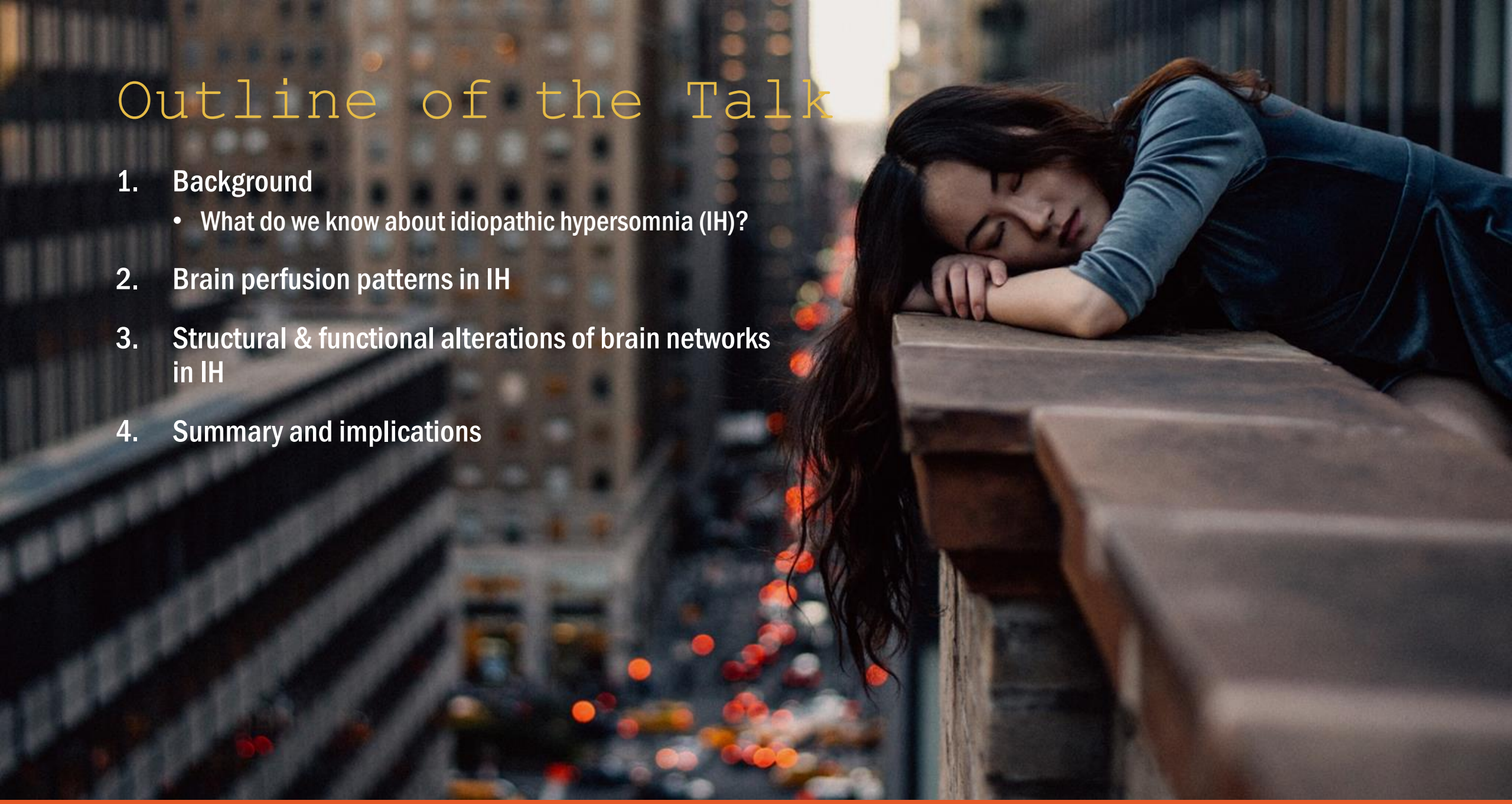
Structural and Functional Brain Alterations in Idiopathic Hypersomnia

Thanh Dang-Vu, MD PhD

Outline of the Talk

1. Background
   - What do we know about idiopathic hypersomnia (IH)?
2. Brain perfusion patterns in IH
3. Structural & functional alterations of brain networks in IH
4. Summary and implications



What is Idiopathic Hypersomnia (IH)?

- Excessive daytime sleepiness
- Unrefreshing nature of sleep periods with difficulty waking up ('sleep drunkenness')
- Total sleep time is often prolonged
- < 2 SOREMPs, no cataplexy
- No consistent hypocretin-1 deficiency
- Clinical overlap with narcolepsy: 18% of narcoleptics have long sleep time and unrefreshing naps
  (Vernet and Arnulf, 2009)

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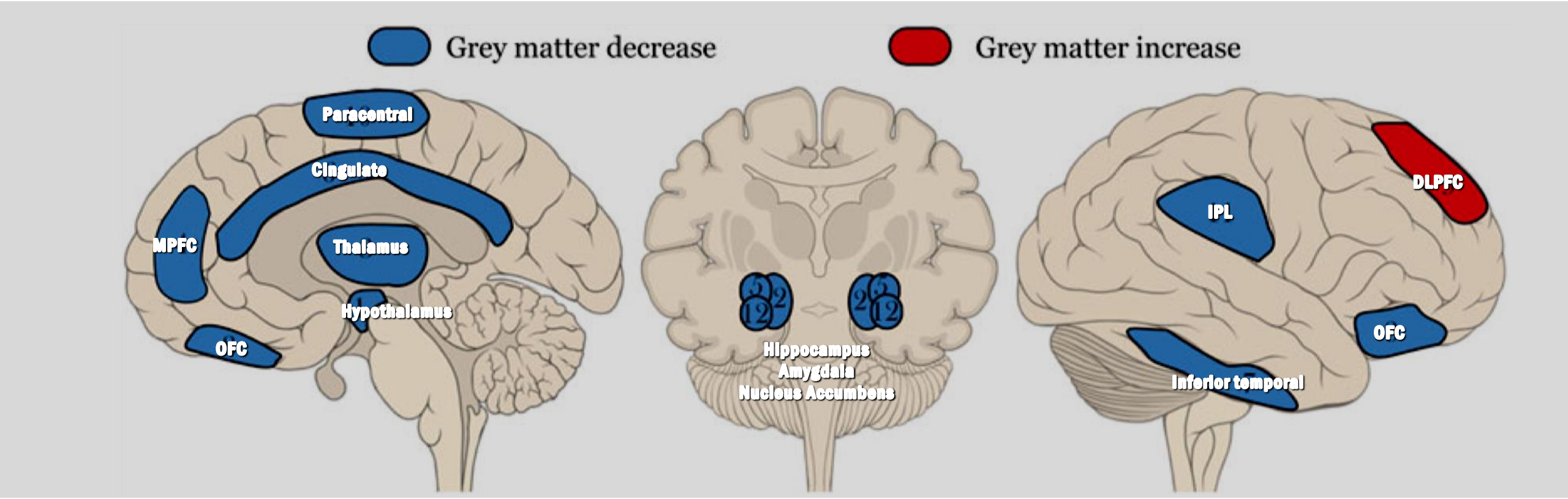
IH is Different From Narcolepsy

Both are central disorders of hypersomnolence

	IH	Narcolepsy
Cataplexy	✗	✓
Early REM sleep onset	✗	✓
Refreshing sleep/naps	✗	✓
Hypocretin (orexin) deficiency	✗	✓

Brain Morphology – Narcolepsy

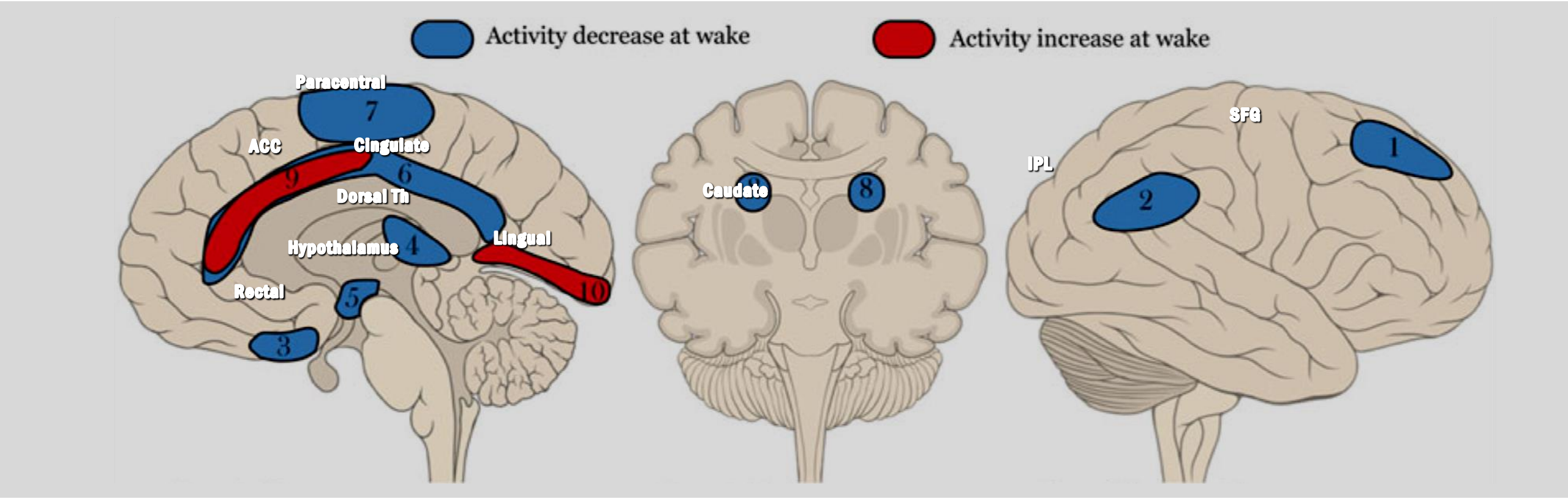


Structural alterations in narcolepsy

Mainly reduced grey matter volume and thickness in hypocretin projection sites and the limbic system

O'Byrne, J. N., Salimi, A., & Dang-Vu, T. T. (2016) Neuroimaging of Narcolepsy. In Narcolepsy (pp. 177–191)

Brain function – Narcolepsy



Functional alterations in narcolepsy

Mainly decreased blood flow or glucose brain metabolism at wake in hypocretin projection sites and the limbic system

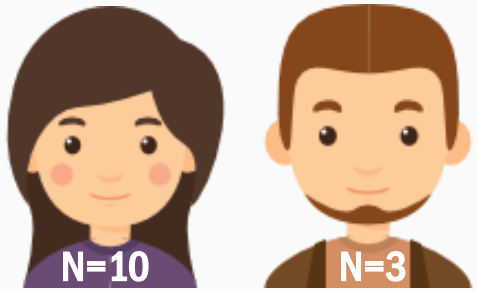
IH?

