Ketamine & Next Generation Therapies With Rapid Antidepressant Effects

Brain & Behavior Research Foundation Webinar
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Experimental Therapeutics & Pathophysiology Branch (ETPB)

Section Neurobiology & Treatment of Mood Disorders (SNMD)

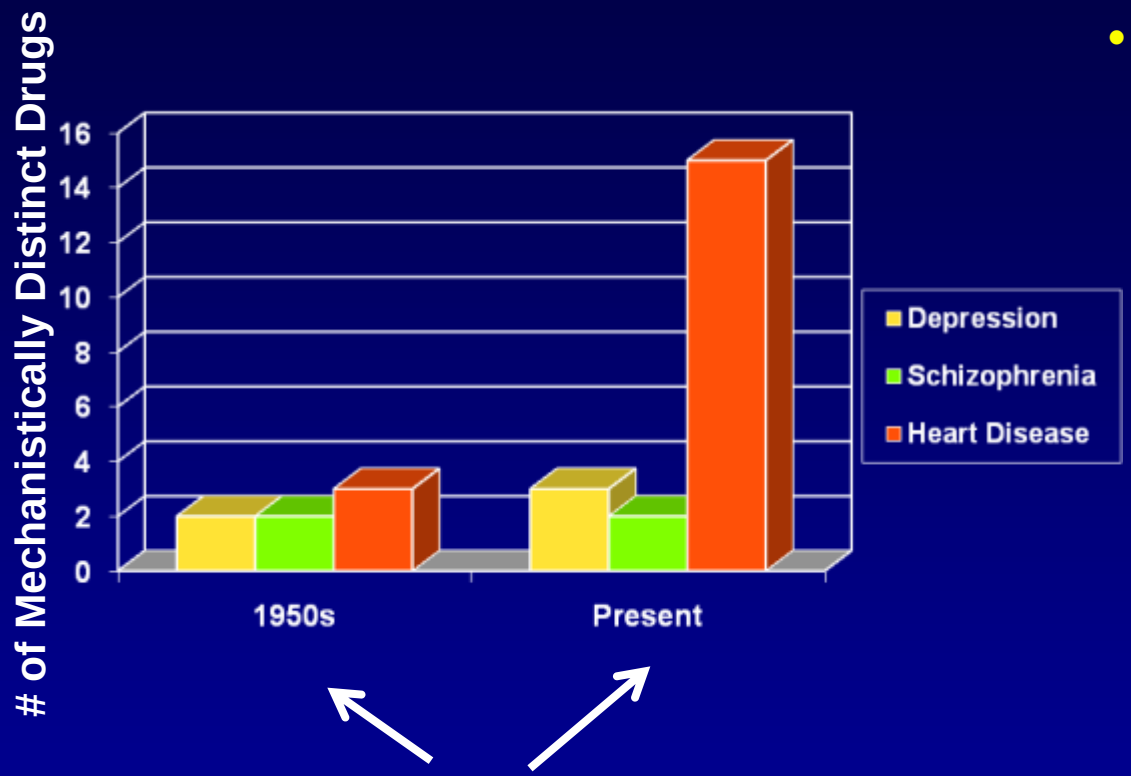
Intramural Research Program

National Institute of Mental Health

Disclosure

- Funding
  - Intramural research program/NIMH
  - No funding from industry
- Listed on a patent application submitted for the use of ketamine and its metabolites in depression. I have assigned my right on the patent to the US government
- Off label use of Scopolamine, Ketamine

Drug Development in the past 50 years



Antidepressants ONLY serotonin and norepinephrine based ('me too drugs')

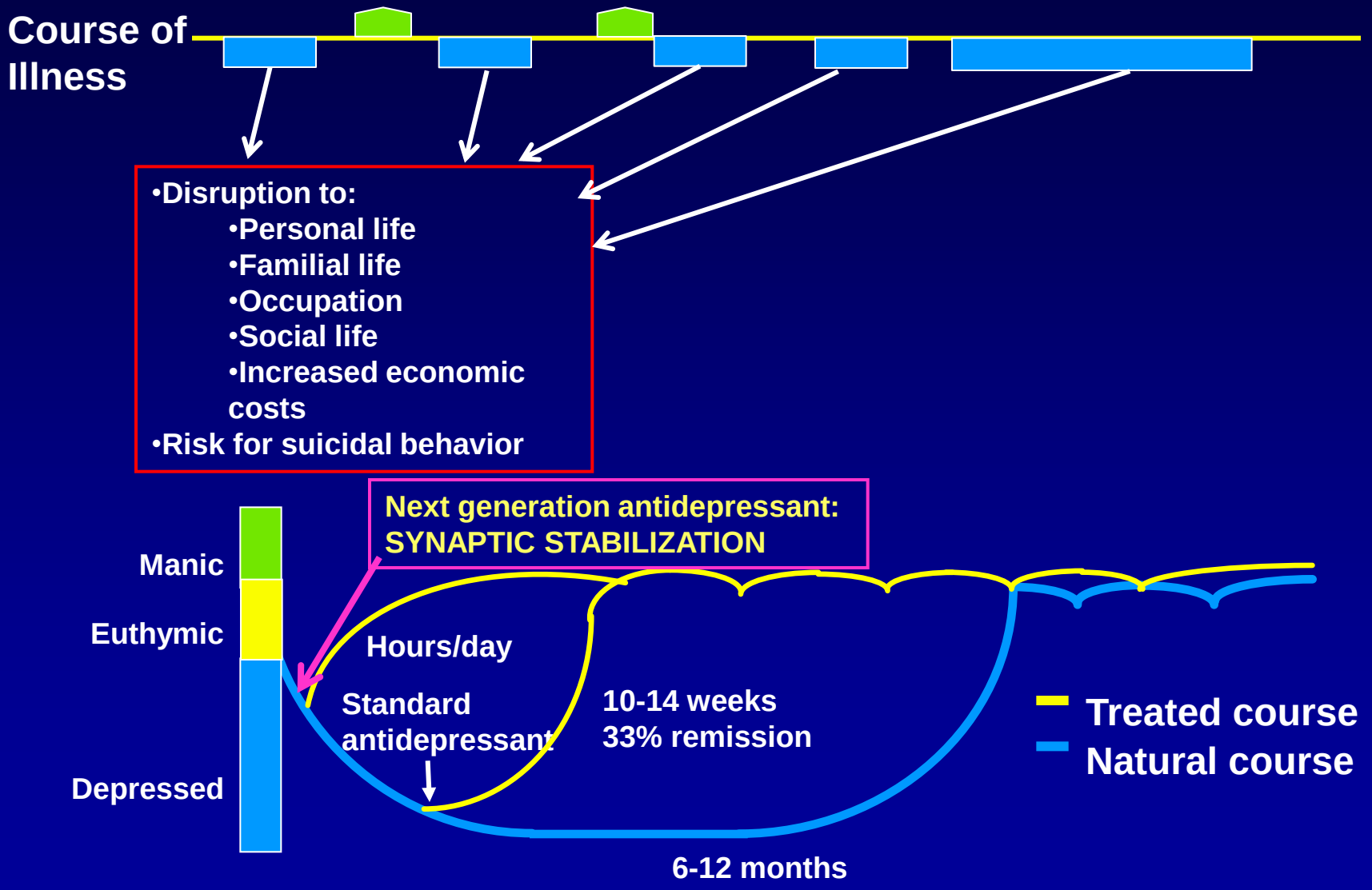
- Except for Li all available FDA approved treatments for Bipolar disorder are anticonvulsants or Antipsychotic drugs
  - Lithium
  - Anticonvulsants
    - Divalproex
    - Carbamazepine
    - Lamotrigine
    - Topiramate
    - Oxcarbazepine
    - Levetiracetam
  - Antipsychotics
    - Clozapine
    - Risperidone
    - Olanzapine
    - Quetiapine
    - Ziprasidone
    - Aripiprazole

Insel and Skolnick Mol Psychiatry 2006;11:11-17

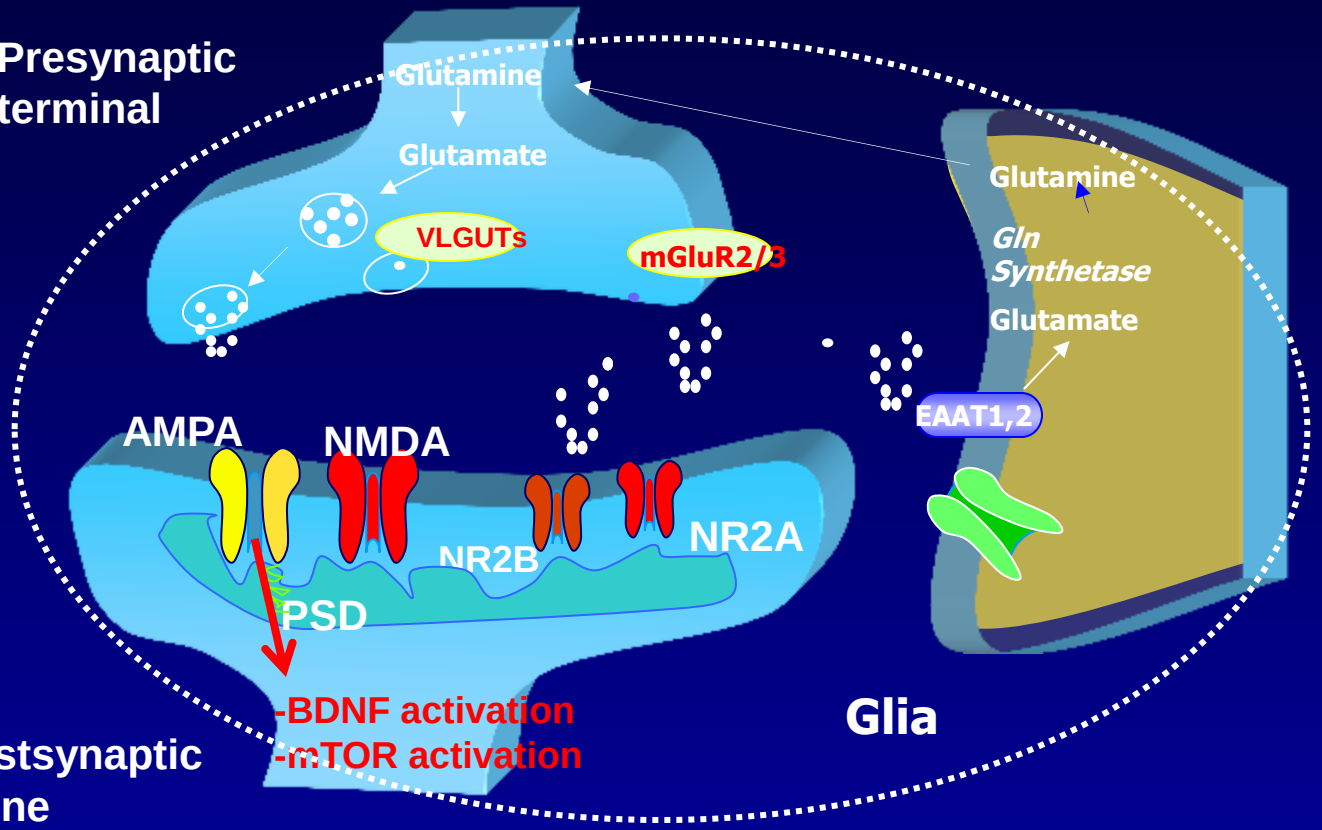
Critical areas to be addressed in translational therapeutic research of mood disorders within ETPB

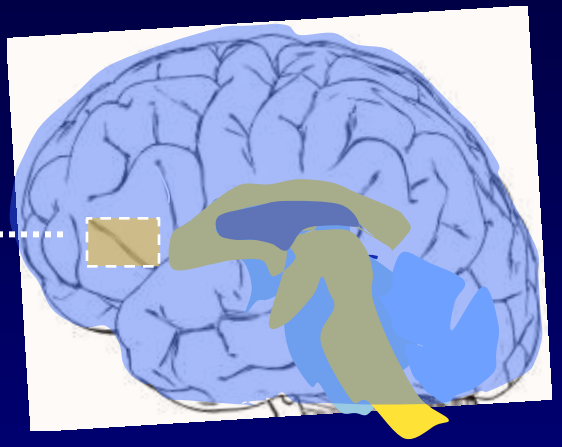
Areas in Need of Study and Treatments
Treatment-resistant depression
No drugs developed specifically for Bipolar disorder
Lag of onset of antidepressants of weeks
Lack of drugs that work rapidly in severe suicidal ideation
Lack of biomarkers predictive of rapid antidepressant response (development of “individualized” or “personalized” txts

Identify a problem: Lag of onset of antidepressant effects

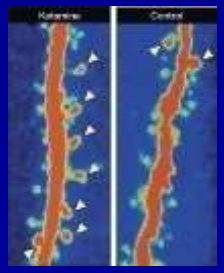


Glutamatergic System: Anatomy, Physiology and Downstream Changes

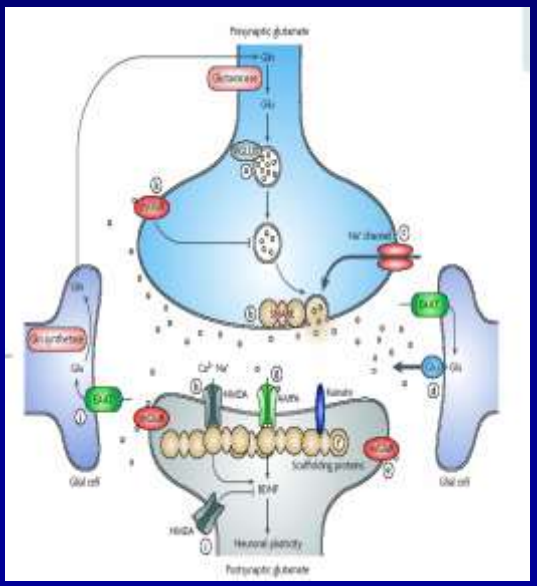




Increase in spine density



Learning
Memory
Plasticity

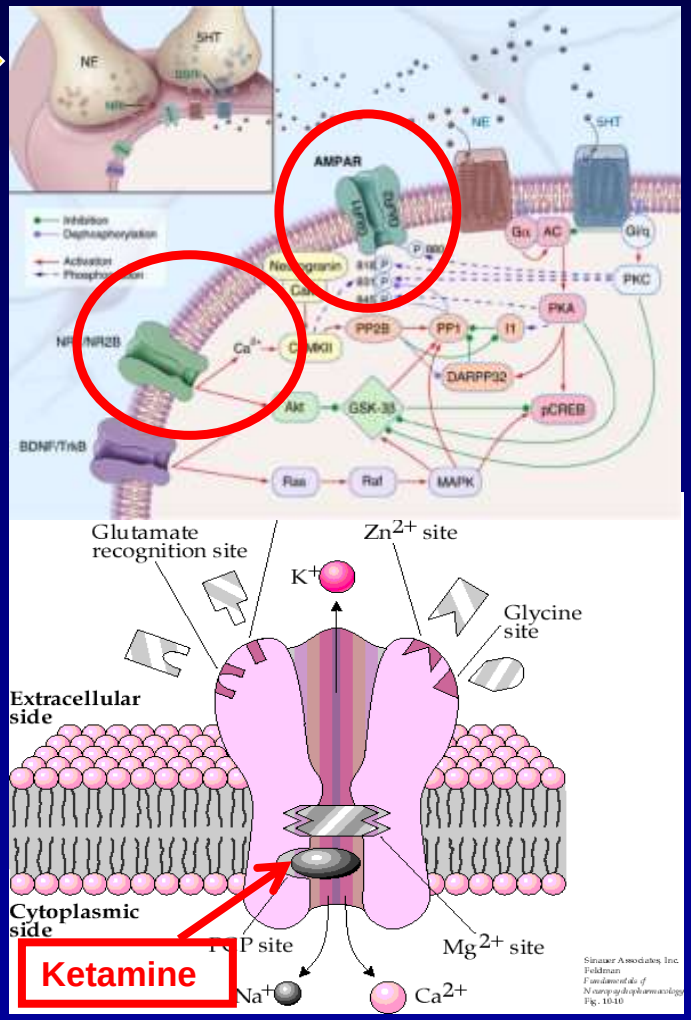


Sanacora, Zarate, Krystal, Manji. Nat Rev Drug Discov 2008

Modification in synaptic AMPA & NMDA receptors

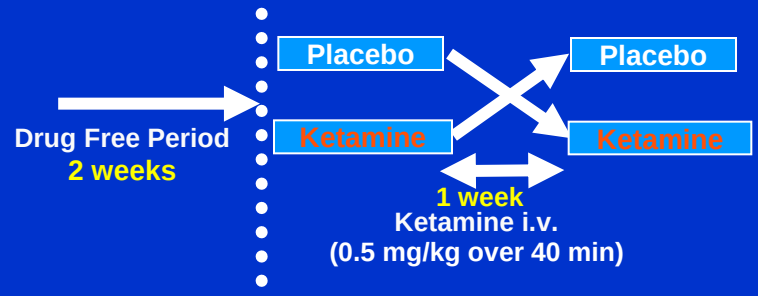
Can the Onset of Action of Antidepressants be Accelerated?

