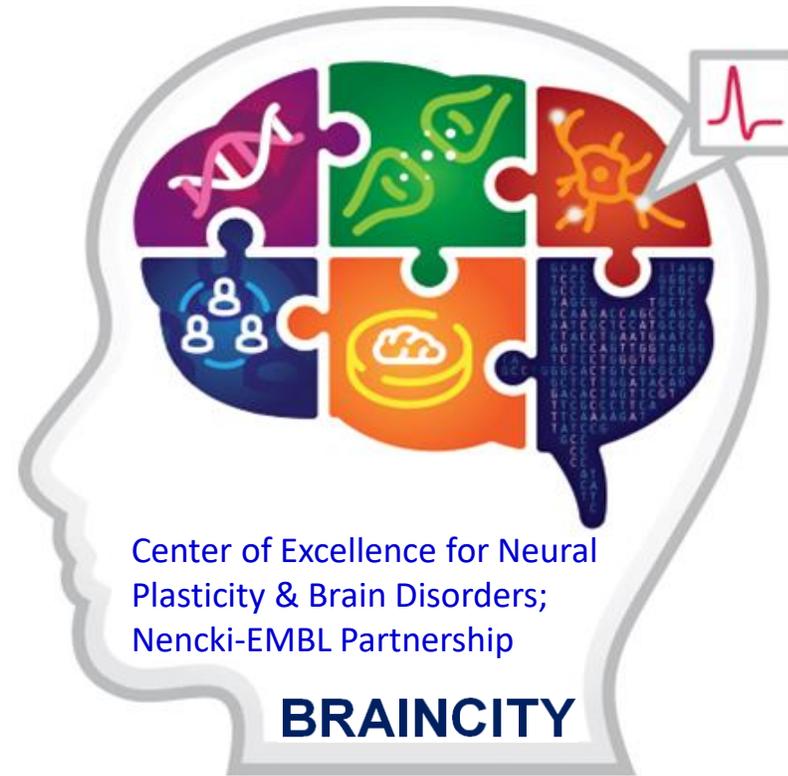
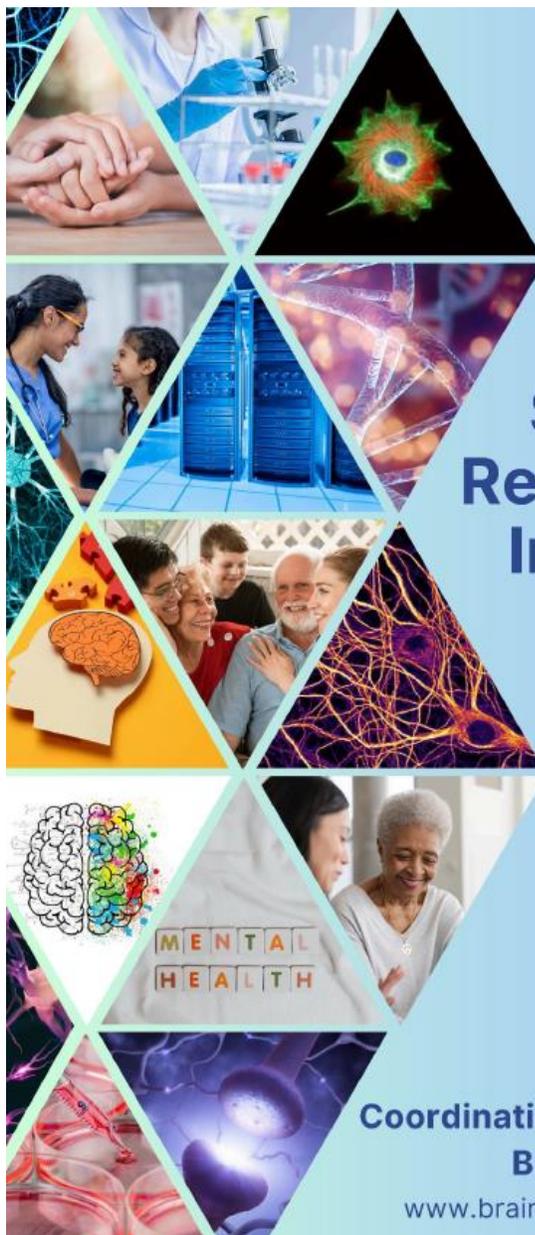


# Grand Challenges in Brain Health and Neurosciences



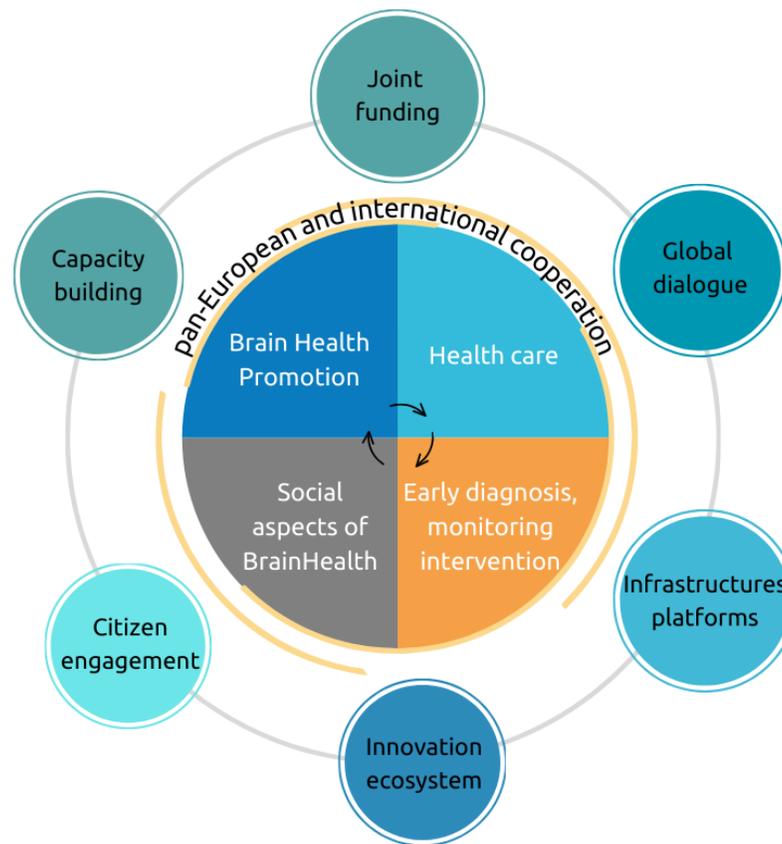
Leszek Kaczmarek, BRAINCITY, Nencki Institute, Warsaw, Poland

