A Heartbeat Away From Consciousness: Heart Rate Entropy can assess Consciousness

Francesco Riganello^{1,2*}, <u>Stephen Karl Larroque</u>^{1*}, Mohamed Ali Bahri³, Lizette Heine⁴, Charlotte Martial¹, Manon Carrière¹, Vanessa Charland-Verville¹, Charlène Aubinet¹, Audrey Vanhaudenhuyse⁵, Camille Chatelle¹, Steven Laureys¹ and Carol Di Perri^{1,6}





¹Coma Science Group, GIGA-Consciousness, University & Hospital of Liege, Belgium; ² Research in Advanced NeuroRehabilitation, Istituto S. Anna, Crotone, Italy; ³ GIGA-Cyclotron Research Center In Vivo Imaging, University of Liege, Belgium; ⁴ Centre de Recherche en Neurosciences, Inserm U1028 - CNRS UMR5292, University of Lyon 1, France; ⁵ Sensation & Perception research Group, GIGA-Consciousness, University & Hospital of Liege, Belgium; ⁶ Centre for

Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK; * These authors contributed equally to this work.



stephen.larroque@uliege.be





Diagnosing consciousness?

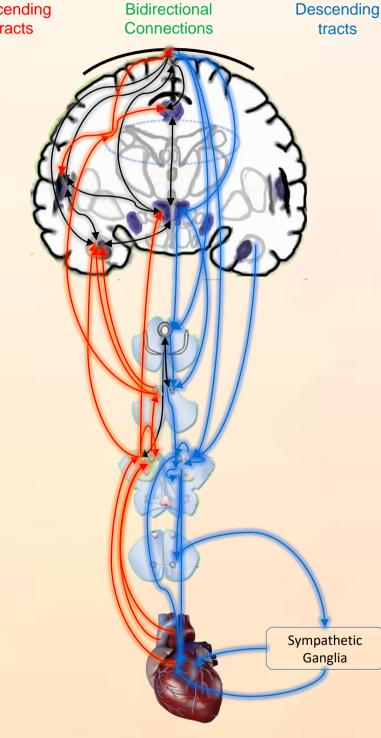


Neuroimaging helps, but is expensive and difficult in daily clinical setting

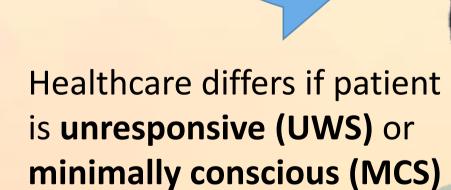




~35% clinical diagnosis error which can impact life and death decisions



→ Can we better diagnose by monitoring the heart?









