

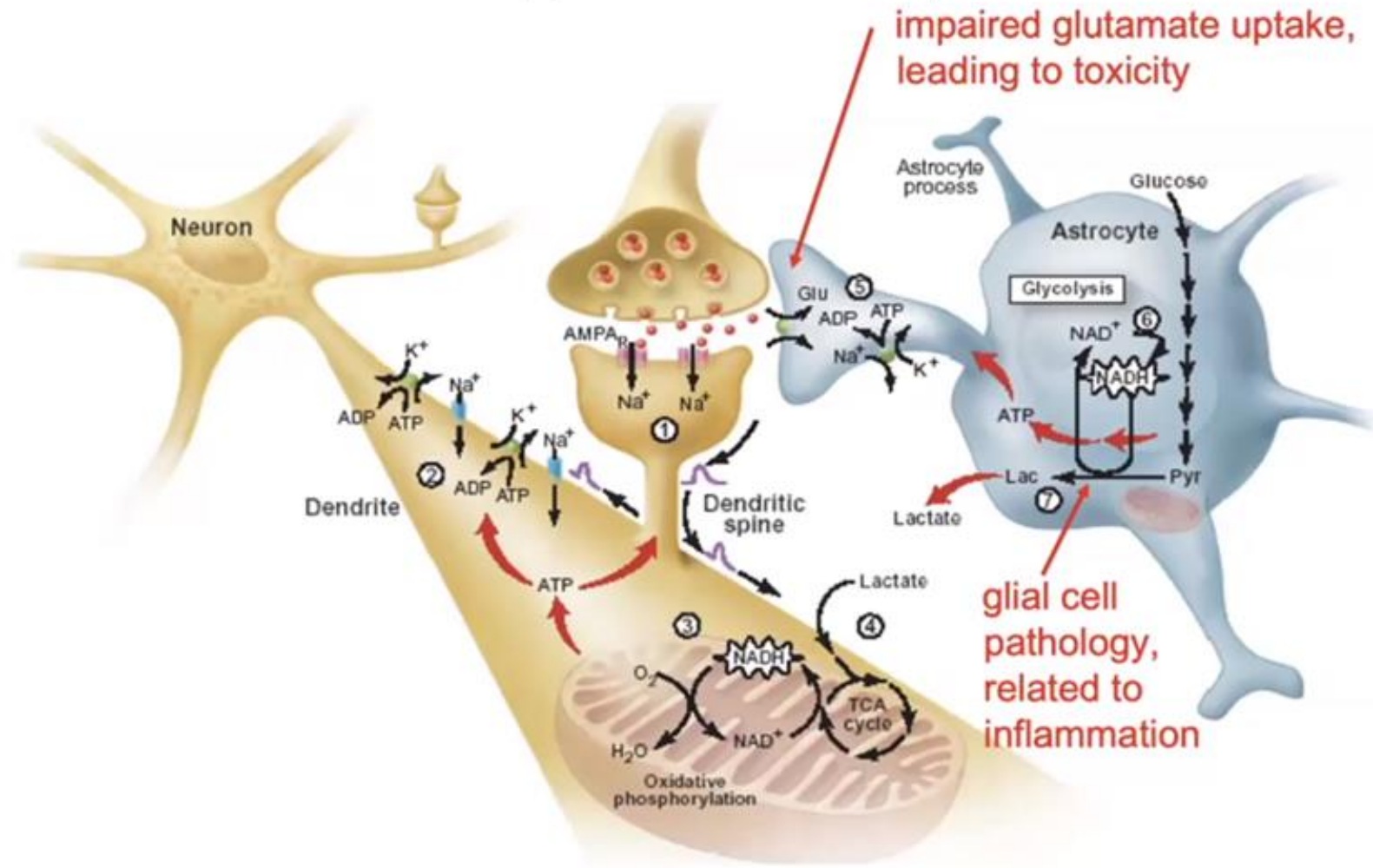
# Highlights ISBD 2021

Nieuwe richtingen voor farmacotherapie

Helene van Gorsel

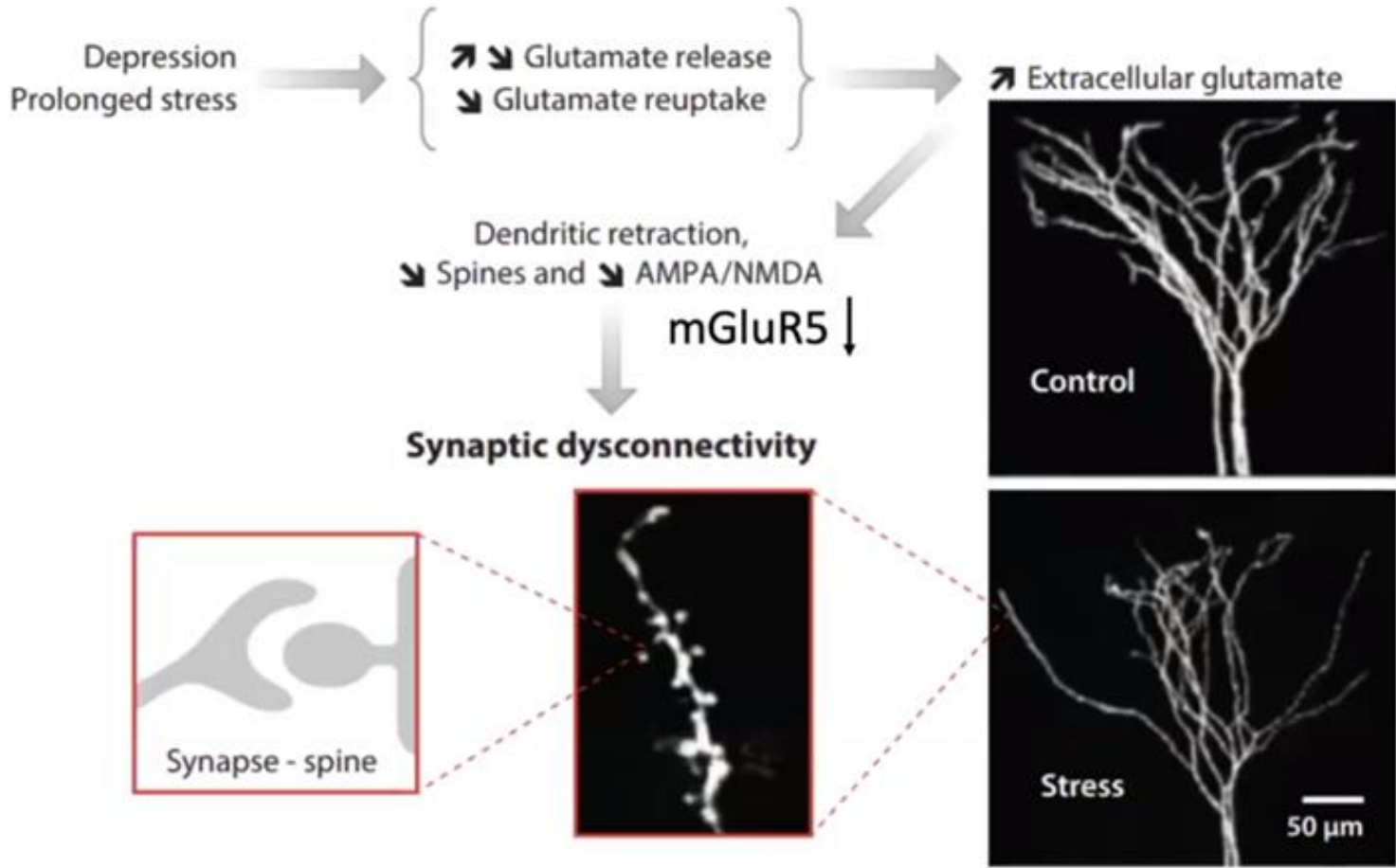


# Glutamate hypothesis of bipolar disorder

