Functional brain imaging in sleep

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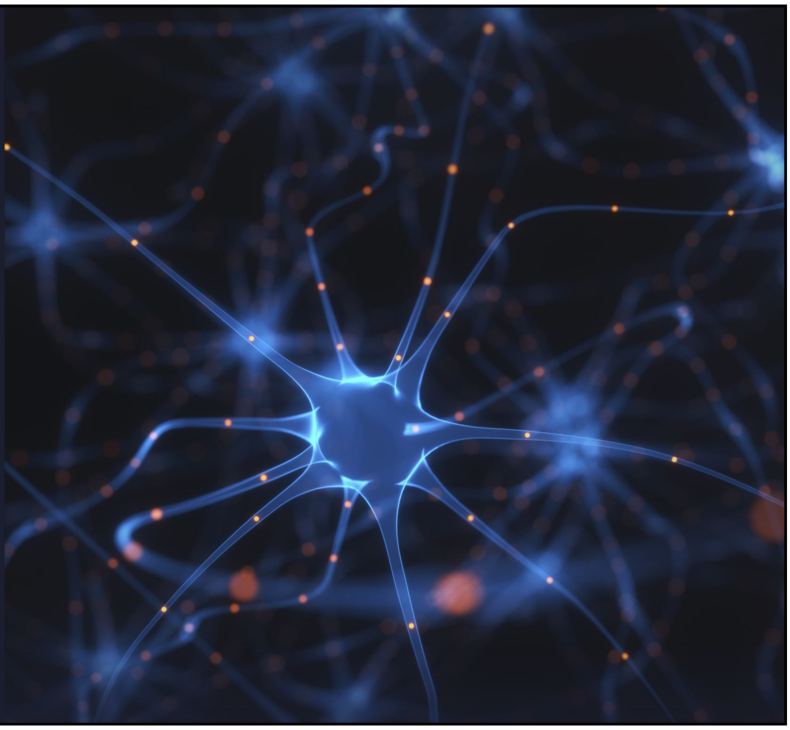


1

Neuroimaging in Sleep

- Functional neuroimaging is a powerful tool to explore regional brain activity in humans.
- It includes a variety of metabolic and hemodynamic techniques such as
  - Positron emission tomography (PET)
  - Single-photon emission computed tomography (SPECT)
  - Functional magnetic resonance imaging (fMRI)
  - Near-infrared spectroscopy
  - Neurophysiologic techniques such as electroencephalography (EEG)
  - Magnetoencephalography (MEG)

2

Functional neuroimaging methods for assessing brain function during sleep

	MEG tomography	fMRI	[^{15}O]H_2O PET	[^{18}F]FDG PET	[^{99m}]Tc-ECD SPECT	Receptor imaging
Measure	Electrical events	Blood flow	Blood flow	Metabolism	Blood flow/ metabolism	5-HT, DA, ACH, GABA, etc.
Spatial resolution	10 mm	<1 cm	Centimetres	Centimetres	Centimetres	Centimetres
Temporal resolution	Milliseconds	Seconds	Minute	10–20 min	Minutes	20–90 min
Sleep in scanner	Yes	Yes	Yes	No	No	Waking
Other	Difficult in sleep, availability, expense	Noise, technically difficult in sleep	Repeated measures possible	Long half-life limits repeated measures	Repeatable in single night	Expensive, labour intensive

3

Neuroimaging in Normal Human Sleep

- PET, SPECT, or fMRI studies demonstrated that global and regional patterns of brain activity during sleep are remarkably different from those during wakefulness
- These studies have also shown the persistence of brain responses to external stimuli during sleep, and plastic changes in brain activity related to previous waking experience.

4

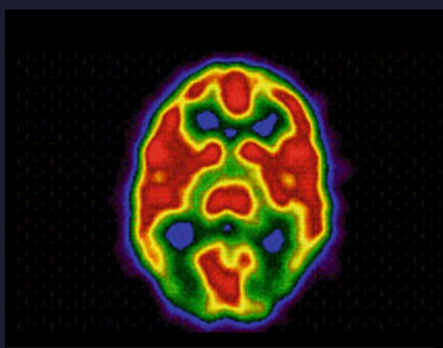
Neuroimaging Insights into the Pathophysiology of Sleep Disorders

- Neuroimaging methods can be used to investigate whether sleep disorders associated with specific changes in brain structure or regional activity.
- These new data might improve our understanding of the pathophysiology underlying adult sleep disorders.
- Functional brain imaging findings in
  - Intrinsic sleep disorders (i.e., idiopathic insomnia, narcolepsy, and obstructive sleep apnea)
  - Abnormal motor behavior during sleep (i.e., periodic limb movement disorder and REM sleep behavior disorder)