SSRIs
NRIs
SNRIs



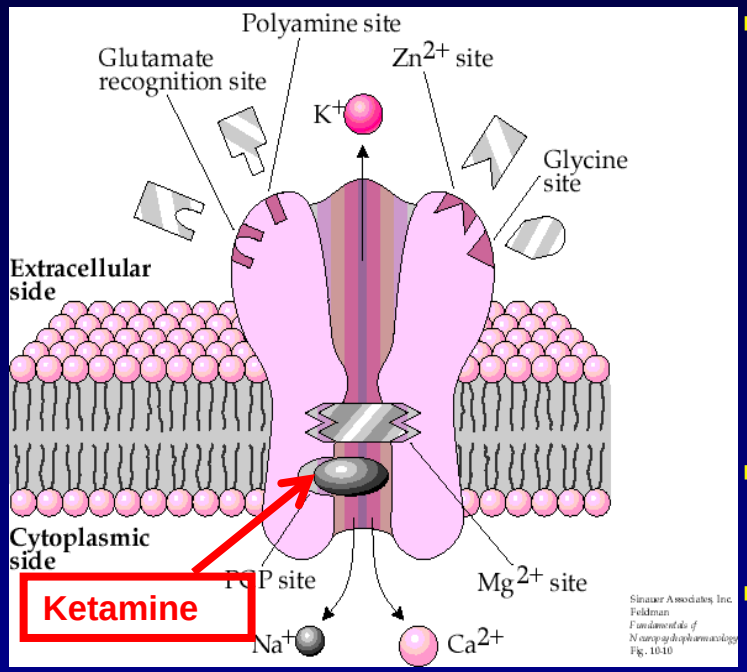
- Synonyms: Ketalar®, Ketaject®, Ketaset®, Vetalar®; K, Special K, Vitamin K, Jet, KitKat
- *Drug Class*: Dissociative anesthetic, hallucinogen, psychotomimetic
- Ketamine is structurally similar to PCP, but 10-50 X less potent at NMDA
- *Medical and Recreational Uses*:
  - In veterinary as a tranquilizer
  - Diagnostic & surgical procedures humans
  - As a short-acting general anesthetic for children and elderly patients
  - Recreationally

Study design 4 studies Unipolar and Bipolar Depression



Ratings: min: 0, 40, 80, 110, 230; Days: 1,2,3, 7

Ketamine psychological and physiological effects



- ***Psychological***: decreased awareness of environment, sedation, dream-like state, vivid dreams, feelings of invulnerability, increased distractibility, generally uncommunicative
  - Pseudo-hallucinations, impaired thought processes, out-of-body experiences, changes in perception about body, surroundings, time and sounds
- ***Physiological***: tachycardia, increased blood pressure, insensitivity to pain, amnesia
- ***Other***: schizophrenic-like symptoms, dizziness, vomiting, and paranoia

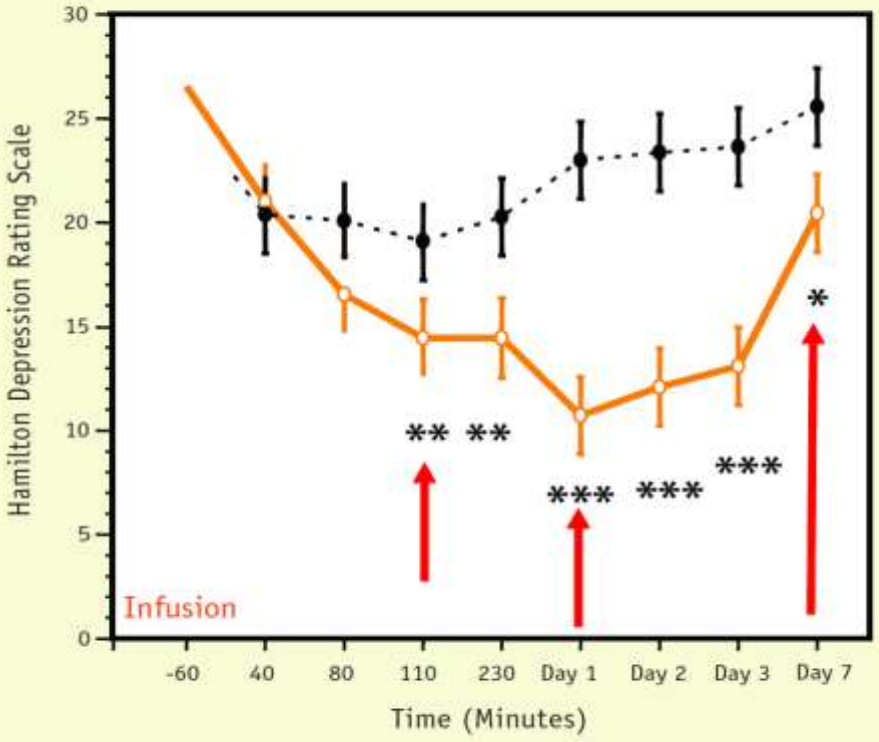
Tolerance, Dependence and Withdrawal Effects: In long-term exposure, high tolerance, drug craving, and flashbacks are described

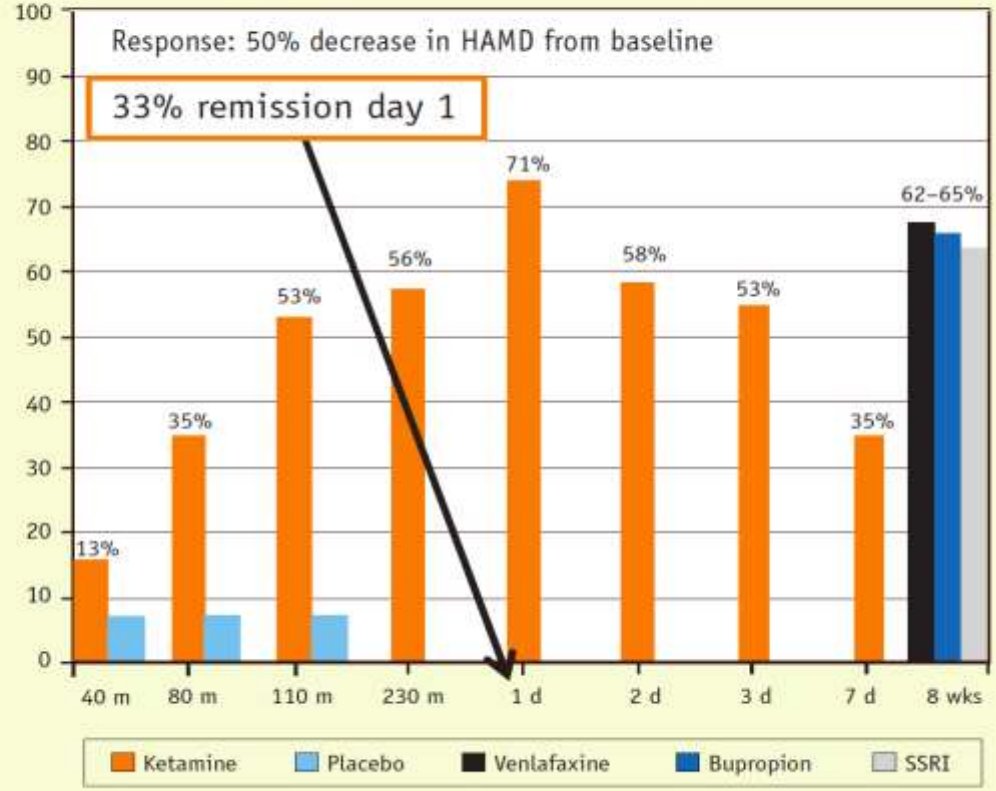
- Little evidence of a physiological withdrawal syndrome unless abrupt discontinuation in chronic users

Bowlde et al. Anesthesiology 1998;88:82-8; Choneim et al. J Clin Psychophopharmacol 1985;5:70-7; Krystal et al. Arch Gen Psych 1994;51:199-214

Rapid Antidepressant Effect Associated with Ketamine

Robust, rapid, and relatively sustained antidepressant effect of low dose ketamine, and response rates to ketamine in a double-blind placebo crossover trial in patients with treatment-resistant major depression.

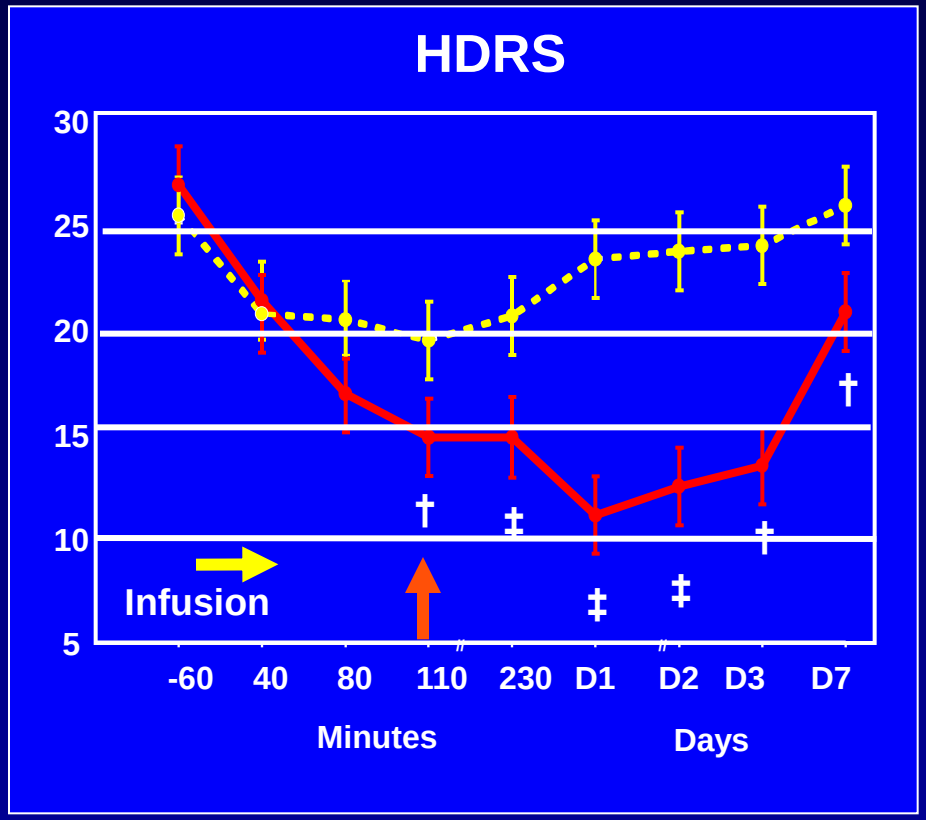




Zarate et al. Arch Gen Psychiatry, 2006

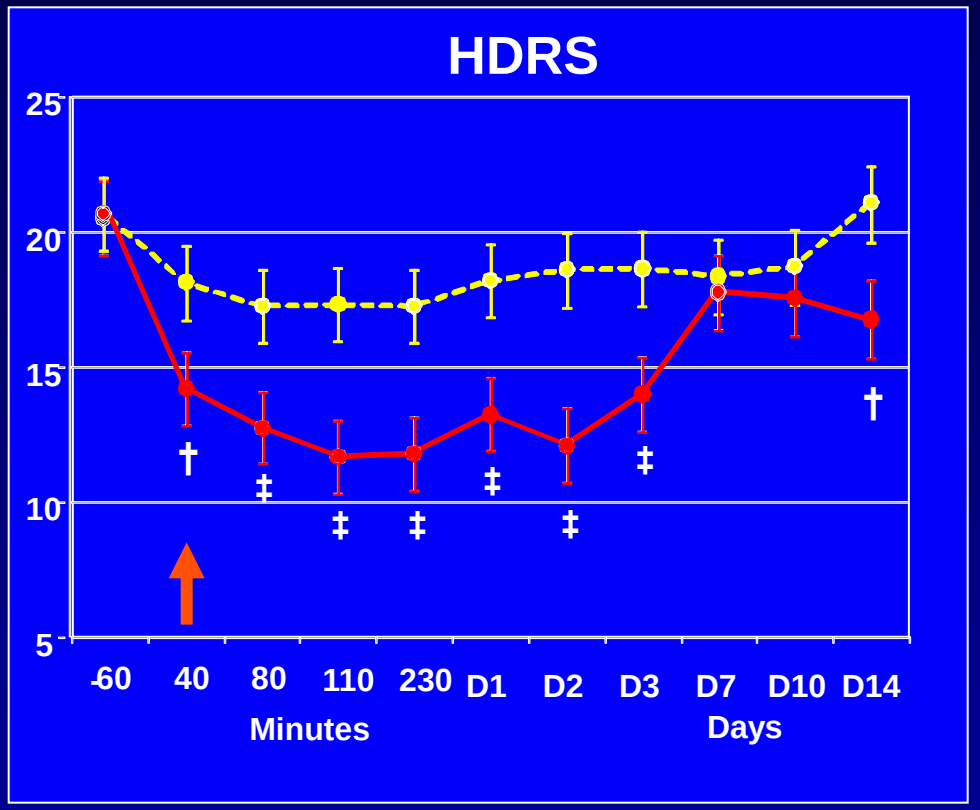
From Discovery to Cure: Report of the National Advisory Mental Health Counsel's Workgroup. August 2010

Change in the Depression Scores Over One Week in Major Depressive Disorder

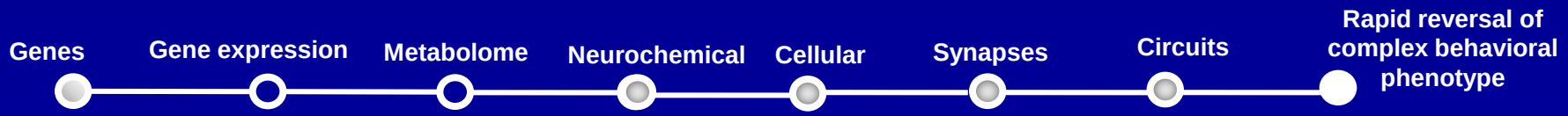


Zarate et al. Arch Gen Psych 2006

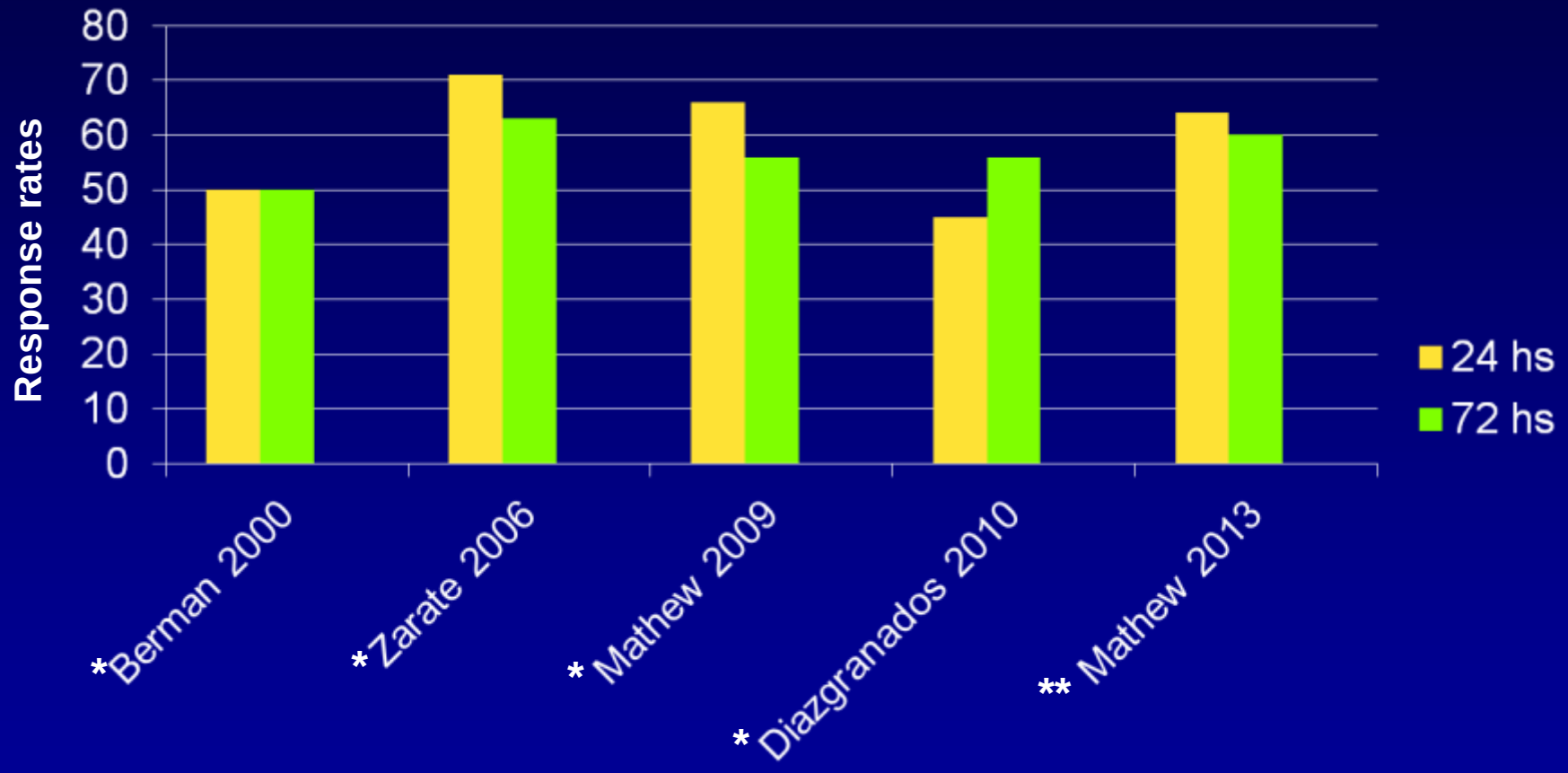
Change in the Depression Scores Over One Week in Bipolar Depression



Diazgranados et al. Arch Gen Psych 2010



Response at 24 and 72 hours Following a Single Ketamine Infusion, controlled studies



* Placebo-controlled

** Midazolam

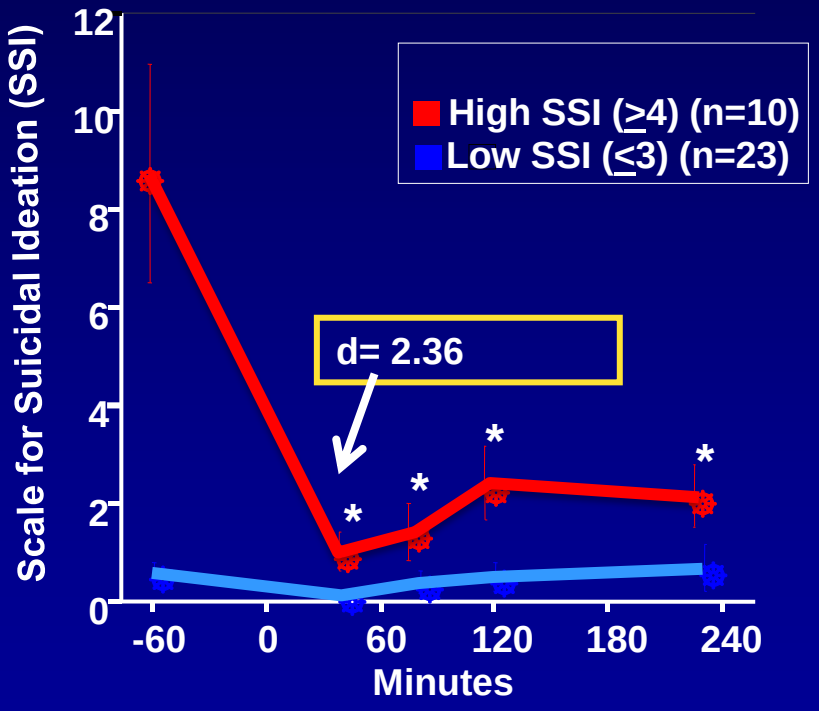
Next Generation Treatments for Acute Severe Suicidal Ideation?

