



# Neural correlates of pain in patients with disorders of consciousness

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# Clinical entities

## CLINICAL EXAMINATION

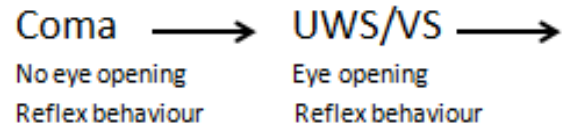
### Coma

No eye opening

Reflex behaviour

# Clinical entities

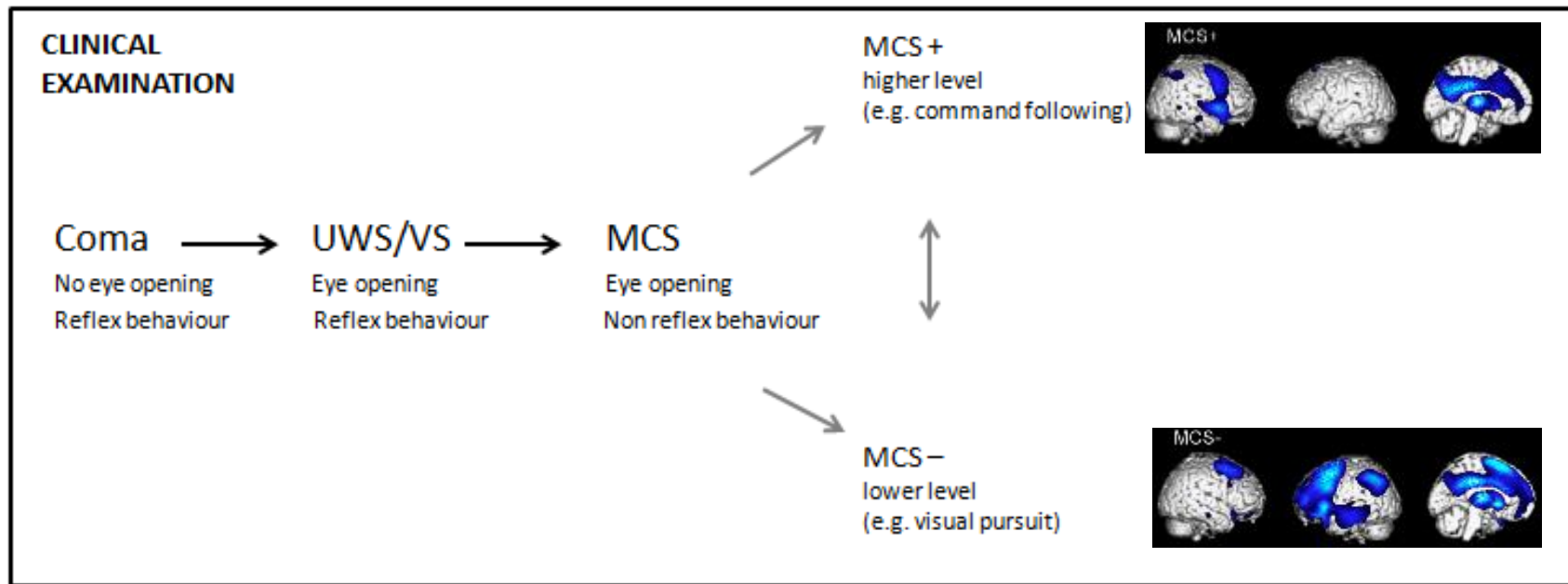
## CLINICAL EXAMINATION



UWS=unresponsive wakefulness syndrome

VS=vegetative state

# Clinical entities

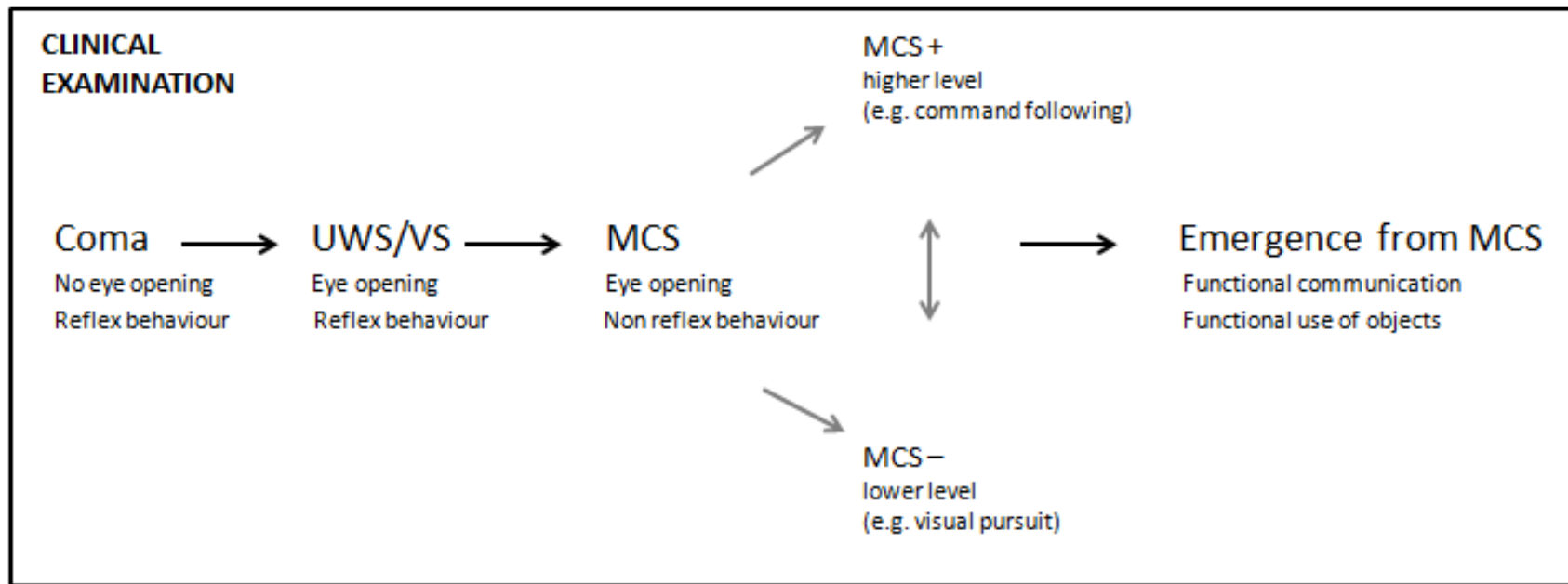


