



Abnormalities in the glutamate synapse in schizophrenia

Evidence from postmortem studies

Lars V. Kristiansen, M.Sc., Ph.D.

Research Laboratory for Stereology and Neuroscience

Bispebjerg University Hospital

Copenhagen, Denmark

E-mail: lkri0062@bbh.regionh.dk



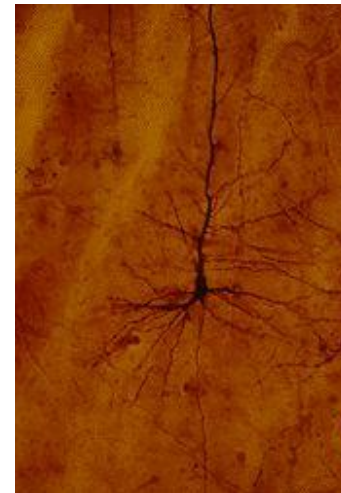
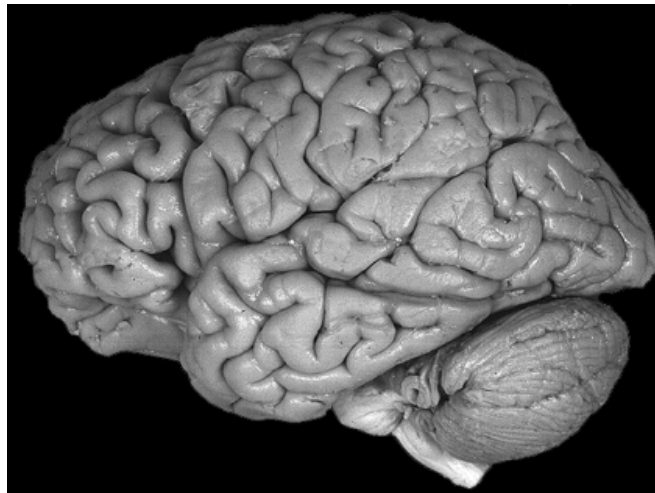
The Bronx VA brain bank

- elderly patients with length history of schizophrenia
- matched elderly comparison group
- most subjects were living in nursing home at time of death
- no neuropathological evidence for neurodegenerative diseases
- stabilized on typical antipsychotics
- no drugs of abuse
- predominantly show negative and cognitive symptoms

What is schizophrenia?



- Defined as *dementia praecox* by Emil Kraepelin (1896) and subsequently renamed *schizophrenia* by Eugen Bleuler (student of Kraepelin).
- “Schizophrenia is a chronic, deteriorating psychotic disorder characterized by rapid cognitive disintegration that affects about 1 percent of the population age 18 and older in a given year”.
- “*Insanity, then, is inordinate or irregular, or impaired action of the mind, of the instincts, sentiments, intellectual, or perceptive powers, depending upon and produced by an organic change in the brain*”. (Dr. W.A.F. Browne (1805–1885) , Director of Crichton Royal lunatic asylum, Dumfries)



“...this noble and enigmatic
cell of thought”
Santiago Ramon y Cajal



Genetic vulnerability

- number of shared genes important risk factor
- Several SNPs found to be associated with increased risk
- Up to 80% risk estimated to be associated with heritability



Developmental insult

- O₂ supply during delivery
- virus/ infection during pregnancy
- season and place of birth
- maternal stress during pregnancy



Neurotransmitter systems

- Dopamine
- Glutamate
- 5-HT
- GABA

Relationship to patient	Risk
General Population	1%
Aunts, Uncles & Cousins	2%
Nieces, Nephews	4%
Grandchildren	5%
Half Siblings	6%
Parents	10%
Siblings	10%
Children	13%
Fraternal Twins	17%
Identical Twins	40-50%

From: www.psychiatric-disorders.com



ØPositive symptoms

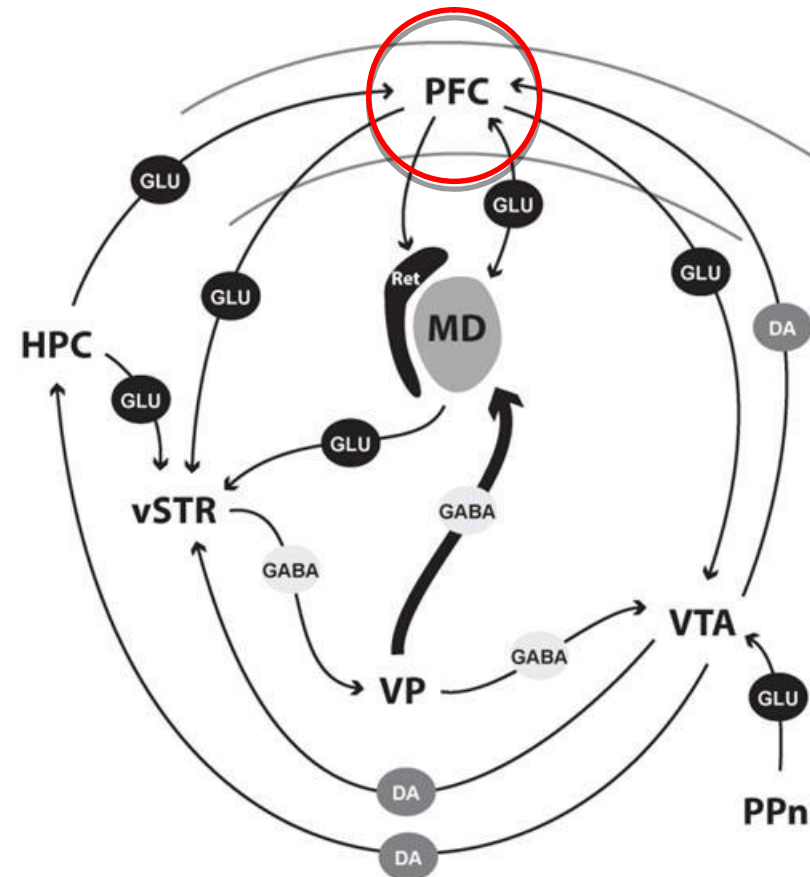
- hallucinations (visual, auditory, gustatory, olfactory, tactile)
- delusions (false perceptions)
- disorganized/ incoherent speech/thinking
- catatonic behavior (stupor and rigidity of limbs)

