

# The Neuroscience of Sleep and its Disorders

Guy Leschziner

Consultant Neurologist, Guy's and St Thomas'  
NHS Trust

Institute of Psychiatry, Psychology and  
Neuroscience, King's College London



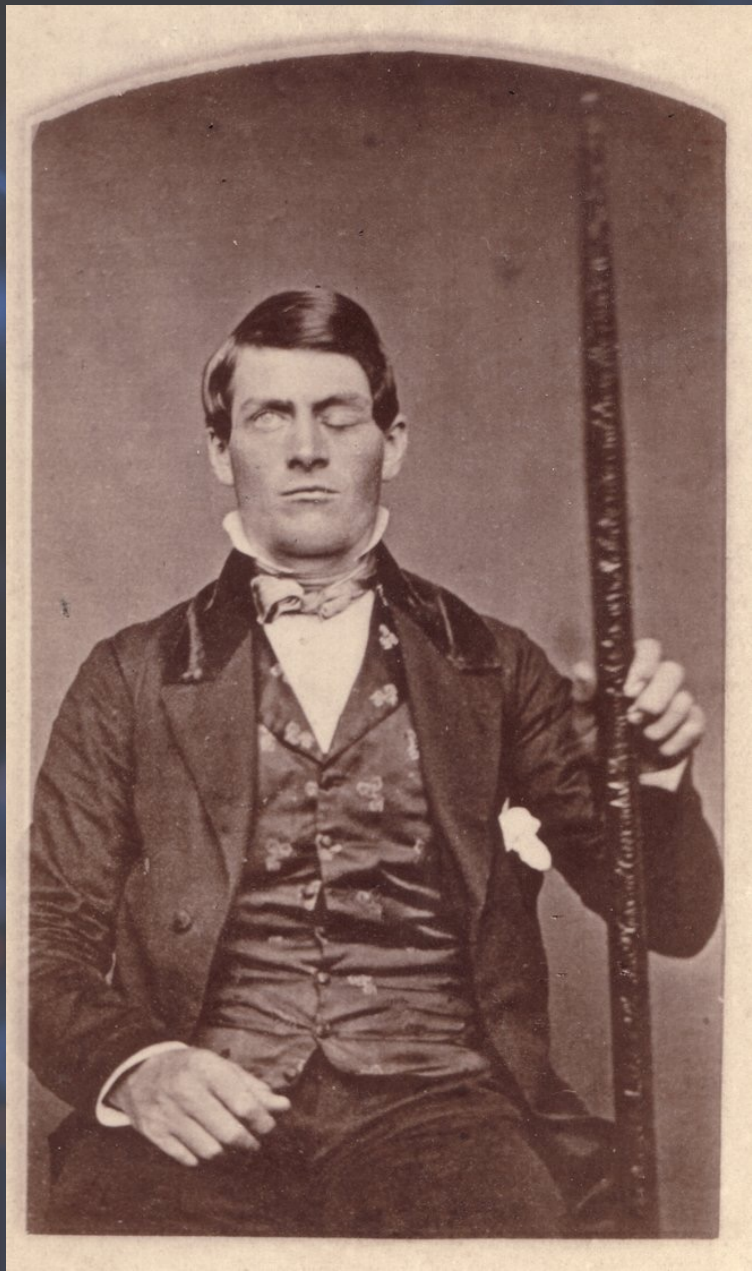
@guy\_lesch

Guy's and St Thomas'   
NHS Foundation Trust

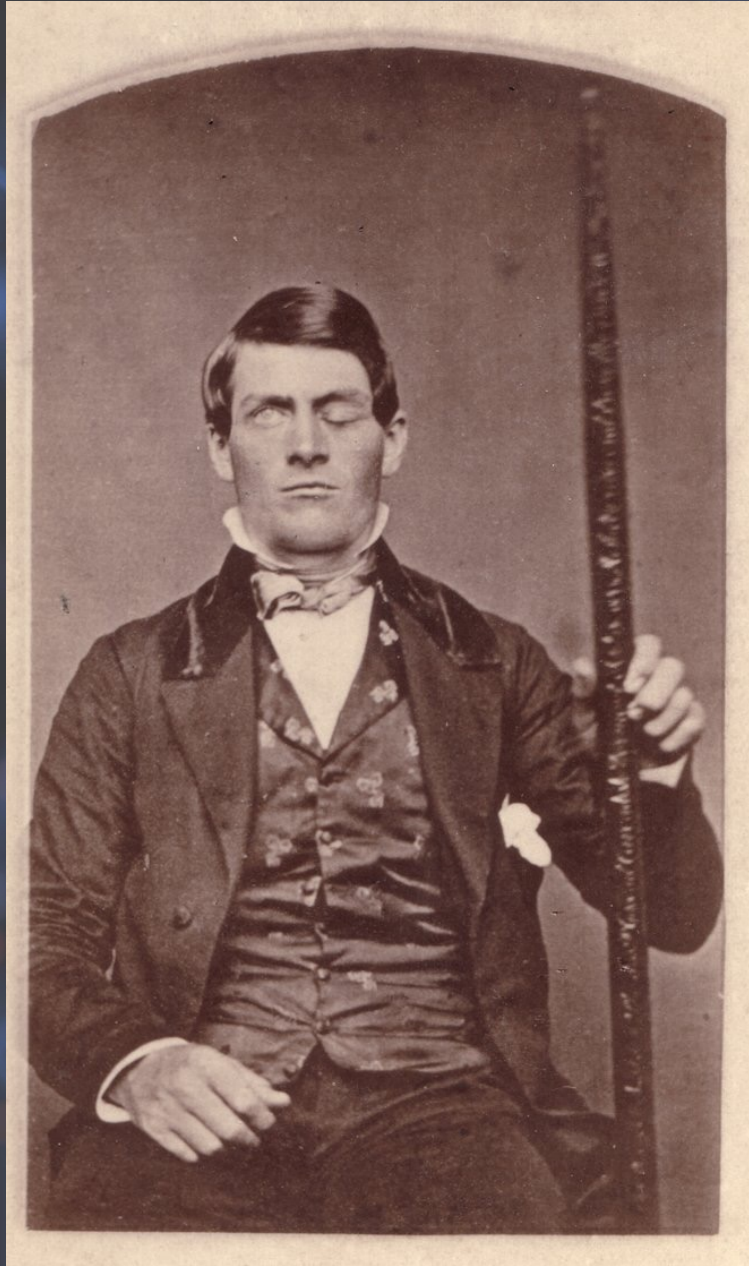
Institute of  
Psychiatry  
at The Maudsley

The logo for King's College London, featuring the text 'KING'S College LONDON' in a red serif font, with 'College' in a smaller, italicized font.





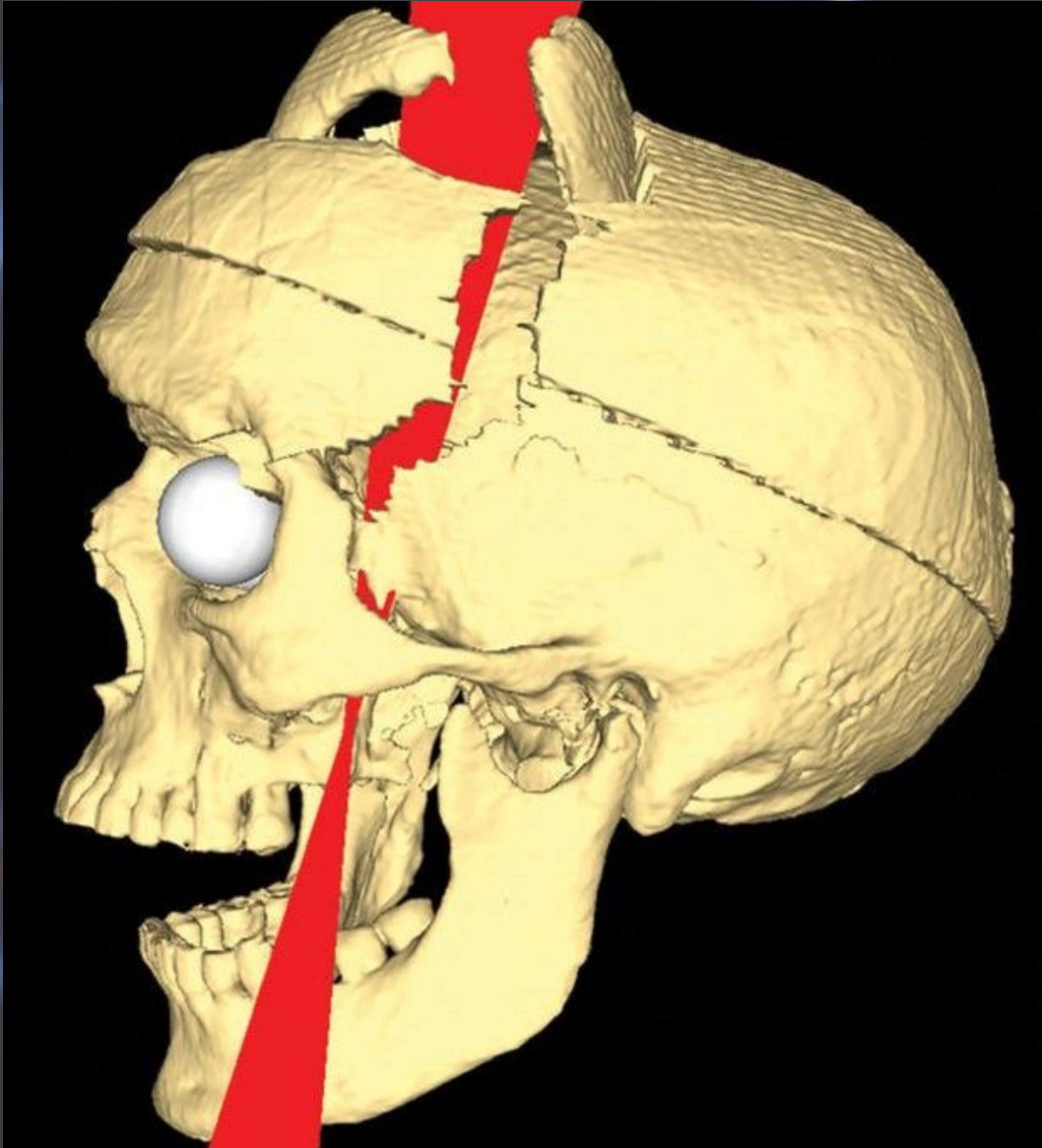




"I first noticed the wound upon the head before I alighted from my carriage, the pulsations of the brain being very distinct. The top of the head appeared somewhat like an inverted funnel, as if some wedge-shaped body had passed from below upward. Mr Gage, during the time I was examining this wound, was relating the manner in which he was injured...I did not believe [his] statement...Mr G got up and vomited; the effort of vomiting pressed out about half a teacupful of the brain, which fell upon the floor"

Phineas Gage, 1823-1860





Van Horn JD, Irimia A, Torgerson CM, Chambers MC, Kikinis R, et al. (2012) Mapping Connectivity Damage in the Case of Phineas Gage. PLoS ONE 7(5): e37454.



“Sleep is of the brain, by the brain and for the brain”  
– J Allan Hobson

Many sleep disorders result from lesions of the brain  
Sometimes transient  
Sometimes functional  
Sometimes microscopic

Some sleep disorders lesion sleep and provide  
insights into the function(s) of sleep



Wake



Sleep

“Each day is a little life: every waking and rising  
a little birth, every fresh morning a little youth,  
every going to rest and sleep a little death”