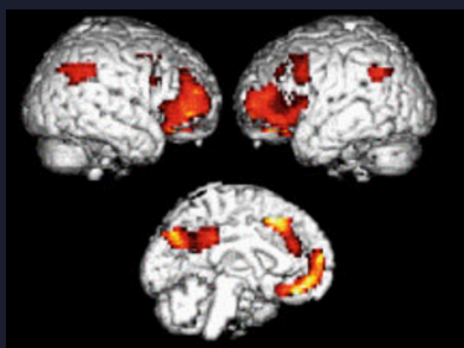
5

Functional Neuroimaging of Normal Human Sleep: Wakefulness

Cerebral glucose metabolism : Prefrontal and parietal lobes (both on the medial wall and convexity)



^{18}F-FDG-PET



^{15}O-PET

Regional cerebral blood flow (CBF) during awake

6

Normal Human Sleep: NREM Sleep

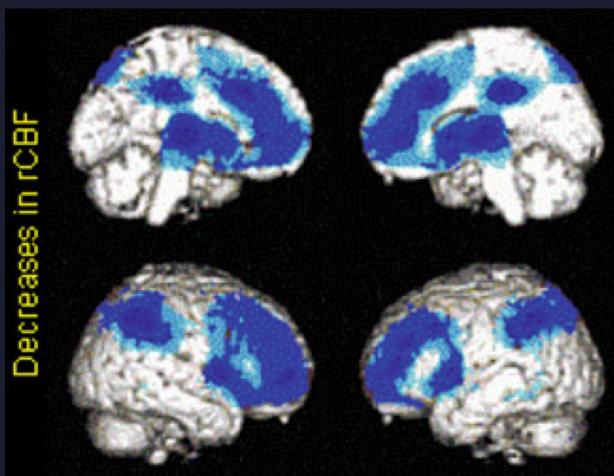
- In mammals, the neuronal activity observed during NREM sleep is sculpted by
  - Cortical slow oscillation that alternates short bursts of firing ("up" states)
  - Long periods of hyperpolarization ("down" states)
  - Slow oscillations organize the synchronization of other NREM sleep rhythms (spindles and delta waves)

Have a major impact on regional cerebral blood flow (rCBF), which when averaged over time decreases in the areas where they prevail

7

Functional Neuroimaging of Normal Human Sleep: NREM Sleep

- PET studies show brainstem and thalamus blood flow decreased during light NREM sleep as well as during SWS
- In human PET data showed pattern of cortical deactivation inhomogeneously distributed throughout the various cortex in SWS
  - Frontal (in particular dorsolateral and orbital prefrontal cortex)
  - Parietal cortex
  - A lesser extent in temporal and insular cortices



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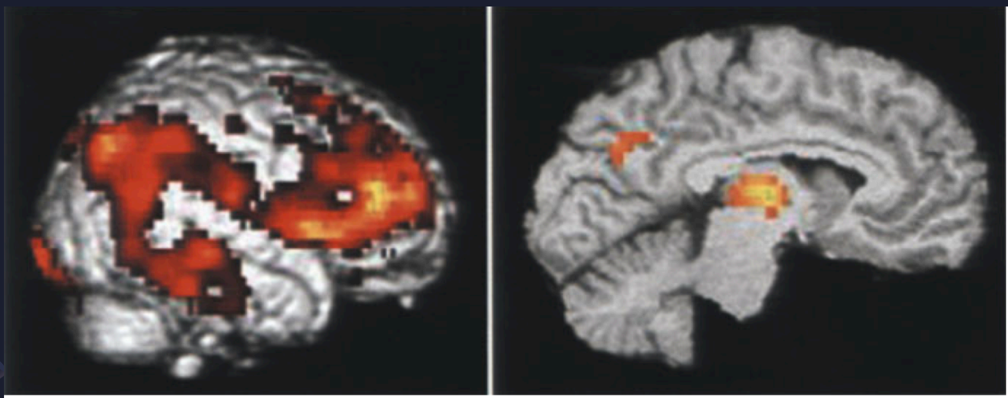
8

Functional Neuroimaging of Normal Human Sleep: NREM sleep

^{18}F-FDG-PET in NREM shows hypometabolism over prefrontal, parietal and temporal cortex. and thalamus



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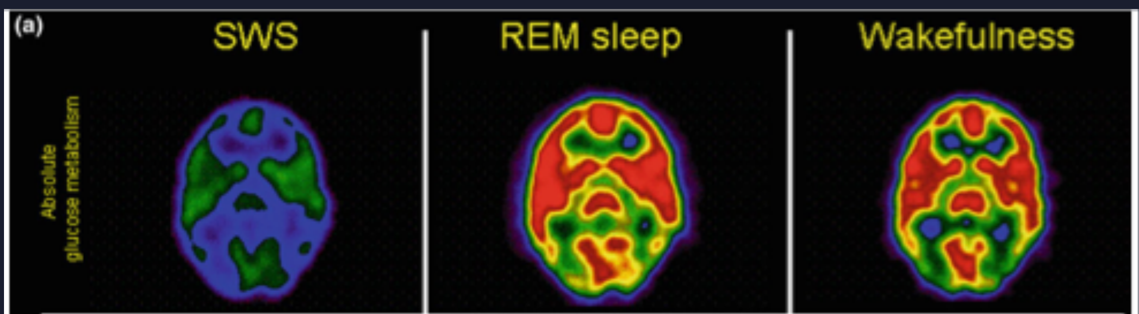
Regions where relative metabolism is less in NREM sleep than in waking.