ØNegative symptoms

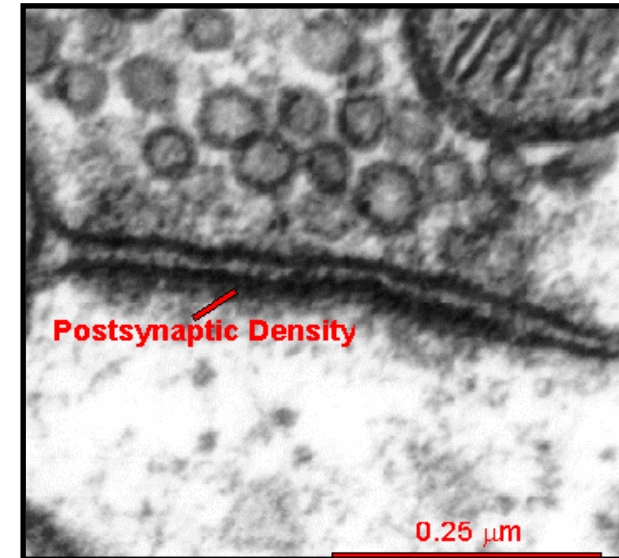
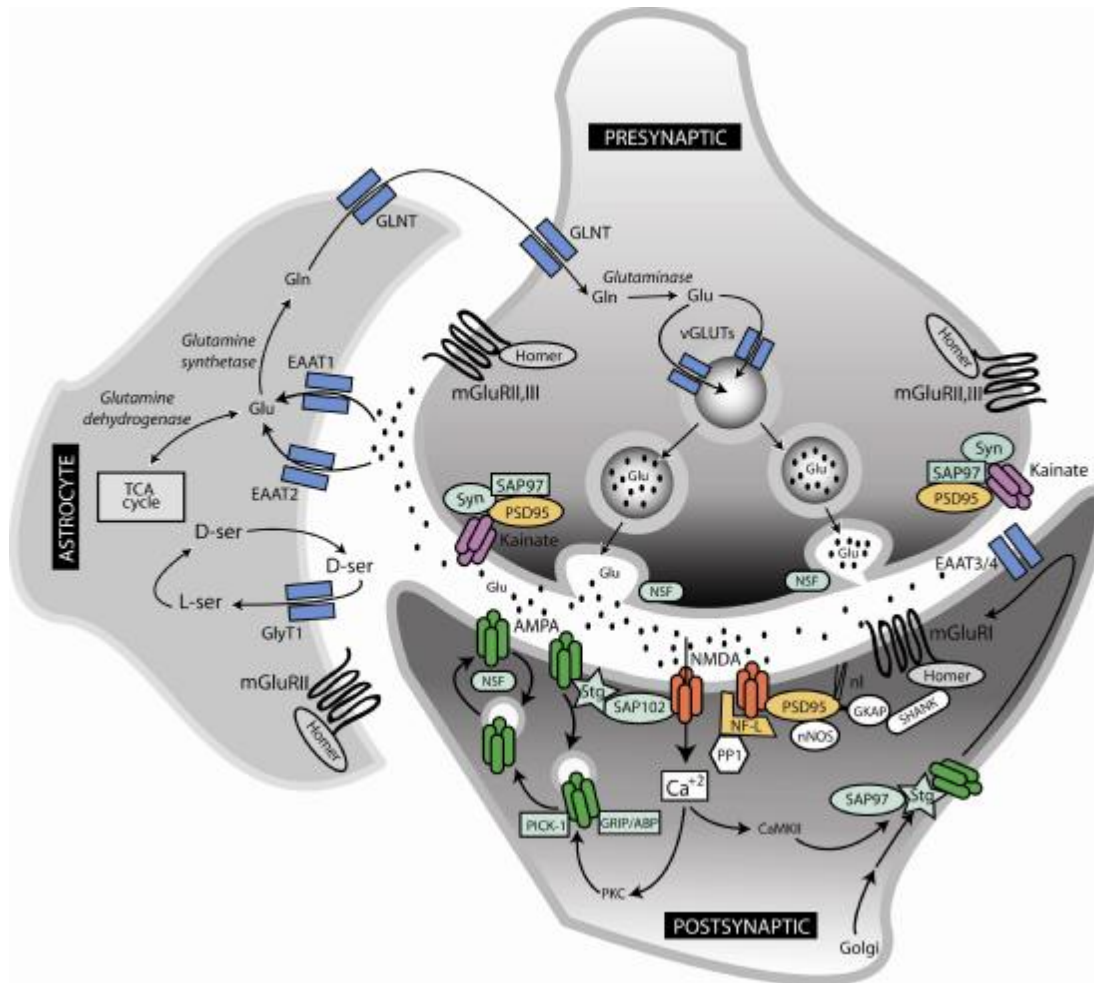
- affective flattening (lack of emotion, apathy)
- low energy (sleeps more than normal)
- alogia (poverty or complete lack of speech)
- avolition (lack of desire, drive, or motivation to pursue meaningful goals)
- lack of social skills
- social isolation and personal neglect

