Bridging neuropsychology with genetic nanotechnologies to treat diseases of the brain

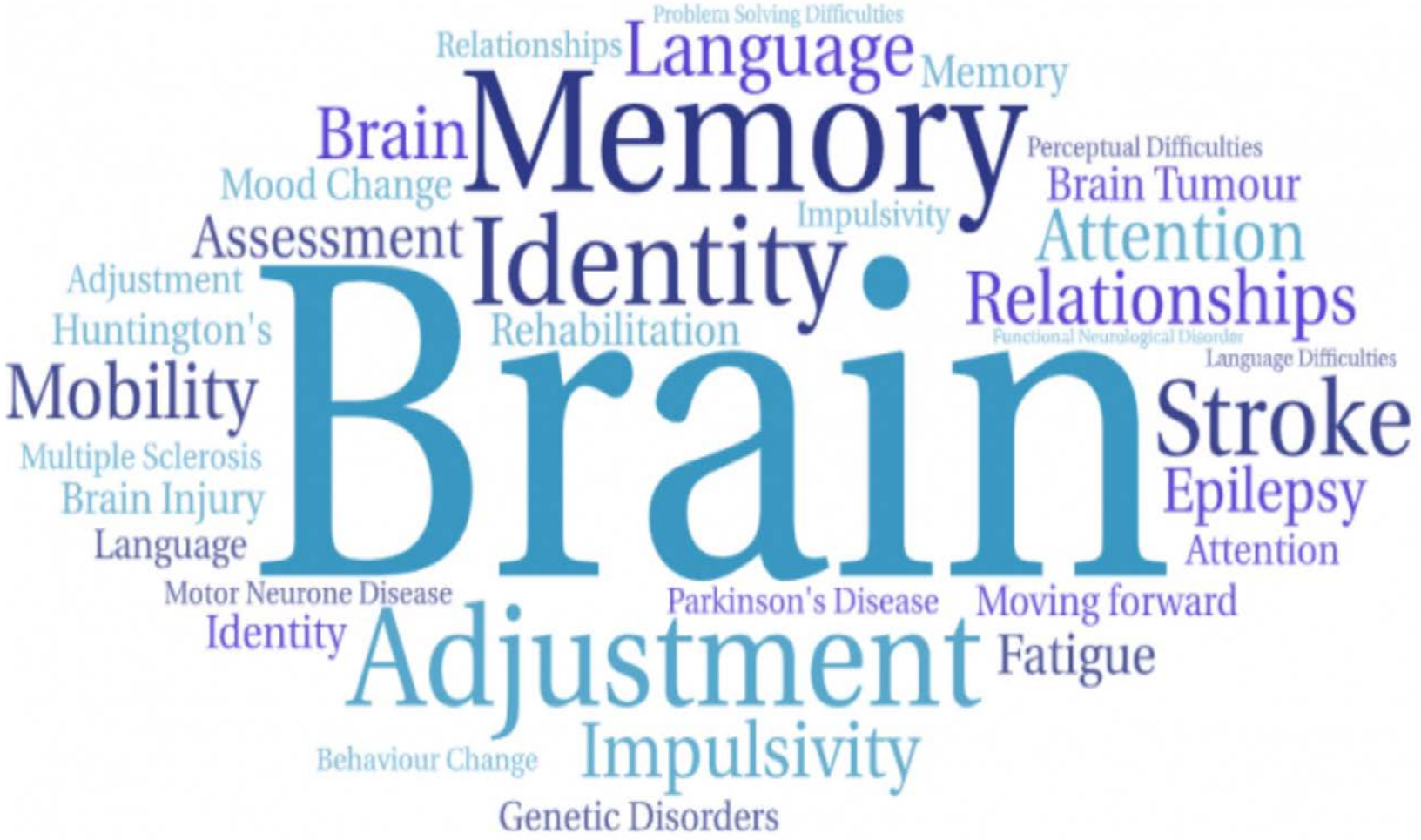
Mazahir T. Hasan, PhD
Ikerbasque Professor

Laboratory of Brain Circuits Therapeutics
Achucarro Basque Center for Neuroscience

“Brain makes us as who we are”

Neuropsychology and beyond…

To understand human psychiatric conditions and neurological disease, and abnormalities induced from birth or by injuries and traumatic experiences, we need to understand how human brain works



WHY STUDY THE HUMAN BRAIN?

IT FORMS
OUR
PERSONALITY,
MAKES US
WHO WE ARE

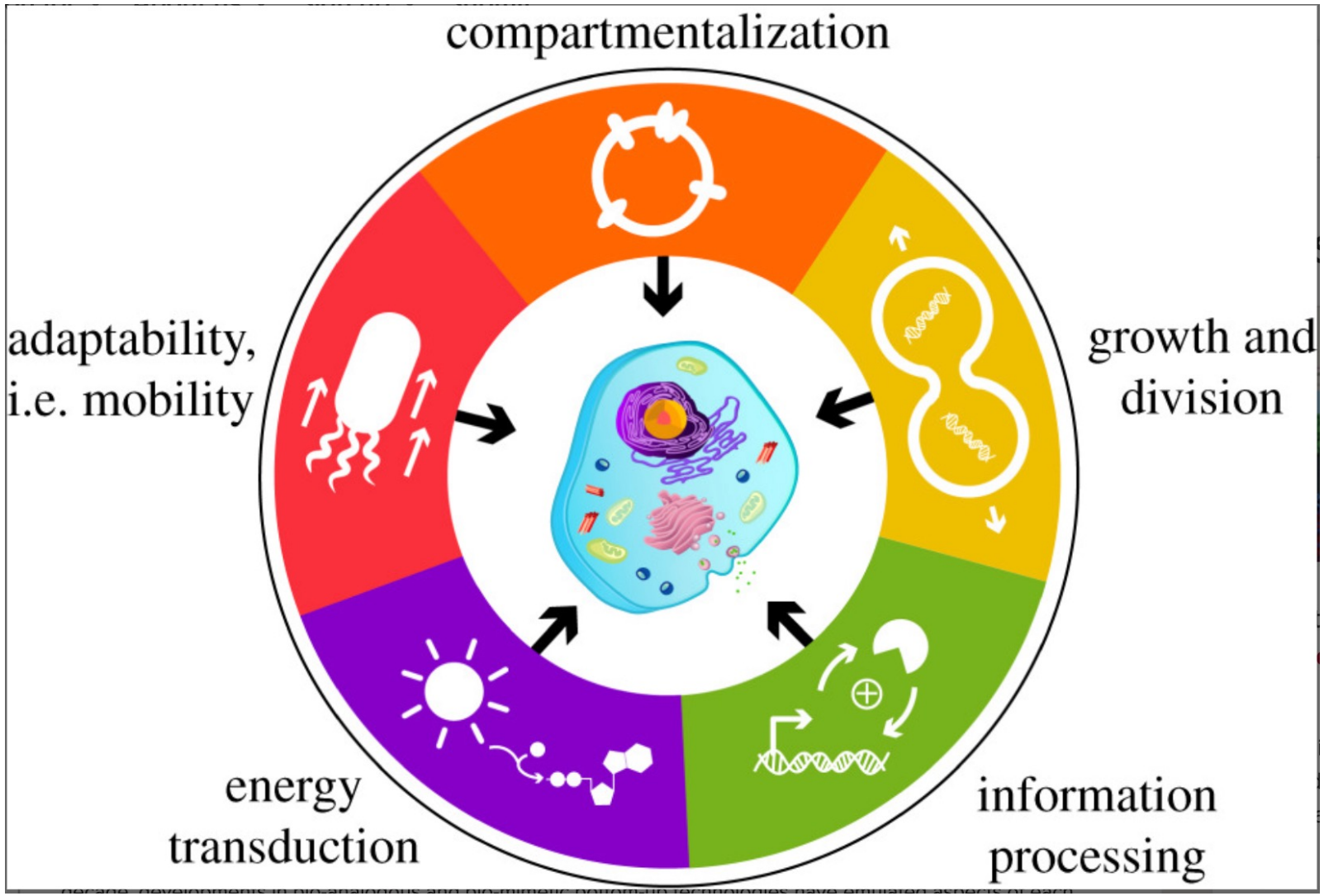

THE HUMAN BRAIN
AN UNRESOLVED
PUZZLE OF OUR TIME


THE HUMAN BRAIN
THE MOST FASCINATING
ENDEAVOR IN MODERN SCIENCE

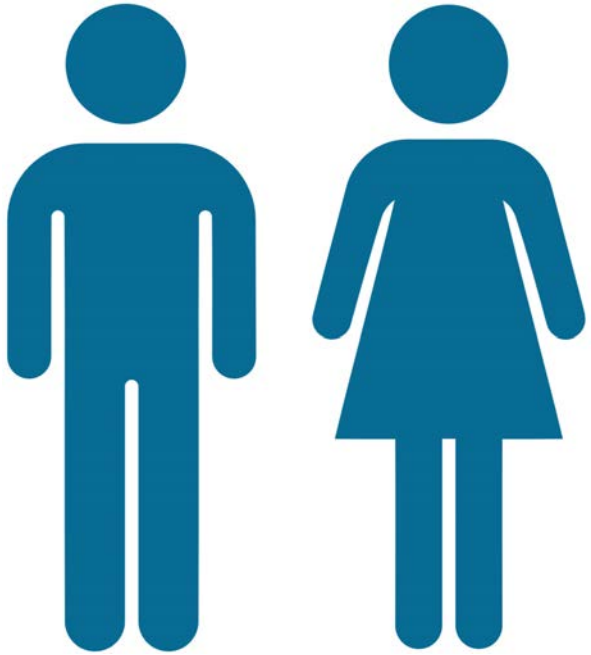
We can understand the human brain by first understanding its building blocks

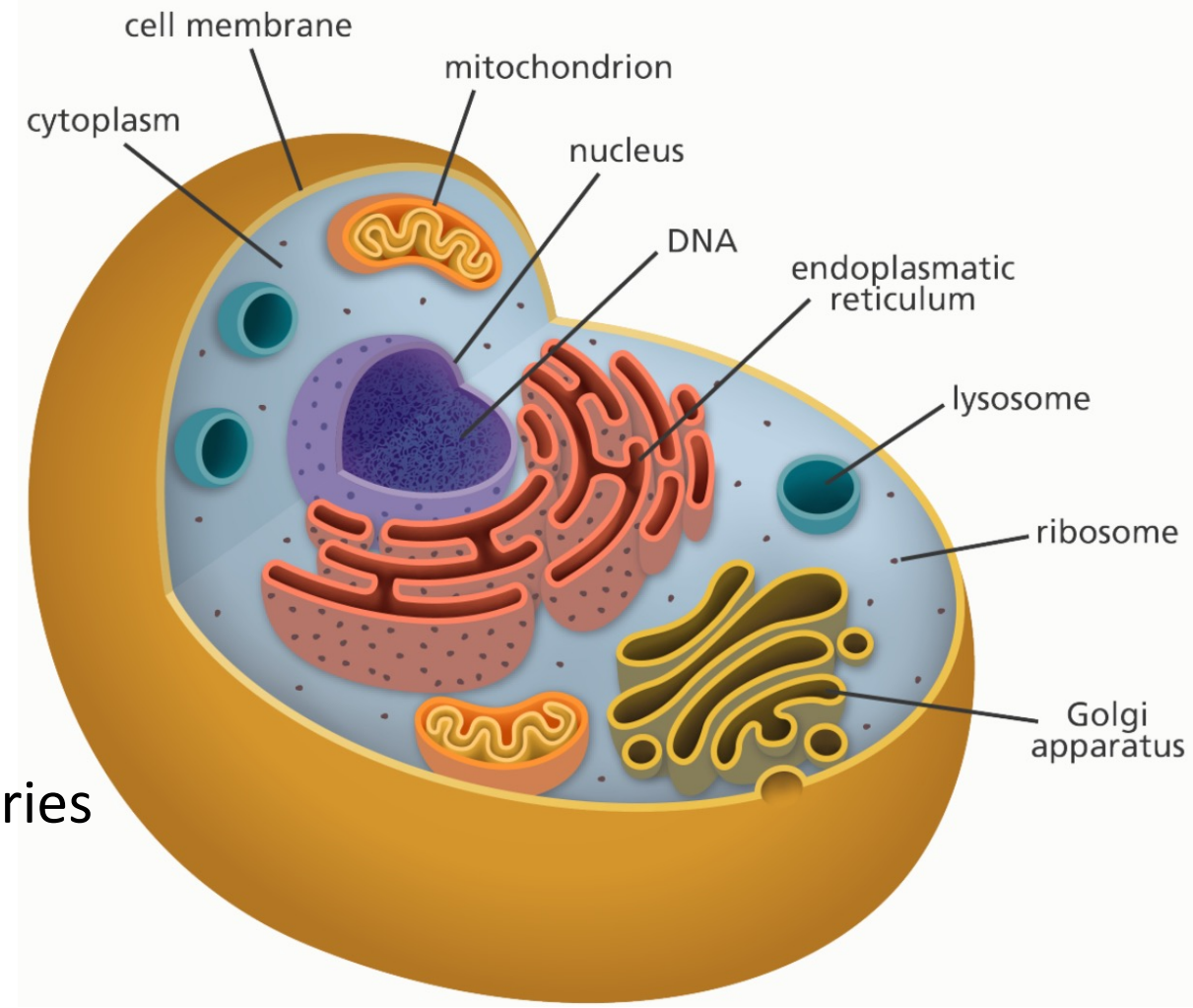
Living species and behavior

A single cell (bacteria), multicellular organisms (worm)
and most complex of all, mammals, (human)



Human has 37.2×10^{12} cells





Cell's molecular machineries operate it's functions

There are ~ 20,000 genes in almost every cell of our body. Small differences in gene expression (1%) makes us uniquely as who we are as individuals.

