Functional Imaging of the Sleeping and Sleep-Disordered Brain

Thanh DANG-VU, MD PhD

Center for Studies in Behavioral Neurobiology
Concordia University

Centre de Recherches de l’Institut Universitaire de Gériatrie de Montréal
Université de Montréal
Functional Neuroimaging of Normal Sleep
- Functional MRI of Non-REM Sleep Oscillations

Functional Neuroimaging of Sleep Disorders
- REM Sleep Behavior Disorder (RBD)
Functional Neuroimaging of Normal Sleep
  Functional MRI of Non-REM Sleep Oscillations

Functional Neuroimaging of Sleep Disorders
  REM Sleep Behavior Disorder (RBD)
Sleep stages: Non-REM sleep

Electroencephalogram (EEG) showing typical brain waves of sleep and wakefulness

- **wakefulness** (relaxed state)
- **stage 1**: theta waves (4–7 Hz)
- **stage 2**: sleep spindle (11–15 Hz), K-complex, slow waves (0.5–2.0 Hz)
- **stage 3** (slow-wave sleep)

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Functional Neuroimaging of Non-REM Sleep

Maquet et al., Brain Res, 1990

Global activation patterns
(PET $^{18}$FDG / glucose metabolism)
Regional brain activity **DECREASES:**

**NREM sleep vs Wakefulness**

(PET $H_2^{15}O$ / blood flow)

- Brainstem
- Thalamus
- Basal ganglia
- Basal forebrain / Hypothalamus
- Prefrontal cortex
- Anterior cingulate
- Precuneus

Maquet et al., J Neurosci, 1997
Functional Neuroimaging of Normal Sleep
   Functional MRI of Non-REM Sleep Oscillations

Functional Neuroimaging of Sleep Disorders & Aging
   SPECT studies of REM Sleep Behavior Disorder (RBD)
Functional Neuroimaging of Non-REM Sleep Oscillations

Ref. : linked mastoids
Functional Neuroimaging of Non-REM Sleep Oscillations

Brain activity during Non-REM sleep

Non-REM sleep oscillations detected as individual EVENTS:
- Spindles
- Slow waves

fMRI / BOLD

EEG
Functional Neuroimaging of SPINDLES

Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep

M. Schabus*, T. T. Dang-Vu†, G. Albouy†, E. Balteau†, M. Boly†, J. Carrier†, A. Darsaud†, C. Degueldre†, M. Desesse,‡, S. Gais†, C. Phillips†, G. Rauchs†, C. Schnakers‡, V. Sterpenich†, G. Vandewalle†, A. Luxen*, and P. Maquet*†

*Estion Research Centre, University of Liège, B-4000 Liège, Belgium; †Departments of Psychiatry and ‡Neurology, Centre Hospitalier Universitaire de Liège, B-4000 Liège, Belgium; †Department of Psychology, University of Salzburg, A-5020 Salzburg, Austria; and Department of Psychology, University of Montreal, Montreal, QC, Canada H3C 3J7

Edited by Marcus E. Raichle, Washington University School of Medicine, St. Louis, MO, and approved June 26, 2007 (received for review April 3, 2007)
Functional Neuroimaging of SPINDLES

Schabus, Dang-Vu et al., PNAS, 2007

Thalamus
Anterior cingulate
Insula

Steriade & Timofeev, Neuron, 2003
Functional Neuroimaging of SPINDLES

- FAST SPINDLES (central): 13-15 Hz
- SLOW spindles (frontal): 11-13 Hz

FAST spindles > SLOW spindles

Schabus, Dang-Vu et al., PNAS, 2007

- Hippocampus
- Sensorimotor cortex
- Medial Prefrontal

Sensorimotor cortex
Functional Neuroimaging of SPINDLES

FAST SPINDLES & MEMORY

Fz
Cz
Pz
Oz

« FAST »
spindles
(central):
13-15 Hz

Bergmann et al, Neuroimage, 2011
Spontaneous neural activity during human slow wave sleep

Thien Thanh Dang-Vu†‡, Manuel Schabus‡, Martin Desseilles‡, Geneviève Albouy†, Mélanie Boly†‡, Annabelle Darsaud†, Steffen Gais†, Géraldine Rauchs†, Virginie Sterpenich†, Gilles Vandewalle‡, Julie Carrier‡, Gustave Moonen‡, Evelyne Balteau†, Christain Degueldre‡, André Luxen†, Christophe Phillips†, and Pierre Maquet†‡