UWS=unresponsive wakefulness syndrome

VS=vegetative state

MCS=minimally conscious state

# Clinical entities

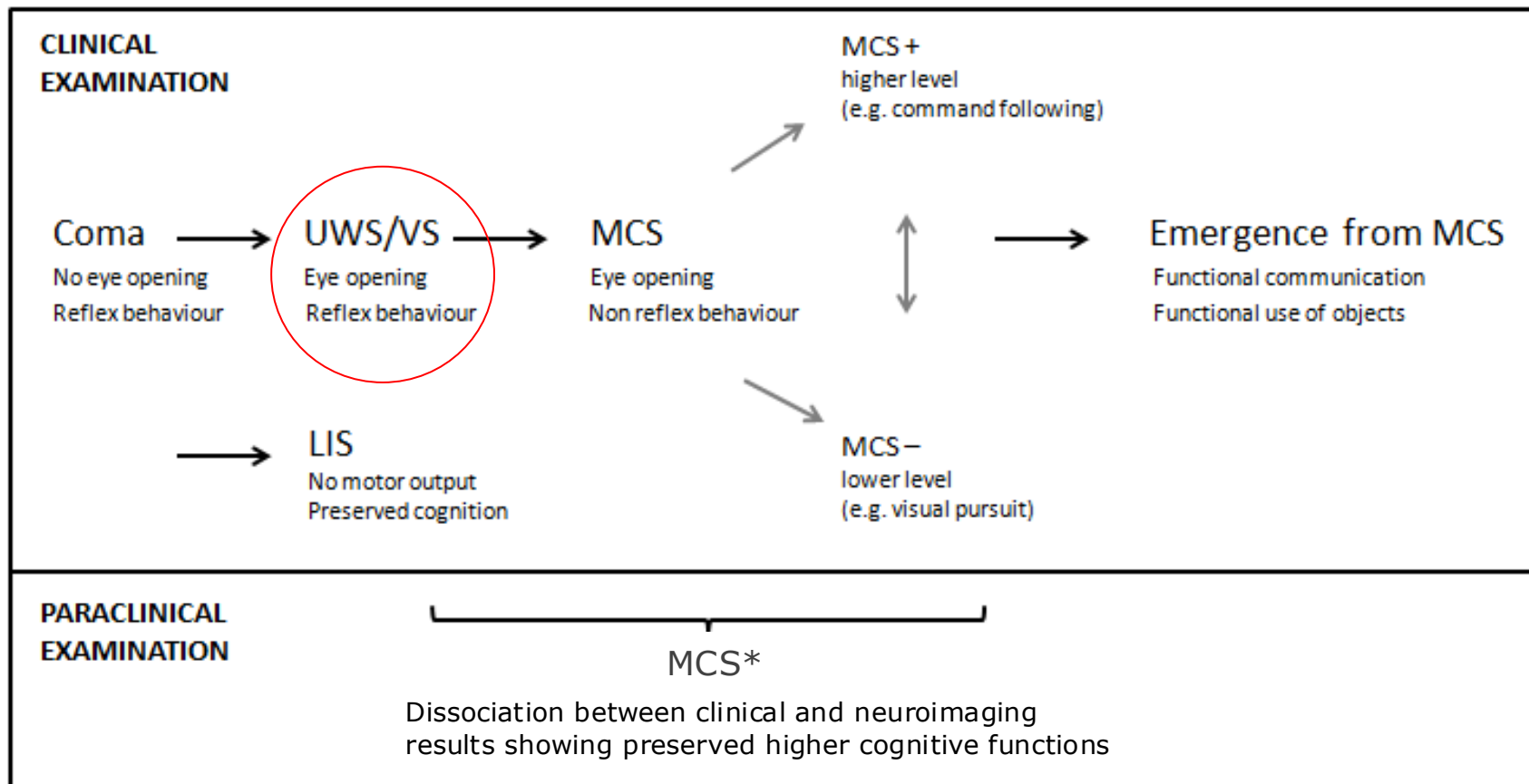


UWS=unresponsive wakefulness syndrome

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# Clinical entities



MCS\* = non-behavioral minimally conscious state

# Difference between pain & nociception



## Pain

“Unpleasant sensory and emotional experience associated with real or potential tissue damage”