Genes control important cellular functions

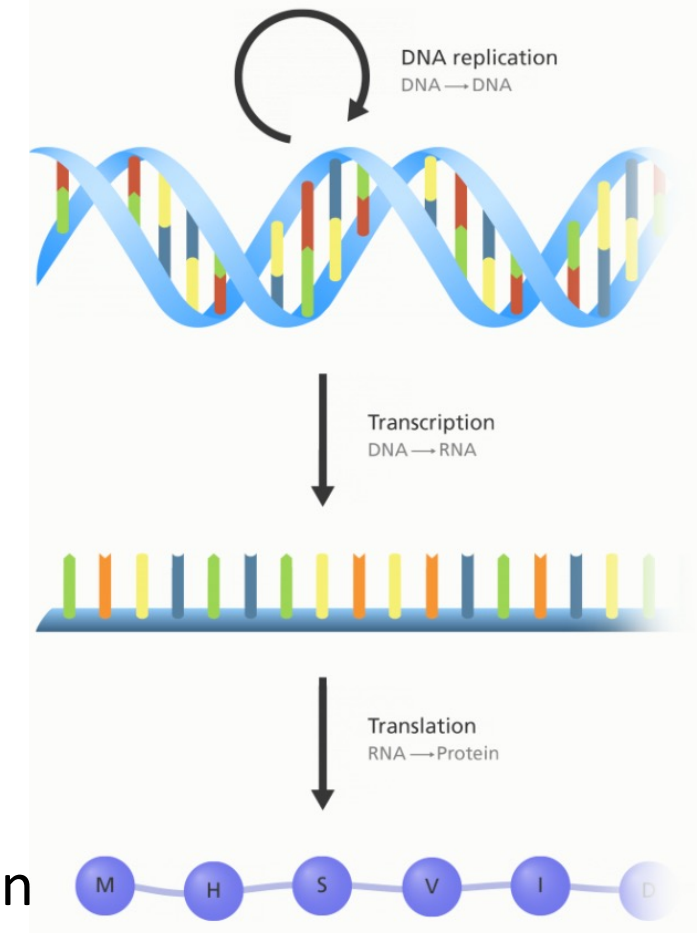
Single change in protein sequence can cause disease

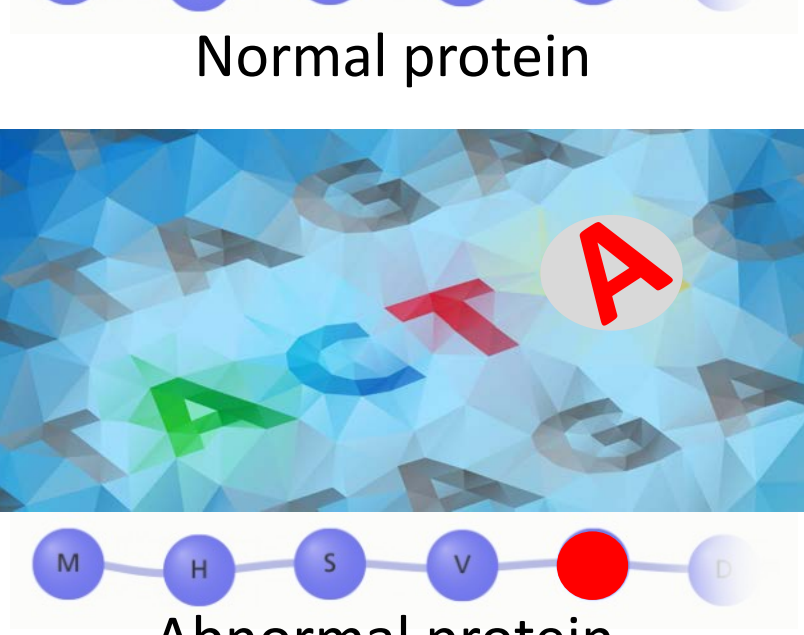
Each cell has

DNA

RNA

Protein





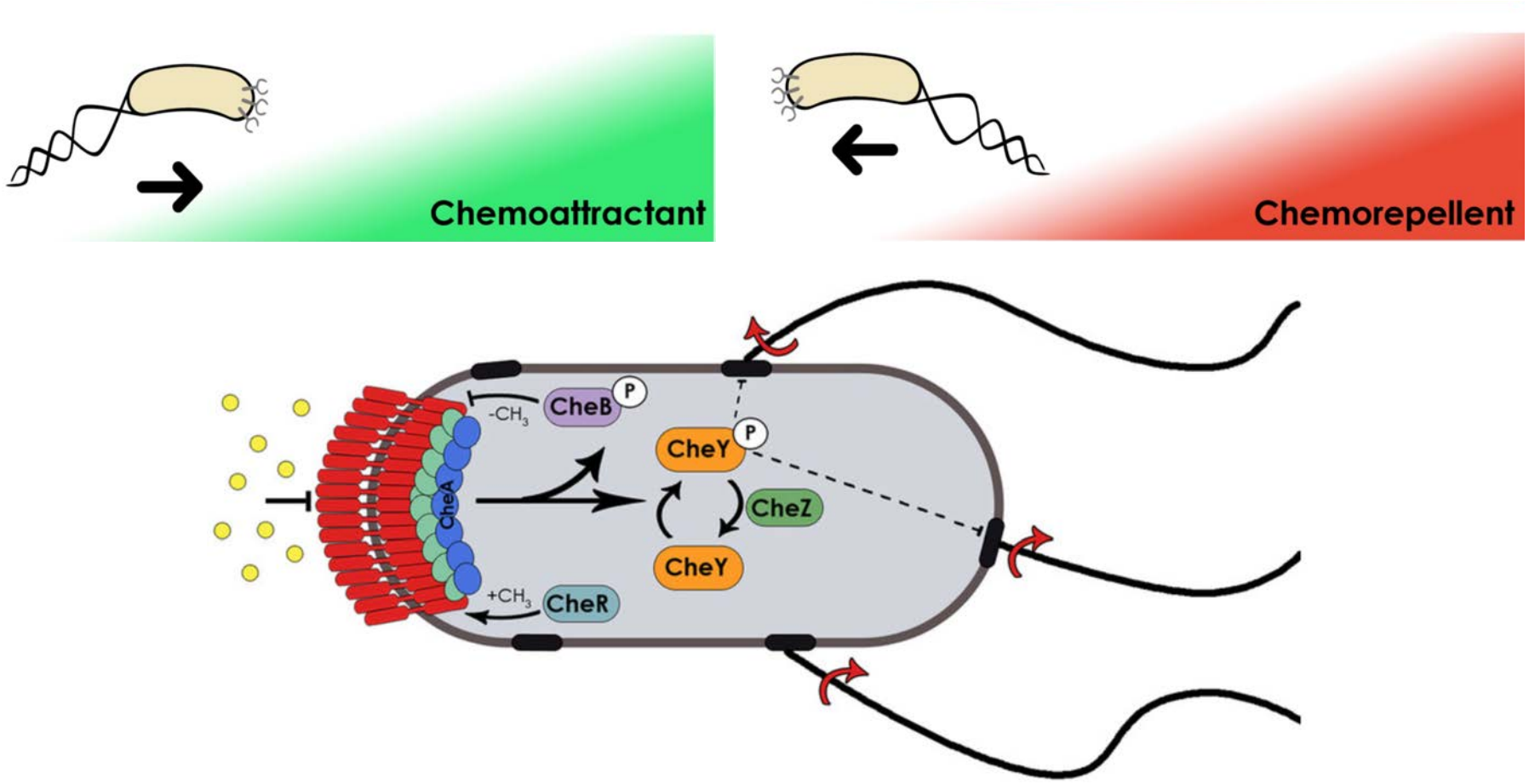
Normal protein

Abnormal protein

Bacteria: biochemical and behavior response

Bacterial size = ~ 1 micrometer

Chemotaxis



Human brain and behavior response

Specialized brain regions and circuits:

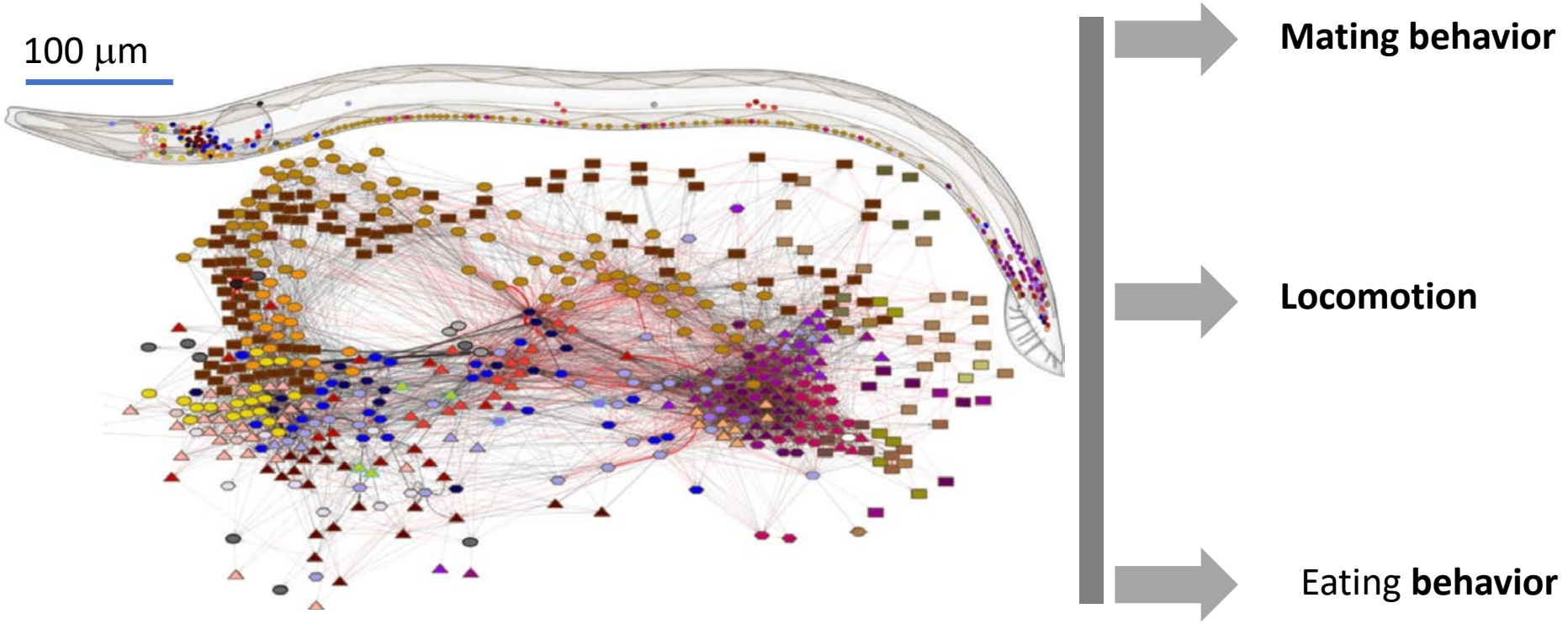
(1) Sensing danger and forming fear memories

(2) Sensing safety and generating positive and reward memories

Happy/Reward

Danger/Fear

Little worm (nematode): neurons and behavior

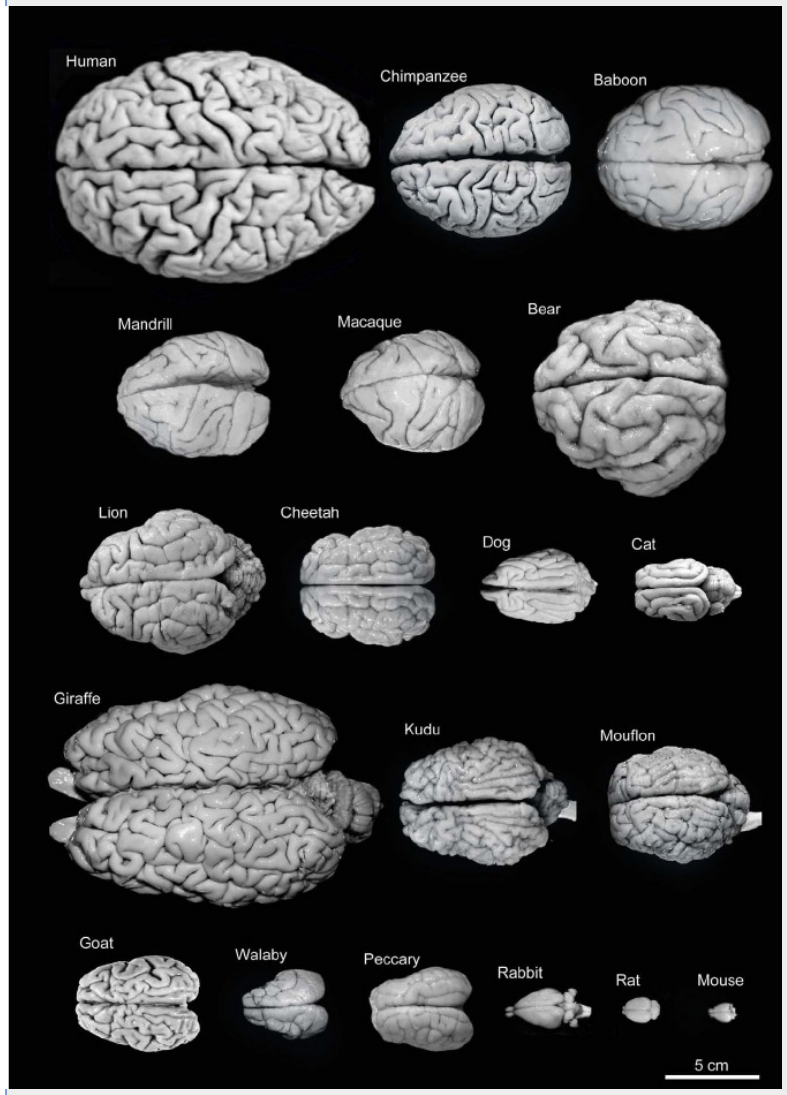


The Big Challenge:

Nematode has 302 neurons that controls multiple behavior.
Their connectivity has been mapped, but we still **don’t** fully understand how the worm's nervous system produces the different behaviors

“The human brain and circuits”

The BRAIN



2,700 X

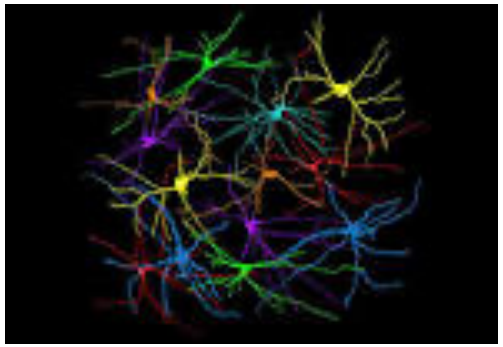
Mouse
Brain volume = 500 mm^3
Hippocampus volume = 26 mm^3
Neocortex volume = 120 mm^3

Human
Brain volume = 1350,000 mm^3
Hippocampus volume = 3,000 mm^3
Neocortex volume = 660,000 mm^3

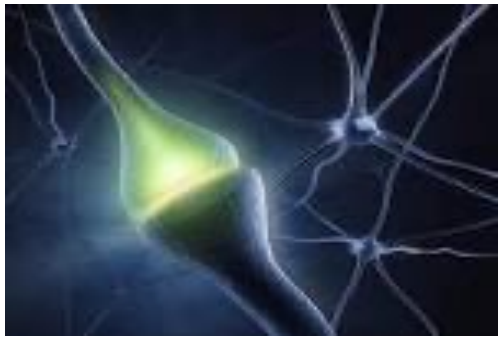
Brain at different spatial scales

Subregions

Neuronal assemblies



Synaptic connections



100 BILLION NEURONS
100 BILLION GLIA

HOW DOES IT WORK?