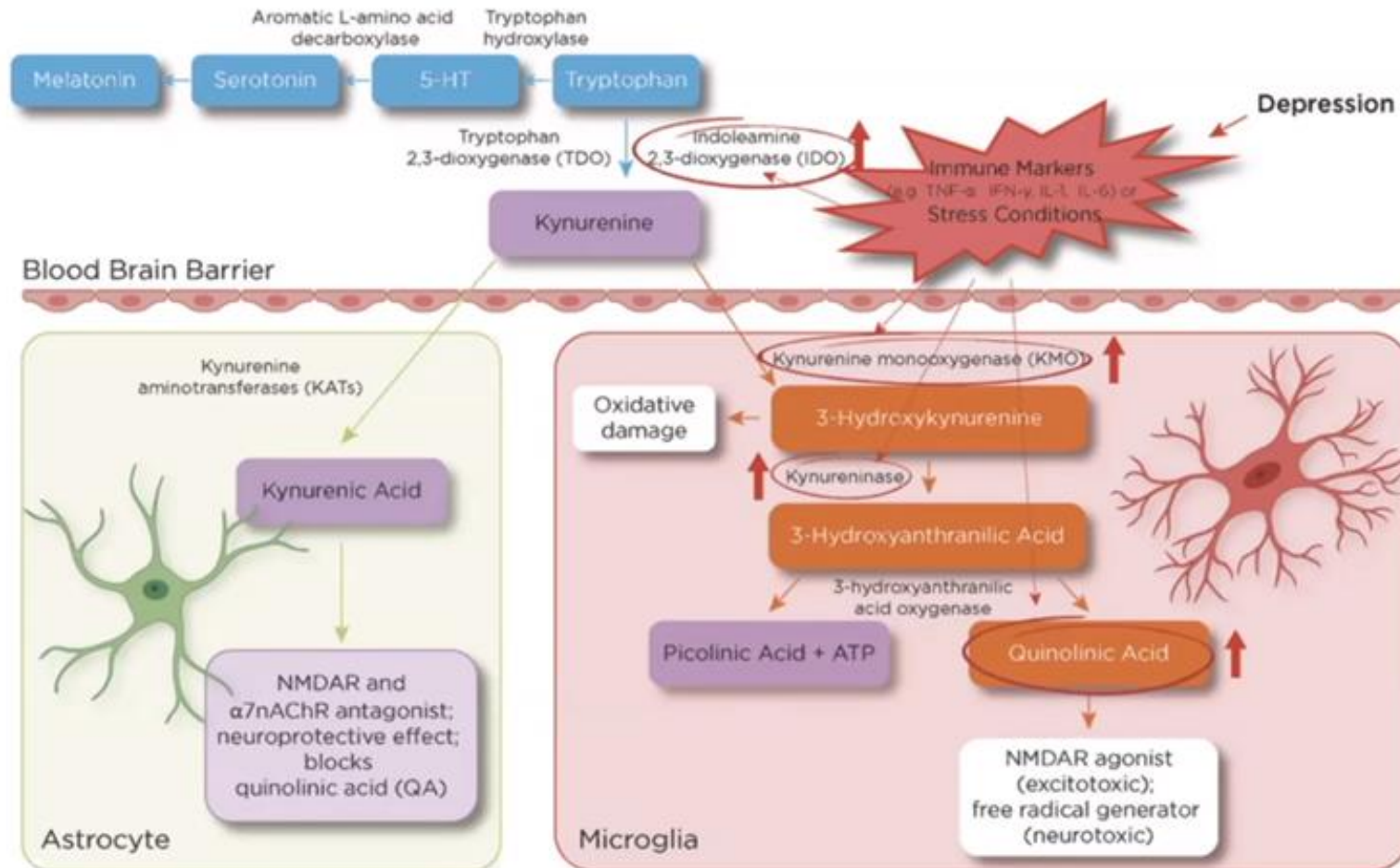


Modified from Pellerin and Magistretti, Science 2004

# Neuroplasticity hypothesis of mood disorder



# The kynurenine pathway and bipolar disorder: intersection of the monoaminergic and glutamatergic systems and immune response



# Middelen met effect op of via glutamaat

- Lamotrigine
- Lithium (neuroprotection via NMDA-R)
- Riluzole
- Asenapine
- Psychedelica (psilocybin, LSD)
- Ketamine

