Age-related declines in nap oscillatory activity are mediated and moderated by grey matter volume

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INTRODUCTION

- The intensity of neuroscillatory activity during sleep varies across brain regions in a frequency-dependent manner
- Regional variation in neuroscillatory activity leads to topographic variability in scalp EEG
- Age-related changes in EEG topography during overnight sleep reflect age-related changes in grey matter volume
  - Delta (0.5-4 Hz) changes are mediated by frontal cortical volume loss from adolescence through senescence *(Goldstone et al., 2018; Mander et al., 2013)*
  - Theta (4-8 Hz) changes reflect neocortical (and possibly hippocampal) grey matter volume during adolescence *(Buchmann et al., 2011; Campbell & Feinberg, 2009)*
  - Sigma (12-16 Hz) changes reflect neocortical and hippocampal grey matter volume in adulthood and senescence *(Fogel et al., 2017; Saletin et al., 2013)*
- Comparisons with overnight sleep may confound age-related changes in basic sleep physiology vs. sleep pressure
- Examining grey matter contributions to age-related changes in scalp EEG activity during a midday nap can separate these concepts

HYPOTHESES

1) Delta, theta, and sigma amplitude during a midday nap will decrease with age, especially over frontocentral scalp

2) Delta/theta declines will reflect frontal cortical grey matter

3) Theta/sigma declines will reflect hippocampal grey matter

METHOD

PARTICIPANTS

- *Young adults (YA):* n=26 (14♀), Ages 18-31 yrs (M=22.42)
- *Older adults (OA):* n=21 (10♀), Ages 58-75 yrs (M=65.29)
- Participants were generally healthy, with no presence of neurological, psychiatric, cardiac, or sleep disorders, depressive symptoms, or diagnosable cognitive decline
- Participants had moderate chronotype (MEQ 20-70), non-poor sleep quality (PSQI > 5), habitual bedtimes <12pm, habitual wake times >5am, and were not habitual nappers

PROCEDURE

- High-density EEG and structural MRI data collected as part of a larger protocol investigating motor sequence learning
- 124-channel scalp EEG collected during a 120 min nap opportunity (1-3pm; $M_{Total\ sleep\ time}$=108 min, p_{Age}=0.25)
- T1 scans (~0.8 mm^3 voxels) acquired same day as nap

ANALYSES

High-density electroencephalography (HD-EEG):

- Averaged mastoid reference, bad channels interpolated, truncated to first 60 min of NREM2/3 sleep
- Power spectra estimated by Welch's method with 10 sec epochs (75% overlap, single Hanning taper), then averaged
- Amplitude envelopes extracted using filter-Hilbert method, averaged into 20 sec epochs within first 60 min of NREM2/3 sleep, averaged across epochs by channel
- OA/YA contrasted using cluster-based permutation tests

Grey matter volume (GMV):

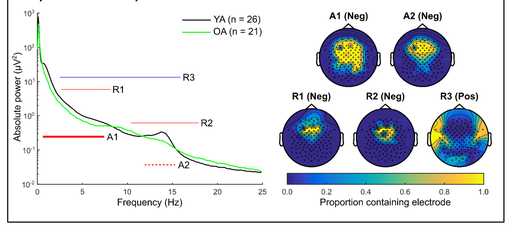
- Voxel-based morphometry performed in FSL-VBM 1.1 with nonlinear registration, randomly selected 21 (of 26) YA
- OA/YA contrasted voxelwise in whole brain using cluster-based permutation tests, and within ROIs using ANCOVA
- Models covaried for estimated total intracranial volume (ETIV)

Structure/function relationships:

- Mediation of age-related declines in EEG amplitude by mean ROI grey matter volume assessed using causal steps method, quantified by bootstrap estimation
- Moderation assessed using interaction models

RESULTS (HD-EEG)

