Decoding ageing brain

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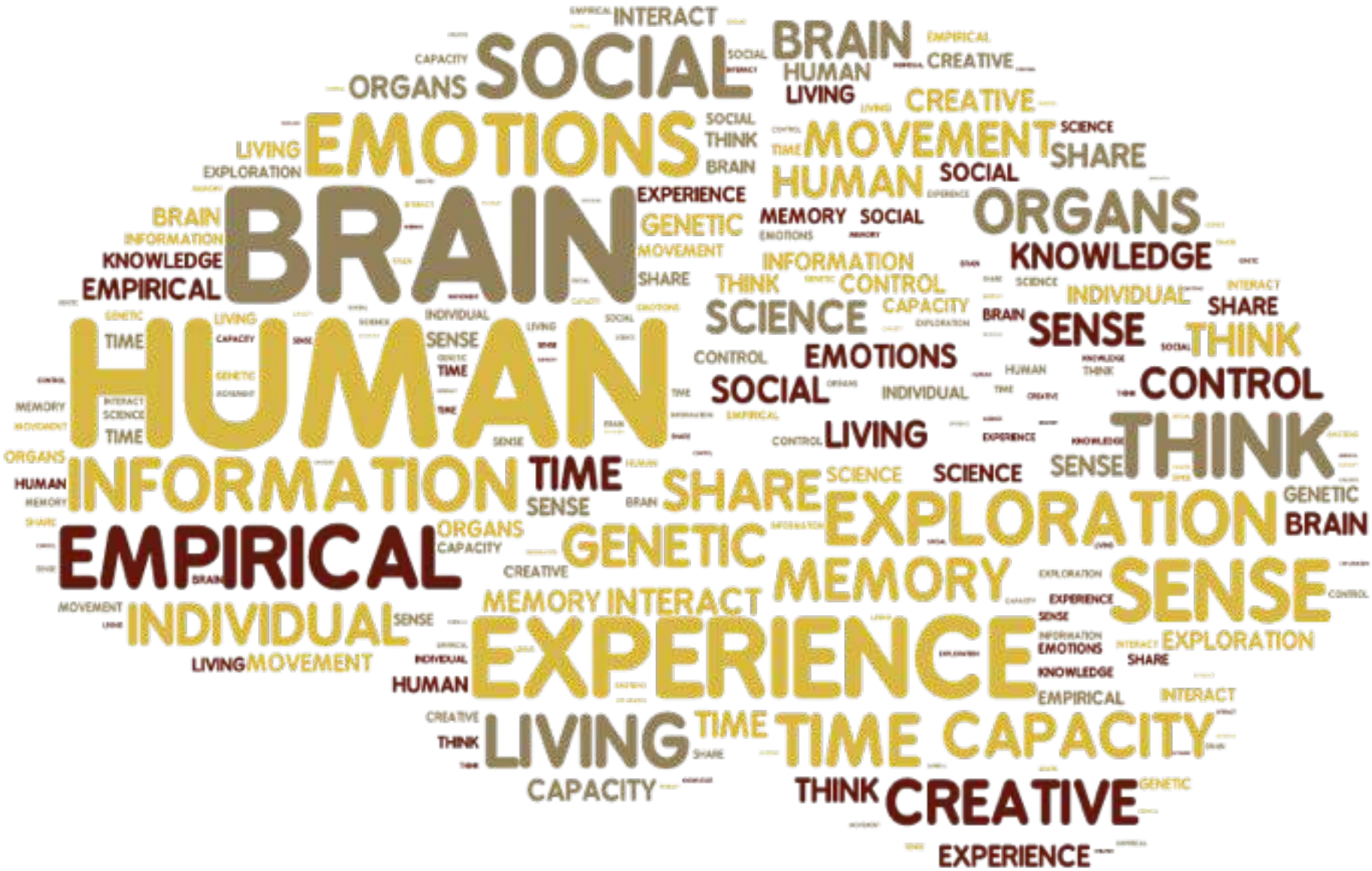
Brain words


INTERACT
SOCIAL
BRAIN
EMPIRICAL
CREATIVE
HUMAN
LIVING
ORGANS
CAPACITY
EMOTIONS
MOVEMENT
SCIENCE
SHARE
LIVING
EXPLORATION
THINK
BRAIN
HUMAN
SOCIAL
EXPERIENCE
BRAIN
GENETIC
MEMORY
SOCIAL
ORGANS
INFORMATION
KNOWLEDGE
KNOWLEDGE
EMPIRICAL
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SHARE
THINK
CONTROL
INDIVIDUAL
SHARE
SCIENCE
CAPACITY
BRAIN
SENSE
THINK
TIME
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EMOTIONS
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CONTROL
LIVING
THINK
ORGANS
INFORMATION
TIME
SHARE
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INDIVIDUAL
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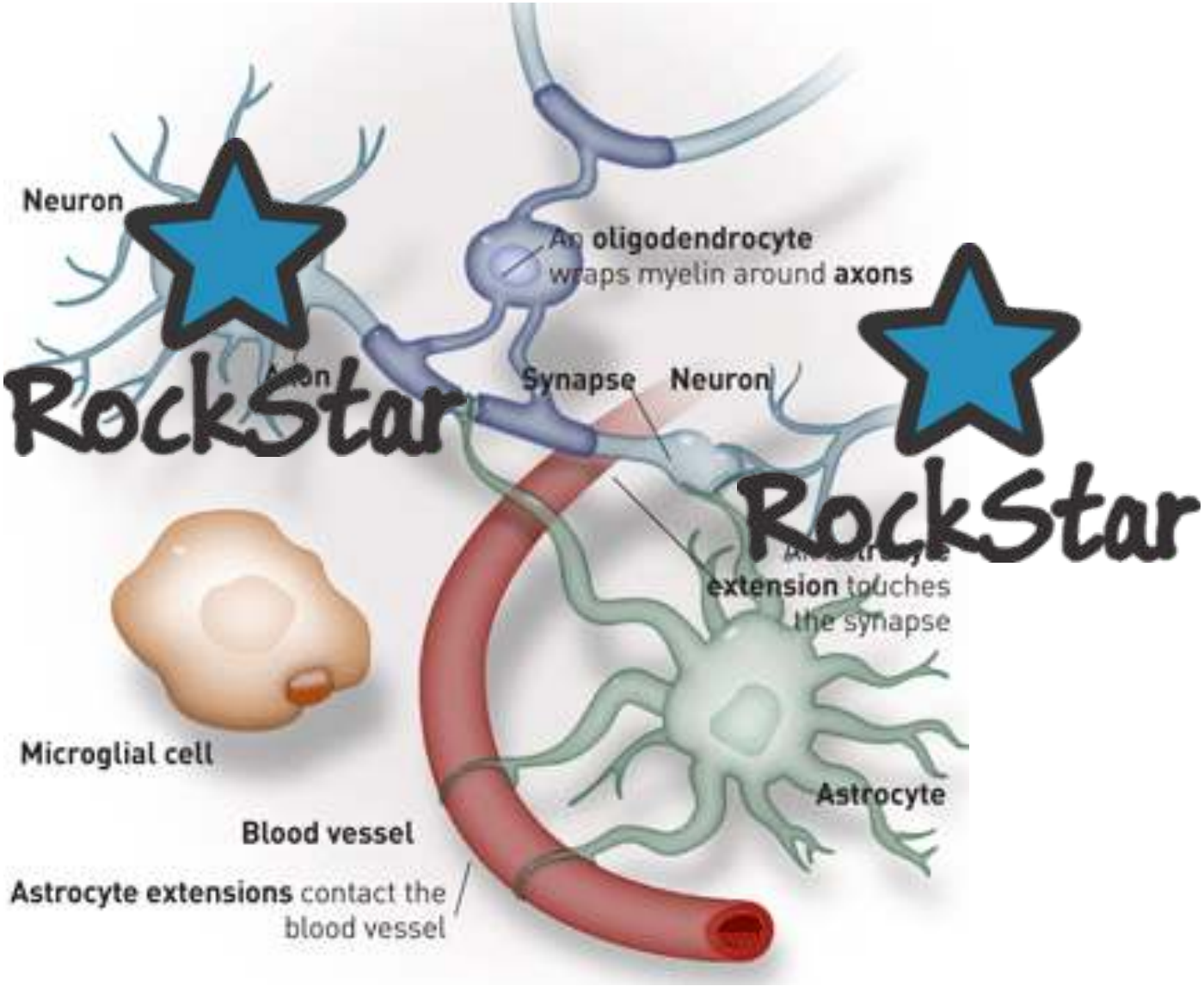
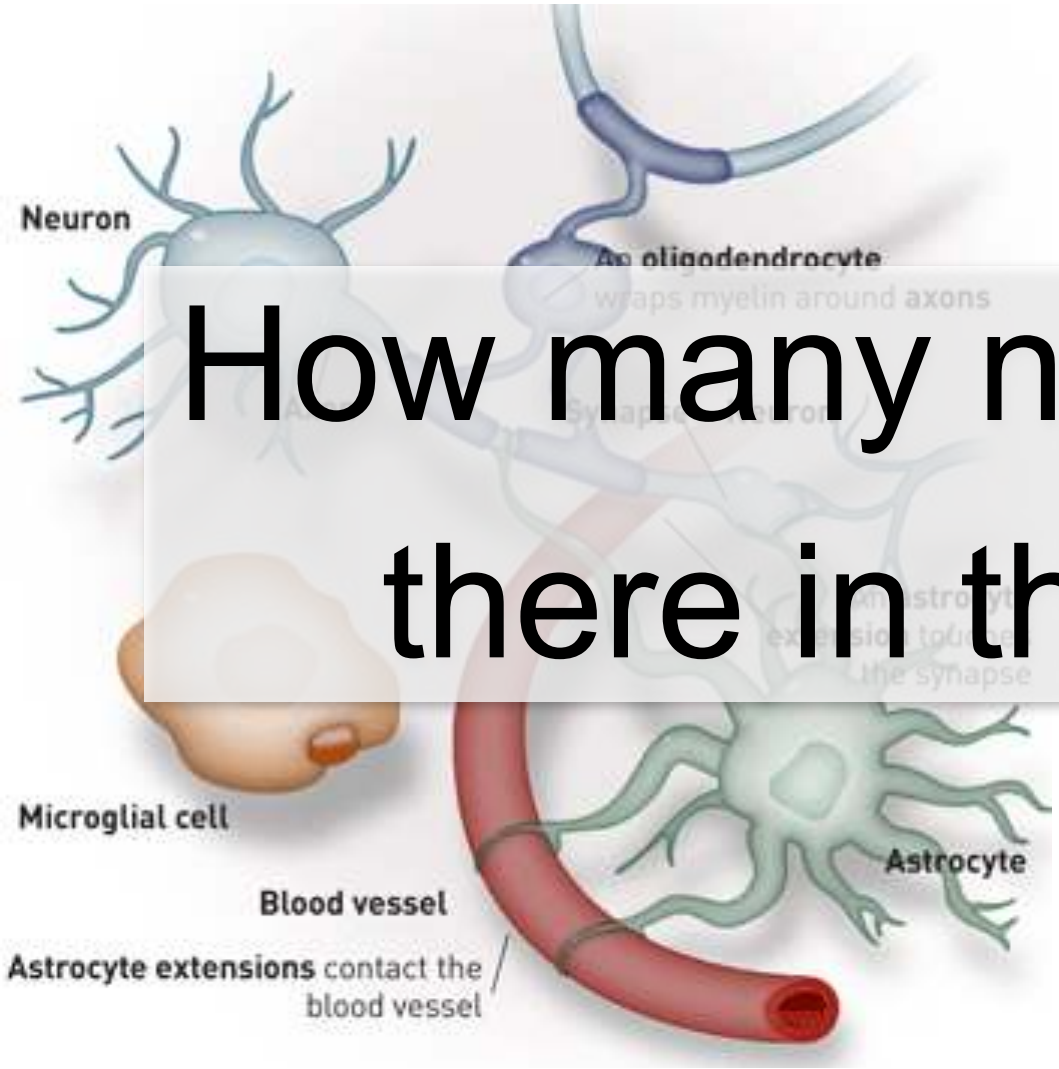
EXPERIENCE
EXPLORATION
LIVING
MOVEMENT
EMOTIONS
SHARE
HUMAN
KNOWLEDGE
EMPIRICAL
INTERACT
CREATIVE
LIVING
TIME
TIME
CAPACITY
THINK
CAPACITY
THINK
CREATIVE
EXPERIENCE

