Recent findings from fMRI and implications for the investigation of people with Prolonged Disorders of Consciousness

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Cambridge University Hospitals NHS Foundation Trust

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Welcome Trust; NIHR; Evelyn trust; JSM

Referring centres;

NHND Putney
The Jacob Centre
Leicester Brain Injury Unit
CERU; Leamington

- Cambridge Group ;
- Professor Lenn Pickard
- Srivas Chenu
- Guy Williams
- Paola Finoa
- Evelyn Kamau
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- Professor David Menon (NCCU)
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- Weill/Cornell Medical College, New York
- Prof. Nicholas Schiff and team
- Spaulding Rehab Unit, Harvard, Boston
- Prof. Jo Giacino and team
- Brain and Mind Institute, University of Western Ontario, Canada
- Prof. Adrian M. Owen/ Damian Cruse

Holycross Meeting 2016

fMRI in PDOC *(>300 papers / year)*

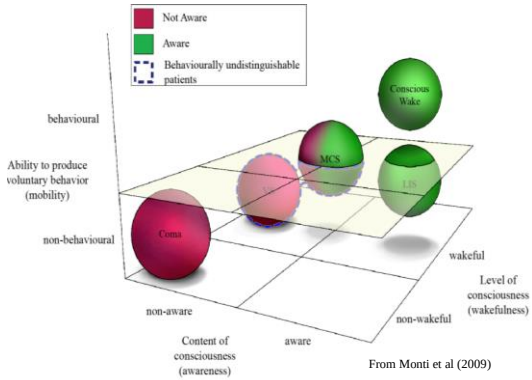
Responses to complex tasks
Sensory stimulation
Effects of medication
Structural studies - DTI
Resting state studies (unstimulated)
Compared with EEG and PET
command following
resting state
Challenges and future directions

Vegetative State

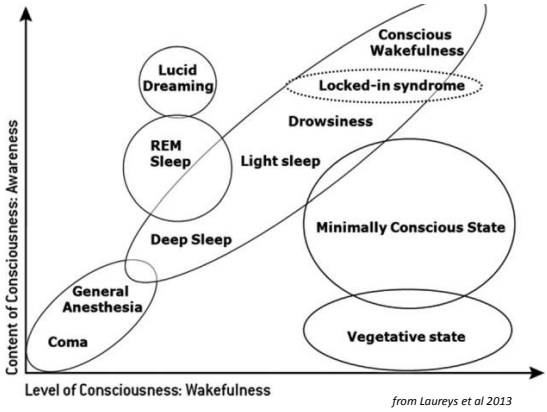
- May be eye opening
- Sometimes have sleep-wake cycles
- No purposeful behaviour
- No communication
- May have tears
- "Continuing VS" after 4 weeks
- "Permanent VS "
  - after 6 months following hypoxia
  - After 12 months following Traumatic Brain Injury (TBI)

Minimally Conscious State

- Tracks with eyes
- Occasional facial expressions
- Occasional sounds / words –
- May display simple emotional responses
- Reproducible but not consistent command following at bedside
- "Continuing MCS" after 4 weeks
- "Permanent MCS" after 5 years

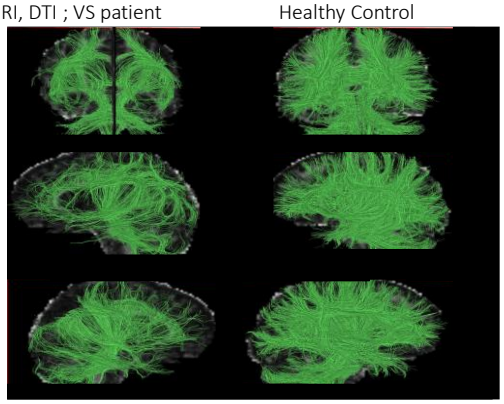


From Monti et al (2009)