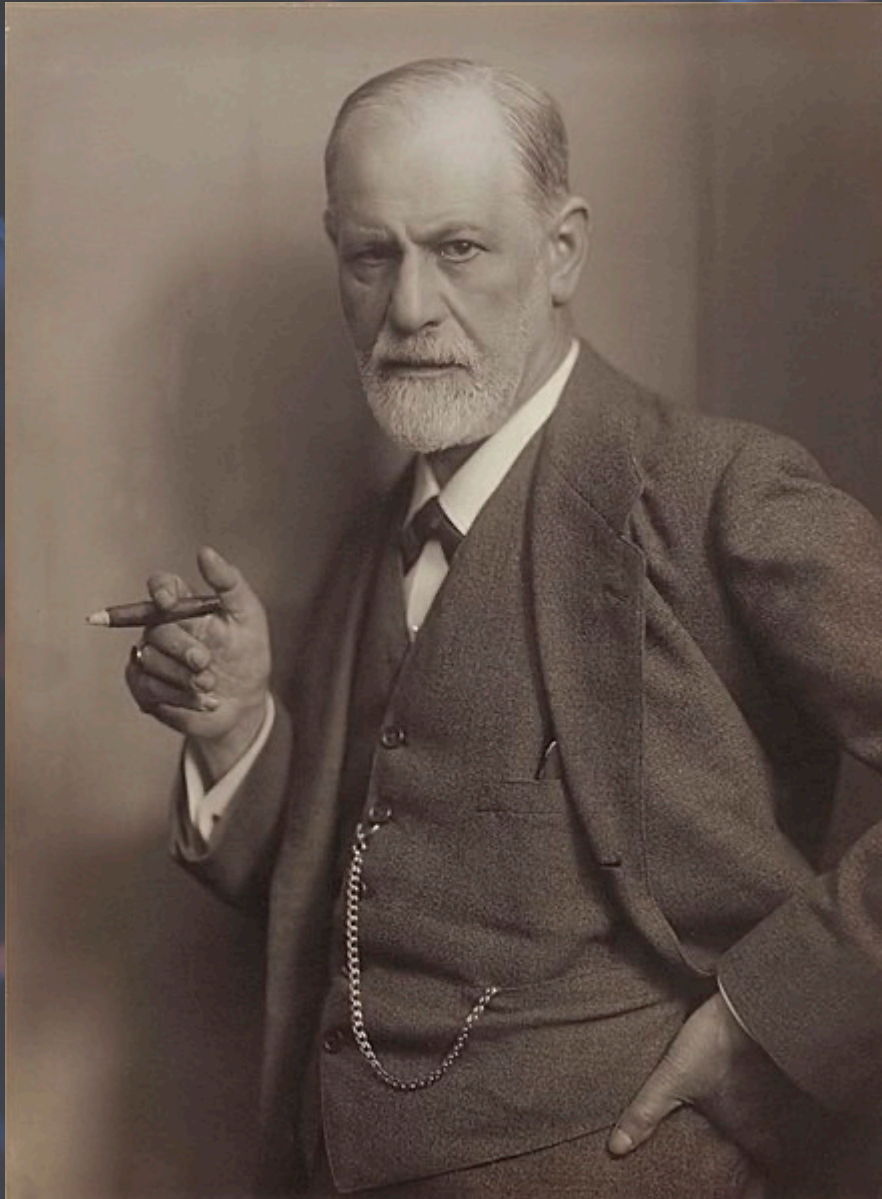
Schopenhauer



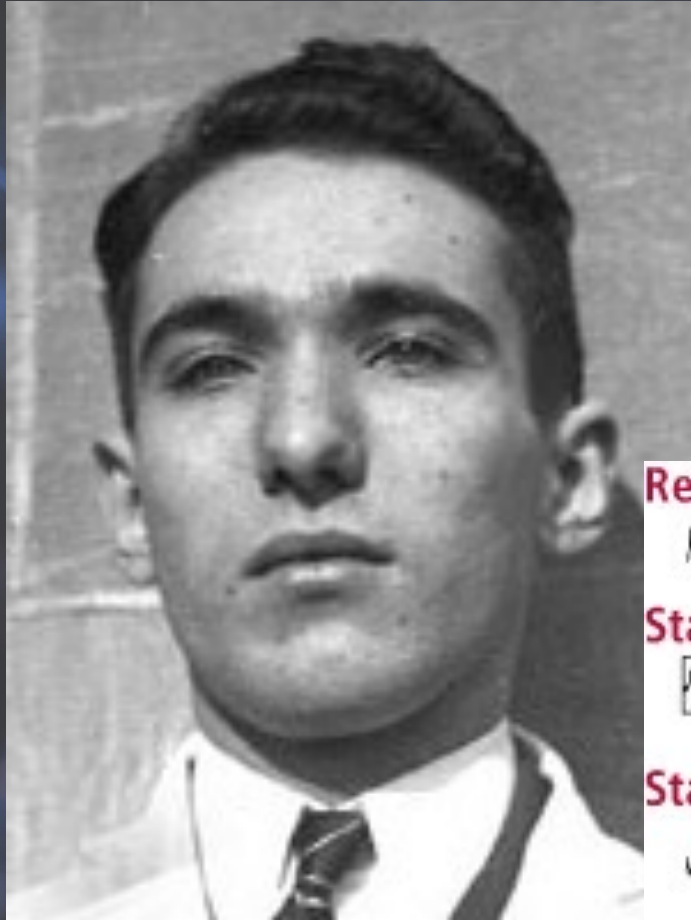


Chester  
Beatty  
Papyri,  
British  
Museum,  
c.1220 BC

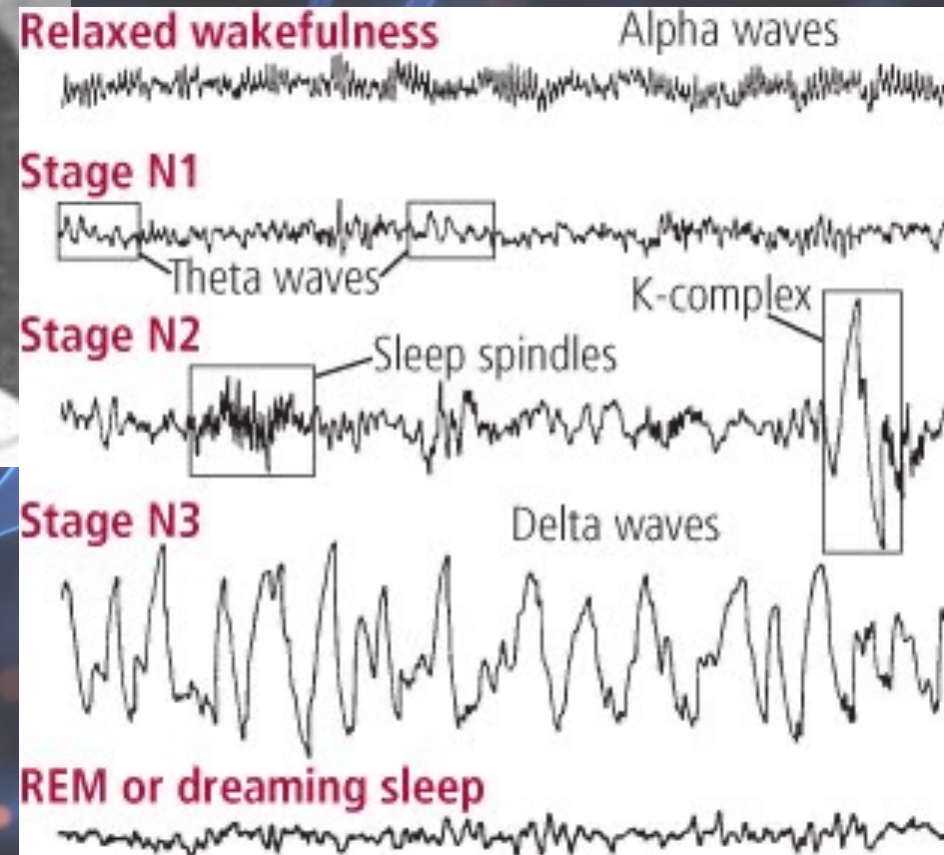
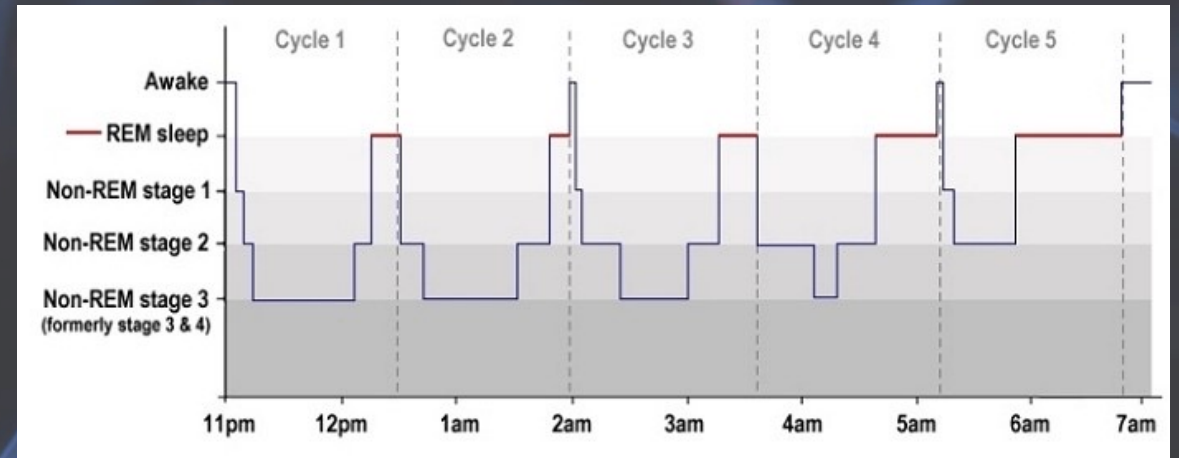








Eugene Aserinsky 1921-1998







A diagram illustrating the stages of sleep. It features three blue circles arranged in a triangle. The top circle is labeled 'Wake'. The bottom-left circle is labeled 'REM Sleep'. The bottom-right circle is labeled 'NREM Sleep'. The background is dark blue with a network of glowing blue lines and orange dots, resembling a neural network or a complex system.

Wake

REM  
Sleep

NREM  
Sleep







# Non-REM Parasomnias

- Spectrum of behaviours arising from slow-wave (N3) sleep
- Range from sleeptalking, confusional arousals, sleep terrors, sleep-eating, sexsomnias, sleep-walking
- Typically arise in first half of night
- Eyes usually open, complex speech or behaviours, directed with interaction with environment
- Amnesia for events, difficult to wake, occasional dream fragments or partial awareness



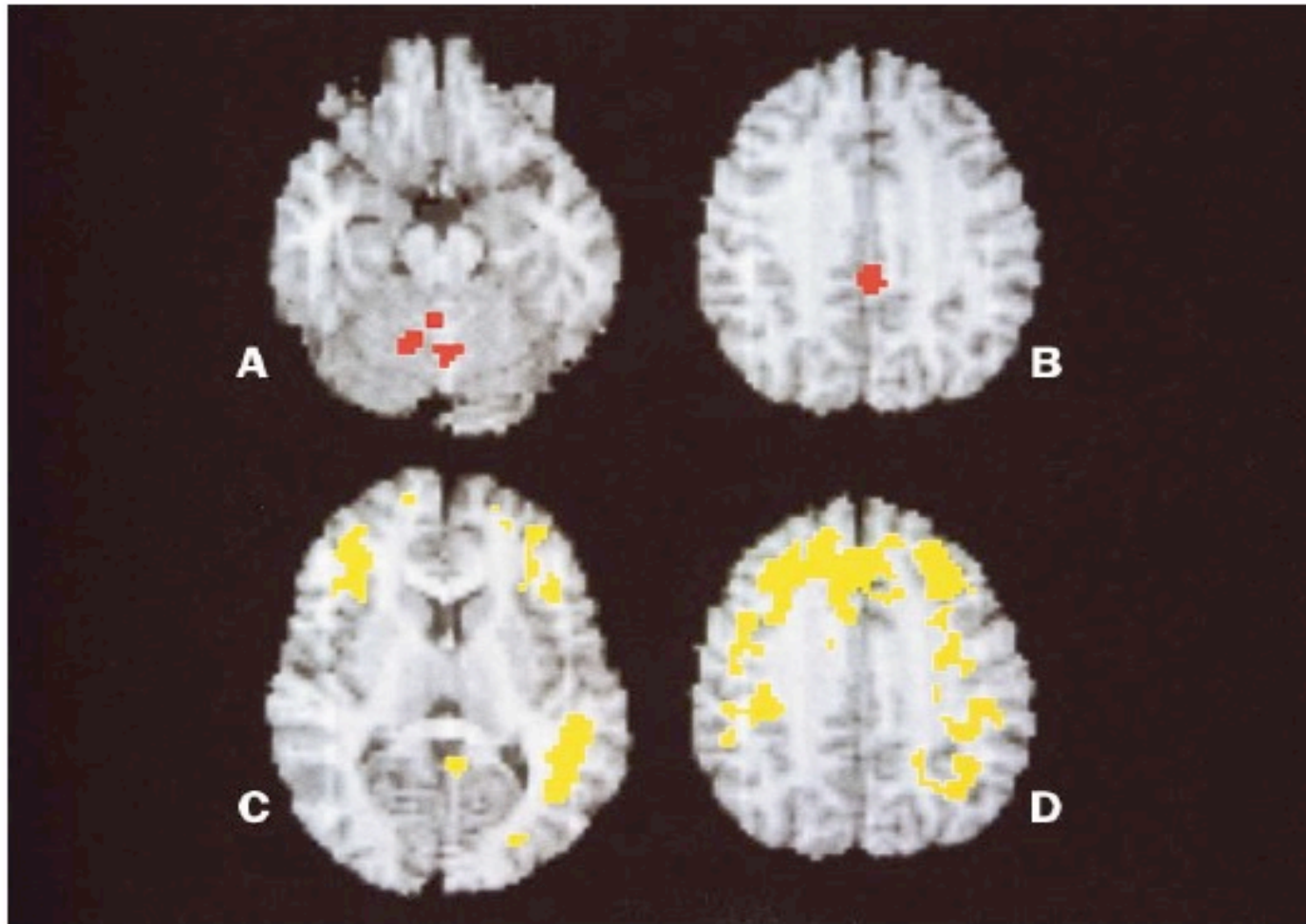
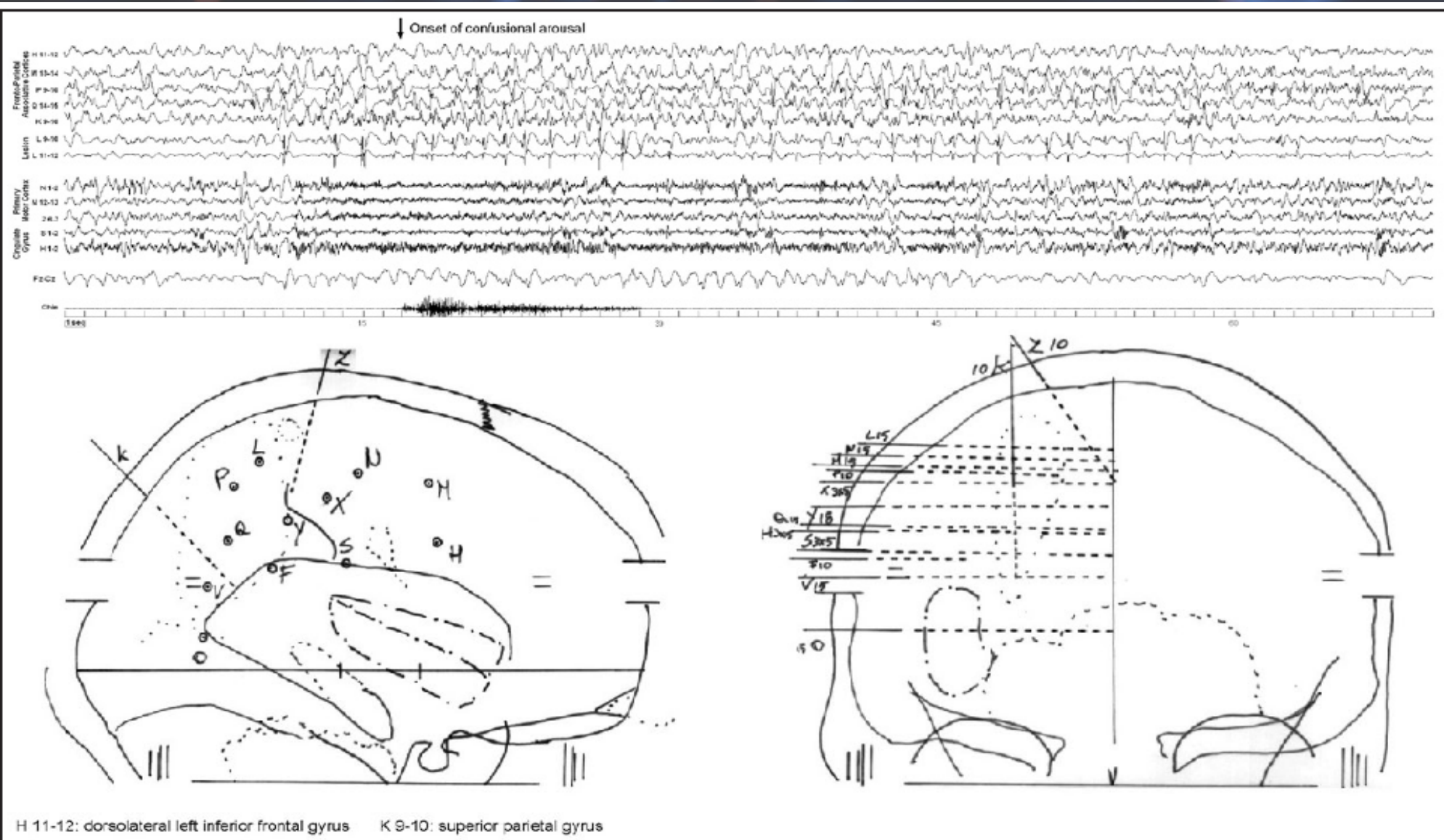


