

How prolonged might PDOC be?

A Very Long term follow up of 72 people with PDOC

Admitted for research investigations 2009-2017

On behalf of the Cambridge Disorders of Consciousness Group (CRIC)

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Holy Cross Conference 2022

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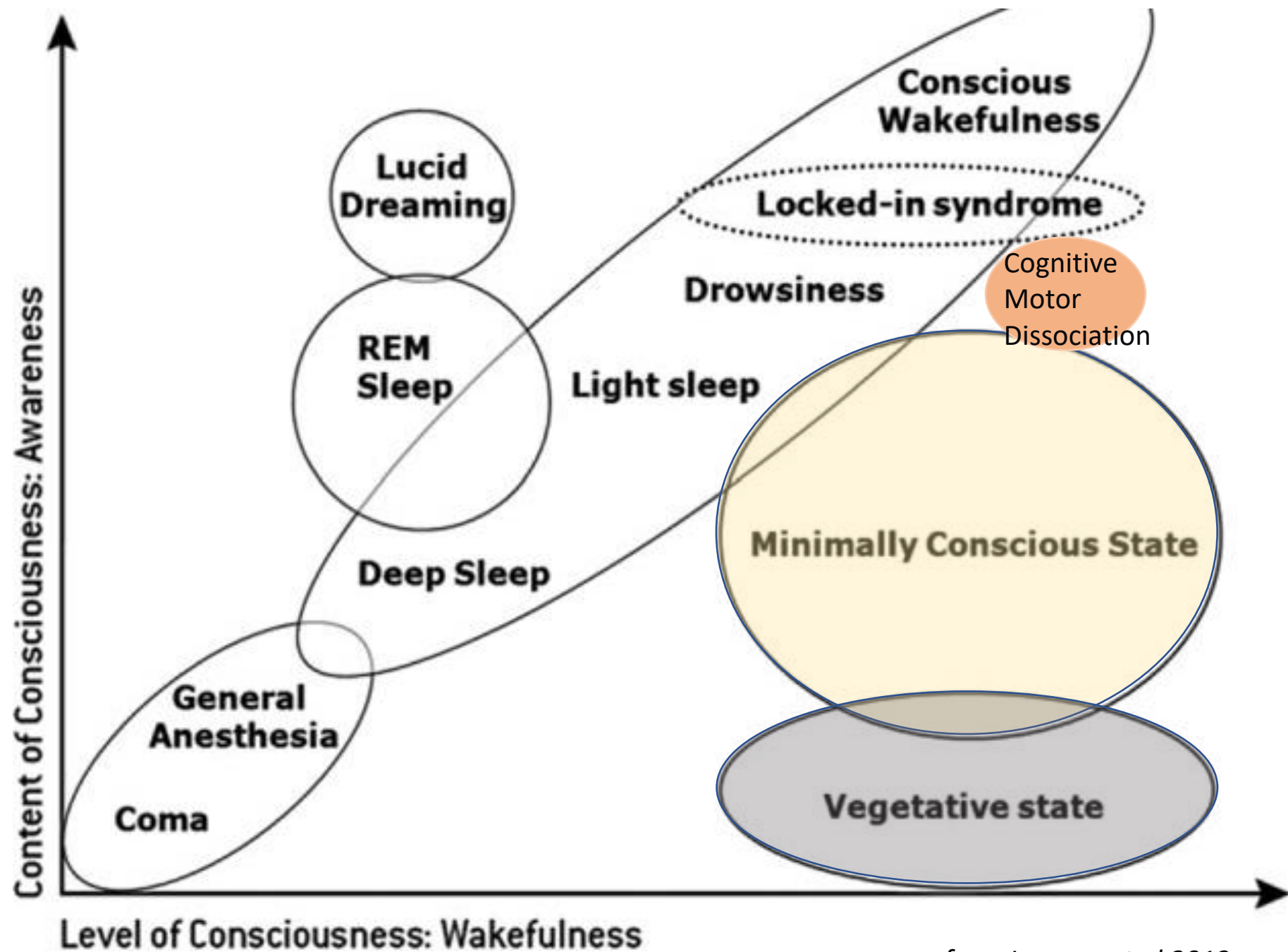
Views expressed are those of the speaker and not of the organisations involved

With thanks to RCP GDG 2013,2019;

Funding; McDonnell Foundation; NIHR; Wellcome; Evelyn Trust; EoE ARC NIHR (CLARHC);

Referring centres; CUH; NHND, Putney; Jacob Centre; CERU; Leicester.

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from Laureys et al 2013

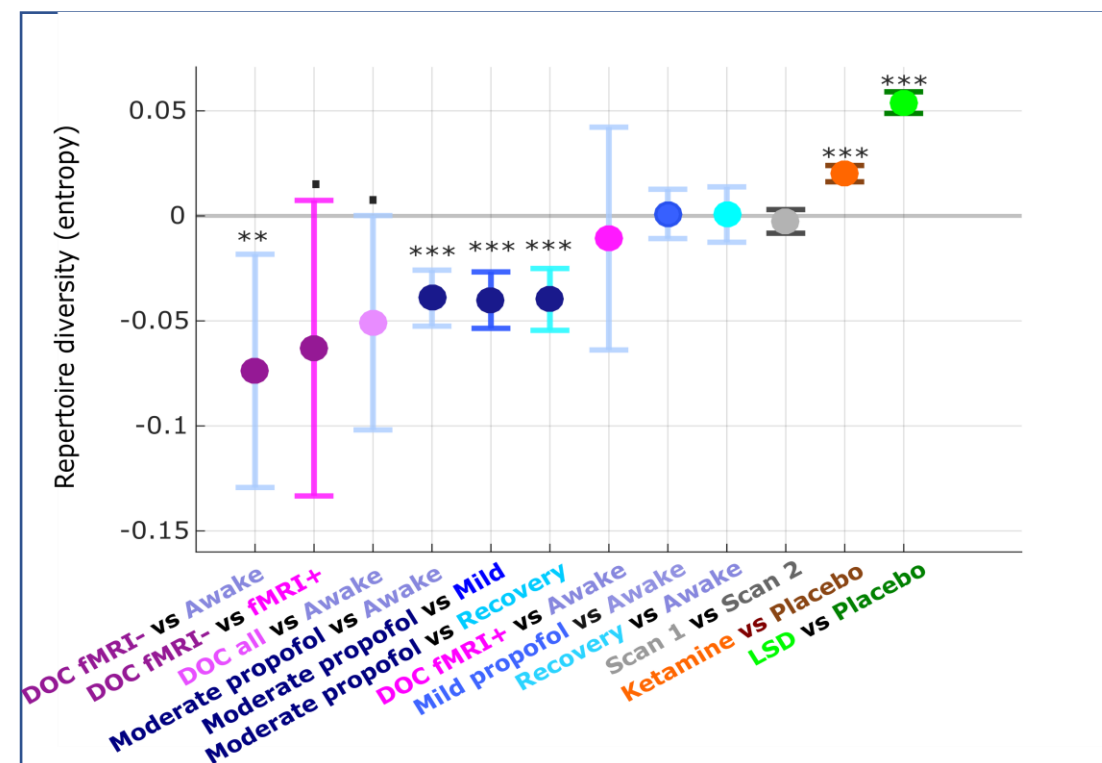
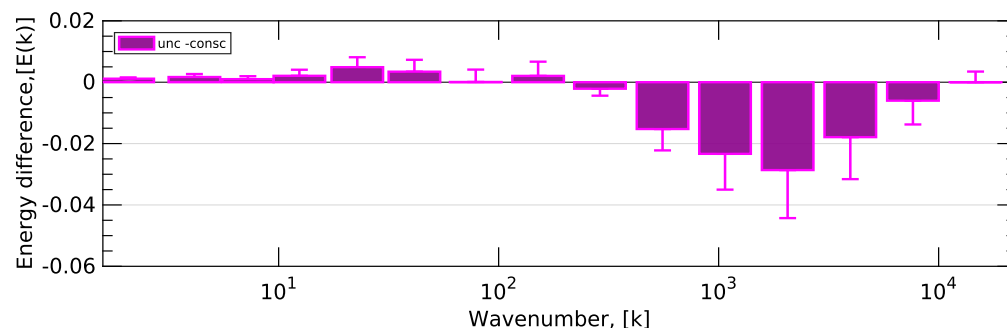
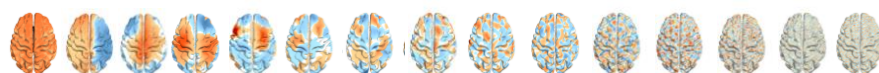
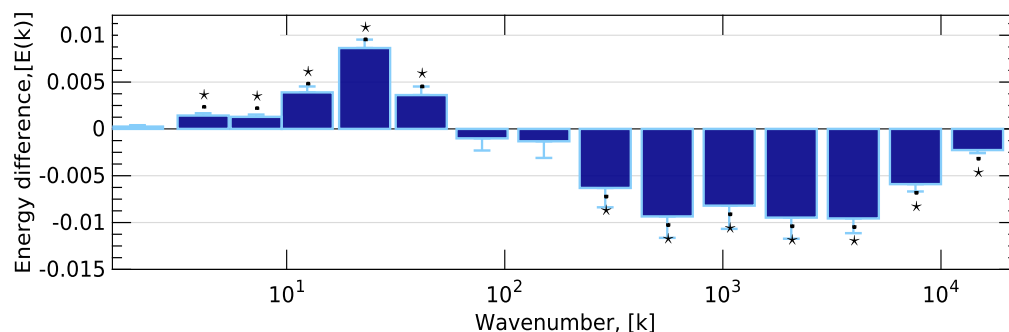
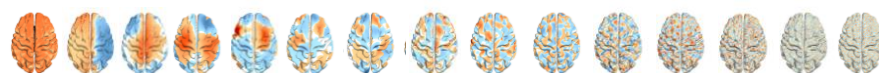


Connectome Harmonic Decomposition of Human Brain Dynamics Reveals a Landscape of Consciousness

A.I. Luppi, J. Vohryzek, M.L. Kringelbach, P.A.M. Mediano, M.M. Craig, R. Adapa, R.L. Carhart-Harris, L. Roseman, I. Pappas, P. Finoia, G.B. Williams, J. Allanson, J.D. Pickard, D.K. Menon, S. Atasoy, E.A. Stamatakis

doi: <https://doi.org/10.1101/2020.08.10.244459>

“both anaesthesia and DOC increase the coupling of functional activity to structural connectivity, and delineates a continuum of complexity (entropy) from unconsciousness to the psychedelic state”.



