

PSYCHOSIS AS A LEARNING AND MEMORY DISORDER*

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Brain & Behavior Research Foundation

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* Supported by NARSAD, Distinguished Investigator Award, 2012

Tracking Psychosis in Schizophrenia

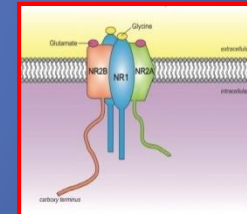
- What is schizophrenia?



- Where is the brain affected?

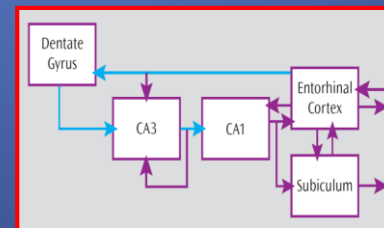


- What is affected in this area?



- How does this pathology generate psychosis?

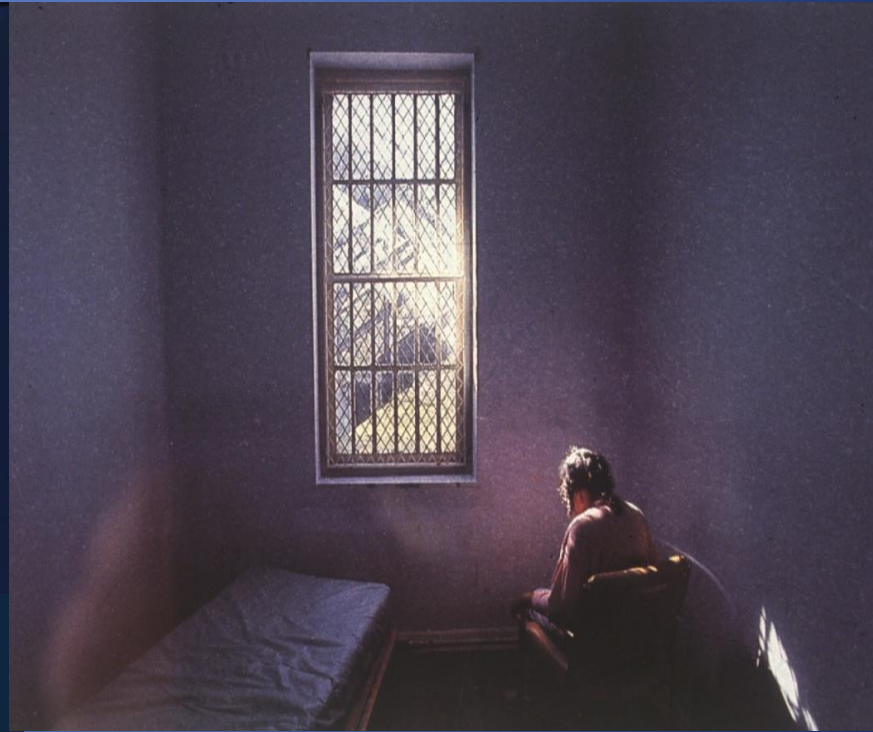
- How can we treat it?



PSYCHOSIS/SCHIZOPHRENIA



1750



1996

WHAT IS THE EXPERIENCE OF PSYCHOSIS/SCHIZOPHRENIA?

“These ideas keep coming into my head and I can’t prevent it. (I) believe there is a conspiracy among military leaders to take over the world, and that (I) am in charge of the takeover. (I) secretly feel that I am the left foot of God. And that God is walking on the earth.”

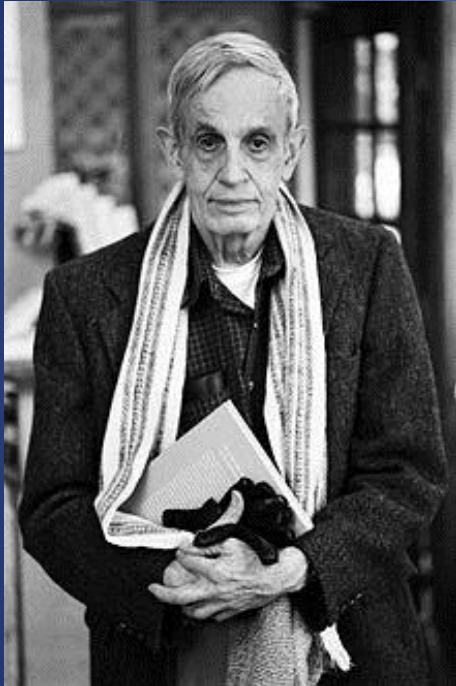
John Forbes Nash, Nobel Prize in Economics, 1994

WHAT IS THE EXPERIENCE OF PSYCHOSIS/SCHIZOPHRENIA?

“Consciousness gradually loses its coherence. The “me” becomes a haze ...reality breaks up like a bad radio signal. There is no longer a sturdy vantage point from which to look out, take things in, assess what’s happening. No core ...lens through which to see the world, to make judgments and comprehend risk. Random moments of time follow one another. Sights, sounds, thoughts, and feelings don’t go together. No organizing principle takes successive moments in time and puts them together in a coherent way from which sense can be made. And it’s all taking place in slow motion.”

The Center Cannot Hold by Elyn R. Saks

Famous and infamous people with SZ



Schizophrenia Characteristics

- Prevalence is approximately 1%, worldwide
- Psychosis begins at 18—26 yrs and lasts a lifetime
- Often earlier cognitive dysfunction
- Psychosis is at its worst between onset and 50 yrs
- Profound psychosocial dysfunction: only <15% are employed, <20% marry, <5% fully recover
- Significant associated health care costs, direct and indirect
- Pathophysiology is not known; treatments are symptomatic—D2 dopamine receptor antagonists
- Cerebral anatomy: prefrontal cortex, hippocampus

PSYCHOTIC SYMPTOMS IN SCHIZOPHRENIA:

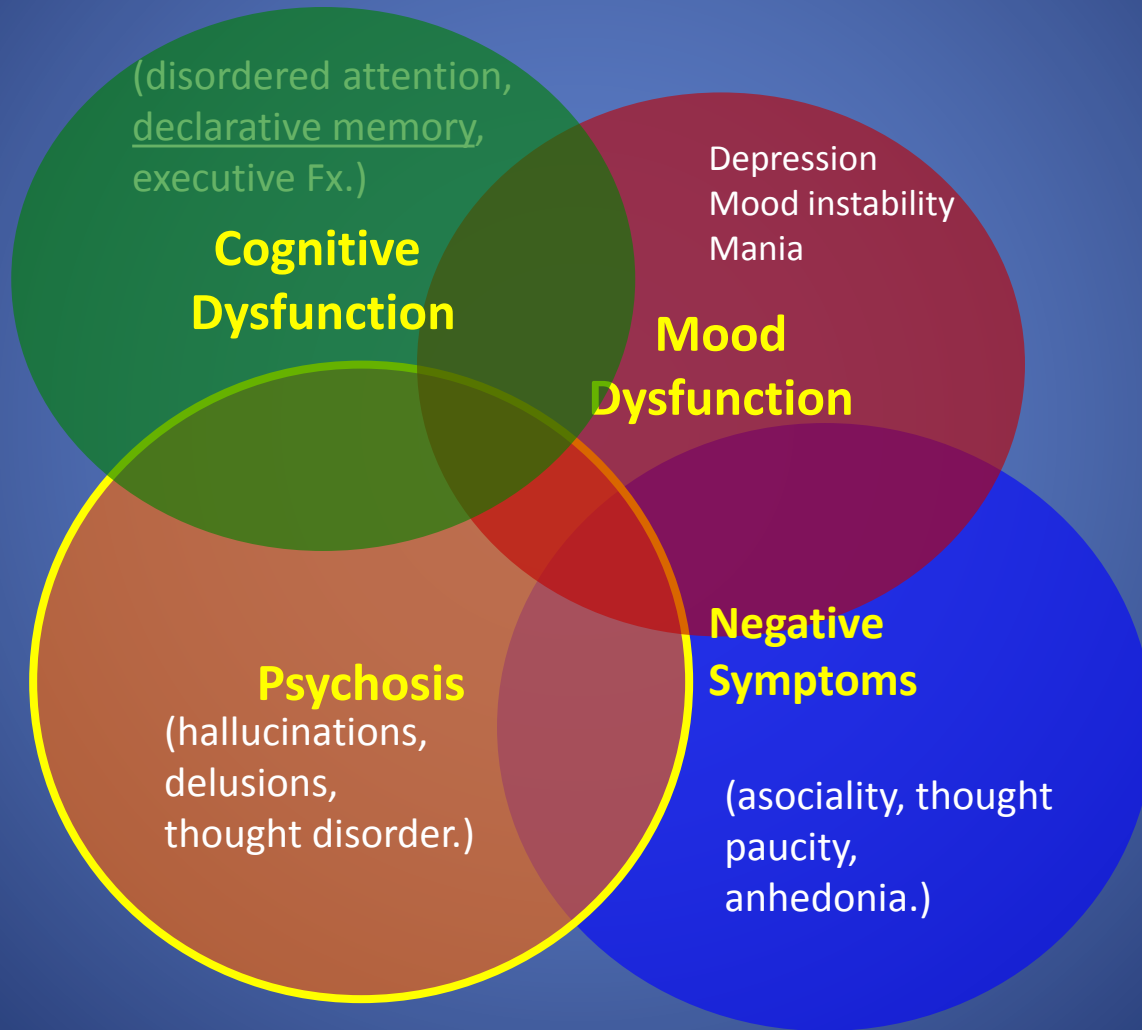
World Health Organization Study

SYMPTOM	FREQUENCY
• LOSS OF INSIGHT	• 97%
• AUDITORY HALLUCINATION	• 74%
• VERBAL HALLUCINATIONS	• 70%
• IDEAS OF REFERENCE	• 70%
• SUSPICIOUSNESS	• 65%
• FLATNESS OF AFFECT	• 65%
• VOICES SPEAKING	• 65%
• PARANOID STATE	• 64%
• THOUGHT ALIENATION	• 52%
• THOUGHTS SPOKEN ALOUD	• 50%