*“The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.”*

# Difference between pain & nociception



## **Pain**

"Unpleasant sensory and emotional experience associated with real or potential tissue damage"

*"The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment."*

## **Nociception**

*"The neural process of encoding noxious stimuli"*  
*(transduced and encoded by nociceptors).*

*"Pain sensation is not necessarily implied".*

# Difference between pain & nociception



## Pain

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## Nociception

*"The neural process of encoding noxious stimuli" (transduced and encoded by nociceptors).*

*"Pain sensation is not necessarily implied".*

➔ « *Pain is always subjective* »

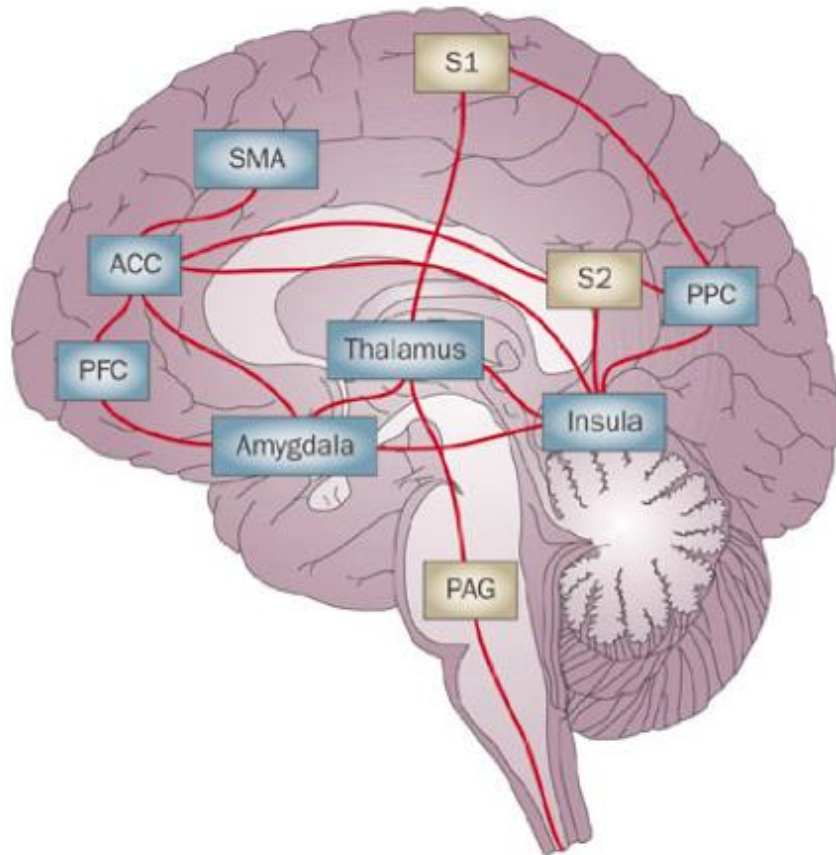
## **No communication**

- cannot assess pain & well-being
- no feedback on treatment

## **Associated disorders**

- spasticity
  - bedsores
  - neuropathic pain
- 
- importance to evaluate pain in DOC