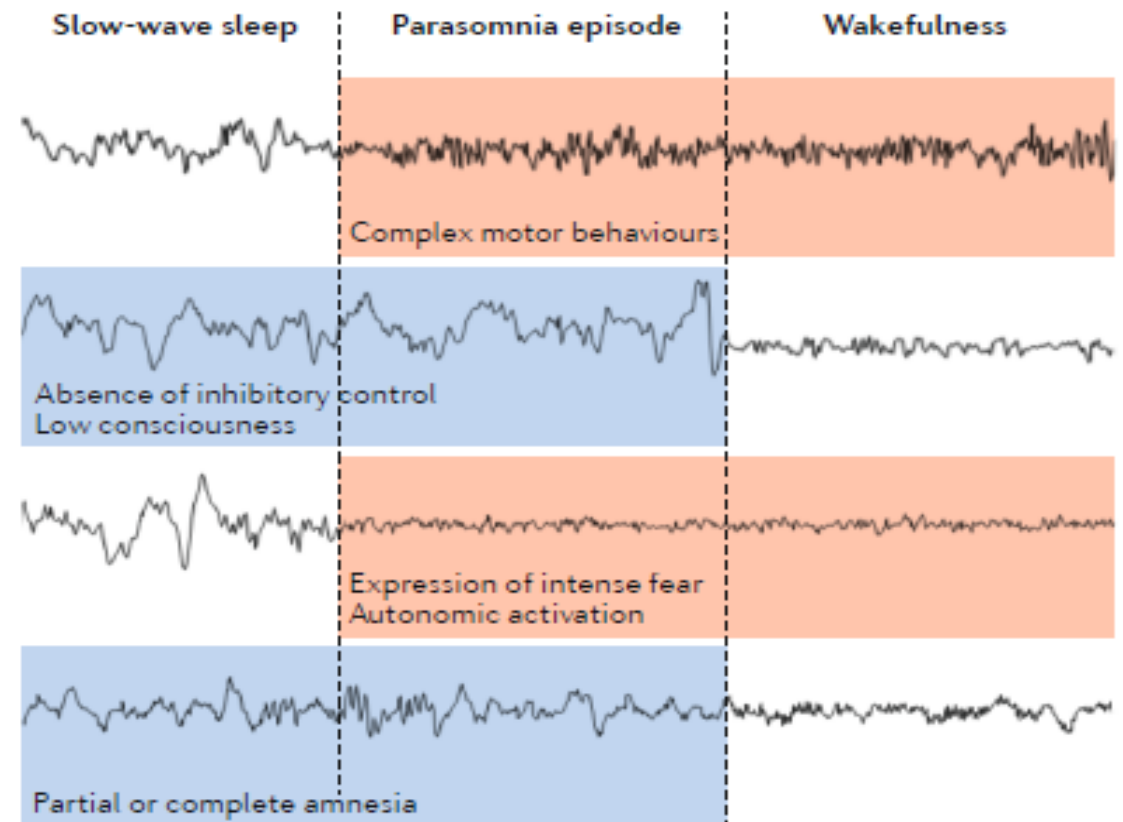
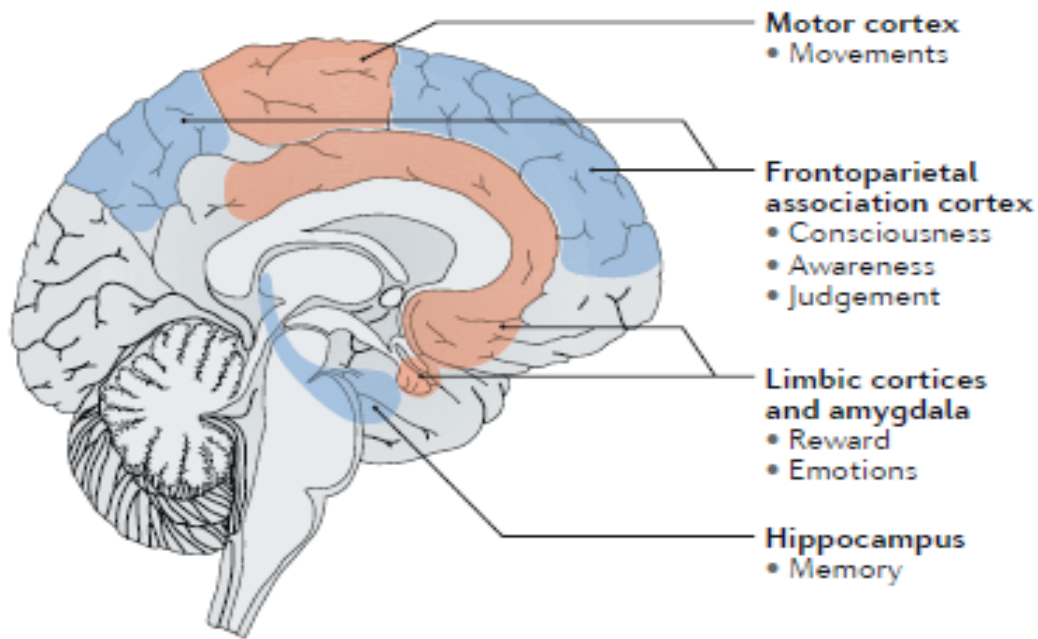
Figure 2: **SPECT** findings during sleepwalking after integration into the appropriate anatomical magnetic-resonance image







# Sleep is Not a Universal Brain State





A diagram illustrating the stages of sleep. Three blue circles are arranged in a triangle. The top circle is labeled 'Wake'. The bottom-left circle is labeled 'REM Sleep'. The bottom-right circle is labeled 'NREM Sleep'. The background is dark blue with a network of glowing blue lines and orange dots, resembling a neural network or a complex system.

Wake

REM  
Sleep

NREM  
Sleep



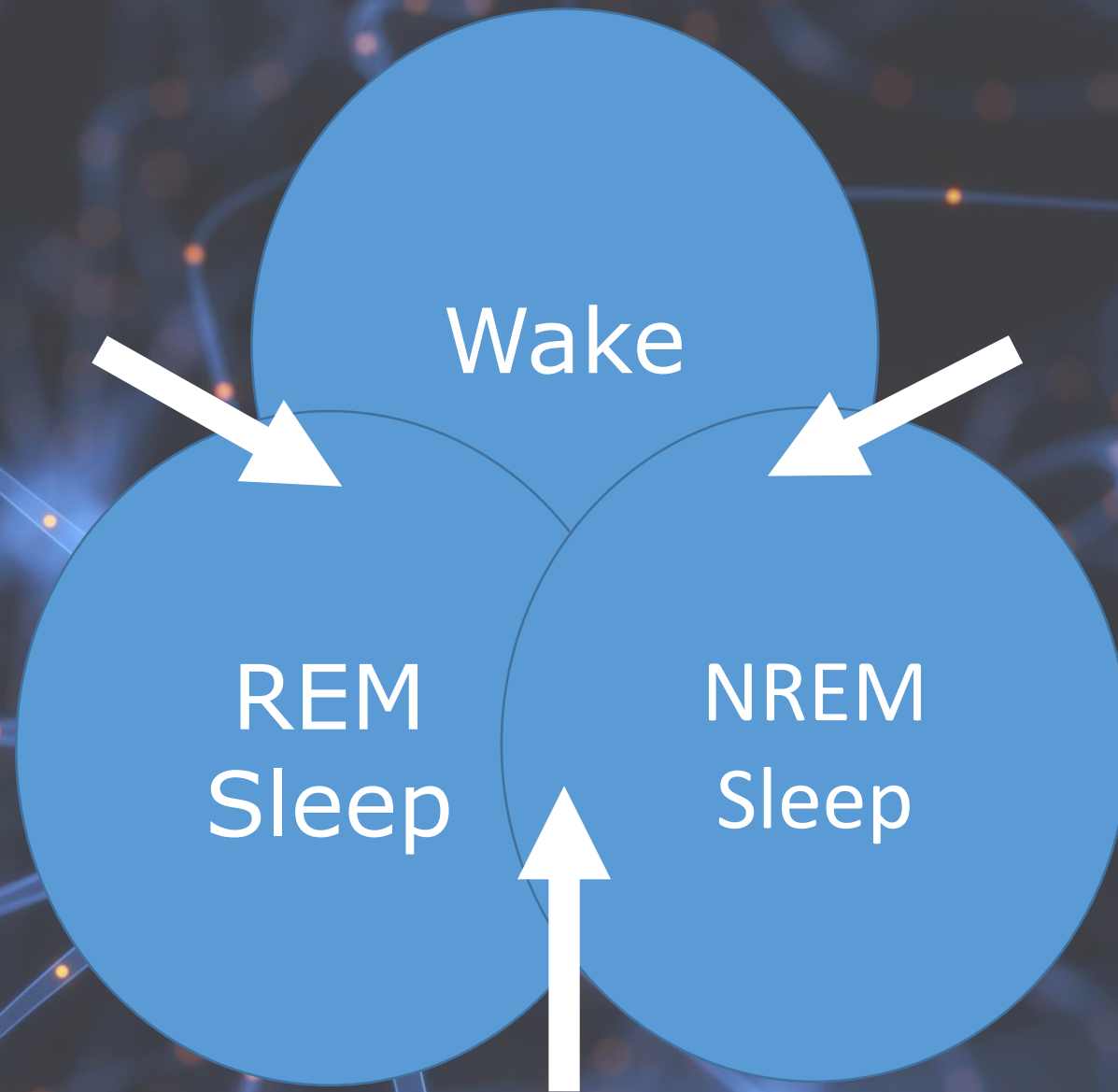


Wake

REM  
Sleep

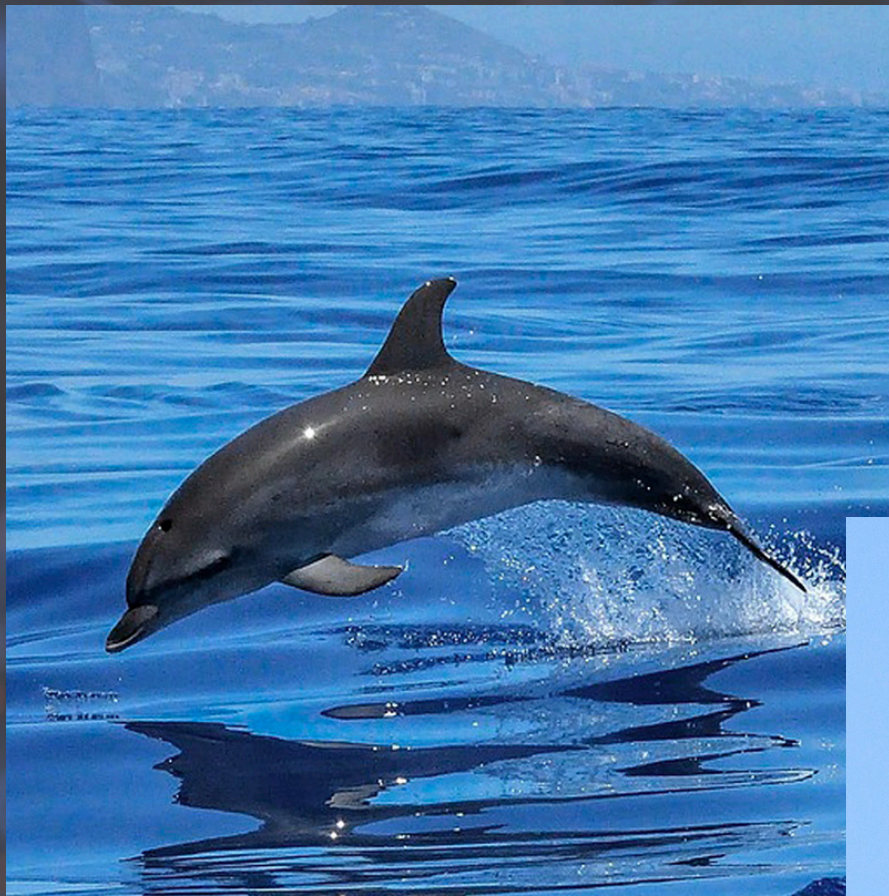
NREM  
Sleep





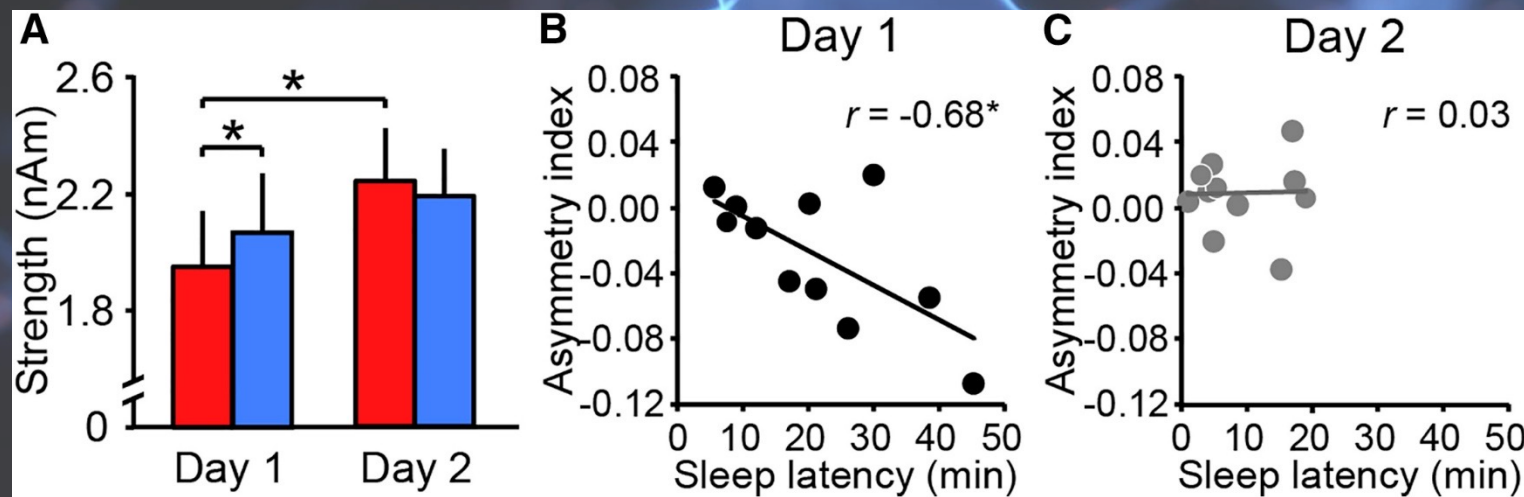
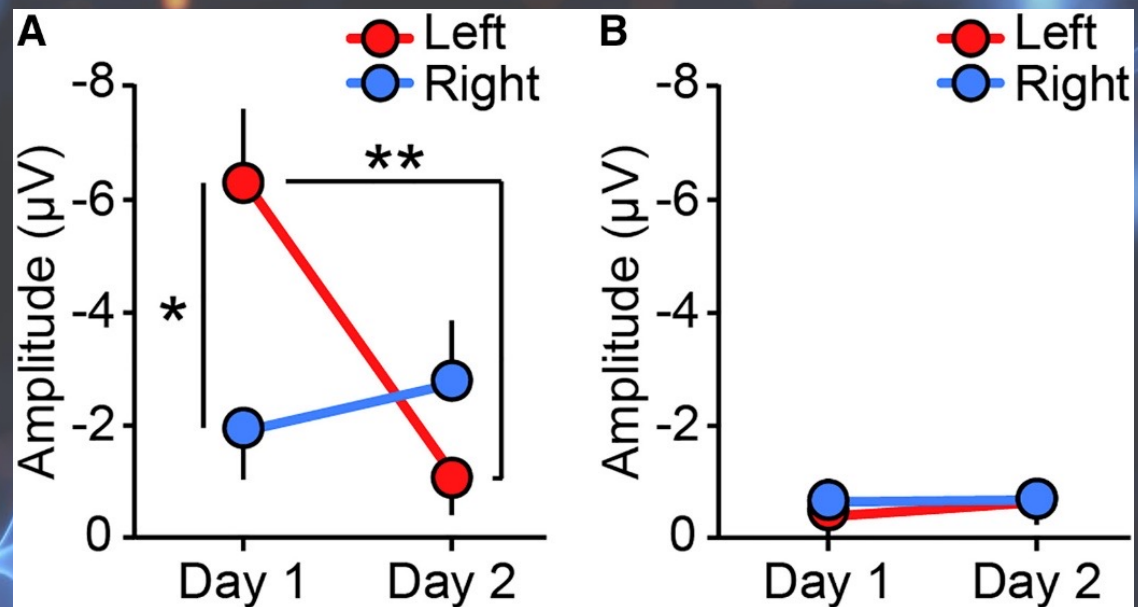


# Blurred Lines





# The First Night Effect



Tamaki et al, 2016, Curr Biol 26 (9): 1190-1194

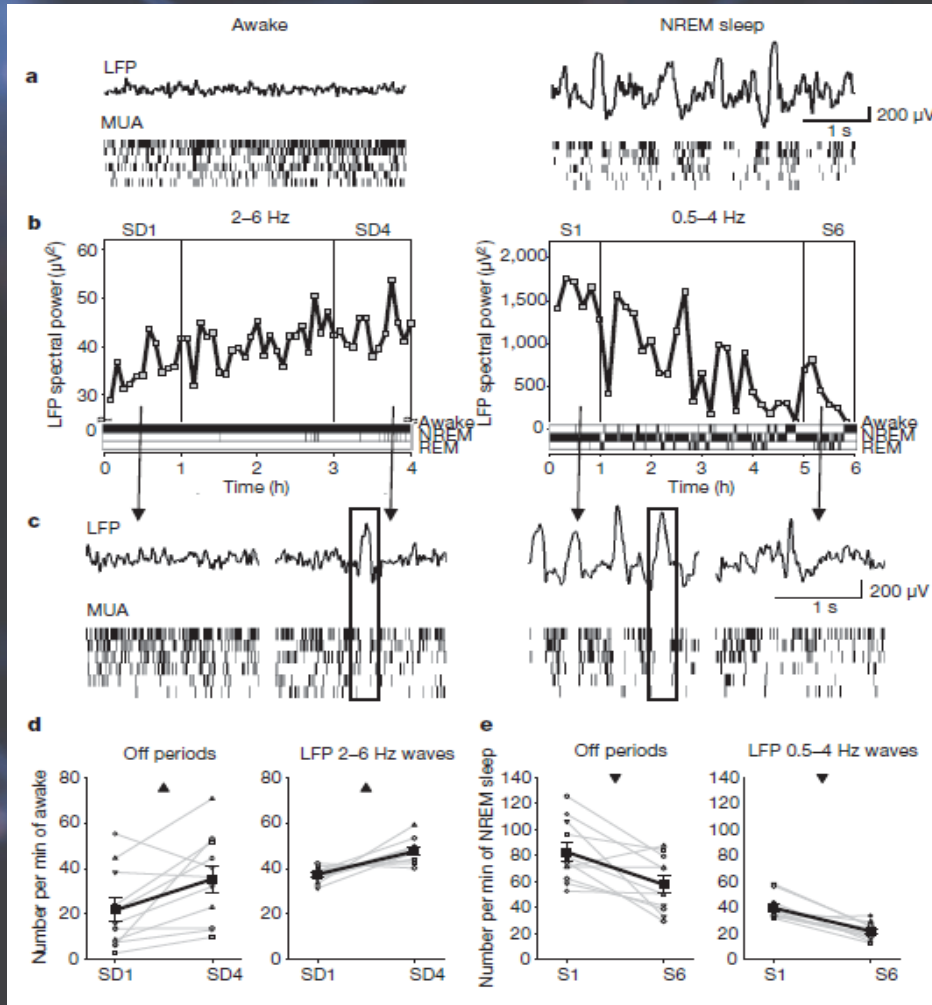


# The Concept of Local Sleep

Brain recordings in rats show “silent areas” in the cortex

These increase in frequency and duration with wakefulness

Correlation with impairment of tasks



Vyazovskiy et al, 2011, Nature, 472 (7344): 443-7.