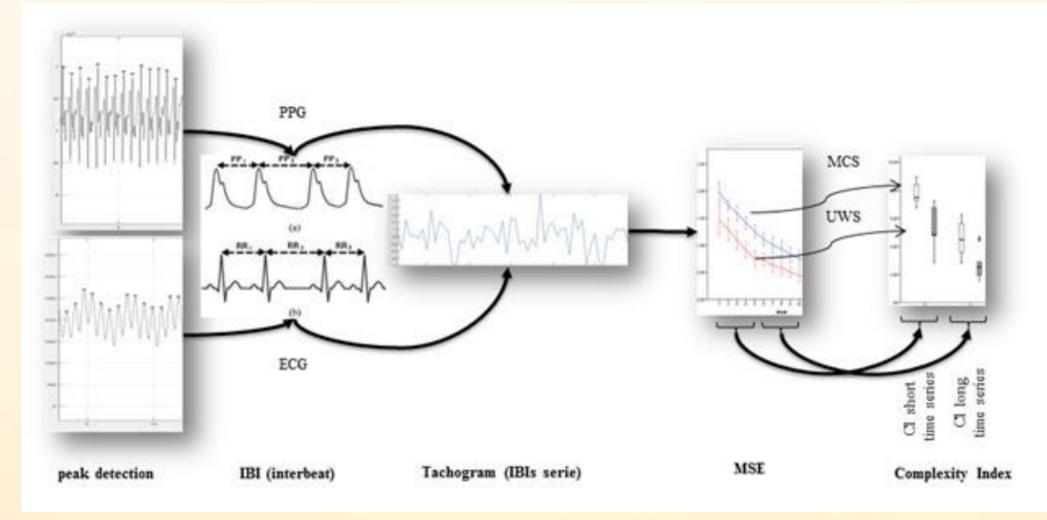




Methods – from heart rate to complexity index

From heart rate to multi-scale entropy to **COMPLEXITY INDEX** in the short term (CI_s) and long

term (CI_I):



- 14 UWS & 16 MCS (n=30) sedated patients, assessed by Coma Recovery Scale Revised (CRS-R).
- Matched for age, gender and onset.
- Electrocardiographic activity (ECG) and photoplethysmographic sensor (PPG) acquired for 10 minutes, simultaneously with MRI (3T Siemens Magnetom TrioTim).
- PPG and ECG cleaned with a Fourier Transform (SigView software).
- CI = area under the sample entropy timescale curve over multi-scale entropy (HRV Advanced Analysis software v2.2).
- MRI T1 and EPI BOLD (n=21) preprocessed with SPM12 and 2^{nd} -level correlation analyses with CONN 17f with CI_s & CI_l as covariates of interest in a parametric regression.









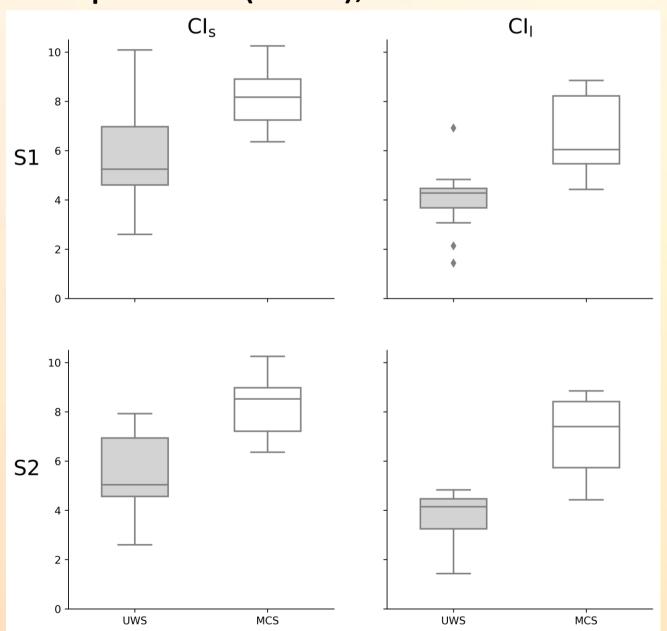
Results

(Riganello & Larroque, 2018)

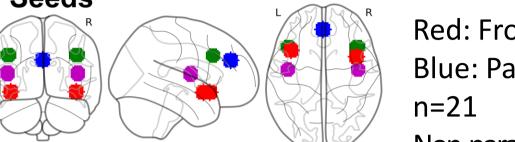
MCS have higher CI than UWS on average

 CI_s (z=-3.346, p<0.001) and CI_l (z=-4.095, p<0.0001) using a Mann-Whitney's test.

