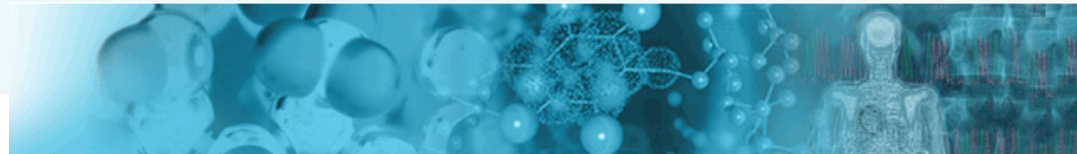
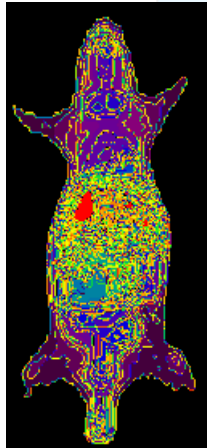
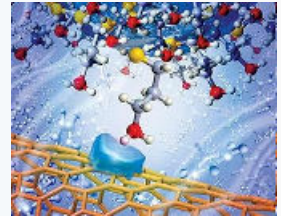


Imagenología funcional y sueño



Dra. Claudia Pascovich



Residente de Medicina Nuclear e Imagenología Molecular.



**Asist. Depto. De Fisiología
Laboratorio de neurobiología del sueño**

Neuroimagen funcional

PET (^{18}F FDG) → **MgluCr**

PET (H_2O^{15}) → **FSCr**

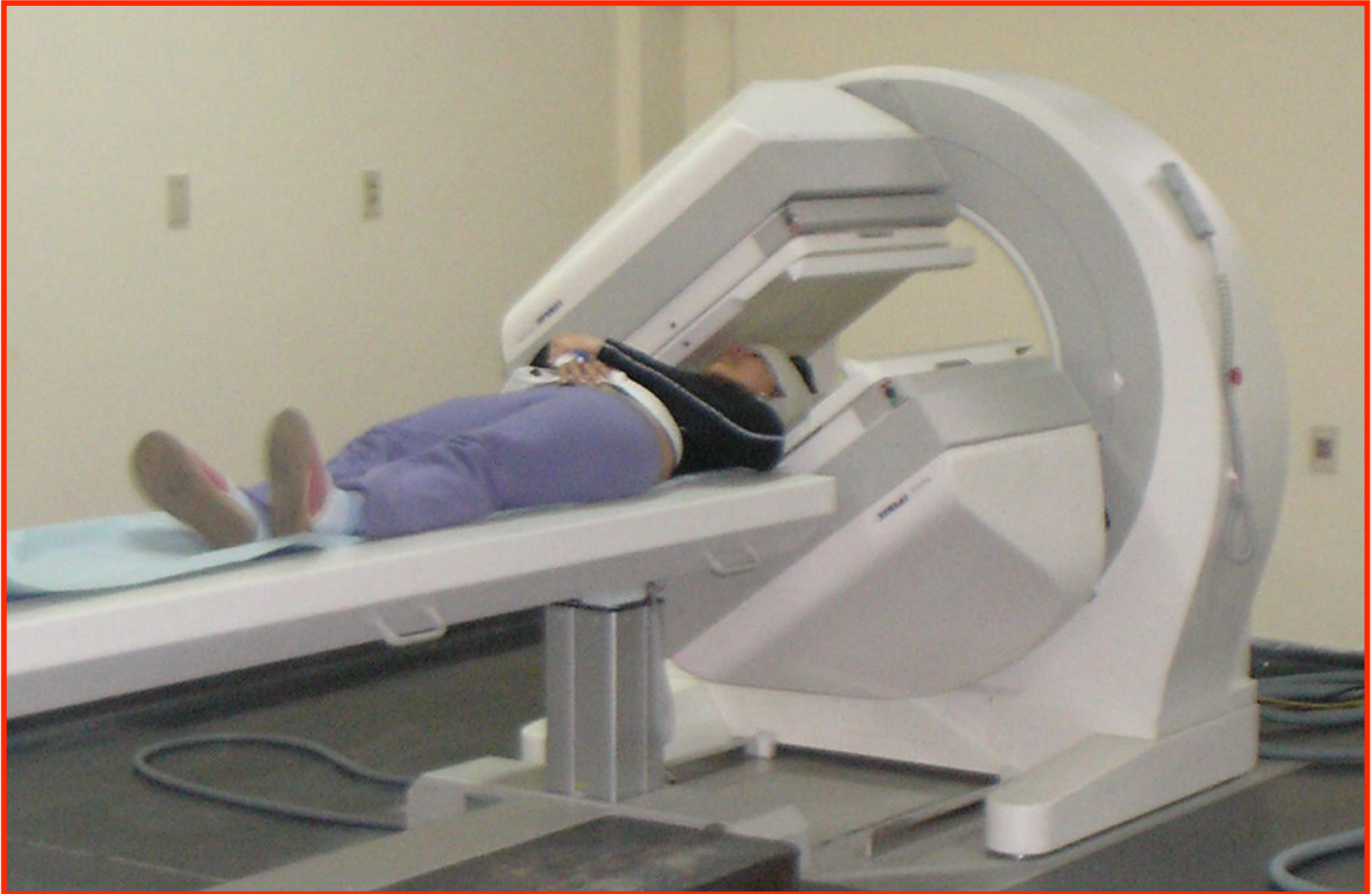
SPECT → **FSCr**

fMRI → **FSCr ~ VSCr**

Neuroimagen funcional

	<i>resolución espacial</i>	<i>resolución temporal</i>	<i>sitio del test</i>
PET (^{18}FDG)	3-4 mm	30 min	lab.
PET (H_2O^{15})	10 mm	2 min	scanner
SPECT	3-10 mm	20 seg	libre
fMRI	3-8 mm	100 ms	scanner sonido

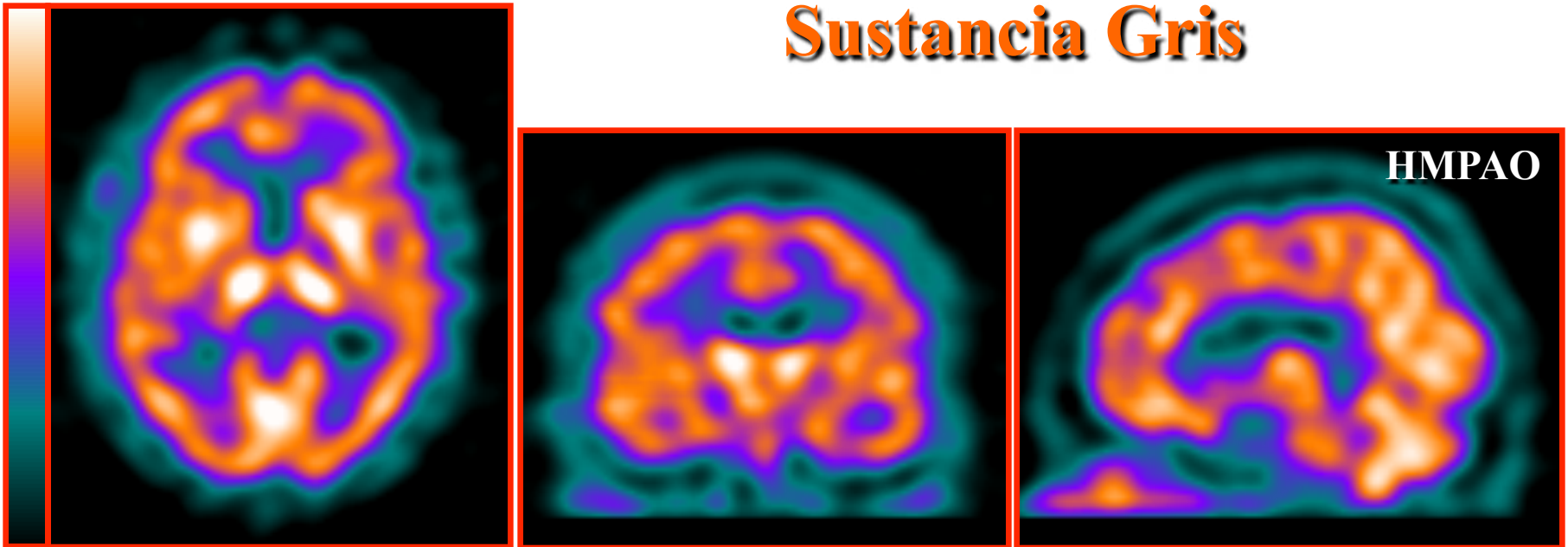
SPECT cerebral



SPECT de perfusión cerebral

Distribución regional del flujo sanguíneo cerebral

Sustancia Gris

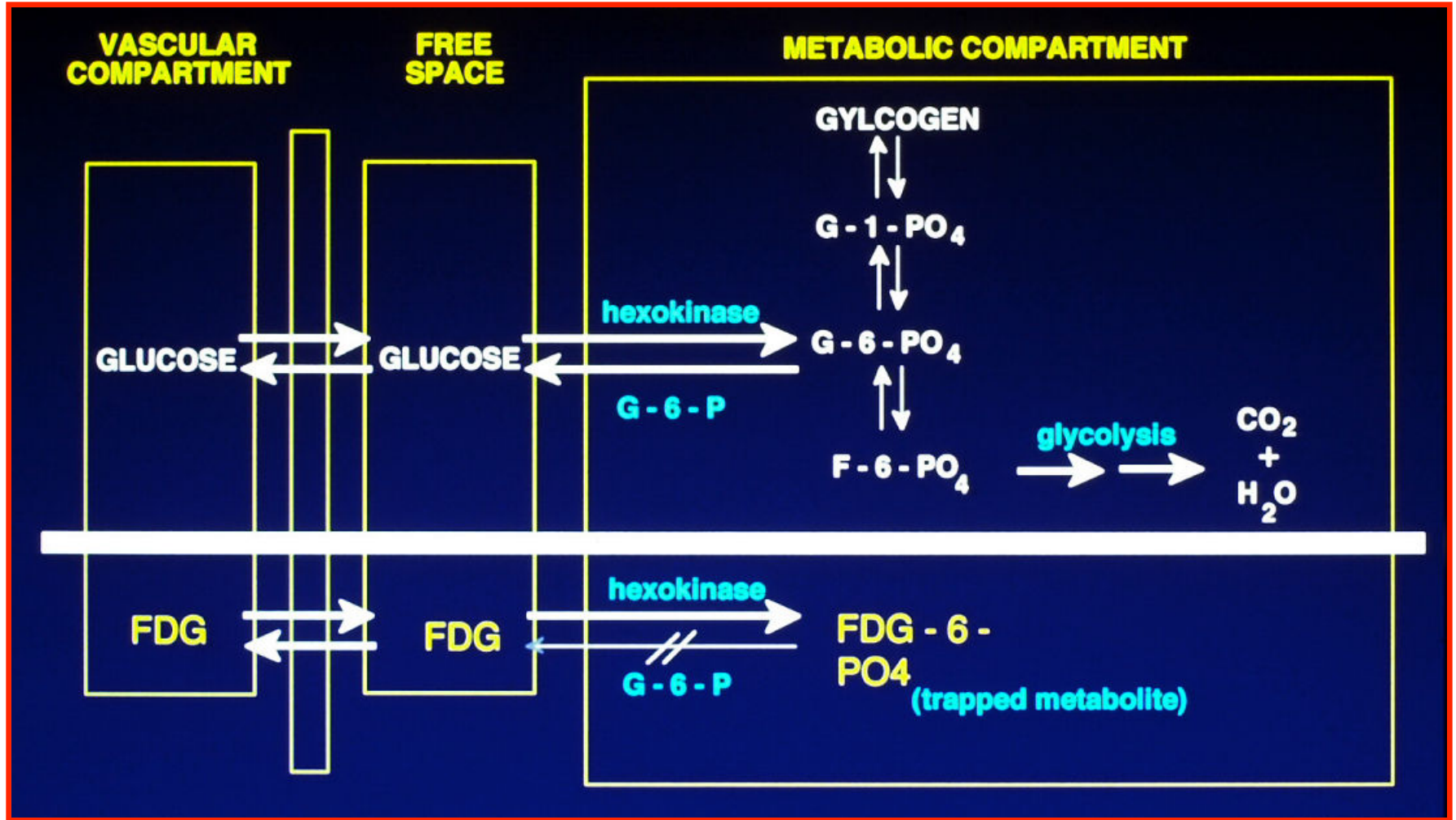


FSCr, metabolismo cerebral y actividad neuronal están estrechamente ligados en casi todas las circunstancias

La base farmacológica del PET

- **Molécula (droga, enzima, glu, aa, nucleósido, etc) marcada con un isótopo emisor de positrones.**
- **La biología de la radiomolécula provee información fisiológica visual y cuantitativa.**
- **FDG es el “caballito de batalla”: glucosa marcada en la 2ª posición con ^{18}F en lugar de un grupo -OH.**

Captación celular del FDG



¿Cómo obtengo la imagen PET ?

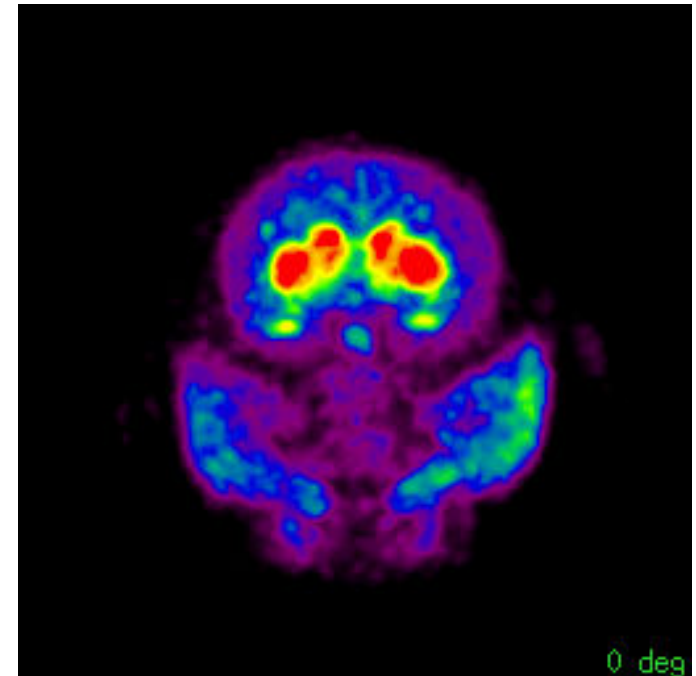
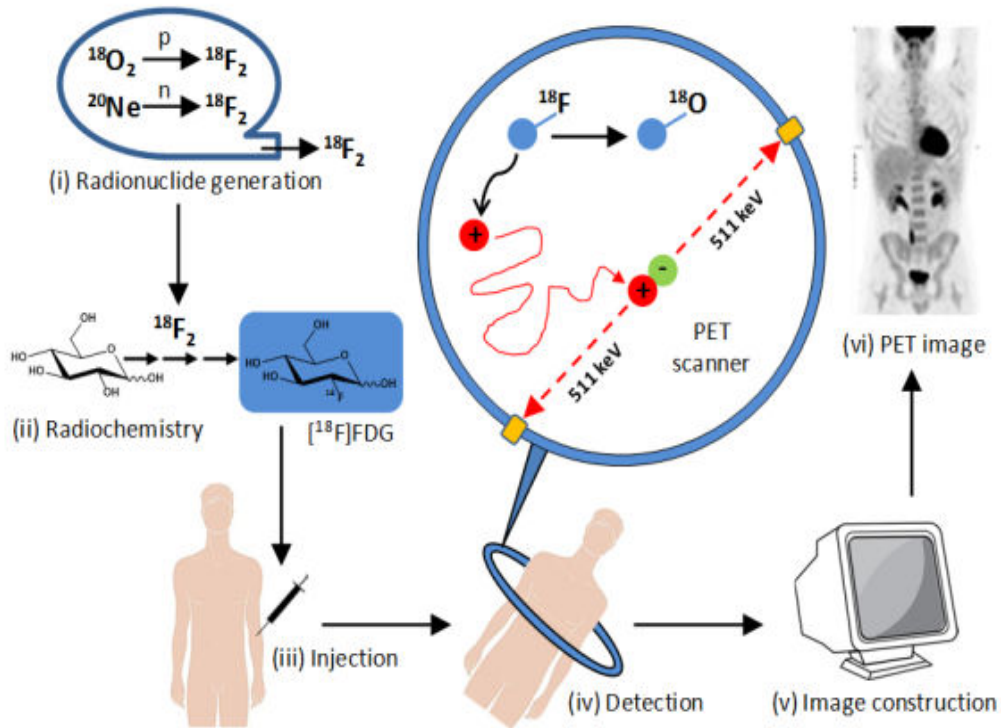


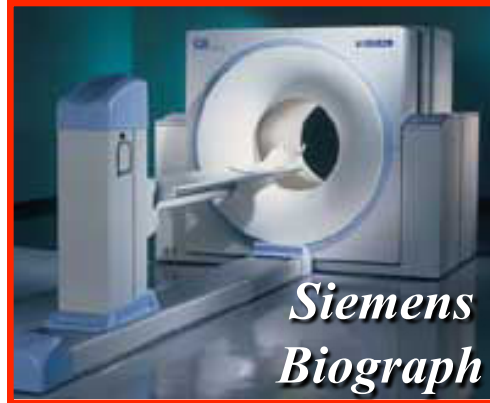
Imagen tomográfica (3D)

PET/CT

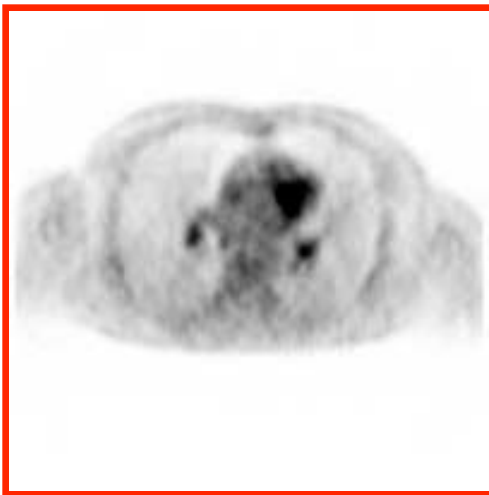
*Philips
Gemini*



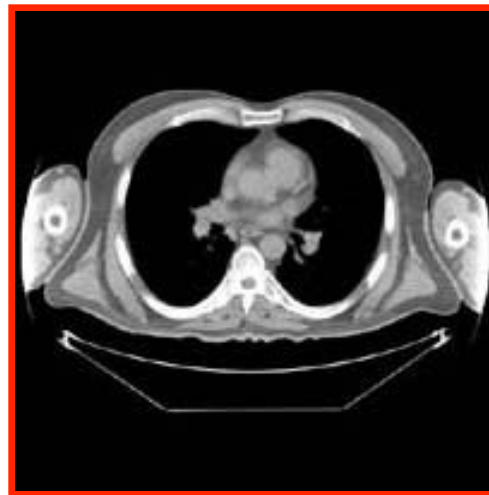
*Siemens
Biograph*



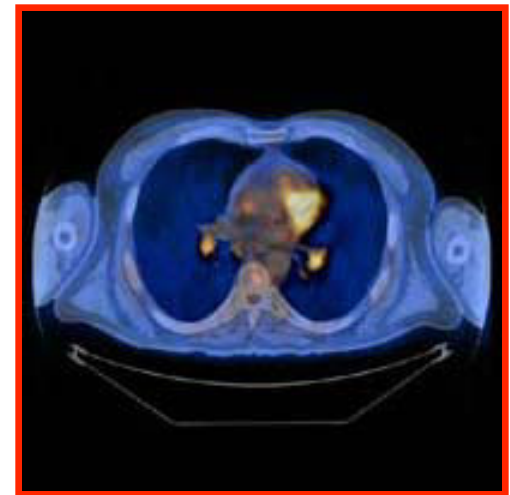
GE Discovery



+



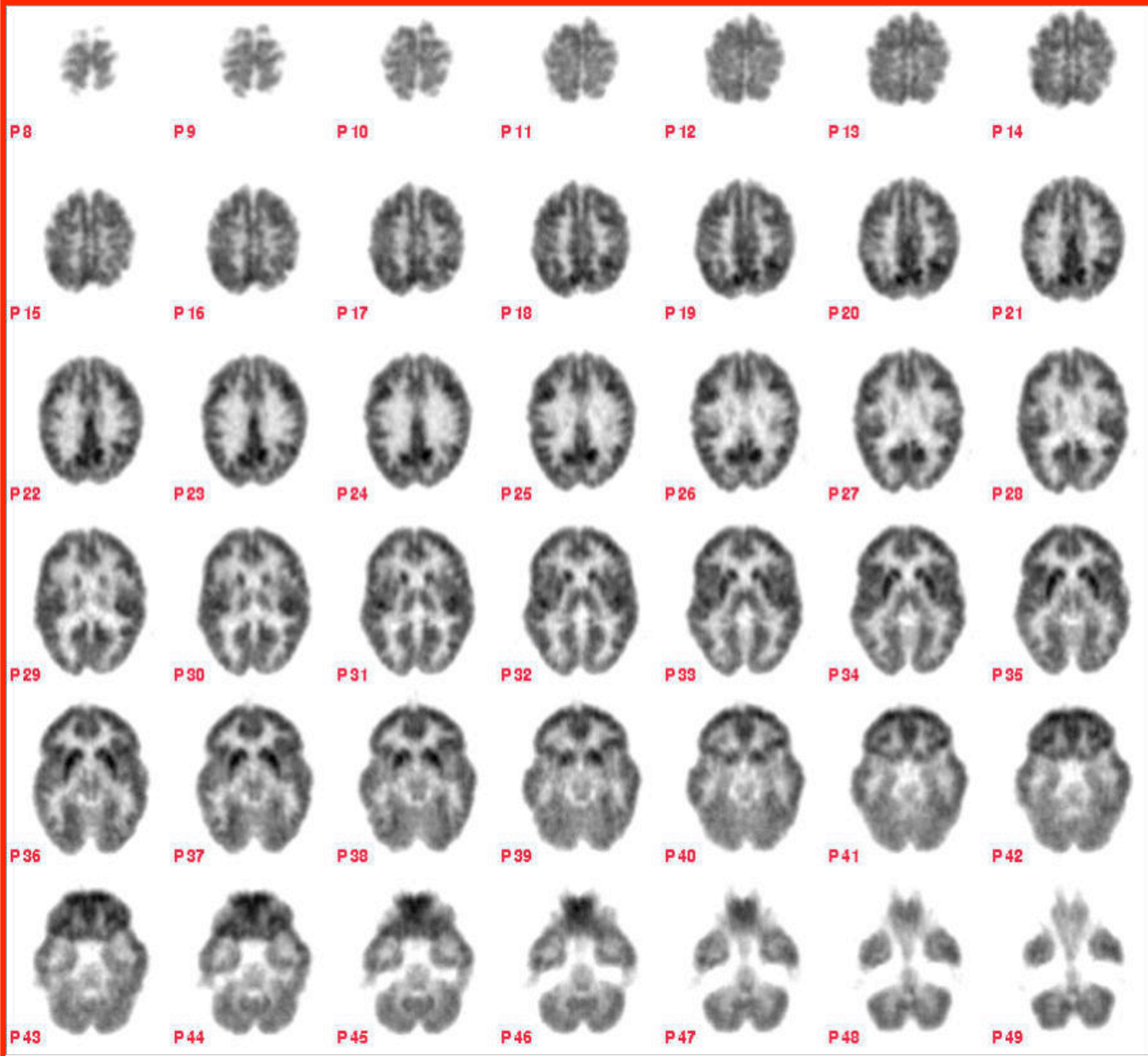
=



Emisores de positrones

<i>Isótopo</i>	<i>Vida media (min)</i>	<i>Energía máx. (MeV)</i>	<i>Rango en agua (mm)</i>	<i>Método de Producción</i>
^{11}C	20.3	0.96	1.1	Ciclotrón
^{13}N	9.97	1.19	1.4	Ciclotrón
^{15}O	2.03	1.70	1.5	Ciclotrón
^{18}F	109.8	0.64	1.0	Ciclotrón
^{68}Ga	67.8	1.89	1.7	Generador
^{82}Rb	1.26	3.15	1.7	Generador

FDG PET
normal



Neurorreceptores

- ❑ Ligandos marcados. Agonistas o antagonistas. Presinápticos o postsinápticos. PET o SPECT.
- ❑ Evaluación in vivo de sistemas neurotransmisores.
- ❑ Asociación con tests de activación.

