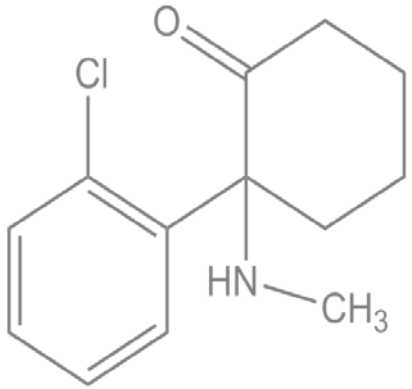
Michigan Medicine

Ketamine: 50 Years of Modulating the Mind



Phillip Vlisides, MD
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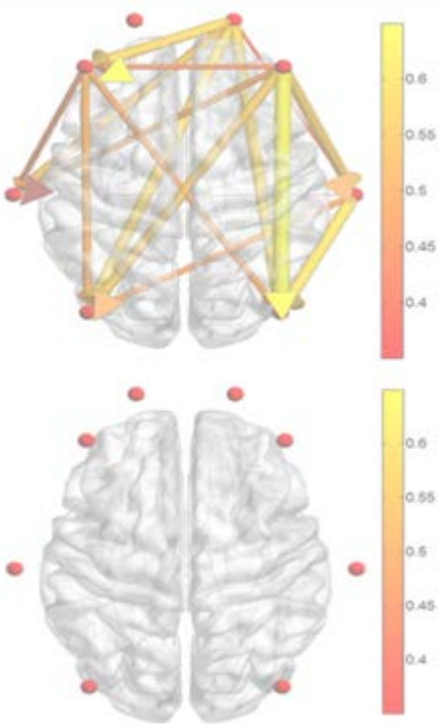
Director, Clinical Neuroscience Research
Department of Anesthesiology
Michigan Medicine



Funding and Disclosures

- <u>Funding</u>

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- <u>Other Disclosures/Conflicts of Interest</u>

  None

Could Party Drug Ketamine Be a Treatment for Depression?

Special K, a Vietnam-era anesthetic favored by ravers looking for an intense high, is being given another chance – this time as legitimate medication

BUSINESS DAY

Special K, a Hallucinogen, Raises Hopes and Concerns as a Treatment for Depression

By ANDREW POLLACK DEC. 9, 2014

Pharmacologic effects of CI-581, a new dissociative anesthetic, in man

Pharmacologic actions of CI-581, a chemical derivative of phencyclidine, were determined in 20 volunteers from a prison population. The results indicate that this drug is an effective analgesic and anesthetic agent in doses of 1.0 to 2.0 mg. per kilogram. With intravenous administration the onset of action is within 1 minute and the effects last for about 5 to 10 minutes, depending on dosage level and individual variation. No tachyphylaxis was evident on repeat doses. Respiratory depression was slight and transient. Hypertension, tachycardia, and psychic changes are undesirable characteristics of the drug. Whether these can be modified by preanesthetic medication was not determined in this study. Recovery from analgesia and coma usually took place within 10 minutes, although from electroencephalographic evidence it may be assumed that subjects were not completely normal until after 1 to 2 hours. No evidence of liver or kidney toxicity was obtained. CI-581 produces pharmacologic effects similar to those reported for phencyclidine, but of shorter duration. The drug deserves further pharmacologic and clinical trials. It is proposed that the words "dissociative anesthetic" be used to describe the mental state produced by this drug.

Edward F. Domino, M.D., Peter Chodoff, M.D., and Guenter Corssen, M.D.
Ann Arbor, Mich.
Departments of Pharmacology and Anesthesiology, The University of Michigan Medical Center

The remarkable analgesic and anesthetic dine, with the formula, 2-(o-chlorophenyl)-

Anesthesiology 2010; 113:678–86

David S. Warner, M.D., Editor

Taming the Ketamine Tiger

Edward F. Domino, M.D.*

Pharmacologic Effects of CI-581, a New Dissociative Anesthetic, in Man. By E. F. Domino, P. Chodoff, G. Corssen. Clin Pharmacol Ther 1965; 6:279–91. Reprinted by permission from Macmillan Publishers Ltd., copyright 1965.

Abstract: Pharmacologic actions of CI-581, a chemical derivative of phencyclidine, were determined in 20 volunteers from a prison population. The results indicate that this drug is an effective analgesic and anesthetic agent in doses of 1.0 to 2.0 mg per kilogram. With intravenous administration the onset of action is within 1 min and the effects last for about 5 to 10 min, depending on dosage level and individual variation. No tachyphylaxis was evident on repeat doses. Respiratory depression was slight and transient. Hypertension, tachycardia, and psychic changes are undesirable characteristics of the drug. Whether these can be modified by preanesthetic medication was not determined in this study. Recovery from analgesia and coma usually took place within 10 min, although from electroencephalographic evidence it may be assumed that subjects were not completely normal until after 1 to 2 h. No evidence of liver or kidney toxicity was obtained. CI-581 produces pharmacologic effects similar to those reported for phencyclidine, but of shorter duration. The drug deserves further pharmacologic and clinical trials. It is proposed that the words "dissociative anesthetic" be used to describe the mental state produced by this drug.

THOSE who anesthetize[1] patients with ketamine (originally given the clinical investigation number CI-581) realize it is a unique pharmacological agent. Ever since its introduction into human clinical anesthesia, ketamine has had a turbulent history. One only has to witness ketamine anesthesia emergence delirium to realize this agent produces unique psychic effects. Nevertheless, the value and safety of ketamine in the anesthetic management of a specific subset of surgical and critical care patients is recognized. After 45 yr of ketamine use in veterinary and human clinical anesthesia, its value and side effects are well known. Why has this drug survived? What can we learn from the past? Can knowledge about ketamine guide us in the future to help in the mission of anesthesiology to relieve pain and suffering? What are its

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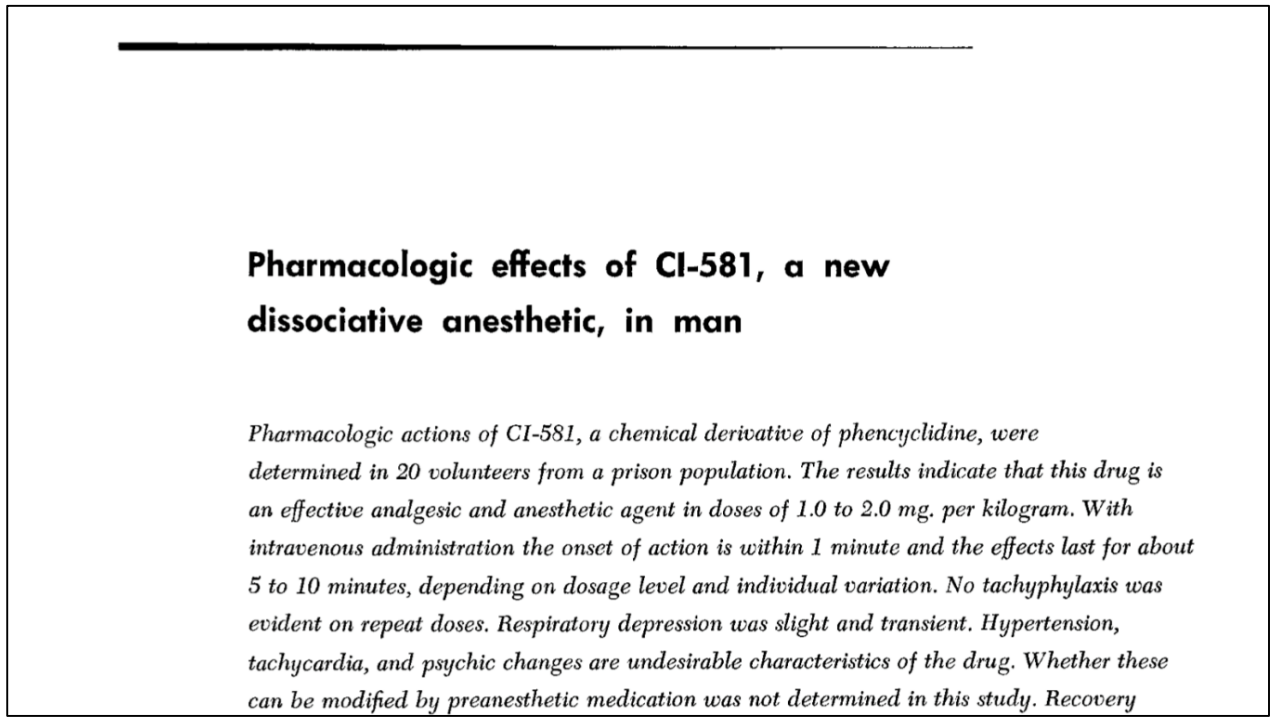

Pharmacologic effects of CI-581, a new dissociative anesthetic, in man

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"The unusual analgesic and anesthetic action of this drug …makes it imperative that a new terminology be developed for drugs of this type. It is suggested that the state produced by this drug be called 'dissociative anesthesia'."

Domino EF et al. Clin Pharmacol Ther. 1965 May-Jun;6:279-91

How does ketamine affect the brain perioperatively?

Ketamine and “Dissociative” Mechanisms

Ketamine and Neurologic Outcomes

How does ketamine affect the brain perioperatively?