WHAT HAPPENS WHEN
SOMETHING GOES WRONG

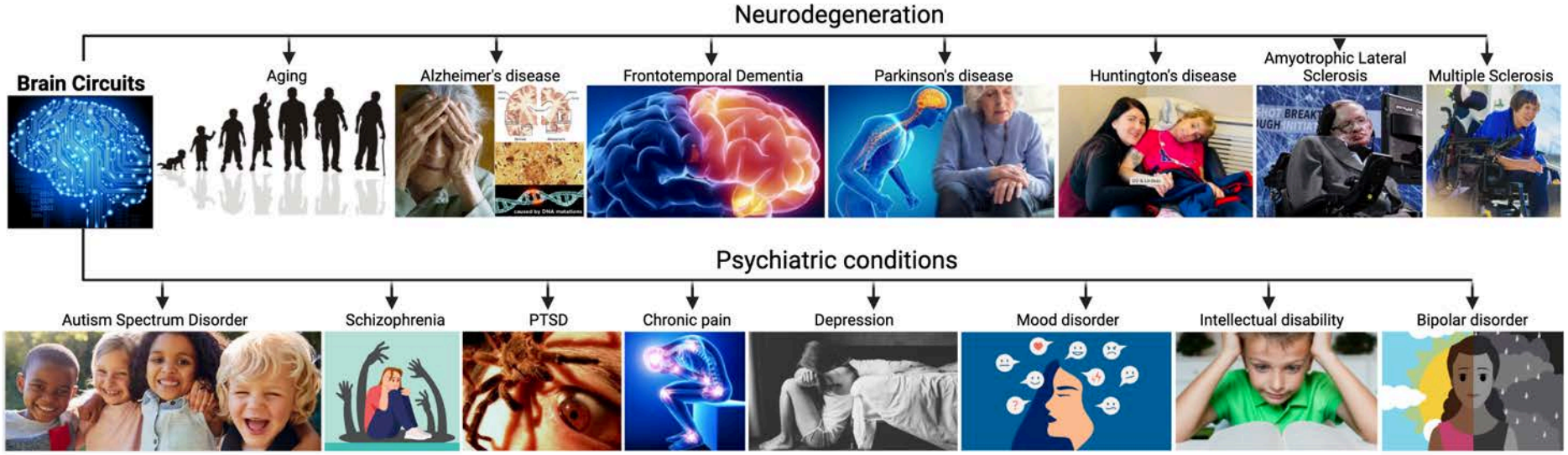
“Brain conditions and diseases: how they emerge”


Diseases of the
Human Brain
>50% of human diseases
affect the nervous system

Neurological and psychiatric diseases: there is no cure

Gene mutations can lead to diseases

Over 4000 human diseases
are caused by a single gene mutation



Why there is no treatment or cure?

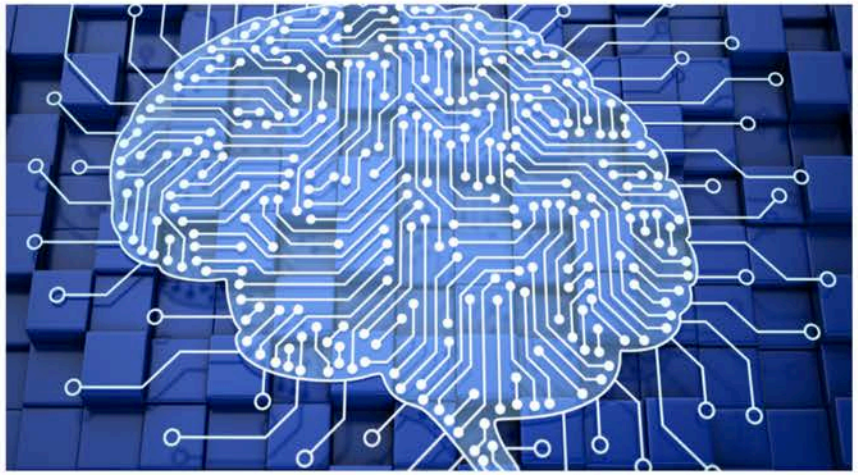
“We really don’t understand how the brain works”

“The state-of-the arts to understand the human brain”

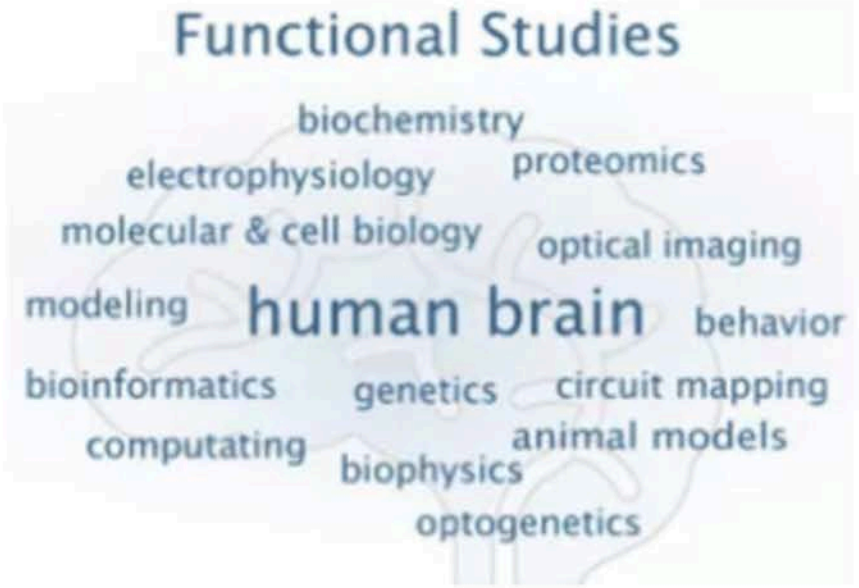

Collaboration
generates ideas
=
Discovery

Mouse as a model to tackle human diseases

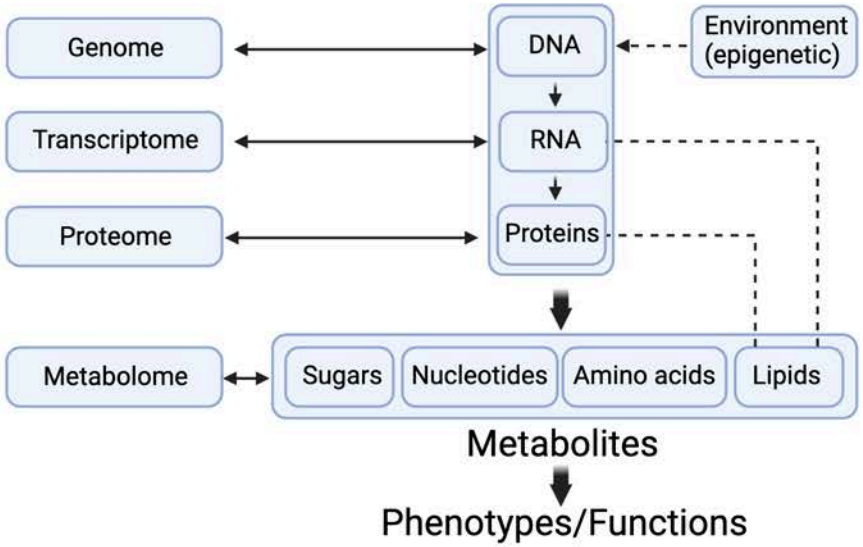
Anatomical and functional brain connectivity