# Strategic Research and Innovation Agenda

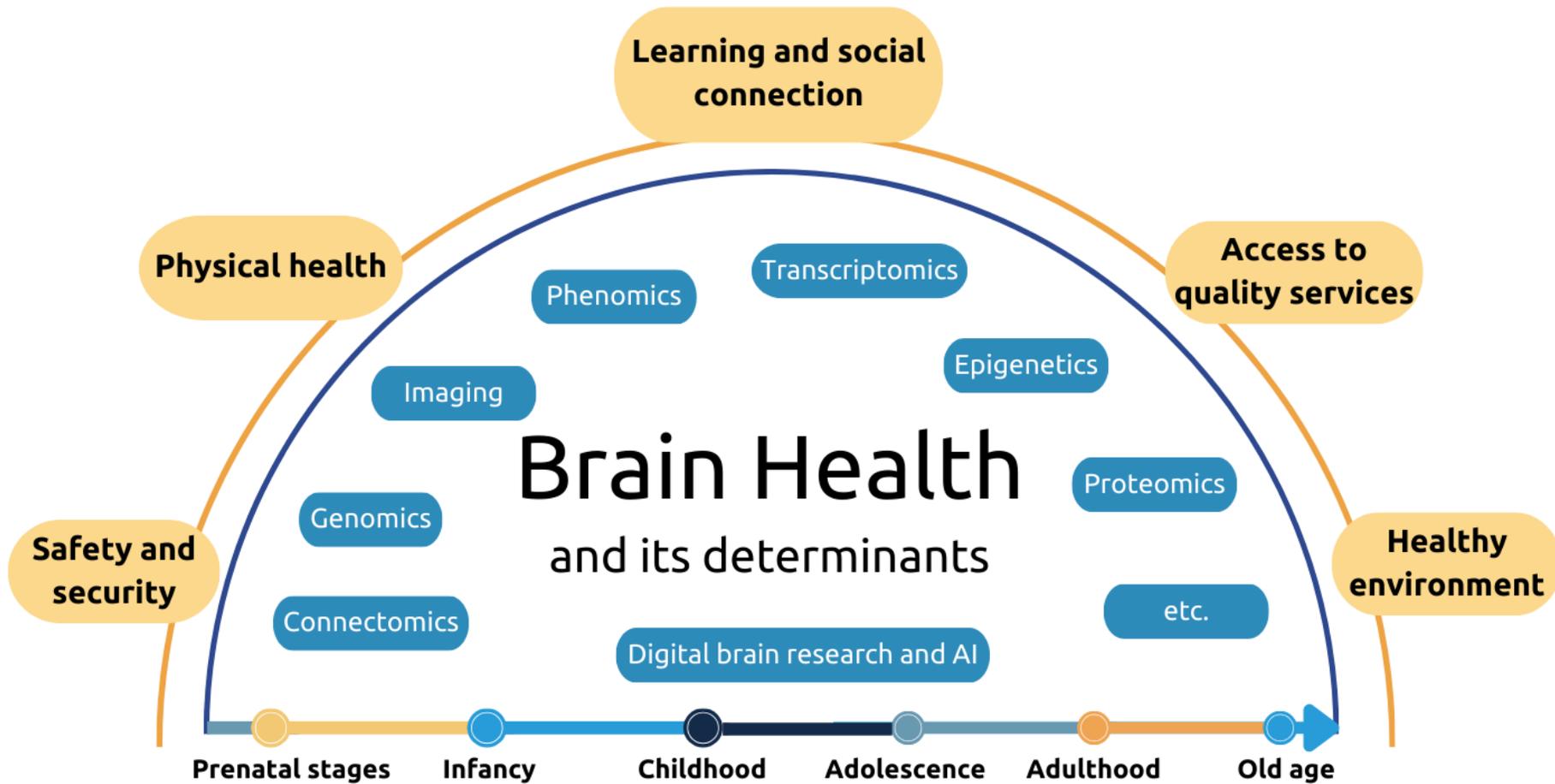
**Coordination & Support Action  
Brain Health**

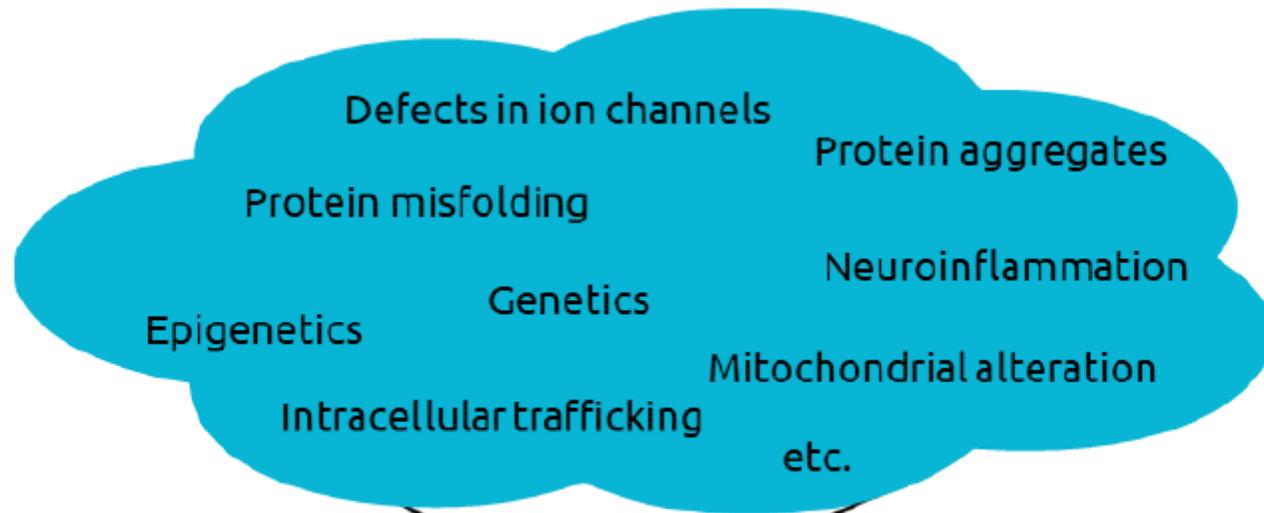
[www.brainhealth-partnership.eu](http://www.brainhealth-partnership.eu)

