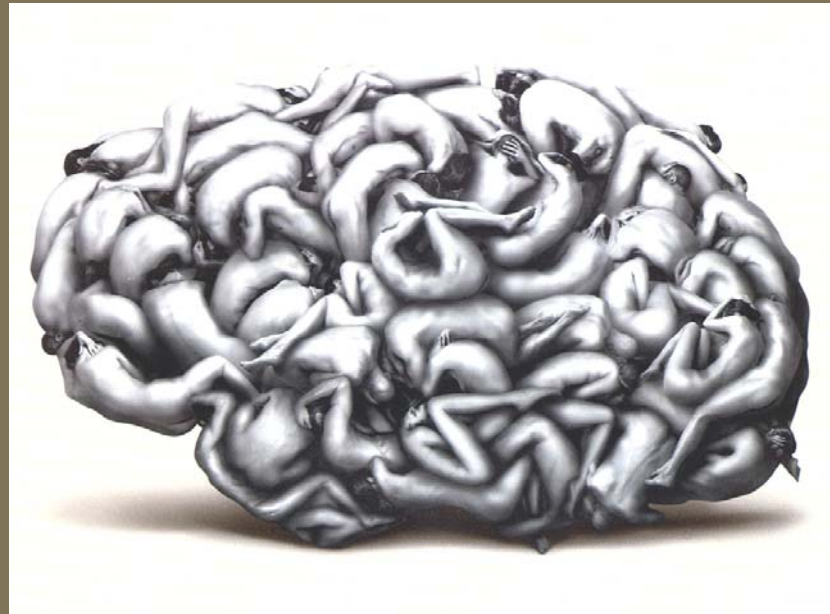


# Chronic disorders of consciousness: medical practice and neuroscientific revolution

Interdisziplinäres Symposium  
über chronische  
Bewusstseinsstörungen

Munich, July 16 2010

Athena Demertzi, MSc  
Neuropsychologist  
PhD candidate



Coma Science Group  
Cyclotron Research Center  
Department of Neurology, CHU  
University of Liège, Belgium



[www.comascience.org](http://www.comascience.org)

# Overview



*'Le scaphandre et le papillon' (2007)*  
Direction: Julian Schnabel

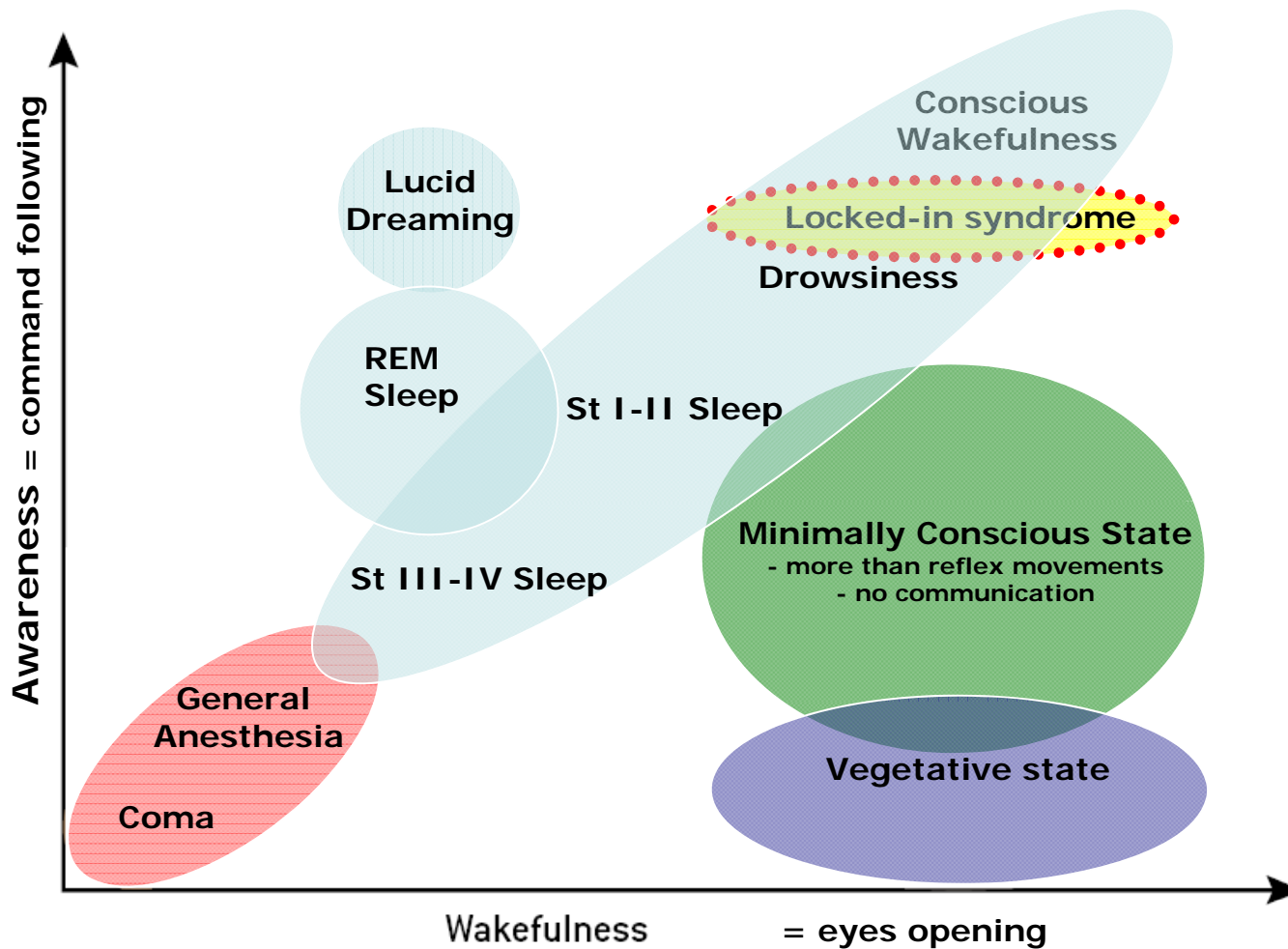
- Definitions
- Scientific perspective
  - Neural correlate of consciousness
- Clinical interest
  - Diagnosis, prognosis, treatment
- Ethical issues
  - End-of-life
  - Quality of life
- Conclusions

# Definitions

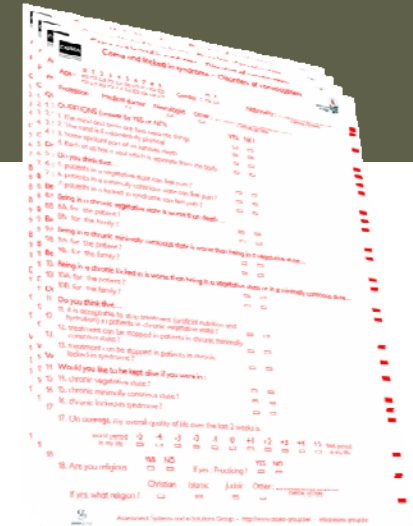


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# Lesion paradigm



# Questionnaire



Age category

Gender

Nationality (NL, BE..)

Profession Other (...)