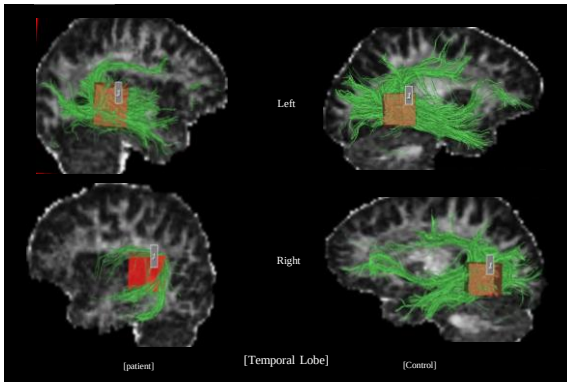


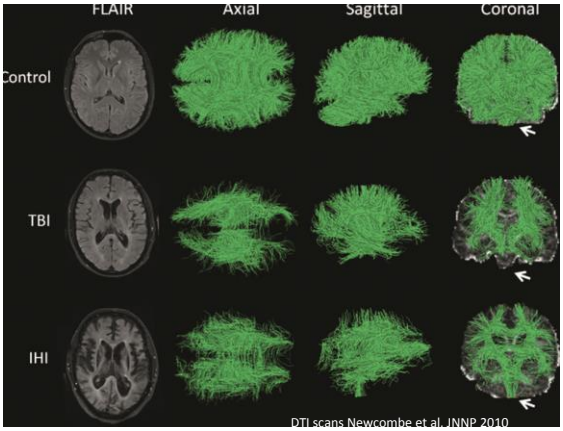
from Laureys et al 2013

MRI, DTI ; VS patient Healthy Control

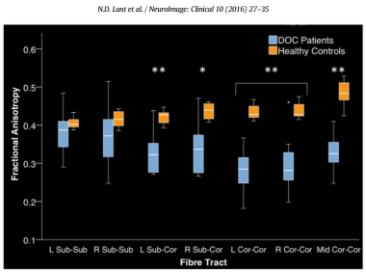


MRI Scan: White matter tractography



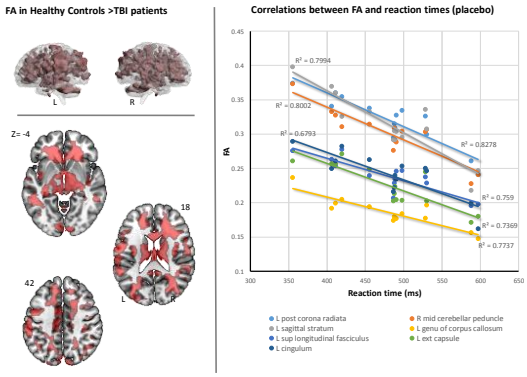


Quantification of DTI;



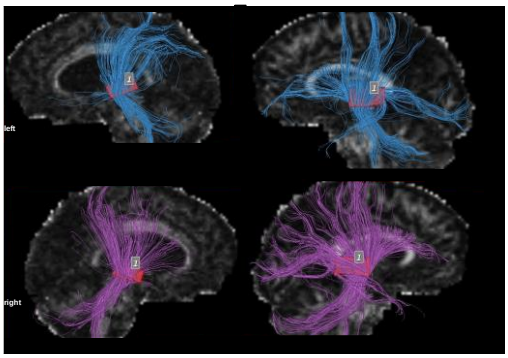
?may be good way of investigating how any drug with long term effects works

Motor Control in TBI; (finger tap in non PDOC)



Dorer, Manktelow, Allanson, Sahakian, Pickard, Bateman, Menon, Stamatakis, under review

Loss of thalamo-cortical structural connectivity on MRI Dti
in patient in Vegetative state (L) compared to Control (R)



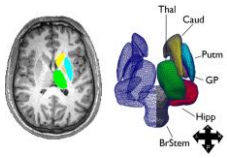
VS - Pathology

- PET ; reduced thalamic glucose metabolism
  - *D Lopez, Spanish/Cambridge study 2010,*
- Glasgow PMs

Jennett of 1500 TBIs	VS/n =55	Sev Dis/n=30
Thalamic Abn	80%	37%
Diff Axonal Inj	80%	50%
Hydrocephalus	77%	73%

Structural MR scans; Thalamic and Extrathalamic Mechanisms of Consciousness after Severe Brain Injury

Lutkenhoff, Pickard, Laureys, Owen, Monti et al
ANN NEUROL 2015;78:68–76



121 after 28 with artefacts removed
CRS-R diagnosis (inc domains)
61 from Cambridge
Compared with 96 controls

Most thalamic atrophy after non traumatic injury

Atrophy in thalamus -> less awareness
Atrophy in basal ganglia -> less arousal

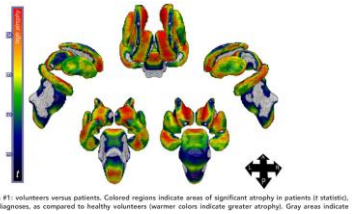
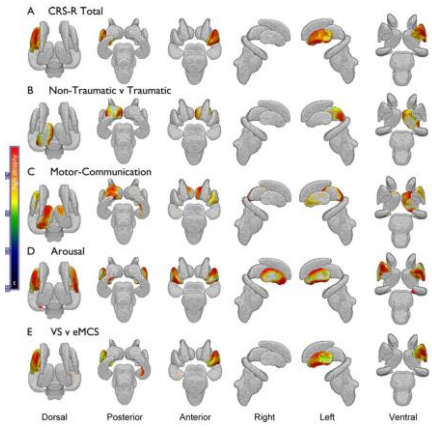


FIGURE 2: Analysis #1: volunteers versus patients. Colored regions indicate areas of significant atrophy in patients (t statistic), collapsing across diagnoses, as compared to healthy volunteers (warmer colors indicate greater atrophy). Gray areas indicate



Structural MRI

one image
high resolution
(1 mm^3)

Functional MRI

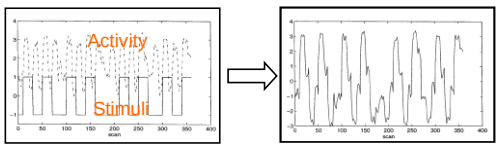
many images
e.g. every 2 seconds
low resolution
~3 mm^3

fMRI uses BOLD ; Blood oxygen level dependent responses

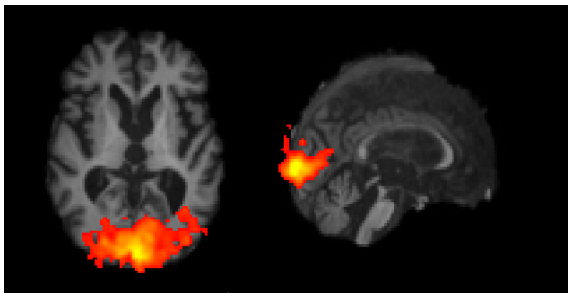
Blood oxygen level changes; spontaneous fluctuations and response to stimuli
Assumes normal behaviour of brain vasculature
Assumes rate of use of oxygen is related to neuronal activity
Comparisons with normal brains (images normalised to analyse)

fMRI, connectivity

Friston KJ, Buechel C, Fink GR, et al. *Neuroimage* 1997;6:218 –229

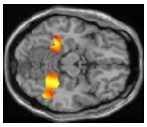


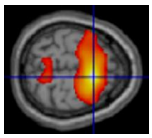
fMRI of PX in VS being shown chequer board;
passive stimulus
Visual cortex response