- Suicidal ideation or attempts in patients with major depression is an emergent condition that requires immediate treatment
- Highest risk period of suicidal behavior is in the first 9 days of starting an antidepressant
- From 1992 to 2001 emergency department visits for suicide attempt/self-injury increased by 47% (0.8 to 1.5 visits per 1000)
- The risk for suicide attempts occurring in inpatient units is the 2nd most common sentinel event reported to the *Joint Commission*
  - ~1/3 of attempts in inpatient units in the US each year take place while the patient is on 15-minute checks
- Military: in the army there are now more deaths by suicide than by combat

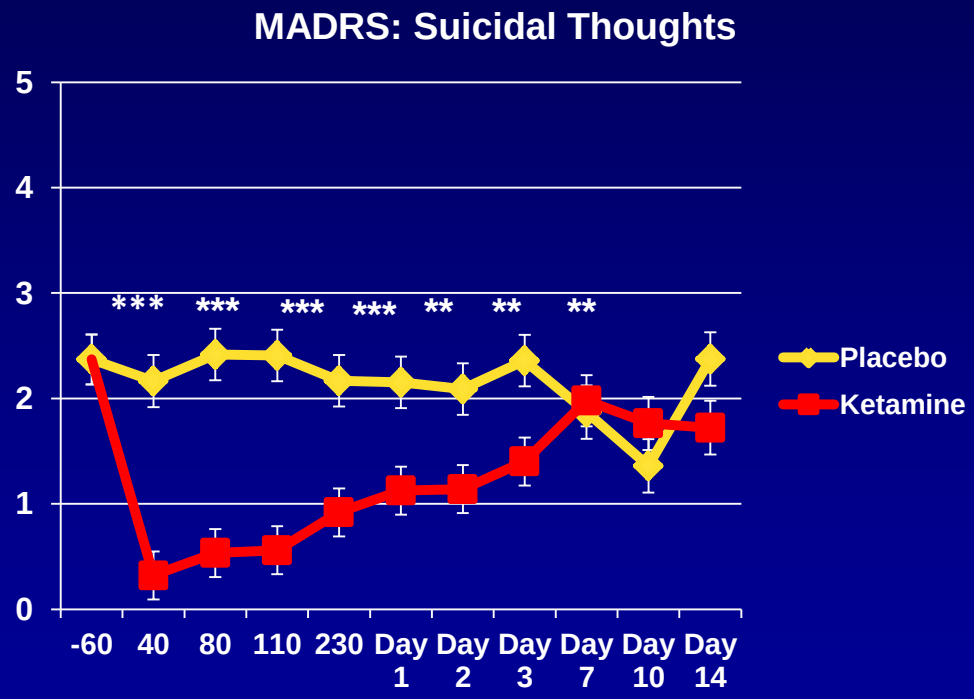
Deisenhammer et al. J Clin Psychiatry 2009; Larkin et al. Crisis 2008; Janofsky J Am Acad Psychiatry Law 2009; Jick et al. JAMA 2004; Diazgranados et al. J Clin Psych 2010

Rapid decreases in suicidal ideation with ketamine in major depressive disorder AND bipolar depression

Unipolar Depression



Bipolar Depression



DiazGranados et al. J Clin Psych 2010; Zarate et al. Biol Psych 2012

Next Steps in Ketamine Research/Treatment

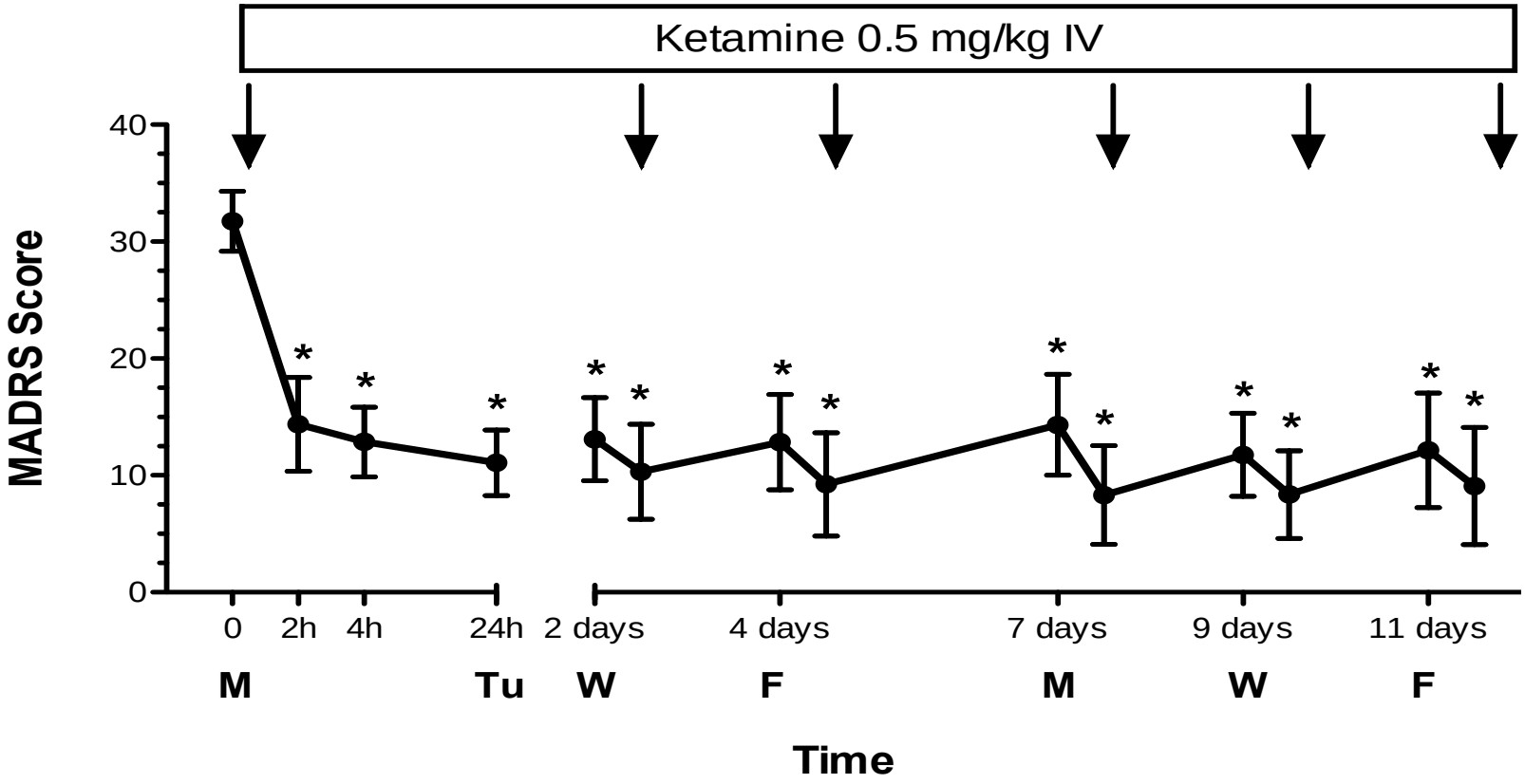
1. Ketamine in Clinical Practice Settings: research/off-label use
   - •Repeat infusions (pulse treatment—ECT)
   - •Slower infusion over 100 min
   - •Combination with lithium
   - •Combination with standard treatments
   - •Combination with ECT
2. Develop ketamine-like drugs (without dissociative side effects)
   - More NMDA subunit selective drugs
3. Understand ketamine's mechanism of action from synapses to through a range of systems
4. Is there more to the story with the "ketamine paradigm": ketamine's metabolites

1. Ketamine in Clinical Practice Settings: Off-label Use

"Psychiatric team at …..Medical Center has begun offering ketamine infusions to patients who are running out of options."

Kaplan, A. Psychiatric Times May, 2011

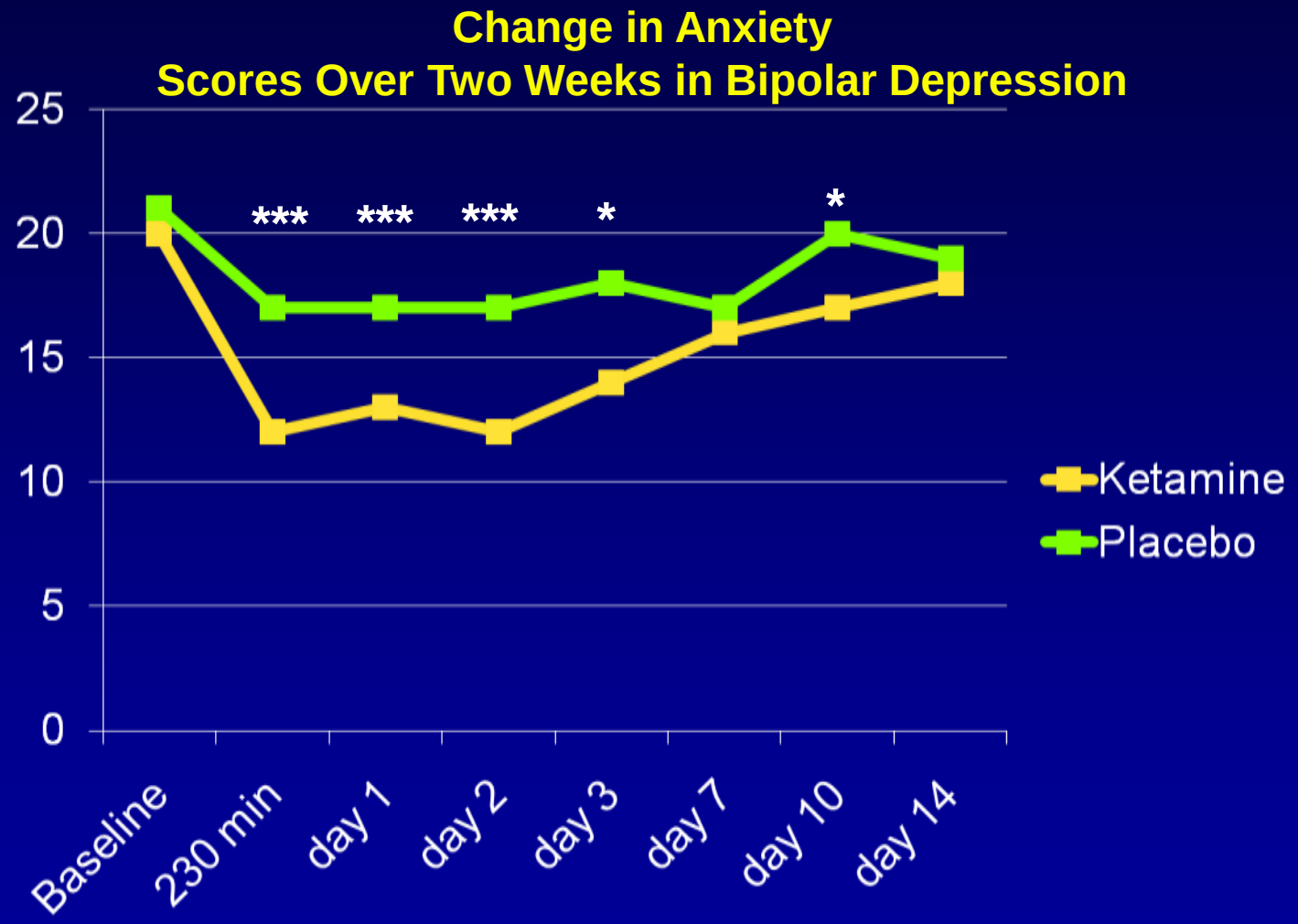
Repeated Ketamine Infusions in Treatment-Resistant Depression: Pilot Experience



24 patients with TRD enrolled in a course of 6 ketamine infusions on a Monday-Wednesday-Friday schedule over two weeks. P values based on the Related-Samples Wilcoxon Signed Rank Test. Error bars reflect 95% CI. Asterisk indicates time-point significantly different from baseline ($p<0.001$)

Murrough et al, Biological Psychiatry 2012

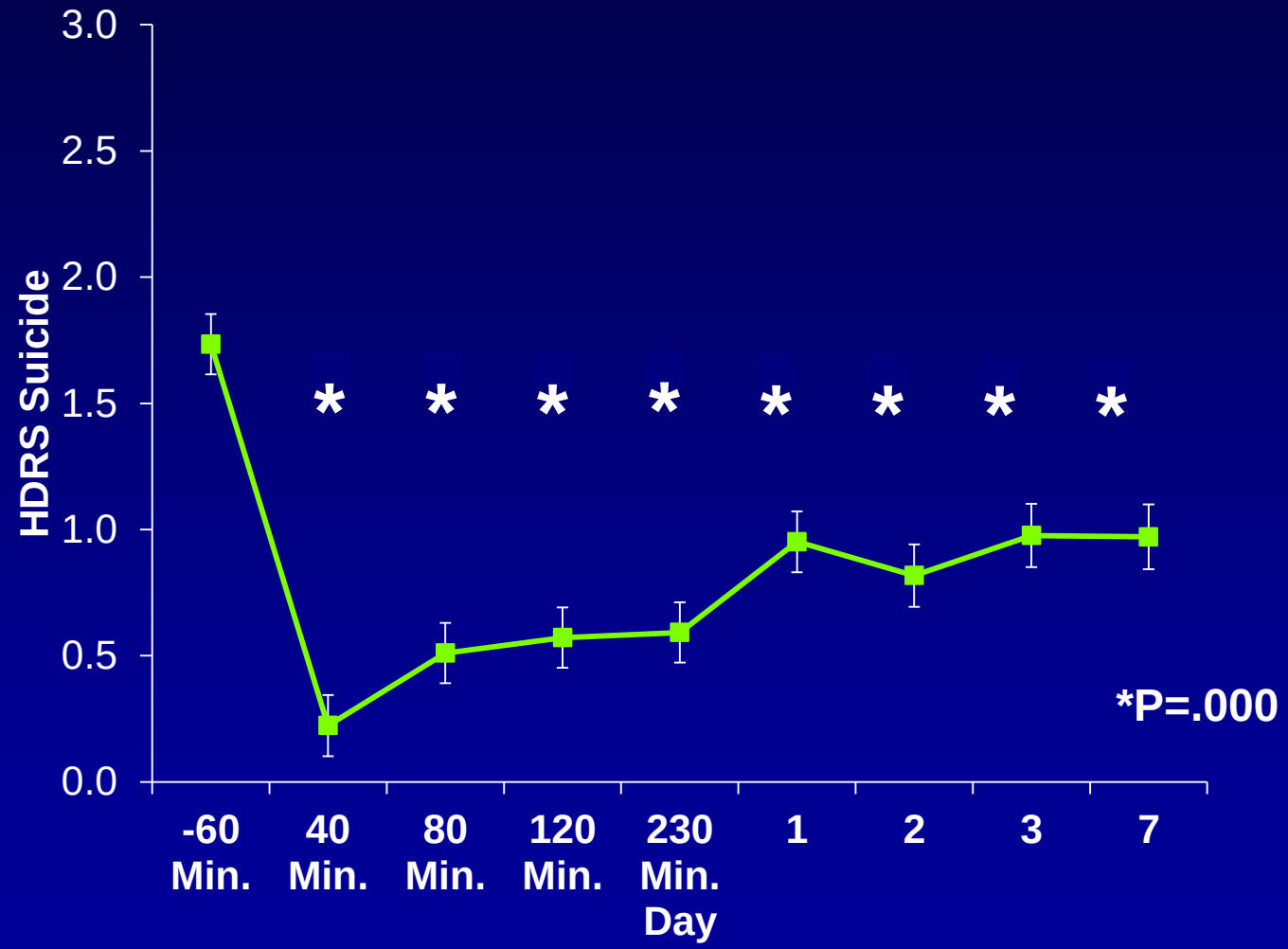
Clinical Observations from Pooled Studies: Ketamine has Robust Anxiolytic Effects



DiazGranados et al. Arch Gen Psych 2010

Clinical Observations from Pooled Studies: Ketamine has Robust Antisuicidal Effects

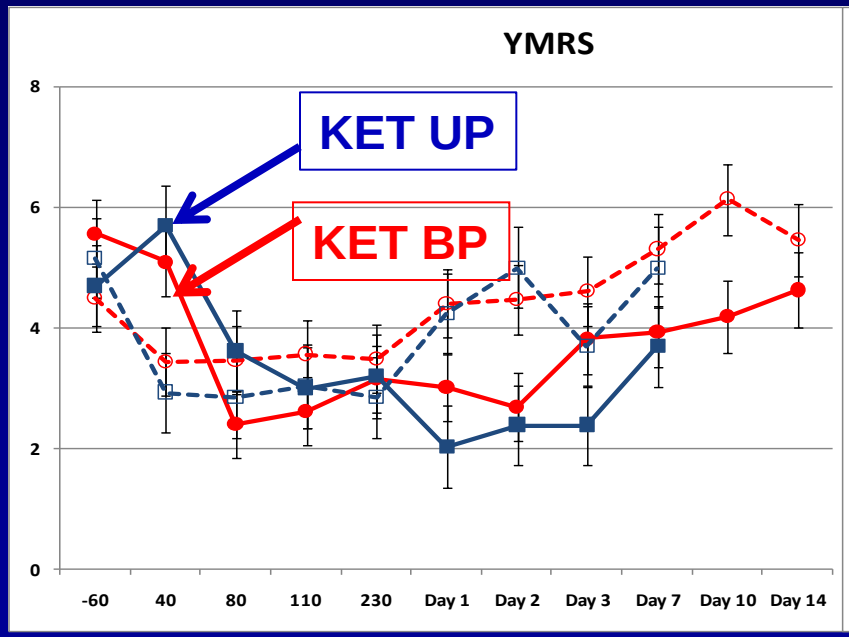
Pooled ketamine studies at NIMH unipolar and bipolar depression (N=111)



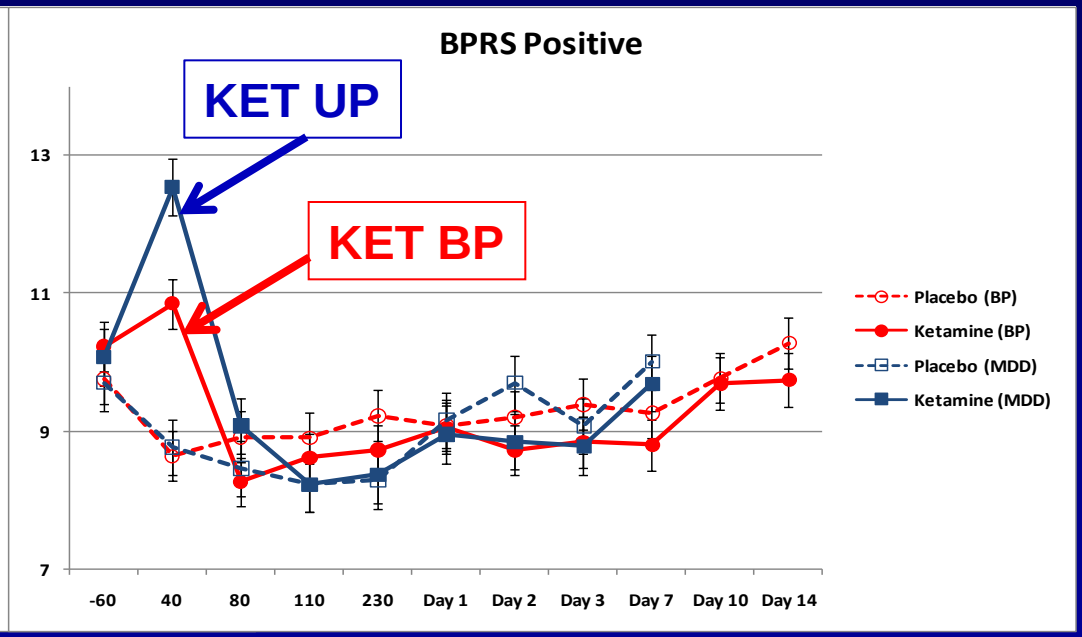
Clinical Observations from Pooled Studies: Ketamine does not appear to:

- induce affective switch in three independent samples of treatment-resistant depression
  - worsen in PTSD and abuse history with a single dose of ketamine

Change in YMRS scores in MDD and Bipolar depression txt'd with ketamine

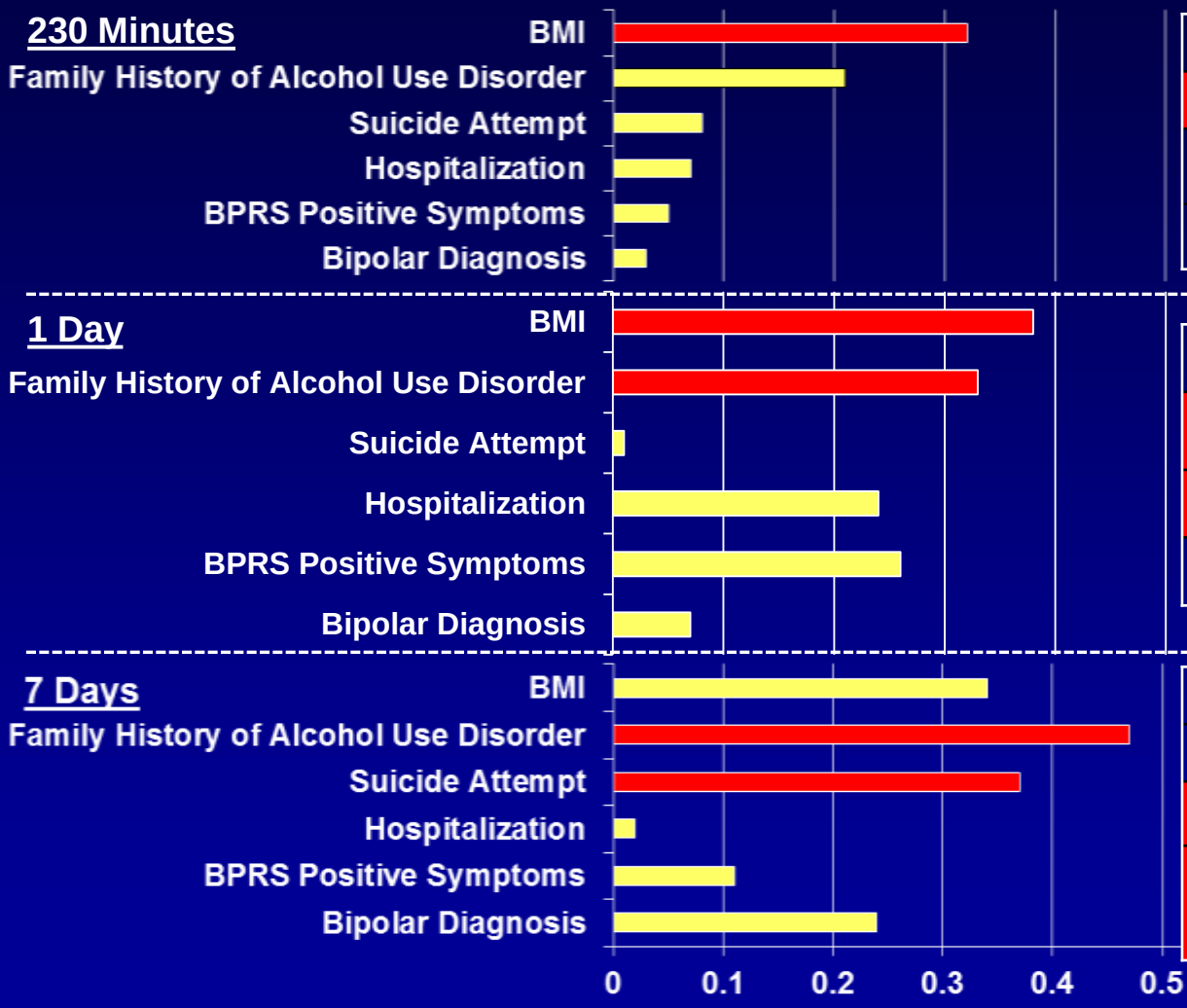


Change in BPRS scores in MDD and Bipolar depression txt'd with ketamine



Diazgranados et al. Arch Gen Psych 2010; Zarate et al. Biol Psych 2012; Zhang et al. Biol Psych 2013; Niciu et al. Biol Psych 2013

