

Complexity-enhancing drugs to treat disorders of consciousness (DoC): a ketamine study

Presenter:

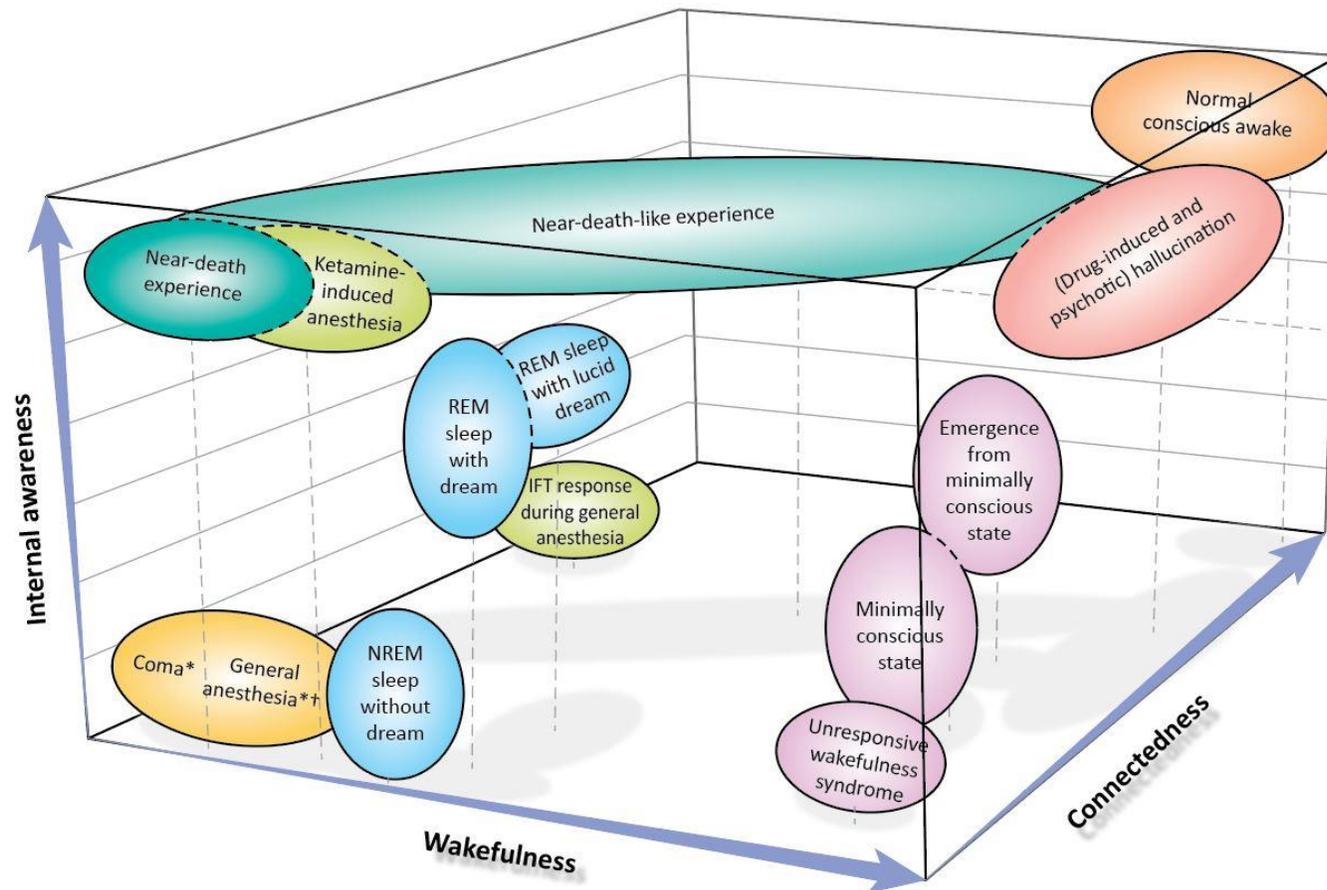
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Clinical representation of consciousness



- Three axis
 - Wakefulness
 - Awareness
 - Connectedness
- Mostly correlated... unless brain damage!