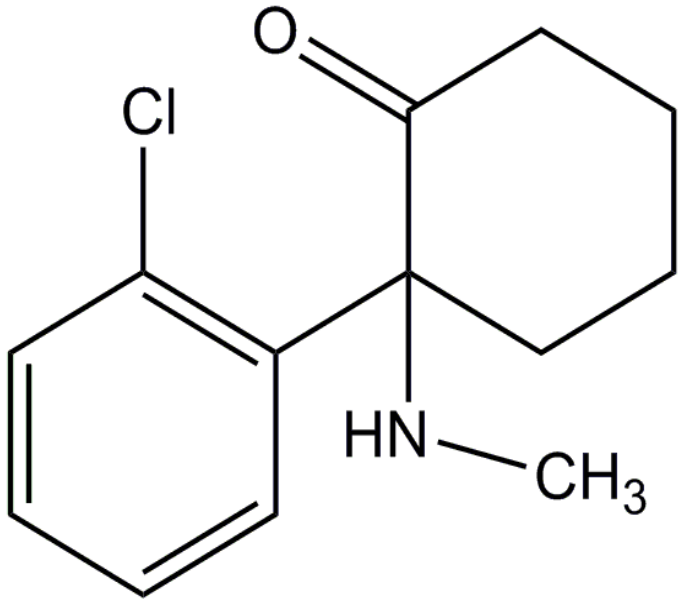
Ketamine and “Dissociative” Mechanisms

Ketamine and Neurologic Outcomes

Ketamine and “Dissociative” Mechanisms…

Ketamine and “Dissociative” Mechanisms…

- Receptor-level
  - NMDA antagonism
  - HCN-1 inhibition
  - AMPA receptor activation
  - Voltage-gated Ca^{2+} inhibition
  - Ca^{2+}-activated K^{+} channel inhibition
  - Nicotinic-AChR inhibition
  - $GABA_A$ agonism



Yamakage M et al. Anesthesiology 1995; 83:1274–82

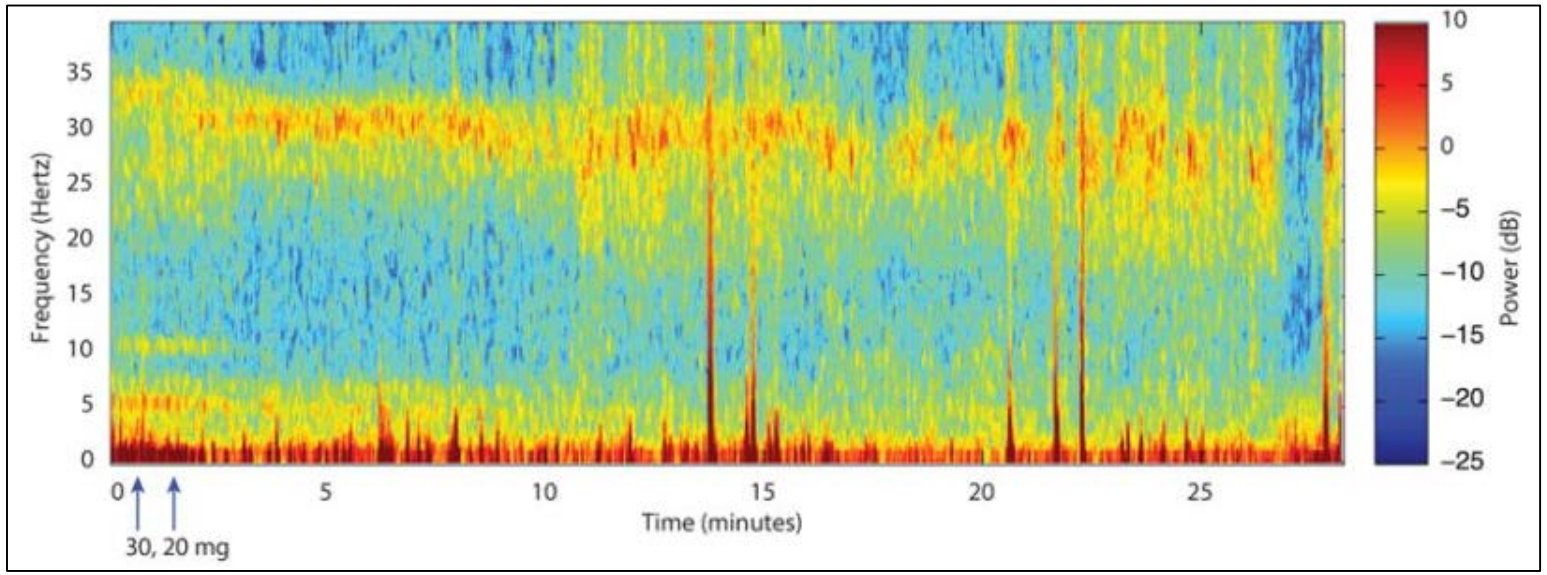
Hayashi Y et al. J Neurosci. 2011 Nov 30;31(48):17370-82

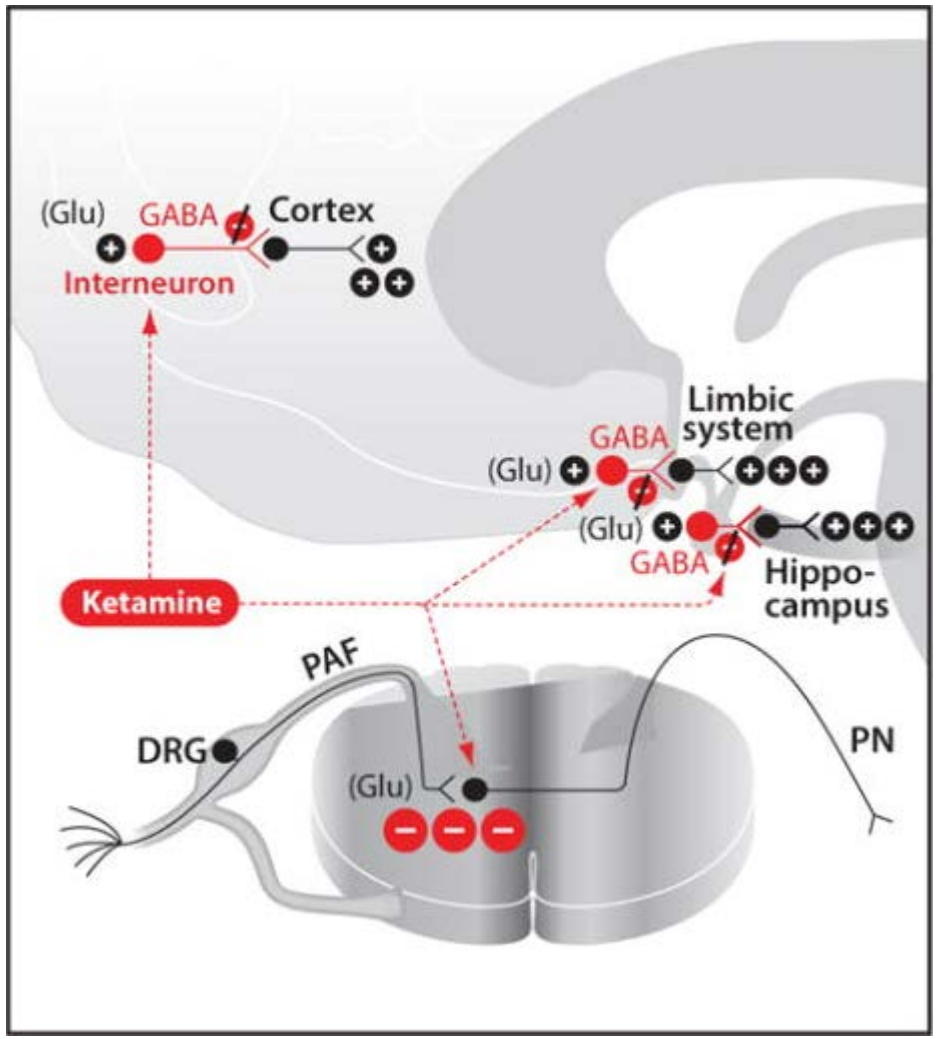
Yamakura T et al. Anesthesiology. 2000 Apr;92(4):1144-53