9

Functional Neuroimaging of Normal Human Sleep

Whole-brain metabolic rates in the waking condition were intermediate between those in REM and nonREM sleep

Cerebral glucose metabolism



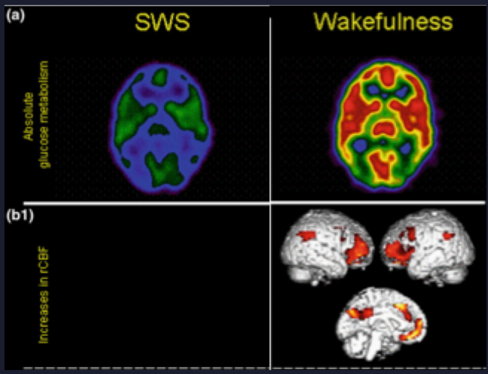
^{18}-F-FDG-PET

Metabolic rate higher throughout the cortex in REM than nonREM sleep, cingulate and frontal cortex, thalamus, and visual association

10

Functional Neuroimaging of Normal Human Sleep: NREM

- **NREM Sleep**
- Compared to wakefulness, average cerebral metabolism and global blood flow levels begin to
  - Decrease in light (stage 1 and stage 2) NREM sleep
  - Reach their nadir in deep (stage 3) NREM sleep (SWS)



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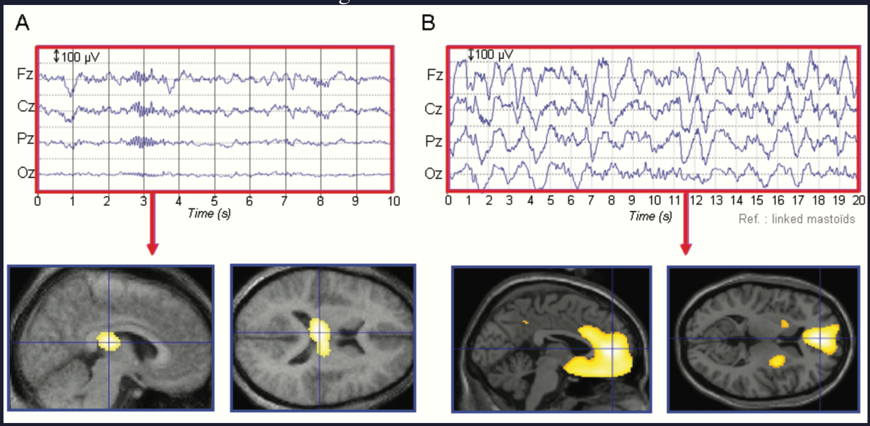
11

Functional Neuroimaging of Normal Human Sleep: NREM sleep

^{15}O-PET rCBF correlated with EEG during NREM



12

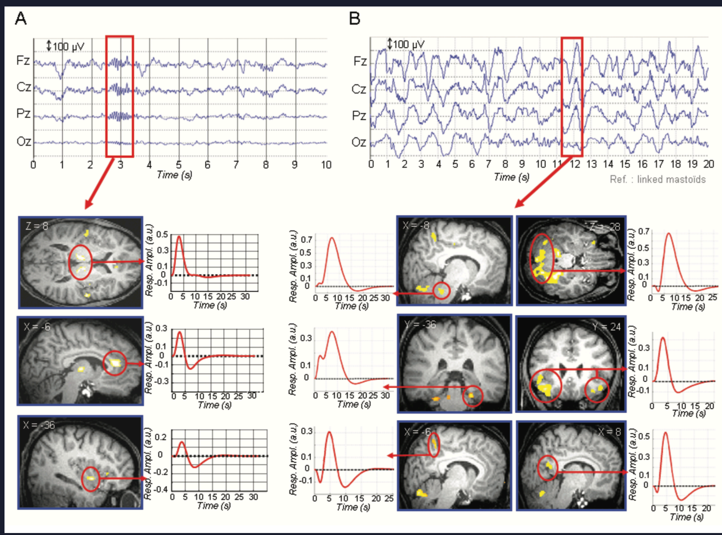
Functional Neuroimaging of Normal Human Sleep: NREM sleep

fMRI correlated with EEG during NREM

PET correlates of spindles

thalamus, anterior cingulate cortex and insula

rCBF during NREM sleep shown to negatively correlate with sigma power in the thalamus bilaterally.



Dang-Vu TT; etal., SLEEP 2010

PET correlates of slow waves. (stage 4) NREM sleep

brainstem, cerebellum, parahippocampal gyrus, inferior frontal gyrus, precuneus and posterior cingulate gyrus

Slow wave activity recorded at the scalp negatively correlated with rCBF in several brain areas (thalamus, brainstem, cerebellum, anterior cingulate, and orbitofrontal cortex).