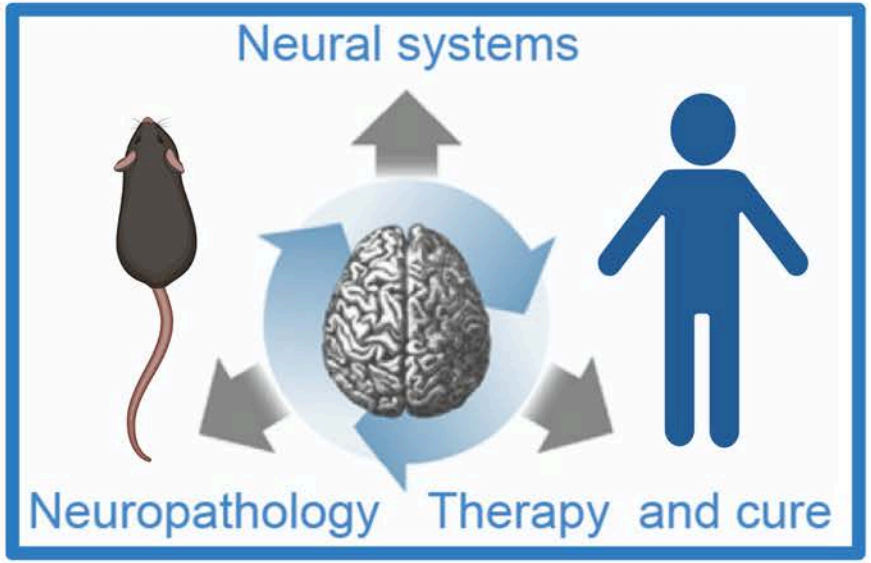


Functional Studies

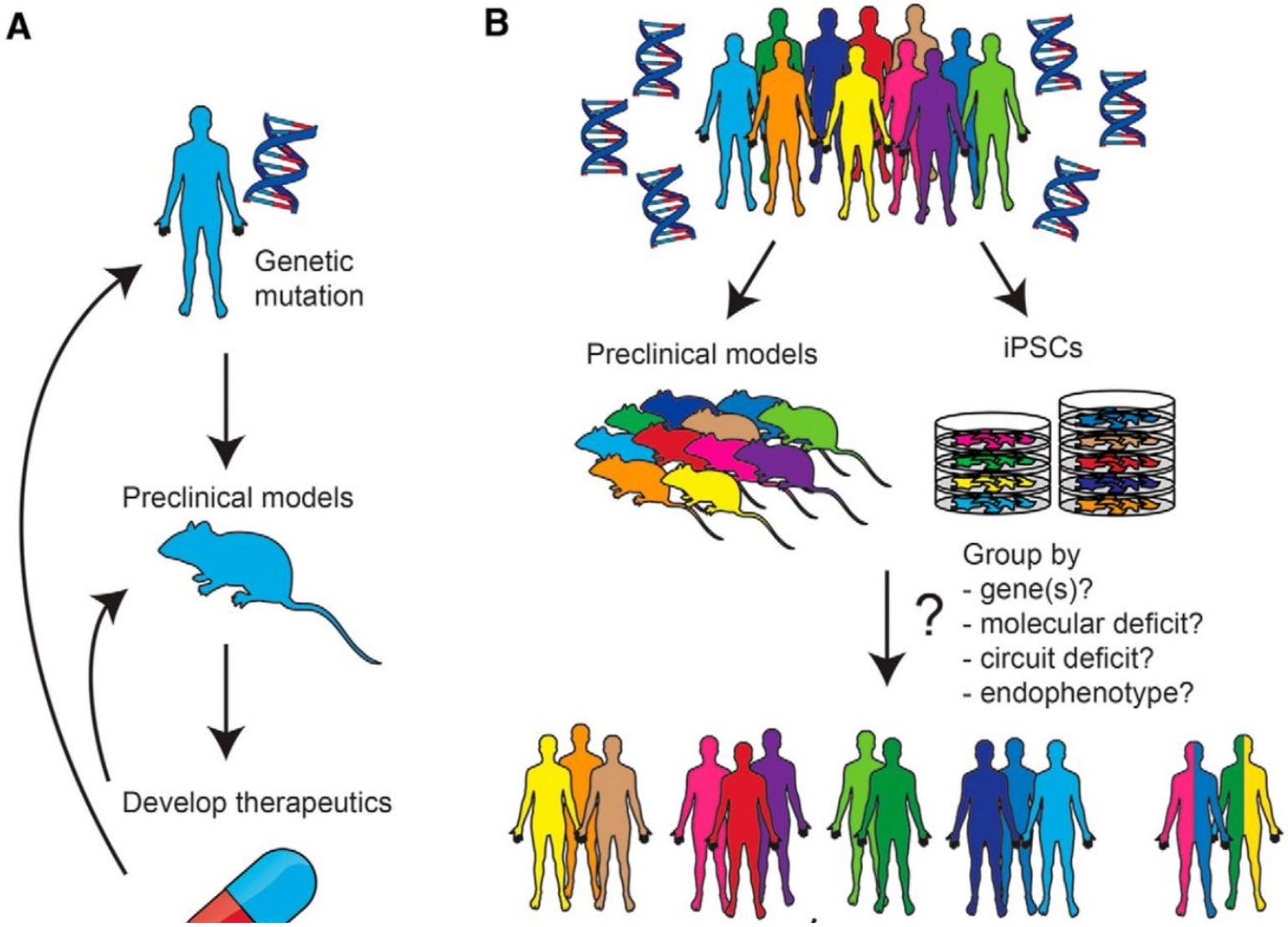


Genetic and environmental factors

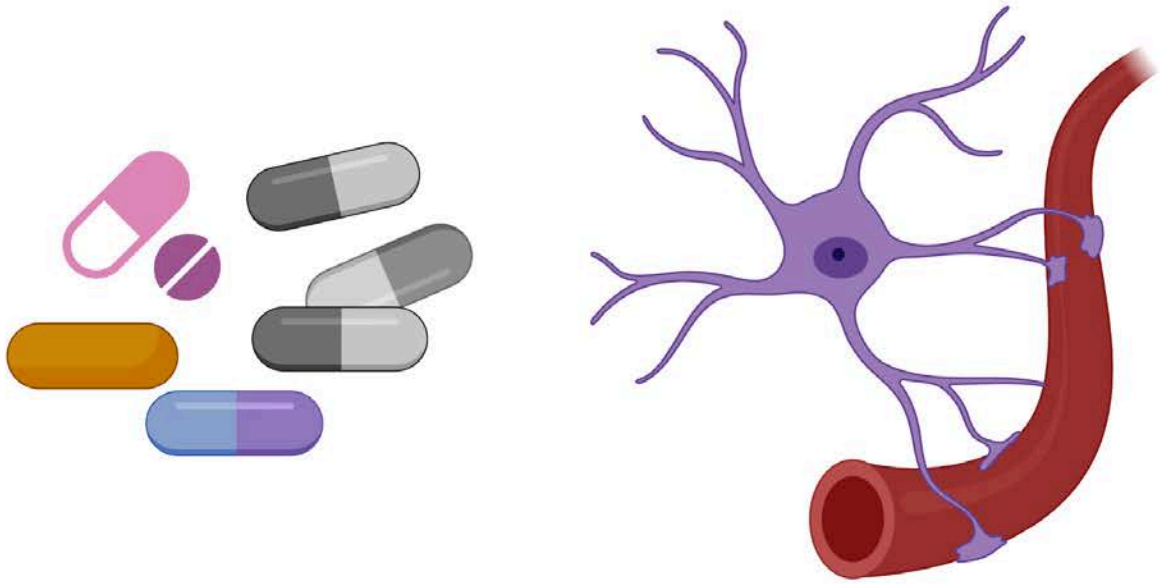




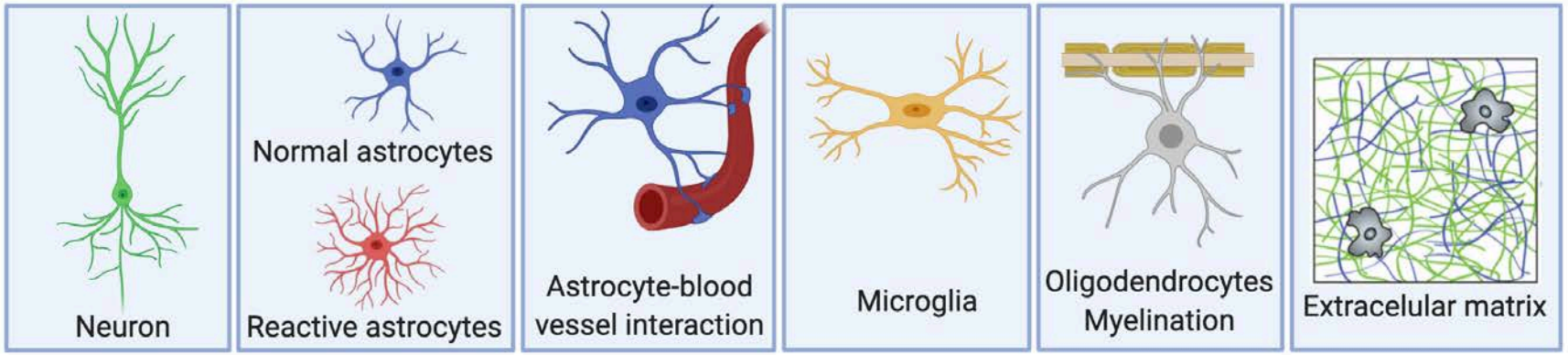
Single gene mutation affects people differently
Precision medicine is needed to serve patient´s needs



Drug delivery to the brain is a major hurdle



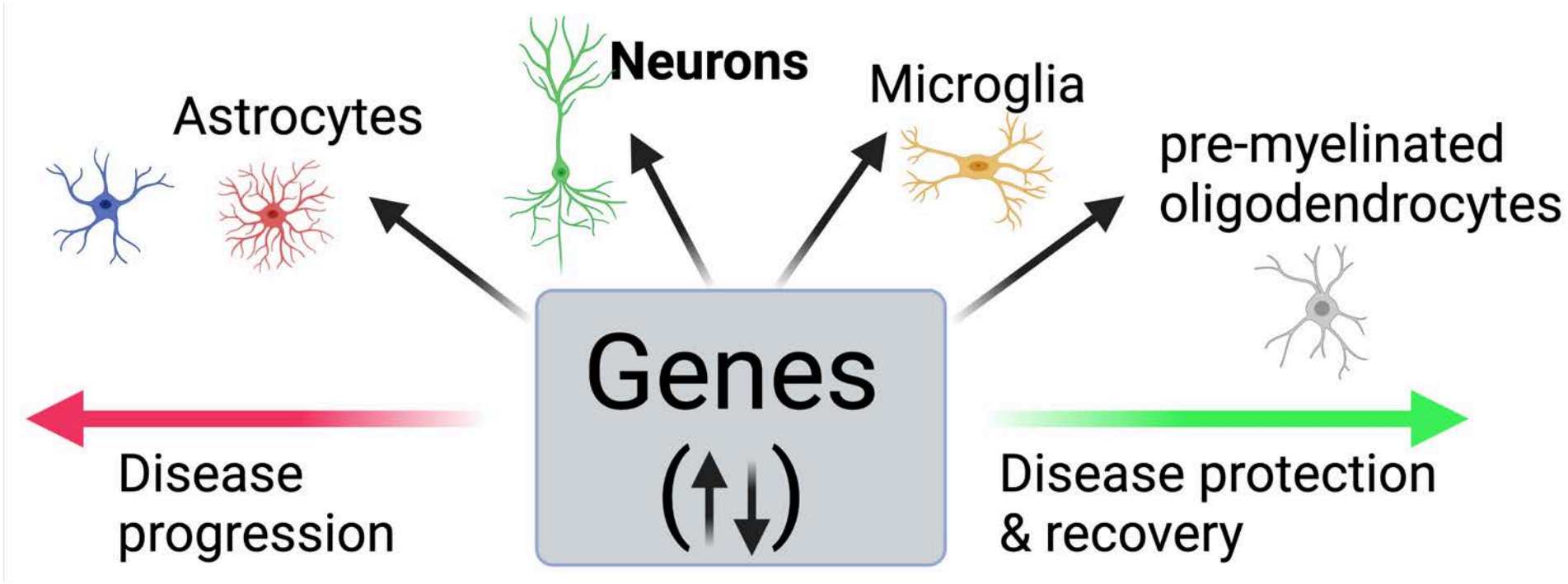
Drugs have non-specific effects on the body and brain;
they affect all brain cell types and components,
thus hindering effective therapeutics



“What is the solution to treat brain diseases and conditions?”

Genetic nanotherapeutics to target disease-specific circuits for precision medicine

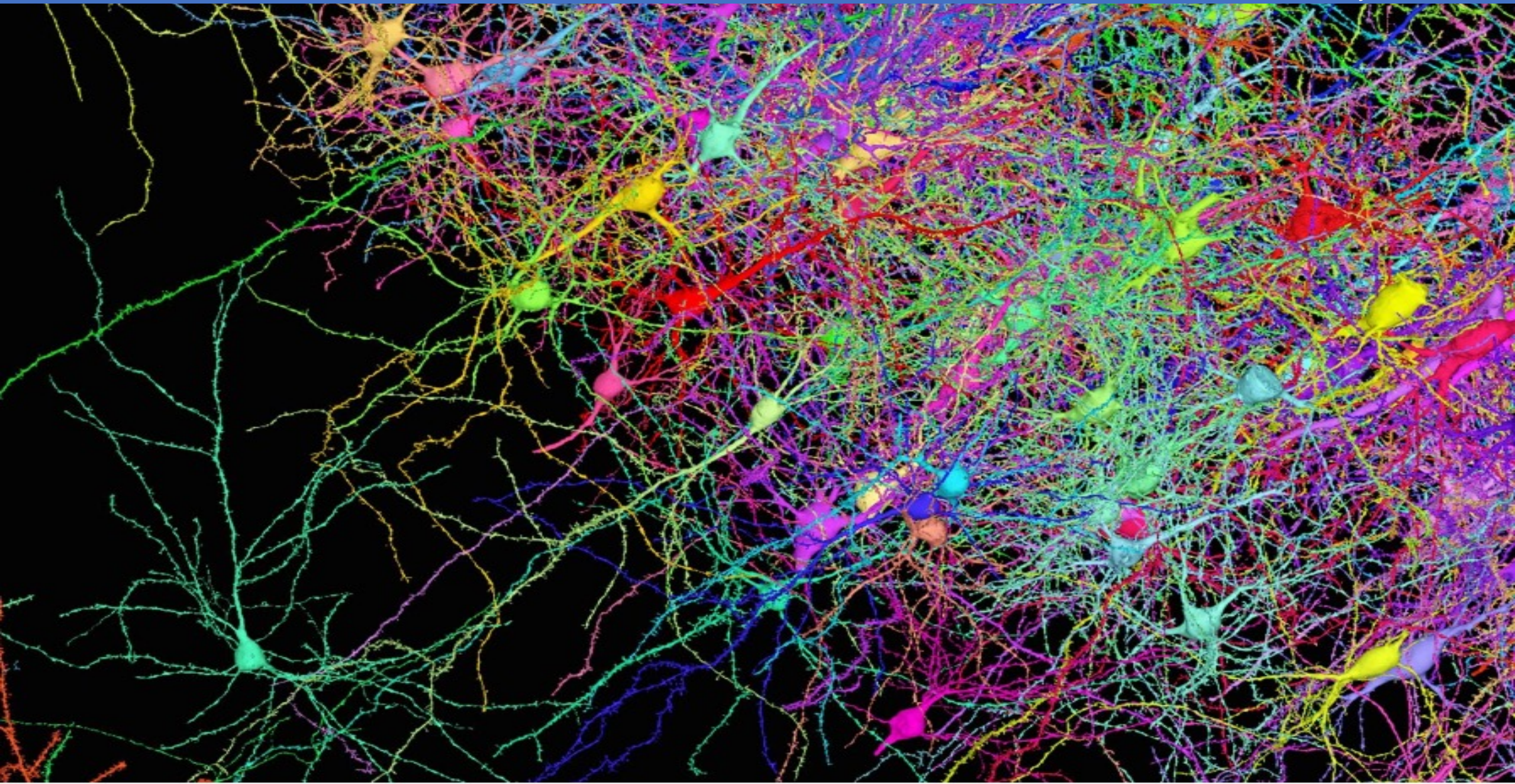
Different brain cell types and circuits perform different functions, which become abnormal during different stages of diseases. To restore their functions, we need to precisely target them and control "**gene activity and circuit functions**".



We need novel technologies for delivering therapeutics to selective neural circuits to treat brain all diseases

We are on our way towards the “golden age” of precision medicine

Anatomical and functional brain connectivity



Piano has 88 keys

52 white keys and 36 black keys

Beautiful music by
Mozart, Beethoven and others

Brain has 100 billion neurons & 100 billion astrocytes

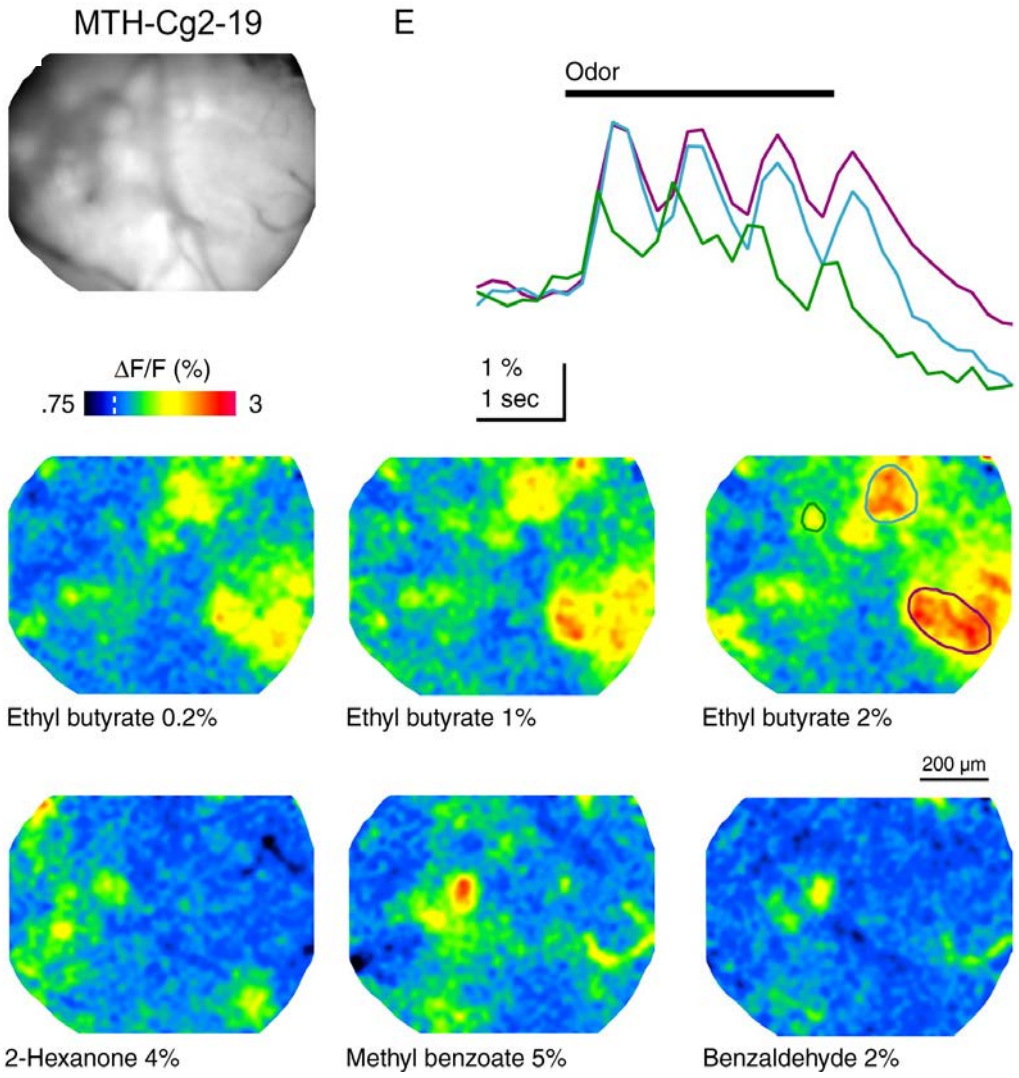
Every neuron can make 1000 connections with other neurons