Risk Factors for Schizophrenia

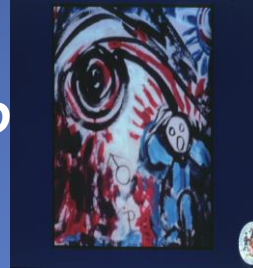
- GENETICS : Creates a vulnerability; 130 risk genes identified from 25,000 cases
- PRENATAL EVENTS: infection, famine
- PERINATAL ACCIDENT: hypoxia
- WINTER BIRTH: summer conception
- EARLY ENVIRONMENT: trauma, stress

SCHIZOPHRENIA PHENOMENOLOGY



Tracking Psychosis in Schizophrenia

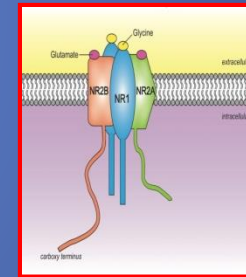
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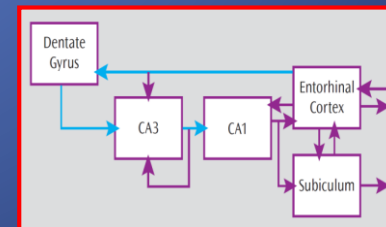


- *What is affected in these areas?*



- *How does this pathology generate psychosis?*

- *How can we treat it?*

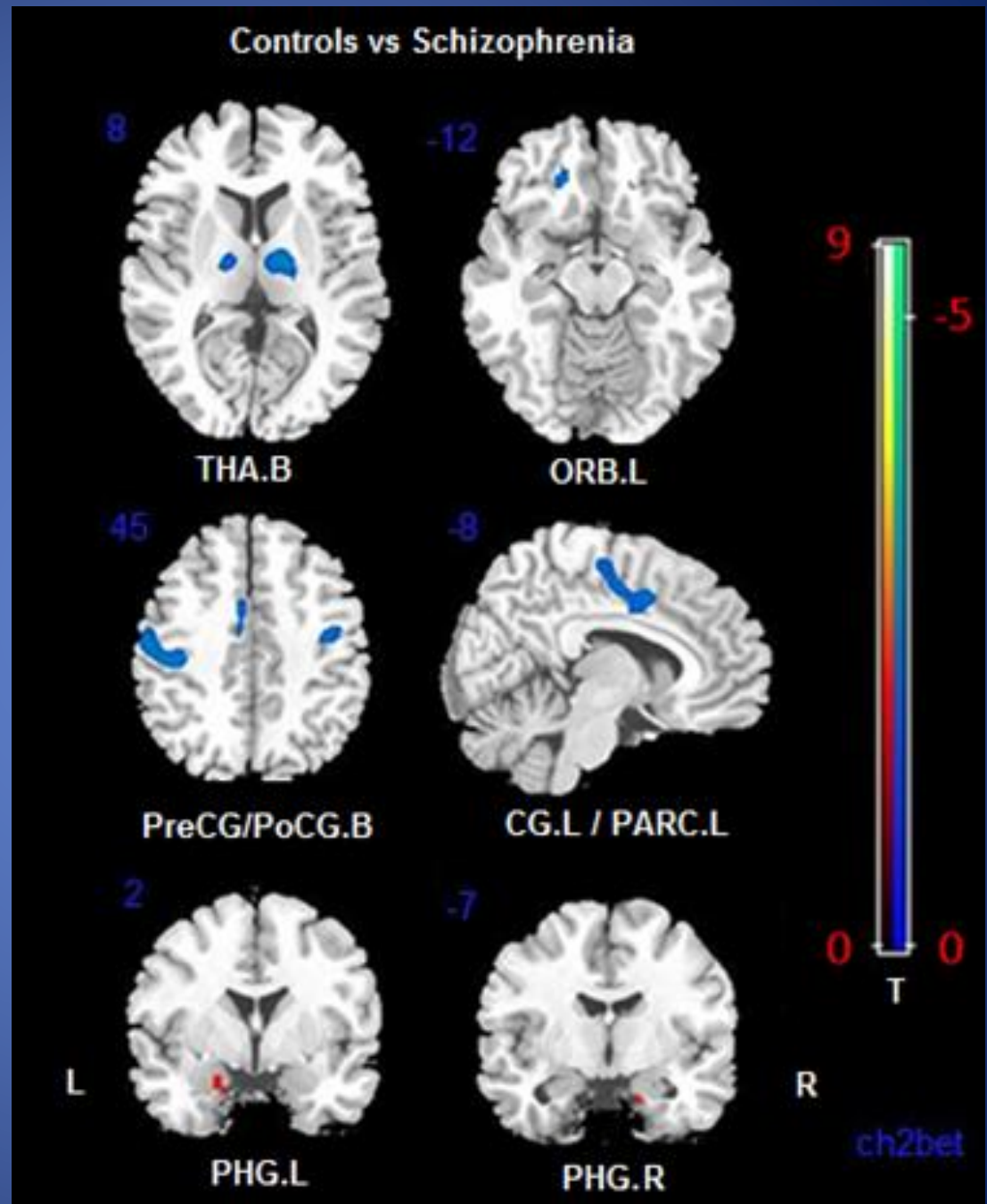


SCHIZOPHRENIA

REDUCED (BLUE) ACTIVITY IN MANY BRAIN REGIONS (BLUE), BUT INCREASED (RED) ACTIVITY IN HIPPOCAMPUS

Individuals with schizophrenia show reduced fMRI (resting) in orbitofrontal cortex, thalamus, pre- and post-central gyrus and cingulate cortex. (BLUE) Only one regions shows ELEVATED fMRI and that is the medial temporal structures including hippocampus. (RED)

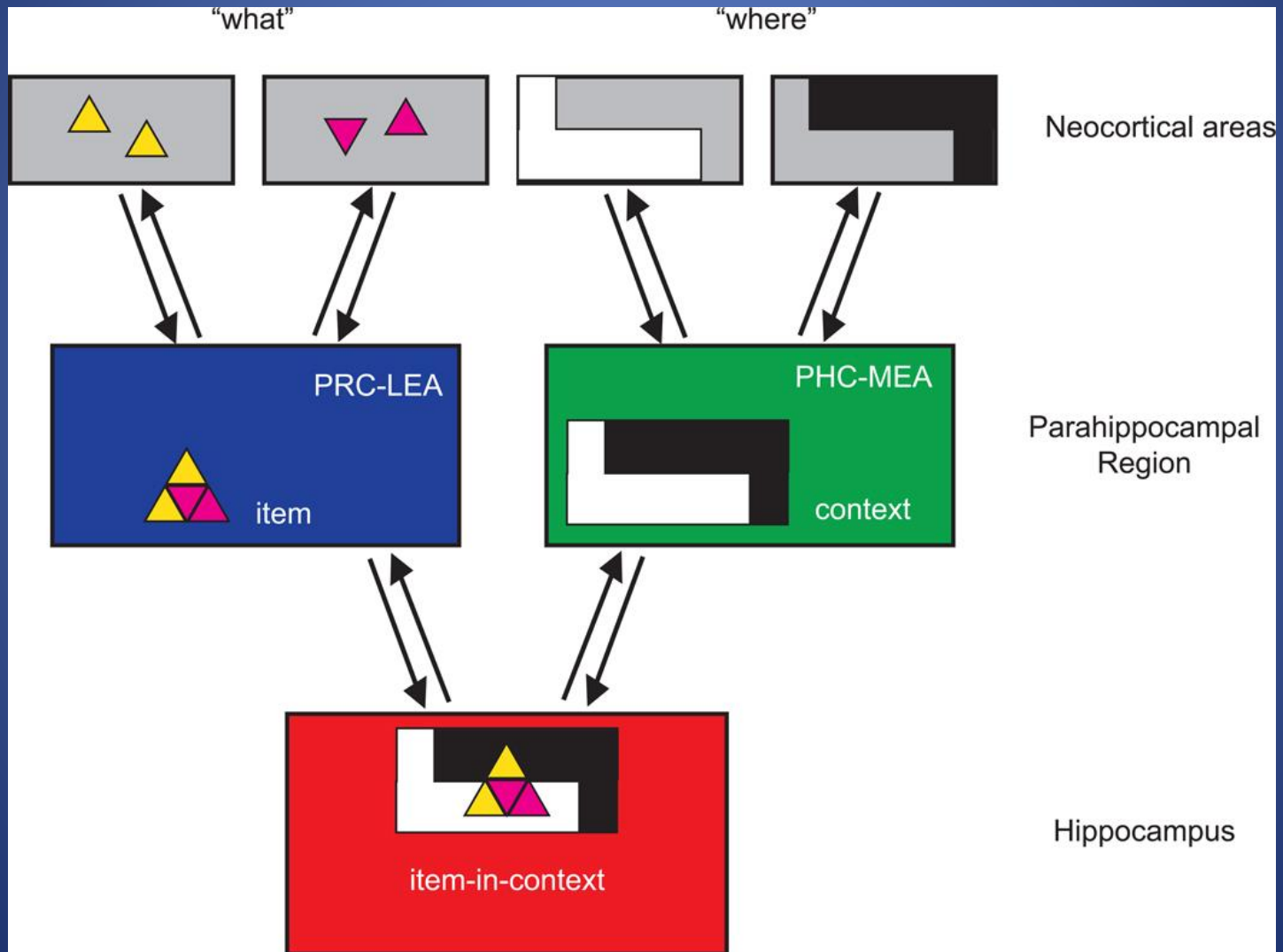
Gong, Sweeney, et al, 2014



**HIPPOCAMPUS IS CRITICAL FOR
EPISODIC MEMORY**



What does hippocampus do for memory?



