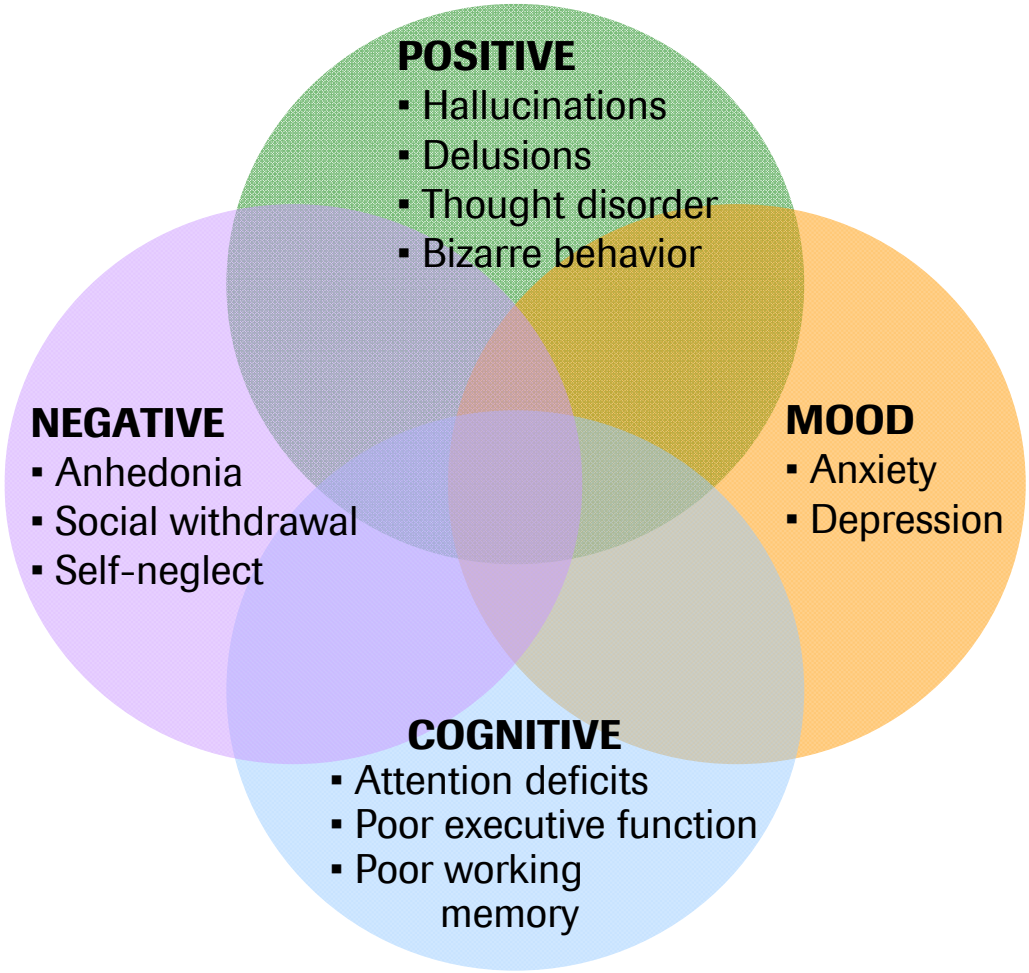
Glycine reuptake inhibitor (GlyT–1)

