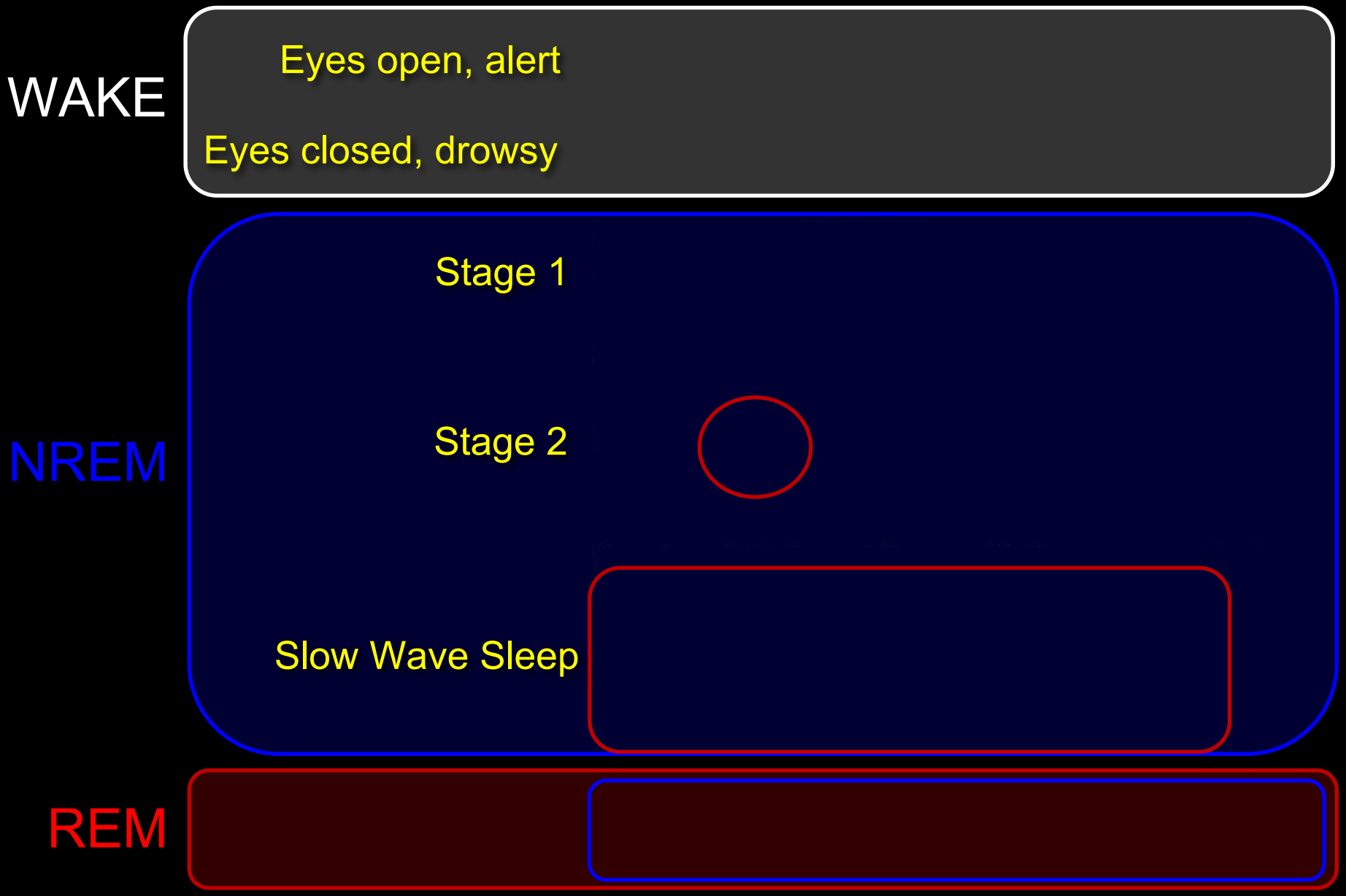
1.
2.
3.

# What Causes Unsuccessful Cognitive Aging?

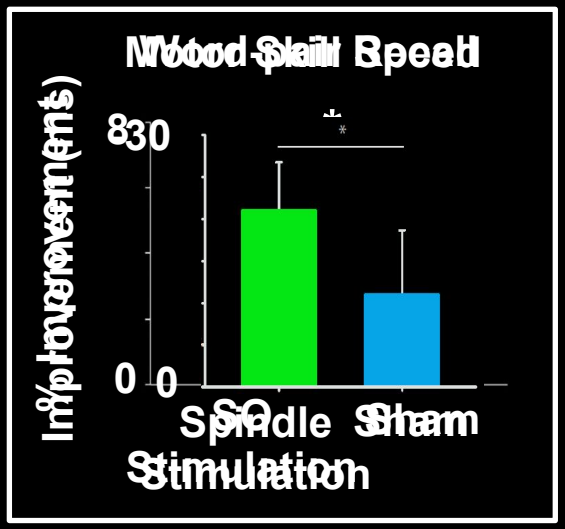



**Could sleep be one factor?**

# EEG changes dramatically with brain state



# Why do we care about NREM slow waves and sleep spindles?







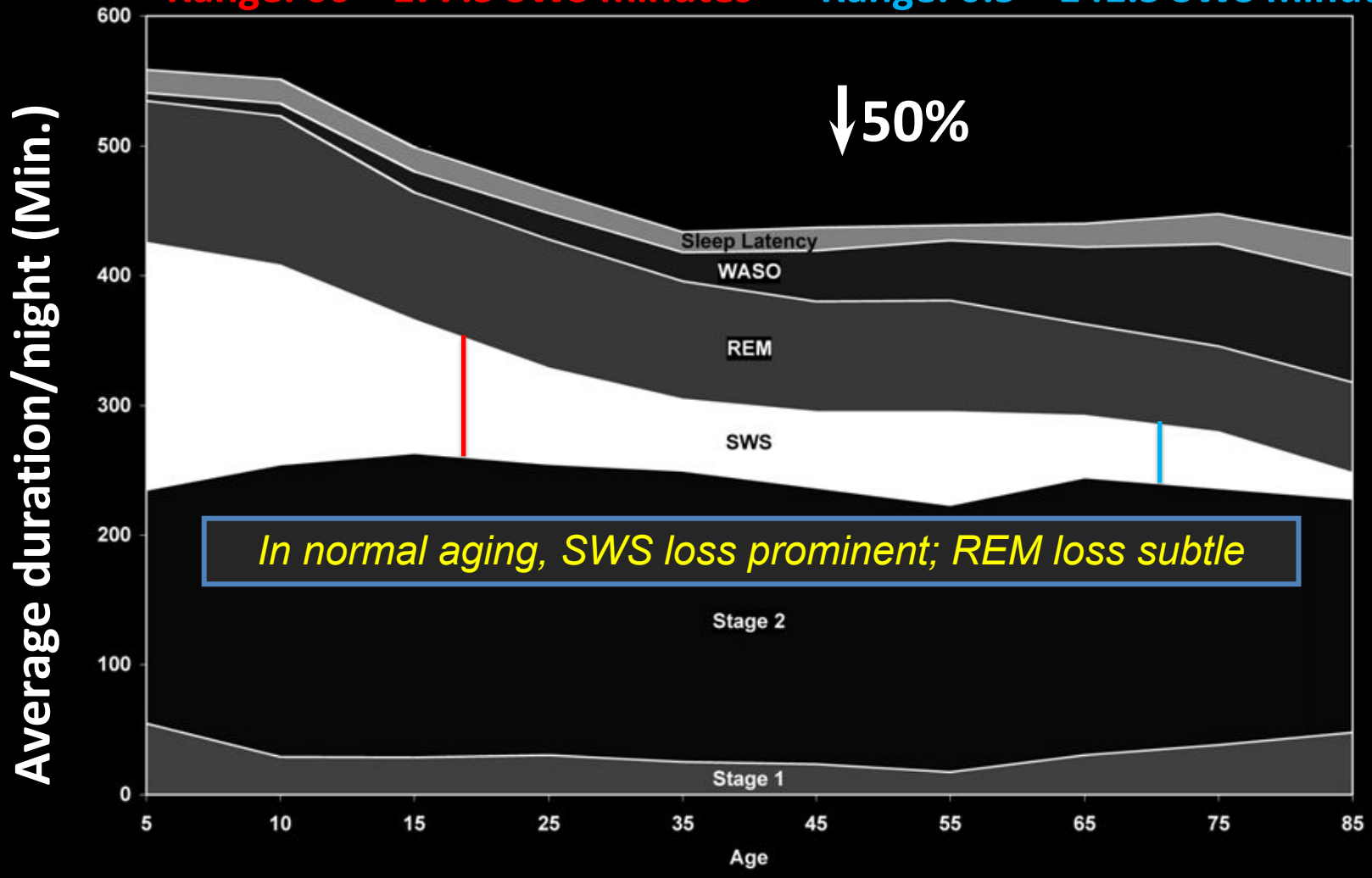
SWS & Slow waves (<1Hz)
- Huber et al, 2004
- Mander et al, 2013, 2015
- Marshall et al, 2004, 2006
- Plihal et al, 1999
- Rasch et al, 2007
- Rudoy et al, 2009
- Westerberg et al, 2015
- Chauvette et al, 2012
- Ladenbauer et al, 2016

Fast sleep spindles (>13Hz)
- Gias et al, 2002
- Fogel et al, 2009
- Saletin et al, 2011
- Nishida et al, 2007
- Morin et al, 2008
- Barakat et al, 2011, 2013
- Fogel et al, 2013
- Lustenberger et al, 2016
- Mander et al, 2016 under revision

