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
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)
**IH is Different From Narcolepsy**

Both are central disorders of hypersomnolence

<table>
<thead>
<tr>
<th></th>
<th>IH</th>
<th>Narcolepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataplexy</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Early REM sleep onset</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Refreshing sleep/naps</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Hypocretin (orexin) deficiency</td>
<td>✗</td>
<td>✓</td>
</tr>
</tbody>
</table>
Background

Brain Morphology - Narcolepsy

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

**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?

---

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

METHODS

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

16 good sleepers
Age: 22-53 y, mean 31 ±9
ESS: 4.8 ±2.3
Clinical Characteristics of IH Compared to Good Sleepers

**METHODS**

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

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

![Reaction Time Graph](image1)

![Omission Errors Graph](image2)

![Commission Errors Graph](image3)
METHODS

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

SPECT RESULTS

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

SPECT RESULTS

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

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)
BACKGROUND

**Default-mode Network**

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

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

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

![Diagram of Default-mode Network]

**WAKE**
- MFC
- IPL-l
- IPL-r
- PC

**SLEEP**
- MFC
- IPL-l
- IPL-r
- PC
Methods Overview

Structural MRI
- Cortical thickness
- Gray matter volume
- Structural covariance

SPECT
- Functional connectivity

Functional MRI
Voxel-based Morphometry

- Gray matter volume
- Functional connectivity
- Cortical thickness
- Structural covariance
Voxel-based Morphometry

METHODS

T1-weighted structural image

native space segmentation

register to standard space using tissue priors

extraction of GM and WM segments

regional grey matter volume
Gray Matter Volume

IH > Good Sleepers

*Increased* gray matter volume in regions of the DMN in IH
RESULTS

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

threshold $T>2.5, k>50$
Cortical Thickness

METHODS

Gray matter volume

Functional connectivity

Cortical thickness

Structural covariance
Cortical Thickness

**METHODS**

- **T1-weighted structural image**
- **register to standard space**
- **inner and outer surface delineation**
- **tissue segmentation**
- **surface mesh**
- **inner surface**
- **outer surface**
- **thickness**
Cortical Thickness

IH > Good Sleepers

Increased cortical thickness in DMN and sensorimotor regions in IH

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

Structural Covariance

Gray matter volume

Functional connectivity

Cortical thickness

Structural covariance
**METHODS**

**Structural Covariance**

Seed region  
Hypersomnia  
Good Sleepers

Mean thickness

- PCC thickness
- IH
- GS

Mean thickness

- IH
- GS
RESULTS

Structural Covariance

IH

PCC seed

Good sleepers

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

**Structural Covariance**

IH > Good Sleepers

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

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

- **Gray matter volume**
- **Cortical thickness**
- **Functional connectivity**
- **Structural covariance**
### Functional Connectivity

**METHODS**

- **Network choice from RSNs**
- **Average timeseries of the network**
- **Connectivity difference**

From Khazaie et al., Neurosci Biobehav Rev 2017
Functional Connectivity

IH > Good Sleepers

*Increased* functional connectivity within regions of the DMN in IH

$T > 2.5 \ (p < 0.001)$

Controlling for age and sex
RESULTS

Functional Connectivity

IH > Good Sleepers

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

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
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!

Contributors
Florence Pomares
Soufiane Boucetta
Jacques Montplaisir
Francis Lachapelle
Jungho Cha

Hosung Kim
Paul Gravel
Jean-Paul Soucy
Antonio Zadra

Affiliations

Funding Sources
Research associate:
Melodee Mograss

Postdoctoral fellows:
Florian Chouchou
Nathan Cross
Aurore Perreault
Florence Pomares
Dylan Smith

Graduate students:
Mehdi Essounni
Aude Jegou
Thomas Lehoux
Alex Nguyen
Oren Weiner

Research coordinators:
Despina Bolanis
Caroline Desrosiers
Undergraduate volunteers
Openings for Postdocs and Graduate Students

Contact: tt.dangvu@concordia.ca