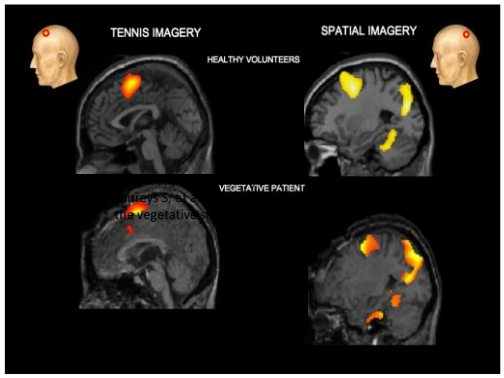


fMRI BOLD response (Owen et al science 2006)

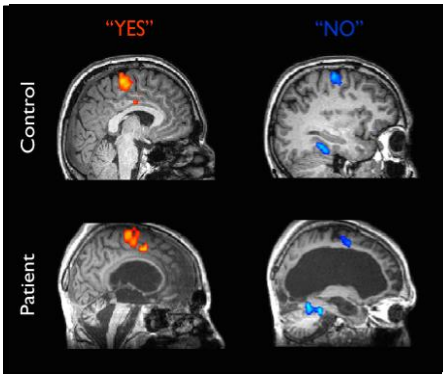
Volition task: "?A measure of awareness"







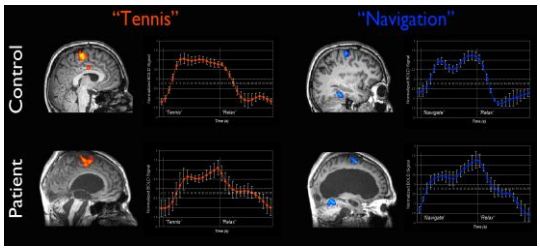
Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, et al. (2006)
Detecting awareness in the vegetative state. Science 313: 1402–1402



fMRI "imagining moving around house or playing tennis" study
Monti, Owen et al NEJM 2010

- 54 patients in VS or MCS
- 5/54 demonstrated wilful modulation of brain activity to spoken request
- 3/5 some response to spoken request at bed side
- 2/5 no voluntary behaviours observed at bed side
- Neuroanatomically specific
- Blood oxygen level dependent (BOLD) responses

- 1/5 could use this imagination to answer YES / NO
- But to date no bedside yes / no established



Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, et al. (2006) Detecting awareness in the vegetative state. Science 313: 1402–1402

Confounders in running and interpreting fMRI

- Fluctuations in arousal
- Spontaneous Motion/ Reflex (especially in people with anoxic injury)
- Fatigue, ? Diff response rates to controls
- Underlying sensory or motor disturbances
  - Impaired vision or hearing
- Language disorder as part of injury
- Medication side effects - anticonvulsants
- Posture;"Syndrome of the Trephine"

- Abnormal brain anatomy – heterogeneous -difficult to normalise

- Not interpretable in real time (yet)
- Need to be wary of questions asked (use ones with predictable answer)

(details of challenges and pitfalls and suggested way of systematic recording; Bodien and Giacino, The Open Neuroimaging Journal, 2016,10)

Cognitive impairments after TBI; to consider in DOC patients

- Fatigue
- Slowing of processing speed (axonal shearing)
- Reduced attention and concentration
- Impaired language comprehension
- Reduced initiation
- Reduced insight
- Impaired memory
- Reduced visual perception

- Requirements for completion of tennis task in MRI
  - MRI compatability
  - Staying still and awake
  - Concentrating
  - Understanding instruction
  - Remembering instruction
  - Ability to change "thinking"
  - Not necessary to have played tennis

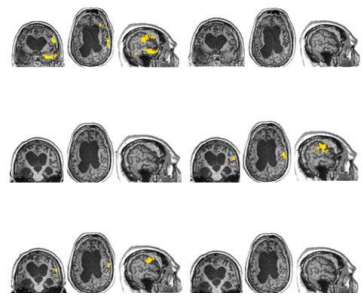
Patient in VS for 16 years. Communicating using attention to yes or no

