Age- and sleep-related changes in brain plasticity and brain architecture in relation with cognition

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Targeting cerebral mechanisms underlying age-related changes in sleep and circadian rhythms is crucial to develop preventive and therapeutic interventions adapted for older individuals.

Sleeping brain is a proxy of cognitive integrity in older individuals and may be used as a biomarker of neurodegeneration.

Improving sleep in the older population may slow down the aging process and neurodegeneration (cognition, oxidative stress, inflammation, amyloid).
During adulthood, increasing age is associated with...

- Earlier bedtimes and waketimes
- Less time in bed
- Less time asleep
- More wakefulness, lower sleep efficiency (especially in second half of the night)
- Less slow-wave sleep (min and %)
- More stage 1 and stage 2 sleep
- *Shorter REM latency; less REM sleep*

NREM sleep EEG
Two electrophysiological markers

NREM sleep oscillations functions
• Sleep and synaptic homeostasis
• Sleep protection against external stimulations
• Learning, memory, cognition

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Frequency</th>
<th>Duration</th>
<th>Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spindles</td>
<td>- N2, + N3</td>
<td>11-15 Hz</td>
<td>&gt; 500 ms</td>
<td>NA</td>
</tr>
<tr>
<td>Slow waves</td>
<td>- N3</td>
<td>&lt; 4 Hz</td>
<td></td>
<td>&gt; 75 µV</td>
</tr>
</tbody>
</table>
Important age-related modifications in NREM sleep EEG oscillations

- ↓SW density
- ↓SW amplitude
- ↓SW slope
- ↓Spindle density
- ↓Spindle amplitude
- ↓Spindle duration

Carrier, Viens et al. 2011. European Journal of Neuroscience
Martin al. (2013). Neurobiology of Aging
Age-related change in NREM sleep is a proxy of cerebral and cognitive health in aging.

- May underlie the difficulty that older people have in recuperating and/or maintaining sleep under challenging conditions

- Cognitive performance, sleep-dependent consolidation, amyloid beta burden, cortical thickness

- Predict the development of dementia in neurodegenerative aging

Latreille et al. 2019, Dube et al., 2015; Fogel et al., 2012; Mander et al., 2016; Mander et al., 2017; Lafortune et al., 2014; Latreille et al., 2015; Fogel et al., 2012; Pace-Schott and Spencer, 2015; Mander et al., 2015; Carrier et al., 2009; Fogel et al., 2012
Sleep become more vulnerable to disturbance with increasing age:
Need to take extra care

Lower ability to enhance slow-wave sleep after sleep deprivation

Lower ability to maintain sleep at an abnormal circadian phase (jet lag, shift work)

Higher sensitivity to caffeine

Lower ability to increase sleep intensity after sleep loss

Higher sensitivity to sleep at an abnormal circadian phase

Sleep, Cognition, and Normal Aging: Integrating a Half Century of Multidisciplinary Research

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What is the link between NREM sleep oscillations and general cognitive ability in healthy older subjects?

In healthy older subjects (between 50-91 y.o):

↑ Spindle density is associated to ↑ performance:
- Declarative memory (Rey verbal learning task)
- Attention (Bell test and Continuous Performance tasks)
- Verbal fluency

↑ SW density is associated to ↑ performance:
- Verbal fluency

NREM/REM EEG: Proxy of neurodegeneration
Do spindles in Parkinson Disease predict the development of dementia?

Spindles at baseline are associated with likelihood of developing dementia at follow-up (4.5 later)


Spindles in patients with PD (Christensen et al. 2014)

Baseline PSG
68 non-demented PD patients
40 healthy individuals

At follow-up (4.5 years)
18 PD patients developed dementia
50 remained dementia free
REM sleep: a window on cholinergic transmission in Parkinson

- Cholinergic degeneration may be especially key to early cognitive impairment in PD (Kehagia et al., 2010; Gratwicke et al., 2015; Bohnen and Albin, 2011; Hall et al., 2014; Liu et al., 2015).

- N-REM sleep: cholinergic activity is nearly absent.