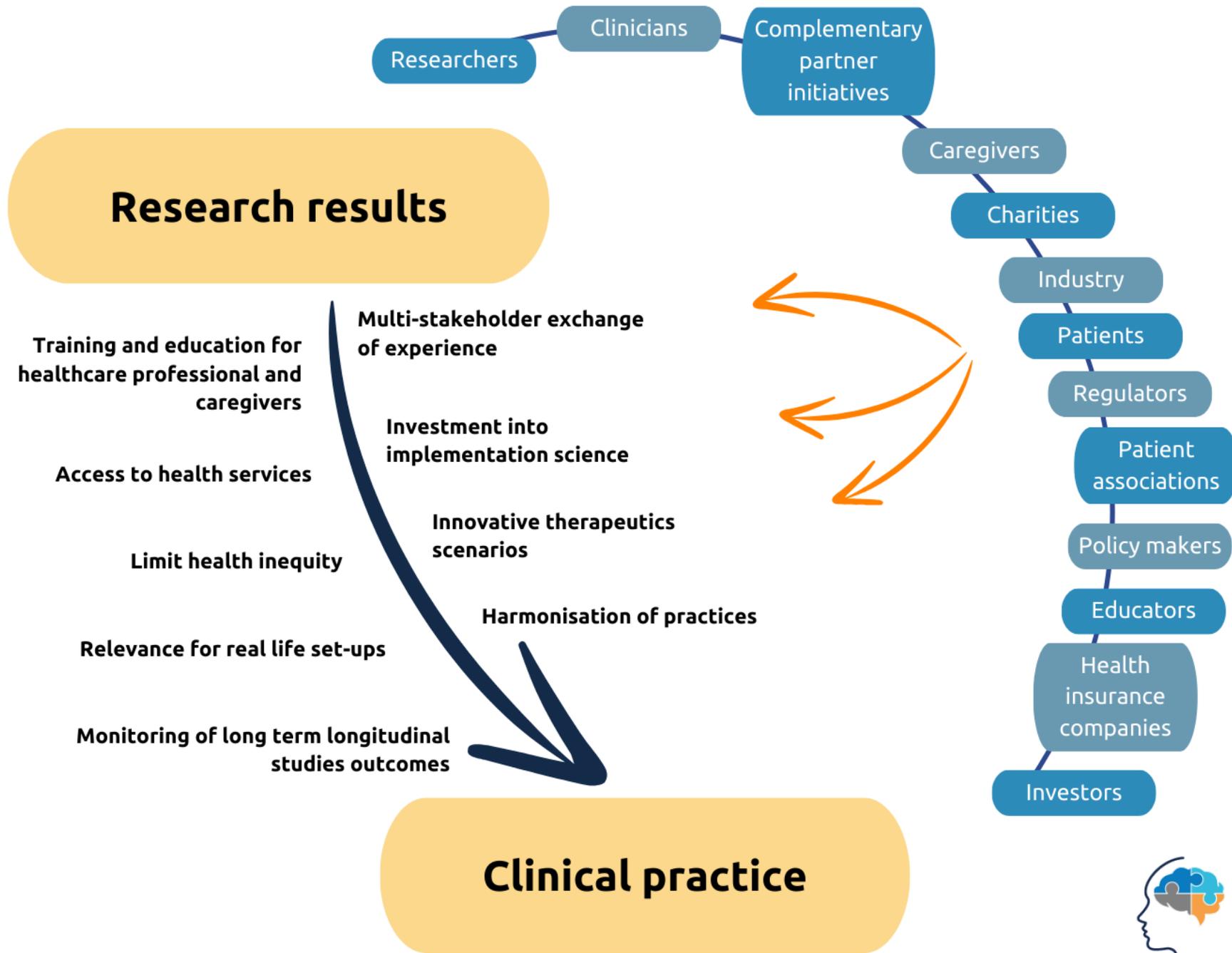



**BrainHealth  
PARTNERSHIP**



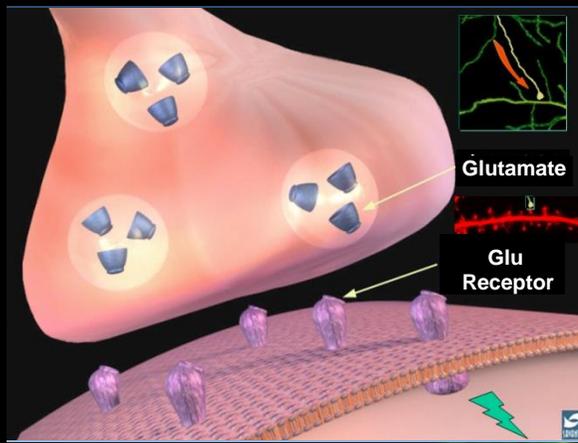




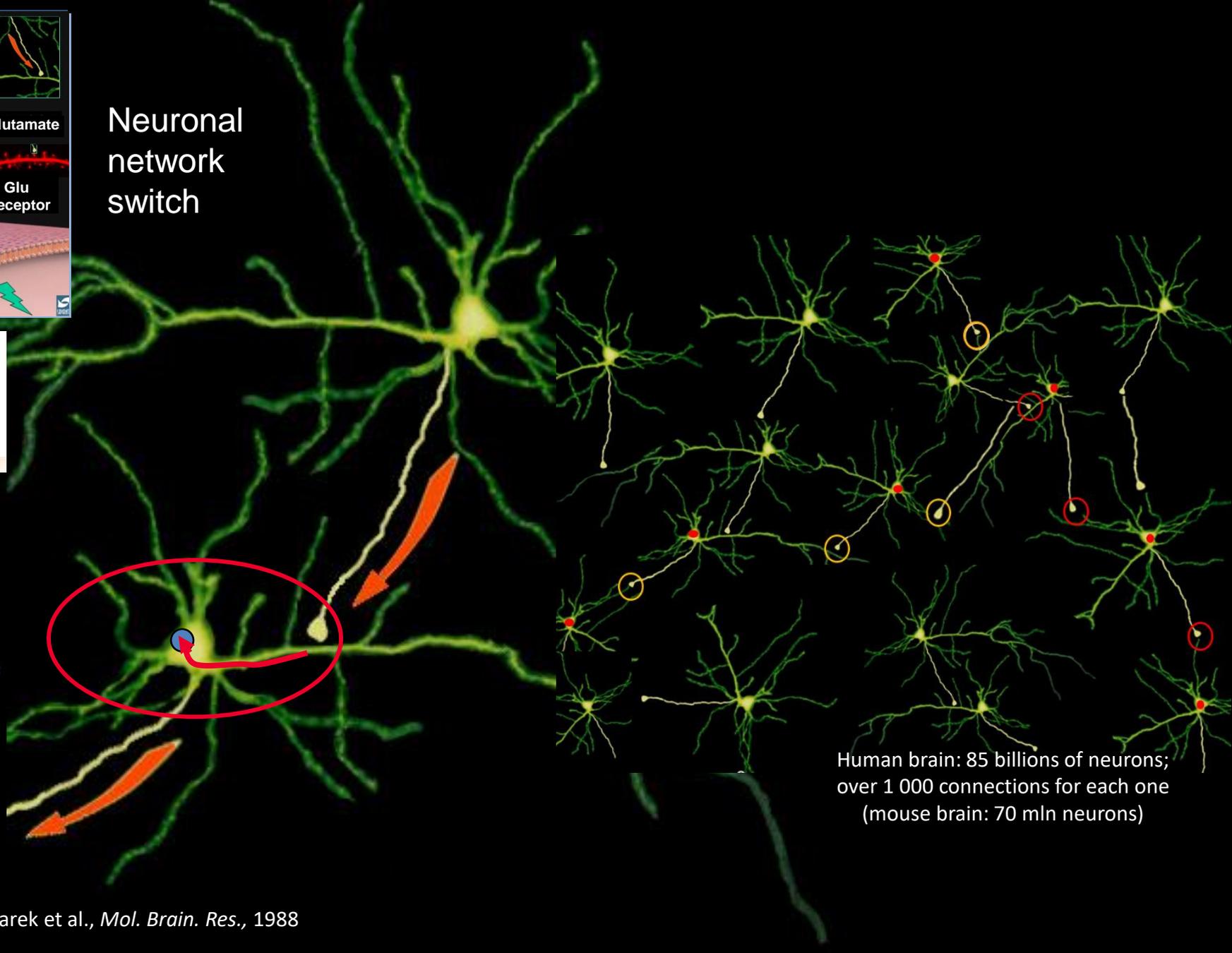
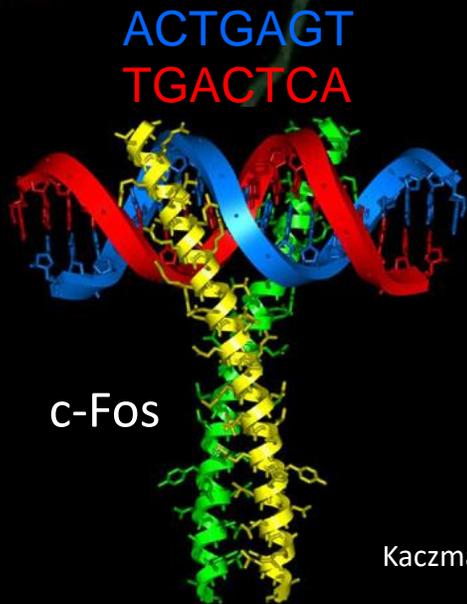
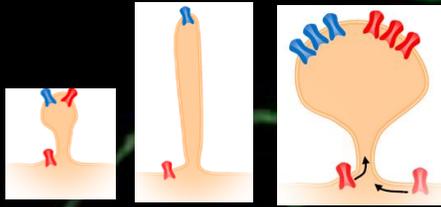


