

Exploring the actions of ketamine: Abnormal fast brain rhythms in freely moving rodents

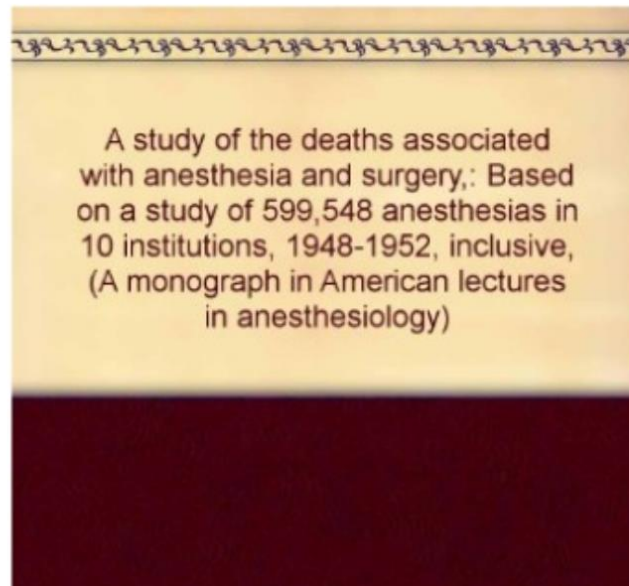
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Laboratory of Neuroinformatics, Nencki Institute of
Experimental Biology, PAN

Historical Background

A study of the deaths associated with anesthesia and surgery,: Based on a study of 599,548 anesthetics in 10 institutions, 1948-1952, inclusive,

Henry K Beecher



**Mortality rate:
1:1560**

**“.....anesthesia
should be viewed
as a major public
health problem”**

1950's Parke-Davis developed phencyclidine as an anesthetic (Sernyl)

Historical Background - Ketamine

- PCP “impressive similarity [to] . . . certain primary symptoms of the schizophrenic process” & uncontrollable emergence (Luby et al., 1959)
- 1962 - Ketamine – derivative of PCP synthesized
- Used as an anesthetic – but milder emergence reactions can occur
- Low doses produce transient psychotic-like state; thought disorders, loose associations, concreteness, delusions of reference, perception distortions
- Reinstates psychoses in stabilised SZ patients (Lahti et al., 1995)

BRIEF REPORTS

Antidepressant Effects of Ketamine in Depressed Patients

Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren,
George R. Heninger, Dennis S. Charney, and John H. Krystal



Does the intensity of dissociation predict antidepressant effects 24 hours after infusion of racemic ketamine and esketamine in treatment-resistant depression? A secondary analysis from a randomized controlled trial

Ana Teresa Caliman-Fontes, Manuela Telles, Lívia N. F. Guerreiro-Costa, Roberta Ferrari Marback, Breno Souza-Marques, Daniel H. Lins-Silva, Cassio Santos-Lima, Taiane de Azevedo Cardoso, Flávio Kapczinski, Acioly L.T. Lacerda, Lucas C. Quarantini

<http://dx.doi.org/10.47626/2237-6089-2022-0593>

Trends Psychiatry Psychother, Ahead of Print, 2023



Research paper

The relationship between subjective effects induced by a single dose of ketamine and treatment response in patients with major depressive disorder: A systematic review

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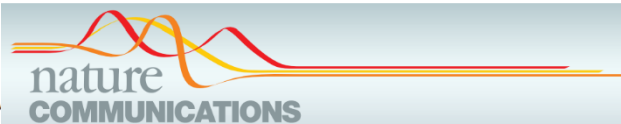


INVITED REVIEW



Are “mystical experiences” essential for antidepressant actions of ketamine and the classic psychedelics?