**Would you like to be kept alive if you were in:**

1. Vegetative state (> 1year)?
2. Minimally conscious state (> 1year)?
3. Locked-in syndrome (> 1year)?

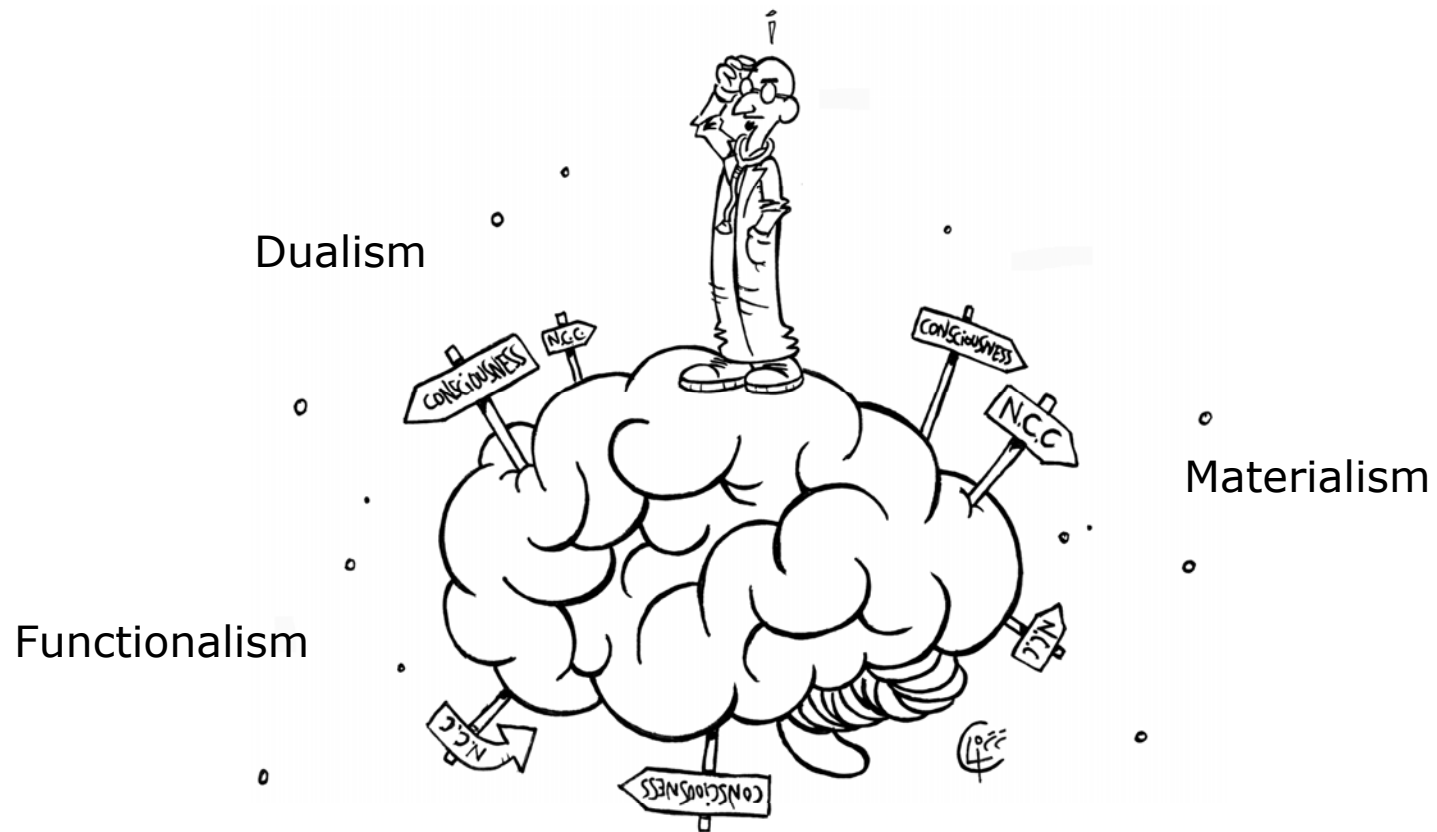
# Scientific perspective



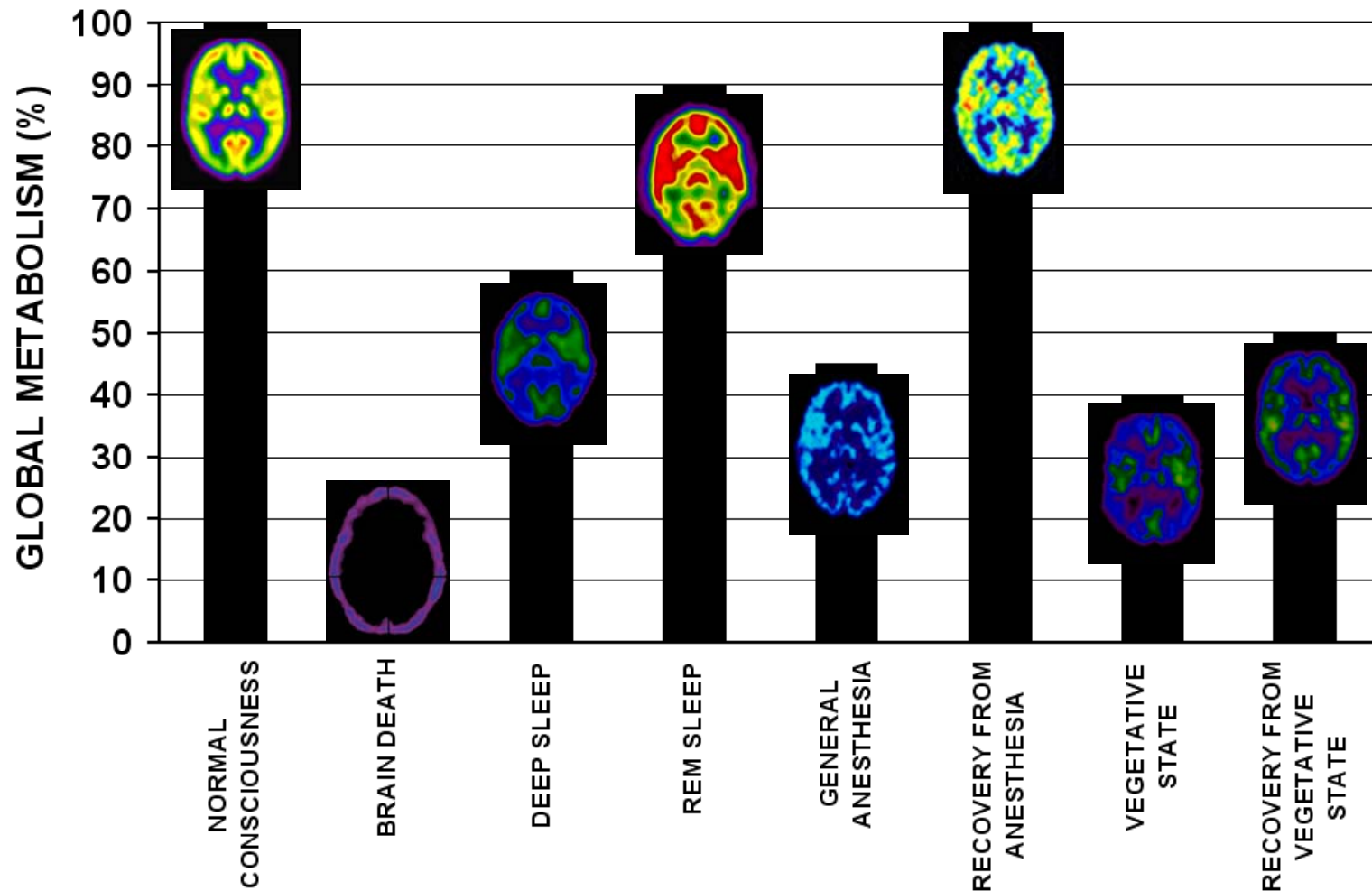
[www.comascience.org](http://www.comascience.org)

# Consciousness in the brain?

Dualism persists in 1/3 of clinicians

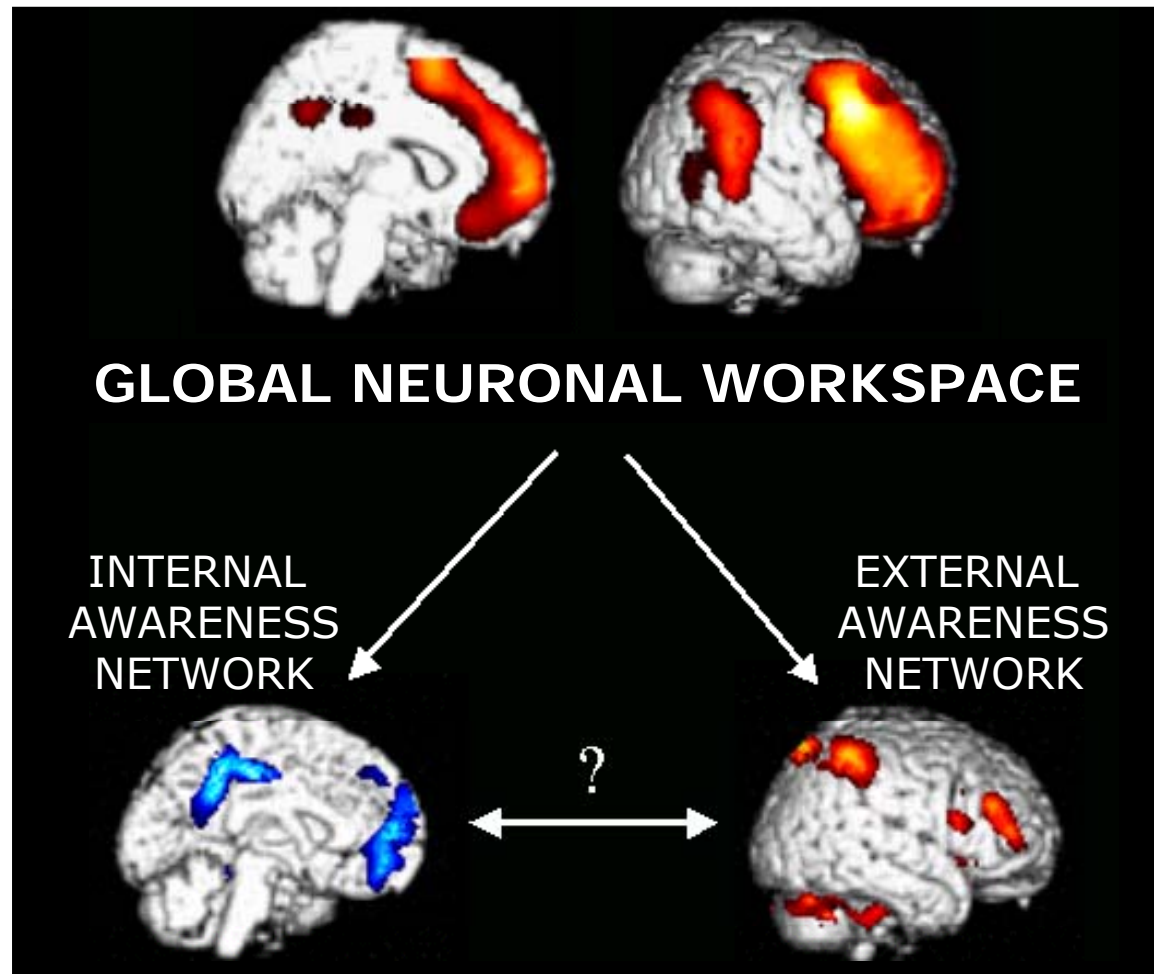


# Consciousness $\neq$ whole brain





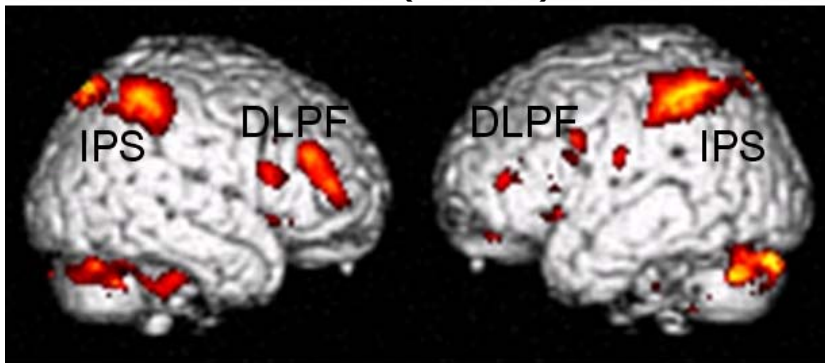
# Two awareness networks



# External and internal awareness

## NEURAL CORRELATE OF EXTERNAL (SENSORY) AWARENESS

Peri-luminal laser stimulation on hand (N=24)



*perceived* ( $433 \pm 23$  mJ) > *unperceived* ( $438 \pm 21$  mJ)

Soddu et al., *Prog Brain Res* 2009

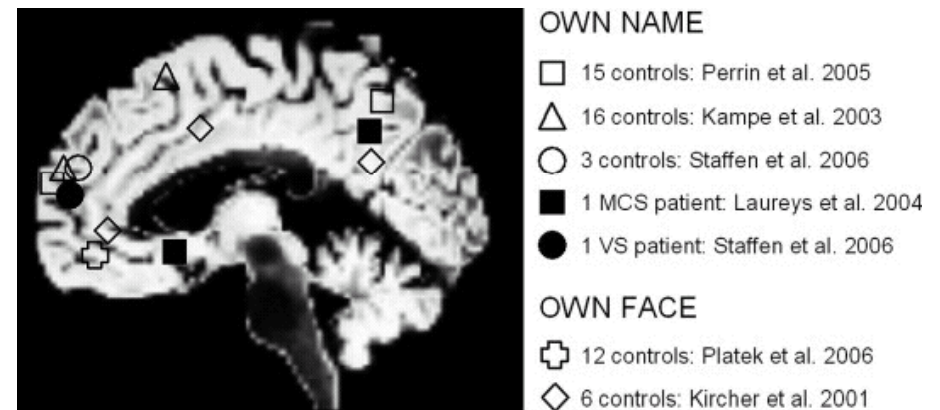
Boly et al, *PNAS* 2007

(also Dehaene et al, *Nat Rev Neuroci* 2001;

Rees et al, *Nat Rev Neuroci* 2001)