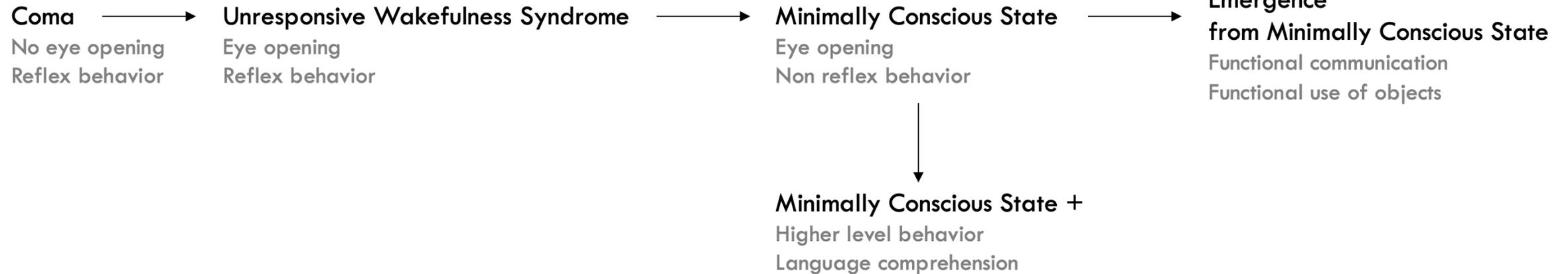
*: Without subjective experience

†: Without isolated forearm technique (IFT) response



Disorder of consciousness

CLINICAL EXAMINATION





Problem with behavioural assessment



Clinician

- Extensive training
- Repeated assessments
- Individual biases

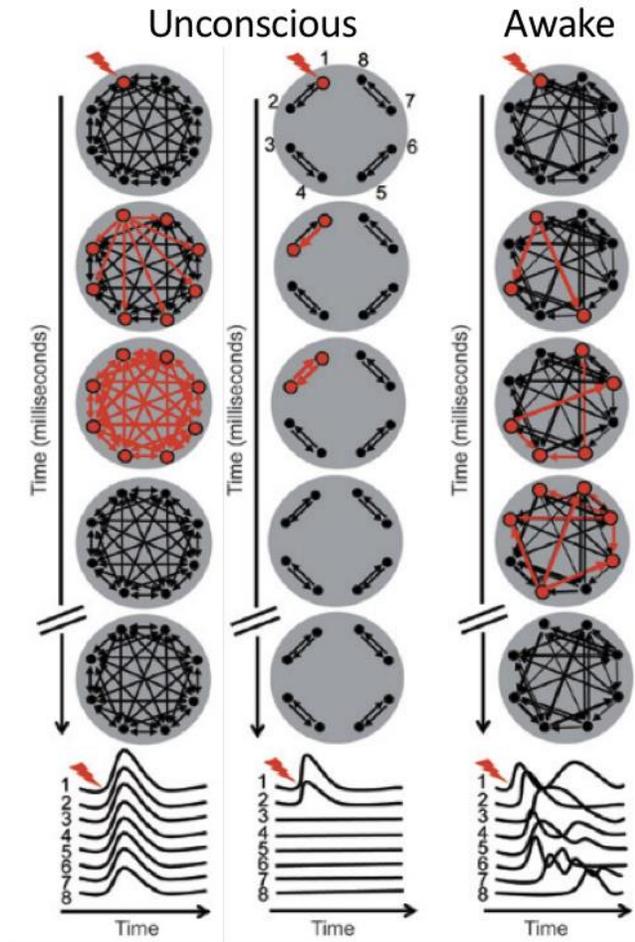


Patient

- Deafness or blindness
- Paralysis
- Aphasia
- Agnosia
- Fluctuating awareness
- Pain
- Medical complication
- Sedation
- Lack of cooperation



