GABA/Glutamaat bij psychose als target voor farmacotherapie

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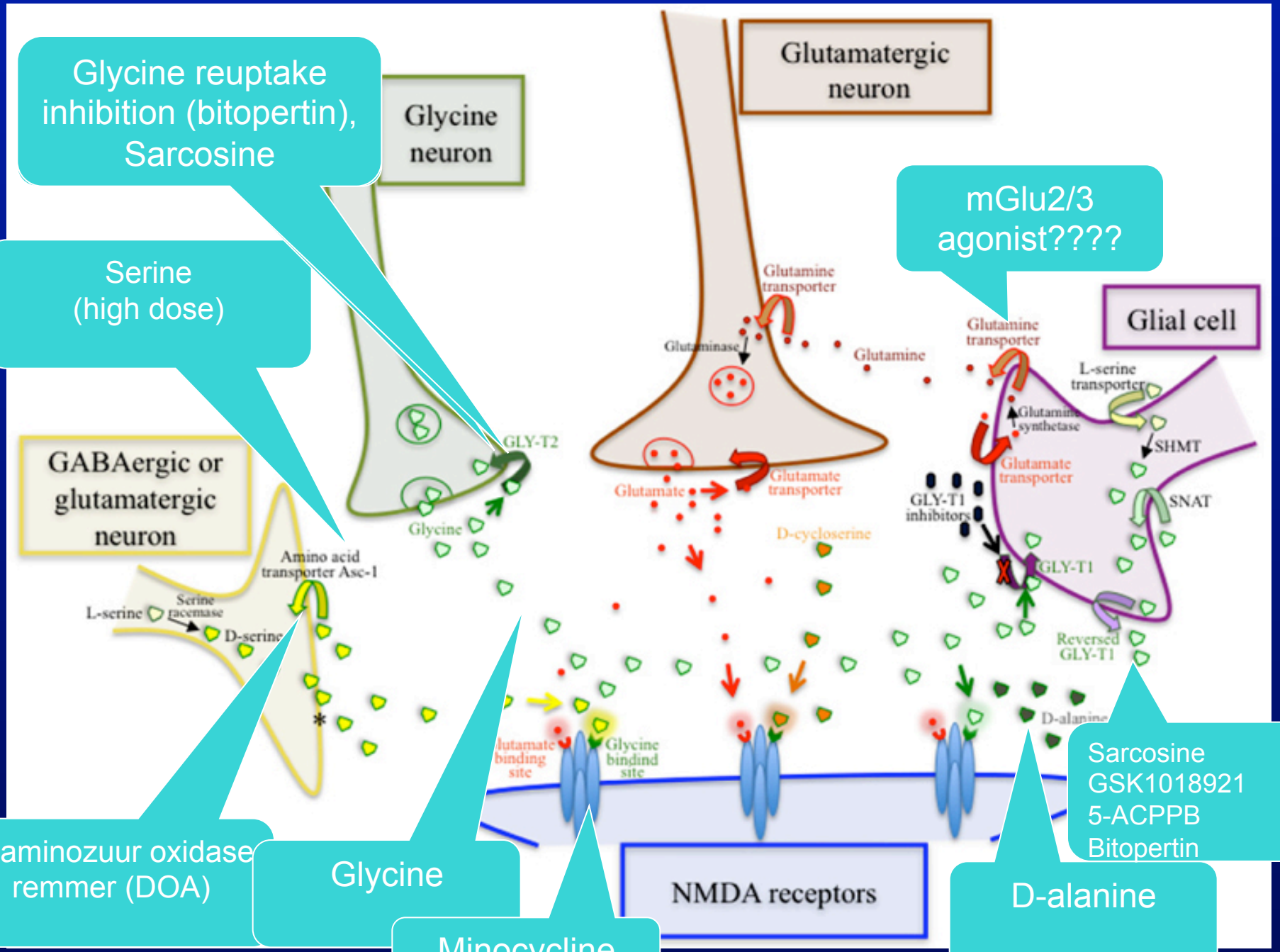
Oranjewoud Heerenveen (voorheen Zwartsluis) 12-03-2015

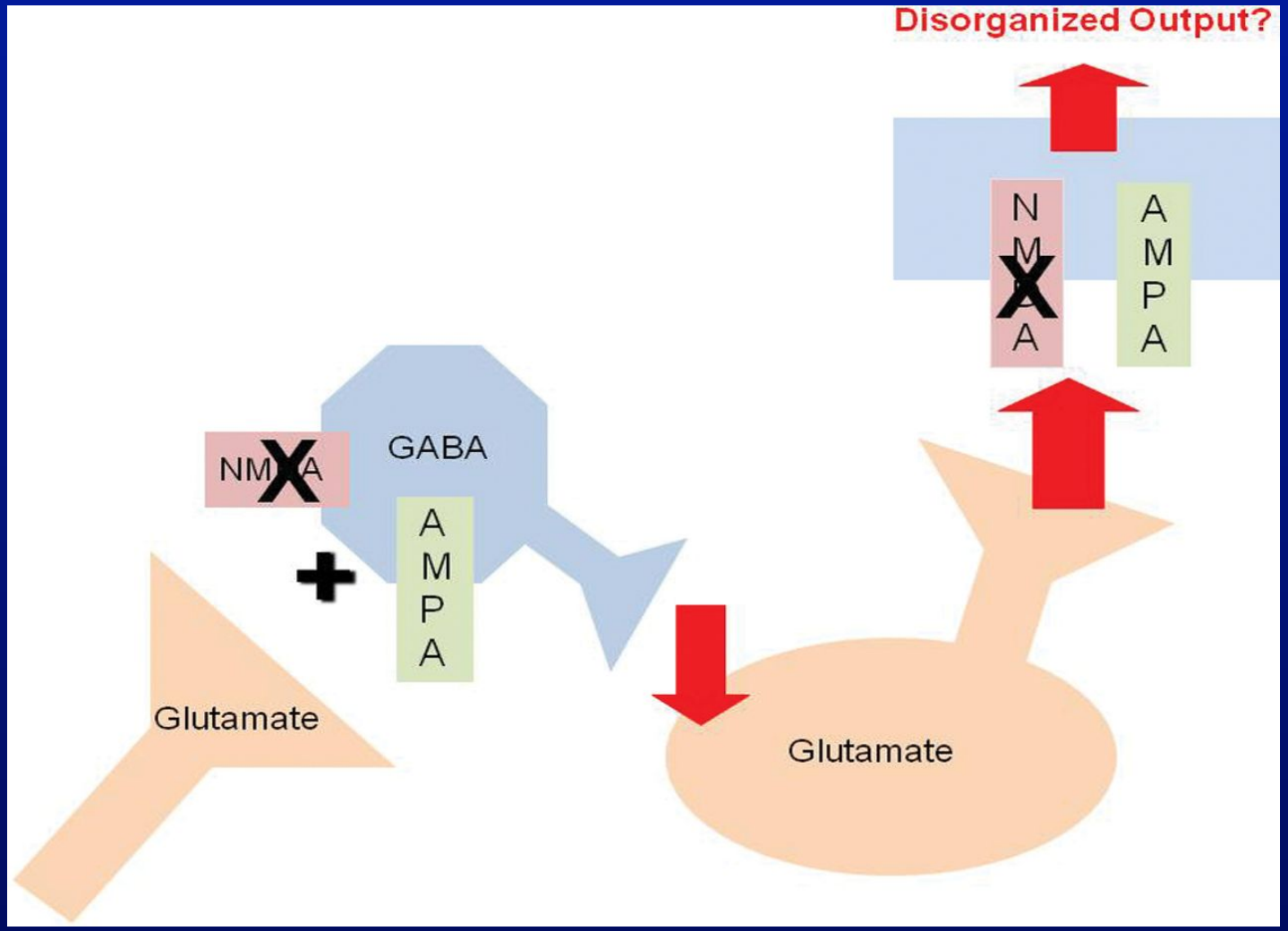
Potentiele toepassingen glutamaat (en GABA) modulatie

- Depressie, bipolaire depressie, therapie resistente depressie en ketamine (met of zonder ECT) (1) of rulizole (2))
- Verbetering van suicidale ideaties (ketamine) (3)
- Farmacotherapie assisted psychotherapy (D-cycloserine bij PTSD (4) of (gegeneraliseerde) angst (5) behandeling)
- Verbeteren cognitief functioneren (GLYX-13)
- Verbeteren negatieve symptomen

1. Fond et al Psychopharmacology (2014) 231:3663–3676
2. Dutti et al Psychiatry Research 225 (2015) 1–13
3. Ballard et al Journal of Psychiatric Research 58 (2014) 161-166
4. Singewald et al Pharmacology and Therapeutics (2015) in press
5. Hofmann et al Curr Psychiatry Rep (2015) 17:532