1Cyclotron Research Centre, University of Liège, B4000 Liège, Belgium; 2Department of Neurology, CHU Sart Tilman, B4000 Liège, Belgium; and 3Department of Psychology, University of Montreal, Montreal, QC, Canada H2V 2S9

Edited by Marcus E. Raichle, Washington University School of Medicine, St. Louis, MO, and approved July 11, 2008 (received for review February 26, 2008)
Functional Neuroimaging of SLOW WAVES

Dang-Vu et al., PNAS, 2008

Inferior frontal gyrus
Precuneus
Posterior cingulate

Massimini et al, J Neurosci, 2004
Functional Neuroimaging of SLOW WAVES

Noradrenergic neurons of the Locus Coeruleus are phase locked to cortical up-down states during sleep in rats.

Brainstem
Cerebellum
Parahippocampal

Dang-Vu et al., PNAS, 2008

Eschenko et al., Cer Cortex, 2011
Functional Neuroimaging of Non-REM Sleep Oscillations

EEG/ fMRI

Schabus, Dang-Vu et al, PNAS, 2007  Dang-Vu et al, Sleep, 2010
Dang-Vu et al, PNAS, 2008
Functional Neuroimaging of Sound Processing during Non-REM Sleep
Functional Neuroimaging of Sound Processing during Non-REM Sleep

Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep

Thien Thanh Dang-Vu¹,¹,²,³, Maxime Bonjean¹,²,³,⁴, Manuel Schabus²,⁵, Melanie Boly³, Annabelle Darsaud³, Martin Desseilles³, Christian Degueldre³, Evelyne Balteau³, Christophe Phillips³, André Luxen³, Terrence J. Sejnowski¹,²,³,⁴, and Pierre Maquet³

¹Cyclotron Research Centre, University of Liège, B-4000 Liège, Belgium; ²Howard Hughes Medical Institute, The Salk Institute, and ³Division of Biological Sciences, University of California at San Diego, La Jolla, CA 92037; and ⁴Laboratory for Sleep and Consciousness Research, Department of Psychology, University of Salzburg, A-5020 Salzburg, Austria

Contributed by Terrence J. Sejnowski, August 5, 2011 (sent for review June 15, 2011)
13 healthy young volunteers
18 - 25 years
Right-handed
Non-smokers
Moderate caffeine and alcohol consumers
No medication
Pittsburgh Sleep Quality Index (PSQI)
Epworth sleepiness scale
Beck Anxiety & Depression Inventories
Horne-Ostberg Questionnaire

**TONES**

*Pure tones (beep, gaussian window)*

*Binaurally (headphones)*

**Duration :** 300 ms

**Frequency :** 400 Hz

70 % probability of occurrence at each scan

**Intensity :** constant, set individually prior to the experiment

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*Dang-Vu et al, PNAS, 2011*
Sound processing during Non-REM sleep and SPINDLES

Tones / WAKE

Tones / Non-REM Sleep

Dang-Vu et al, PNAS, 2011
Functional Neuroimaging of Sound Processing during Sleep and Non-REM Sleep Oscillations

Spindles distort responses to sounds

Dang-Vu et al, PNAS, 2011
Functional Neuroimaging of Sound Processing during Sleep and Non-REM Sleep Oscillations

Spindle rate predicts sleep stability from sounds

Dang-Vu et al, Curr Biol, 2010
Functional Neuroimaging of Sound Processing during Non-REM Sleep

Dang-Vu et al, PNAS, 2011
Sound processing during Non-REM sleep and K-COMPLEXES

Fig. 1. Top and Middle. Population. * TNK TN0
Fig. 2. Top and Middle. Population. * TNK TN0
Fig. 3. Top and Middle. Population. * TNK TN0
Fig. 4. Top and Middle. Population. * TNK TN0

Dang-Vu et al, PNAS, 2011
Functional Neuroimaging of Sound Processing during Non-REM Sleep

Schabus, Dang-Vu et al., Frontiers Neurol, 2012
Sound processing during Non-REM sleep and SLOW WAVES

A – Tone responses independent of SW phase

B – SW phase dependent response (TPost > TPre)

Schabus, Dang-Vu et al., Frontiers Neurol, 2012
Functional Neuroimaging of Sound Processing during Sleep and Non-REM Sleep Oscillations