The case of complexity

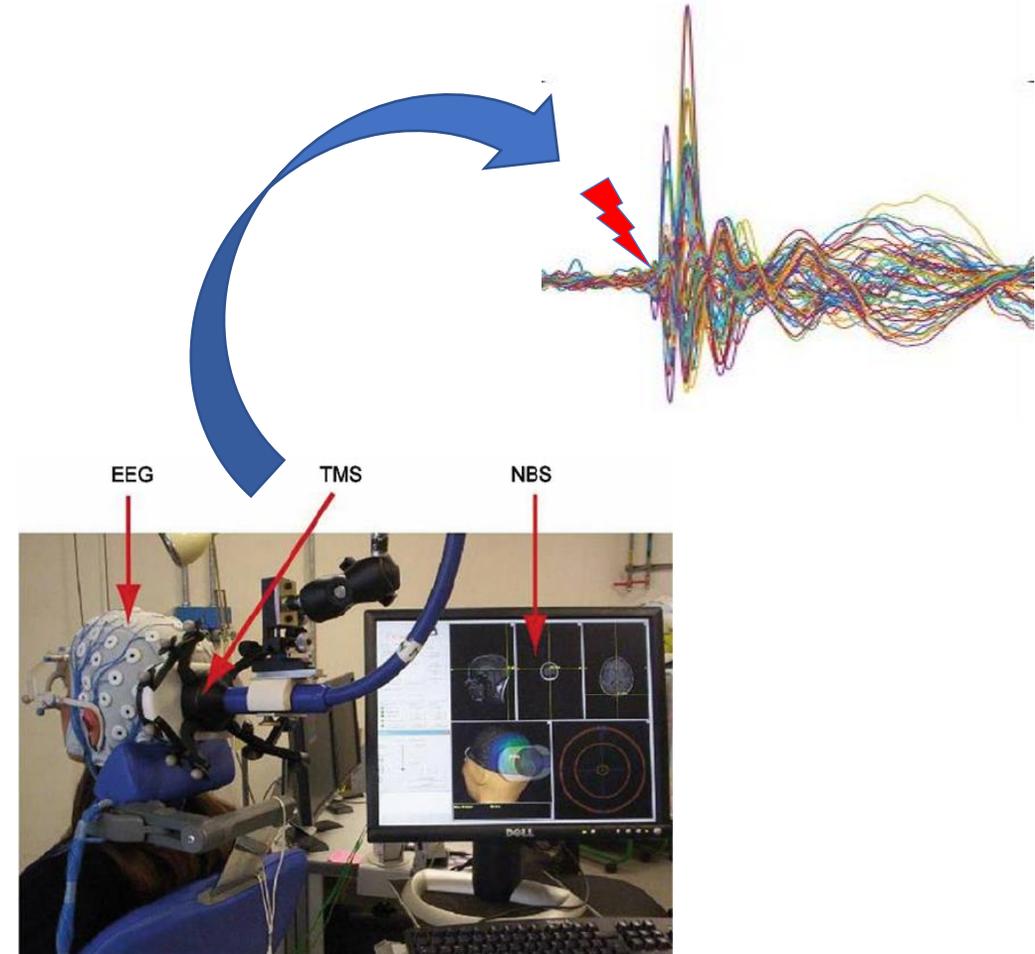


- Graph theory representation
- Degree of integration and information
- Wakefulness is complex over **time and space**



How to measure it in humans?

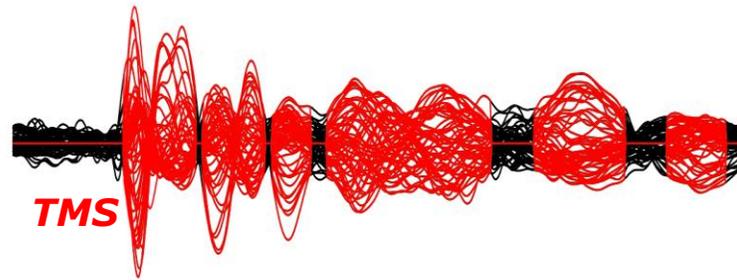
- Transcranial magnetic stimulation coupled with electroencephalography (TMS-EEG)
- Neuronavigation
 - Online modelling to know where we target