# Sleep changes across the lifespan

**Young Adults (18-23y.o.)**
**Range: 60—177.5 SWS minutes**

**Older Adults (62-81y.o.)**
**Range: 0.5—141.5 SWS minutes**

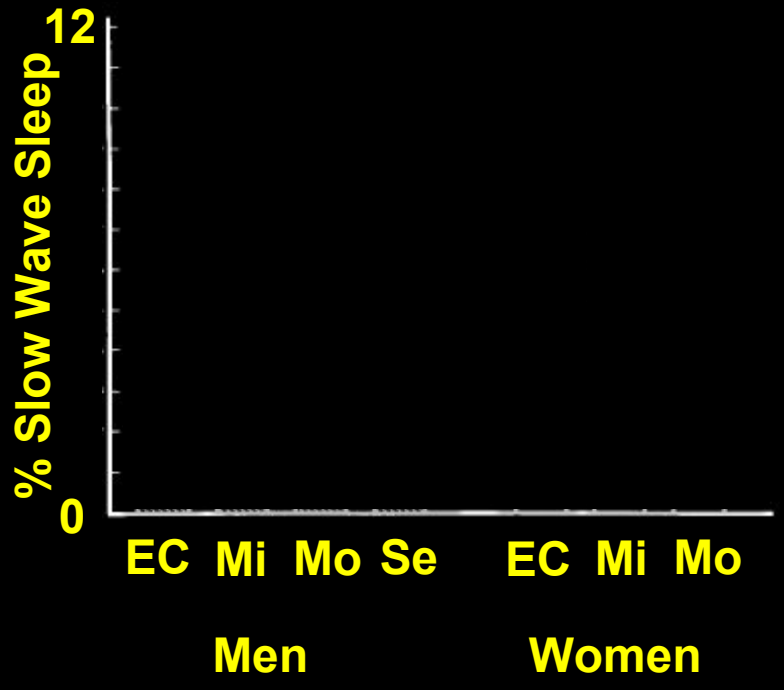


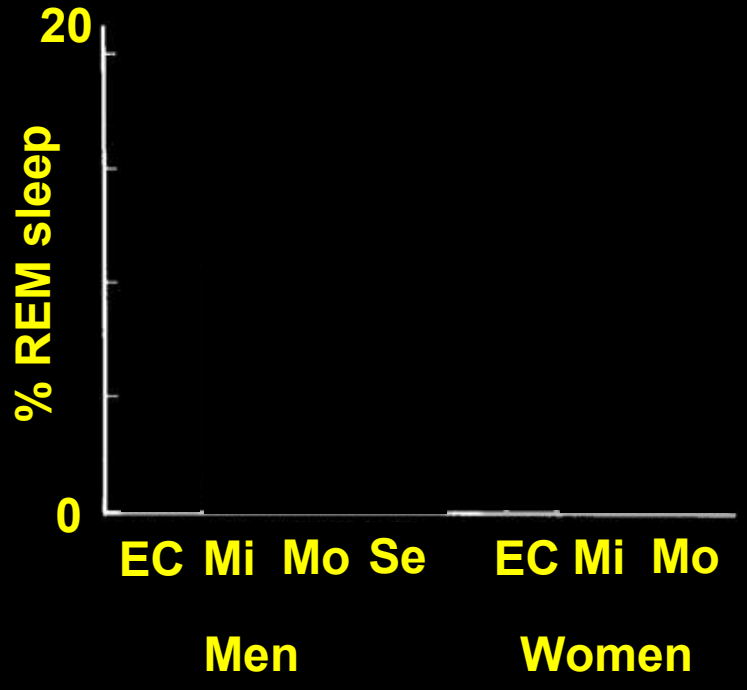

*In normal aging, SWS loss prominent; REM loss subtle*

Ohayon et al, 2004

# Sleep in Alzheimer's Disease

EC – Elderly Control
Mi – Mild AD
Mo – Moderate AD
Se – Severe AD

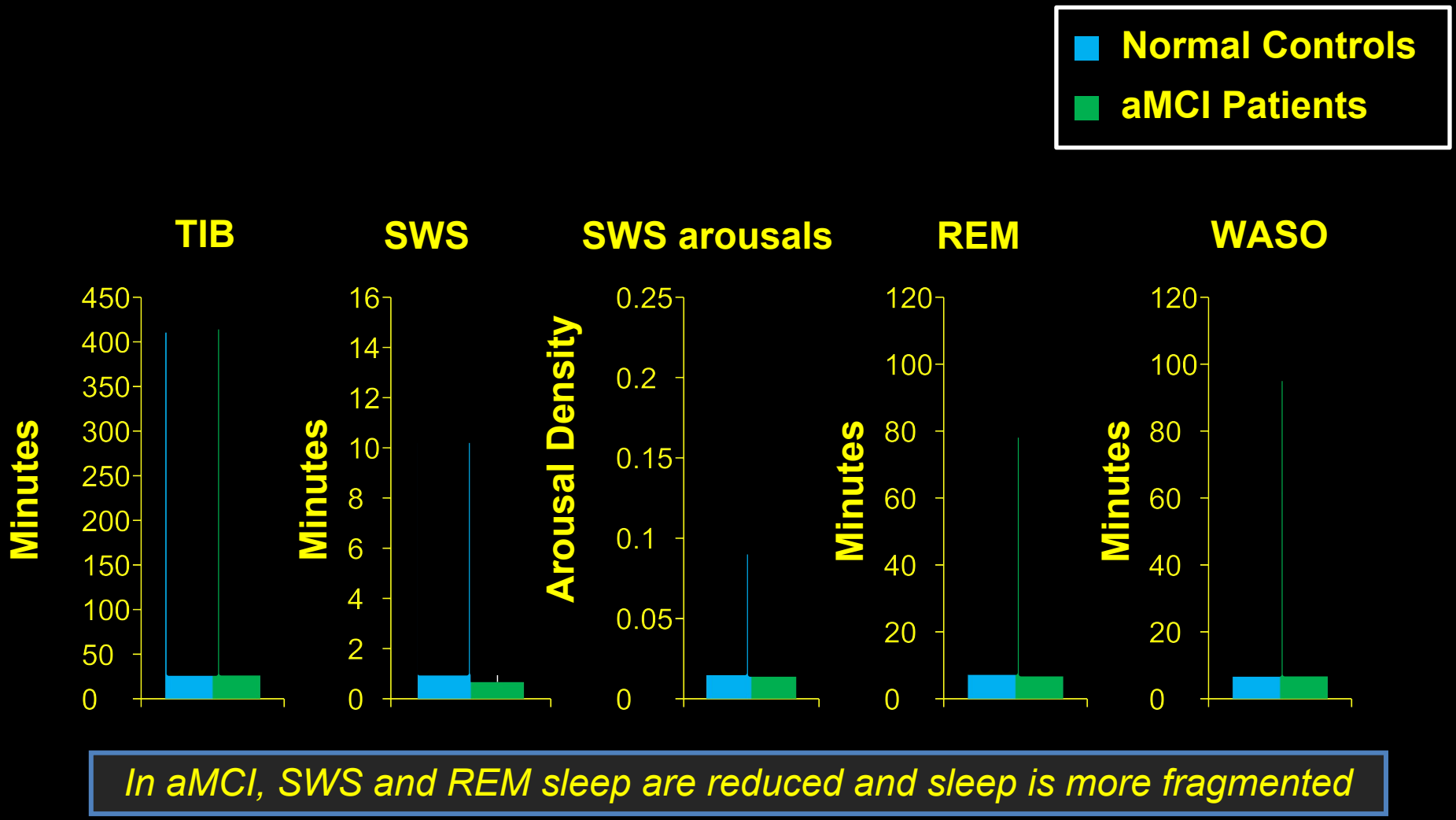



*Lost SWS and REM sleep replaced with sleep fragmentation and more time awake*

From Prinz et al, 1982

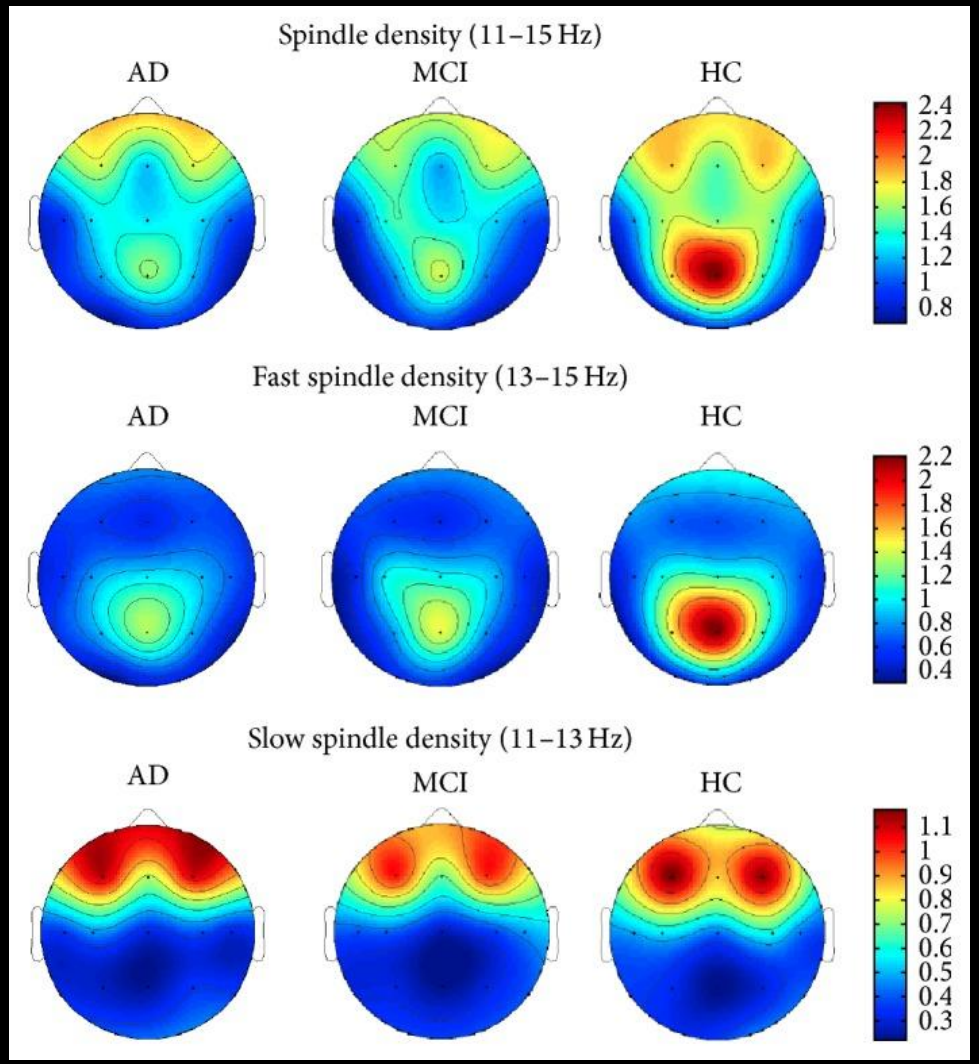
# Sleep in Mild Cognitive Impairment




*In aMCI, SWS and REM sleep are reduced and sleep is more fragmented*

**Adapted from Westerberg et al, 2012 and Hita-Yanez et al, 2012**

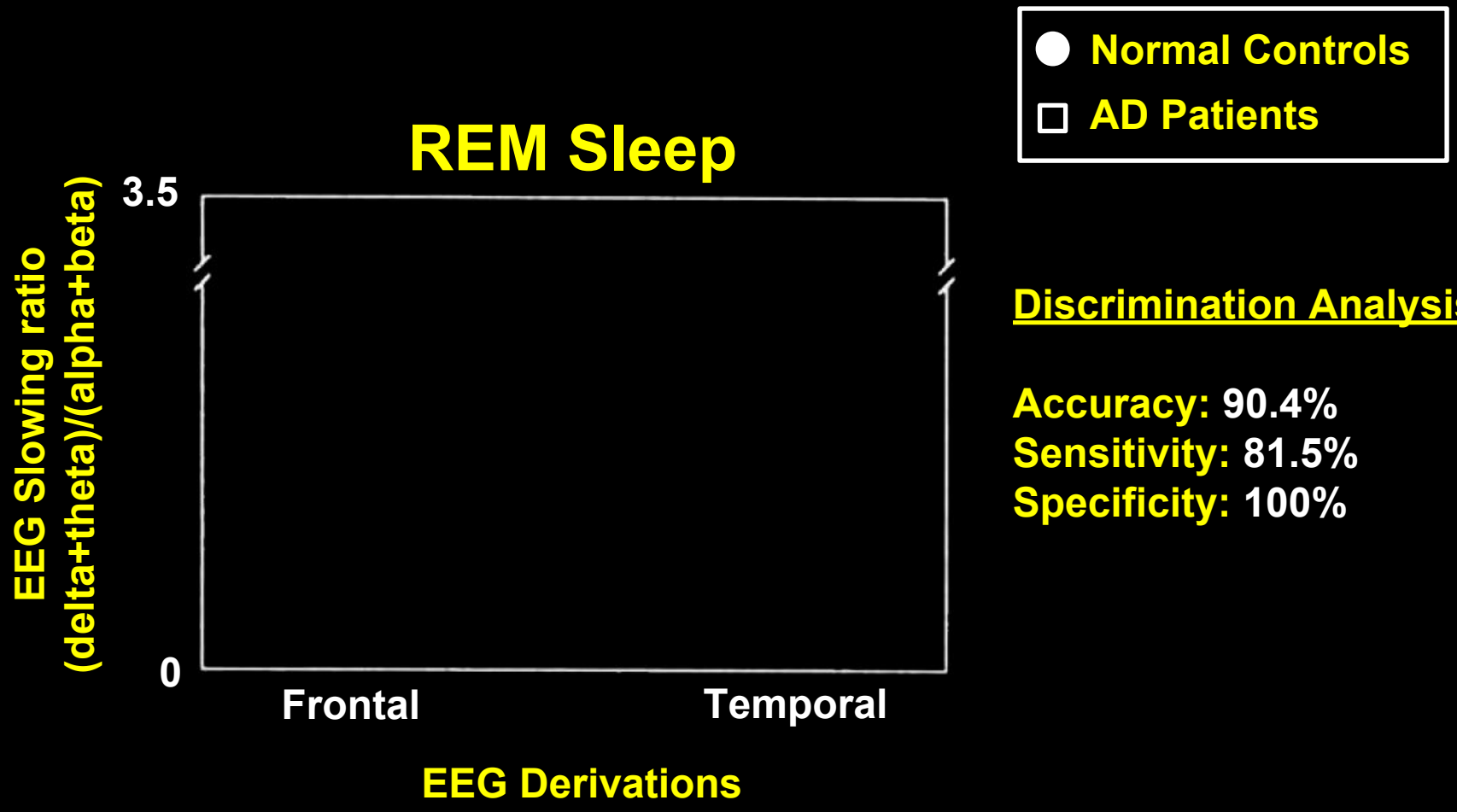
# Sleep spindles in AD and MCI


*AD & MCI patients have fewer parietal fast sleep spindles (13-15Hz)*