Memory is dependent on hippocampus

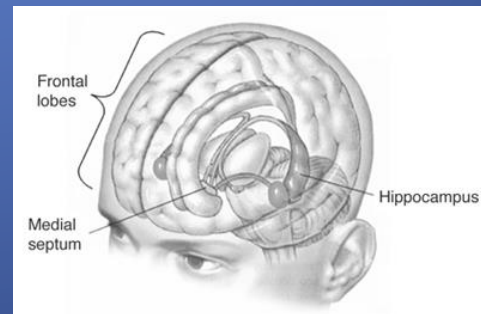
What is episodic memory?

- Episodic memory is *long term memory* for general facts and specific events.
- It includes both the *encoding* and the *retrieval* of episodic events, independent of consciousness.
- Hippocampus *binds the distinct elements* of an event into memory, such that it captures the *relationships* between those elements.
- *Mnemonic flexibility* allows for novel use of stored knowledge, consciously or unconsciously.

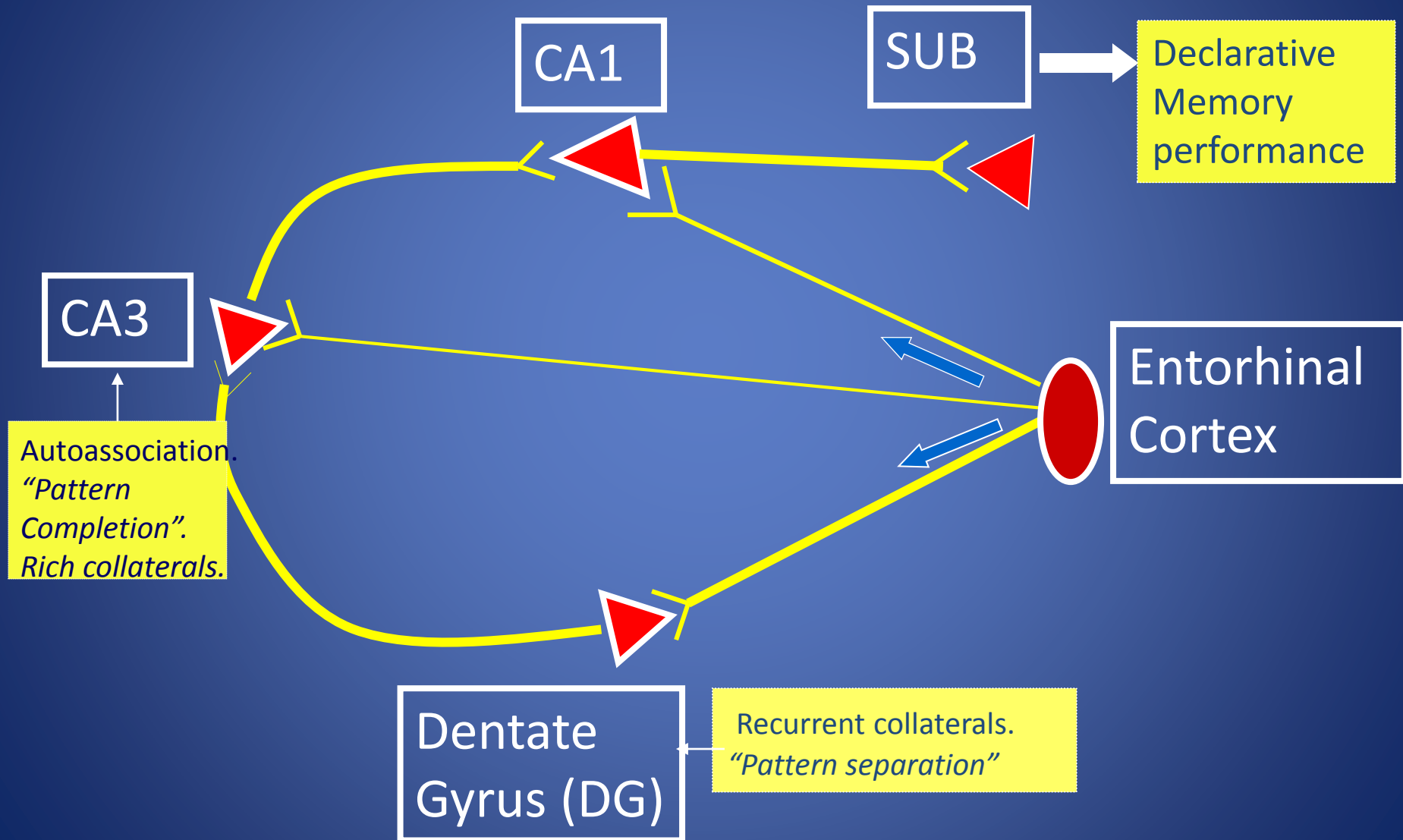
Henry Moliason (HM):

Who is HM? What did HM teach us?

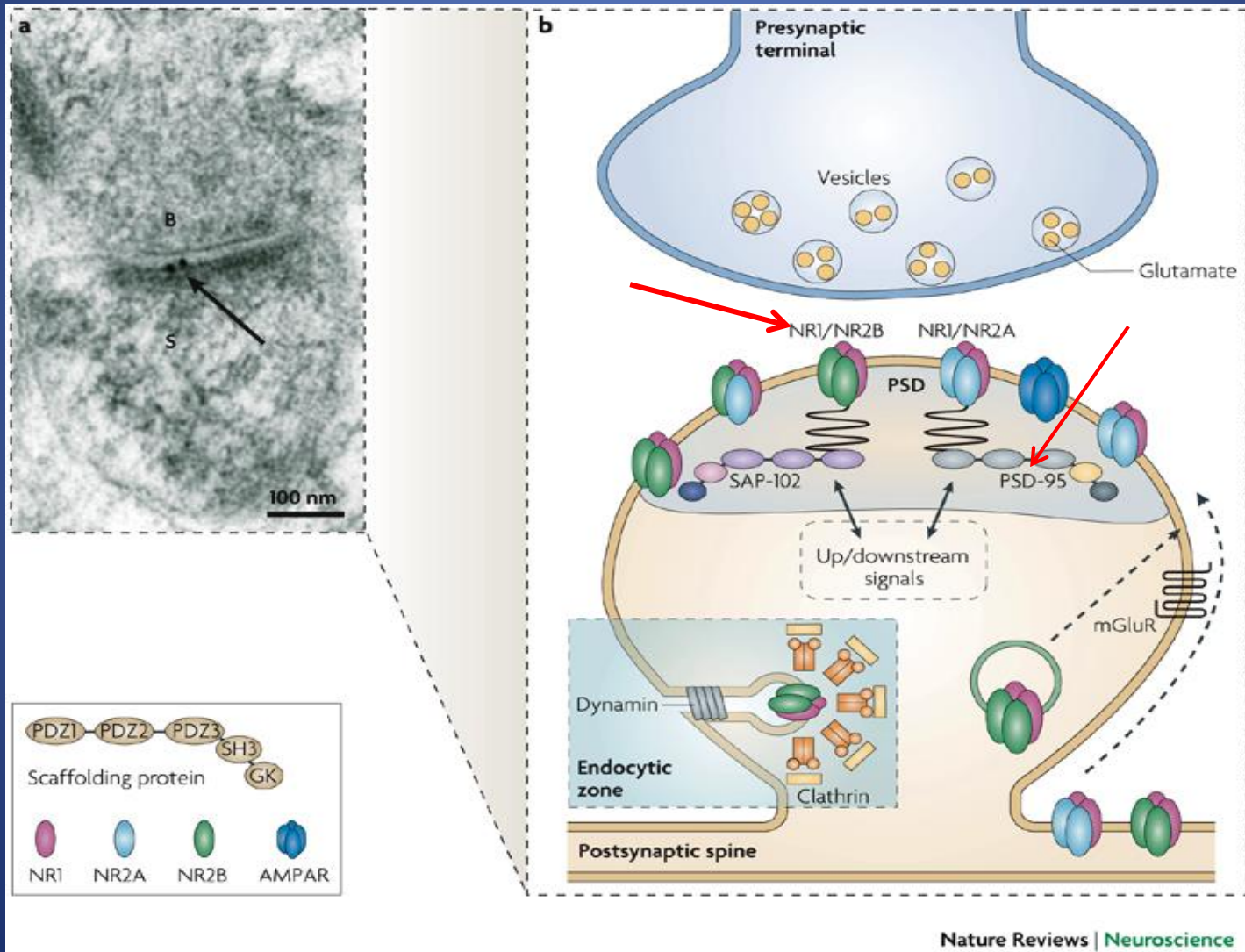
- MEMORY is a distinct psychological function
- Amnesia is an impairment of episodic memory
- Amnesia spares short-term and working memory
- Hippocampus is a core brain structure supporting declarative memory
- Hippocampus supports the permanent consolidation of memories



The Anatomy of Memory: Hippocampus



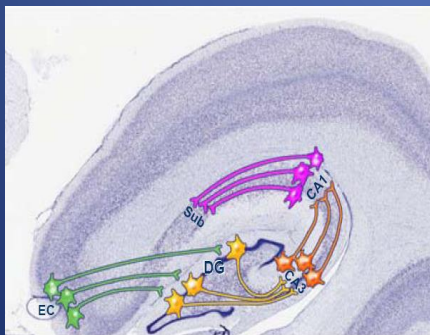
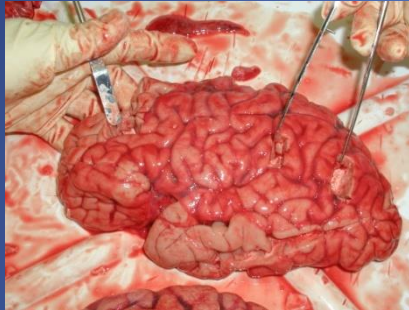
Synaptic Basis of Memory/CA3