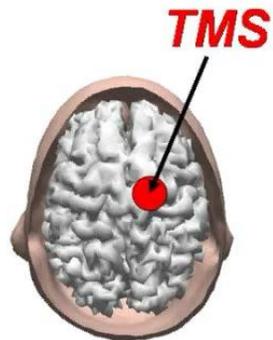


Brain responses and consciousness

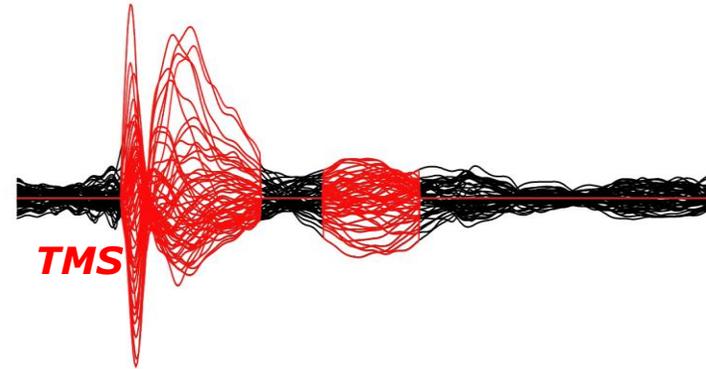
Conscious



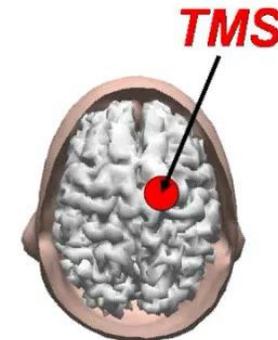
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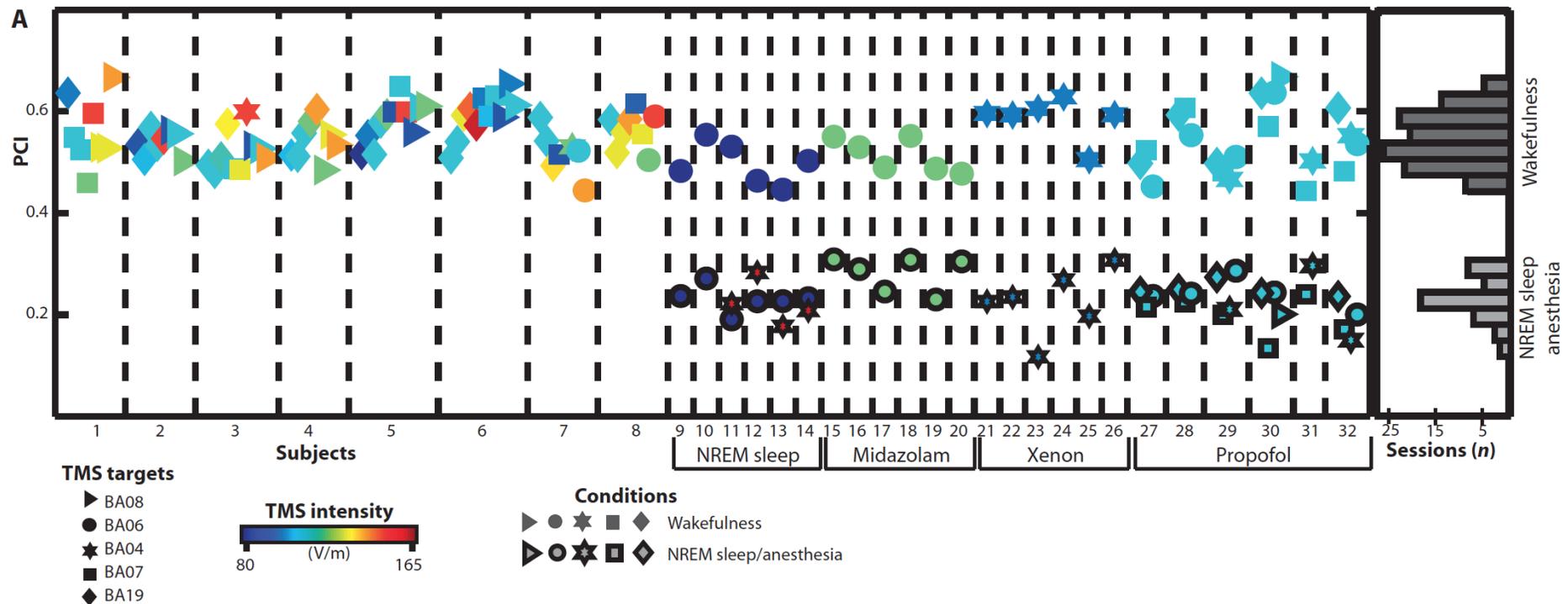
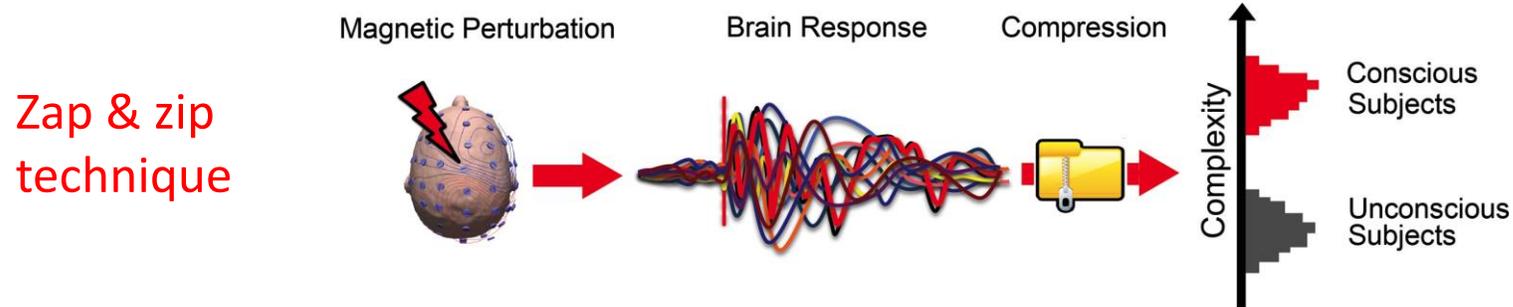
Unconscious