S1 includes all patients (n=30), S2 fMRI included (n=21)

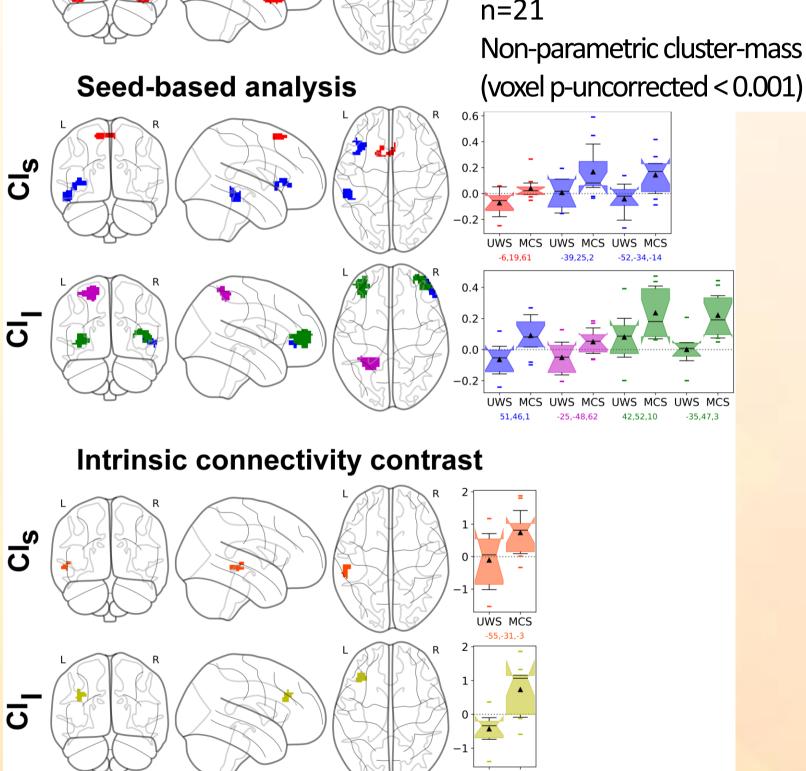


CI correlates with CAN fMRI connectivity recovery



Red: Fronto-Insular Blue: Paracingulate Magenta: STG Green: DLPFC

Non-parametric cluster-mass p-FWE < 0.05













Results

CI reliably discriminates MCS from UWS

Using a One-R classifier with 10-fold cross-validation:

- → Cl_I selected as the best predictor
- → 90% accuracy, 7% false positive and 13% false negative rates
- → In comparison:
 - Zero-R (always predicting MCS) = 53% accuracy
 - Clinical consensus without CRS-R ≈ 35% false negative
- → Lower error than clinical consensus

Confusion Matrix	
MCS	MCS as UWS
(true positive)	(false negative)
15	1
1	13
UWS as MCS	UWS
(false positive)	(true negative)

Conclusion

- → Complexity Index has **high discriminative power** and low false negative & positive rates
- → Might provide an inexpensive way to diagnose MCS & UWS and screen/monitor CAN connectivity changes
- → Works even if extensive brain damage
- → Future: investigate in a bigger cohort and in non-sedated patients

Reference: Riganello & Larroque, et al. "A Heartbeat Away From Consciousness: Heart Rate Variability Entropy can discriminate disorders of consciousness and is correlated with resting-state fMRI brain connectivity of the Central Autonomic Network." *Frontiers in Neurology* 9 (2018): 769.

This research was supported by: University and Hospital of Liège, F.R.S.-F.N.R.S., French Speaking Community Concerted Research Action (ARC 12-17/01), Center-TBI (FP7-HEALTH- 602150), Human Brain Project (EU-H2020-fetflagship-hbp-sga1-ga720270), Luminous project (EU-H2020-fetopen-ga686764), James McDonnell Foundation, Mind Science Foundation, IAP research network P7/06 of the Belgian Government (Belgian Science Policy), Public Utility Foundation "Université Européenne du Travail", "Fondazione Europea di Ricerca Biomedica", Bial Foundation, Belgian National Plan Cancer (139), European Space Agency, Belspo and European Commission.