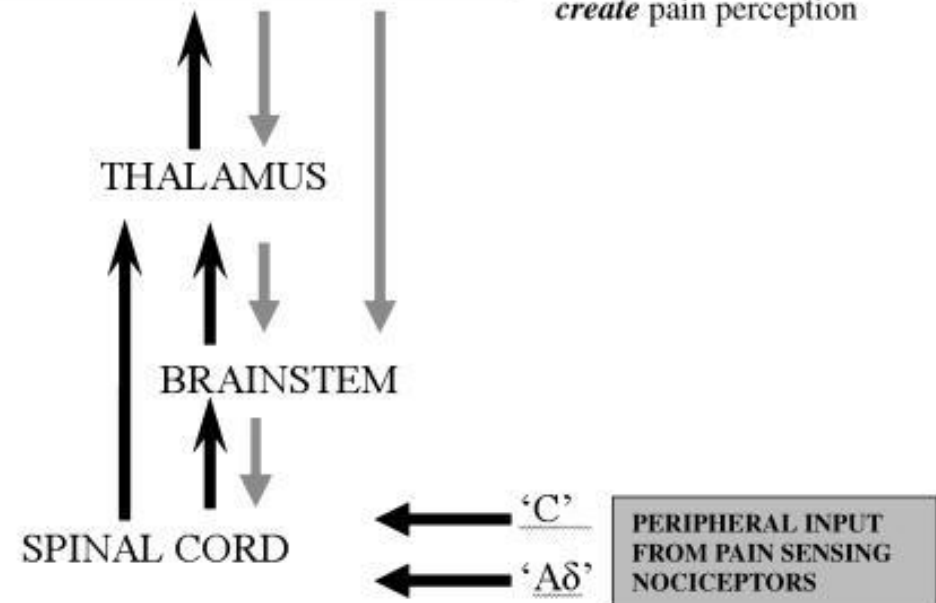
# Pain network



- INSULA  
- SOMATOSENSORY CORTICES  
- ANTERIOR, MIDDLE & POSTERIOR CINGULATE  
- BASAL GANGLIA  
- POSTERIOR PARIETAL CORTEX  
- AMYGDALA  
- HYPOTHALAMUS  
- PREFRONTAL CORTEX

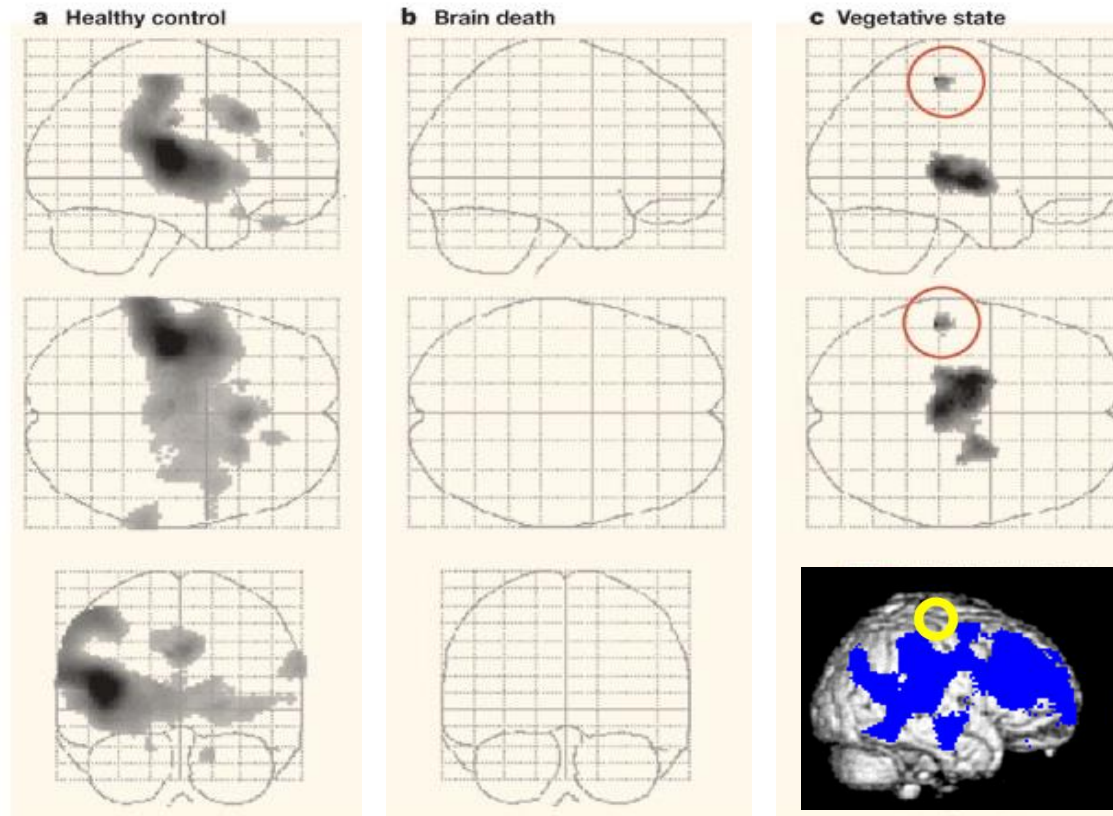
- Conscious perception of event being painful created by central **processsing** of incoming signals