Clinical Observations from Pooled Studies: Baseline Predictors of Response



Multivariate

	B	p
BMI	-0.30	0.004
Family History ETOH	-0.17	0.080
Suicide Attempt	-0.01	0.916

	B	p
BMI	-0.37	0.001
Family History ETOH	-0.27	0.014
Suicide Attempt	-0.14	0.196

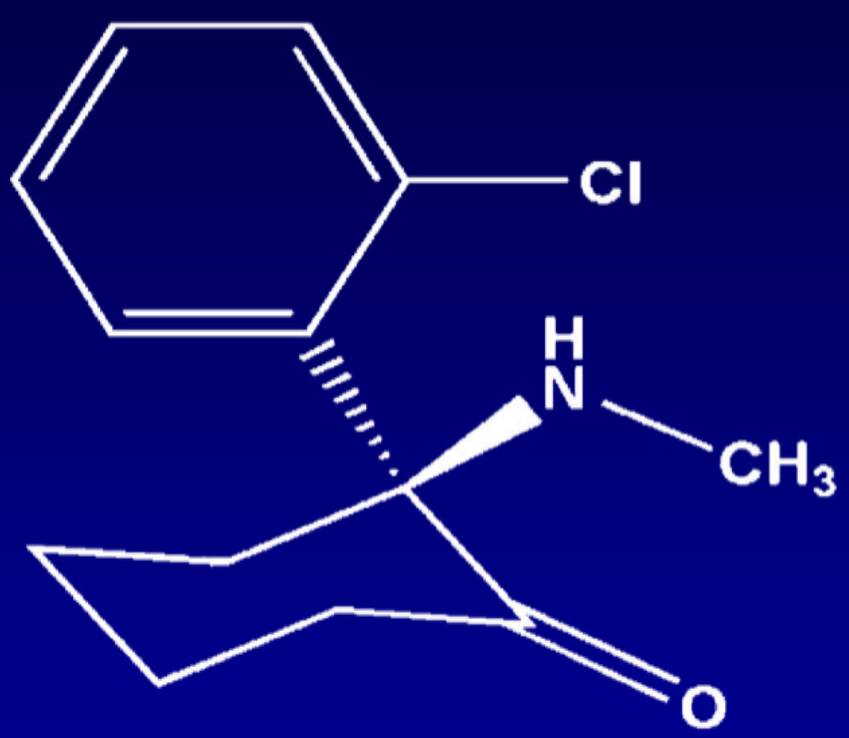
	B	p
BMI	-0.18	0.098
Family History ETOH	-0.41	0.000
Suicide Attempt	0.28	0.012

2. Develop ketamine-like drugs (without dissociative side effects)

Glutamate modulation in TRD: pipeline (Partial List)

Compound (Manufacturer)	Mechanism of Action	Phase	Route	
Esketamine	S-ketamine	I/II	IV, IN	J & J; Completed
MK-0657*(Merck); Cerecor	NR2B Antagonist	IIa	p.o.	Completed; Cerecor new program
CP101,606 (Pfizer)	NR2B antagonist	IIa	IV	+ response; discontinued
mGlu negative allosteric modulators (Roche)	mGlu2 and mGlu5	IIa	p.o.	Ongoing study
AZD6765*(AstraZeneca)	NR2AB Antagonist	IIb	IV	Completed NIMH AZ ongoing
EVT 101 (Evotec) (J &J)	NR2B antagonist	IIa	p.o.	Study halted; Compounds picked up by J&J

The Optical Isomers of Ketamine



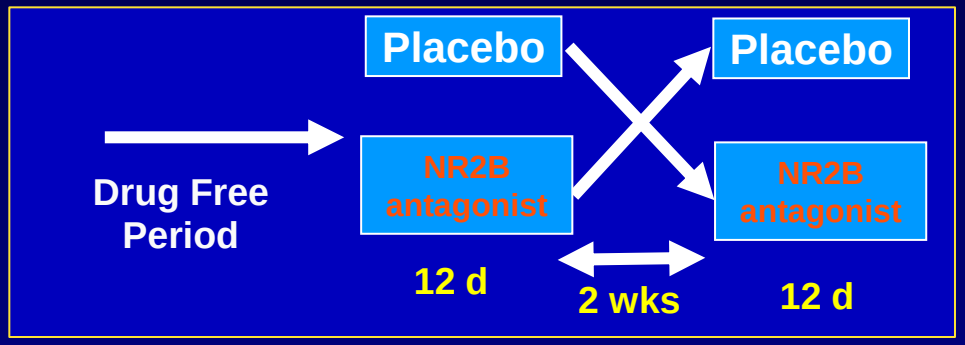
R-(–)- ketamine

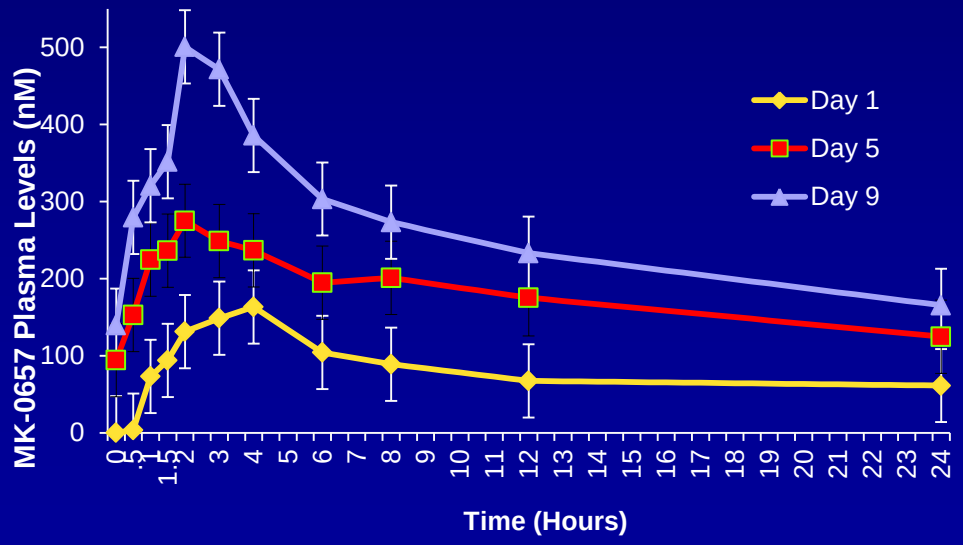
S-(+)- ketamine

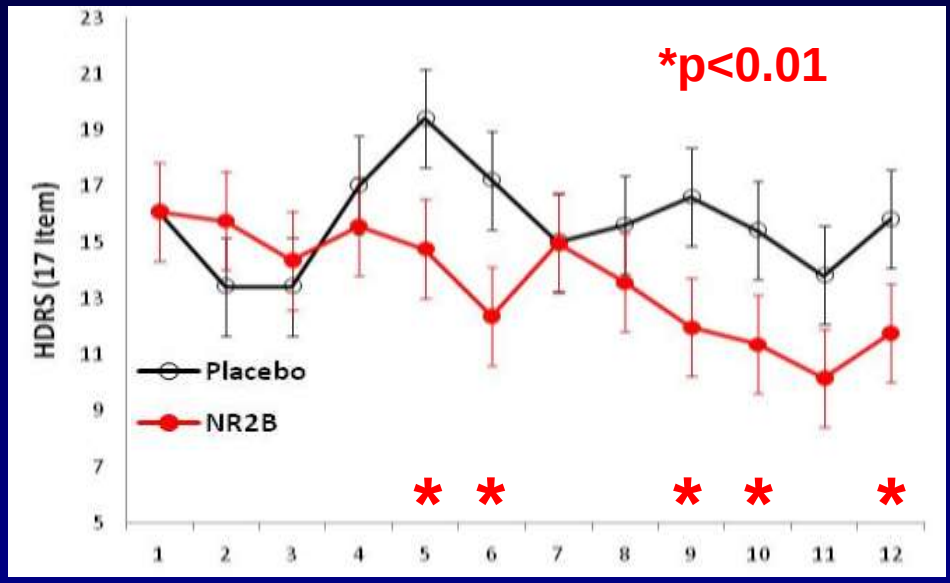
Pai A , Heining M 2007

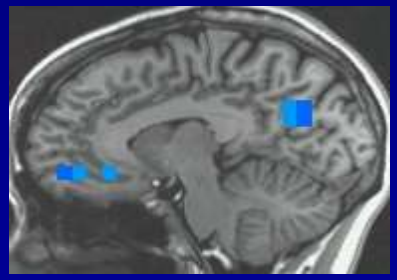
Preliminary data on an NR2B in antagonist (MK-0657) in major depressive disorder: efficacy, neurotrophic factors (BDNF), and ACC activity

- Oral doses (4-8 mg/day)
- No psychotomimetic effects

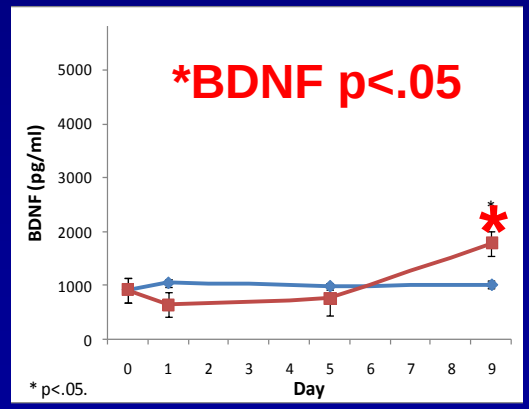








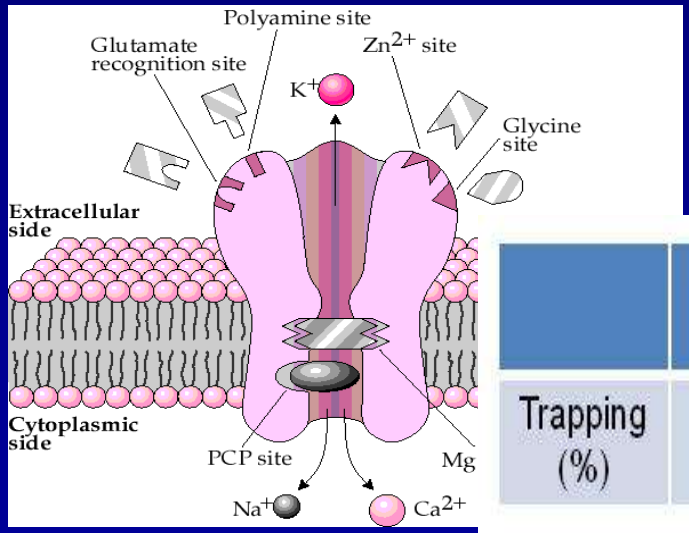
MEG: NR2B vs placebo
N back



Ibdrahim et al. J Clin Psychopharmacol 2012

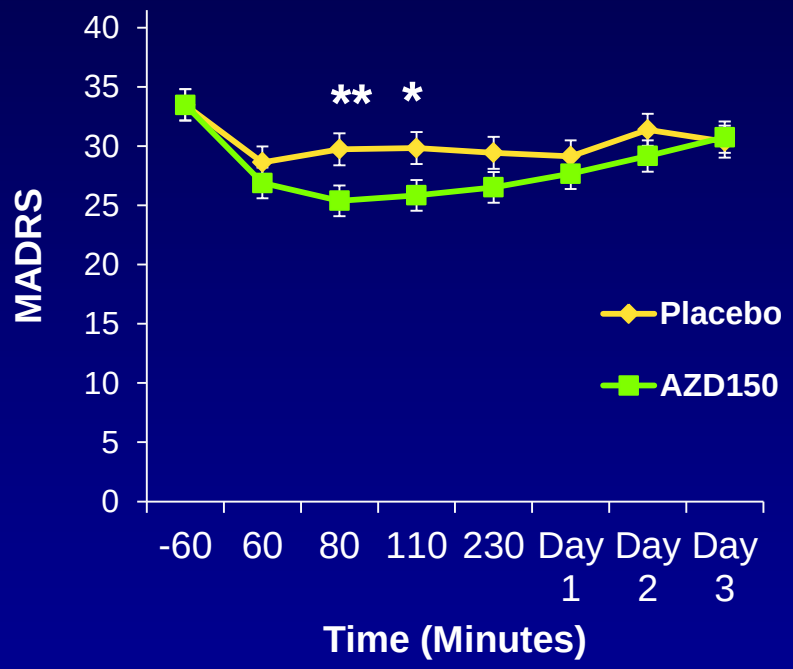
AZD6765: A low-affinity NMDA channel blocker

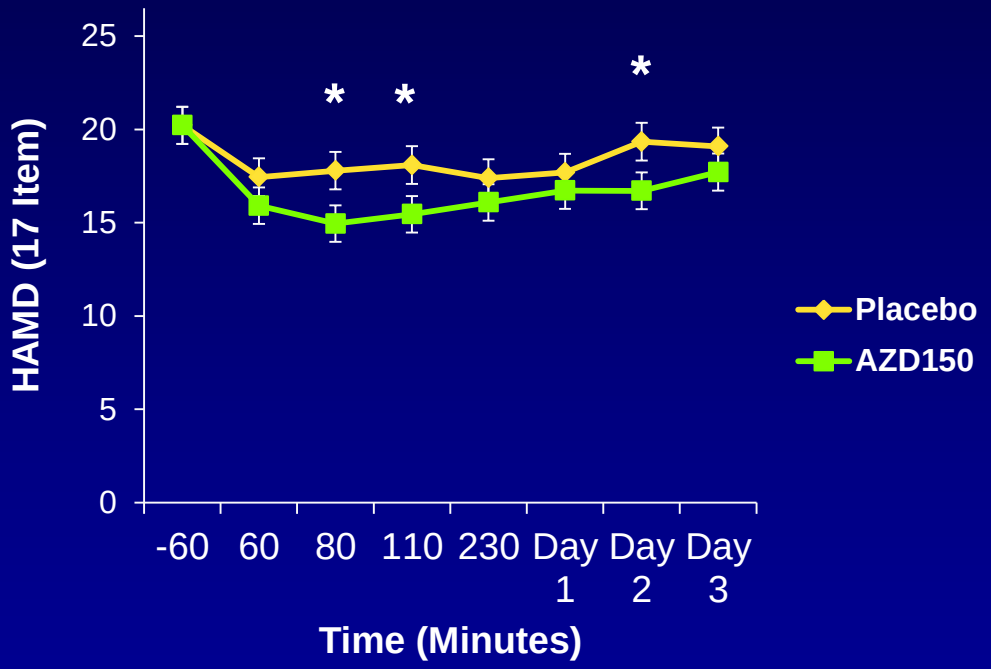
- AZD6765 was developed in Europe as an intravenous txt for stroke but was not further pursued because of a lack of efficacy
- AZD6765 is a low-trapping NMDA channel blocker, NMDA receptor antagonist. It is blood-brain penetrant
- AZD6765 well tolerated with dizziness, nausea, and vomiting, being the most common AEs. No psychotomimetic effects up to 160 mg
- Antidepressant effects in learned helplessness, FST
- Anxiolytic activity in the rat punished responding model



	Ketamine	MK-801	Memantine	Active Remacemide	AZD6765
Trapping (%)	82%	76%	70%	64%	52-59 %

A double-blind placebo-controlled study of NMDA antagonist (AZD6765) in treatment-resistant depression (N=22)

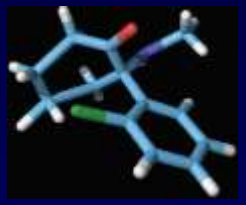




No dissociative, psychotomimetic or euphoric effects

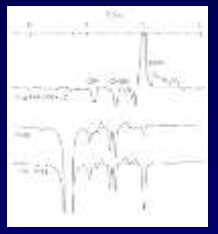
Zarate et al. Biol Psych 2012

3. Study of ketamine's mechanism of action from synapses through a range of systems



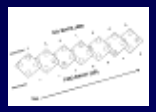
Polysomnography

MRS

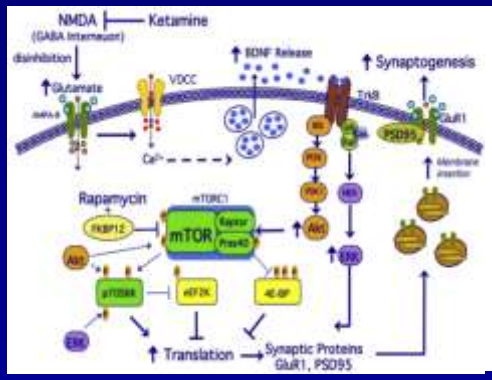


PET & MEG

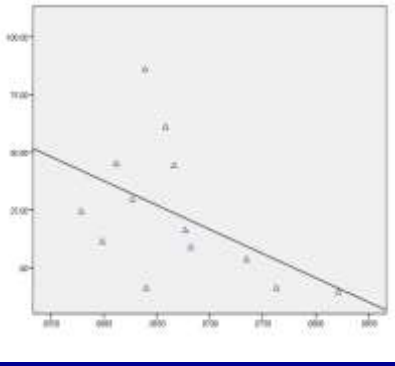
MEG



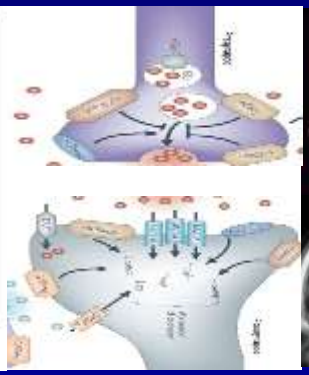
Synaptic Plasticity
(mTOR, eEF2, GSK-3B inh)

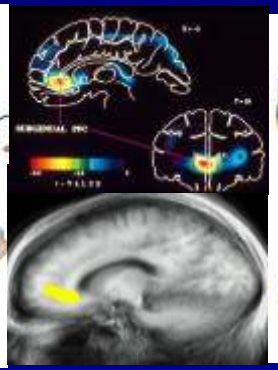


Neurochemicals
(Glx DM/DA-PFC
Glx/Glu ratio)