Definitions; “PDOC”; prolonged disorders of consciousness

- Vegetative state (UWS unresponsive wakefulness)

- Replaced “apallic syndrome, total dementia, akinetic mutism” ; “unresponsive wakefulness”
- Jennet and Plum 1972
- “awake but unaware”, “no (**behavioural**) evidence of a working mind”
- Need **cause** and no persisting effects of medication, metabolic disturbance, or other complications such as hydrocephalus
- Sleep wake cycle
- “No evidence of awareness or self or environment at any time”
- **No responses** to visual, auditory, or noxious stimuli “of a kind **suggesting volition or conscious purpose**”
- **No evidence of language** comprehension or meaningful expression
- P for persistent (continuing) (not permanent) if longer than 4 weeks

- How common is VS (In adults)?

- Prevalence **4-25** / per million population (UK), (Israel 4-5)
- Glasgow series 6% of those admitted with severe TBI -> VS
- Multi Soc Task Force (USA); if VS after 4 years mean survival 12.5 years more

PDOC Adults; Outcome studies

- *Belgium* 20% of 186 cases VS at 1/12 returned to work
- *Naples* mean 2 years 50 VS (36% TBI)
 - 21 died (42%)
 - 17 VS
 - 2 recovered responsiveness
 - 10 late recovery (12% to consciousness)
- *Boston, Katz 2009* 1-4 year follow up
 - 36 VS/MCS admitted to “slow to recover programme”
 - 72% MCS emerged
 - ~45% day time indept at home at 12/12
 - 22% returned to work / school
 - Worst outcome if VS > 8 weeks
- Predictors of better prognosis
 - Young (< 39years), tbi, AEPs,
 - BVT (if not present 80% still in VS 2 years) (Lieges , New York)

Recent American Follow up studies

- *Nakase-Richardson, Whyte et al*

- From US model systems data base 1988-2009
- 396, all TBI, 268 emerged during rehab

- **128 left rehab still in PDOC**
- **37 /128 followed to 5 years**
- **28/37 command following by 5 years**

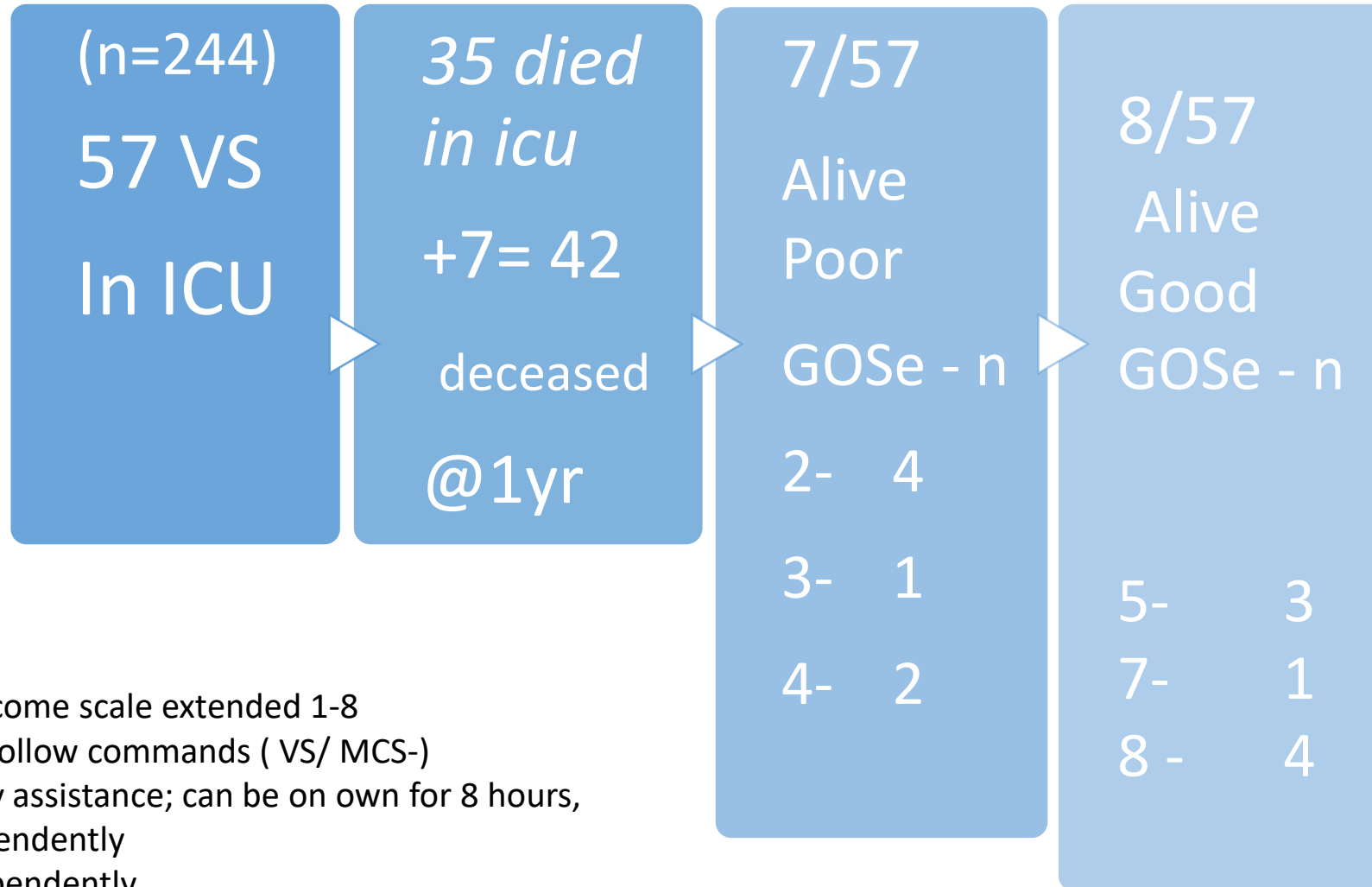
le at least
20%
emergence

- *Hammond, Giacino et al 2018 J Neurotrauma*

- 10 year follow up of 110 TBI from same data base
- Not command following at admission to rehab directly from Acute care
- 78 not following commands after 28 days rehab

- **58 of 110 were high functioning at one year (median time to emerge 37 days)**
- 46/78 had emerged at 1 year
- 31/47 emerged at 2 years
- 25/34 emerged at 5 years

1yr Outcome of comatose survivors of Cardiac Arrest (*paris / lieges ICU MRI study 2013*)



GOS e

Glasgow Outcome scale extended 1-8

1- unable to follow commands (VS/ MCS-)

2- needs daily assistance; can be on own for 8 hours,

3-shop independently

4-travel independently

5 -restricted social participation; supported work; family disruption

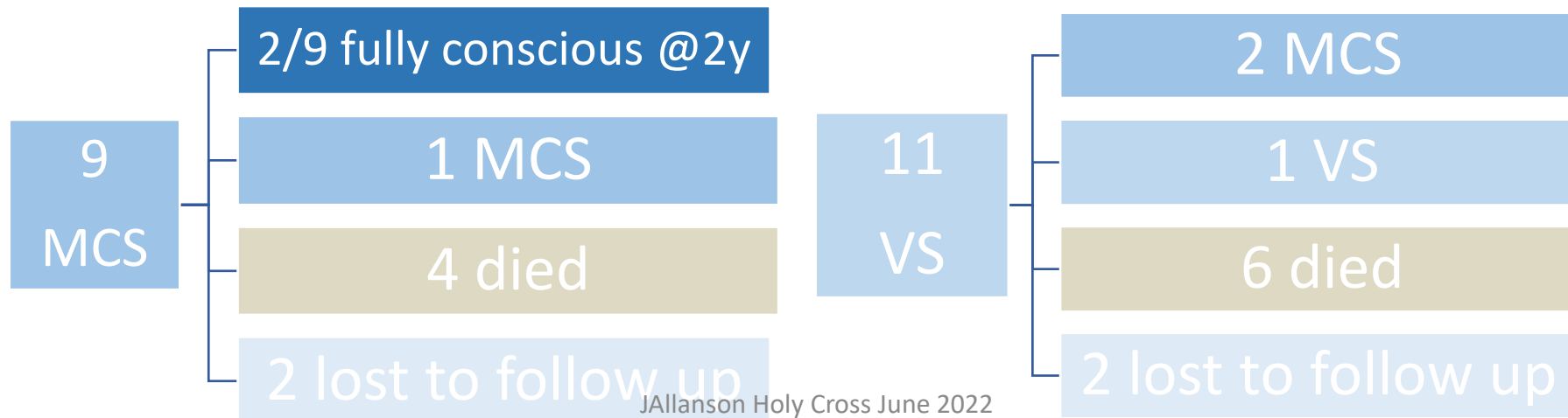
11/57 in VS post arrest
had high functional outcome
at 12/12