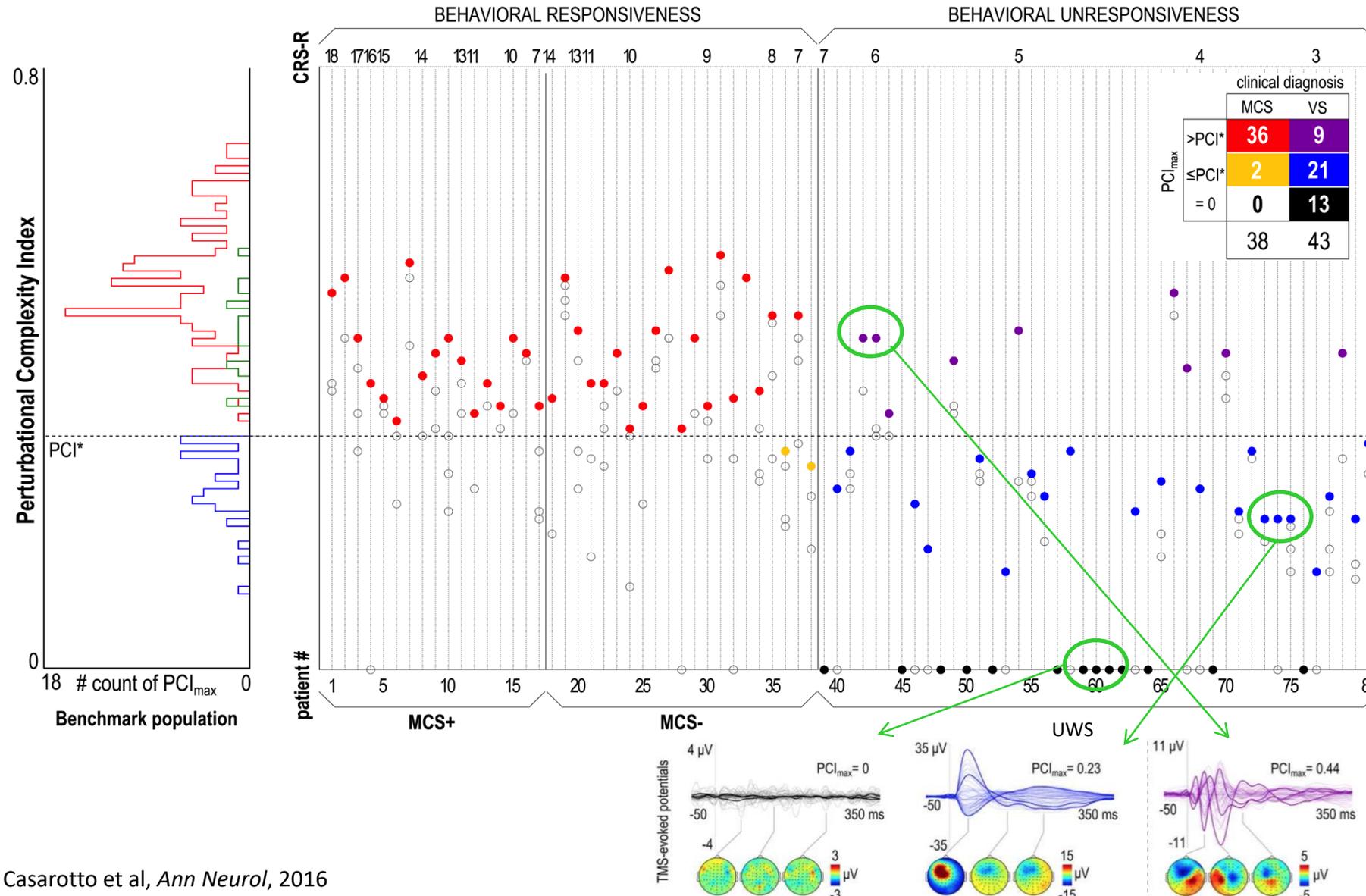
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Perturbational Complexity Index (PCI)