13

Normal Human Sleep: REM sleep

- REM sleep is characterized by desynchronized neuronal activity and, correspondingly, by high cerebral energy requirements and blood flow
- In this active but sleeping brain, some areas are particularly active, even more than during wakefulness, while others have lower than average regional activity

14

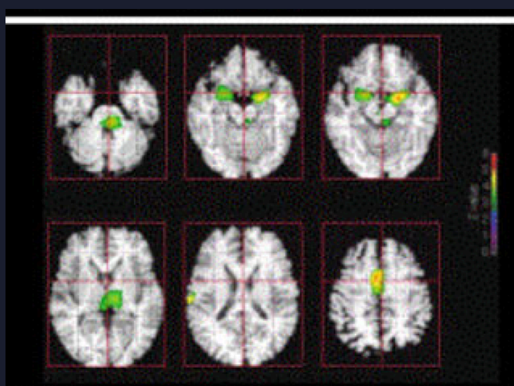
Normal Human Sleep: Functional neuroimaging in REM sleep

- PET studies show significant rCBF increases during REM sleep in
  - Pontine tegmentum, thalamic nuclei, limbic and paralimbic areas, amygdaloid complexes, hippocampal formation, anterior cingulate cortex, and orbitofrontal and insular cortices
  - Posterior cortices in temporo-occipital areas also found to be activated

15

Functional Neuroimaging of Normal Human Sleep: REM sleep

- PET studies have shown significant rCBF increases during REM sleep in
  - Pontine tegmentum
  - Thalamic nuclei
  - Limbic and paralimbic areas, amygdaloid complexes, hippocampal formation
  - Anterior cingulate cortex
  - Orbitofrontal and insular cortices



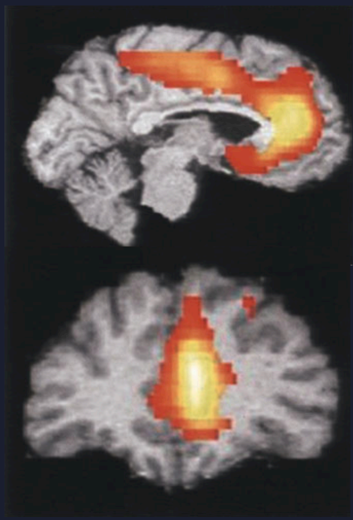
Increase rCBF during REM sleep

16

Functional Neuroimaging of Normal Human Sleep: REM sleep

REM Sleep shows hypermetabolism

- Ventral striatum, subgenual, pregenual and dorsal anterior cingulated cortex, medial prefrontal cortex, supplementary motor area (SMA) and primary sensorimotor cortex
- Basal forebrain, basal ganglia, premotor cortex, cerebellum, insular cortex, mesial temporal cortex including the hippocampus, amygdala, and uncus, and brainstem reticular formation



18F-FDG-PET

17

Functional Neuroimaging of Normal Human Sleep: REM sleep

Regional brain activity in subcortical mesopontine and thalamic regions during human REM sleep is in keeping with our current understanding of sleep generation in animals

REM sleep is generated by neuronal populations of the mesopontine reticular formation that activates the thalamic nuclei, which in turn activate the cortex

18

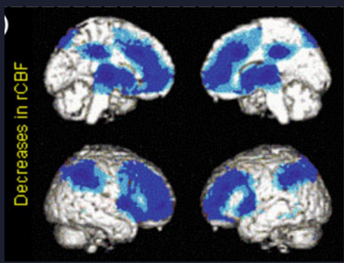
Functional Neuroimaging of Normal Human Sleep: rCBF in NREM and REM

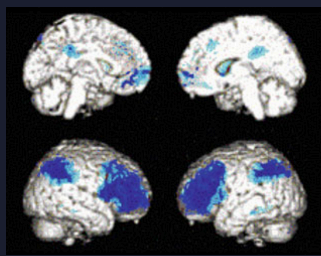
^{15}O-PET

NREM **REM**

Frontal (in particular dorsolateral and orbital prefrontal cortex)

Parietal cortex
A lesser extent in temporal and insular cortices





inferior and middle dorsolateral prefrontal gyri, the inferior parietal cortex, and the posterior cingulate cortex and precuneus were the least active brain regions

