Aberrant cognitive processing in schizophrenia:

Insights from fMRI research

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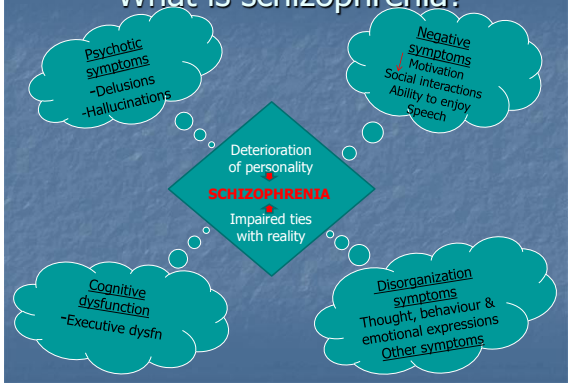
- Life time prevalence of 0.5 to 1.5 % in all known populations
  - The relative numbers affected are the same in all races and all continents
- Origins of schizophrenia related to the speciation event and origins of language
  - (Crow, 1993, Lancet)

- *"The biochemical features of schizophrenia are what made us human"*
  - Horrobin, 1998
- *"We are human…because some members of the human race are schizophrenic"*
  - Horrobin, 1998
- But, at what costs to the sufferers???

What is schizophrenia?



Schizophrenia—History

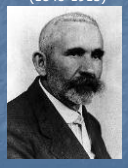
- Egyptian Book of Hearts, part of the Ebers papyrus (2000 BC)
  - Psychological symptoms thought to emanate from heart and uterus, blood vessels, purulent or fecal matter, poisons or demons
- Hindu descriptions—in Atharva Veda (1400 BC)
  - Imbalance between the 5 bhuthas (elements) and 3 doshas (humors)
- Chinese text—Yellow Emperor's Classic of Internal Medicine (1000 BC)
  - Demonic or supernatural possession was implicated to cause psychotic behaviours

Schizophrenia: Biblical description

Lycanthropy: King Nebuchadnezzar, King of Babylon, 6th century B.C.

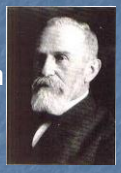
Pioneers of the modern concept

Emil Kraeplin
(1848-1915)



Dementia praecox
(1893)

Schizophrenia
(1911)



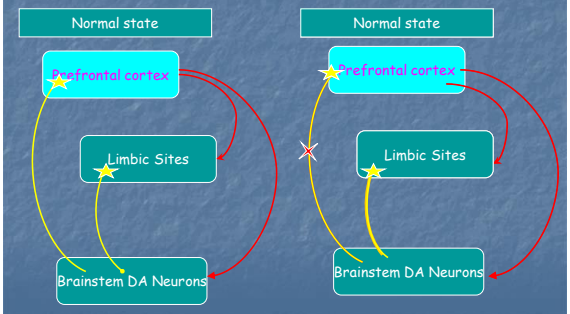
Eugen Bleuler
(1857-1939)

Major advances in the 20th century

Arvid Carlsson
(Nobel Prize in Physiology or Medicine, 2000)

- Dopamine: a neurotransmitter in the brain
- Antipsychotics: exert their action by blocking dopamine receptors
- First-generation antipsychotics
  - Effective against positive symptoms
  - Ineffective for / possibly worsen negative symptoms
- Second generation antipsychotics
  - Serotonin-Dopamine antagonists

DA model of schizophrenia pathophysiology



Pitfalls of the DA model

- No demonstrable intrinsic DA deficits
- "Subcortical hyperdopaminergia co-existing with cortical hypodopaminergia"— paradoxical mechanism
- DA dysfunction, in general, accounts poorly for symptom classes in schizophrenia other than positive symptoms
  - Thus, alternative conceptual models of schizophrenia are required.