❑ *DOPAMINERGICOS*

- ❑ *D1*. Circuito órptico-estrio-talámico. ^{123}I -FISCH y TISCH
- ❑ *D2*. ^{132}I -Iodobenzamida (IBZM), ^{11}C -raclopride, etc.
- ❑ *Transportadores*. ^{11}C -cocaína, ^{123}I -BCIT, etc.

❑ *GABA-BZD* ^{11}C -flumazenil, ^{123}I -iomazenil

❑ *ACETILCOLINERGICOS*

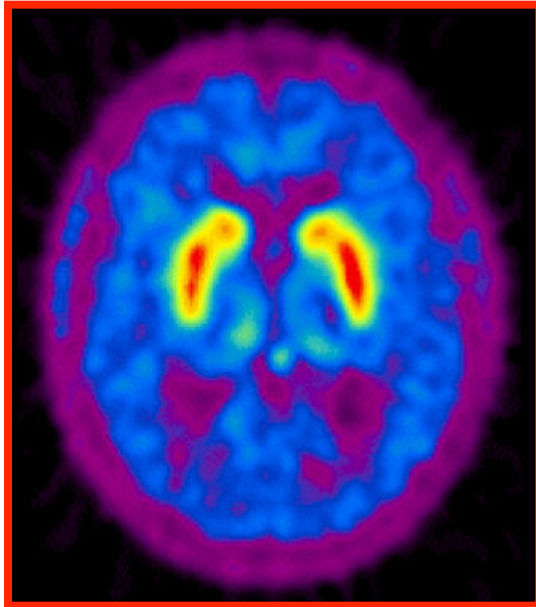
- ❑ *Muscarínicos*. ^{123}I -QNM o IDEX
- ❑ *Nicotínicos*. ^{11}C -nicotina

❑ *OPIOIDES* ^{11}C -diprenofina y carfentanil

❑ *SEROTONINA* Receptores 5HT

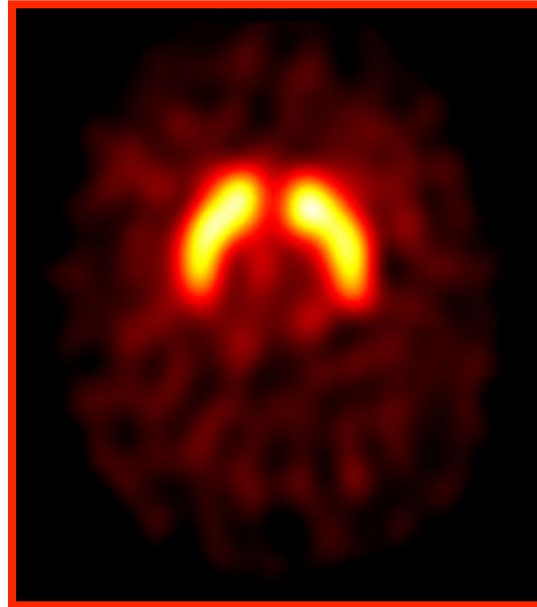
Imagen de neuroreceptores

DDC



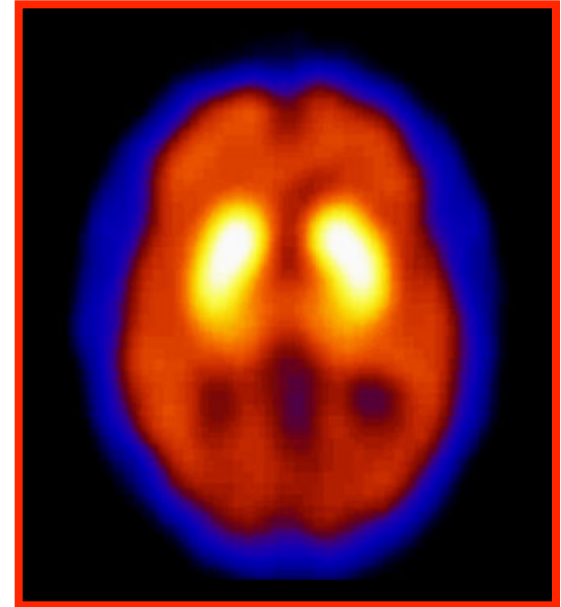
¹⁸F-DOPA

DAT



¹²³I-FP CIT

D2

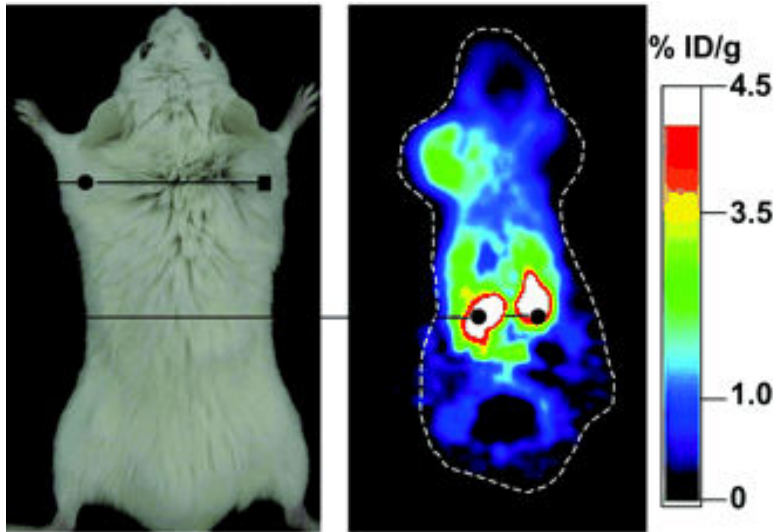


¹²³I-IBZM

Tomógrafos microPET: pasado y presente

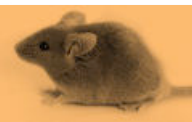
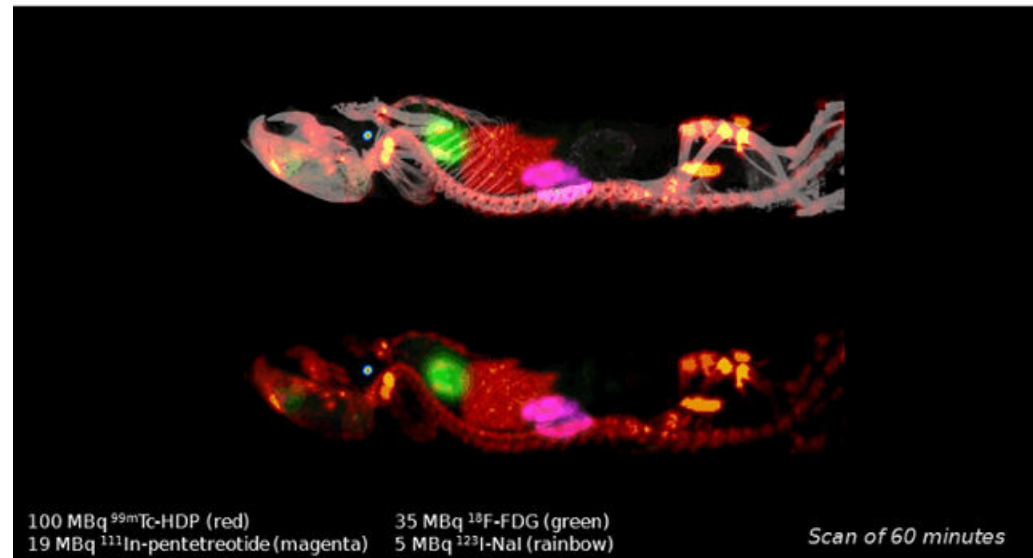


Ratón



Proc Natl Acad Sci USA. 2003;100:1232-1237

Simultaneous multi-isotope SPECT & PET Imaging

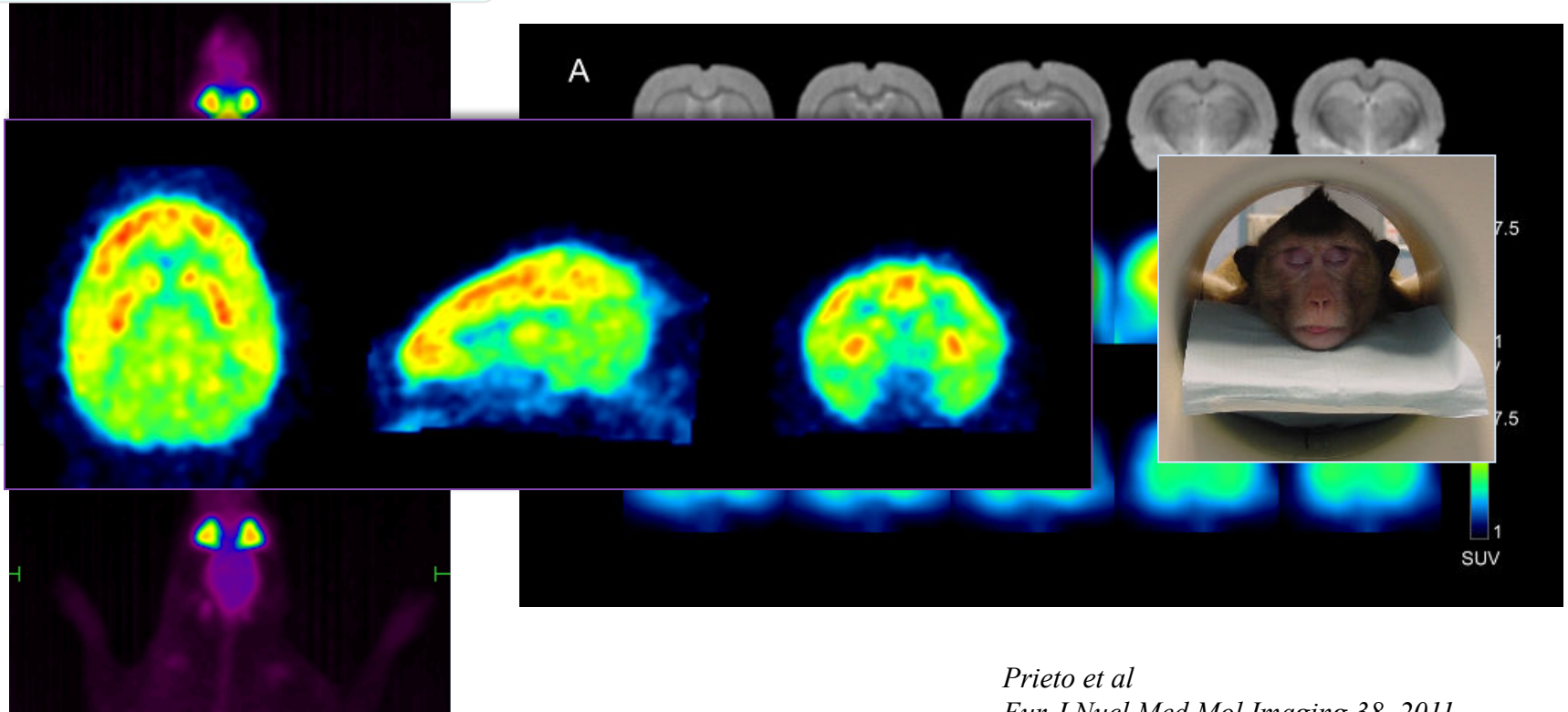


La importancia de la anestesia



^{18}F -FDG: actividad neuronal

Incorporación despierta



Prieto et al
Eur J Nucl Med Mol Imaging 38, 2011



Claves imagen PET en animales

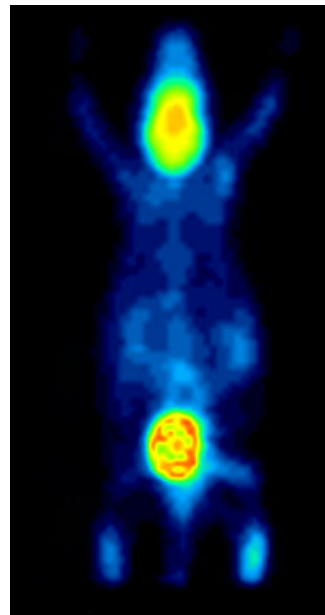
La importancia de la anestesia



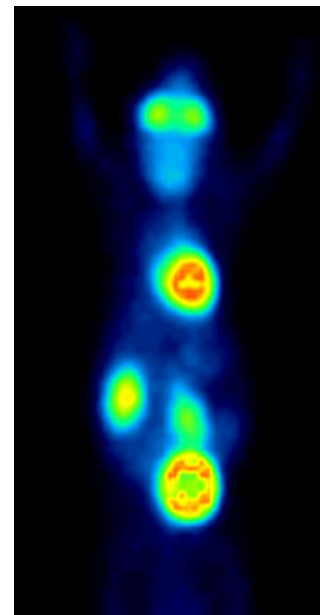
^{18}F -FDG: metabolismo

- ✓ cerebral
- ✓ cardiaco
- ✓ renal
- ✓ muscular
- ✓ glandular

Etc...



Incorporación despierto



Incorporación dormido

5 SUV



0

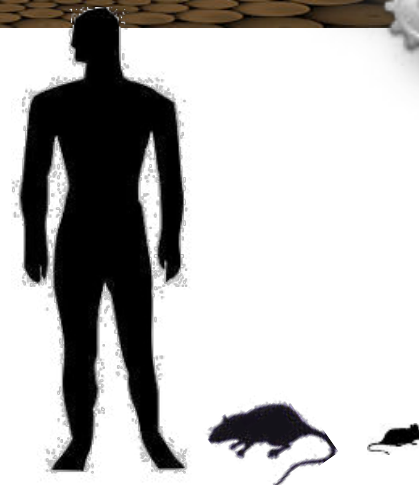


Claves imagen PET en animales

Tomógrafos microPET

- Gran reto técnico: RESOLUCIÓN

Hombre	70000 g - 1,70 m	↔	$10^2 - 10^3$
Rata	250 g - 17-27 cm		
Ratón	20 g - 10 cm		



- Primer equipo para animales: 1995
- Resoluciones cercanas a 1 mm
- ▶ Equipos híbridos comerciales: PET/SPECT/CT y **PET/MRI**



Bioscan



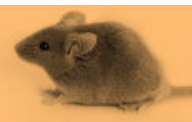
Milabs



Albira



Mediso



Un ejemplo: Unidad de Investigación Micro-PET

UBICACIÓN

- Unidad de soporte a la Investigación
 - Centro de Investigación Médica Aplicada
 - Clínica Universidad de Navarra (Medicina Nuclear)



Facultades de:

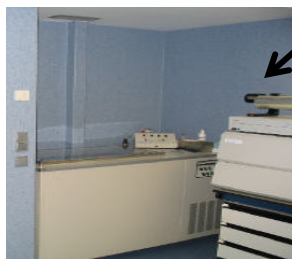
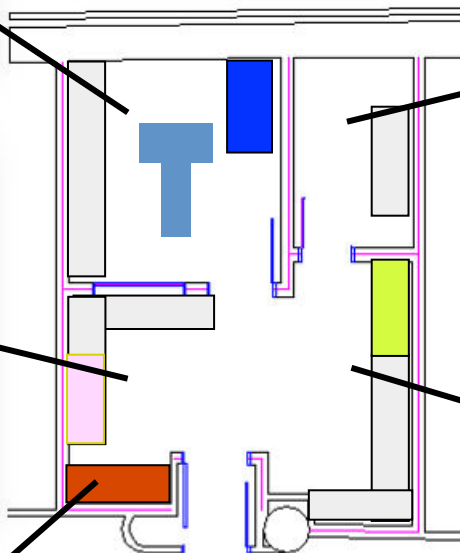
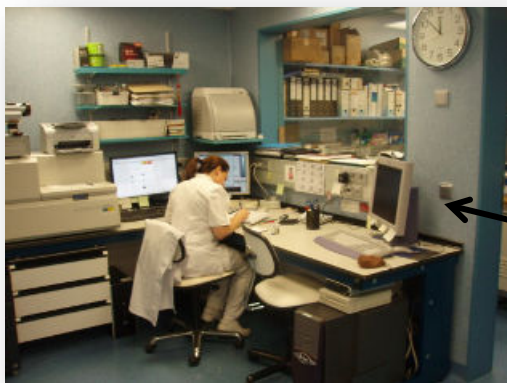
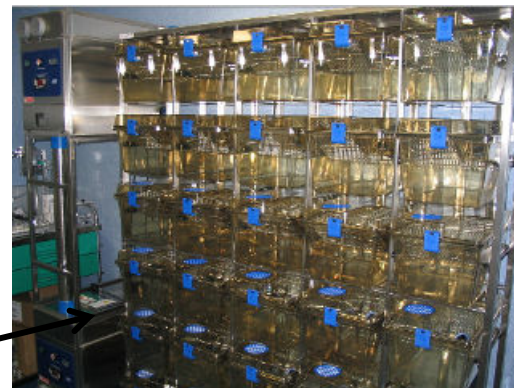
- Medicina
- Farmacia
- Química
- Biología



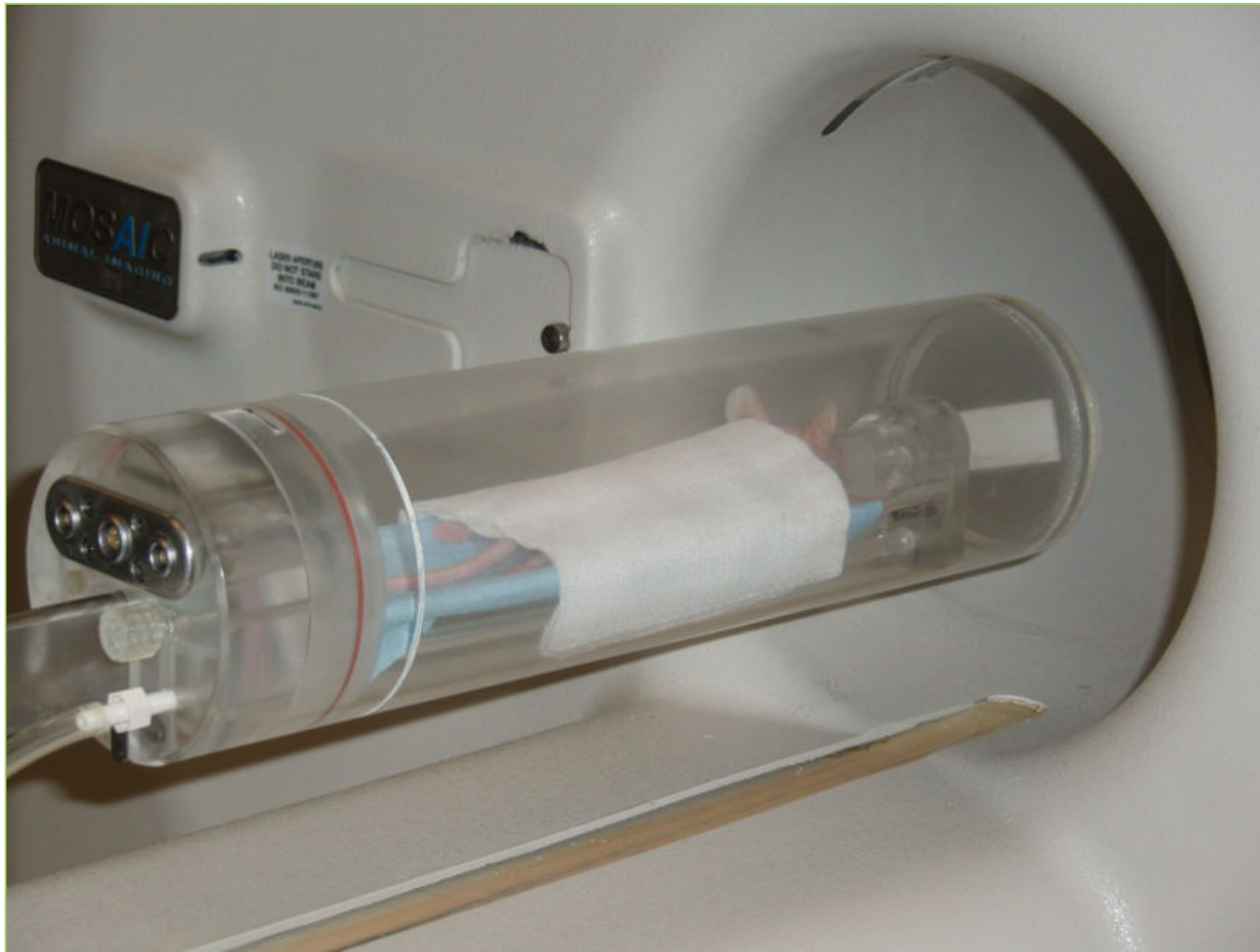
Instalación



Un ejemplo: Unidad de Investigación Micro-PET



Procedimientos con rata/ratón



Procedimientos con primates



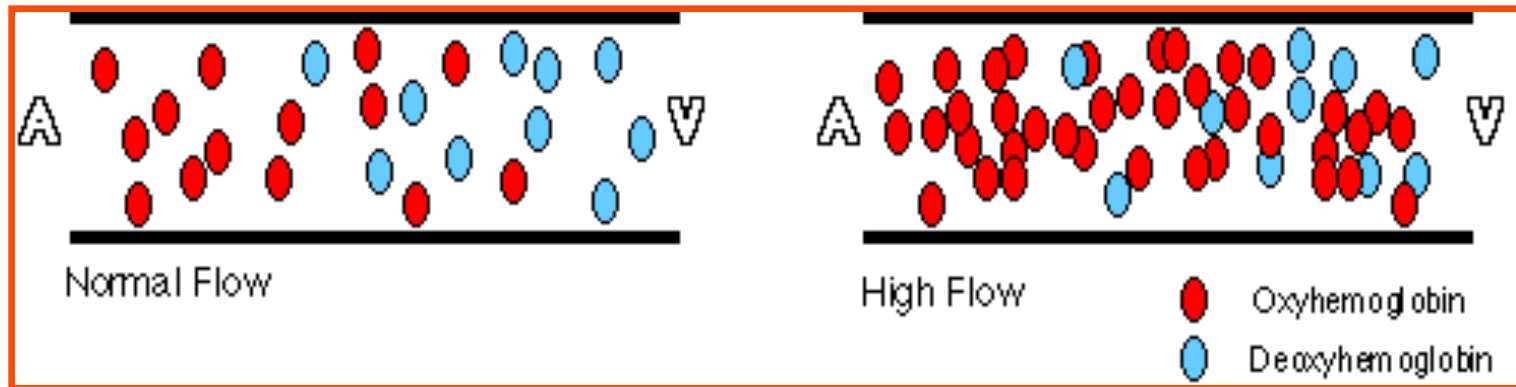
- ✓ Animal llega a instalación para el estudio PET
- ✓ Anestesia: ketamina/midazolam o isofluorano
- ✓ Inyección radiotrazador en vena safena



fMRI (Resonancia magnética funcional)

La señal **BOLD**

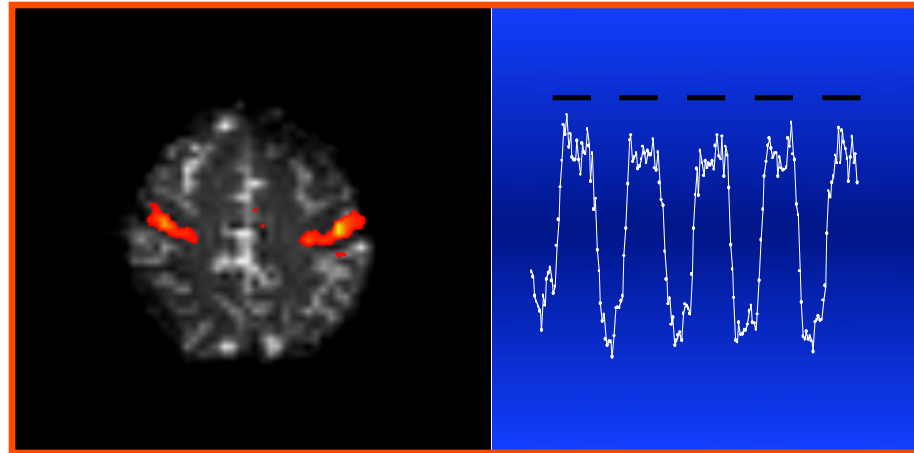
Blood Oxigenation Level Dependent



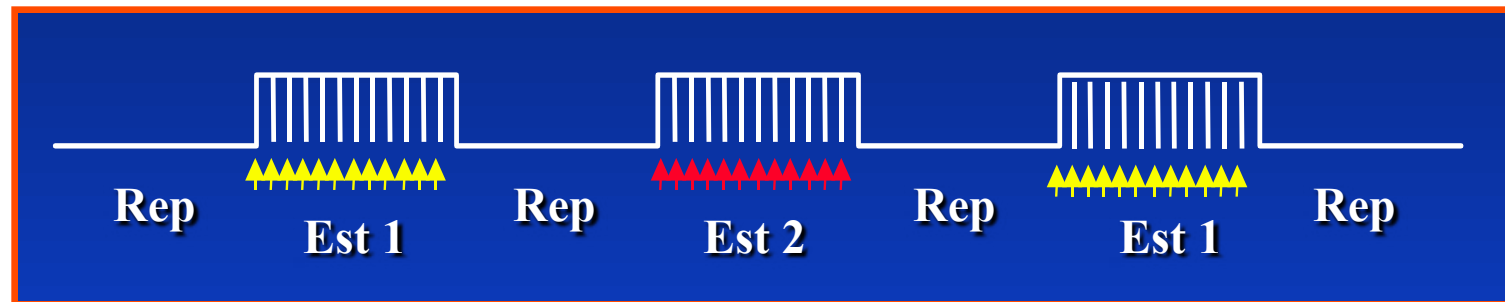
En las áreas cerebrales que se activan el aumento del flujo sanguíneo excede al consumo de O_2 , con lo cual disminuye la proporción de Hb desoxigenada (decaimiento rápido de la señal magnética) con respecto a la oxigenada (decaimiento lento) dando como resultado un aumento local de la señal.