ØCognitive symptoms

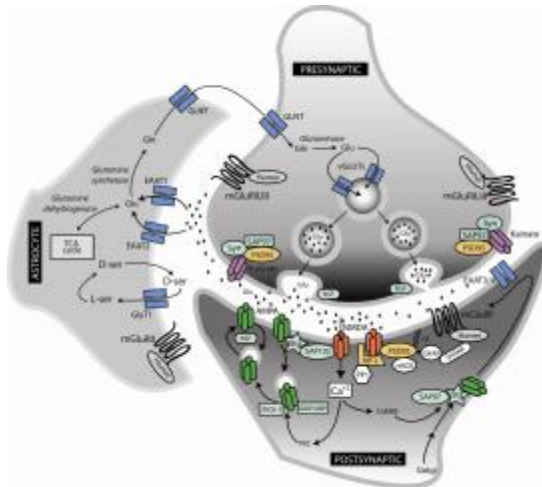
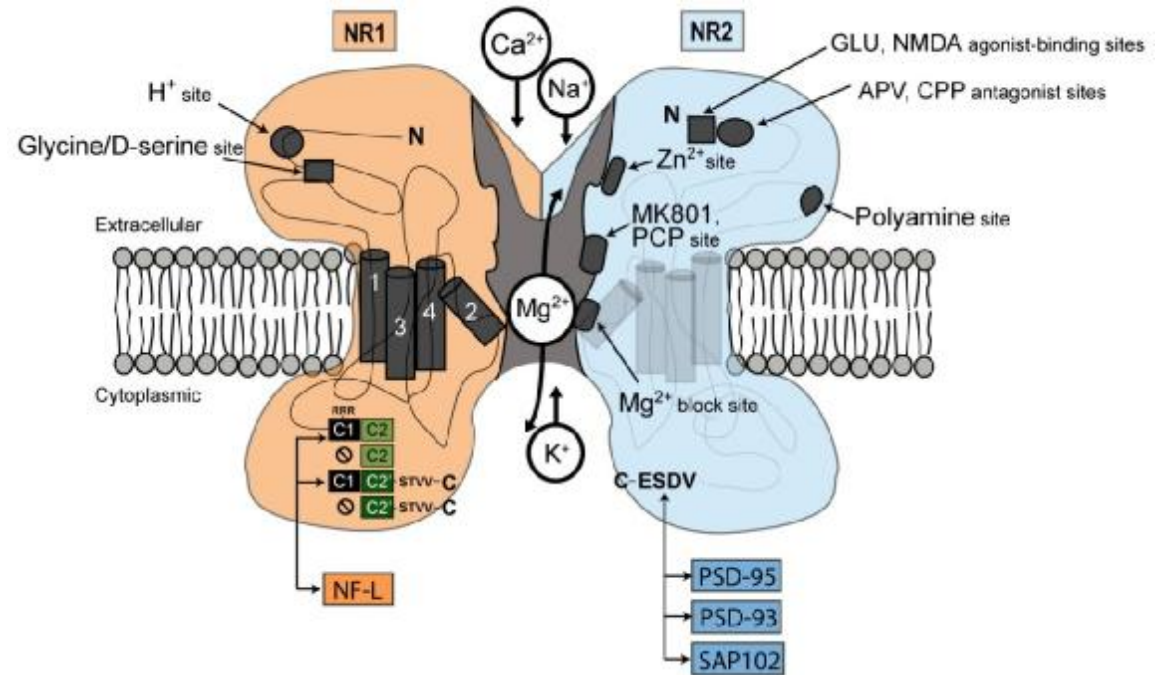
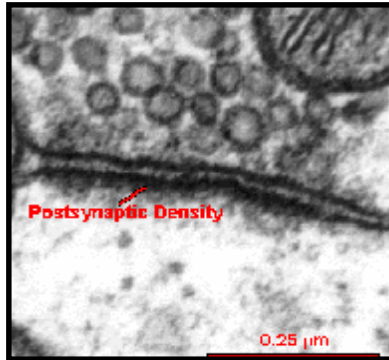
- disorganized thinking and expression of thoughts
- slow thinking
- poor concentration
- poor memory
- attention deficit
- difficulty integrating thoughts, feelings and behavior (executive dysfunction)



The glutamate synapse



The glutamate synapse



IONOTROPIC			
RECEPTOR SUBUNITS	NMDA	AMPA	Kainate
	NR1 NR2A-D NR3A,B	GluR1 GluR2 GluR3 GluR4	GluR5 GluR6 GluR7 KA1 KA2
BINDING SITES	Glutamate Glycine/D-serine Polyamines PCP/MK801 Proton Zinc ion	AMPA	Kainate