Glutamate hypothesis of schizophrenia

Testing the glutamate hypothesis of schizophrenia

Joshua A Gordon

Gordon, 2010, Nature Neuroscience

A study in this issue presents a new mouse model that directly tests the glutamate hypothesis of schizophrenia. The study reports that a decrease in NMDA receptor signaling during a particular developmental window in interneurons can induce cellular and behavioral changes similar to those seen in schizophrenia.

Modeling psychiatric illness in mice is a tricky business, especially for diseases such as schizophrenia, which is marked by disturbances in cognition, social function and reality testing. Schizophrenia disrupts functions at the core of what seems to make us human, and even the notion of producing a model of schizophrenia in an animal as lowly as the mouse can offend our sensibilities. However, evidence indicates that schizophrenia is, at least in part, a genetic disease. Thus, the promise of genetic mouse models to enrich our understanding of the neurobiology of schizophrenia is tremendous, as is the number of mouse models of schizophrenia presented in the literature. Can they all be valid? How is one to evaluate whether any given animal is a good model of schizophrenia? Although some models, such as those with the strongest genetic validity, might more faithfully represent the causality of schizophrenia than others, attempts to define a 'good' model often miss the point. Science uses models not to represent diseases in all their complexity, but rather as tools to test hypotheses. In the current issue, Belforte *et al.*[1] present a mouse model that tests an important hypothesis about a specific aspect of schizophrenia pathogenesis. The study

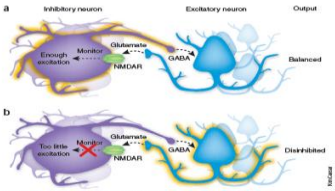
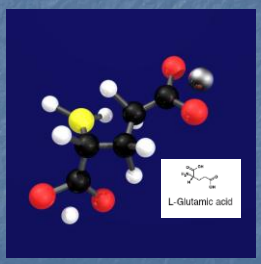


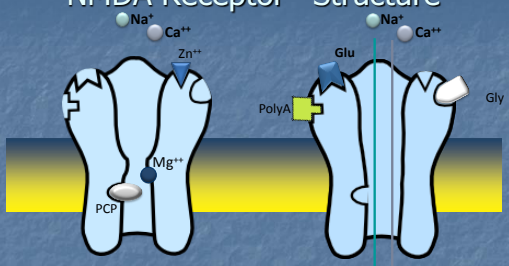
Figure 1 Glutamate hypothesis of schizophrenia pathogenesis. (a) Inhibitory neurons monitor levels of excitatory activity via NMDA receptor (NMDAR) signaling. Normally, the inhibitory neuron maintains sufficient GABA release to balance inhibition with excitation. (b) In the cortex of individuals with schizophrenia, decreased NMDA receptor signaling disrupts this monitoring function, fooling inhibitory neurons into acting as if there is insufficient excitatory activity. The inhibitory neurons downregulate their output, disinhibiting the excitatory neurons.

L-Glutamate

- The most abundant endogenous amino acid excitatory neuro-transmitter
- Plays an important role in functions of learning and memory
- Under abnormal conditions, may behave as neurotoxin



NMDA Receptor—Structure



NMDA receptor modulators

Magnesium	Glycine
Phencyclidine	Polyamines
Zinc	

NMDA hypofunction theory of schizophrenia

- Initial studies conducted with PCP in the early 1960s showed psychiatric symptoms and cognitive deficits that are highly reminiscent of schizophrenia
- Impaired working memory, response inhibition and executive processing
- These findings support the etiological involvement of NMDA dysfunction in the pathophysiology of schizophrenia