# Ketamine

## Studies on ketamine in bipolar depression



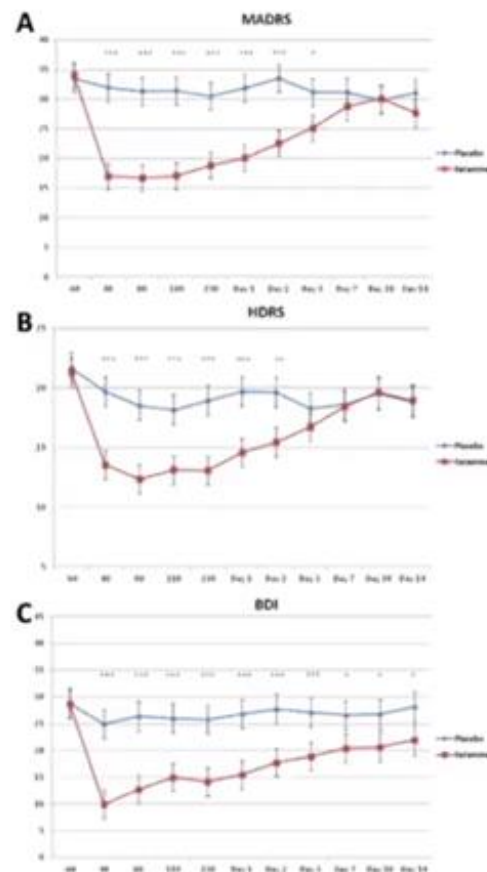
Author	Design	Main Measurement	Results	Side Effects
Diazgranados et al. (2010)	Placebo controlled (n=18)	MADRS (Montgomery-Asberg Depression Rating Scale)	Ketamine improved depressive symptoms compared to placebo (71% responded to ketamine, 6% to placebo, defined as $\geq 50\%$ reduction in MADRS score)	Manic symptoms induced by ketamine (n=1) and by placebo (n=1), most common were dissociative symptoms
Zarate et al. (2012)	Placebo controlled (n=15)	MADRS	Ketamine improved depressive symptoms compared to placebo (79% responded to ketamine, 0% to placebo, defined as $\geq 50\%$ reduction in MADRS score)	No serious adverse effects, most common were dissociative symptoms, ketamine did not increase manic symptoms
Lally et al. (2014)	Placebo controlled (n=36)	MADRS and SHAPS (Snaith-Hamilton Pleasure Scale)	Ketamine rapidly reduced levels of anhedonia independent from reductions in general depressive symptoms	not mentioned
Nugent et al. (2014)	Placebo controlled (n=21)	MADRS	43% responders (defined as $\geq 50\%$ reduction in MADRS score)	dissociative symptoms
Rybakowski et al. (2013)	Open label (n=25)	HDRS (Hamilton Depression Rating Scale)	52% responders (defined as $\geq 50\%$ reduction in HDRS score), 12 patients remitted (defined as $\leq 7$ score in HDRS) after 14 days	not mentioned
Permoda-Osip et al. (2013)	Open label (n=20)	HDRS	50% responders (defined as $\geq 50\%$ reduction in HDRS score)	not mentioned
Permoda-Osip et al. (2014)	Open label (n=42)	HDRS	Ketamine significantly improved depressive symptoms, 52% responders (defined as $\geq 50\%$ reduction in HDRS score)	No serious adverse effects, most common were dissociative symptoms
Ionescu et al. (2014)	Open label (n=36)	MADRS and HDRS	Ketamine induced an antidepressant response regardless of baseline anxiety status	dissociative symptoms
Rybakowski et al. (2017)	Open label (n=53)	HDRS	51% responders (defined as $\geq 50\%$ reduction in HDRS score)	Depersonalization experienced by 1/3 of patients during infusion