RG1678, the first GRI in schizophrenia

Schizophrenia
Disease and epidemiology

Multiple symptoms

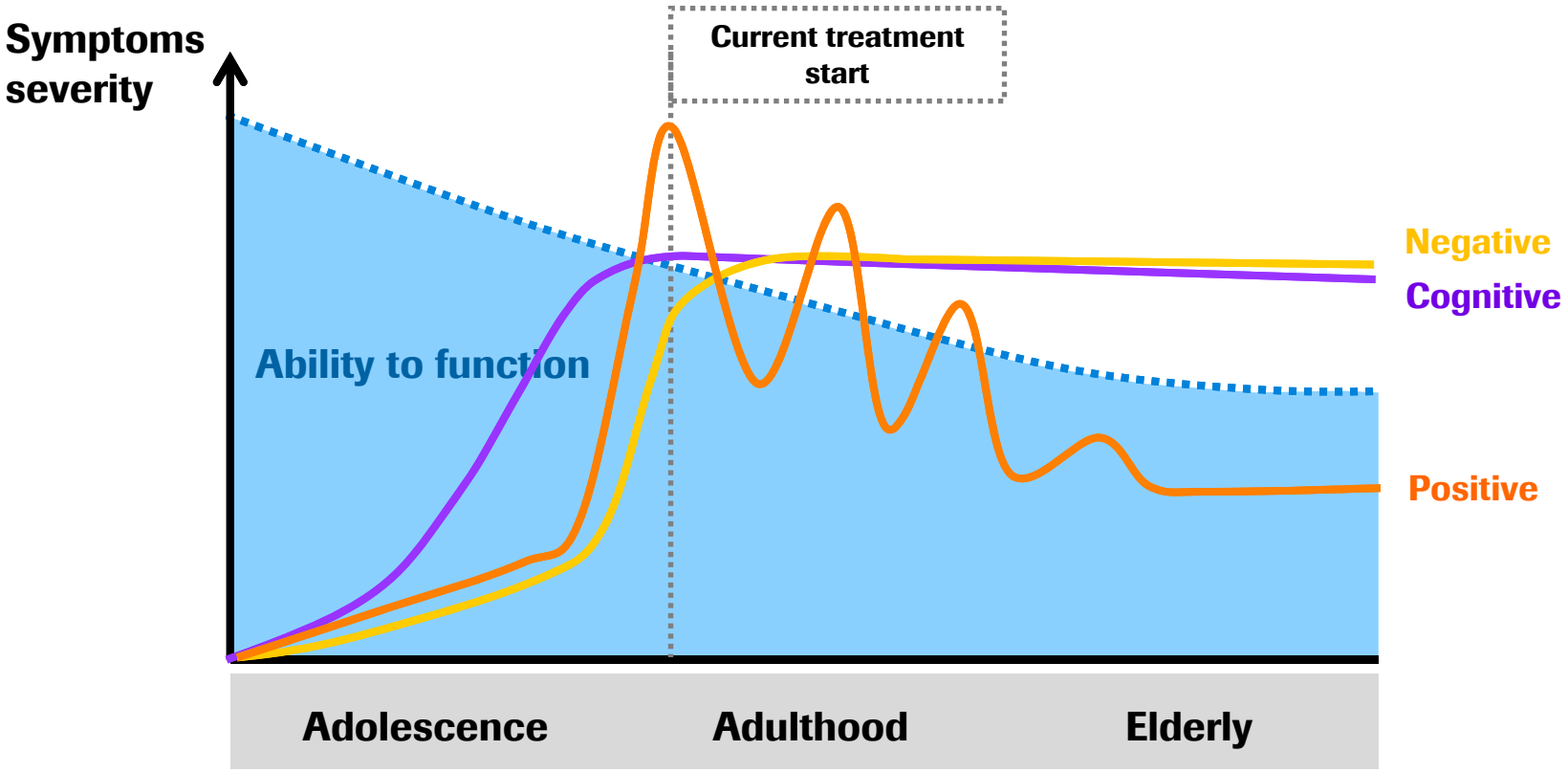


Epidemiology*

Country	Diagnosed Prevalence (%)
US	0.7
Japan	0.8
France	0.7
Germany	0.8
Italy	0.8
Spain	0.7
UK	0.8

* Source: Decision Resources, Jan. 2010

Addressing untreated symptoms in schizophrenia



Available treatment options

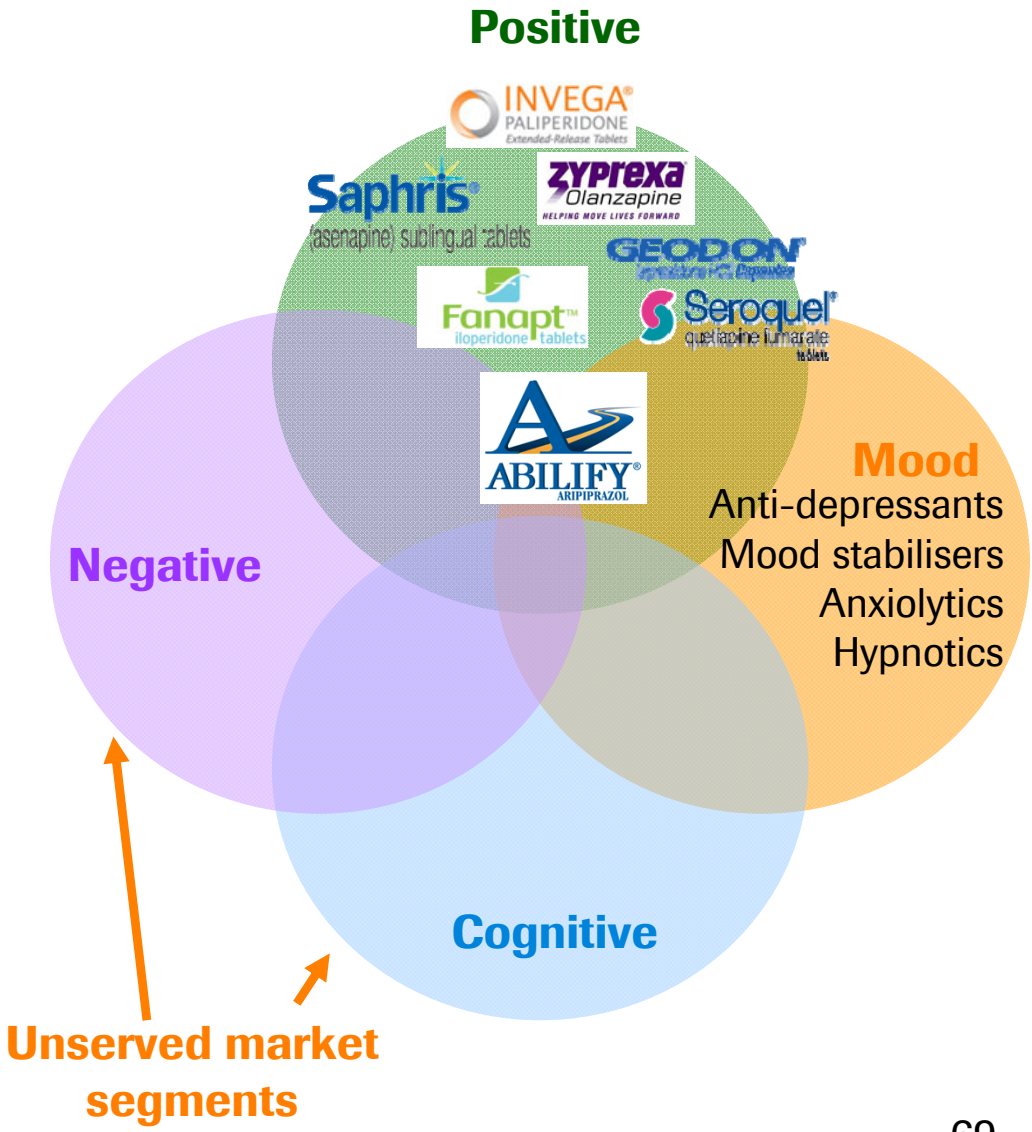
Only positive symptoms addressed by antipsychotics