- antagonists of the NMDA glutamate receptor induce schizophreniform psychosis in healthy individuals and exacerbate symptoms in patients (Krystal (1994), Lahti (2001))
- Altered CSF levels of glutamate and other relevant metabolites in patients with schizophrenia (glutamine, glutathione etc)
- Genetic evidence (SNPs etc. in “glutamate genes”)
- Efficacy of glutamate modulating compounds in the treatment of patients with schizophrenia (mGluR_{2/3} agonists, D-serine, EAAT2 blockers, GlyT antagonists, AMPAkinases, etc)
- Animal models (neurodevelopmental lesion models (surgical/pharmacological), acute, genetic (knock-out/ overexpression models)
- Human postmortem studies.
 - Expression of transporters and interacting proteins (EAATs, EAATips, GS, vGluTs, and xCT)
 - Expression of receptors (AMPA, mGluRs, NMDA) and interacting PSD proteins
 - Ultrastructure and synaptic organization of the glutamate postsynaptic density and dendritic tree (pyramidal neurons in PFC)



Expression of NMDA receptor subunits in schizophrenia

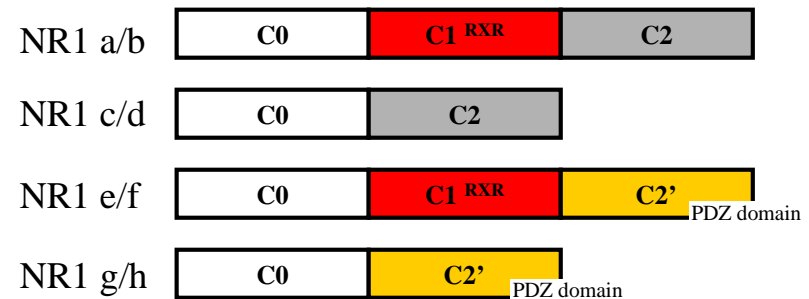
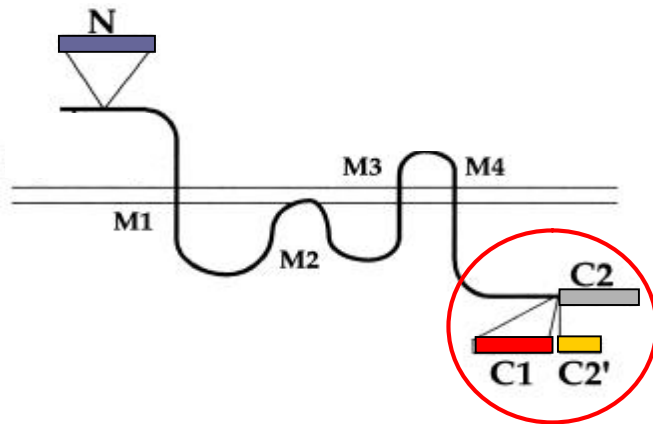
Brain Region	Subarea	NR1	NR2A	NR2B	NR2C	NR2D	NR3A	References	NF-L	PSD-95	PSD-93	SAP102
Cortex	Frontal pole	■ - ■	■ -	■ -	↓	↑		42, 48		■ -		
	DLPFC	↑ ↓ ■	■ - ■	■ - ■	■ -	■ -	↑	43, 45, 47, 49	↑ ↓	↓ ■ -	■ - ■	■ - ■
	Anterior Cingulate	↑ *	■ -	■ -	■ -	■ -		49	■ - ■	↑ ↓	↑ ↓	■ - ■
	Temporal	■ ↑ ↓ ■	■	■	■	■	■	44, 46, 47, 50				
	Parietal lobe	■	■	■	■	■		42				
	Occipital	↑	↑	■				43		↑ ■	■	■
Hippocampus	Hippocampus	■ ↓ ■	■ - ■	↑ ■	■	■		48, 61, 62, 63	■	■ - ■ ↓	■ - ■	■ ↓
Thalamus	Thalamus	↓ ■	■	↓ ↑	↓ ■	■		64, 65	↓ ↑	↓ ↑	■	↓ ↑
	Dorsomedial	■	■	↑				66	■	↑		■
	Ventral	■	■	■				66	■	■		■
Basal Ganglia	Striatum	■	■	■	■	■		69	■	↓	■	↓
	Accumbens									↑		
	Substantia nigra	↑	■	■	■	■	■	71	■	■	■	■

■ Transcript study ■ Protein study

Splicing of the NR1 subunit

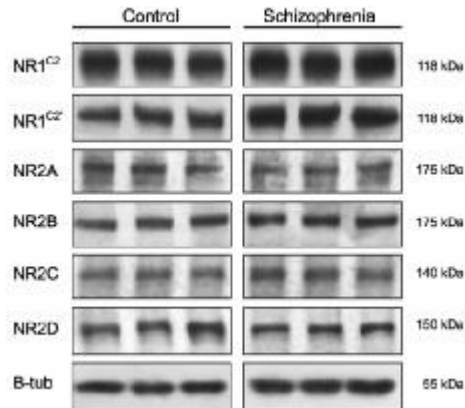
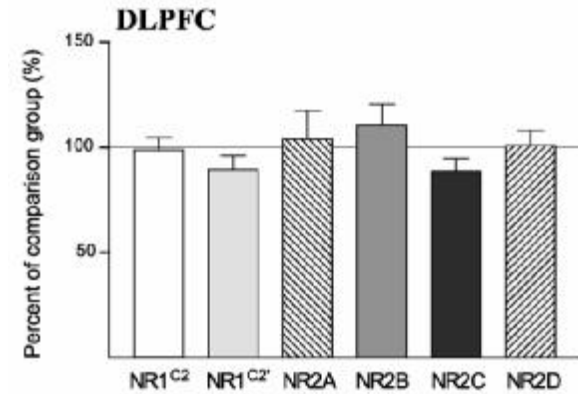
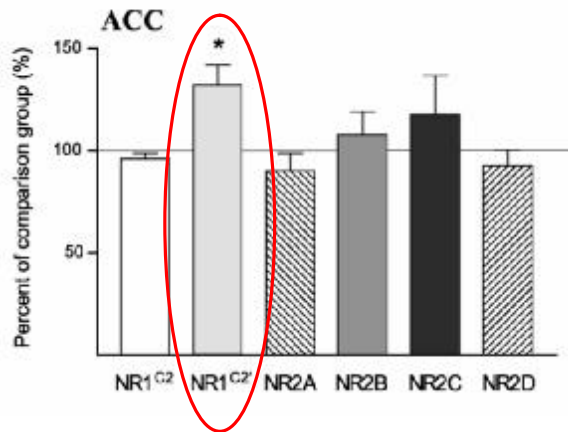