## NEURAL CORRELATE OF INTERNAL (SELF) AWARENESS

Self-referential stimuli



OWN NAME

□ 15 controls: Perrin et al. 2005

△ 16 controls: Kampe et al. 2003

○ 3 controls: Staffen et al. 2006

■ 1 MCS patient: Laureys et al. 2004

● 1 VS patient: Staffen et al. 2006

OWN FACE

⊕ 12 controls: Platek et al. 2006

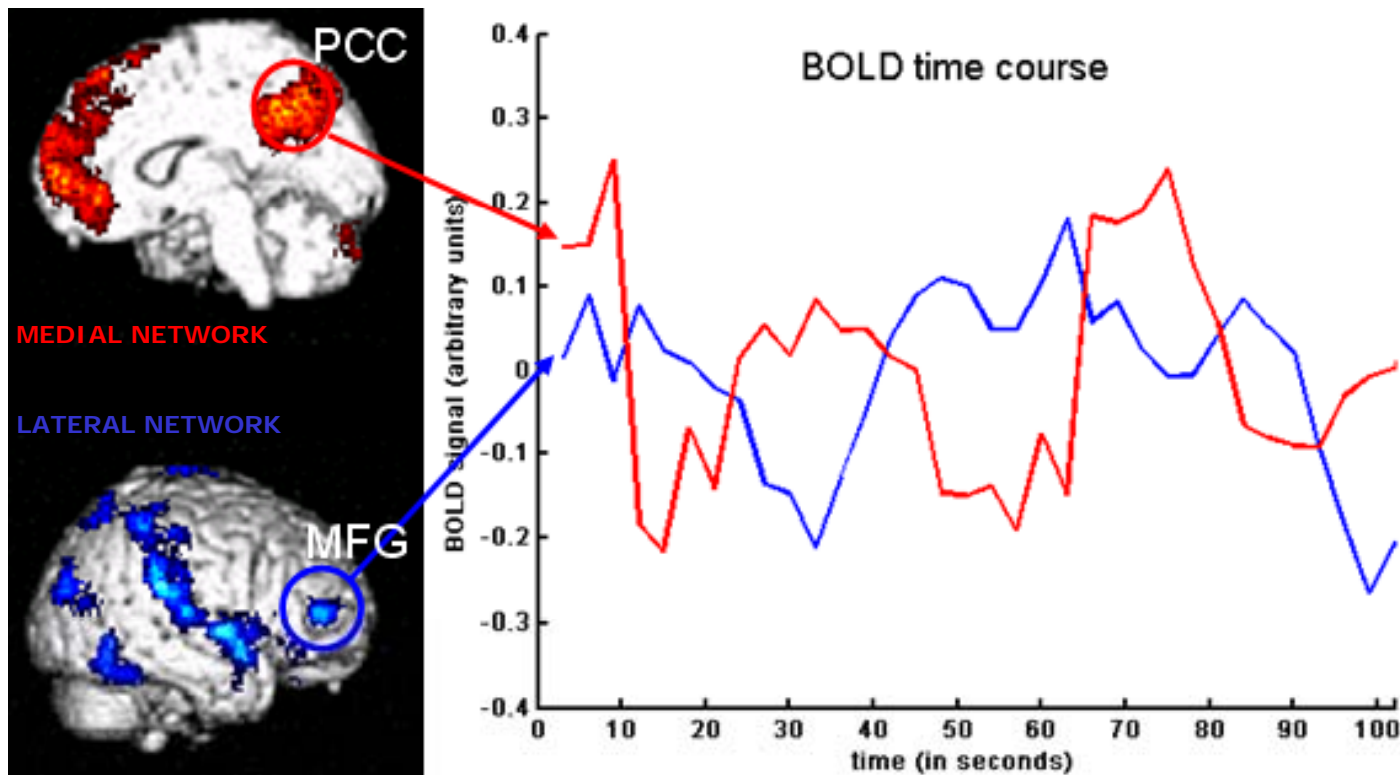
◇ 6 controls: Kircher et al. 2001

Laureys et al, *Consciousness & Cognition* 2007

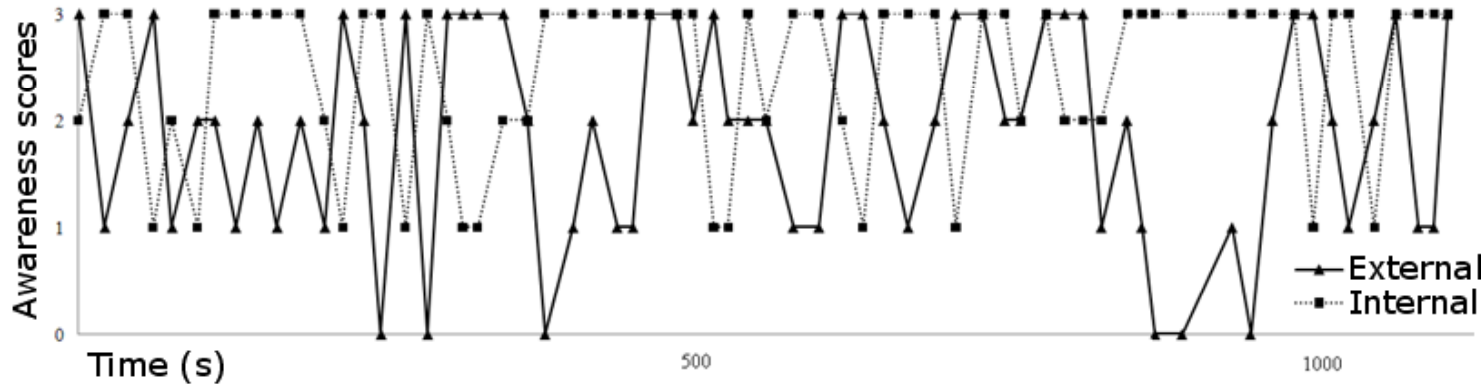
(also Mason et al, *Science*, 2007;

Golland et al, *Neuropsychologia* 2008)

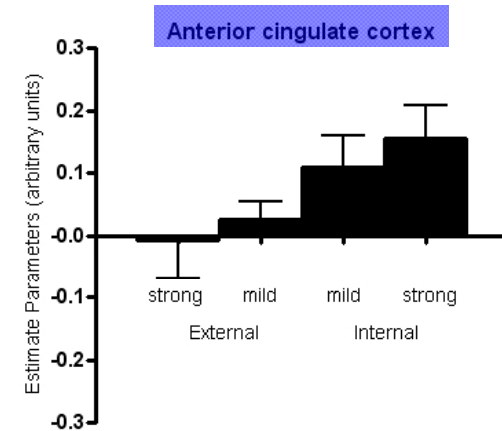
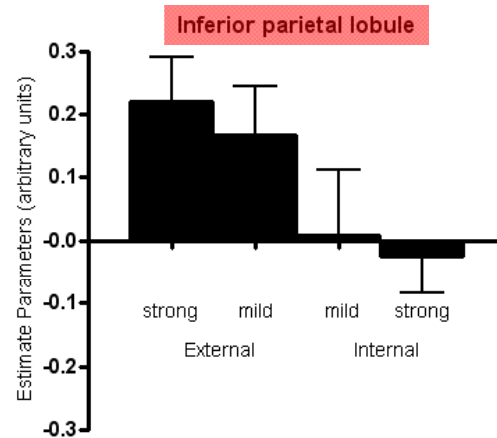
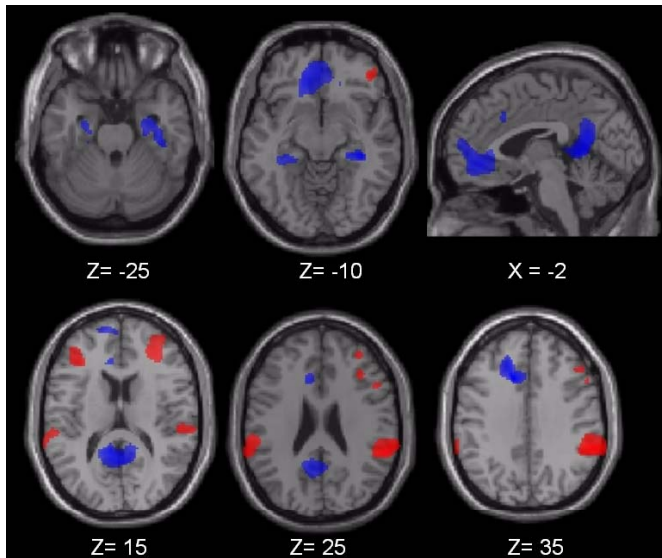
# “Resting state” default brain activity



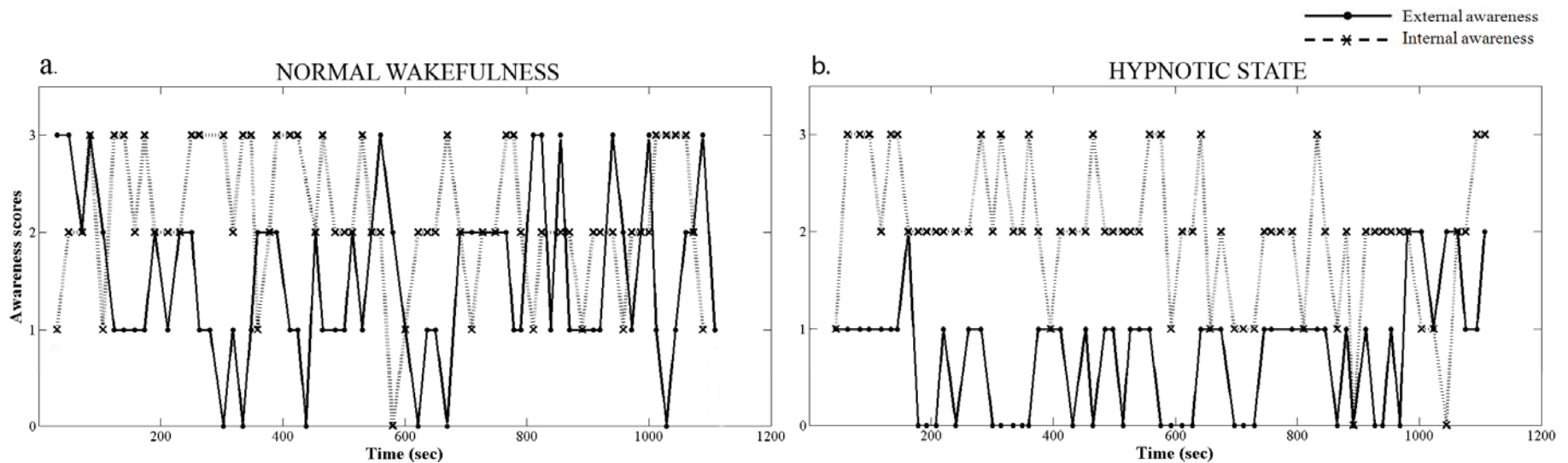
# Functional role to behavior



Anti-correlated  
Switching 0.05 Hz  
(range 0.01-0.1Hz)  
1/20 s  
(range 10-100 s)



# Flexibility of resting networks



$r = -0.41$

Switching of 0.05Hz (range 0.04-0.05Hz)

1/20 s

$r = -0.24$

Switching 0.03Hz (range = 0.02 0.05Hz)

1/33 s

# Questionnaire

4A. Do you think functional neuroimaging can differentiate between the vegetative and minimally conscious states?

4B. If a behaviorally vegetative patient would show normal activation of functional neuroimaging would this change your diagnosis?