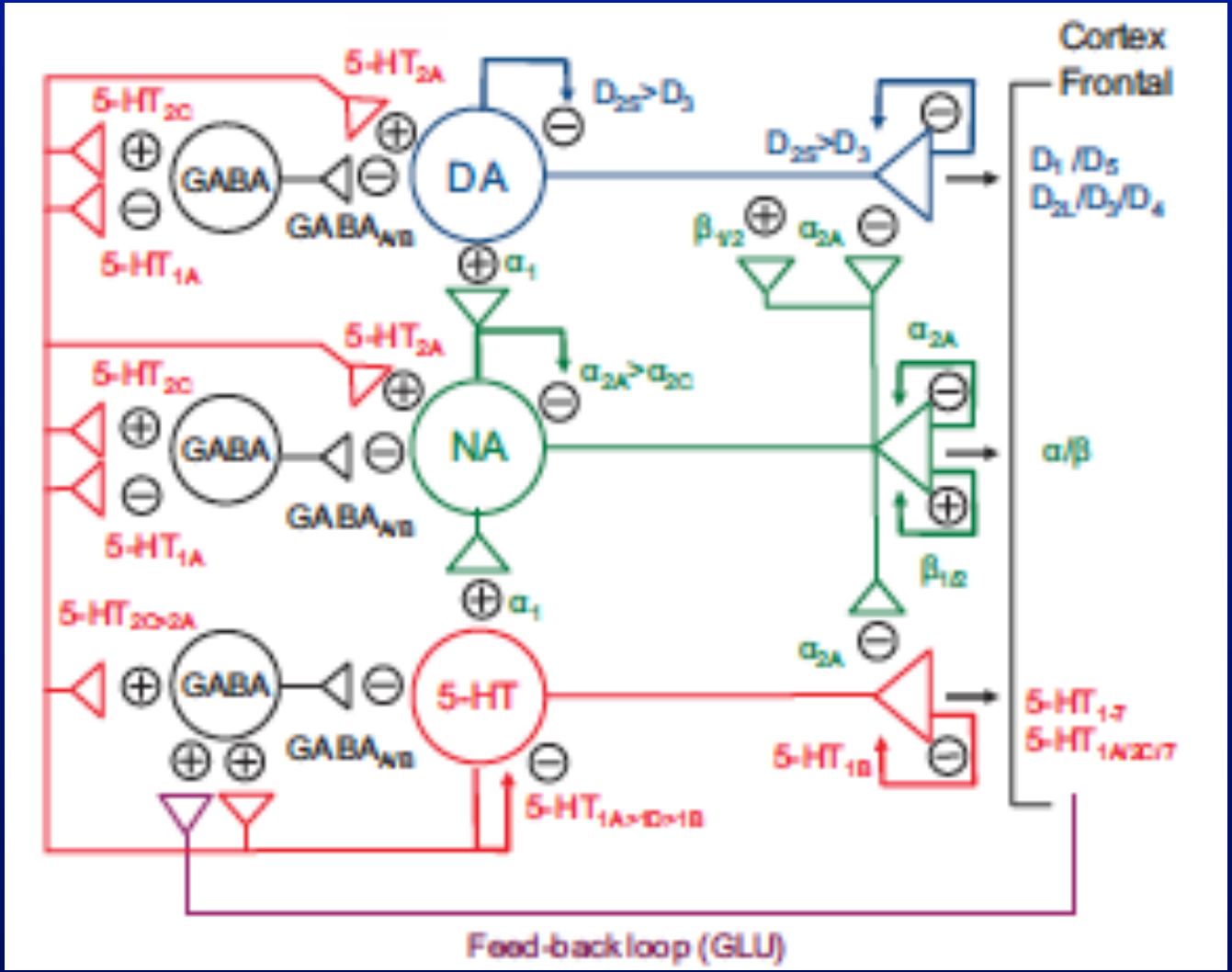

Glycine reuptake inhibition (bitopertin), Sarcosine
Glycine neuron
Glutamatergic neuron
mGlu2/3 agonist????
Serine (high dose)
Glial cell
GABAergic or glutamatergic neuron
Glutamine transporter
Glutaminase
Glutamine
GLY-T2
Glycine
Glutamate
Glutamate transporter
Amino acid transporter Asc-1
Serine racemase
L-serine
D-serine
D-cycloserine
GLY-T1 inhibitors
GLY-T1
Glutamine synthetase
L-serine transporter
SHMT
SNAT
Reversed GLY-T1
D-alanine
Glutamate binding site
Glycine bindind site
NMDA receptors
D-aminozuur oxidase remmer (DOA)
Glycine
Minocycline
Sarcosine
GSK1018921
5-ACPPB
Bitopertin
D-alanine

NMDA receptor deficits on GABA interneurons disinhibit glutamate release in PFC and hippocampus promoting disorganized cortical activity.



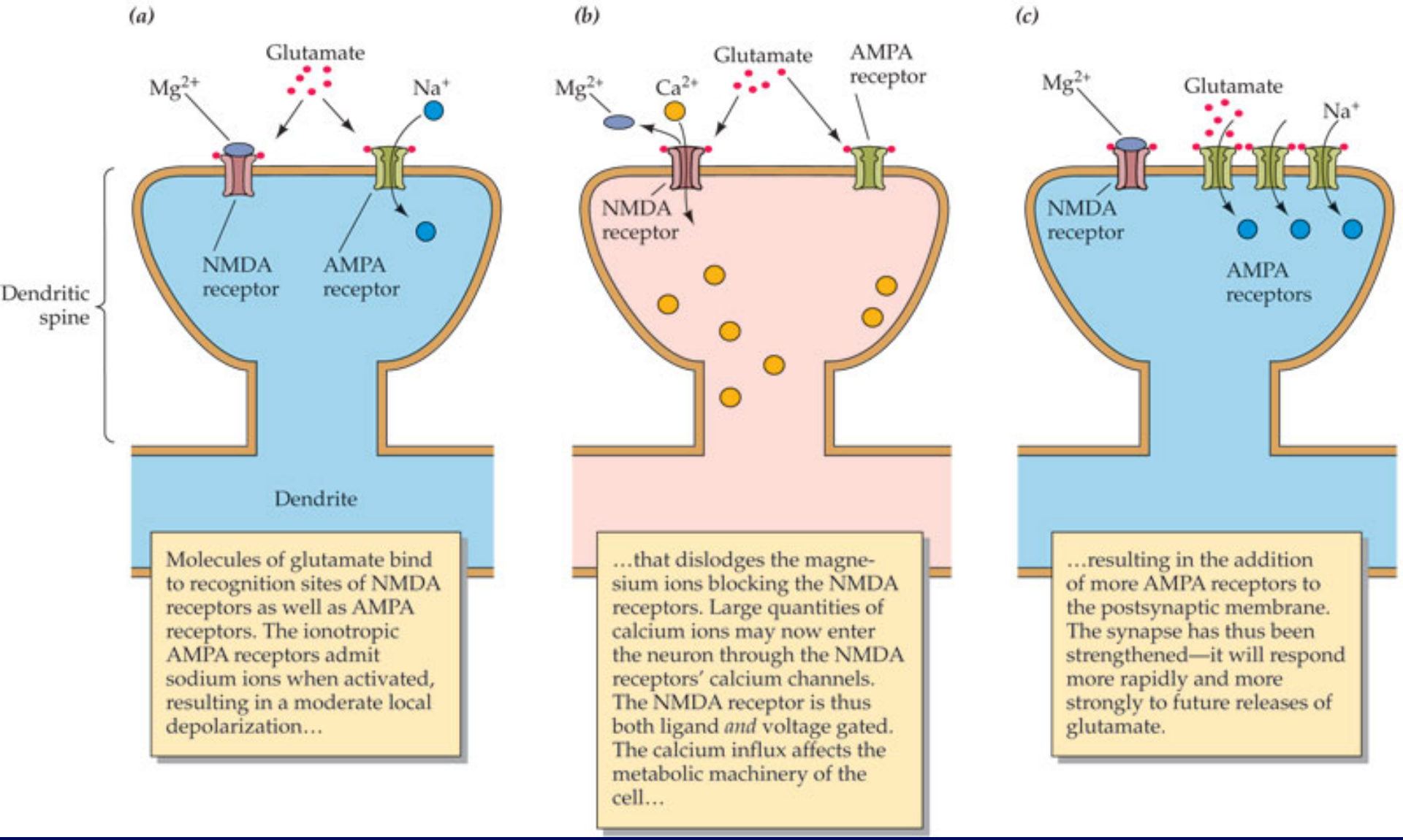
Moghaddam B and Krystal J H Schizophr Bull 2012;38:942-949

Networks in the brain



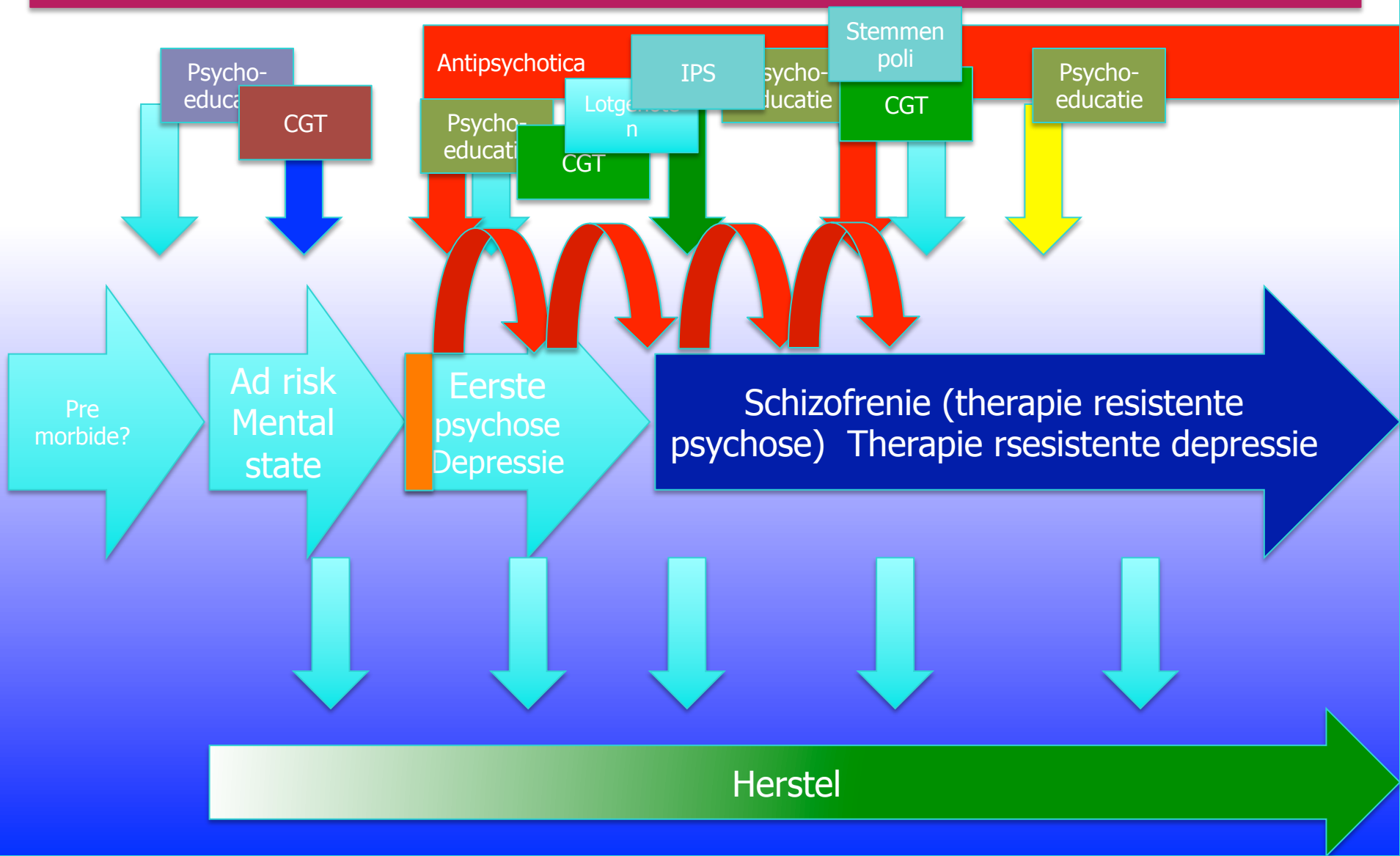
Adapted from Millan: Pharmacology and Therapeutics 2006

NMDA AMPA and Learning (LTP)