The basic idea that some type of change in synapses might be important for learning had been proposed by Cajal in 1894. ... A modern form of this hypothesis was put forward in 1948 by the Polish neuropsychologist Jerzy Konorski (who) argued that a sensory stimulus leads ... changes in the nervous system. The first, which he called excitability ....(and the) second, more interesting change, which **Konorski called plasticity, or plastic change**, leads, he wrote, to „permanent functional transformations ... in particular systems of neurons as a result of appropriate stimuli or their combination.”

E.R. Kandel: IN SEARCH OF MEMORY  
The Emergence of a New Science of Mind

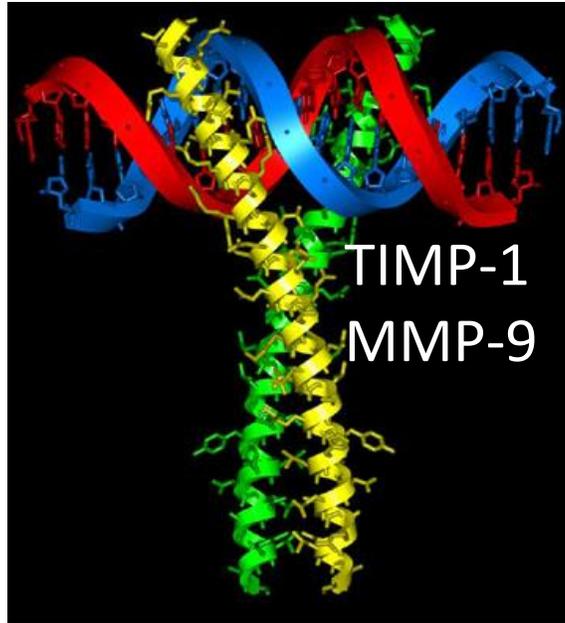


# Neuronal network switch

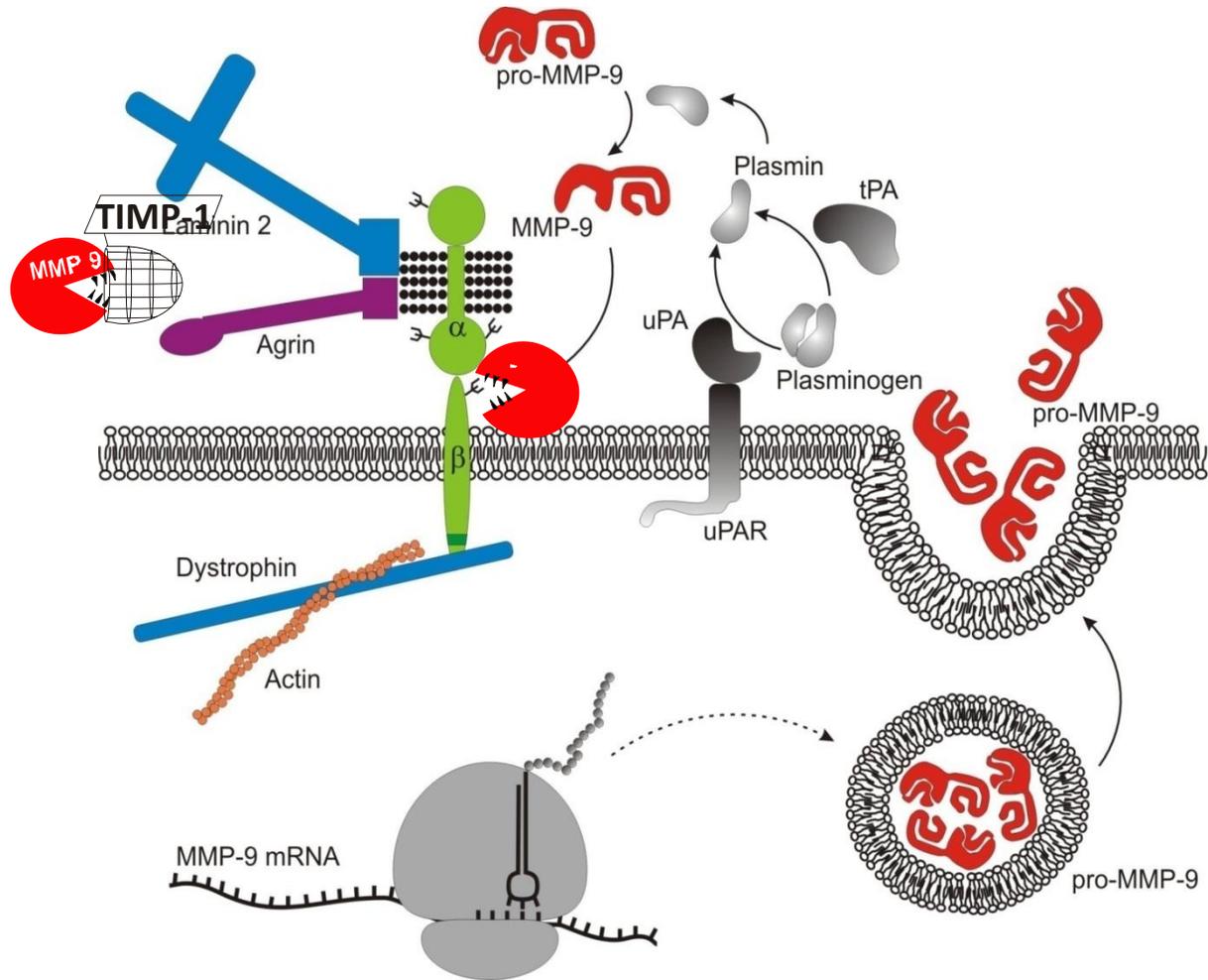


Human brain: 85 billions of neurons;  
over 1 000 connections for each one  
(mouse brain: 70 mln neurons)