N-terminal exon regulates agonist binding (Durand et al 1993).



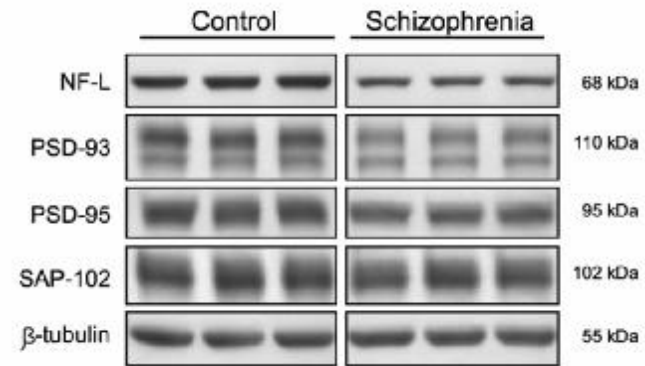
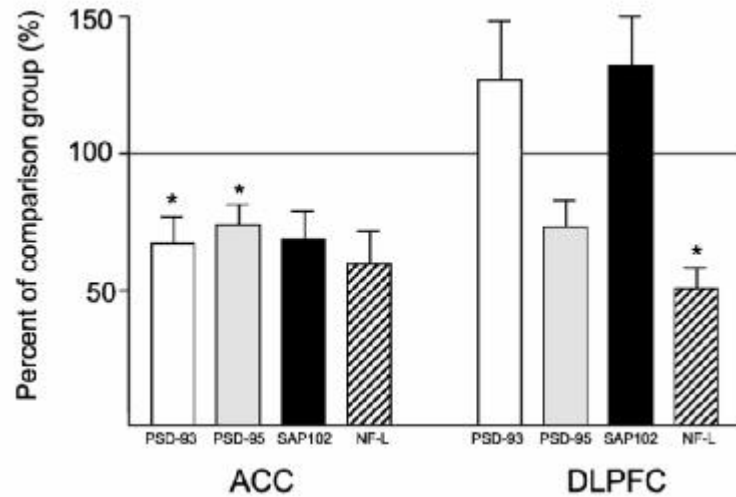
- Activity dependent **alternative splicing** of the C2/C2' domains regulates ER exit and trafficking. C2' is associated with increased/faster synaptic targeting of newly synthesized NMDA receptor (Mu et al 2003).
- NF-L binds only to C1 containing receptors, stabilizing the receptor in the cell membrane (Ratnam et al 2005). The C1 exon contains the **S896/S897** amino acids that are phosphorylated by PKC/PKA (Scott et al, 2003, Tingley et al. 1997).

NMDAR subunits in schizophrenia



An increase in C2' expression is consistent with altered synthesis/splicing/assembly of the NMDA receptor in ACC resulting in faster forward trafficking of the NMDA receptor in schizophrenia.