Inside the brain



Brain is extremely complex structure



How many neurons are there in the brain?

majority of nerve cells in our brain and spinal cord are born before birth and will last a lifetime

http://www.brainhealthandpuzzles.com/brain_plasticity.html

All might kill neurons

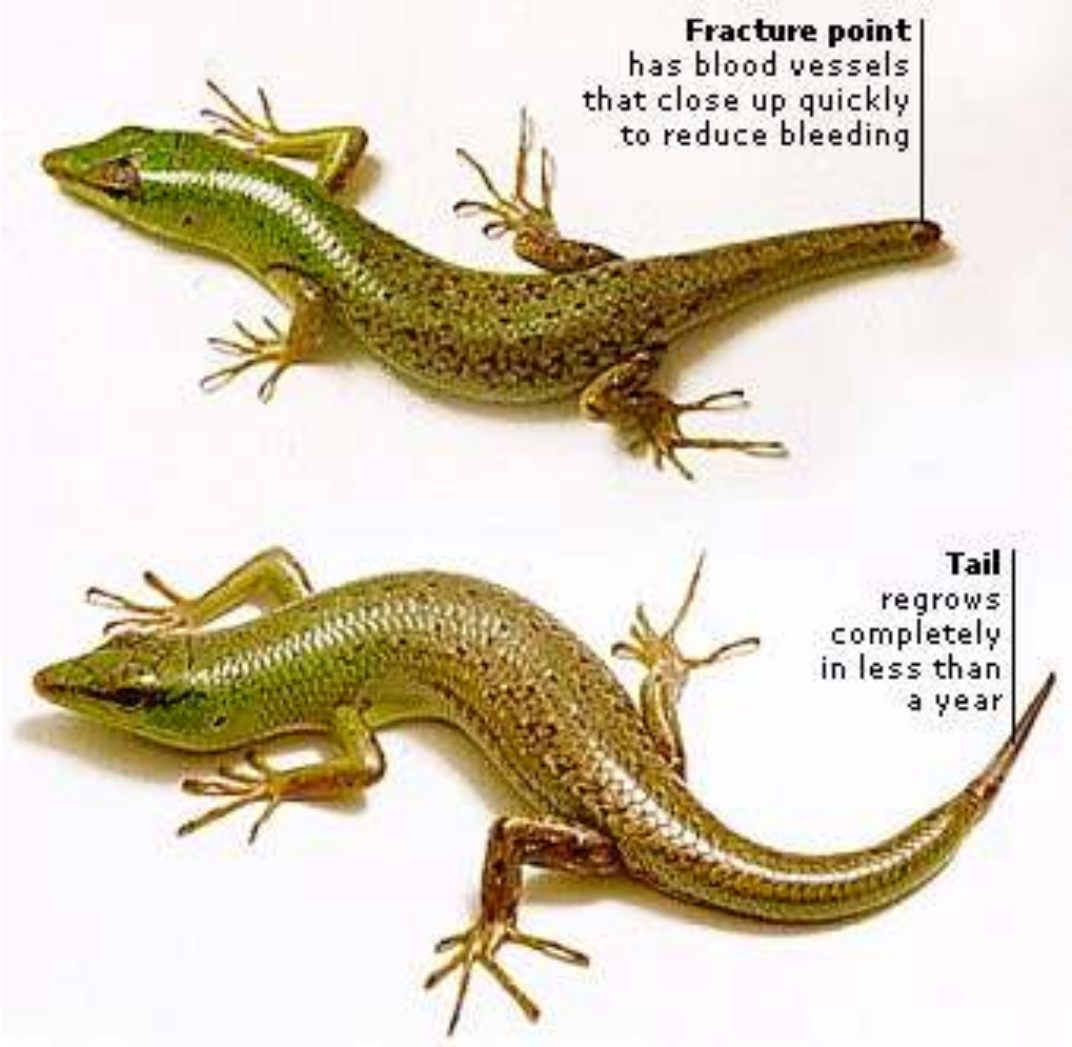
Stress

Sleep deprivation

Ageing

Disease

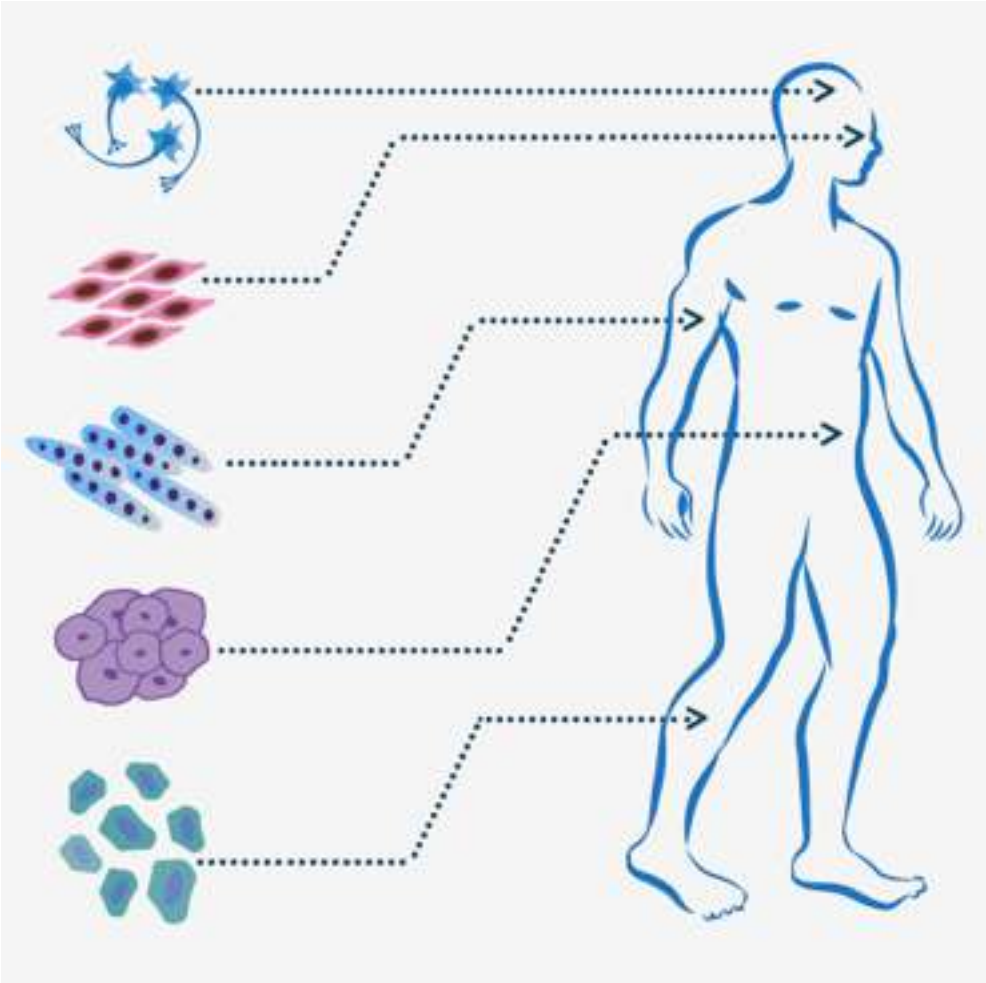
Regeneration in animals



Ability to regenerate

Ability of our body to repair the damaged parts

- Skin
- Bones
- Liver
- Etc.