Irifune M et al. Anesth Analg. 2000 Jul;91(1):230-6

Ketamine and “Dissociative” Mechanisms…

- Neurophysiologic-level
  - *Disinhibition of inhibitory synaptic transmission*

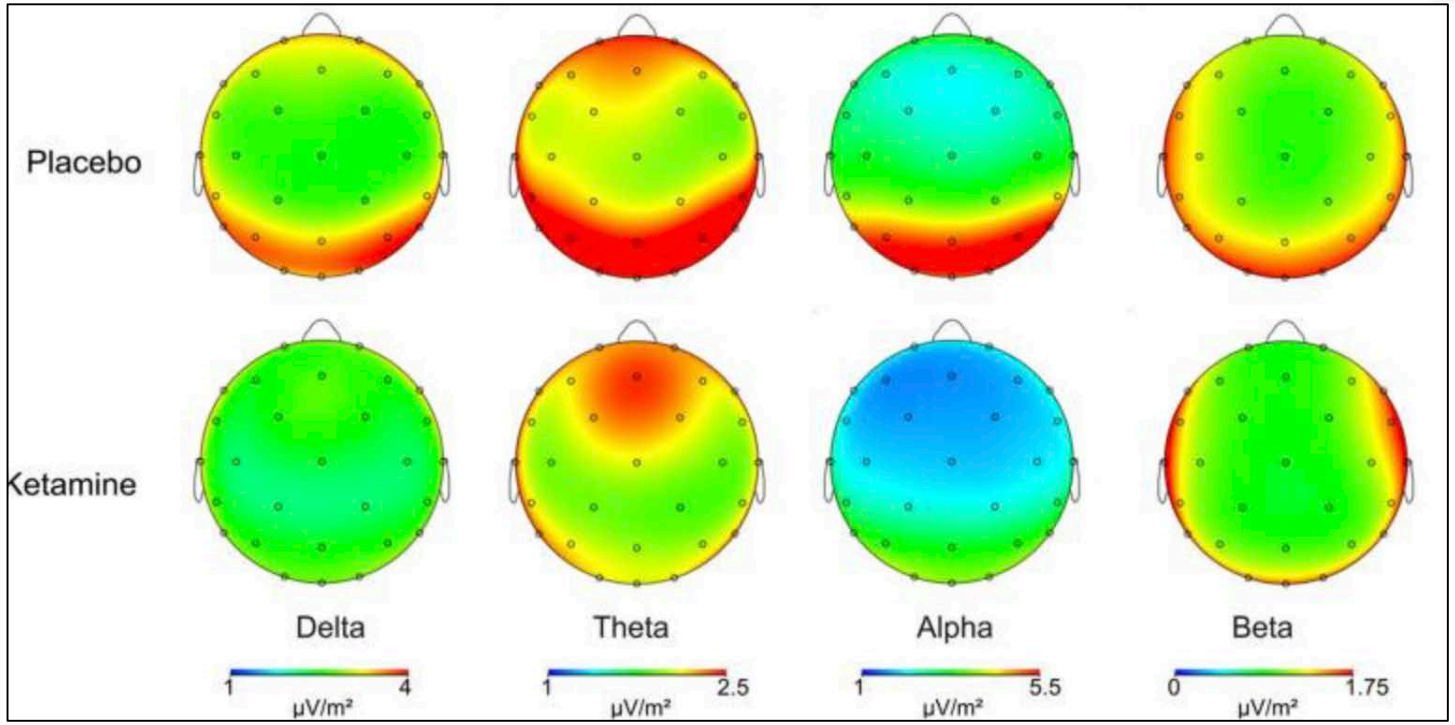


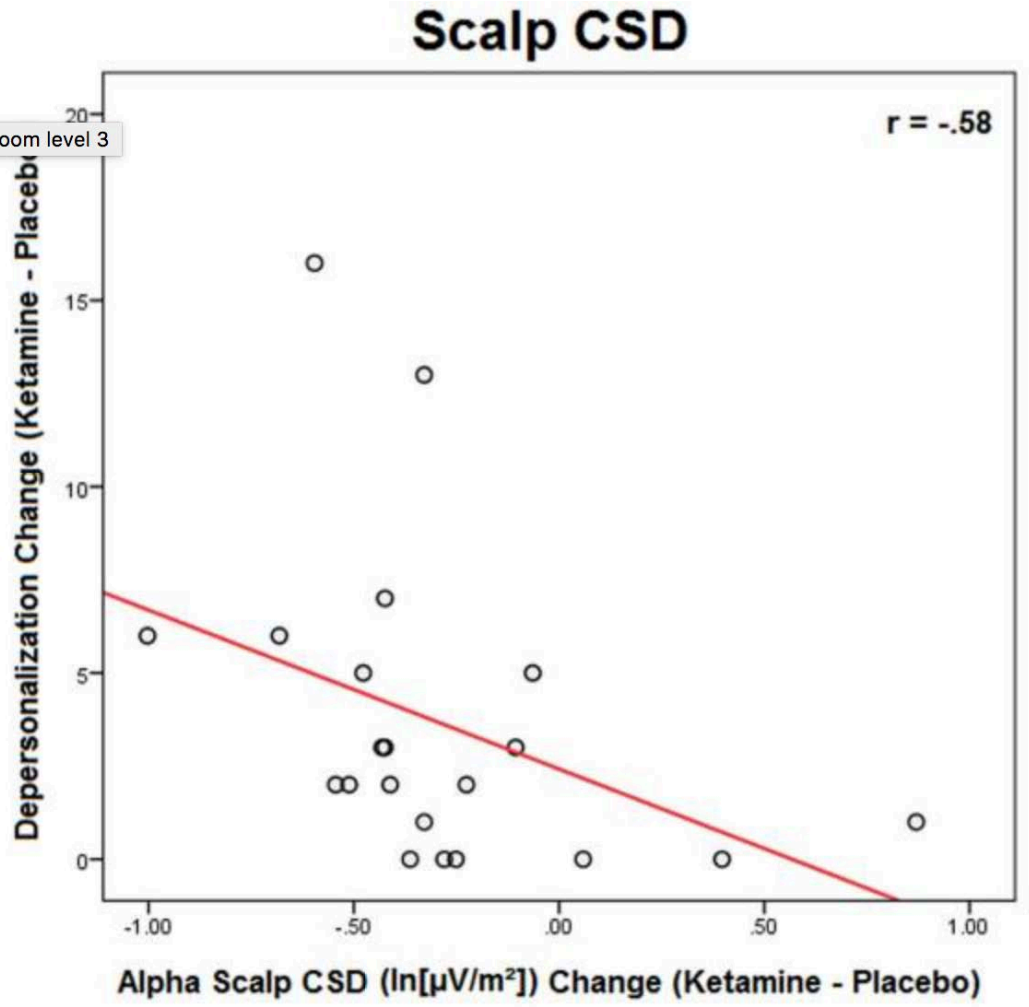


Purdon PL et al. Anesthesiology. 2015 Oct;123(4):937-60

Ketamine and “Dissociative” Mechanisms…

- Neurophysiologic-level
  - *Reduced alpha power and connectivity*

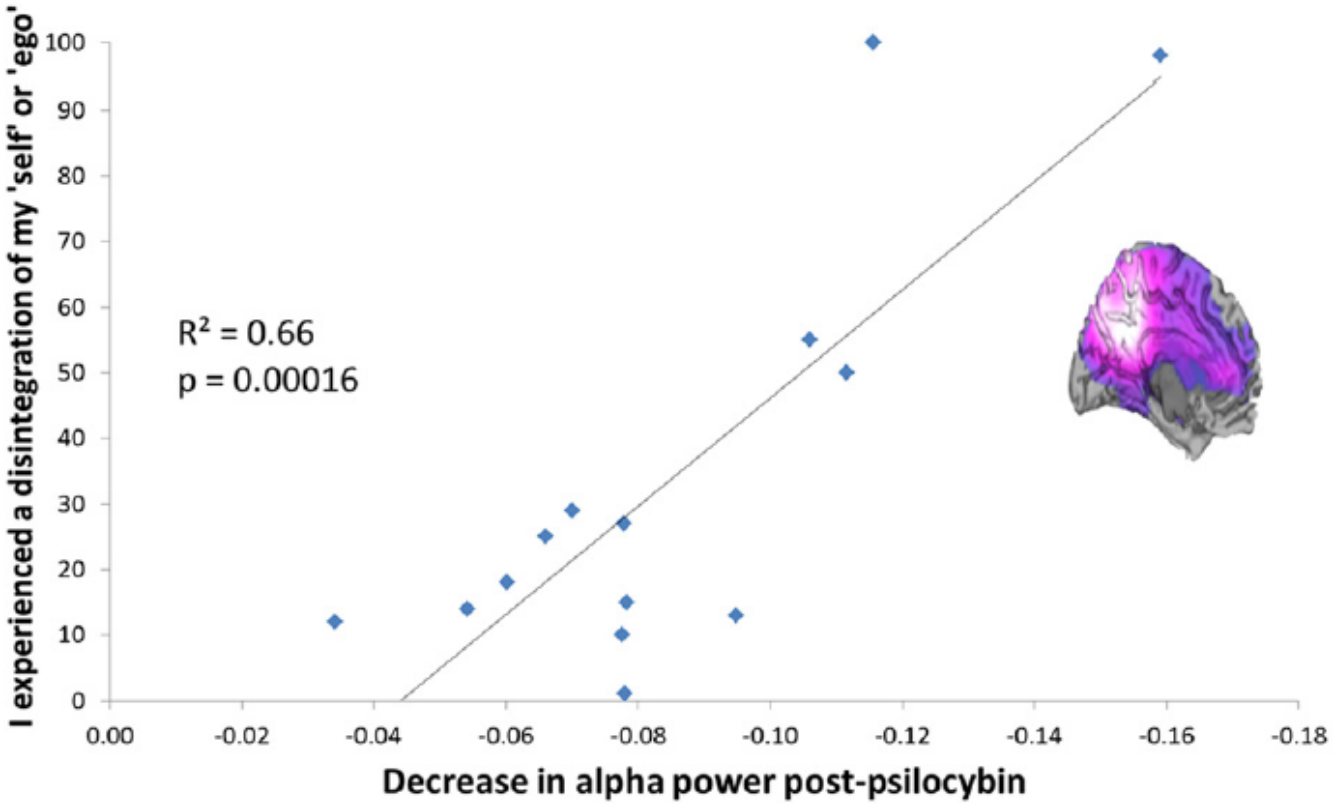




de la Salle S et al. Front Pharmacol. 2016 Sep 27;7:348

Ketamine and “Dissociative” Mechanisms…

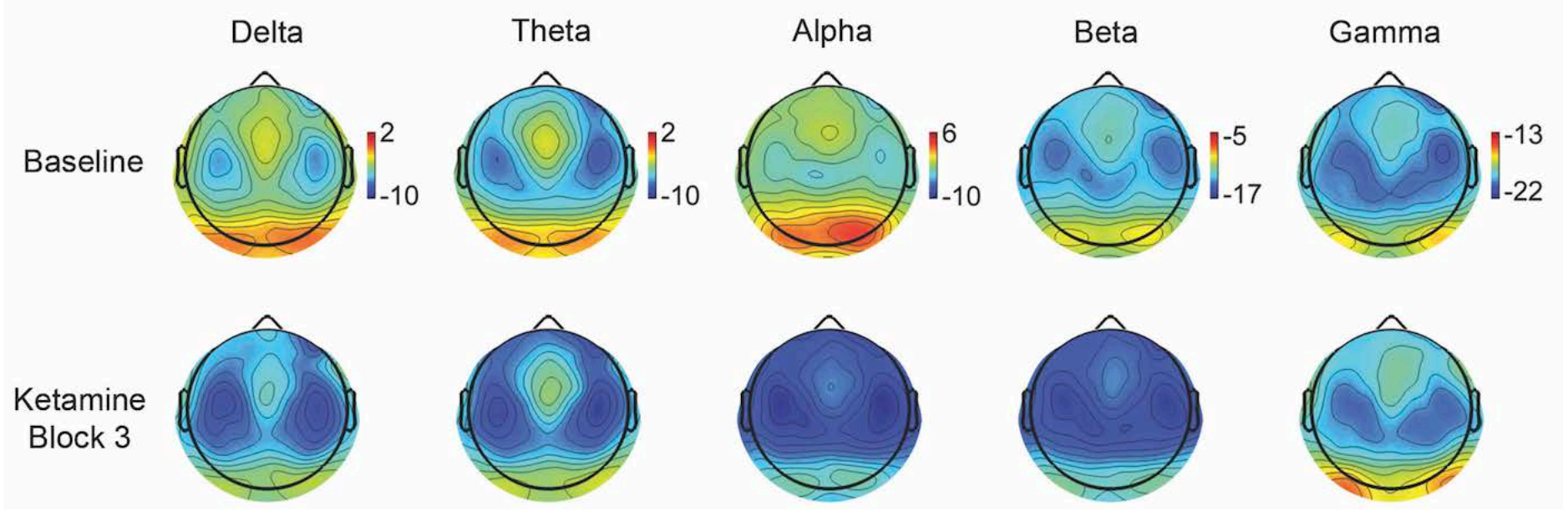
- Neurophysiologic-level
  - *Reduced alpha power and connectivity*