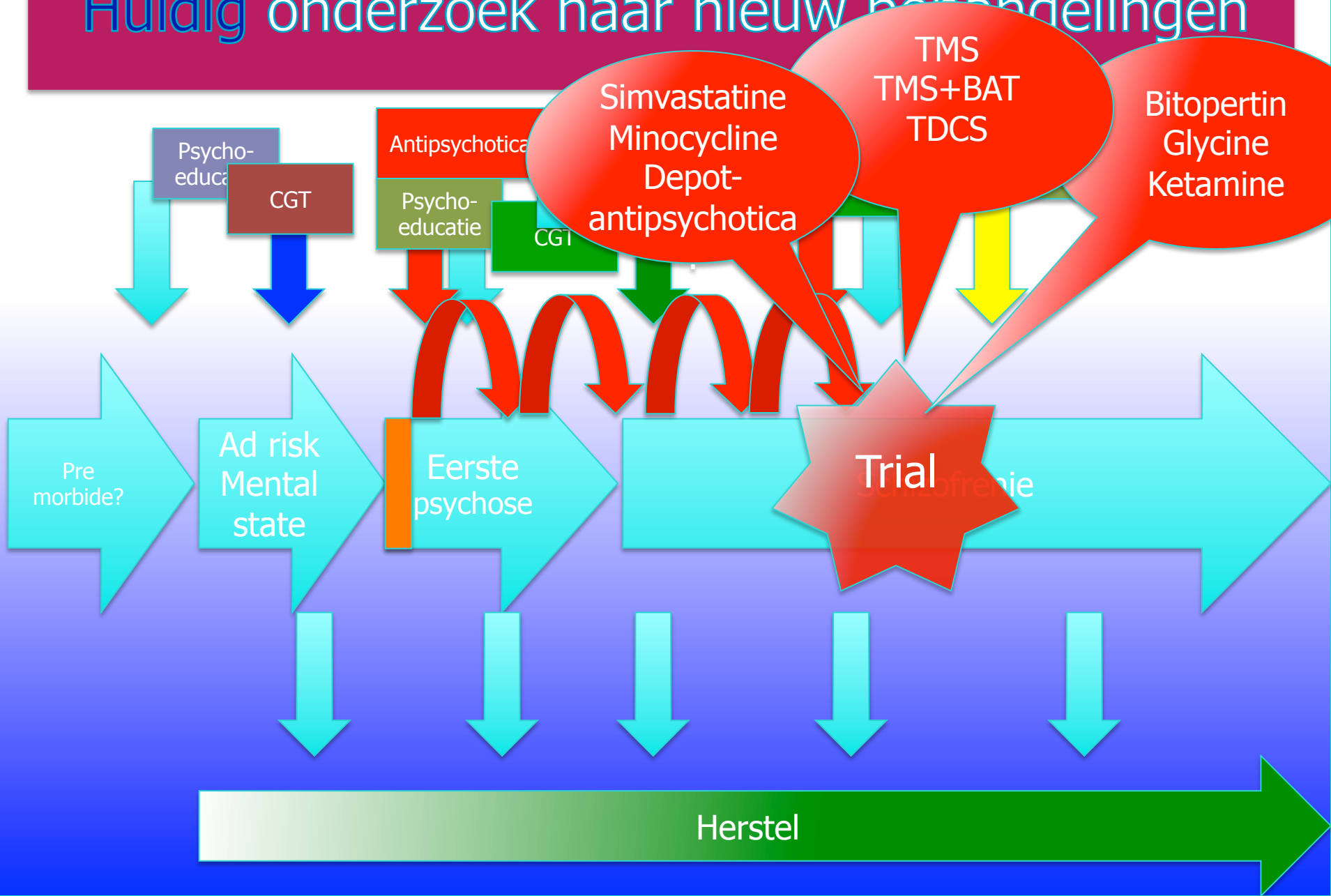


http://www.biopsychology.com/6e/step0402.html

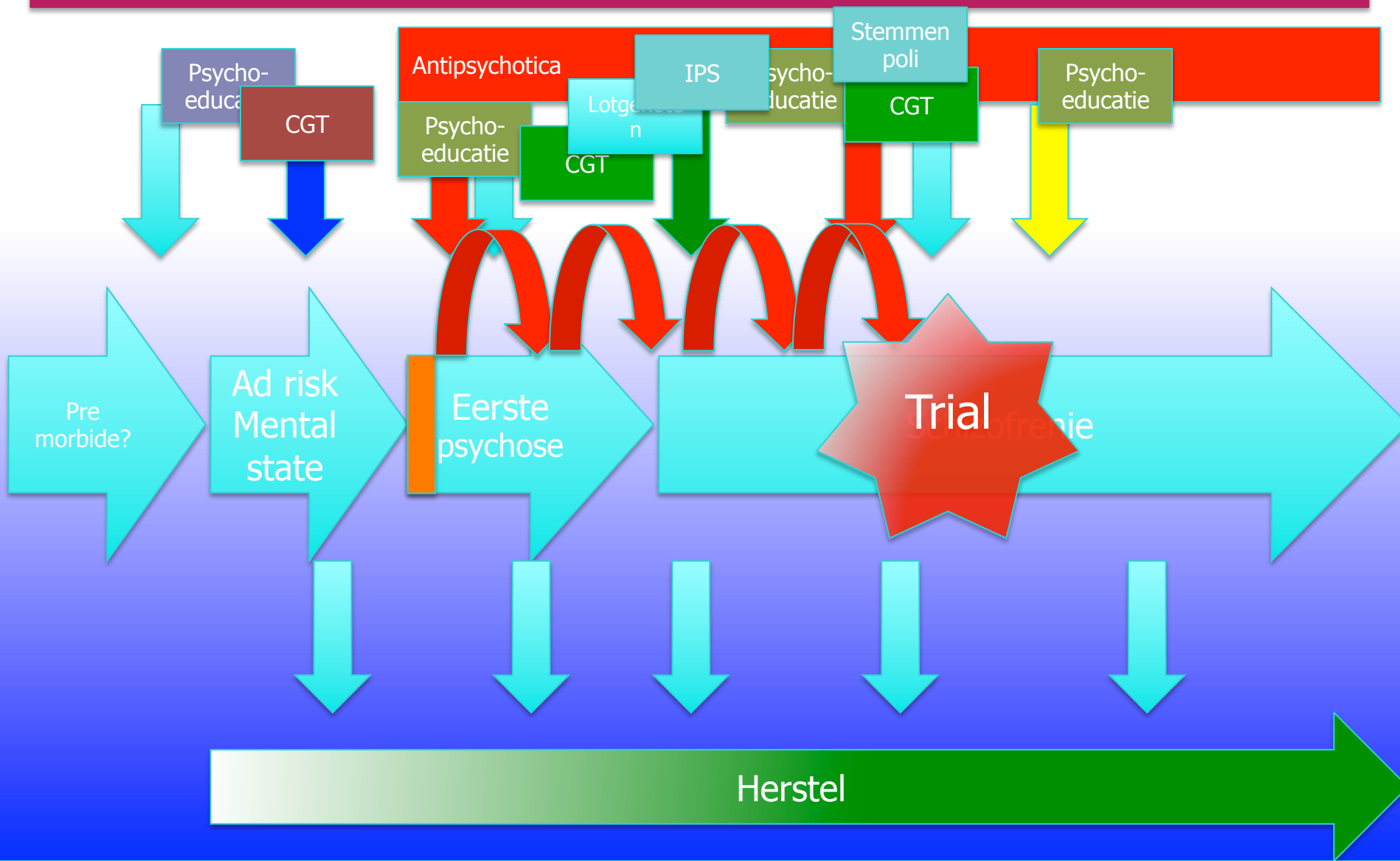
Huidig onderzoek naar nieuw behandelingen



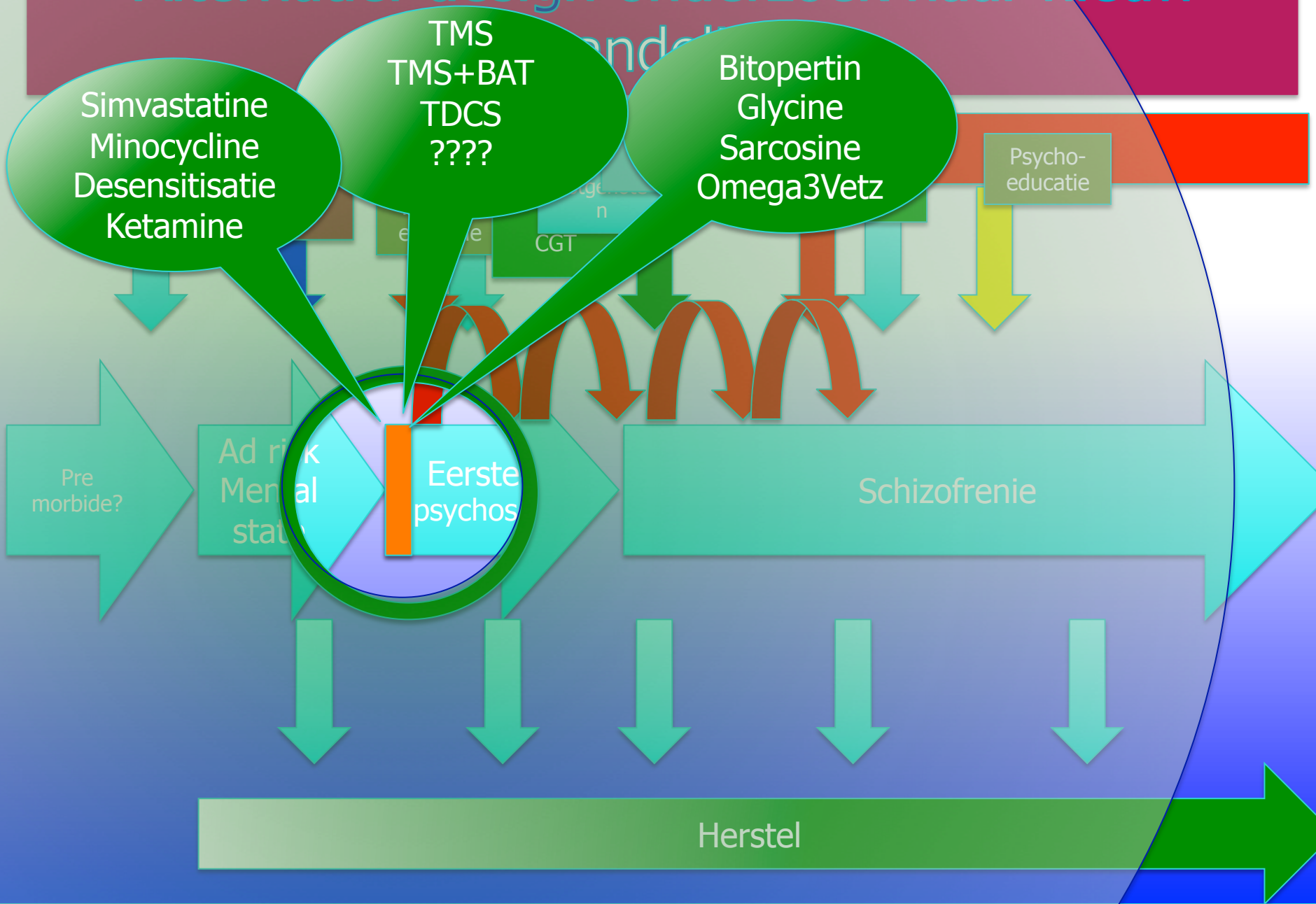
Huidig onderzoek naar nieuw behandelingen



Huidig onderzoek naar nieuw behandelingen



Alternatief design onderzoek naar nieuw



Glutamaat NMDA **anta**gonisten

- (Es)ketamine (therapie resistente depressie, suicidaliteit?)
- Rulizone (therapie resistente depressie)
- Tiletamine
- PCP (Phencyclidine)
- Dextromethorphan, methorphan
- AP5
- MK801 (dizocilpine)
- Memantine (partieel antagonist) (Dementie)

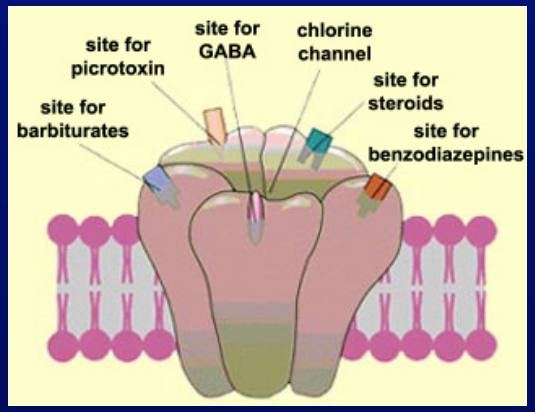
Glutamaat NMDA agonisten
(Positieve Allosterisch Modulatie)

- Glycine (negatieve symptomen)
- D-cycloseride (angst behandeling)
- Serine (negatieve symptomen)
- Sarcosine (negatieve symptomen)
- Minocycline (antibioticum, negatieve symptomen?)
- Bitopertin (negatieve symptomen, psychose)
- MGlu2/3 agonist (negatieve symptomen?)