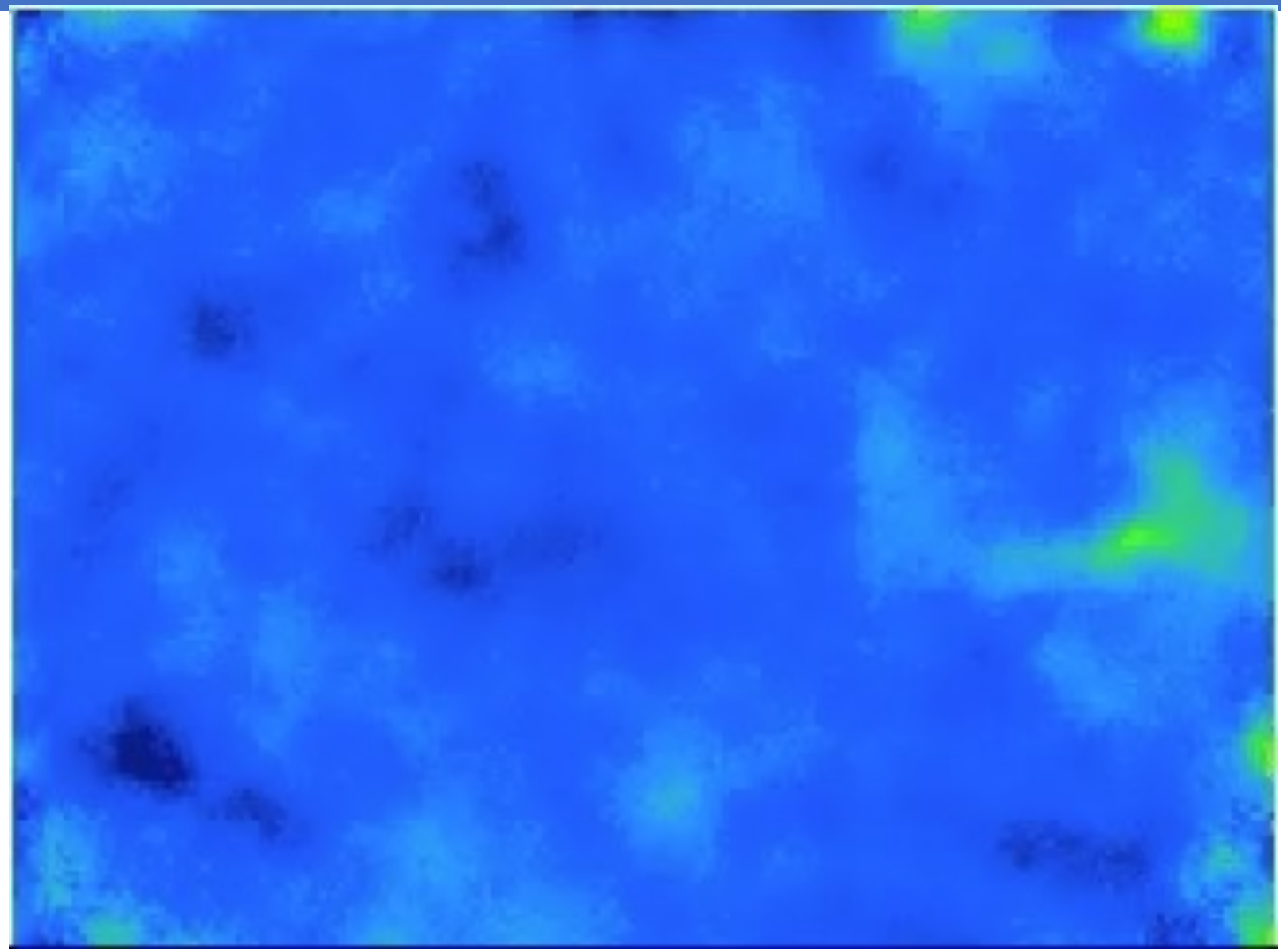
Each astrocyte contacts 2 million synapses at a time

$10^{11} \times 10^{3} \times 10^{6} = 10^{20} =$ **100×10^{18} keys**

It is this "brain symphony" orchestrated with **100×10^{18}** keys that allows us to see, hear, smell, taste, and touch. Makes us feel, learn, memorize and behave. **It give us consciousness and makes us as who we are as individuals.**

Mapping activity in response to different types of smell molecules in the brain



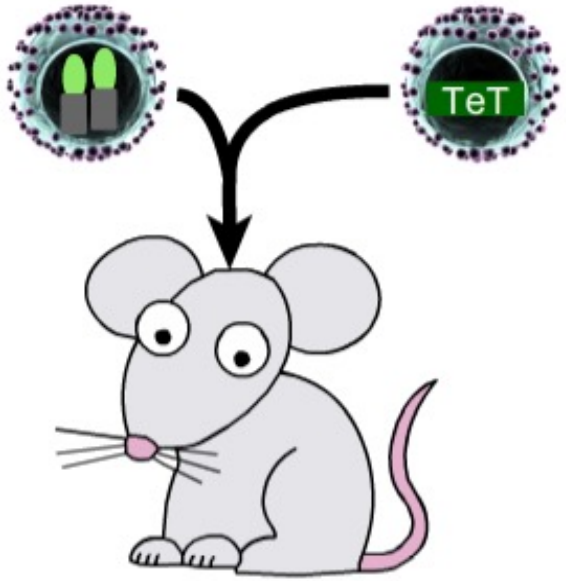


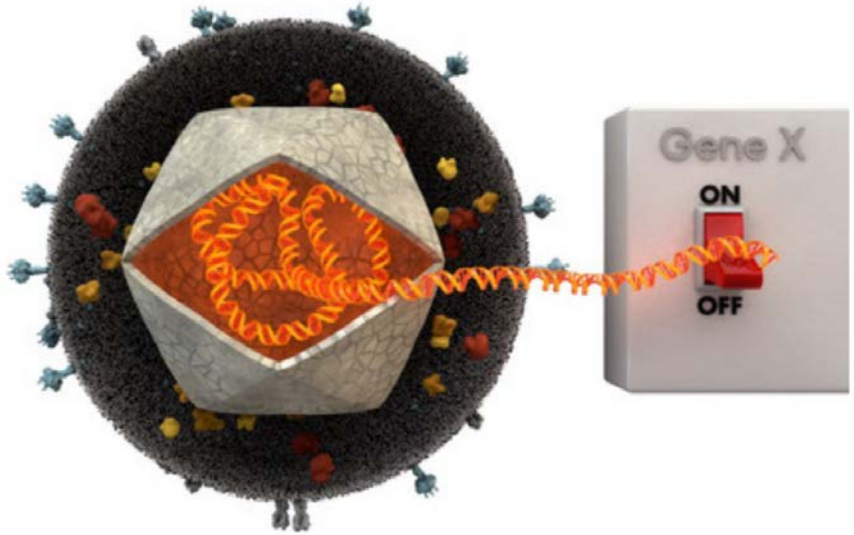
Hasan et al.,, *PLoS* 2:763-775, 2004.

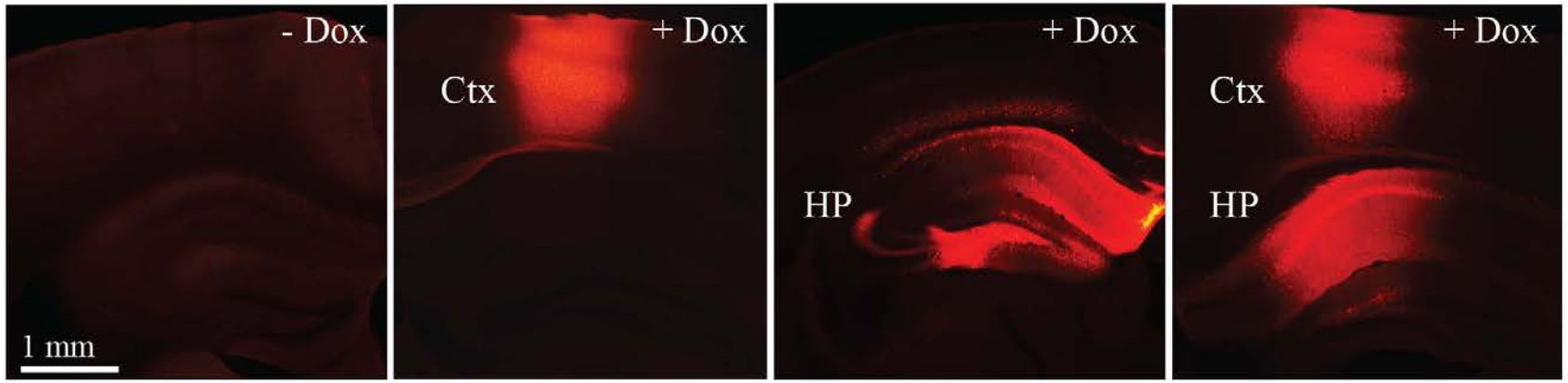
Large-scale, multi-region, microcircuit imaging

“The emergence of genetic NEURO-technologies to control excitation-inhibition”

Switchable genetic nanotechnologies to target brain circuits for precision medicine





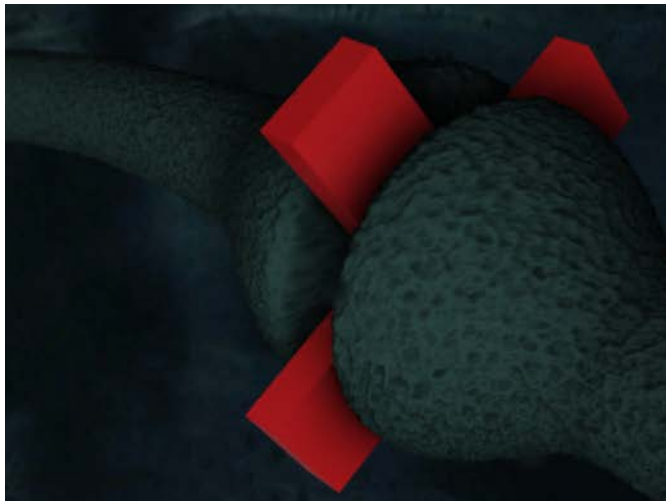


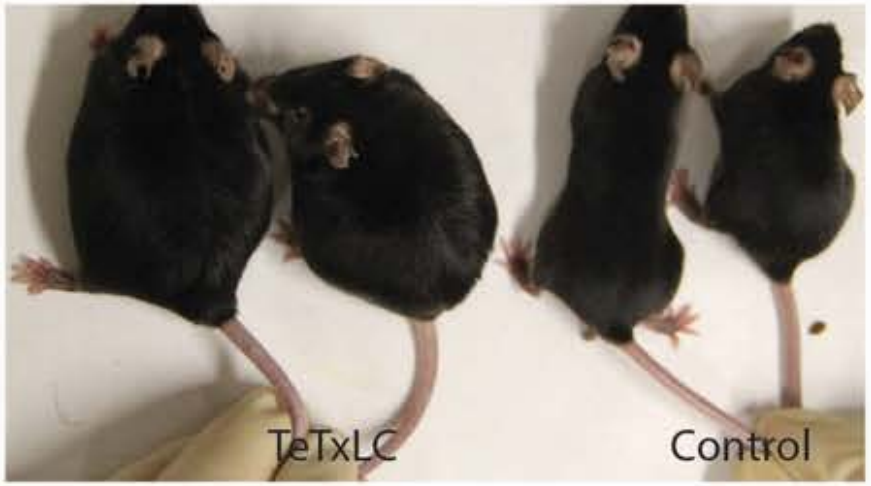
Dogbevia el al., *Front Cell Neurosci* 2015, Dogbevia et al., *Mol Ther Nucleic Acids* 2016

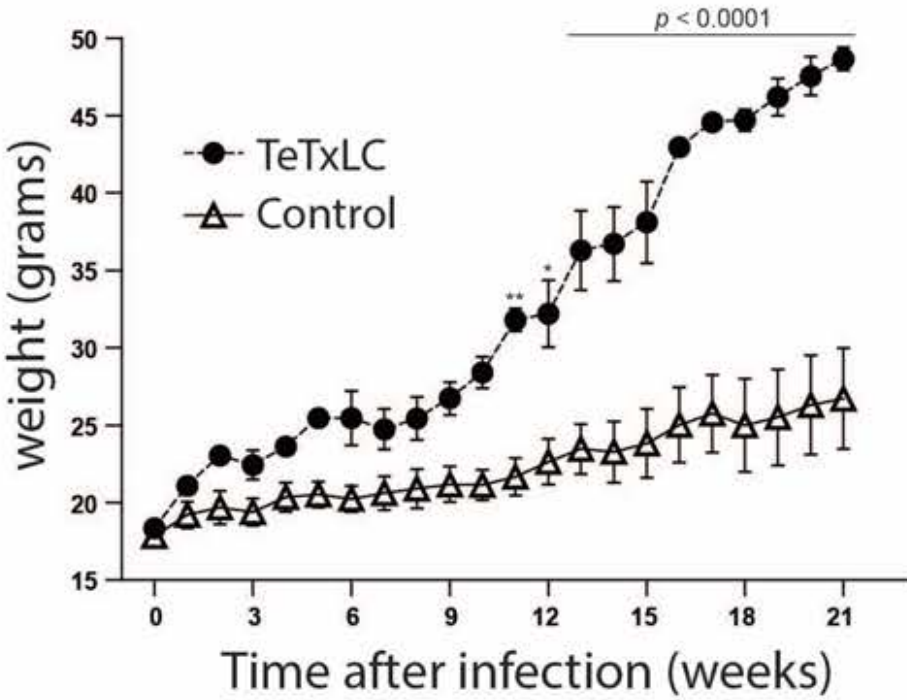
Reversible silencing of synaptic transmission

Hasan lab (work in progress)