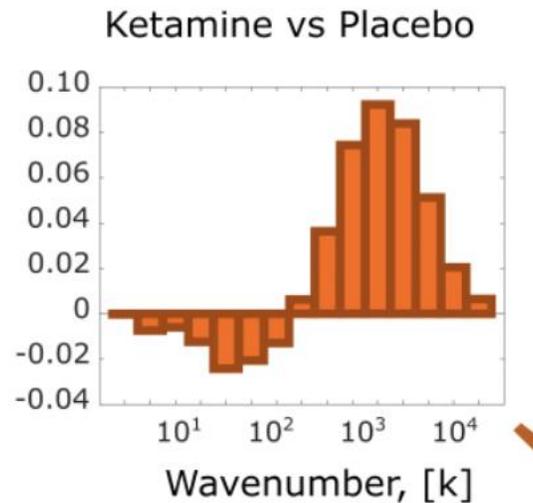
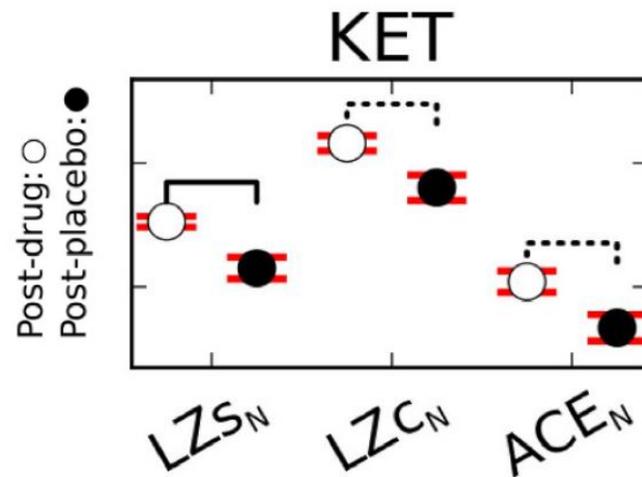


Complexity and DoC





Could we increase complexity?