fMRI (Resonancia magnética funcional)

Test de activación motora



Diseño de Bloque



Neuroactivación

- ❑ *Comparación de 2 condiciones: basal y test de activación*
- ❑ *SPECT de perfusión, $^{15}\text{O}\text{-H}_2\text{O}$ PET, fMRI*

➤ **Test farmacológicos**

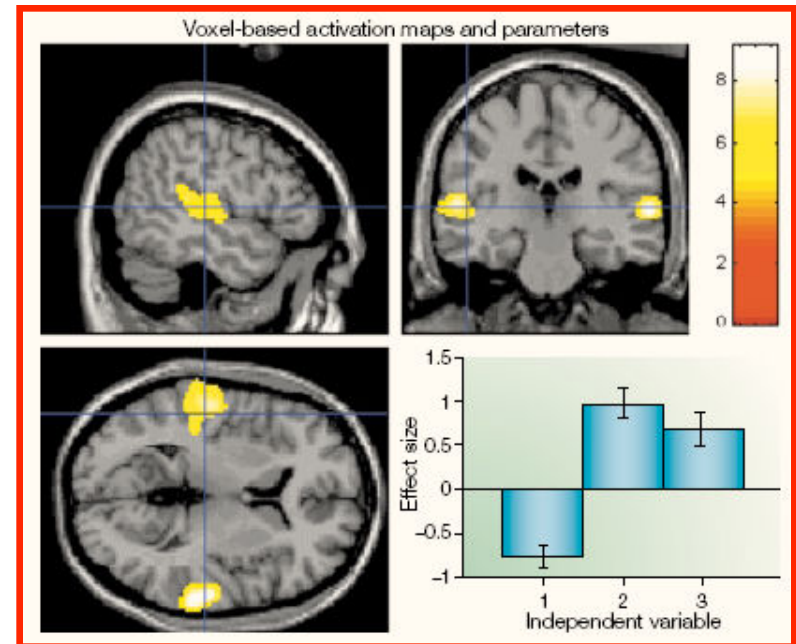
❑ *Ej: ACZ, AMP*

➤ **Test sensoriales**

➤ **Test cognitivos**

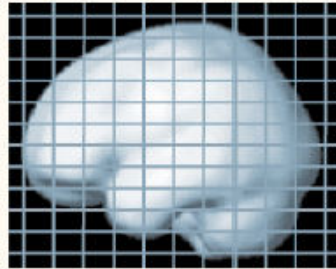
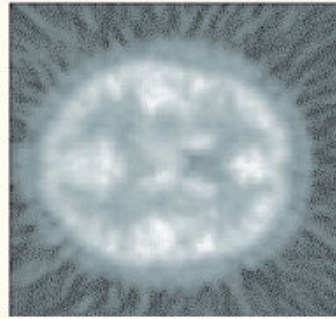
❑ *Ej: WCST, Stroop Test*

➤ **Test asociados**



Análisis estadístico de neuroimágenes

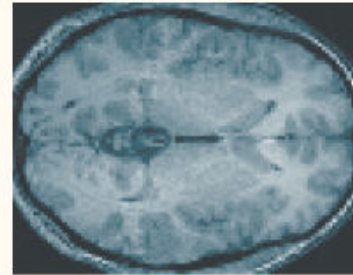
Functional images



Target template in stereotaxic space

Realignment

Coregistration

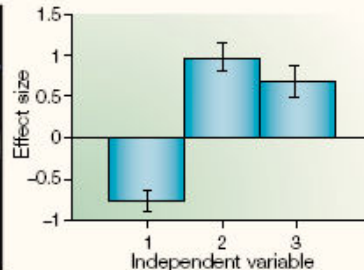
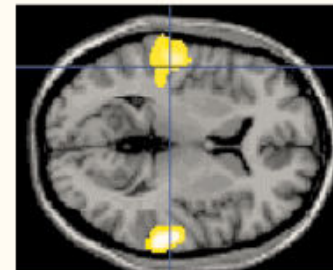
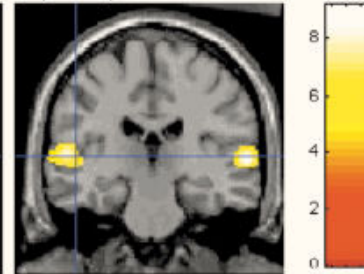


Structural image

Spatial normalization

Statistical analysis

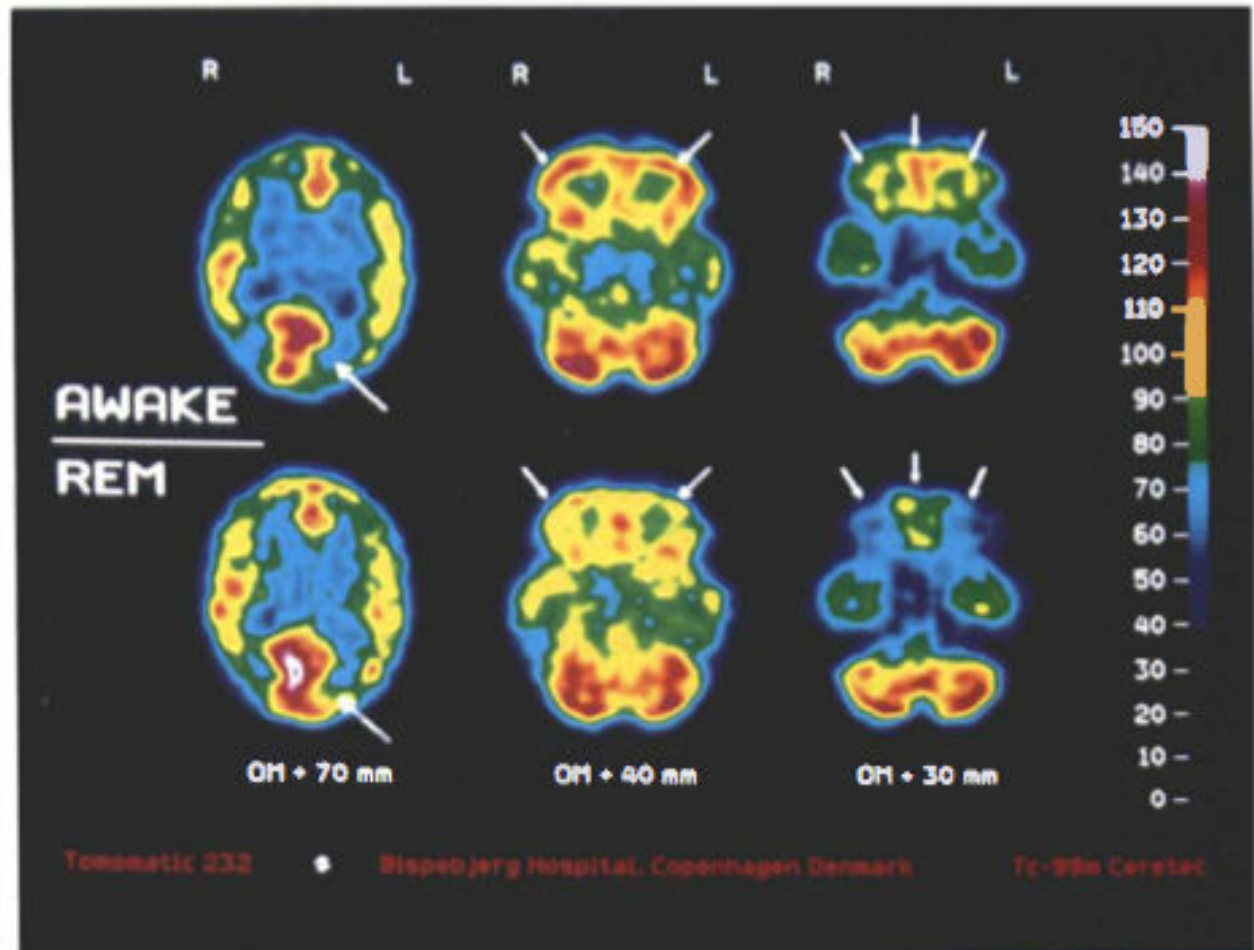
Voxel-based activation maps and parameters



Aportes de la neuroimagen funcional a la fisiología del sueño

- ❑ Áreas se más activas o menos activas durante las distintas etapas del sueño
- ❑ El cerebro durante el sueño es capaz de procesar estímulos externos
- ❑ Sueño y memoria
- ❑ Privación de sueño
- ❑ Patologías del sueño
- ❑ Nuevos aportes con imagenología molecular

FSCr con Tc^{99m} -HMPAO SPECT durante el sueño NREM

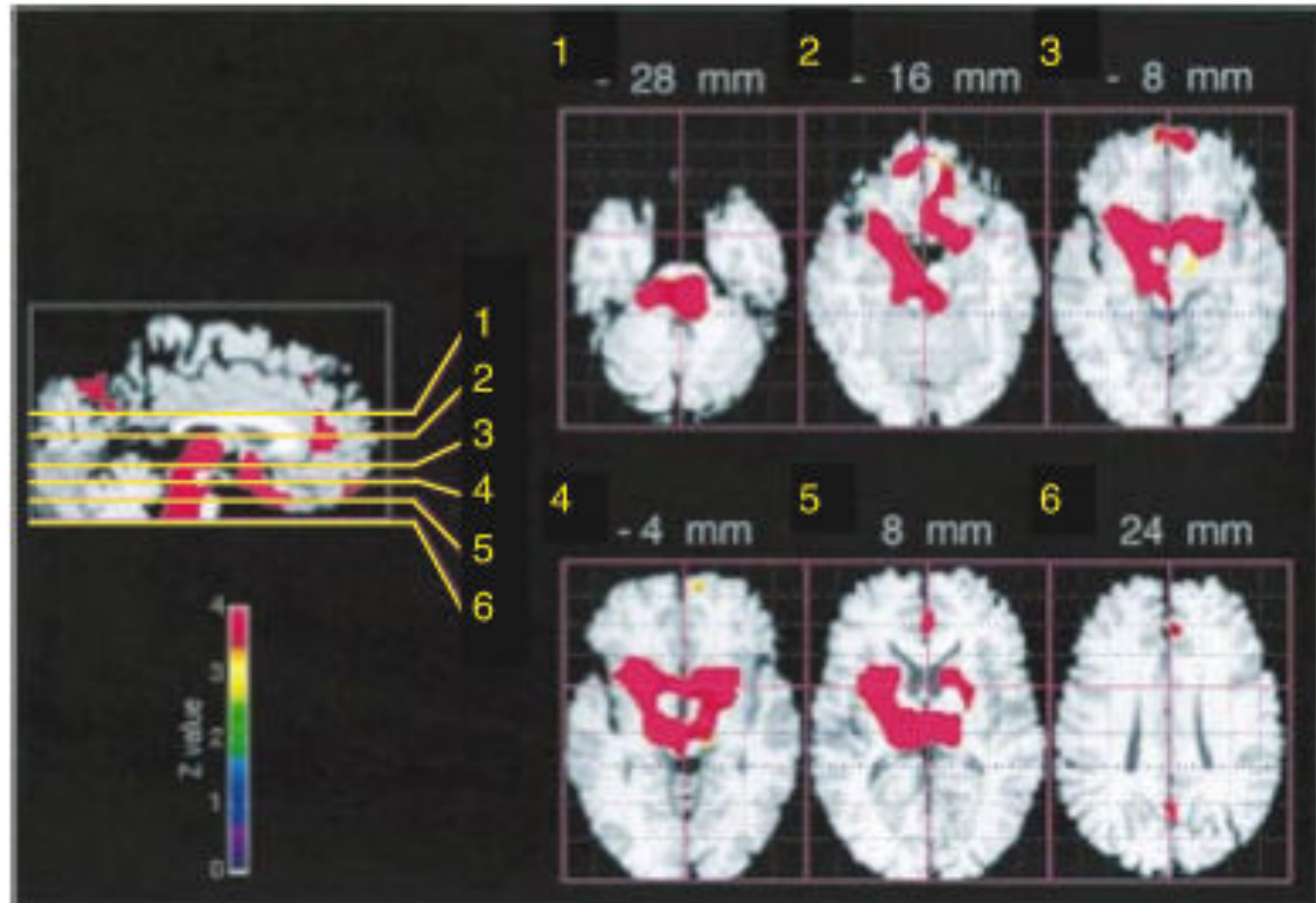


Madsen et al, 1991.

Disminución del FSCr durante el sueño NREM con con $H_2^{15}O$ PET

Deactivation of the central core structures (brainstem and thalamic nuclei)

- basal forebrain
- basal ganglia
- orbito-frontal cortex
- anterior cingulate cortex
- precuneus



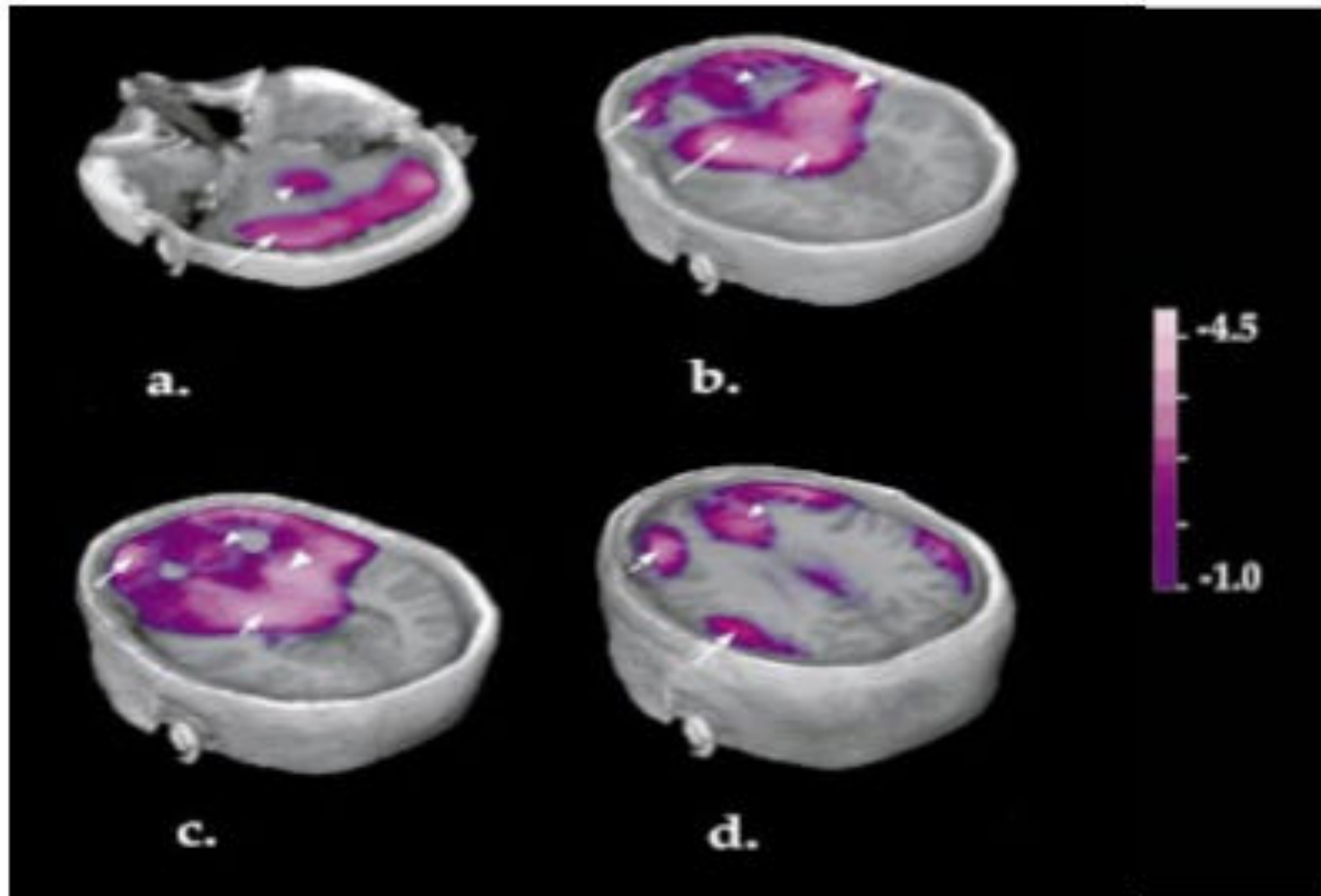
Maquet et al. 1997.

Disminución del FSCr durante el sueño NREM con con $H_2^{15}O$ PET

Contrast: presleep W
 \pm SWS.

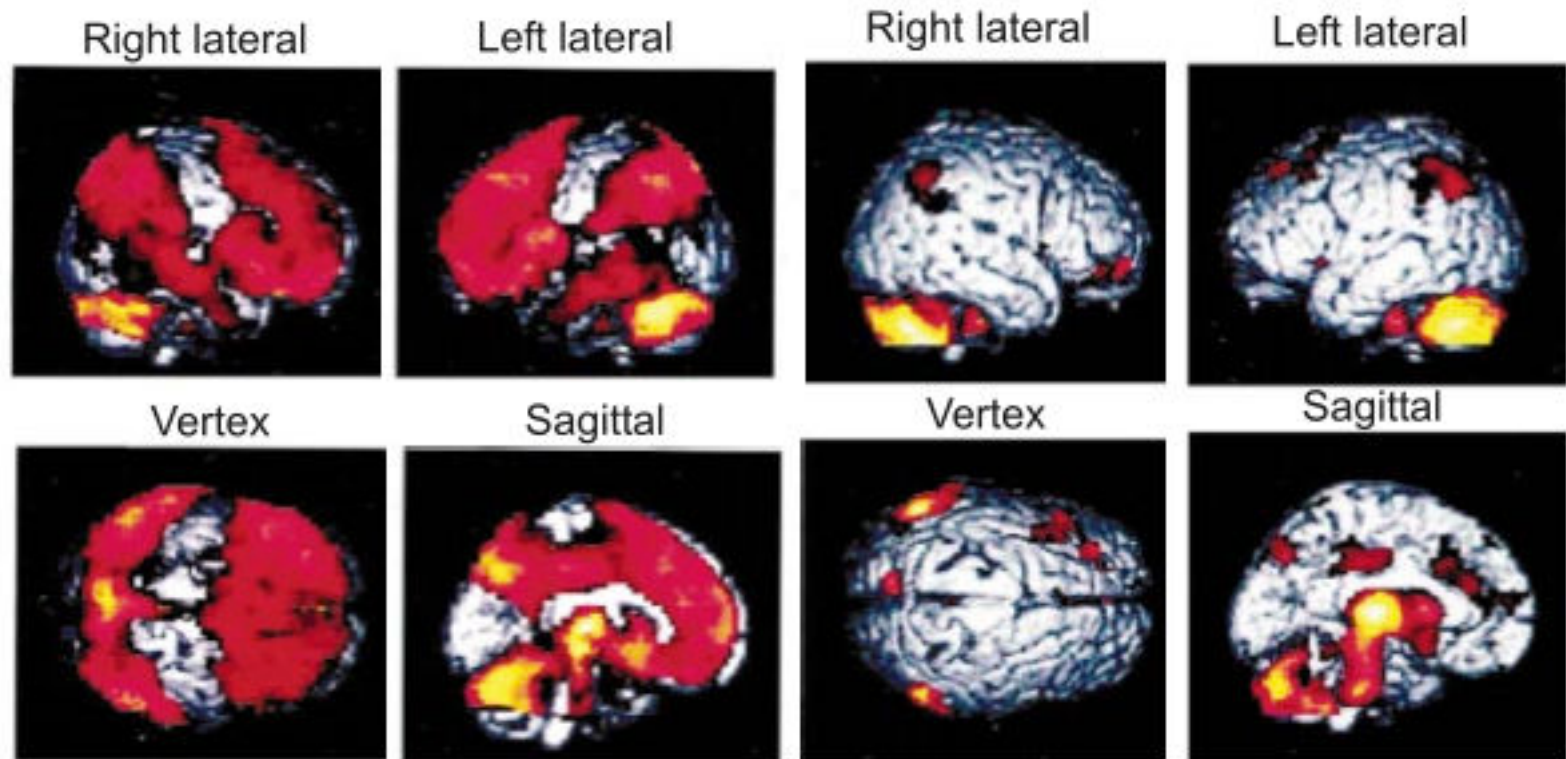
Transverse sections
showing deactivation
of the:

- brainstem
- thalamus
- basal forebrain
- basal ganglia
- orbito-frontal cortex
- frontal and parietal cortices on the convexity.



Broun et al. 1997.

Disminución del FSCr durante el sueño NREM con con $H_2^{15}O$ PET

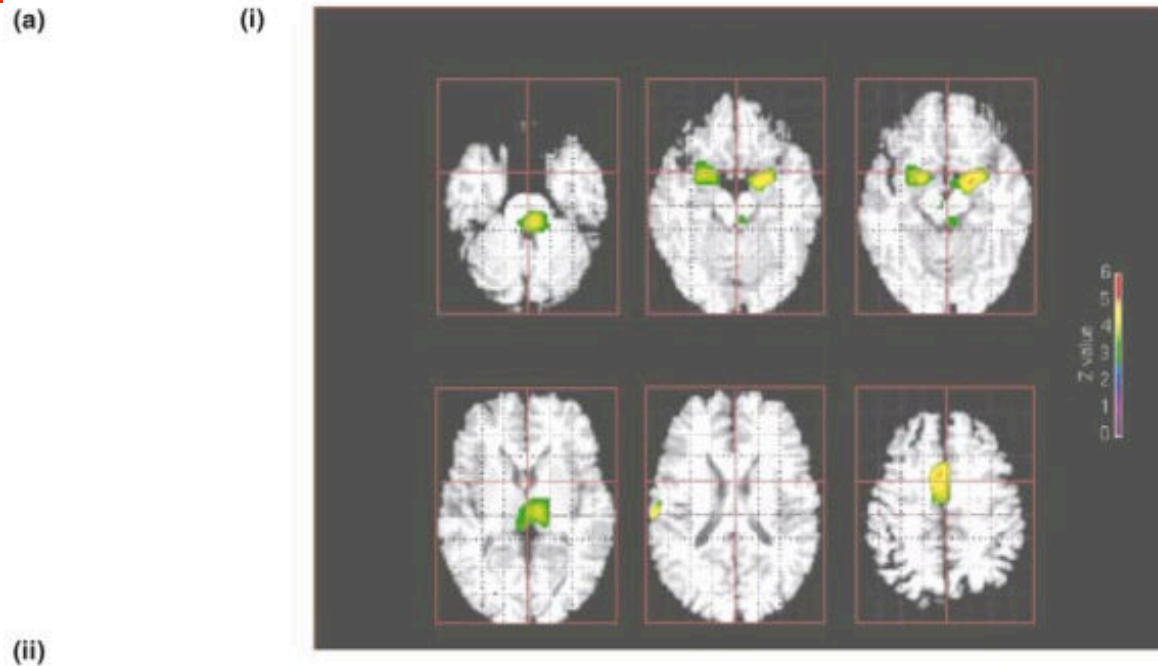


Kajimura et al, 1999.

Aumento del FSCr durante el sueño REM con con $H_2^{15}O$ PET

Contrast: REMS \pm [(W + SWS)/2].

Transverse sections showing activation of pontine tegmentum, the thalami, the anterior cingulate cortices and the right parietal operculum.