Stem Cells

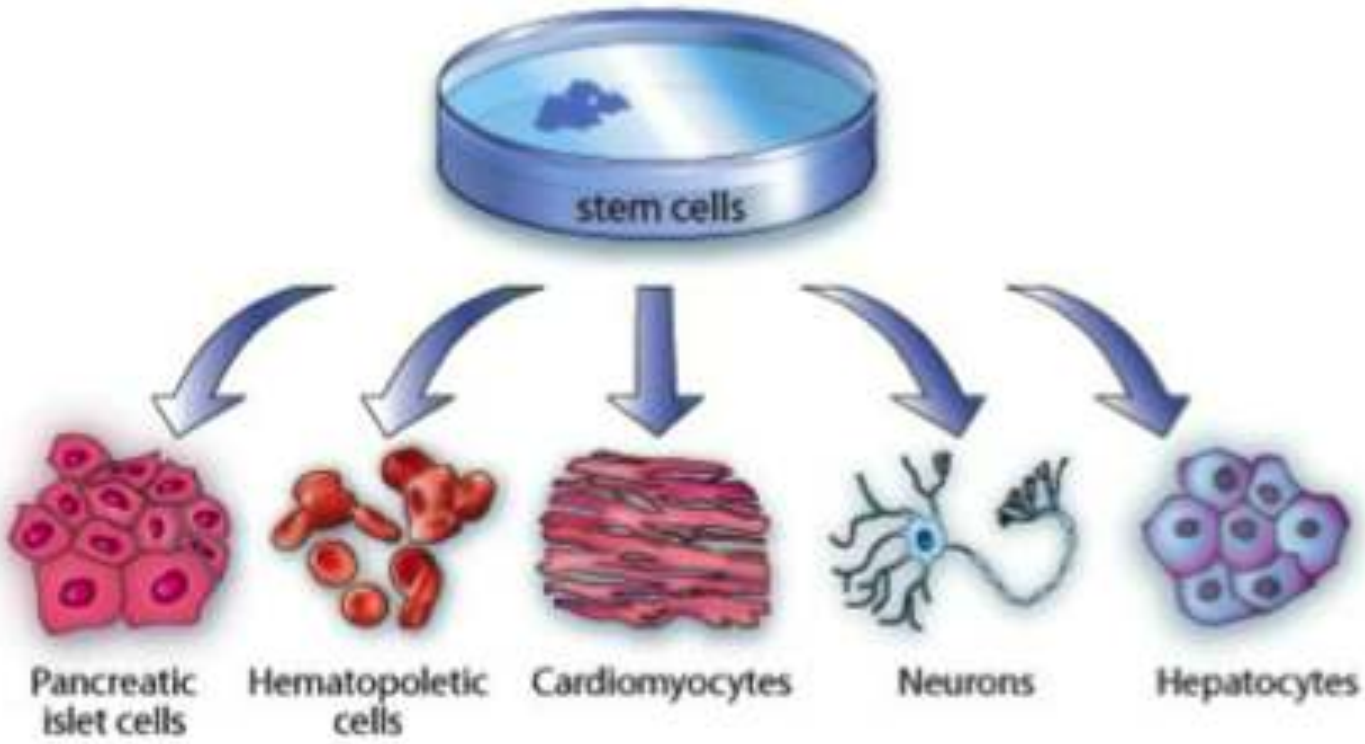


Image is modified illustration from Cell Imaging Core

Neural Stem Cells

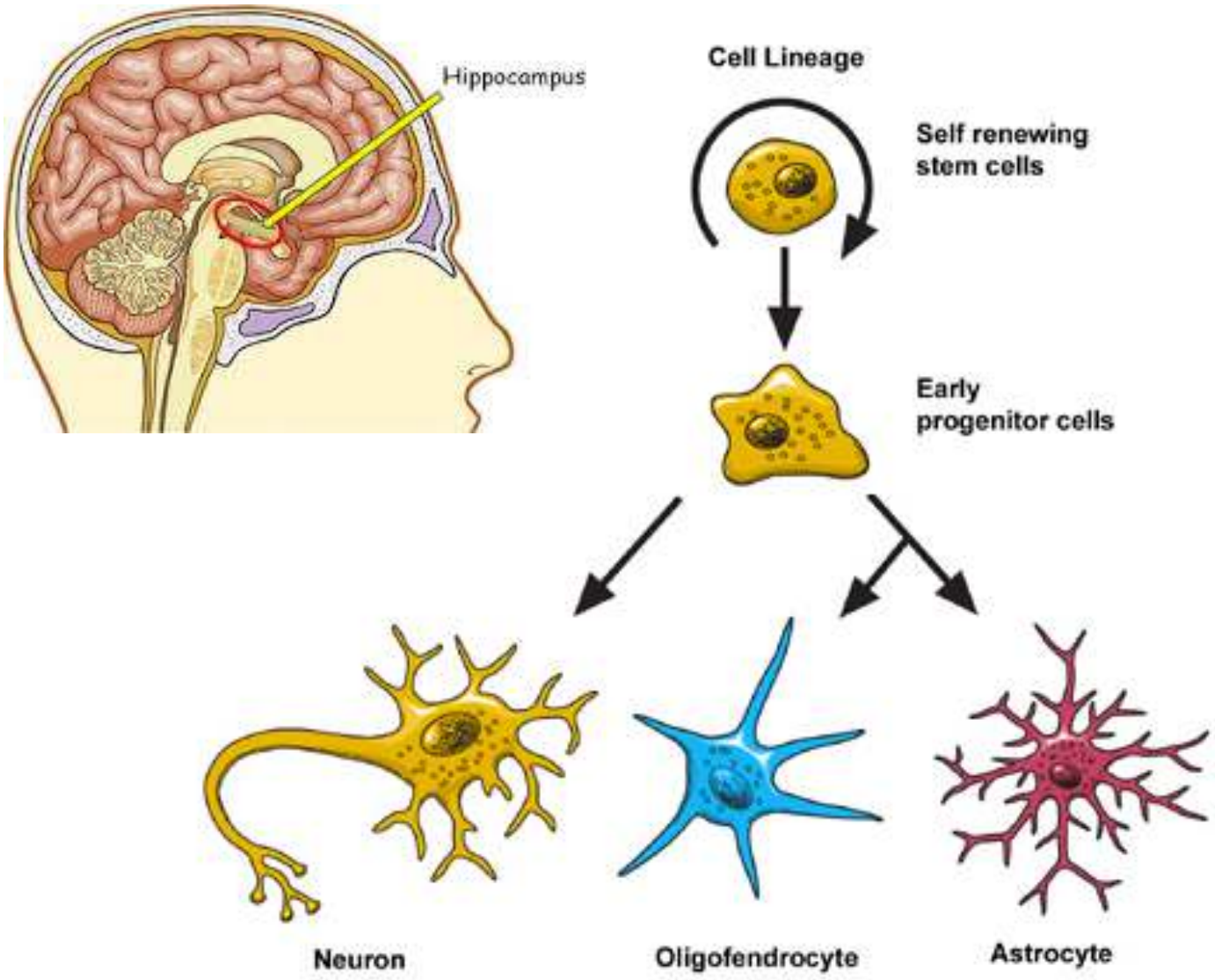
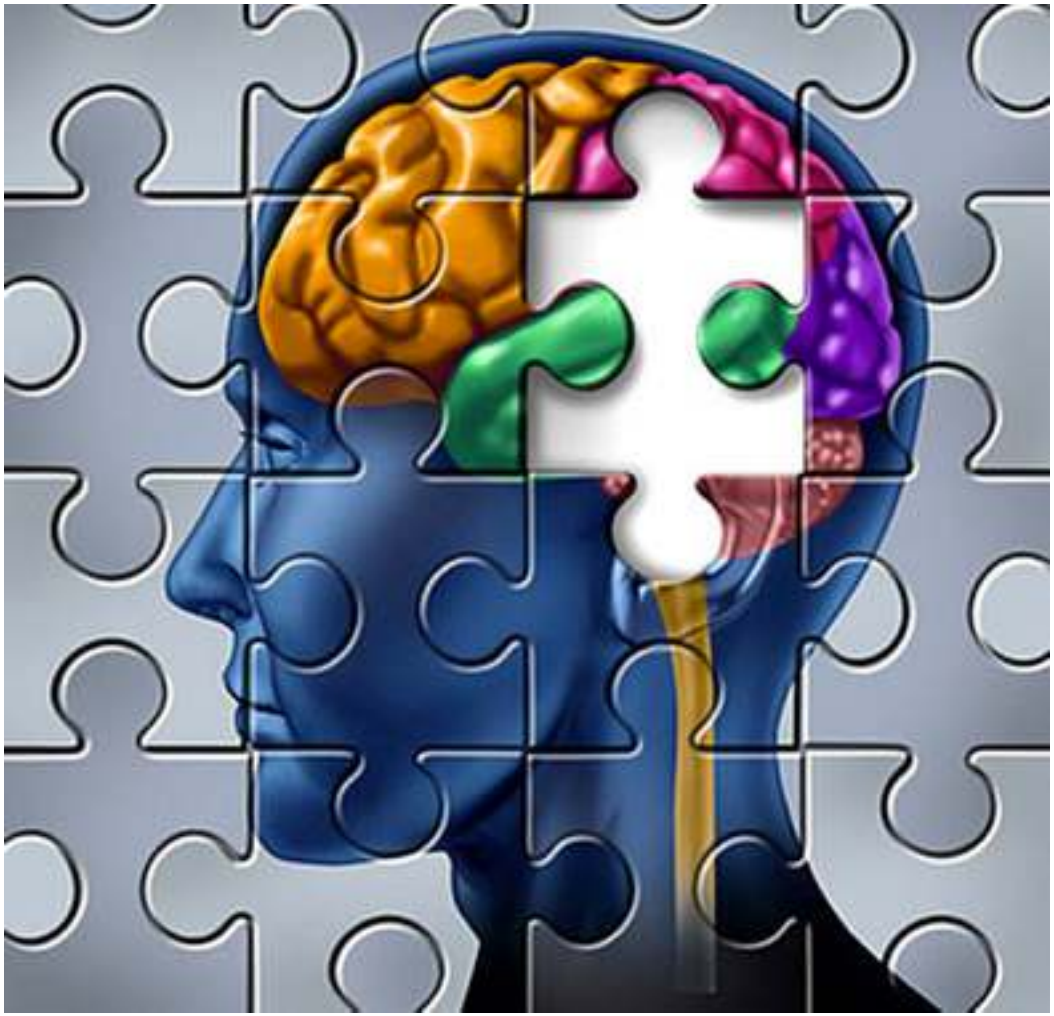


Image is modified, illustration is from http://www.ninds.nih.gov/disorders/brain_basics/ninds_neuron.htm

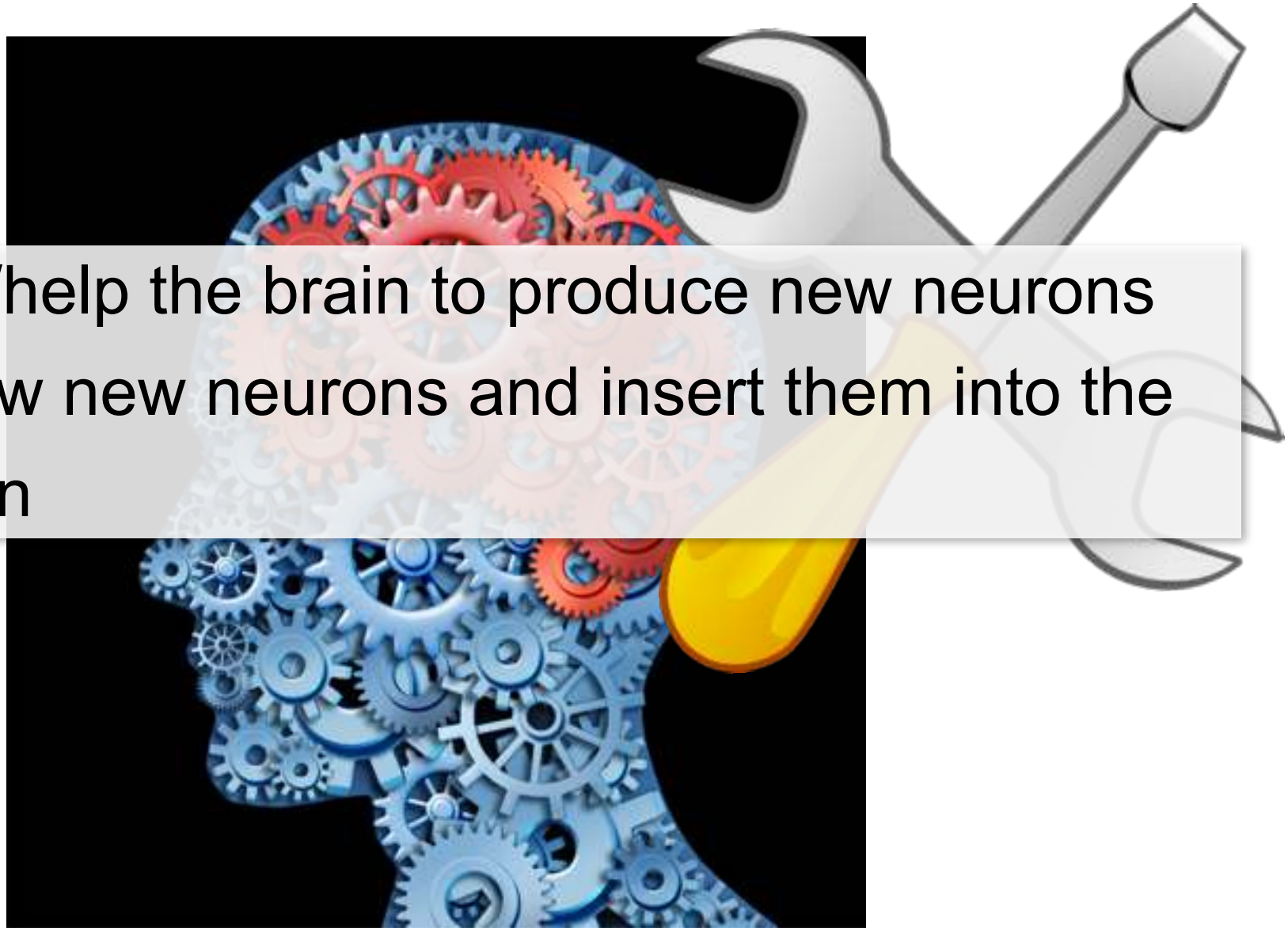
Why are they important?
Curing with stem cells

- Brain injury
- Neurodegenerative disorders (Parkinson's, Huntington's, Alzheimer's)
- Other brain diseases (multiple sclerosis, etc.)

Brain own capacity is not enough



What can we do?