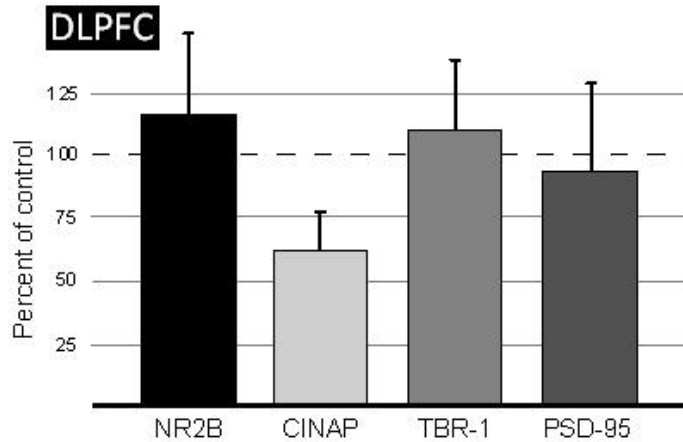
Expression of NMDA binding PSD proteins



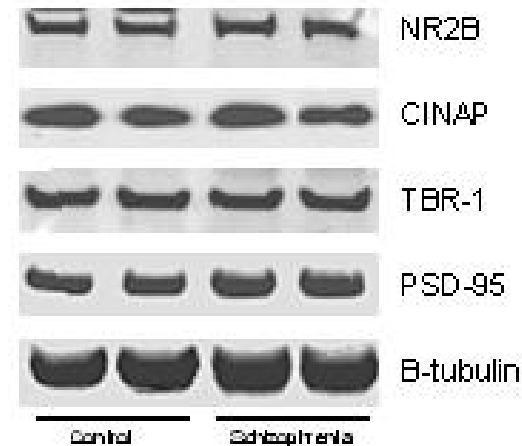
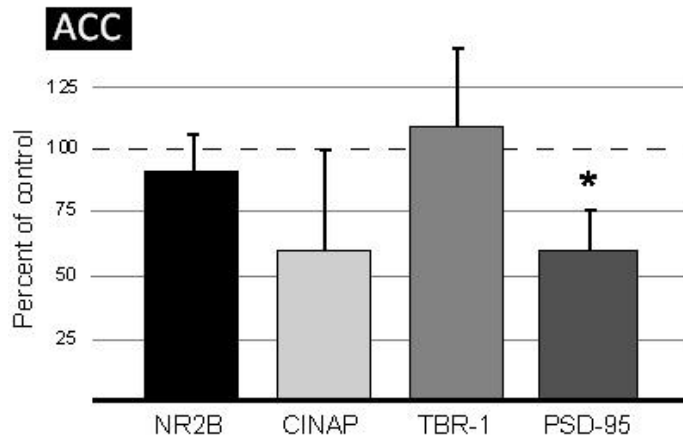
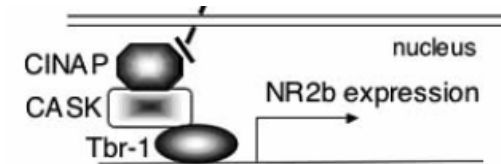
	ACC		DLPFC	
	mRNA	Protein	mRNA	Protein
PSD-93	↑	↓	NC	NC
PSD-95	↑	↓	NC	NC
SAP-102	NC	NC	NC	NC
NF-L	NC	NC	↑	↓

Could altered neuronal processing in schizophrenia include synthesis and dendritic trafficking?

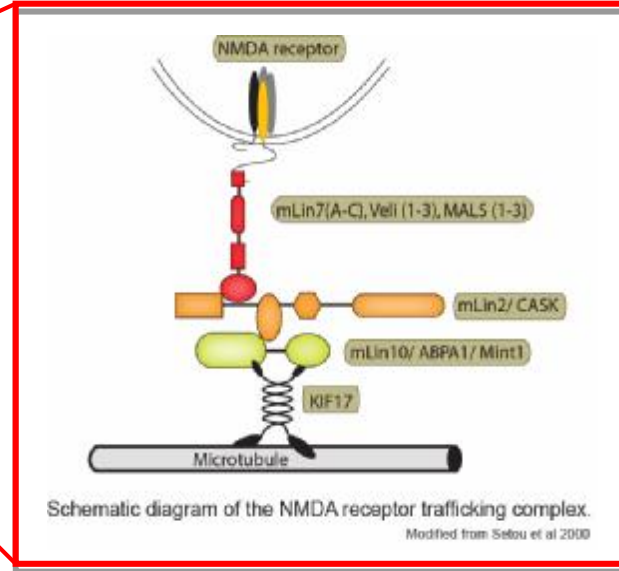
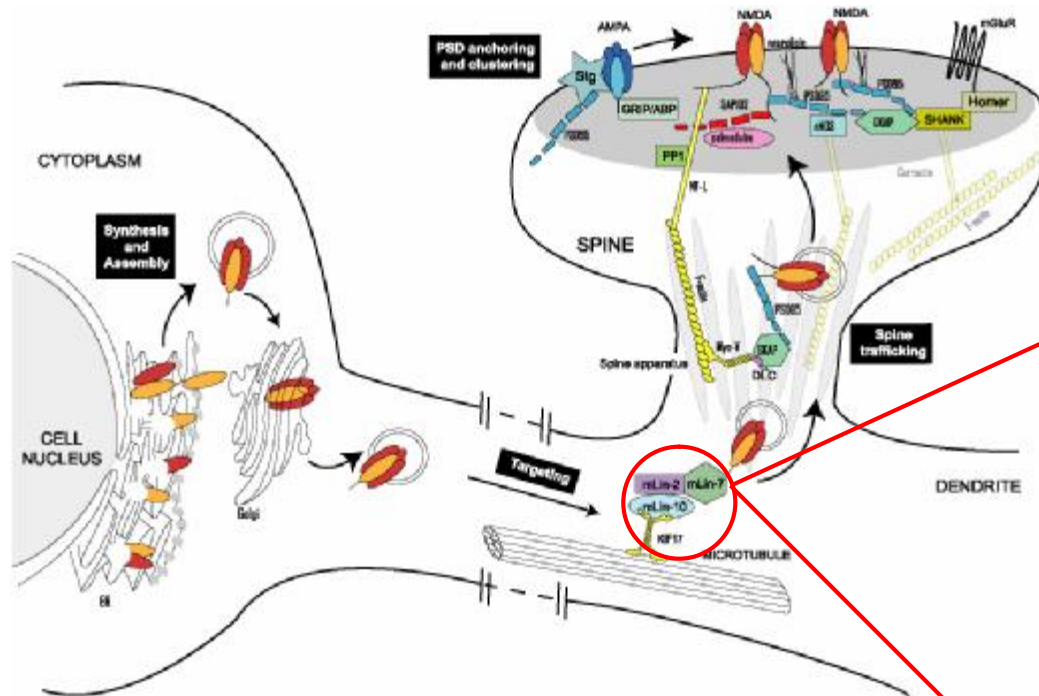
Synthesis of the NR2B receptor in schizophrenia