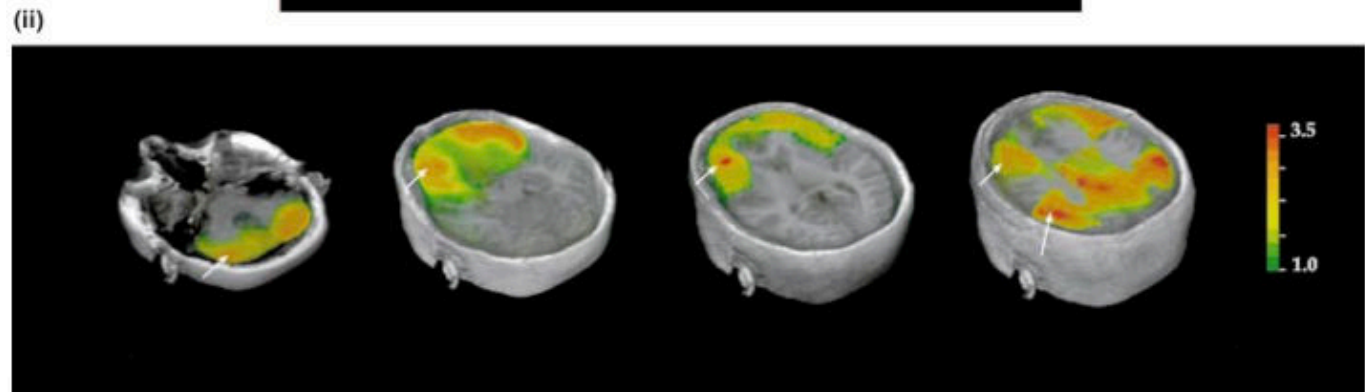
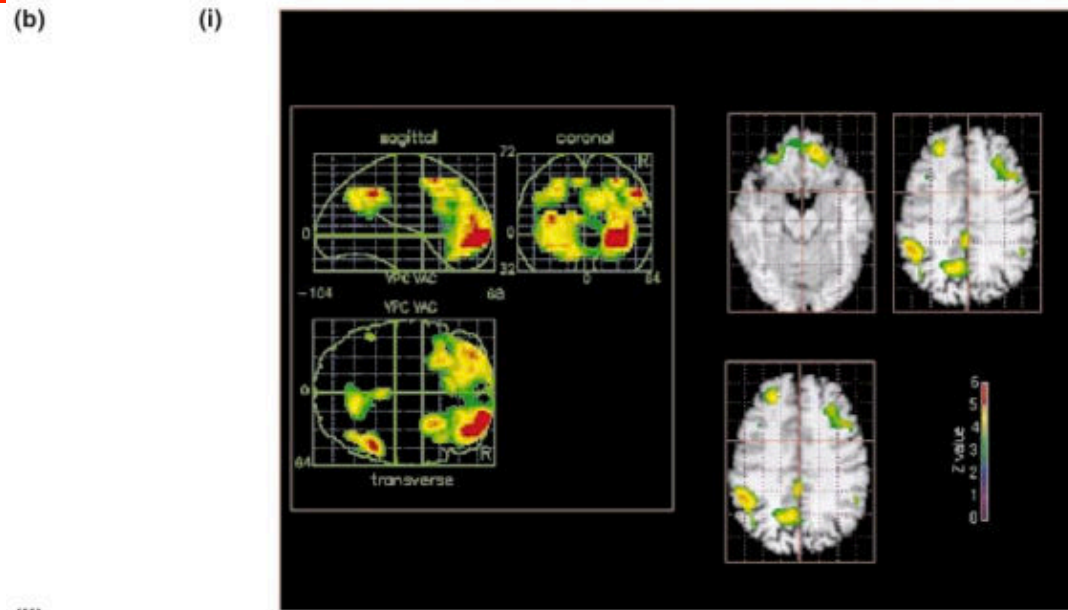


Disminución del FSCr durante el sueño REM con con $H_2^{15}O$ PET

Contrast: REMS \pm SWS.

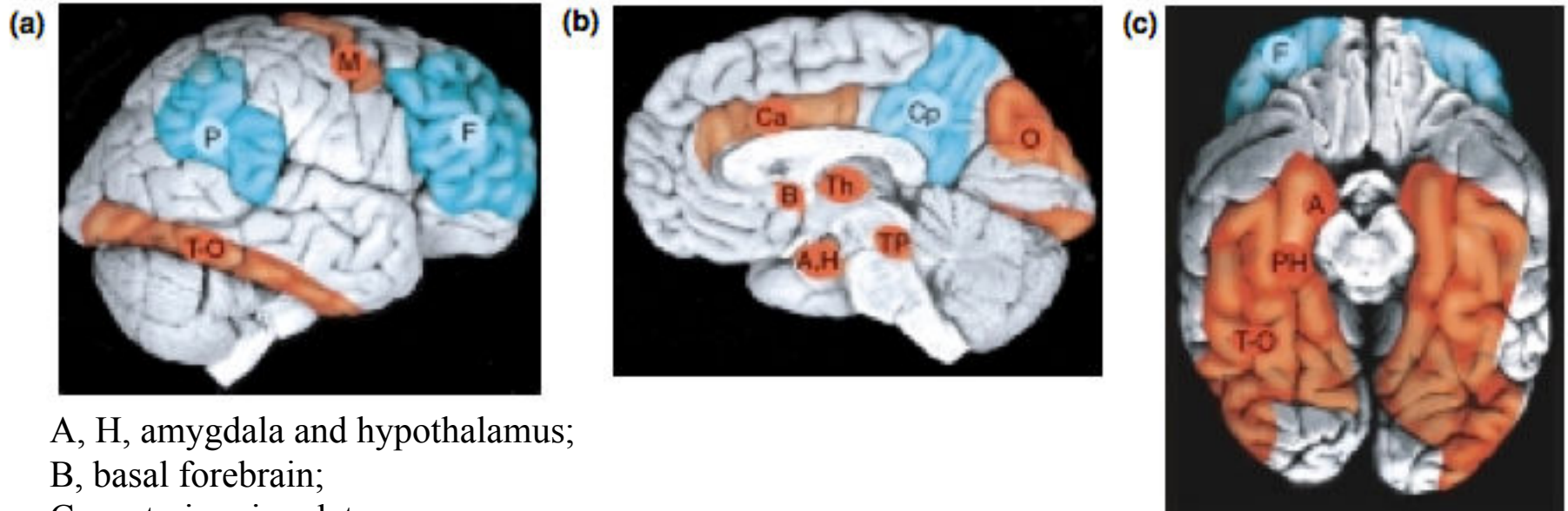
Activation of:

- Brainstem
- thalamus
- orbito-frontal
- anterior cingulate and insular cortices.



Braun et al, 1997.

Sueño REM



A, H, amygdala and hypothalamus;
B, basal forebrain;
Ca, anterior cingulate gyrus;
Cp, posterior cingulate gyrus and precuneus;
F, prefrontal cortex;
M, motor cortex;
P, parietal supramarginal cortex;
PH, parahippocampic gyrus;
O, occipital-lateral cortex; Th, thalamus;
T-O, temporo-occipital extrastriate cortex;
TP, pontine tegmentum.

TRENDS in Cognitive Sciences

Schwartz et al, 2002.

Resumen

Table 2 Increases in rCBF during REM sleep

	<i>Maquet et al. (1996)</i>	<i>Braun et al. (1997)</i>	<i>Nofzinger et al. (1997)</i>
Quantification	-	+	+
Global activity adjustment	+	+	+
Brainstem	↑	↑	
Thalami	↑	↑	↑
Basal forebrain		↑	↑
Amygdala	↑		↑
Hippocampal formation		↑	↑
Orbito-frontal cortex			↑
Parietal lobule	↑		
Extrastriate cortex		↑	
Anterior cingulate cortex	↑	↑	↑
Insula-temporal cortex		↑	↑
Cerebellum		↑	
Remarks	CBF REMS - [(W + SWS)/2]	CBF REMS - SWS	Glucose metabolism REMS - W

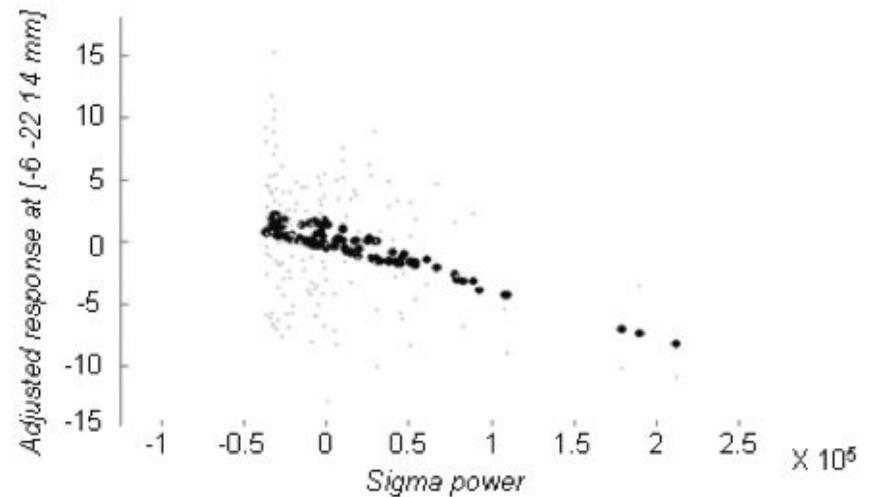
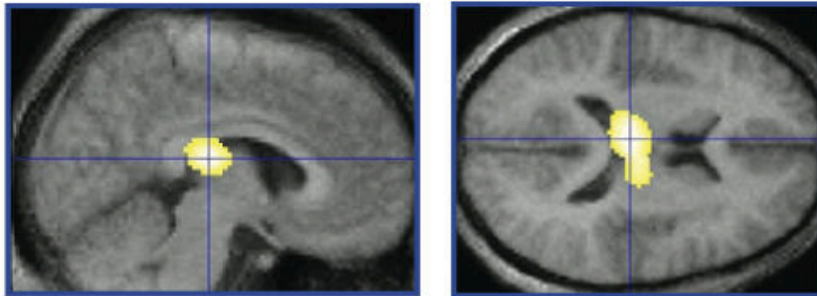
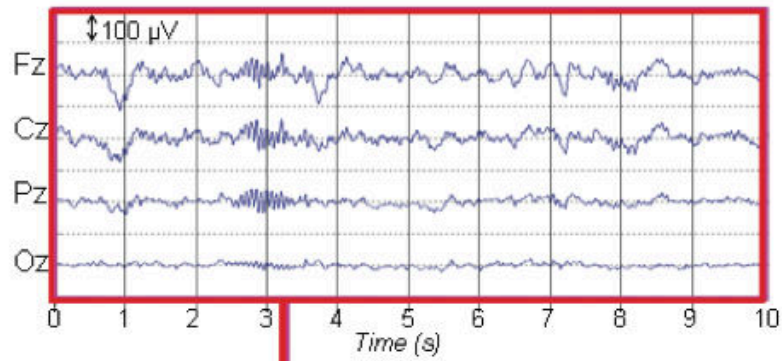
Table 3 Decreases in rCBF during REM sleep

	<i>Maquet et al. (1996)</i>	<i>Braun et al. (1997)</i>
Quantification	-	+
Global activity adjustment	+	+
Preformal cortex	↓	↓
Parietal cortex	↓	↓
Precunes/posterior cingulate cortex	↓	↓
Remarks	CBF REMS - [(W + SWS)/2]	CBF REMS - SWS

Componentes fásicos del sueño

FSCr con $H_2^{15}O$ PET durante el sueño NREM

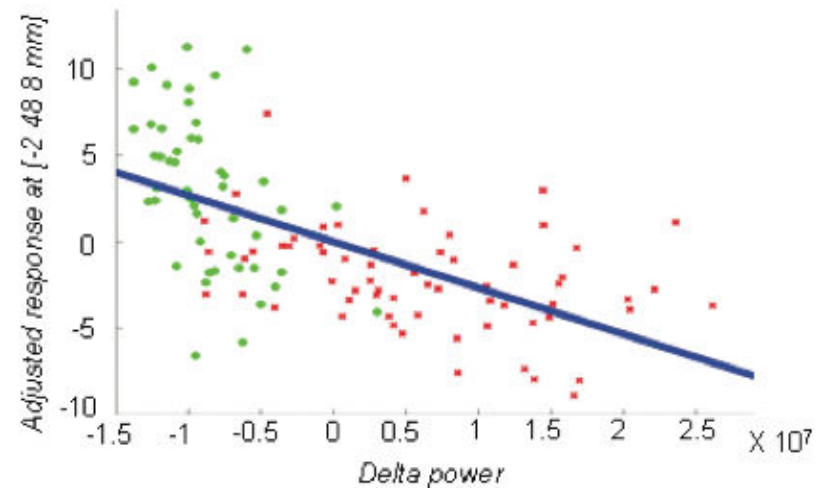
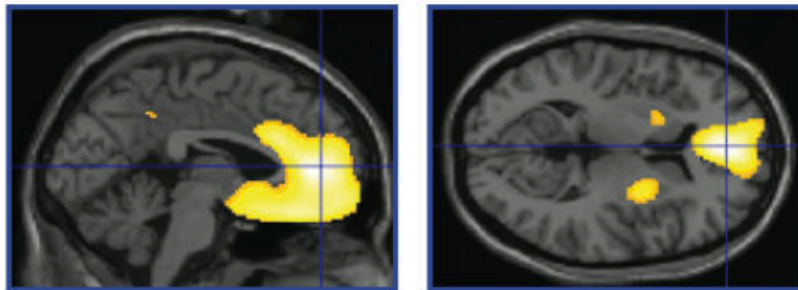
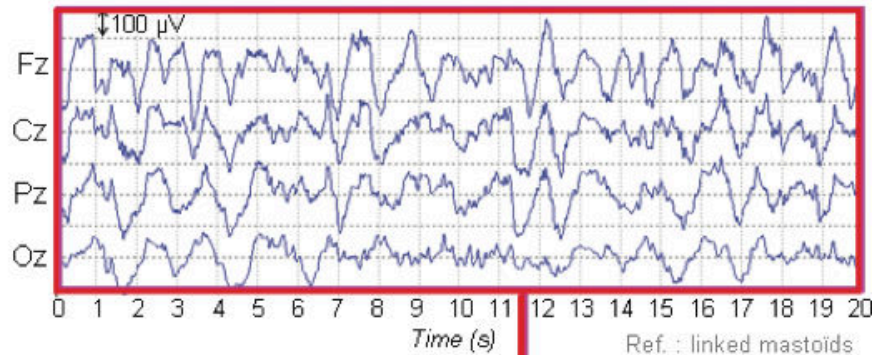
A



Hofle et al. 1997

FSCr con $H_2^{15}O$ PET durante el sueño NREM

B

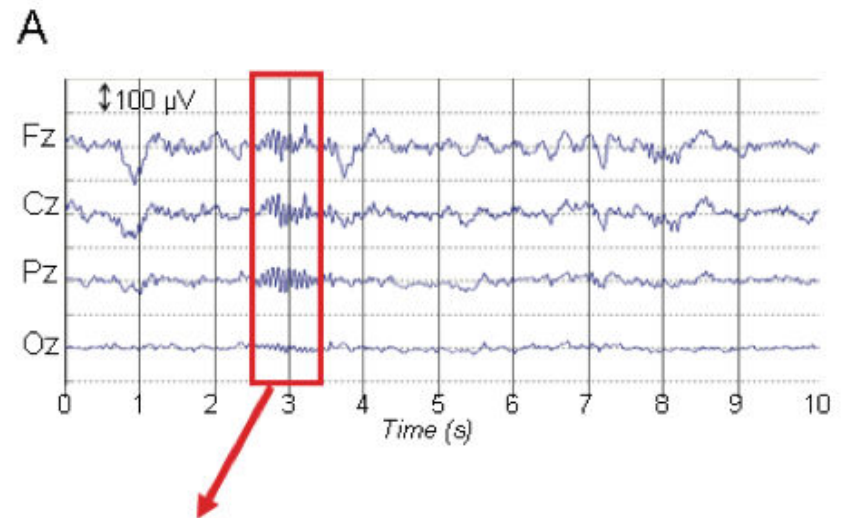
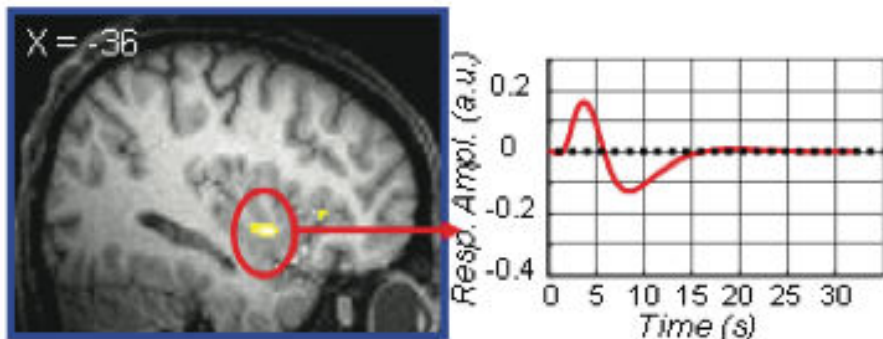
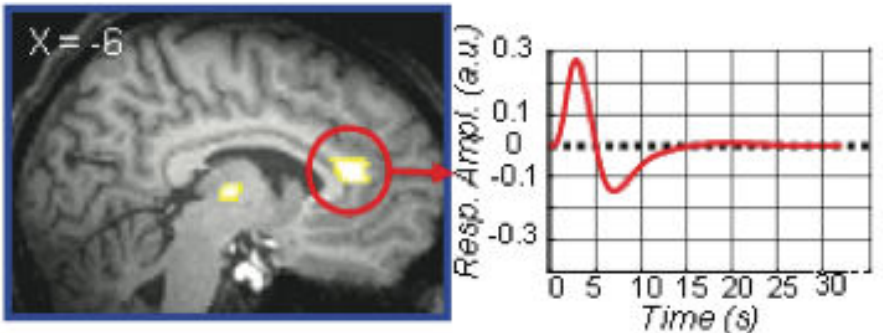
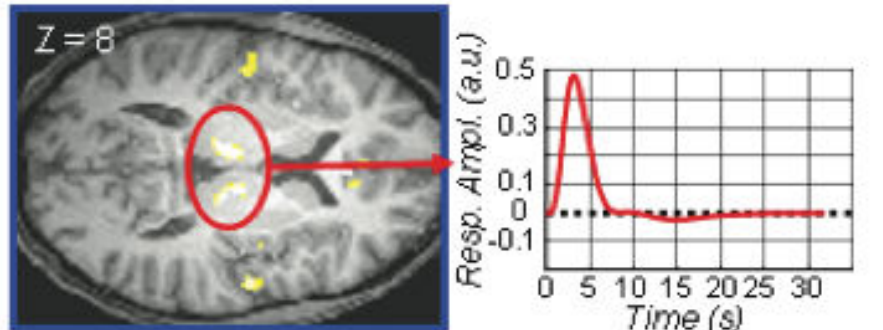


Hofle et al. 1997

FSCr con $H_2^{15}O$ PET durante el sueño REM

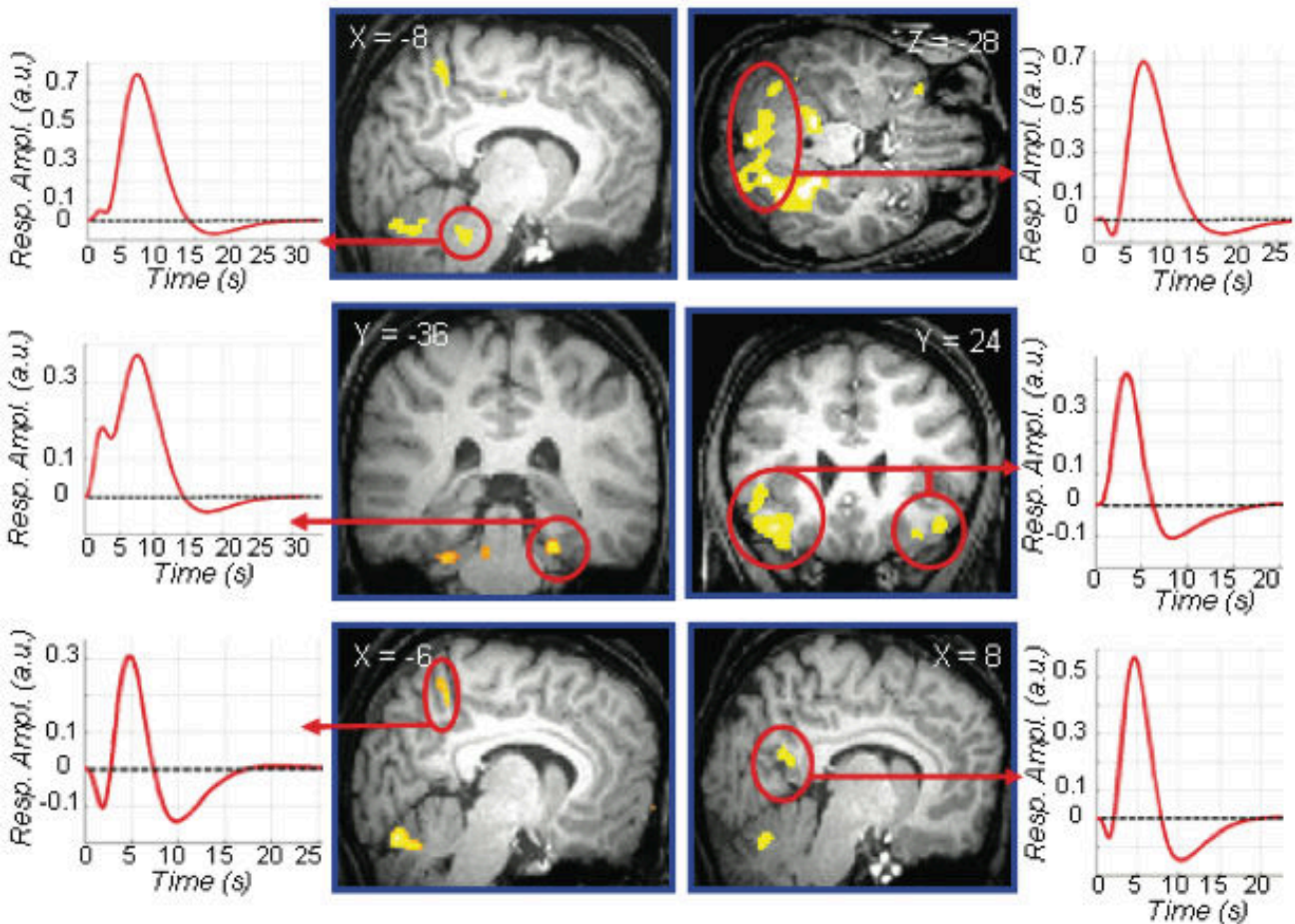
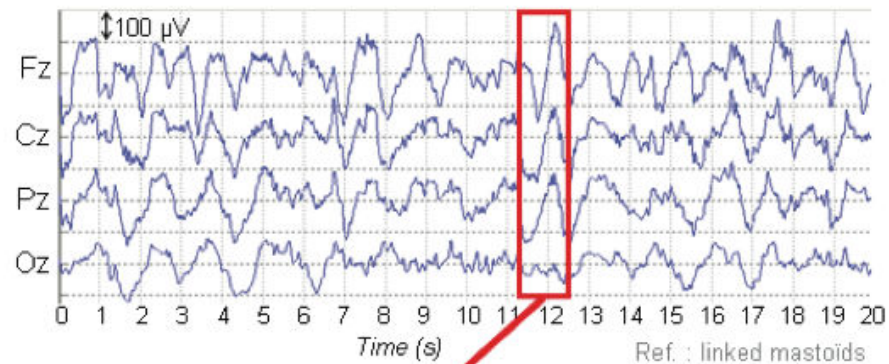
- ❑ **Correlación entre la densidad de movimientos oculares rápidos y el FSCr en la corteza occipital y los cuerpos geniculados laterales del tálamo (Peigneux P, 2001).**
- ❑ **Correlación positiva entre la variabilidad de la FC y el FSCr en complejo amigdalino derecho (Henderson 2002).**
- ❑ **La corteza insular derecha covaría con la amígdala.**