Javitt, 2010

NMDA hypofunction theory of schizophrenia

Confirmation using a knock-out mouse model

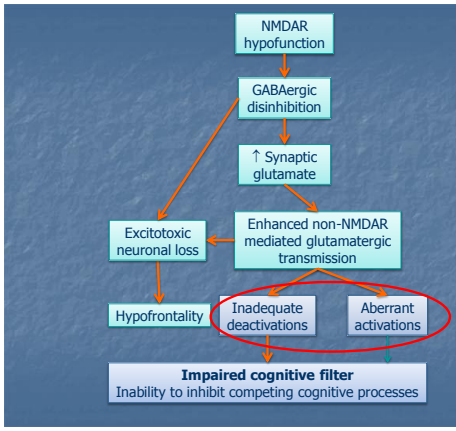
ARTICLES

nature neuroscience

Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes *Belforte et al., 2010, Nature Neuroscience*

Juan E Belforte[1,2,5], Veronika Zsiros[1], Elyse R Sklar[1,5], Zhihong Jiang[1], Gu Yu[3], Yuqing Li[4], Elizabeth M Quinlan[3] & Kazu Nakazawa[1]

Cortical GABAergic dysfunction may underlie the pathophysiology of psychiatric disorders, including schizophrenia. Here, we characterized a mouse strain in which the essential NR1 subunit of the NMDA receptor (NMDAR) was selectively eliminated in 40–50% of cortical and hippocampal interneurons in early postnatal development. Consistent with the NMDAR hypofunction theory of schizophrenia, distinct schizophrenia-related symptoms emerged after adolescence, including novelty-induced hyperlocomotion, mating and nest-building deficits, as well as anhedonia-like and anxiety-like behaviors. Many of these behaviors were exacerbated by social isolation stress. Social memory, spatial working memory and prepulse inhibition were also impaired. Reduced expression of glutamic acid decarboxylase 67 and parvalbumin was accompanied by disinhibition of cortical excitatory neurons and reduced neuronal synchrony. Postadolescent deletion of NR1 did not result in such abnormalities. These findings suggest that early postnatal inhibition of NMDAR activity in corticolimbic GABAergic interneurons contributes to the pathophysiology of schizophrenia-related disorders.

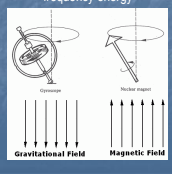


Functional Magnetic Resonance Imaging (fMRI)

Nuclear Magnetic Resonance (NMR)

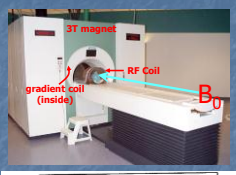
- Atoms with odd number of protons/neutrons spin in a magnetic field
- NMR
  - Nuclear: properties of nuclei of atoms
  - Magnetic: magnetic field required
  - Resonance: interaction between magnetic field and radio frequency

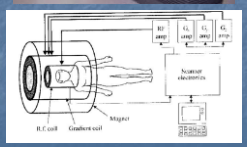
1946: Block and Purcell
Atomic nuclei absorb and re-emit radio frequency energy



Magnetic Resonance Imaging

- Very strong magnetic field (B_0)=3 Tesla
- Earth's magnetic field: 0.5 Gauss
- 1 Tesla=10,000 Gauss
- 3 Tesla = 3 x 10,000 ÷ 0.5 = 60,000 x Earth's magnetic field



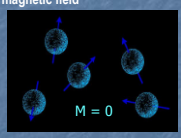


Source: Robarts Research Institute 3T Joe Gati

^1H aligns with B_0

Protons are abundant: high concentration in human body
have high sensitivity: yields large signals

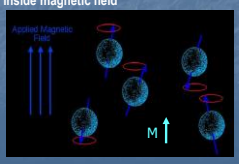
Outside magnetic field



- randomly oriented

Longitudinal magnetization

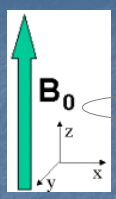
Inside magnetic field

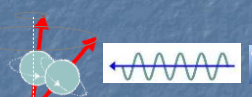


- spins tend to align parallel or anti-parallel to B_0
- net magnetization (M) along B_0
- spins precess with random phase
- no net magnetization in transverse plane
- only 0.0003% of protons/T align with field

