Restoring complexity via psychedelics in patients with DoC: study protocol for two placebo-controlled RCTs

Paolo Cardone[1,2], Arthur Bonhomme[1], Vincent Bonhomme[3,4], Gregory Scott[5], Naji Alnagger[1,2], Christopher Timmermann[5,6], Johannes G. Ramaekers[7], Franz X. Vollenweider[8,9], Robin L. Carhart-Harris[5,6], Steven Laureys[1,2], Charlotte Martial[1,2*], Olivia Gosseries[1,2*]

[1]Coma Science Group, GIGA-Consciousness, University of Liège, Belgium; [2]Centre du Cerveau², University Hospital of Liège, Belgium; [3]Anesthesia and Intensive Care Laboratory, GIGA-Consciousness, GIGA Institute, University of Liège, Belgium; [4]Department of Anesthesia and Intensive Care Medicine, Liege University Hospital, Liege, Belgium; [5]The Computational, Cognitive and Clinical Neuroimaging Laboratory, Department of Brain Sciences, Imperial College London, UK; [6]Department of Medicine, Centre for Psychedelic Research, Department of Brain Sciences, Imperial College London, UK; [7]Faculty of Psychology and Neuroscience, Maastricht University, The Netherlands; [8]Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Switzerland; [9]Center for Neuroscience Research, University and ETH Zurich, Switzerland; *Contributed equally

Introduction

- Brain complexity is high in conscious states and low in unconscious ones.[1-3]
- Patients with post-comatose disorders of consciousness (DoC) have low complexity.
  - Increasing complexity should increase conscious level.[4]
- Ketamine and psilocybin increase complexity in healthy participants.
  - Possible treatment for DoC.[4-7]

Methods

Two double-blind, randomized, placebo-controlled clinical trials (**Figure 1**):

- Sub-anesthetic dose of IV ketamine (0.5mg/Kg)
- Moderate dose of oral psilocybin (25mg)
- 30 patients with DoC in each RCT

Each RCT has three phases (Observational, Experimental and Follow-up). See **Figure 2**

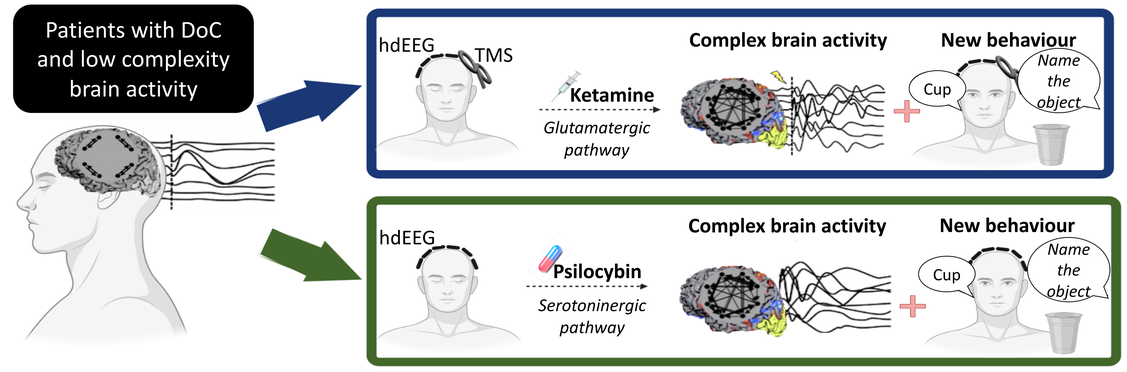

Figure 1 - Graphical abstract : Patients with DoC have low brain complexity which is linked to their impairments. We will use sub-anesthetic doses of ketamine and psilocybin to increase brain complexity and conscious level.

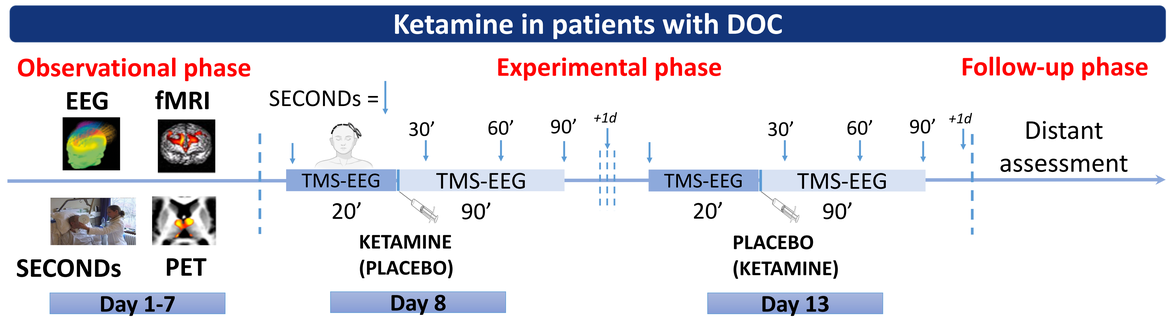

Figure 2 – Protocol: Patients undergo (1) a baseline observational phase with multimodal testing, (2) an experimental phase, whereby they receive the drug and the placebo, and (3) follow-up via distant assessment.

Expected results

- Primary outcome:
  - New conscious behaviours and ↑ brain complexity = Responders
  - ↑ Brain complexity in patients who have memories of the session
- Secondary outcomes:
  - EEG, fMRI and PET: Responders ≠ Non-responders

Conclusion

Our project addresses several questions (**Figure 2**):

1. Do ketamine and psilocybin increase conscious level in patients with DoC?
2. What predict responsiveness to ketamine and psilocybin?
3. What is the serotoninergic and glutamatergic contribution to complexity?
4. What is the link between complexity and consciousness?

Bibliography

1. Sarasso S, Casali AG, Casarotto S, Rosanova M, Sinigaglia C, Massimini M. *Neurosci Conscious*. (2021)
2. Casali AG, Gosseries O, Rosanova M, et al. *Sci Transl Med*. (2013)
3. Sarasso S, Boly M, Napolitani M, et al., *Curr Biol*. (2015)
4. Scott G, Carhart-Harris RL.. *Neurosci Conscious*. (2019)
5. Schartner MM, Carhart-Harris RL, Barrett AB, Seth AK, Muthukumaraswamy SD., *Sci Rep*. (2017)
6. Farnes N, Juel BE, Nilsen AS, Romundstad LG, Storm JF., *PLoS One*. (2020)
7. Peterson A, Tagliazucchi E, Weijer C., *Neurosci Conscious*. (2019)
8. Comolatti R, Pigorini A, Casarotto S, et al., *Brain Stimul*. (2019)
9. Aubinet C, Cassol H, Bodart O, et al. *Ann Phys Rehabil Med* (2020).
10. Oizumi M, Albantakis L, Tononi G., *PLOS Comput Biol*. (2014)

p.cardone@uliege.be