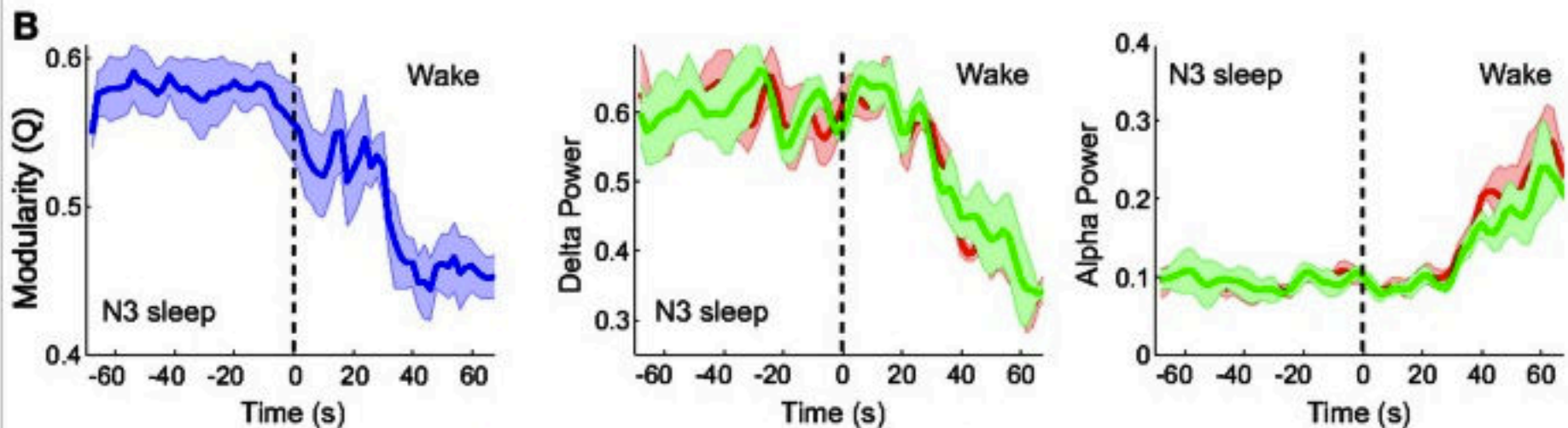
fMRI durante el sueño



fMRI durante el sueño

B

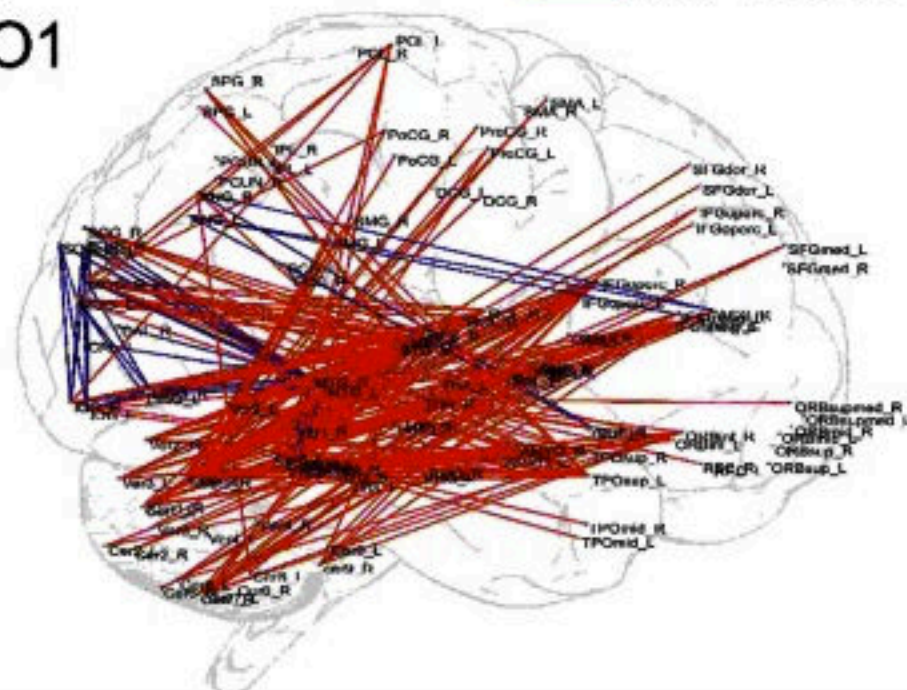




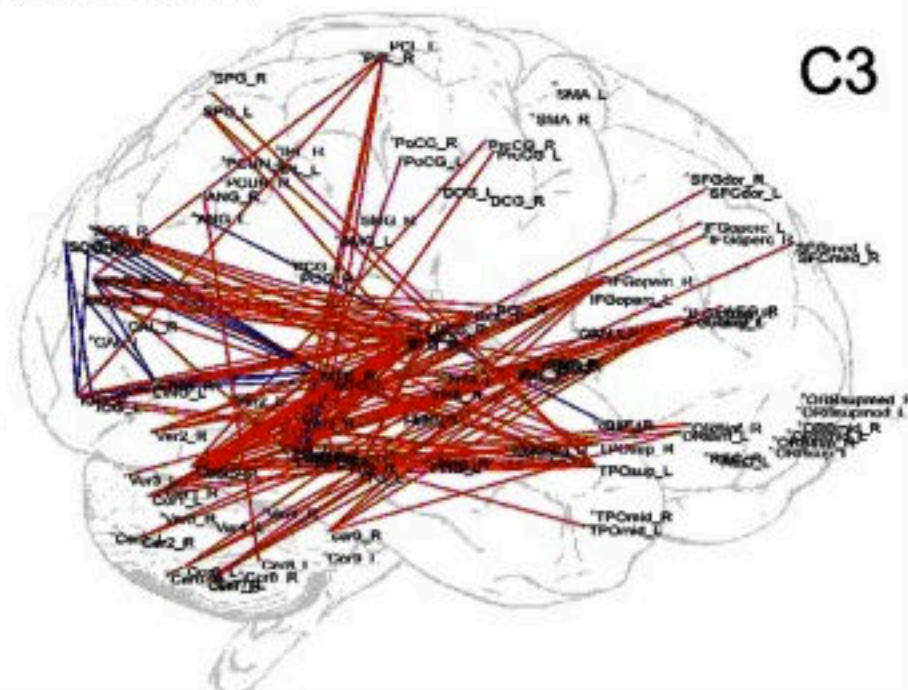
■ Intra-module correlation
■ Inter-module correlation

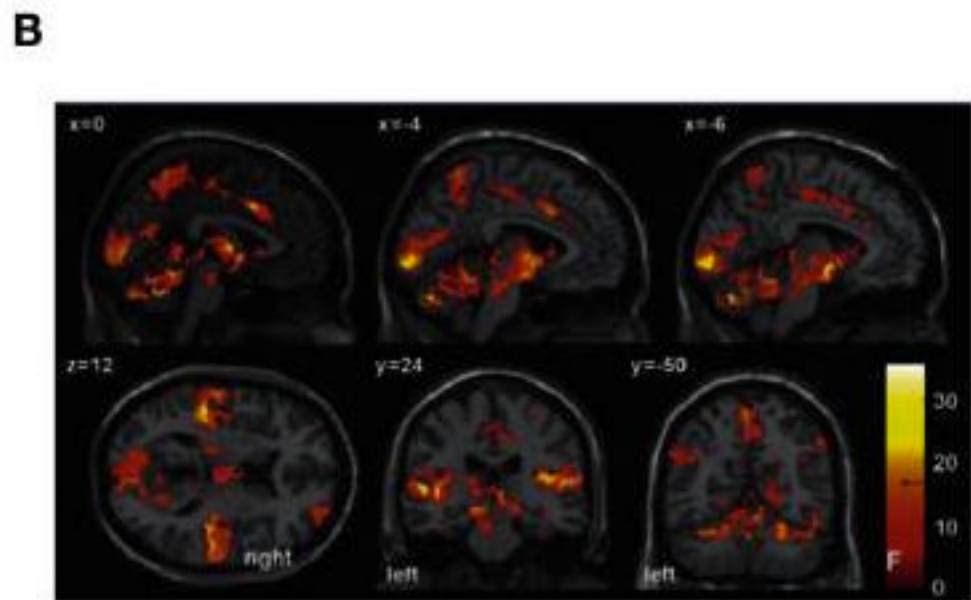
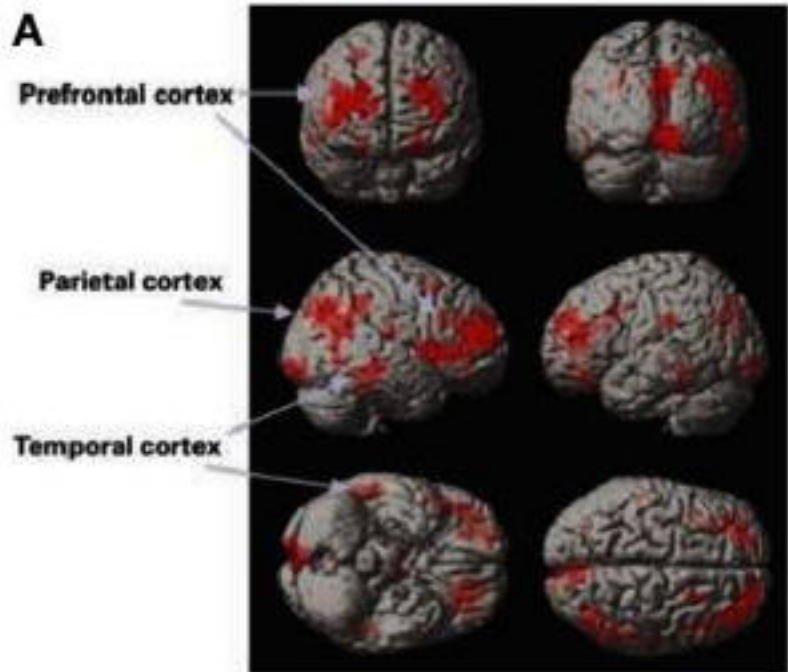
C

O1



C3

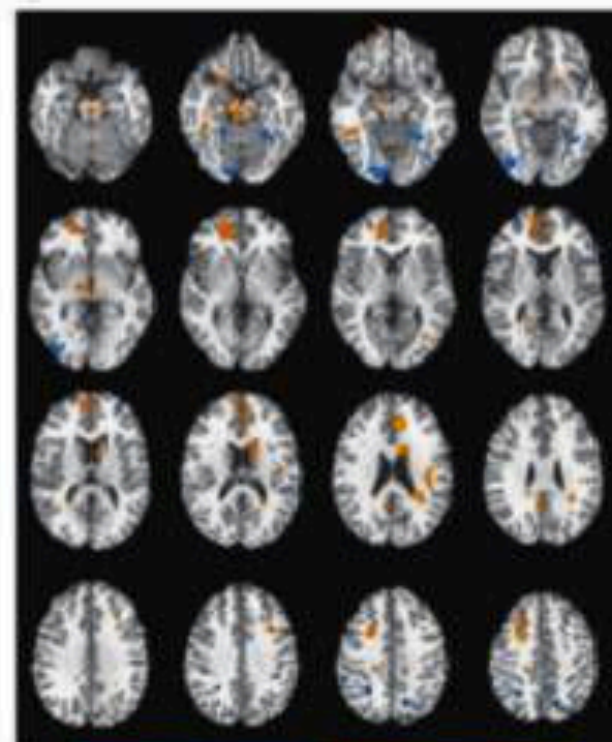
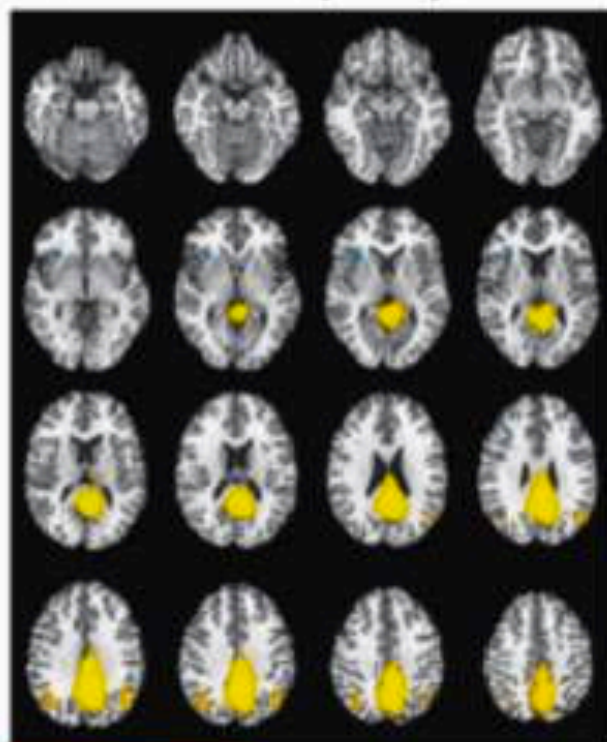
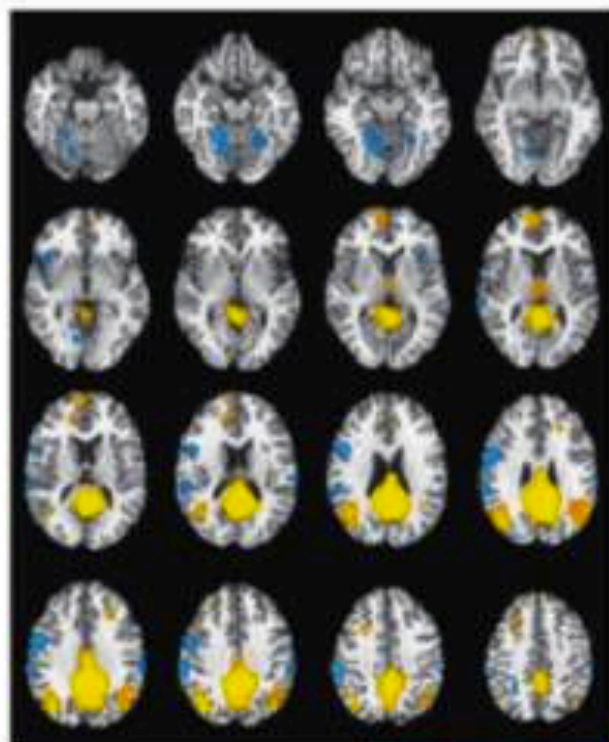




wake

deep sleep

t-test

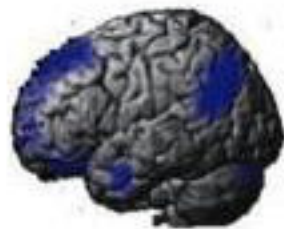


<-8 -5 5 >8
z-score

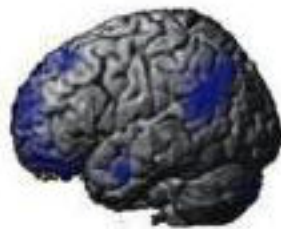
<-8 -3.5 3.5 >8
t-value

D

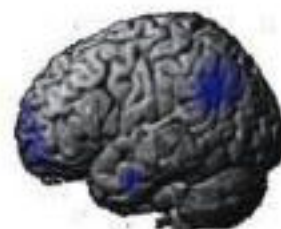
Wakefulness



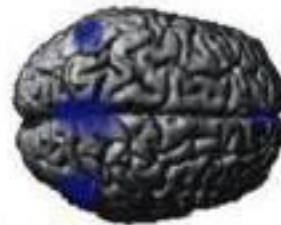
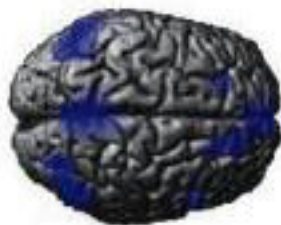
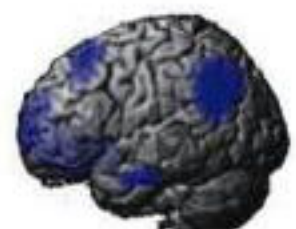
N1 sleep



N2 sleep



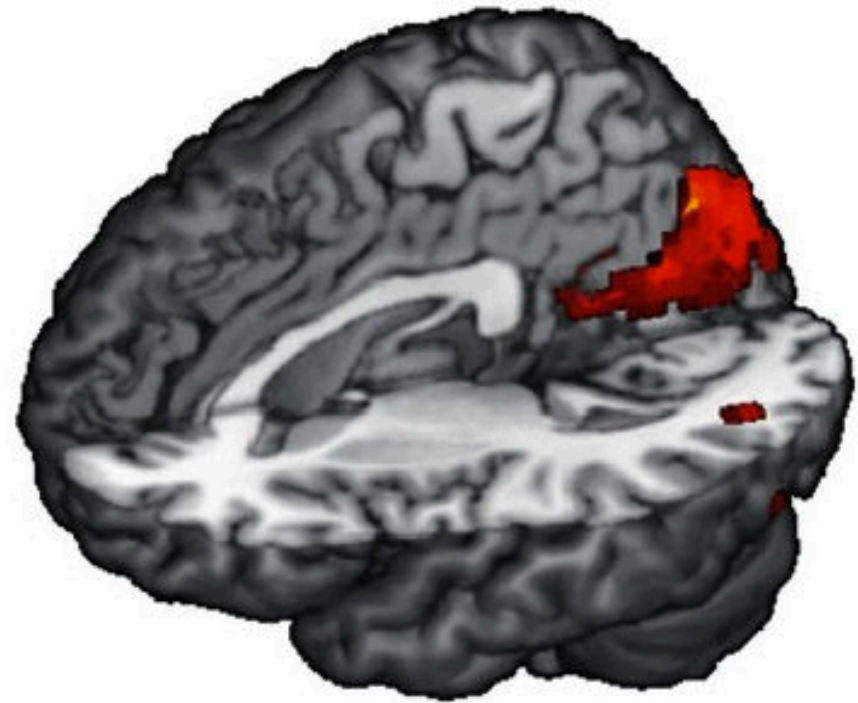
N3 sleep



Inner speech



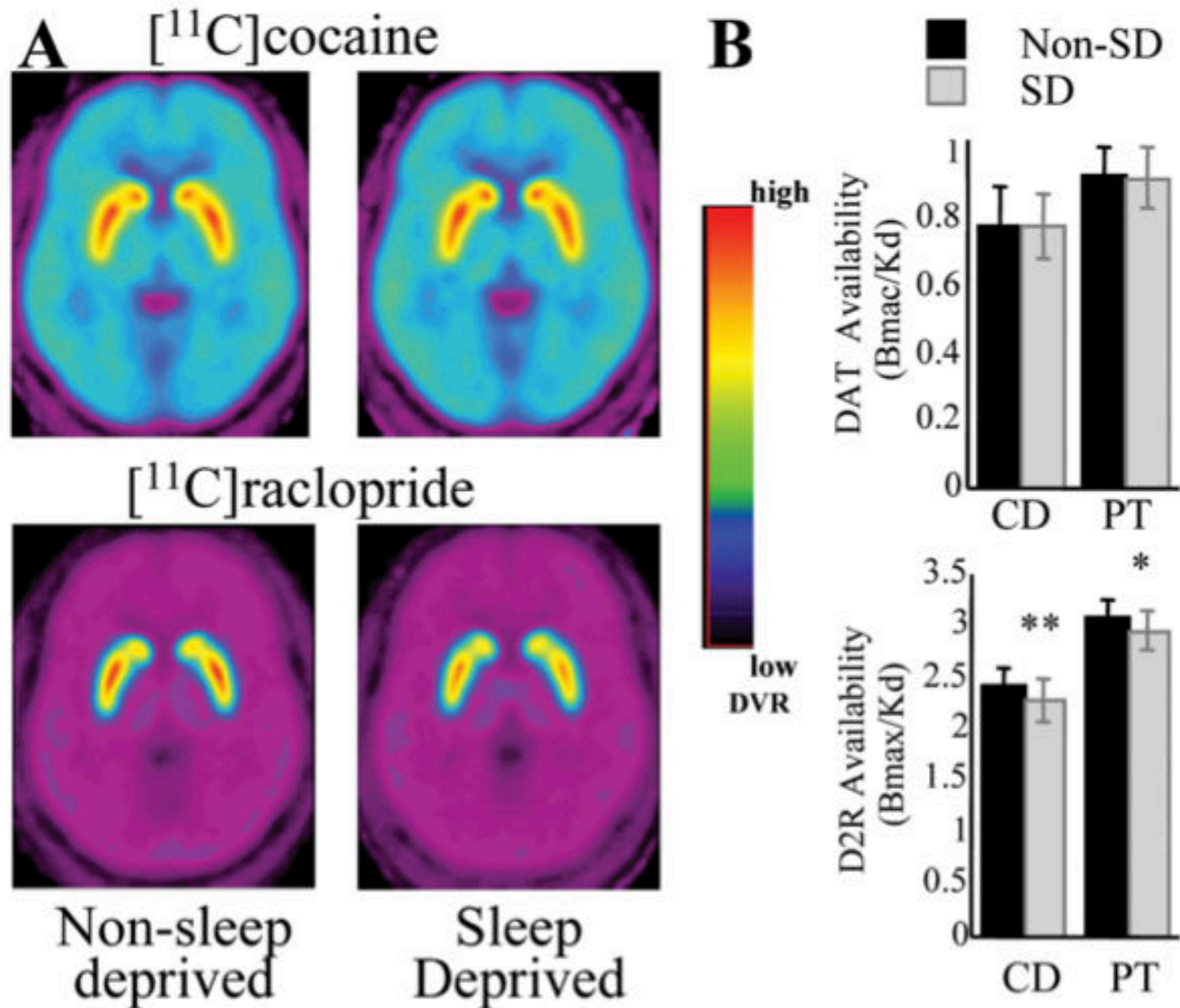
Visual imagery



Aportes a la patología del sueño

Privación de sueño y sistema dopaminérgico

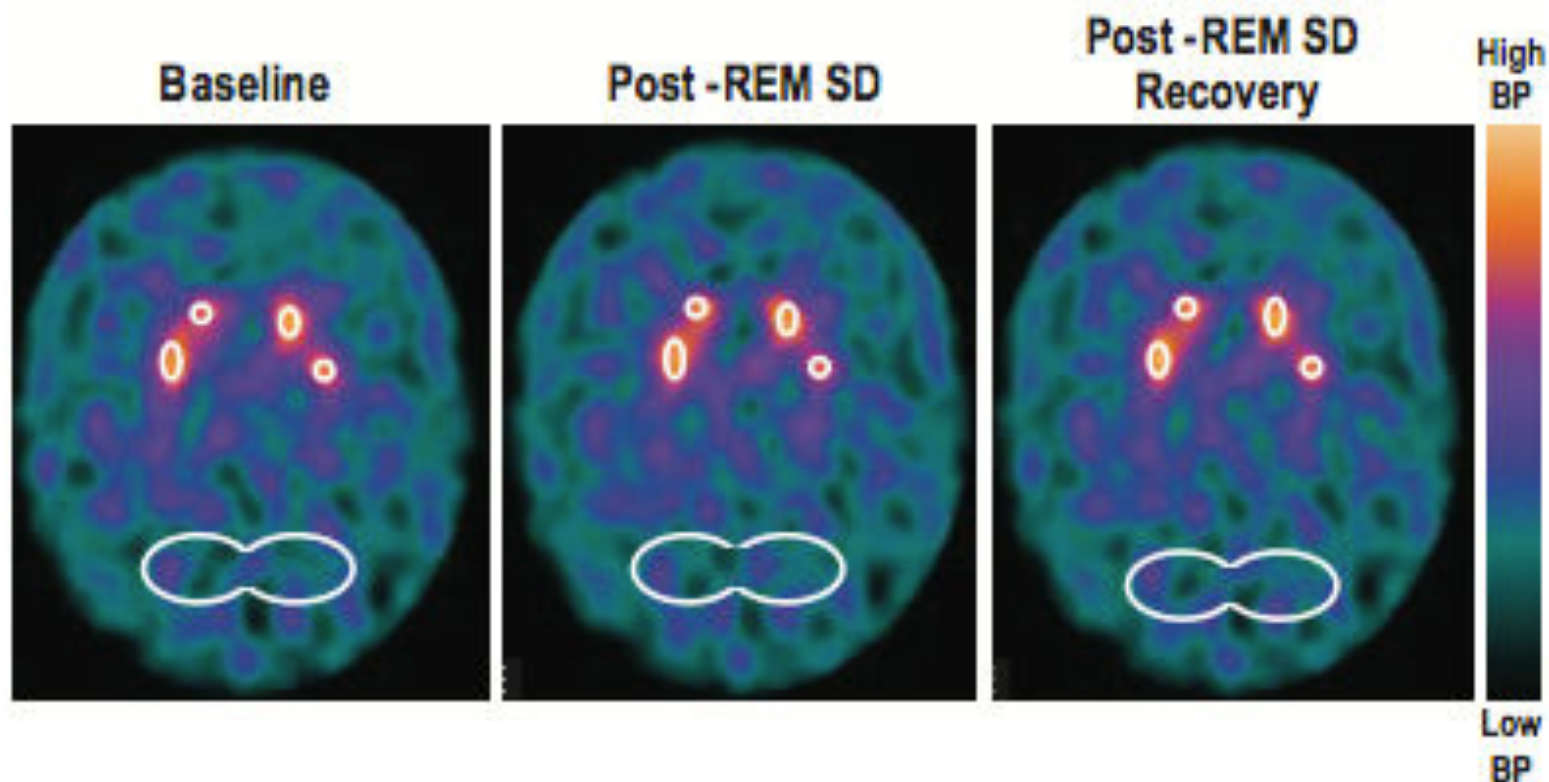
- [11C]cocaine (dopamine transporter radioligand)
- [11C]raclopride (dopamine D2/3 receptor radioligand)