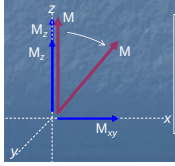
Source: Mark Cohen's web slides
Source: Robert Cox's web slides

NMR





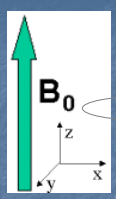
Excitation

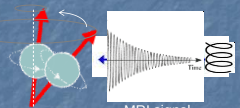


Excitation at resonance frequency

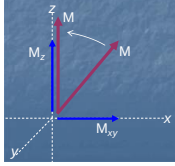
- increased angle of precession axis (tilts towards XY plane), becomes more synchronized
- Reduces longitudinal magnetization (along Z axis)
- increases transverse magnetization (along XY plane)

NMR





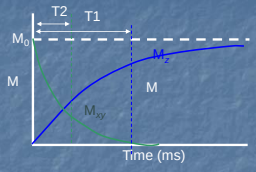
Relaxation

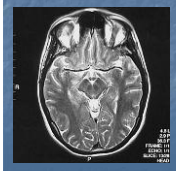


- Dephasing of spins – rapid
- Transverse relaxation – T2 relaxation
- ↓overall magnetization vector in the XY plane

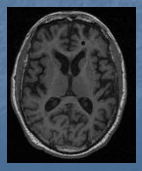
- Return of spin axis to vertical
- Longitudinal relaxation – T1 relaxation
- ↑overall magnetization vector in the Z direction

Contrast in MRI



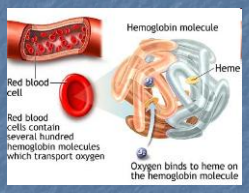


- RF excitation and reading sequences are referred to as "MRI protocols"
- MRI protocols can be tweaked to bias towards
  T1 relaxation predominance or T2 relaxation predominance
  (T1 weighted images or T2 weighted images)



BOLD: basis

- Inhomogeneities in magnetic field can result from changes in blood O_2 level
- DeoxyHb: paramagnetic (weakly magnetic)
- OxyHb: diamagnetic (not magnetic or weakly anti-magnetic)



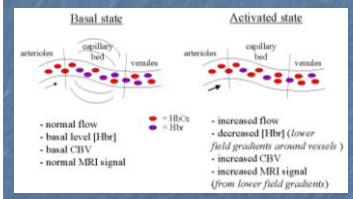
Hb + O_2 ↔ HbO_2
(deoxyHb) (oxyHb)

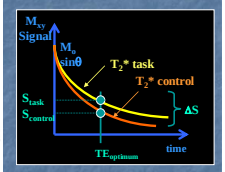
Ogawa

BOLD signal

1992: Ogawa and colleagues - first functional images using BOLD signal

→neural activity → ↑ blood flow → ↑ oxyhemoglobin → ↑ T2* → ↑ MR signal





Source: Brief Introduction to fMRI by Irene Tracey

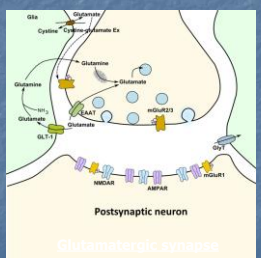
Source: Jorge Jovicich

BOLD: basis
Neuro-vasuclar coupling

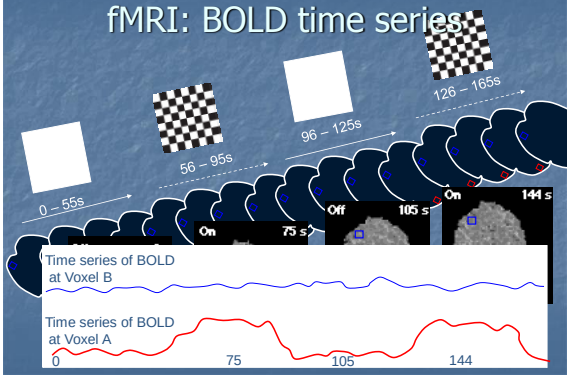
- Vascular density proportional to synaptic density