**From Rauchs et al, 2008**
**And Gorgoni et al, 2016**

# quantitative REM sleep EEG in AD

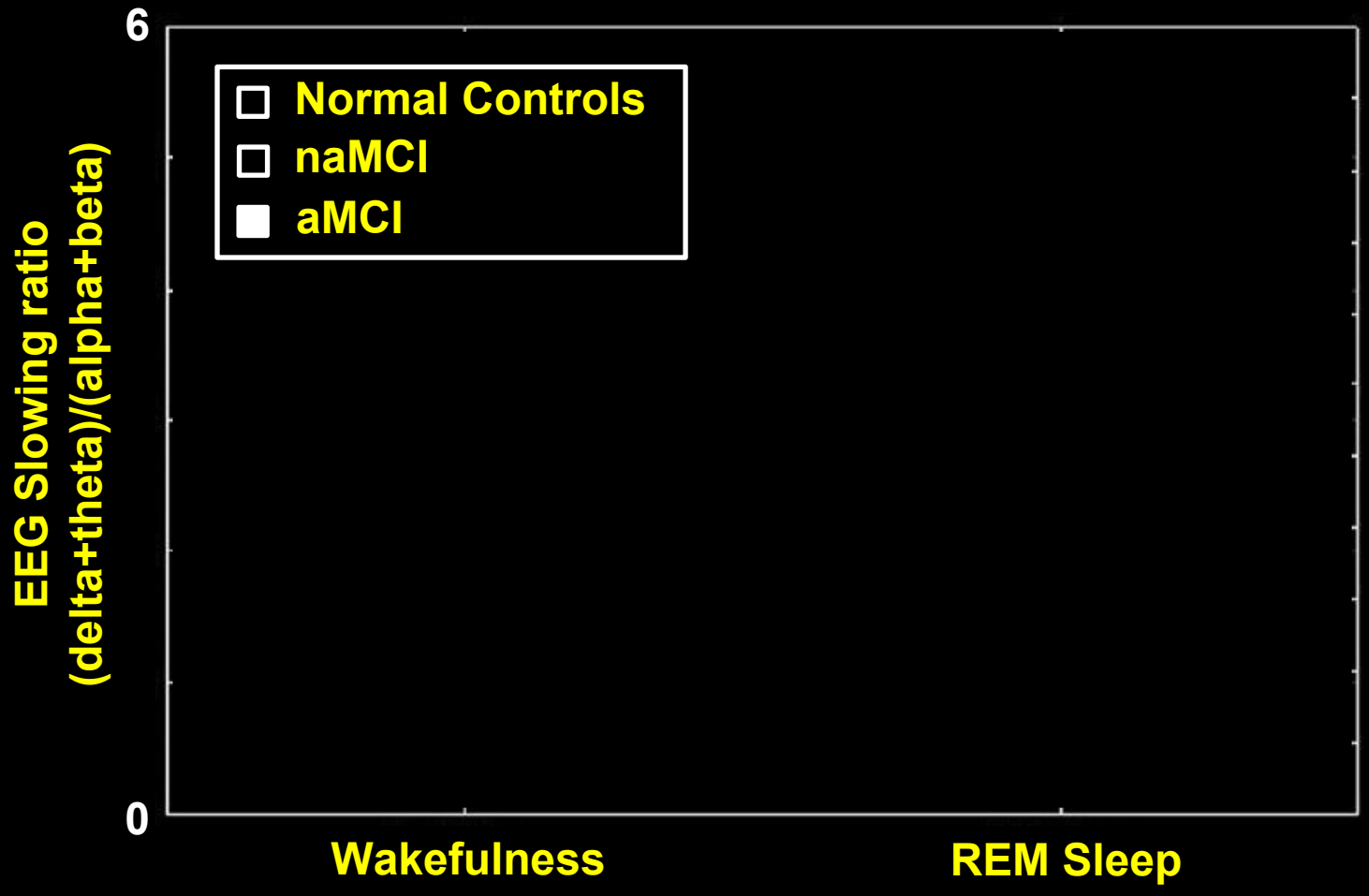



**Discrimination Analysis**

**Accuracy:** 90.4%
**Sensitivity:** 81.5%
**Specificity:** 100%

From Hassainia et al, 1997

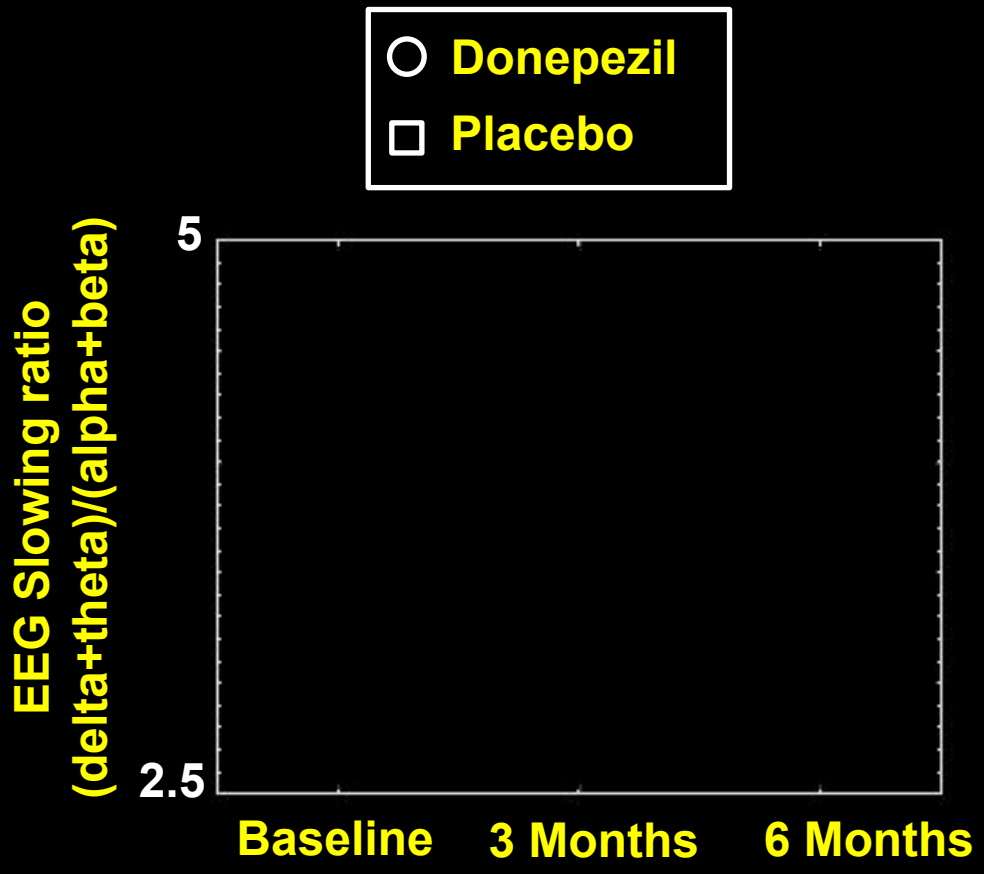
# quantitative REM sleep EEG in MCI

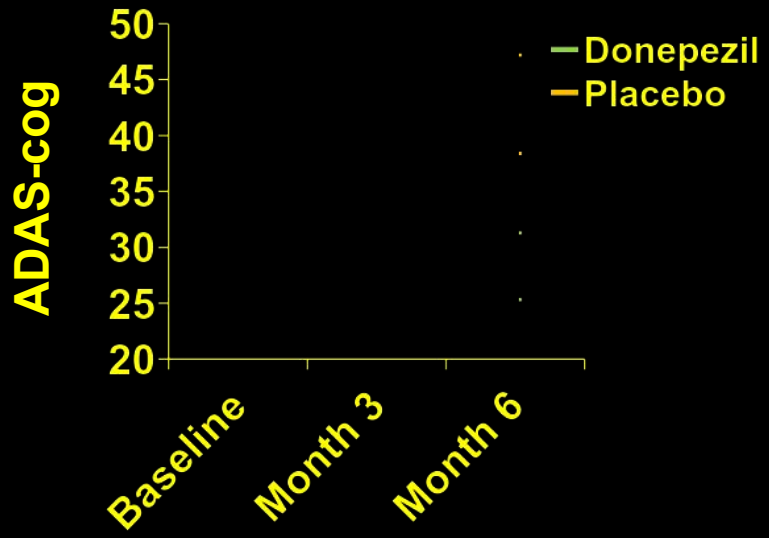



*aMCI differs from Controls and naMCI*

From Brayet et al, 2015

# Mechanism of REM EEG slowing

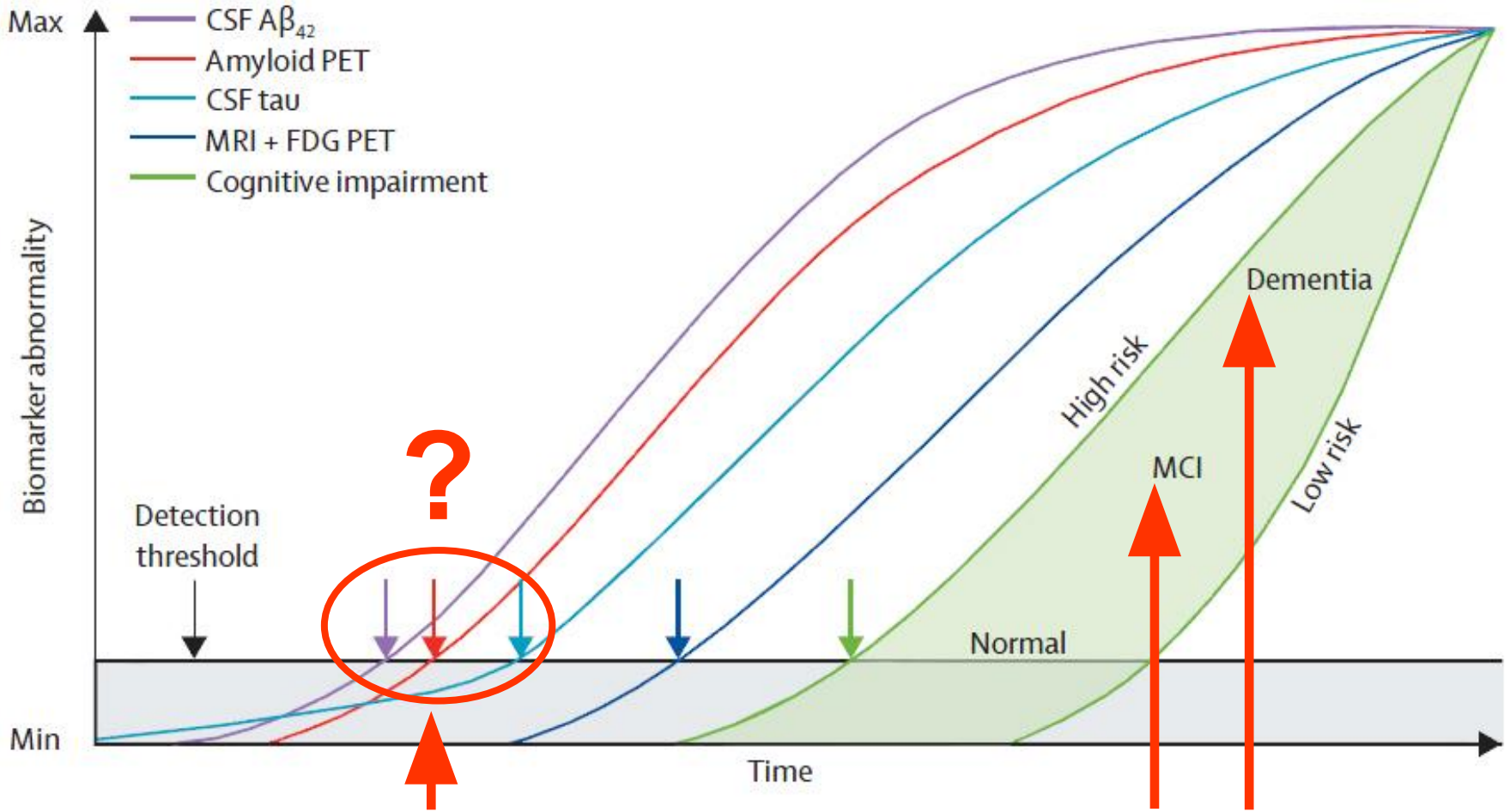



*ACh system degeneration likely cause; linked to cognitive decline?*

From Moraes et al, 2006

# The Cascade Hypothesis of Alzheimer's Disease



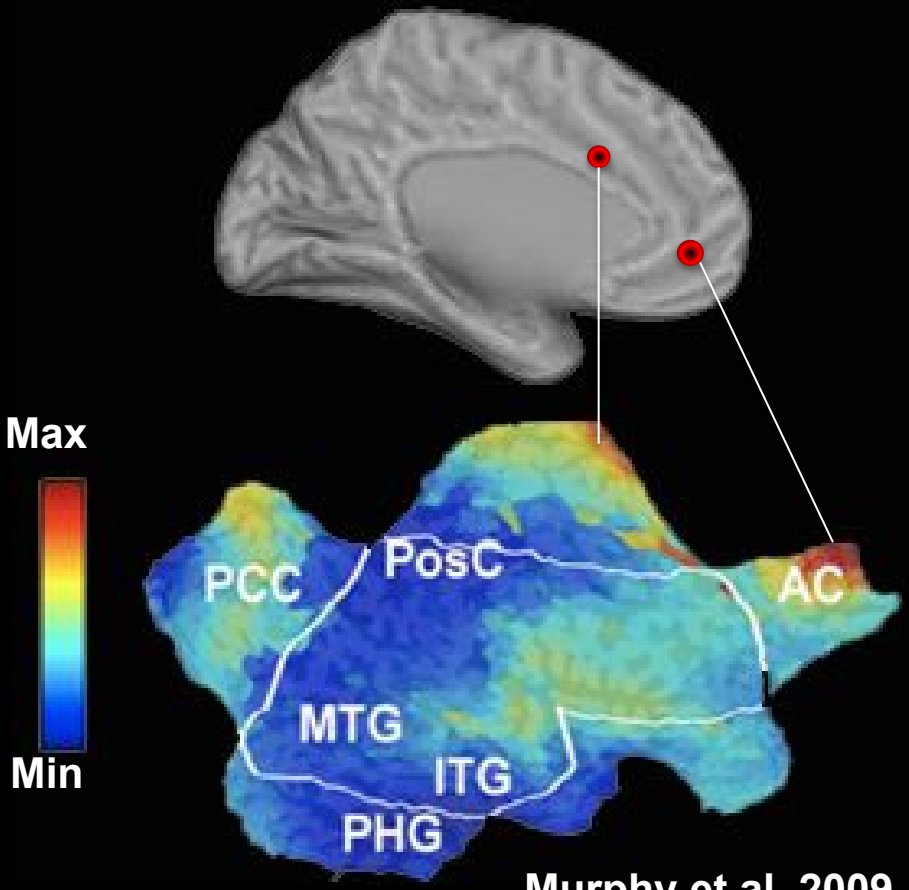

From Jack et al, 2013

# Aβ and NREM slow waves before MCI?

**β-amyloid pathology**

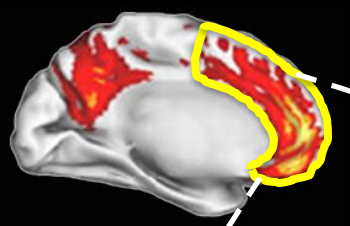
Buckner et al, 2005

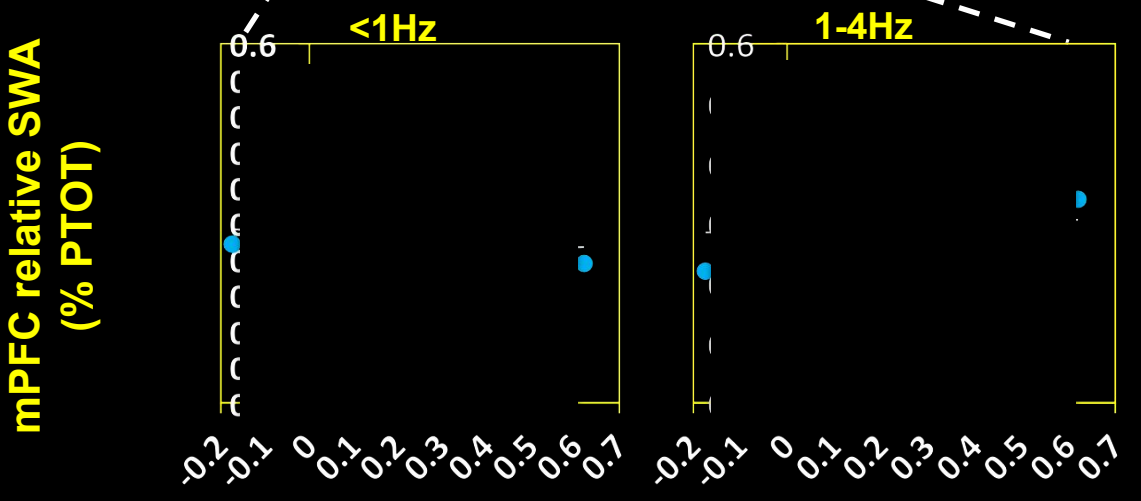
**Cortical generators of NREM slow waves**