Decreased rCBF in NREM and REM sleep

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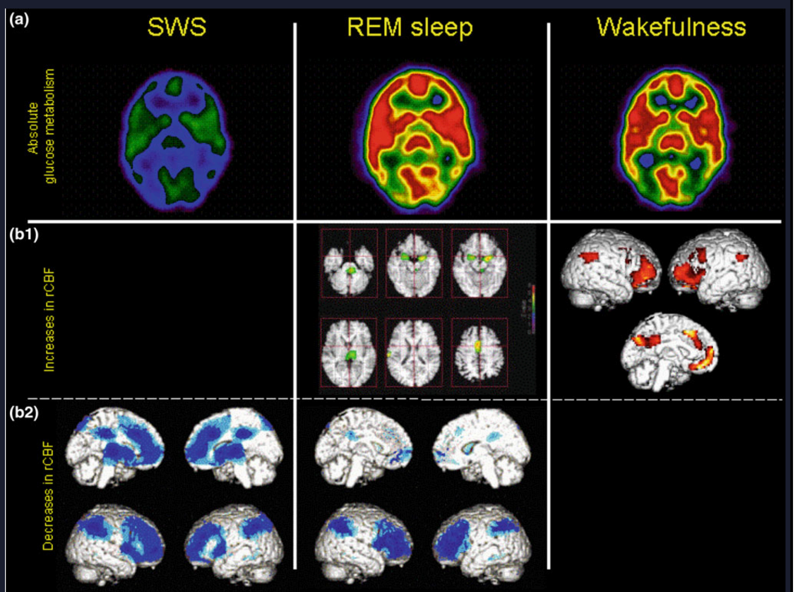
19

Functional Neuroimaging of Normal Human Sleep:

Cerebral glucose metabolism (CGM) and regional cerebral blood flow (CBF) during

- deep NREM sleep (first column)
- REM sleep (second column)
- wakefulness (third column).



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20

Functional Neuroimaging of Normal Human Sleep: REM sleep

- fMRI study demonstrated REM sleep connectivity is also different from NREM sleep connectivity, specifically in the set of brain areas known as the default-mode network
- The default-mode network consists of regions activated when the brain is not engaged in externally oriented behavior
- The functional connectivity within the default-mode network diminished in NREM sleep, but in REM sleep, it is comparable to that in wakefulness

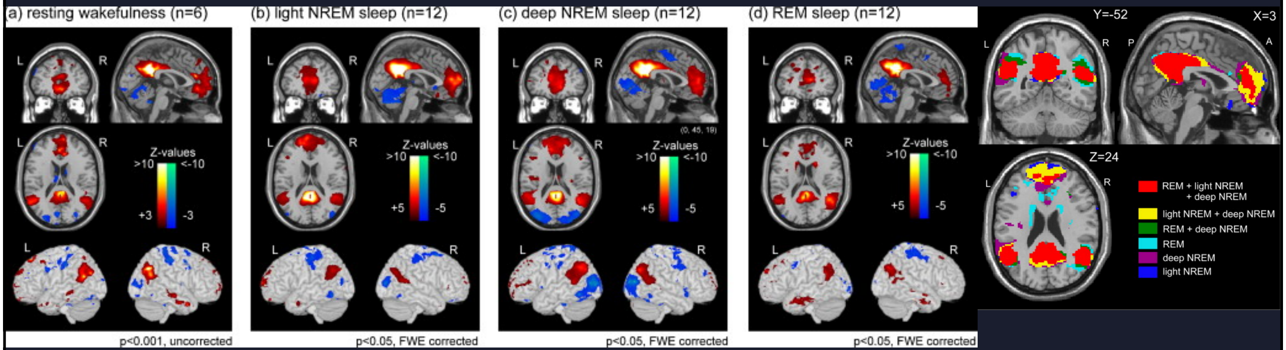
21

Functional Neuroimaging of Normal Human Sleep: REM sleep

- DMN in (REM) sleep with that in (NREM) sleep is useful for revealing relationship between arousal level
- Arousal level is at its lowest during deep NREM, while during REM sleep it is as high as wakefulness
- Functional connectivity among the DMN core regions - the posterior cingulate cortex, rostral anterior cingulate cortex, and inferior parietal lobule - remained consistent across sleep states.
- In contrast, connectivity involving the DMN subsystems of REM sleep differs from that of NREM sleep, and the change well accounts for the characteristics of REM sleep

22

Default-mode network during sleep



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23

Neuroimaging of Sleep Disorders

- It can help characterize the cerebral consequences of sleep disruption due to intrinsic sleep disorders and extrinsic environmental or medical causes
- To better characterize the pathogenic mechanisms of sleep disorders, or at least their cerebral correlates
- Help to establish the nosography of sleep disorders.
  - For instance, neuroimaging could help classify different subtypes of insomnia in terms of their underlying characteristic patterns of regional brain activity, an approach that may prove complementary to clinical observation.

24

Functional Neuroimaging in Sleep Disorders

- Sleep may be disrupted in a number of conditions ranging from
  - Medical diseases (e.g., endocrine disorders, chronic pain, brain lesions, and sleep apnea)
  - Psychiatric disorders (e.g., anxiety, depression, and schizophrenia)
  - Environmental situations (e.g., jet lag, shift work, and noisy environment)

25

Functional Neuroimaging: Idiopathic Insomnia

- Idiopathic Insomnia is a lifelong inability to obtain adequate sleep that is presumably due to an abnormality in the neurologic control of sleep–wake regulation systems
- This disorder probably caused from imbalance between arousal system and various sleep-inducing and sleep-maintaining systems.