Eating disorder: oxytocin control by hypothalamus



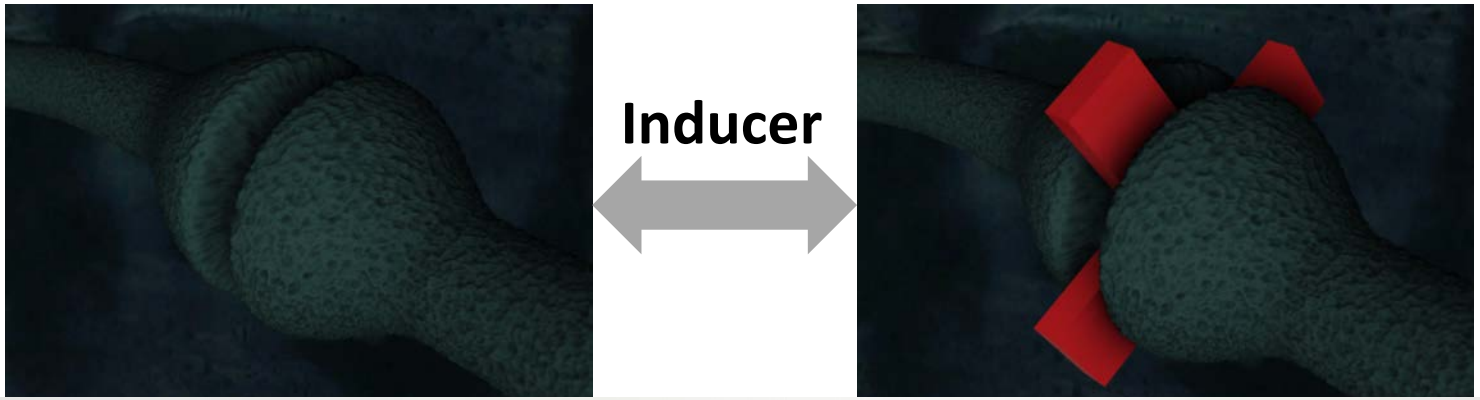


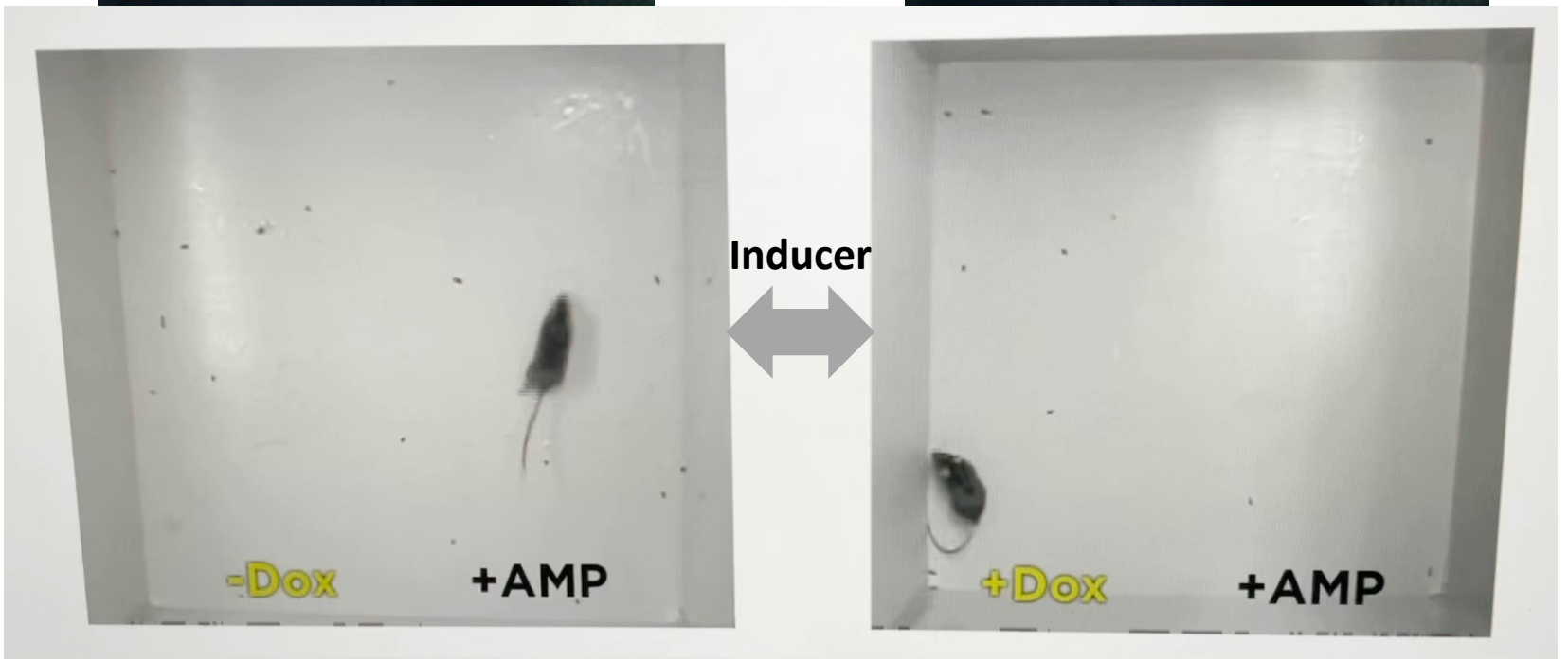


Hasan lab (work in progress)

Control of motor movement by genetic NEURO-therapeutics to treat Parkinson's disease

Control of motor movement by genetic NEURO-therapeutics to treat Parkinson's disease



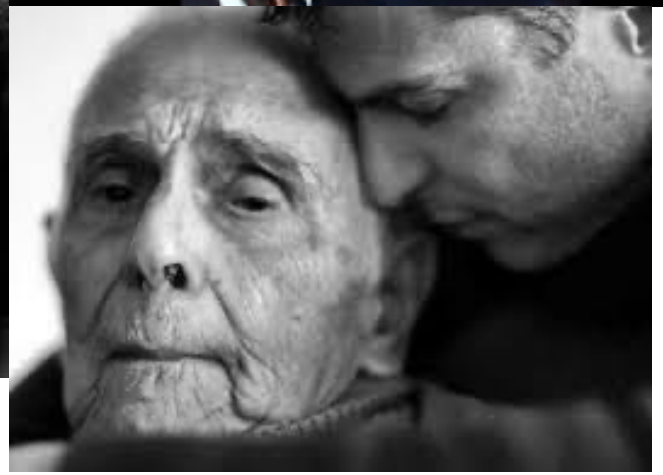


Hasan lab (work in progress)

“What are memories made of and how they are related to brain diseases”


MEMORIES

Memories makes us as who we are



We are our brain

How are memories formed, stored, maintained and retrieved in the brain?

On Memory and Reminiscence

By Aristotle

Commentary: A few comments have been posted about On Memory and Reminiscence.

Download: A 27k text-only version is available for download.

On Memory and Reminiscence

By Aristotle

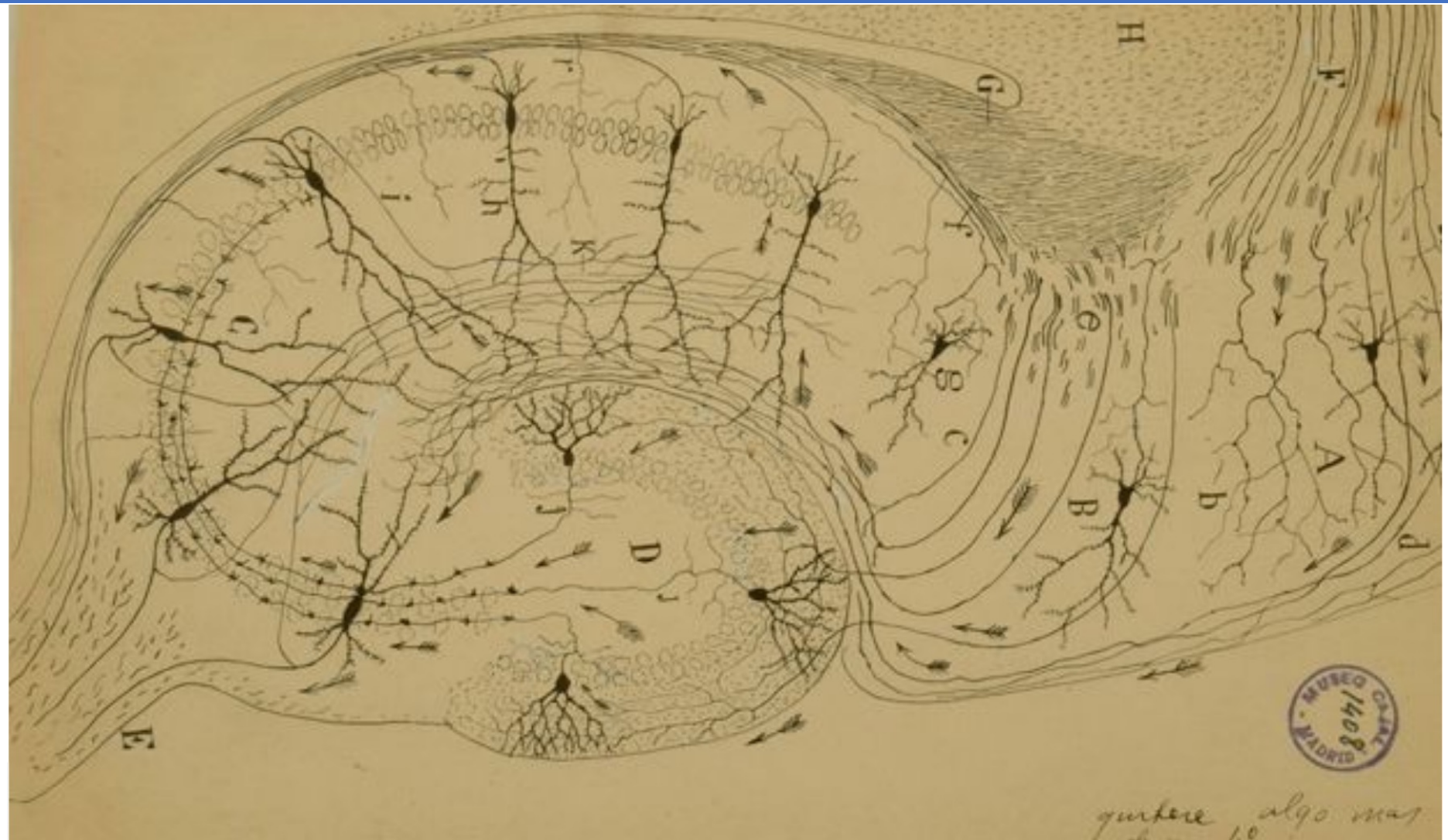
Written 350 B.C.E

Translated by J. I. Beare

The process of movement sensory stimulation involved the act of perception stamps in as it were a sort of **impression of the percept** just as persons do who make **an impression with a seal**.

Ramón y Cajal – The Neuron Doctrine (1889)

law of dynamic polarization - unidirectional transmission of nerve impulses



Search for a memory engram

Richard Wolfgang Semon
A German zoologist and evolutionary biologist, and a memory researcher

Semon proposed the psychophysiological parallelism according to which each psychological state corresponds to alterations in the nerves.

In 1904, he proposed that the engram is the biological basis for long-term memory

ENGRAM is an IMPRINT of "what we know"

Search for a memory engram

Wilder Penfield – 1940

Brain stimulation and memory

Stimulated the cortex of patients undergoing surgery for epilepsy 8% of the patients experienced specific memories when their temporal lobes were stimulated.

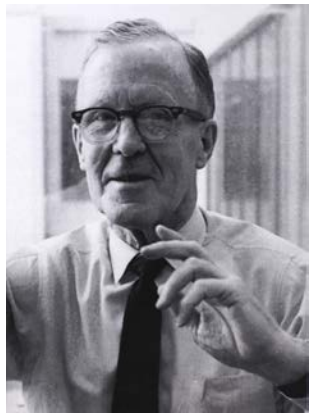
Memories could be “localized” in the brain

Search for a memory engram

- **Karl Lashley** – 1950
  - Wanted to know where memories are located
  - Studied rats who had learned a maze
  - Lesioned a part of the brain, watched in maze
    - What he found?
      - No localized memories! Rats could still go through the maze even with parts of the brain removed

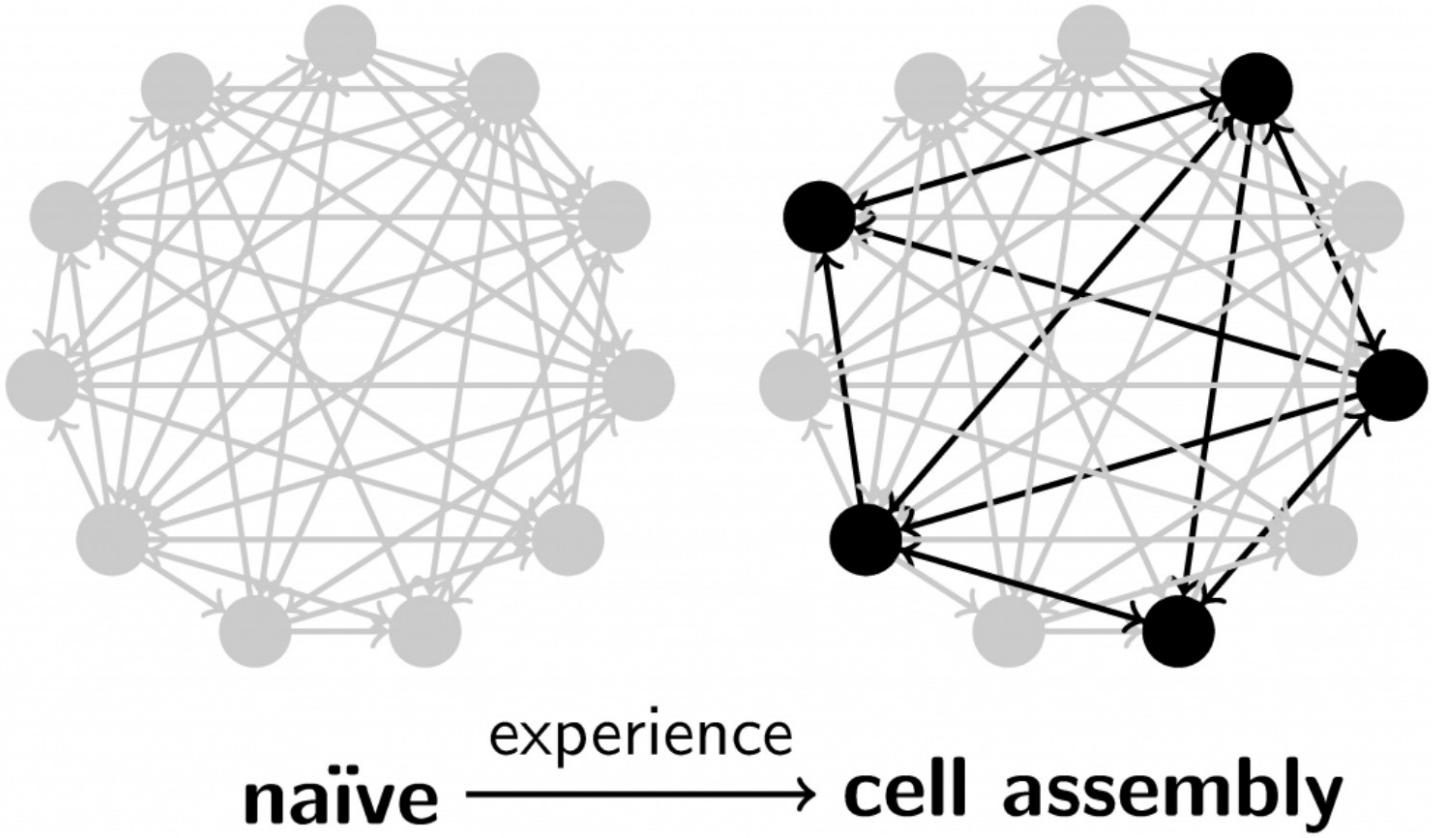
Memories could be “distributed” in the brain