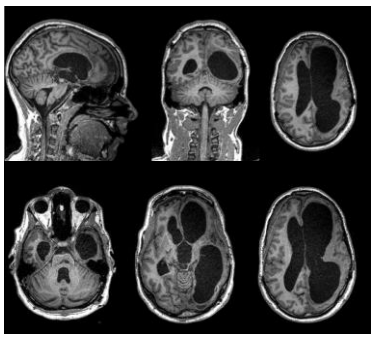
Naci, Owen et al, 2013

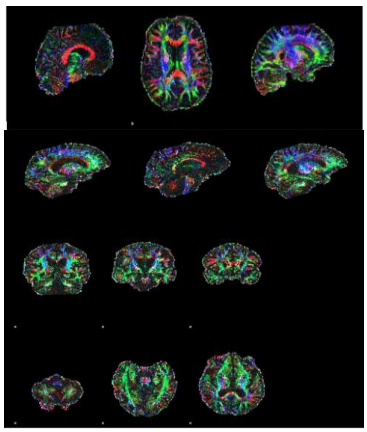
?Name is

Place?
Supermarket

? hospital





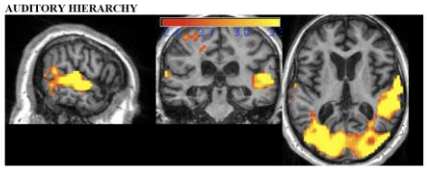


DTI

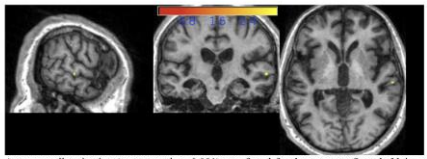
Healthy volunteer

Patient with CRS-9

AUDITORY HIERARCHY

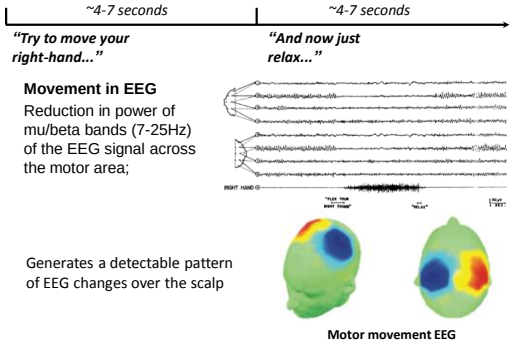


A strong significant activation was found in the left primary auditory cortex for the contrast Sounds>Silence together with activations in areas not usually connected with auditory tasks.

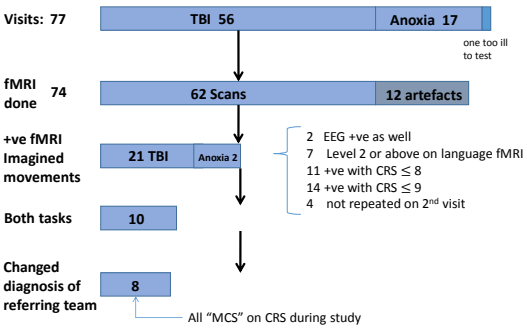


A very small activation (uncorrected, p=0.001) was found for the contrasts Speech>Noise and no significant activation was found for the Ambiguous>Unambiguous contrast.

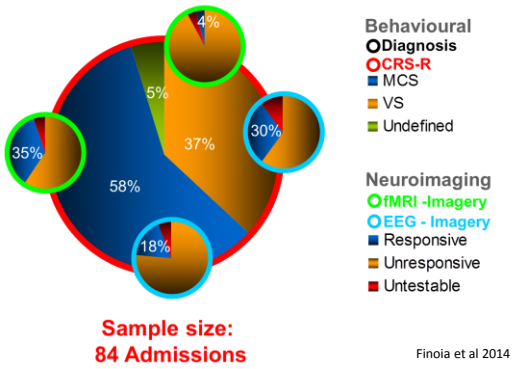
Detecting Attempted Movement with EEG



CRIC group; Positive fMRI Findings 2009-2014



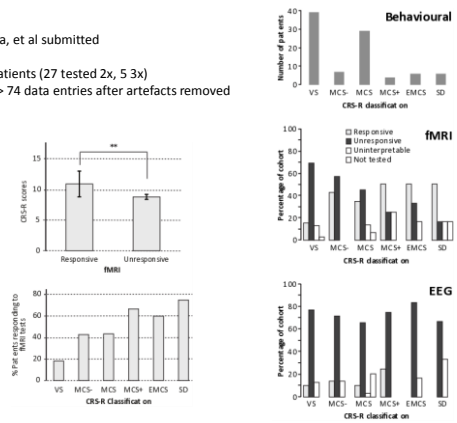
CRS-R



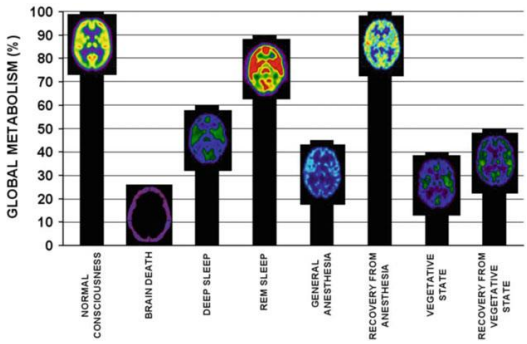
Finoia et al 2014

Finoia, et al submitted

59 patients (27 tested 2x, 5 3x)
91 –> 74 data entries after artefacts removed

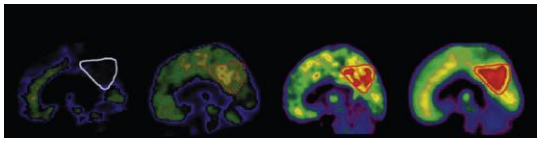


FDG-PET (levels of brain metabolism in PDOC)



Laureys et al. Lancet 2000 355: 1825-1826

PET scan images to show reduced metabolism at rest in UWS/VS MCS LIS Healthy Control



normally the highest activity is in the medial posterior cortex ;includes the precuneus and the adjacent posterior cingulate cortex (in red) ; Part of Default Mode Network

S. Laureys, A. M. Owen, and N. D. Schiff, "Brain function in coma, vegetative state, and related disorders," *The Lancet Neurology*, vol. 3, no. 9, pp. 537–546, 2004.