The background is a dark blue field filled with a complex network of glowing, translucent blue lines. These lines are interconnected and branch out in various directions, creating a web-like structure. Small, bright orange-yellow dots are scattered along these lines, acting as nodes or points of interest. The overall effect is one of dynamic energy and interconnectedness, reminiscent of a neural network or a data visualization.

Other Examples of Blurred Lines?



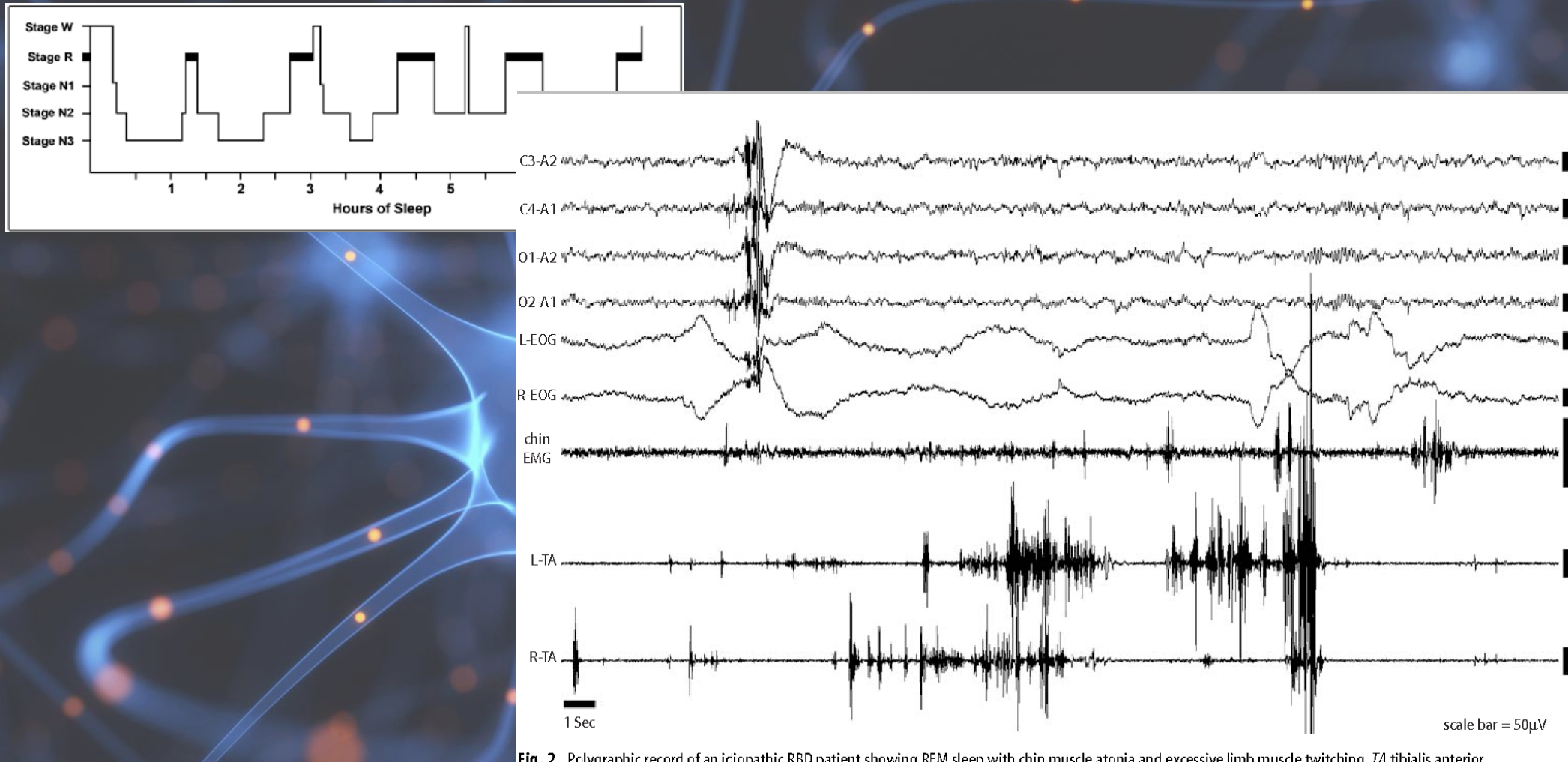


# REM Sleep Behaviour Disorder

- Estimated prevalence of <1%
- Usually towards latter half of night
- Lashing out, crying, swearing, shouting
- Eyes closed
- Speech usually unintelligible
- Pts do not leave bed, no purposeful interaction
- If woken may have dream recall
- Can occur every night, several times a night
- Injuries to self or bed partner a real risk



# Muscle Paralysis in REM Sleep

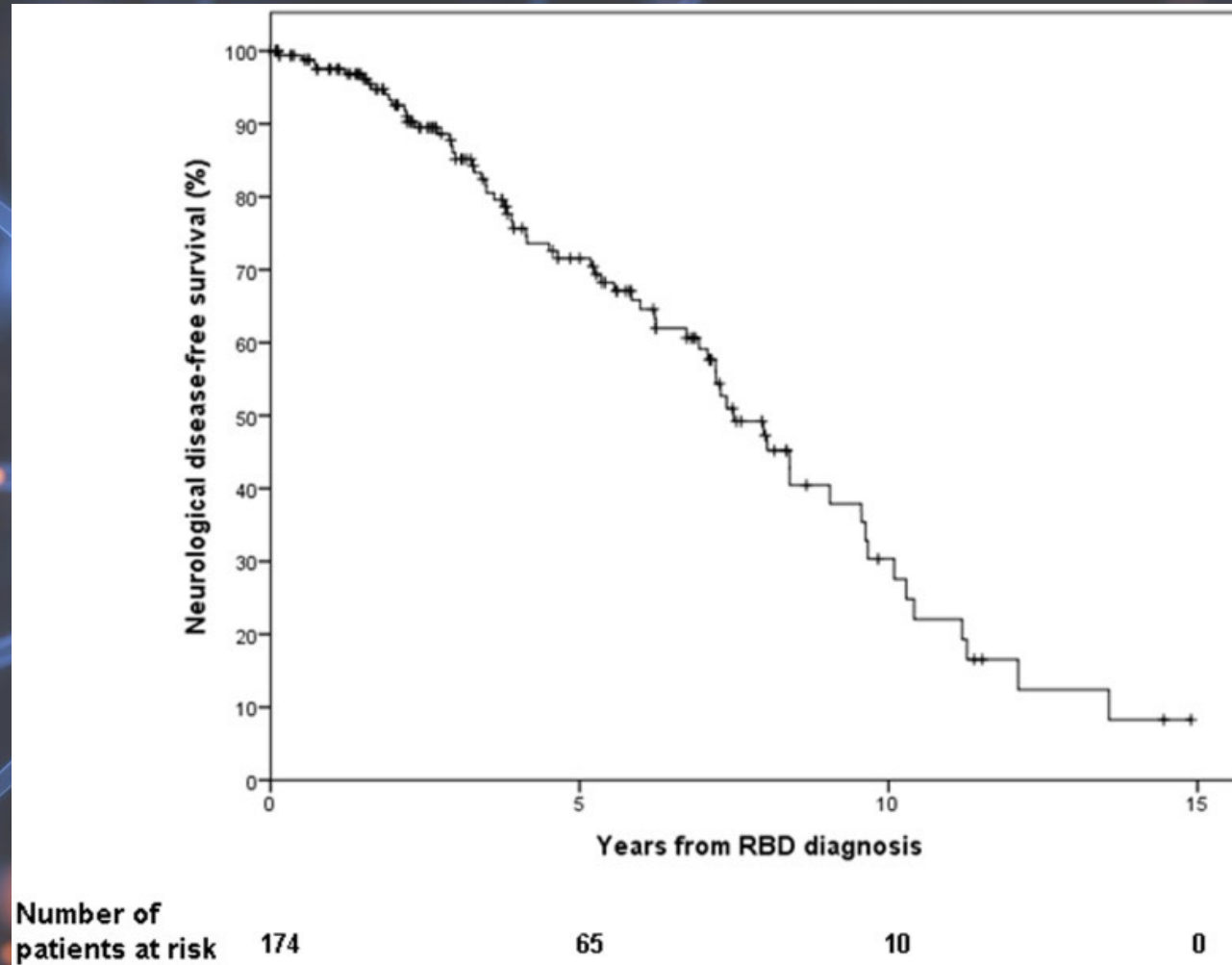


**Fig. 2** Polygraphic record of an idiopathic RBD patient showing REM sleep with chin muscle atonia and excessive limb muscle twitching. TA tibialis anterior