Dual-dopamine/5HT2 antagonists:

- Poor efficacy in negative and cognitive symptoms
- Low tolerability: EPS (movement disorders), hypotension, obesity, diabetes, QTc prolongations

Better treatment for positive symptoms needed:

- Widespread use of combination therapy (app. 60 % *)
- No safety data for D2 combinations
- No controlled studies with combinations in schizophrenia

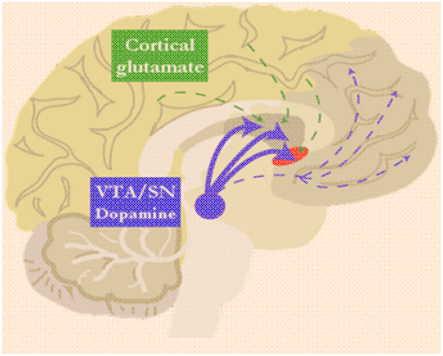


* Faries D, Ascher-Svanum H, Zhu B, Correll C, Kane J. BMC Psychiatry. 2005

Mechanism-based drug discovery for personalised therapy

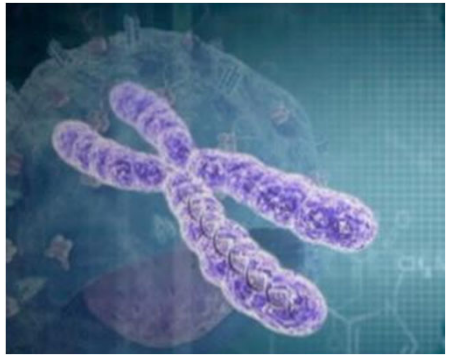
Therapeutic areas of focus

Psychiatry
Schizophrenia and Depression



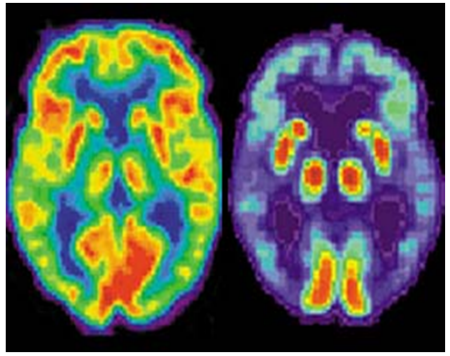
Leading glutamatergic approaches aimed at specific neural circuits

Neurodevelopmental disorders
Fragile X, down syndrome and autism



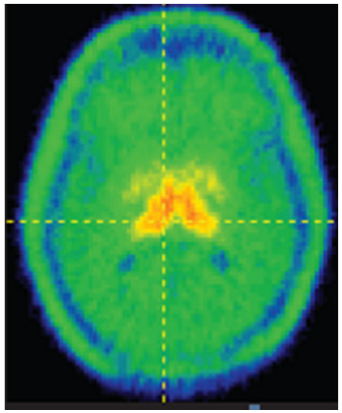
Recent advances in genetics allow to target the disease pathophysiology

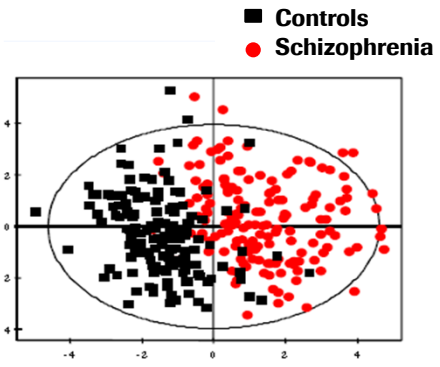
Neurodegeneration
Alzheimer's and Parkinson's

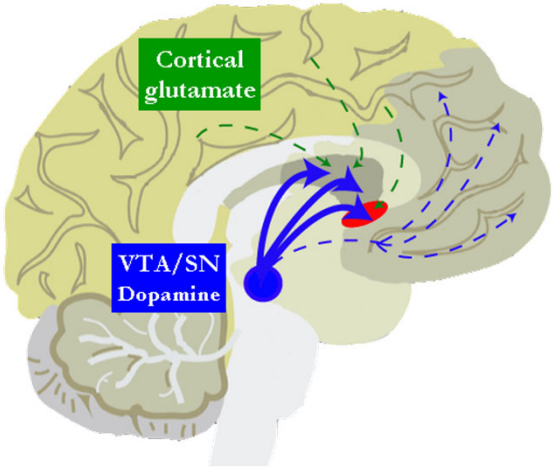


Intervene at an early disease stage, co-develop molecular DX to identify patients