- Brain and spinal cord can **modulate**, but also **create** pain perception

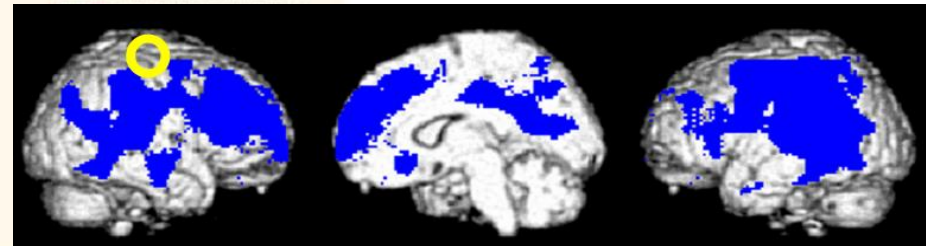


# Pain in unresponsive wakefulness syndrome

## Noxious electrical stimulation

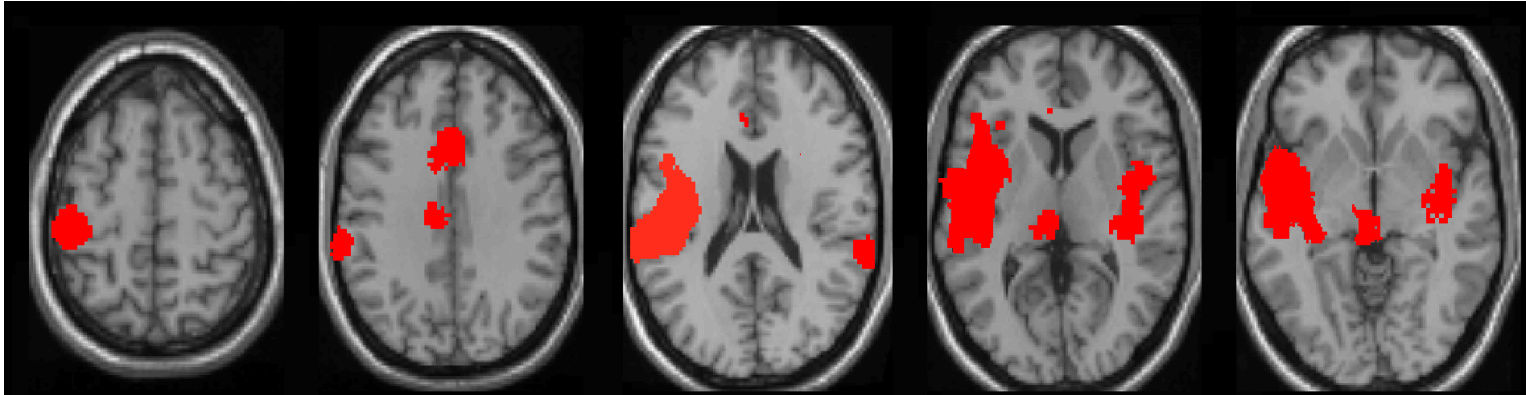


Low level  
disconnected  
cortical activation

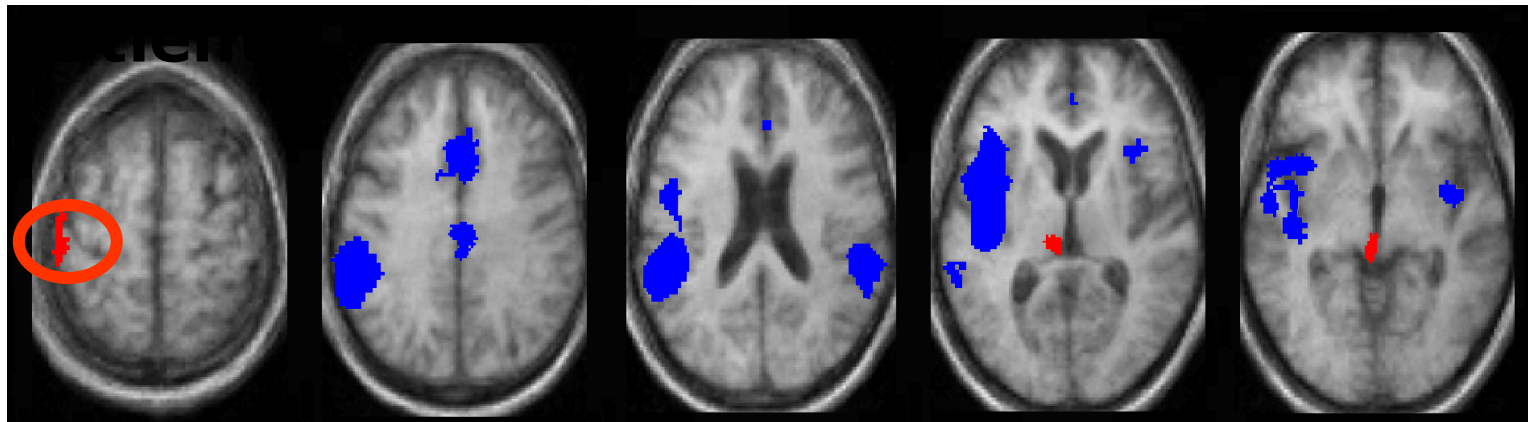


# Pain in unresponsive wakefulness syndrome

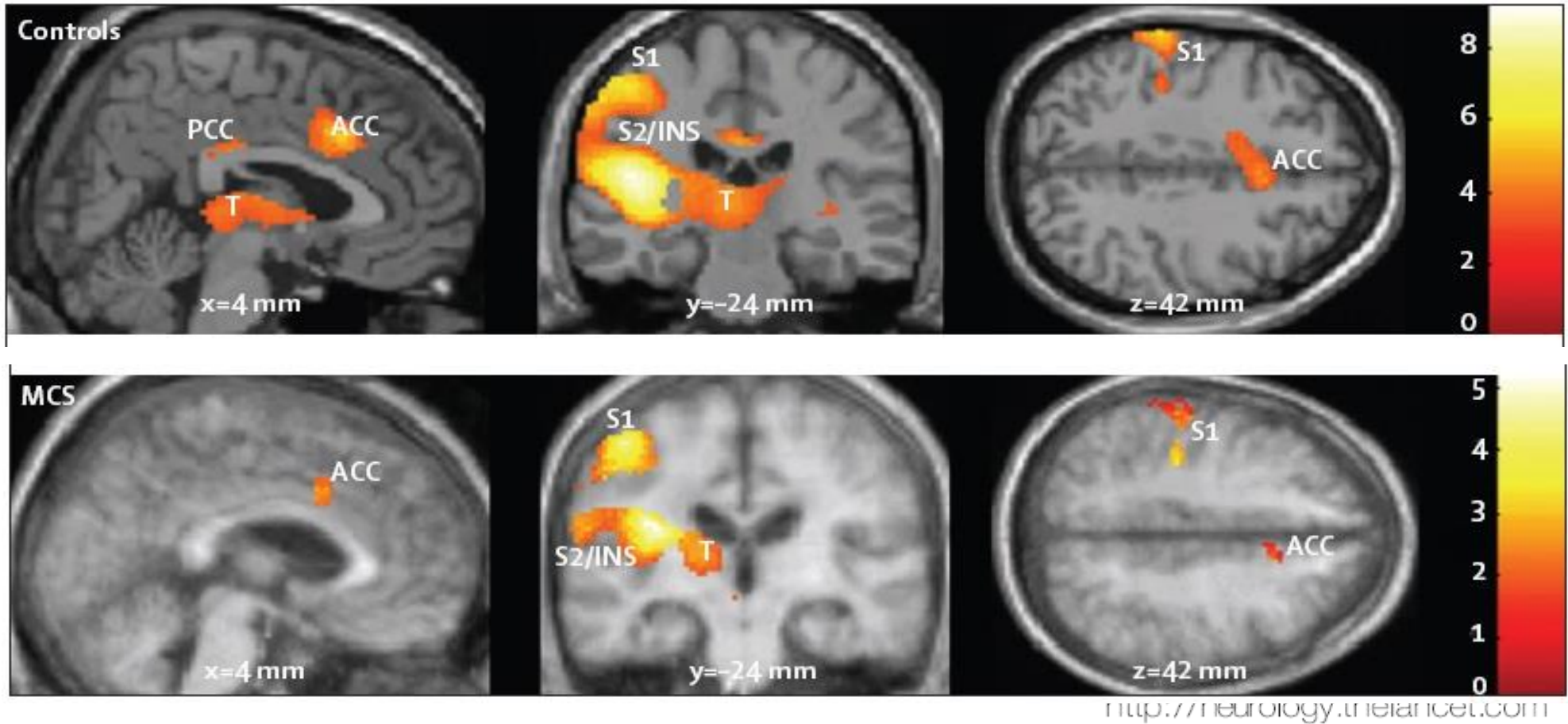
## Controls



## Unresponsive



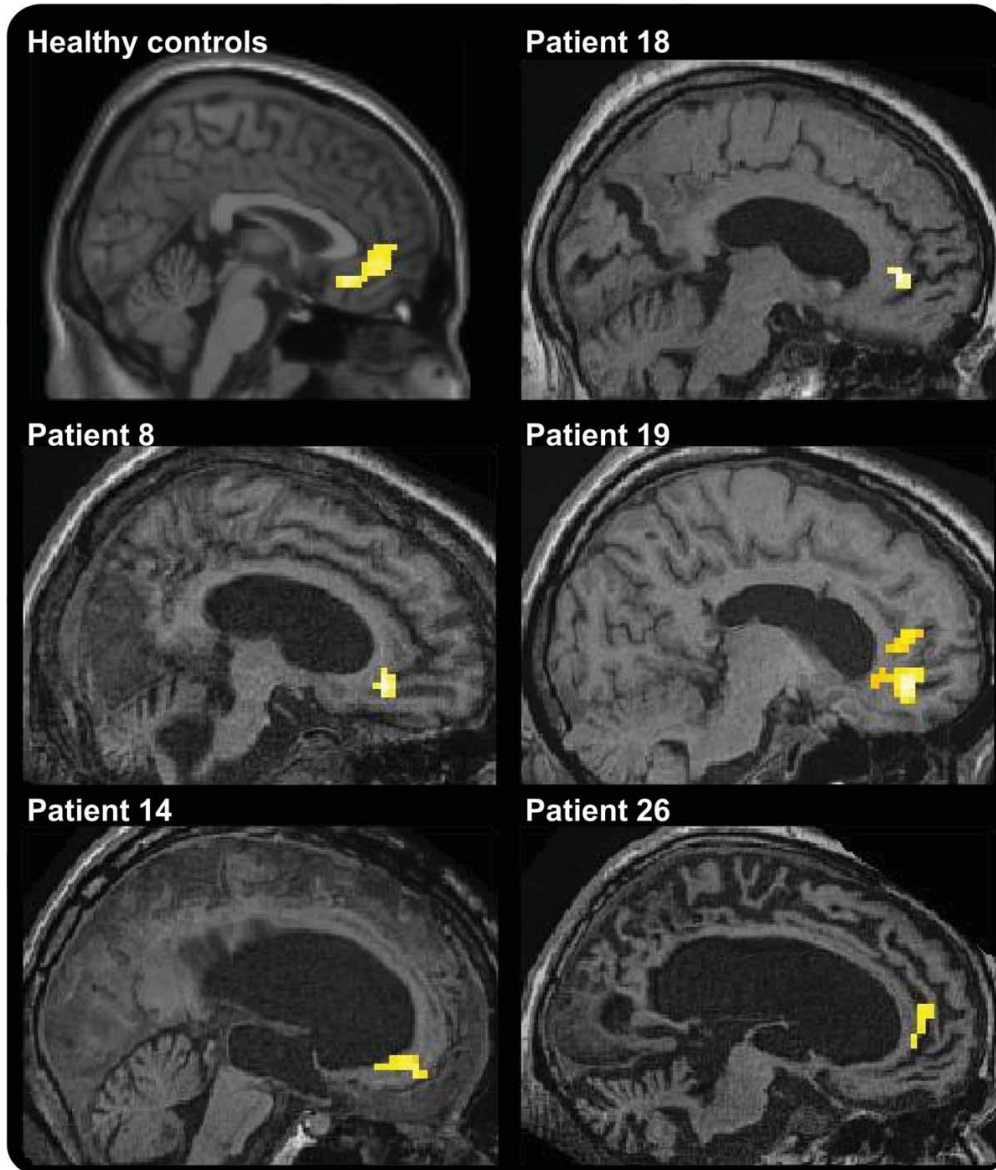
# Pain in minimally conscious state



# BUT...

| Subject number | Sex | Age | ACC | AI | S2 | S1 | Thalamus | PI | Cerebellum |
|----------------|-----|-----|-----|----|----|----|----------|----|------------|
| 1              | F   | 52  | —   | —  | +  | +  | —        | —  | +          |
| 2              | F   | 29  | —   | +  | +  | +  | +        | +  | +          |
| 3              | M   | 46  | —   | —  | +  | —  | +        | —  | +          |
| 4              | M   | 29  | +   | +  | +  | +  | +        | +  | +          |
| 5              | F   | 31  | +   | +  | +  | +  | +        | +  | +          |
| 6              | F   | 35  | +   | +  | +  | —  | —        | +  | —          |
| 7              | M   | 32  | +   | +  | +  | +  | +        | +  | —          |
| 8              | M   | 62  | —   | —  | +  | —  | —        | +  | —          |