# RBD is a Herald of Brain Degeneration

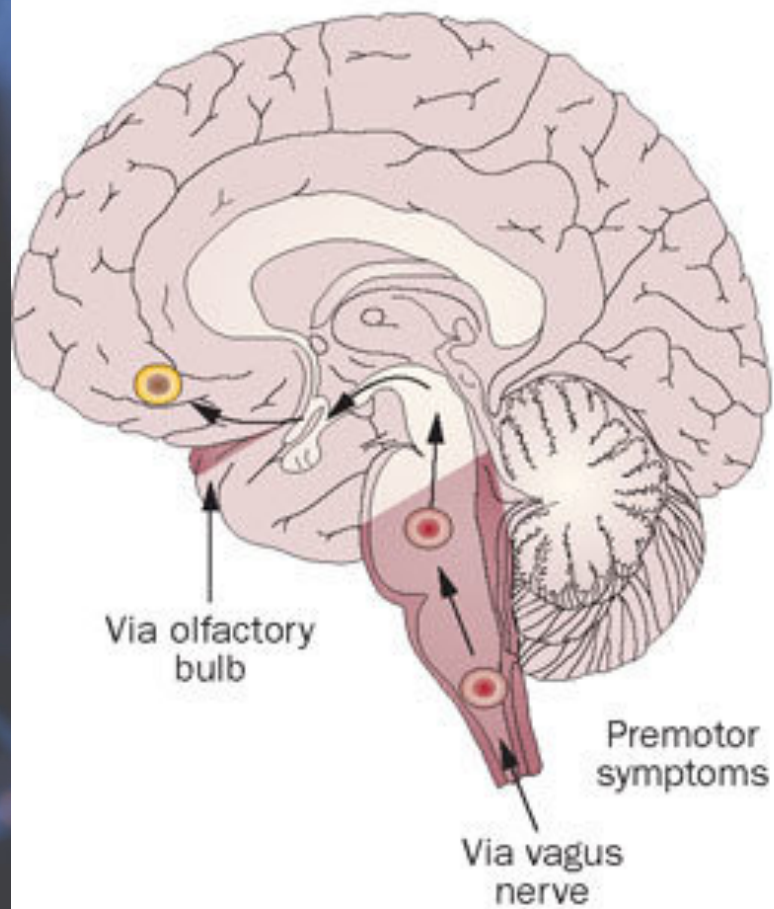


Iranzo et al ,  
2014



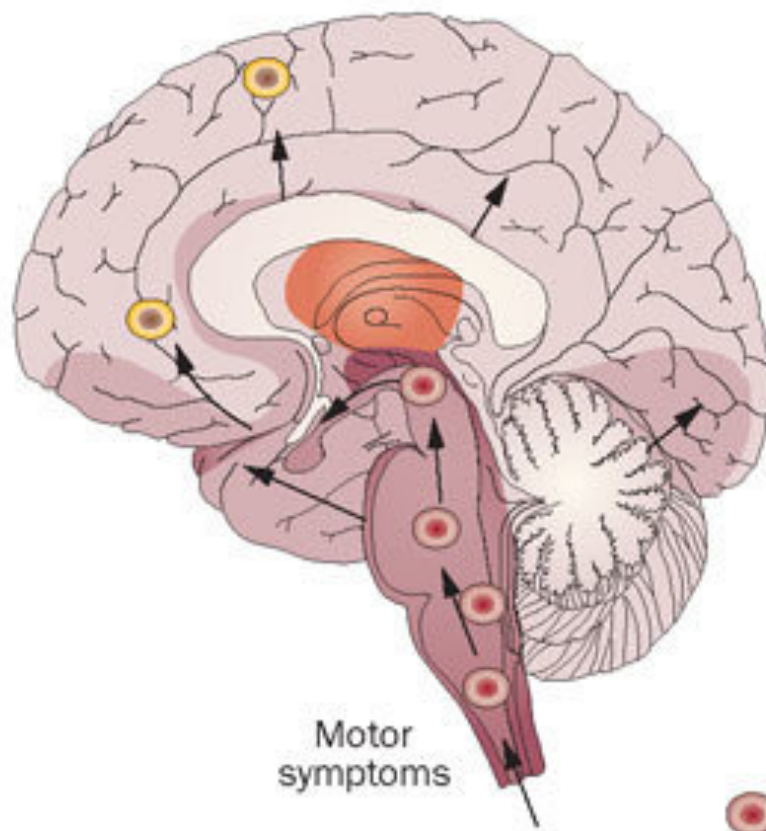
### Braak stages 1 and 2

Autonomic and olfactory disturbances



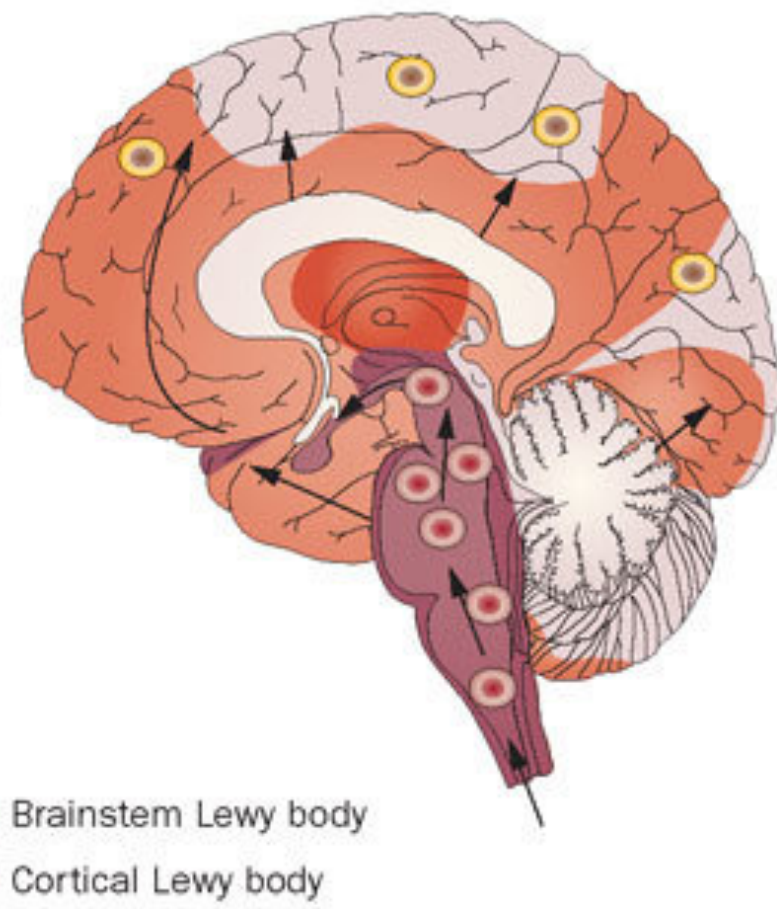
### Braak stages 3 and 4

Sleep and motor disturbances



### Braak stages 5 and 6

Emotional and cognitive disturbances





# So does Isolated RBD Exist?

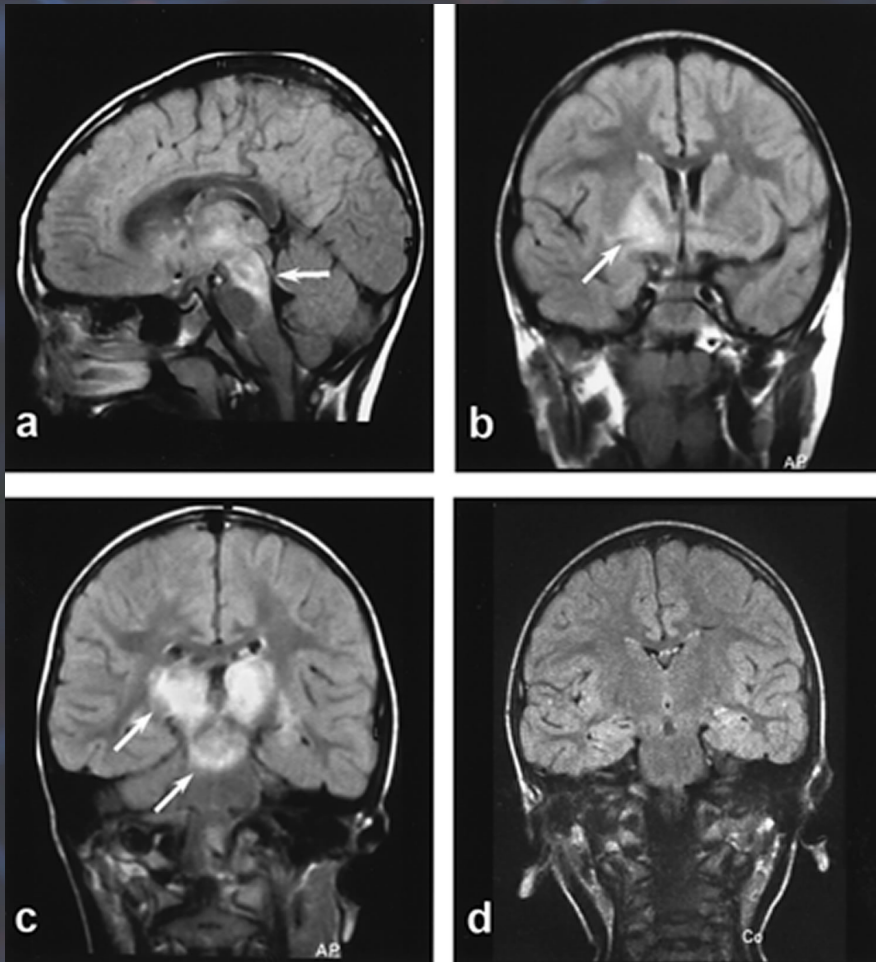
- People with RBD have higher rates of:
  - Abnormalities in smell, bladder, gut and cardiovascular function
  - Higher rates of alpha-synuclein in a variety of tissue biopsies
  - Constipation, anosmia, subtle Parkinsonian signs, abnormal brain scans
  - Subtle problems with cognition
- Is RBD therefore really prodromal neurodegenerative disorder?
- Are patients with RBD candidates for disease-modifying drugs?



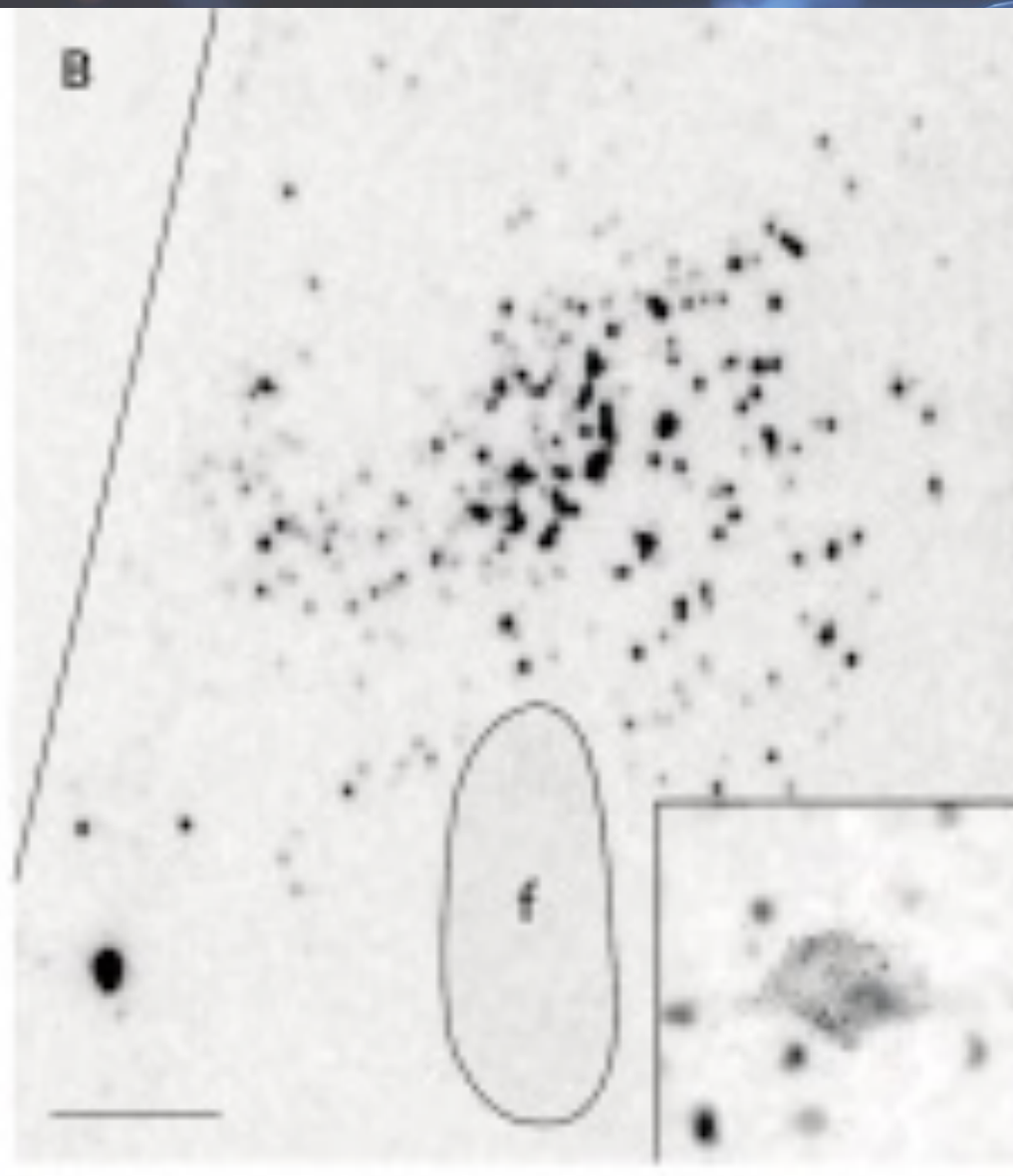
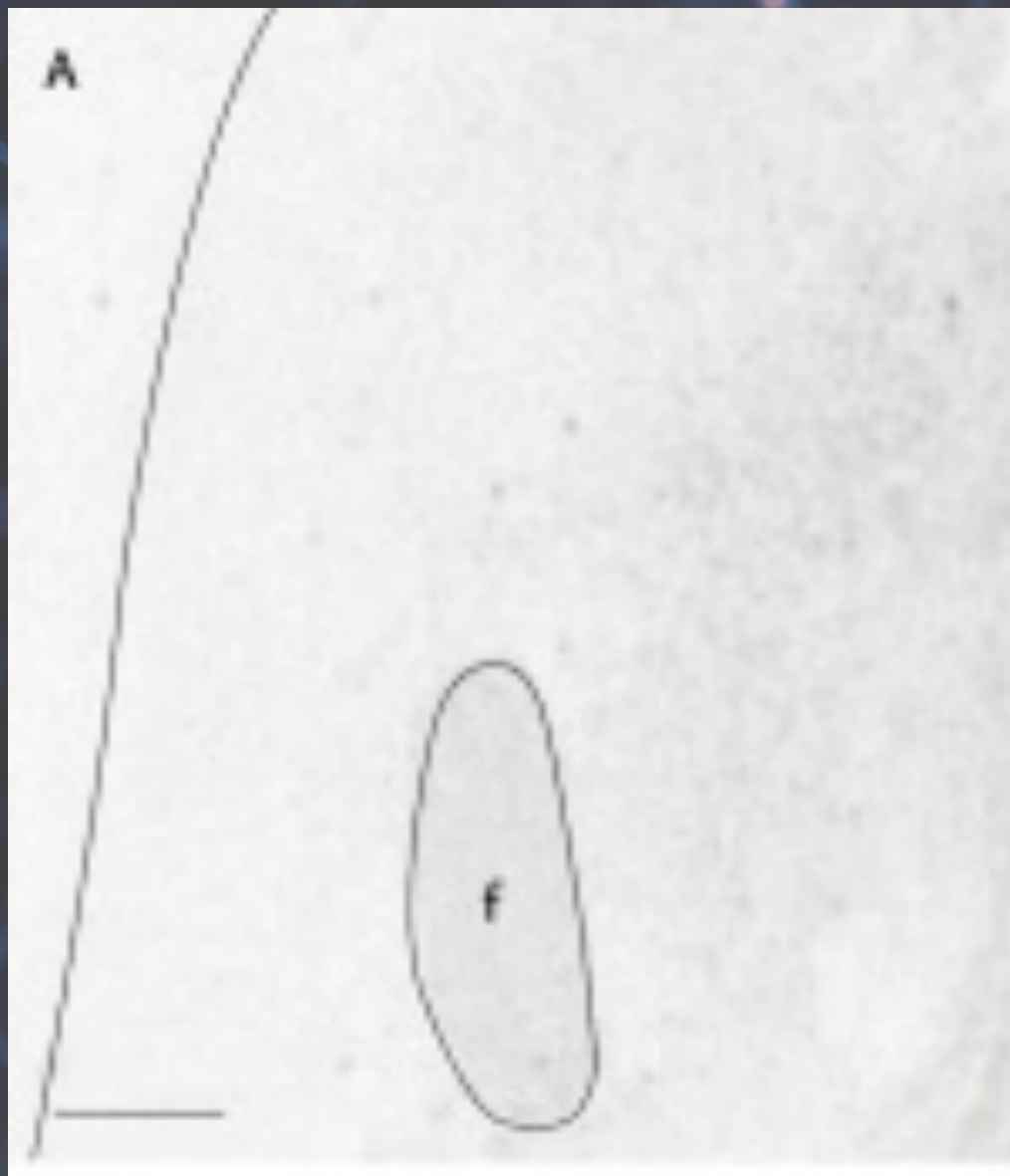


Courtesy of Seven Wonder and Channel 4

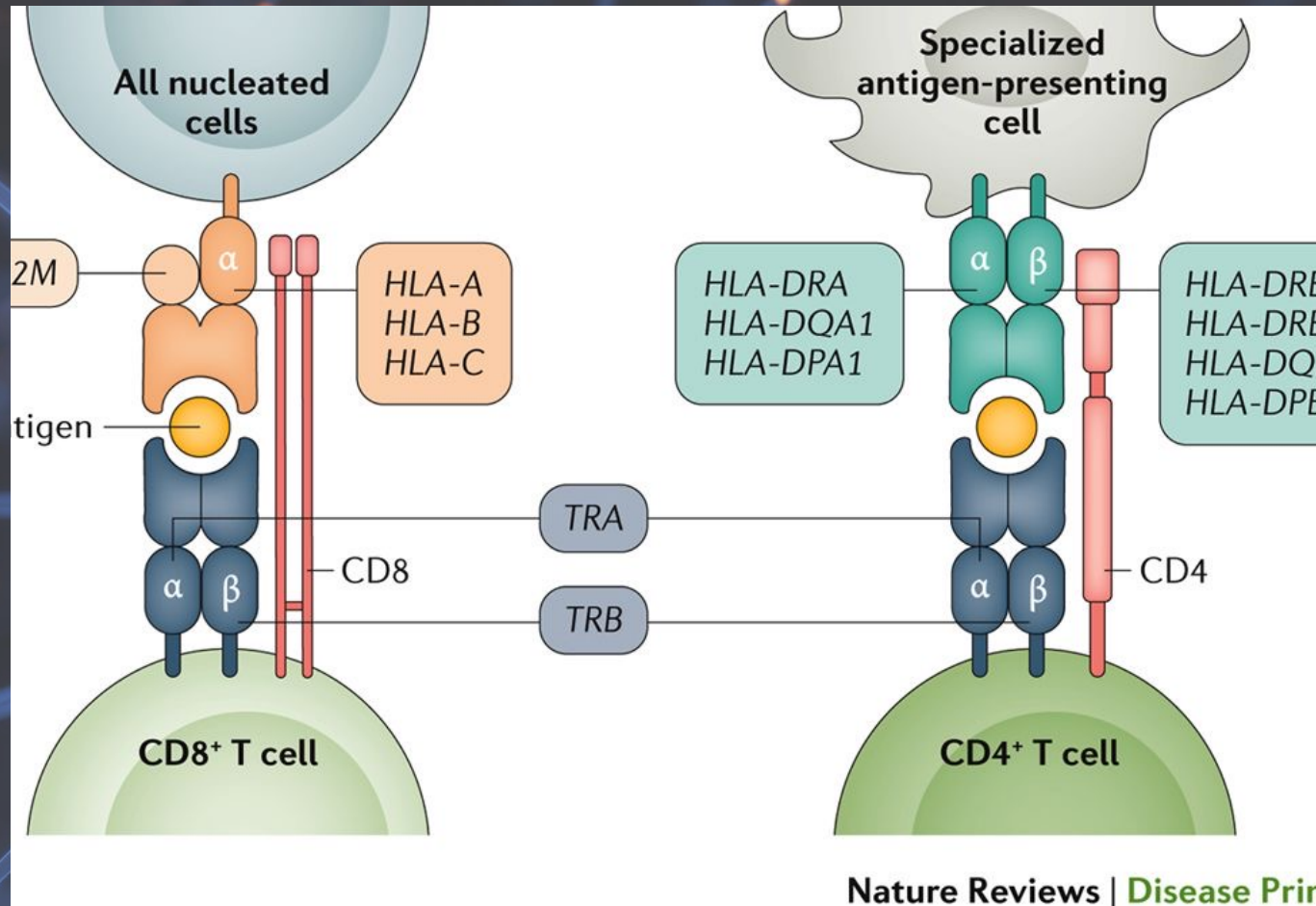
# Origins of Narcolepsy?