15/57 with GOSe>1

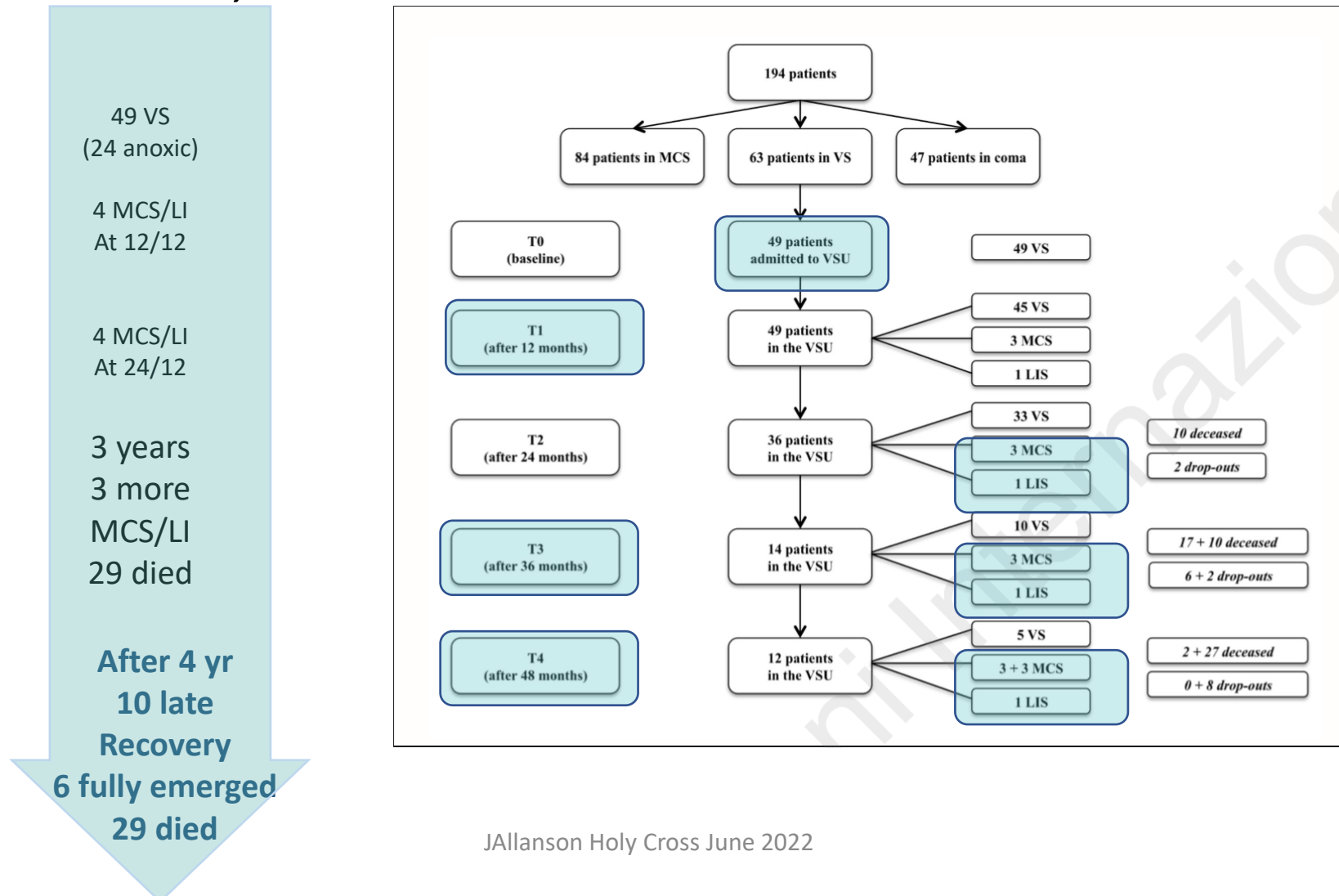
Netherlands 10-12 year follow up; *Eilander 2016*

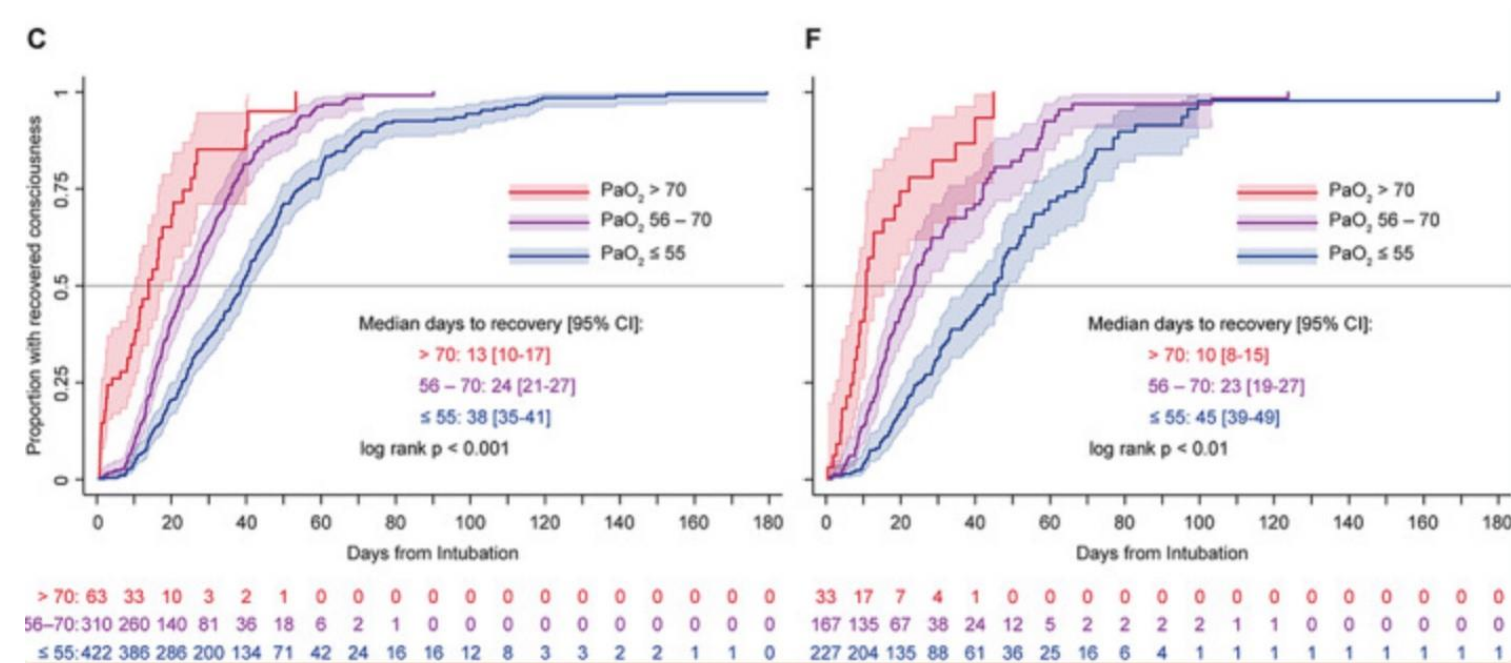
Brain Injury

- 0-25 year olds with < 6/12 tbi or <3/12 anoxic;
- 44 admitted (32 TBI 12 non TBI); 33 in VS, 11 MCS
- All had up to 3/12 intensive treatment;
- 24/44 fully conscious by discharge, (inc 22/33 VS)
- 26% still had SLT; All had PT after discharge



194 Italian VS patients in a rehab unit; Longterm Outcomes from “slow to recover programme” *Functional Neurology; Baricich, Estraneo et al 2017;* *If VS < 56 days 3x more likely to emerge*





–Meier cumulative incidence curves for recovery of command-following by hypoxemia category ($\text{PaO}_2 \leq 70$) and minimal PaO_2 value for initial surge (March–July 2020) and second surge (October 2020 to April 2021)

PDOC after covid

Ann Neurol. 2022 Jun; 91(6): 740–755.

Published online 2022 Apr 21. doi: 10.1002/ana.26342

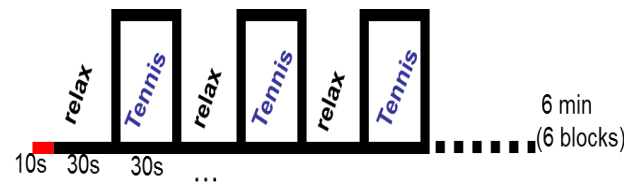
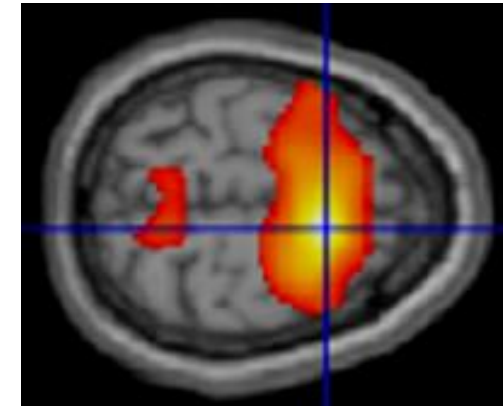
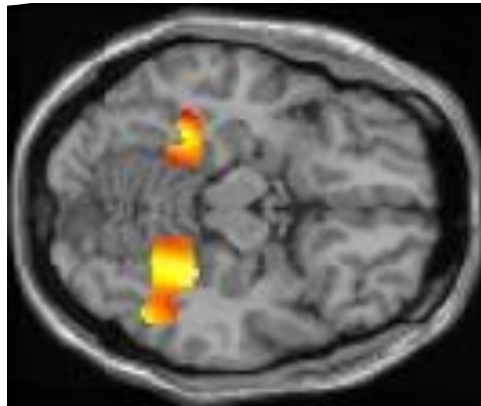
Waldrop ,...Claassen, Schiff, Edlow,