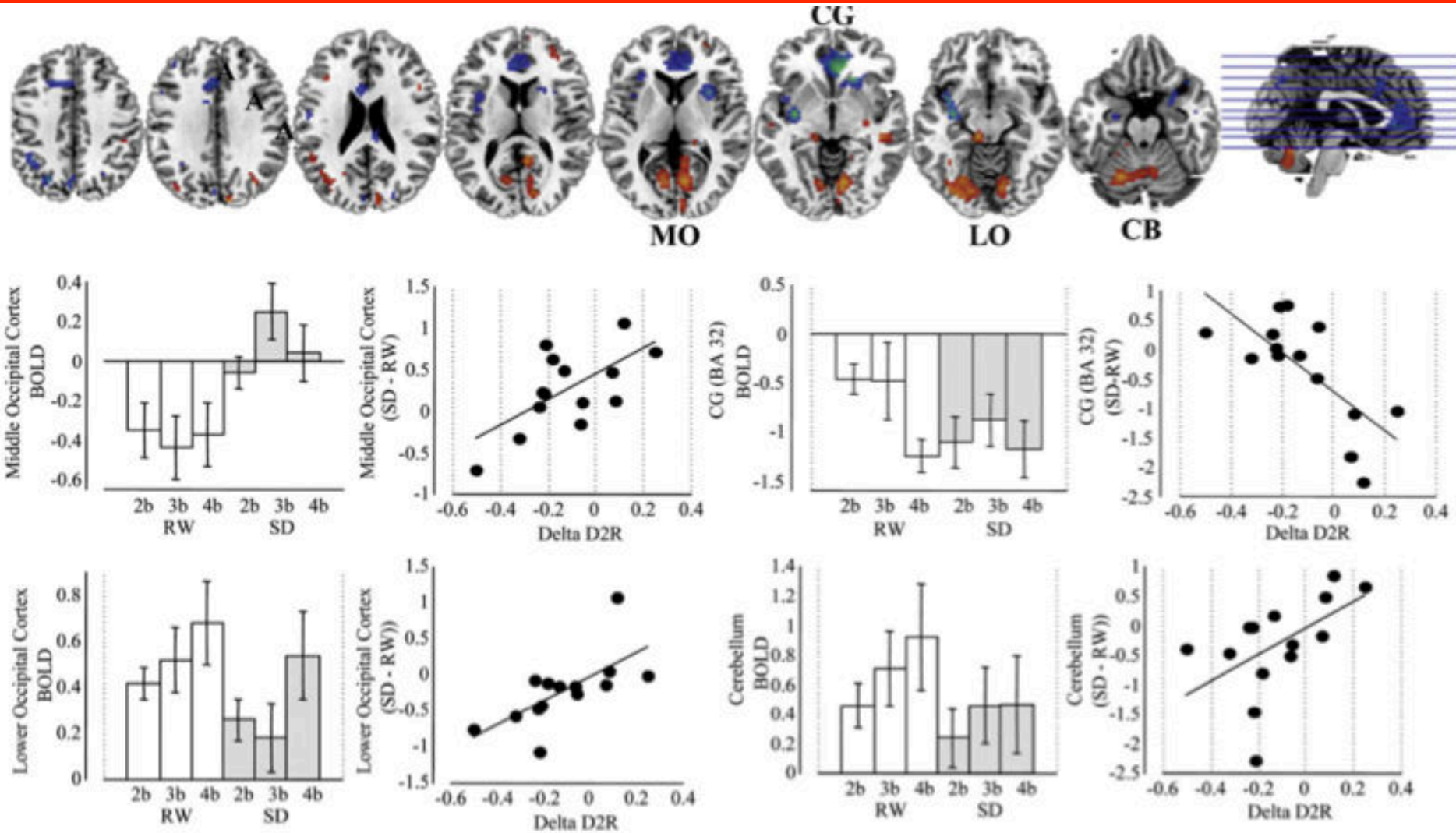
Dopamine Transporter Regulation during Four Nights of REM Sleep Deprivation Followed by Recovery – An *in vivo* Molecular Imaging Study in Humans

RCS Martins, MS¹; ML Andersen, PhD¹; SA Garbuio, MS¹; LR Bittencourt, PhD, MD¹; C Guindalini, PhD^{1,2}; MC Shih, PhD²; MQ Hoexter, MD²; RA Bressan, PhD²; MLV Castiglioni, MD³; S Tufik, PhD, MD¹

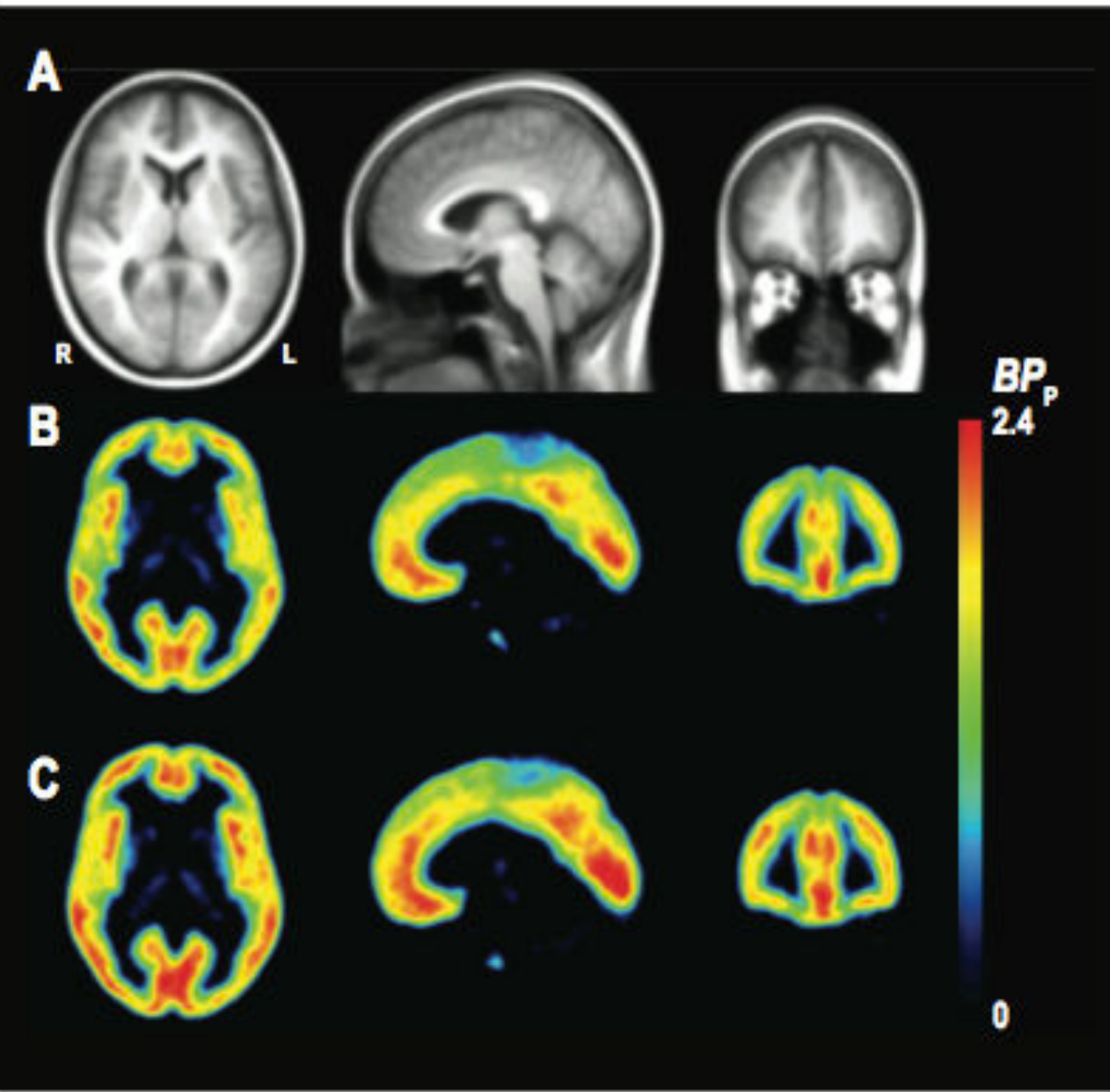
¹Department of Psychobiology–Universidade Federal de São Paulo, Escola Paulista de Medicina (UNIFESP/EPM); ²LiNC–Laboratório Interdisciplinar de Neuroimagem e Cognição, Departamento de Psiquiatria - Universidade Federal de São Paulo (UNIFESP/EPM); ³Department of Radiology–Universidade Federal de São Paulo, Escola Paulista de Medicina (UNIFESP/EPM)



Privación de sueño y alteraciones cognitivas



Sleep Deprivation Increases Cerebral Serotonin 2A Receptor Binding in Humans

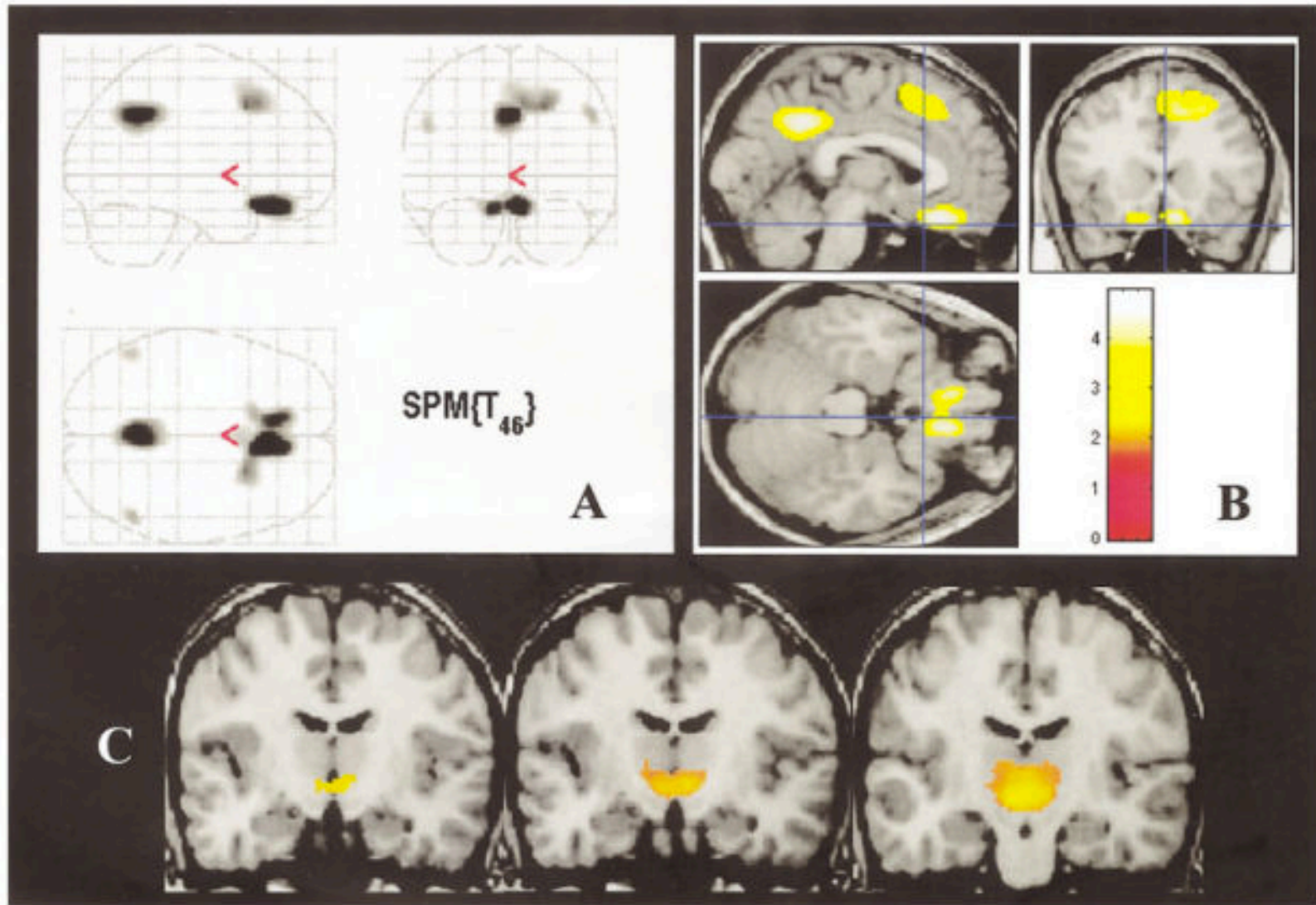


- [18F]Altanserin-PET
- Hypothesis that sleep deprivation induces global molecular alterations in the cortical serotonergic receptor system.
- A total of 24 hours of sleep deprivation led to a 9.6% increase of [18F]altanserin binding on neocortical 5-HT_{2A} receptors.
- Medial inferior frontal gyrus, insula, and anterior cingulate, parietal, sensorimotor, and ventrolateral prefrontal cortices.

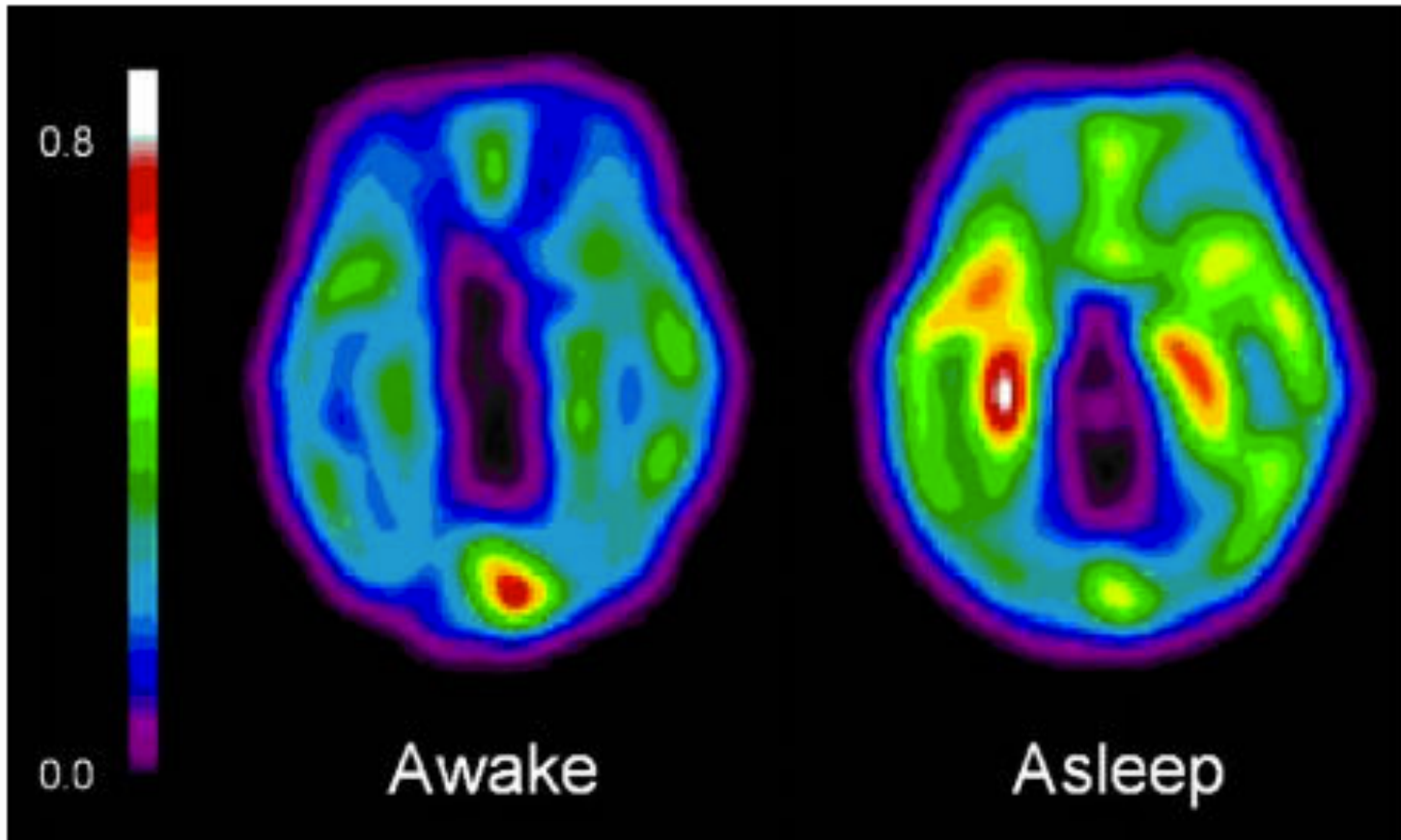
Glucose Hypometabolism of Hypothalamus and Thalamus in Narcolepsy

Eun Yeon Joo, MD¹ Woo Suk Tae, MS¹
Jee Hyun Kim, MD¹ Byung Tae Kim, MD²
and Seung Bong Hong MD¹

This study showed cerebral glucose hypometabolism of the hypothalamus-thalamus-orbitofrontal pathways in the narcoleptic brain.

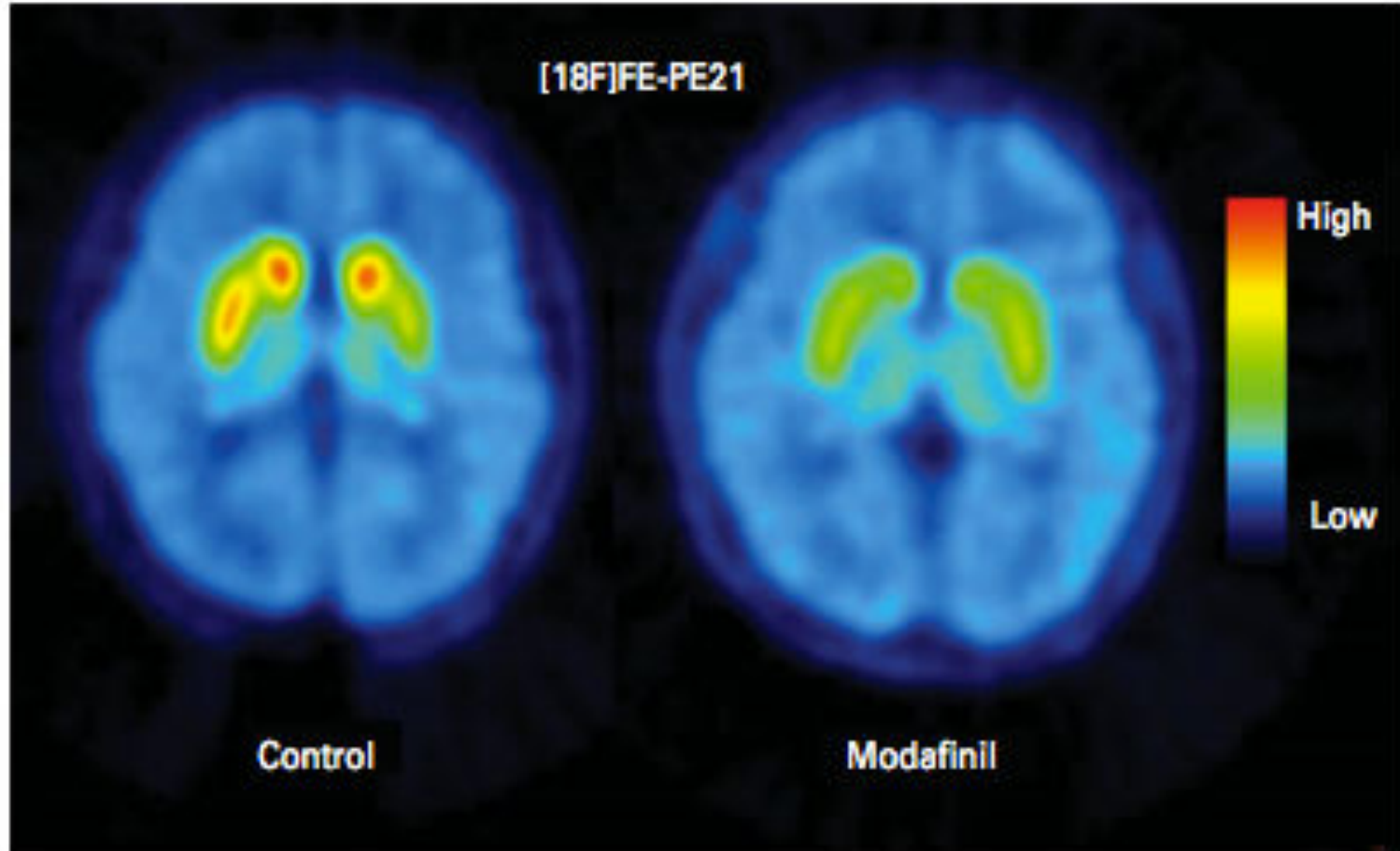


Increased serotonin receptor availability in human sleep: Evidence from an [^{18}F]MPPF PET study in narcolepsy

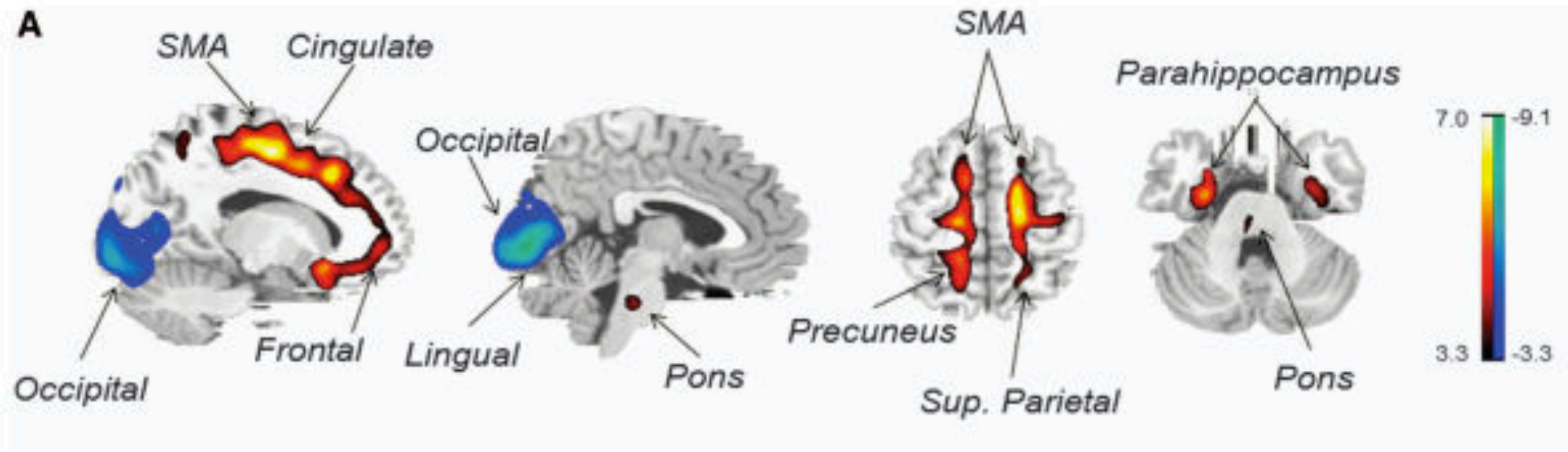


These findings indicate that serotonin receptor availability is increased in sleep compared to wakefulness in narcoleptic humans.