| 9              | F   | 47  | —   | —  | —  | +  | —        | +  | —          |
| 10             | M   | 52  | —   | +  | +  | +  | —        | +  | —          |
| 11             | F   | 58  | —   | —  | +  | +  | —        | —  | —          |
| 12             | M   | 48  | +   | +  | +  | +  | —        | —  | —          |
| 13             | F   | 28  | +   | +  | +  | +  | +        | +  | +          |
| 14             | M   | 33  | —   | +  | +  | +  | —        | +  | +          |
| 15             | M   | 54  | —   | —  | +  | —  | —        | —  | —          |

# BUT...



fMRI response to pain-related sounds  $>$   $<$  neutral

About 50% of clinically UWS patients exhibited reliable brain responses (ACC) to pain-related sounds

# Clinical assessment

## Coma Recovery Scale Revised (CRS-R)

| JFK COMA RECOVERY SCALE - REVISED ©2004   |       |  |  |  |  |  |  |  |  |
|-------------------------------------------|-------|--|--|--|--|--|--|--|--|
| Record Form                               |       |  |  |  |  |  |  |  |  |
| Patient:                                  | Date: |  |  |  |  |  |  |  |  |
| <b>AUDITORY FUNCTION SCALE</b>            |       |  |  |  |  |  |  |  |  |
| 4 - Consistent Movement to Command *      |       |  |  |  |  |  |  |  |  |
| 3 - Reproducible Movement to Command *    |       |  |  |  |  |  |  |  |  |