O'Byrne, J. N., Salimi, A., & Dang-Vu, T. T. (2016) Neuroimaging of Narcolepsy. In Narcolepsy (pp. 177–191)

Participants

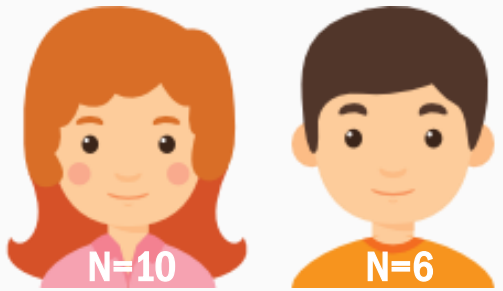
Inclusion criteria for IH

- Excessive daytime sleepiness > 3 months
- Daytime mean sleep latency < 8 min (MSLT). Not required if TST > 11 h
- Number of SOREMPs < 2
- Absence of cataplexy
- Absence of other causes of hypersomnia



13 IH

Age: 22-59 y, mean 33 ±10
ESS: 17.3 ±4.3
MSLT: 7.3 ±3.2 min



Designed by Freepik

16 good sleepers

Age: 22-53 y, mean 31 ±9
ESS: 4.8 ±2.3

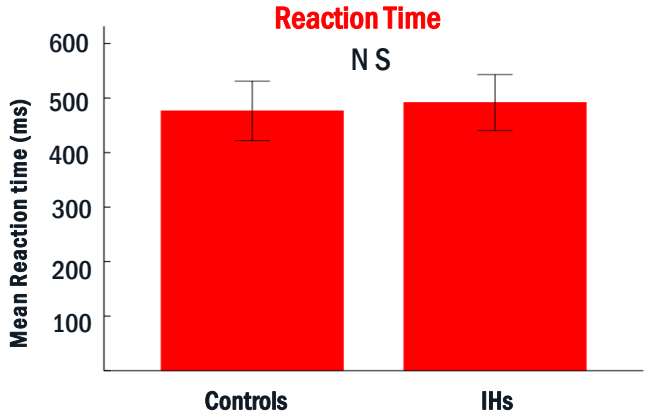
Clinical Characteristics of IH Compared to Good Sleepers

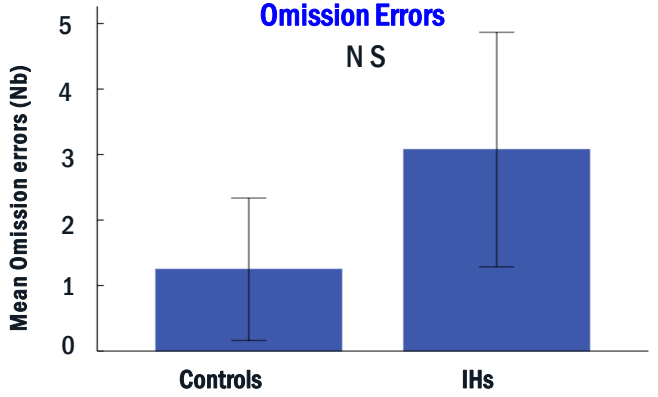
Parameters	IH (N = 13)	HC (N = 16)	p-value
Demographics:			
Age	33.31 ± 9.72	31.00 ± 9.47	0.526
Sex (M:F)	3:10	6:10	0.454
Education (Years)	15.69 ± 2.72	16.38 ± 1.93	0.454
BMI	23.88 ± 4.38	23.30 ± 2.42	0.674
Clinical characteristics:			
Symptoms duration (years)	11.46 ± 8.56	-	-
Average sleep latency at MSLT (min)	7.28 ± 3.20	-	-
SOREMPs at MSLT (Nb)	0.23 ± 0.44	-	-
Polysomnography:			
Total sleep time (min)	454.13 ± 39.06	416.61 ± 56.72	0.050
Sleep latency (min)	12.91 ± 8.56	13.95 ± 7.96	0.744
Sleep efficiency (%)	91.55 ± 5.25	90.57 ± 4.20	0.595
Wake after sleep onset (min)	32.18 ± 19.72	22.65 ± 17.26	0.190
N1 sleep (% of total sleep time)	8.25 ± 5.25	5.29 ± 2.43	0.098
N2 sleep (% of total sleep time)	59.72 ± 10.06	56.91 ± 5.34	0.379
N3 sleep (% of total sleep time)	12.88 ± 6.57	14.53 ± 5.11	0.471
REM sleep (% of total sleep time)	19.19 ± 7.24	23.07 ± 6.27	0.146
Questionnaires:			
Pittsburgh Sleep Quality Index (PSQI)	4.84 ± 0.99	3.06 ± 1.12	0.000
Epworth Sleepiness Scale (ESS)	17.31 ± 4.25	4.75 ± 2.35	0.000
Beck Depression Inventory (BDI)	9.61 ± 7.10	2.88 ± 3.03	0.002
Beck Anxiety Inventory (BAI)	9.64 ± 9.77	2.38 ± 3.16	0.025
Morningness–Eveningness Questionnaire (MEQ)	48.77 ± 8.02	53.31 ± 10.14	0.189

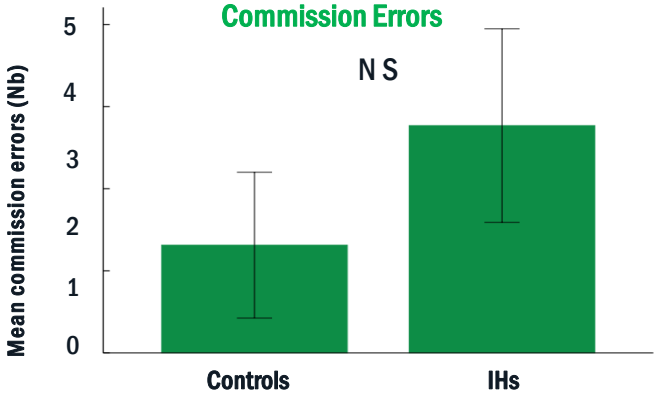
METHODS

Continuous Performance Test

	IH Patients (N = 13)	Controls (N = 16)	p-value
Reaction time (ms):			
Total	514.21 ± 109.66	477.44 ± 93.59	0.348
1/4	491.73 ± 92.62	476.42 ± 109.23	0.686
2/4	526.02 ± 118.85	470.52 ± 95.57	0.186
3/4	518.86 ± 125.82	470.25 ± 98.29	0.267
4/4	518.85 ± 127.43	486.15 ± 93.38	0.448
Omission errors (Nb):			
Total	3.08 ± 3.23	1.25 ± 2.18	0.096
1/4	0.38 ± 1.12	0.44 ± 1.03	0.897
2/4	0.69 ± 0.75	0.25 ± 0.77	0.132
3/4	0.92 ± 1.12	0.25 ± 0.58	0.056
4/4	1.08 ± 1.26	0.31 ± 0.48	0.065
Commission errors (Nb):			
Total	2.77 ± 2.13	1.31 ± 1.78	0.061
1/4	1.15 ± 1.14	0.56 ± 1.09	0.170
2/4	0.46 ± 0.66	0.25 ± 0.58	0.373
3/4	0.46 ± 0.78	0.19 ± 0.40	0.265
4/4	0.69 ± 1.11	0.31 ± 0.60	0.282





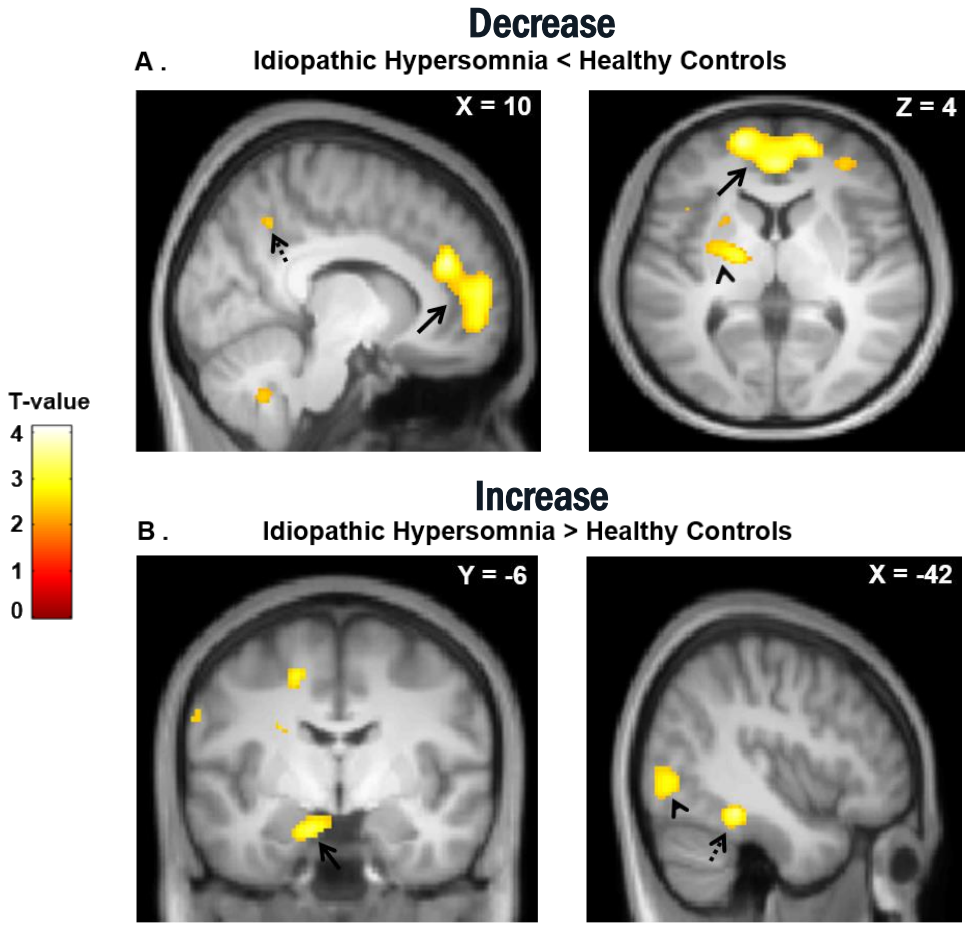


SPECT

- **Single photon emission computed tomography (SPECT)** with Tc-99m ethyl cysteinate dimer (ECD)
- Assessment of **brain perfusion** (regional cerebral blood flow, rCBF)
- Participants were scanned in the morning during resting **wakefulness** (absence of sleep was monitored)
- Comparison of rCBF between IH and good sleepers ($p < 0.05$, corrected for multiple comparisons)
- Correlations between rCBF and clinical characteristics to assess the functional correlates of brain perfusion patterns. (controlling for age, education and disease duration)