PET and fMRI in diagnosis of PDOC

Lancet 2014, Stender, Gosseries, Laureys et al

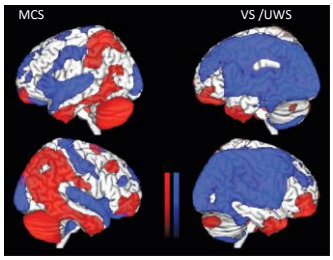


Figure 1: Statistical parametric mapping-analysis of fluorodeoxyglucose PET scans
(A) Minimally conscious state. (B) Unresponsive wakefulness syndrome. Areas where cerebral glucose metabolism is decreased and preserved in individual patients in a minimally conscious state and or vegetative state (unresponsive wakefulness syndrome), compared with 39 healthy patients. Blue=areas with significantly lowered metabolism. Red=areas with preserved metabolism (p<0·05).

Lancet 2014 ctd;
Compared PET and fMRI "tennis" results with CRS-R

	Coma Recovery Scale-Revised results		
	UWS	MCS	Total
Clinical consensus diagnosis			
VS/UWS	33 (37%)	18 (20%)	51 (57%)
MCS	2 (2%)	36 (40%)	38 (43%)
Total	35 (39%)	54 (61%)	89 (100%)
^{18}F-FDG PET			
VS/UWS	24 (21%)	5 (4%)	29 (26%)
MCS	12 (11%)	71 (63%)	83 (74%)
Total	36 (32%)	76 (68%)	112 (100%)
Mental imagery fMRI			
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

Comparison of FDG-PET and fMRI ctd
PET most sensitive

	Clinical consensus diagnosis	^{18}F-FDG PET	Mental imagery fMRI
Completed examinations (of 122)	122 (100%)	112 (91%)	72 (59%)
Number of interpretable examinations (of all completed)	89 (73%)	112 (100%)	70 (97%)
Overall congruence with Coma Recovery Scale-Revised (95% CI)	78% (68–85%)	85% (77–90%)	63% (51–73%)
Congruence with Coma Recovery Scale-Revised diagnoses of UWS (95% CI)	95% (82–99%)	67% (49–81%)	89% (71–98%)
Sensitivity to MCS (95% CI)	67% (52–79%)	93% (85–98%)	45% (30–61%)
Overall outcome prediction (95% CI)	..	74% (64–81%)	56% (43–67%)
Positive outcome prediction (95% CI)	..	67% (55–77%)	63% (41–81%)
Negative outcome prediction (95% CI)	..	92% (76–98%)	52% (38–66%)

FDG PET=fluorodeoxyglucose PET. UWS=unresponsive wakefulness syndrome. MCS=minimally conscious state. Outcome=conscious/unconscious, according to GOS-E at 12 months. Positive outcome=GOSE >2, and negative outcome=GOS-E ≤2.

Table 3: Diagnostic characteristics by modality

PET and active task based fMRI; summary

- 48 TBI (Interesting to note that 4 excluded at start as psychologists could not reach consensus)
- 33 clinical diagnosis sent with was not always a conventional one eg post comatose state
- Unable to do fMRI scan in 41% of group due to spontaneous movements

- **CRS-R and PET agreed in 95 of 112 scanned (85% agreement on diagnosis)**

- fMRI demonstrated 3 with activity suggestive of MCS when CRS-R suggestive of VS

- **12 month outcomes**
- **36 / 65 who had fMRI**; outcomes predicted by fMRI findings;

- **75 /102 who had PET** scanning had outcomes predicted by initial diagnosis;

- 13 of 41 VS patients had activity compatible with MCS in one or other scanning
- 9 of these 13 were MCS or better at 12/12; 3 died, 1 remained in VS
- None of the other 41 diagnosed as VS on imaging and CRS-R had emerged at one year

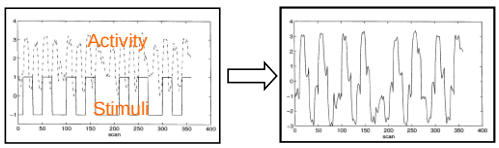
- **51 of 76** diagnosed as in MCS using PET recovered to conscious (nb 24% had died)
- Less agreement in MCS group than VS group

fMRI uses BOLD ; Blood oxygen level dependent responses

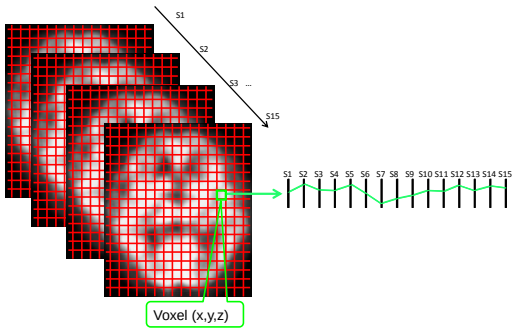
Blood oxygen level changes; spontaneous fluctuations and response to sti,uli
Assumes normal behaviour of brain vasculature
Assumes rate of use of oxygen is related to neuronal activity
Comparisons with normal brains (images normalised to analyse)