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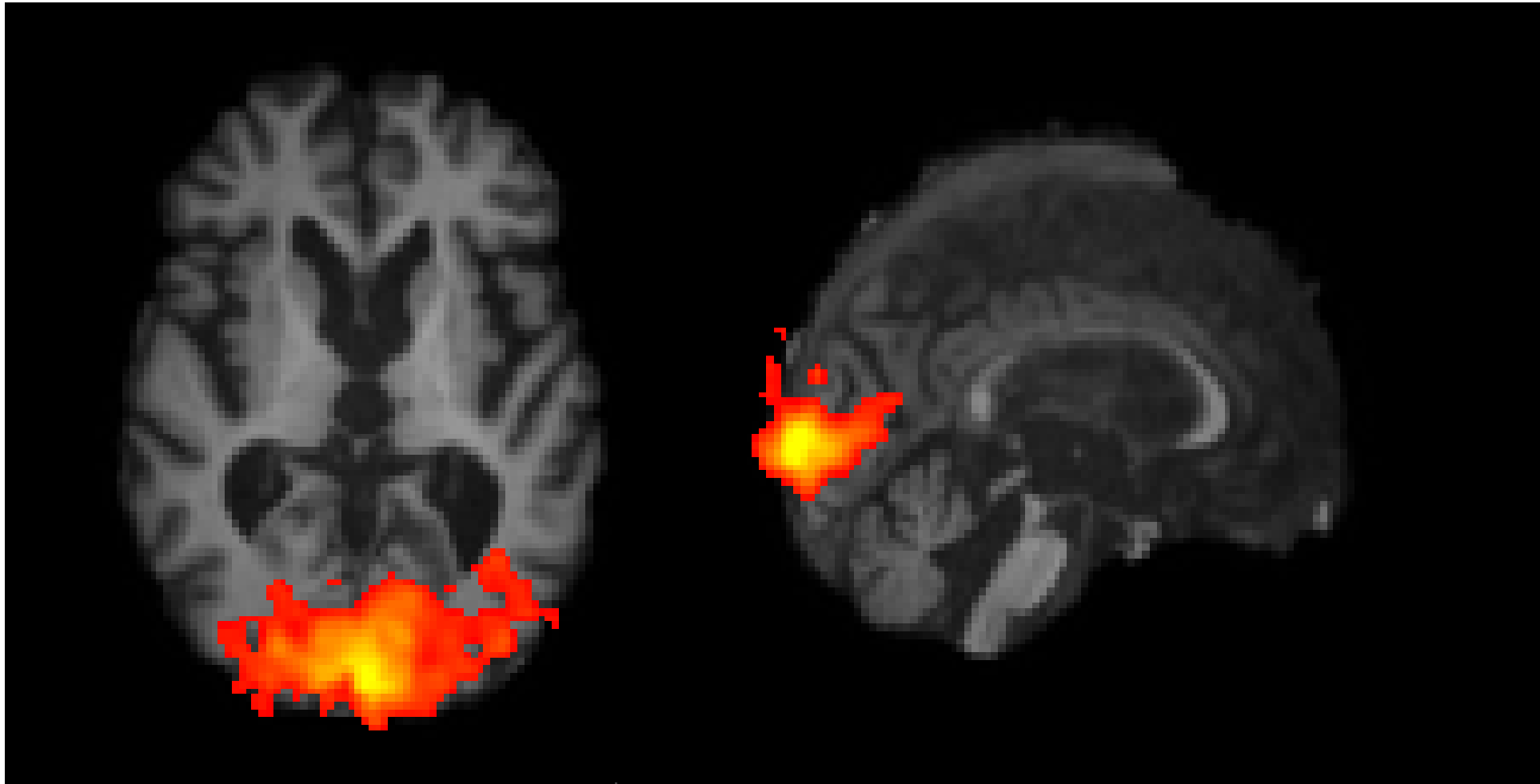
- 3 NY hospitals centres n=1284
- ICU admission, with Sars 19 infection, intubated for at least 7 days
- GCS<6
- 2 pandemic surges in Newyork march-July 2020 and oct 2020 –April 2021
- Analysis focused on levels of hypoxaemia
- Worst outcomes if there had been significant hypoxia (ARDS)
- Outcomes were reported at dc from hospital
- 140/775 – home
- 145 rehab and 133 skilled nursing facility
- 265 had died before dc
- **10% emerged more than 23 days after ventilation stopped**
- **Note many emerged to CF later than 25 days after extubation and some much later**
- **Up to 120 days -**

fMRI BOLD (blood oxygen level dependent) response

Volition task (command following) : “?A measure of awareness”



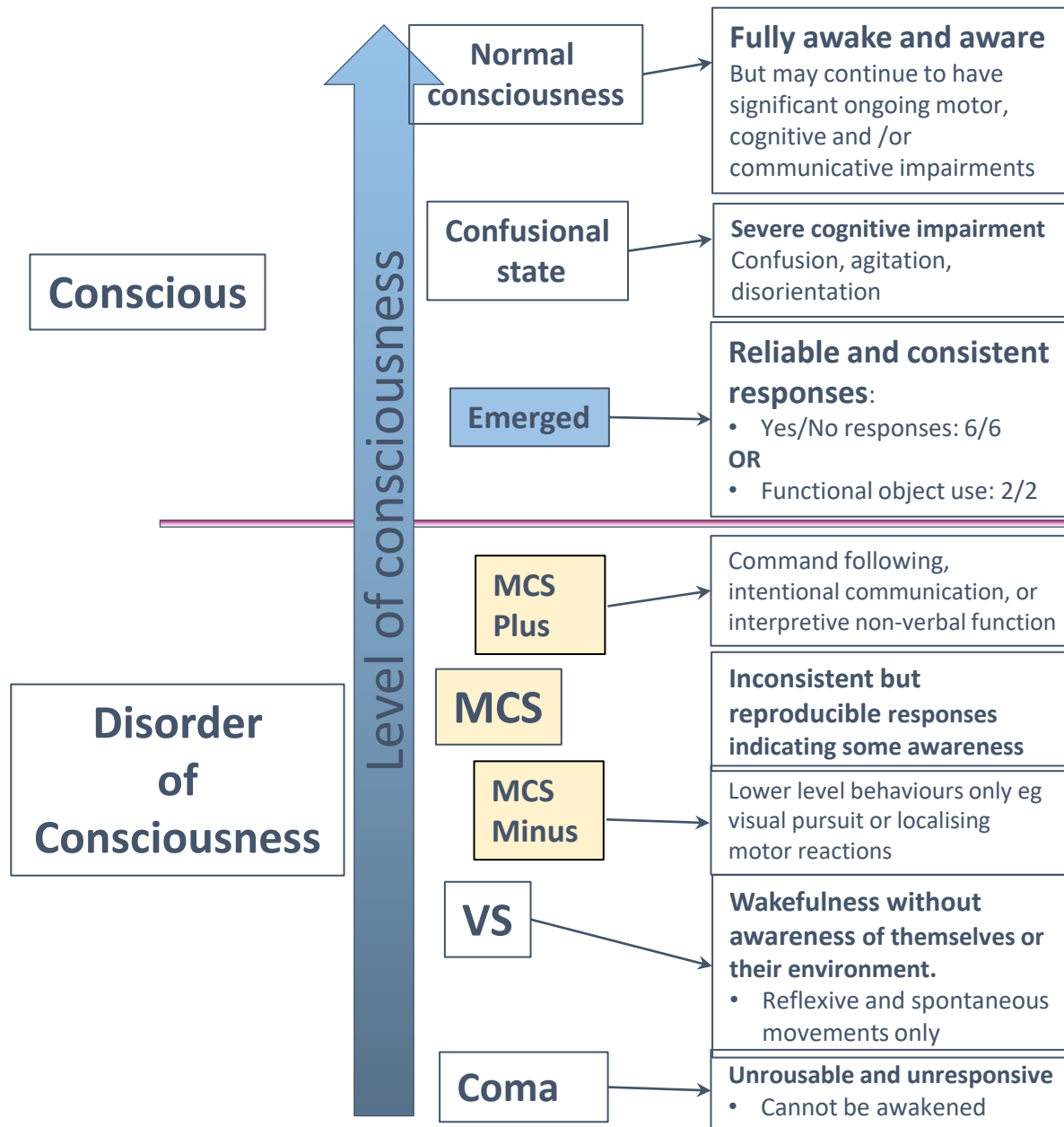
fMRI of PX being shown chequer board
using “BOLD” response



Long term outcomes of Prolonged Disorders of Consciousness;

*2-10 year retrospective follow up study of a Cambridge research cohort
funded by CLARHC fellowship using data from CRIC group admissions
(JA, EK, CB, PF, ES, VL, GW, DKM, JDP, SB, TH)*

- Initial admission;
 - Transferred from specialist rehab units/SNH to CRF for 5 days. (3 from neuroscience ward)
 - 49 TBI; 16 isolated hypoxia; 7 other injuries; 53 M;19 F;
 - Collated clinical history; inc 1st GCS; craniectomy; shunting; seizures; medication;
 - Neuro exam; daily behavioural assessments; PT; fMRI + EEG n=72
 - Mean time since injury when initially included;20 months. (range 3-157)
 - Level of behaviour using daily CRS-R charts;26 VS; 25 MCS-; 20 MCS+; (1 already emerged at scanning)
 - Ethics LREC 99/391 and IRAS 191739 / REC 18/EE/0030
- All 72 scanned between 2010-2017 (n=72) were then traced between 2019-20.
 - National mortality data on spine / or current clinically managed patients/referrers/ families
 - ftf with neuro exam and CRS-R or CRS-R phone with family/ professional ; video; therapy reports
 - current activity/ residence



Coma Recovery Score

JFK- CRS-R, 2004, updated 2020

Giacino, Kalmar and White (free on COMBI website)