# c-Fos drives TIMP-1 & MMP-9: Extracellular proteolytic system

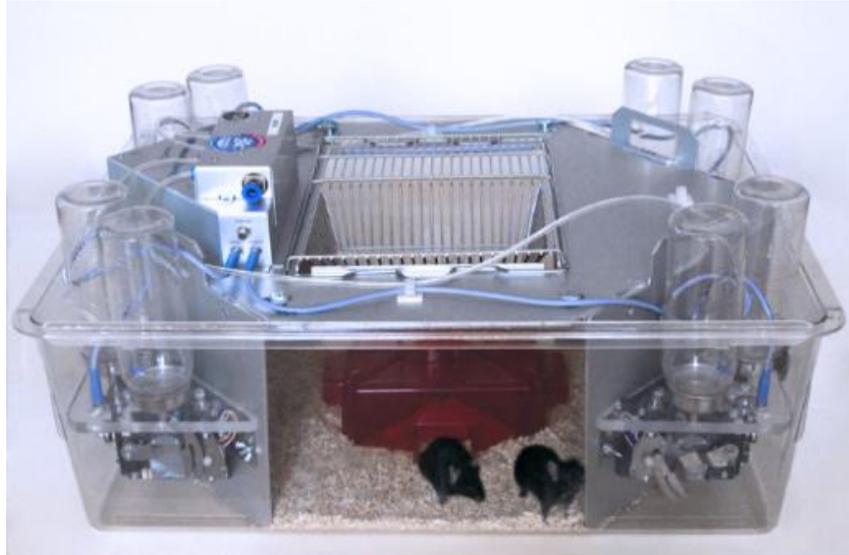


Jaworski et al., *J.Biol.Chem.*, 1999  
Kaczmarek et al., *EMBO J.*, 2002  
Kuzniewska et al., *Mol. Cell. Biol.*, 2013



Based on: Michaluk & Kaczmarek *Cell Death Differ.*, 2007

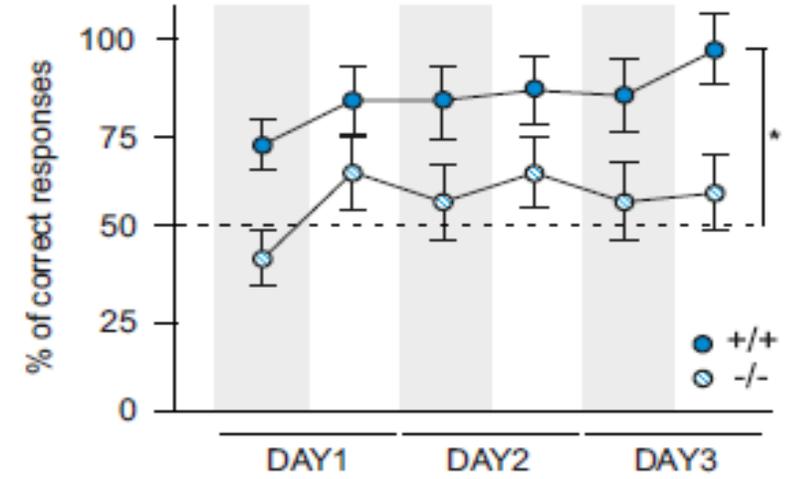
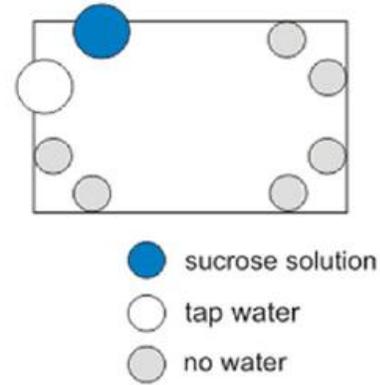
# Appetitive but not aversive learning depends on MMP-9



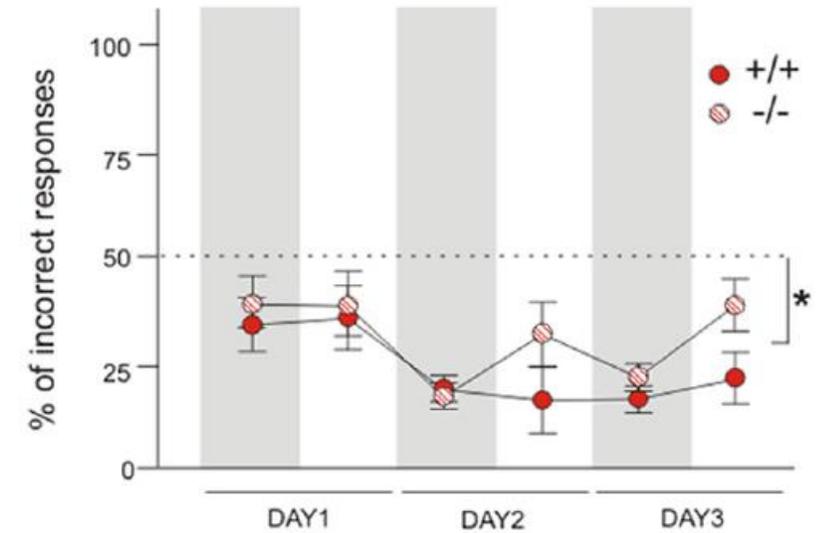
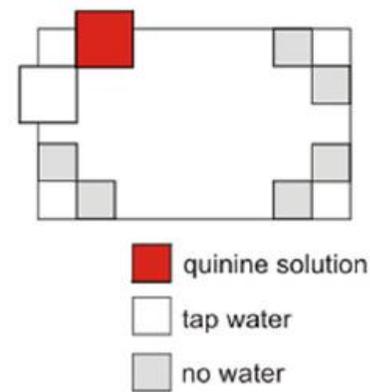
corner