- REM sleep differs from wakefulness: sustain activity mainly cholinergic, with very little input from other neurotransmitter systems (i.e., noradrenaline, serotonin, and dopamine).

- REM sleep is the ideal state to investigate cholinergic transmission integrity in PD.
Electroencephalographic prodromal markers of dementia across conscious states in Parkinson’s disease

Véronique Latreille,1,2 Julie Carrier,1,2 Benjamin Gaudet-Fex,1,2 Jessica Rodrigues-Brazête,1,2 Michel Panisset,3 Sylvain Chouinard,3 Ronald B. Postuma1,4 and Jean-François Gagnon1,5
REM sleep EEG slowing predicts dementia in PD


Baseline PSG
68 non-demented PD patients
40 healthy individuals

At follow-up (4.5 years)
18 PD patients developed dementia
50 remained dementia free

Figure 1: PDD patients showed higher REM sleep EEG slowing. Absolute spectral power in the delta (A) and theta (B) frequency bands, and slow-to-fast frequencies ratio (C) for each derivation in PDD patients (red), PDnD patients (dark blue), and controls (light blue). Post hoc analyses: *P < 0.05. Results are expressed as mean (± standard error of the mean).

[(delta + theta)/(alpha + beta)]
Are age-related modifications in NREM EEG oscillations associated with anatomical and functional changes in the brain?

Multimodal approach using MRI, fMRI-EEG, MEG-EEG

May underlie age-related changes in brain plasticity and cognition
Are age-related changes in NREM EEG oscillations associated with cortical grey matter?

changes in grey matter

Distance (mm) between cortical layers
- External: cerebrospinal fluid
- Internal: white matter

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Lemaître et al., 2012 – Hutton et al., 2009

Bushmann et al. 2011

Marjolaine Lafortune
Jonathan Dubé
Does cortical thickness explain age-related change in slow waves?

Mediation model

Step 2

Cortical thickness

Step 1

Frontal SW density and amplitude

Age

\[ b_{\text{frontal sw density}} = -0.25; \ p < 0.001 \]

\[ b_{\text{frontal sw amplitude}} = -0.09; \ p < 0.001 \]

Step 3: Indirect effect of age (through cortical thickness):

Preacher & Hayes, 2013

Cortical thickness is associated to SW density and SW amplitude

**SW density (nb/min)**
- Infero-parietal
- Middle temporal
- Superior temporal
- Middle frontal

**SW amplitude (µV)**
- Right superior parietal lobule
- Left Cuneus
- Left Lingual gyrus
- Right middle frontal gyrus

**Corrected p-values**
- Corrected-p = 0.05
- Corrected-p = 0.001
Most cortical regions associated to SW show lower cortical thickness in older subjects.

<table>
<thead>
<tr>
<th>SW density</th>
<th>SW amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle frontal</td>
<td>Middle frontal</td>
</tr>
<tr>
<td>Middle temporal</td>
<td>Superior parietal lobule</td>
</tr>
<tr>
<td>Infero-temporal</td>
<td>Cuneus</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>Lingual</td>
</tr>
</tbody>
</table>
Integrative model

Parallel mediation analysis → p<0.05 → p<0.05 (parallel model)

Model 1: SW density

- Middle frontal gyrus
- Middle temporal gyrus
- Superior temporal gyrus
- Infero-parietal gyrus

Age → SW density

\[ b_{\text{age}} = -0.25, p<0.001 \]

Cuneus
- Global cortical thickness
- Middle frontal gyrus

Age → SW amplitude

\[ b_{\text{age}} = -0.25, p<0.001 \]
Conclusions

Thinning in a network of cortical regions involved in SW generation and propagation, but also in cognitive functions, explained the age-related decrease in SW density and amplitude.

Dubé et al. (2015) Journal of Neuroscience
Age-related changes in relative spectral power in REM and NREM sleep

Latreille et al. (2019). Neurobiology of Aging
After controlling for age, spectral power is associated with cortical thickness in both REM and non-REM sleep.