# Clinical interest

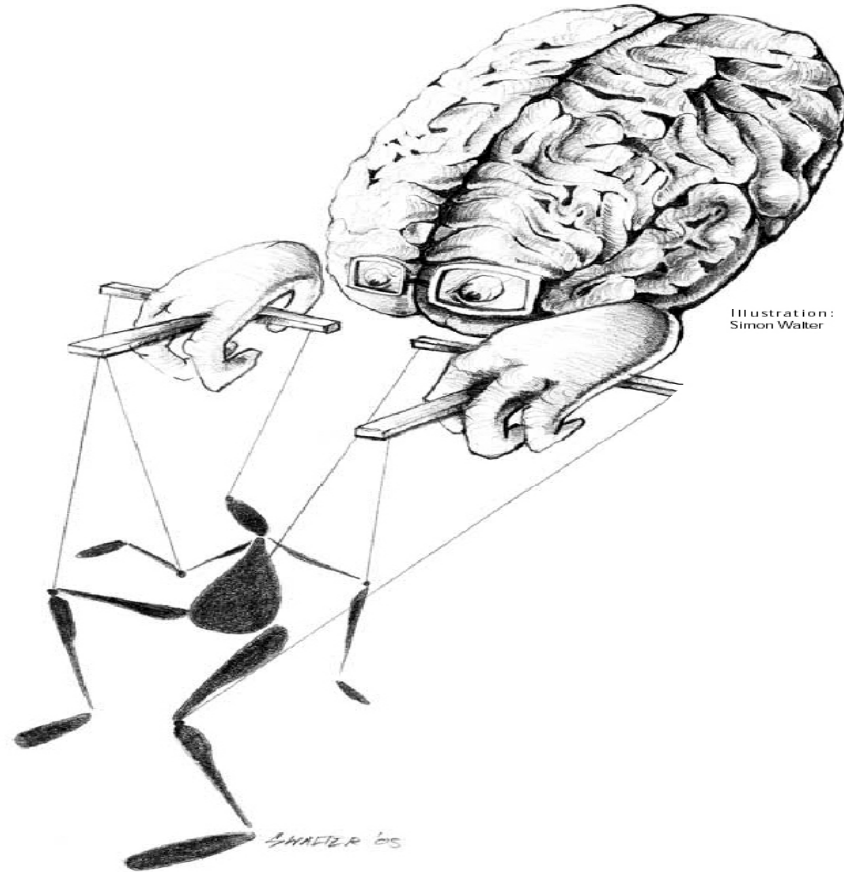


**COMA**

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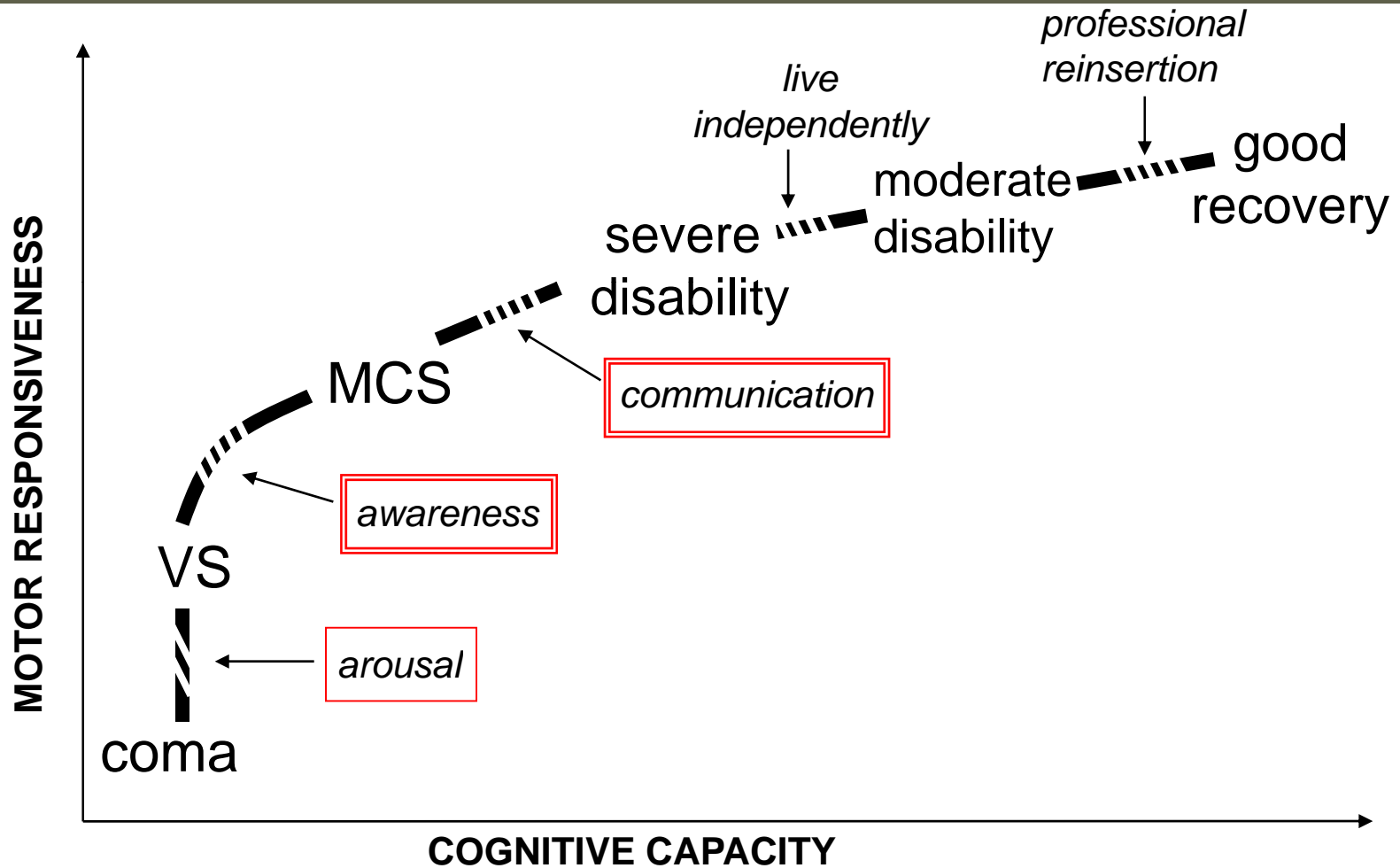
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# Reflex versus voluntary





# Assessing consciousness



# Misdiagnosis of vegetative state

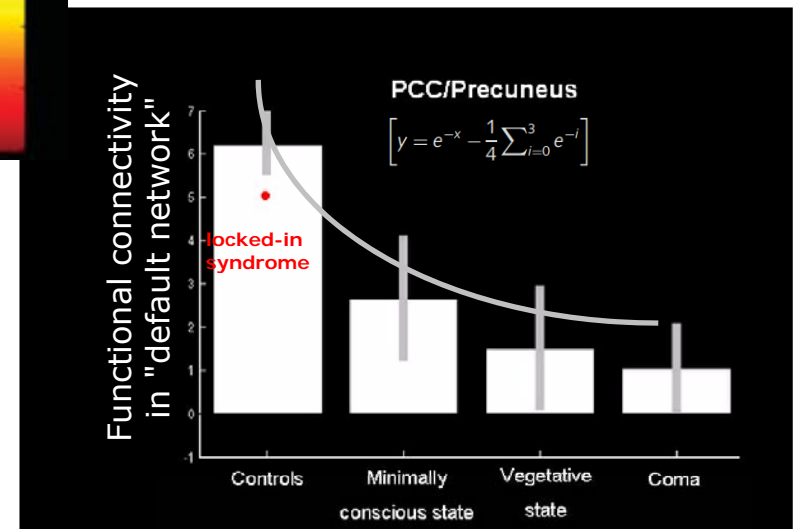
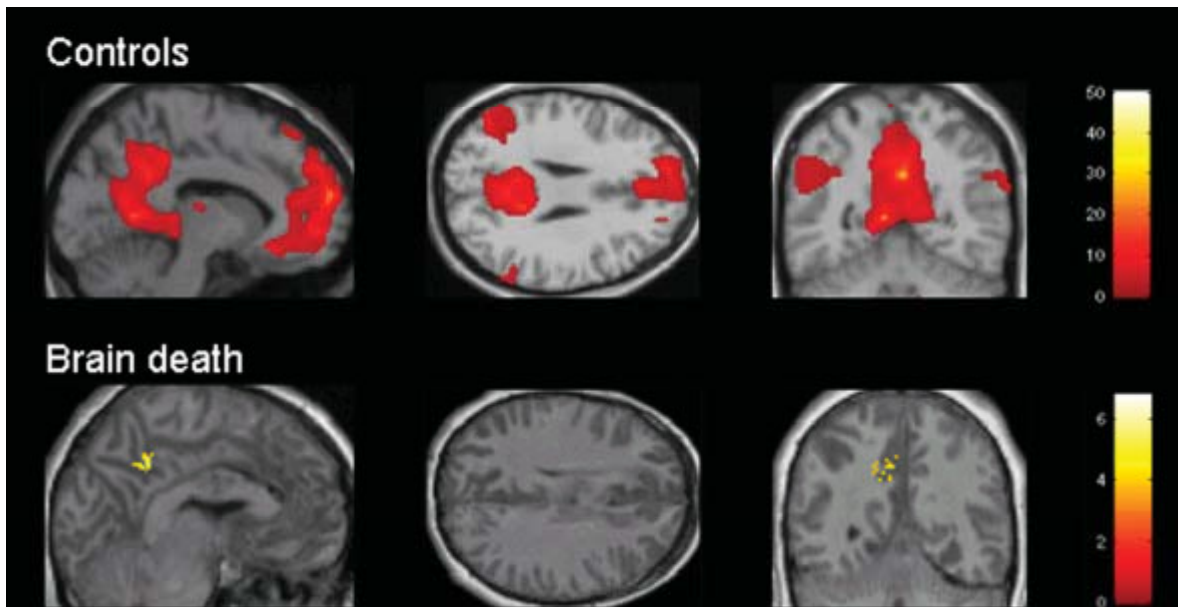
n=103 post-comatose patients

45 clinical diagnosis of “vegetative state”