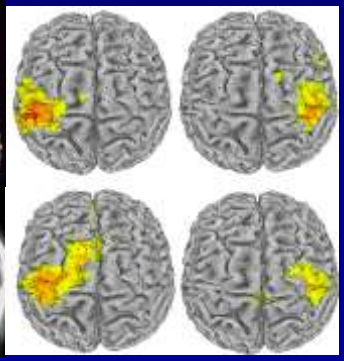


•Glucose changes
(glutamate signal)
•Circuits/connectivity





Cortical excitability

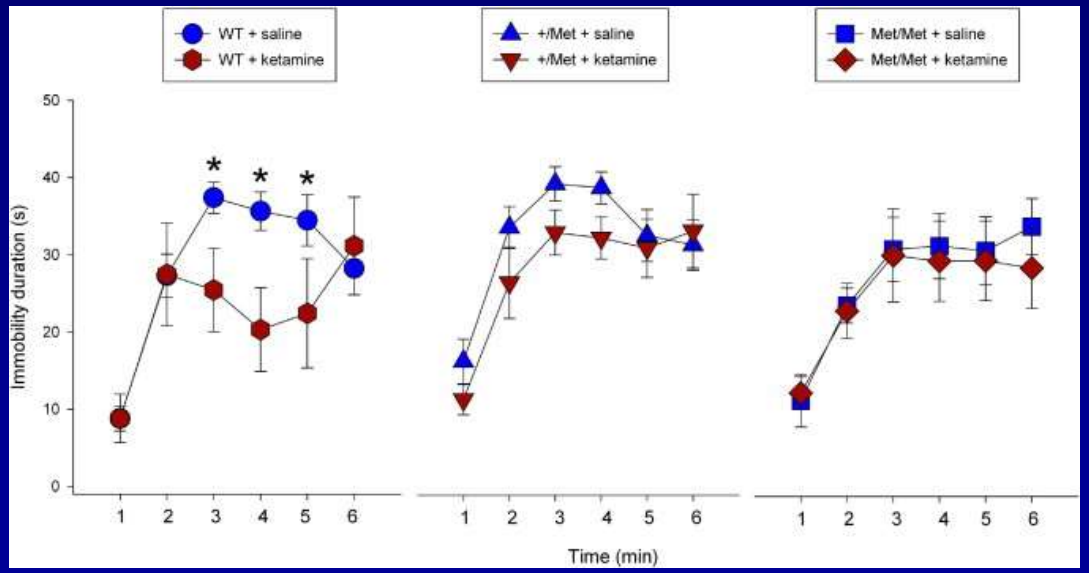


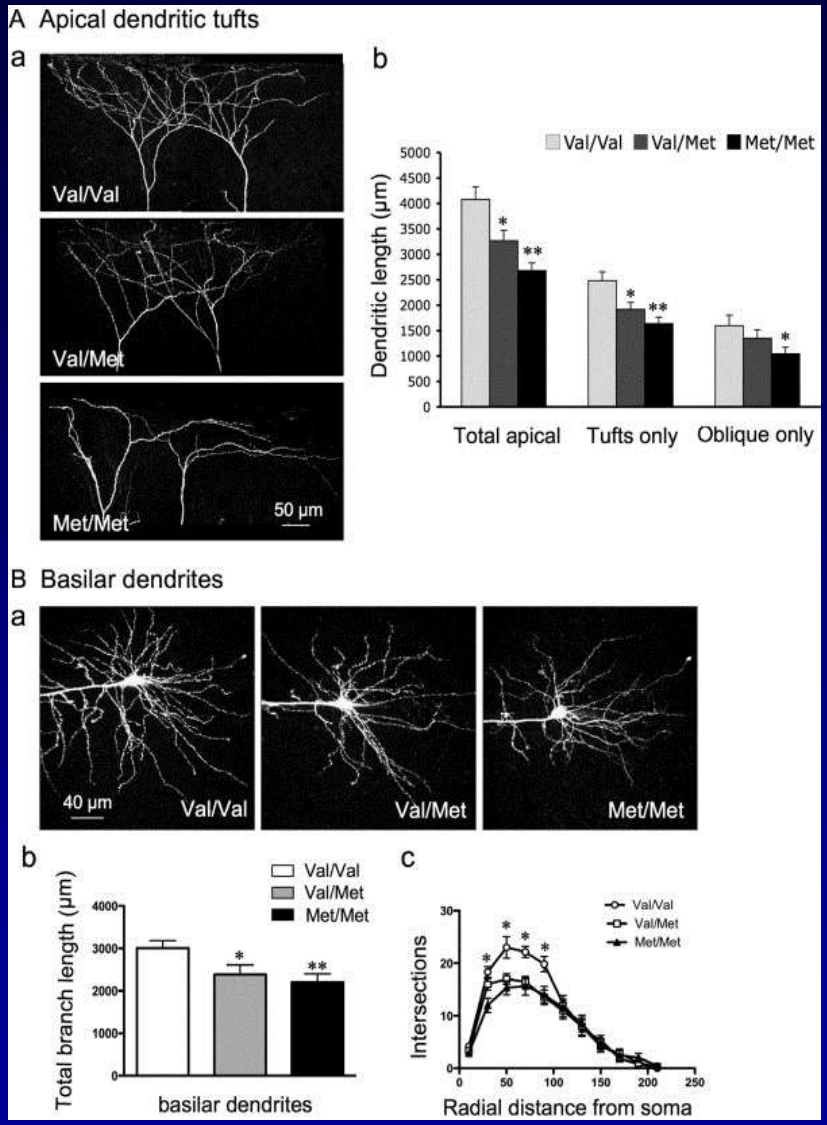
Genes → Gene expression → Metabolome → Neurochemical → Cellular → Synapses → Circuits → Rapid reversal of complex behavioral phenotype

Zarate et al. Biol Psych 2013

Medial prefrontal cortex layer V pyramidal cells in brain-derived neurotrophic factor Val66Met knock-in mice have both apical and basilar dendritic atrophy

Antidepressant response to Ket in the forced swim test is attenuated in brain-derived neurotrophic factor Val66Met knock-in mice

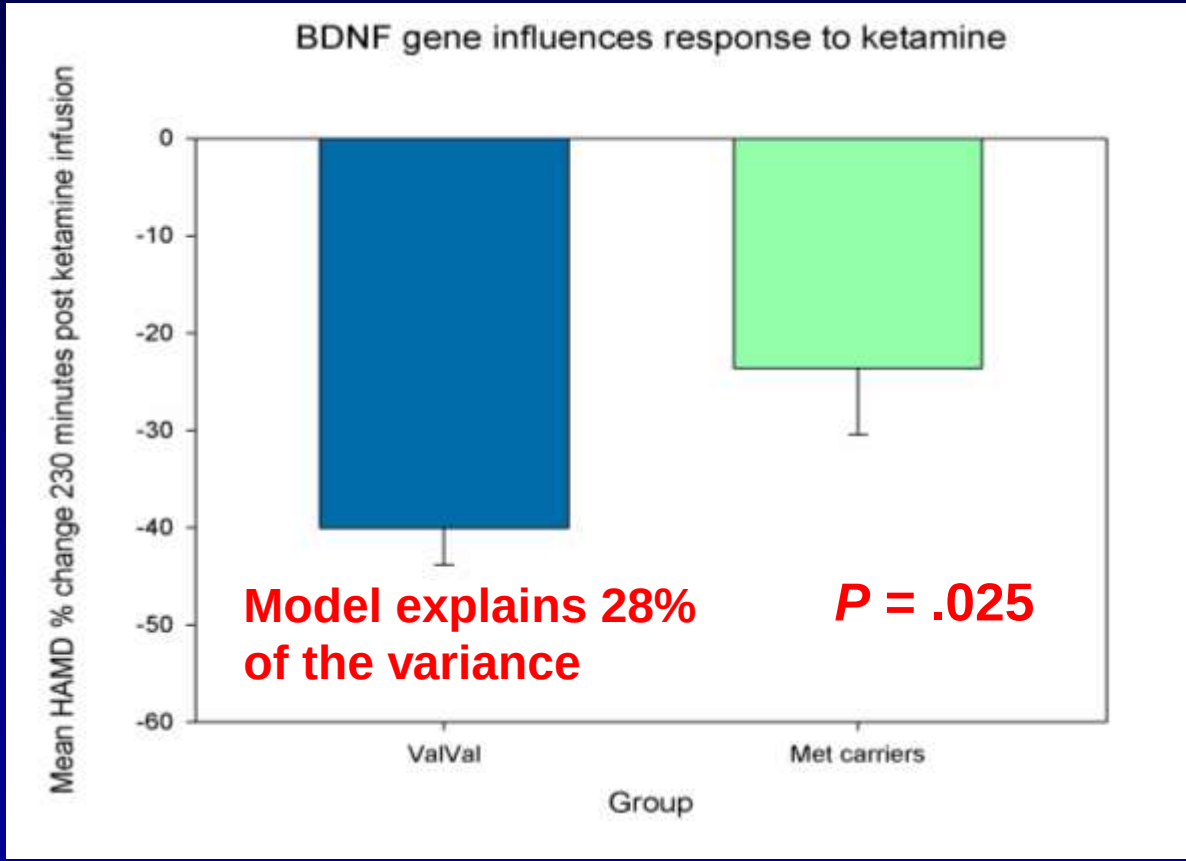




Liu et al. Biol Psychiatry 2012

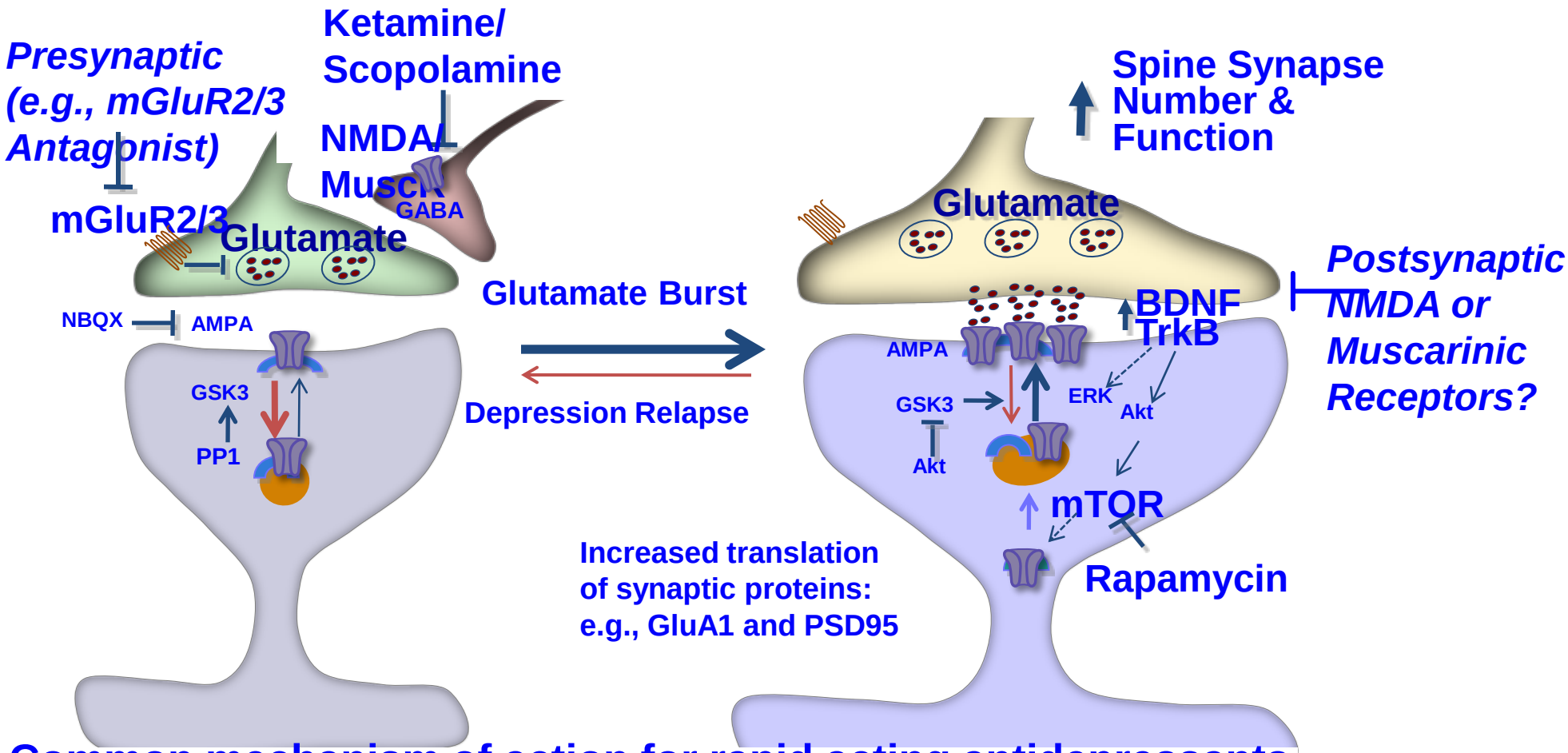
Genetics: Brain-Derived Neurotrophic Factor Val66Met polymorphism and antidepressant efficacy of ketamine in MD

- 62 patients (NIMH, Yale) with BDNF SNP data and HAMD score at 230 minutes post ketamine infusion
- 41 ValVal, 19 MetVal, 2 MetMet



Laje, Lally, McMahon et al. Biol Psych 2013

Rapid acting antidepressants: NMDA and muscarinic-antagonists increase synaptogenesis: SYNAPTIC STABILIZATION TO MOOD STABILIZATION

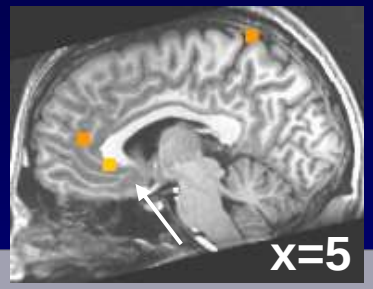


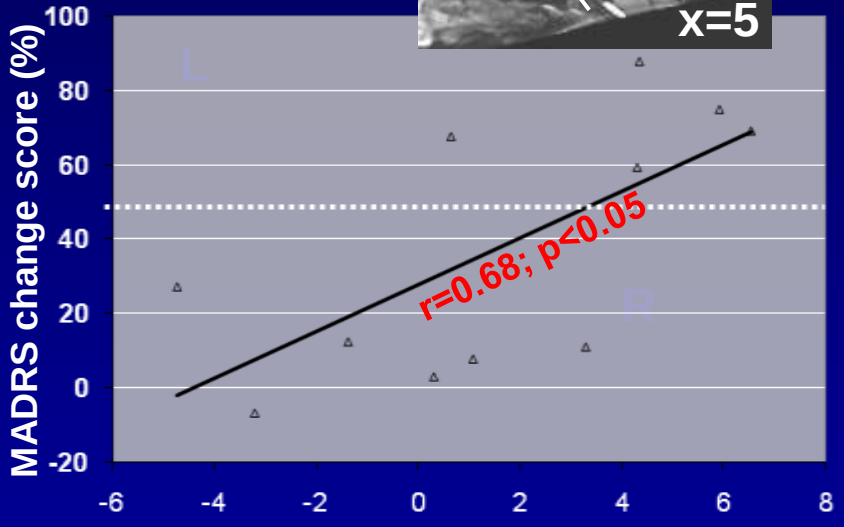
-Common mechanism of action for rapid acting antidepressants

-Rapid reversal of the Synaptic Loss Caused by Stress and Depression

Experiment 1 (affective task): rostral ACC activity is positively correlated with AD response to ketamine

Rostral ACC pretreatment activity (Emotion)





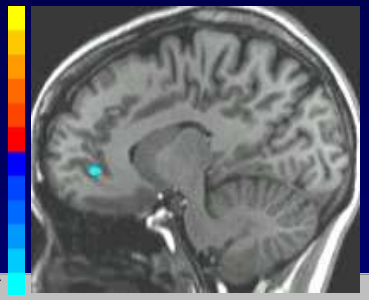
Linear change in ACC activity

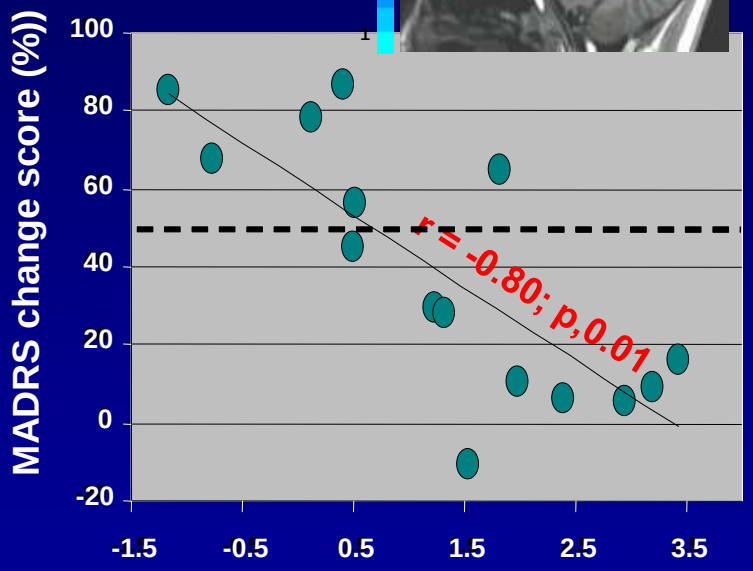
Salvadore et al., Biol Psychiatry 2010

+

Experiment 2 (a cognitive task): rostral ACC activity is negatively correlated with AD response to ketamine

Rostral ACC pretreatment activity (Cognition)





Salvadore et al. Neuropsychopharmacology 2010

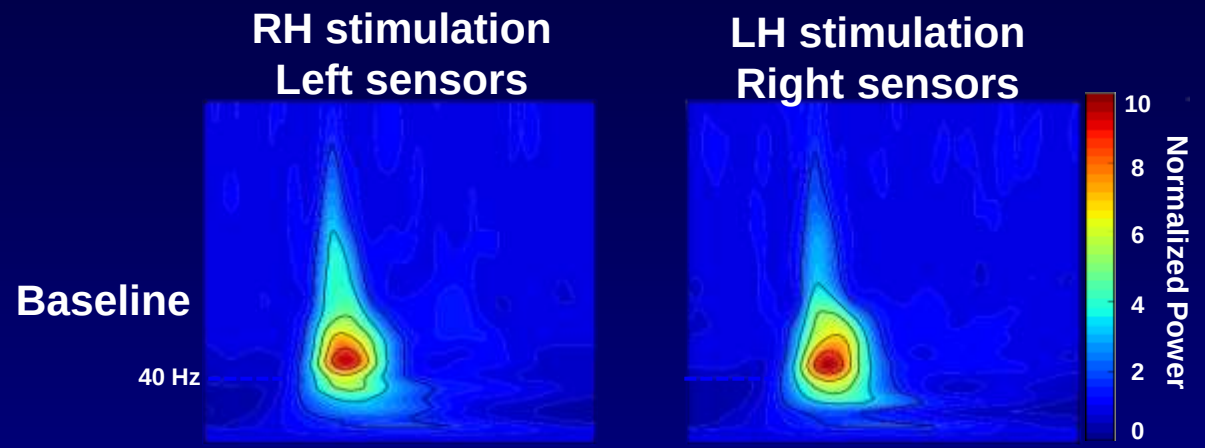
Genes → Gene expression → Metabolome → Neurochemical → Cellular → Synapses → Circuits → Rapid reversal of complex behavioral phenotype

MEG: A sensory cortical signature of ketamine's rapid antidepressant effects

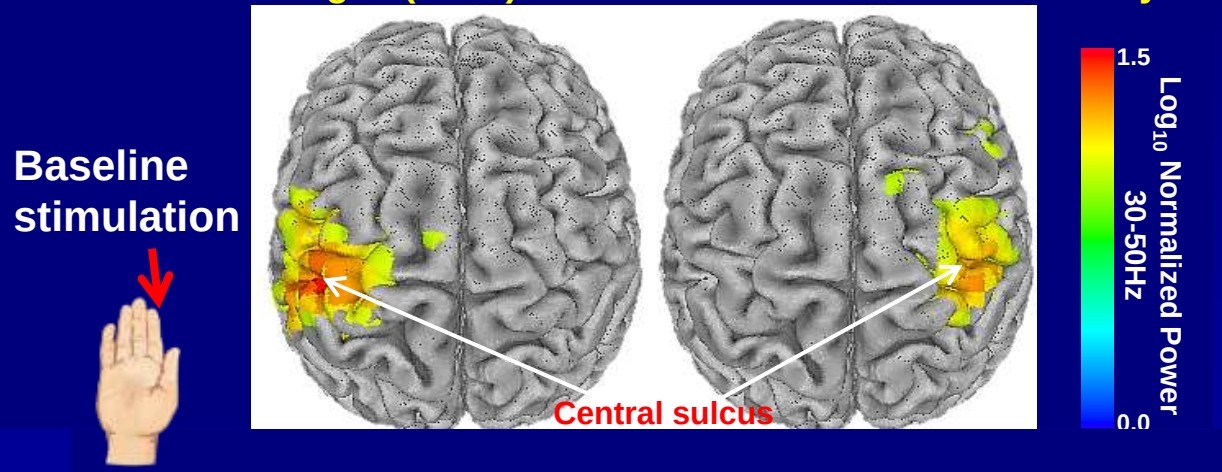
Somatosensory stimuli

- Gamma rhythms are involved in many aspects of cognitive function from 1• sensory representation through selective attention and short-term memory.
- They possess the ability to facilitate synchrony of neuronal activity occurring in many, anatomically distant areas at the same time.
- Using ketamine in rodents produces an increase in gamma rhythm generation (frontoparietal, hippocampus).