### REM sleep
- **Delta: Central**
  - Left superior frontal gyrus
  - Left lateral orbitofrontal cortex
  - Right rostral anterior cingulate cortex
- **Delta: Temporal**
  - Left superior frontal gyrus
- **Delta: Parietal**
  - Left/right superior frontal gyrus
  - Right superior temporal gyrus
- **Delta: Occipital**
  - Left superior frontal gyrus

### NREM sleep
- **Delta: Central**
  - Left medial orbitofrontal cortex
- **Theta: Occipital**
  - Right lateral occipital cortex

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*Fig 1. Mediation model illustrating how cortical thickness may mediate the relationship between age and sleep EEG.*

Latreille et al. (2019). Neurobiology of Aging
Cortical thickness explains age-related changes in REM and NREM sleep

Latreille et al. (2019). Neurobiology of Aging

Sup. frontal gyrus

Sup. temporal gyrus

Medial orbital frontal cortex

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Latreille et al. (2019). Neurobiology of Aging
Are age-related changes in REM sleep associated to grey matter?

Fig 4. Conjunction maps of delta power correlates across REM and NREM sleep.

Thinning of the left superior frontal gyrus (spreading to the anterior cingulate and medial orbitofrontal cortices) drives EEG desynchrony during both REM and NREM sleep with aging.

Common mechanisms for both REM and NREM

**Medial frontal and cingulate cortices**: major hubs of the human brain, in synchronizing neuronal assemblies during sleep

Latreille et al. (2019). Neurobiology of Aging.
Are age-related changes in NREM EEG oscillations associated with white matter integrity?

Diffusion tensor imaging (DTI): water diffusion in each voxel (tensor)

Anisotropy of the diffusion = one preferential direction

Tract-Based Spatial Statistics:

4 metrics: radial diffusivity (RD), axial diffusivity (AD), mean diffusivity (MD), fractional anisotropy (FA)

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In the young: ^sigma spectral power and ^spindle density is associated with higher AD (Piantoni et al 2013)

White Matter older adults moderates the benefit of sleep spindles on motor memory consolidation (Mander et al. 2018)
Older individuals show lower white matter integrity than young individuals.

- **FA (↓)**
  - Forceps Minor
  - Inferior fronto-occipital fasciculus (IFOF)

- **MD (↑)**
  - Left anterior thalamic radiation
  - Minor Forceps
  - IFOF
  - Left Uncinate fasciculus
  - Part of cingular

- **AD (↓)**
  - Minor Forceps
  - Right Corticospinal track
  - Major Forceps
  - IFOF

- **RD (↑)**
  - Anterior thalamic radiation
  - Forceps Minor
  - IFOF
  - SLF
  - Right Inferior longitudinal fasciculus
  - Part cingular

Gaudreault et al. SLEEP (2018)
Are frontal and central spindle characteristics associated with white matter integrity after controlling for age?

No mediation effect:
White matter does not explain lower spindles in older individuals
Frontal spindle amplitude and sigma spectral power are associated to WM diffusion metrics only in the young individuals.

- Frontal spindle amplitude
  - **FA (+)**
  - Inferior fronto-occipital fasciculus (IFOF)
  - Superior Longitudinal fasciculus (SLF)
  - Uncinate fasciculus
  - Anterior thalamic radiation (left)
  - Corticospinal track (right)

- **MD (-)**
  - Forceps Minor
  - Superior Longitudinal fasciculus (SLF)
  - AD (-)
  - Forceps Minor
  - Forceps Major

- **RD (-)**
  - Inferior fronto-occipital fasciculus (IFOF)
  - Superior Longitudinal fasciculus (SLF)
  - Uncinate fasciculus gauche
  - Anterior thalamic radiation (left)
  - Corticospinal track (right)

- Frontal Sigma
  - **MD (-)**
  - Superior Longitudinal fasciculus (SLF) bilatéral
  - **RD (-)**
  - Anterior thalamic radiation (left)
  - Inferior fronto-occipital
Moderation analyses: the association between white matter and sleep spindles differs in young and older individuals.