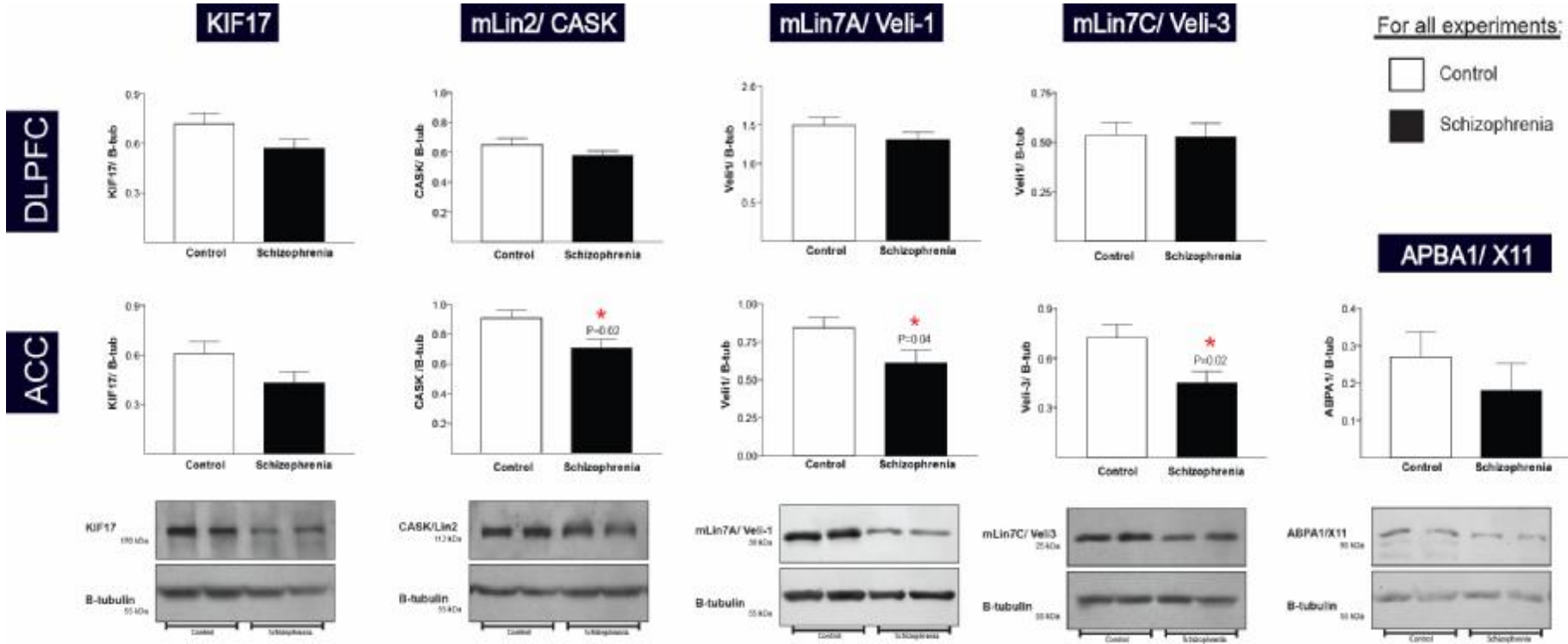
- The CASK, CINAP/TBR-1 proteins form a nuclear complex that regulates NR2B synthesis in the brain (Wang et al. 2004, Hsueh 2006)