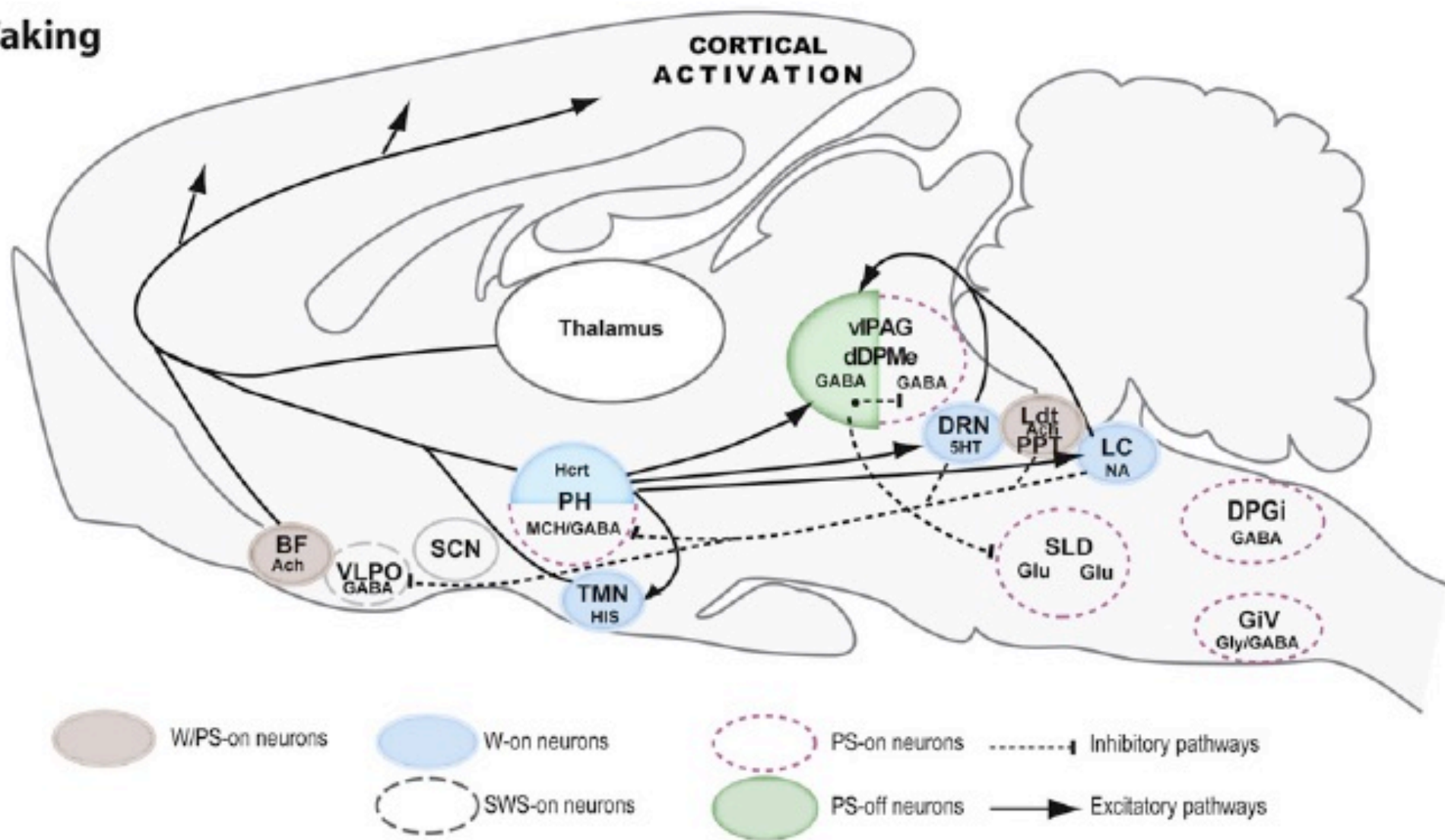
# What Causes This Loss?

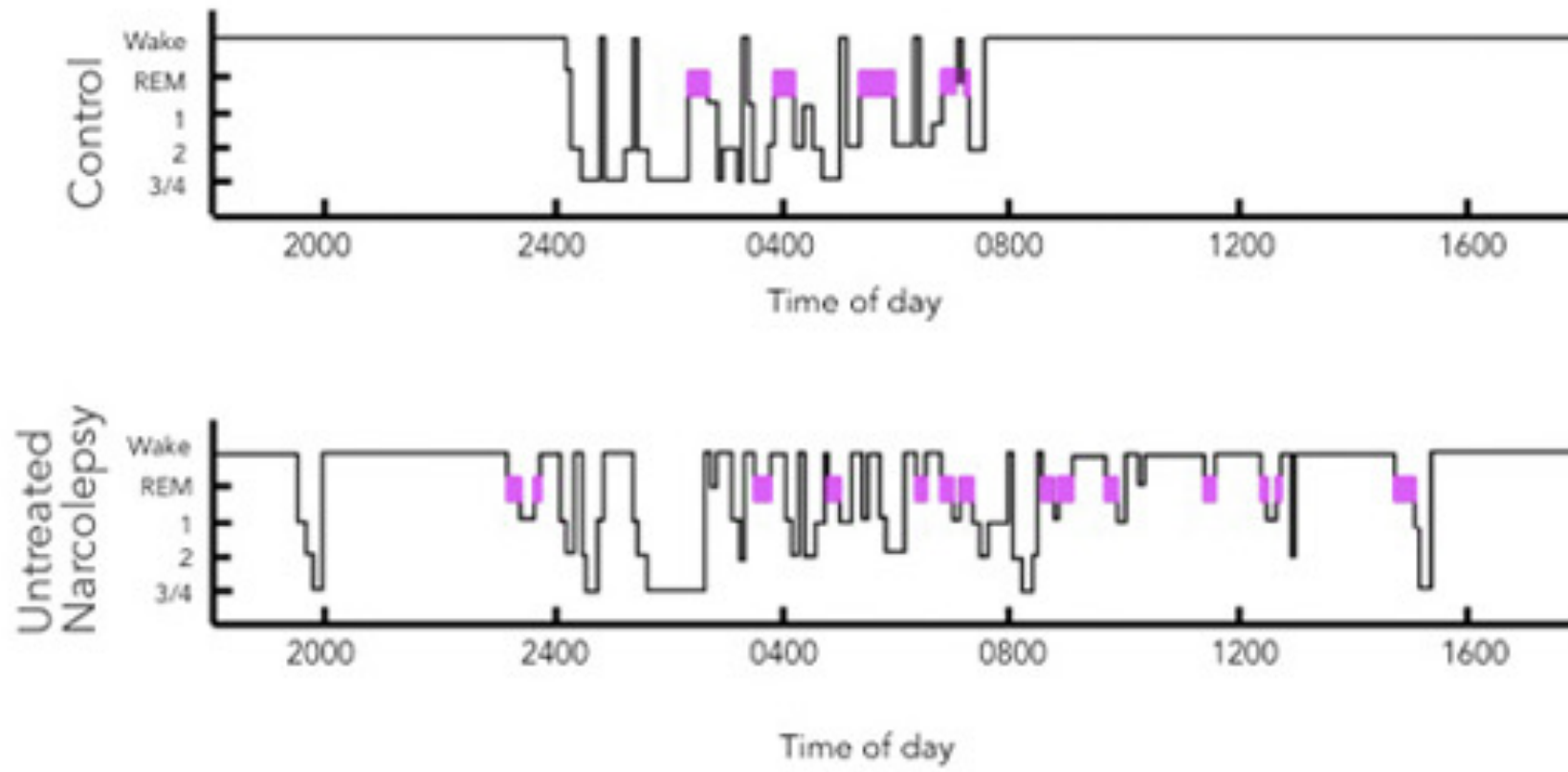


Korhum et al,  
Nature Rev  
Disease Primers,  
2017, 3: 16100



# Waking





Adapted from Rogers et al. Sleep 1994; 17:590



# And Cataplexy?





# Lucid Dreaming – More Blurred Lines



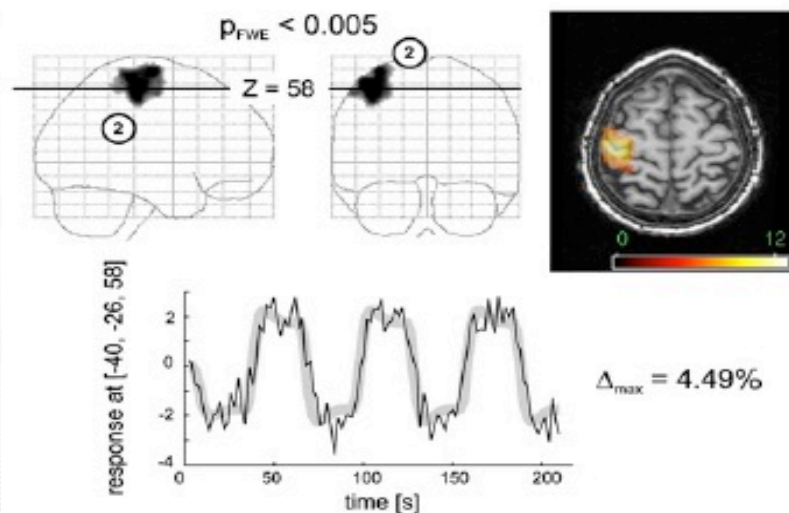
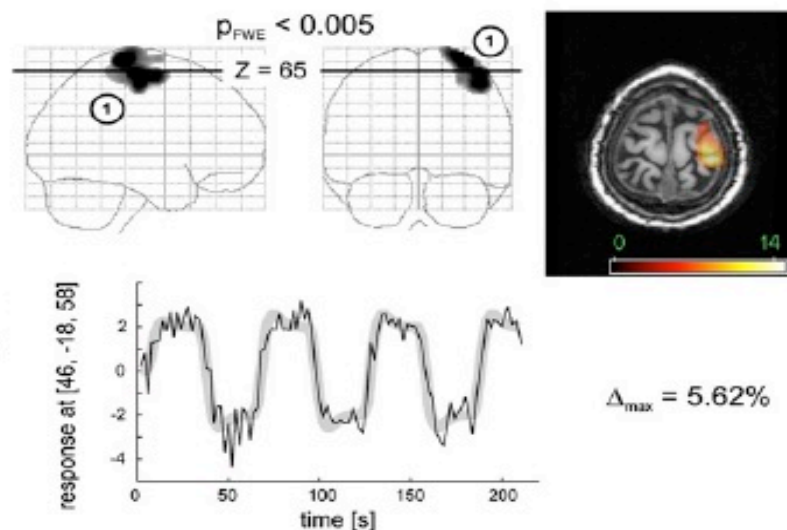


Left hand > right hand

Right hand > left hand

A

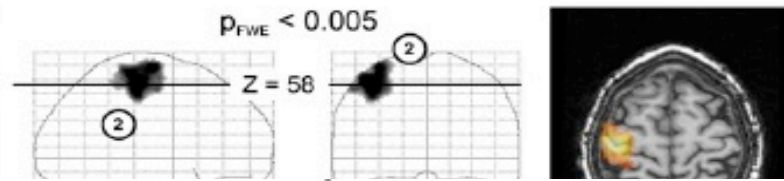
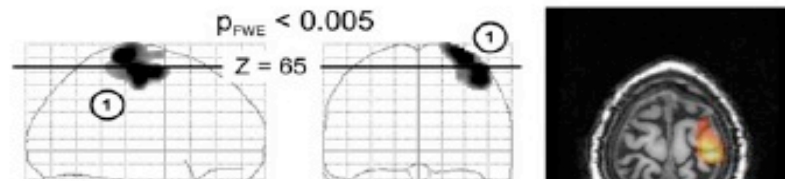
real hand movement  
during wakefulness



Left hand > right hand

Right hand > left hand

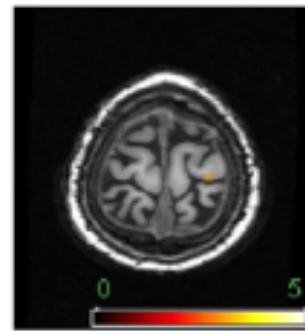
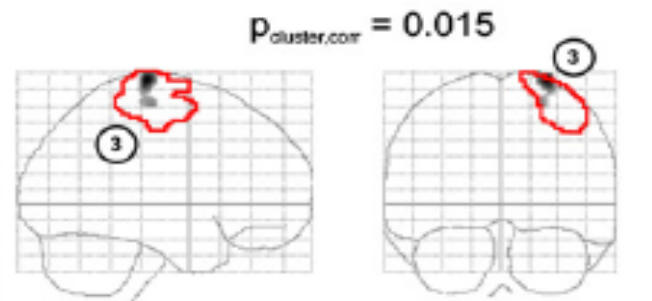
**A**



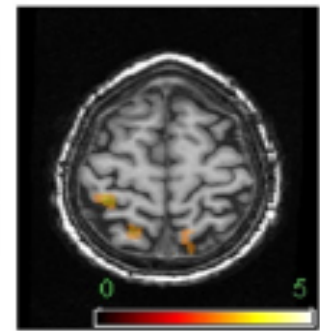
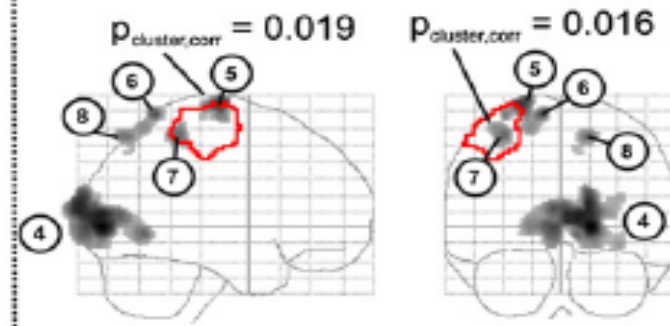
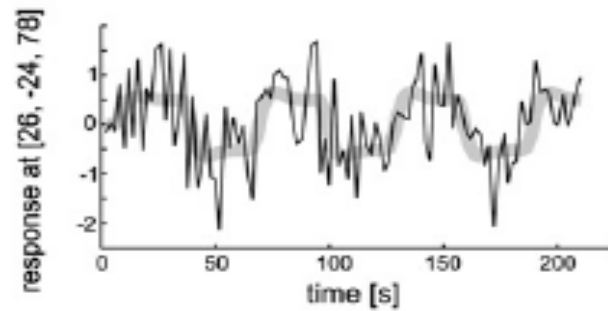
real hand movement  
during wakefulness

Imagined hand movement  
during wakefulness

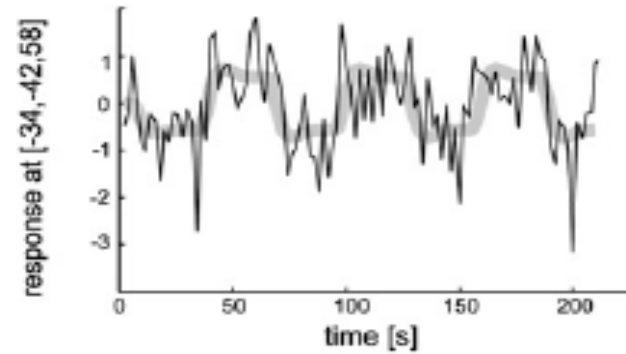
**B**



$\Delta_{max} = 1.31\%$



$\Delta_{max} = 1.44\%$



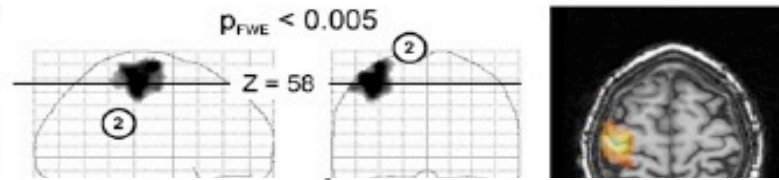
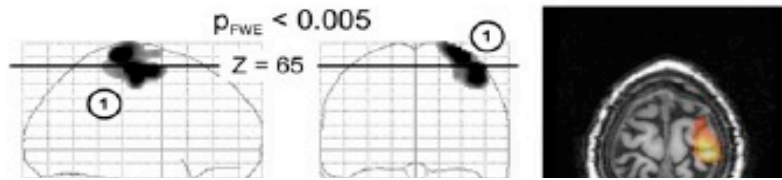