Bonus slides





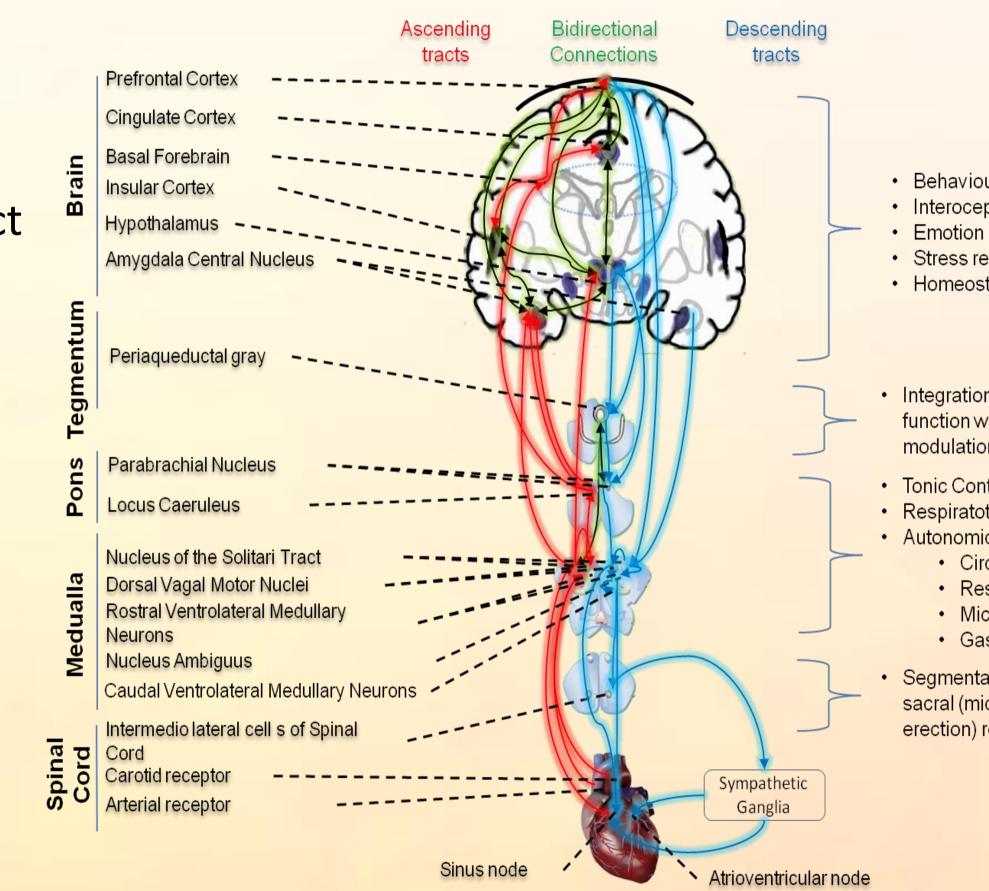






Background

- Healthcare differs if patient is unresponsive (UWS) or minimally conscious (MCS)
- ~35% clinical diagnosis error which can impact life and death decisions
- Neuroimaging helps, but is expensive and difficult in daily clinical setting
- Heart and brain's Central Autonomic Network (CAN) are connected in a two-way dynamic interaction through the Autonomic Nervous System (ANS).
 - → Can we better diagnose by monitoring the heart?



- Behavioural arousal
- Interoceptive awareness
- Stress response
- Homeostasis
- Integration of automatic function with arousal and pain modulation
- · Tonic Control of blood pressure
- · Respiratoty Rhythms
- Autonomic Reflexes
 - Circulation
 - Respiration
 - Micturition
 - Gastrointestinal
- Segmental sympathetic and sacral (micturition, defecation, erection) reflexes











Results 3 - CI reliably discriminates MCS from UWS

One-R classifier with 10-fold cross-validation:

- → Cl_I selected as the best predictor
- → 90% accuracy, 7% false positive and 13% false negative rates
- → In comparison, Zero-R (always predicting MCS) has 53% accuracy
- → Lower error than clinical consensus

Confusion Matrix	
MCS	MCS as UWS
(true)	(false negative)
15	1
1	13
UWS as MCS	UWS
(false positive)	(true)