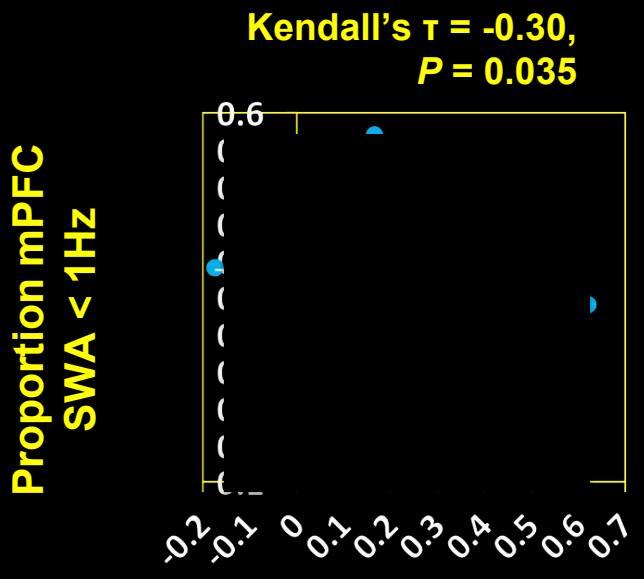



Murphy et al, 2009

# Aβ effects on SWA in healthy controls






**ANCOVA**

**Frequency: *P* = 0.009**

**mPFC PIB DVR: *P* = 0.087**

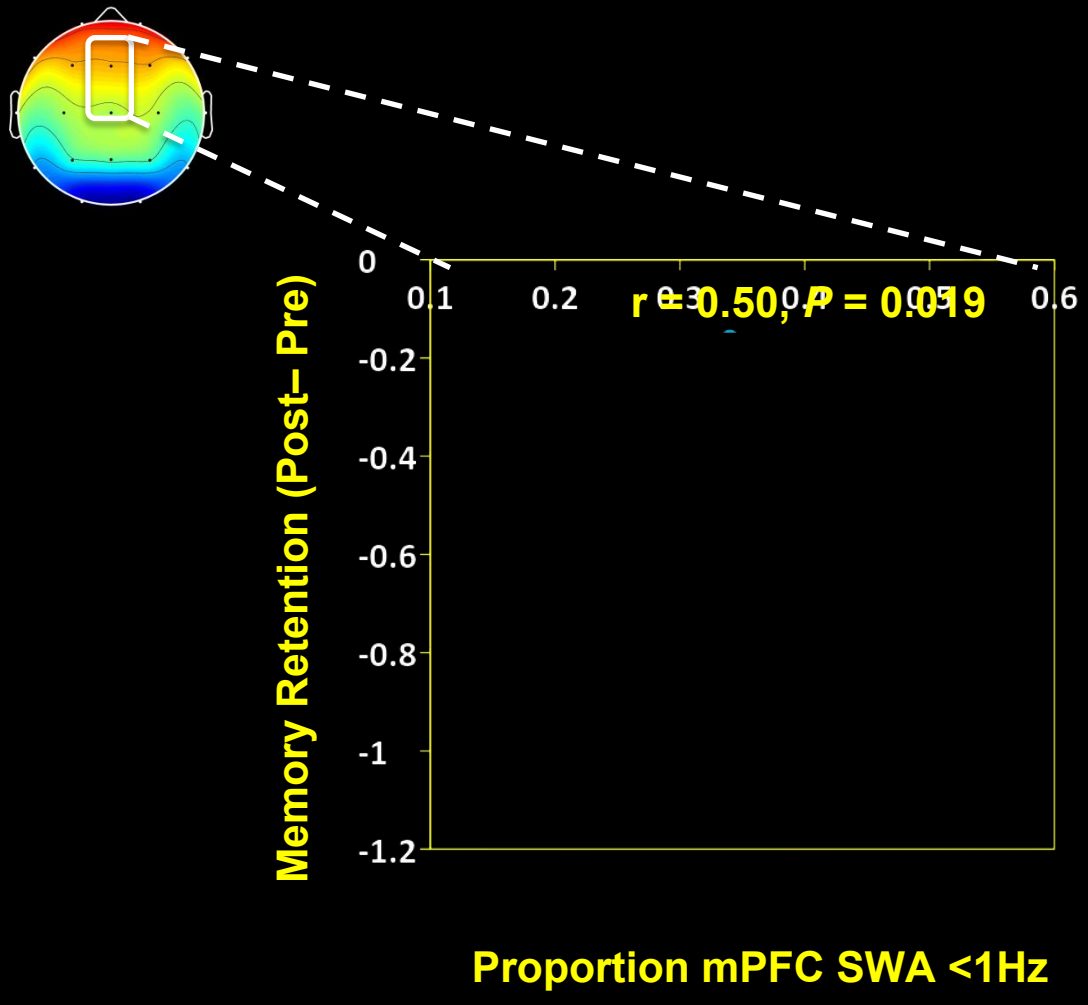
**Frequency×mPFC PIB DVR: *P* = 0.032**

*Aβ deposition disrupts SWA <1Hz within mPFC*

**From Mander et al, 2015**

# Preliminary Findings:
# Is this NREM SWA signature a biomarker?

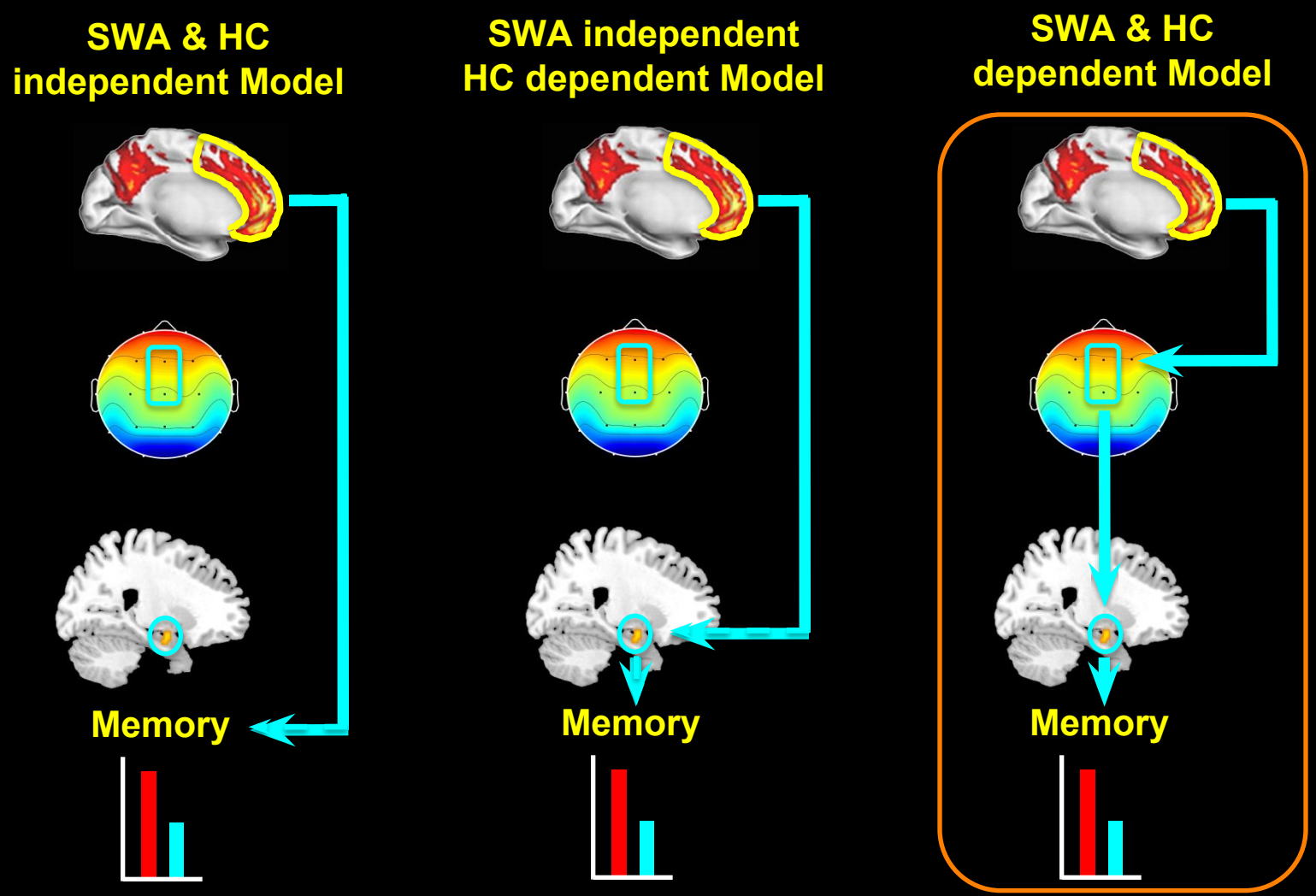
# Does SWA explain Aβ impact on memory?




*mPFC SWA <1Hz predicts overnight memory retention*

**From Mander et al, 2015**

# Path Analysis Models




*mPFC Aβ influences memory through SWA*

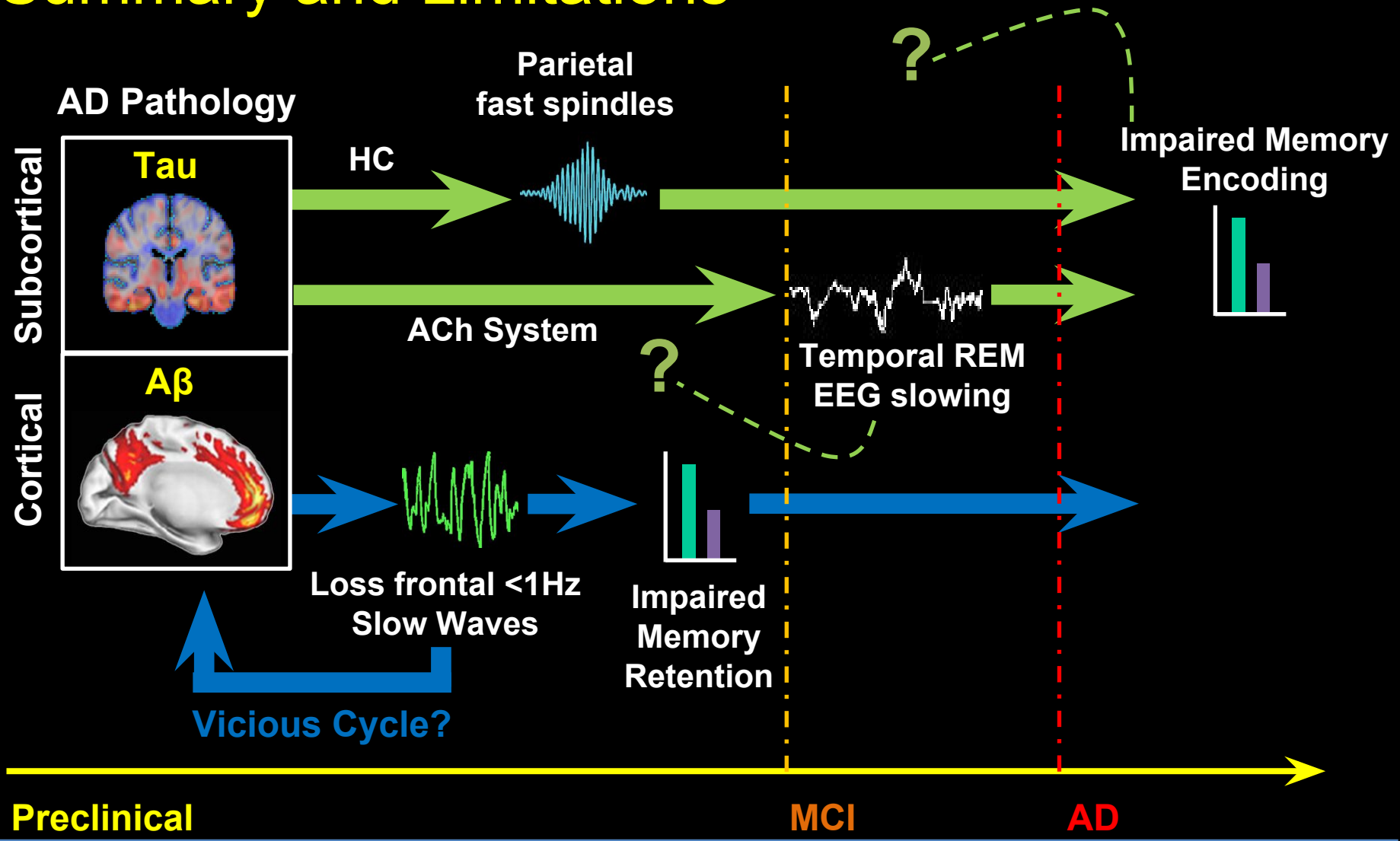
From Mander et al, 2015

# Preliminary Findings:
# Impact of Aβ and Tau on NREM SW density

# Preliminary Findings:
# Impact of Aβ and Tau on NREM sleep spindles

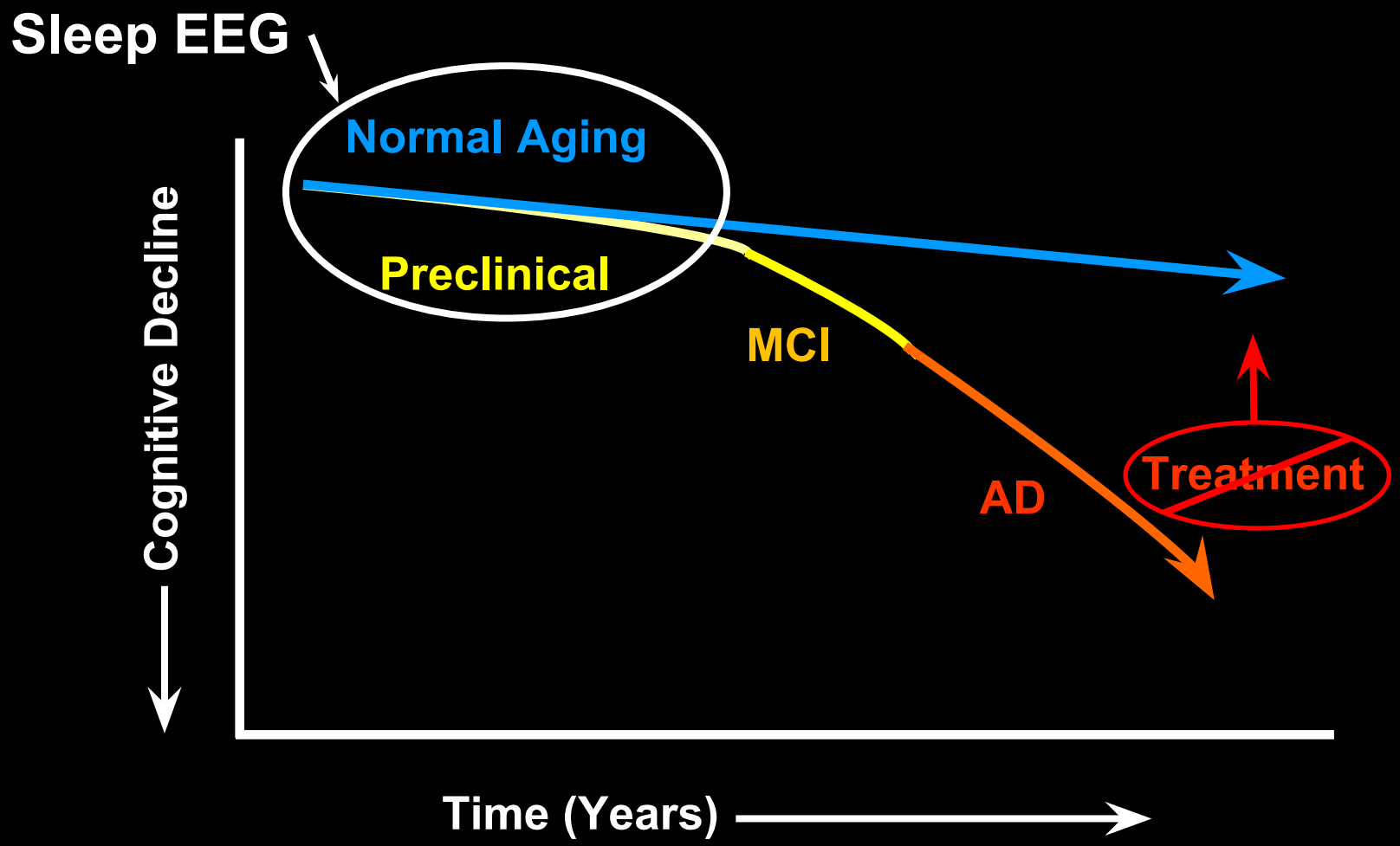
# Preliminary Findings:
# Impact of Aβ and Tau on NREM sleep spindles

# Summary and Limitations




1) *Longitudinal data with AD biomarkers, PSG, and cognition limited*
2) *No studies have used sleep stimulation in MCI, AD patients or at risk populations*
3) *Understanding of mechanisms limited*

# Could Sleep EEG aid early detection and prevention?



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Sleep Well… !