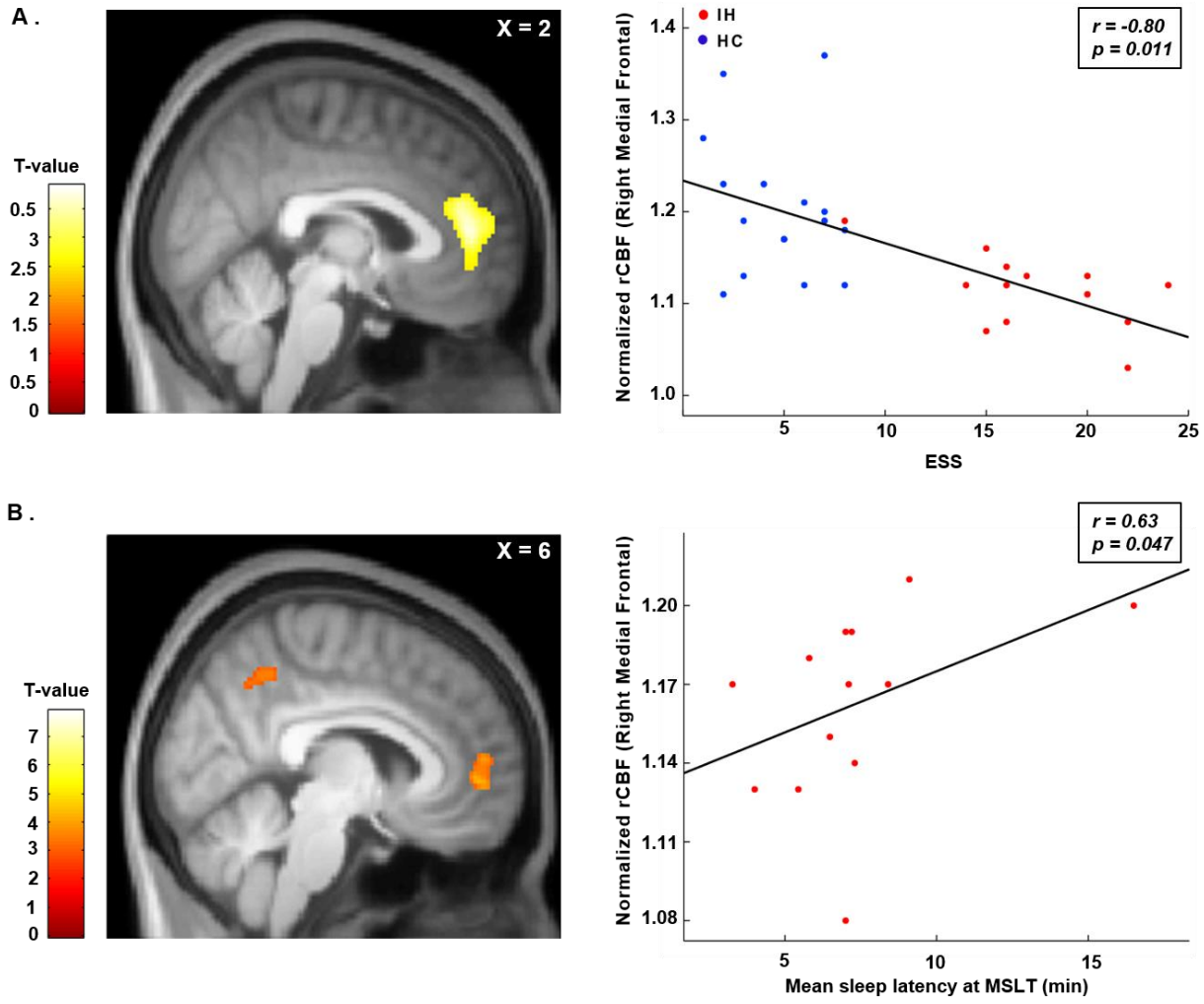
Brain Perfusion Changes in IH

- Regional CBF is altered in idiopathic hypersomnia
- Decrease of rCBF mainly in the **default-mode network (DMN)**: medial prefrontal, anterior cingulate, posterior cingulate
- Increase of rCBF in the amygdala and temporo-occipital regions



Boucetta, Montplaisir, Zadra, Lachapelle, Soucy, Gravel and Dang-Vu, SLEEP, 2017

Brain Perfusion Changes in IH

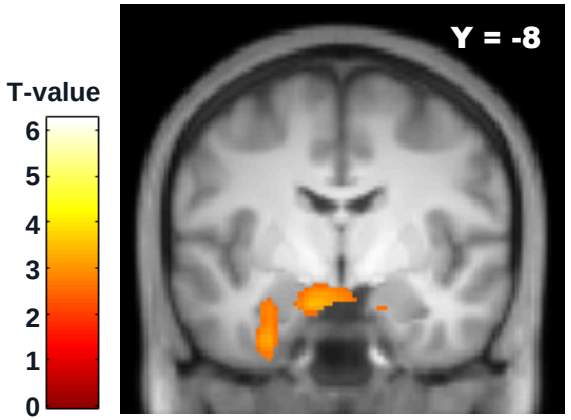


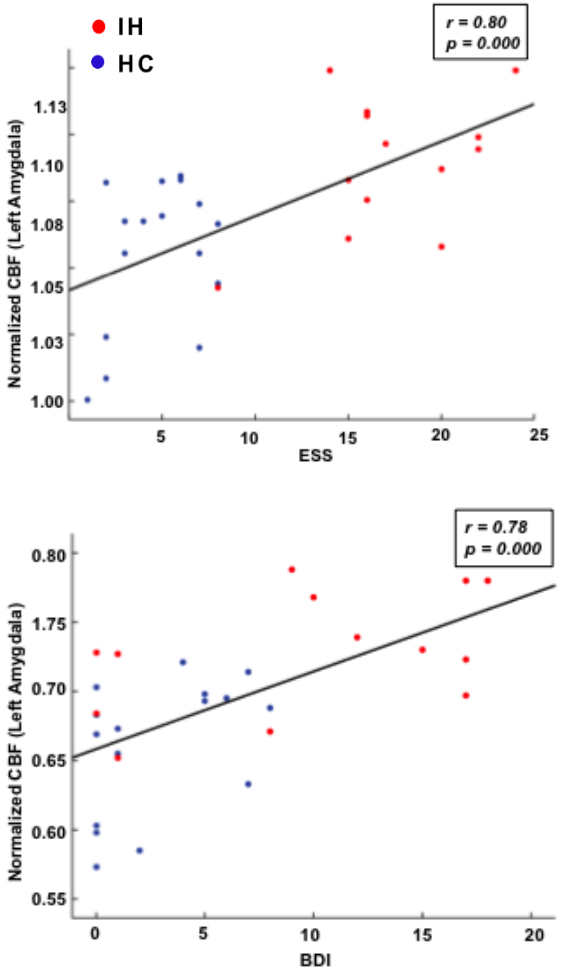
Decreased rCBF in the DMN is associated with higher self-reported sleepiness (ESS)

Decreased rCBF in the DMN is associated with higher objective sleepiness (mean sleep latency, MSLT)

Boucetta, Montplaisir, Zadra, Lachapelle, Soucy, Gravel and Dang-Vu, SLEEP, 2017

Brain Perfusion Changes in IH

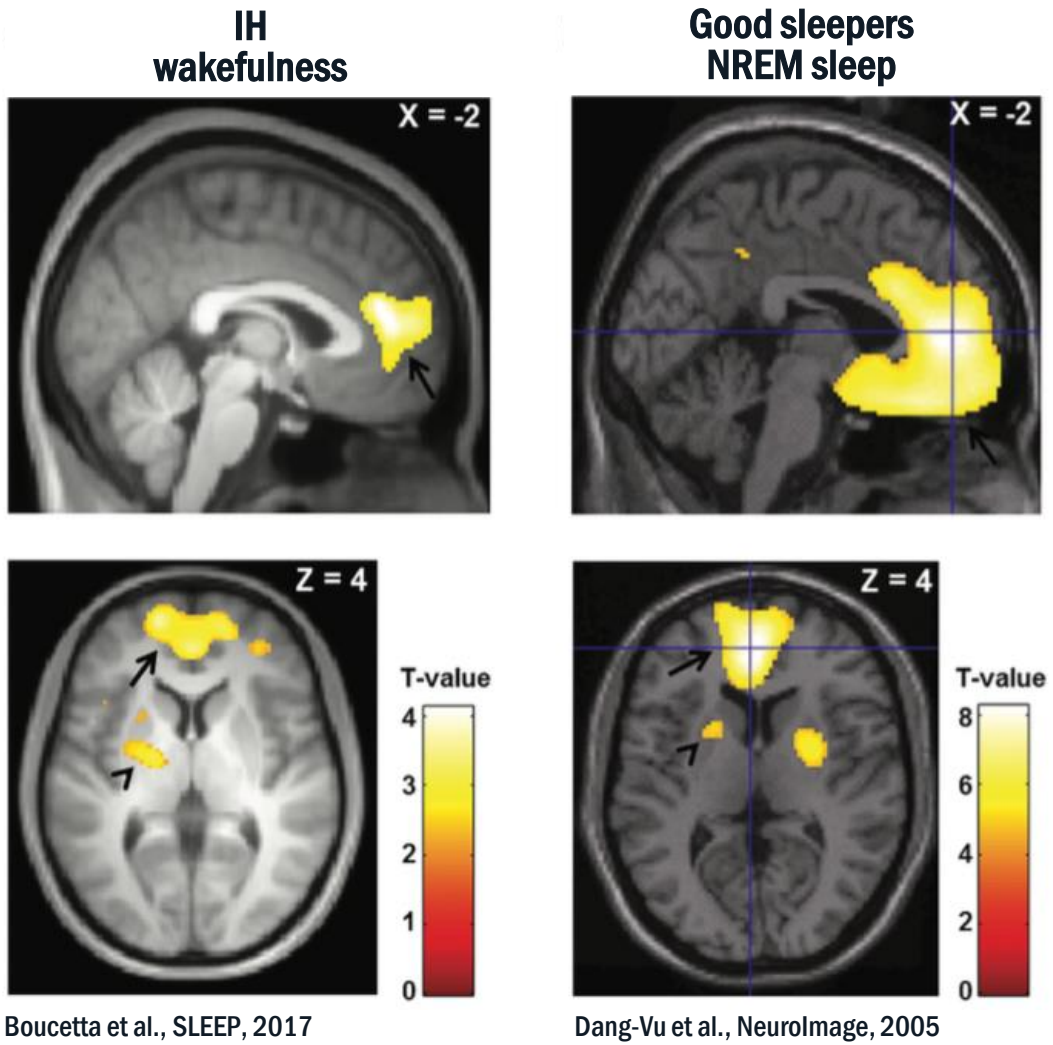




Increased rCBF in the amygdala is associated with higher self-reported sleepiness (ESS) and depression scores (BDI)