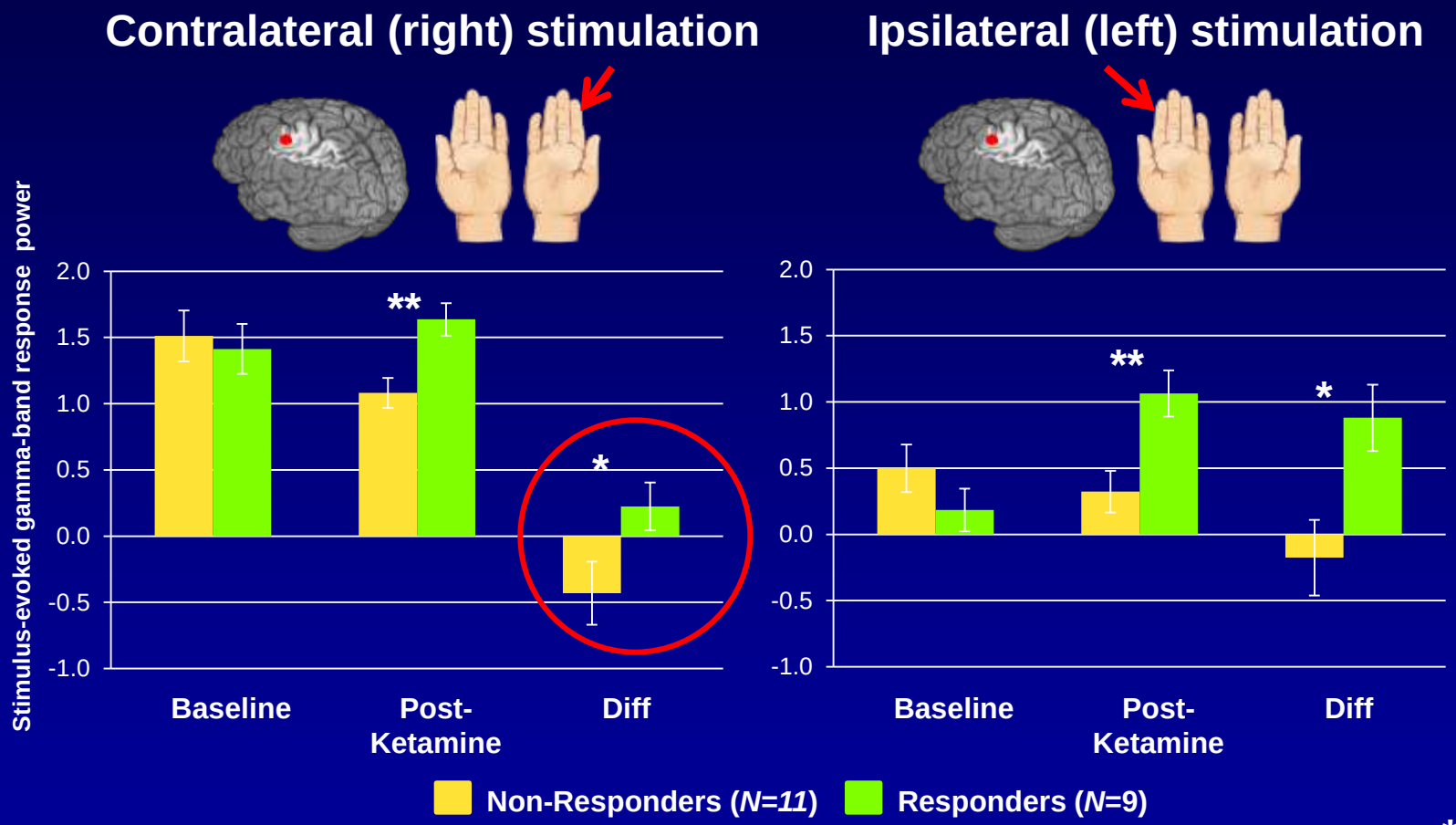
MEG: Grand Averaged (N=20) Time-frequency plots



Grand Averaged (N=20) Evoked Gamma-Band Source Analyses



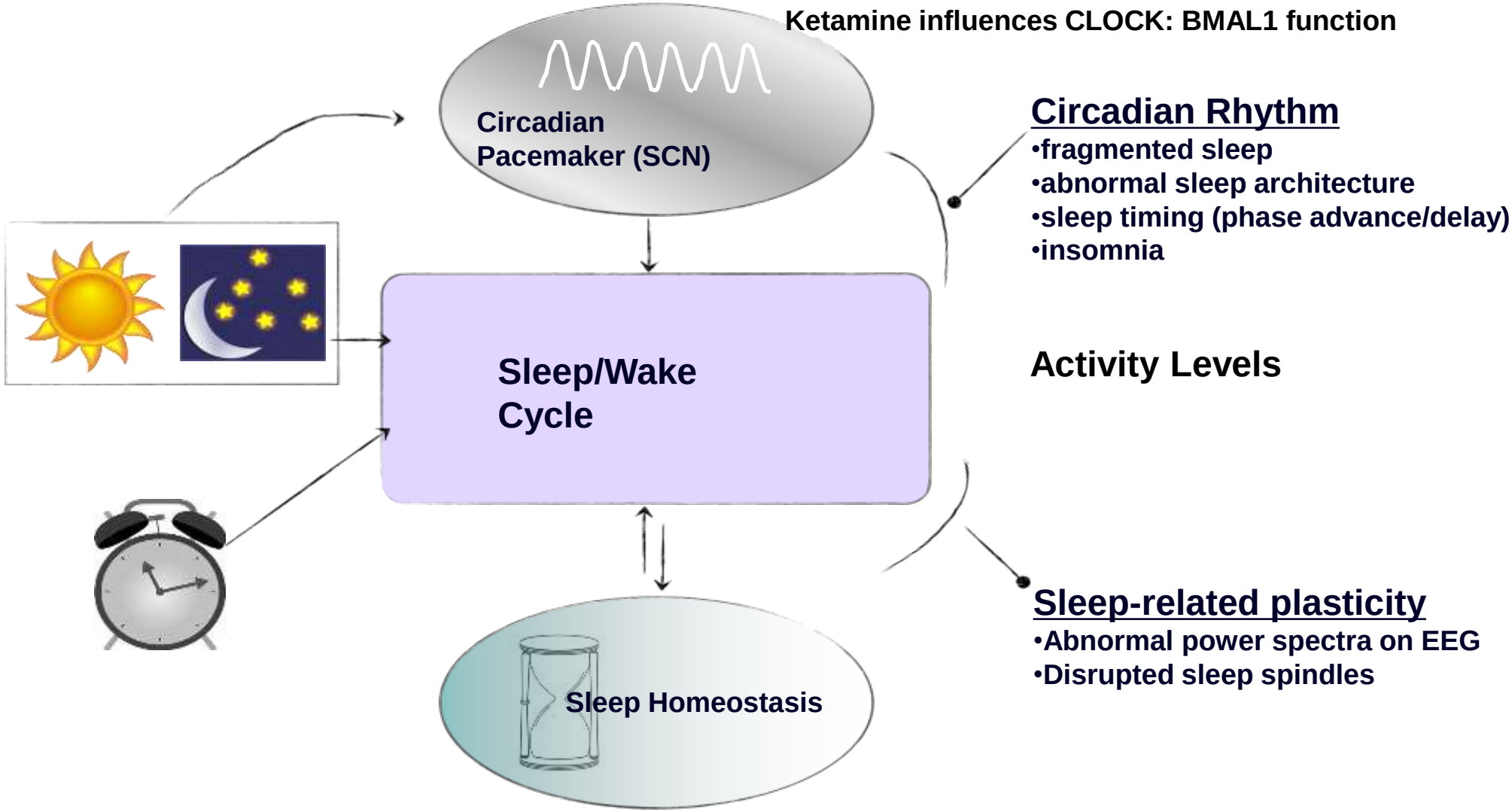
Mean primary somatosensory cortical evoked gamma-band (30-50 Hz) response to tactile stimulation for non-responders an responders before (pre) and 5-7 h after ketamine administration (POST)



*p < .05
**p < .01

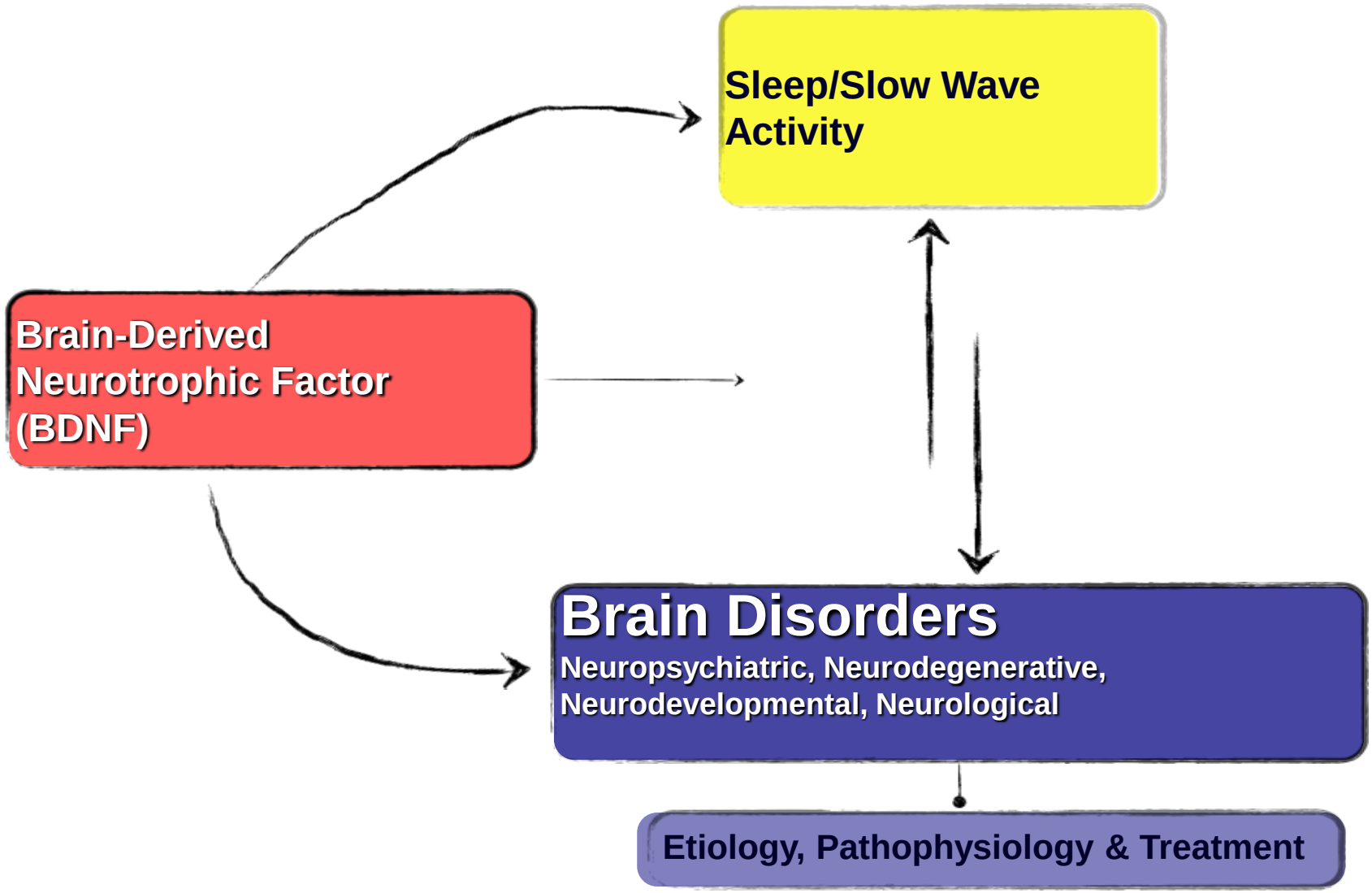
Cornwell et al. Biol Psych 2012

Ketamine, Sleep, and Depression

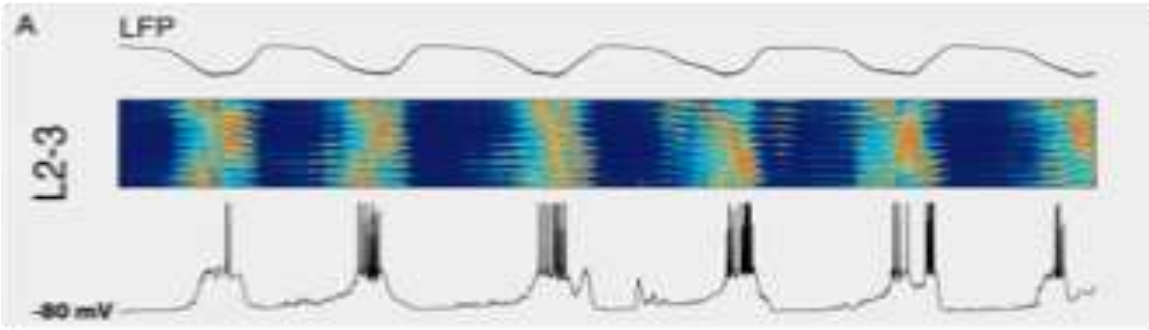


The synaptic homeostasis hypothesis:

slow wave activity (SWA) as a marker of synaptic potentiation

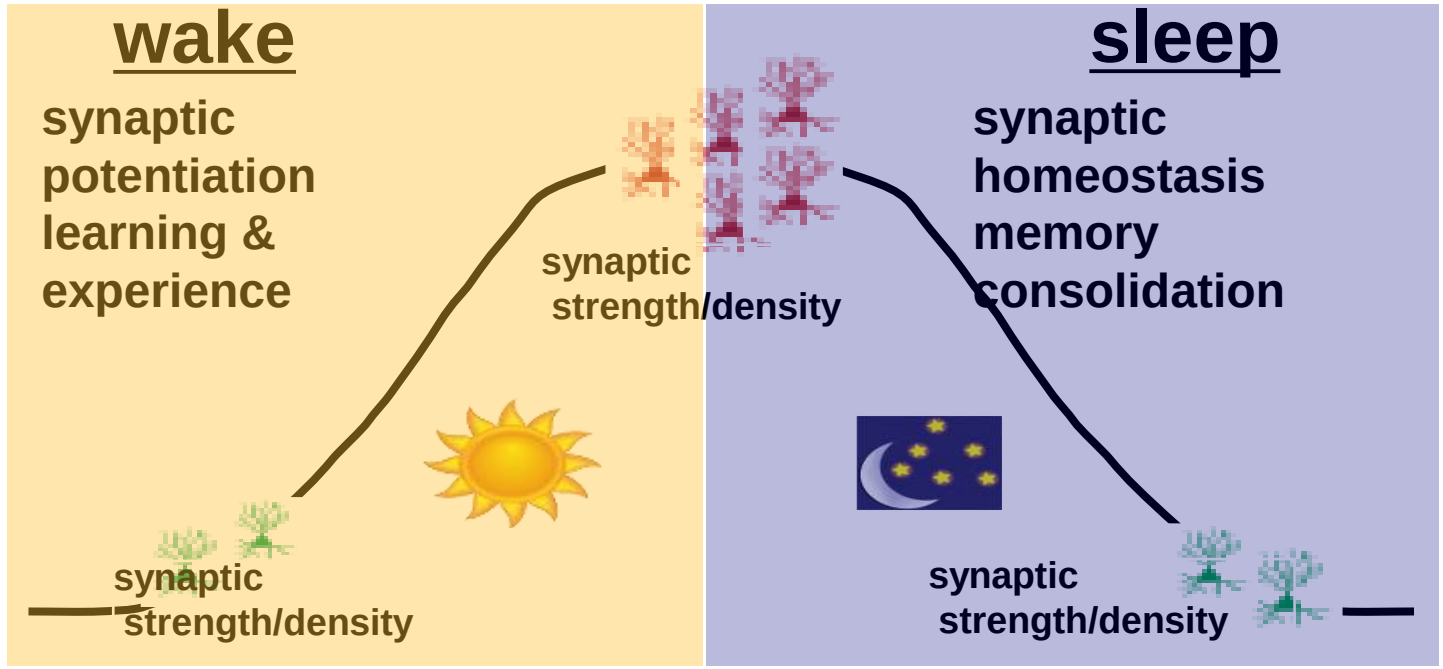


Slow wave oscillations



Hill S , Tononi G J Neurophysiol 2005;93:1671-1698

- cortically generated 0.5-4.5 Hz oscillation
- power represents synchronization across circuits
- reflect synaptic density, strength, efficacy



The synaptic homeostasis hypothesis:

slow wave activity (SWA) as a marker of synaptic potentiation

Animal studies

•Exploratory behaviors increase the amount of SWA and the expression of plasticity-related genes, ***BDNF***, *Arc*, *Homer* (Huber et al., 2007)

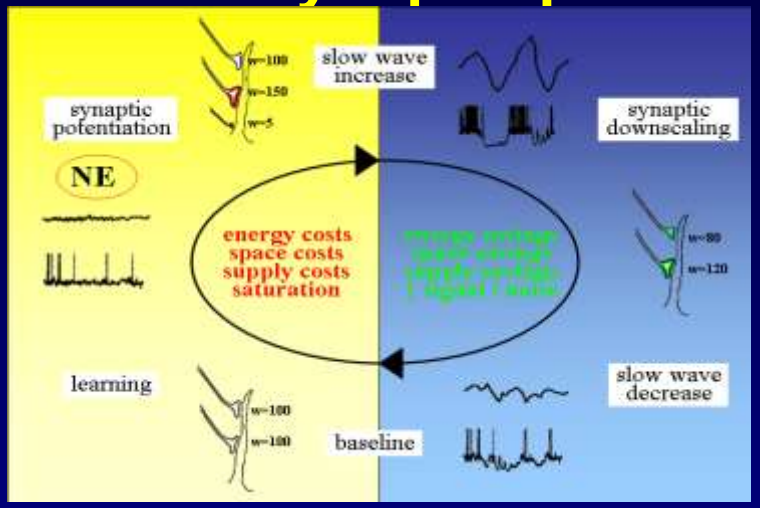
•Whisker stimulation elicits a greater increase in EEG SWA during non-REM sleep in the stimulated hemisphere than in the control hemisphere (Vyazovskiy et al., 2004).