Targeting brain circuits to treat negative and cognitive symptoms

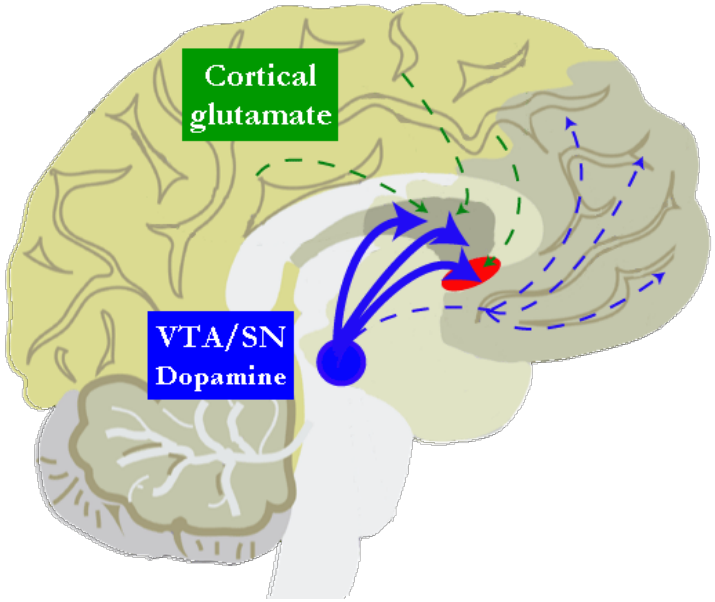






Glutamate hypothesis of schizophrenia:
Reduced signaling through NMDA receptor

- **NMDA blockers (PCP / ketamine)**
  - Induce schizophrenia-like symptoms in normals
  - Aggravate symptoms in schizophrenia
- **NMDA enhancers (glycine / serine / D-cyclo-serine / sarcosine)**
  - Ameliorate symptoms in schizophrenia, in particular negative symptoms
- **Genetics**
  - Most of the identified and confirmed schizophrenia susceptibility genes have an impact on NMDA activity



- **Cortical glutamate input exerts inhibitory control of sub-cortical dopamine through NMDA receptors on GABA neurons.**
- **In schizophrenia deficient inhibitory control due to NMDA hypofunction assumed to result in an abnormal dopamine system**

Schizophrenia and depression: World-leading expertise in targeting the glutamatergic system

Depression

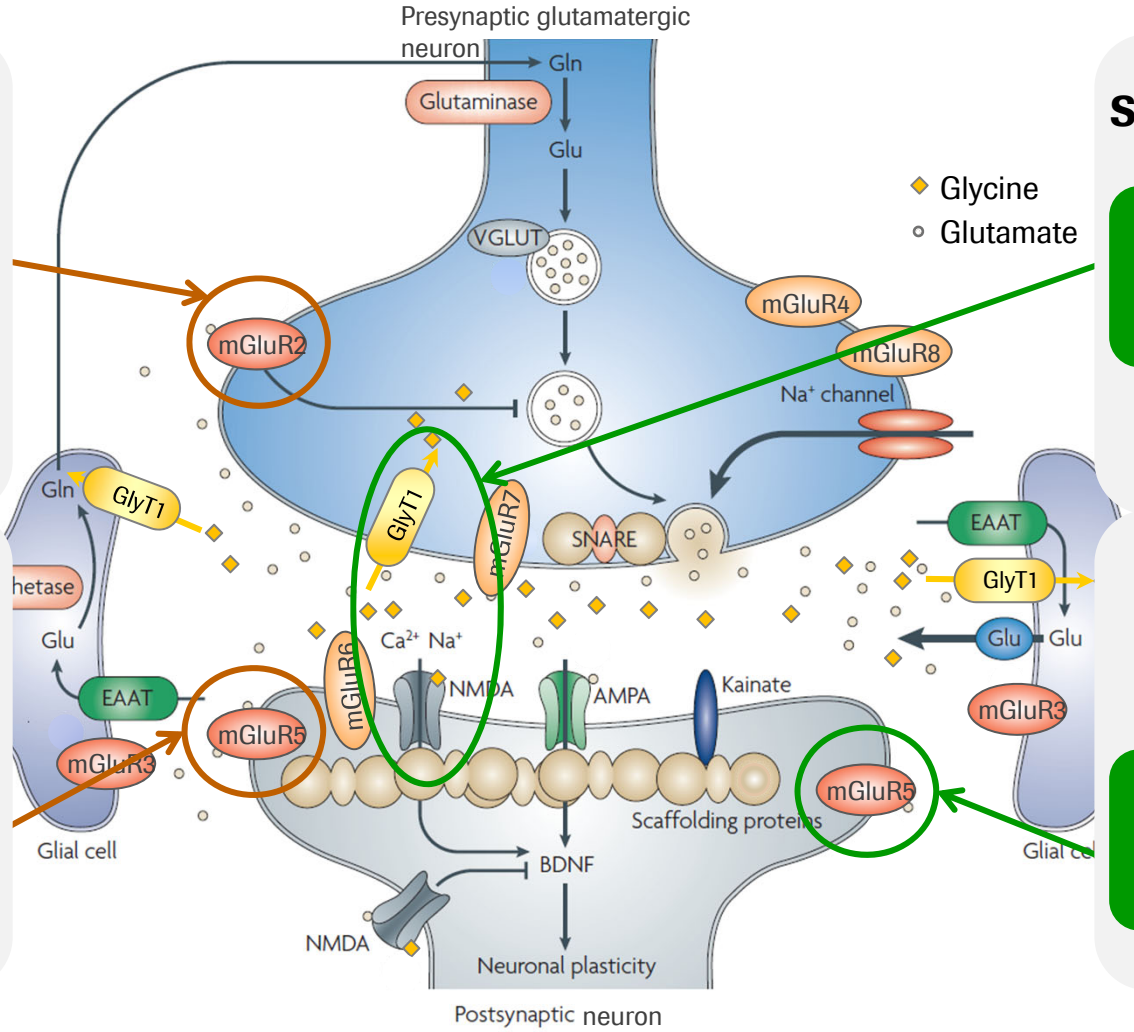
mGluR2 antagonist RG1578 P2

mGluR5 antagonist RG7090 P2

Schizophrenia

bitopertin (GlyT1 inh) P3

mGluR5 PAM preclinical



GlyT-1=type-1 glycine transporter, mGluR2/5=metabotropic glutamate receptor2/5, PAM=positive allosteric modulator
Adapted from Sanacora et al, Nature Reviews Drug Discovery 2008