# Comparison between Bipolar I and Bipolar II Disorder

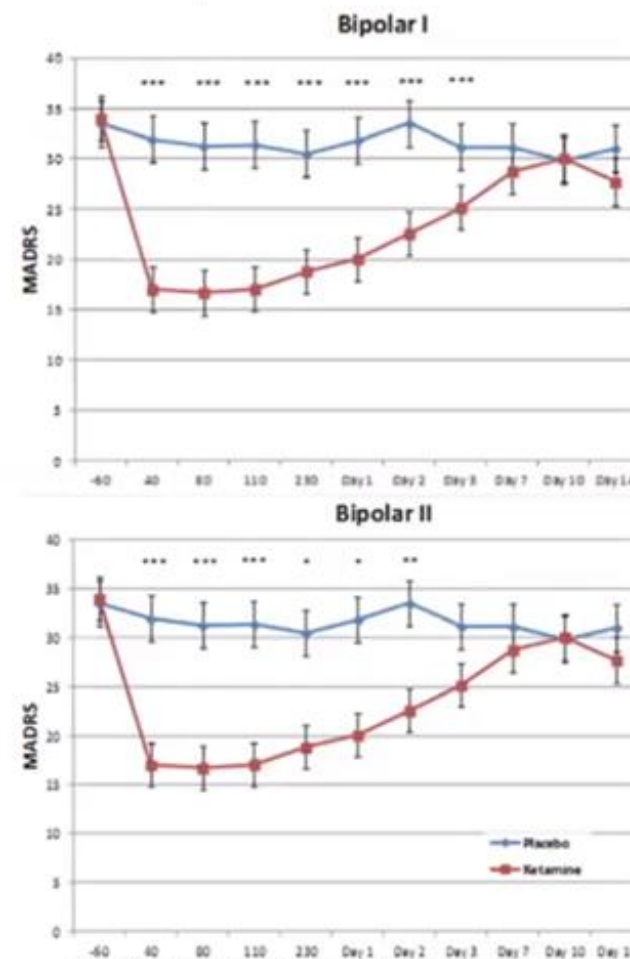


Single ketamine infusion in **bipolar I and II depression:**

- Rapid reduction in depressive symptoms
- Rapid improvement in suicidal ideation
- No significant drug effect on YMRS



**Figure 1.** (A) Change in Montgomery-Asberg Depression Rating Scale (MADRS) over two weeks (n = 15). (B) Change in 17-item Hamilton Depression Rating Scale (HDRS) over 2 weeks. (C) Change in Beck Depression Inventory (BDI) over two weeks. Values are expressed as generalized least squares means and standard errors for the intent to treat analysis. \*p < .05, \*\*p < .01, \*\*\*p < .001.