26

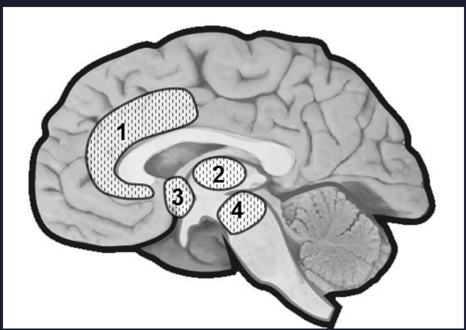
Functional Neuroimaging: Idiopathic Insomnia

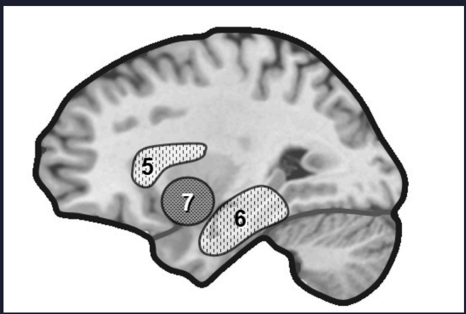
- Patients with insomnia showed major rCBF decrease in the basal ganglia, medial frontal cortex, occipital cortex, and parietal cortex.
- These results suggest that idiopathic insomnia is associated with an abnormal pattern of regional brain activity during NREM sleep that particularly involves a dysfunction in basal ganglia
- 18FDG PET: Insomniac patients showed
  - Increased global CMRglu during sleep, suggesting an overall cortical hyperarousal in insomnia.
  - A smaller decline, in relative CMRglu from waking to sleep states in the ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices

27

Functional Neuroimaging: Idiopathic Insomnia

Metabolic increase during NREM Sleep
Metabolic decrease during NREM Sleep





Insomnia patients showed increased global CMRglu during transition from waking to sleep onset as compared to healthy subjects, suggesting there is an overall cortical hyperarousal in insomnia

Metabolic increase in ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices

28

Functional Neuroimaging: Narcolepsy

- Narcolepsy is a disorder characterized by excessive sleepiness that is typically associated with several manifestations of so-called dissociated or isolated REM sleep features, such as
  - Muscle atonia (i.e., cataplexy), sleep paralysis, and hallucinations

- Human narcolepsy has been found to be associated with reduction in or loss of the hypothalamic peptide hypocretin (also called orexin) implicated in arousal systems

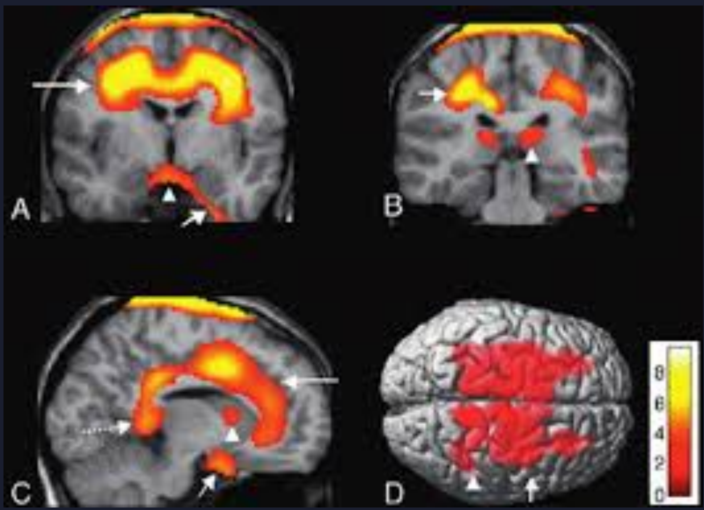
29

Functional Neuroimaging: Narcolepsy

- 18FDG PET studies shows reduced CMRglu bilateral posterior hypothalami, mediodorsal thalamic nuclei, and frontal and parietal cortices
- CMRglu of FDG-PET increase in the cingulate and visual association cortices in patients also suffering from cataplexy
- SPECT study revealed hypoperfusion during wakefulness in several areas including the bilateral anterior hypothalami, caudate nuclei, pulvinar, parahippocampal gyri, cingulate gyri, and prefrontal cortices

30

Functional Neuroimaging: Narcolepsy



hypermetabolism in narcolepsy–cataplexy in fully awake condition in the limbic cortex specifically in the anterior and mid cingulate cortex, in the right cuneus and lingual gyrus.