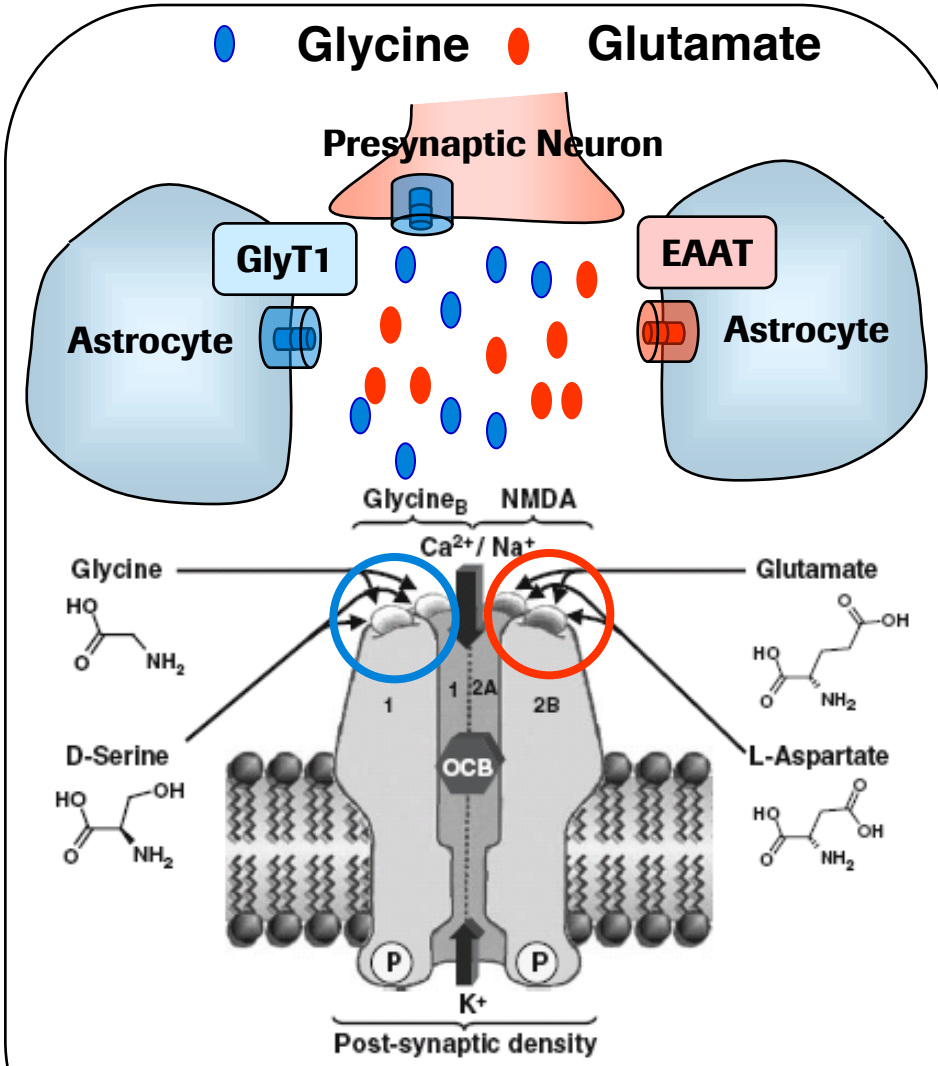
NMDA receptors: modulatory strategies

1. Glycine-site agonists

Chemically intractable target

2. Glycine transporter 1 (GlyT1) inhibitors

Chemically tractable target and reduced potential for excitotoxicity (modulatory site)