GABA

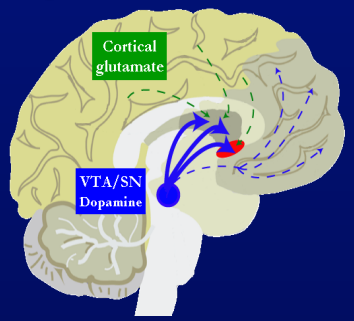
(Positieve Allosterische Modulatie (PAM))

- Benzodiazepines (anxiolytica, slaap, katatonie, antiepileptica
- Z-drugs (slaapmiddelen)
- Pregabaline (GABA agonist) (neuropatische pijnen, gegeneraliseerde angststoornis



NMDA receptor dysfunctie in schizofrenie?

- Mogelijke lagere serine en glycine spiegels bij mensen met schizofrenie
- NR2A subunit van NMDA receptoren was in 49-73% niet aantoonbaar in parvabumin bevattende cellen GABA-erge interneuronen in de prefrontale cortex
- Genetica: Associaties Dysbindin-1a, GRIN2B, GRIN1, GRIN2A-D, MAG12 polimorfismen en NMDA dysfunctie en schizofrenie

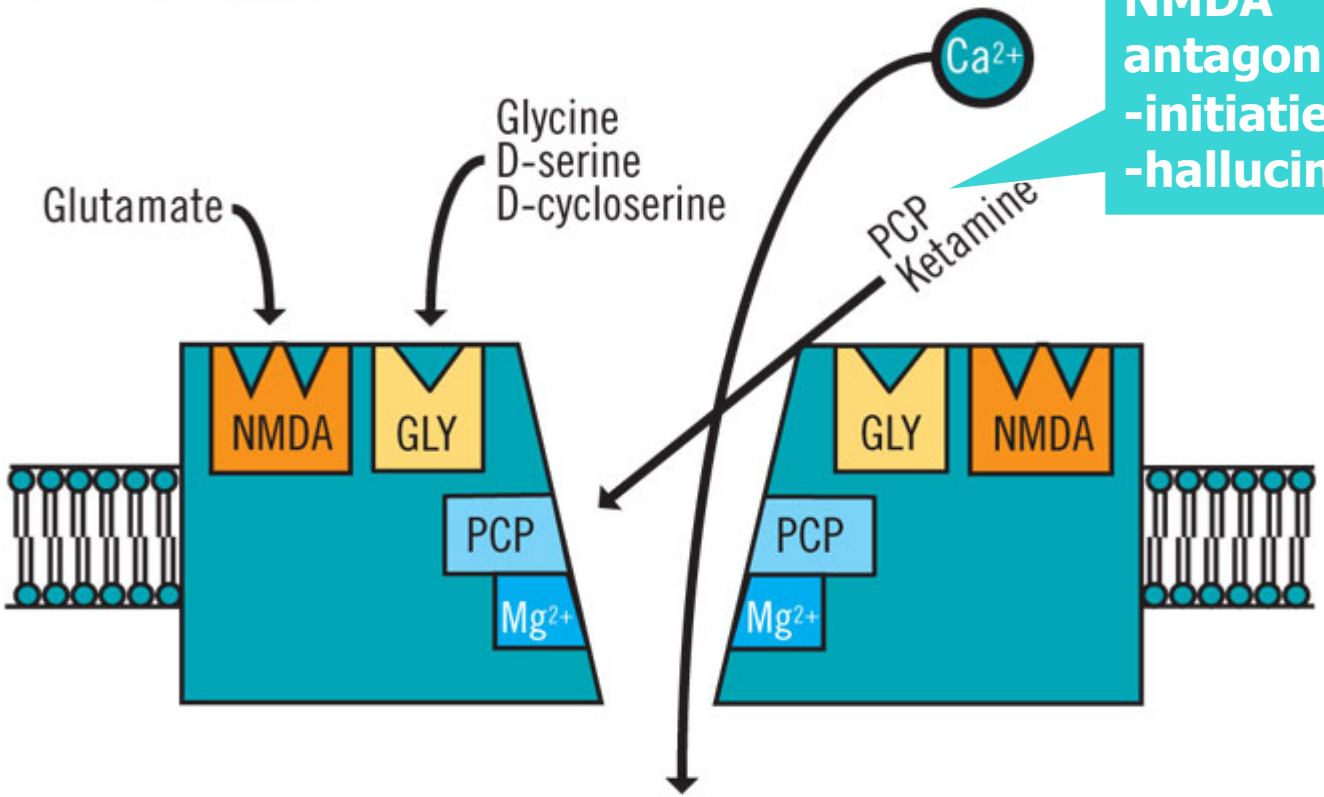


Calcia et al 2012; Schiz Research. Bitanihirwe et al 2009 BMC Psychiatry. Yamamori e.a. 2014: Neurosc lett Oct 17: 582:93-98

FIGURE 1

SCHEMATIC MODEL OF THE NMDA RECEPTOR COMPLEX, SHOWING THE BINDING SITES FOR GLUTAMATE, GLYCINE, AND D-SERINE

NMDA antagonisten
-initiatief verlies
-hallucinaties



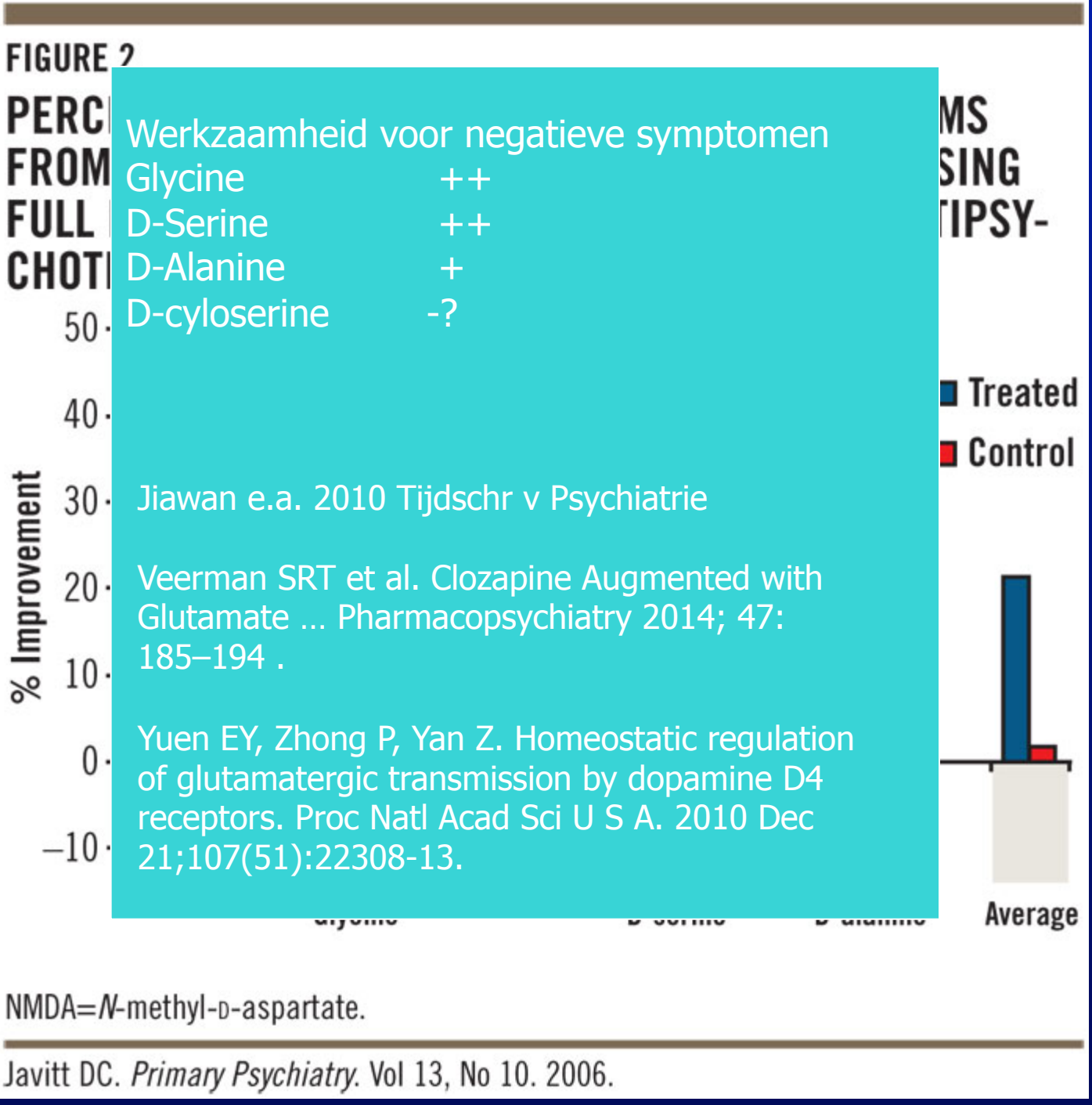
PCP and ketamine induce their psychotomimetic effects by binding to a site within the ion channel formed by the NMDA receptor complex.

NMDA=*N*-methyl-D-aspartate; GLY=glycine; PCP=phencyclidine; Ca=calcium; Mg=magnesium.

Javitt DC. *Primary Psychiatry.* Vol 13, No 10. 2006.

Interventies op NMDA hypo?functie

- DAAOI-1 (een D-amino acid oxidase (DAAO) inhibitor) (DAO)
- M-glu2/(3) agonist (presynaptisch)
- Glutamaat co-agonisten (postsynaptisch)
  - Glycine
  - Serine (hoge dosis)
  - D-alanine
  - D-cycloserine (wrs onwerkzaam)
- GlyT1 transporter antagonisten (presynaptisch)
  - Sarcosine
  - GSK1018921 (1e studie 2010 afgerond)
  - ACPPB
  - Bitopertin



Werkzaamheid voor negatieve symptomen

Glycine	++
D-Serine	++
D-Alanine	+
D-cyloserine	-?

Jiawan e.a. 2010 Tijdschr v Psychiatrie

Veerman SRT et al. Clozapine Augmented with Glutamate … Pharmacopsychiatry 2014; 47: 185–194 .

Yuen EY, Zhong P, Yan Z. Homeostatic regulation of glutamatergic transmission by dopamine D4 receptors. Proc Natl Acad Sci U S A. 2010 Dec 21;107(51):22308-13.