- Tell/help the brain to produce new neurons
- Grow new neurons and insert them into the brain

Reprogramming body cells

Cell

Cell, Volume 126, Issue 4, 663-676, 25 August 2006

doi:10.1016/j.cell.2006.07.024

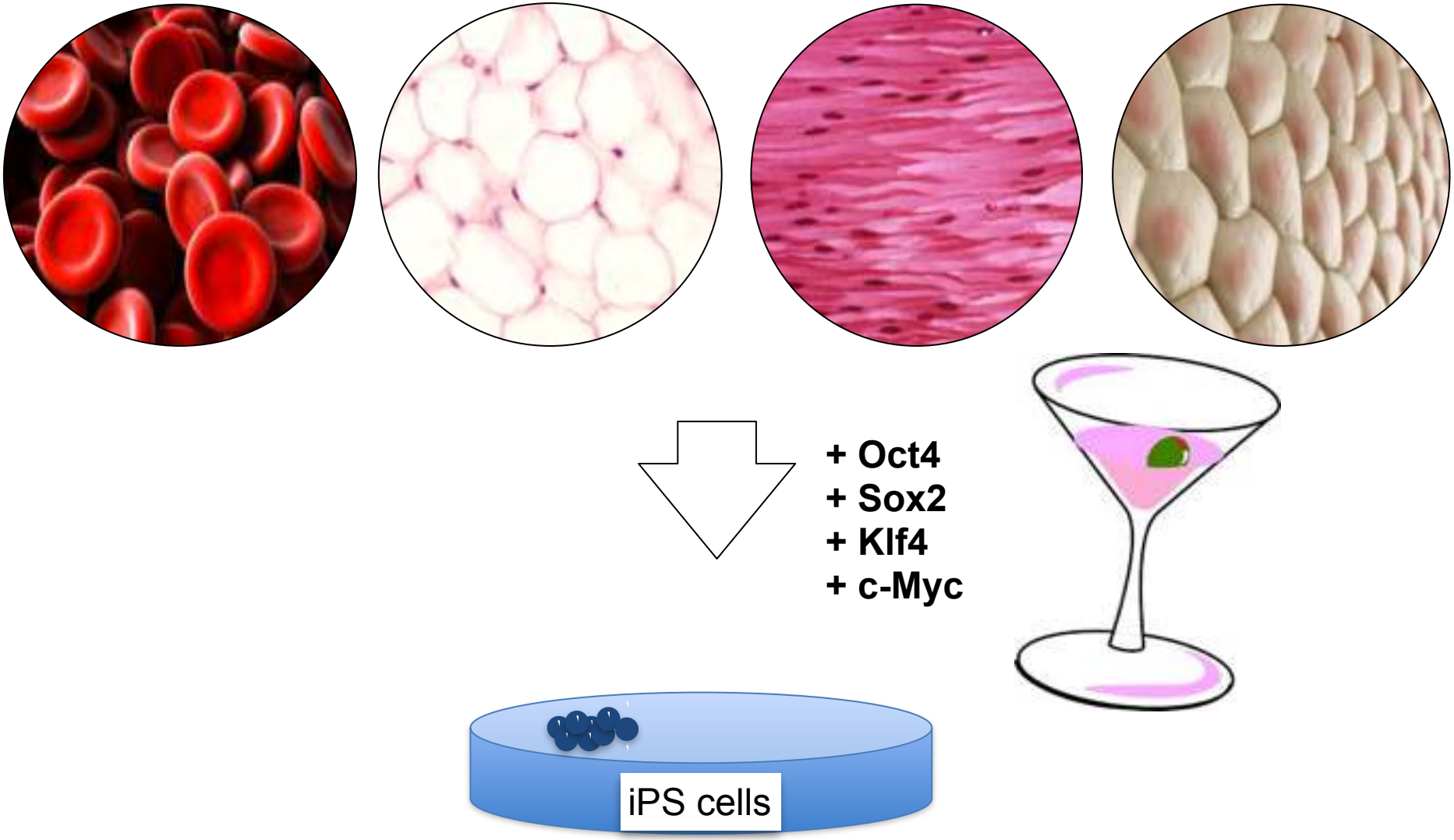
Article

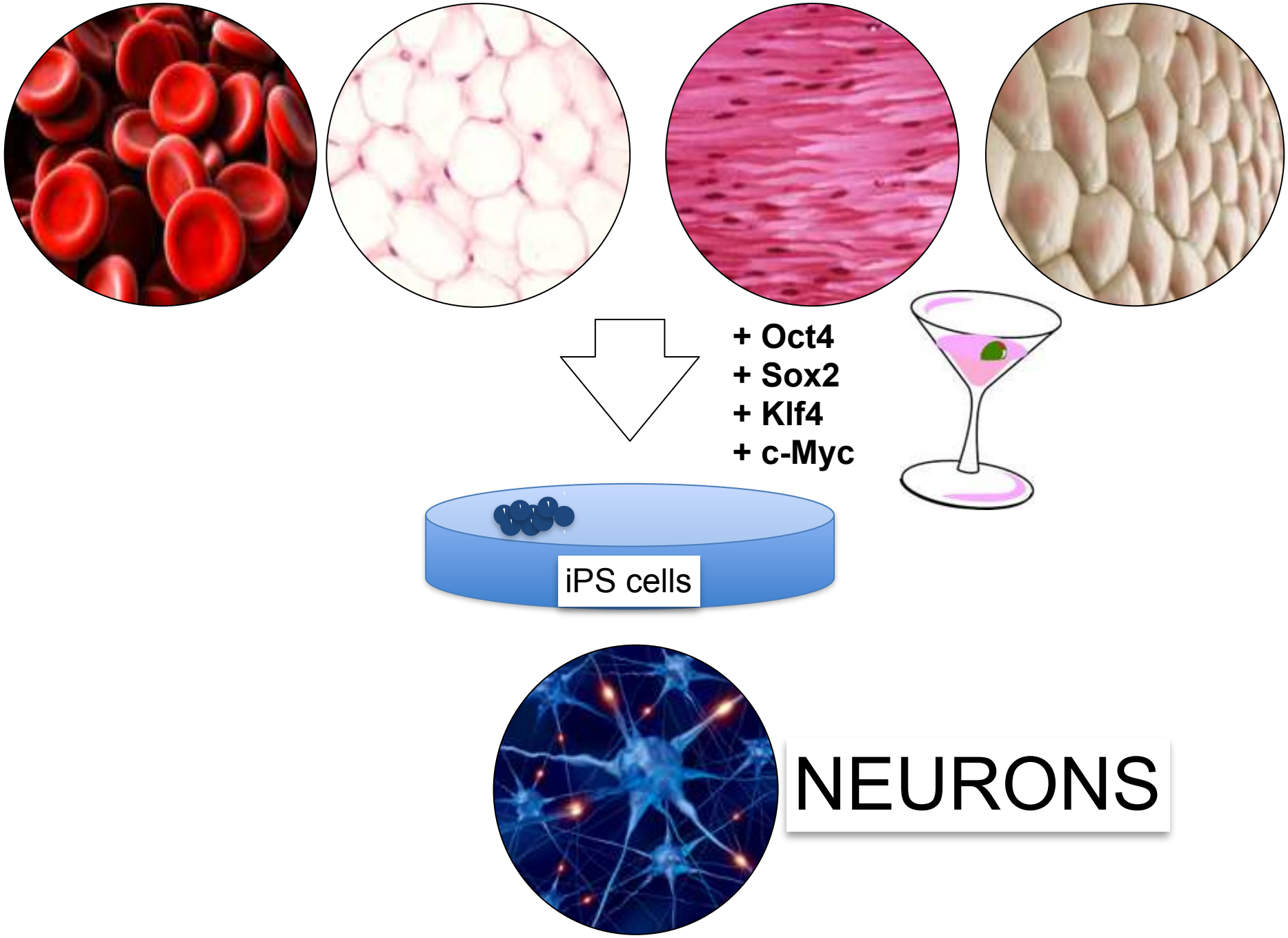
Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] and Shinya Yamanaka[1, 2,]

[1] Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2] CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan

Cell reprogramming

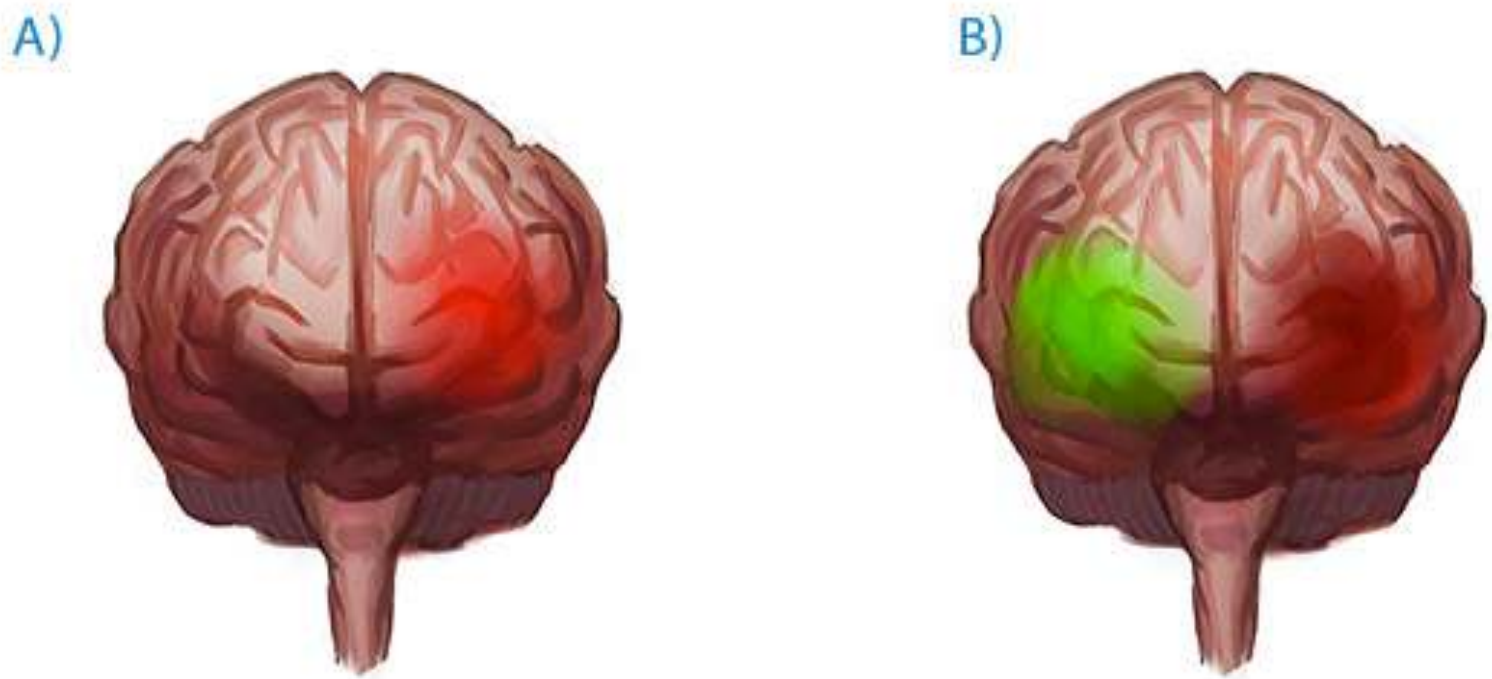



+ Oct4
+ Sox2
+ Klf4
+ c-Myc
iPS cells
NEURONS

Silly brain

Smart brain

Neuroplasticity

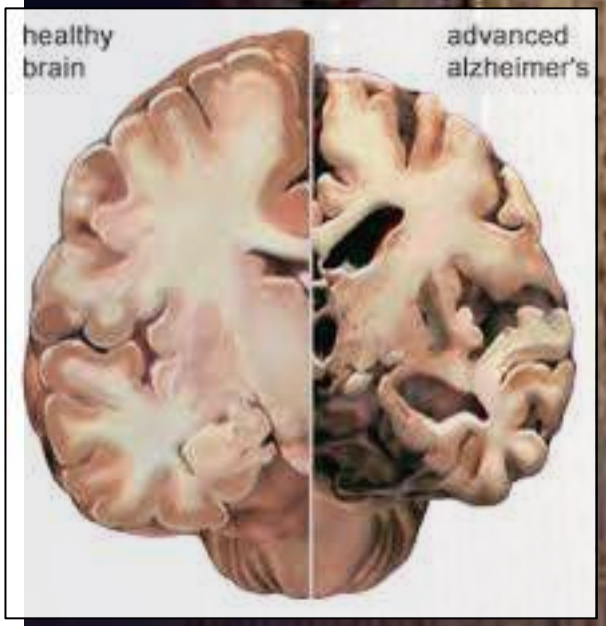


A) A segment of one brain hemisphere is damaged (shown in red), resulting in a loss of a particular function.
B) Over time, the opposite hemisphere can take over the lost function in the damaged hemisphere (shown in green).

http://www.stanford.edu/group/hopes/cgi-bin/wordpress/wp-content/uploads/2010/06/hemisphere3.jpg