Dang-Vu et al, PNAS, 2011

Schabus, Dang-Vu et al., Frontiers Neurol, 2012
Functional Neuroimaging of Normal Sleep
- Functional MRI of Non-REM Sleep Oscillations

Functional Neuroimaging of Sleep Disorders
- REM Sleep Behavior Disorder (RBD)
Figure 15-2. Functional and structural neuroimaging of sleep disorders

A1 Idiopathic Insomnia: Functional Studies
- Activity increase during NREM sleep
- Activity decrease during wake
- Activity increase during wake
- Activity decrease during wake

A2 Idiopathic Insomnia: Structural Studies
- Increased volume
- Reduced volume

B1 Narcolepsy: Functional Studies
- Activity increases at wake
- Activity decreases at wake
- Activity increase during cataplexy
- Activity decrease during cataplexy

B2 Narcolepsy: Structural Studies
- Gray matter decrease

C1 Obstructive Sleep Apnea Syndrome: Functional Studies
- Activity increase during cognitive performance
- Activity decrease during cognitive performance
- Activity decrease at wake

C2 Obstructive Sleep Apnea Syndrome: Structural Studies
- Gray matter decrease

D Restless Legs Syndrome
- Activity increase during RLS
- Gray matter increase
- Gray matter decrease
- Decreased iron concentration

E Rapid-eye-movement sleep behavior disorder
- Activity increase at wake
- Activity decrease at wake
- Gray matter increase
- Gray matter decrease
Functional Neuroimaging of Normal Sleep
  Functional MRI of Non-REM Sleep Oscillations

Functional Neuroimaging of Sleep Disorders
  REM Sleep Behavior Disorder (RBD)
REM Sleep Behaviour Disorder (RBD)
Rapid-eye-movement sleep behavior disorder

- Activity increase at wake
- Activity decrease at wake
- Gray matter increase
- Gray matter decrease

**Dang-Vu, O’Byrne, et al., in Sleep Disorders Medicine, 2014**

- Mazza et al., 2006
  1. Pons
  2. Superior frontal
  3. Hippocampus
  4. Temporoparietal
  5. Putamen
- Vendette et al., 2011
  1. Pons
  2. Superior frontal
  3. Hippocampus
  4. Precuneus

- Hanyu et al., 2011
  4. Precuneus
  6. Cerebellum
- Dang-Vu et al., 2012
  1. Pons
  3. Hippocampus
- Ellmore et al., 2010
  7. Putamen
- Scherfler et al., 2011
  8. Hippocampus
Structural Neuroimaging of RBD: Pontine Structures

MRI with Diffusion Tensor Imaging (DTI)

Scherfler et al, Ann Neurol, 2011

Dang-Vu et al, in Sleep and Movement Disorders (2013)
Structural Neuroimaging of RBD: Pontine Structures

MRI with neuromelanin-sensitive sequences

Garcia-Lorenzo et al, Brain, 2013
Structural Neuroimaging of RBD: Dopaminergic Nigro-Striatal System

Substantia nigra hyperechogenecity (ultrasound)

Iwamani et al, Sleep Med, 2010

Dang-Vu et al, in Sleep and Movement Disorders (2013)
Functional Neuroimaging of RBD: Dopaminergic Nigro-Striatal System

Presynaptic DA dysfunction (PET / SPECT with DAT ligands)

Control | RBD patient 1 | RBD patient 2

Albin et al, Neurology, 2000
### Functional Neuroimaging of RBD: Dopaminergic Nigro-Striatal System