Glycine to treat at risk mental states: risk syndrome for psychosis

Woods et al 2012 European Neuropsychopharmacology

Glycine to treat at risk mental states: risk syndrome for psychosis

Two small studies

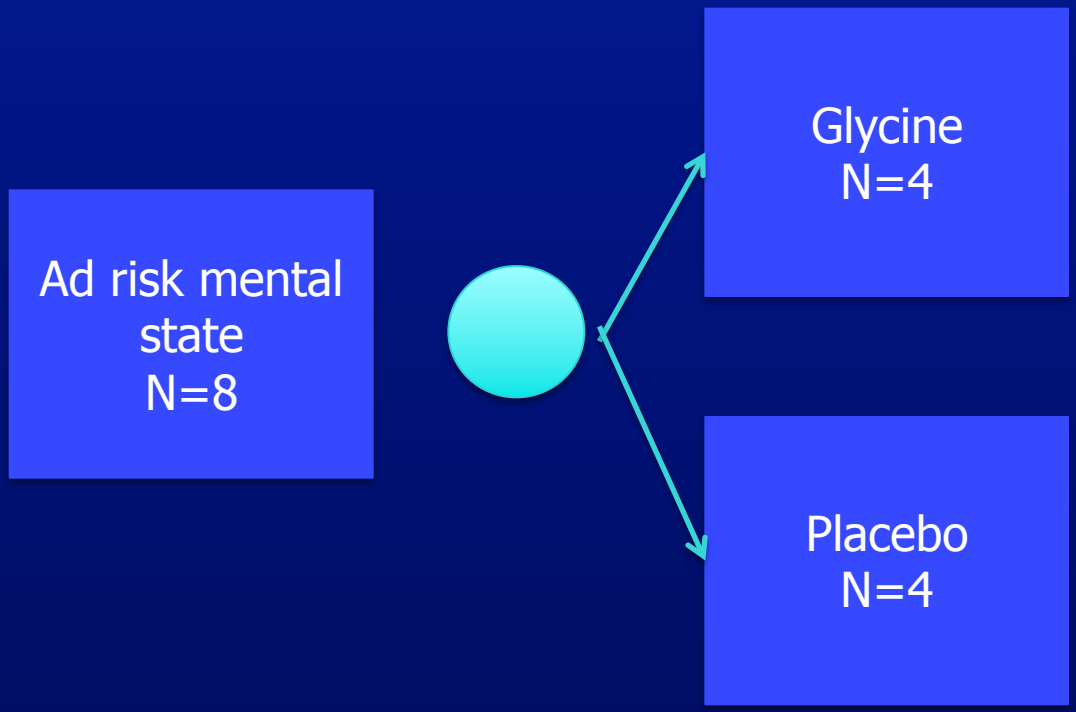
1. N=10, 8 weeks open label add on to antipsychotics glycine dose up to 0,8gr/kg/dag and 16 weeks discontinuation follow-up

2. N=8, double blind randomised glycine versus placebo trial 12 weeks and 12 weeks open label continuation

Woods et al 2012 European Neuropsychopharmacology

Glycine to treat at risk mental states: risk syndrome for psychosis

2. N=8, double blind randomised glycine versus placebo trial 12 weeks and 12 weeks open label continuation
POM: Scale Of Psychosis Risk Symptoms (SOPS) every two weeks



Positive symptoms
Effect size -1.11

Negative symptoms
Effect size -0.79

Cognitive improvement

No safety concerns

Woods et al 2012 European Neuropsychopharmacology

Interventies op NMDA hypo?functie

- DAAOI-1 (een D-amino acid oxidase (DAAO) inhibitor) (DAO)
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  - ACPPB
  - Bitopertin

Glycine transport inhibitors (GTIs)

- Glycine transport inhibitors (GTIs) functioneren door het blokkeren glycine transport out synapsspleet, met als netto gevolg versterking van NMDA activatie

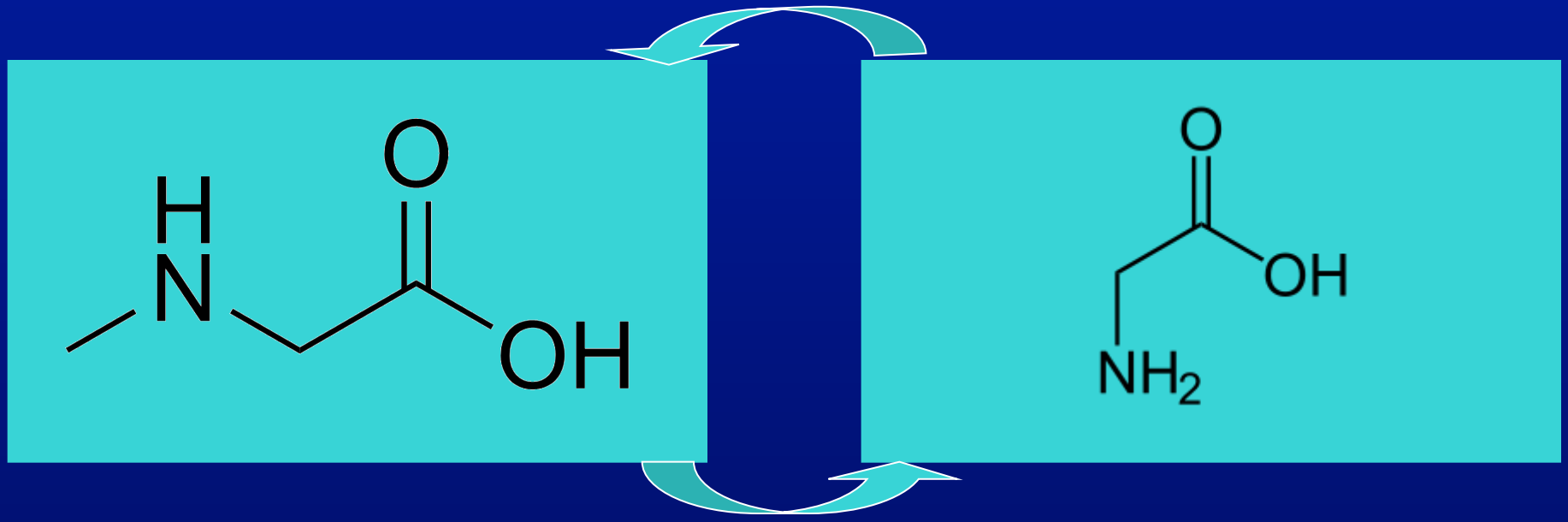
GlyT 1 transporter inhibitors

- Sarcosine (***N*-methylglycine**)
- ASP2535
- Bitopertin RG1678
- ORG 25935

- Possible applications
  - Alzheimer
  - Schizophrenia (negative symptoms, residual symptoms)
  - (alcohol) dependency
  - Anticonvulsant

Sarcosine

glycine-*N*-methyl transferase



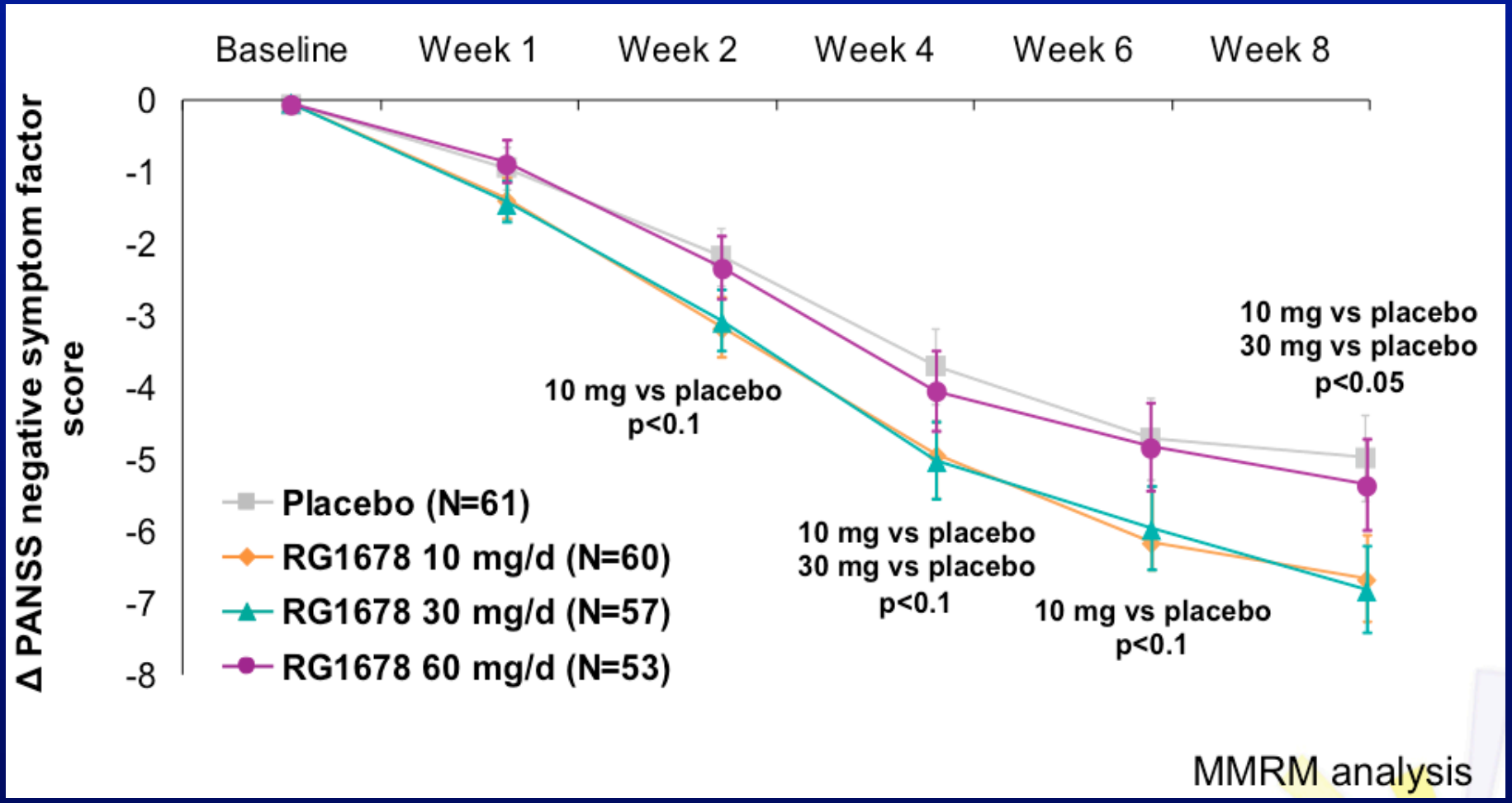
Sarcosine | sarcosine dehydrogenase | Glycine

Sarcosine=***N*-methylglycine**

Goff e.a. MI **April 2008** vol. 8 no. 2**99-107**

Significante vermindering van de PANSS negatieve symptomen factor met bitopertin 10 en 30 mg

RG1678 (Bitopertin) of Placebo in combinatie met AP



ITT at 8 weeks: 10 mg/d vs. placebo: p=0.07; 30 mg/d vs. placebo: p=0.09

Bitopertin 2014-2015

- Studies gestopt wegens onvoldoende effect op negatieve symptomen en therapie resistente positieve symptomen
- Maar
  - Aantal patienten melden….
  - Wat te doen bij patienten die een gunstig effect melden….