Coma Recovery Score Revised

23
21
19
9
5

AUDITORY FUNCTION SCALE	#	TCC
4 – Consistent Movement to Command*		
3 – Reproducible Movement to Command*		
2 – Localization to Sound		
1 – Auditory Startle		
0 – None		
VISUAL FUNCTION SCALE	#	TCC
5 – Object Recognition*		
4 – Object localization: Reaching*		
3 – Visual Pursuit*		
2 – Fixation*		
1 – Visual Startle		
0 – None		
MOTOR FUNCTION SCALE	#	TCC
6 – Functional Object Use†		
5 – Automatic Motor Response*		
4 – Object Manipulation*		
3 – Localisation to Noxious Stimulation*		
2 – Flexion Withdrawal		
1 – Abnormal Posturing		
0 – None		
OROMOTOR/VERBAL FUNCTION SCALE	#	TCC
3 – Intelligible Verbalization*		
2 – Vocalization/Oral Movement		
1 – Oral Reflexive Movement		
0 – None		
COMMUNICATION SCALE	#	TCC
2 – Functional: Accurate†		
1 – Non-functional: Intentional*		
0 – None		
AROUSAL SCALE	#	TCC
3 – Attention		
2 – Eye Opening w/o Stimulation		
1 – Eye Opening with Stimulation		
0 – Unarousable		
TOTAL SCORE		

* Denotes Minimally Conscious State Minus (MCS-)

* Denotes Minimally Conscious State Plus (MCS+)

† Denotes emergence from Minimally Conscious State (eMCS)
TCC Test Completion Code

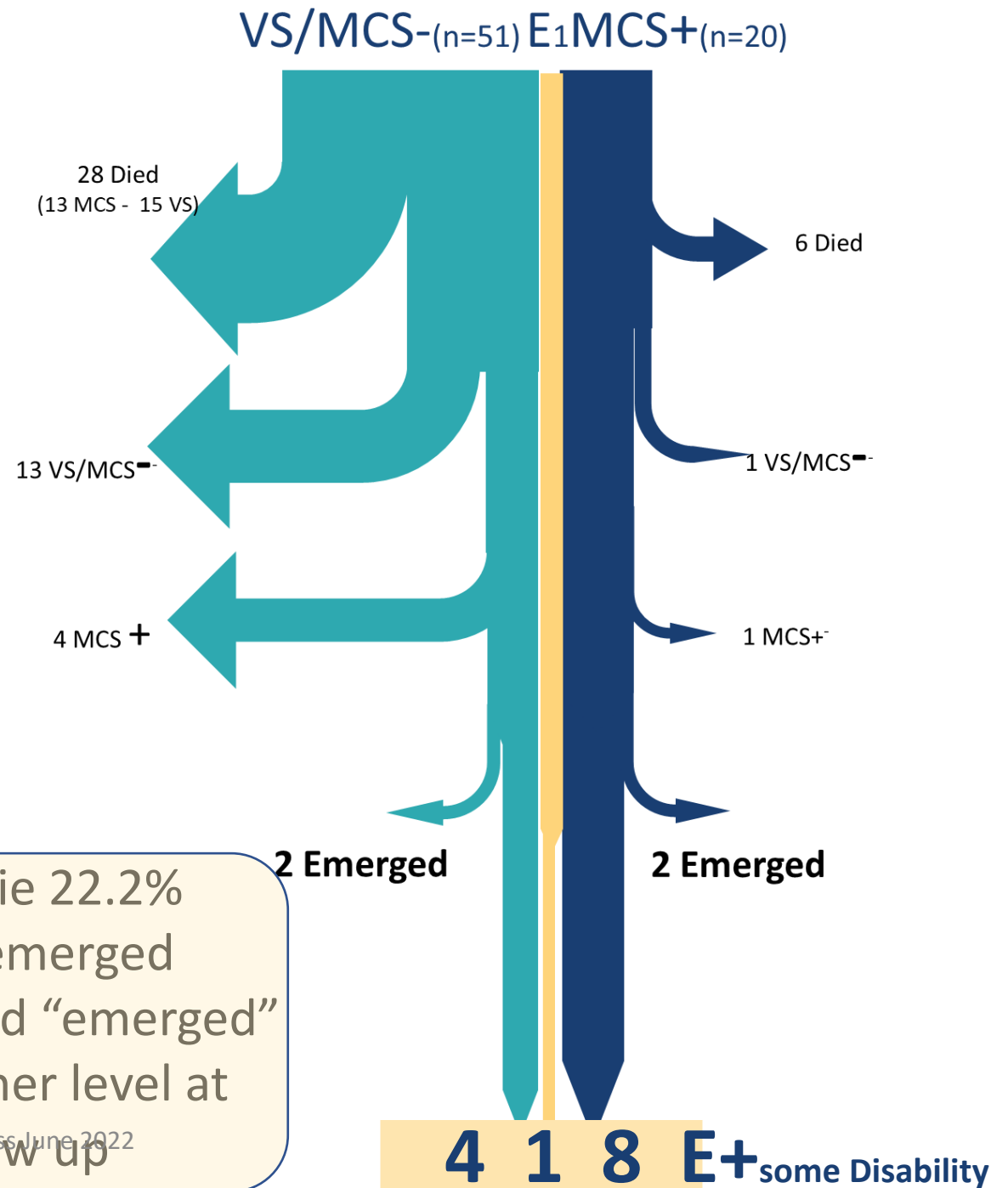
Prolonged Disorders of Consciousness; What might the future hold?

- Traced 72 scanned sequential recruits to CRIC study 2010-17
- 49 had had TBI;
- 16 isolated hypoxia;
- 7 other injuries.
- 53 M;19 F;
- mean age at Injury 35y (15-77y);
- Mean time since injury when admitted for research scans ;20 months. (range 3-157 months post injury);
- CRS-R had been recorded 3-5 x during initial admission;
- used highest CRS-R for grouping
- **Follow up study; 2019;**
- **Mean time since see in study 2-9 years;**
- **Checked national mortality data**
- **CRS-R ftf or phone**

CRIC JA, JDP, DKM, ES et al 2020; JNNP spplt.

Total of 16/72 ie 22.2%
Who had not emerged
at first visit had “emerged”
or were at higher level at
long term follow up

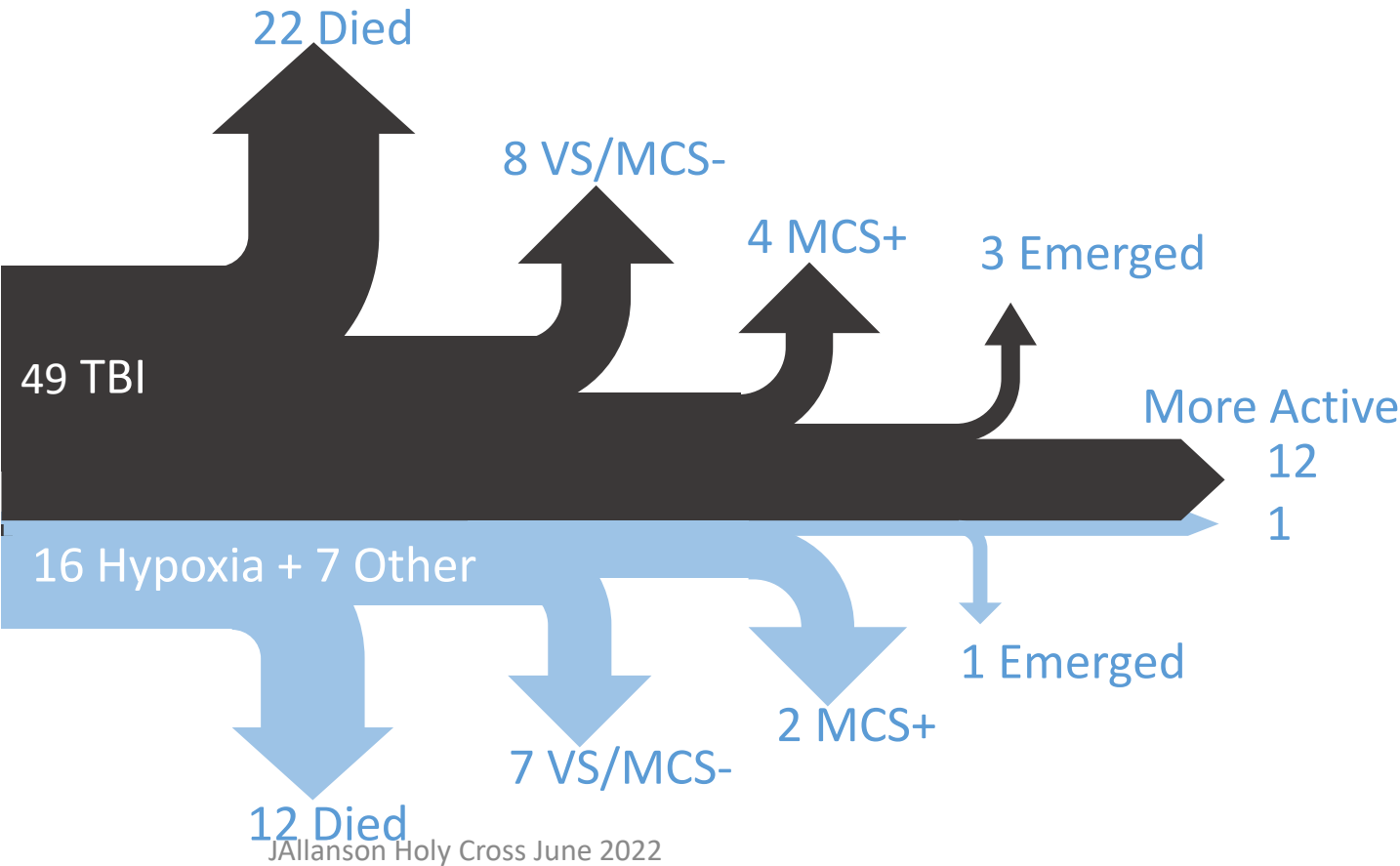
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Results 2