Diffusion metrics explained between 14% and 39% of SS amplitude and sigma power variance in the young subjects only.

Gaudreault et al. SLEEP (2018)
To connect or not connect during sleep: this is the question!

Cognitive and mental functions emerge from the brain’s complex networks.

Most conclusions on functional connectivity during human sleep come from studies in young individuals.

Age-related change in functional connectivity during sleep may very well underlie cerebral and cognitive health in aging.
fMRI functional connectivity (FC) during NREM

EEG/fMRI studies in the young: NREM sleep induces important modifications in cortical and sub-cortical networks underlying sensory awareness, information transfer, memory consolidation and executive control.

Fading of consciousness: greater local cortical FC, but a breakdown of long range cortico-cortical FC during NREM sleep with the descent from wakefulness to SWS sleep.

Our fMRI study

NREM sleep in older individuals: Important modifications including lighter sleep, lower slow-waves and spindle density/amplitude.

Objective: to investigate changes in fMRI FC that occur during NREM sleep in aging.

Hypothesis: Older individuals will show a lower breakdown of FC during NREM sleep than young participants
Methodology (fMRI)

Participants:
Young (20-30 y) = 16(8F); mean = 23.3±3.3
Older (52-69 y) = 14(9F); mean = 59.5±5.9

Data acquisition (90 minutes) after a 26-hour sleep deprivation
EEG (32-electrode cap)

Scanner gradient EEG artifacts: Adaptive subtraction; Residual artifacts removed using ICA.

Ballistocardiographic artifacts: Constrained cICA (Leclercq et al., 2009).

Sleep scoring
fMRI (BASC-GLM)

Bootstrap analysis of stable clusters (BASC): (Bellec et al., 2010): identify brain regions that consistently exhibited similar spontaneous activity in individual subjects, and were spatially stable across both young and older participants.

Cerebral functional connectivity analyses: Standard correlation measures based on Bold signal fluctuations

Nicolas Martin, Ph.D.  Pierre Bellec, Ph.D.  Pierre Orban, Ph.D.  Véronique Daneault, Ph.D.
Data-driven parcellization
20 regions

20 homogeneous regions in terms of fluctuations of the BOLD signal
NREM2 vs Wake
Similar effects in young and older

Lower FC in NREM2

Higher FC in NREM2
NREM2 vs NREM1
Similar effects in young and older

Lower FC in NREM2
Higher FC in NREM2
NREM2 vs NREM1
Stronger FC ↓ in young and ↑ FC in older

Less FC in NREM2
More FC in NREM2

inferior dlPFC
superior dlPFC
basal ganglia

inf/med/sup temporas
basal ganglia
sup. temporal
OFC
inf. mpfc
med/int/lat insula
occipital

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Conclusions (1)

- **Young and older individuals:** Very similar decreases in cortico-cortical fMRI FC between wakefulness and NREM2 and globally, between NREM1 and NREM2.

- **Age-related difference in FC:** Between NREM2 and NREM1 in specific brain networks (16%)

- **Older subjects:** Shallower ↓ fMRI FC or ↑ FC between NREM2 and NREM1 between networks underlying sensory awareness, information transfer, memory consolidation, executive control
Age related changes in EEG coherence during sleep

- How two EEG sensors (brain regions) show similar neuronal oscillatory activity (frequency specific).
- Complete night study
- All sleep stages
- More ecological environment

Jean-Marc Lina, Ph.D., ETS, CÉAMS
Maude Bouchard, B.Sc., Ph.D. student
Bouchard et al. (2019). SLEEP.
Imaginary EEG coherence

- The “strength” of functional interactions between two cortical areas in different frequency bands (delta, theta, sigma, alpha, beta).
- Removal of 0 lag contribution

Castro et al., 2014
EEG coherence differences between older and younger individuals

Bouchard et al. (2019) SLEEP
Changes in EEG coherence (2-4 Hz) across the night

Global connectivity index: the sum of the differences in connectivity between two conditions, across all the significant pairs of electrodes

Bouchard et al. 2019 (SLEEP)
Older individuals showed lower EEG connectivity in N2 than the young (linked to spindles density).