Umbricht et al. CINP congress June 2012, Florence April 2014

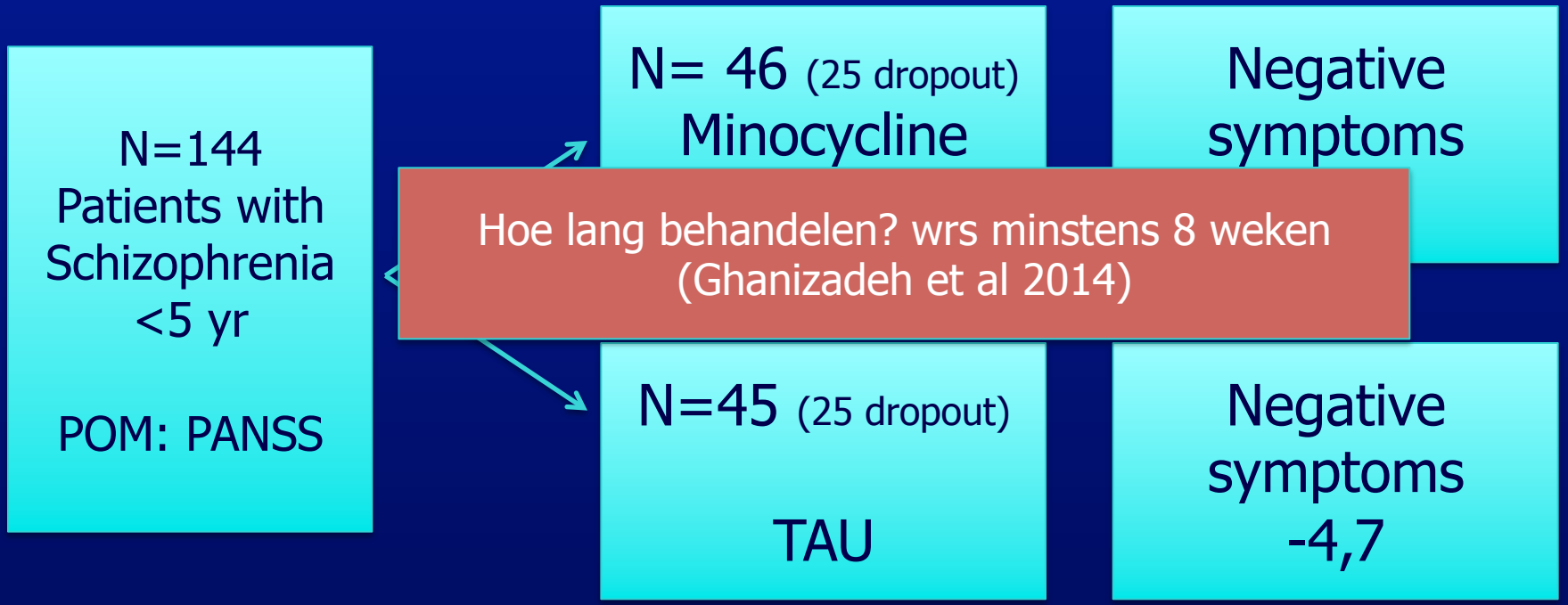
Minocycline

Neuroscience Volume 170, Issue 3, 27 O ctober 2010, Pages 901-912

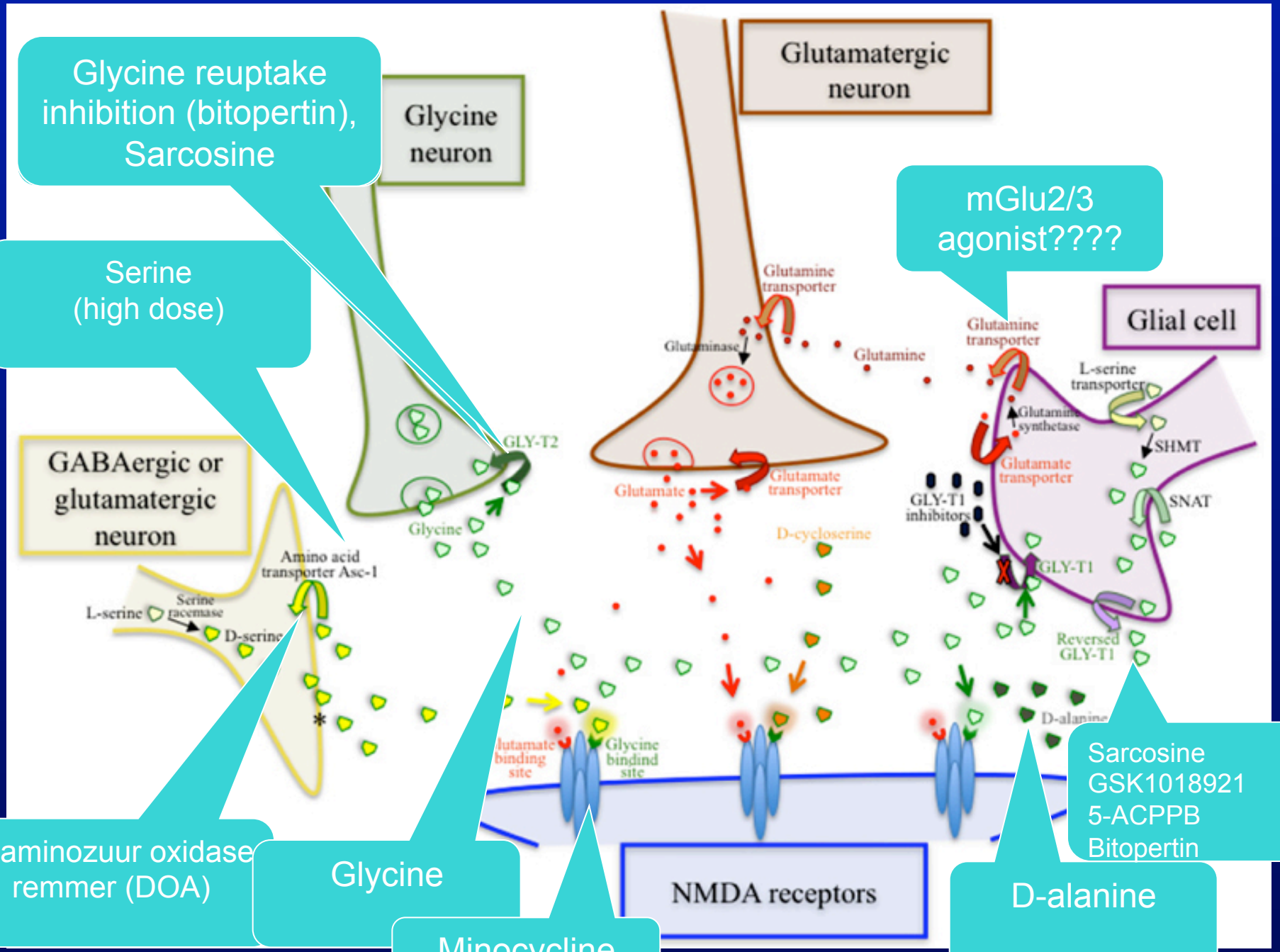
C. Chaves et al,Braz J Med Biol Res, November 2009, Volume 42(11) 1002-1014

Minocycline in schizophrenia

- Minocycline may improve negative symptoms



Chaudhry I B et al. J Psychopharmacol 2012;26:1185-1193
(Ghanizadeh et al 2014. Recent Pat Inflamm Allergy Drug Discov. 2014 Oct 29. [Epub ahead of print] .)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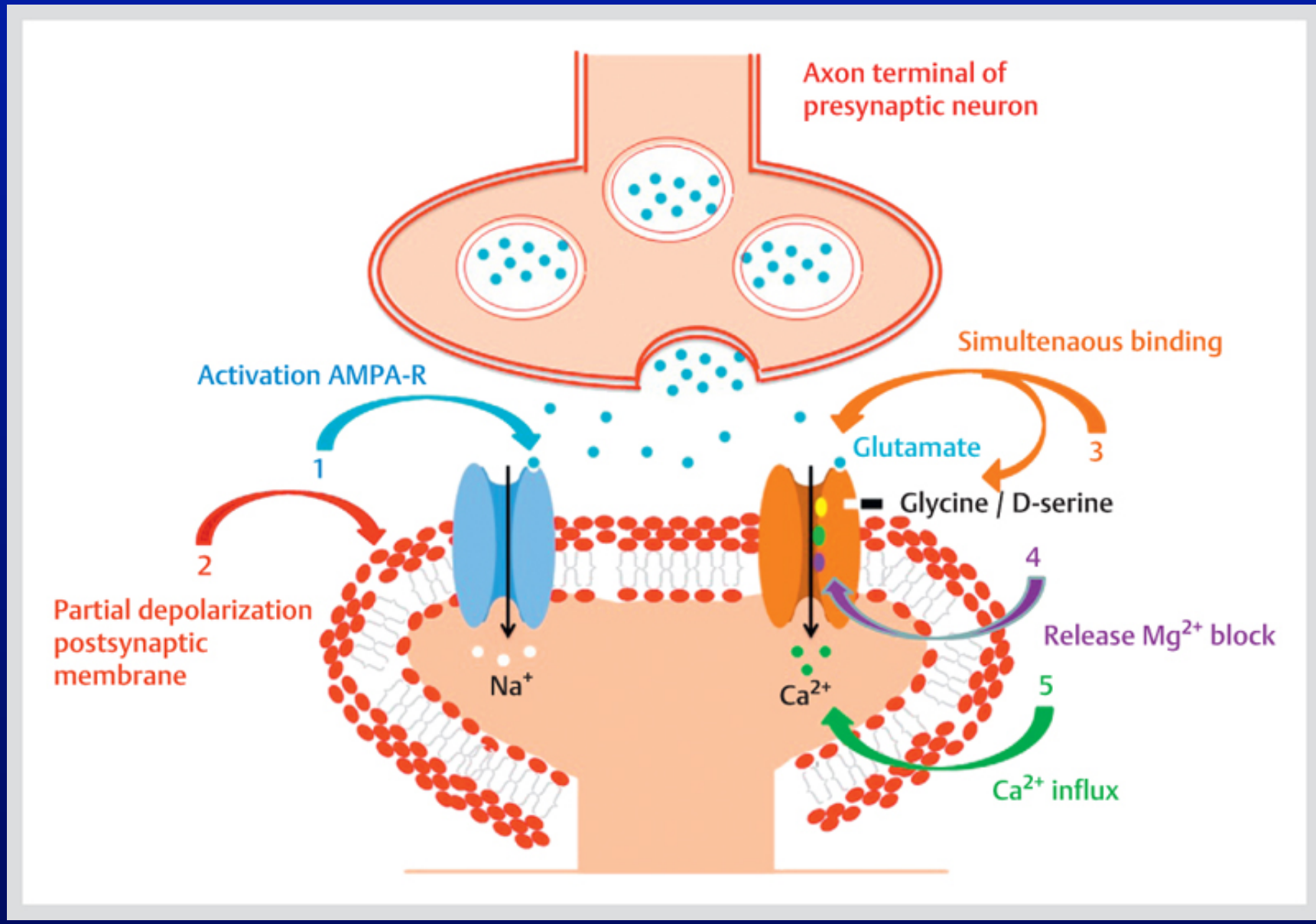
NMDA receptors
D-aminozuur oxidase remmer (DOA)
Glycine
Minocycline
Sarcosine
GSK1018921
5-ACPPB
Bitopertin
D-alanine