Boucetta, Montplaisir, Zadra, Lachapelle, Soucy, Gravel and Dang-Vu, SLEEP, 2017

Brain Perfusion Changes in IH



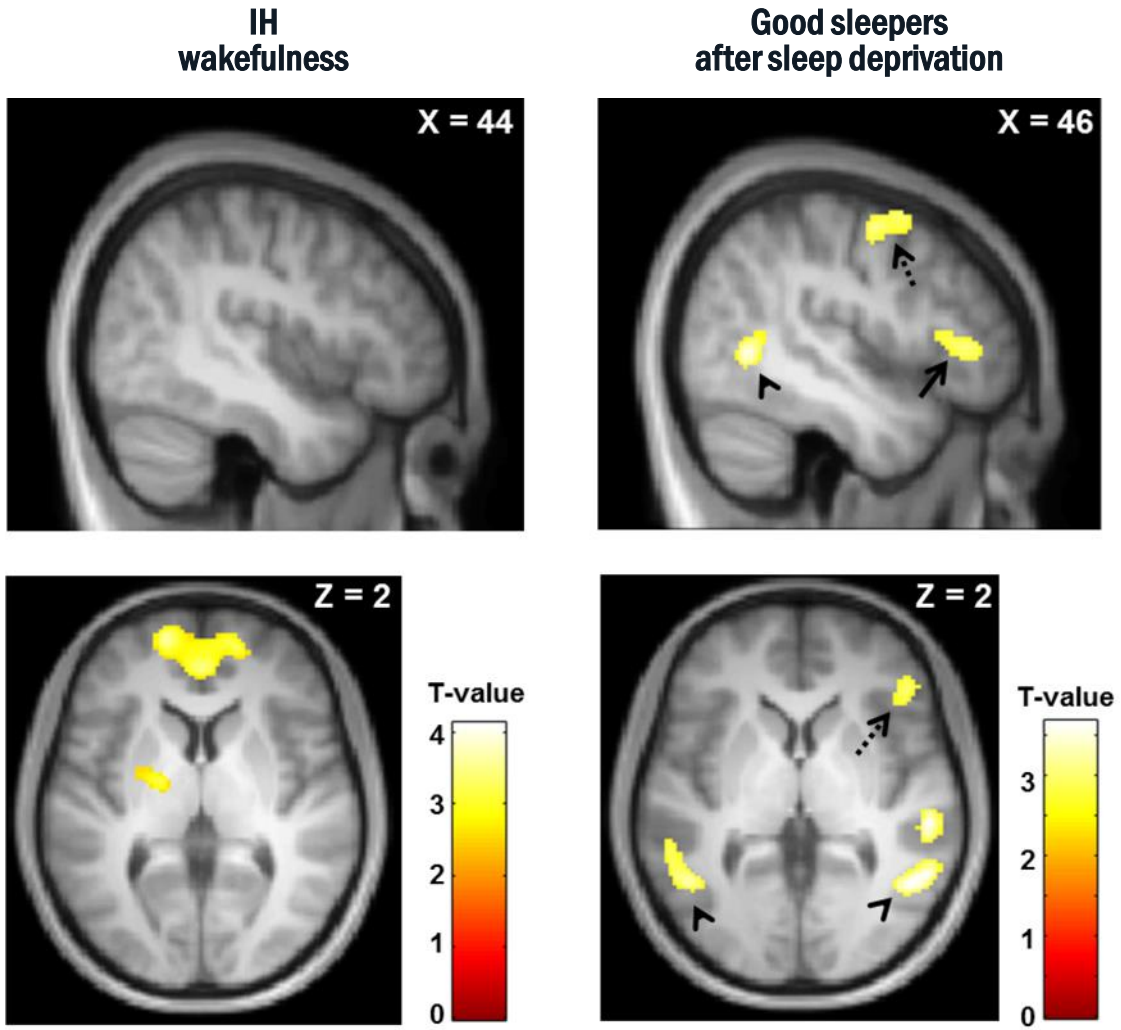
Boucetta et al., SLEEP, 2017

Dang-Vu et al., NeuroImage, 2005

Similarity of rCBF distribution between IH at wake and good sleepers during NREM sleep

Altered rCBF in DMN in IH → incomplete sleep-wake transitions?

Brain Perfusion Changes in IH



Distinct rCBF distribution between IH at wake and good sleepers after acute sleep deprivation

Changes in IH likely reflect trait rather than state (sleepiness) effects

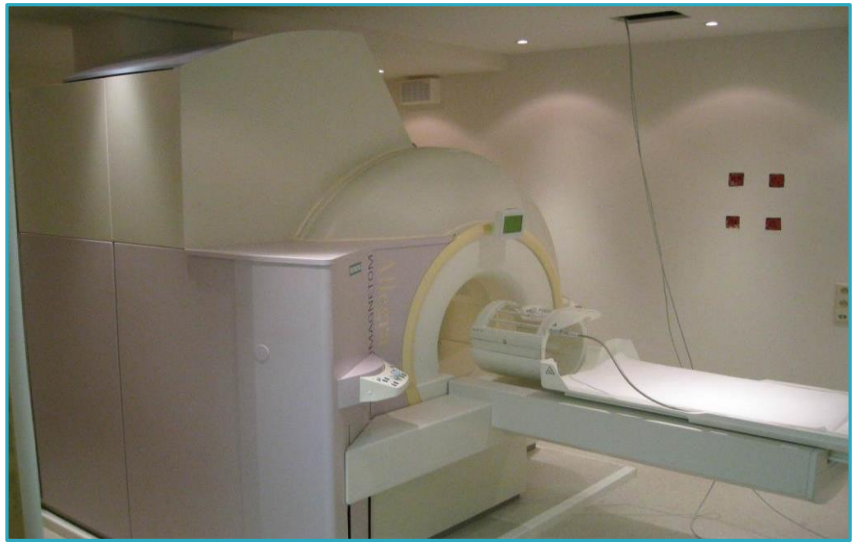
Boucetta, Montplaisir, Zadra, Lachapelle, Soucy, Gravel and Dang-Vu, SLEEP, 2017

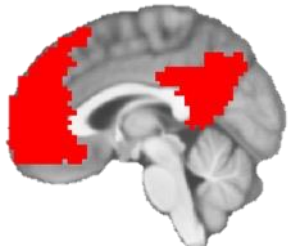
SPECT (RCBF) During Wake In IH: Summary

- IH showed a disruption of cortical networks involved in alertness (**DMN**) and emotion regulation (amygdala), which may contribute to the excessive daytime sleepiness and mood disturbances
- No significant changes in the hypothalamic region, in line with the preservation of the hypocretin-1 system
- Distribution of rCBF during wakefulness in IH showed striking similarity with rCBF during NREM sleep in good sleepers (decreased perfusion in medial frontal, precuneus, putamen), suggesting incomplete sleep-wake transitions
- Distribution of rCBF during wakefulness in IH did not overlap with rCBF distribution after sleep deprivation in good sleepers, suggesting that these results reflect trait abnormalities associated with IH rather than a mere non-specific state of sleepiness

Brain Networks – IH

- No visible structural alterations but rCBF alterations in the DMN
- **Magnetic resonance imaging (MRI)** study of IH, including structural MRI (grey matter volume, cortical thickness, structural covariance) and functional MRI (resting state fMRI connectivity)
- Same participants
- Focus on the DMN





Default-mode network (DMN)

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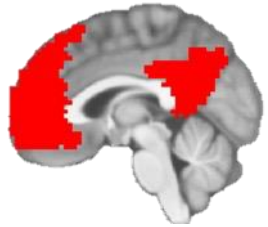
Default-mode Network



Regions

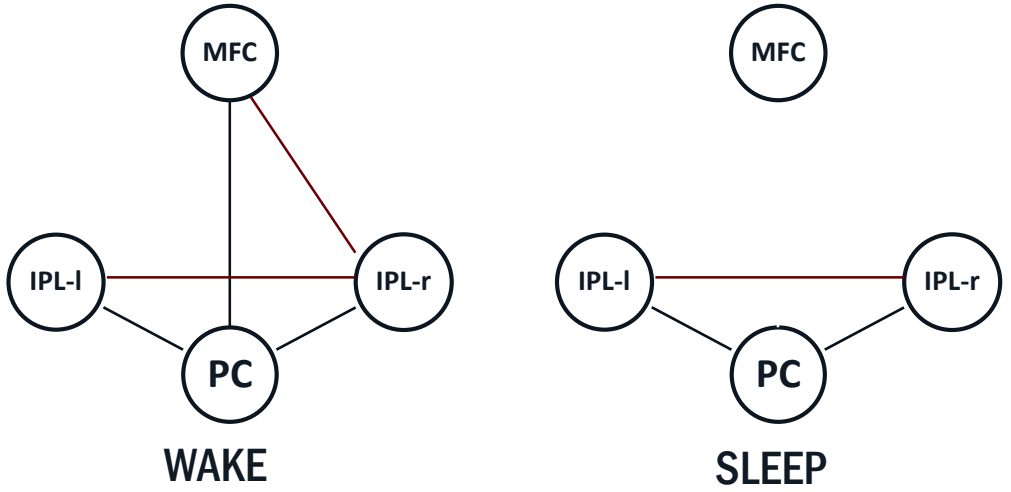
- medial prefrontal cortex
- posterior cingulate cortex
- precuneus
- bilateral inferior parietal lobule

Sleep

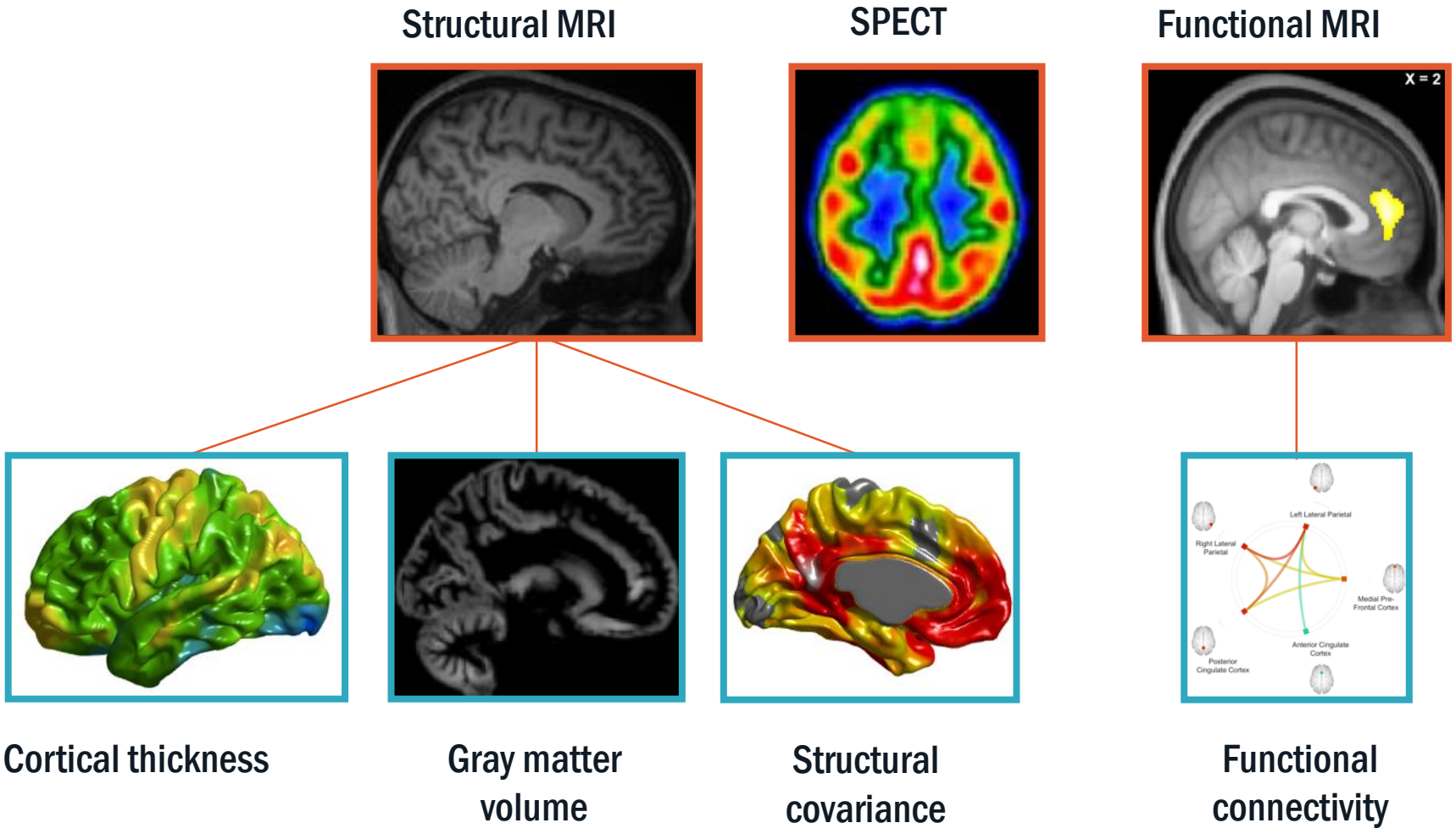
- Activity decreases
- posterior DMN disconnects from frontal regions during sleep