In vivo activity of modafinil on dopamine transporter measured with positron emission tomography and [¹⁸F]FE-PE2I



Assessing cerebral glucose metabolism in patients with idiopathic rapid eye movement sleep behavior disorder

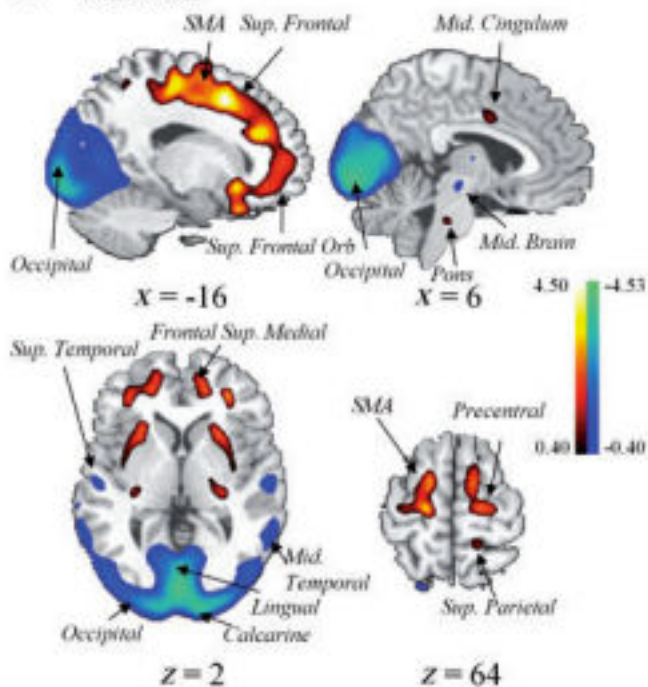


Patients with RBD showed increased metabolism in the hippocampus/ parahippocampus, cingulate, supplementary motor area, and pons, but decreased metabolism in the occipital cortex/lingual gyrus

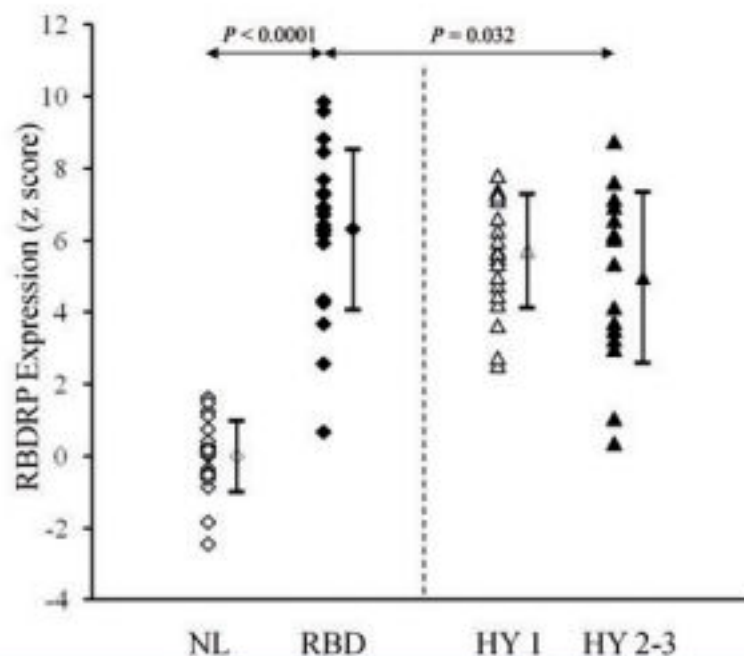
Consistent abnormalities in metabolic network activity in idiopathic rapid eye movement sleep behaviour disorder

Ping Wu,^{1,*} Huan Yu,^{2,*} Shichun Peng,³ Yves Dauvilliers,⁴ Jian Wang,² Jingjie Ge,¹ Huiwei Zhang,¹ David Eidelberg,³ Yilong Ma^{3,†} and Chuantao Zuo^{1,†}

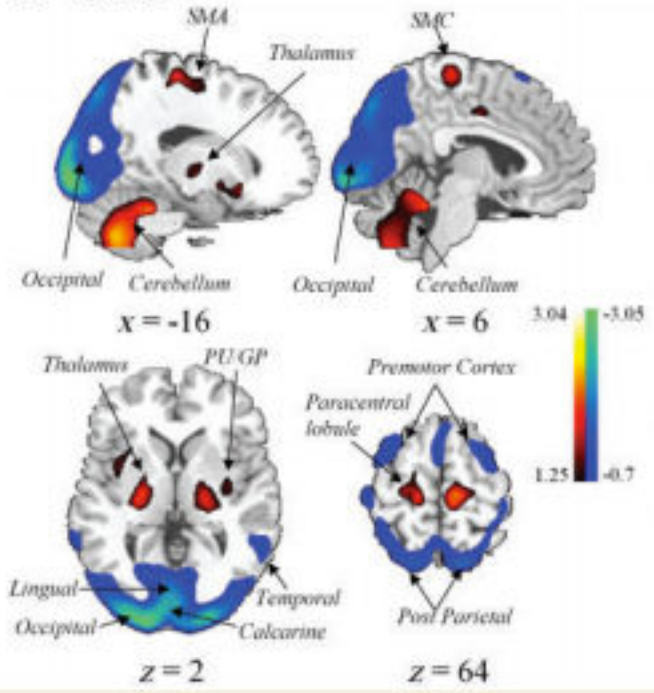
A RBD RP



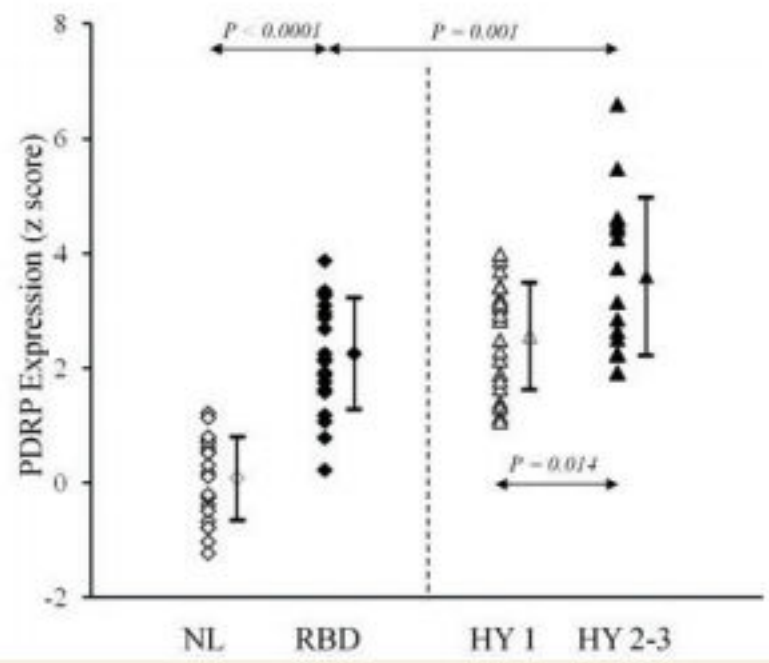
B Changes in RBD RP activity



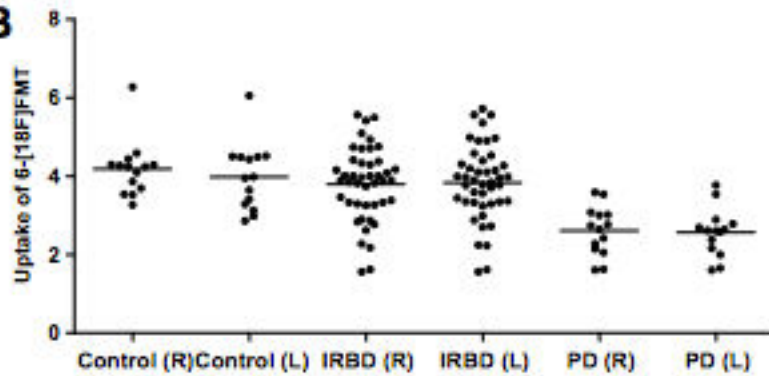
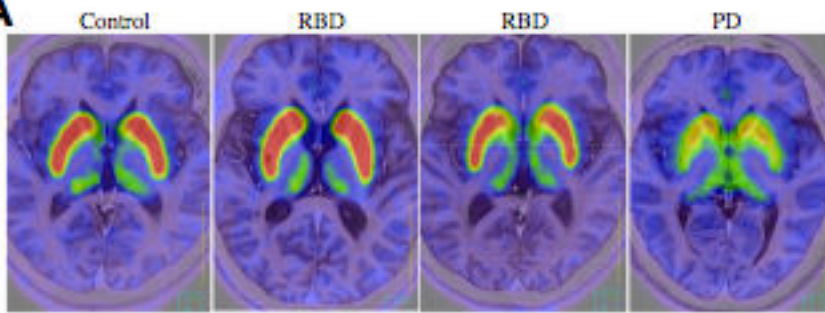
A PDRP



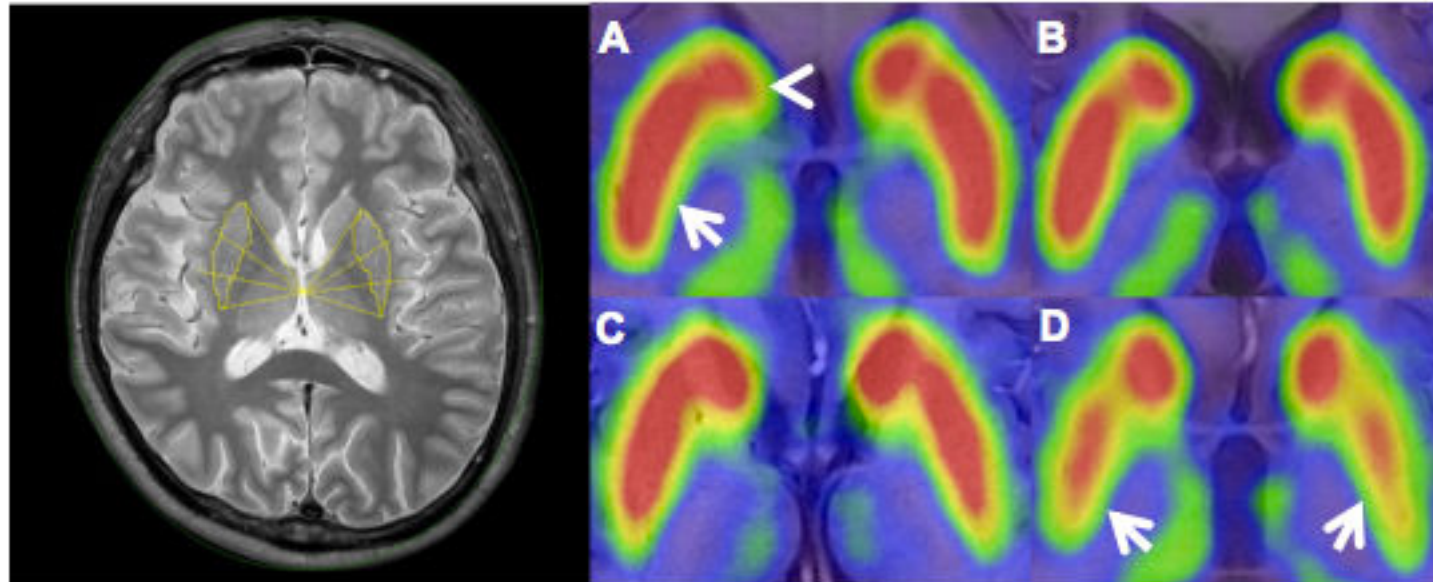
B Changes in PDRP activity



Trastorno del sueño REM y Parkinson



M. Miyamoto, T. Miyamoto/Sleep Medicine 14 (2013) 739–743

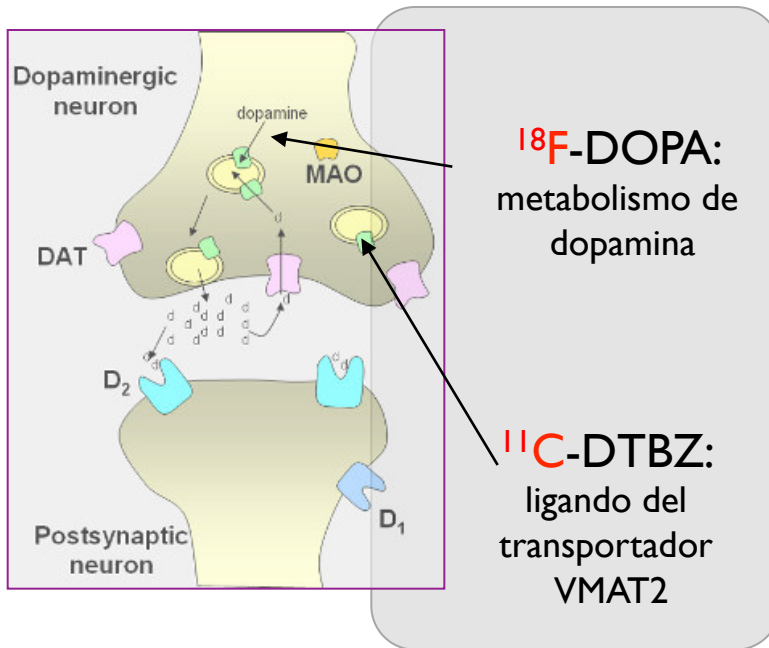


Miyamoto et al. Sleep Medicine 14 (2013) 739–743

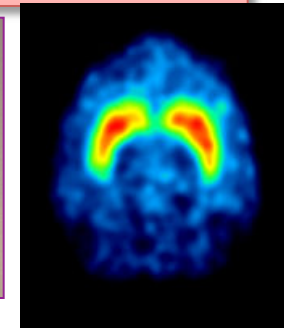


Neurología (Parkinson)

✓ Estudio de SISTEMA DOPAMINÉRGICO



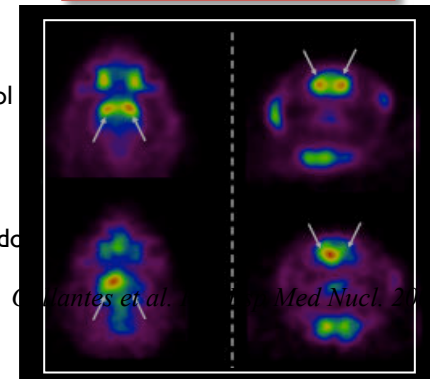
*Macaca
fascicularis*



Rata

Animal control

Animal lesionado
unilateral

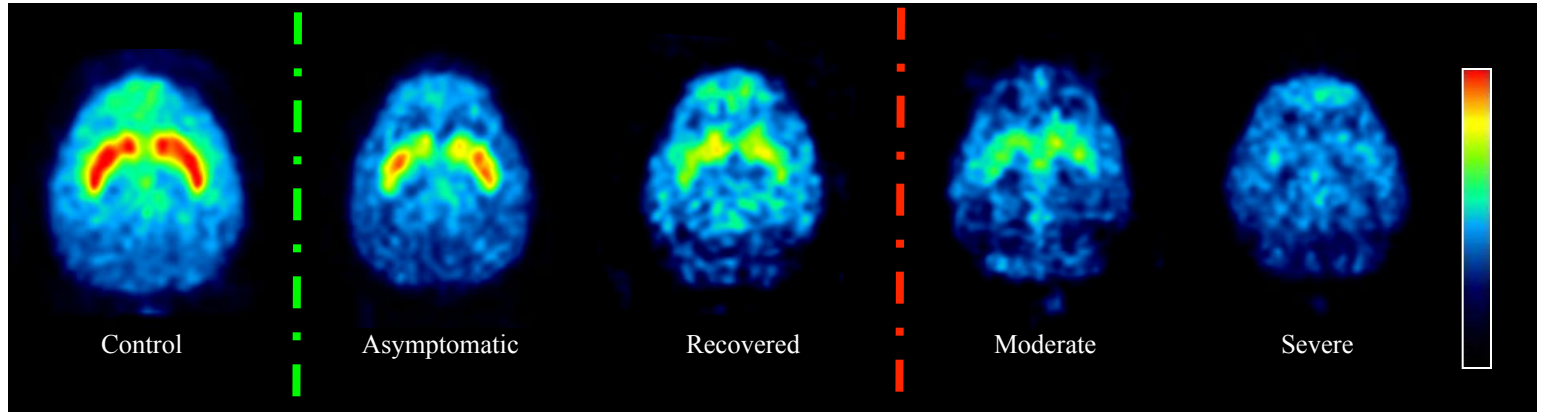
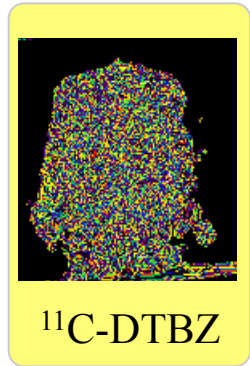


Quantes et al. J Nucl Med Nucl, 2008



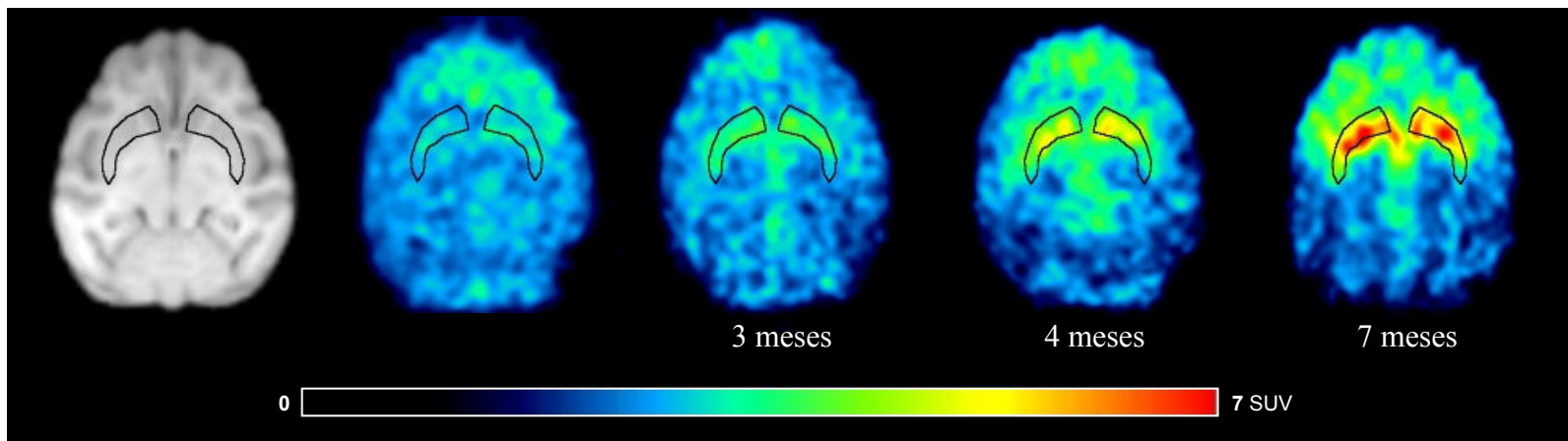
Neurología (Parkinson)

✓ Monos: tratamiento con MPTP, seguimiento longitudinal



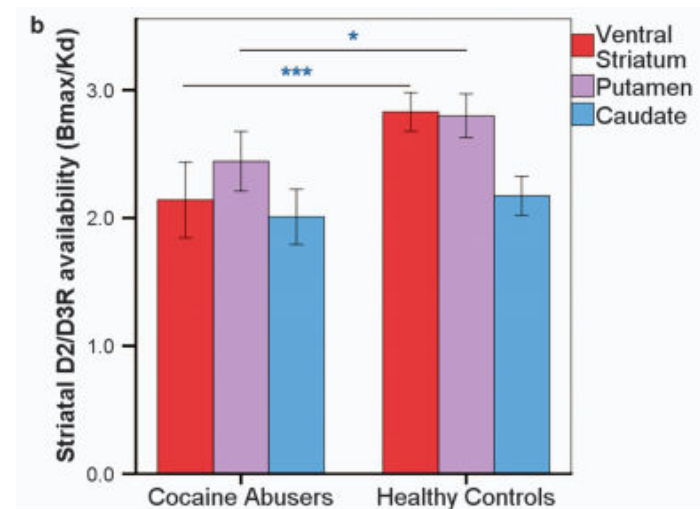
Collantes et al, Neuroimage. 2009; Blesa et al. NeurobiolDis. 2010; Blesa et al. NeurobiolDis. 2012

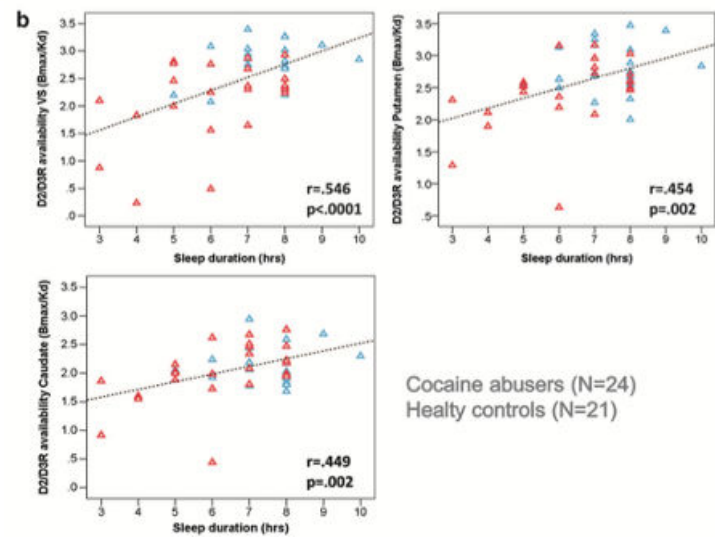
✓ Efecto de un tratamiento: recuperación



Reduced sleep duration mediates decreases in striatal D2/D3 receptor availability in cocaine abusers

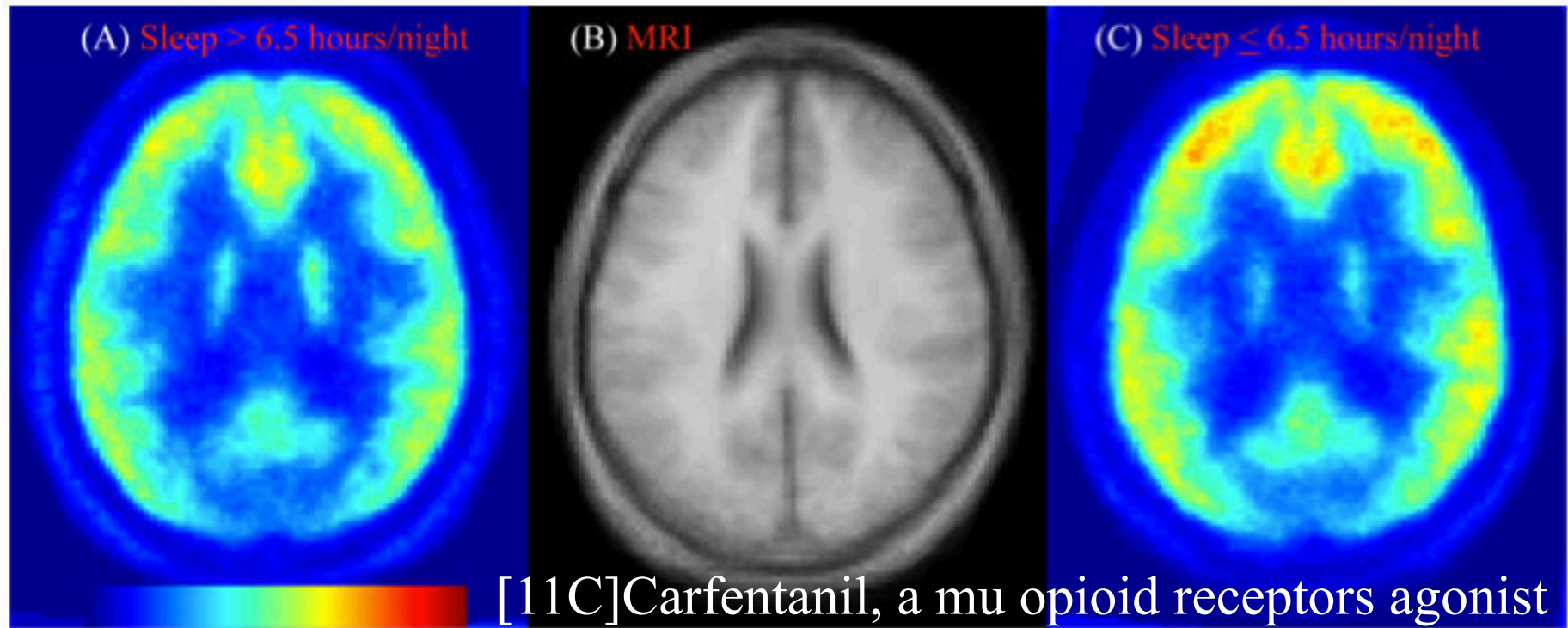
These findings suggest that impaired sleep patterns contribute to the low striatal D2/D3R availability in cocaine abusers. As sleep impairments are similarly observed in other types of substance abusers (for example, alcohol and methamphetamine), this mechanism may also underlie reductions in D2/D3R availability in these groups.