Dilemma’s in het voorschrijven van niet geregistreerde geneesmiddelen

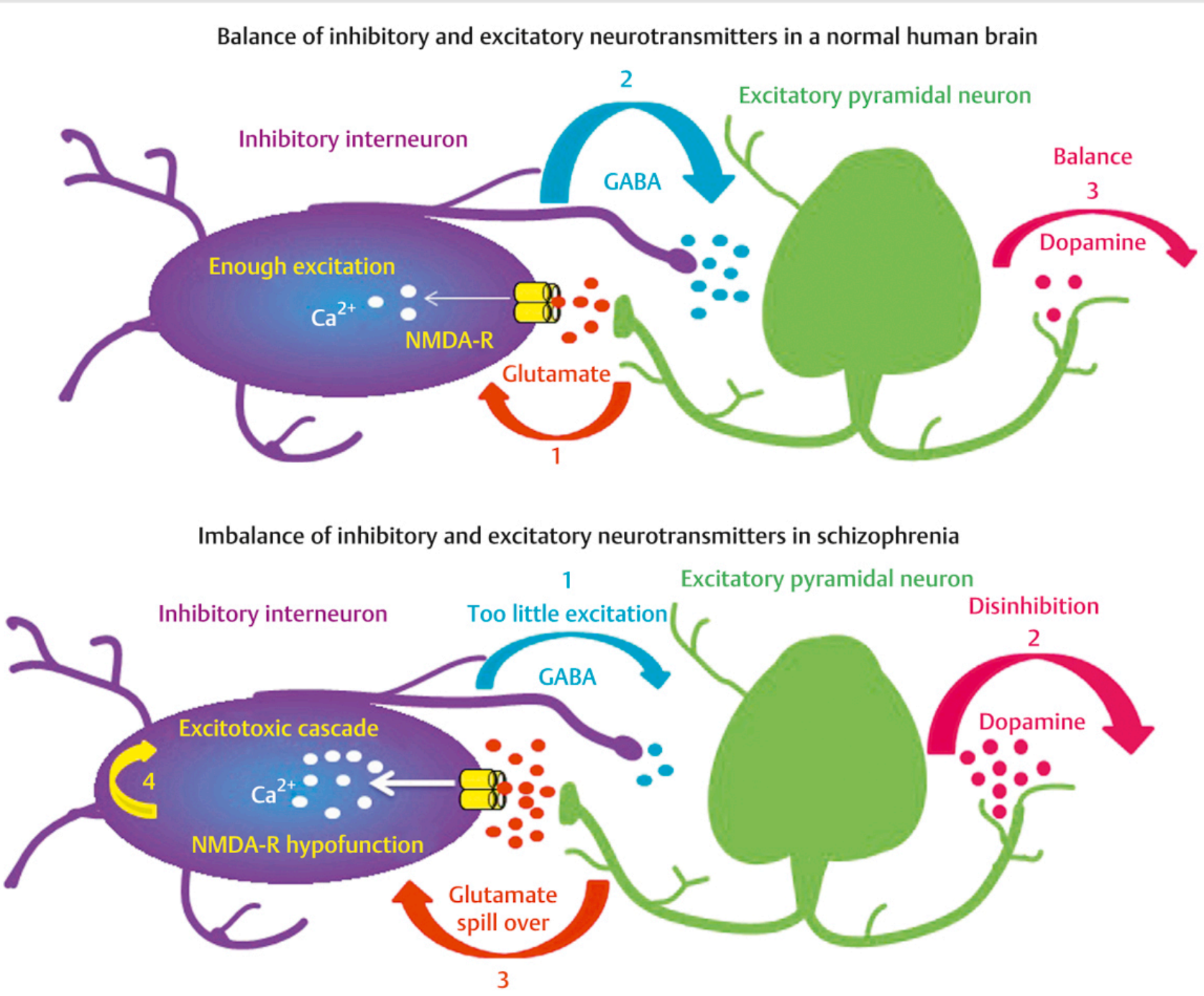
Wat als clozapine niet werkt

Rikus Knegtering

12-3-15



Veerman e.a. Pharmacopsychiatry 2014; 47(04/05): 121-130


Balance of inhibitory and excitatory neurotransmitters in a normal human brain
2
Excitatory pyramidal neuron
Inhibitory interneuron
GABA
Balance
3
Dopamine
Enough excitation
Ca2+
NMDA-R
Glutamate
1
Imbalance of inhibitory and excitatory neurotransmitters in schizophrenia
1
Excitatory pyramidal neuron
Inhibitory interneuron
Too little excitation
Disinhibition
2
GABA
Dopamine
Excitotoxic cascade
4
Ca2+
NMDA-R hypofunction
Glutamate
spill over
3

Clozapine Augmented with Glutamate Modulators in Refractory Schizophrenia: A Review and Metaanalysis

Authors S. R. T. Veerman[1], P. F. J. Schulte[2], M. J. H. Begemann[3], F. Engelsbel[4], L. de Haan[5]

Effecten van clozapine op glutamaat

- Clozapine is a glutamate agonist,
  - affecting the glycine site of the NMDA receptor by inducing the release of D-serine by glial cells and activating mGlu receptors through subsequent release of glutamate by glial cells.
- Clozapine results in upregulation of NMDA receptors. Through antagonist activity at *D 4 receptors in the PFC* -clozapine *may* induce upregulation of AMPA receptors.

Veerman SRT et al. Clozapine Augmented with Glutamate … Pharmacopsychiatry 2014; 47: 185–194 . Yuen EY, Zhong P, Yan Z. Homeostatic regulation of glutamatergic transmission by dopamine D4 receptors. Proc Natl Acad Sci U S A. 2010 Dec 21;107(51):22308-13.

Clozapine additie met een NMDA agonist (glycine, sarcosine, D-serine, D-cylcoseride)

- Treatment-resistant patients do not benefit from the combination of clozapine and a NMDA receptor-related agonist, as shown by 6 negative trials .
  - Ongoing synaptic activity results in persistent downregulation of NMDA receptors, which are hypothesized to be hypofunctional in schizophrenia.

Table 1A Double-blind, placebo-controlled randomized trials of clozapine augmentation with glutamate agonists in refractory schizophrenia.

Study Statistical analysis	Adjunctive agent (maximum dose)	N (phase 1/2)	Trial duration (weeks)	Outcome of measure	ES	P-Value	Significance
Potkin et al., 1999	Glycine (30 g)	9	12	Positive symptoms (BPRS-P)	−1.052	0.025	−
	Placebo	10		Negative symptoms (SANS)	−0.228 ■	0.605	=
Completer analysis				Overall clinical symptoms (BPRS)	−	0.326	=
Evins et al., 2000	Glycine (60 g)	14	8	Positive symptoms (PANSS-P)	−0.545	0.152	=
	Placebo	13		Negative symptoms (SANS)	0.186	0.619	=
Completer analysis				Overall symptoms of schizophrenia (Total PANSS)	−0.075	0.840	=
				Cognitive functioning (*)	x	x	=
Diaz et al., 2005	Glycine (60 g)	5/6	14 + 14	Positive symptoms (PANSS-P)	−0.444	0.286	=
	Placebo	6/5	(cross-over)	Negative symptoms (PANSS-N)	−0.237	0.564	=
Completer analysis				Overall symptoms of schizophrenia (Total PANSS)	−0.022	0.956	=

Clozapine additie met een NMDA agonist (glycine, sarcosine, D-serine, D-cycloseride)

- Treatment-resistant patients do not benefit from the combination of clozapine and a NMDA receptor-related agonist, as shown by 6 negative trials .
  - Ongoing synaptic activity results in persistent downregulation of NMDA receptors, which are hypothesized to be hypofunctional in schizophrenia.
- Ampakine CX516, in one small trial, seems to be the only glutamate agonist to have significant benefits, especially on negative symptoms, as an adjunct to clozapine.

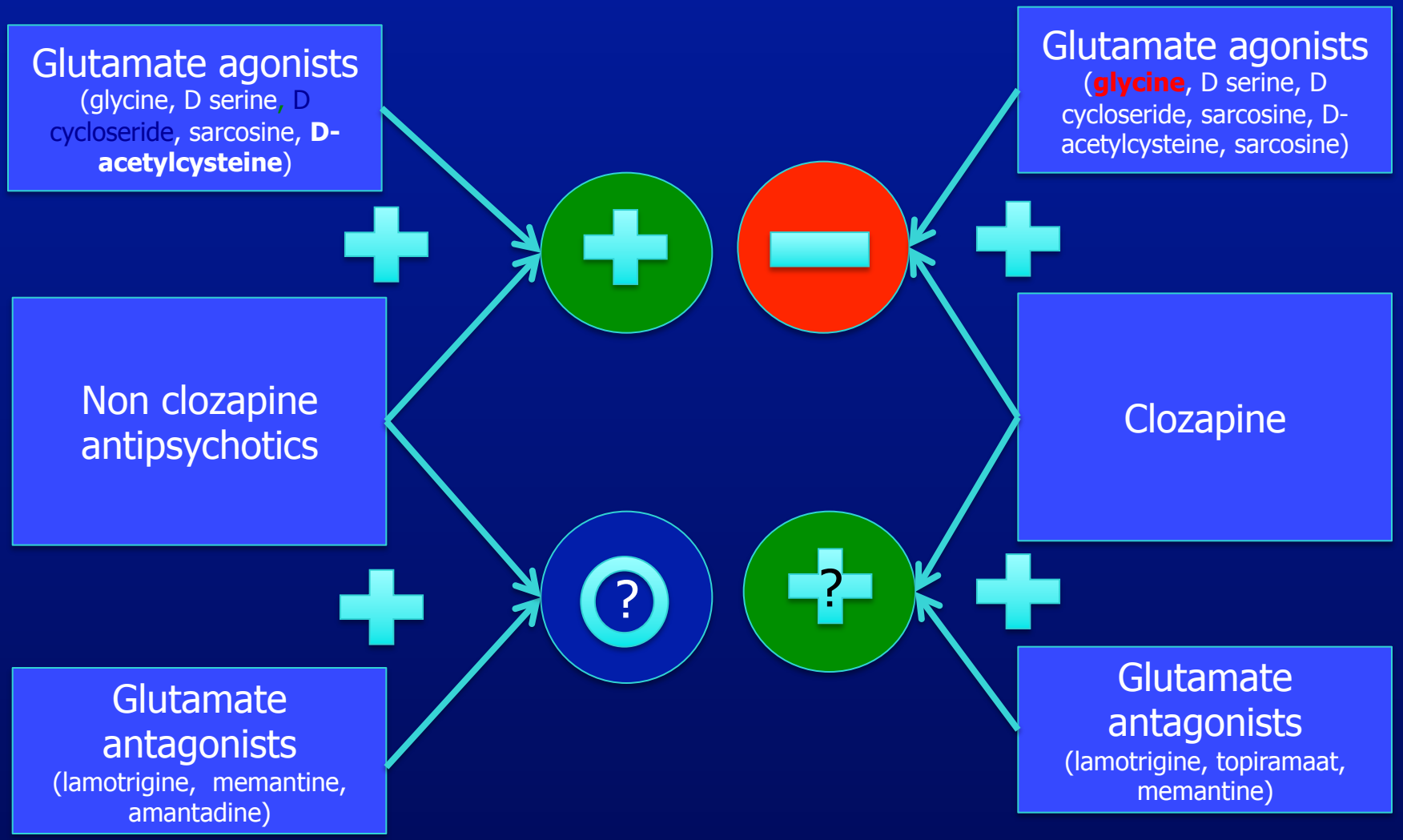
Clozapine additie met een NMDA antagonist (memantine)

Table 4 Double-blind, placebo-controlled randomized trials of clozapine augmentation with memantine in refractory schizophrenia.