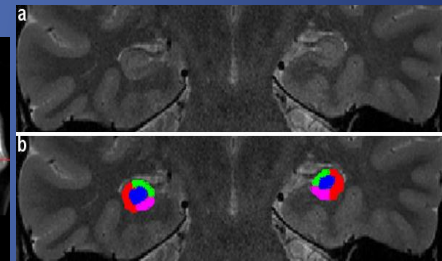
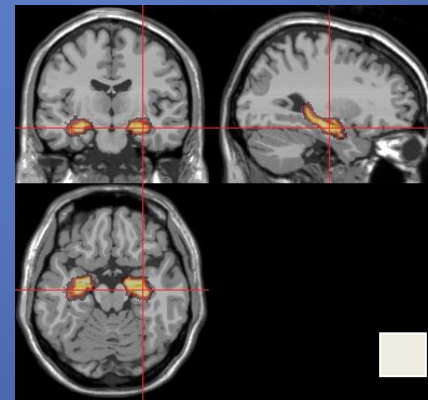
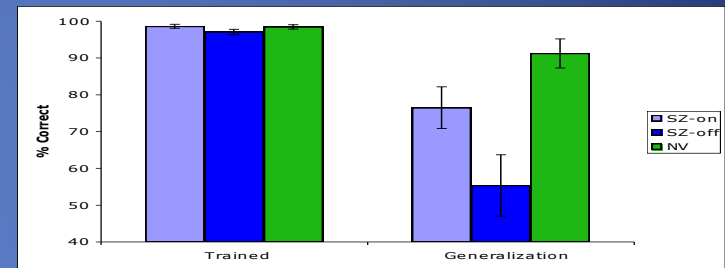
What about Episodic Memory and
Hippocampal Function
in Schizophrenia?

Learning and Memory Methods for Human Hippocampus

Human postmortem brain



Human brain imaging and memory performance

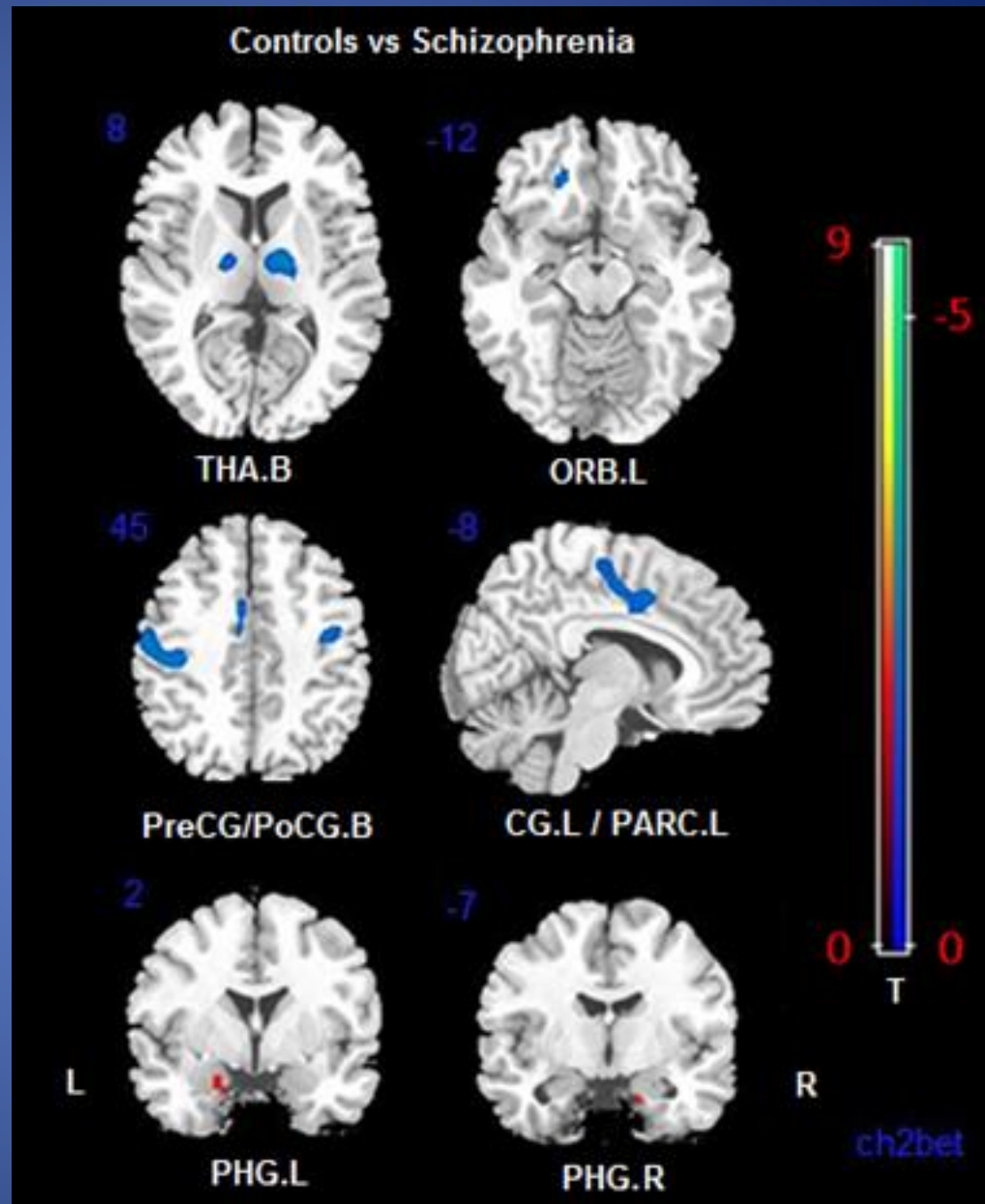


SCHIZOPHRENIA

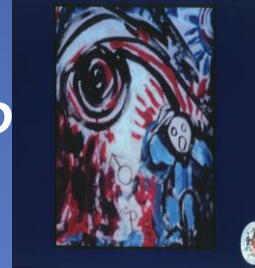
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Tracking Schizophrenia Psychosis

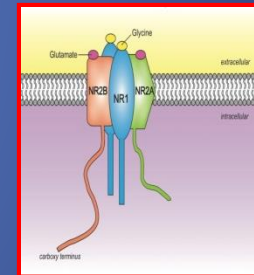


- *What is schizophrenia?*

- *Where is the brain affected?*

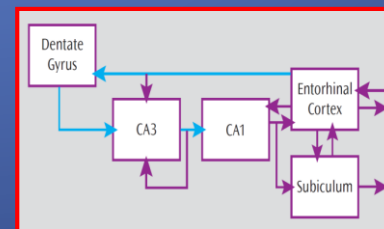


- *What is affected in hippocampus?*



- *How does this pathology generate psychosis?*

- *How can we treat it?*



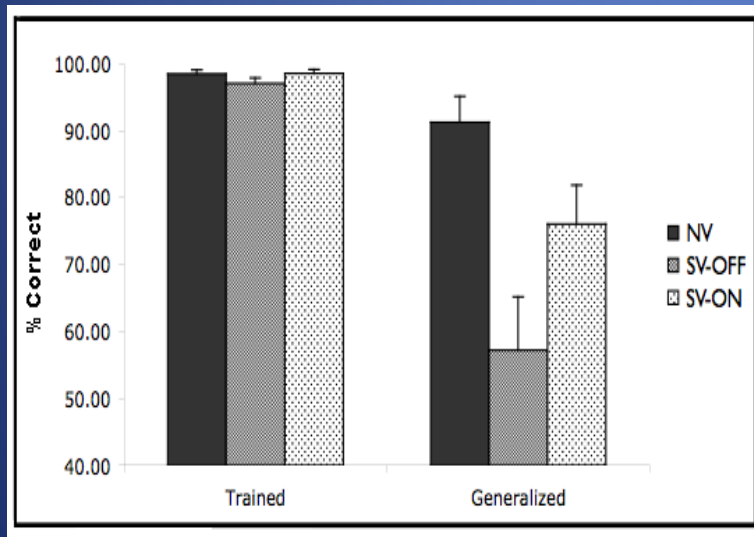
Reported hippocampal alterations in SZ: relational memory

- (1) a consistent, albeit small (4-5%), reduction in hippocampal volume;
- (2) impairment in memory performance in SZ, particularly in relational memory and in pattern separation;
- (3) an increase in hippocampal basal perfusion,
- (4) an activation deficit during declarative memory tasks,
- (5) decreased neurogenesis in dentate gyrus and altered efferent excitatory signaling from DG granule cells.
- *These changes correlate with psychotic symptoms, and thus appear functionally relevant.*
- *Therefore, the hippocampus is affected in schizophrenia*

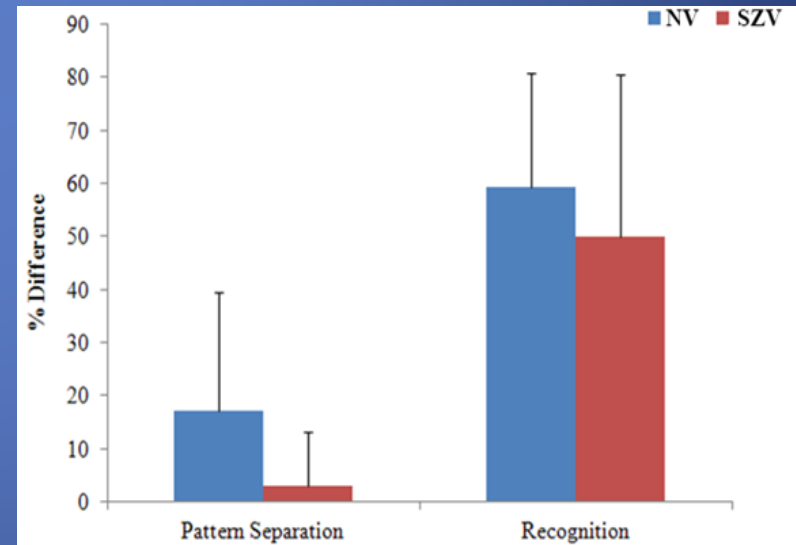
What do we know about memory performance in schizophrenia?