Role

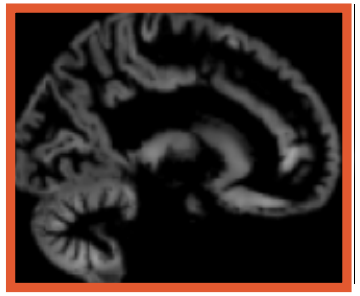
- self
- attention
- introspection
- awareness
- internal oriented tasks



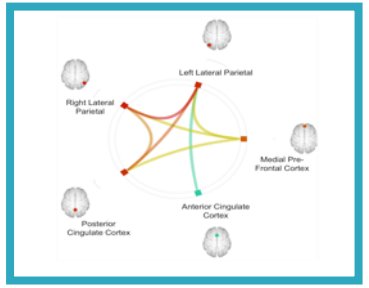
Methods Overview



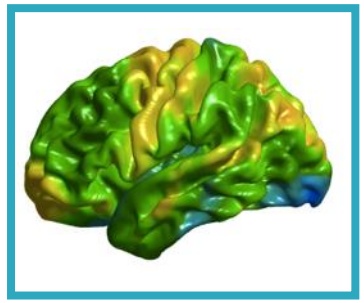
Voxel-based Morphometry



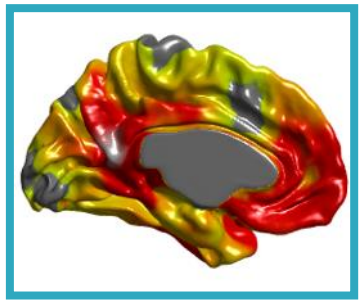
Gray matter volume



Functional connectivity

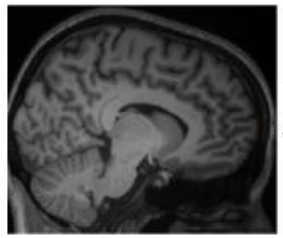


Cortical thickness

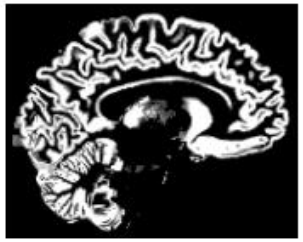


Structural covariance

Voxel-based Morphometry

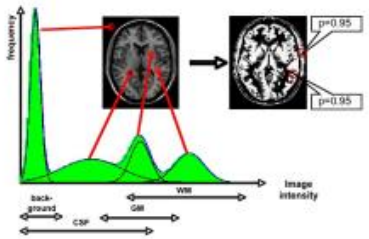


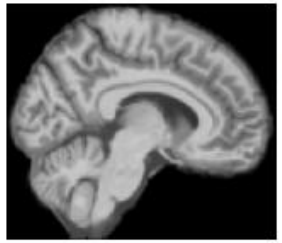
T1-weighted
structural image



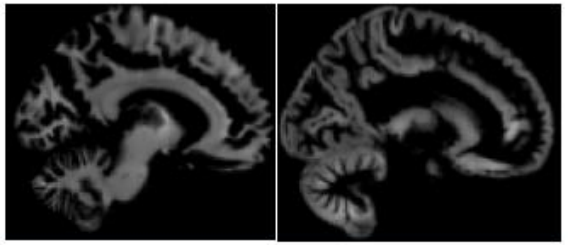
native space
segmentation

Computational Anatomy Toolbox

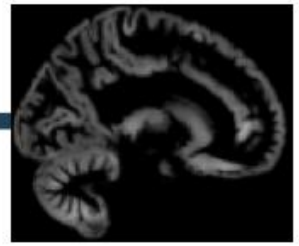




register
to standard space
using tissue priors



extraction of
GM and WM
segments



regional
grey matter
volume

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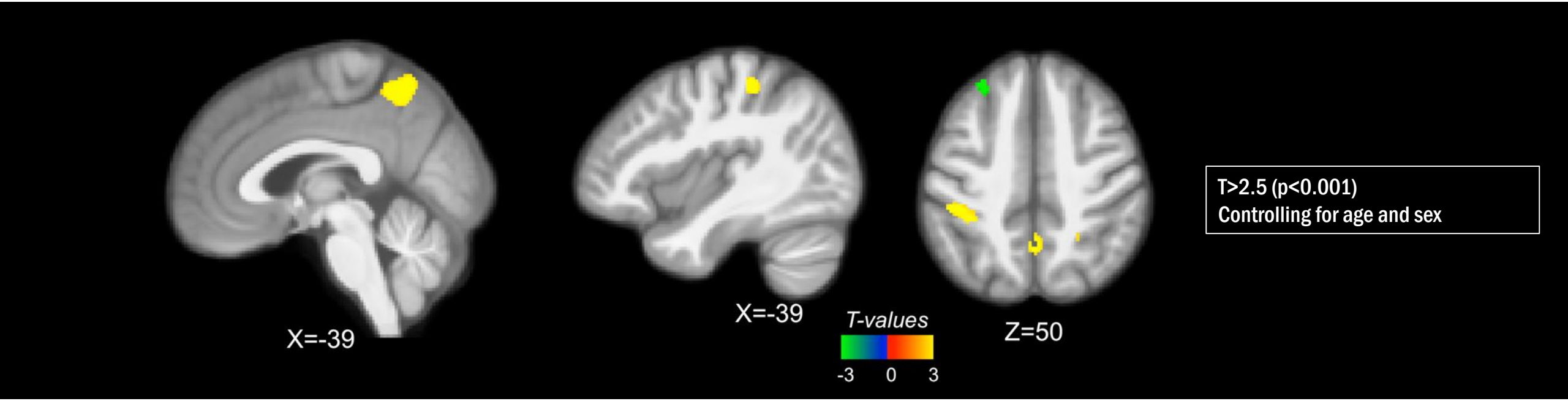
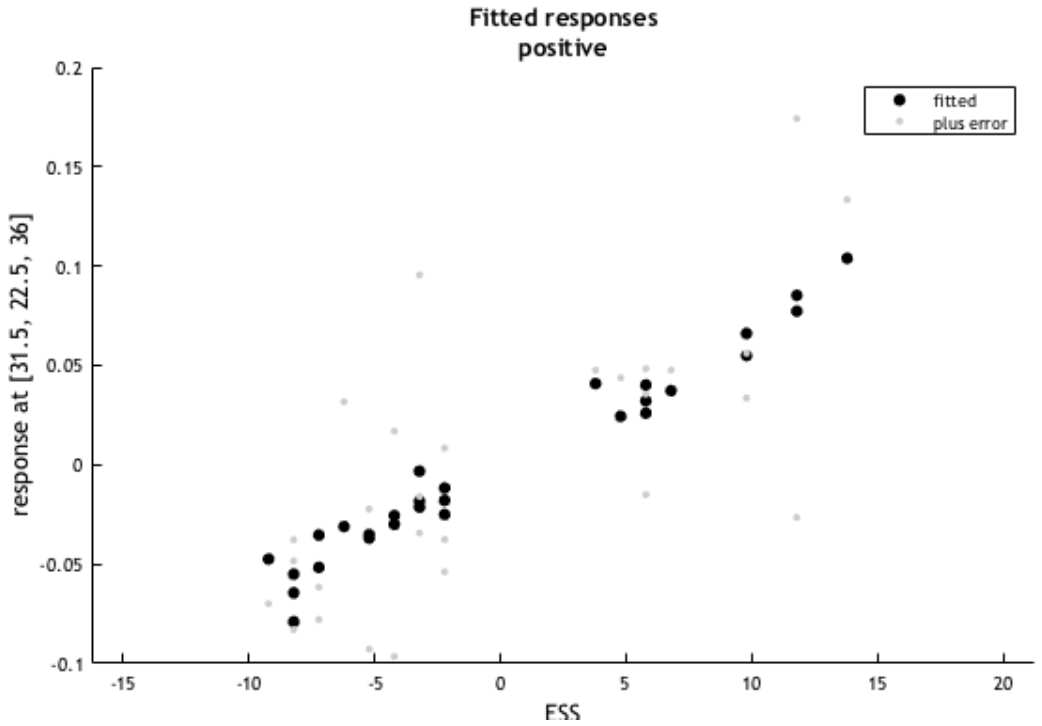
Gray Matter Volume

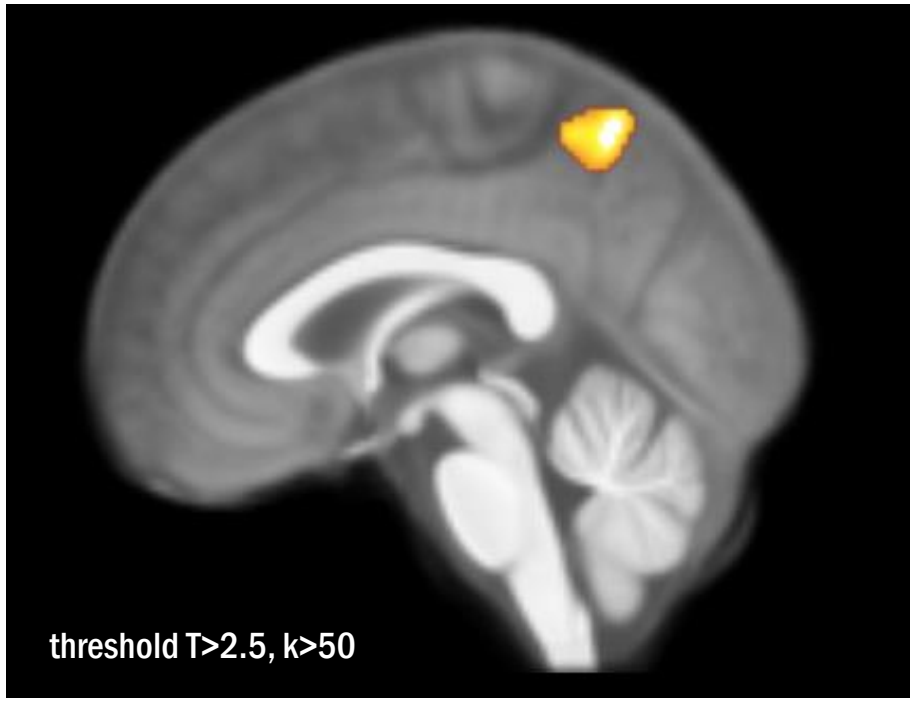
IH > Good Sleepers



Increased gray matter volume in regions of the DMN in IH

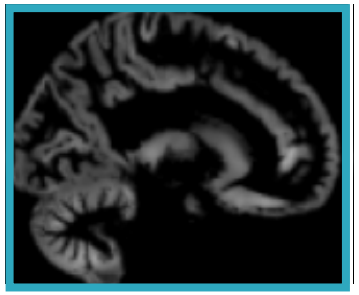
Grey Matter Volume Correlation With Sleepiness