Kenji Hashimoto¹



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PERSPECTIVE

<https://doi.org/10.1038/s41467-020-20190-4>

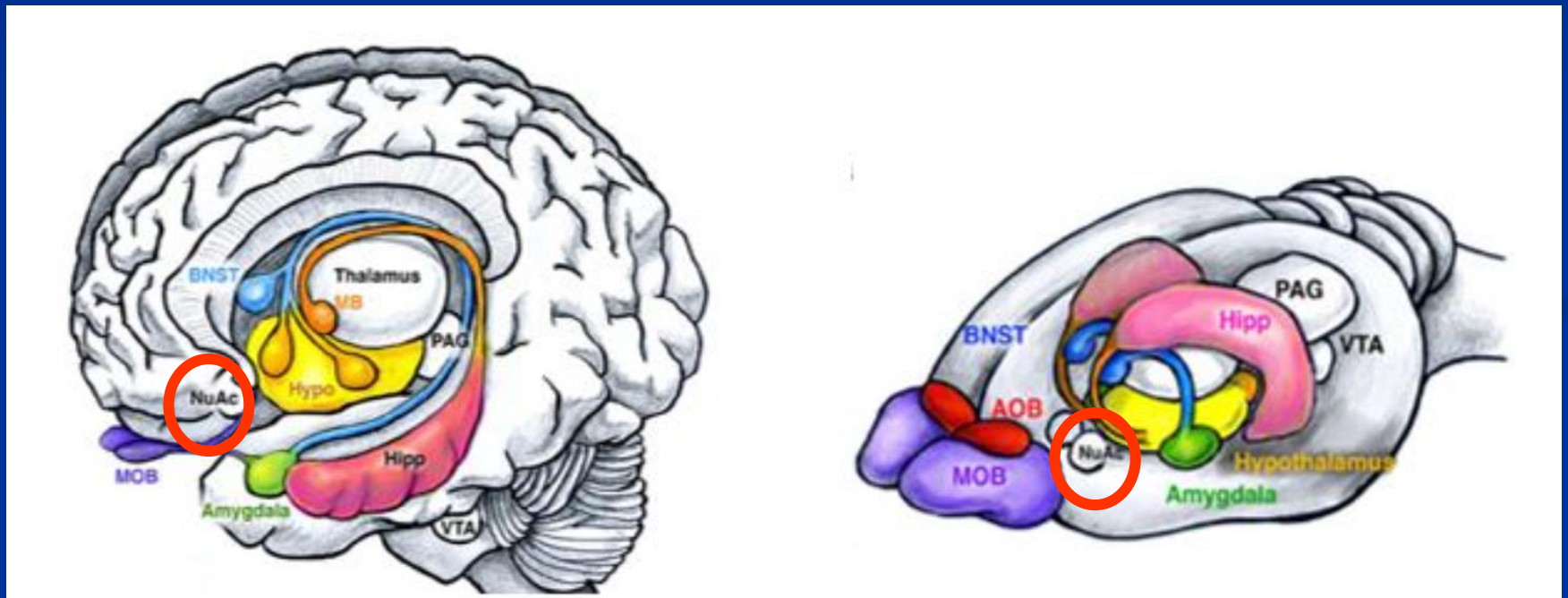
OPEN

The role of dissociation in ketamine’s antidepressant effects

Elizabeth D. Ballard ¹ & Carlos A. Zarate Jr.¹

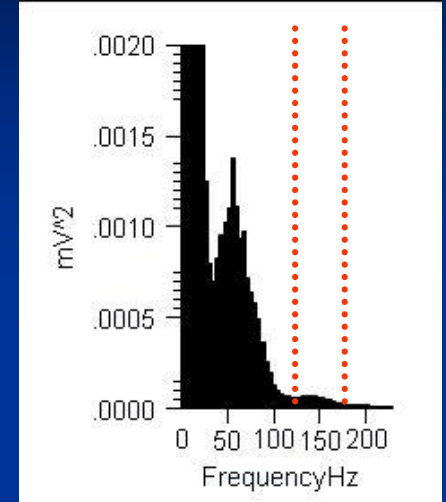
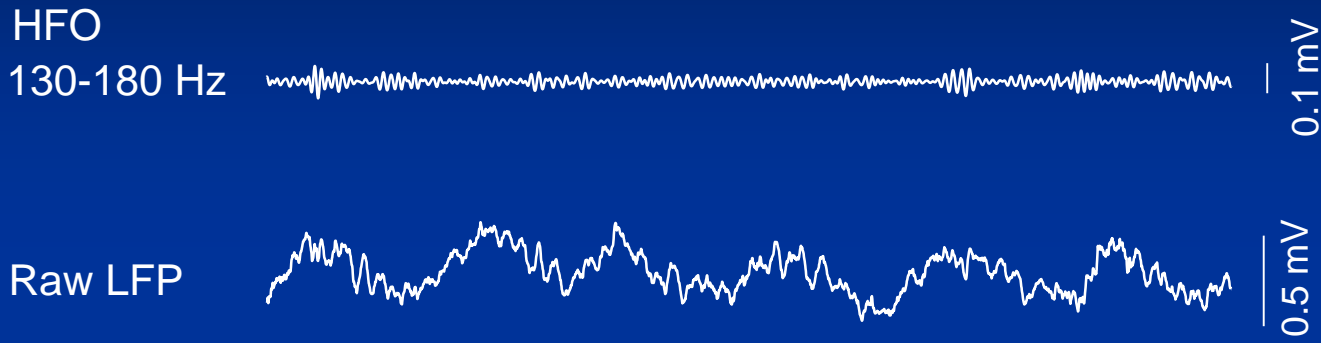
“...it remains unknown whether the dissociative experiences associated with ketamine administration represent a core feature of the antidepressant response or a side effect”

Use experimental rodents to understand how ketamine affects brain activity

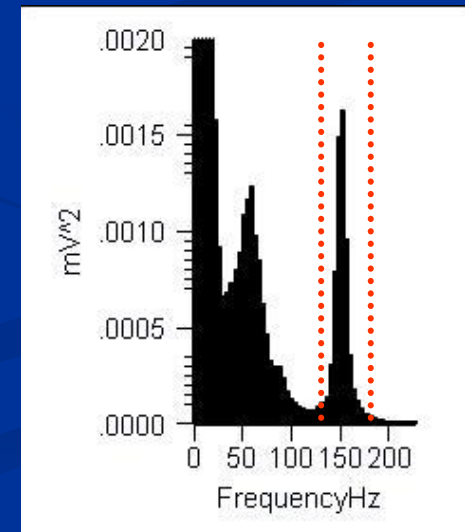
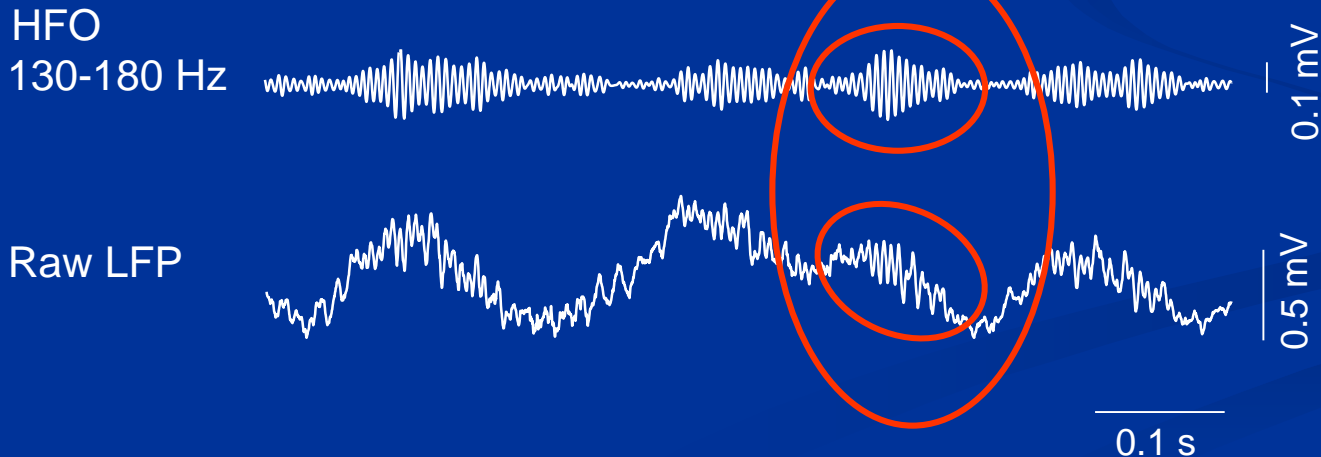