Human studies

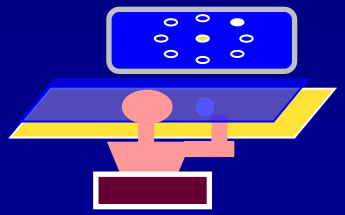
•The amount of SWA is locally increased after learning a visuomotor task (Huber et al., 2004) {lower right panel}

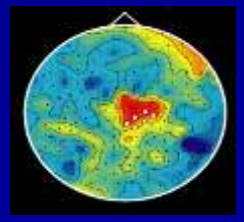
•After rTMS, the amount of SWA increases in the area stimulated

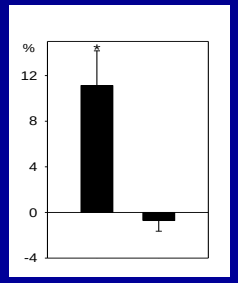
•Conversely, amount of SWA is locally decreased after arm immobilization (Huber et al., 2006)



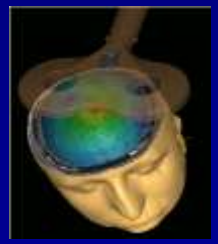
Visuomotor Task: Local SWA Increase

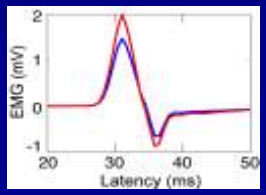


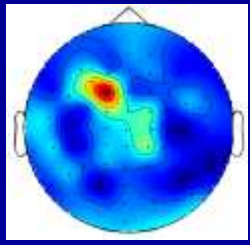




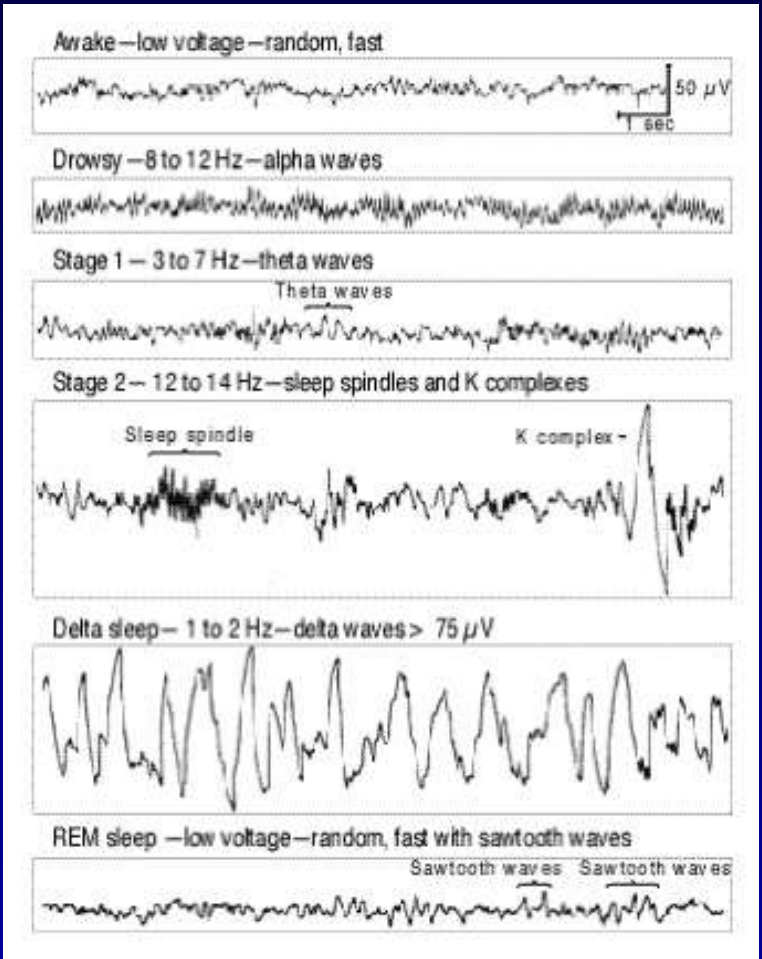
rTMS: LTP and Local SWA Increase



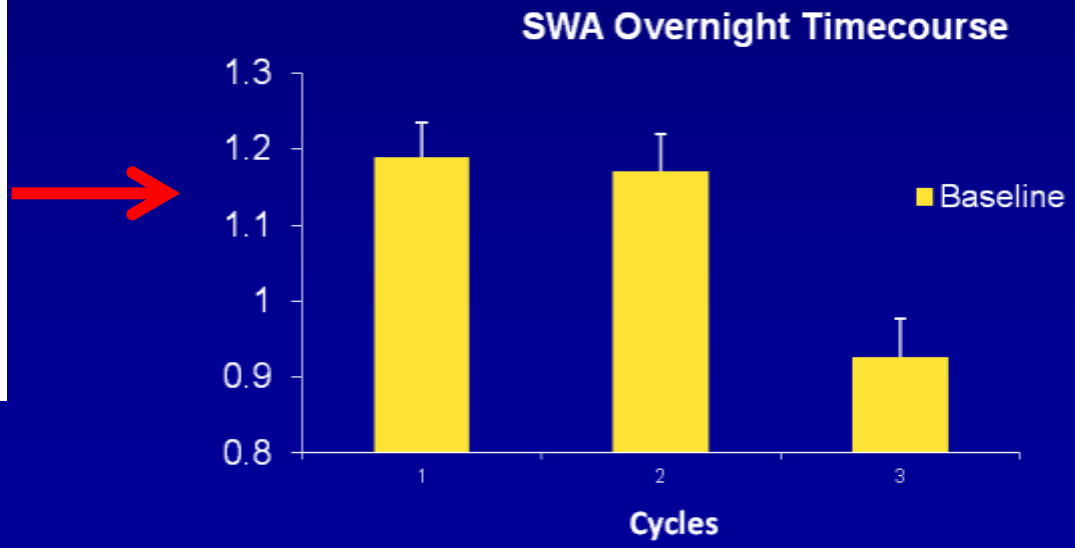




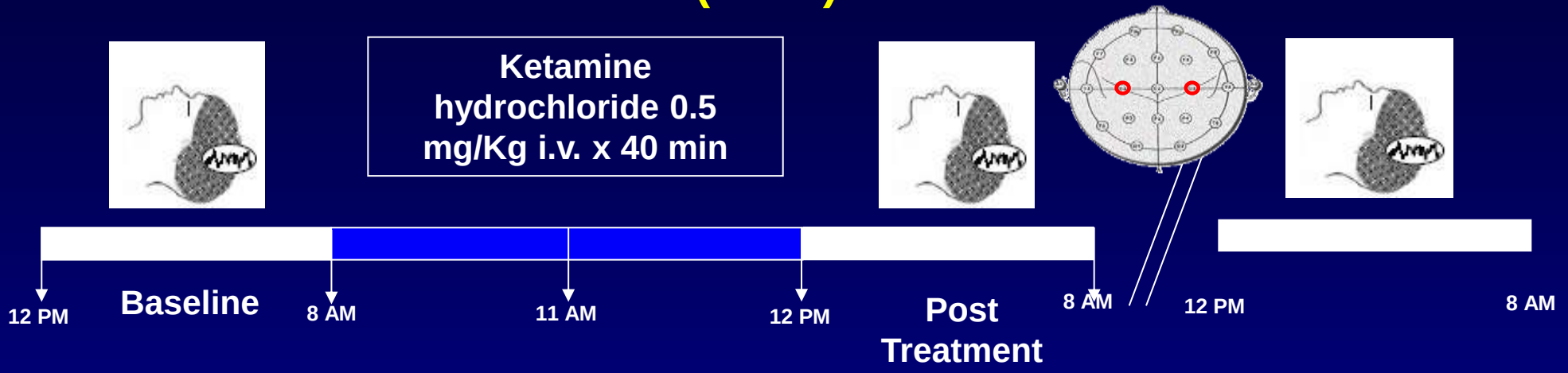
PSG: Ketamine affects SWA



- **Slow wave activity (SWA) as a marker of synaptic potentiation**
- **Ketamine injections in rat PFC are associated with increases in synaptic strength (Li et al., 2010)**
- **Injections of ketamine in rats increase SWA during NREM sleep**
- **SWA could be a marker for synaptic plasticity which is a potential mechanism for ketamine's antidepressant effect**



PSG: Experimental Procedures SWA & BDNF : Acute Changes (N=30)

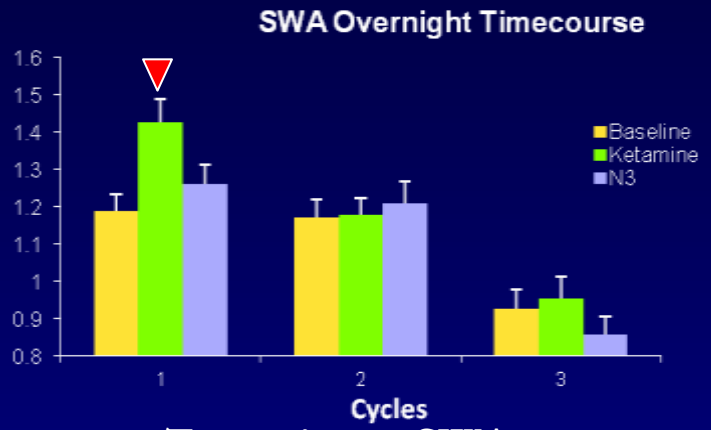


- 2 Sleep recordings (Baseline/Post Treatment night)
- 4 mood ratings (MADRS) and sample collection:
  - 1 hour Pre infusion (BDNF, VEGF plasma)
  - 4 hours Post infusion (BDNF, VEGF plasma)
  - After a night of sleep in the morning (Day 1)
  - After a second night of sleep in the morning (Day 2

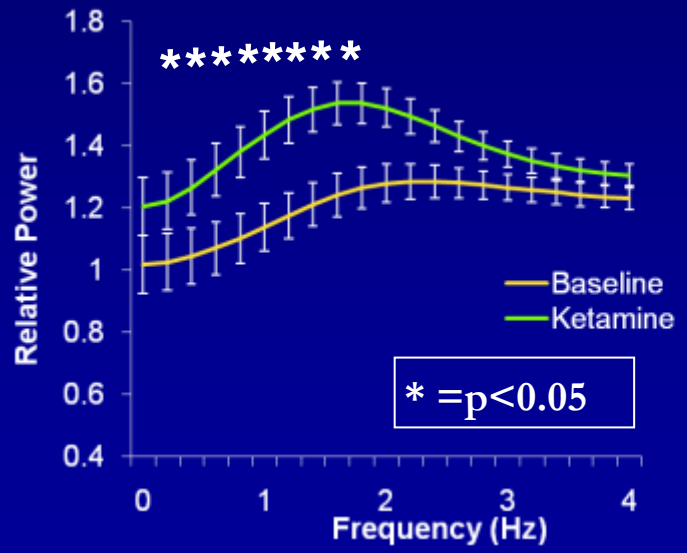
SWA analysis:

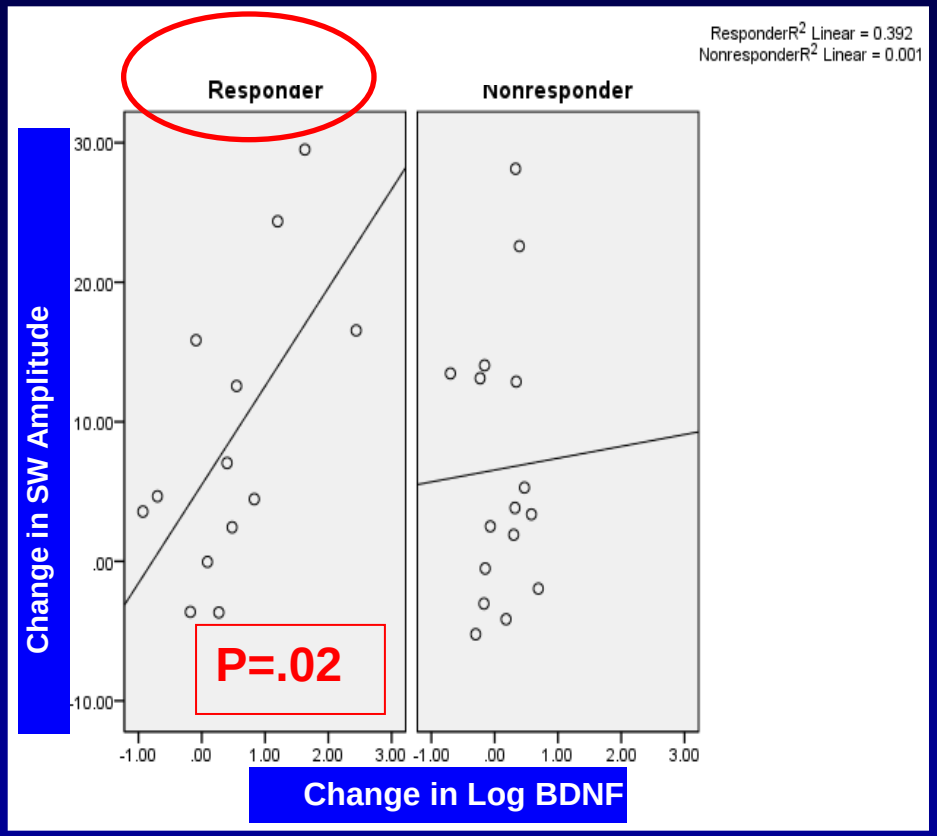
- SWA (0.6-4 Hz) calculated as FFT averages over consecutive 5 sec epochs
- Average of the 2 channels

Ketamine increases slow wave amplitude (N=30) ketamine responder versus non responder differences



Zoom in on SWA range

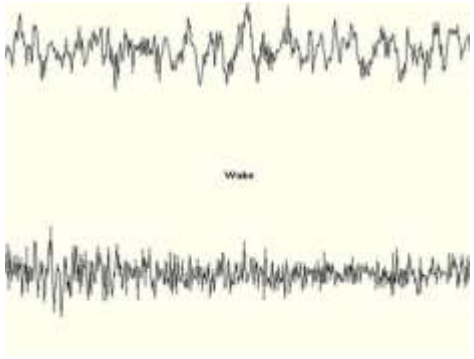




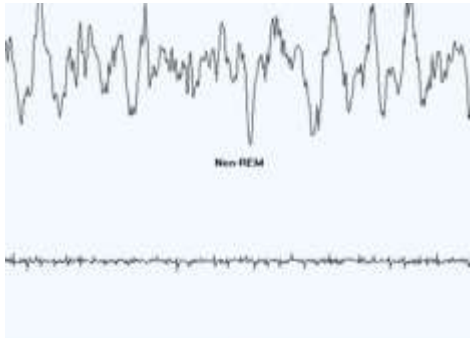
Duncan et al. Int J Neuropsychopharmacol 2013

Recording sleep EEG in rodents

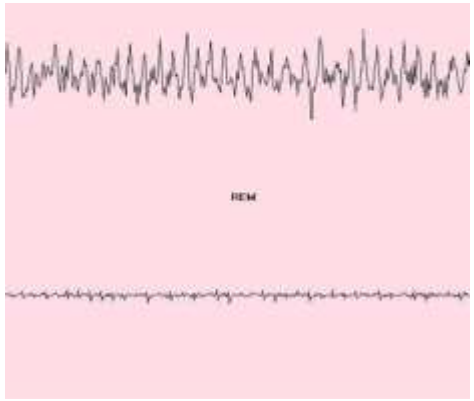
Wake: EEG (upper), EMG (lower)

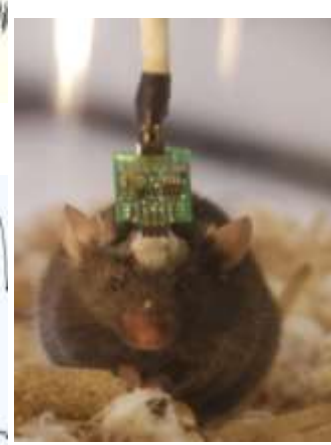


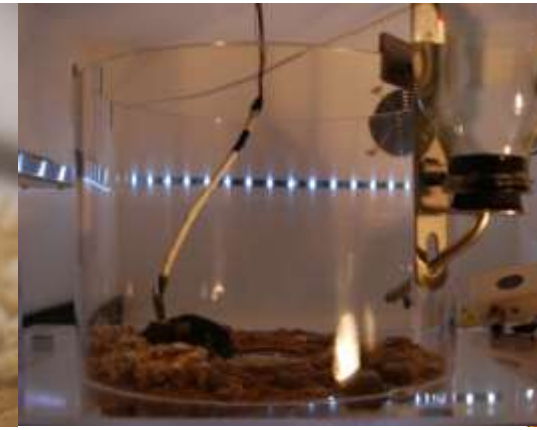
SWA: EEG (upper), EMG (lower)

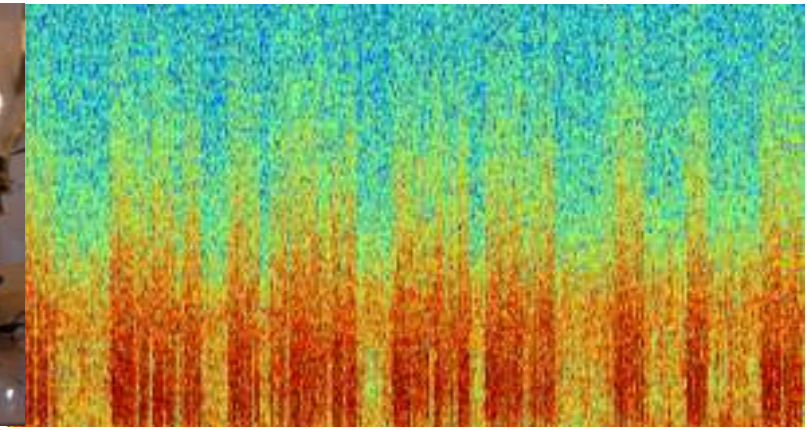


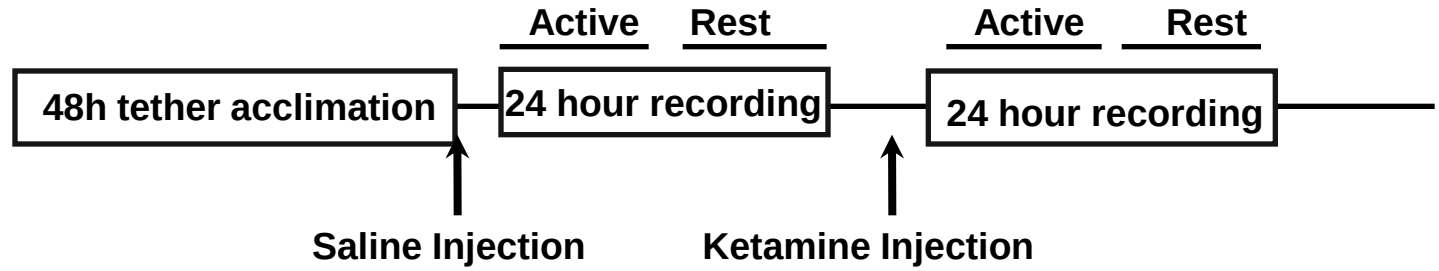
REM: EEG (upper), EMG (lower)