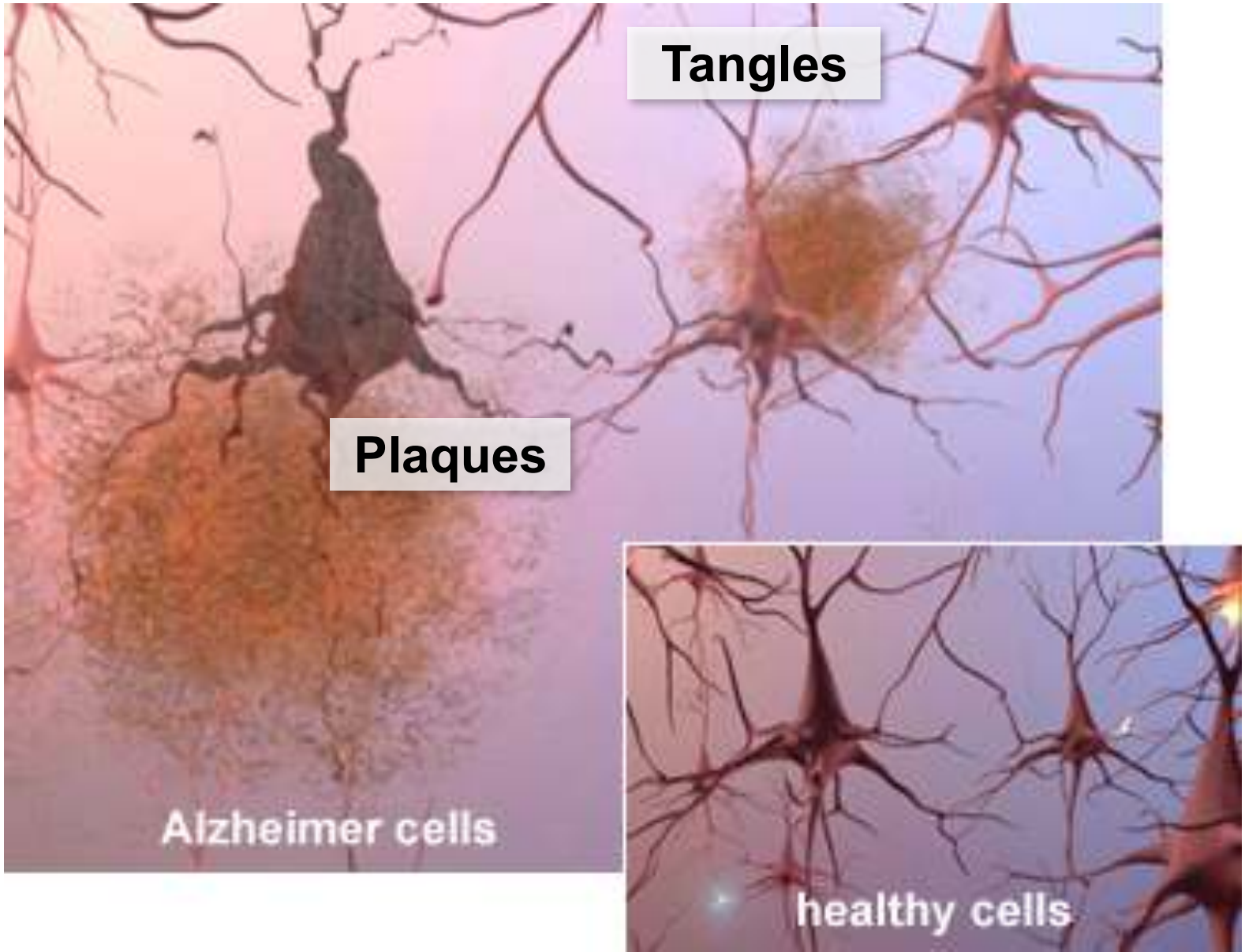
Ageing & Alzheimer's

Nearly 50% of adults over 85 afflicted with Alzheimer



http://www.alzheimers.net/resources/alzheimers-statistics/

Look from inside

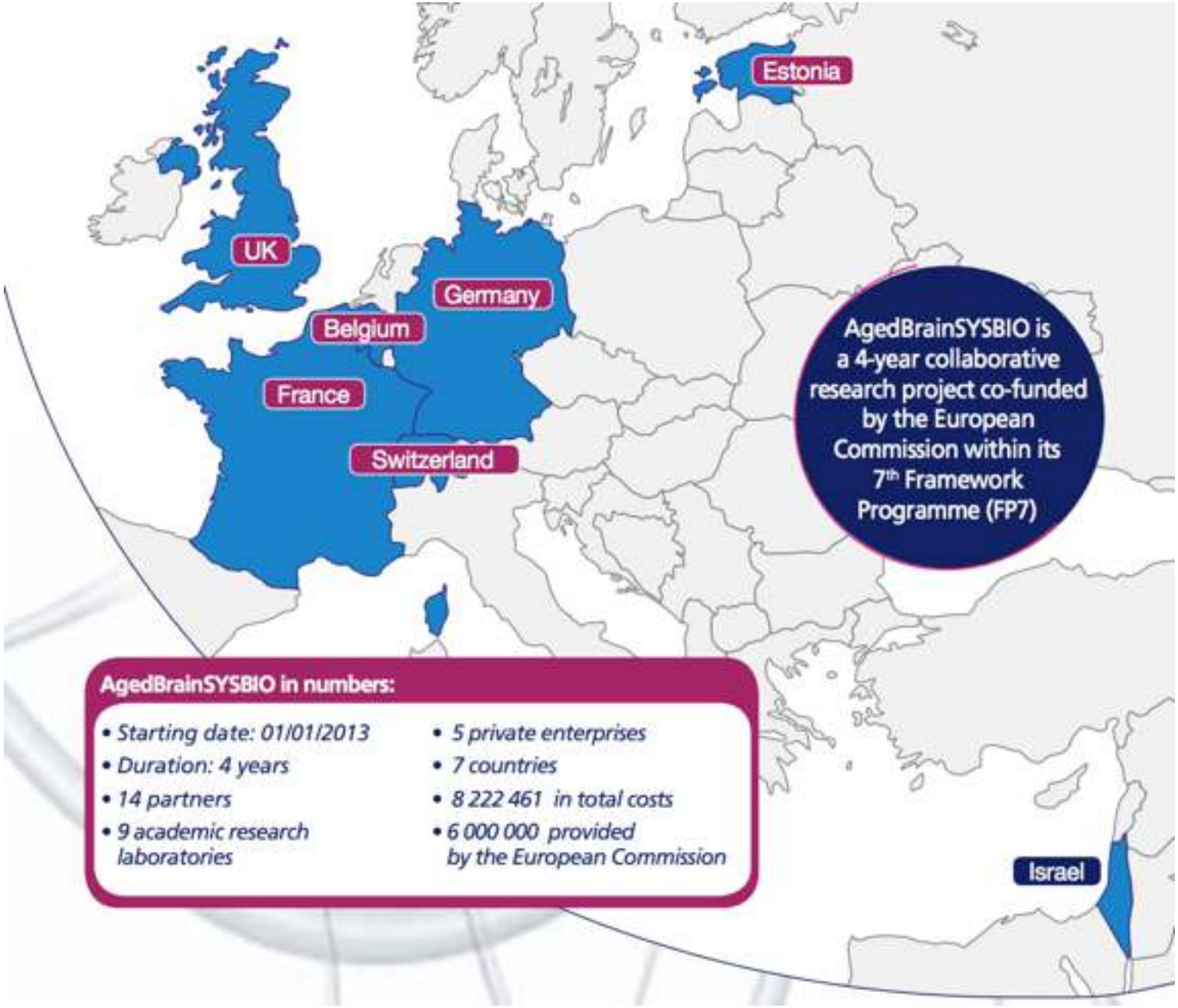


What do we do to understand?

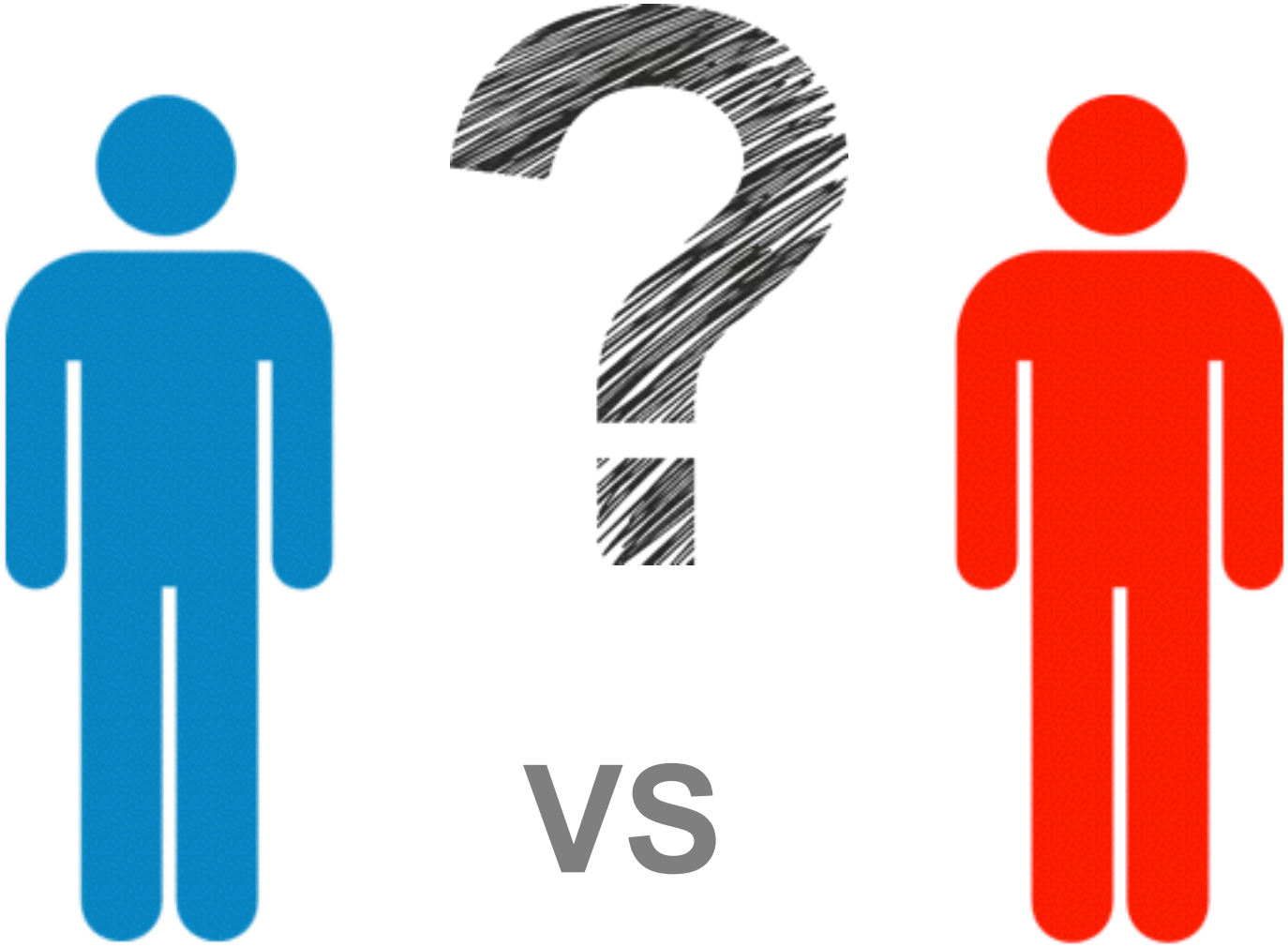