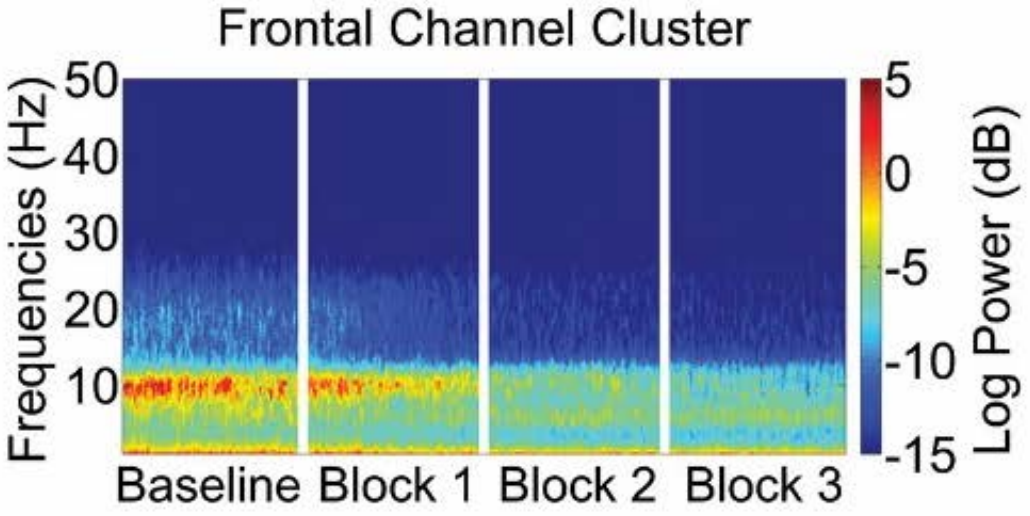


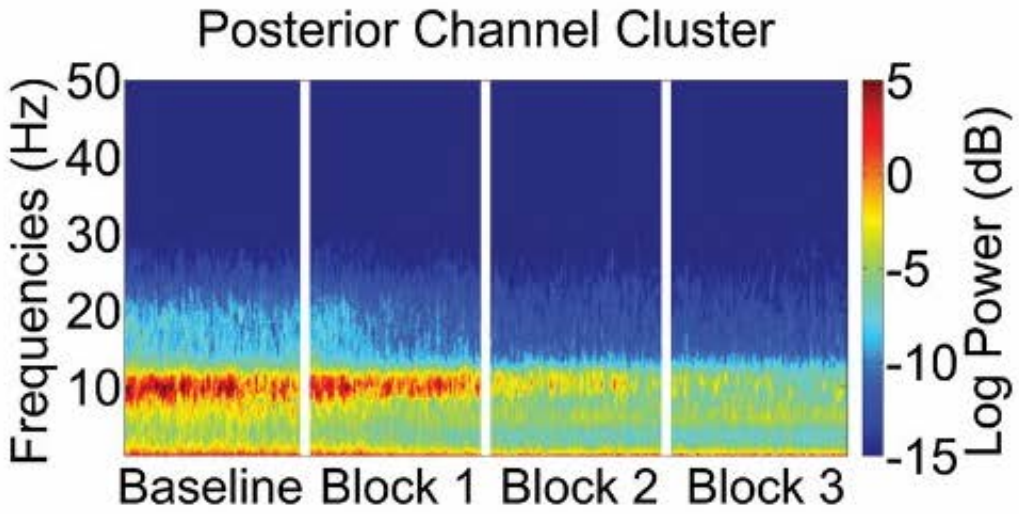
“Ego integrity”

Muthukumaraswamy et al, J Neurosci, 2013;33:15171

Carhart-Harris RL. Front Hum Neurosci. 2014 Feb 3;8:20







Vlisides PE, Bel-Bahar T, et al. – in press, Br J of Anaesth

		Study Score			Lifetime Score					
Scale Name	**Items**	**α**	**M**	**SD**	**α**	**M**	**SD**	**Difference**	**T**	
Experiences of Unity	4	0.64	4.76	2.12	0.87	0.95	0.95	**3.81**	5.81	***
Disembodiment	3	0.72	6.72	2.07	0.72	0.52	0.57	**6.20**	10.97	***
Transcendence of Time and Space	6	0.84	6.62	2.08	0.83	1.21	0.99	**5.41**	8.75	***

Vlisides PE, Bel-Bahar T, et al. – in press, Br J Anaesth

****P<0.001, Cronbach's Alpha*

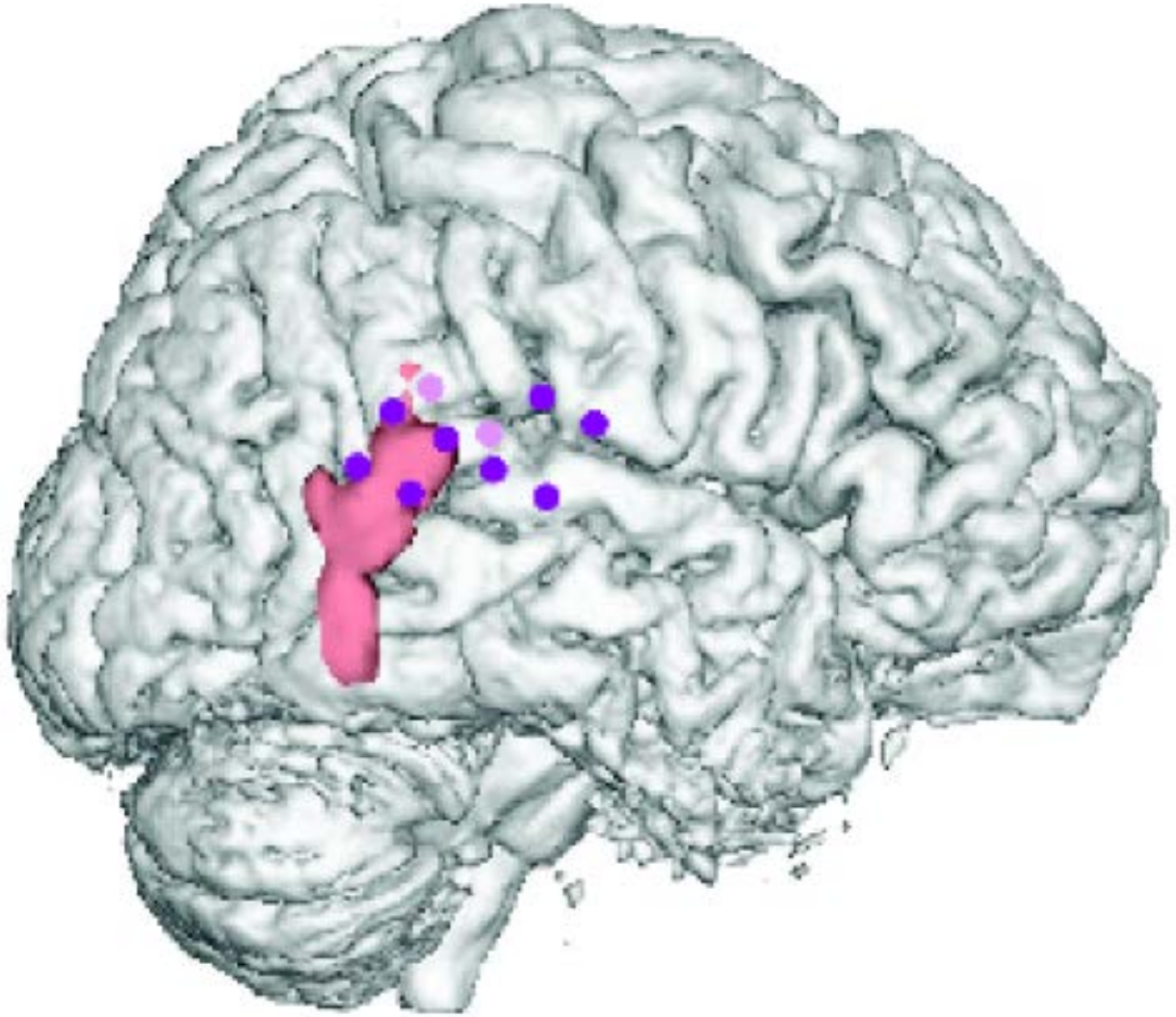
the investigators. After analgesia disappeared and the subject was in full contact with his environment, there still were no alpha waves. This rhythm was not re-established until at least a half to one hour after drug injection. The lower right-hand