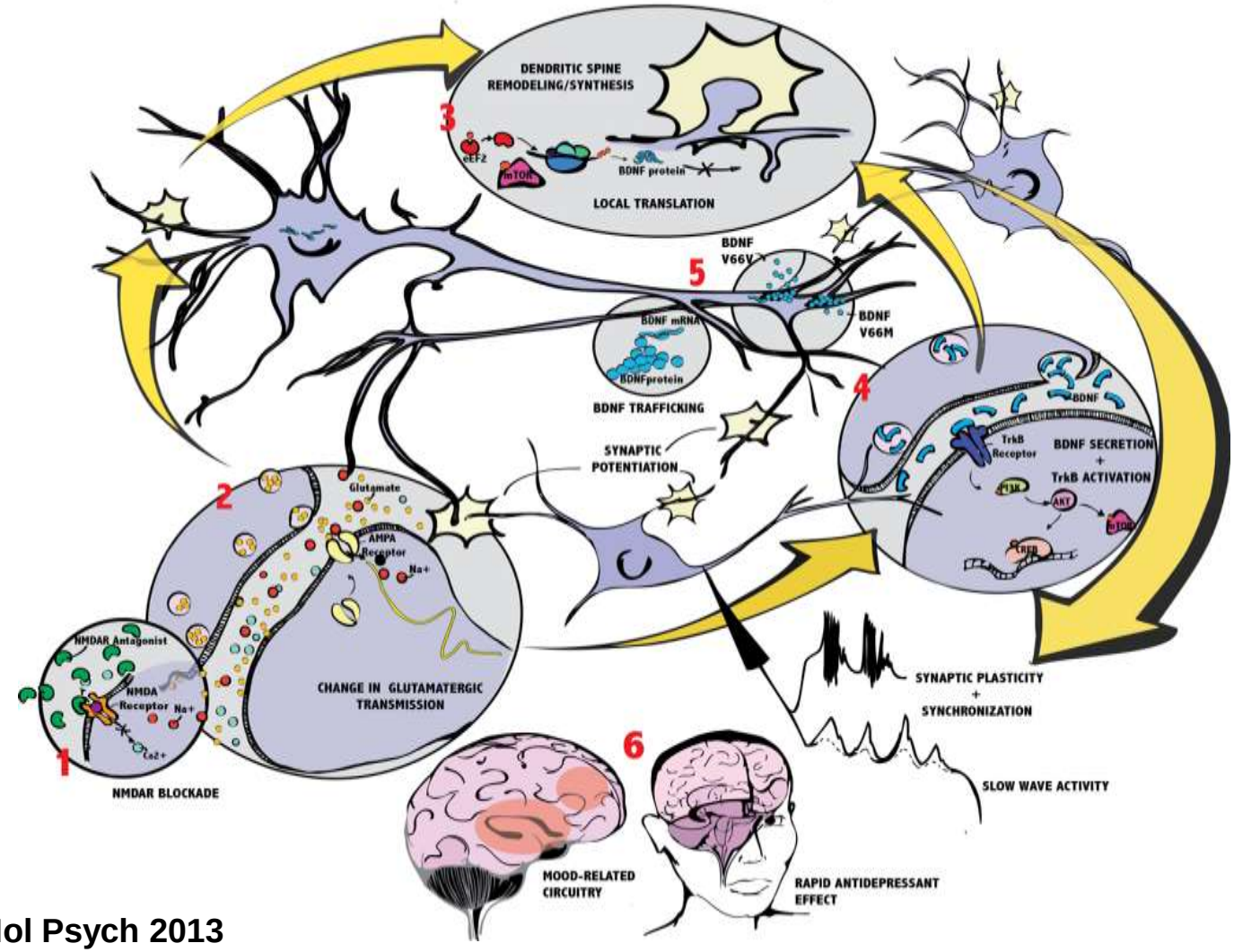
Keri Martinowich
2013 NARSAD Young Investigator Grant

Schematic model of acute and subchronic (Day 1 and Day2) ketamine-induced changes in mood, molecular, sleep and slow-wave variables in MDD w treatment resistant depression. Note the parallel change of BDNF and EEG slow wave measures on Day 1 and 2, as well as the parallel change of mood and sleep measures on Day 1 and 2

VARIABLE	BASELINE	Day 1 (<24 h)	Day 2 (≥24 h)
Mood	↑MADRS	↓MADRS	↓MADRS
Cellular/Molecular	↓Spine density	↑Spine density	↑Spine density
Neurotrophic	↓BDNF	↑BDNF	↓BDNF*
Sleep	↓Total Sleep, ↑Wake	↑Total Sleep, ↓Wake	↑Total Sleep, ↓Wake
EEG Slow Wave Measures	↓SWA, ↓Amplitude, ↓Slope	↑SWA, ↑Amplitude, ↑Slope	↓SWA, ↓Amplitude, ↓Slope

Duncan & Zarate, Current Psych Report, in press

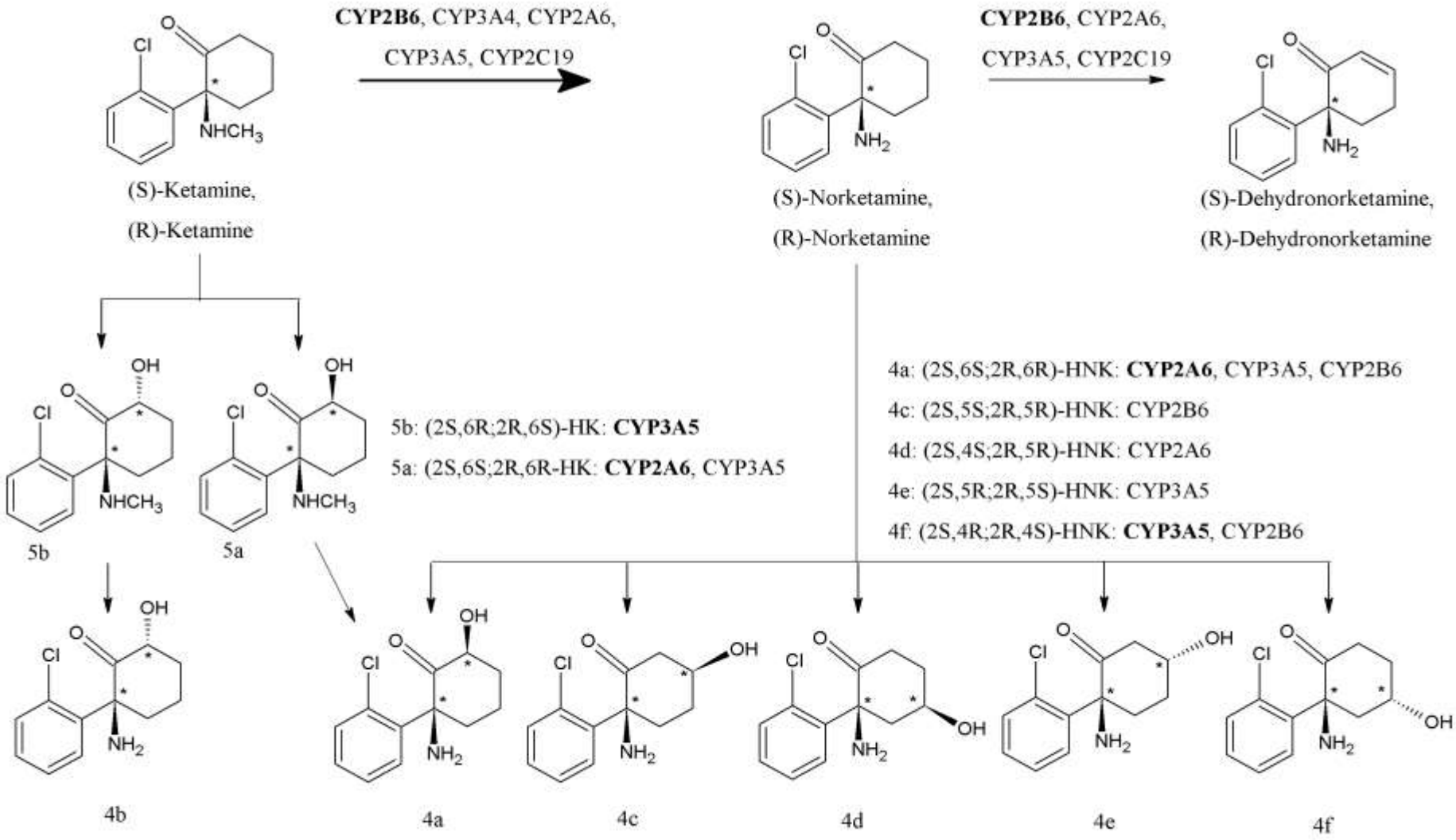
rAD Effects of Ketamine: BDNF/Synchronization Hypothesis



Martinowich et al. Mol Psych 2013

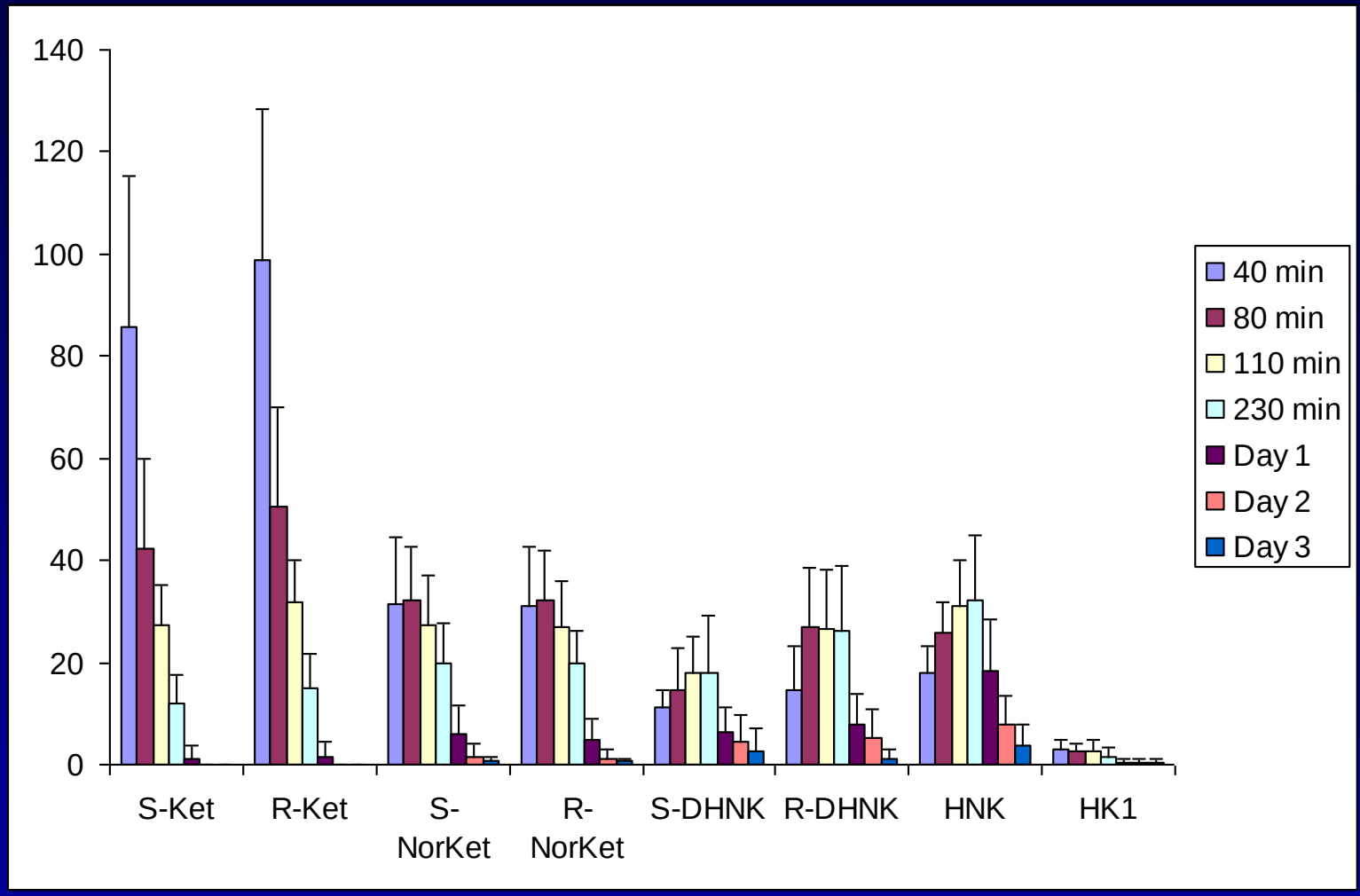
4. Is there more to the story with the "ketamine paradigm": Ketamine's metabolites

(R,S)-Ket is extensively metabolized by cytochrome P450 enzymes



Zhao et al. Br J Phamacol 2012

The average plasma concentrations of the stereoisomers of (R,S)-Ket and its major metabolites in patients treated with a 0.5 mg/kg dose of (R,S)-Ket

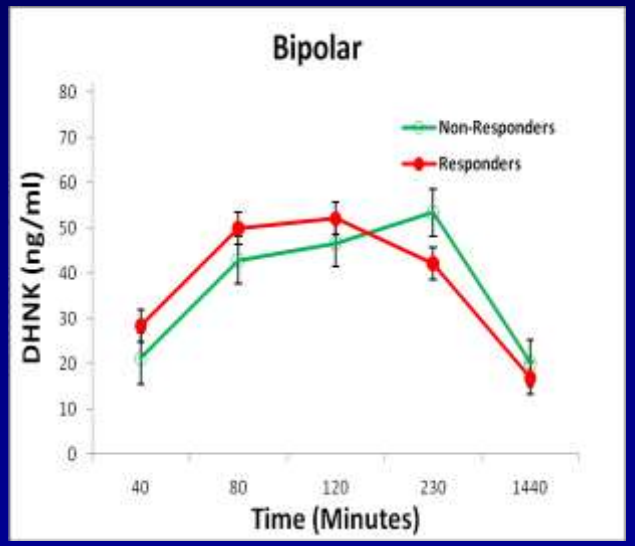


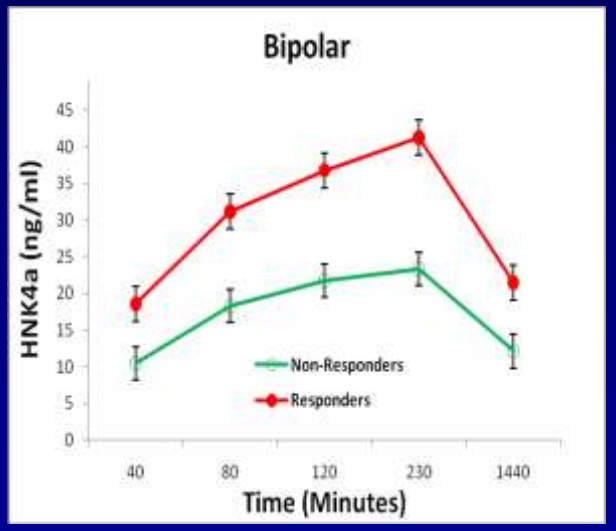
Zhao et al. Br J Phamacol 2012

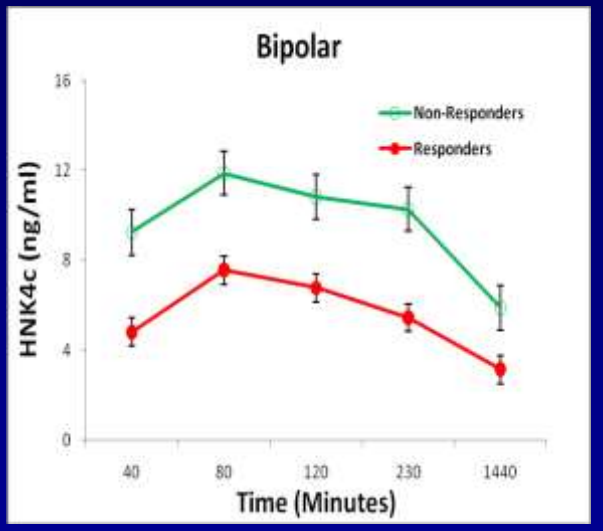
Relationship of Ketamine's Plasma Metabolites with Response, Diagnosis, and Side Effects in Major Depression

-(2S,5S;2R,5R)-HNK (HNK4c) was associated with nonresponse in patients with bipolar depression

-(R,S)-DHNK, (2S,6S;2R,6R)-HNK (HNK4a) and (2S,4R;2R,4S)-HNK (HNK4f) were associated with reduced psychotic and dissociative symptoms at 40 min





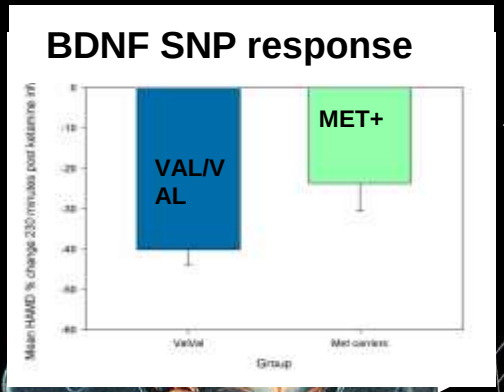


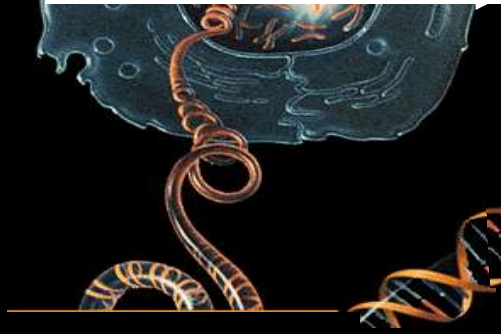
Zarate et al. Biol Psych 2012

Ketamine metabolites inhibit α7-nAChR activity

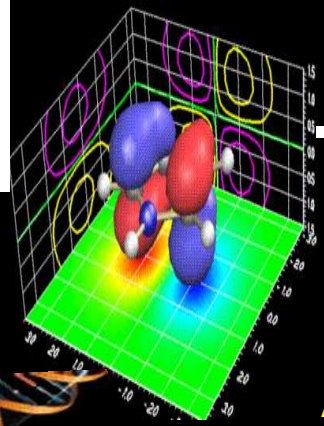
Tran et al. Eur J Pharmacol 2013

The Neurobiology of Mood Disorders
Understanding the Mechanism of Ketamine Across Different Systems

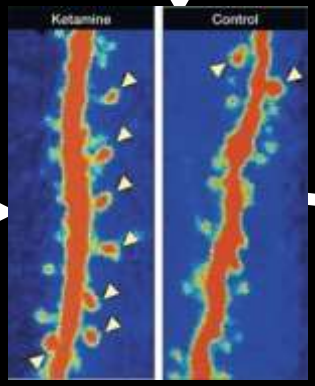




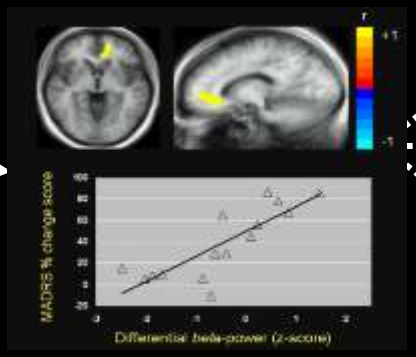
Genes
Multiple susceptibility alleles each of small effect
? Ketamine effects



Cellular Programming
Gene and Protein Expression
? Ketamine effects

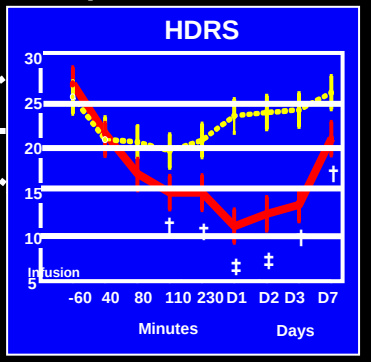


Cells:
Ketamine enhances AMPA:NMDA throughput in critical neuronal circuits and activates the mTOR pathway: increased synaptic signaling proteins and increased number and function of new spine synapses in the PFC of rats



Systems:
ACC desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine

Depression



Behavior:
Rapid reversal of Complex Phenotype

Genes → Gene expression → Metabolome → Neurochemical → Cellular → Synapses → Circuits → Rapid reversal of complex behavioral phenotype

Intramural Research Program/NIMH

Mark O. Hatfield Clinical Research Center

Collaborators

Intramural Research Program

NARSAD awards

Brain & Behavior Foundation Award

Mogens Schou Bipolar Award

Patient and their families

http://patientinfo.nimh.nih.gov

1-877-MIND-NIH (1-877-646-3644)

moodresearch@mail.nih.gov

zaratec@mail.nih.gov