AgedBrainSYSBIO

- Address the basis of brain ageing in normal and in disease conditions
- Identify and validate new drug targets for Alzheimer's Disease

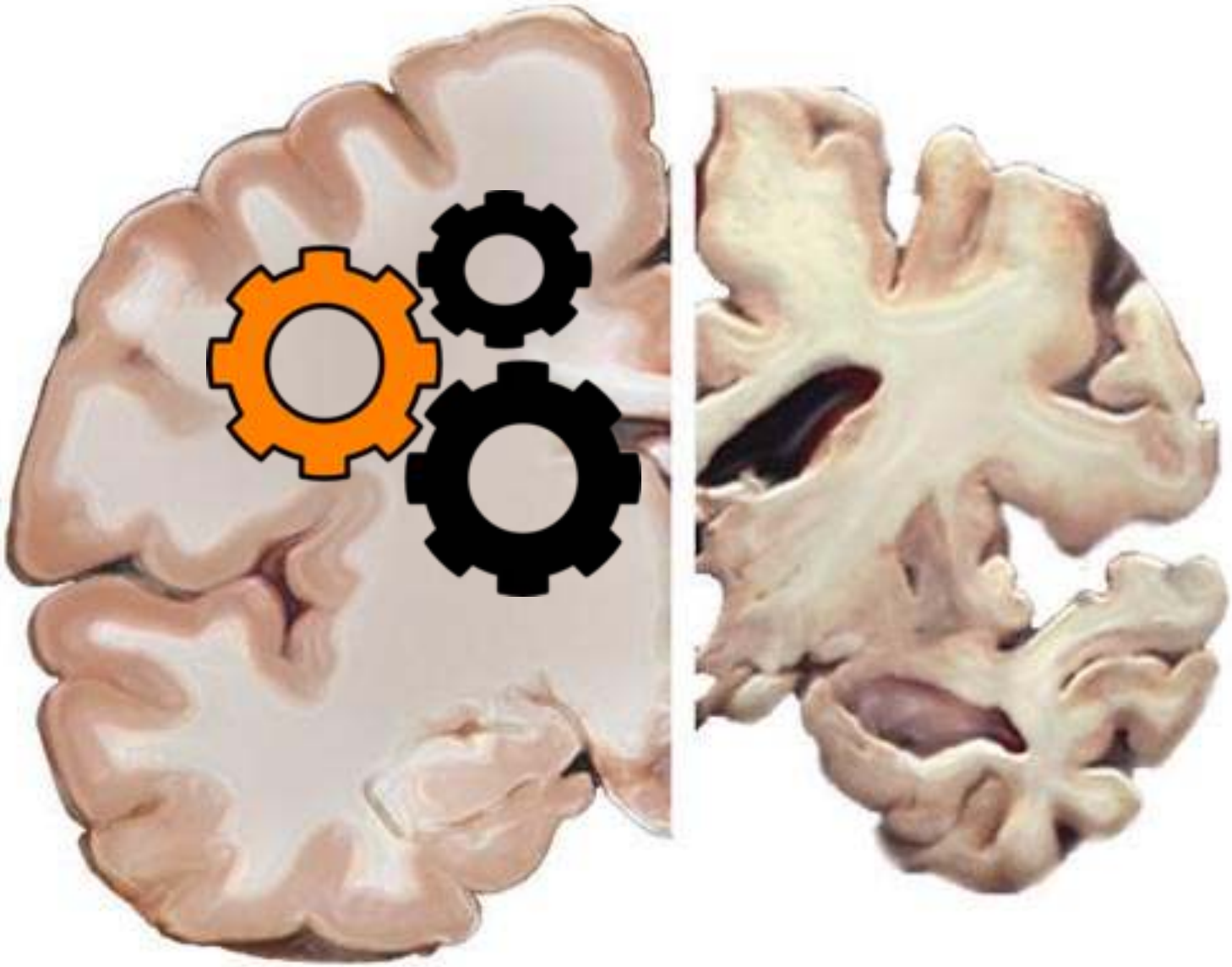
AgedBrainSYSBIO is funded by the European Commission within its FP7 Programme; Contract number HEALTH-F2-2012-305299