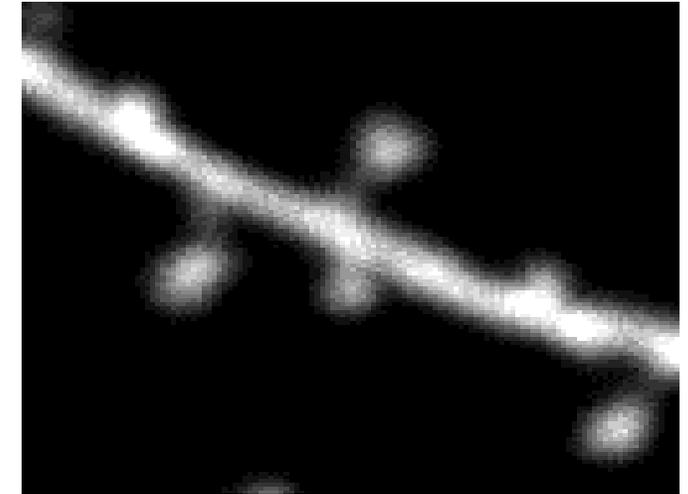
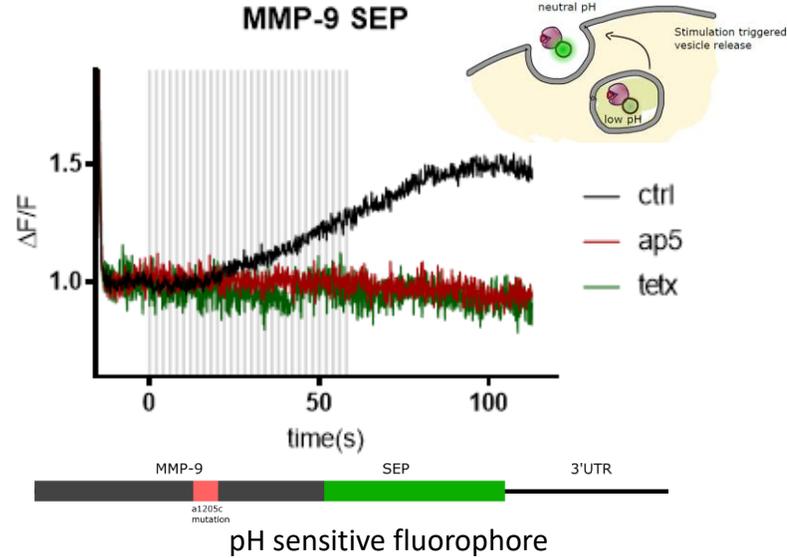
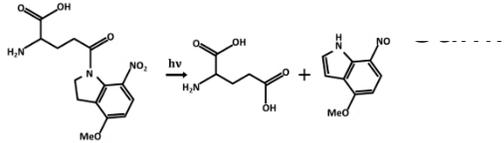
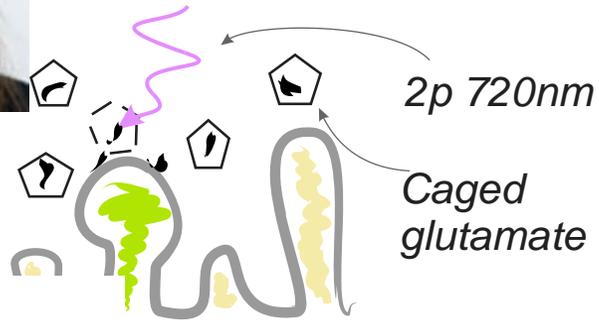
DISCRIMINATIVE  
APPETITIVE LEARNING



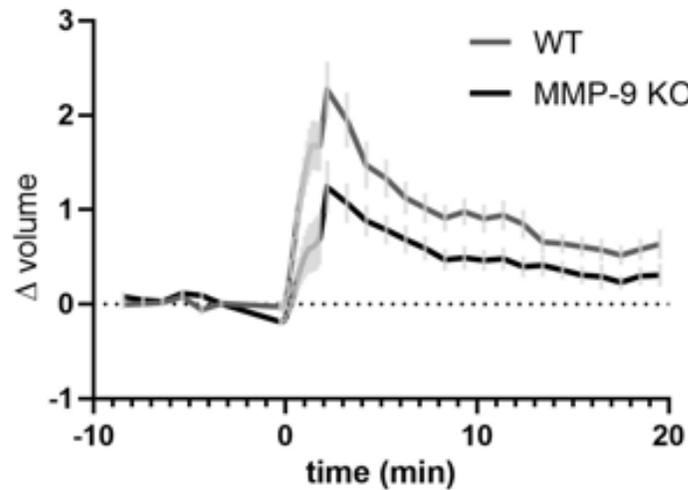
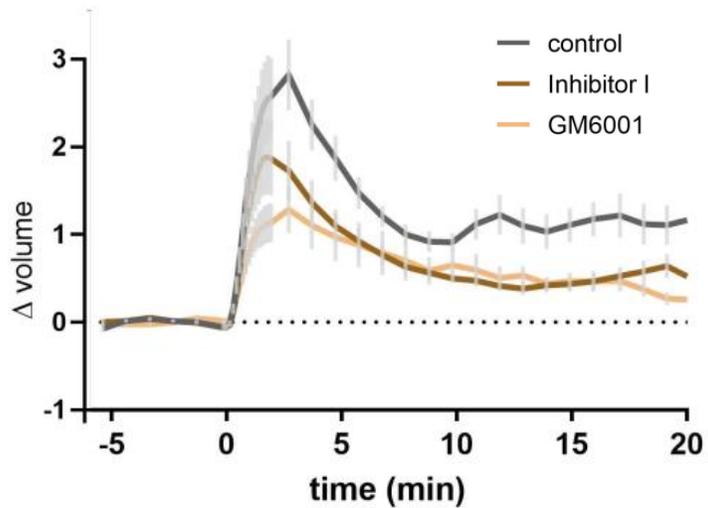
DISCRIMINATIVE  
AVERSIVE LEARNING



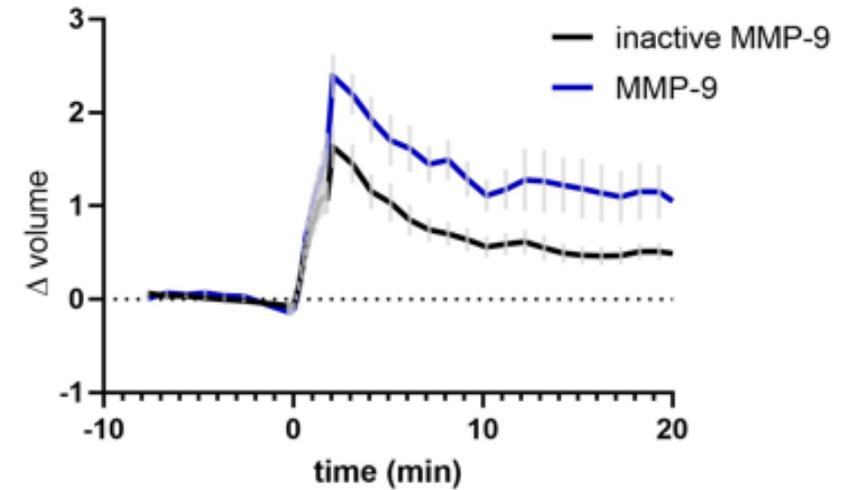
# MMP-9 plays a major role in structural LTP of the dendritic spine