Cell Essembles: "what fire together, wires together"



Donald O. Hebb

The Organization of Behavior (1949)



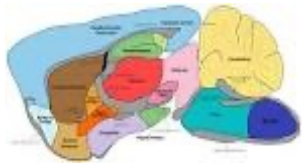
Dynamics at different spatial scales

Multi-scale systems

Whole brain

↕

Subregions



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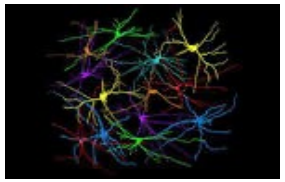
Neuronal circuits



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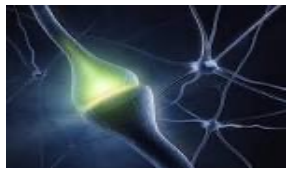
Synaptic circuits



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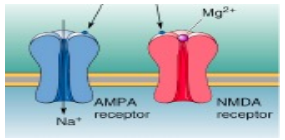
Genes/products



Key questions we aim to tackle

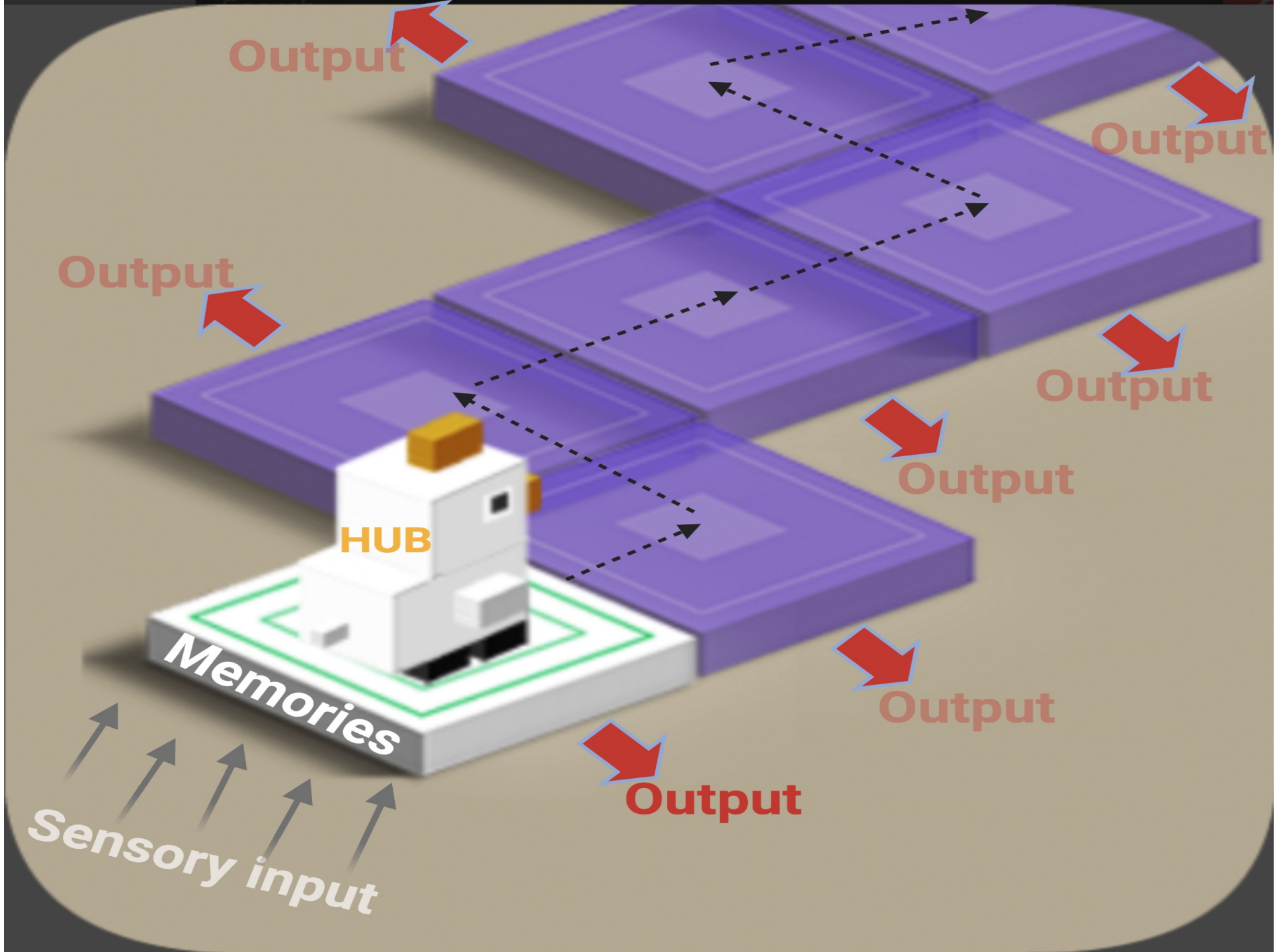
Where is memory formed and stored in the brain?

Is memory ‘engram’ localized or distributed?

How to identify “activated” brain circuit for activity manipulation?

Is memory retrieval enabled by precisely organized synaptic connections or synaptic weights?

What is the synaptic and molecular basis of engram formation and maintenance?


Output
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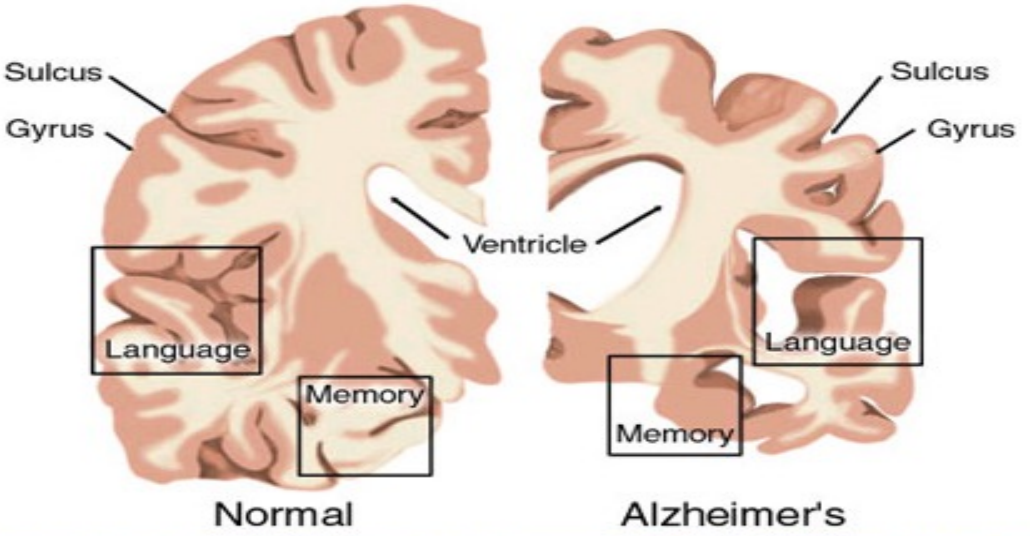
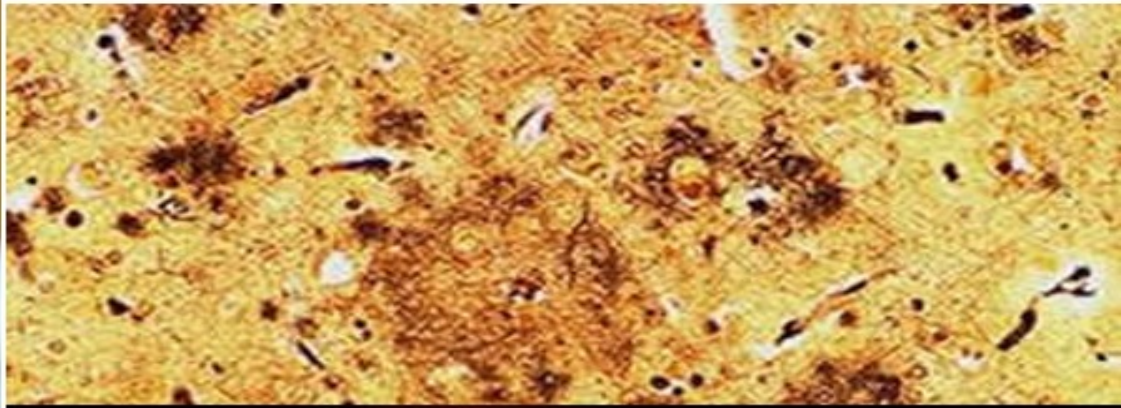
HUB
Memories
Sensory input

Alzheimer's
shrinks the brain



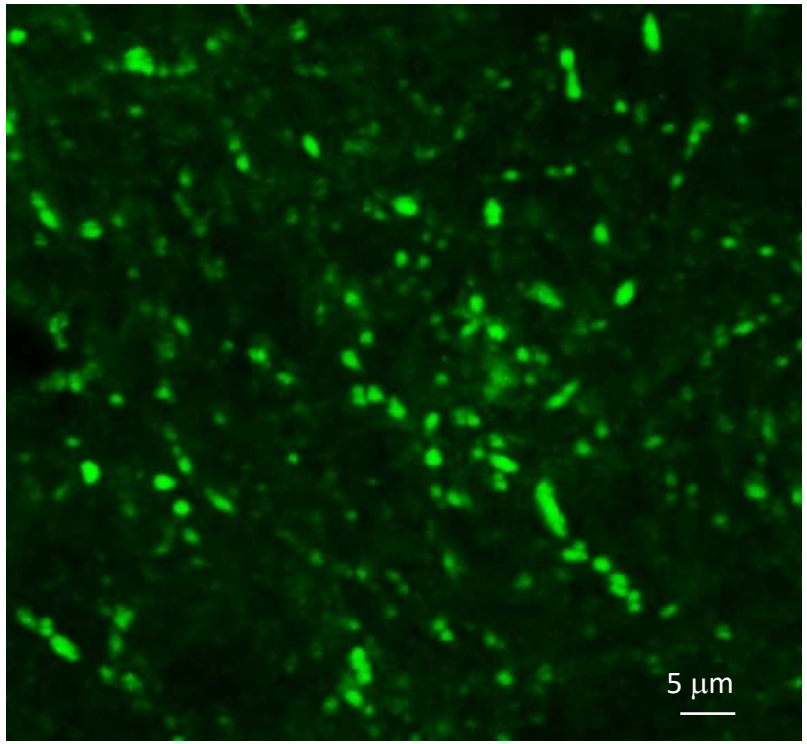
Normal Alzheimer's

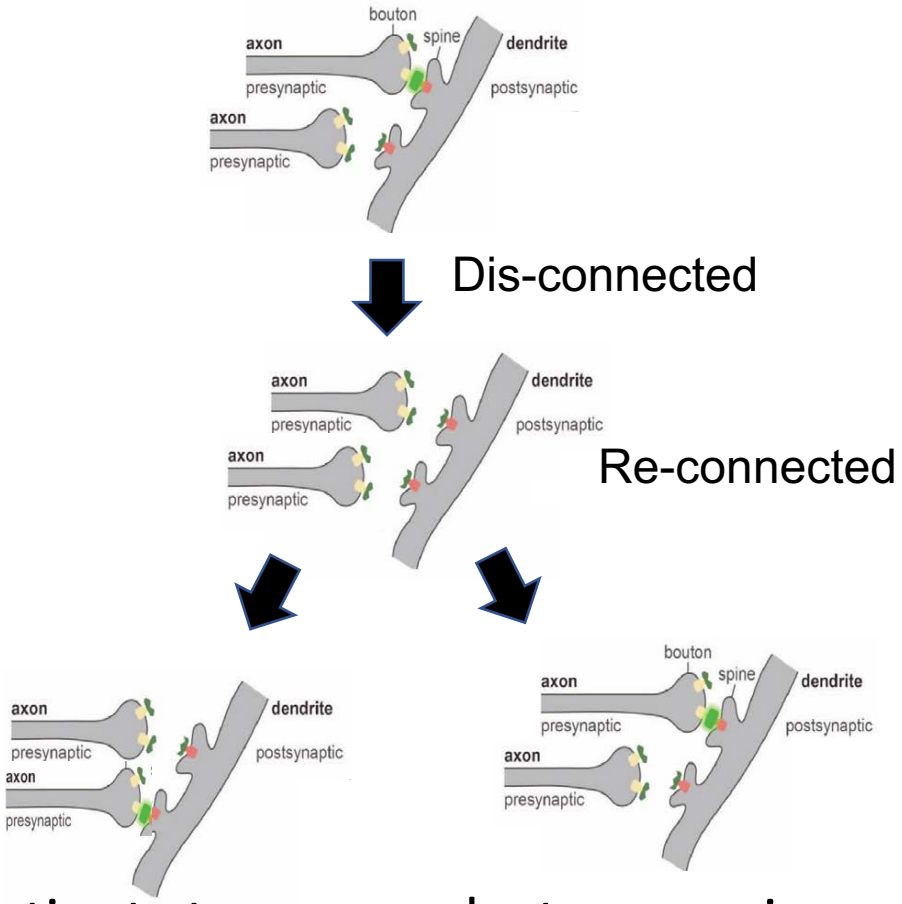


Is memory retrieval enabled by precisely organized synaptic connections?