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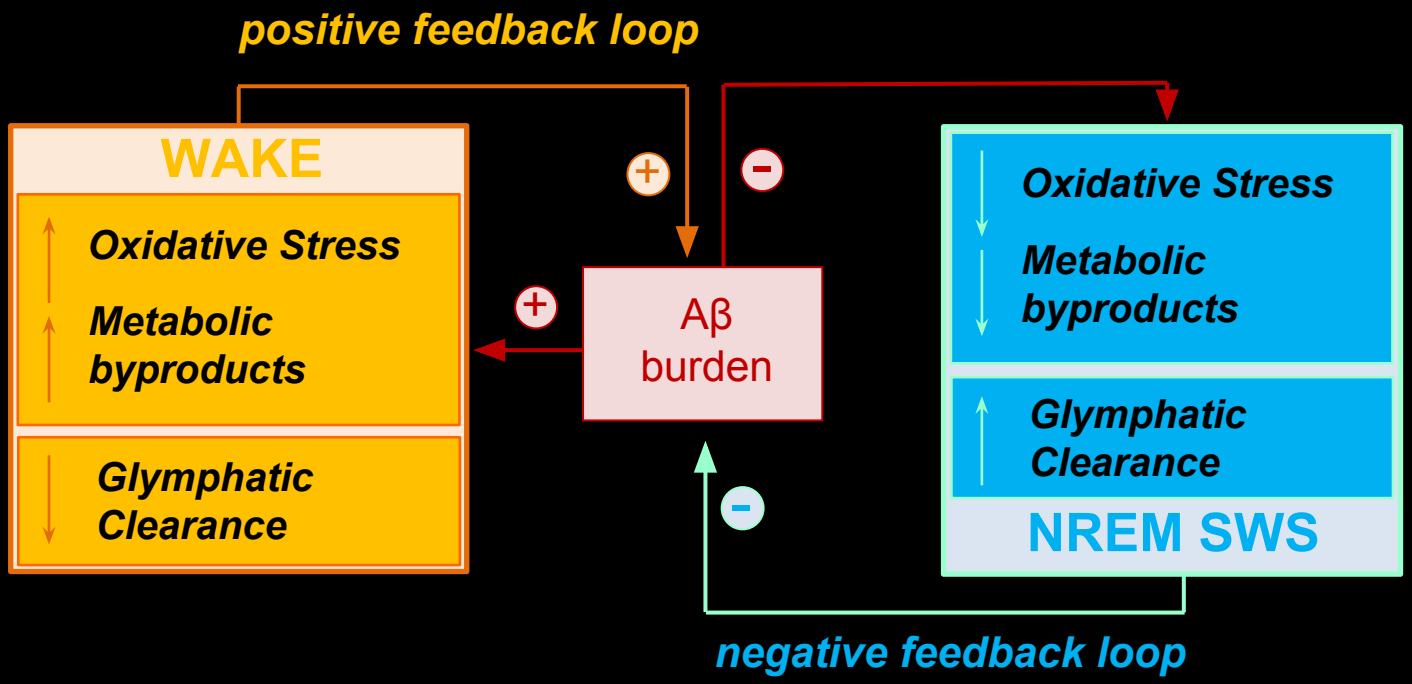
# EXTRA SLIDES