Domino EF, et al. Clin Pharmacol Ther. 1965 May-Jun;6:279-91

TPJ Modulation by Subanesthetic Ketamine

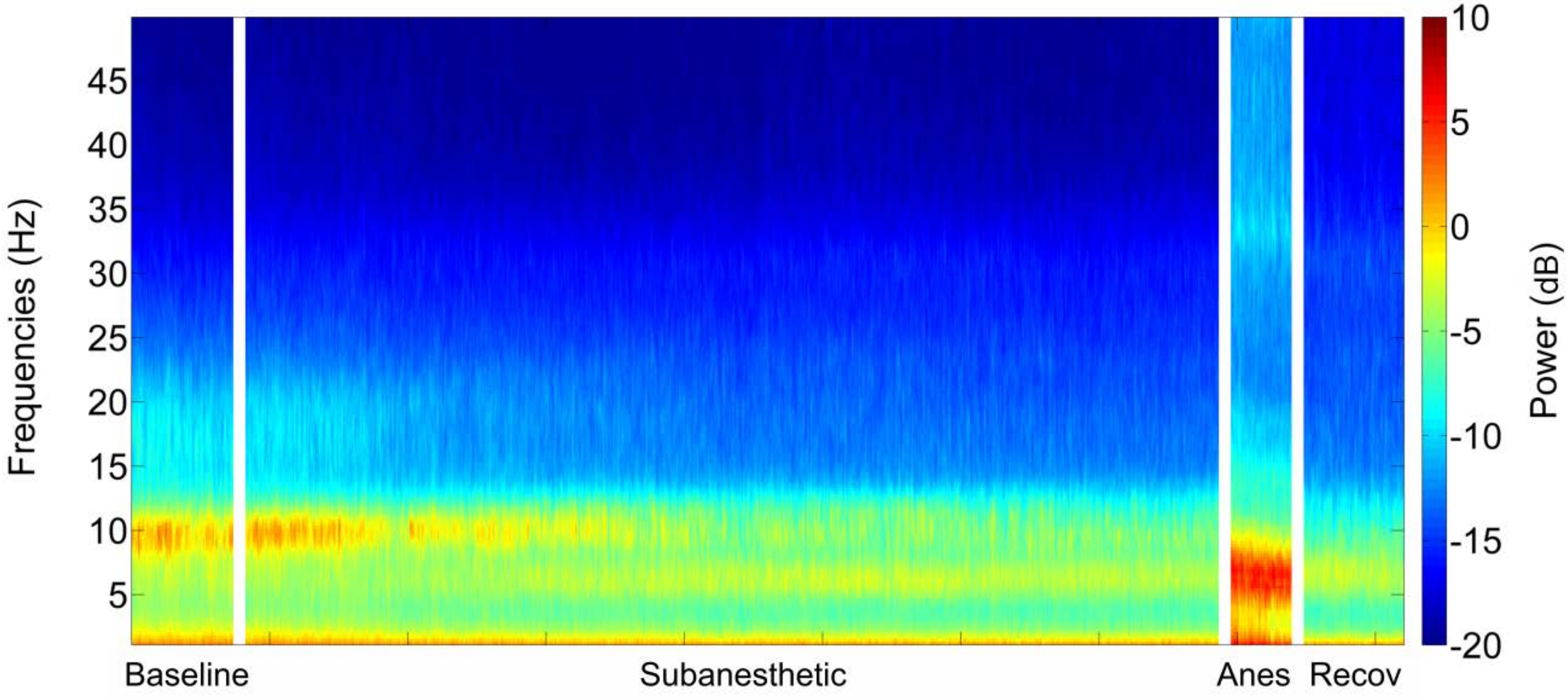
Vlisides PE, Bel-Bahar T, et al. – in press, Br J Anaesth

TPJ Lesions Cause Out-of-Body Experiences

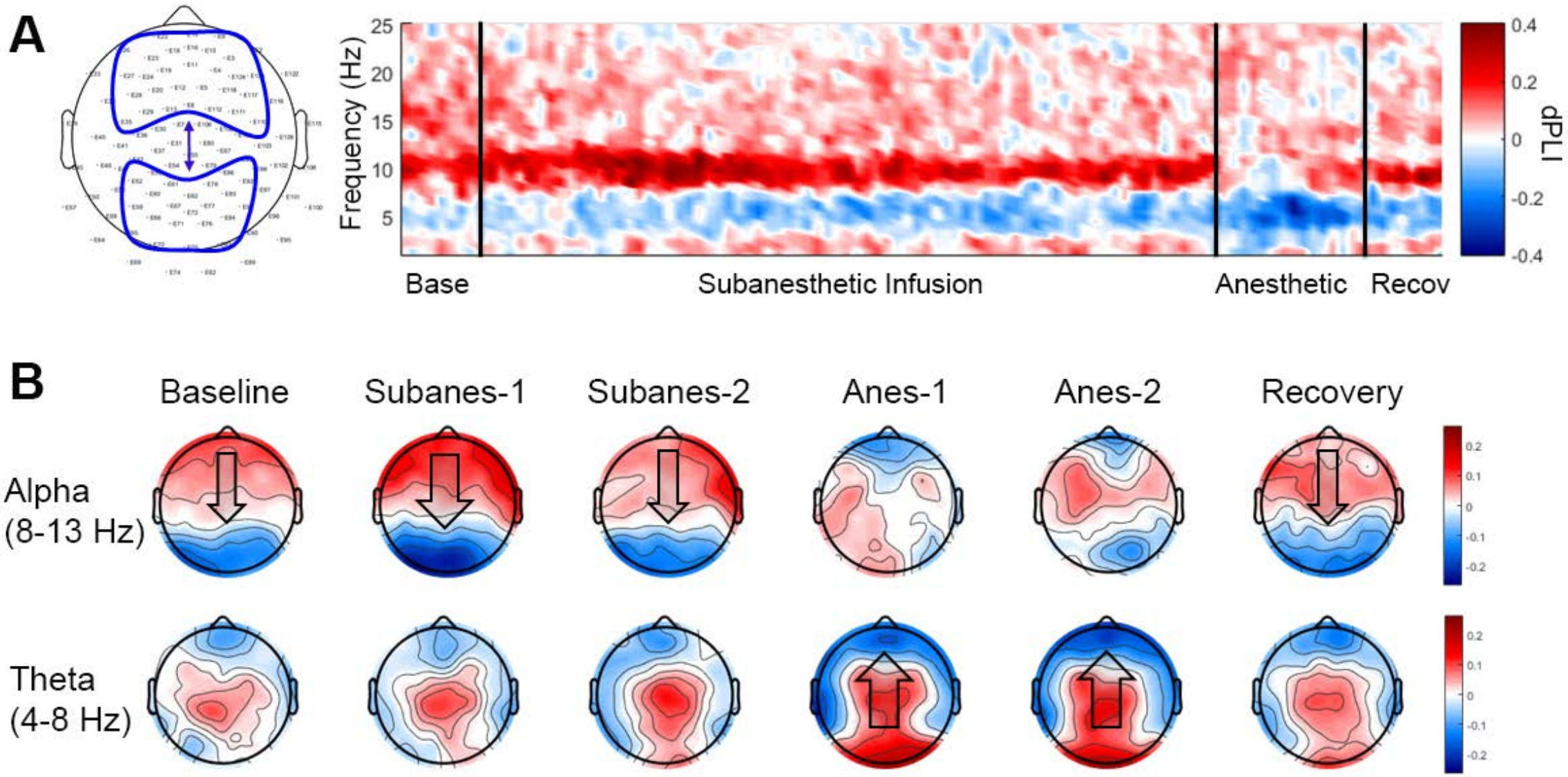


Blanke et al., Brain 2004;127:243

Ketamine Dose-Dependency



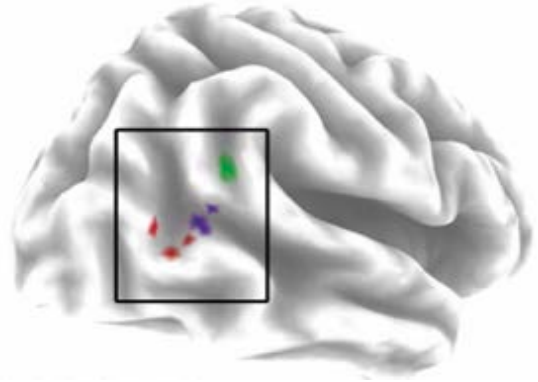
Vlisides PE, Bel-Bahar T, et al. *Anesthesiology.* 2017 Jul;127(1):58-69



Vlisides PE, Bel-Bahar T, et al. *Anesthesiology.* 2017 Jul;127(1):58-69

Ketamine Mechanisms - Summary

- Alpha power inversely correlates with measures of dissociation (e.g., ego dissolution, transcendence of space and time)
- Ketamine reduces low-frequency power (particularly alpha), increases gamma
- Ketamine-induced alpha reductions – and dissociative characteristics – may involve the TPJ
- Dose-dependent oscillatory, connectivity changes



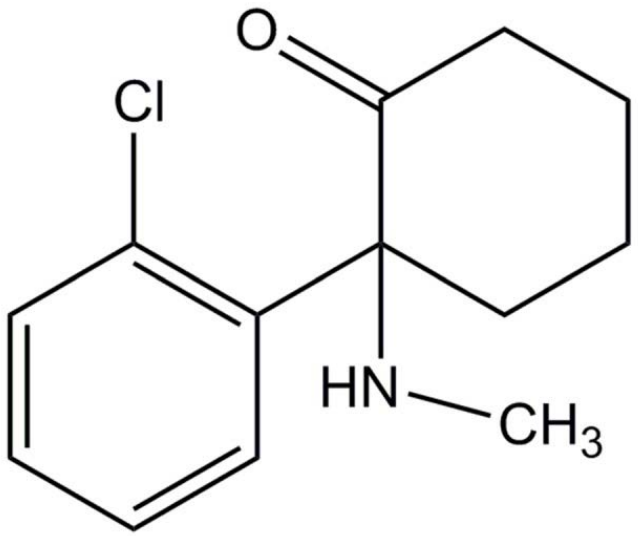
How does ketamine affect the brain perioperatively?