In our ongoing work, we have discovered that lost memories can be recovered by re-connecting broken connections in the brain

Two-photon imaging of synaptic connections

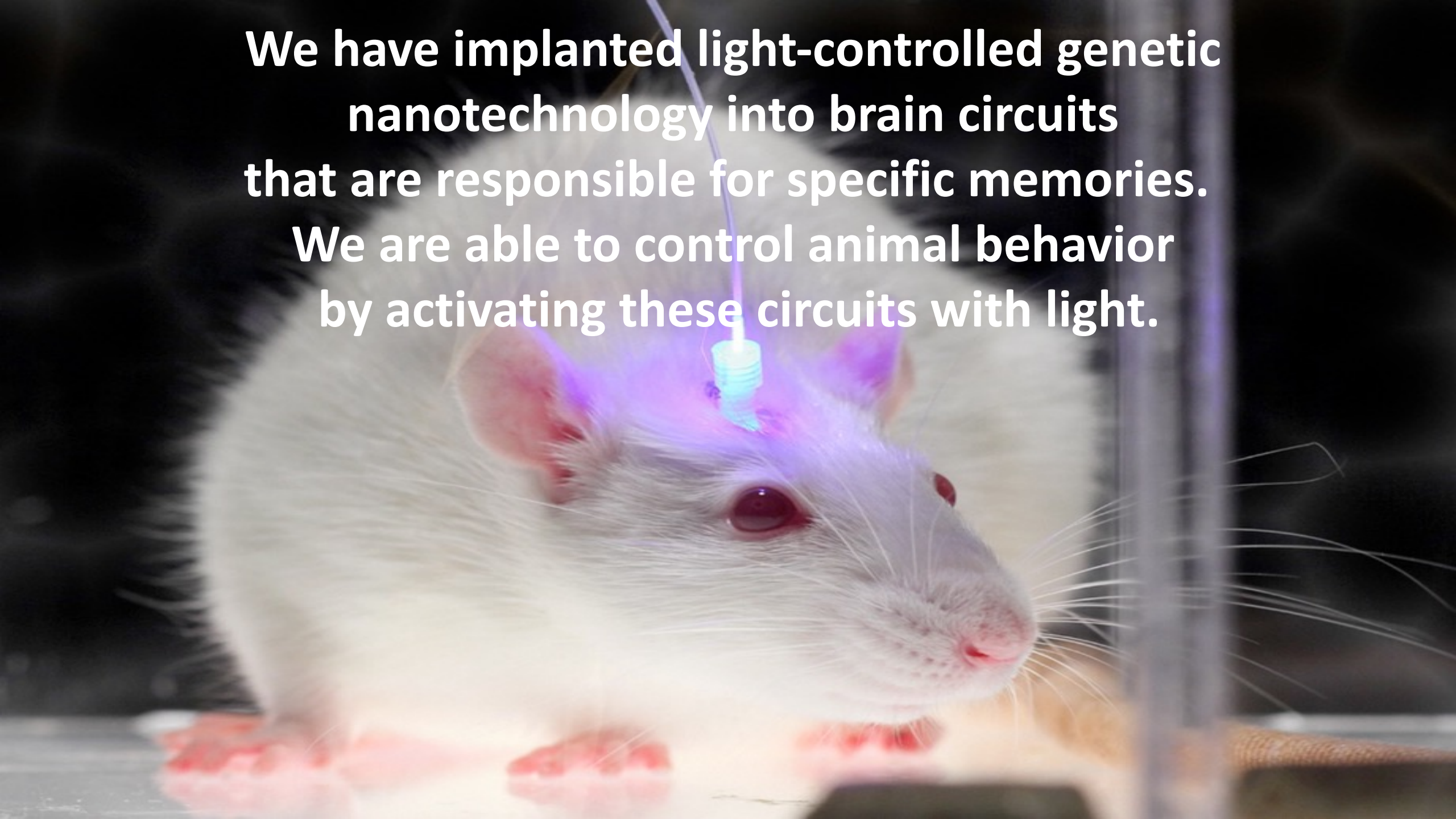




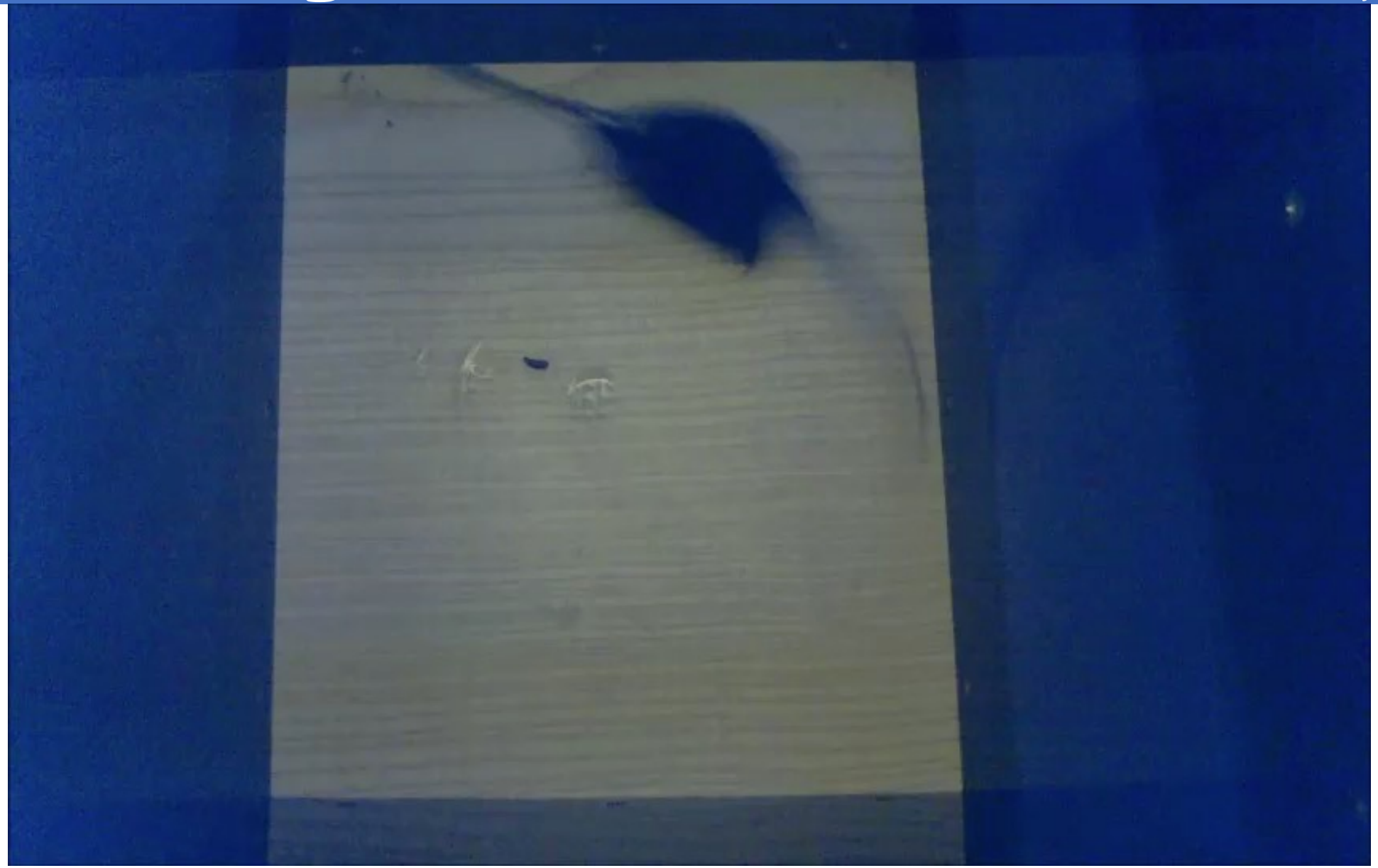
Impact: Hope for the Alzheimer's patients to recover lost memories.

Hasan lab (work in progress)


PTSD


We have implanted light-controlled genetic
nanotechnology into brain circuits
that are responsible for specific memories.
We are able to control animal behavior
by activating these circuits with light.

"Activating" trauma-induced fear memory



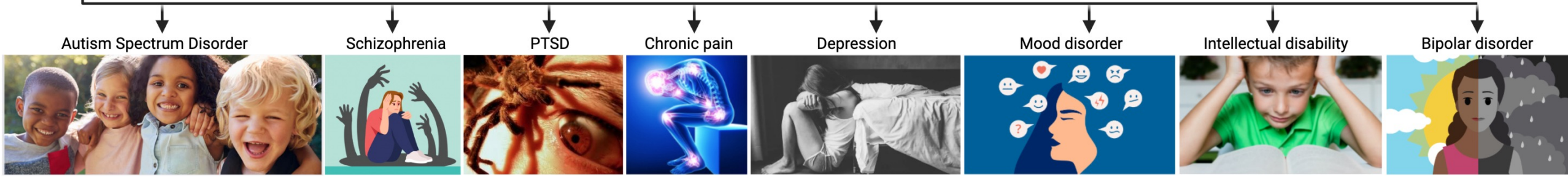
Hasan lab (work in progress)

"Erasing" trauma-induced fear memory

Hasan et al., "A Fear Memory Engram and Its Plasticity in the Hypothalamic Oxytocin System". *Neuron*. 2019;103(1):133-146.e8".

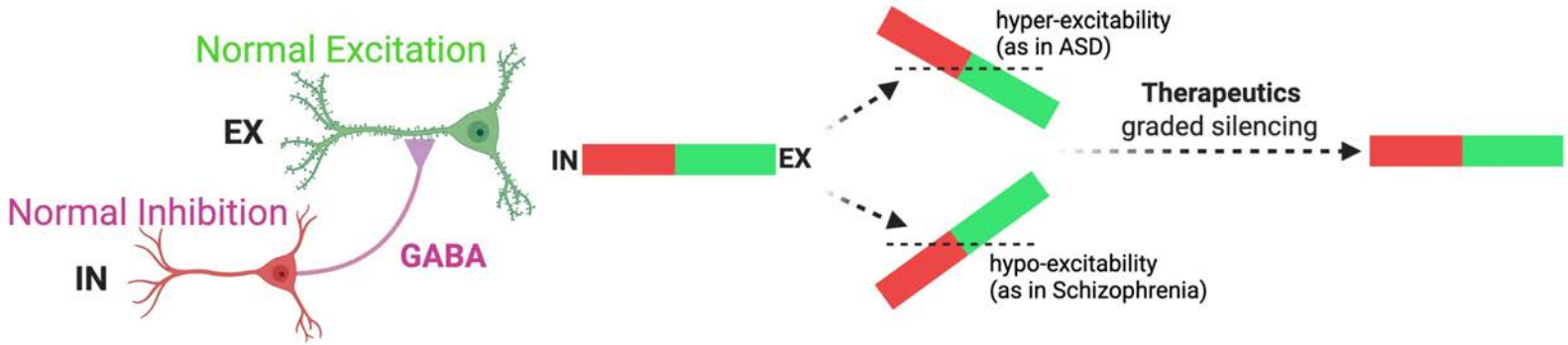
Genetic nanotechnologies to treat psychiatric conditions

Psychiatric conditions



"Unifying" hypothesis for psychiatric conditions

Abnormal expression of specific genes shifts the excitation-inhibition balance towards either hypoexcitability or hyperexcitability. Restoring excitation-inhibition balance by genetic therapeutics can correct psychiatric condition(s)

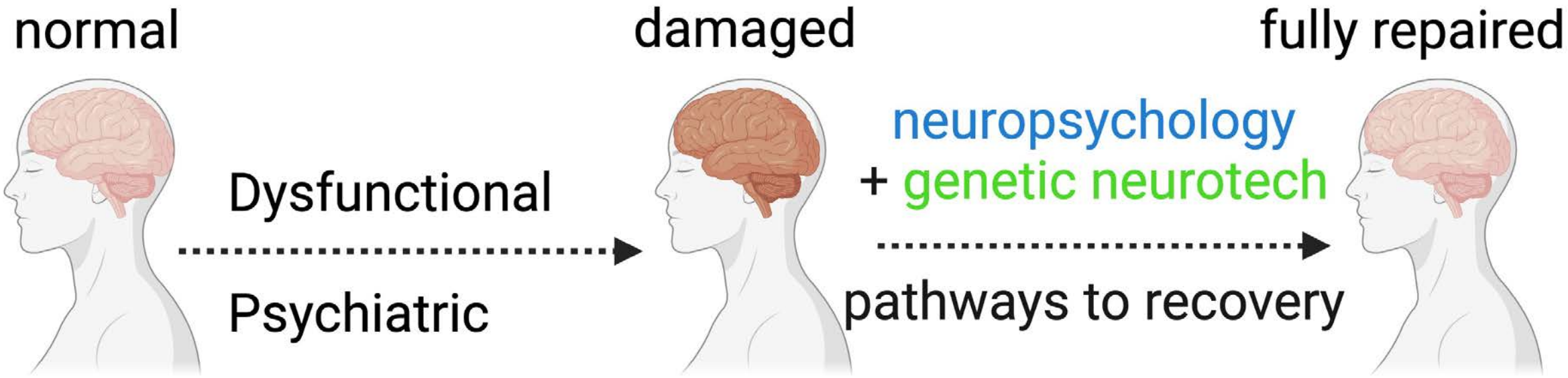


“Integrating NEURO-psychology with genetic NEURO-technologies”


Collaboration
generates ideas
=
Discovery

A vision towards the "golden age" of "precision medicine"

Integrating psychotherapy
with targeted brain circuits therapeutics



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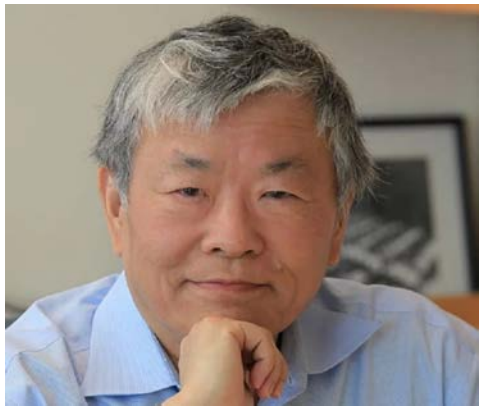

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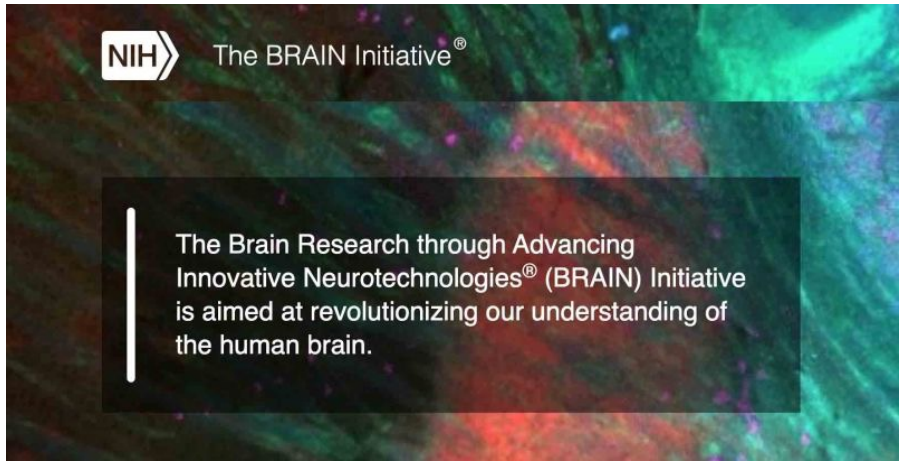

NATIONAL INSTITUTES OF HEALTH

“Off the beaten road to new directions”

Interdisciplinary collaboration

Neuropsychology

Brain Circuits Therapeutics

Thank you!

Mazahir T. Hasan, PhD, Ikerbasque Professor
Laboratory of Brain Circuits Therapeutics - Achucarro Basque Center for Neuroscience
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