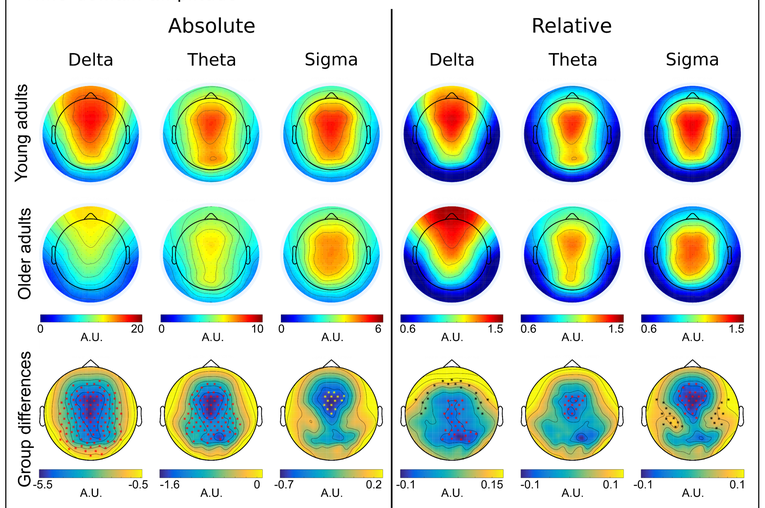
Spectral amplitude



Summary

- Age-related differences were observed in the delta, theta, and sigma frequency bands
- Older adults had lower absolute delta, theta, and sigma amplitude
  - Delta and theta reductions were topographically broad
  - Sigma reductions were constrained to frontocentral
- Delta was relatively more frontal in older adults
  - Relative delta amplitude reduced over posterior scalp in older adults, but increased over frontal scalp
- Theta and sigma relatively less frontocentral in older adults

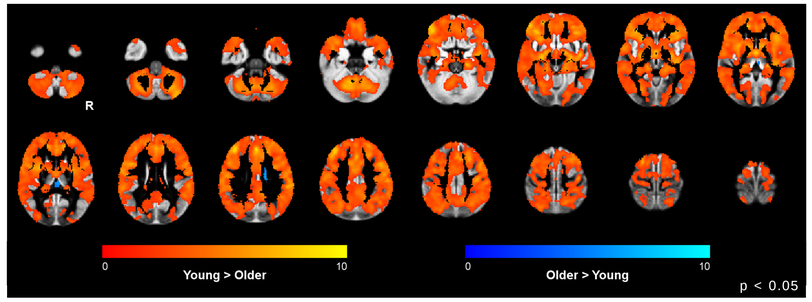
Time-domain amplitude



* = OA > YA (p < 0.025); * = OA < YA (p < 0.025); * = OA < YA (p < 0.05)

RESULTS (GMV)

Voxel-based morphometry (voxelwise)



Voxel-based morphometry (within-ROI)

ROI	Hemi	EMM_{OA}	EMM_{YA}	p	Sig.
Frontal medial cortex	-	0.468	0.571	< 0.001	***
Premotor cortex	L	0.325	0.383	< 0.001	***
	R	0.300	0.353	< 0.001	***
Primary motor cortex (Anterior)	L	0.298	0.336	0.001	**
	R	0.275	0.311	0.001	**
Primary motor cortex (Posterior)	L	0.295	0.349	< 0.001	***
	R	0.279	0.337	< 0.001	***
Hippocampus	L	0.530	0.568	0.017	*
	R	0.527	0.560	0.004	**
Caudate	L	0.356	0.402	< 0.001	***
	R	0.343	0.378	0.011	*
Putamen	L	0.310	0.357	< 0.001	***
	R	0.344	0.393	< 0.001	***
Pallidum	L	0.137	0.162	< 0.001	***
	R	0.155	0.185	< 0.001	***
Thalamus	L	0.328	0.355	0.004	**
	R	0.349	0.362	0.125	n.s.
Cerebellum	L	0.413	0.459	< 0.001	***
	R	0.411	0.452	< 0.001	***
Cerebellum (Vermis)	-	0.447	0.497	0.002	**