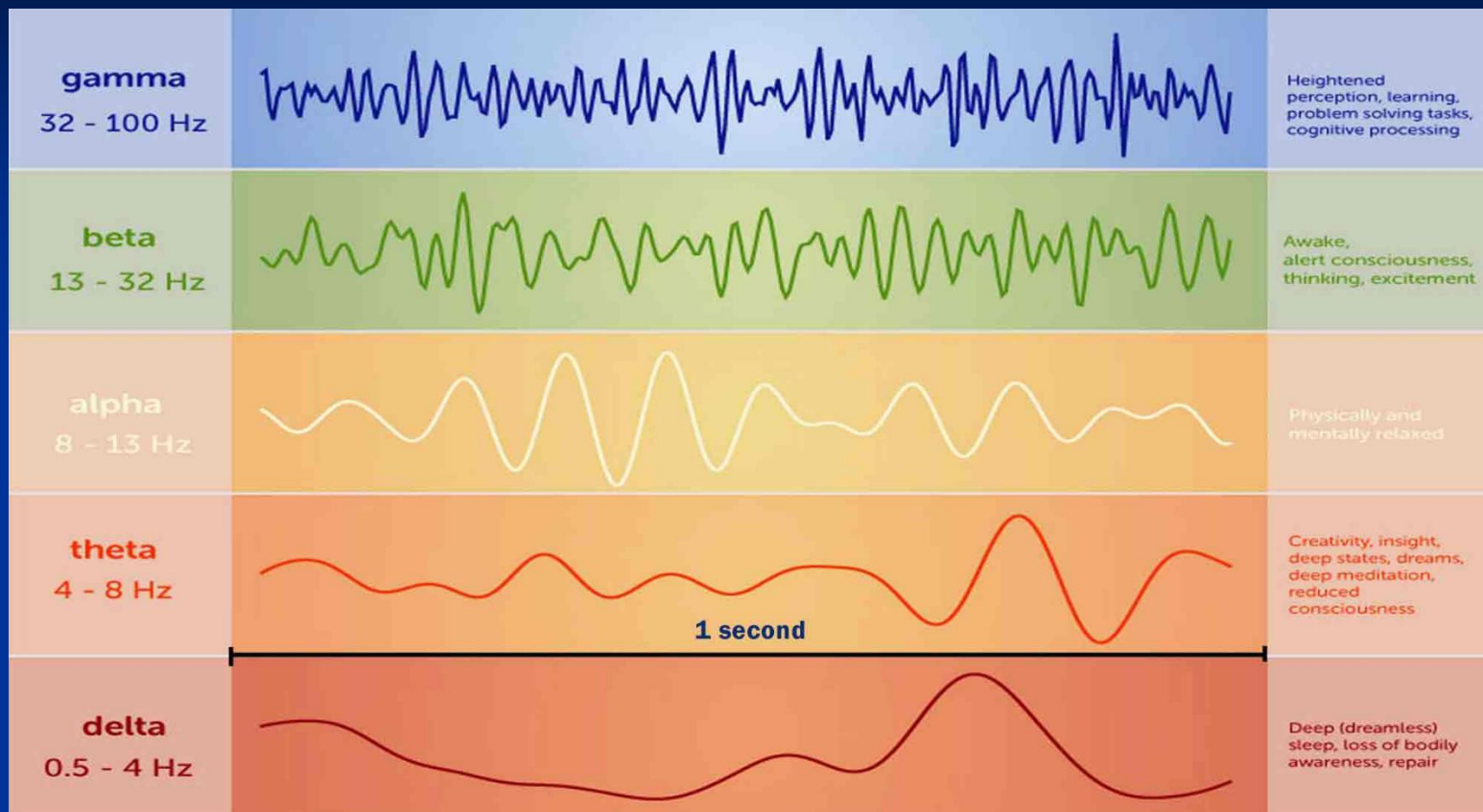
Ketamine increases HFO power in the ventral striatum