Long term Outcomes at Follow up by aetiology (CRIC, in prep)

N= 72 av age at BI 37y
31 repeat scan visits
Needed CRS-R Phone
Questionnaire
11 in own Homes
(3 VS/MCS-)
Families remarkable
Gradual Changes
Over years,
Many moved several x
Stresses re funding
All except 1 needed
care (some only occ)
Periods of challenging
behaviours as emerged



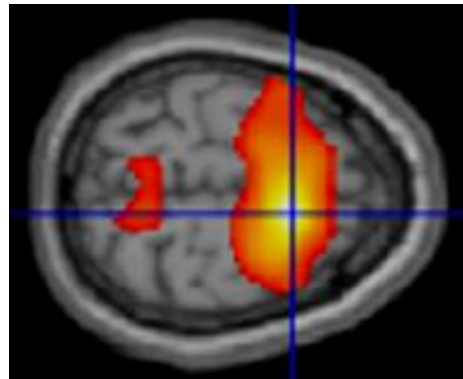
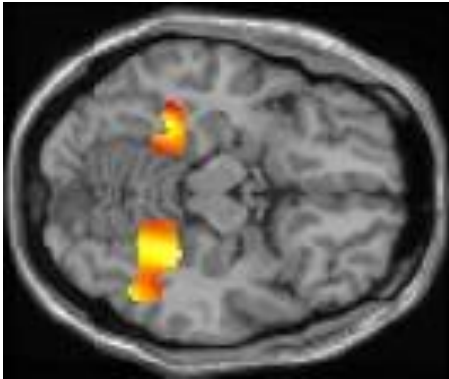
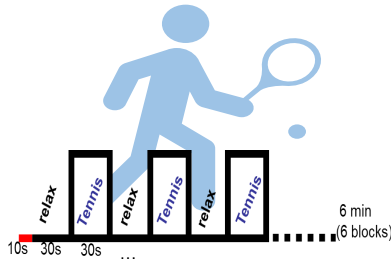
Additional info from long term follow up (*CRIC in prep*)

- 17 of those in VS died by follow up ie 53%
- 50% of those who had primary hypoxic injury had died
- 43% of those who had sustained a TBI had also died
- Mean time after injury to death 48 months (for TBI cohort 53 months)
- 11 in MCS- died
- 6 of 19 in MCS+ died
- **Thus 19% still in VS/MCS- at long term**

- Of the 38 who were still alive at long term follow up 16 had emerged (ie 22% of the initial cohort were still alive)
- Of the total of 16/71 who had emerged since inclusion for research scanning (1 already emerged at research admission) 10 of those 16 had been found to be in PDOC after full detailed assessments at 17 or more months post injury
- 10/19 in MCS+ had emerged (53%)

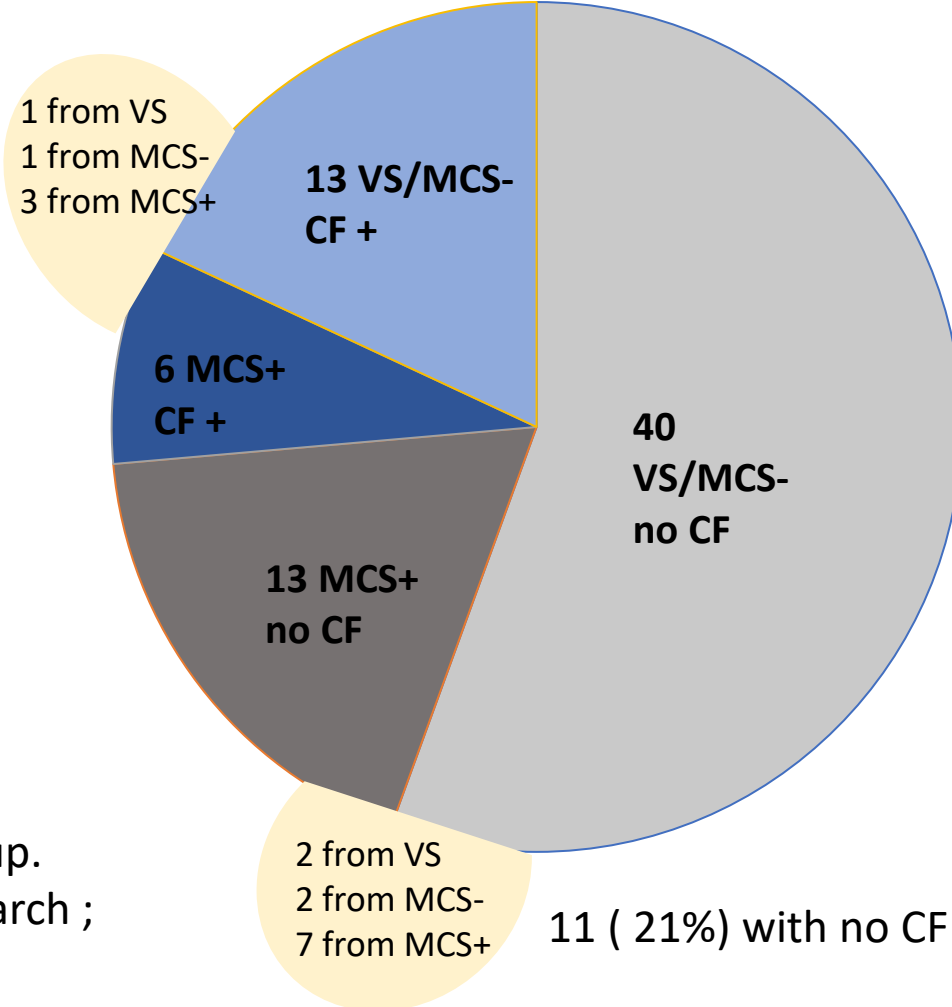
- Of those 19 who had displayed changes on fMRI suggestive of command following
 - 6 were recorded as being in MCS+ at scanning and 3 of those emerged
 - 13 were recorded as being in VS (4)or MCS- using crs-r ;1 in VS emerged and 1 MCS- emerged
- Of the 53 who had not displayed changes suggestive of command following during research admission 11 had emerged at fu.

fMRI BOLD responses/command following predicting long term emergence? *(from CRIC 2019 data, BSRM 2021 and in prep)*



- Of those 19 who had displayed BOLD changes on fMRI suggestive of command following
- 6 were in MCS+ at scanning;
- 3/6 of those in MCS+ had emerged at long term follow up.
- 13/19 of those with CF were in VS(4) or MCS- (9) at research ;
- ie 13/72 had covert cognition
- Of these 1 person in VS, 1 in MCS- had emerged at follow up

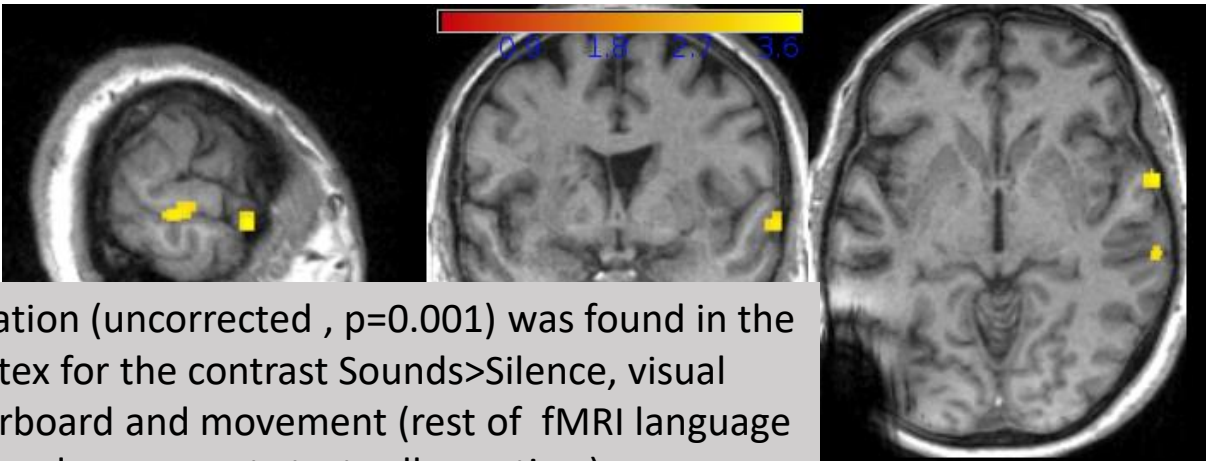
5 (26%) with CF emerged



Pn at 11/12 post bleed,

Function Scale	Highest Scores one time only	Lowest scores
Auditory (0-4)	3- reproducible movement to command (thumbs up and also did spontaneously	2-localisation to sound
Visual (0-5)	4-object recognition ? Reached x1 to block??	3-Visual pursuit
Motor (0-6)	??4 – object manipulation Touched a wooden block with fingers	2-flexion withdrawal
Oromotor/Verbal (0-3)	1-oral reflexive movements	1-Oral reflexive movements
Communication (0-2)	1. Non functional intentional	1-Non functional intentional
Arousal (0-3)	2-Eye opening without stimulation	2-Eye opening without stimulation
Total Score (Max = 23)	??15	11
Behaviours suggesting MCS	+	+