## Time course of spine volume change



## MMP-9 KO

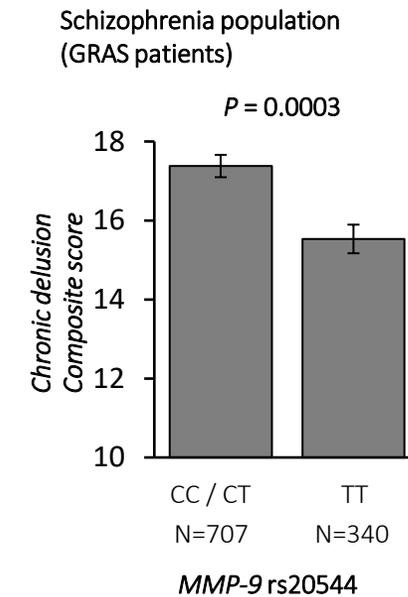


# MMP-9 in schizophrenia: Delusions

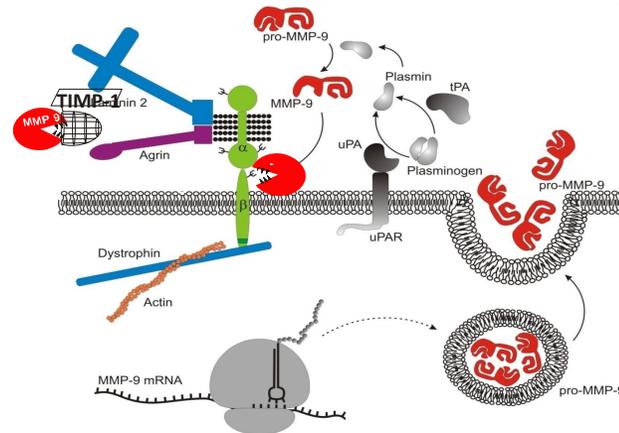


The GRAS (Göttingen Research Association for Schizophrenia) data collection was initiated in 2005. With >3000 phenotypical data points per patient, it comprises the world-wide largest currently available schizophrenia database (N > 1200), combining genome-wide SNP coverage and deep phenotyping under highly standardized conditions.

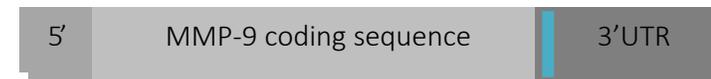
MMP-9 rs20544	GRAS patients N (%)	GRAS controls N (%)
CC*	220 (20.2)	232 (18.8)
CT	514 (47.3)	604 (48.9)
TT	353 (32.5)	399 (32.3)
Genotypic P = 0.623 Allelic P = 0.659		



Ehrenreich & Nave, *Genes*, 2014



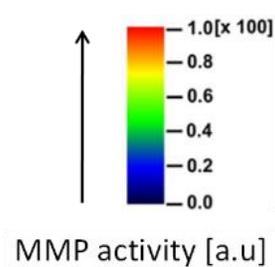
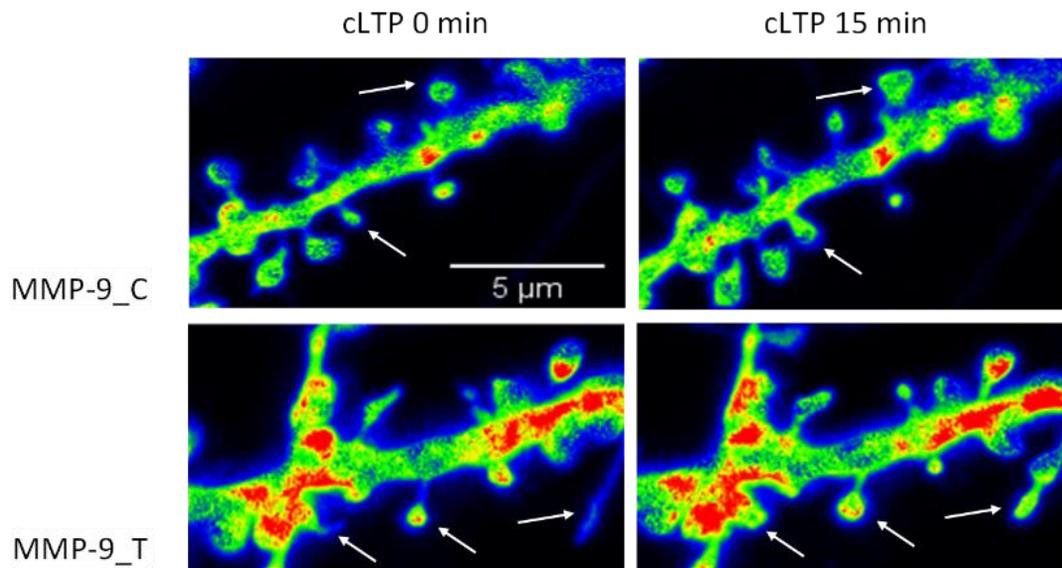
Based on: Michaluk & Kaczmarek *Cell Death Differ.*, 2007