31

Functional Neuroimaging: OSA

- OSAS is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with reduction in blood oxygen saturation
- Population-based epidemiologic, high prevalence (1–5 % of adult men).
- OSAS with significant morbidity, such as hypertension, cardiovascular disease, stroke, and motor vehicle accidents

- OSAS may lead to functional and structural brain alterations.
- Functional alterations such as sleep fragmentation often associated with neuropsychological deficits that can be reversible after treatment of OSAS

32

Functional Neuroimaging: OSA

- Functional imaging studies of OSAS patients used fMRI to evaluate BOLD contrasts during performance on cognitive tasks
- The studies have found deactivations in various regions, while some instead showed increases in activation or mixed results
  - Inactivation in OSAS patients across Parietal, cingulate
  - OSAS severity correlated with increased activation of right parietal lobe during a working memory task

33

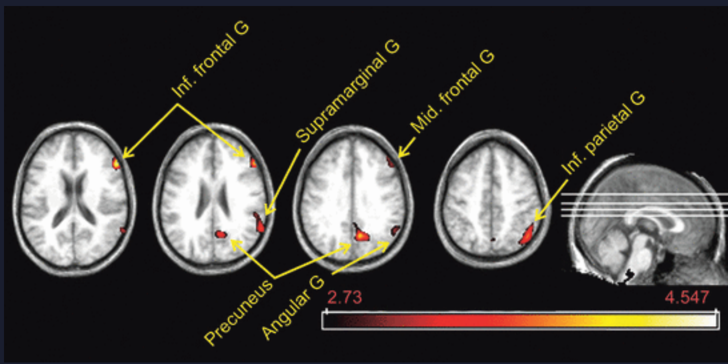
Functional Neuroimaging: OSA

- More recent studies focused on resting-state functional connectivity changes,, found regional reductions in connectivity in medial and dorsolateral prefrontal cortices
- 99mTc-ECD SPECT study observed decreased baseline rCBF in parahippocampal and lingual gyri in OSAS patients
- 18FDG PET showed reduced CMRglu in prefrontal, parieto-occipital, and cingulate gyri of OSAS

34

Functional Neuroimaging: OSA

18FDG PET showed decrease in brain metabolism involved precuneus, the middle and posterior cingulate gyrus, and the parieto-occipital cortex, as well as the prefrontal cortex.

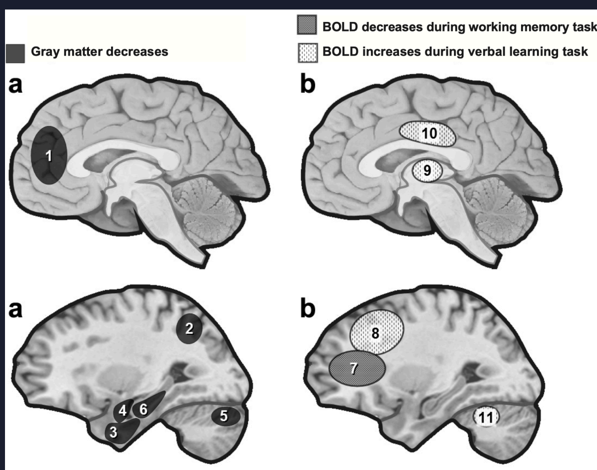


35

Functional Neuroimaging: OSA

Regional gray matter loss in OSAS patients. VBM results in OSAS patients revealed gray matter loss

left hippocampus or extending to regions involved in cognitive functions and motor regulation of the upper airway



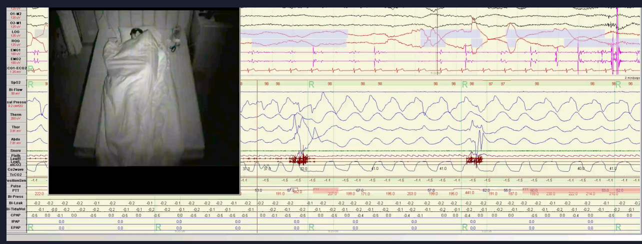
Functional MRI in OSAS patients during a 2-back working memory task was associated with reduced dorsolateral prefrontal activity

while verbal learning was associated with increases in frontal cortex, thalamus and cerebellum.

36

Functional Neuroimaging: RLS

- Periodic limb movements (PLM) during sleep and restless legs syndrome (RLS) are distinct but overlapping disorders.
- RLS is typified by an irresistible urge to move the legs (and less often, the arms), especially during sleep onset.
  - The compulsion associated with relentless feelings of discomfort from deep inside the limbs



- PLM characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep
- While these movements disturbed sleep and can result in awakening, patients mostly unaware of movements or even that their sleep disturbed.

37

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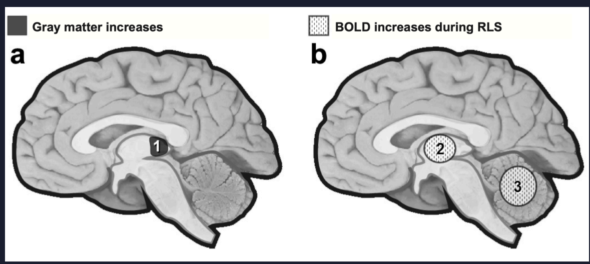
38

Functional Neuroimaging: RLS

Cortical gray matter changes in RLS.

VBM in RLS patients revealed bilateral gray matter increase in the pulvinar



BOLD increases during RLS.