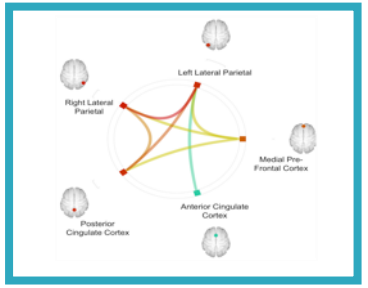


Whole group: GLM to look at correlation between grey matter volume and ESS, controlling for total intracranial volume, age and sex

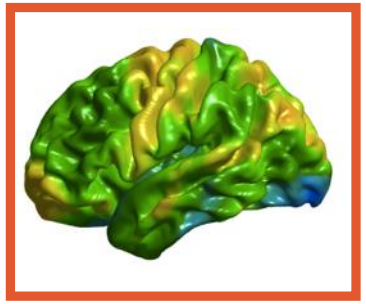
Cortical Thickness



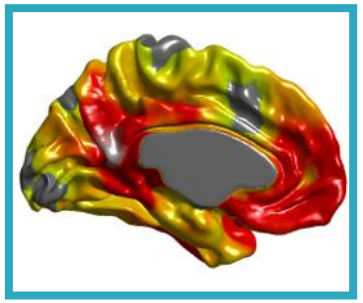
Gray matter volume



Functional connectivity

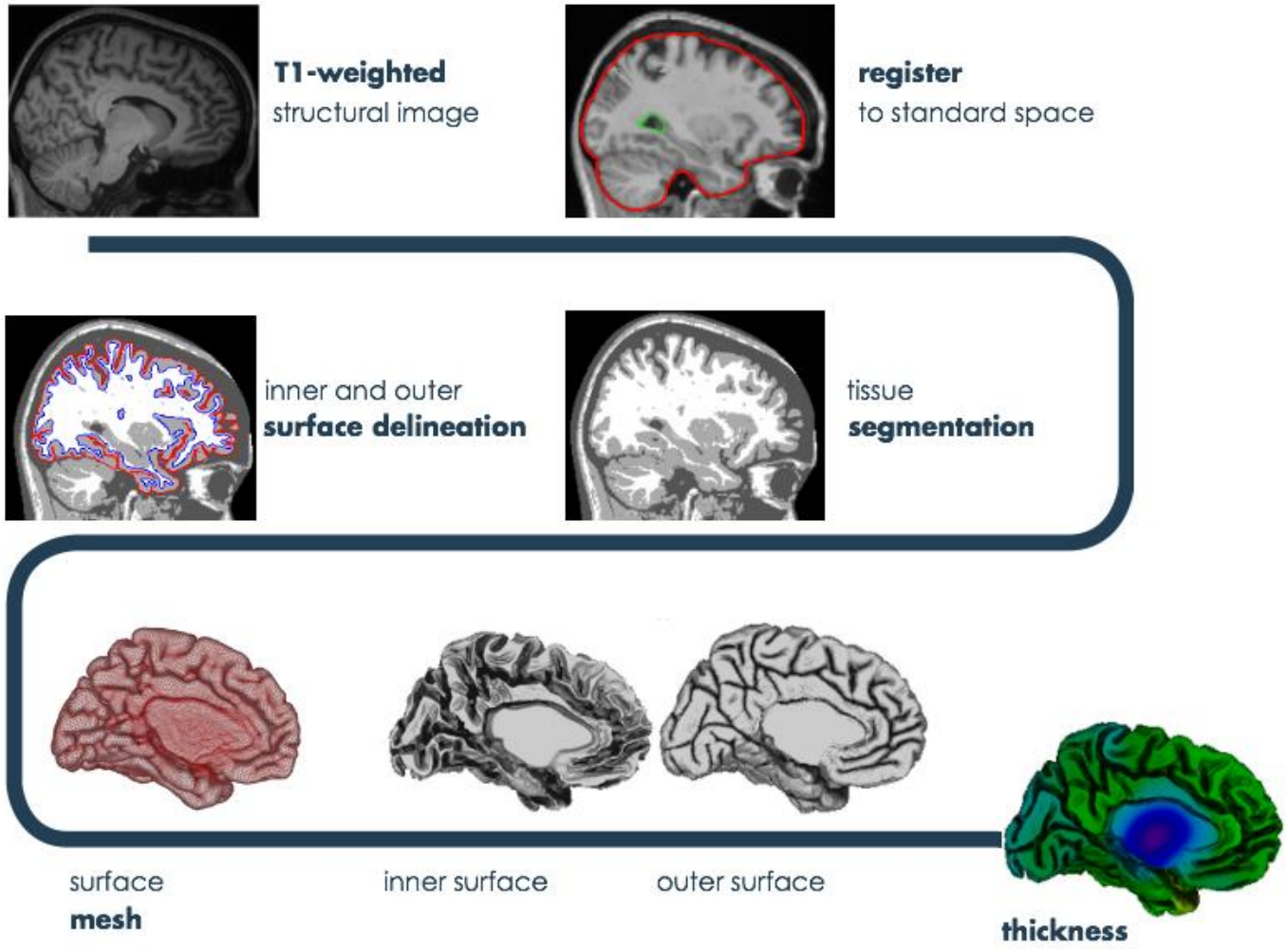


Cortical thickness



Structural covariance

Cortical Thickness



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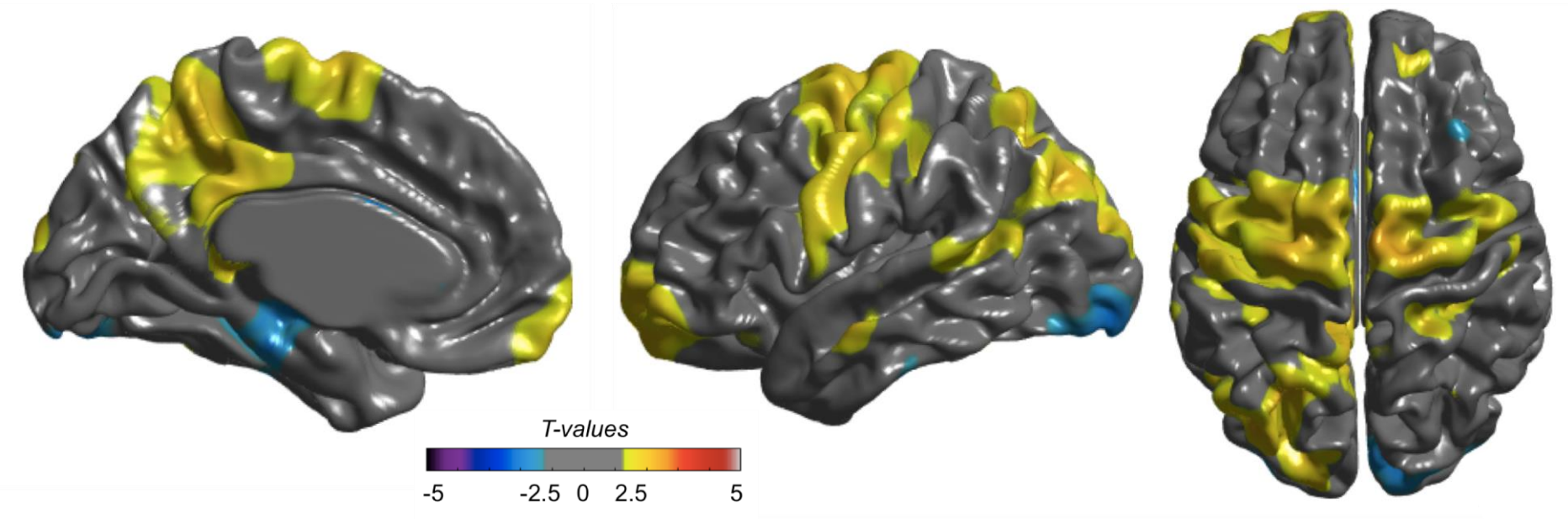
Cortical Thickness

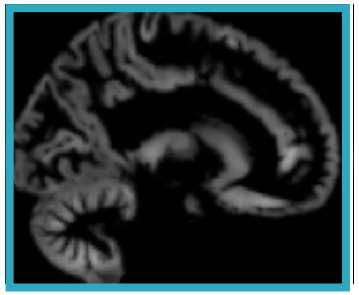
IH > Good Sleepers



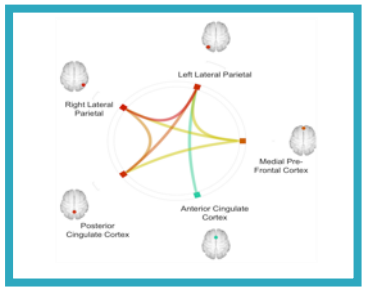
T>2.5 (p<0.001)
Controlling for
age and sex