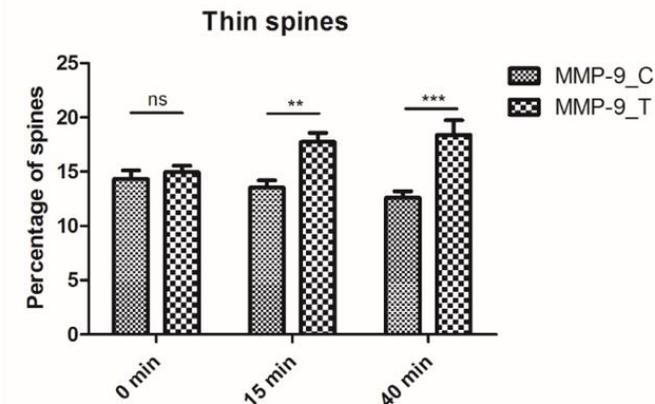
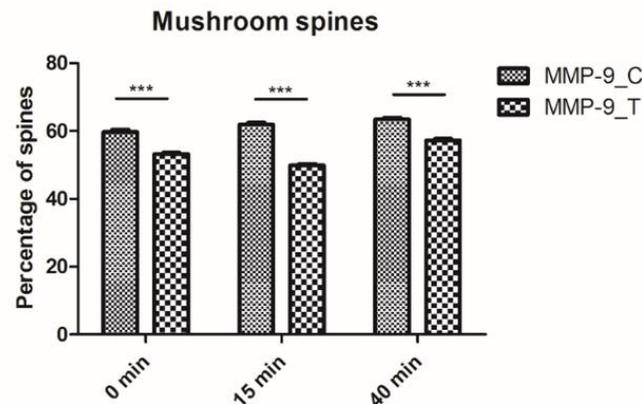
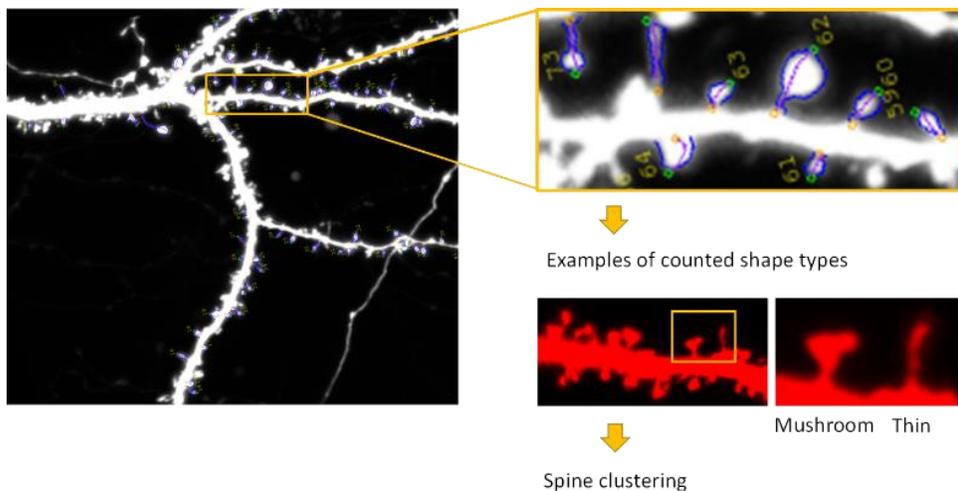
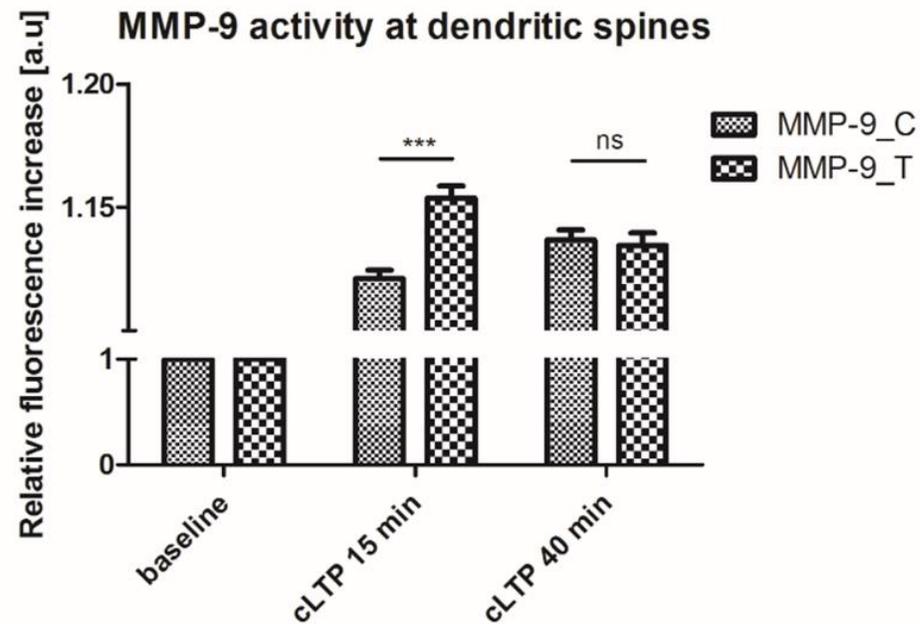
SNP rs20544: „C” or „U (T)”

Lepeta et al., *EMBO Mol. Med.*, 2017

# MMP-9 mRNA 3'UTR polymorphism affects spines

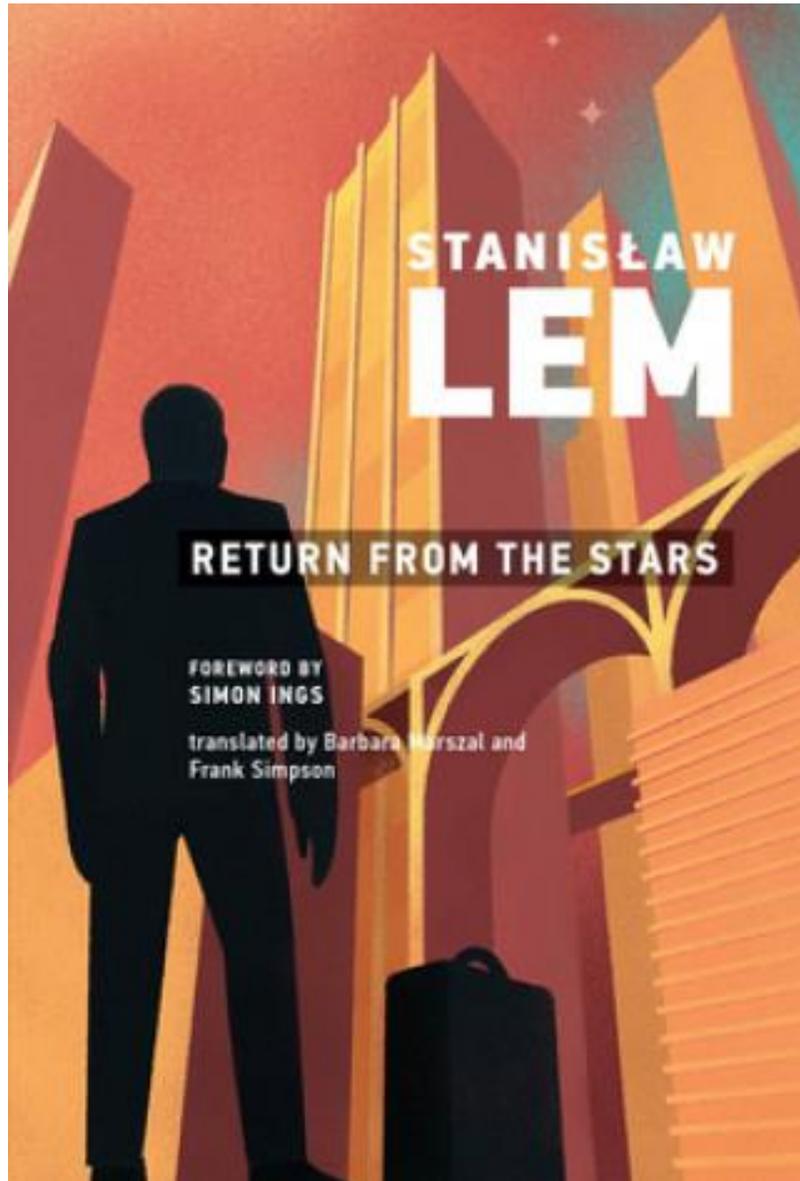


cLTP:  
Rolipram  
Forskolin  
Picrotoxin



- Synaptic plasticity and extracellular proteolysis are pivotal underpinnings of the brain-mind connection in neuronal physiology and pathology
- Expanding our understanding of those phenomena and harnessing this knowledge for benefit of science and society is a major brain health and disease research challenge

## Betrisation



The developing forebrain was affected at an early stage of life, through a group of **proteolytic enzymes**. The effects were selective: **reduction aggressive drives** in 80 to 88 percent compared to non-betrisized children; exclusion of the formation of associative relationships between acts of aggression and the sphere of **positive feelings**; reducing the possibility of taking personal life risks by an average of 37%. The greatest achievement was said to be that the changes did not have a negative impact on development of intelligence or the formation of personality, and what is perhaps even more important - the resulting limitations did not operate on the principle of anxiety feedback. In other words, subject didn't kill because he was afraid of the act itself. This would be the result of neurotization, fear infection of all humanity. He didn't do it because "it couldn't occur to him." (S. Lem, 1961)