Saline



Ketamine

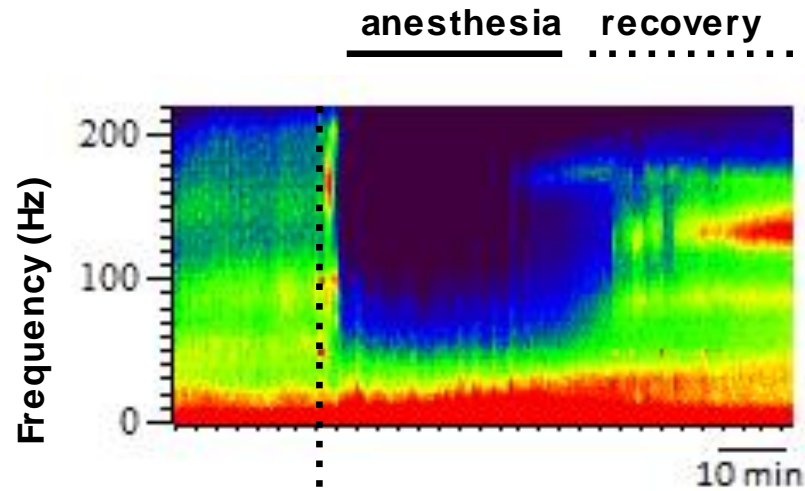




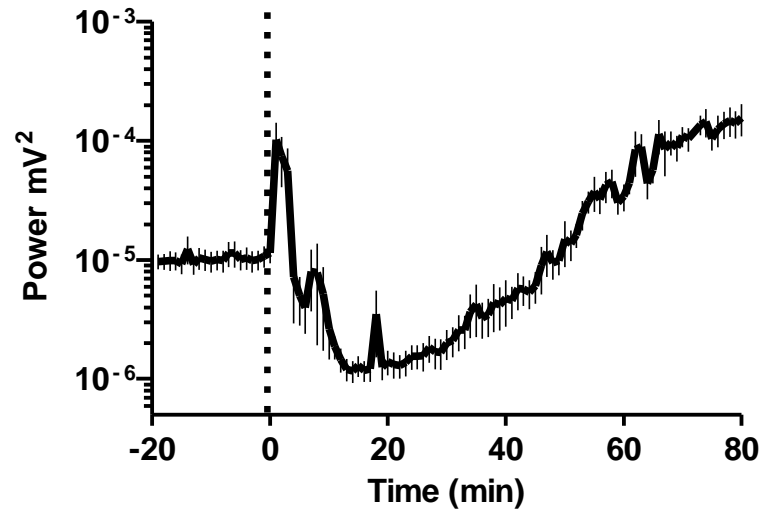
<https://psychedelicreview.com/altered-oscillations-the-modulatory-effect-of-dmt-on-brain-waves/>

HFO increases during emergence from ketamine anesthesia

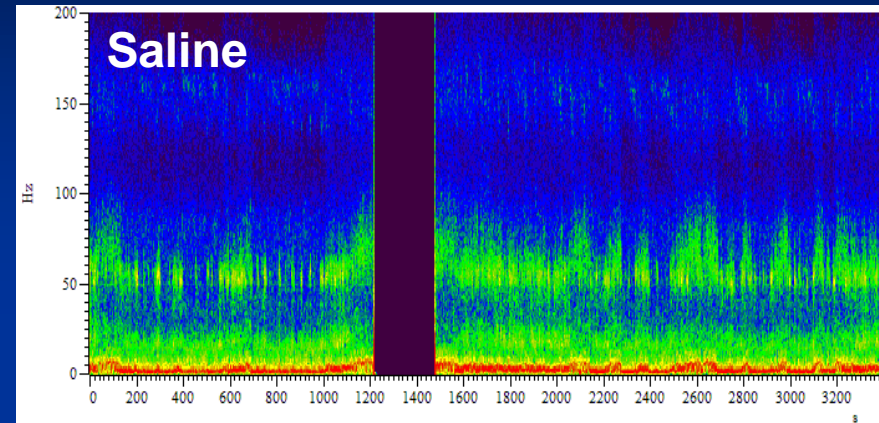
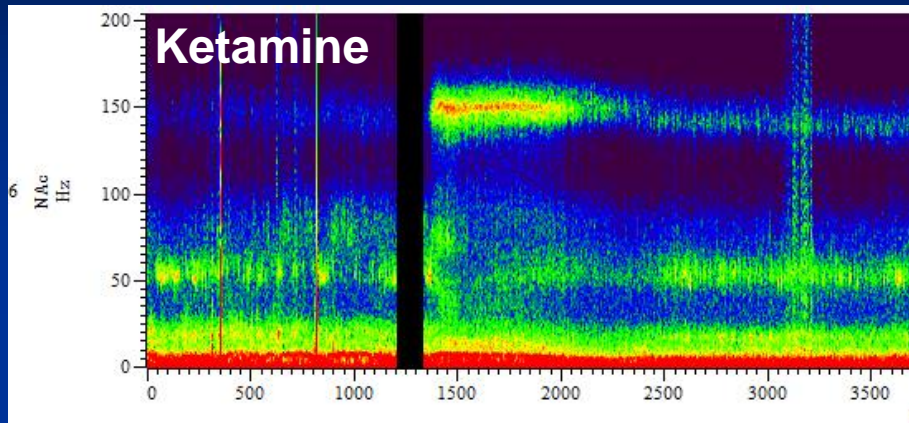
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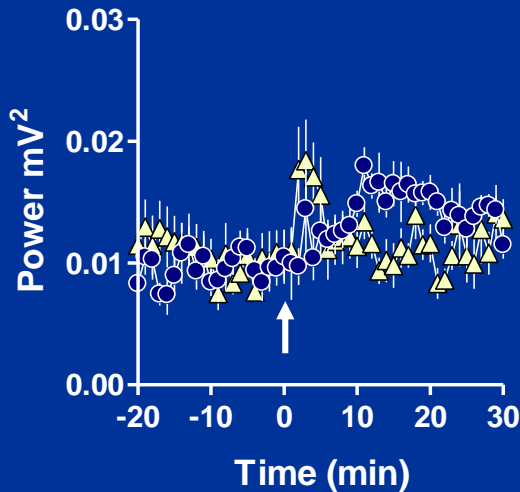


Increases in HFO power are the dominant oscillatory change after ketamine injection