27 Coma Recovery Scale diagnosis

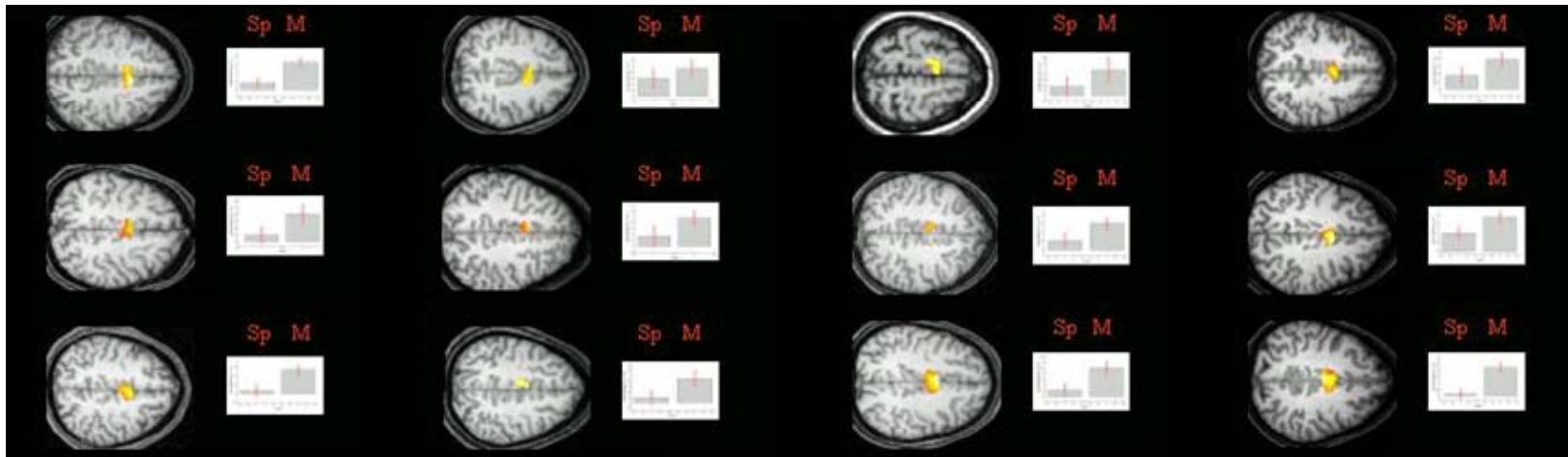
 40% misdiagnosis

# "Resting state" default brain activity

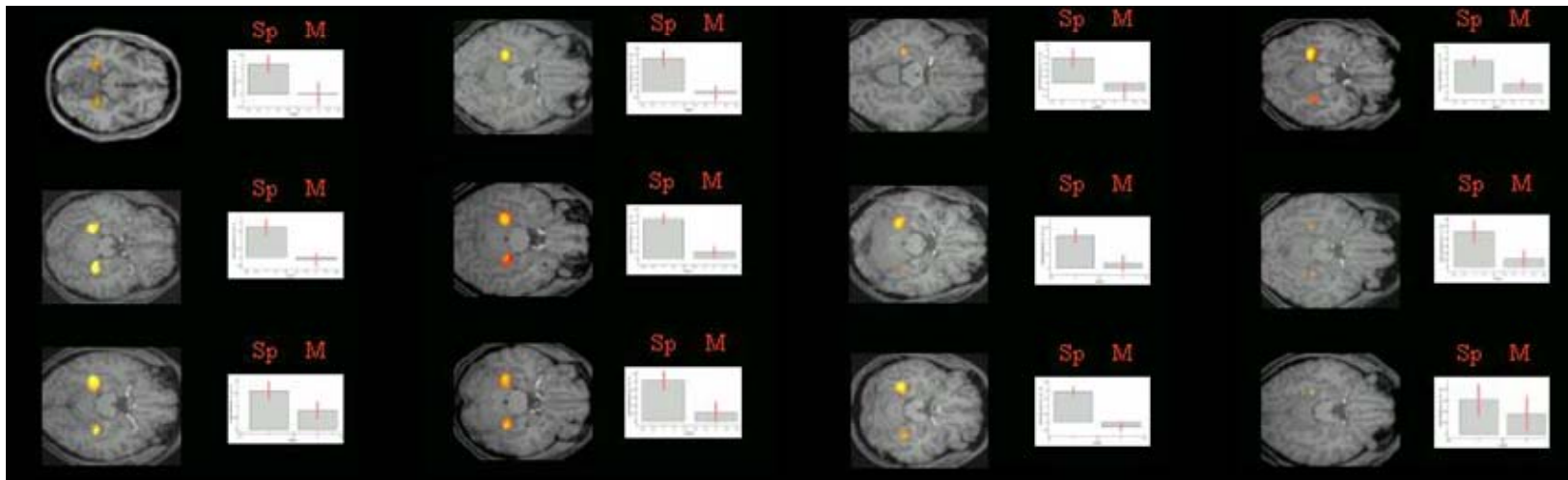


# “Mindreading”

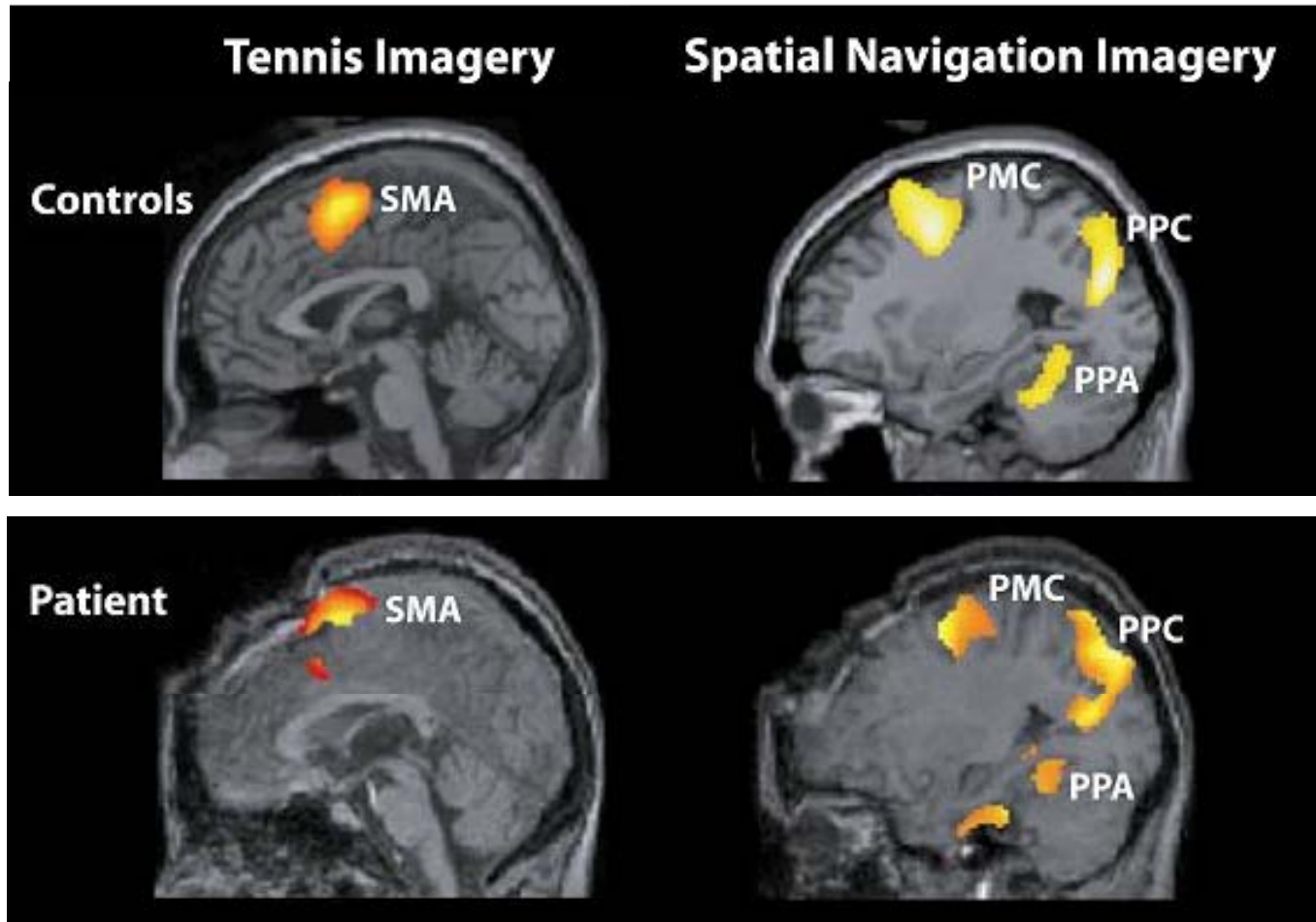
TENNIS



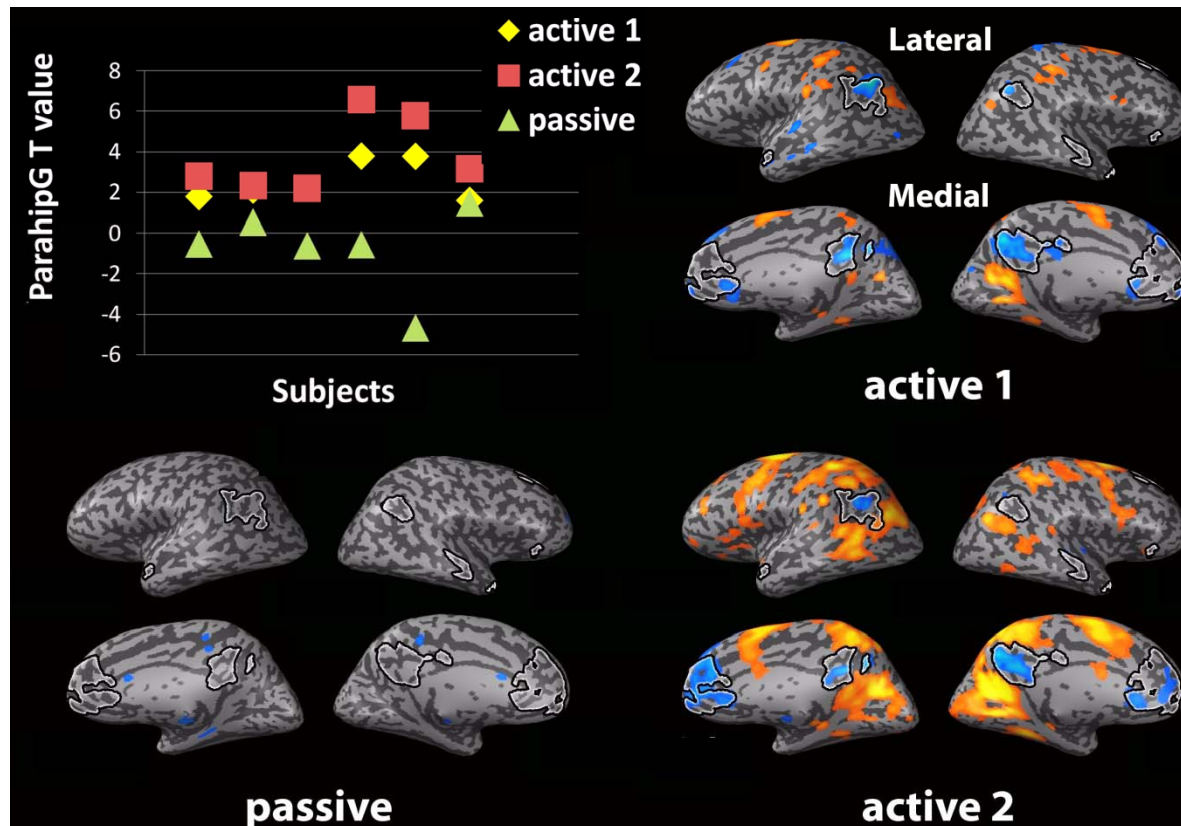
NAVIGATION



# Signs of consciousness on fMRI

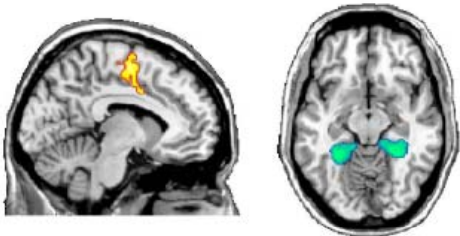


# ≠ “automatic” brain response

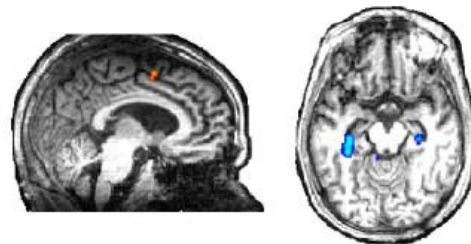


# Yes-No communication with fMRI

Healthy Controls

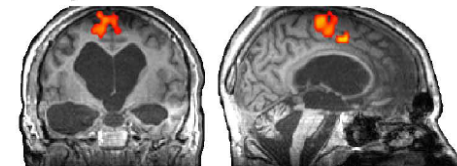


L25 TBI

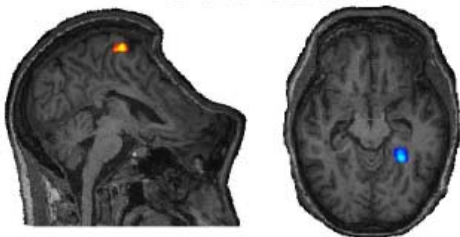


Imagine **Tennis** to answer 'YES'  
Imagine **Navigating** to answer 'NO'

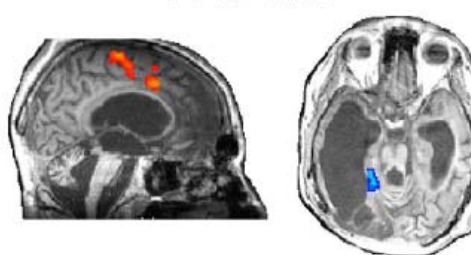
Is your father's name Alexander ?