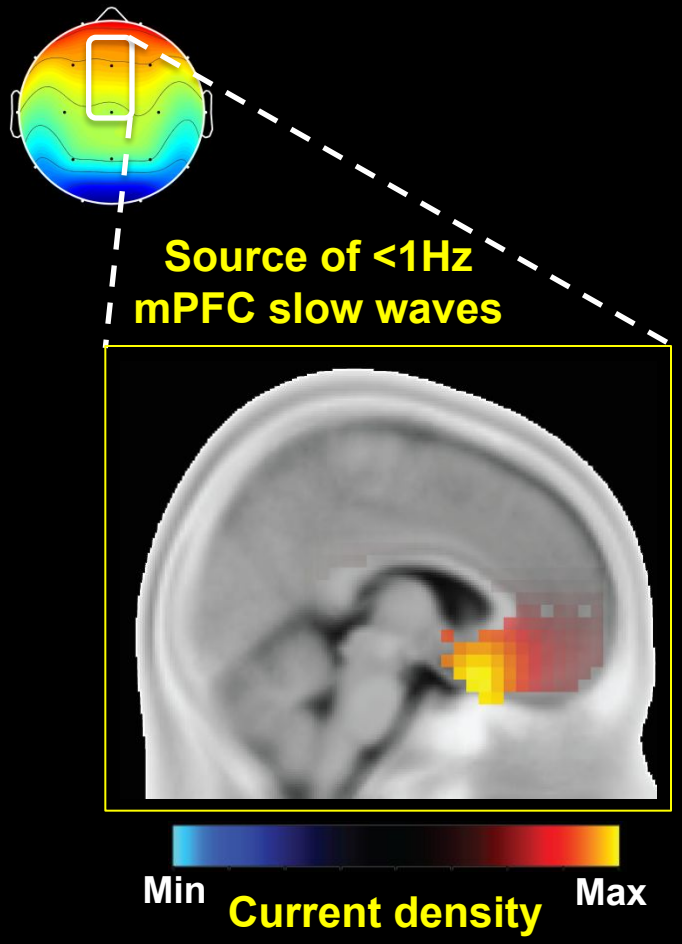
# Aβ and Sleep: Hypothetical Mechanisms




***BUT…What about Tau?***

From Mander et al, 2016

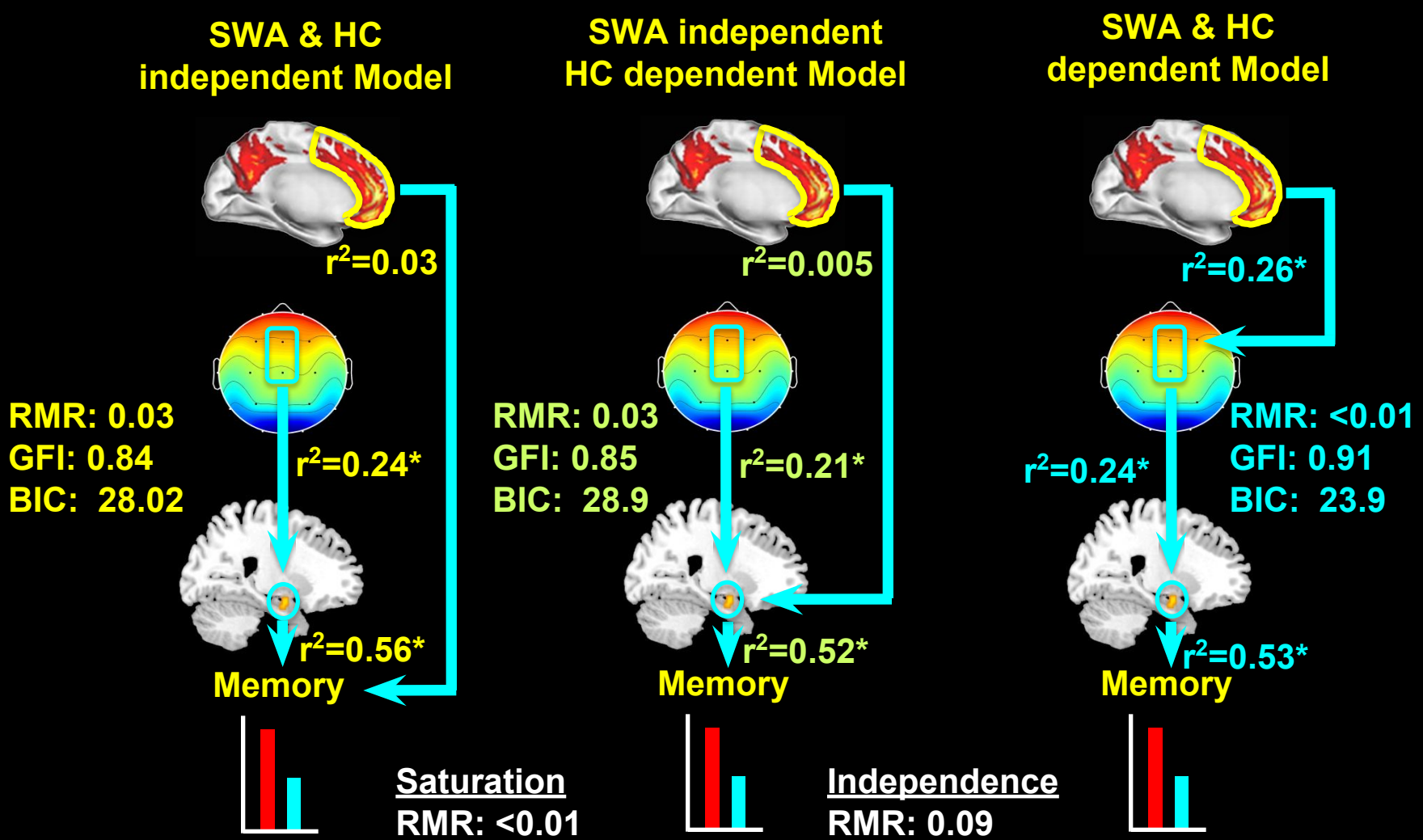
# Source of NREM SW <1Hz




*CZ and FZ Slow waves <1Hz sourced to mPFC*

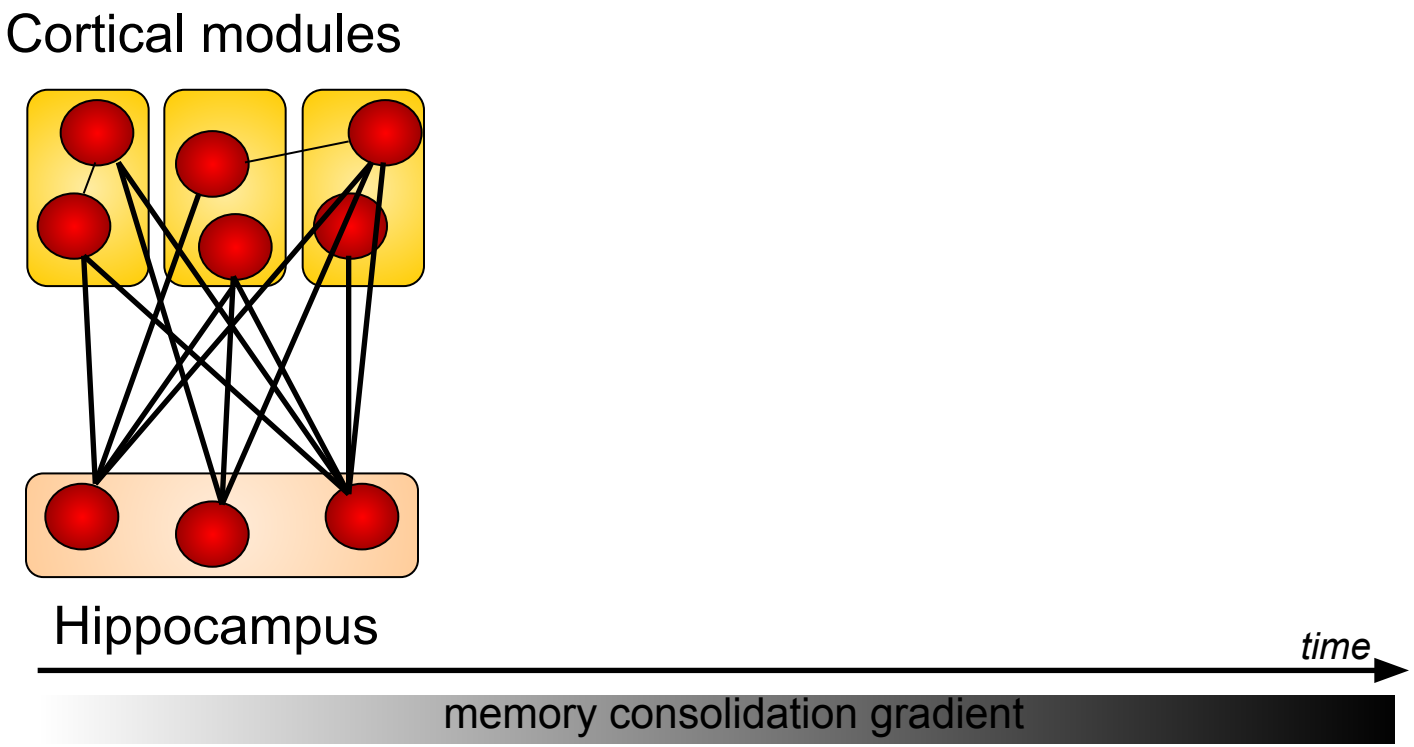
**From Mander et al, 2015**

# Path analysis models details

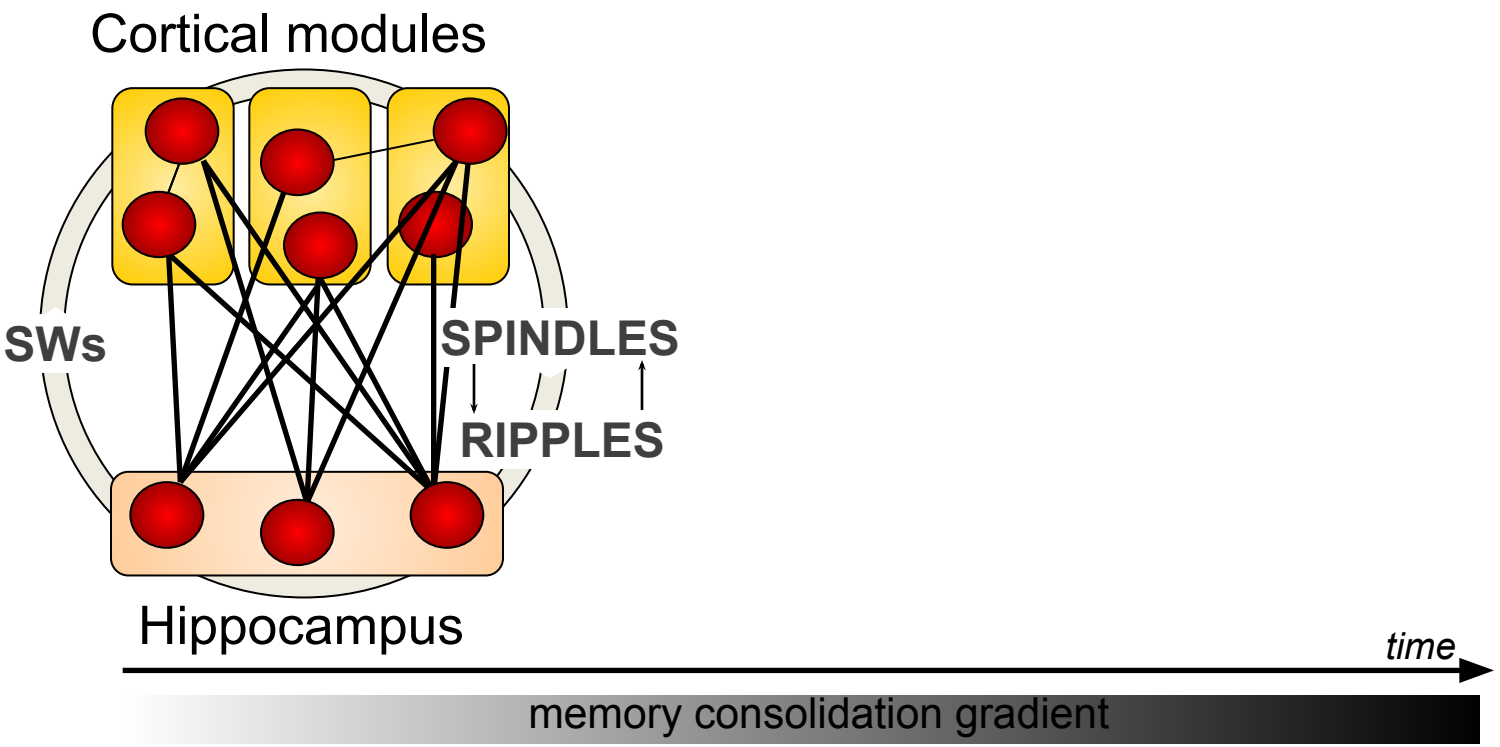