Impaired

Acquired Equivalence Performance



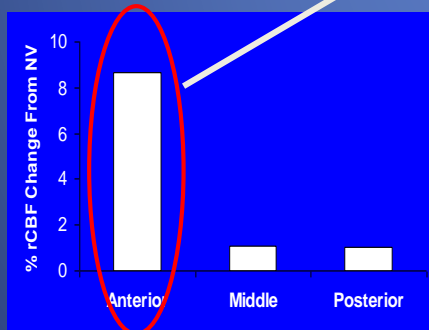
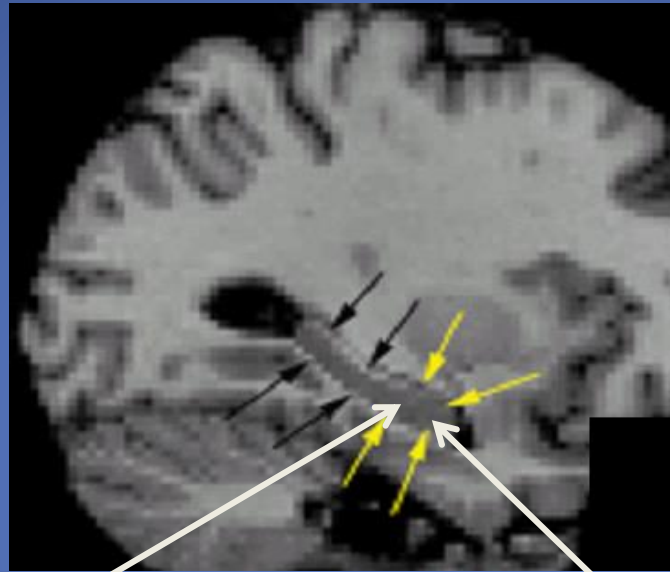
Pattern Separation Performance



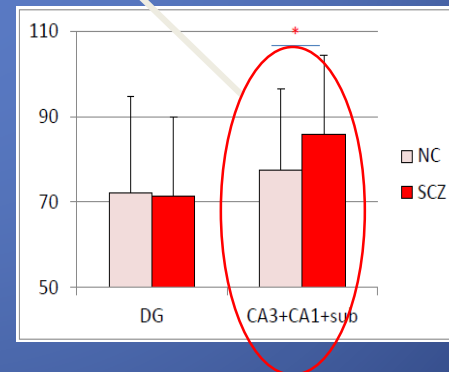
Regional blood flow is an indirect measure of neuronal activity.

We find increased neuronal activity in hippocampus in schizophrenia.

Increased hippocampal blood flow in SZ

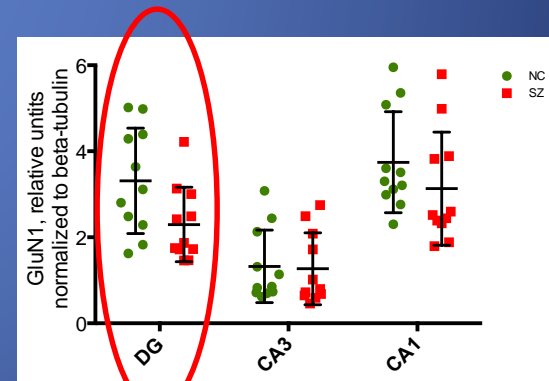
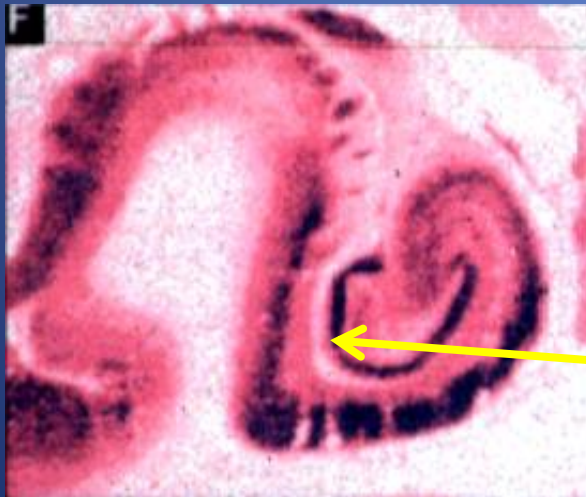


rCBF is increased in Hipp in SZ

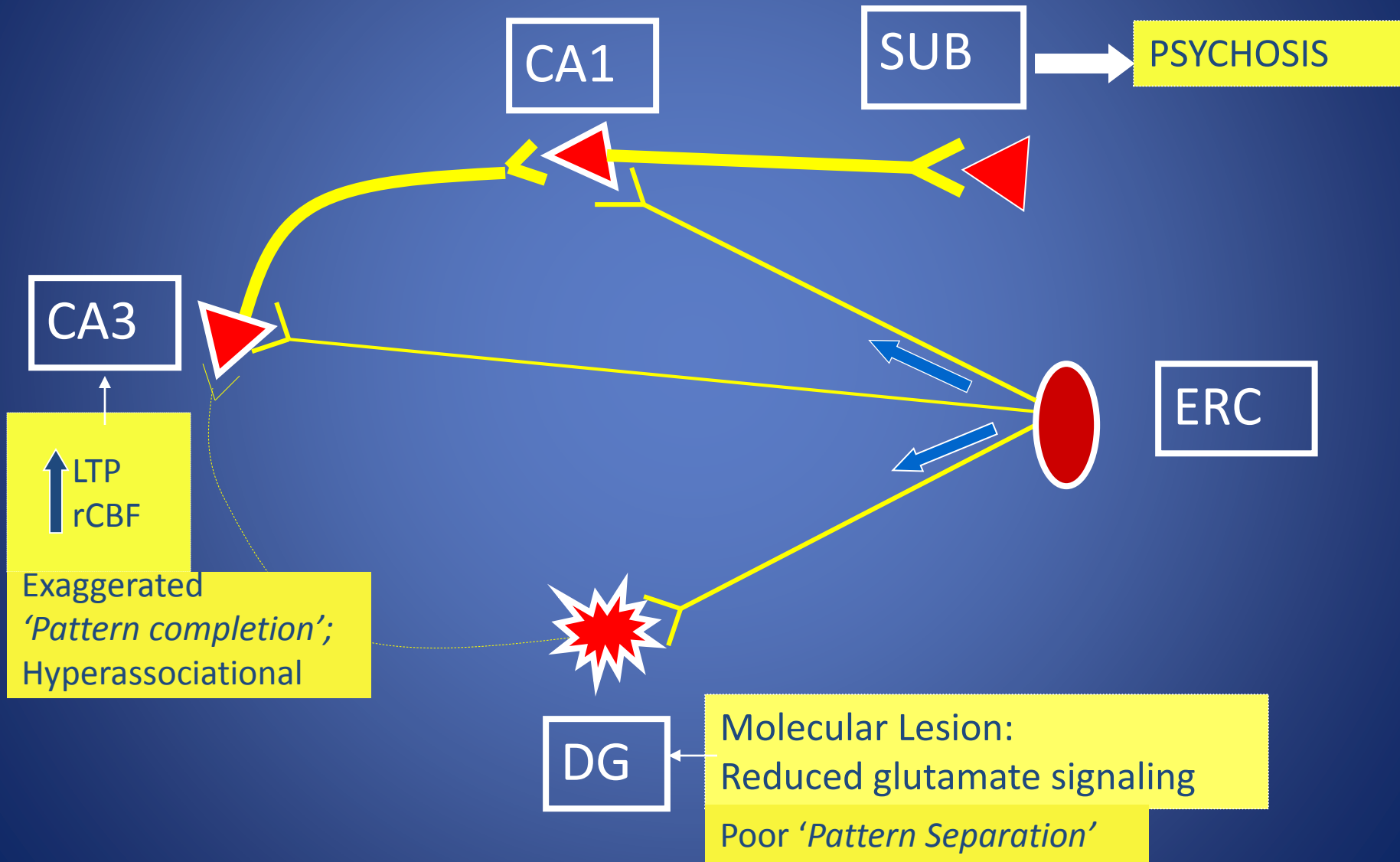


rCBV is increased in CA3/CA1 in SZ

However, tissue measures of glutamate are decreased in dentate gyrus in schizophrenia: GluN1
What is going on?



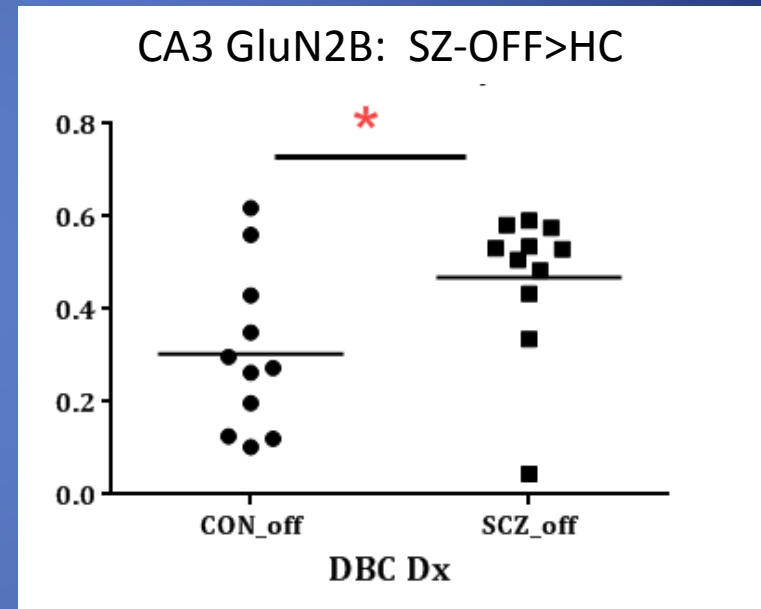
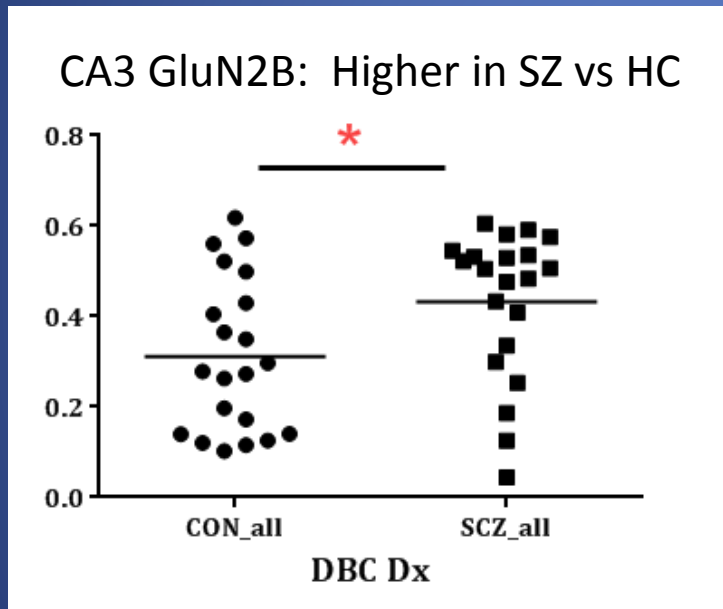
Model of Psychosis in Schizophrenia