**Presynaptic DA dysfunction (PET / SPECT with DAT ligands)**

**Table 19.4. SPECT- and PET-Ligand Studies in REM Sleep Behavior Disorder**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>IMAGING</th>
<th>TARGET</th>
<th>NO. PAT. // CTRL. MEDICATION*</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisensehr et al. 92</td>
<td>SPECT 123I-IPT &amp; 123I-IBZM</td>
<td>DAT &amp; D2</td>
<td>5 // 7</td>
<td>No</td>
</tr>
<tr>
<td>Eisensehr et al. 93</td>
<td>SPECT 123I-IPT &amp; 123I-IBZM</td>
<td>DAT &amp; D2</td>
<td>8 // 11</td>
<td>No</td>
</tr>
<tr>
<td>Albin et al. 94</td>
<td>PET 11C-DTBZ</td>
<td>DAT</td>
<td>6 // 19</td>
<td>Yes</td>
</tr>
<tr>
<td>Gilman et al. 95</td>
<td>PET 11C-DTBZ</td>
<td>DAT</td>
<td>13** // 15</td>
<td>No</td>
</tr>
<tr>
<td>Stiasny-Kolster et al. 96</td>
<td>SPECT 123I-FP-CIT</td>
<td>DAT</td>
<td>11 // 10</td>
<td>Yes</td>
</tr>
<tr>
<td>Unger et al. 91</td>
<td>SPECT 123I-FP-CIT</td>
<td>DAT</td>
<td>5 // 0</td>
<td>No</td>
</tr>
<tr>
<td>Kim et al. 97</td>
<td>SPECT 123I-FP-CIT</td>
<td>DAT</td>
<td>14 // 12</td>
<td>No</td>
</tr>
<tr>
<td>Iranzo et al. 84</td>
<td>SPECT 123I-FP-CIT</td>
<td>DAT</td>
<td>43 // 18</td>
<td>No</td>
</tr>
<tr>
<td>Iranzo et al (link to Iranzo 2011)</td>
<td>SPECT 123I-FP-CIT</td>
<td>DAT</td>
<td>20 // 20</td>
<td>No</td>
</tr>
<tr>
<td>Miyamoto et al. 98</td>
<td>PET 11C-CFT</td>
<td>DAT</td>
<td>1 // 6</td>
<td>No</td>
</tr>
</tbody>
</table>

*Dang-Vu et al, in Sleep and Movement Disorders (2013)*
Mazza et al, Neurology, 2006:
- 99mTc-ECD SPECT *(wakefulness)*
- 8 patients / 9 ctrls
- Perfusion increases: pons, putamen, hippocampus *(right)*
- Perfusion decreases: frontal and temporoparietal areas

Vendette et al, Mvt Dis, 2011:
- 99mTc-ECD SPECT *(wakefulness)*
- 20 patients / 20 ctrls
- Perfusion increases: pons, putamen, hippocampus, temporal areas
- Perfusion decreases: frontal and parietal areas
Patients with idiopathic RBD are at risk for developing synucleinopathies:
- Parkinson’s disease
- Dementia with Lewy bodies
- Multiple system atrophy

5 year-risk: approx. 50% (Schenck et al, 1996; Iranzo et al, 2006; Postuma et al, 2009)

Interval: variable, up to 50 years (Claassen et al, 2010)

Predictors for development of neurodegenerative disorder in RBD?
RBD and neurodegenerative disorder

† Predictors for development of neurodegenerative disorder in RBD?

† Neuroimaging (Iranzo, Lancet Neurol 2010)
  † Decreased striatal DAT uptake ($^{123}$I-FP-CIT SPECT)
  † Midbrain hyperechogenicity (TCS)

<table>
<thead>
<tr>
<th>Age at neuroimaging (years)</th>
<th>RBD duration at neuroimaging (years)</th>
<th>Reduced striatal $^{123}$I-FP-CIT uptake</th>
<th>Hyperechogenicity of substantia nigra</th>
<th>Echogenic substantia nigra size (cm$^2$)</th>
<th>Diagnosis 2-5 years after neuroimaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>Yes</td>
<td>Yes</td>
<td>0.24</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>Yes</td>
<td>No</td>
<td>0.05</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>Yes</td>
<td>No</td>
<td>0.10</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>Yes</td>
<td>Yes</td>
<td>0.12</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>No</td>
<td>Yes</td>
<td>0.25</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>No</td>
<td>Yes</td>
<td>0.34</td>
<td>Dementia with Lewy bodies</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>Yes</td>
<td>Yes</td>
<td>0.26</td>
<td>Dementia with Lewy bodies</td>
</tr>
<tr>
<td>8</td>
<td>73</td>
<td>Yes</td>
<td>No</td>
<td>0.10</td>
<td>Multiple system atrophy</td>
</tr>
</tbody>
</table>
Functional Neuroimaging of RBD: Predictive Brain Perfusion Patterns

Methods

- 99mTc-ECD SPECT at baseline
- Clinical follow-up: 3 years on average
  - 20 RBD patients:
    - 10 stable (8M & 2F)
    - 10 evolving (8M & 2F)
    - 5 to Parkinson disease (PD)
    - 5 to Lewy body dementia (LBD)
- SPM8 analysis: comparison of SPECT data between groups
Functional Neuroimaging of RBD: Predictive Brain Perfusion Patterns