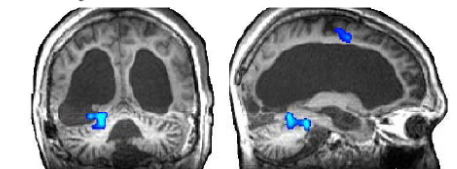
C04 TBI



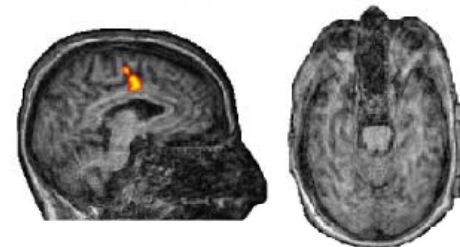
L23 TBI



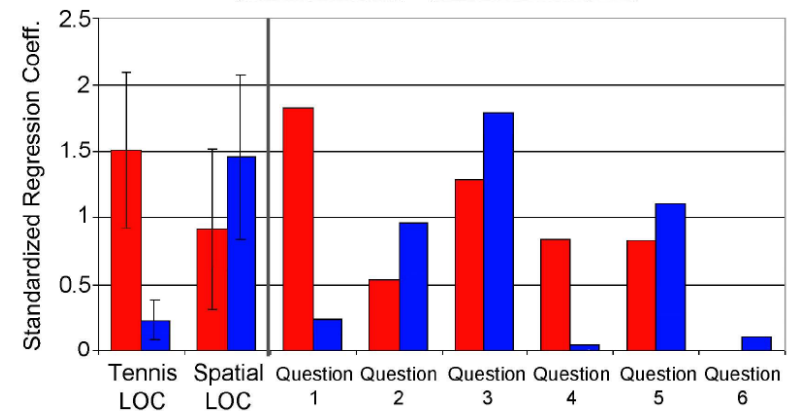
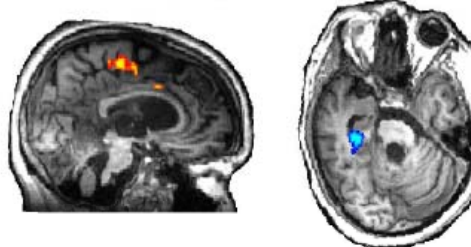
Is your father's name Thomas ?



C06 TBI



L22 TBI



# Questionnaire

**Do you think that:**

- 5A. Patients in a VS can feel pain?
- 5B. Patients in a VS should receive pain medication?
  
- 6A. Patients in a MCS can feel pain?
- 6B. Patients in a MCS should receive pain medication?
  
- 7A. Patients in a LIS can feel pain?
- 7B. Patients in a LIS should receive pain medication?

**Assuming surrogate informed consent, is it acceptable to do functional neuroimaging studies on:**

- 8A. Pain perception in the VS?
- 8B. Perception of thirst and hunger in the VS?
  
- 9A. Pain perception in the MCS?
- 9B. Perception of thirst and hunger in the MCS?

**Do you think invasive interventions are justified to...**

- 10A. Diagnose and study disorders of consciousness or to provide prognostic information?
- 10B. Develop treatments for disorders of consciousness?



# Treatment

- symptomatic
- curative



"...a (woman's) brain is a mystery...  
and even more so in this state"

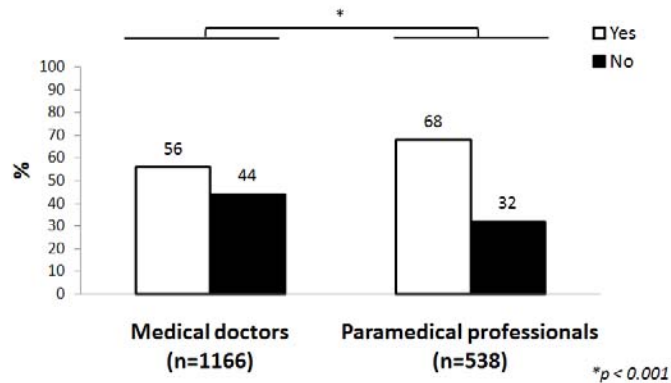
Pedro Almodovar - Hable con ella



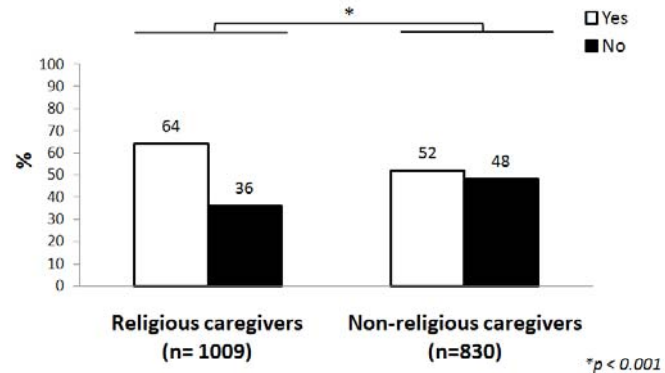
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# Nociception and pain

Do you think that patients in a vegetative state can feel pain?



Do you think that patients in a vegetative state can feel pain?



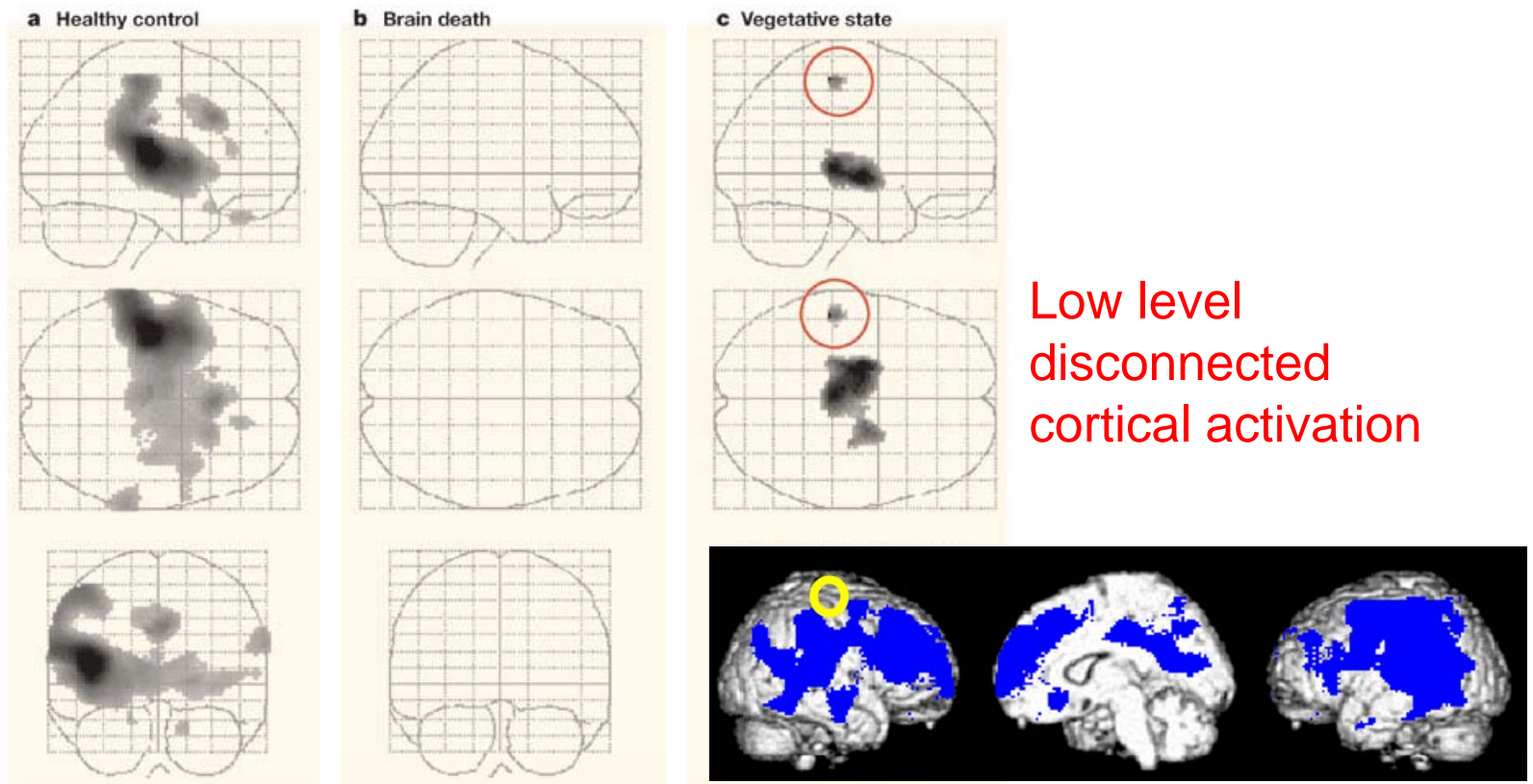
## Nociception Coma Scale

Score	Item	Response
<b>MOTOR RESPONSE</b>		
3	<i>Localization to Noxious Stimulation</i>	The non-stimulated limb must locate and make contact with the stimulated body part at the point of stimulation.
2	<i>Flexion Withdrawal</i>	There is isolated flexion withdrawal of at least one limb. The limb must move away from the point of stimulation.
1	<i>Abnormal Posturing</i>	Slow, stereotyped flexion or extension of the upper and/or lower extremities occurs immediately after the stimulus is applied.
0	<i>None/Flaccid</i>	There is no discernible movement following application of noxious stimulation, secondary to hypertonic or flaccid muscle tone.
<b>VERBAL RESPONSE</b>		
3	<i>Intelligible Verbalization</i>	Production of words in response to noxious stimulation. Each verbalization must consist of at least 1 consonant-vowel-consonant (CVC) triad. For example, "that hurts" would not be acceptable, but "that hurts" would be.
2	<i>Vocalization / Oral Movement</i>	Vocalization in response to noxious stimulation.
1	<i>Groans</i>	Groans in response to noxious stimulation.
0	<i>None</i>	No response to noxious stimulation.
<b>VISUAL RESPONSE</b>		
3	<i>Fixation</i>	Fixation on the point of stimulation.
2	<i>Eyes movements</i>	Eyes movements in response to noxious stimulation.
1	<i>Startle</i>	Startle response to noxious stimulation.
0	<i>No change</i>	There are no discernible changes in response to noxious stimulation.
<b>FACIAL EXPRESSION</b>		
3	<i>Cry</i>	Cries are observed not spontaneously but in response to noxious stimulation.
2	<i>Grimace</i>	Grimaces are observed not spontaneously but in response to noxious stimulation.
1	<i>Oral reflexive movement/Startle response</i>	Clamping of jaws, tongue pumping, yawning, chewing movement.
0	<i>None</i>	There is no discernible facial expression following application of noxious stimulation.