Study Statistical analysis	Adjunctive agent (maximum dose)	N	Trial duration (weeks)	Outcome of measure	ES	P-Value	Significance
Lucena et al., 2009	Memantine (20 mg)	10	12	Positive symptoms (BPRS-P)	1.325	0.002	+
	Placebo	11		Negative symptoms (BPRS-N)	3.197	<0.001	+
No drop outs				Overall clinical symptoms (BPRS)	2.640	<0.001	+
				Cognitive functioning (MMSE)	1.267	0.003	+

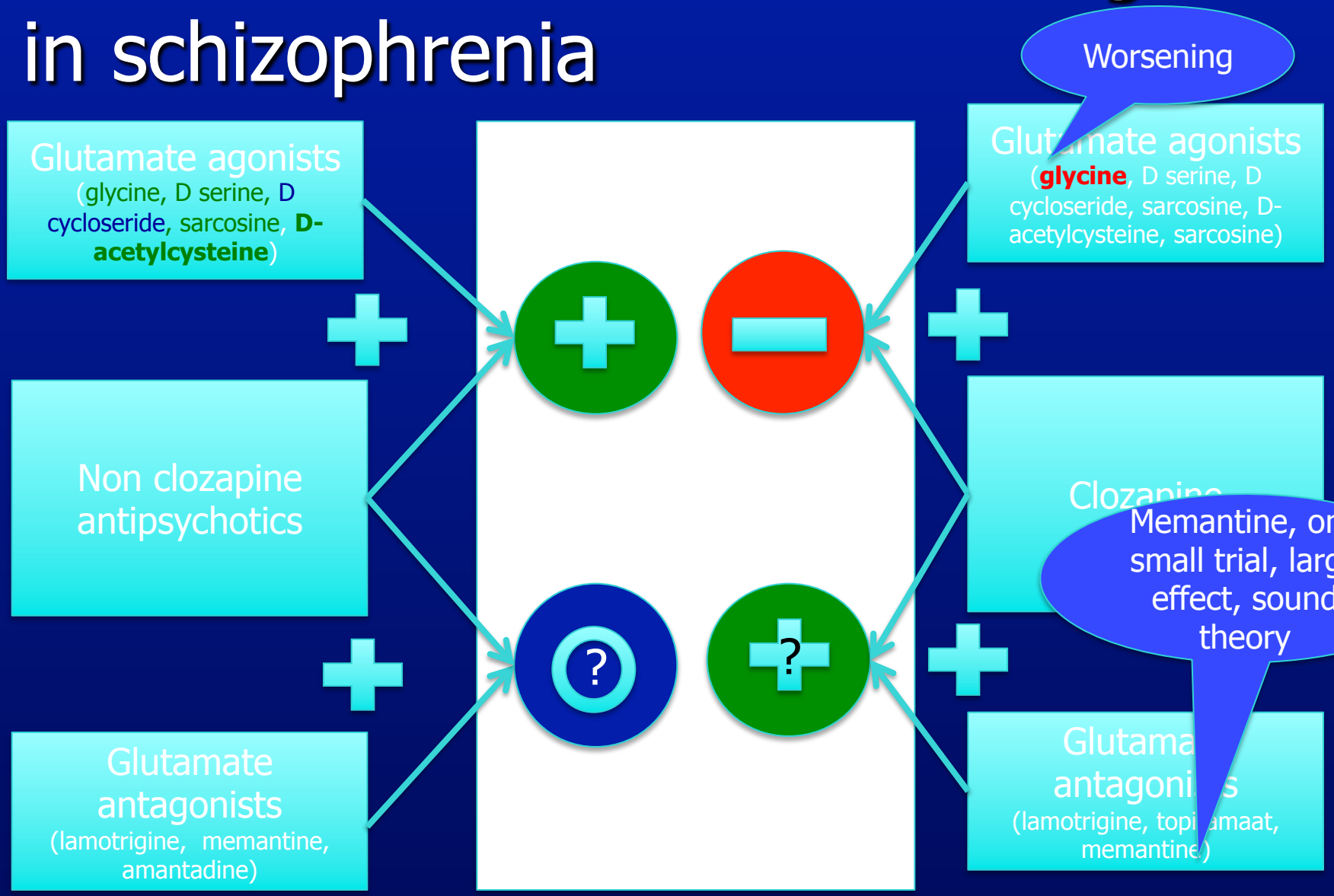
Veerman SRT et al. Clozapine Augmented with Glutamate … Pharmacopsychiatry 2014; 47: 185–194

Conclusions on addition strategies in schizophrenia



Veerman SRT et al. The Glutamate Hypothesis … Pharmacopsychiatry 2014; 47: 121–130. Singh SP and Singh V. Meta-analysis of the efficacy of adjunctive NMDA receptor modulators in chronic schizophrenia. CNS Drugs 2011. Oct 1;25(10):859-85. Bewerking

Conclusions on addition strategies in schizophrenia



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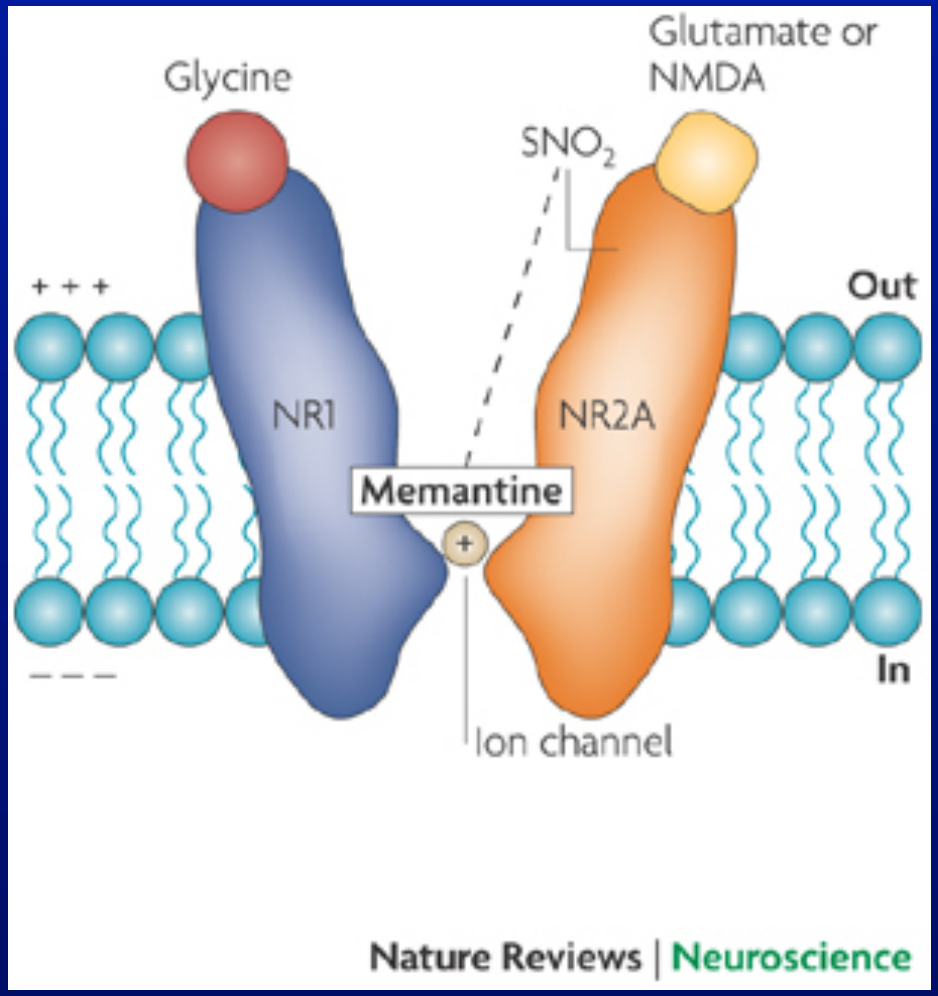
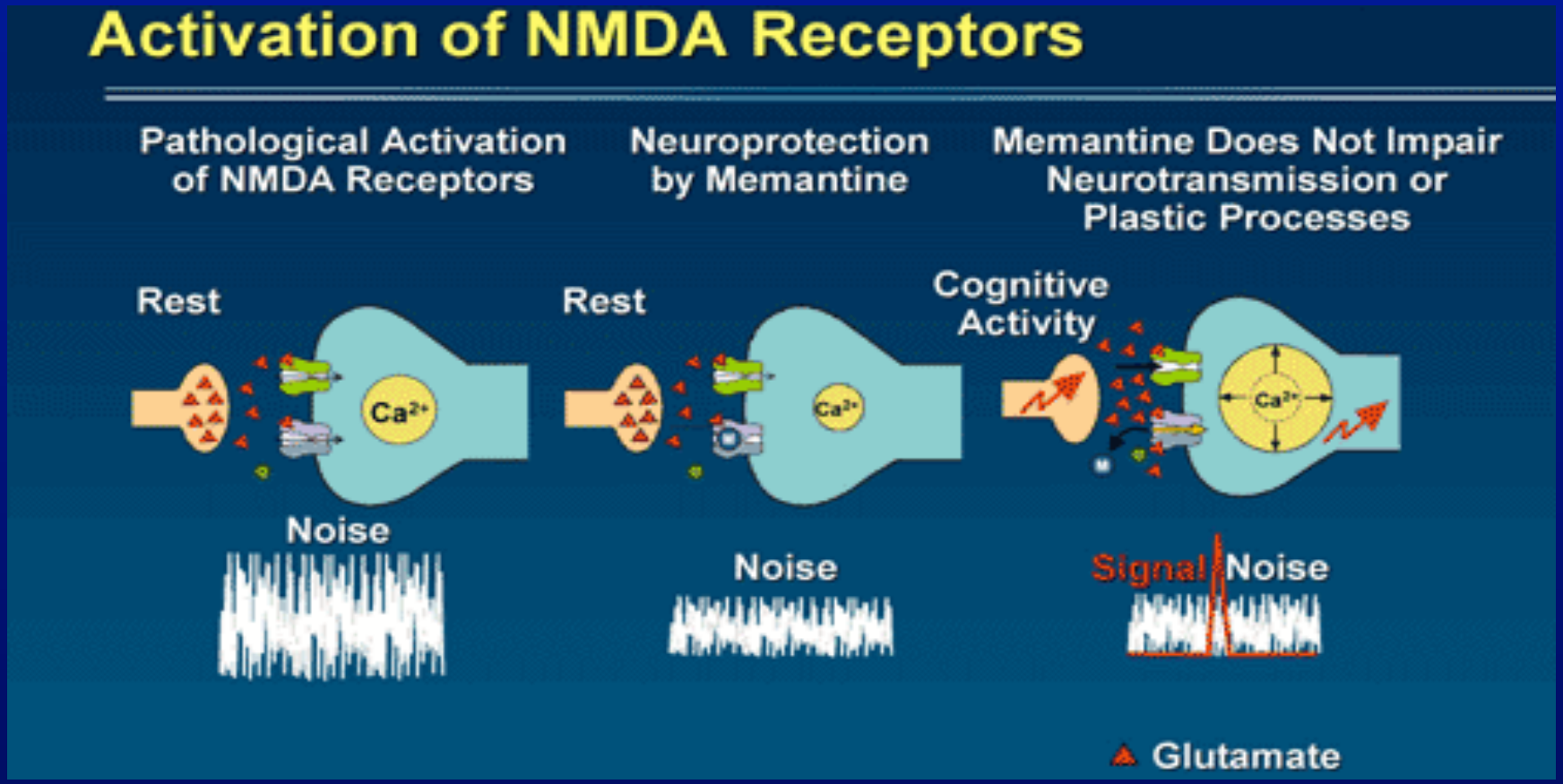
Memantine

- Memantine acts as a low to moderate affinity type of uncompetitive, nonselective NMDA receptor antagonist
- Memantine is a voltage dependent antagonist.
- Memantine exerts its subtle effect on the NMDA receptor by binding at or near the Mg 2 + site within the ion channel.
- Memantine binds somewhat stronger than Mg 2 + ,
- decreasing Ca 2 + influx.
- Through reduction of overstimulation of NMDA receptors in the presence of excessive glutamate in thesynaptic cleft, a homeostatic state is restored.
- D2 agonist, 5HT3 antagonist, fast dissociating antagonist fornicotinereceptors including alpha 7 nAChR.

Memantine


Glycine
Glutamate or
NMDA
SNO_2
+ + +
Out
NR1
NR2A
Memantine
+
In
– – –
Ion channel
Nature Reviews | Neuroscience

Memantine


Activation of NMDA Receptors
Pathological Activation of NMDA Receptors
Neuroprotection by Memantine
Memantine Does Not Impair Neurotransmission or Plastic Processes
Rest
Rest
Cognitive Activity
Ca2+
Ca2+
Ca2+
Noise
Noise
Signal
Noise
Glutamate