Stable > Evol

Evol > Stable

Stable: n=10
Evol: n=10

$P < .05$, corrected (SVC)

Dang-Vu et al., Neurology, 2012
Functional Neuroimaging of RBD: Predictive Brain Perfusion Patterns

Evol > Stable

Stable: n=10  Evol: n=10  \( P < .05, \text{ corrected (SVC)} \)

Dang-Vu et al., Neurology, 2012
Stable vs Ctrl: n=10
Evol: n=10
Ctrls: n=10

\( P < .05, \text{ corrected (SVC)} \)

Dang-Vu et al., Neurology, 2012
RBD and neurodegenerative disorder

- Predictors for development of neurodegenerative disorder in RBD?
  - Clinical signs:
    - Motor signs (UPDRS)
    - Colour vision abnormalities (FM-100)

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*Postuma et al, Ann Neurol, 2011*
Functional Neuroimaging of RBD: Predictive Brain Perfusion Patterns

Regression with motor score (UPDRS-III) (n=19)

\[ x = 36 \]
\[ y = -12 \]

\[ P < .05, \text{ corrected (SVC)} \]

Dang-Vu et al., Neurology, 2012
Functional Neuroimaging of RBD: Predictive Brain Perfusion Patterns

Regression with colour vision score (FM-100) (n=19)

P < .05, corrected (SVC)

Dang-Vu et al., Neurology, 2012
Structural neuroimaging of RBD

Gray matter density increases in hippocampus (VBM)

Scherfler et al, Ann Neurol 2011
Functional neuroimaging of Parkinson

Table 3 lists the peaks of the most significantly decreased. In patients with stage I or II disease, the adjusted rCBF significantly increased in both cerebral cortical regions except the right lower temporal. In patients with stage III and IV disease, adjusted rCBF showed a significant reduction, whereas basal ganglia, a significant increase in adjusted rCBF in Parkinson’s thalami, brain stems, hippocampi and cerebellums showed no disease patients compared with healthy volunteers (no voxels significant reduction). Table 4 shows the voxels with cortex showed a significant reduction, whereas basal ganglia, a significant increase in adjusted rCBF in Parkinson’s thalami, brain stems, hippocampi and cerebellums showed no disease patients compared with healthy volunteers (no voxels significant reduction). Table 3 lists the peaks of the most significantly decreased. In patients with stage I or II disease, the adjusted rCBF significantly increased in both cerebral cortical regions except the right lower temporal.

FIGURE 2. Adjusted regional cerebral blood flow (rCBF) increase shown by statistical parametric mapping (SPM) in patients with Parkinson’s disease compared with healthy volunteers. MIP = maximum intensity projection.

Imon et al., J Nucl Med 1999
Structural and functional studies have demonstrated alterations in the pons, supporting the involvement of pontine nuclei in RBD pathophysiology.

Structural and functional studies suggest degenerative changes of the SN and presynaptic dysfunction of DA nigro-striatal pathways in RBD, which are in agreement with the view of RBD as an early stage of a neurodegenerative disease (PD).
Neuroimaging of RBD: conclusion (2)

- It is possible with neuroimaging to predict the short-term development of neurodegenerative disease in RBD patients.
- Disease progression can be predicted by abnormal perfusion in the hippocampus at baseline.
Functional neuroimaging with EEG-fMRI identifies brain areas involved in the generation of sleep spindles and slow waves.

EEG-fMRI studies demonstrate that sleep oscillations modulate the processing of external stimulation during sleep:
- Filtering of information at the thalamic level during spindles
- Cortical processing of information during K-complexes
- Facilitation of cortical processing during the ‘up’ state of the slow oscillation

Functional neuroimaging in the pathophysiology and prospective evaluation of sleep disorders:
- Neuroimaging biomarkers of evolution towards neurodegenerative diseases
ACKNOWLEDGEMENTS

- S. Boucetta, J. O’Byrne, L. Reed, O. Malhi, V. Zhang, A. Arcelin, A. Salimi, M. Berman, V. Delvecchio, K. Wenzel, F. Lachapelle, V. Discepola

- Canadian Institutes of Health Research (CIHR)
- Fonds de Recherche du Québec – Santé (FRQS)
- Natural Sciences and Engineering Research Council of Canada (NSERC)
- Sleep Research Society Foundation (SRSF)