Increased cortical thickness in DMN and sensorimotor regions in IH

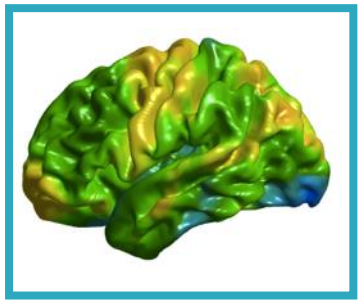
Structural Covariance



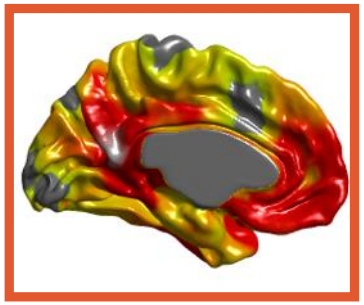
Gray matter volume



Functional connectivity

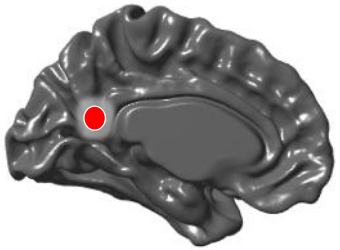


Cortical thickness

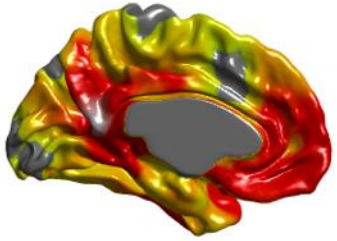


Structural covariance

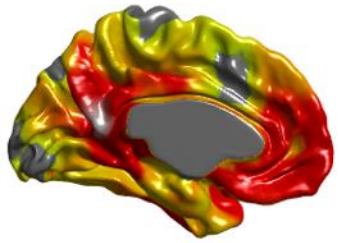
Structural Covariance



Seed region

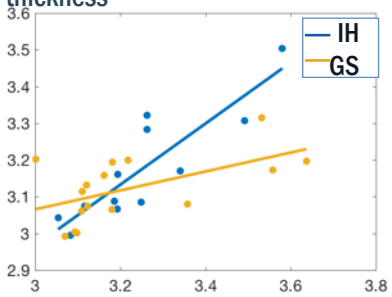


Hypersomnia

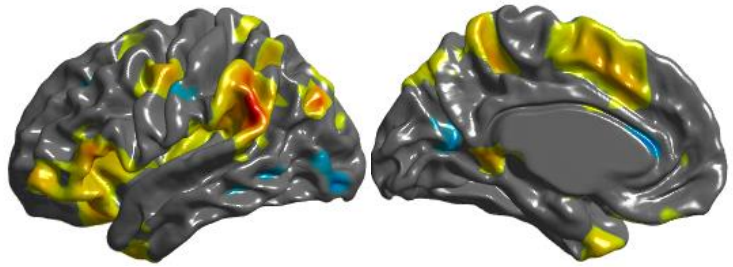


Good Sleepers

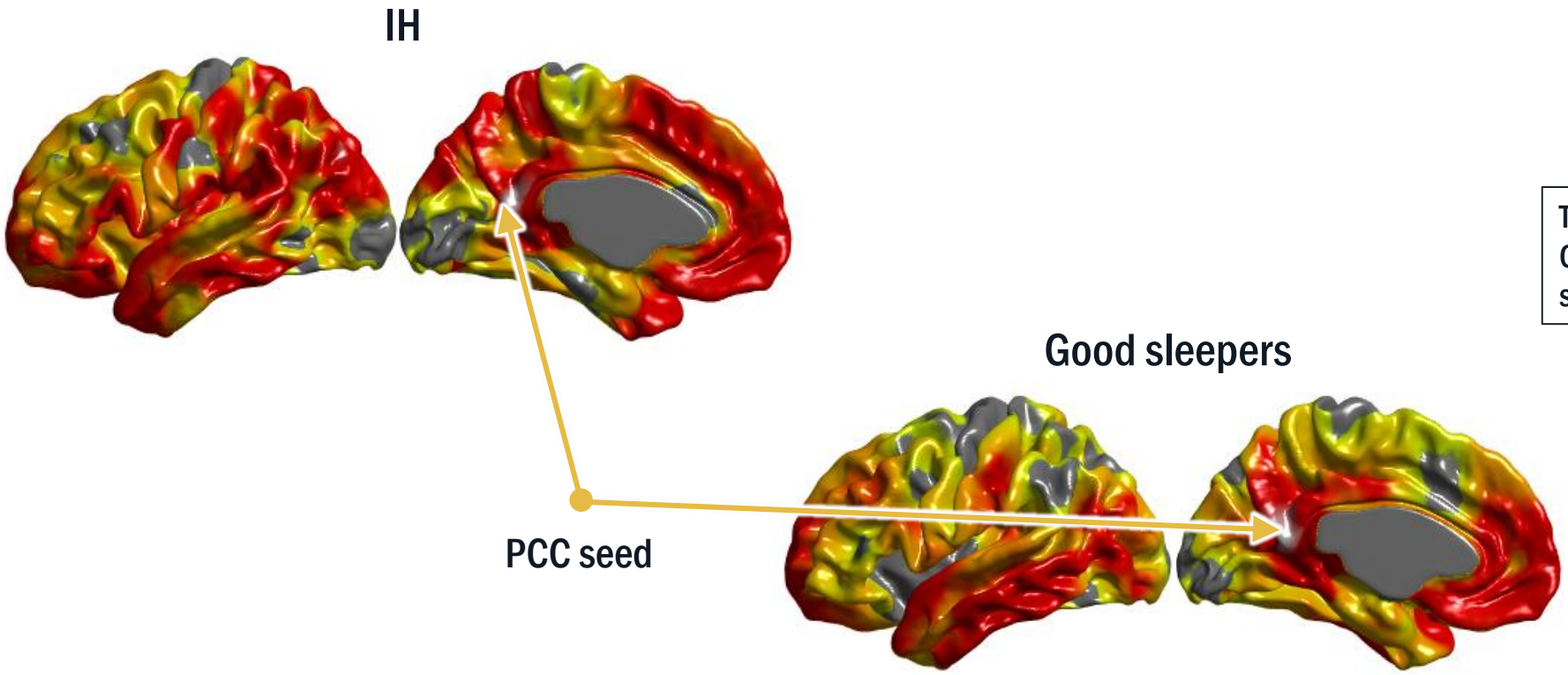
Mean thickness



PCC thickness



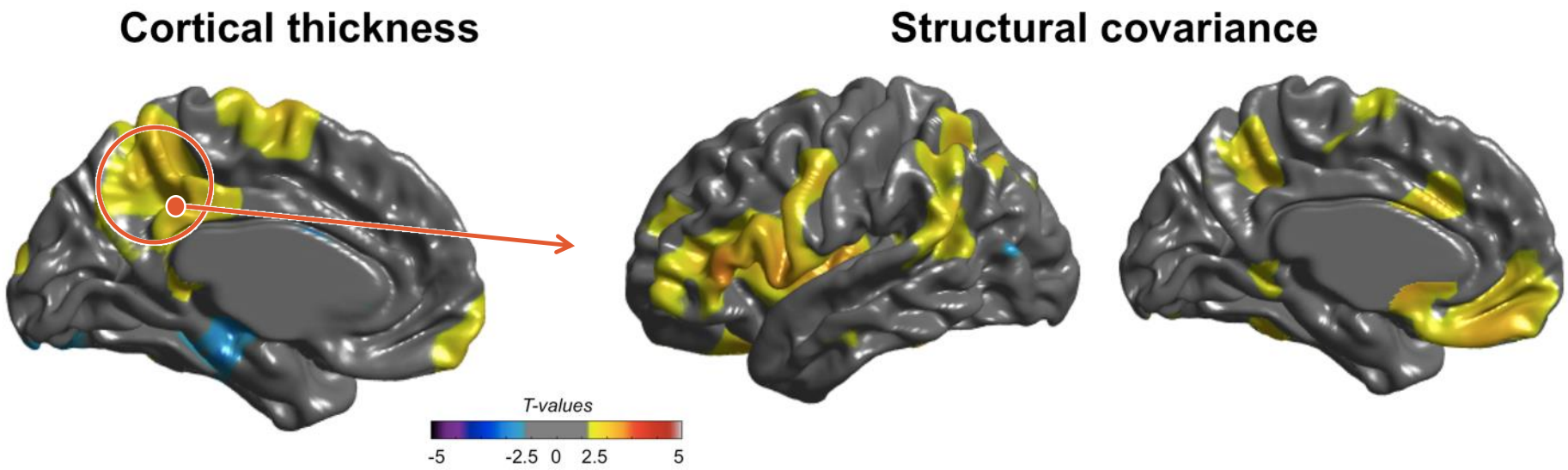
Structural Covariance



T>2.5 (p<0.001)
Controlling for age and sex

Structural Covariance

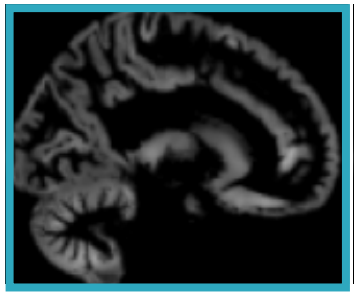
IH > Good Sleepers



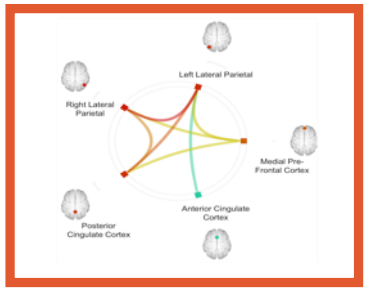
T>2.5 (p<0.001)
Controlling for age and sex

Increased structural covariance between regions of the DMN and other cortical regions (within and outside the DMN) in IH