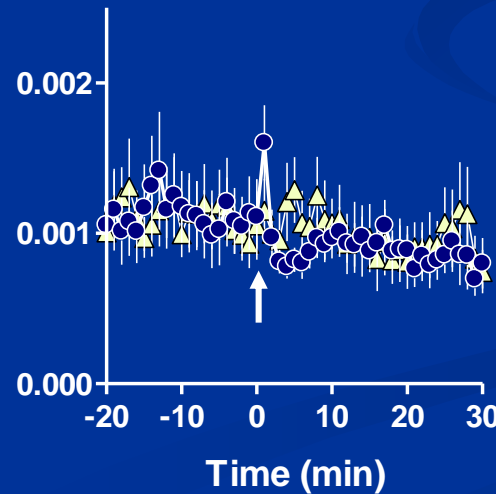


○ Ketamine ▲ Saline

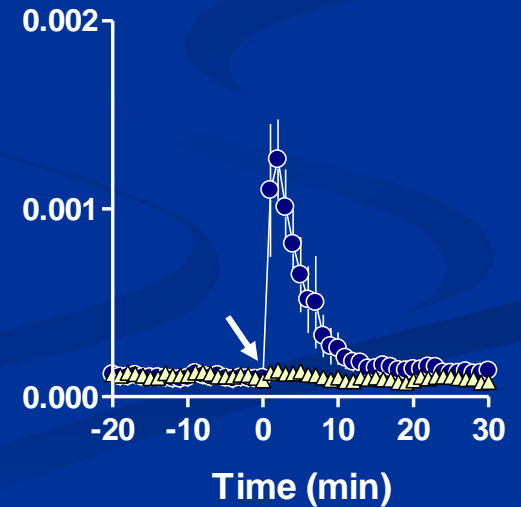
Delta



Gamma



HFO



NMDAR antagonist (ketamine, PCP, MK801) HFO in other rodent brain regions

Cortex – Motor/Visual/Prefrontal/Retrosplenial

Nicolas et al., 2011; Jones et al., 2012; Kulikova et al., 2012; Phillips et al., 2012; Olszewski et al., 2013; Hiyoshi et al 2014; Cordon et al., 2015; Flores et al., 2015; Sapkota et al., 2016; Schmitt et al. 2016 SfN Abs. Lee et al., 2017; Pittman-Polletta et al., 2017

Ventral Striatum/nucleus accumbens

Hunt et al., 2006; Hunt et al., 2008; Hunt et al., 2011; Olszewski et al., 2013; Schmitt et al. 2016 SfN Abs.; Lee et al 2017

Dorsal Striatum

Nicolas et al., 2011; Hunt et al., 2011; Olszewski et al., 2013; Cordon et al., 2015; Schmitt et al., 2016 SfN Abs.; Kealy et al., 2017

Hippocampus

Hunt et al., 2011; Caixeta et a., 2013; Kealy et al., 2017; Lee et al., 2017


Amygdala

Hakami et al., 2009; Rejniak et al in preparation

Subthalamic Nucleus/Substantia Nigra




Nicolas et al., 2011; Cordon et al., 2015

Cats

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Cortical high-frequency oscillations (≈ 110 Hz) in cats are state-dependent and enhanced by a subanesthetic dose of ketamine

 Santiago Castro-Zaballa,  Joaquín González, Matías Cavelli, Diego Mateos,  Claudia Pascovich, Adriano Tort, Mark Jeremy Hunt, Pablo Torterolo

doi: <https://doi.org/10.1101/2023.05.31.543142>

scientific reports



OPEN **Network and synaptic mechanisms underlying high frequency oscillations in the rat and cat olfactory bulb under ketamine-xylazine anesthesia**

Władysław Średniawa^{1,2}, Jacek Wróbel¹, Ewa Kublik¹, Daniel Krzysztof Wójcik^{1,3}, Miles Adrian Whittington⁴ & Mark Jeremy Hunt^{1,4,5}


Monkeys

Electrocorticographic effects of acute ketamine on non-human primate brains


Tianfang Yan¹, Katsuyoshi Suzuki², Seiji Kameda¹, Masashi Maeda³, Takuma Mihara³, Masayuki Hirata^{3,4,5}

Humans

Psychopharmacology (2023) 240:59–75
<https://doi.org/10.1007/s00213-022-06272-9>

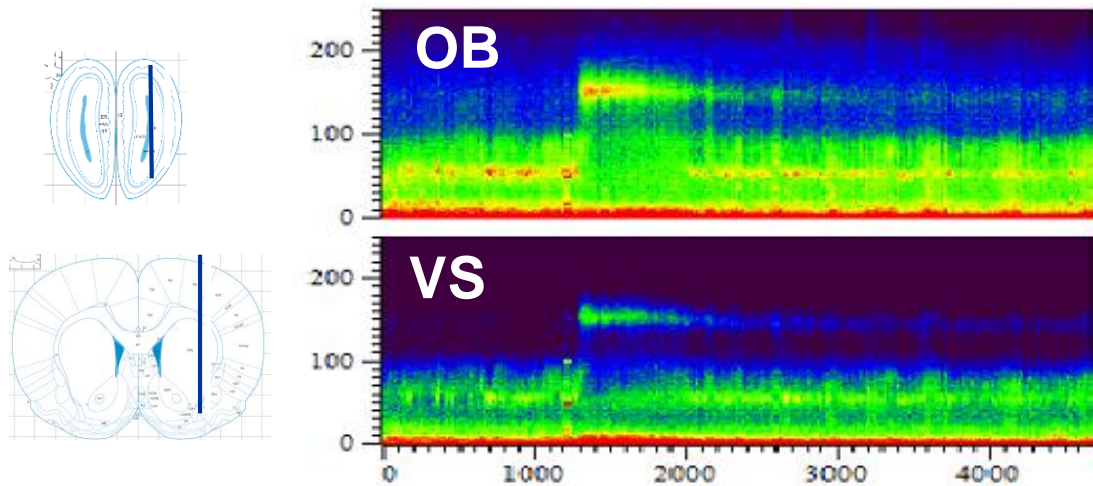
ORIGINAL INVESTIGATION 

The effect of ketamine and D-cycloserine on the high frequency resting EEG spectrum in humans