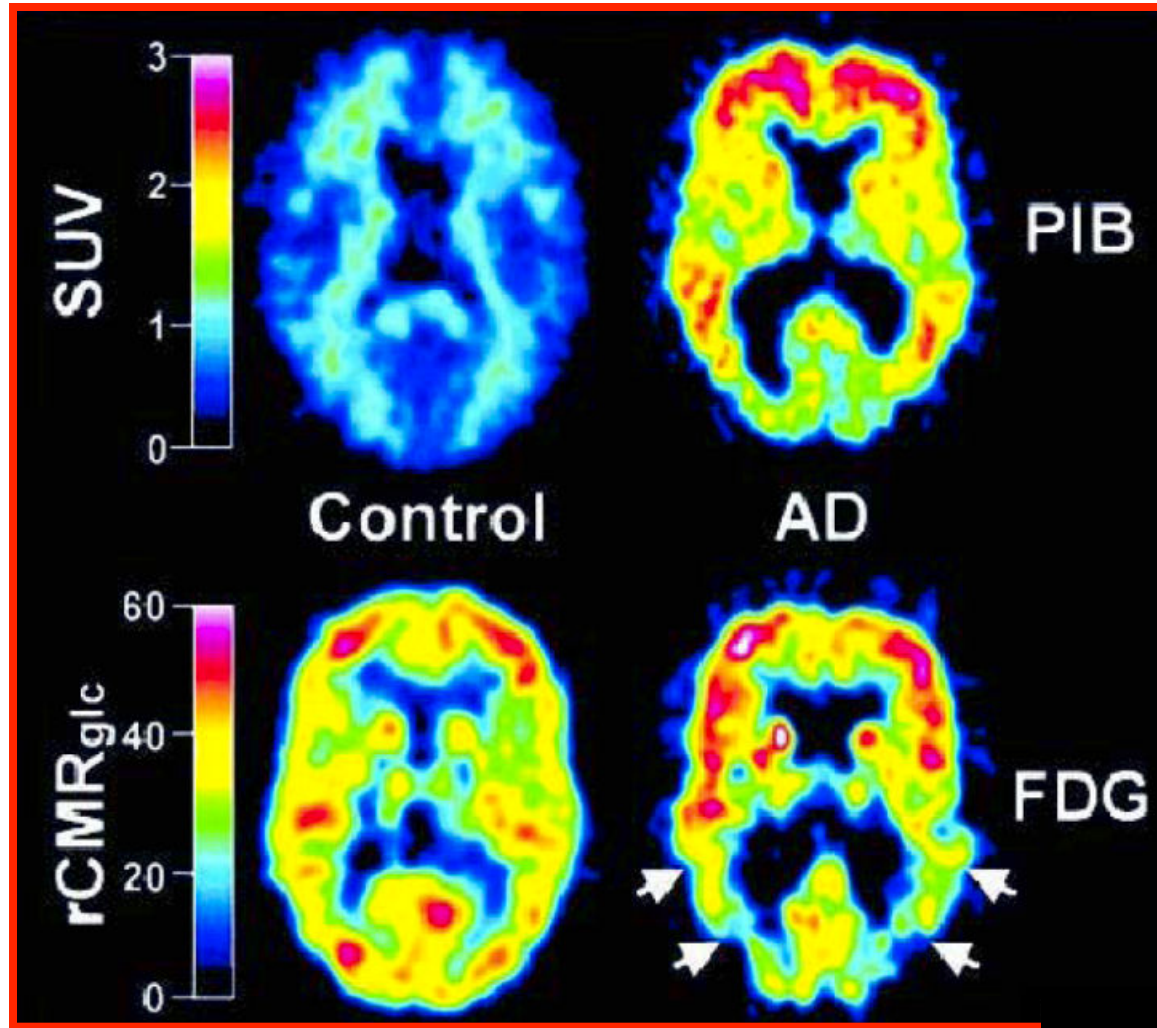
Últimos aportes de la imagenología molecular

Individual Variation in Sleep Quality and Duration Is Related to Cerebral Mu Opioid Receptor Binding Potential during Tonic Laboratory Pain in Healthy Subjects



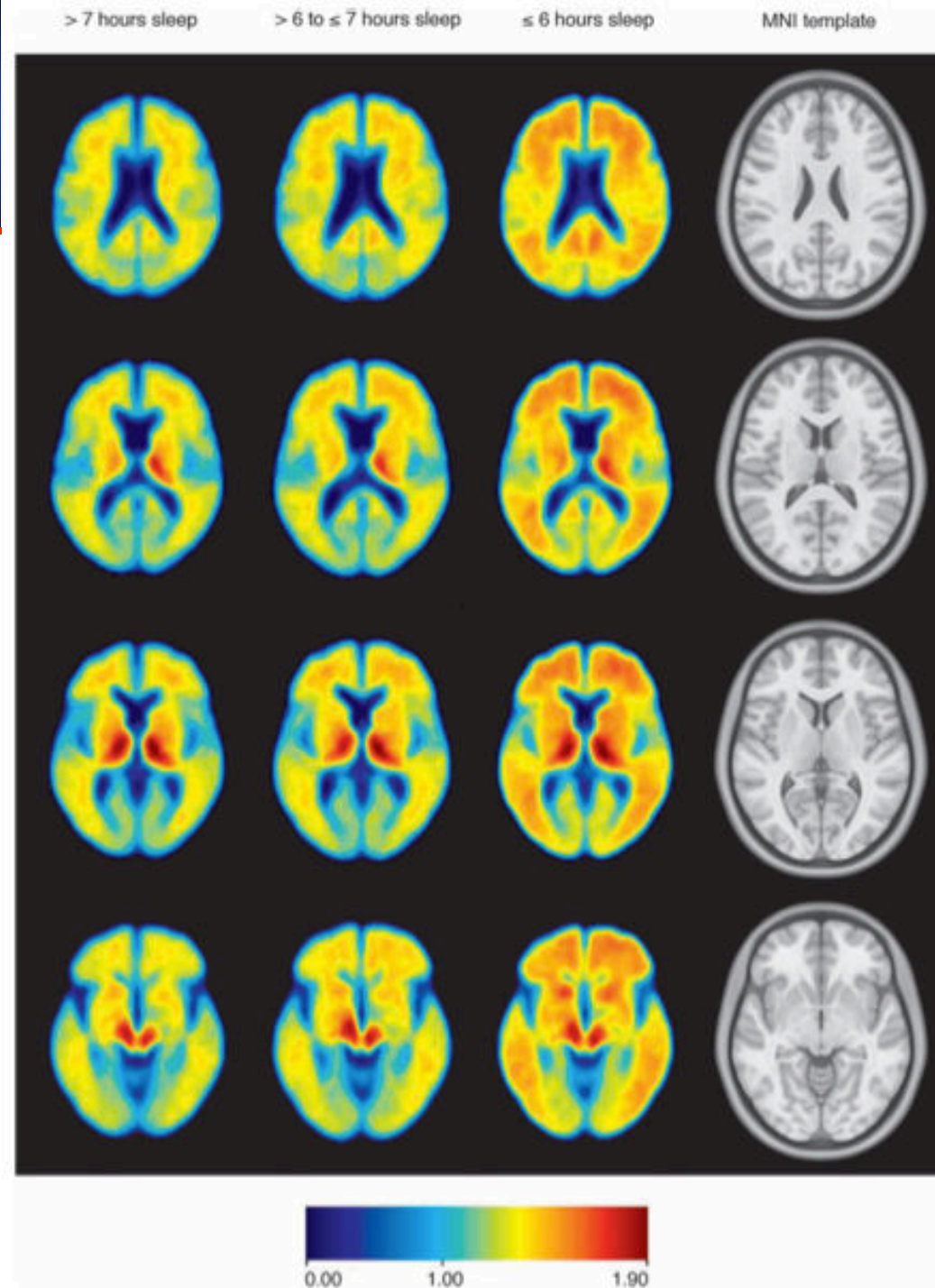
Poor sleep quality (PSQI) was positively associated with greater BP in regions within the frontal lobes. In addition, sleep duration was negatively associated with BP in these areas as well as the temporal lobe and anterior cingulate.

Imagen del β -amiloide



β -amiloide y sueño

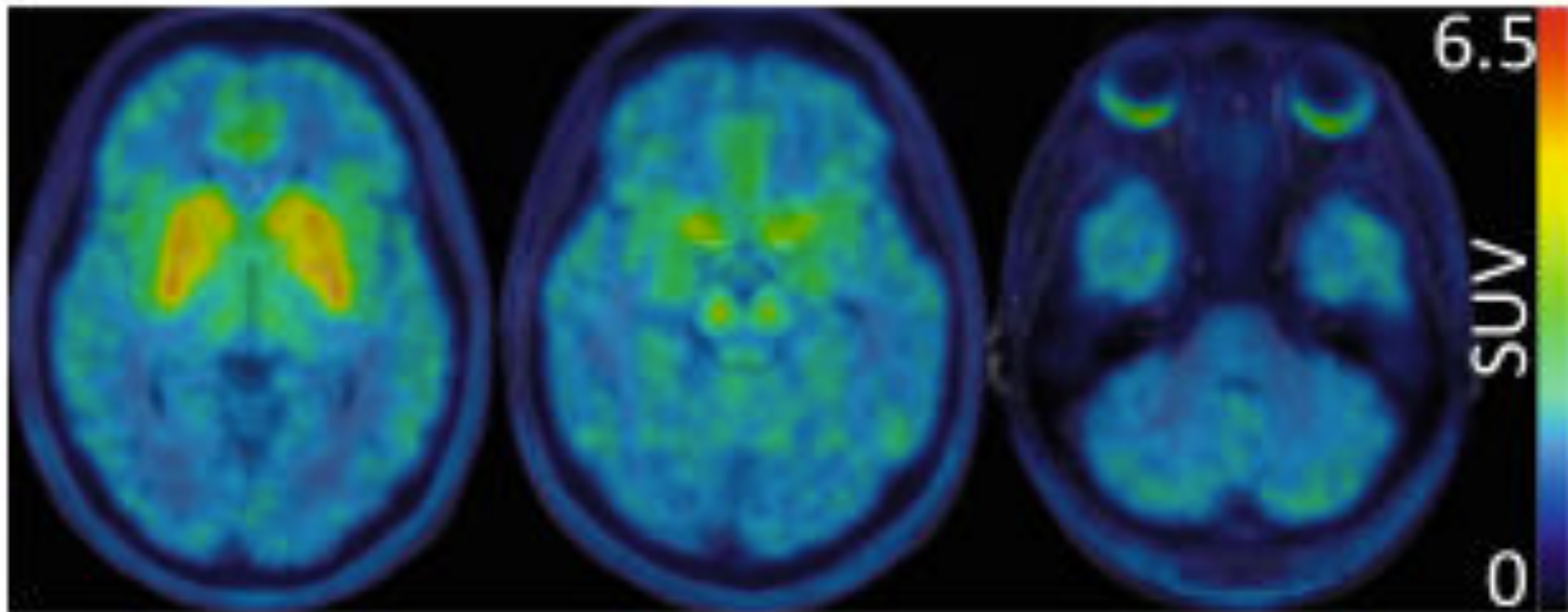
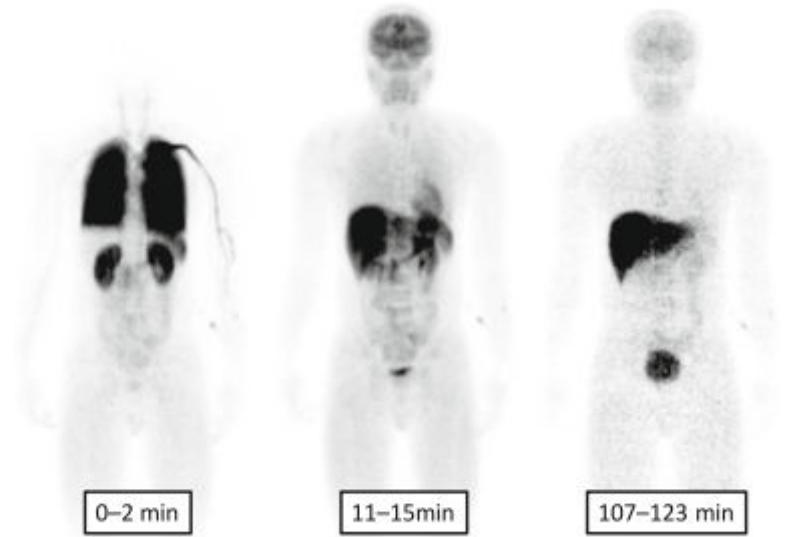
Among community-dwelling older adults, reports of shorter sleep duration and lower sleep quality are associated with greater β -amyloid burden.



Spira et al. Neurol 2013

[¹¹C]TASP457, a novel PET ligand for histamine H₃ receptors in human brain

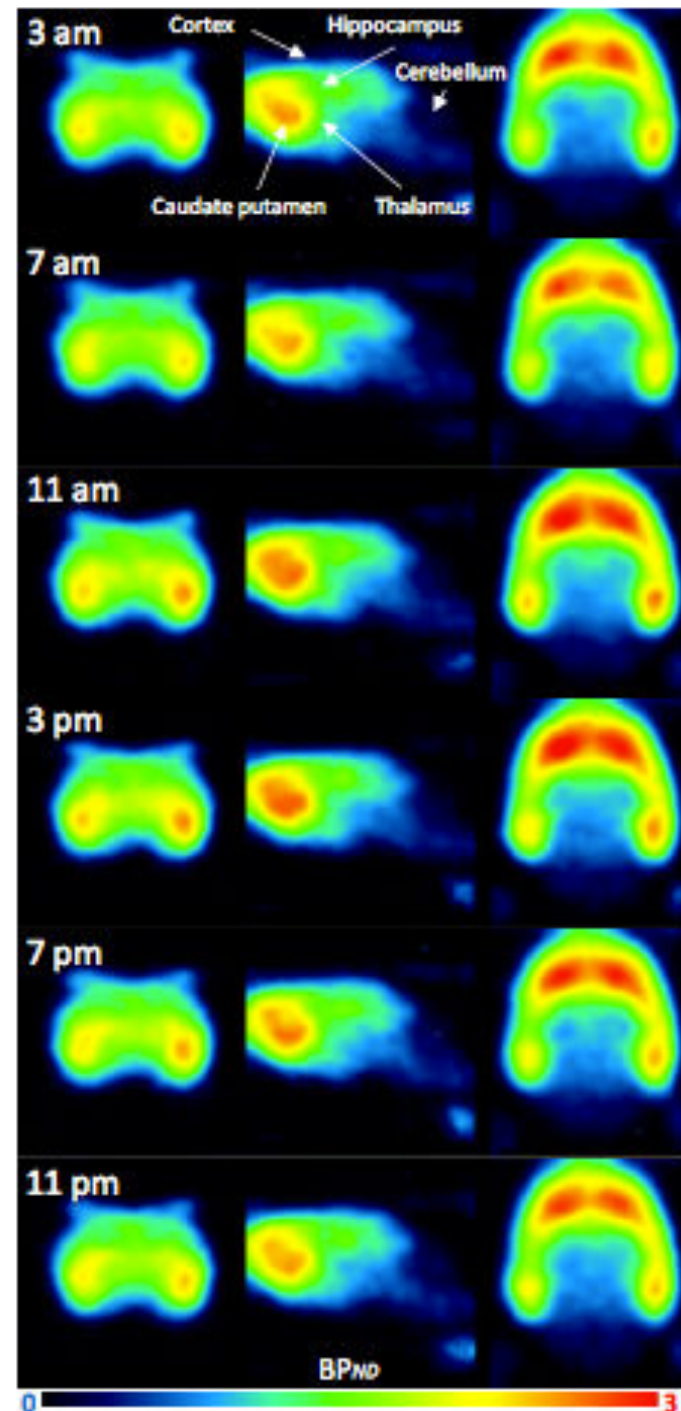
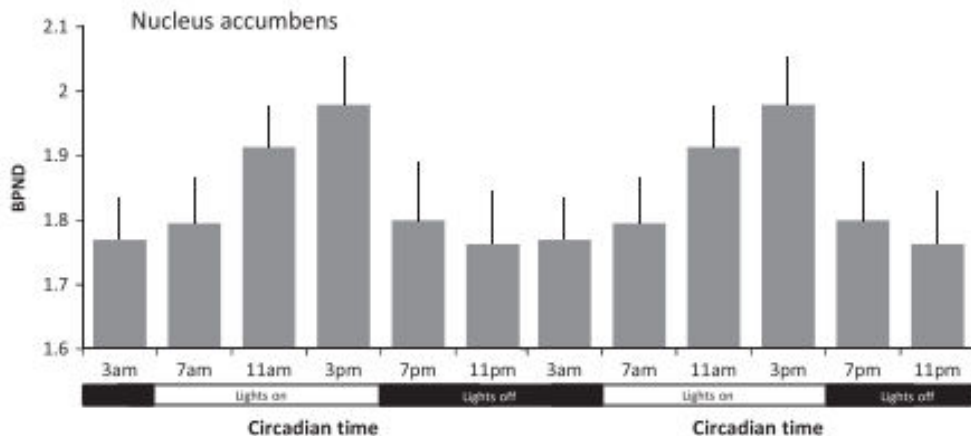
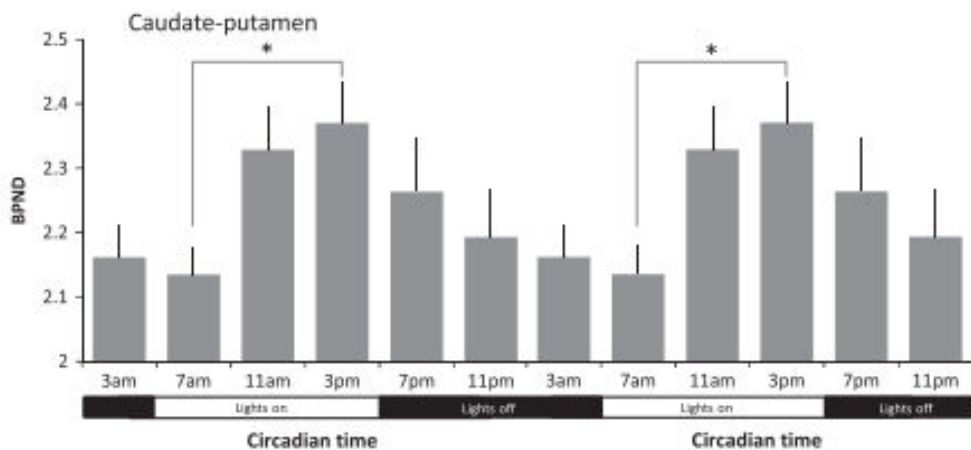
[(11)C]TASP457 is a useful novel PET ligand for the investigation of the density of histamine H₃ receptors in human brain.



Circadian variation of metabotropic glutamate receptor 5 availability in the rat brain

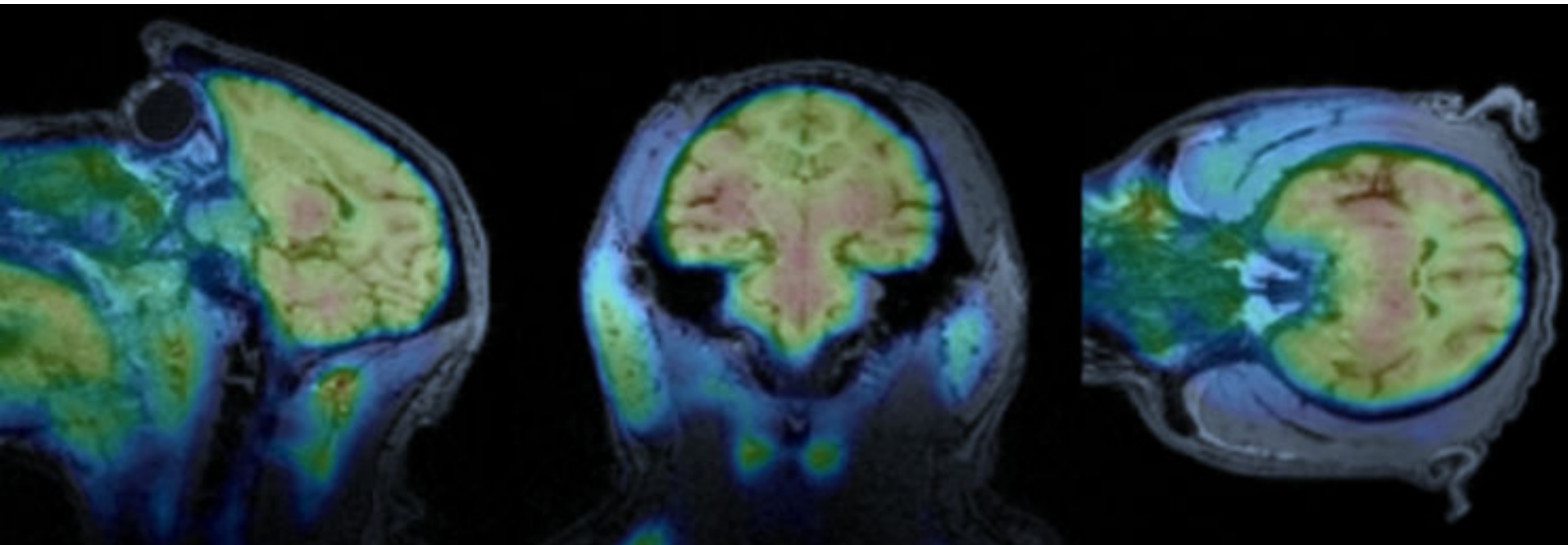
[11C]ABP688 – PET

This study shows that mGluR5 availability is increased during the light-on, or sleep phase, of rodents by approximately 10%.

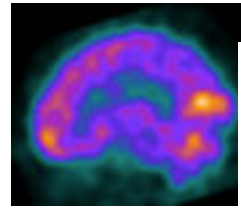
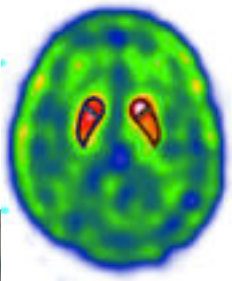


Evaluation of Potential PET Imaging Probes for the Orexin 2 Receptors

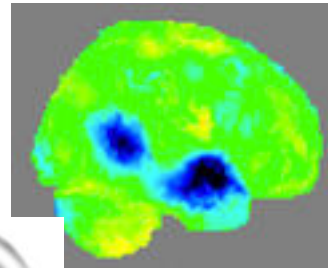
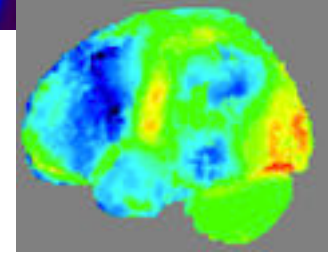
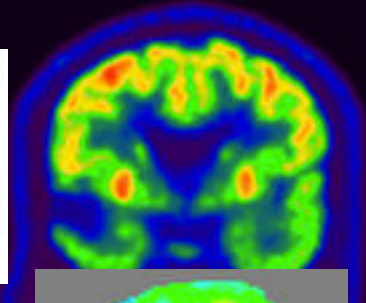
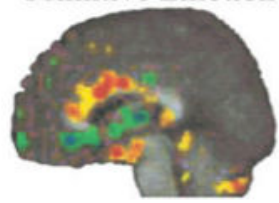
Changning Wang^a, Colin M. Wilson^a, Christian K. Moseley^a, Stephen M. Carlin^a, Shirley Hsu^a, Grae Arabasz^a, Frederick A. Schroeder^{a,b}, Christin Y. Sander^{a,c}, and Jacob M. Hooker^{a,*}



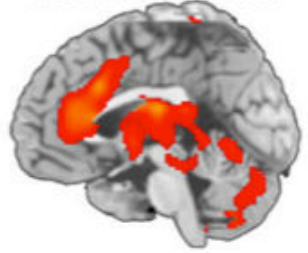
from Sleep



Primitive Emotion

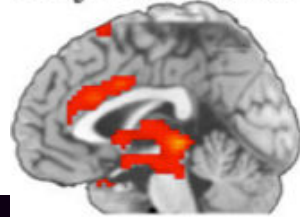


from Anesthesia



Gracias!

Subjective Arousal



VECJ