Ketamine and “Dissociative” Mechanisms

Ketamine and Neurologic Outcomes

Ketamine and Surgery

- Reported to reduce postoperative inflammation, pain, and opioid consumption after surgery



- NMDA antagonism
- HCN inhibition

Excitotoxicity

Neuroinflammation

Dale O et al., *Anesth Analg* 2012. Oct;115(4): 934-4
Laskowski K et al., *Can J Anaesth* 2011. Oct;58(10): 911-23


↓Excitotoxicity
↓Neuroinflammation
Cognition?
Pain?

Ketamine and Cognition

Ketamine and Cognition

- Reduced of emergence agitation in children (RR 0.30, 95% CI 0.13 to 0.69)

Cochrane Database Syst Rev. 2014 Sep 12;(9):CD007084

Ketamine and Cognition

Ketamine Attenuates Delirium After Cardiac Surgery With Cardiopulmonary Bypass

Judith A. Hudetz, PhD, Kathleen M. Patterson, PhD, Zafar Iqbal, MD, Sweeta D. Gandhi, MD,
Alison J. Byrne, PhD, Anthony G. Hudetz, DBM, PhD, David C. Warltier, MD, PhD, and Paul S. Pagel, MD, PhD

Objective: **To determine if ketamine attenuates postoperative delirium concomitant with an anti-inflammatory effect**

The incidence of postoperative delirium was lower ($p = 0.01$, Fisher exact test) in patients receiving ketamine (3%) com-

Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery

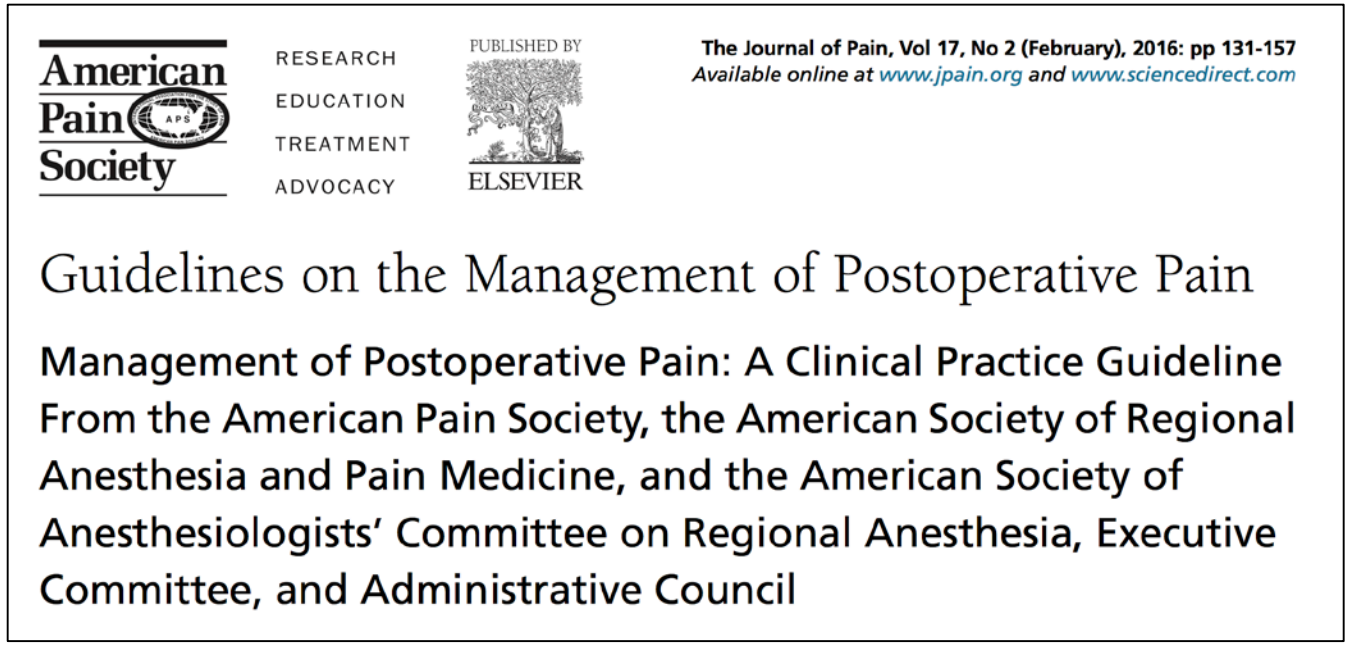
J. A. Hudetz, Z. Iqbal, S. D. Gandhi, K. M. Patterson, A. J. Byrne, A. G. Hudetz, P. S. Pagel and D. C. Warltier
Department of Anesthesiology, Clement J. Zablocki Veterans Administration Medical Center, Milwaukee, WI

Background: Post-operative cognitive dysfunction (POCD) commonly occurs after cardiac surgery. Ketamine exerts neuroprotective effects after cerebral ischemia by anti-excitotoxic

the placebo group and only in seven patients in the ketamine group compared with the nonsurgical controls ($P < 0.001$, Fisher's exact test). Cognitive performance was

Ketamine and Cognition

- Psychoactive effects
- Increased association with hallucinations and nightmares



Recommendation 18

- The panel recommends that clinicians consider i.v. ketamine as a component of multimodal analgesia in adults (weak recommendation, moderate-quality evidence).

I.v. ketamine has been evaluated as a part of multimodal analgesia. In adults and children, studies found i.v. ketamine infusions were associated with decreased postoperative pain medication use compared with placebo, and in some studies with decreased postoperative pain scores.[1,22,59,75,173,213] I.v. ketamine was also associated with decreased risk of persistent postsurgical pain.[198] In the trials, ketamine was administered preoperatively, intraoperatively, and/or post
widely varying doses (ranging from bo
2 mg/kg before incision and at closure, wi
infusions ranging from 12 mg/kg/h [2
2 mg/kg/h). There was insufficient evidence
the optimal method for dosing ketamine,
suggests using a preoperative bolus of .5 m
by an infusion at 10 μg/kg/min intraoperatively, with or without a postoperative infusion at a lower dosage.[183]
Ketamine was associated with increased risk of hallucinations and nightmares. Clinicians who administer ketamine should be familiar with its use and adverse effects, and the panel suggests that ketamine be reserved for major surgeries. Some situations in which ketamine might be particularly useful include management of highly opioid-tolerant patients[183] and patients who have difficulty tolerating opioids.

"Ketamine was associated with increased risk of hallucinations and nightmares."

Ketamine and Pain

Ketamine and Pain

- Elia N and Tramèr MR, 2005 (Pain)
- *Prophylactic IV ketamine:*
  - *16 Trials, data from 850 adults, variable perioperative dosing*
  - *Pain intensity, VAS: decreased, all time points through 48 hours (data from 9 trials)*
  - *Morphine consumption at 24 hours: -15.7mg, [-20.9 to -10.5], (7 trials, n=135)*

Elia N and Tramer MR. Pain. 2005; 113:61-70

Ketamine and Pain

- Laskowski K et al., 2011 (Can J Anaesth)
- *Prophylactic IV ketamine:*
  - *70 Trials, IV perioperative ketamine (variable dosing)*
  - *Total opioid dose consumed, SDM: -0.646; 95% CI (-0.797 to -0.495; P<0.001)*
  - *Low risk of publication bias*

Laskowski K et al. Can J Anaesth. 2011 Oct;58(10):911-23

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 17, No 2 (February), 2016: pp 131-157
Available online at www.jpain.org and www.sciencedirect.com

Guidelines on the Management of Postoperative Pain

Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council

“The panel recommends that clinicians consider i.v. ketamine as a component of multimodal analgesia in adults (weak recommendation, moderate-quality evidence).”

The Journal of Pain, Vol 17, No 2 (February), 2016: pp 131-157
Available online at www.jpain.org and www.sciencedirect.com

Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial

*Michael S Avidan, Hannah R Maybrier, Arbi Ben Abdallah, Eric Jacobsohn, Phillip E Vlisides, Kane O Pryor, Robert A Veselis, Hilary P Grocott, Daniel A Emmert, Emma M Rogers, Robert J Downey, Heidi Yulico, Gyu-Jeong Noh, Yonghun H Lee, Christine M Waszynski, Virendra K Arya, Paul S Pagel, Judith A Hudetz, Maxwell R Muench, Bradley A Fritz, Witold Waberski, Sharon K Inouye, George A Mashour, on behalf of the PODCAST Research Group**

- >600 patients, nine international sites, triple-blinded RCT
- Three arms: placebo, ketamine 0.5 mg/kg, ketamine 1 mg/kg

One time, single bolus dose

- Standardized delirium training (K07AG041835)

- Subjective pain assessments (10-cm VAS)
- Objective pain assessments (BPS, BPS-NI)
- Opioid Consumption
- Internal audits (to review data accuracy, study procedures, etc.)