BOLD: basis

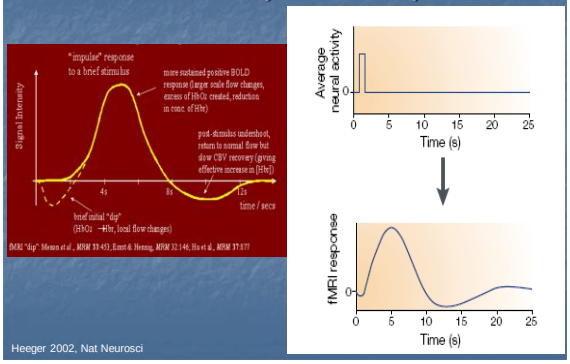
- Most energy is spent on glutamate re-uptake



fMRI: BOLD time series



fMRI: hemodynamic response



Heeger 2002, Nat Neurosci

Semantic word generation

- *The best candidate cognitive endophenotype of schizophrenia*
  - Szoke et al., 2008
- Semantic verbal fluency has higher discriminatory power than phonological verbal fluency
  - to differentiate schizophrenia *v.* healthy subjects

Word generation vs. word repetition

- Experimental condition
  - Overt, paced, visually-cued, *semantic category word generation* task with clustered volume acquisition
  - Categories: animals, vegetables, birds, fruits, flowers, trees
- Baseline condition
  - Overt, paced, visually-cued, *word repetition* task with clustered volume acquisition
  - Repeat the word 'pass'

Verbal fluency fMRI task design

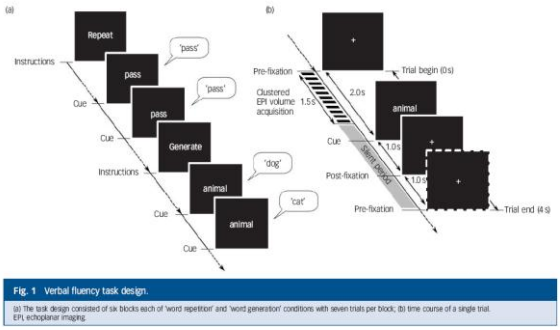
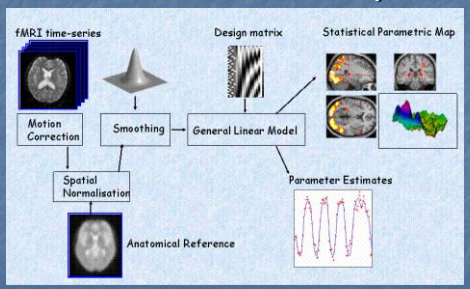


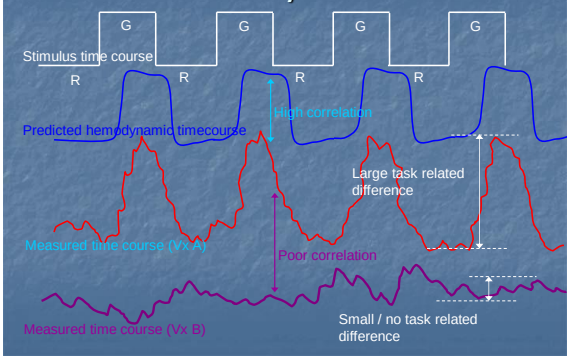
Fig. 1 Verbal fluency task design.

(a) The task design consisted of six blocks each of 'word repetition' and 'word generation' conditions with seven trials per block; (b) time course of a single trial. EPI, echoplanar imaging.