- In healthy participants psychedelics increase complexity

- Results replicate through different modalities and studies

Schartner et al. ,*Sci. Rep.*, 2017

Luppi et al.. *BioRxiv*, 2020

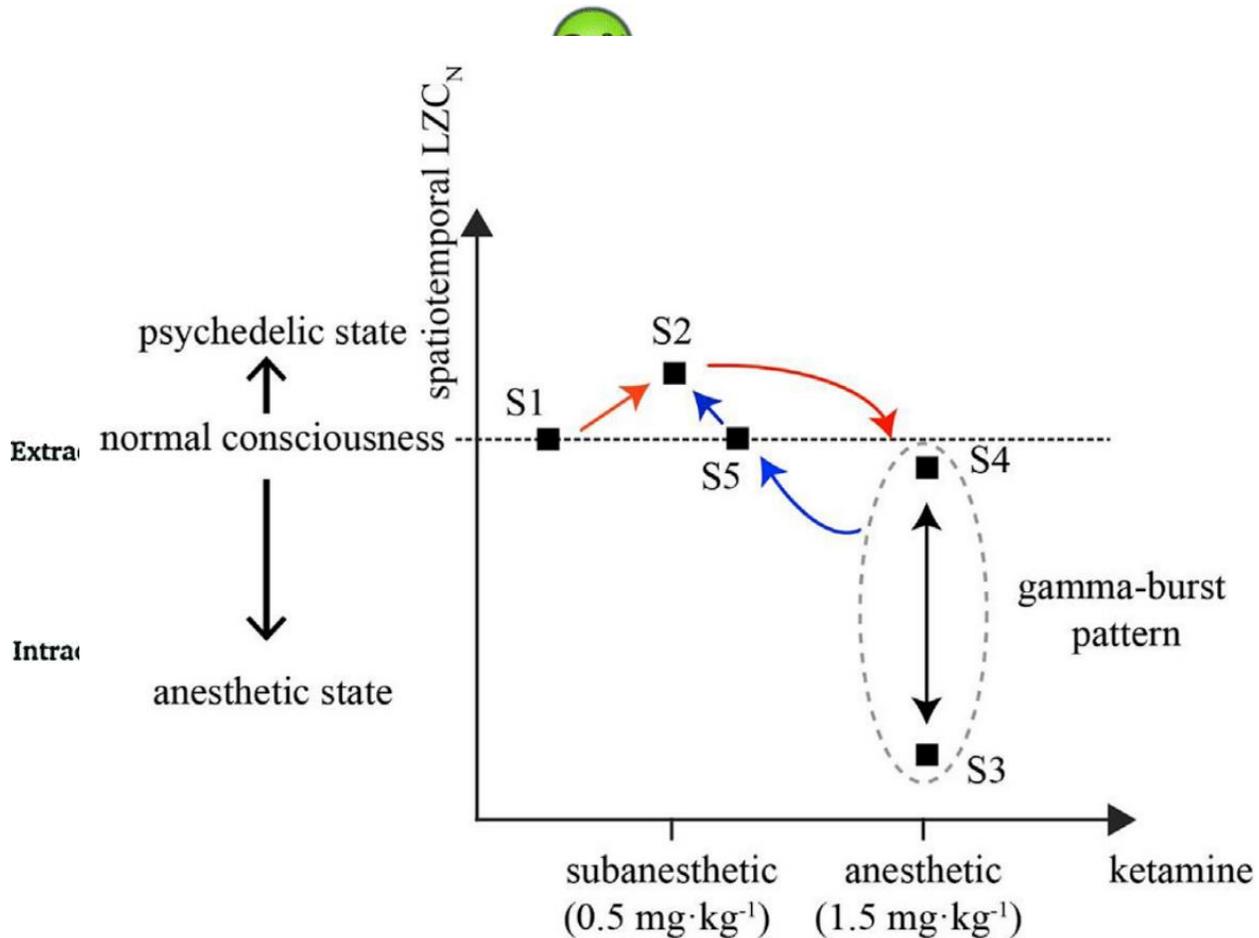


Aims of the project

- Psychedelics as treatment
 - Can ketamine ameliorate conscious state in DoC patients?
- Look for baseline biomarkers of efficacy
 - Future predictions on responsiveness?



Why ketamine?

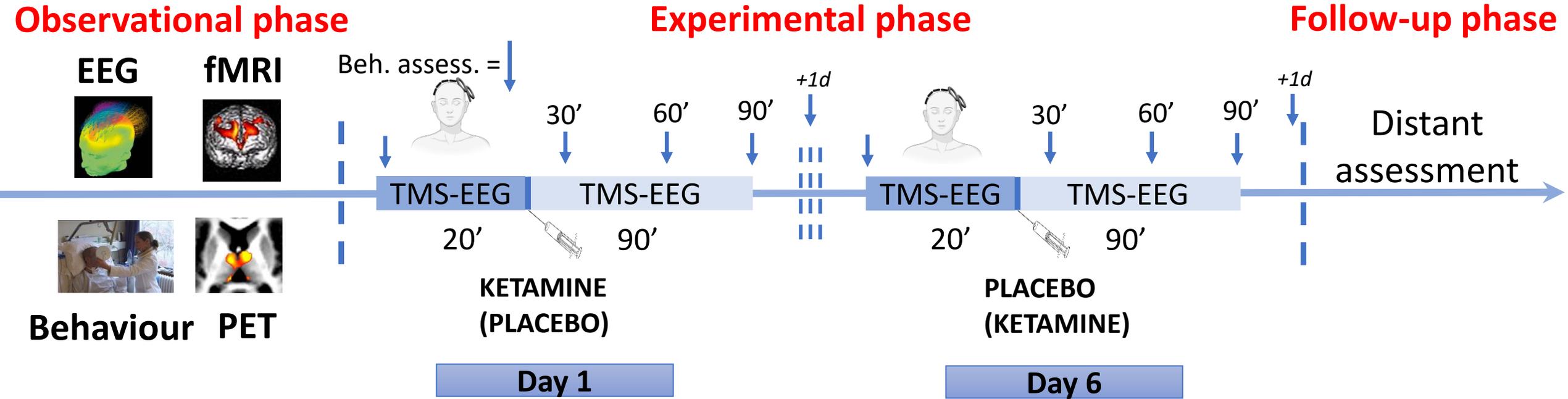


- Anesthetic agent
 - NMDA antagonist
- Psychedelic effects in subanesthetic doses
- Ketamine is widely used in clinical settings

Protocol – Visual representation



Ketamine in patients with DoC



- Additional info:

- 30 patients stratified by diagnosis (UWS/MCS)
- Ketamine given through a targeted-controlled infusion (TCI)



Hypothesis

1. Complexity proportional to Ket concentration
2. New signs of consciousness
3. Baseline differences between responders and non-responders



Our expectations

	Increased complexity	Same complexity
New signs of consciousness	New treatments	Independent phenomena
No novel signs of consciousness	Independent phenomena or disconnected consciousness	Psychedelics need an already complex system?



