

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

Francesco Riganello^{1, 2}, Stephen K. Larroque^{1*}, Mohamed Ali Bahri³, Lizette Heine⁴, Charlotte Martial¹, Manon Carrière¹, Vanessa Charland-Verville¹, Charlène Aubinet¹, Audrey Vanhauzenhuysse⁵, Camille Chatelle¹, Steven Laureys¹ and Carol Di Perri^{1, 6}

¹ Coma Science Group, University of Liège, Belgium

² Ricerca in Advanced NeuroRehabilitation, Istituto S. Anna, Italy

³ GIGA-Cyclotron Research Center In Vivo Imaging, University of Liege, Belgium

⁴ INSERM U1028 Centre de Recherche en Neurosciences de Lyon, France

⁵ Sensation & Perception Research Group, GIGA-Consciousness, University hospital of Liege, Belgium

⁶ Centre for Clinical Brain Sciences (CCBS), University of Edinburgh, United Kingdom

Motivation:

Heart rate variability (HRV) reflects the heart-brain two-way dynamic interactions[1-5]. HRV entropy analysis quantifies the unpredictability and complexity of the heart rate beats intervals and over multiple time scales using multiscale entropy (MSE)[6-8]. The complexity index (CI) provides a score of a system's complexity by aggregating the MSE measures over a range of time scales[8]. Most HRV entropy studies have focused on acute traumatic patients using task-based designs[9]. We here investigate the CI and its discriminative power in chronic patients with unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS) at rest, and its relation to brain functional connectivity.

Methods:

We investigated the CI in short (CIs) and long (CII) time scales in 16 UWS and 17 MCS sedated. CI for MCS and UWS groups were compared using a Mann-Whitney exact test. Spearman's correlation tests were conducted between the Coma Recovery Scale-revised (CRS-R) and both CI. Discriminative power of both CI was assessed with One-R machine learning model. Correlation between CI and brain connectivity (detected with functional magnetic resonance imagery using seed-based and hypothesis-free intrinsic connectivity) was investigated using a linear regression in a subgroup of 12 UWS and 12 MCS patients with sufficient image quality.

Results and Discussion:

Significant differences were found between MCS and UWS for CIs and CII ($0.0001 \leq p \leq 0.006$). Significant correlations were found between CRS-R and CIs and CII ($0.0001 \leq p \leq 0.026$). The One-R classifier selected CII as the best discriminator between UWS and MCS with 85% accuracy, 19% false positive rate and 12% false negative rate after a 10-fold cross-validation test. Positive correlations were observed between CI and brain areas belonging to the autonomic system.

CI was found to be significantly higher in MCS compared to UWS patients, with high discriminative power and lower false negative rate than the reported misdiagnosis rate of human assessors, providing an easy, inexpensive and non-invasive diagnosis tool. CI is correlated to functional connectivity changes in brain regions belonging to the autonomic nervous system, suggesting that CI can provide an indirect way to screen and monitor connectivity changes in this neural system. Future studies should investigate further the extent of CI's predictive power for other pathologies in the disorders of consciousness spectrum.

Figure 1

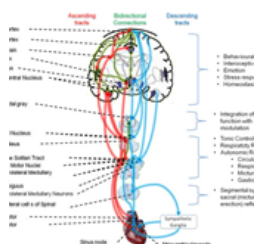


Figure 2

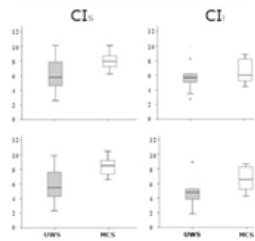
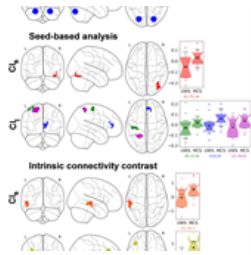


Figure 3



Acknowledgements

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), Mind Science Foundation, IAP research network P7/06 of the Belgian Government (Belgian Science Policy), Belgian National Plan Cancer (139), European Space Agency, Belspo and European Commission.

References

- [1] Palma J-A, Benarroch EE. Neural control of the heart: Recent concepts and clinical correlations. *Neurology* (2014) 83:261–271. doi:10.1212/WNL.0000000000000605 [2] Porges SW. The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. *Cleve Clin J Med* (2009) 76:S86–S90. doi:10.3949/ccjm.76.s2.17 [3] Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord* (2000) 61:201–216. [4] Kleiger RE, Miller JP, Bigger Jr. JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* (1987) 59:256–262. doi:10.1016/0002-9149(87)90795-8 [5] Harrison NA, Cooper E, Voon V, Miles K, Critchley HD. Central autonomic network mediates cardiovascular responses to acute inflammation: Relevance to increased cardiovascular risk in depression? *Brain Behav Immun* (2013) 31:189–196. doi:10.1016/j.bbi.2013.02.001 [6] Costa M, Goldberger AL, Peng CK, others. Multiscale Entropy Analysis (MSE). (2000). [7] Voss A, Schulz S, Schroeder R, Baumert M, Caminal P. Methods derived from nonlinear dynamics for analysing heart rate variability. *Philos Trans R Soc Math Phys Eng Sci* (2009) 367:277–296. doi:10.1098/rsta.2008.0232 [8] Costa M, Goldberger AL, Peng C-K. Multiscale entropy analysis of biological signals. *Phys Rev E* (2005) 71: doi:10.1103/PhysRevE.71.021906 [9] lula [9] Riganello F, Garbarino S, Sannita WG. Heart Rate Variability, Homeostasis, and Brain Function: A Tutorial and Review of Application. *J Psychophysiol* (2012) 26:178–203. doi:10.1027/0269-8803/a000080 [10] Cechetto DF, Shoemaker JK. Functional neuroanatomy of autonomic regulation. *NeuroImage* (2009) 47:795–803. doi:10.1016/j.neuroimage.2009.05.024 [11] Napadow V, Dhond R, Conti G, Makris N, Brown EN, Barbieri R. Brain Correlates of Autonomic Modulation: Combining Heart Rate Variability with fMRI. *NeuroImage* (2008) 42:169–177. doi:10.1016/j.neuroimage.2008.04.238

Keywords: disorders of consciousness (DOC), fMRI – functional magnetic resonance imaging, ECG, heart rate variability (HRV) analysis, machine learning (artificial intelligence), unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS), Central autonomic network, coma recovery scale-revised (CRS-R)

Conference: Belgian Brain Congress 2018 – Belgian Brain Council, LIEGE, Belgium, 19 Oct - 19 Oct, 2018. **Presentation Type:** e-posters

Topic: NOVEL STRATEGIES FOR NEUROLOGICAL AND MENTAL DISORDERS: SCIENTIFIC BASIS AND VALUE FOR PATIENT-CENTERED CARE

Citation: Riganello F, Larroque SK, Bahri M, Heine L, Martial C, Carrière M, Charland-Verville V, Aubinet C, Vanhudenhuysse A, Chatelle C, Laureys S and Di Perri C (2018). 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. *Front. Neurosci. Conference Abstract: Belgian Brain Congress 2018 – Belgian Brain Council*. doi: 10.3389/conf.fnins.2018.95.00018

Received: 30 Jul 2018; **Published Online:** 09 Aug 2018.

* **Correspondence:** Mr. Stephen K Larroque, Coma Science Group, University of Liège, Liège, Liège, 4000, Belgium, lrq3000@gmail.com