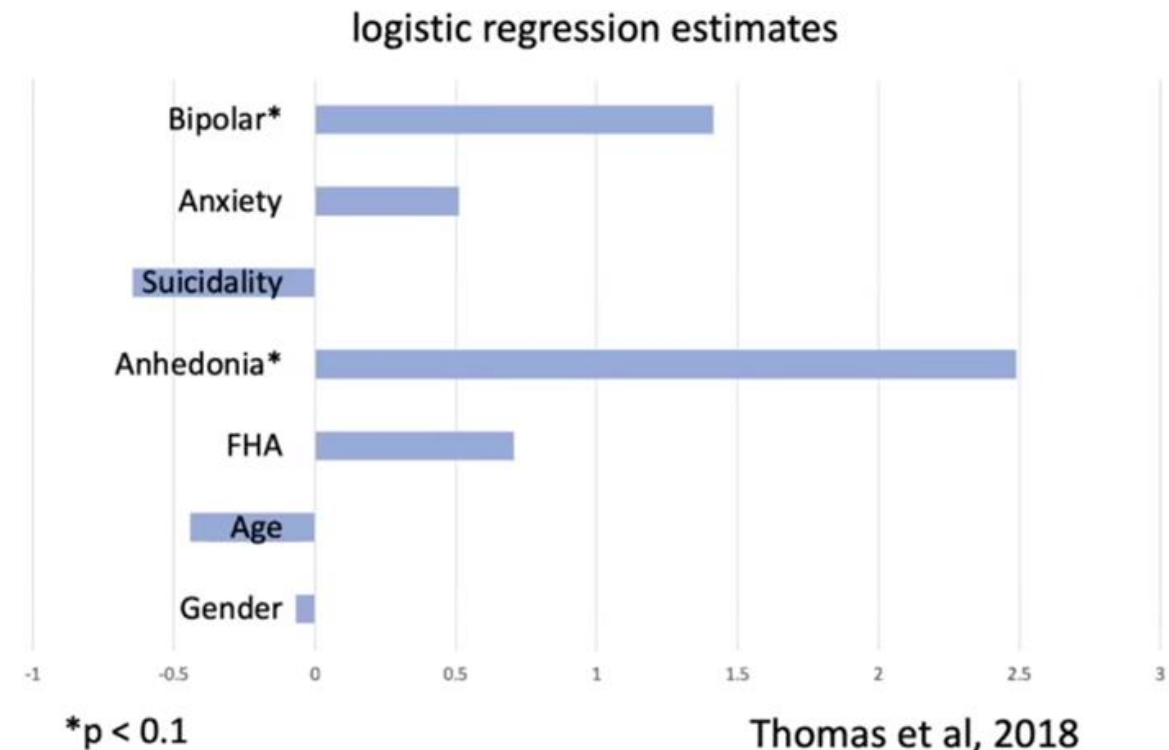


**Figure 4.** Change in Montgomery-Asberg Depression Rating Scale (MADRS) scores over 2 weeks by bipolar disorder subtype (I vs. II; n = 15). Error bars reflect one Standard error (SE).



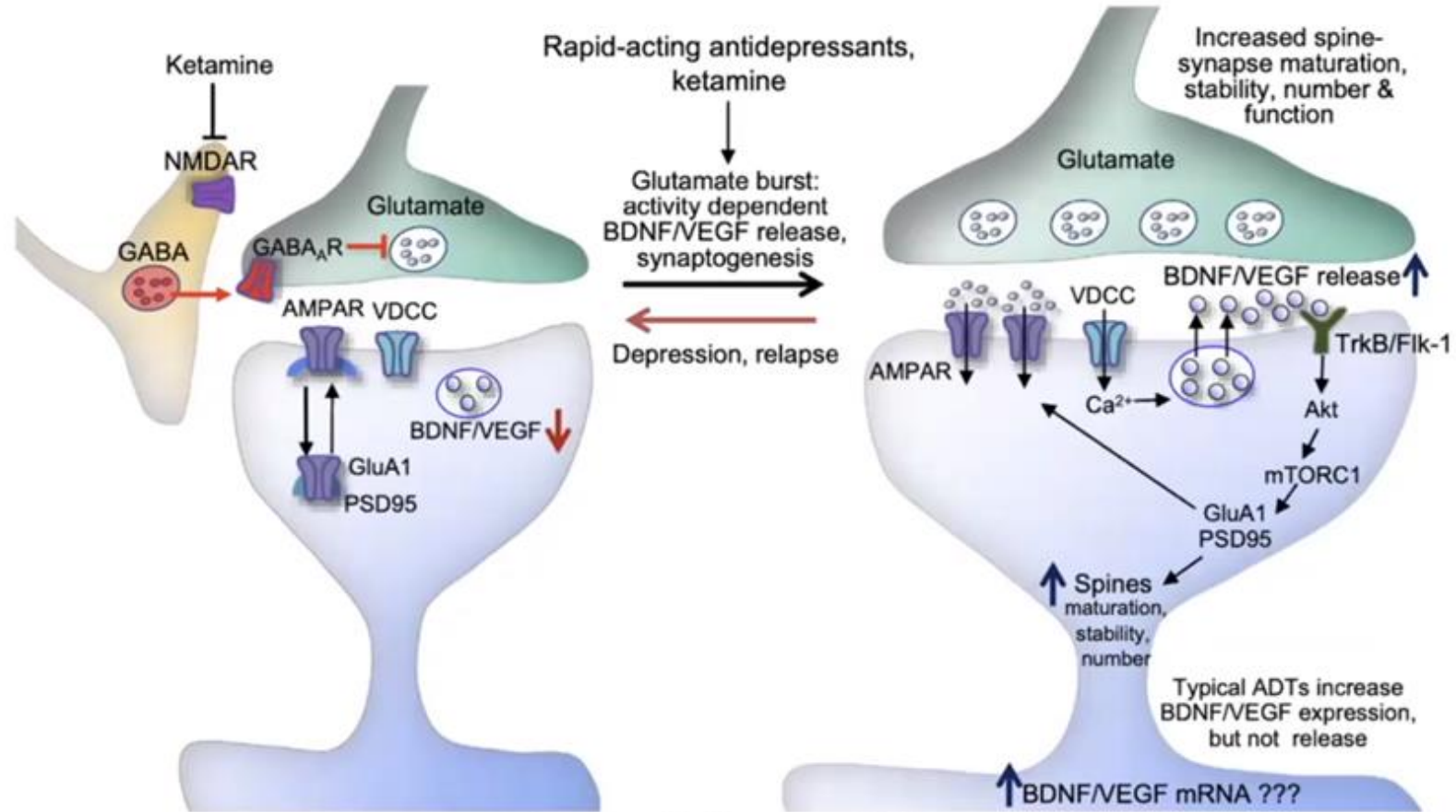
## Six ketamine infusions over 2-3 weeks in major depressive and bipolar disorder (N=50)