From Mander et al, 2015

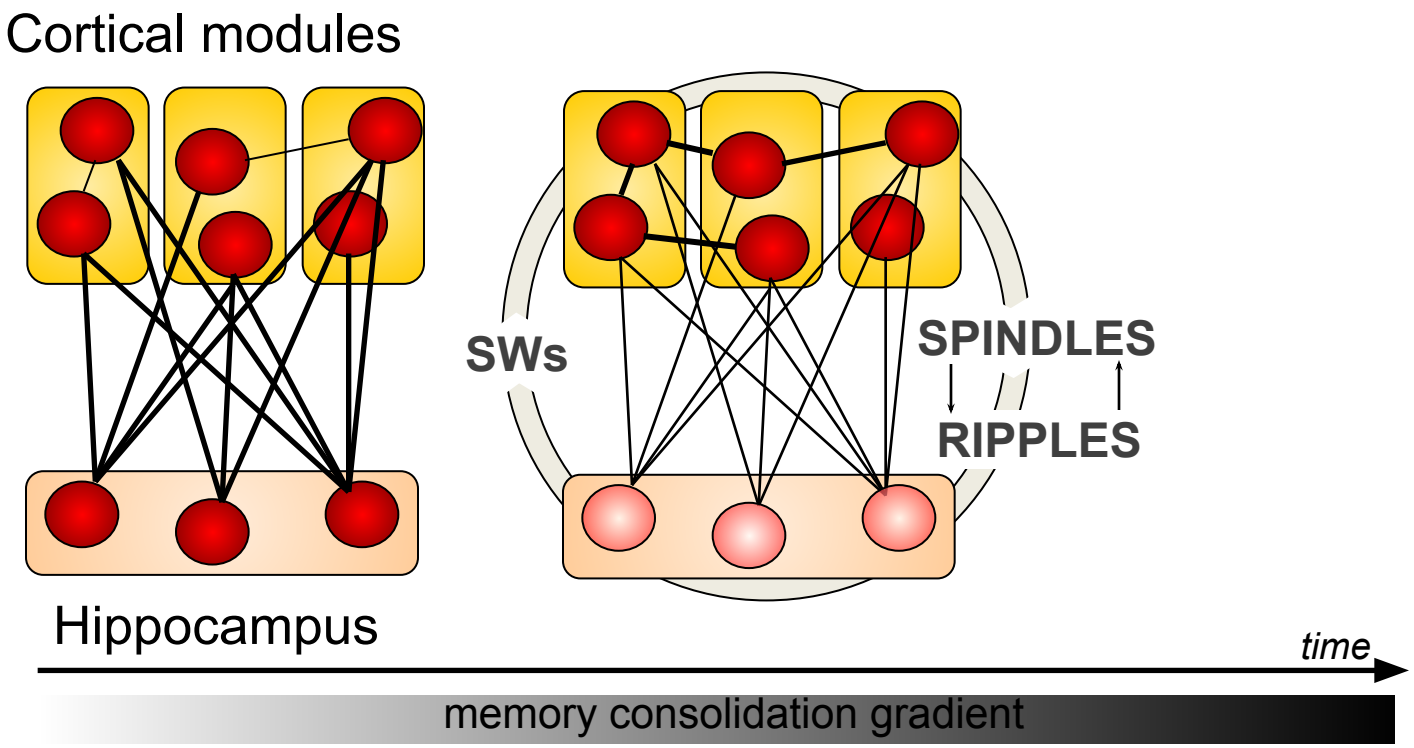
# Hippocampal-Neocortical Model of Memory Processing



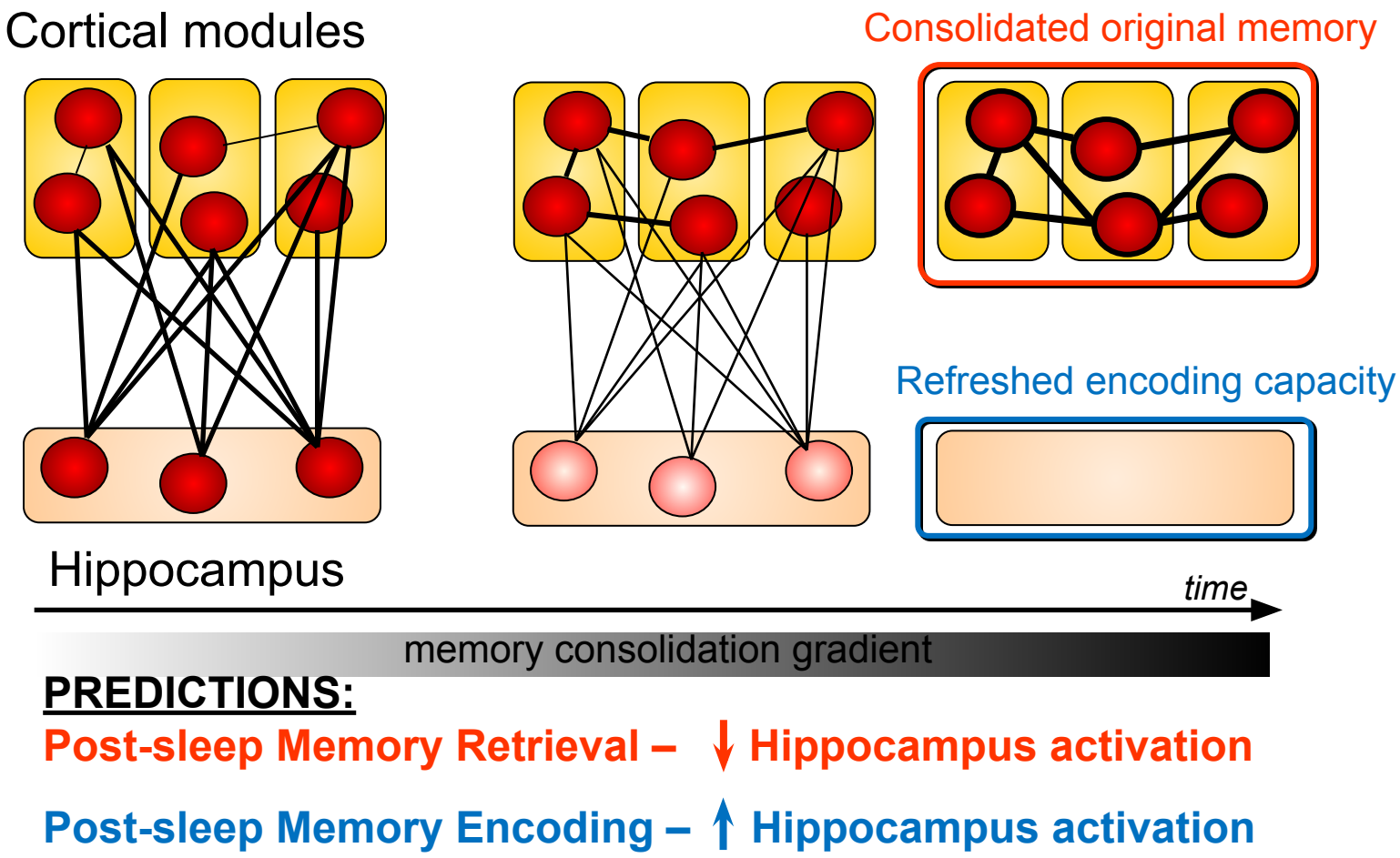
# Hippocampal-Neocortical Model of Memory Processing



# Hippocampal-Neocortical Model of Memory Processing

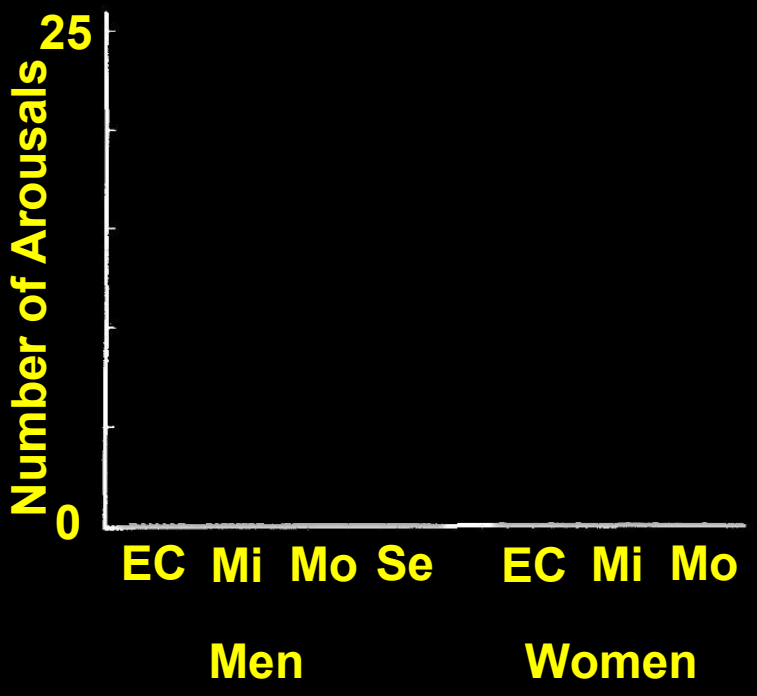


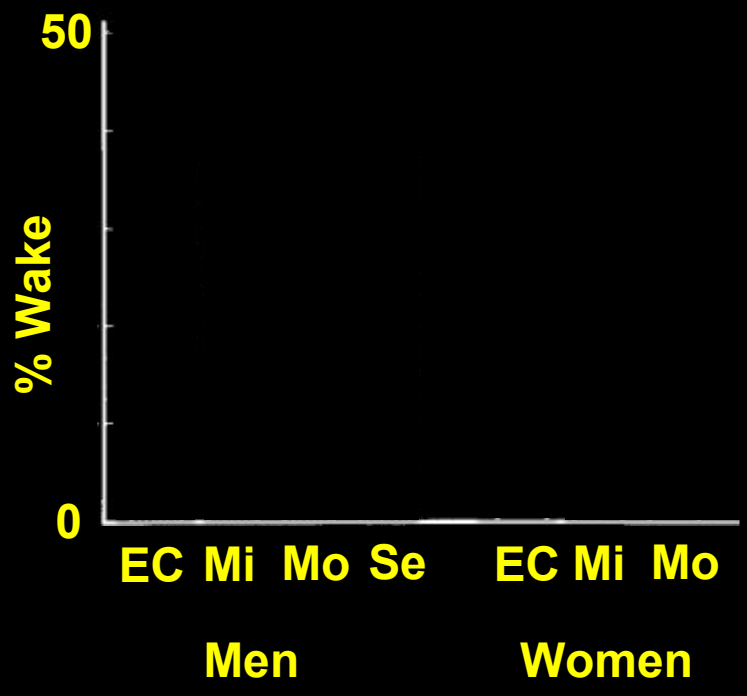
# Hippocampal-Neocortical Model of Memory Processing