Overview of SPM analysis

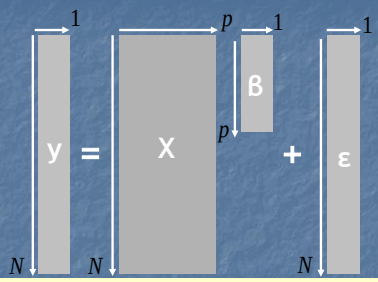


fMRI analysis: GLM



The General Linear Model

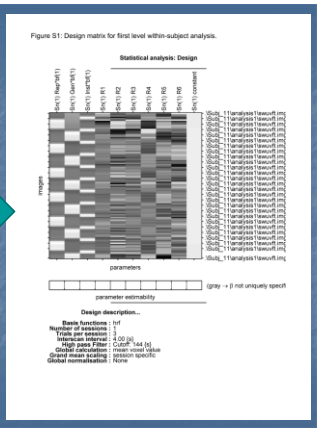
$y = X\beta + \varepsilon$



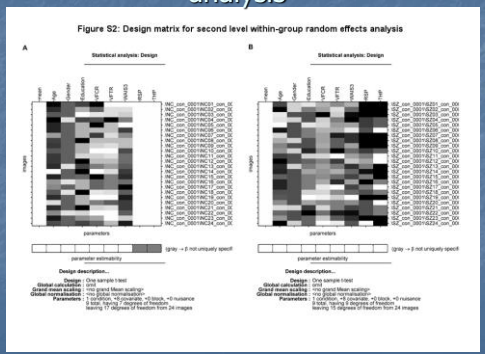
Observed data	=	Predictors	*	Parameters	+	Error
eg. Image intensities		Also called the design matrix.		How much each predictor contributes to the observed data		Variance in the data not explained by the model

Design matrix for first-level within-subject analysis

John et al., British J Psychiatry, 2011



Design matrices for second-level analysis



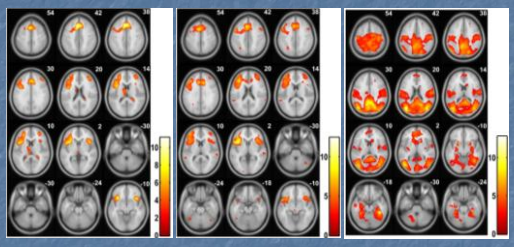
Choosing a statistical threshold

- Uncorrected threshold of p < .001
- Familywise Error (FWE)
- Bonferroni correction
  - E.g.: .05/100,000 = .0000005
- False Discovery Rate (FDR)
  - Adjusts the criterion used based on the amount of signal present in the data
- Reduce the number of comparisons
  - E.g.: Instead of examining the entire brain, examine just a small region

  IMPORTANCE of taking into account the multiple comparisons across voxels BUT also the multiple comparisons across contrasts (i.e., the number of contrasts tested)

40

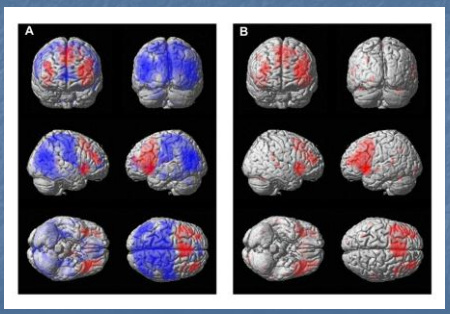
Aberrant activations and deactivations during semantic word generation



BOLD activations in Healthy Controls N=24	BOLD activations in Schizophrenia subjects N=24	BOLD deactivations in Healthy Subjects N=24

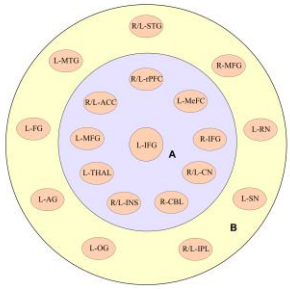
John et al 2011, *British Journal of Psychiatry*