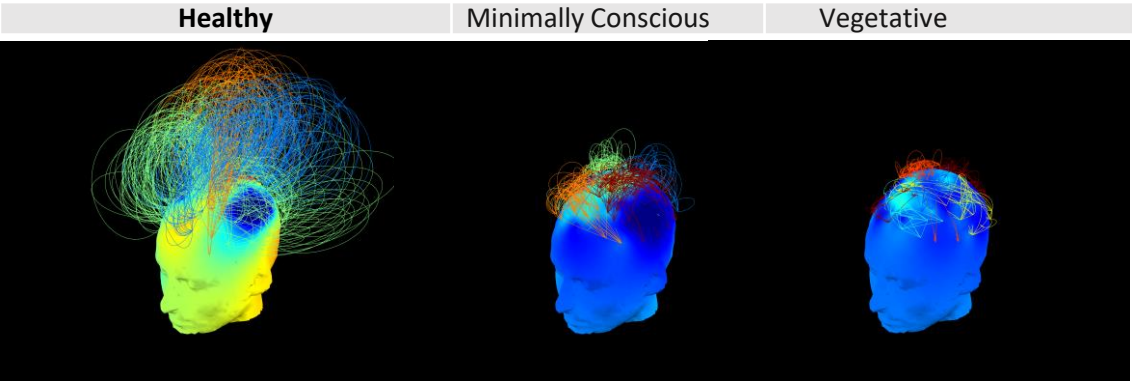
2019; called her family; suggested I call pt;
Well; wanting PT and a splint for her R hand



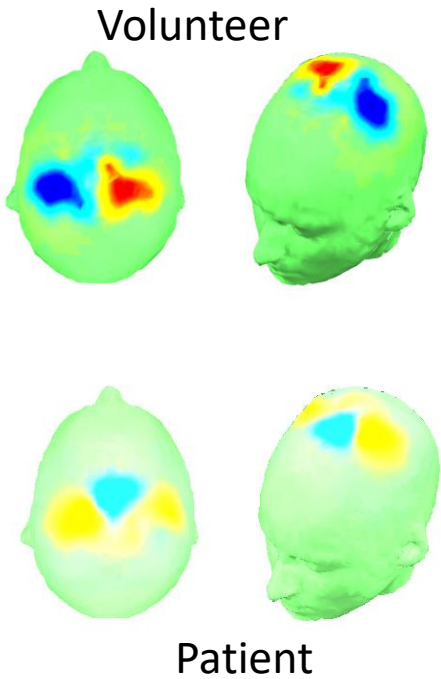
fMRI ; A very small activation (uncorrected , $p=0.001$) was found in the left primary auditory cortex for the contrast Sounds>Silence, visual cortex reacted to checkerboard and movement (rest of fMRI language paradigm neg, and imagined movements tests all negative,)

Resting state EEG

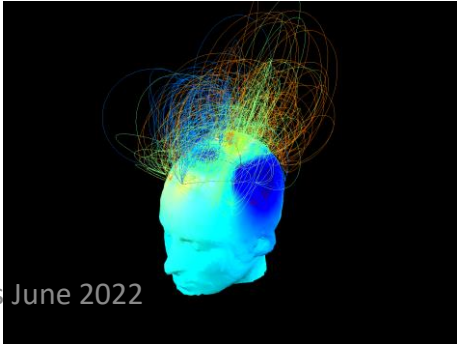
Alpha-band brain networks in healthy volunteers and patients measured during rest



“Active” EEG imaging
Making fist with R hand



Patient

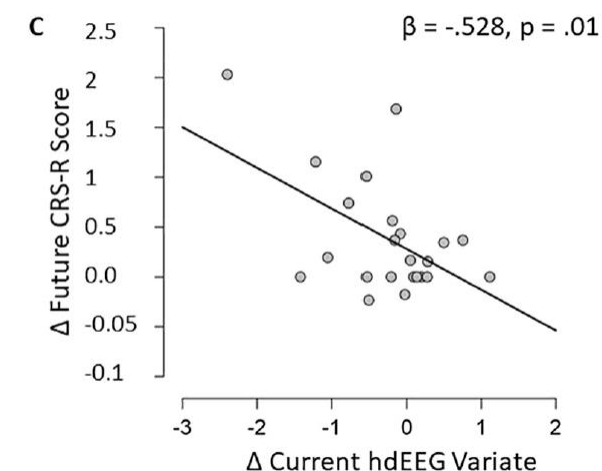
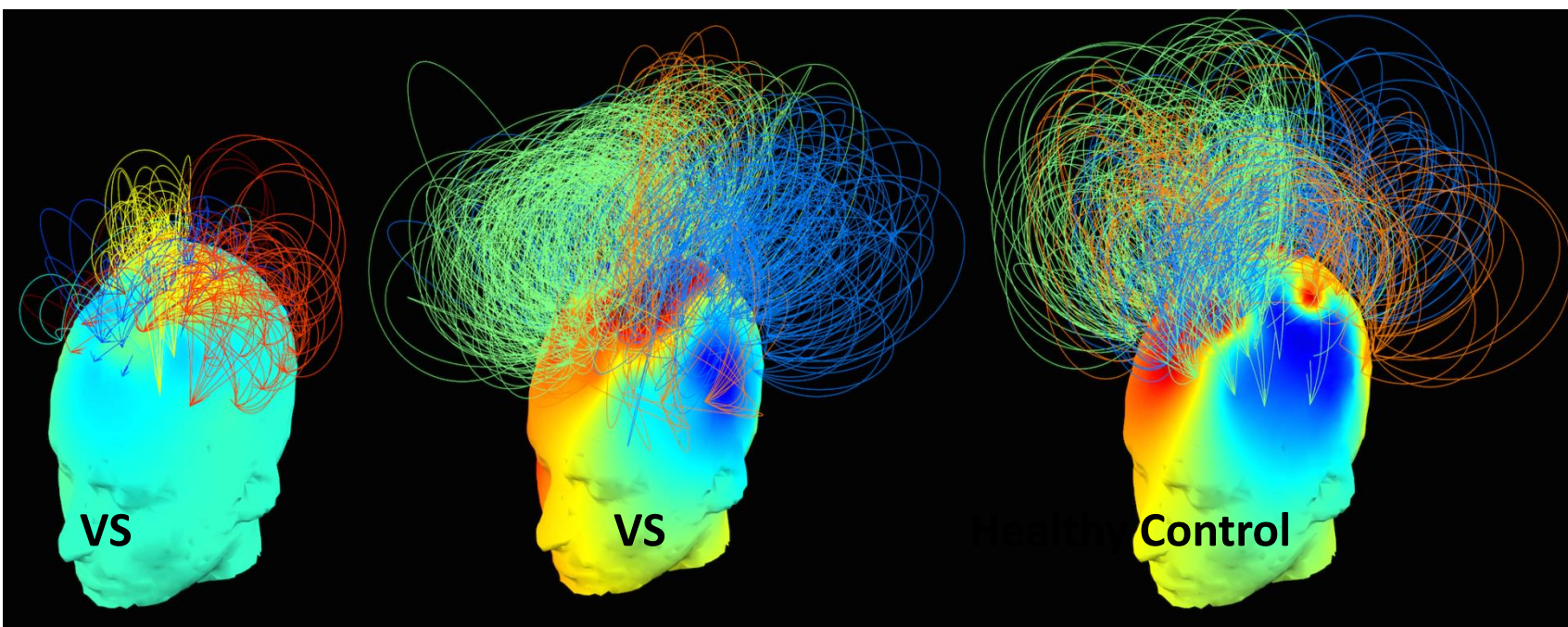
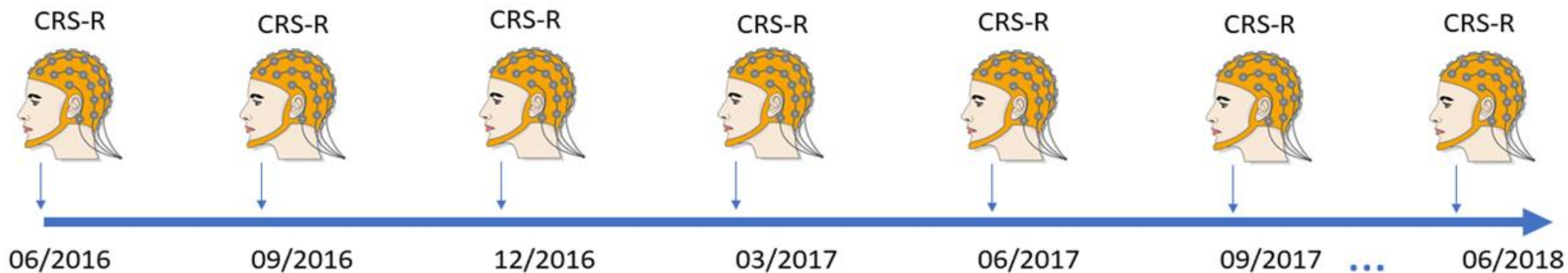


Notes re the cohort *(CRIC 2019 data in preparation)*

- Large range of age and time since injury
- 35 of the 72 scanned were seen in PDOC at >12 months post injury
- Mean when seen 20 months; median 11 months;
 - 8 seen @ < 6 months post injury
- 18 of 35 alive seen face to face
- Others video/ professionals and family / telephone with patient
- Interventions for injury
- 17/72 had had a VP shunt (2 further had had EVD) ;
- 31/ 72 had had craniectomy - > 12 then had a cranioplasty
- Outcomes from all combinations of initial level of CRS-R and fMRI CF might be emergence or death
- Of those 16 who had emerged
 - 7 had had a shunt, (1 further had emerged to walk 12/12 after shunt but died 2y later of tumour recurrence)
 - 4/16 had had a craniectomy, shunt and cranioplasty
 - 2/16 had had craniectomy and cranioplasty but no shunt

Conclusions / Future

- This study is not epidemiological but does look at what can happen “after rehab”/ (mean 20 months post injury)
- One of few UK based studies
- It does illustrate that a whole range of trajectories do occur
- May be reassuring to see that only a small proportion of people and their families remain in a state of perpetual ambiguous loss
- “active” paradigms in Functional MRI not predictive in our series
- EEG and fMRI passive /”resting state” (ie not reliant on language, recall or attention) may be useful
- Importance of considering the individual and their individual injury
- Personalised assessments and interventions
- We need a registry to increase our understanding of prognosis
- At the same time it is important not to stop exploring ways of facilitating recovery and communication as both can occur