Using brain tissue to test subfields for
increased cellular activity

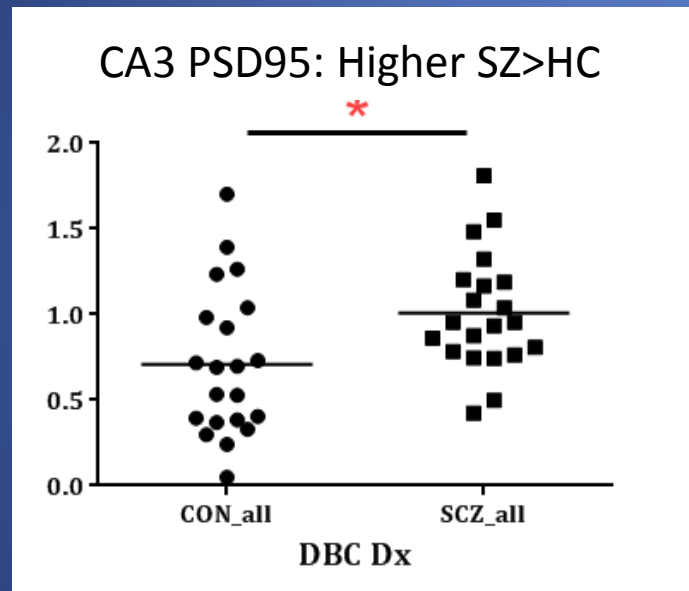


GluN2B-containing NMDA Receptors are Increased in SZ: CA3, not CA1

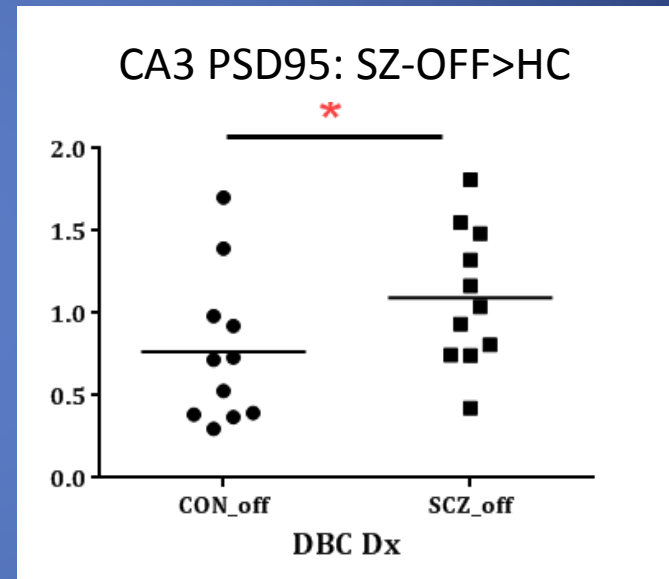


In CA3, GluN2B-containing NMDA receptors were increased, in 'all' and 'off', indicating INCREASED synaptic strength.

Postsynaptic Density Protein, PSD95 increased in SZ: CA3 not CA1

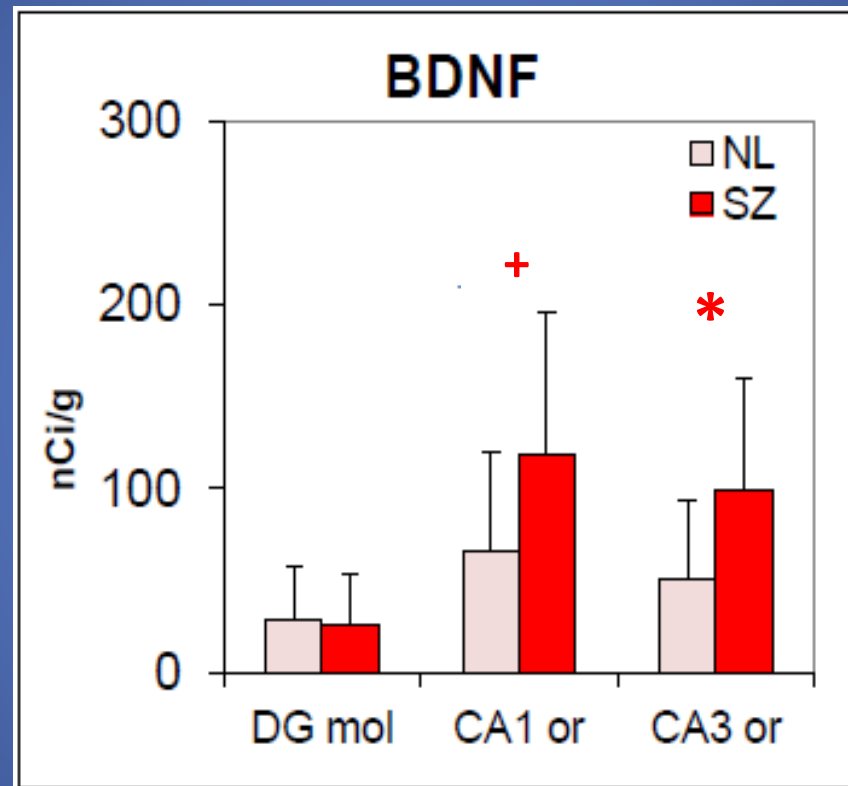


The INCREASE in PSD95 in CA3 in SZ (all and off) suggests an INCREASE in synaptic strength.



There is no significant change in PSD95 in CA1 in SZ.

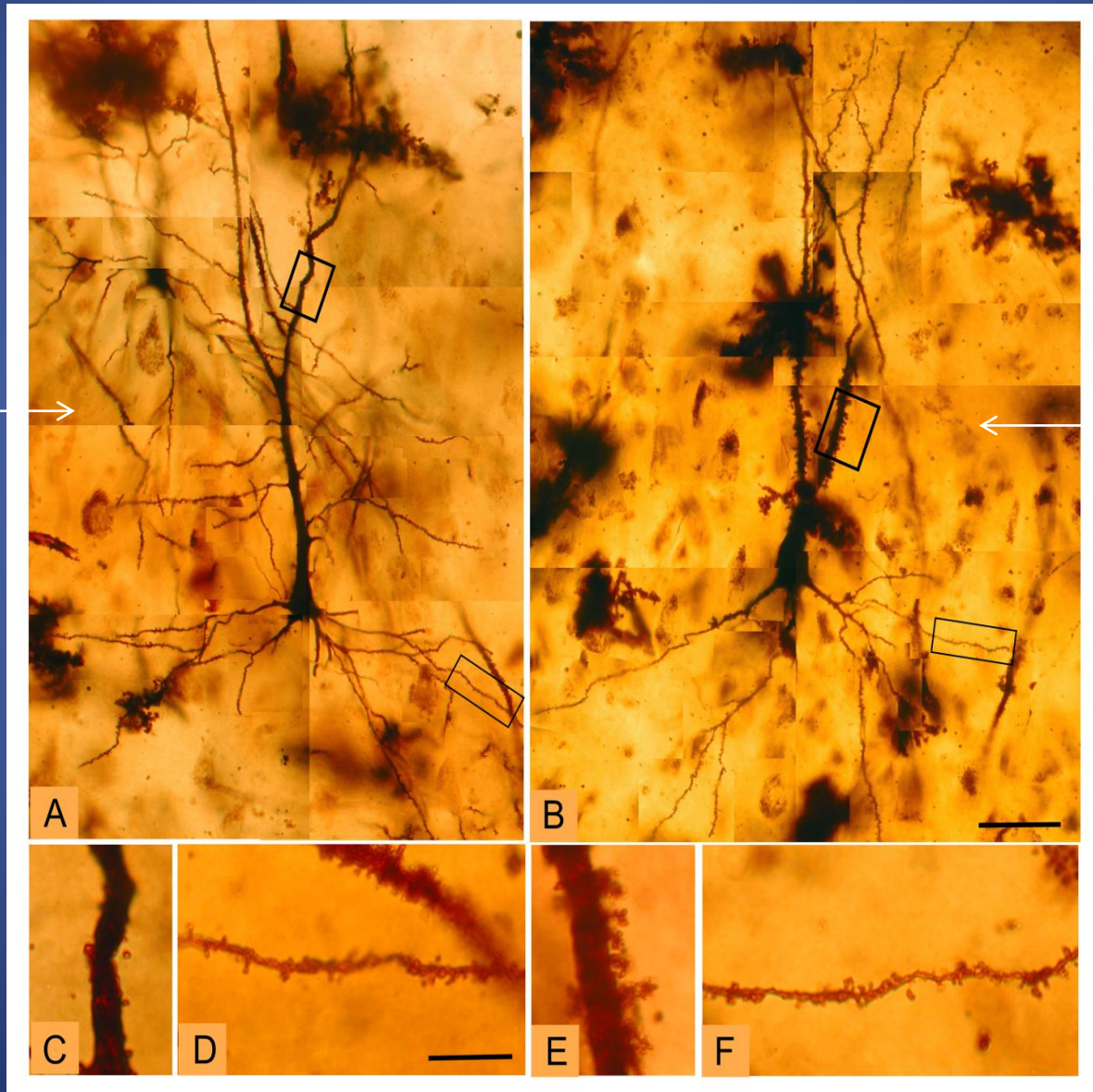
BDNF mRNA: CA3 and CA1



BDNF mRNA in CA3 st oriens in NL vs SZ. BDNF increase in SZ compared to NL in Hipp CA3 ($p=.028$) and CA1 ($p=0.06$).