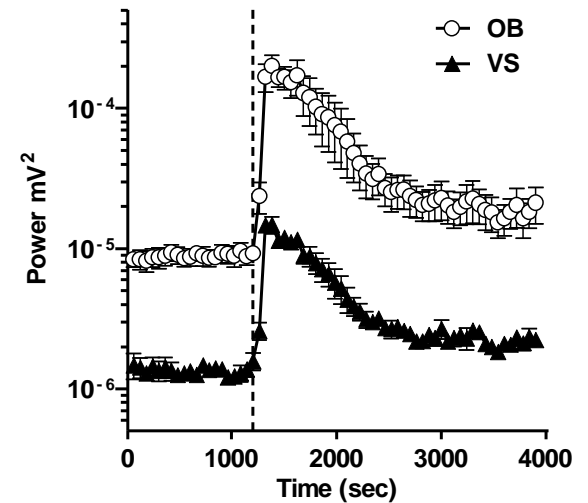
J. F. Nottage^{1,2}  · A. Gabay³ · K. De Meyer² · K. F. Herrik⁴ · J. F. Bastlund⁴ · S. R. Christensen⁴ · S. Gijsen^{5,6} · M. A. Mehta²

Ketamine HFO are larger in the olfactory bulb vs. ventral striatum

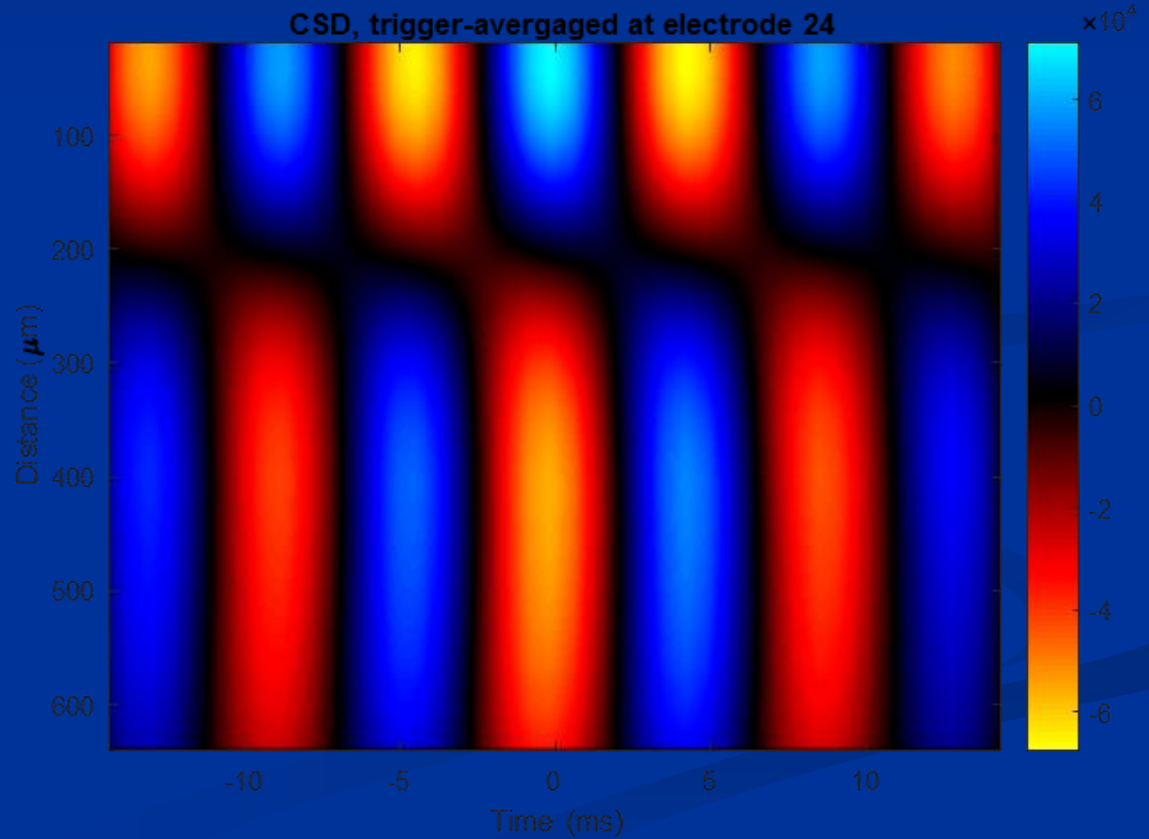