Resting state Brain networks from EEG

In two patients in the vegetative state (VS; left and middle), and a healthy adult (right). Both VS patients were behaviourally identical on clinical examination, and CRS-R but the patient in the middle panel showed specific brain activity in appropriate brain regions when asked to imagine playing tennis during an fMRI study, while the patient on the left showed no such response¹⁰

PLOS one Cruse, Chennu et al 2015

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Bedside EEG predicts longitudinal behavioural changes in disorders of consciousness

Neuroimage Aug 2020, 28

Corinne Anne Bareham Neil Roberts; Judith Allanson; Peter J Hutchinson;

John D Pickard; David K Menon; Srivas Chennu



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JAllanson Holy Cross June 2022

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NHS Foundation Trust

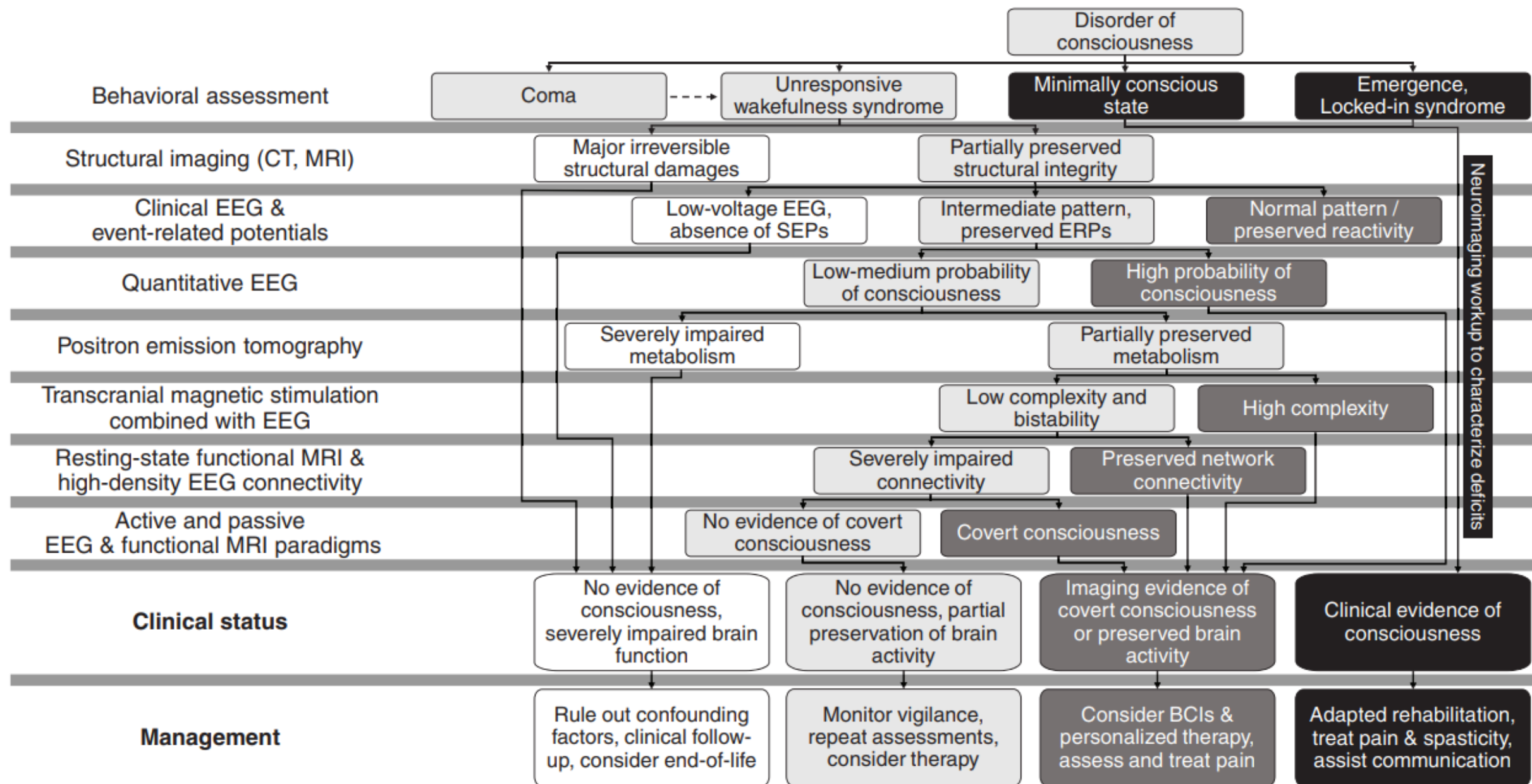


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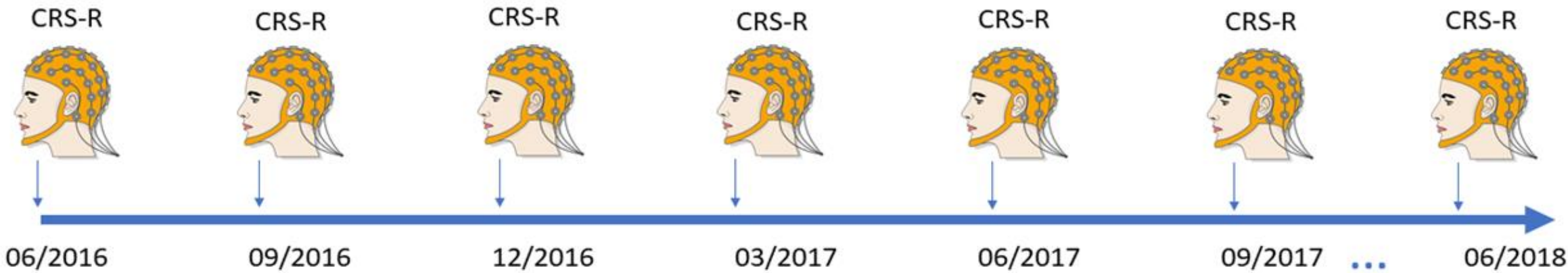


Summary

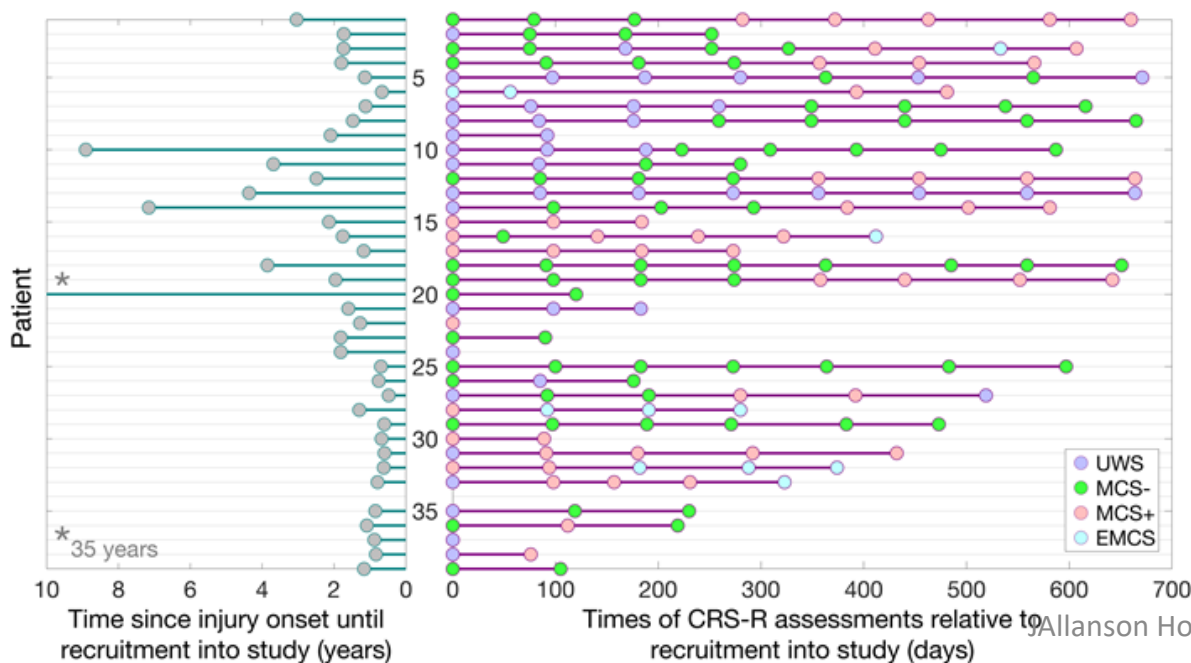
- New information about mechanisms ; Dopamine
 - Implications for further drug trials
- Update of behavioural scale
- New legal framework for Clinically assisted hydration and nutrition;
- New information about imaging; Resting state; PET;
- Complex command following; still for research;
- EEG (espec Resting state); feasible in situ;
- Key is to understand the pathology and anatomy;
- Personalised interventions

A Bedside EEG predicts longitudinal behavioural changes in disorders of consciousness

Neuroimage Aug 2020, 28
Corinne Anne Bareham Neil Roberts; Judith Allanson; Peter J Hutchinson; John D Pickard; David K Menon; Srivas Chennu



B



C

- canonical correlation analysis was used to relate clinical variables and CRS-R values with EEG power and connectivity between “nodes – specified regions”
- revealed that the patient’s age, and the hdEEG theta band power and alpha band connectivity, contributed most significantly to the relationship between hdEEG and clinical variables.
- Further, we found that hdEEG measures recorded at the time of assessment augmented clinical measures in predicting CRS-R scores at the next assessment.
- Moreover, the rate of hdEEG change not only predicted later changes in CRS-R scores, but also outperformed clinical measures in terms of prognostic power