fMRI, connectivity

Friston KJ, Buechel C, Fink GR, et al. *Neuroimage* 1997;6:218 –229



Voxel-level statistical analysis - Cross-sectional study



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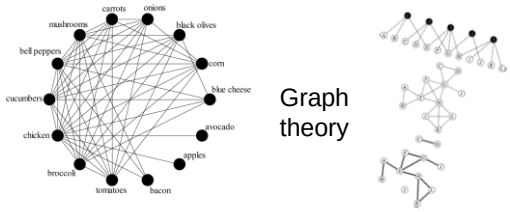
fMRI, functional connectivity

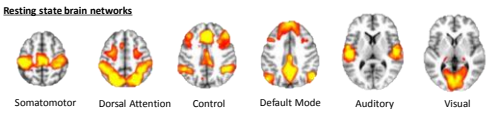
•How do regions within the network influence each other in time?

Friston KJ, Buechel C, Fink GR, et al. Neuroimage ,1997



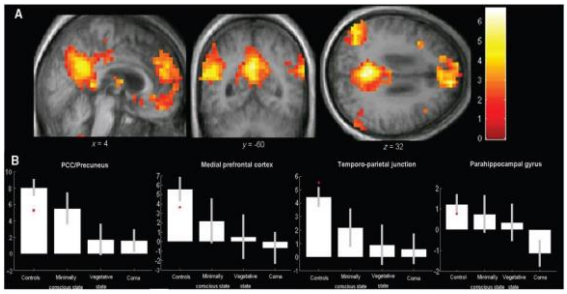
Newman ME. Phys Rev E Stat Nonlin Soft Matter Phys. 2003

Brain networks at rest " resting state networks"



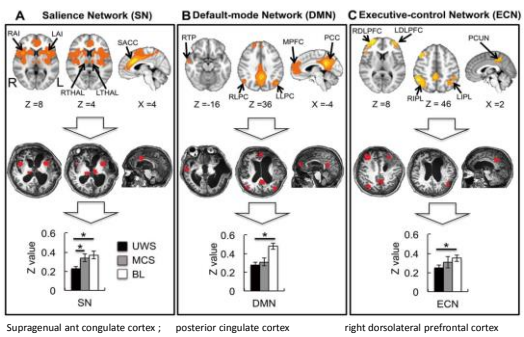
Beckmann, DeLuca, Devlin, Smith. Philosophical Transactions of the Royal Society B: Biological Sciences, 2005

Spatially separated "Networks" in resting state MRI
(10 min scanning; no need for language / vision)



Boly, Laureys et al

Functional Connectivity in 3 MRI resting state networks ; differences in VS and MCS



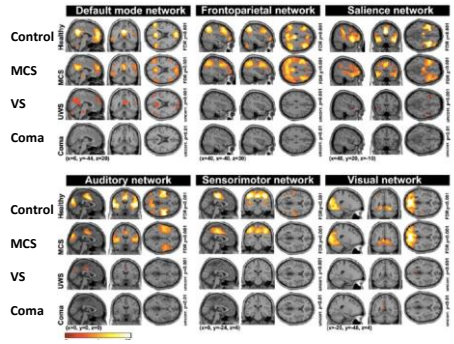
Supragenual ant congulate cortex ; "seed regions" in yellow

posterior cingulate cortex

right dorsolateral prefrontal cortex

Qin, Northoff et al Annals of Neurology 2015

Resting state connectivity networks in PDOC



Gosseries et al, The Open Neuroimaging Journal, 2016, *10*, (Suppl-1, M5) 52-68

Increased connectivity patterns from VS to MCS

Demertzi, Laureys et al Brain 2016

group level Resting state fMRI; 51 patients mixed diagnosis, patterns were predictive of CRS scores and tested in further 22

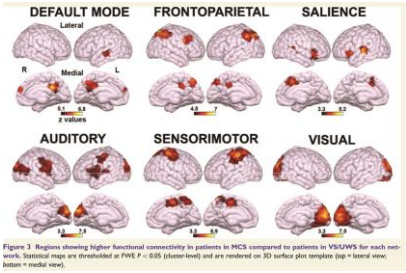


Figure 3 Regions showing higher functional connectivity in patients in MCS compared to patients in VS/UWS for each network. Statistical maps are thresholded at FWE $P < 0.05$ (cluster-level) and are rendered on 3D surface plot template (top = lateral view; bottom = medial view).