Results

Results

Ketamine Groups: **19·45%**

Placebo Group: **19·82%**

Absolute Difference 0·36%

95% CI, [−6·07 to 7·38], p=0·92

	Coefficient	P>|z|	Odds Ratio (95% CI)
0.5 mg/kg group	-0.106	0.686	0.900 (0.539–1.501)
1.0 mg/kg group	-0.028	0.914	0.973 (0.58–1.611)
Age*	0.066	0.000	1.068 (1.037–1.100)
Depression	0·778	0·011	2.176 (1.19–3.955)
Cardiac surgery	1.018	0.000	2.768 (1.645–4.658)

**Age: per year over 60. C-statistic: 0.697*

Delirium – Duration

Duration (days)	Placebo (n=222)	0.5 mg/kg (n=227)	1 mg/kg (n=223)
None	80%	82%	79%
One	11%	12%	11%
Two	6%	4%	6%
Three	4%	2%	5%

Delirium – Severity

Day	Placebo (n=222)	0.5 mg/kg (n=227)	1 mg/kg (n=223)
POD1	**7**(6 – 9)	**7**(6 – 9)	**8**(6 – 8)
POD2	**8**(5 – 10)	**6**(5 – 8)	**8**(6 – 9)
POD3	**7**(6 – 9)	**7**(6 – 9)	**8**(6 – 9)

Range: 0 – 19
N (IQR)

Ketamine and Delirium

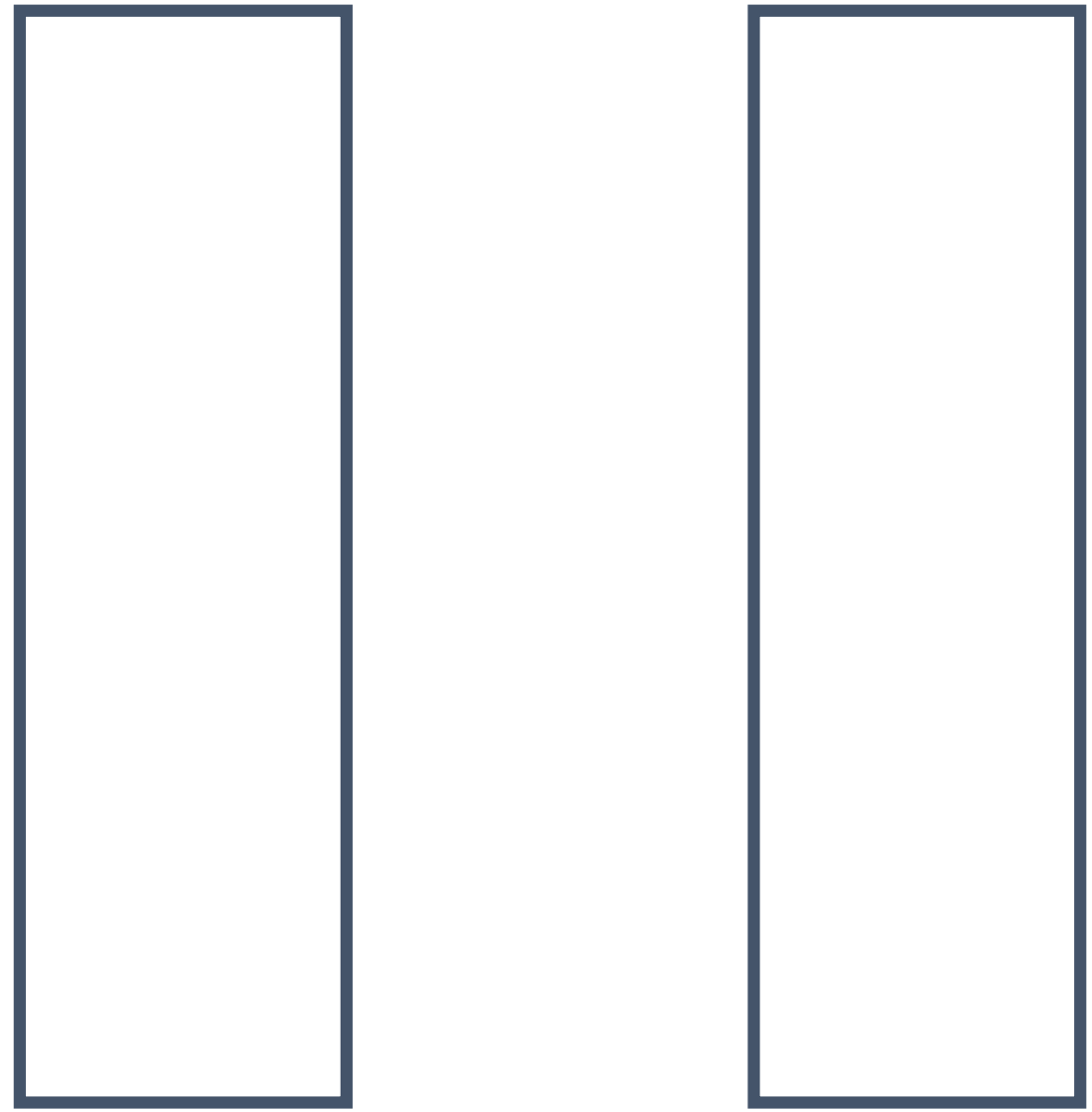
Otherwise stated, ketamine had no discernable influence on the incidence, recurrence, or severity of delirium

Ketamine and Pain

Ketamine and Pain

	All groups (n=672)	Placebo (n=222)	0·5 mg/kg ketamine (n=227)	1·0 mg/kg ketamine (n=223)
Morphine equivalents POD0 (n=598)	18 (8–48)	17 (8–49)	17 (8–50)	18 (8–42)
Morphine equivalents POD1 (n=605)	32 (17–68)	33 (17–78)	32 (18–63)	30 (16–59)
Morphine equivalents POD2 (n=559)	24 (12–48)	25 (12–52)	24 (12–44)	22 (12–49)
Morphine equivalents POD3 (n=450)	19 (8–40)	22 (10–42)	17 (8–39)	16 (8–38)

Data are median (IQR). Numbers are rounded to the nearest mg. The conversion table that was used to convert opioids to morphine equivalents in mg is provided in the appendix. Data were not available after hospital discharge.
POD=postoperative day.



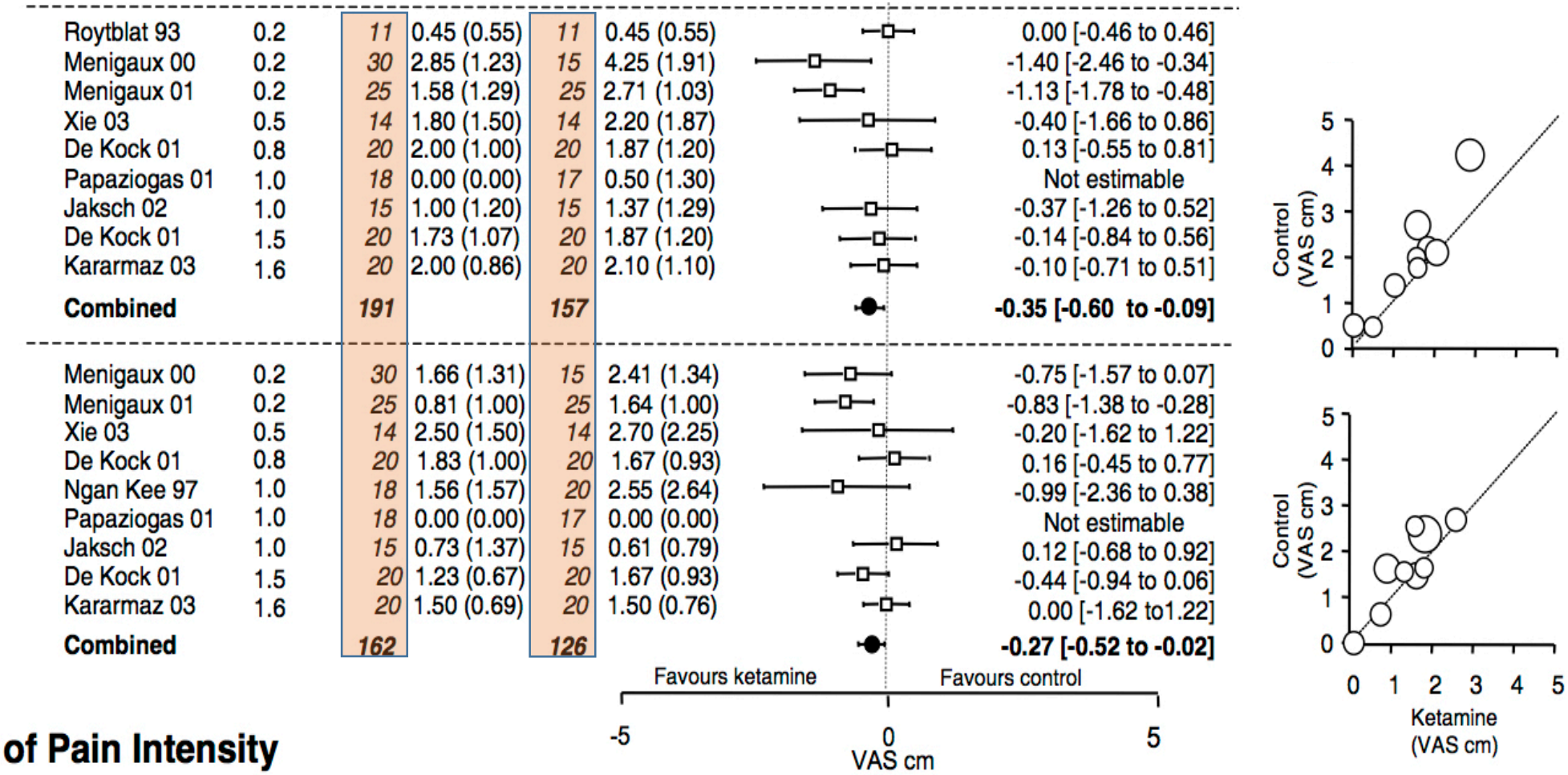
Postoperative day 2				
am				
Pain level at rest (n=519)	14 (3–40)	15 (4–38)	13 (3–42)	15 (3–38)
Pain level when taking a deep breath (n=517)	35 (11–60)	34 (18–64)	35 (10–56)	36 (8–64)
Pain level when moving (n=516)	42 (19–71)	42 (21–70)	44 (17–72)	42 (18–71)
pm				
Pain level at rest (n=504)	11 (2–33)	12 (3–35)	10 (1–32)	10 (2–33)
Pain level when taking a deep breath (n=503)	33 (11–58)	35 (13–62)	29 (9–54)	33 (10–55)
Pain level when moving (n=502)	41 (16–69)	43 (18·5–69)	37 (15–69)	42 (14–68)

Postoperative day 3				
am				
Pain level at rest (n=487)	10 (1–30)	10 (1–30)	10 (0–27)	10 (2–29)
Pain level when taking a deep breath (n=517)	35 (11–60)	34 (18–64)	35 (10–56)	36 (8–64)
Pain level when moving (n=488)	36 (12–1)	36 (14–60)	34 (15–60)	38 (10–63)
pm				
Pain level at rest (n=452)	10 (1–28)	10 (2–25)	8 (0–29)	10 (2–29)
Pain level when taking a deep breath (n=453)	29 (8–53)	30 (10–53)	28 (8–53)	33 (7–54)
Pain level when moving (n=450)	35 (10–60)	38 (13–63)	33 (10–59)	35 (8–60)

…No Analgesic Effects?...