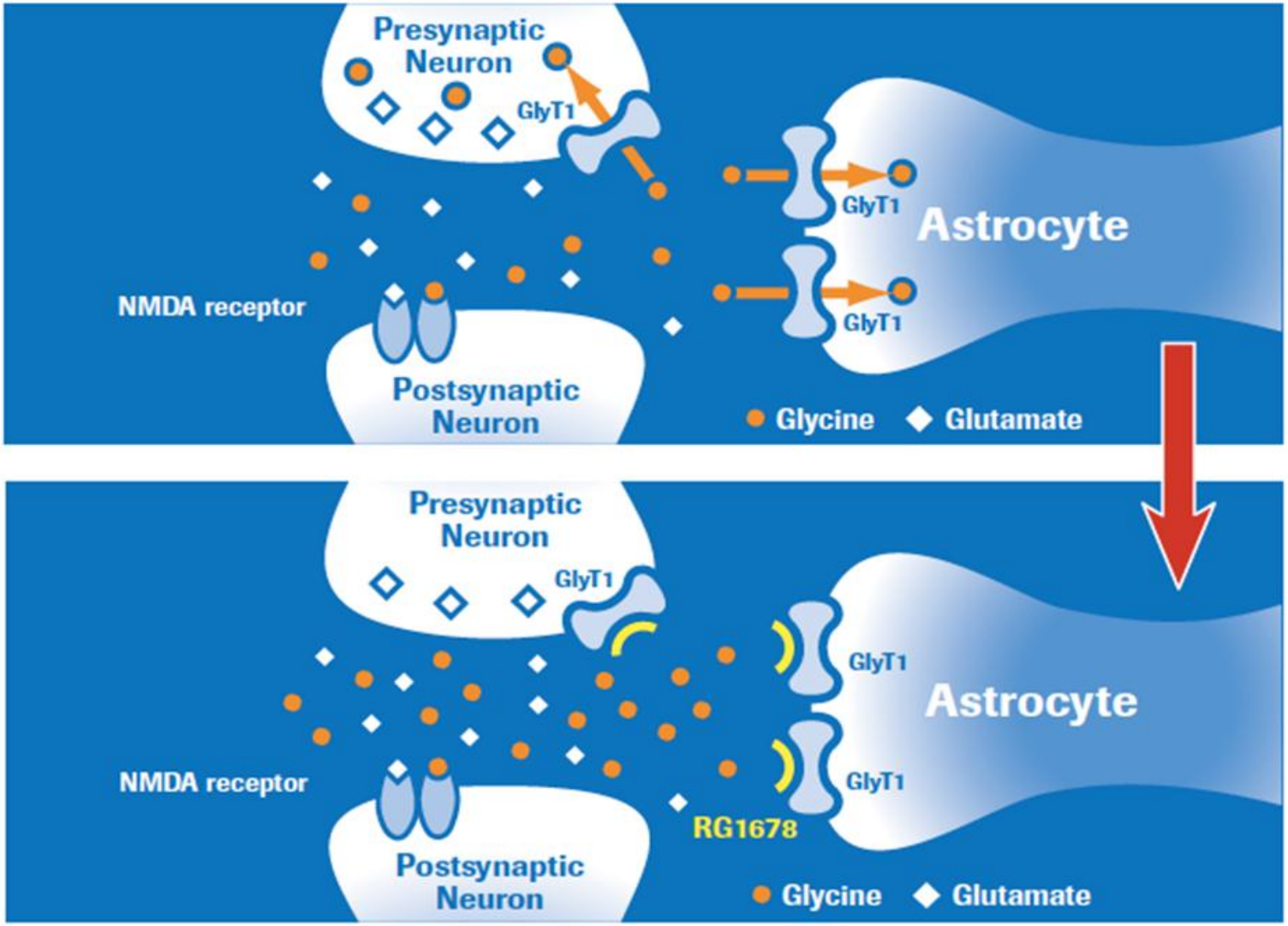
1. Glutamate-site agonists

Potential for excitotoxicity

2. Excitatory amino acid transporter (EAAT) inhibitors

Potential for excitotoxicity

Mechanism of action of a Glycine Reuptake Inhibitor (GRI)



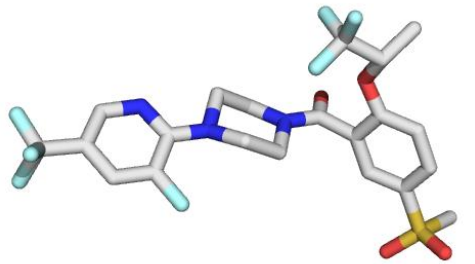
Glycine is a co-agonist at the NMDA receptor

RG1678 is a potent, highly selective inhibitor of the Glycine Transporter (GlyT1)

By increasing intrasynaptic glycine RG1678 enhances NMDA functioning and glutamate transmission