Healthy vs. Schizophrenia subjects



John et al 2011, *British Journal of Psychiatry*

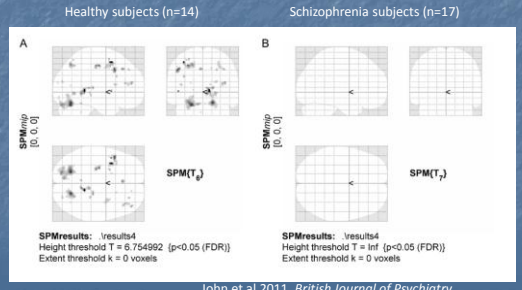
Brain regions underlying semantic word generation



Core / essential brain regions and cognitive/ associated processes underlying overt, semantic category word generation

1. L-IFG - Semantic search, word retrieval and selection
2. R-IFG - Suppression of inappropriate responses
3. ACC - Control functions (e.g., selective attention; facilitation and suppression of within-category responses; task adherence; monitoring of conflicting responses and errors; recruiting essential brain regions)
4. MeFC - Higher-order motor control processes such as setting up goals or internal selection of individual actions (pre-SMA); motor preparation for oral expression (SMA)
5. rPFC - Executive control and maintainence of internally generated cognitive operations in word generation
6. INS - Sensory, motor and mental control of selection and suppression mechanisms
7. L-MFG - Updating generated words in verbal working memory
8. THAL/CN - Speech production and articulation; generation of mental images and visual details (THAL)
10. R-CBL - Sustained search for serial word generation

Regression analysis— lat_{gen}-lat_{rep} on deactivation maps

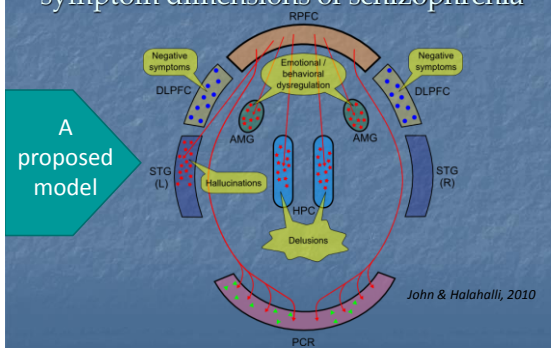


John et al 2011, *British Journal of Psychiatry*

Implications for schizophrenia pathophysiology

- Inefficient activations and deficient deactivations
  - ? the core neurophysiological disturbance in schizophrenia
  - deficient deactivations--? neurophysiological signature of the 'defective cognitive filter' in schizophrenia
- ? Aberrant Glu-signalling underlying the above aberrant neurophysiology

Aberrations in Glu signaling and symptom dimensions of schizophrenia



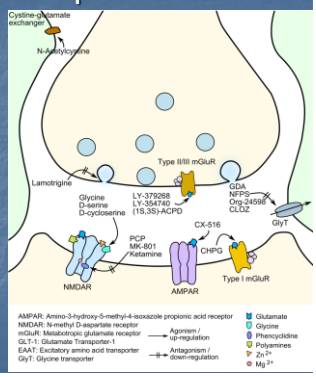
John & Halahalli, 2010

Clinical implications

- Provides a more comprehensive and ?accurate model of schizophrenia pathophysiology
- Potential to guide future drug development

Therapeutic implications

1. NMDA receptor
   - Gly site full agonists
   - Gly site partial agonists
   - Gly/D-Ser transport inhibitors
2. AMPA receptor
   - AMPAkines
3. Metabotropic receptors
   - Gr I mGluR modulators
   - Gr II mGluR modulators
4. Ion-channel blockers/ Glu release inhibitors
   - Lamotrigine
   - Riluzole



Take home points!!

- Schizophrenia—a heterogeneous disorder
- Aberrant cognitive processing
- Probably mediated by aberrant glutamatergic signaling with involvement of other neurotransmitters
- NMDA hypofunction results in excessive activations and deficient deactivations

Take home points!!

- fMRI research provides *in vivo* evidence for excessive activations and deficient deactivations in schizophrenia
- The above findings constitute supportive evidence for the glutamate-centric hypothesis of schizophrenia
- Implications for schizophrenia pathophysiology and therapeutics

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