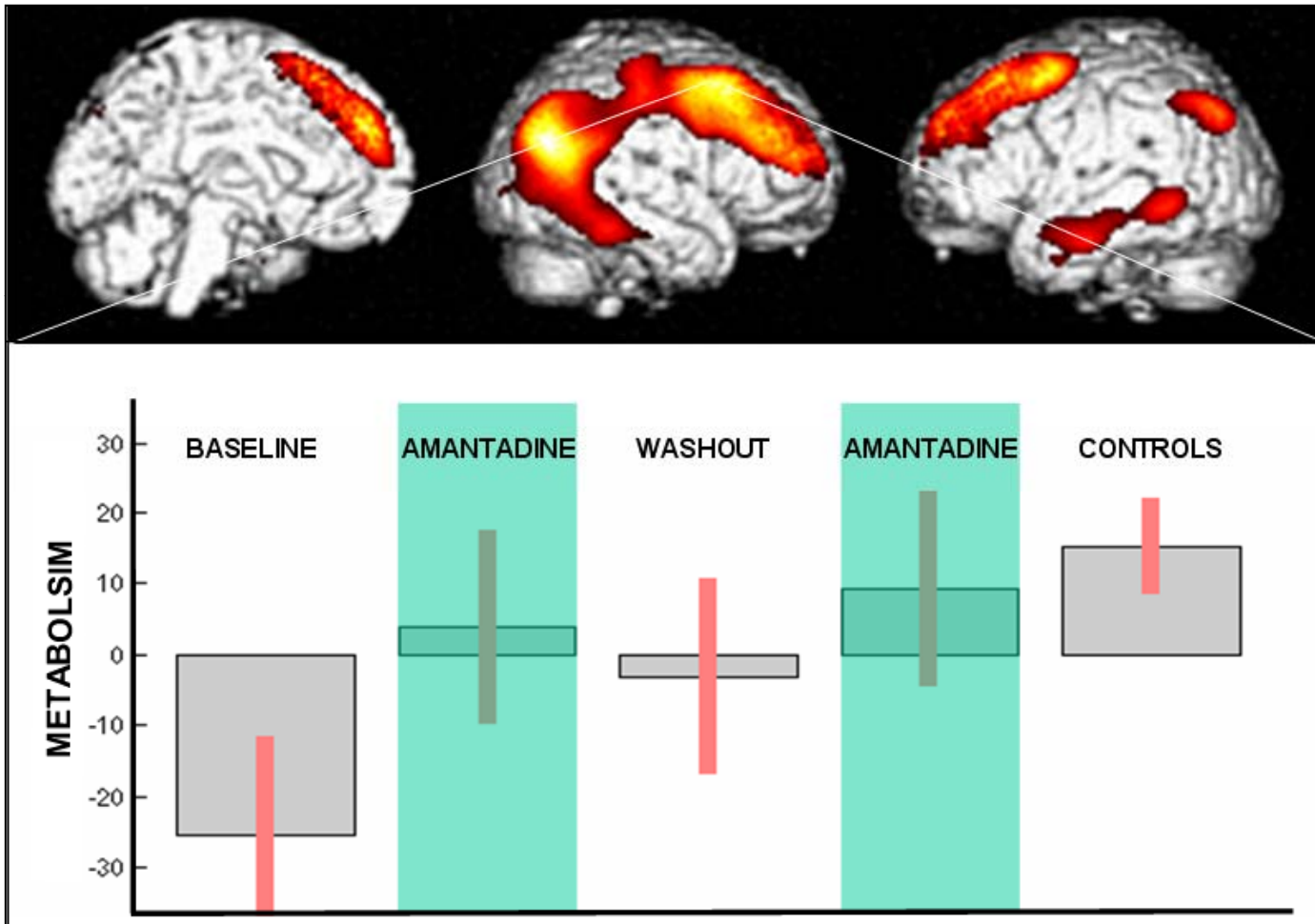


# Do they feel pain ?

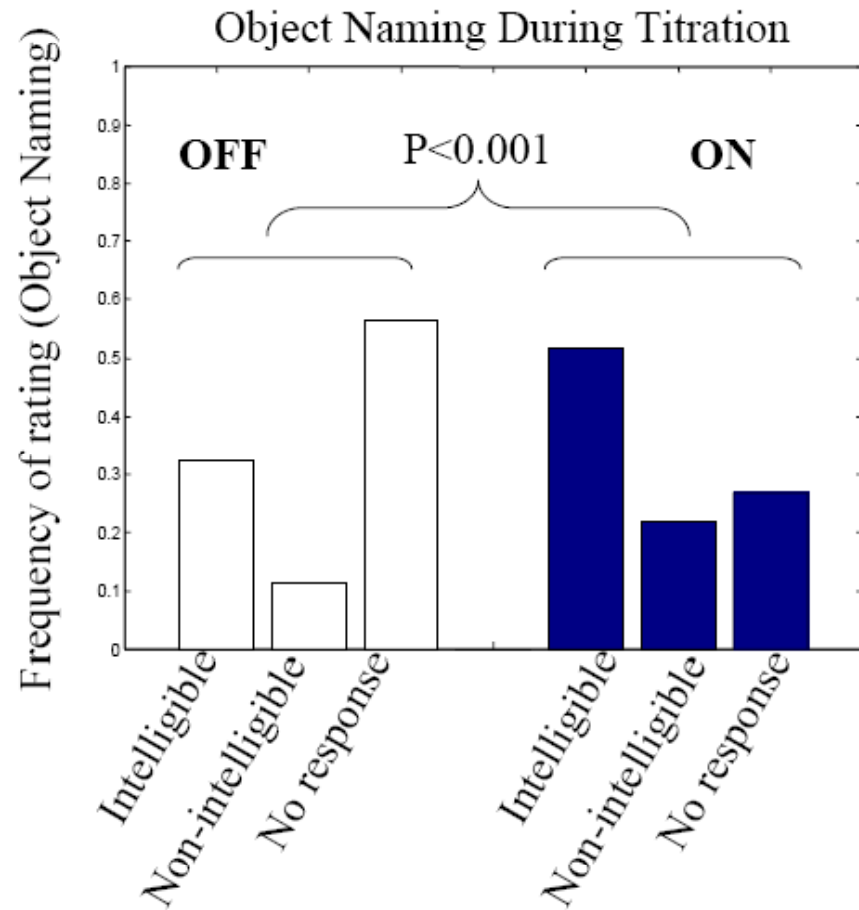
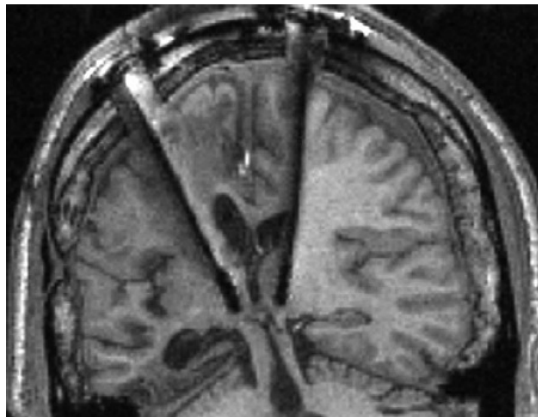
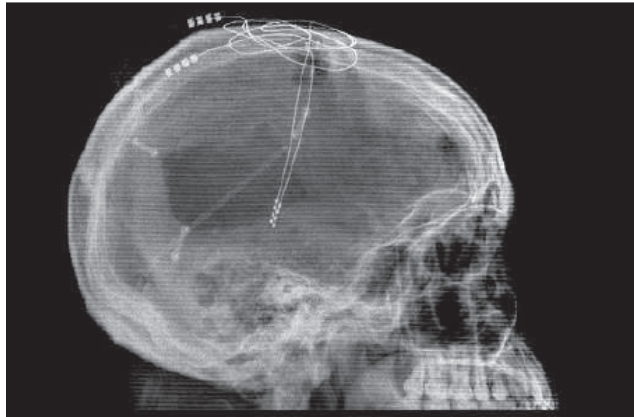
## Noxious electrical stimulation



# Curative treatment: Drugs? no evidence based therapy



# Curative treatment: Deep brain stimulation?



# Questionnaire

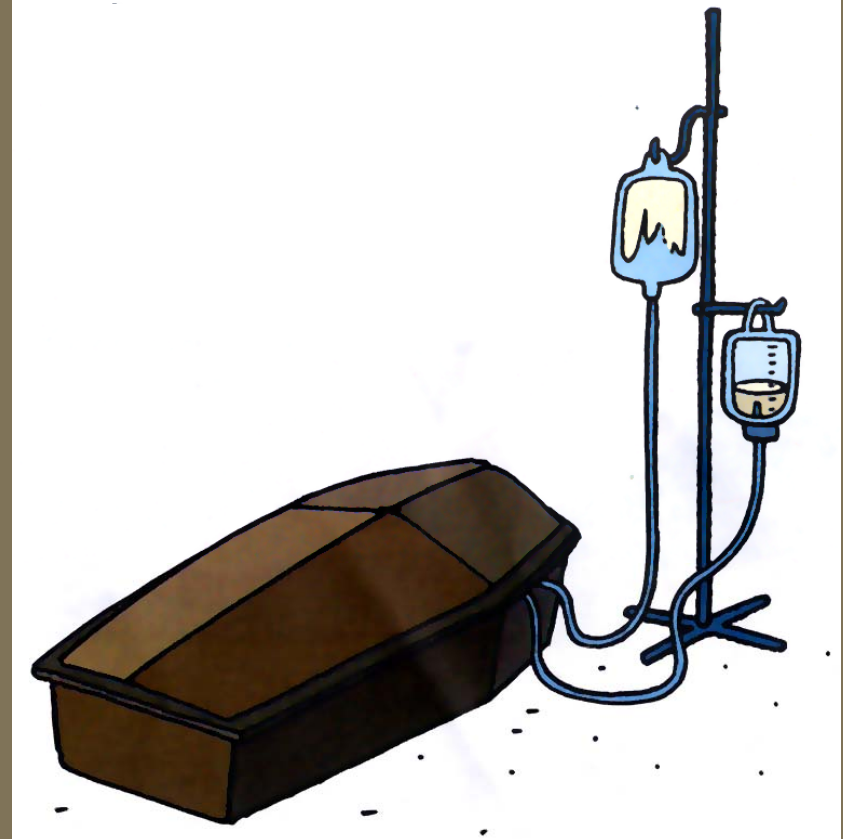
**Do you think it is acceptable to withhold or withdraw treatment in patients:**

11. In the vegetative state?
12. In the minimally conscious state?
13. In the locked-in syndrome?

**Are you religious?**

**If yes, please state your affiliation**

# Ethical challenges



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# End-of-life decisions in VS