RG1678: preclinical characteristics

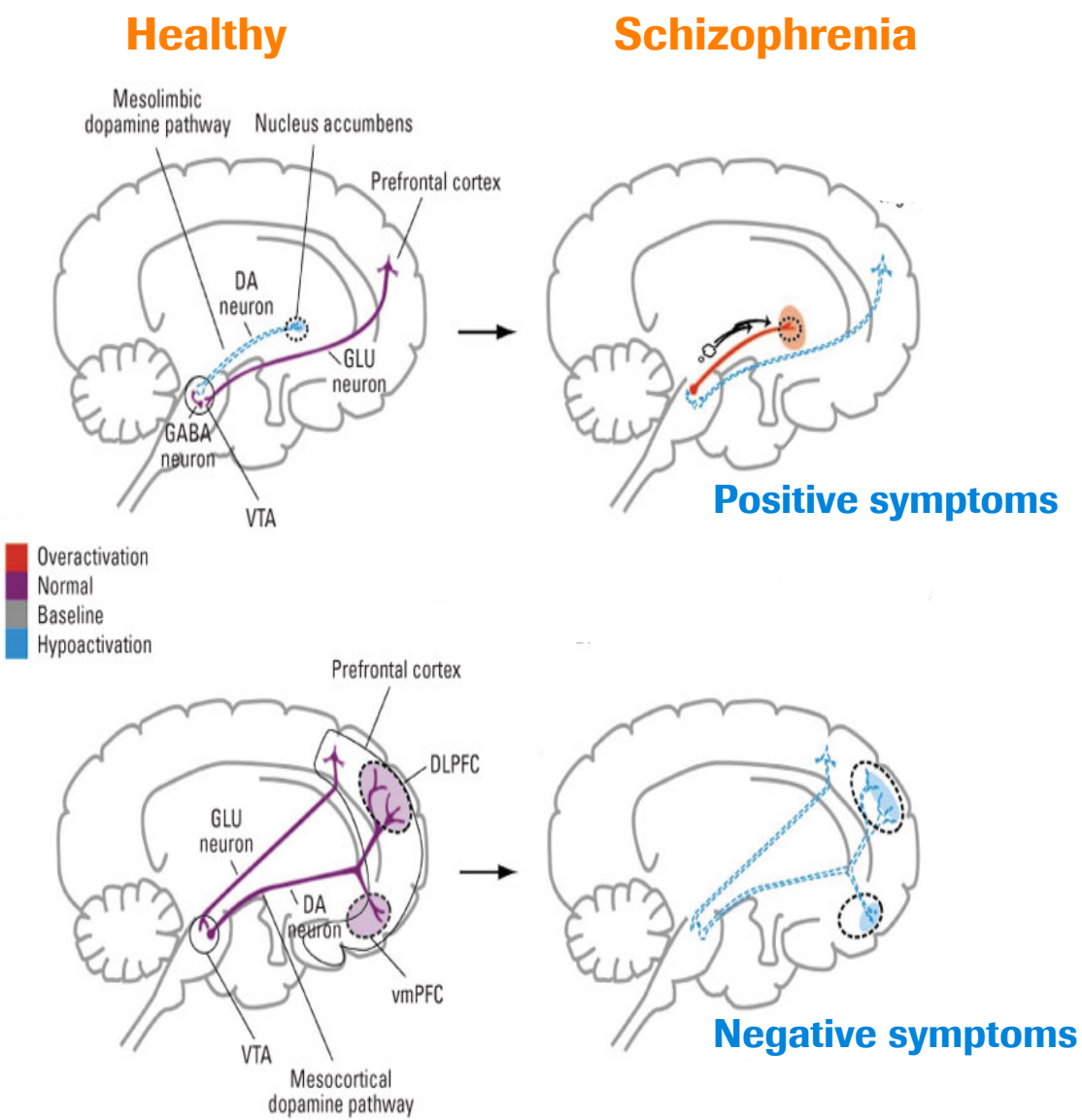
- [4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2 trifluoro-1-methyl-ethoxy)-phenyl]-methanone OR RG1678



- Non-sarcosine derivative
- Potent, non-competitive and selective GlyT1 inhibitor (EC_{50} GlyT1 = 25 nM)
- More than 1000-fold selectivity for human GlyT1 versus GlyT2
- More than 700-fold selectivity versus 86 other binding sites.
- At least 300-fold selectivity for GLyT1 versus 16 other enzymes/ transporters

⇒ See poster 218 Alberati et al, Wednesday

GlyT-1 potentially benefits both positive and negative symptoms



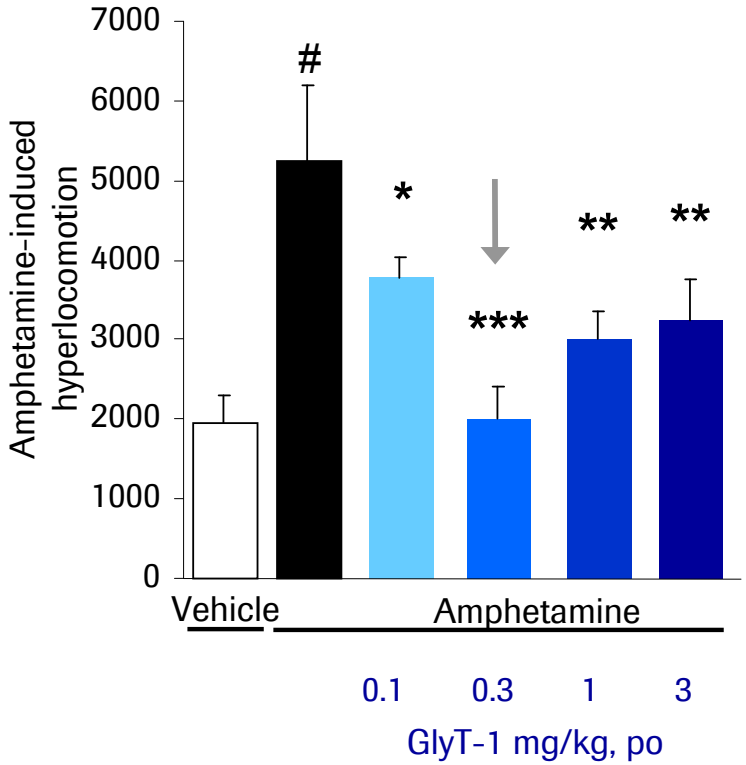
GlyT-1 activates NMDA receptors on GABA and dopaminergic neurons and excite them

- Decreases dopamine levels in the striatum (nucleus accumbens) where it **impacts positive symptoms**
- Increases dopamine levels in the prefrontal cortex where it **benefits negative symptoms**

Modified from: Stahl SM, Stahl's Essential Psychopharmacology, 3rd ed.