| 2 - Localization to Sound                 |       |  |  |  |  |  |  |  |  |
| 1 - Auditory Startle                      |       |  |  |  |  |  |  |  |  |
| 0 - None                                  |       |  |  |  |  |  |  |  |  |
| <b>VISUAL FUNCTION SCALE</b>              |       |  |  |  |  |  |  |  |  |
| 5 - Object Recognition *                  |       |  |  |  |  |  |  |  |  |
| 4 - Object Localization: Reaching *       |       |  |  |  |  |  |  |  |  |
| 3 - Visual Pursuit *                      |       |  |  |  |  |  |  |  |  |
| 2 - Fixation *                            |       |  |  |  |  |  |  |  |  |
| 1 - Visual Startle                        |       |  |  |  |  |  |  |  |  |
| 0 - None                                  |       |  |  |  |  |  |  |  |  |
| <b>MOTOR FUNCTION SCALE</b>               |       |  |  |  |  |  |  |  |  |
| 6 - Functional Object Use †               |       |  |  |  |  |  |  |  |  |
| 5 - Automatic Motor Response *            |       |  |  |  |  |  |  |  |  |
| 4 - Object Manipulation *                 |       |  |  |  |  |  |  |  |  |
| 3 - Localization to Noxious Stimulation * |       |  |  |  |  |  |  |  |  |
| 2 - Flexion Withdrawal                    |       |  |  |  |  |  |  |  |  |
| 1 - Abnormal Posturing                    |       |  |  |  |  |  |  |  |  |
| 0 - None/Flaccid                          |       |  |  |  |  |  |  |  |  |