MRI functional connectivity ability to predict VS/MCS (diagnosed by CRS-R and FDG PET)

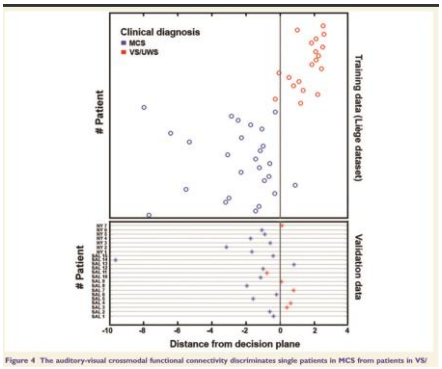
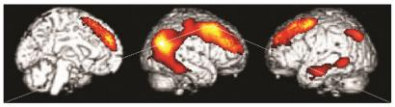


Figure 4 The auditory-visual crossmodal functional connectivity discriminates single patients in MCS from patients in VS/

Demertzi, Laureys et al Brain 2015;

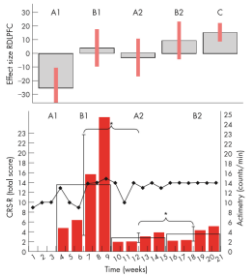


Amantadine 200mg od ABAB

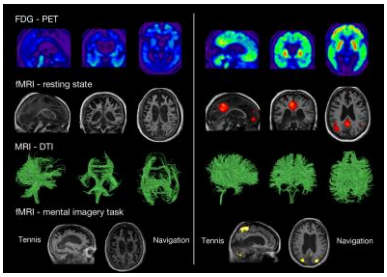
in MCS 2 years after Anoxic injury

Schnakers et al , JNNP, 2008

Increased nos of high CRS scores
Increased metabolic changes captured by PET scanning in fronto temporal parietal areas



Role of Neuroimaging techniques in establisghing diagnosis, prognosis and therapy in DOC
Gosseries et al, The Open Neuroimaging Journal, 2016 (10)



VS/ UWS typical pattern

VS/UWS on CRS-R but suggests non behavioural MCS

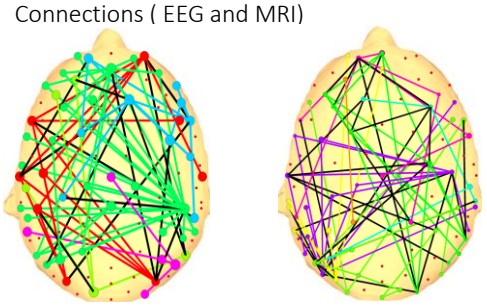
Challenges of fMRI

- normalising brains
- motion
- shunts / cranioplasty
- statistics used in analysis

Variation between research centres

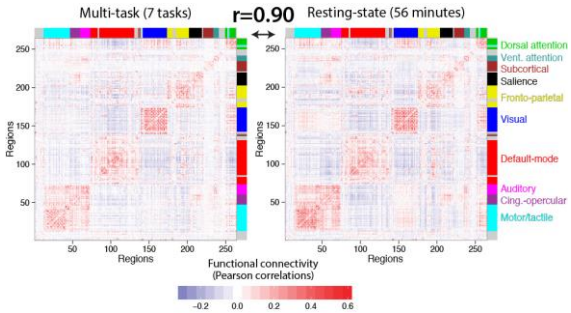
- Patients
  - Acute – chronic (eg Lieges include many <1/12, few >12/12
  - Family referrals
  - Payment for visits
- PET access (radioactivity, use 2 anaesthetists, arterial sampling)
- Sedation for MRI
- Length of stay / travel to scanners
- Proportions excluded for abnormal brain shapes / motion

Current Research: Connections (EEG and MRI)



Healthy Adult **Patient**

Comparisons with task networks



Cole, Bassett, Power, Braver and Petersen, Neuron, 2014

Future directions

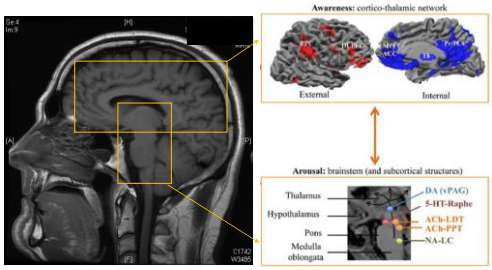
fMRI Resting state
EEG resting state

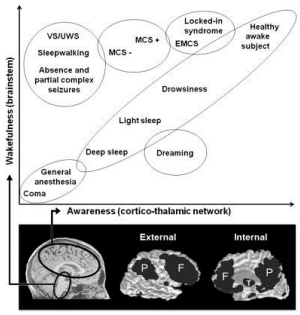
Pharmacology driven by anatomy/ loss of function

PUK network and registry
Towards standardised interventions

Illustration of awareness and arousal systems

(from Demertzi, Laureys et al, Current opinion in Neurobiol 2013)
for right hemisphere





C. Di Perri , Laureys et al. / Epilepsy& Behavior 30 (2014) 28 –32

Figure 3: Alpha-band brain networks in healthy volunteers and patients measured during rest

Healthy **Minimally Conscious** **Vegetative**

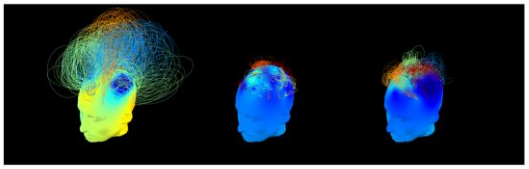
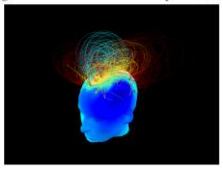
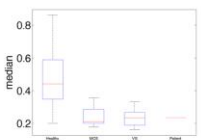


Figure 4: Brain network in this patient, compared with healthy volunteers and other patients





From CRIC group; admission report 2015

Thank you

Patients and Families
Referrers

Cambridge Research on Impaired Consciousness Group;