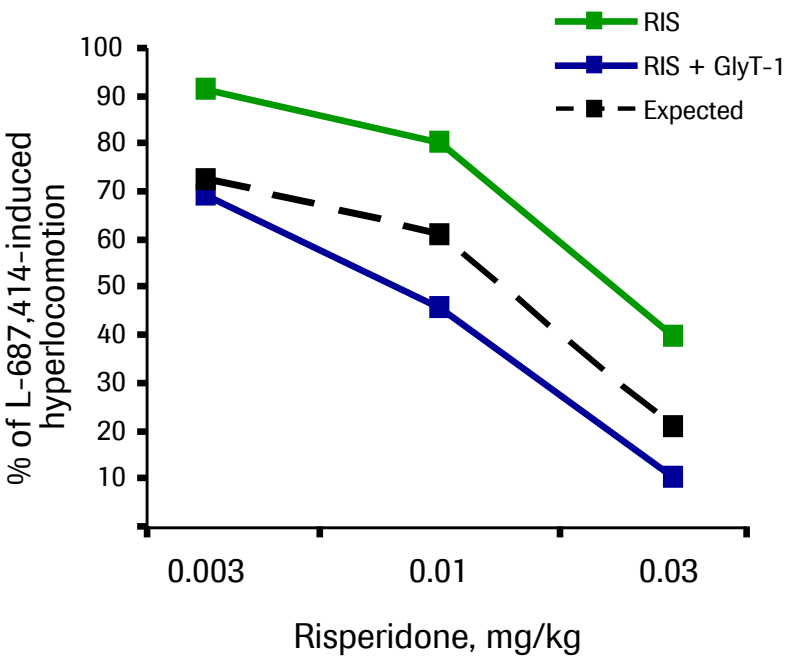
GlyT-1 shows efficacy in pre-clinical models thought to predict efficacy in positive symptoms

GRI modulates dopamine transmission without blocking D2 receptors



Compound	ED90, mg/kg
GlyT-1	**0.3**
Clozapine	5
Olanzapine	0.55
Aripiprazole	0.6
Risperidone	0.2

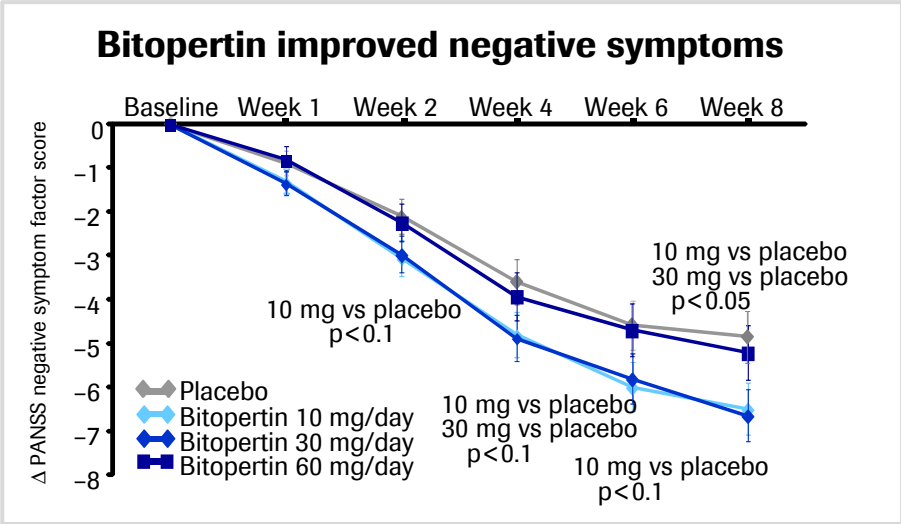
GRI can enhance the efficacy of antipshychotics

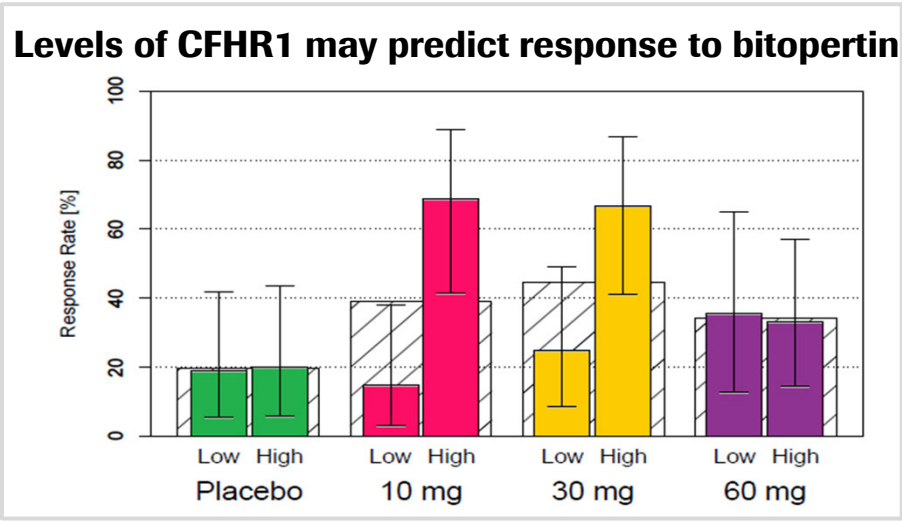


#=p< 0.05 vs Vehicle; *= p< 0.05; **= p< 0.01; ***=p<0.001 vs Amphetamine

Bitopertin phase II proof-of-concept study

Recruited 320 patients in EU/US/JP





Patient population & design

- Predominant negative symptoms, stabilised on antipsychotics (add-on)
- 8-week treatment

Results

- Significant reduction in negative symptoms* (PANSS-NSFS)
- Significantly greater improvement of negative symptoms* (CGI-I)
- Trend in functional improvement (PSP)

Potential biomarker discovered in phase II

- Hypothesis for biomarker validated in phase III
- *In vitro* diagnostic assay in development at Roche Dx

*PP population; PANSS-NSFS=PANSS-negative factor symptome score; CGI-I=Clinical Global Impression-Improvement; PSP=personal and social performance scale; CFHR1=complement factor H-related protein 1