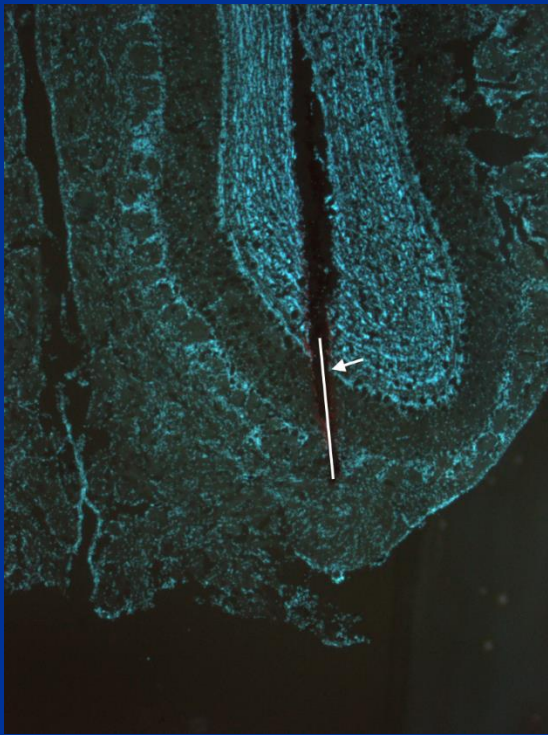
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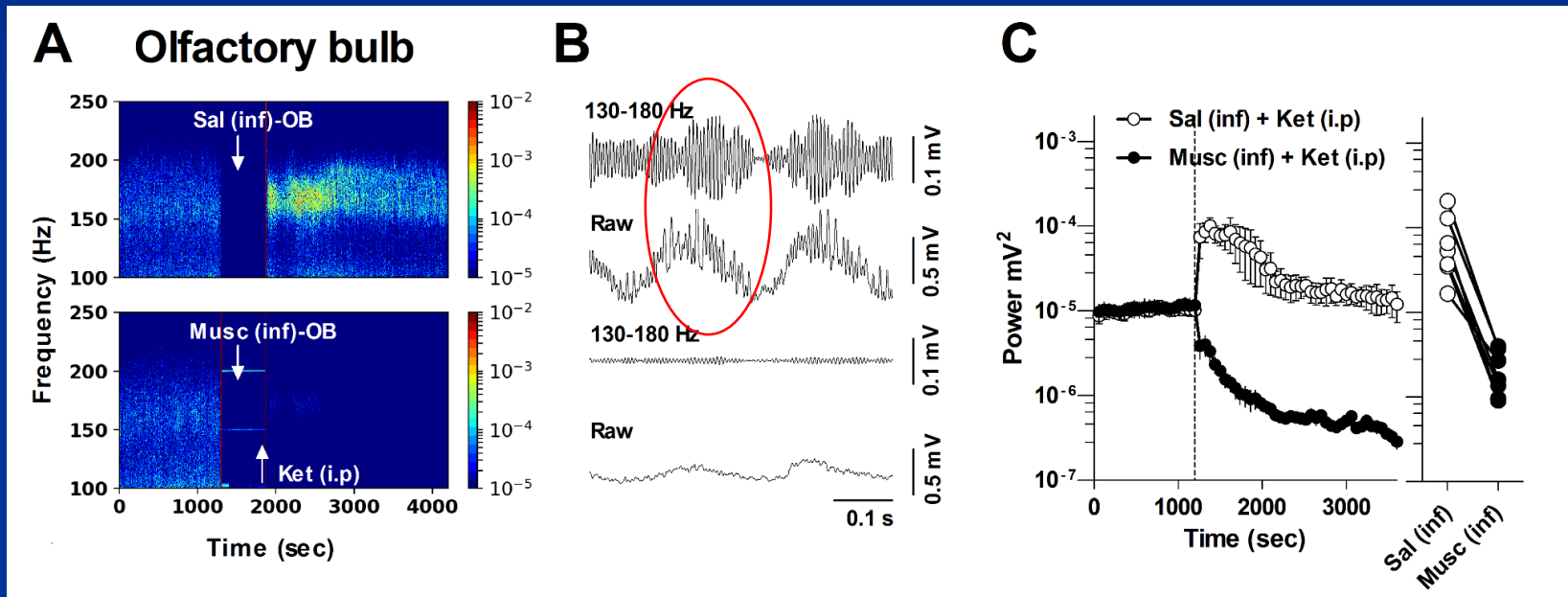
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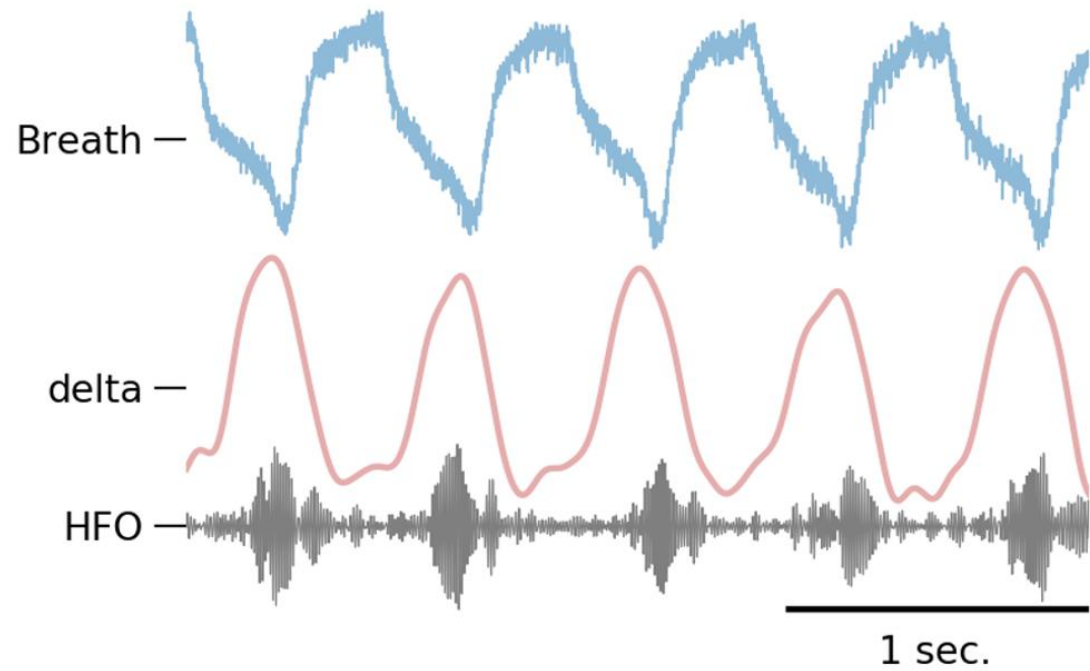
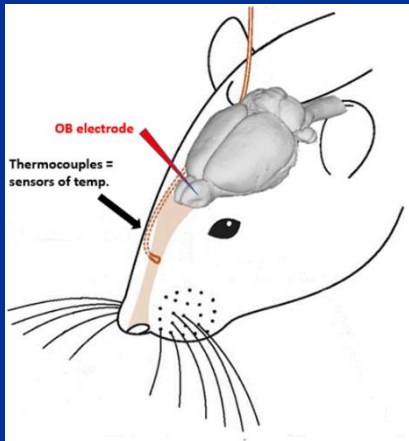