NR2B trafficking

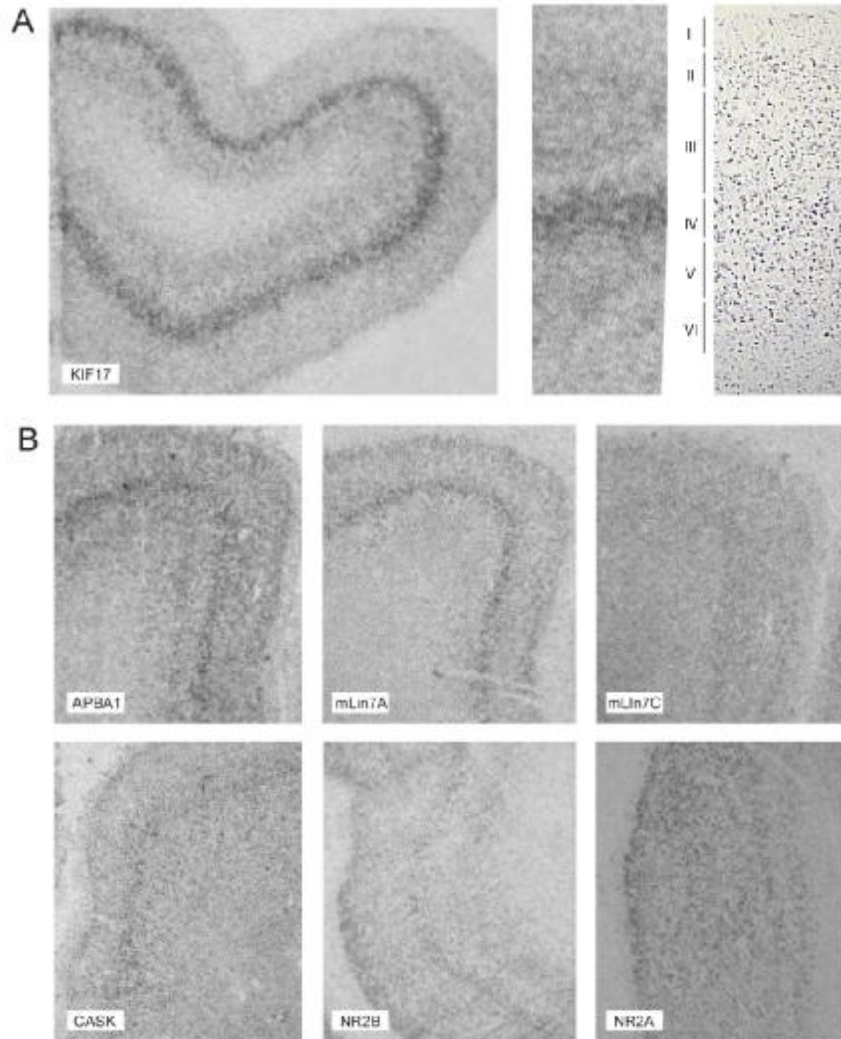


Protein expression



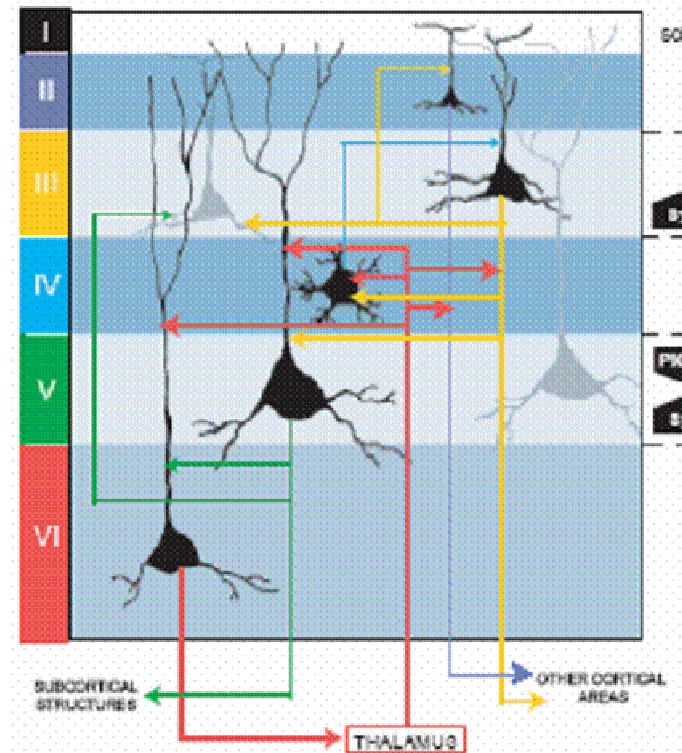
Decreased CASK and Veli-3 protein expression

Expression of the NR2B trafficking complex in ACC



- expression pattern for KIF17 restricted to layer III/IV in ACC in the human brain.

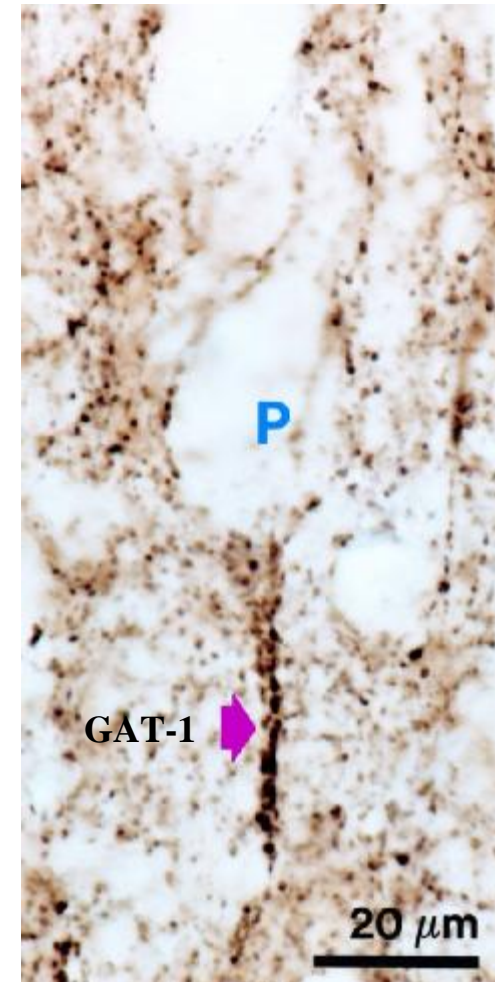
Layer III/IV corresponds to cortical input region for thalamo-cortical projections.



Conclusions



- ∅ Altered expression/splicing of the NMDAR and its associated PSD proteins in schizophrenia
- ∅ No evidence for altered NR2B synthesis in schizophrenia
- ∅ Pathophysiology likely involves compromised PSD delivery of NR2B-NMDA receptors in ACC.
- ∅ The cortical expression pattern of NR2B in deep layer III/IV might indicate an overlapping GABA/glutamate abnormality of spiny stellate and chandelier neurons of the input zone for thalamo-cortical projections?



Pierri et al. 1999



UNIVERSITY OF ALABAMA AT BIRMINGHAM

James H. Meador-Woodruff

Chairman of Psychiatry and Behavioral Neurobiology,
University of Alabama at Birmingham

JMW- Laboratory

- Robert McCullumsmith
- Monsheel Sohti
- Monica Beneyto
- Rita Cowell
- Miguel Biscaia
- Deborah Bauer
- Amy Steffek
- Elizabeth Lucas
- **Charlotte Hammond**
- Jana Drummond
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