Increased synapses in human SZ hippocampus

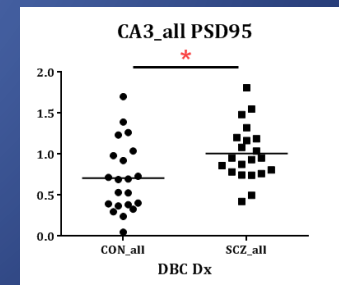
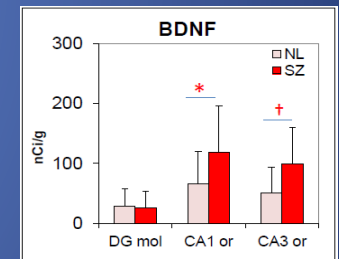
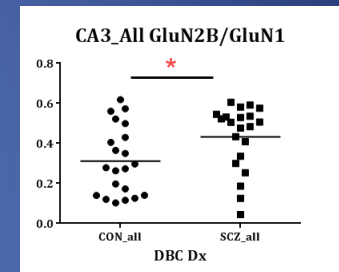
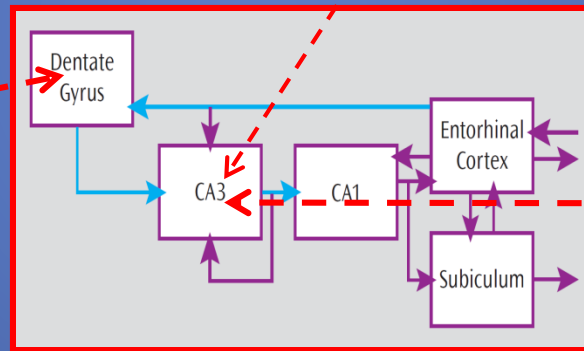
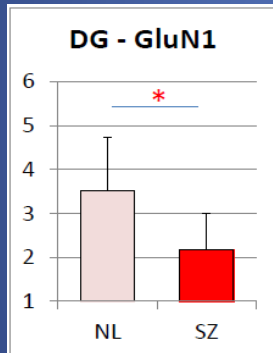
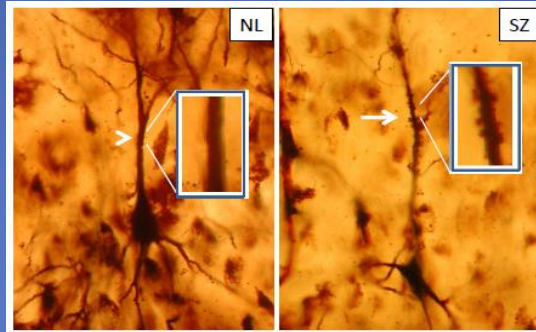
Control →



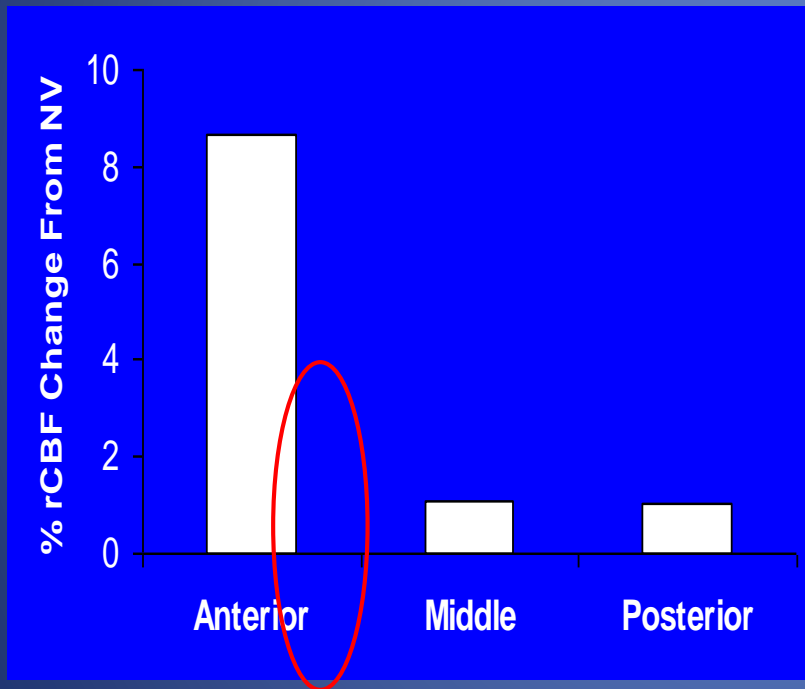
← Schizophrenia

CA Tamminga
L. Selemon, et al.
Am J Psych, 2015

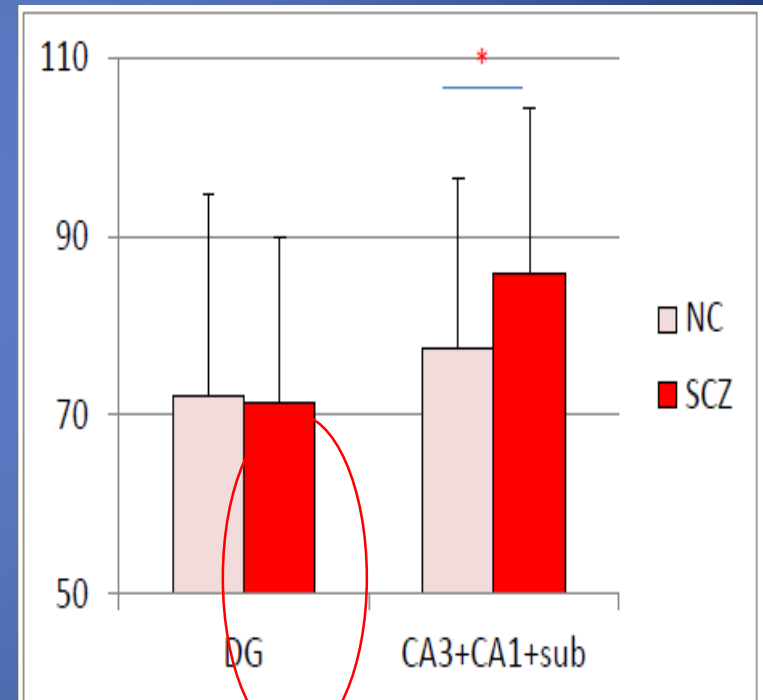
Schizophrenia and Hippocampus



Increased hippocampal rCBF can be explained by hippocampal pathology



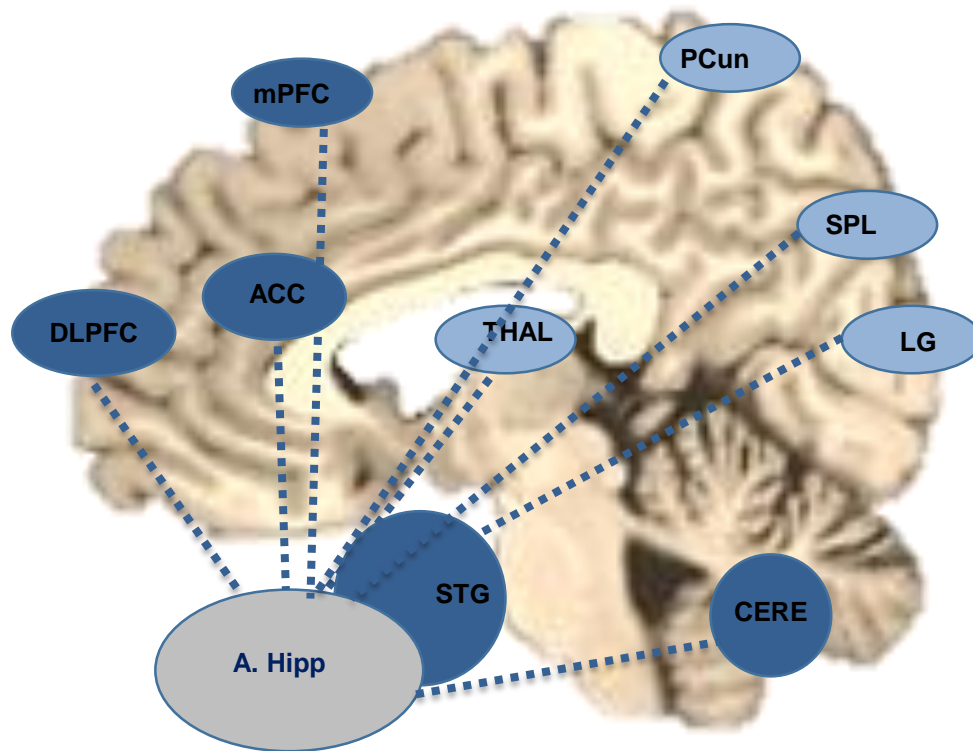
rCBF is increased in Hipp in SZ



rCBV is increased in CA3/CA1 in SZ

*How does hippocampal
hyperactivity affect brain function
in OTHER brain regions?*