Cerebellum and thalamus are more activated (fMRI) when RLS patients experience leg discomfort

39

Functional Neuroimaging: PLM

- A few studies have focused specifically on PLM
- An fMRI study combining PLM and sensory leg discomfort showed activity in
  - Cerebellum and thalamus
  - With additional activation in the red nuclei and brainstem close to the reticular formation

40

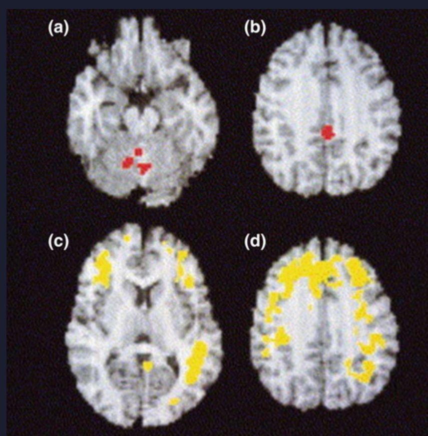
Functional Neuroimaging in Sleep walking

- Sleepwalking, also known as somnambulism, is an arousal parasomnia consisting of a series of complex behaviors result in large movements during sleep
- It is perceived a dissociation state whereby most of the brain exhibits non-REM sleep patterns, except motor-related areas

41

Functional Neuroimaging in Sleep walking

- SPECT findings during sleepwalking subtracted from normal subject co-registered with MRI shows
  - Increases rCBF (>25 %) during sleepwalking over the anterior cerebellum (i.e., vermis) and posterior cingulate cortex
  - Deactivation over frontal and parietal association cortices



Bassetti et al. 2000, The Lancet)

42

Functional Neuroimaging : RBD

- Characterized by brisk movements of the body associated with dream mentation during REM sleep that usually disturbs sleep continuity
- During the nocturnal spells, patients behave as if they were acting out their dream, in the absence of muscle atonia
- This disease may be idiopathic (up to 20 %) but mostly associated with neurodegenerative disorders.

- A sizeable proportion of patients with RBD will develop extrapyramidal disorders, Lewy body dementia (LBD), and multiple system atrophy
- A strong association between RBD and a-synucleinopathies, often preceding clinical onset of neurodegenerative disease

43

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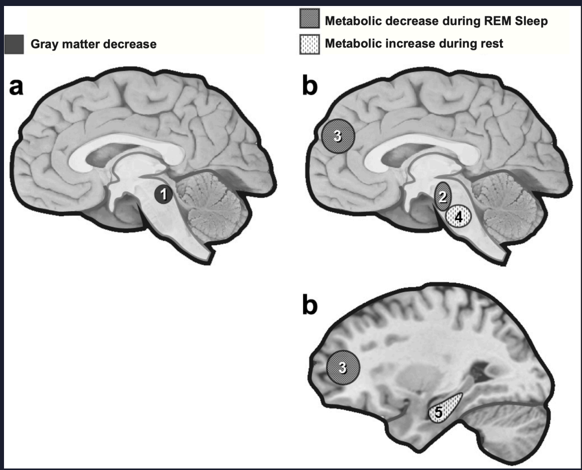
44

Functional Neuroimaging: RBD

Patients with RBD have lesions affecting the dorsal mesopontine tegmentum



Metabolic changes during REM sleep, patients with RBD show

- Decreased blood flow (SPECT) in the pons and superior frontal regions,
- Increased activity in the pons, putamen and hippocampus during rest at wake

45

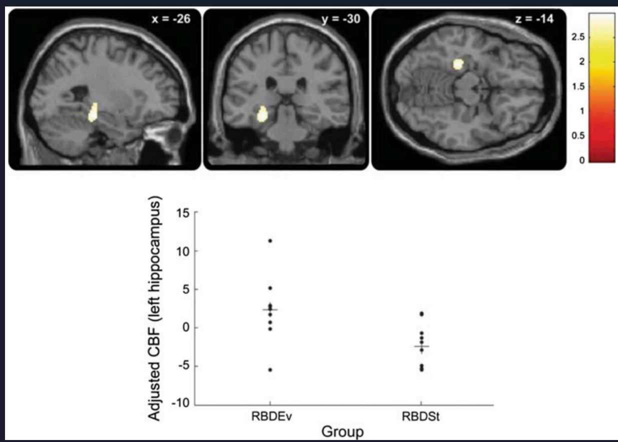
Functional Neuroimaging in RBD:

- A SPECT study in RBD patients during waking rest showed decreased activity in the frontal and temporoparietal cortices, but found increased activity in the pons, putamen, and right hippocampus
- A longitudinal study in idiopathic RBD using 99mTc-ECD SPECT
  - After the three-year period, the patients had developed PD or LBD.
  - Regression analysis revealed that hyperperfusion in the hippocampus predicted the subsequent development of LBD or PD in RBD patients

46

Functional Neuroimaging in RBD: who develop/or not develop synucleinopathy

- Left hippocampal hyperperfusion is noted in REM sleep behavior disorder patients who did (RBDEv) (develop synucleinopathy) compared who did not (RBDSt) develop synucleinopathy.



Dang-Vu et al. 2012, American Academy of Neurology

47