Srivas Chennu
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Evelyn Kamau
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Victoria Lupson
Stewart Fuller
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University of Cambridge

UNIVERSITY OF CAMBRIDGE

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Prof. John Pickard


Prof DK Menon

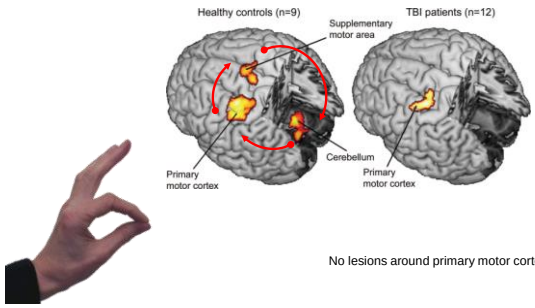

Prof. Adrian M. Owen


Dr. Tristan A. Bekinschtein

Motor task 2 (thumb-finger opposition)

- fMRI for patients on two separate occasions (randomised):
  - Methylphenidate (30mg)
  - Placebo
- White matter assessment

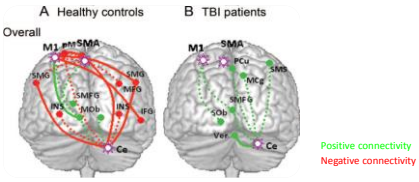
Motor task 1 (Index index-thumb opposition)



No lesions around primary motor cortex

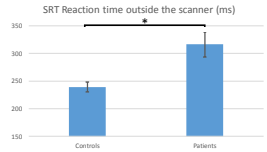
Kasahara M, Menon DK, Outtrim JG, Pickard JD, Sahakian BJ, Stamatakis EA. ***Neurology,*** 2010

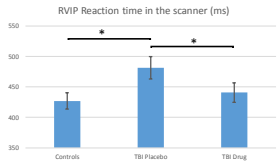
Motor Control in TBI



Kasahara M, Menon DK, Pickard JD, Sahakian BJ, Stamatakis EA. Neurology, 13;75(2):168-76. 2010

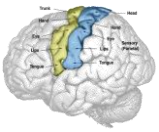
Motor Control in TBI

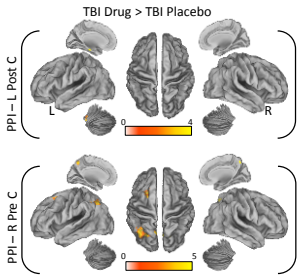




Dorer, Manktelow, Allanson, Sahakian, Pickard, Bateman, Menon, Stamatakis, in preparation

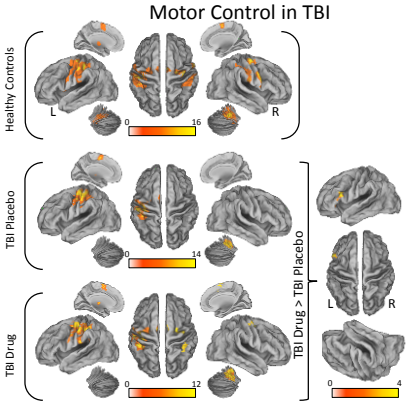
Motor Control in TBI





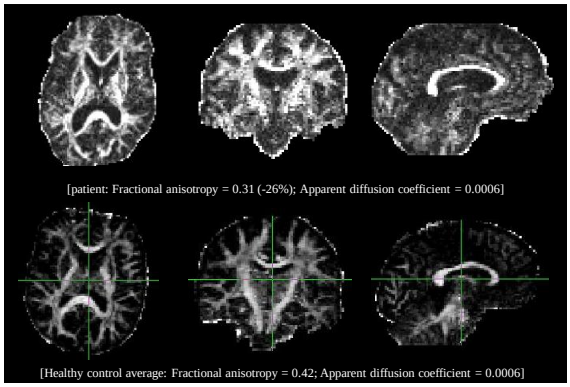
Dorer, Manktelow, Allanson, Sahakian, Pickard, Bateman, Menon, Stamatakis, in preparation

Motor Control in TBI

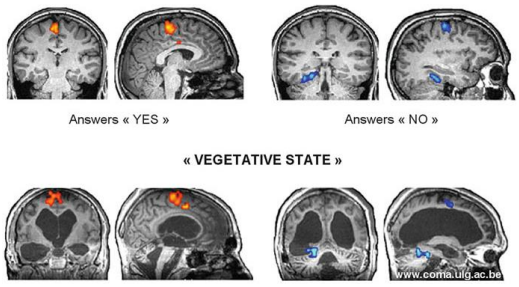


Dorer, Manktelow, Allanson, Sahakian, Pickard, Bateman, Menon, Stamatakis, in preparation

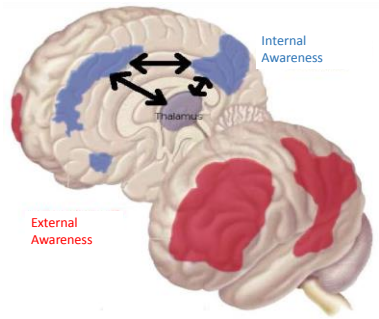
MRI Scan: White matter tractography



Tennis Walking round house



Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, et al. (2006) Detecting awareness in the vegetative state. Science 313: 1402–1402



J Cogn Neurosci 2011; 23: 570–578