Tony Blant, °1970,  
vegetative 1989, † 1993  
UK



Terry Schiavo °1963,  
vegetative 1990, † 2005  
US



Eluana Englaro °1970,  
vegetative 1992, † 2009  
IT

*When the diagnosis of a permanent VS is considered definite, it should be discussed with the relatives, [...] who should then be given the time to consider the implications, including the possibility of withdrawing artificial means of administering nutrition and hydration.*

(The Royal College of Physicians, 2003)



# Attitudes' survey

## Aim:

1. Debrief and update attitudes towards VS
2. Determine attitudes for MCS

A 16-item questionnaire (Yes-No responses)

Attendees at conferences and meetings

32 European countries

September 2007 -October 2009

## Statistical Analysis (SPSS v.16)

- Chi-square tests ( $p= .05$ )
- Multiple Logistic Regression models (method: Enter)
  - Predicted outcome: Agreement
  - Predictors: age, gender, region, profession and religiosity



# Attitudes' survey (n=2475)

## Demographic data

Age, mean  $\pm$ SD (range) 39 $\pm$ 14 (18-88)

### Gender, no. (%)

Women 1314 (53%)

Men 1098 (44%)

Missing 63 (3%)

### Respondents by European Region, no (%)

Northern 402 (16%)

Central 1213 (49%)

South 855 (35%)

Missing 5 (0%)

### Profession, no. (%)

Medical professionals 1608 (65%)

Paramedical professionals 651 (26%)

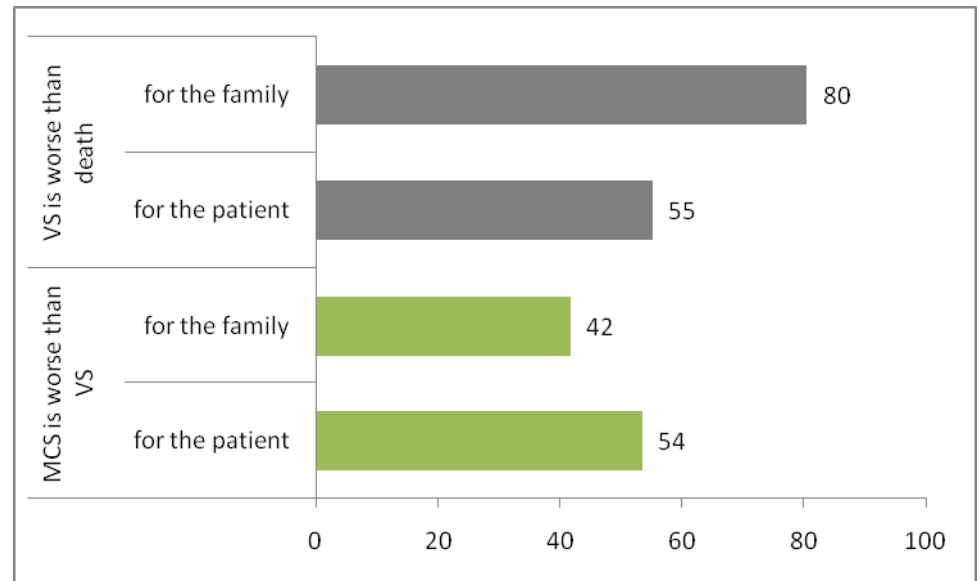
Missing 216 (9%)

### Religiosity, no. (%)

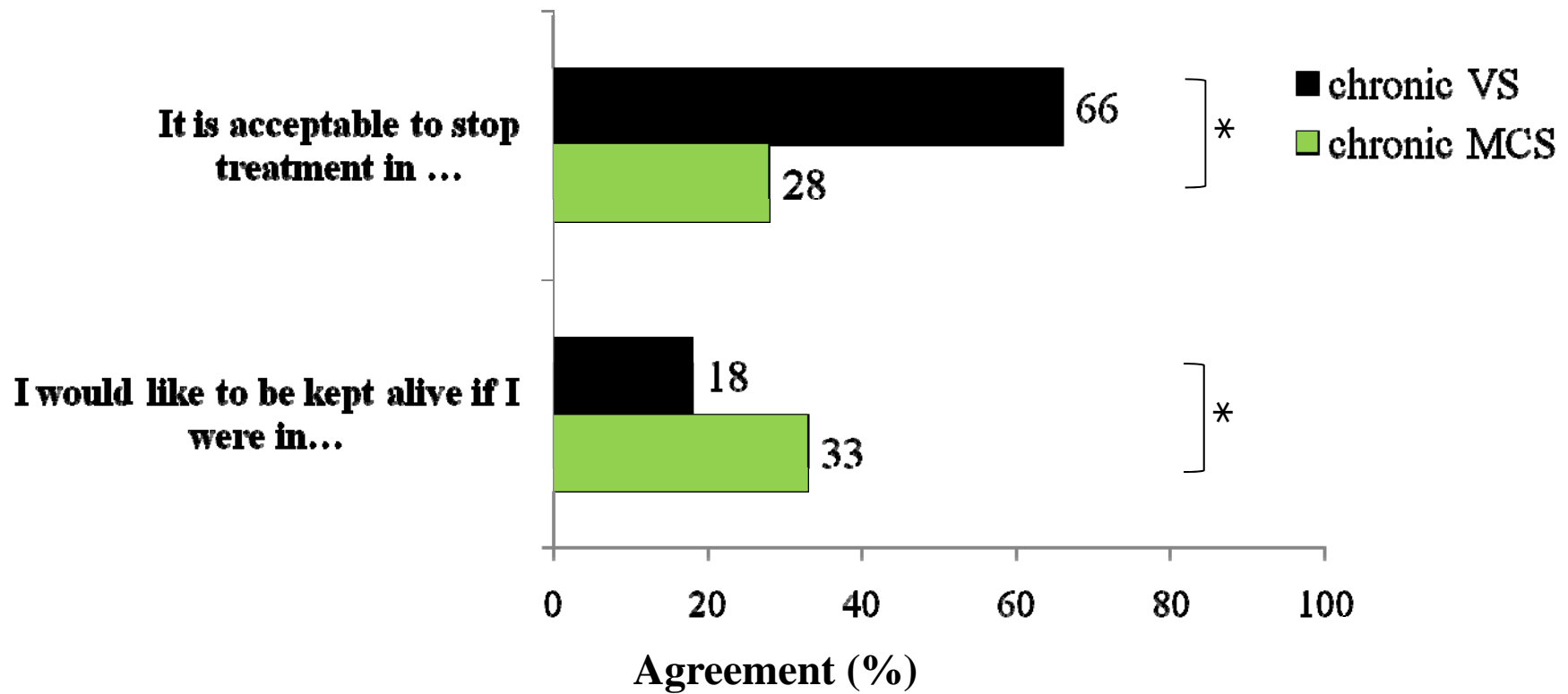
Religious respondents 1407 (57%)

Non-religious respondents 1004 (40%)

Missing 64 (3%)



# End-of-life attitudes (n=2475)



\*  $p < .001$

# End-of-life attitudes: predictors

Predictor variable	It is acceptable to stop ANH in a chronic VS	It is acceptable to stop ANH in a chronic MCS	I would like to be kept alive in a chronic VS	I would like to be kept alive in a chronic MCS
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Age†	0.98 (0.97-0.99)**	0.98 (0.98-0.99)**	1.01 (1.01-1.02)*	1.00 (0.99-1.01)
Women	0.79 (0.64-0.97)*	0.91 (0.73-1.13)	0.87 (0.67-1.12)	0.92 (0.75-1.13)
<b>Southern Europe</b>	1	1	1	1
<b>Northern Europe</b>	3.36 (2.38-4.74)**	3.82 (2.79-5.23)**	0.34 (0.21-0.55)**	0.47 (0.34-0.66)**
<b>Central Europe</b>	1.84 (1.49-2.26)**	2.24 (1.77-2.83)**	0.72 (0.56-0.92)*	0.69 (0.56-0.85)**
Medical professionals	1.18 (0.94-1.49)	0.91 (0.73-1.15)	1.18 (0.88-1.59)	1.28 (1.02-1.62)*
<b>Religious respondents</b>	0.45 (0.37-0.55)**	0.46 (0.37-0.55)**	2.20 (1.70-2.85)**	2.24 (1.84-2.73)**

\*\* p< 0.001, \* p< 0.05;

Note: Predicted response: 'agreement'. An odds ratio higher than 1 signifies more agreement with the statement, whereas an odds ratio less than 1 notifies less agreement.

†For continuous variables, the odds ratio equals the relative change in the odds ratio when the variable is increased by one unit.

# Conclusions

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# Translational research

Neural correlates of conscious awareness

- ≈ fronto-parietal neuronal 'global workspace'
- ≈ cortico-thalamo-cortical functional connectivity

Diagnostic use

- ≈ 40% signs of consciousness in vegetative state

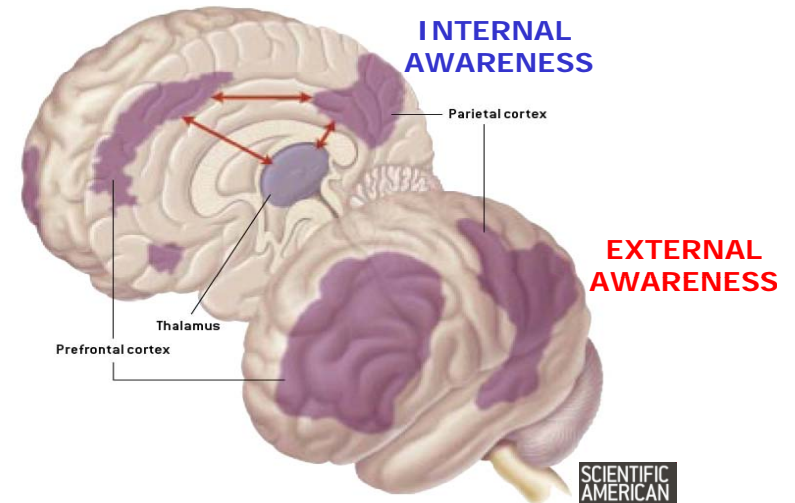
Prognostic use

- (f)MRI prospective multicenter studies

Therapeutic use

- symptom & pain treatment / curative thalamic DBS

↙ ↘ Ethical issues





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# THANK YOU

Slides can be downloaded from [www.comascience.org](http://www.comascience.org)

## PhD candidates:

Marie-Aurélie Bruno  
Olivia Gosseries  
Pierre Boveroux MD  
Muriel Kirsch MD  
Audrey Maudoux  
Camille Chatelle  
Marie Thonnard  
Victor Cologan

## PhDs:

Melanie Boly MD  
Andrea Soddu  
Quentin Noirhomme, Ing  
Didier Ledoux MD  
Audrey Vanhaudenhuyse  
Caroline Schnakers

## Also:

Christophe Phillips, PhD Ing  
Pierre Maquet, MD PhD

the patients & families

## Collaborations:

NY J Giacino, N Schiff, J Fins  
Cambridge A Owen  
Milano M Massimini  
Wisconsin G Tononi  
Tubingen & Wurzburg A Kübler  
Paris L Puybasset  
Hangzhou China H Di  
Salzburg M Schabus  
Lyon F Perrin



Université  
de Liège



James S. McDonnell Foundation



## The Neurology of Consciousness

Cognitive Neuroscience and Neuropathology



Steven Laureys • Giulio Tononi



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