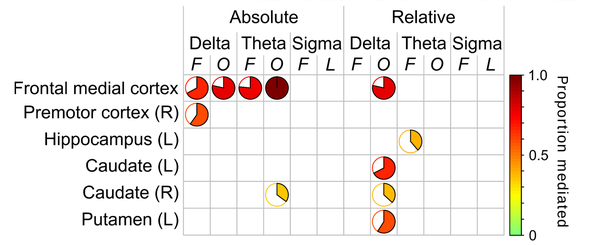
Summary

- Older adults had reduced grey matter volume across most brain regions

STRUCTURE/FUNCTION RELATIONSHIPS

Mediation

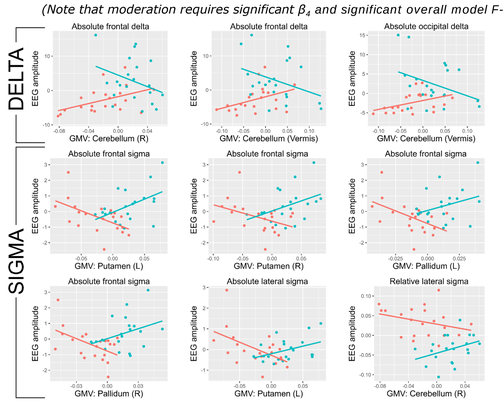
Base model: EEG = $\beta_0 + \beta_1$(Age) + β_2(ETIV)
Mediator model: GMV = $\beta_0 + \beta_1$(Age) + β_2(ETIV)
Outcome model: EEG = $\beta_0 + \beta_1$(Age) + β_2(ETIV) + β_3(GMV)
(Note that mediation requires significant β_{1_Base}, $\beta_{1\_Mediator}$, $\beta_{3\_Outcome}$, and that $\beta_{1\_Outcome} < \beta_{1\_Base}$)



- Age-related declines in delta amplitude were mediated by grey matter loss in neocortex and striatum
  - Absolute frontal delta mediated by frontal medial, right premotor cortices
  - Absolute occipital delta mediated by frontal medial cortex
  - Relative occipital delta mediated by frontal medial cortex, bilateral caudate, left putamen
- Age-related declines in theta amplitude were mediated by grey matter loss in neocortex, striatum, and hippocampus
  - Absolute frontal theta mediated by frontal medial cortex
  - Absolute occipital theta mediated by frontal medial cortex and right caudate
  - Relative frontal theta mediated by left hippocampus

Moderation

Model: EEG = $\beta_0 + \beta_1$(Age) + β_2(ETIV) + β_3(GMV) + β_4(Age*GMV)
(Note that moderation requires significant β_4 and significant overall model F-test)



- Age moderated delta relationships with cerebellar GMV
  - **OA:** increased cerebellar GMV == increased delta amplitude
  - **YA:** increased cerebellar GMV == decreased delta amplitude
- Age moderated sigma relationships with striatal, cerebellar GMV
  - **OA:** increased striatal, cerebellar GMV == decreased sigma amplitude
  - **YA:** increased striatal, cerebellar GMV == increased sigma amplitude

RESULTS SUMMARY

High-density electroencephalography (HD-EEG):

- Older adults have less delta (0.5-4 Hz), theta (4-8 Hz), and sigma (12-16 Hz) activity during a midday nap than young adults
- With age, delta becomes more relatively frontal, whereas theta and sigma become less relatively frontocentral

Grey matter volume (GMV):

- Older adults have lower grey matter volume than young adults across most of the brain

Structure/function relationships:

- Age-related declines in delta activity are mediated by grey matter loss in frontal medial and premotor cortices, and in bilateral caudate and left putamen
- Age-related declines in theta activity are mediated by grey matter loss in frontal medial cortex, right caudate, and left hippocampus
- Age and grey matter volume have interactive effects on neuroscillatory activity during a nap
  - Cerebellar grey matter positively predicts delta in older adults, negatively predicts delta in young adults
  - Striatal and cerebellar grey matter negatively predict sigma in older adults, positively predict sigma in young adults

CONCLUSIONS

- Age-related declines in sleep neuroscillatory activity are not dependent on age-related changes in sleep pressure
- Mediation of age-related declines in sleep neuroscillatory activity by grey matter volume is not dependent on age-related changes in sleep pressure
- Delta activity during sleep reflects large contributions from frontal medial cortex
  - Delta during sleep may additionally reflect contributions from generators active prior to sleep (e.g., premotor cortex, striatum, cerebellum after motor learning)
- Theta activity during sleep reflects contributions from frontal medial cortex and hippocampus
  - Supports developmental hypothesis that sleep theta reflects maturation of allocortical structures
  - Indicates frontal medial cortex contributions to sleep neuroscillatory activity are not exclusive to delta band
  - Theta during sleep may be less influenced by task-related activations prior to sleep than delta
- Sigma activity during sleep may reflect different generator networks in young and older adults
  - Young adult sigma network may be better able to take advantage of increased striatal, cerebellar contributions

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