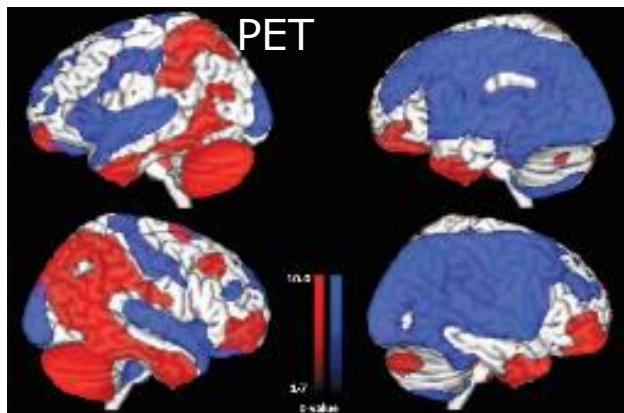
Clinical diagnosis  
30-40% of misdiagnosis

|                                       |  |  |  |  |
|---------------------------------------|--|--|--|--|
| <b>OROMOTOR/VERBAL FUNCTION SCALE</b> |  |  |  |  |
| 3 - Intelligible Verbalization *      |  |  |  |  |
| 2 - Vocalization/Oral Movement        |  |  |  |  |
| 1 - Oral Reflexive Movement           |  |  |  |  |
| 0 - None                              |  |  |  |  |
| <b>COMMUNICATION SCALE</b>            |  |  |  |  |
| 2 - Functional: Accurate †            |  |  |  |  |
| 1 - Non-Functional: Intentional *     |  |  |  |  |
| 0 - None                              |  |  |  |  |
| <b>AROUSAL SCALE</b>                  |  |  |  |  |
| 3 - Attention                         |  |  |  |  |
| 2 - Eye Opening w/o Stimulation       |  |  |  |  |
| 1 - Eye Opening with Stimulation      |  |  |  |  |
| 0 - Unarousable                       |  |  |  |  |
| <b>TOTAL SCORE</b>                    |  |  |  |  |

# FDG-PET as a diagnostic tool

## 128 patients

81 MCS, 41 UWS, 4 LIS  
110 chronic, 50 TBI



PET, MRI, EEG  
20-35% MCS\*

|                                     | Coma Recovery Scale-Revised results |          |            |
|-------------------------------------|-------------------------------------|----------|------------|
|                                     | UWS                                 | MCS      | Total      |
| <b>Clinical consensus diagnosis</b> |                                     |          |            |
| VS/UWS                              | 33 (37%)                            | 18 (20%) | 51 (57%)   |
| MCS                                 | 2 (2%)                              | 36 (40%) | 38 (43%)   |
| Total                               | 35 (39%)                            | 54 (61%) | 89 (100%)  |
| <b><sup>18</sup>F-FDG PET</b>       |                                     |          |            |
| VS/UWS                              | 24 (21%)                            | 5 (4%)   | 29 (26%)   |
| MCS                                 | 12 (11%)                            | 71 (63%) | 83 (74%)   |
| Total                               | 36 (32%)                            | 76 (68%) | 112 (100%) |
| <b>Mental imagery fMRI</b>          |                                     |          |            |
| VS/UWS                              | 25 (36%)                            | 23 (33%) | 48 (69%)   |
| MCS                                 | 3 (4%)                              | 19 (27%) | 22 (31%)   |
| Total                               | 28 (40%)                            | 42 (60%) | 70 (100%)  |

UWS=unresponsive wakefulness syndrome. MCS=minimally conscious state.

**Table 2: Diagnostic results by modality**

35% clinical misdiagnosis

33% CRS-R misdiagnosis

75% recovered csc

THE  
LANCET

# Conclusions

- Sensitive clinical scales are warranted (CRS-R)
- 30% of clinically unresponsive patients are (minimally) conscious → need of neuroimaging exams to complement behavioural tools
- Patients in MCS perceive pain
- About 30-50% of UWS (clinically unresponsive) patients present neural activity to pain (or emotional) stimuli suggesting pain (and emotional) perception



# Thank you!



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Human Brain Project