# Sleep in Alzheimer's Disease

EC – Elderly Control
Mi – Mild AD
Mo – Moderate AD
Se – Severe AD



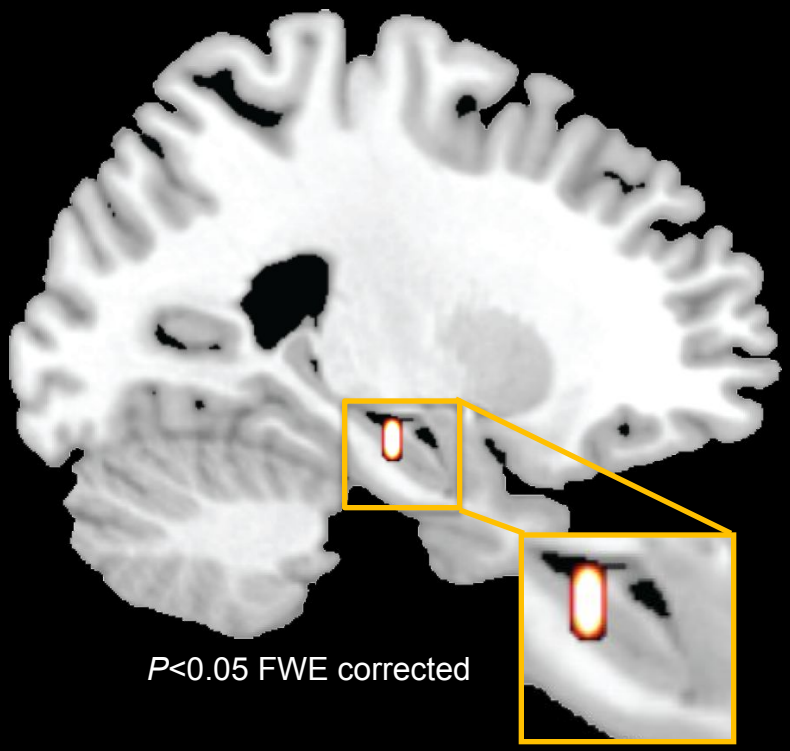

From Prinz et al, 1982

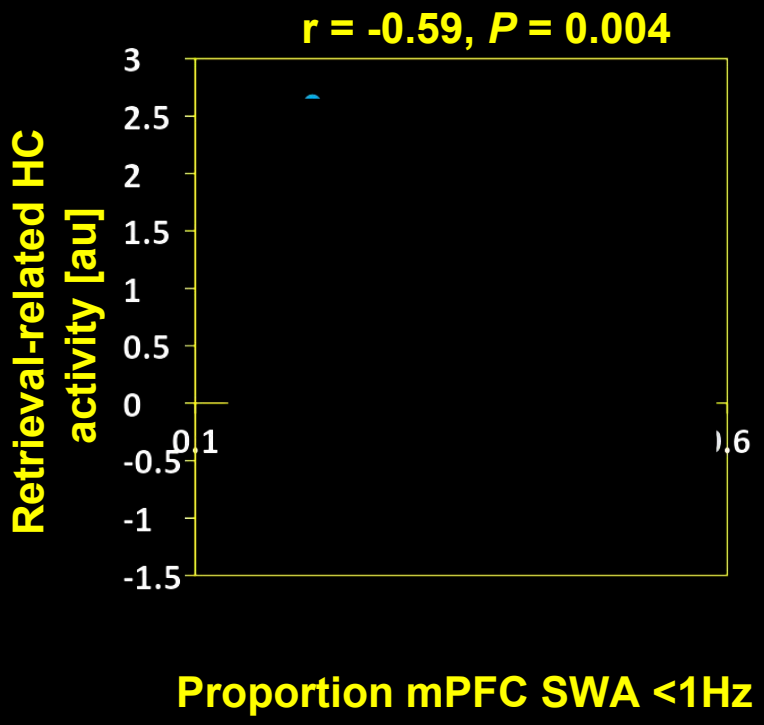
# REM EEG slowing predicts conversion to other dementias, too


*Idiopathic REM behavior disorder increases risk for Parkinson's Disease.*
*REM EEG slowing in iRBD increases risk for PD, MSA, and DLB in 3.5 years.*

**From Rodrigues-Brazète et al, 2016**

# Does SWA explain Aβ impact on memory?

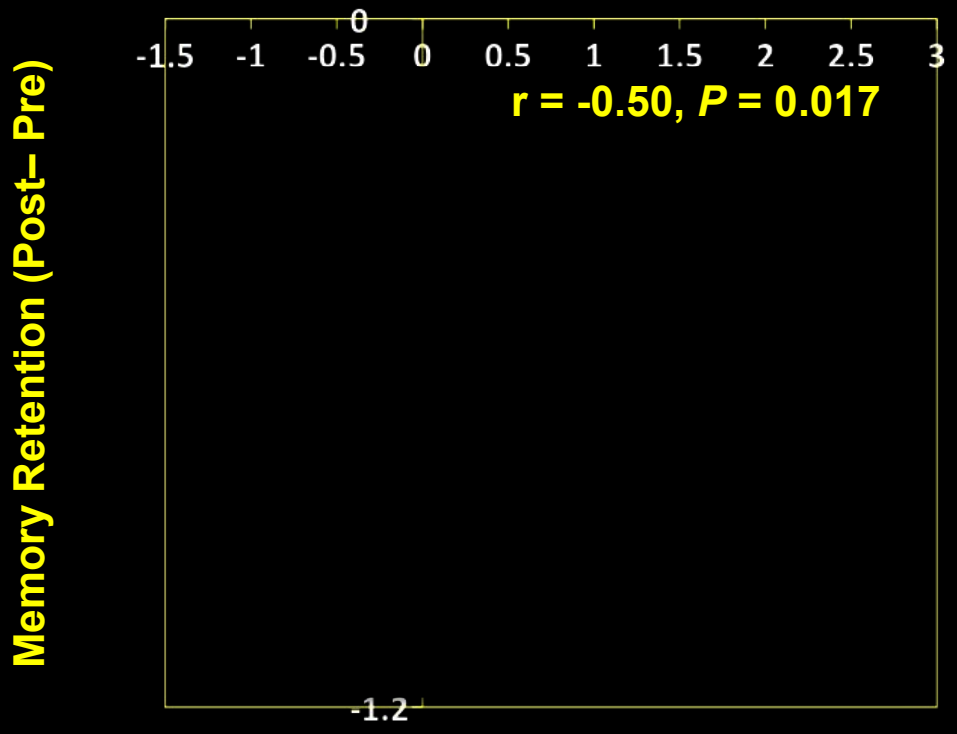



*mPFC SWA <1Hz predicts next day HC activation during retrieval*

**From Mander et al, 2015**

# Does SWA explain Aβ impact on memory?



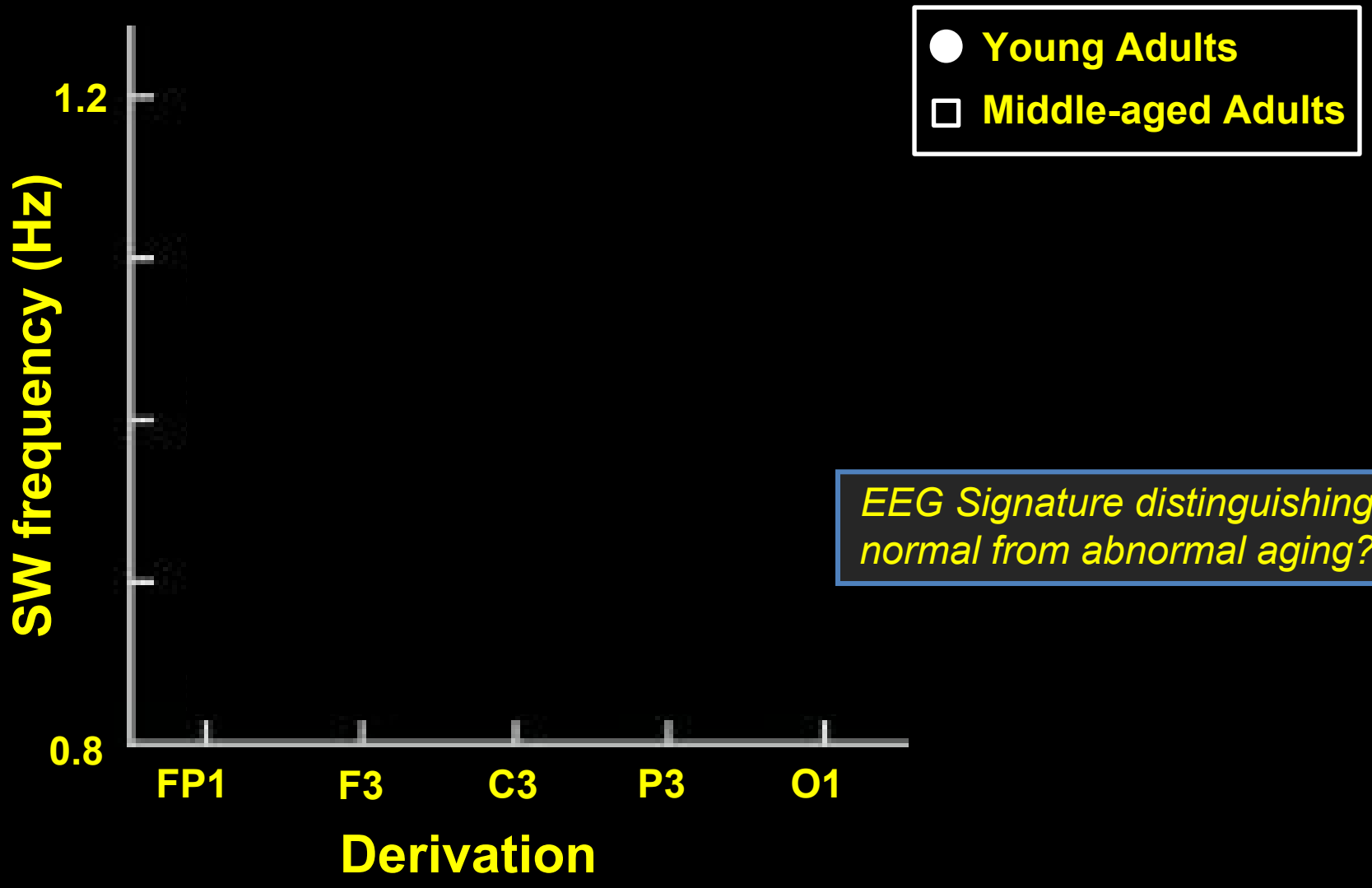

*Reliance on HC during retrieval indexes*
*failure of overnight memory consolidation*

**From Mander et al, 2015**

# Preliminary Findings:
# Does this NREM sleep EEG signature predict future Aβ?

# Preliminary Findings:
# Does this NREM sleep EEG signature predict Aβ change?

# Aβ effects on SWA distinct from normal aging?




*EEG Signature distinguishing normal from abnormal aging?*

Carrier et al, 2011