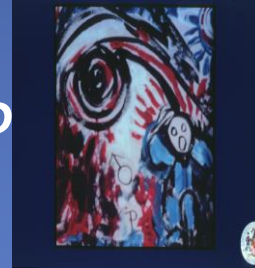
Reduced Hippocampal Connectivity in Schizophrenic Psychosis



A. Hipp – anterior hippocampus
MFG – medial frontal gyrus
ACC – anterior cingulate cortex
DLPFC – dorsal lateral prefrontal cortex
STG – superior temporal gyrus
Cb – cerebellum
PCun – precuneus
SPL – superior parietal lobule
thal – thalamus
LG – lingual gyrus

Tracking Psychosis in Schizophrenia

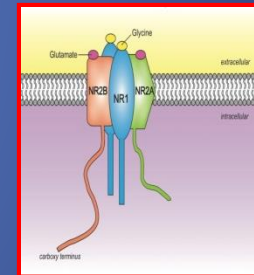
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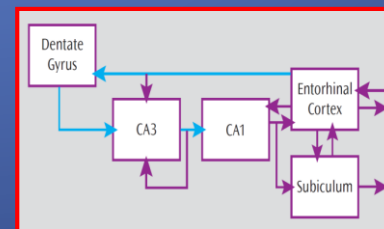


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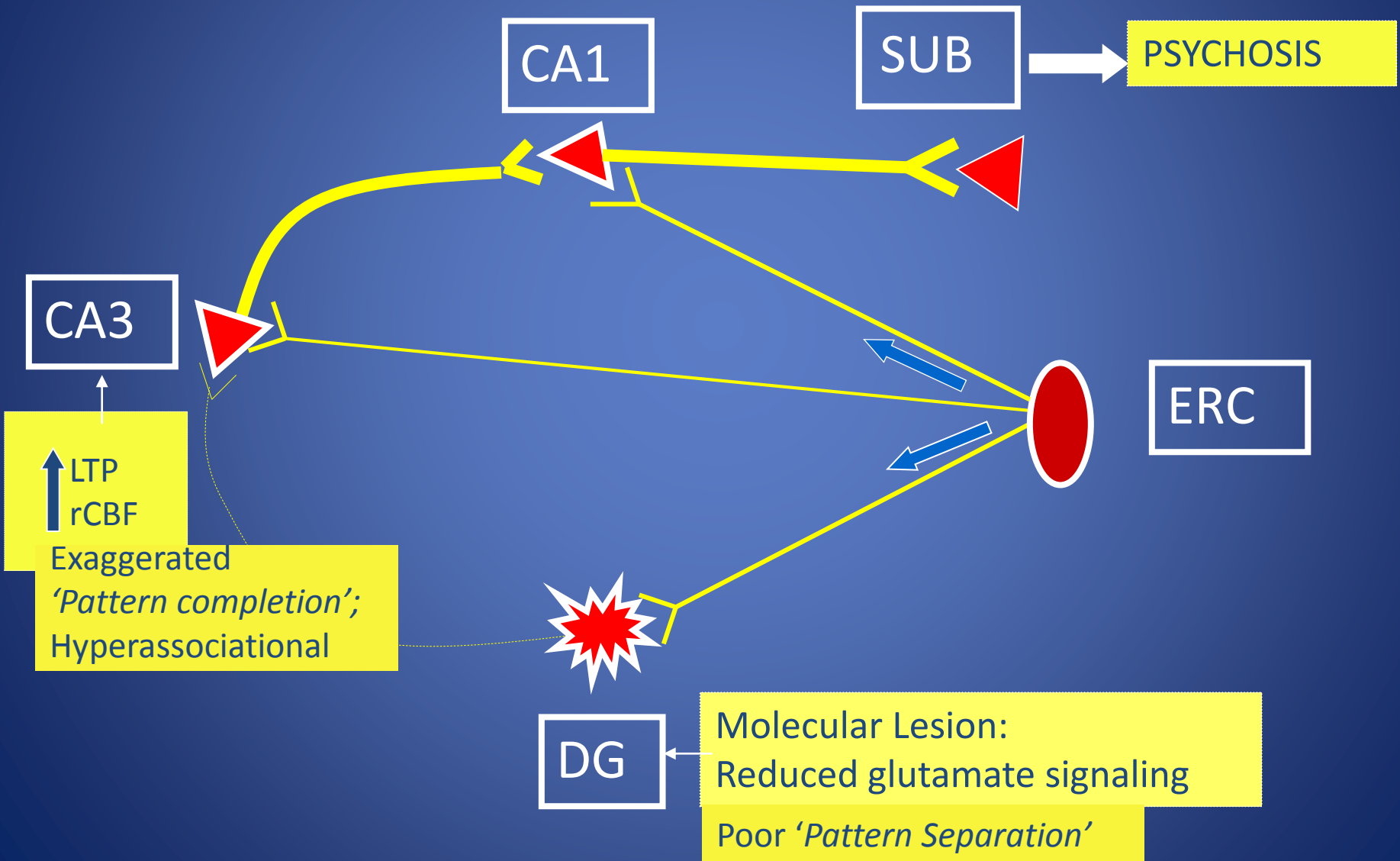
- *How can we treat it?*



Psychosis and Hippocampus

- Increased hippocampal blood flow, consistent with increased neuronal activity
- Increased synaptic strength in CA3
- Increased spines and terminal insertions in CA3, consistent with increased synaptic strength
- Psychosis could be associated with hippocampal hyperactivity, which exceeds hippocampal capacity and generates hyper-associations and false memories, some with psychotic content

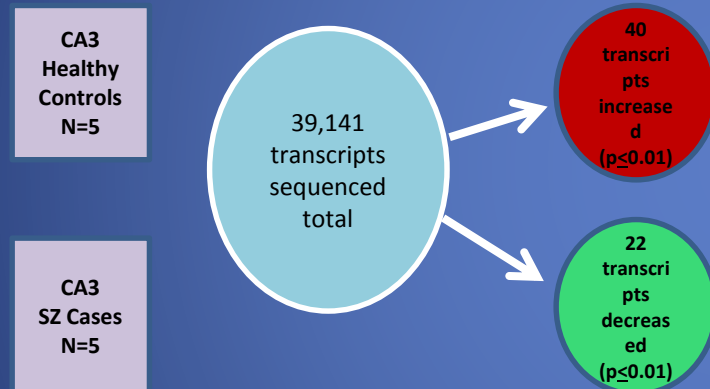
CA3 hyperactivity in hippocampus generates false memories with psychosis



Schizophrenia psychosis is a
learning and memory disorder
associated with the establishment of
false memories, with psychotic content

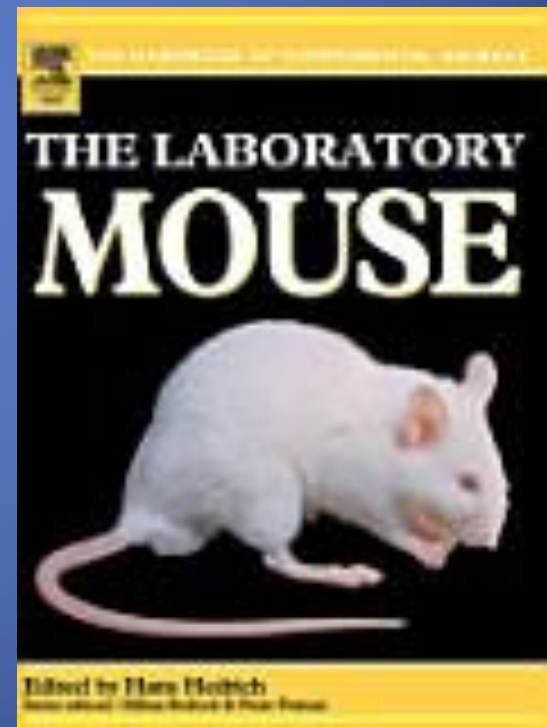
Ongoing experiments

Transcriptome analysis for novel proteins in CA3



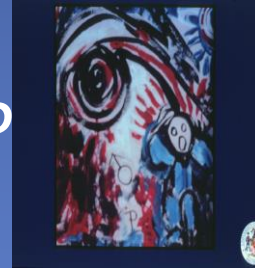
RNA Transcripts Increased	Literature Review	RNA Transcripts Decreased	Lit. Review
<i>SZ-associated</i>		<i>Non-Coding</i>	
1	Neuregulin-associated	6	lncRNA
1	Dysbindin-associated	1	snoRNA
2	Located in 22q11	1	scaRNA
<i>Synaptic activity related</i>			
2	PSD95-associated		
1	CREB associated		
<i>Non-Coding</i>			
6	lncRNA		

Animal model



Tracking Psychosis in Schizophrenia

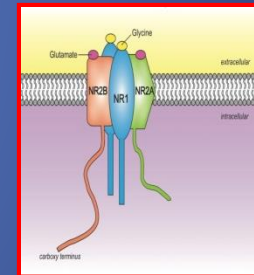
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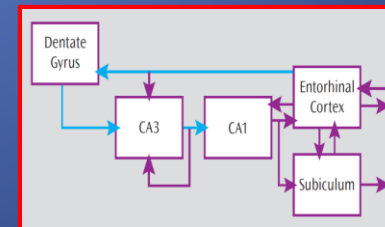


- *What is affected in hippocampus?*



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Treating a hyperactive hippocampus in SZ to reduce psychosis

- Antipsychotic drugs (antidopaminergic)
- Direct Current Stimulation (tDCS): a neuromodulation approach
- tDCS neuromodulation during active psychosis
- GluN2B-specific NMDA antagonists: Ifenprodil; Ro 25-6981; CP101,606; several additional novel drugs in development
- PSD95 antagonist: NA-1 (Tat-NR2B9c)

COLLABORATORS

PSYCHOSIS STUDIES/UTSW

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- Sarah Hendrix
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- Tanusree Das
- Hanzhang Lu
- Tae Kyung Kim
- Anthony Wagner
- John Sweeney
- Dallas Medical Examiner
- UTSW Tissue Transplant