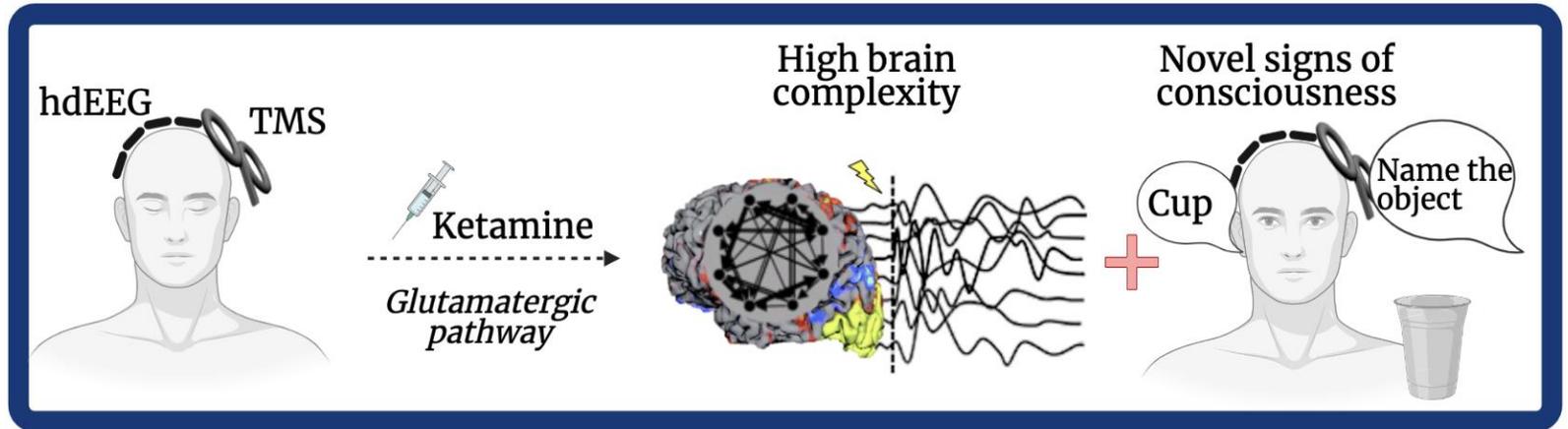
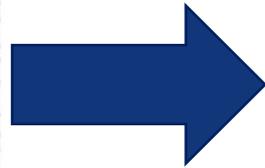
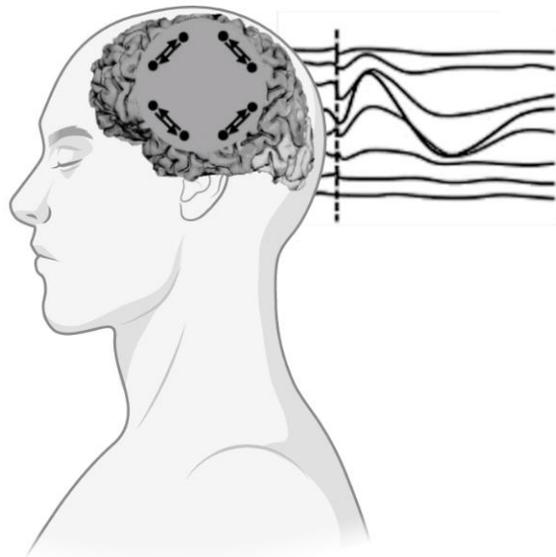
Where are we at

- Approved by the local and national ethical committee
 - EudraCT number: 2021-002321-23
- First pilot in May!



Summary

Patients with DOC
and low brain
complexity





Take home messages

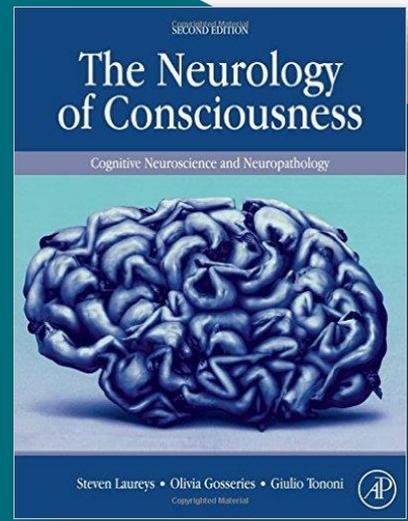
- Complexity and consciousness are intertwined
- Complexity is low in DoC patients
- Psychedelics increase complexity in healthy participants
- Ketamine might be used as a treatment for DoC



Thank you for your attention !



Patients & families



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