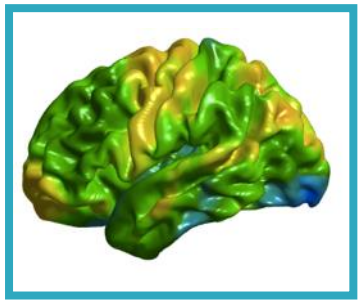
Functional Connectivity



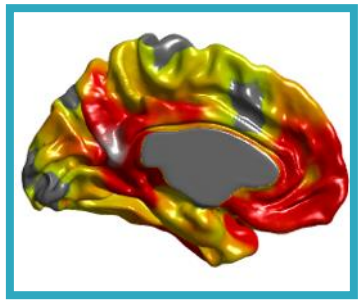
Gray matter volume



Functional connectivity

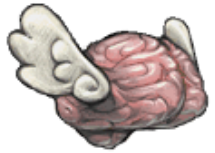


Cortical thickness

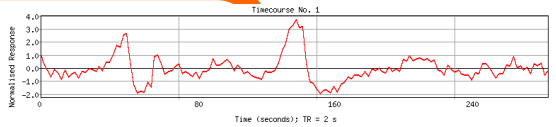


Structural covariance

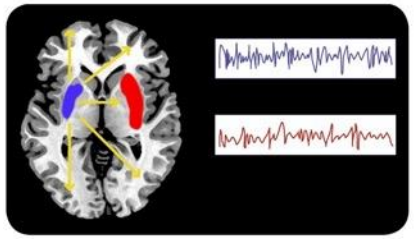
Functional Connectivity



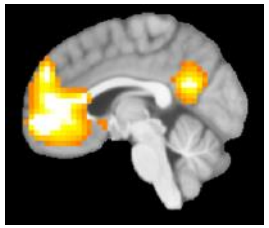
Network choice from RSNs



Average timeseries of the network

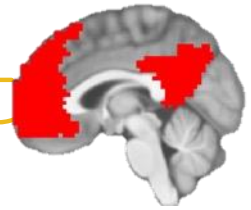


From Khazaie et al., Neurosci Biobehav Rev 2017

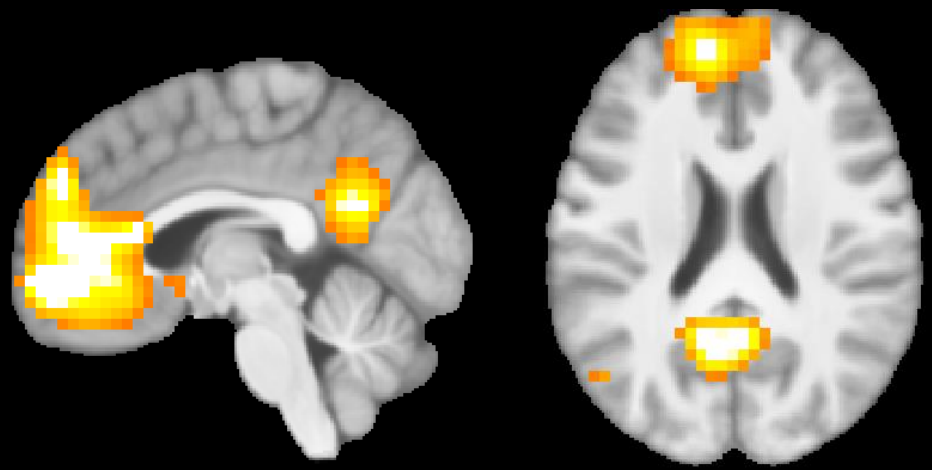


Connectivity difference

Functional Connectivit



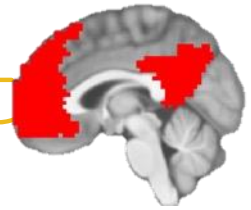
IH > Good Sleepers



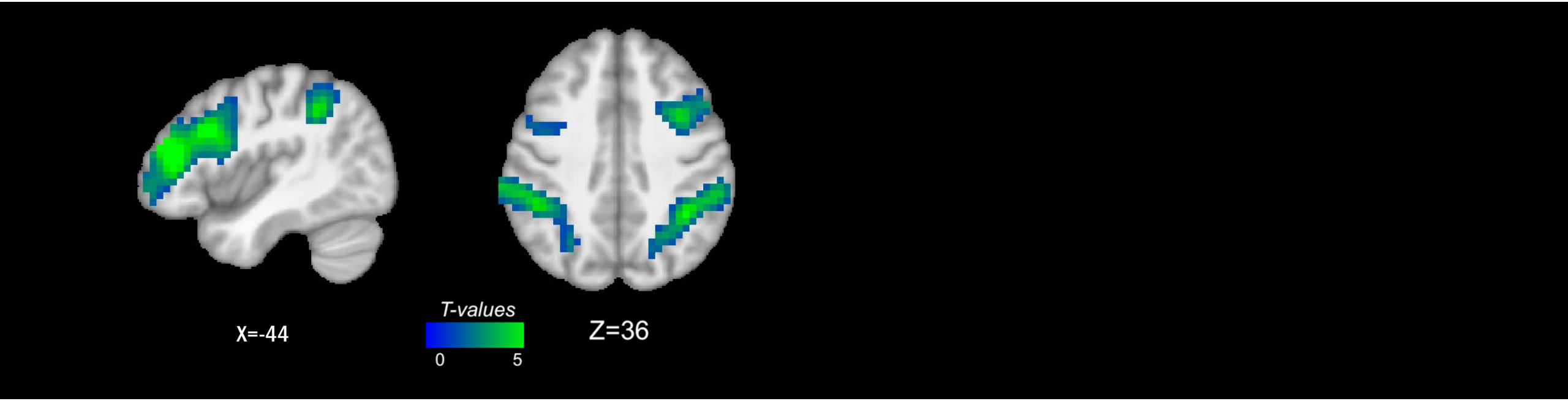
T>2.5 (p<0.001)
Controlling for age and sex

Increased functional connectivity within regions of the DMN in IH

Functional Connectivit

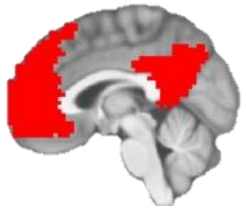


IH > Good Sleepers



Decreased functional connectivity between regions of the DMN and those of the dorsal attention network (DAN) in IH

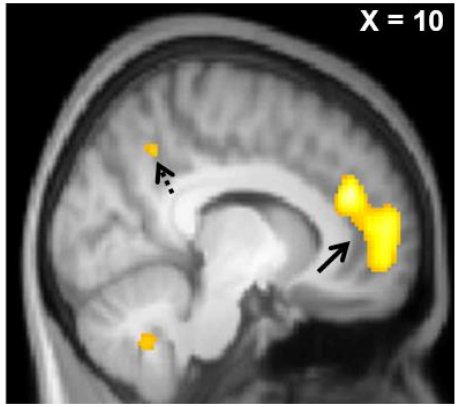
Default-mode Network

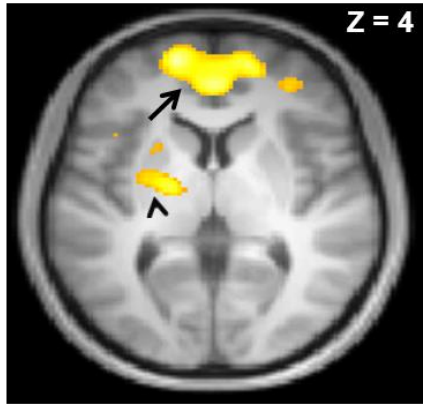


Idiopathic Hypersomnia:

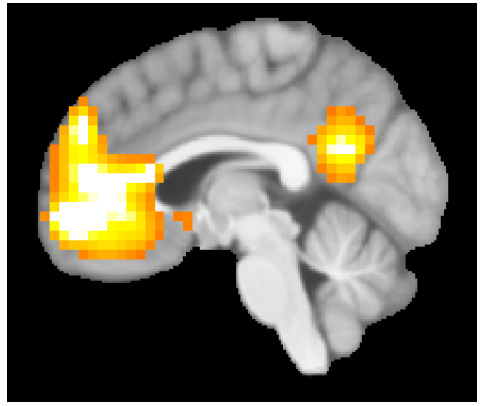
- ↗ grey matter and cortical thickness
- ↗ structural and functional connectivity within DMN
- ↘ functional connectivity between DMN & DAN

rCBF decreases





FC within DMN increases



hypersomnia foundation.org

Summary

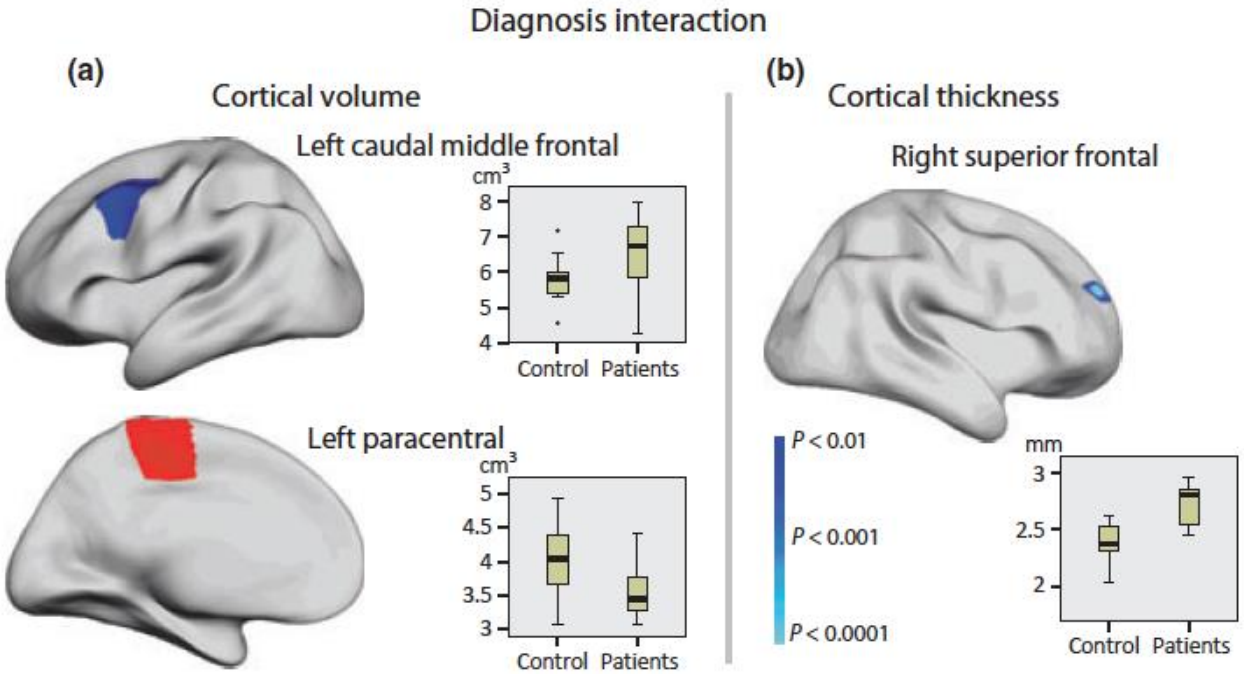
Decreased brain perfusion in regions of the **DMN**, indicating possible **persistent NREM sleep** features during wakefulness

Increased volume, thickness and connectivity in the **DMN**, indicating possible **compensatory** changes

Summary

Different findings in the DMN compared to **narcolepsy**

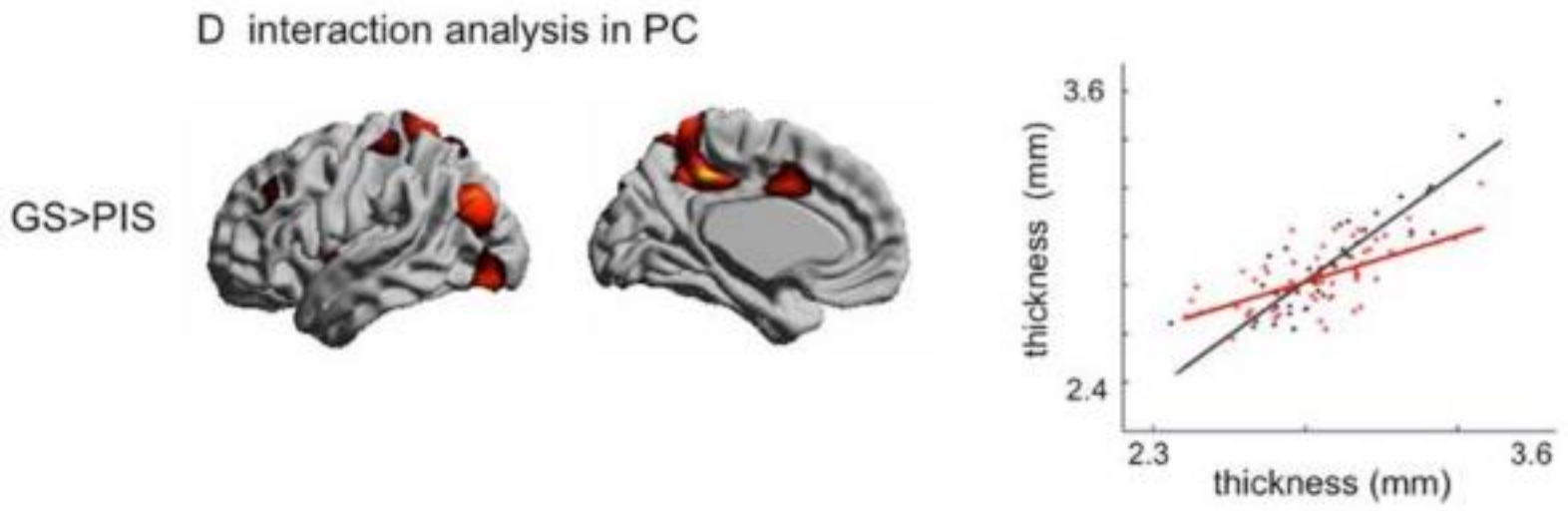
- **Distinct patterns of volume and thickness differences**
  (Schaer et al., 2012)



Summary

Different findings in the DMN compared to **insomnia**

- **Opposite patterns of structural connectivity**
  (Suh et al., 2016)



Limitations

- Small sample size
- Participants scanned at wake, not when symptoms are present or during sleep
- No direct comparison with narcolepsy

Thank You for Your Attention!

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Université Concordia University

cshn

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NSERC CRSNG

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Openings for Postdocs and Graduate Students

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