- Moderate/Severe anhedonia increased response probability by 55% (OR=1.21)
- Bipolar disorder increased antidepressant response probability by 54% (OR=1.18)





# Neuroplastic mechanisms underlying the rapid and sustained antidepressant actions of ketamine



Deyama & Duman, 2020

## The Altered-State-of-Consciousness Aspect of a Feeling of Lightness Is Reported to Be Associated with Antidepressant Benefits by Depressed Individuals Receiving Ketamine Infusions: A Systematic Analysis of Internet Video Testimonials

*Kurt Stocker<sup>a-c</sup> Gregor Hasler<sup>d</sup> Matthias Hartmann<sup>c,e</sup>*

- 1 “After my first treatment I woke up the next morning and I had less heaviness in my throat and my chest. The heaviness that you feel on an ongoing basis saps your energy (0:10)” (T4).
- 2 “The weight was gone. The heaviness, the darkness, the weird, awful thoughts, the sadness – I had completely forgotten what it felt like (2:22)” (T21).
- 3 “I felt happy and light (2:31)” (T19).
- 4 “Bubbles are rising from the back of my neck (3:24) ... all the pressure in my head just starts to feel light and normal again (4:47)” (T11).

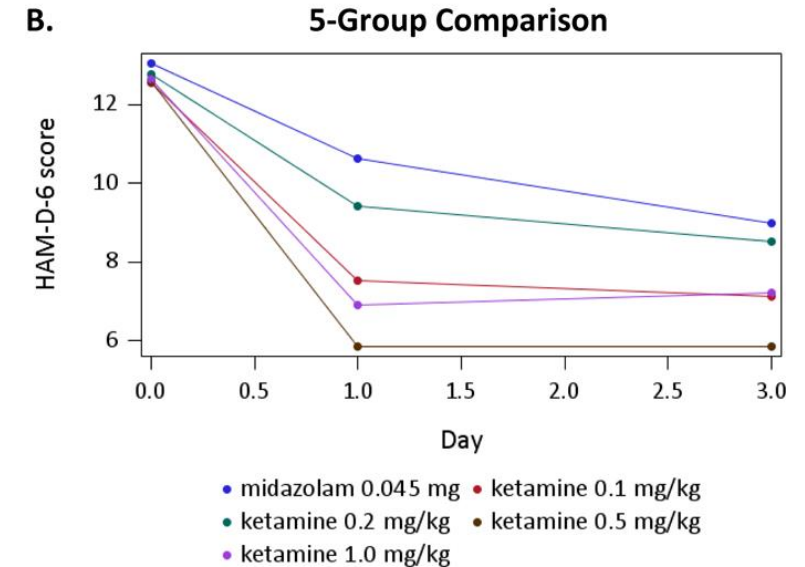
Psychotherapy & Psychosomatics 2019

Atypical depression symptoms: leaden paralysis, hypersomnia



# Behandelopties Nederland

- IV ketamine
  - 0,5 mg/kg infusie 40 minuten
- Esketamine neusspray (Spravato)
  - EMA en CBG goedkeuring december 2019
  - Positief advies ZiN i.v.m. vergoeding september 2020
  - Huidige status 'in de sluis' i.v.m. kosten
  - Overleg over behandeling in gespecialiseerde centra



Fava et al. 2018