Older individuals showed higher EEG connectivity than younger ones in both REM and N3 sleep.

Older individuals do not show reduced EEG connectivity in N3 as compared to N2 during the first NREM sleep cycle.

EEG connectivity during REM sleep is lower than in N3 (data not shown).

EEG connectivity in N2 and REM sleep linked to cognition (data not shown).
PLI during the transition between SW hyperpolarization and depolarization (constant delay).

Global connectivity index: the sum of the differences in connectivity between two conditions, across all the significant pairs of electrodes.
To connect or not connect during sleep: this is the question!

Brain imaging (EEG, MEG, MRI, fMIR): new insights on brain areas involved in the functions of human sleep.

**Next step**: to understand how brain areas interacts to give rise to human sleep functions.

**Functional connectivity** is estimated by **several metrics at different time scale** (e.g. during all night vs SW): unique information and processes to understand the complexity of the sleeping brain.

**Age-related changes** in fMRI functional connectivity, NREM EEG coherence, synchronization during slow-waves.

Age-related change in functional connectivity during sleep may very well underlying cerebral and cognitive health in aging.
NREM/REM sleep: Age-related changes in sleep dependent consolidation

Neuron
Old Brains Come Uncoupled in Sleep: Slow Wave-Spindle Synchrony, Brain Atrophy, and Forgetting

Impaired Prefrontal Sleep Spindle Regulation of Hippocampal-Dependent Learning in Older Adults

White Matter Structure in Older Adults Moderates the Benefit of Sleep Spindles on Motor Memory Consolidation

fMRI and Sleep Correlates of the Age-Related Impairment in Motor Memory Consolidation

Cerebral Activation During Initial Motor Learning Forecasts Subsequent Sleep-Facilitated Memory Consolidation in Older Adults

Sleep benefits consolidation of visuo-motor adaptation learning in older adults

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Enhancing slow-waves and spindles to enhance memory consolidation during sleep in the older population

Transcranial Alternating Current Stimulation

Acoustic Stimulation during sleep

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Enhancing slow-waves and spindles
Acoustic stimulations

Acoustic enhancement of sleep slow oscillations in mild cognitive impairment
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Acoustic Enhancement of Sleep Slow Oscillations and Concomitant Memory Improvement in Older Adults
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Using Oscillating Sounds to Manipulate Sleep Spindles
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Introduction: EEG oscillations known as sleep spindles have been linked with various aspects of cognition, but the specific functions they signal remain controversial. Two types of EEG sleep spindles have been distinguished: slow spindles at 1 S13.5 Hz and fast spindles at 13.5–16 Hz. Slow spindles exhibit a frontal scalp topography, whereas fast spindles exhibit a posterior scalp topography and have been preferentially linked with memory consolidation during sleep. To advance understanding beyond that provided from correlative studies of spindles, we aimed to develop a new method to systematically manipulate spindles.

Aims and Methods: We presented brief bursts of oscillating white noise to people during a 90-min afternoon nap. During stage 2 and slow-wave sleep, oscillations were embedded within contiguous 10-s stimulation intervals, each comprising 2 s of white noise amplitude modulated at 12 Hz (targeting slow spindles), 15 Hz (targeting fast spindles), or 50 Hz followed by 8 s of constant white noise.

Results: During oscillating stimulation compared to constant stimulation, parietal EEG recordings showed more slow spindles in the 12-Hz condition, more fast spindles in the 15-Hz condition, and no change in the 50-Hz control condition. These effects were topographically selective, and were absent in frontopolar EEG recordings, where slow spindle density was highest. Spindles during stimulation were similar to spontaneous spindles in standard physiological features, including duration and scalp distribution.

Conclusions: These results define a new method to selectively and noninvasively manipulate spindles through acoustic resonance, while also providing new evidence for functional distinctions between the 2 types of EEG spindles.

Keywords: sleep spindles, oscillations, memory consolidation.
Precious collaborators

Undergraduate, graduate, post-graduate students, research, research associate

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