How to reconcile these findings with previous systematic reviews and meta-analyses…

- No subgroup analyses
- Pooled data from much smaller trials – “small study effects”



VAS of Pain Intensity

n: number of patients analysed; sd: standard deviation; CI: confidence interval; VAS: visual analogue scale of pain intensity; cm: centimeters
The comparisons are arranged according to increasing ketamine regimens; on the L 'Abbé plot, the sizes of the symbols represent the sizes of the trials

Elia et al. Pain. 2005 Jan;113(1-2):61-70

…No Analgesic Effects?...

"Studies that show a significant effect of treatment are more likely to be published, be published in English, be cited by other authors, and produce multiple publications than other studies. Such studies are therefore also more likely to be identified and included in systematic reviews, which may introduce bias…

…All these biases are more likely to affect small studies than larger ones."

Sterne JA et al. BMJ. 2001 Jul 14;323(7304):101-5

…No Analgesic Effects?...

“In six of 13 meta-analyses [of osteoarthritis trials], the overall pooled estimate suggested a clinically relevant, significant benefit of treatment, whereas analyses restricted to large trials and predicted effects in large trials yielded smaller non-significant estimates.”

Nüesch E et al. BMJ. 2010 Jul 16;341

Ketamine and Additional Outcomes

Subanesthetic, bolus dose – outcome incidence across *all three postoperative days*

	Placebo	*0.5 mg/kg*	*1 mg/kg*
Hallucinations:	18%	20%	28% (p=0.01)
Nightmares:	8%	12%	15% (p=0.03)

Recommendation 18

- The panel recommends that clinicians consider i.v. ketamine as a component of multimodal analgesia in adults (weak recommendation, moderate-quality evidence).

I.v. ketamine has been evaluated as a part of multimodal analgesia. In adults and children, studies found i.v. ketamine infusions were associated with decreased postoperative pain medication use compared with placebo, and in some studies with decreased postoperative pain scores.[1,22,59,75,173,213] I.v. ketamine was also associated with decreased risk of persistent postsurgical pain.[198] In the trials, ketamine was administered preoperatively, intraoperatively, and/or post
widely varying doses (ranging from bo
2 mg/kg before incision and at closure, wi
infusions ranging from 12 mg/kg/h [2
2 mg/kg/h). There was insufficient evidence
the optimal method for dosing ketamine,
suggests using a preoperative bolus of .5 m
by an infusion at 10 μg/kg/min intraoperatively, with or without a postoperative infusion at a lower dosage.[183]
Ketamine was associated with increased risk of hallucinations and nightmares. Clinicians who administer ketamine should be familiar with its use and adverse effects, and the panel suggests that ketamine be reserved for major surgeries. Some situations in which ketamine might be particularly useful include management of highly opioid-tolerant patients[183] and patients who have difficulty tolerating opioids.

"Ketamine was associated with increased risk of hallucinations and nightmares."

REPORTS OF ORIGINAL INVESTIGATIONS

A systematic review of intravenous ketamine for postoperative analgesia

Revue méthodique de l'utilisation de la kétamine intraveineuse pour l'analgésie postopératoire

Kevin Laskowski, MD · Alena Stirling, MD · William P. McKay, MD · Hyun J. Lim, MD

Received: 9 November 2010 / Accepted: 8 July 2011 / Published online: 20 July 2011

“Overall, there was an increase in such [neuropsychiatric] side effects with the treatment of ketamine ($P = 0.018$), which becomes more prevalent with treatment efficacy ($P < 0.001$)…Many papers commented that the psychological effects were well tolerated.”

Laskowski et al. 2011. Can J Anaesth. 2011 Oct;58(10):911-23

Ketamine and Neurologic Outcomes - Summary

- Single-center efficacy studies may be subject to bias; outcomes often not replicated in large-scale effectiveness trials
- Ketamine unlikely to prevent postoperative delirium
- For older patients: subanesthetic, intraoperative bolus dose unlikely to reduce postoperative pain, opioid requirements
- Net effect: increased hallucinations, nightmares

Take Home Points…

- Ketamine sedation – alpha reductions, TPJ may be involved with dissociative states

- Single bolus-dose unlikely to confer meaningful postoperative neurologic benefits (e.g., delirium, pain)

…but may increase risk of hallucinations, nightmares postoperatively

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- National Institutes of Health

Washington University in St. Louis
School of Medicine

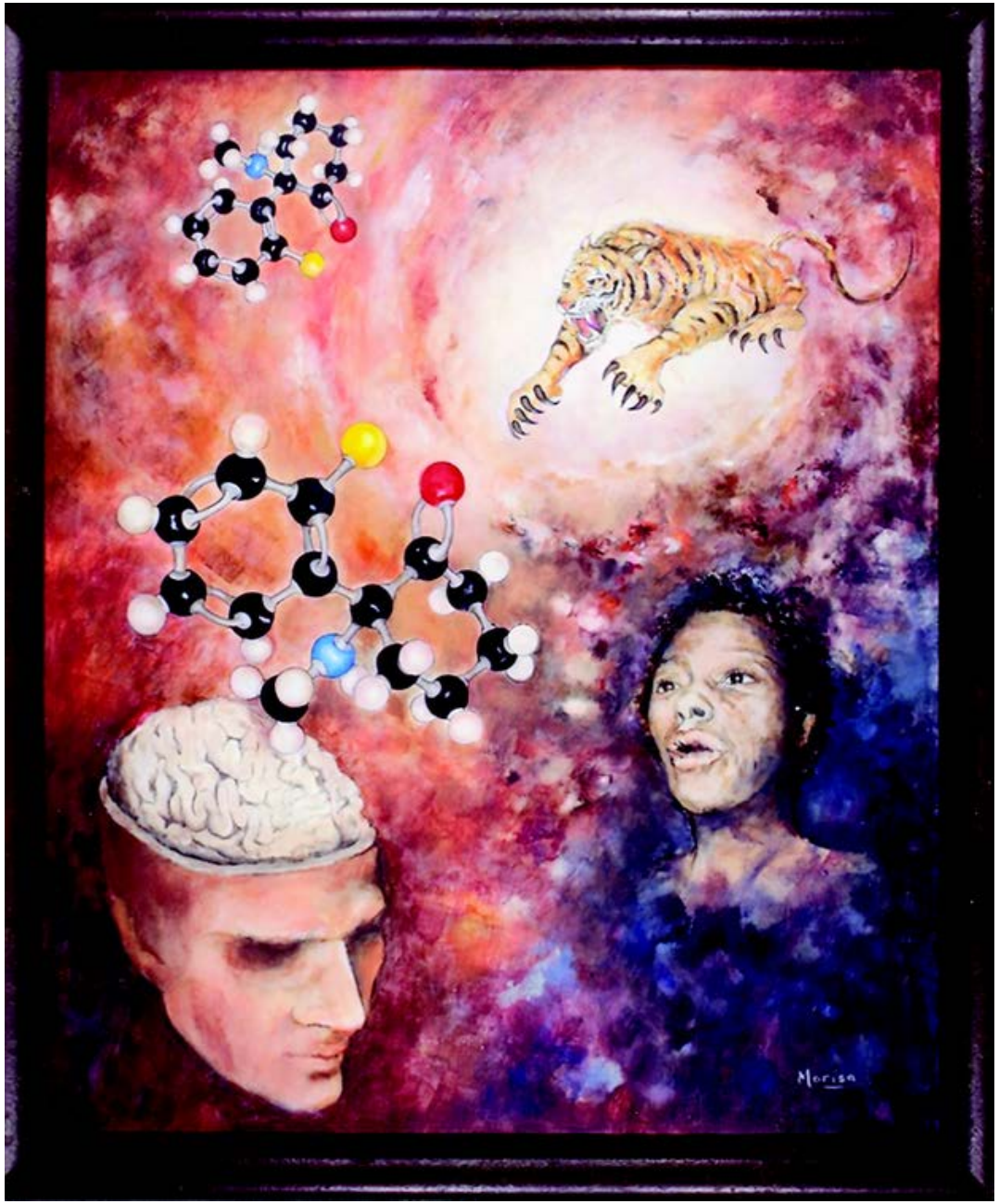
NIH National Institute of General Medical Sciences

NIH National Institute on Aging

NIH NATIONAL CANCER INSTITUTE

“In the meantime you, the reader, must decide what is truth or fiction in your clinical use of ketamine or its separate enantiomers. But always be aware of that tiger…it needs to be tamed.”

– Dr. Edward Domino



Domino EF. Anesthesiology. 2010 Sep;113(3):678-84