Ketamine-HFO reverses phase at/close to mitral layer

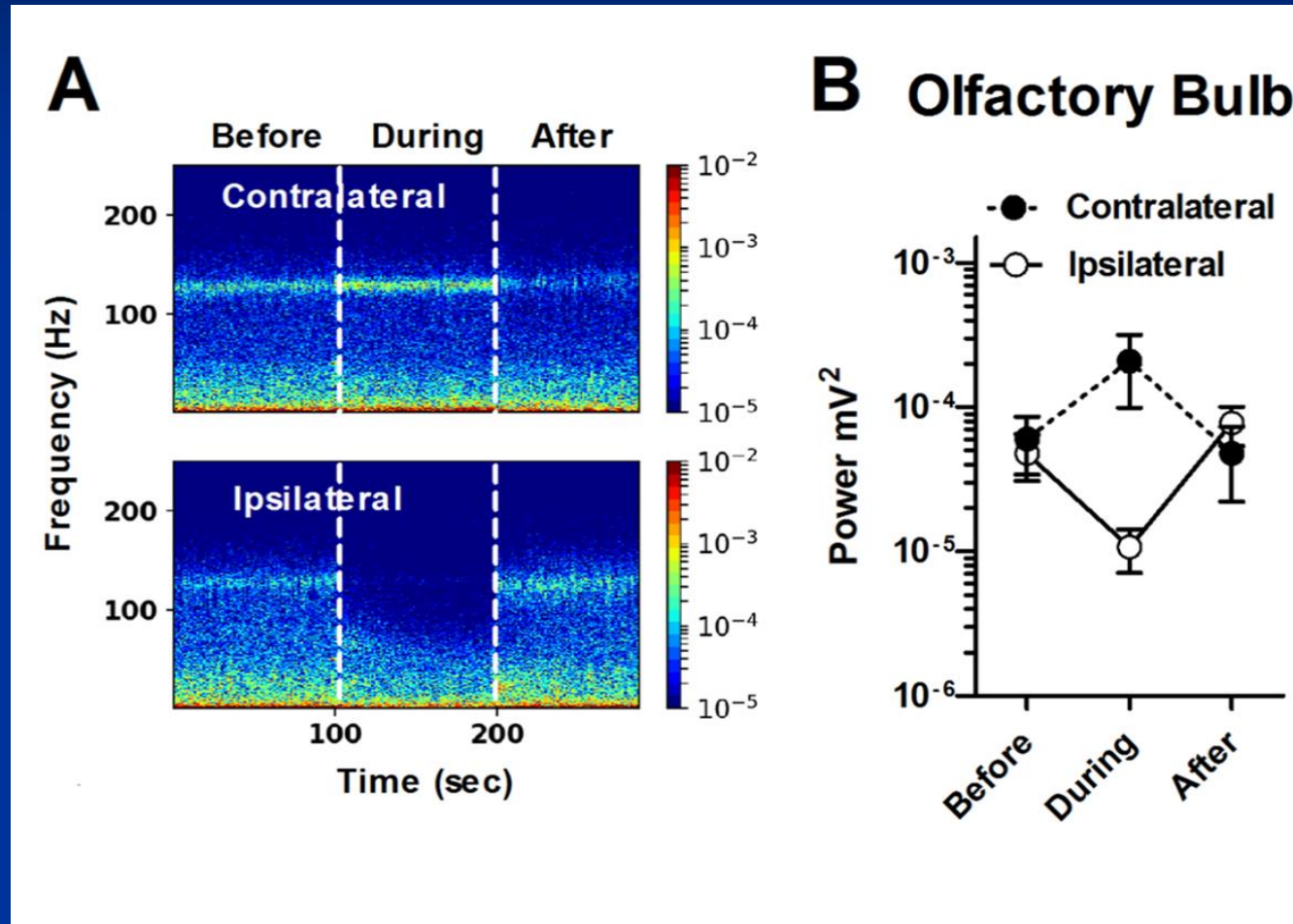


Reversible inhibition of the OB reduces ketamine HFO





Naris blockade reduces ketamine-associated HFO



Summary

- Ketamine increases HFO in many brain regions of rats
- The olfactory bulb can orchestrate transmission in other brain areas
 - Brain-wide hypersynchronization
- Sensory input, nasal respiration, drives this rhythm
- Functional relevance of ketamine-HFO needs investigating
 - Abnormal increased HFO power may be associated with the dissociative effects

Acknowledgements

Nencki Institute: Jacek Wrobel, Wiktoria Podolecka, Stefan Kasicki, Daniel Wójcik

University of York: Miles Whittington, Natalie Adams, Anna Simon

University of Nice: Rene Garcia

Ketamine in Healthy People: Examples

- 'There were thoughts that were happening that I wouldn't normally think about and it just seems that someone is putting them on there'.
- It felt like there were more people in the room than two, presence of four people. I could hear people talking but I couldn't tell who was doing the talking – so it could have been something inside my head, I don't know. But I was definitely hearing things that I couldn't just place to any specific person or thing'
- [Telling the story of Little Red Riding Hood] There's a girl who wears a cape that was red, and it has a red hood. And her grandmother knitted – made it for her. She goes into the woods, there's a wolf there. And a woodcutter and... her grandmother... of the girl, Red Riding Hood. It's all just spinning around in my mind... and... if you want me to put it into a story... .There was a ... I'm getting confused with the little boy who cried wolf. [Long pause] I don't know what to think, I thought I knew it but I didn't.