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

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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:

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<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
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<td>Grant/Research Support</td>
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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?

Diagram showing the progression from Normal Aging to Preclinical, MCI, and dementia, with an arrow pointing to Treatment.
EEG changes dramatically with brain state

**WAKE**
- Eyes open, alert
- Eyes closed, drowsy

**NREM**
- Stage 1
- Stage 2
- Slow Wave Sleep

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

SWS & Slow waves (<1Hz)
- Huber et al, 2004
- 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
- Fogel et al, 2013
- Lustenberger et al, 2016
- Mander et al, 2016 under revision
Sleep changes across the lifespan

In normal aging, SWS loss prominent; REM loss subtle

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

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

Ohayon et al, 2004
Sleep in Alzheimer’s Disease

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

From Prinz et al, 1982
Sleep in Mild Cognitive Impairment

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

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

Frontal

Temporal

EEG Derivations

REM Sleep

EEG Slowing ratio
(delta+theta)/(alpha+beta)

0

3.5

Discrimination Analysis
Accuracy: 90.4%
Sensitivity: 81.5%
Specificity: 100%

Normal Controls
AD Patients

From Hassainia et al, 1997
quantitative REM sleep EEG in MCI

From Brayet et al, 2015

Wakefulness
REM Sleep

EEG Slowing ratio
(delta+theta)/(alpha+beta)

Normal Controls
naMCI
aMCI

aMCI differs from Controls and naMCI

From Brayet et al, 2015
Mechanism of REM EEG slowing

From Moraes et al, 2006

Baseline
Donepezil
Placebo

EEG Slowing ratio
(delta+theta)/(alpha+beta)

5

Baseline 3 Months 6 Months

ADAS-cog

20
30
40
50

Baseline Month 3 Month 6

ACh system degeneration likely cause; linked to cognitive decline?

From Moraes et al, 2006
Where and when is sleep affected?

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

β-amyloid pathology

Max

Min
Aβ effects on SWA in healthy controls

**ANCOVA**
Frequency: \( P = 0.009 \)
mPFC PIB DVR: \( P = 0.087 \)
Frequency×mPFC PIB DVR: \( P = 0.032 \)

**Kendall’s τ = -0.30, \( P = 0.035 \)**

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?

Proportion mPFC SWA <1Hz predicts overnight memory retention

From Mander et al, 2015
Path Analysis Models

SWA & HC independent Model

SWA independent HC dependent Model

SWA & HC dependent Model

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

AD Pathology

Cortical
Aβ

Subcortical
Tau

HC

Parietal fast spindles

Temporal REM EEG slowing

Impaired Memory
Encoding

Impaired Memory Retention

Vicious Cycle?

Loss frontal <1Hz
Slow Waves

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?

Sleep EEG

Normal Aging

Preclinical

MCI

AD

Treatment

Cognitive Decline

Time (Years)
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Sleep Well…!
References

References

References

References

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

**SWA & HC independent Model**
- $r^2 = 0.03$
- RMR: 0.03
- GFI: 0.84
- BIC: 28.02

**SWA independent HC dependent Model**
- $r^2 = 0.005$
- RMR: 0.03
- GFI: 0.85
- BIC: 28.9

**SWA & HC dependent Model**
- $r^2 = 0.26^*$
- RMR: <0.01
- GFI: 0.91
- BIC: 23.9

From Mander et al, 2015
Hippocampal-Neocortical Model of Memory Processing
Hippocampal-Neocortical Model of Memory Processing
Hippocampal-Neocortical Model of Memory Processing

Cortical modules

Hippocampus

memory consolidation gradient

time

SWs

SPINDLES

RIPPLES
Hippocampal-Neocortical Model of Memory Processing

PREDICTIONS:
Post-sleep Memory Retrieval – ↓ Hippocampus activation
Post-sleep Memory Encoding – ↑ Hippocampus activation
Sleep in Alzheimer’s Disease

From Prinz et al, 1982

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

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<th>Women</th>
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<td>Number of Arousals</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>EC</td>
<td>Mi</td>
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<tr>
<td>% Wake</td>
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</tr>
<tr>
<td>0</td>
<td>EC</td>
<td>Mi</td>
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<tr>
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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?

Proportion 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?

Carrier et al., 2011

EEG Signature distinguishing normal from abnormal aging?