Dresler et al Curr  
Biol 2011, 21 (21):  
1833-7

Left hand > right hand

Right hand > left hand

A

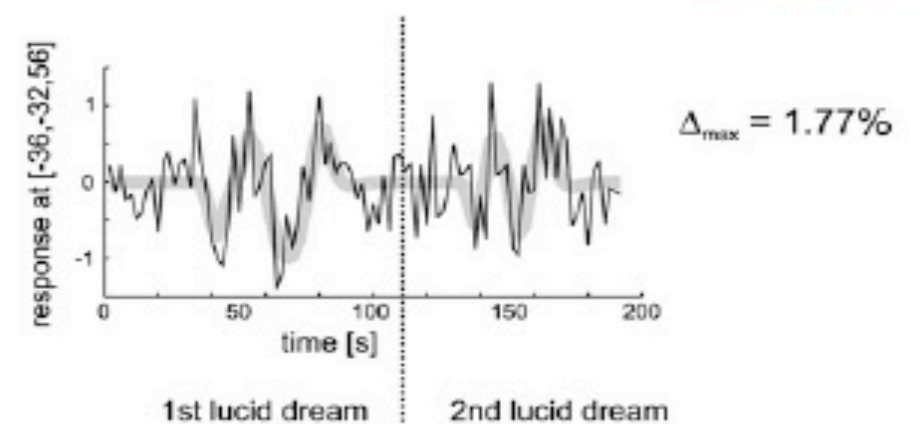
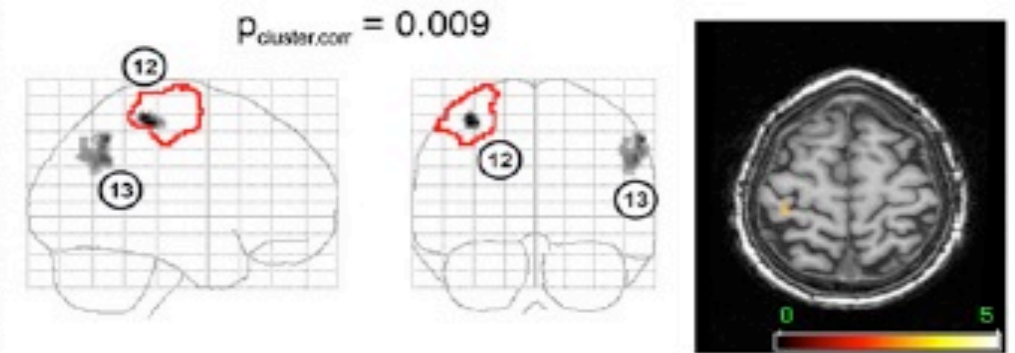
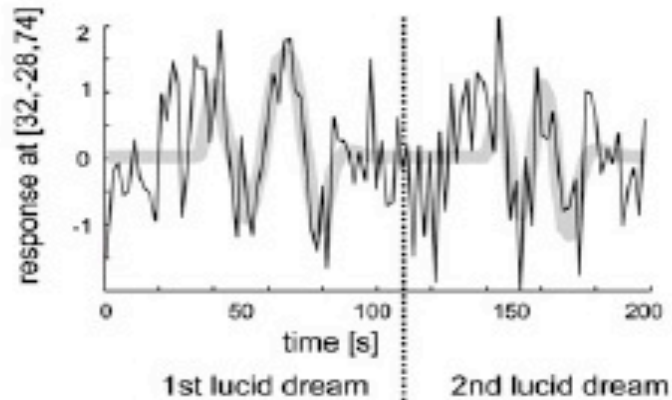
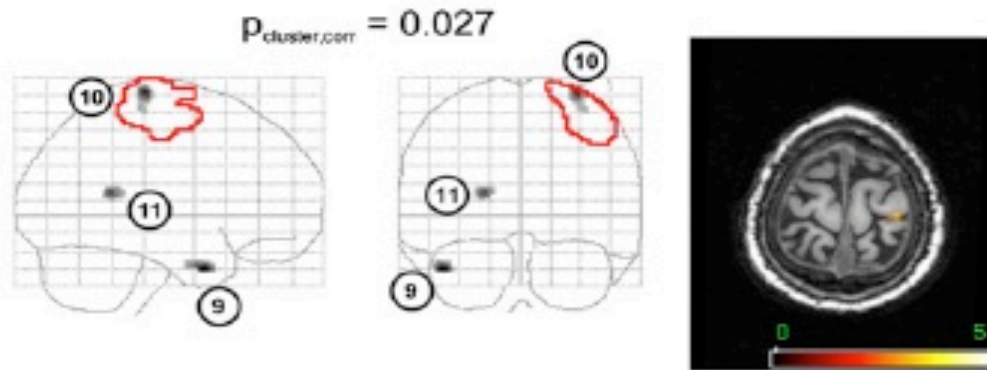


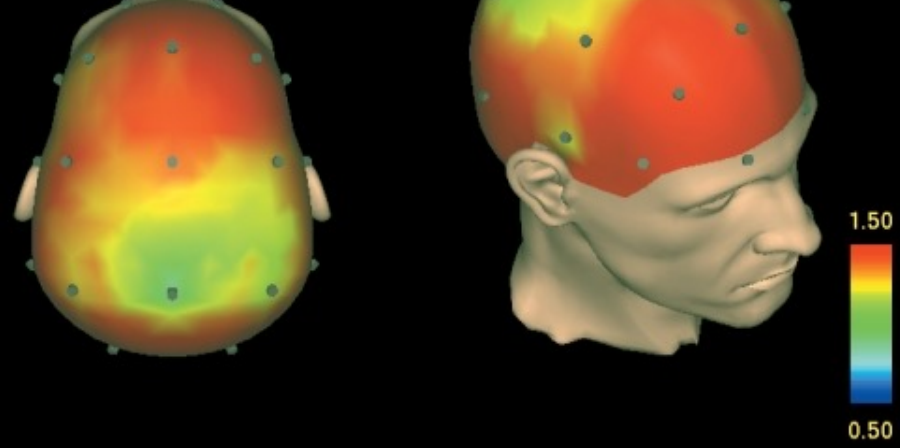
real hand movement  
during wakefulness

Imagined hand movement  
during wakefulness

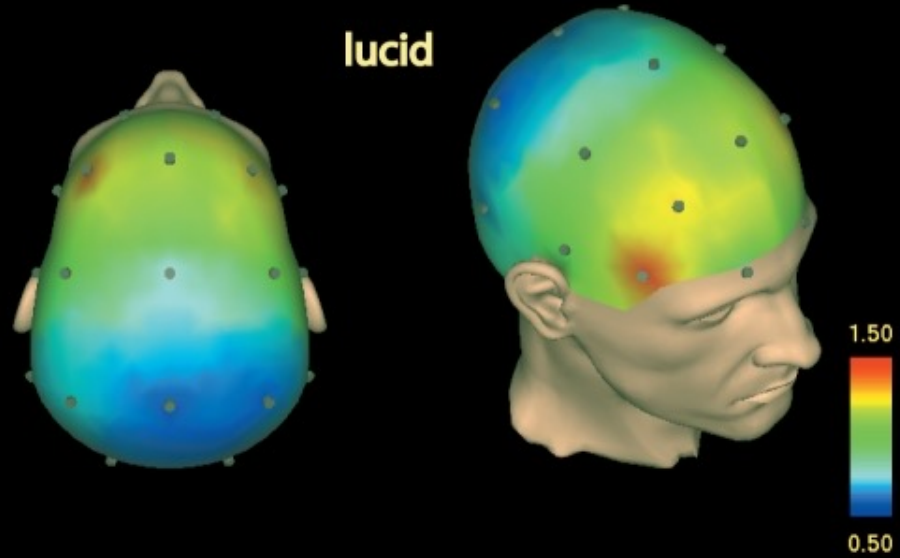
C

dreamed hand movement

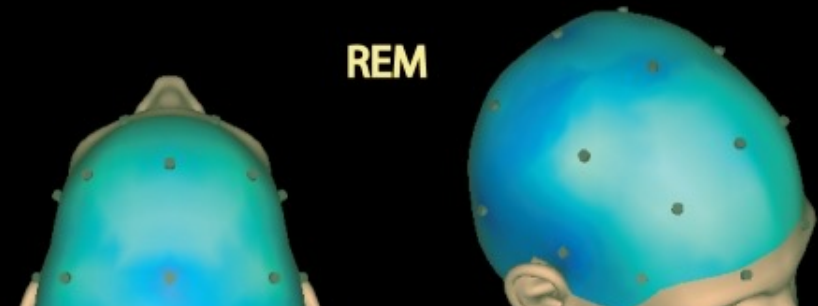




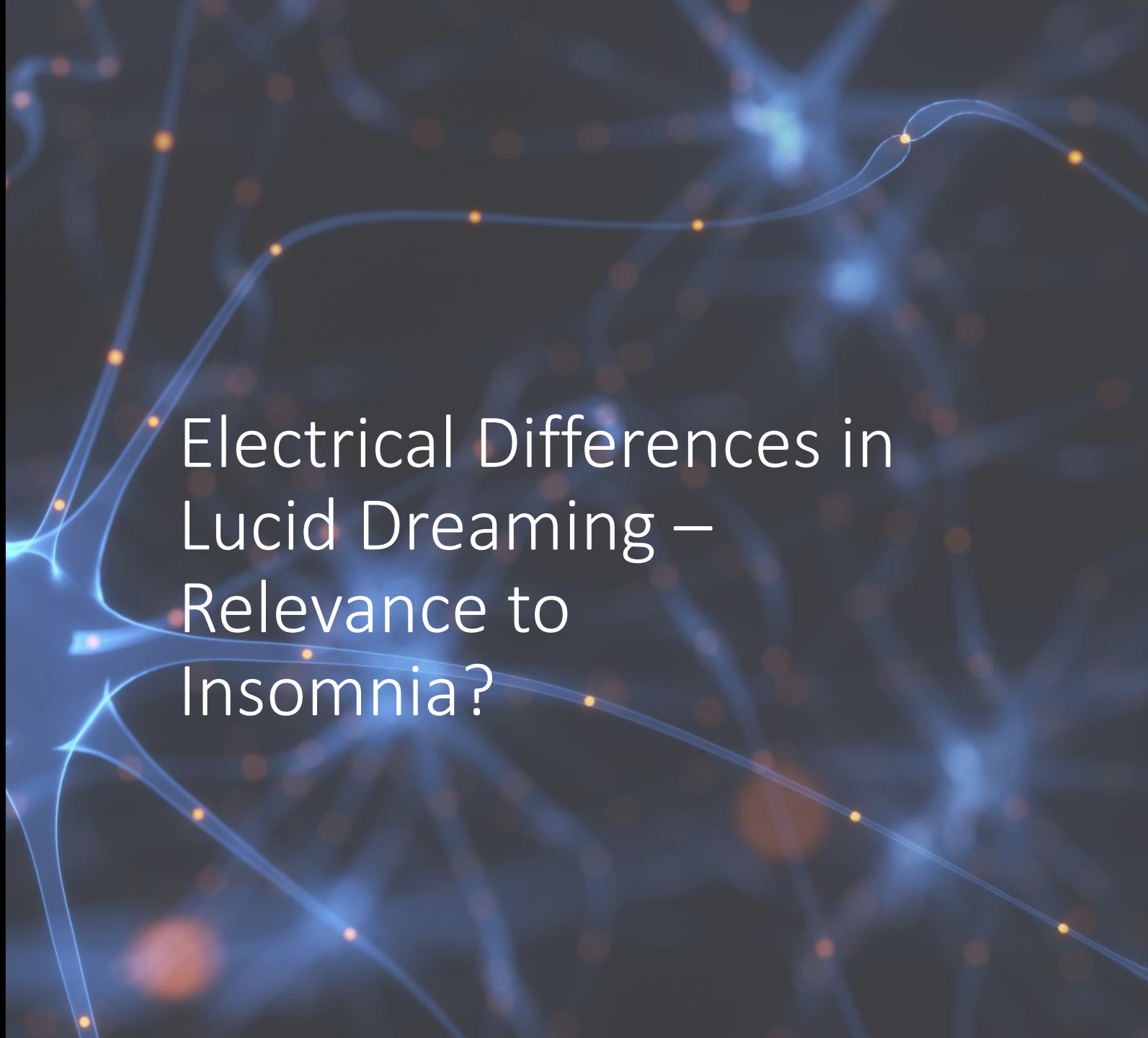
lucid



REM



Electrical Differences in  
Lucid Dreaming –  
Relevance to  
Insomnia?

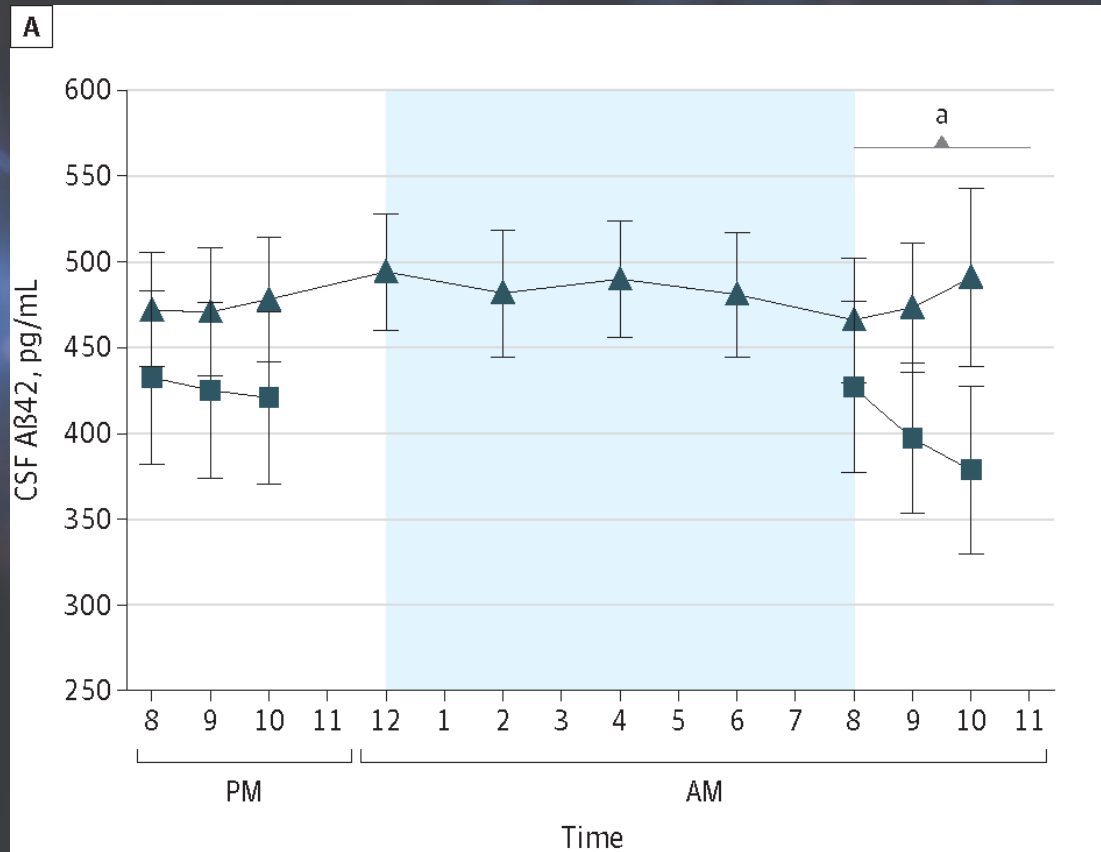




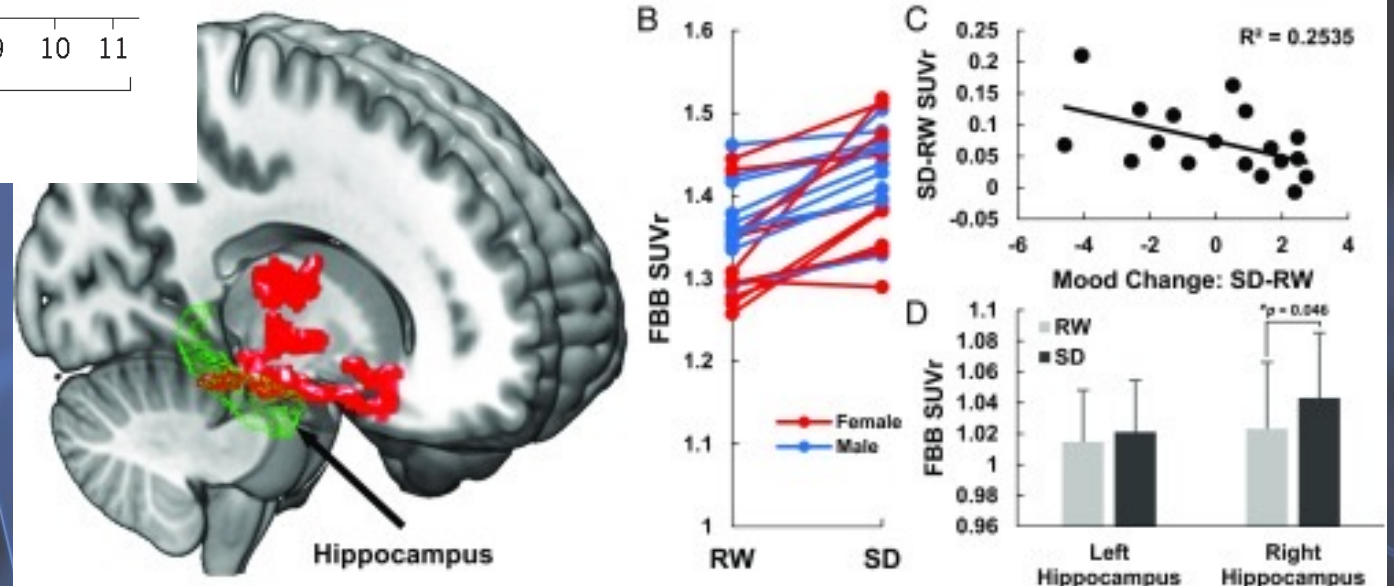
# What About Lesioning Sleep Itself?

- Wide range of conditions “lesion” sleep
  - Chronic Sleep Deprivation
  - Insomnia
  - Obstructive Sleep Apnoea
  - Periodic Limb Movement Disorder
- Sleep disorders associated with an array of neurological consequences
  - Cognitive and mood problems
  - Stroke
  - Dementia

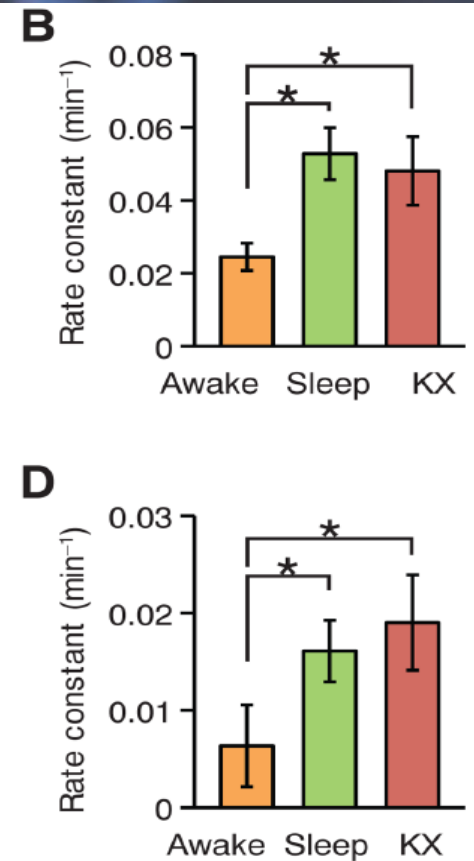
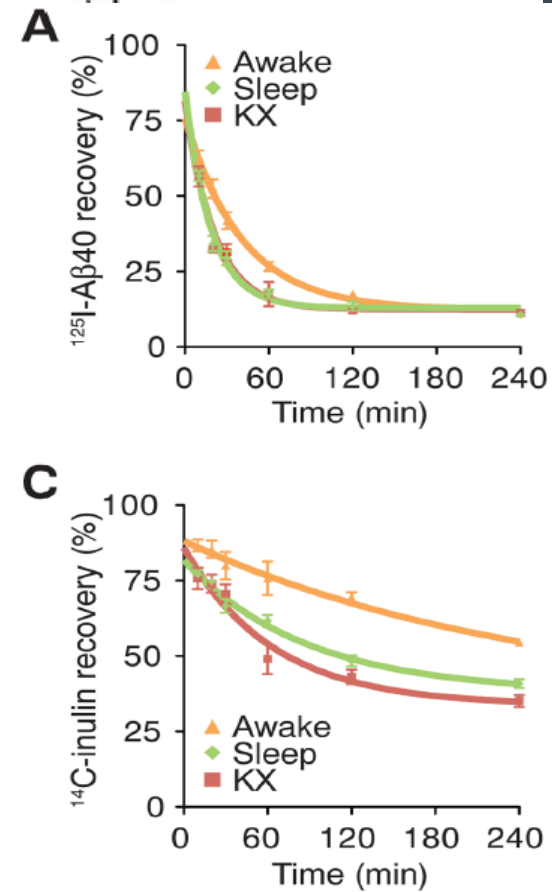
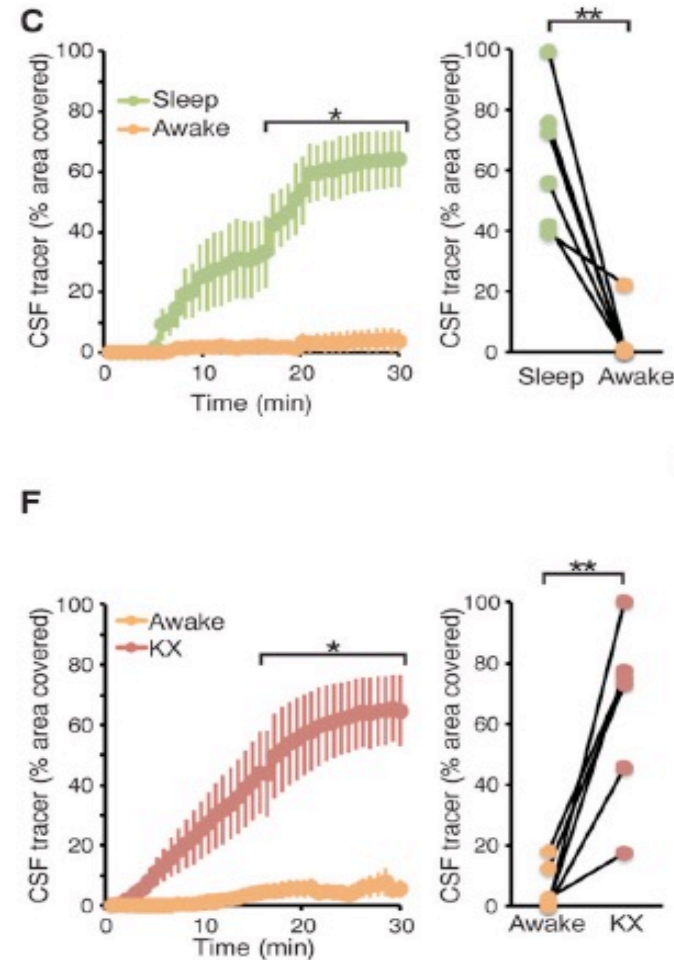
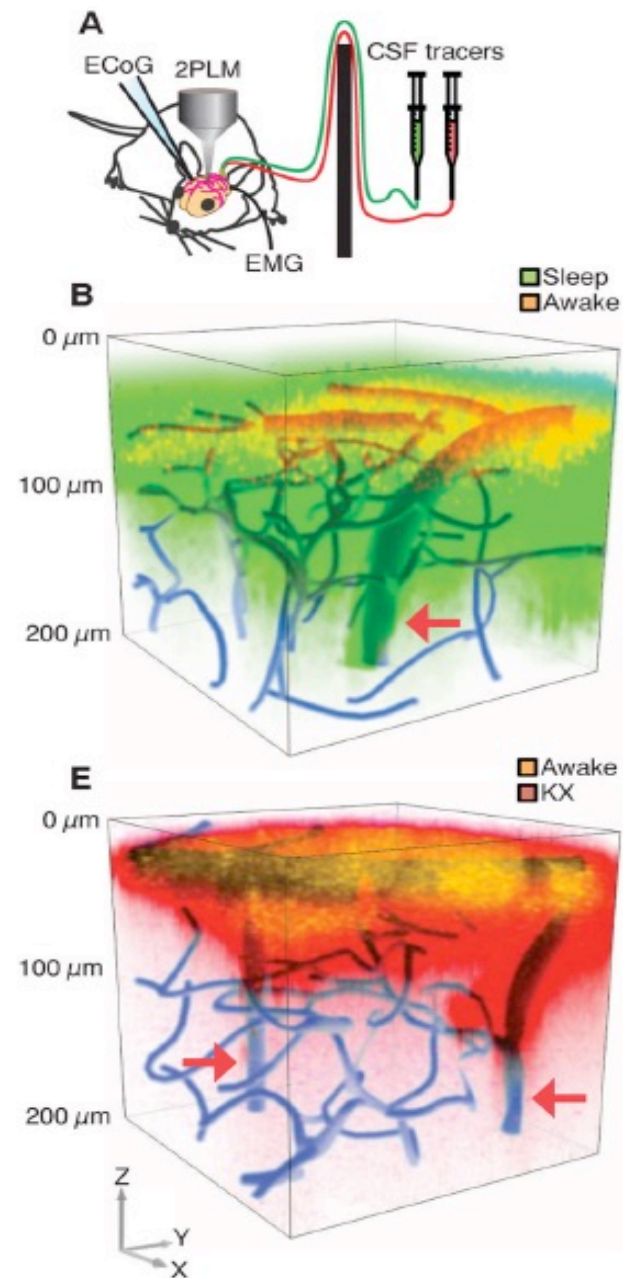
Ooms et al, JAMA  
Neurology 2014, 71 (8):  
971-977.



Ehsan-Shokri et al, PNAS  
2018, 115 (17).







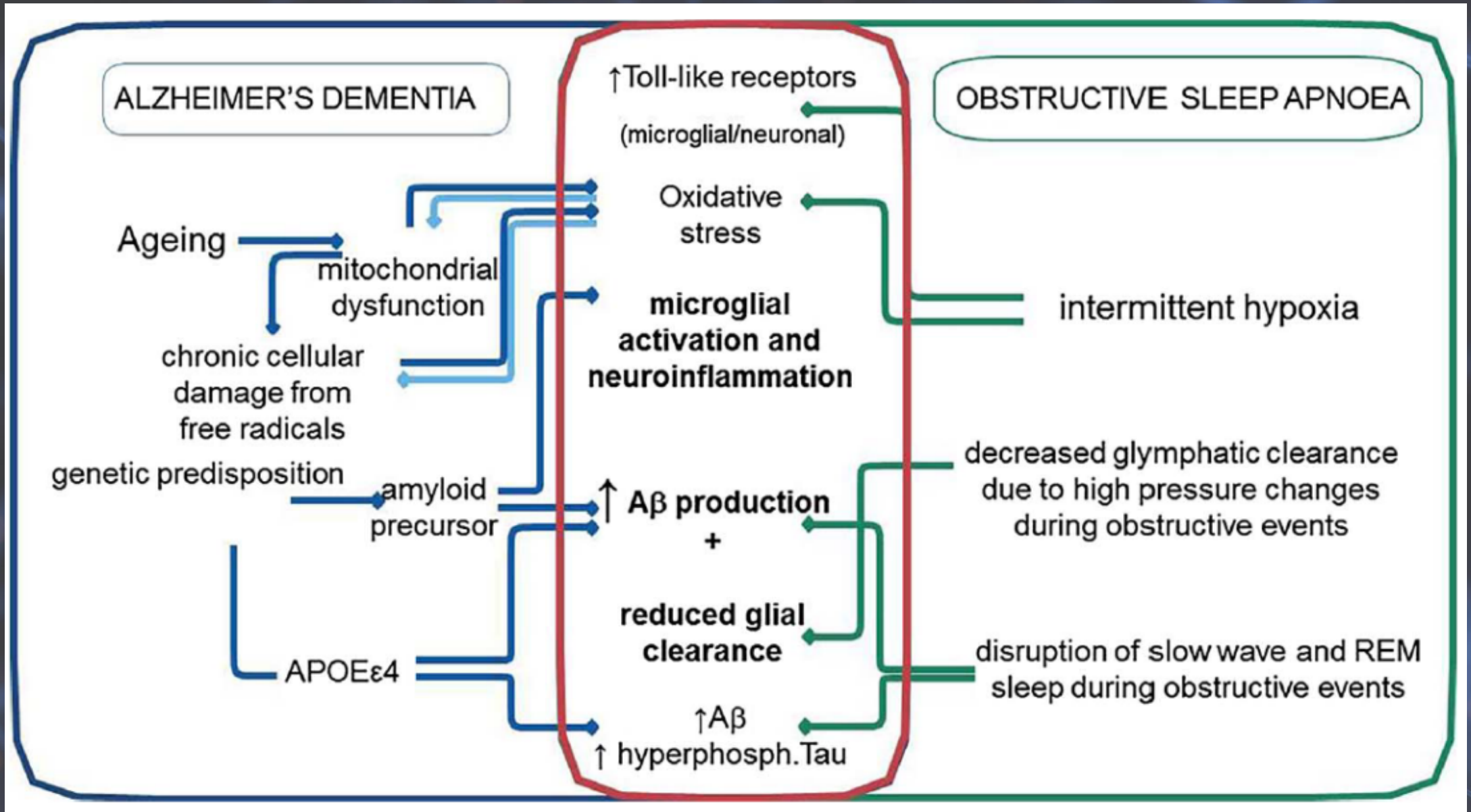
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Science. 2013 October 18; 342(6156): . doi:10.1126/science.1241224.

## Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie<sup>1,\*</sup>, Hongyi Kang<sup>1,\*</sup>, Qiwu Xu<sup>1</sup>, Michael J. Chen<sup>1</sup>, Yonghong Liao<sup>1</sup>, Meenakshisundaram Thiyagarajan<sup>1</sup>, John O'Donnell<sup>1</sup>, Daniel J. Christensen<sup>1</sup>, Charles Nicholson<sup>2</sup>, Jeffrey J. Iliff<sup>1</sup>, Takahiro Takano<sup>1</sup>, Rashid Deane<sup>1</sup>, and Maiken Nedergaard<sup>1,†</sup>

<sup>1</sup>Division of Glial Disease and Therapeutics, Center for Translational Neuromedicine, Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY 14642, USA

<sup>2</sup>Department of Neuroscience and Physiology, Langone Medical Center, New York University, New York, NY 10016, USA





# Conclusions

Sleep is not a single brain state  
Sleep is not even a global brain state  
Sleep disorders provide important insights into the regulation and functions of sleep  
Phenomena that we may all experience, even in good health, can be explained in these terms