Estonia
UK
Germany
Belgium
France
Switzerland
Israel
AgedBrainSYSBIO is a 4-year collaborative research project co-funded by the European Commission within its 7th Framework Programme (FP7)
AgedBrainSYSBIO in numbers:
• Starting date: 01/01/2013
• Duration: 4 years
• 14 partners
• 9 academic research laboratories
• 5 private enterprises
• 7 countries
• 8 222 461 in total costs
• 6 000 000 provided by the European Commission

We want to understand

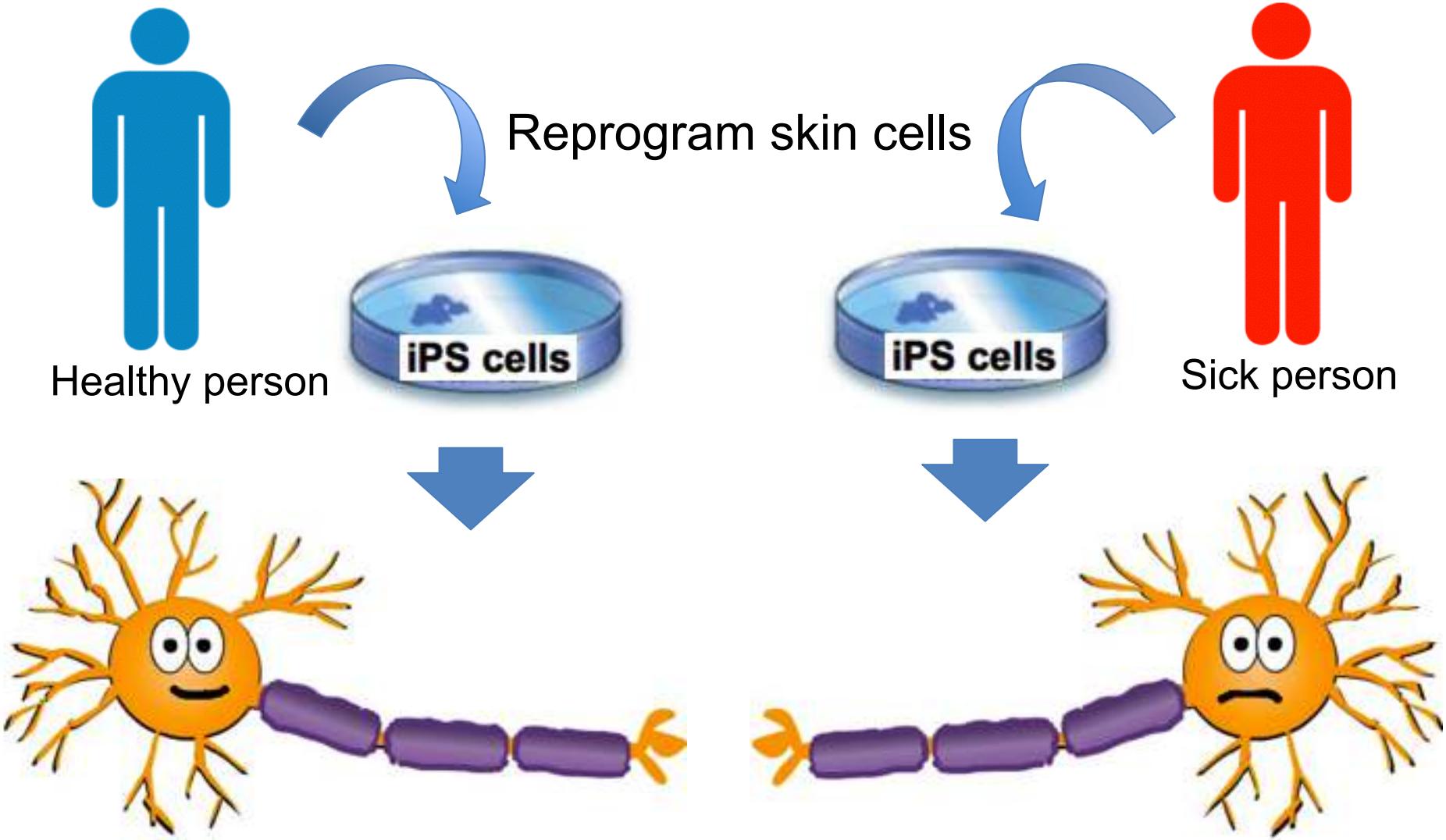


We want to understand

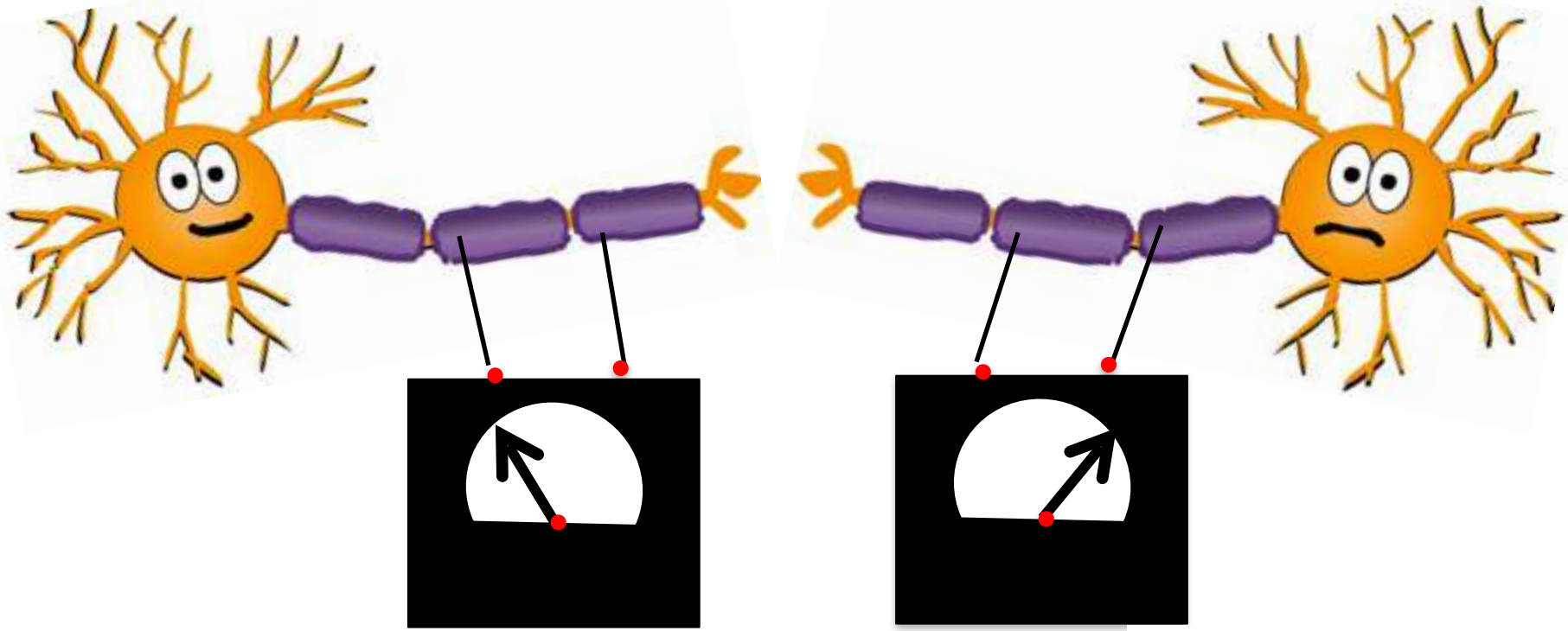


Experiments

Reprogram cells to study disease

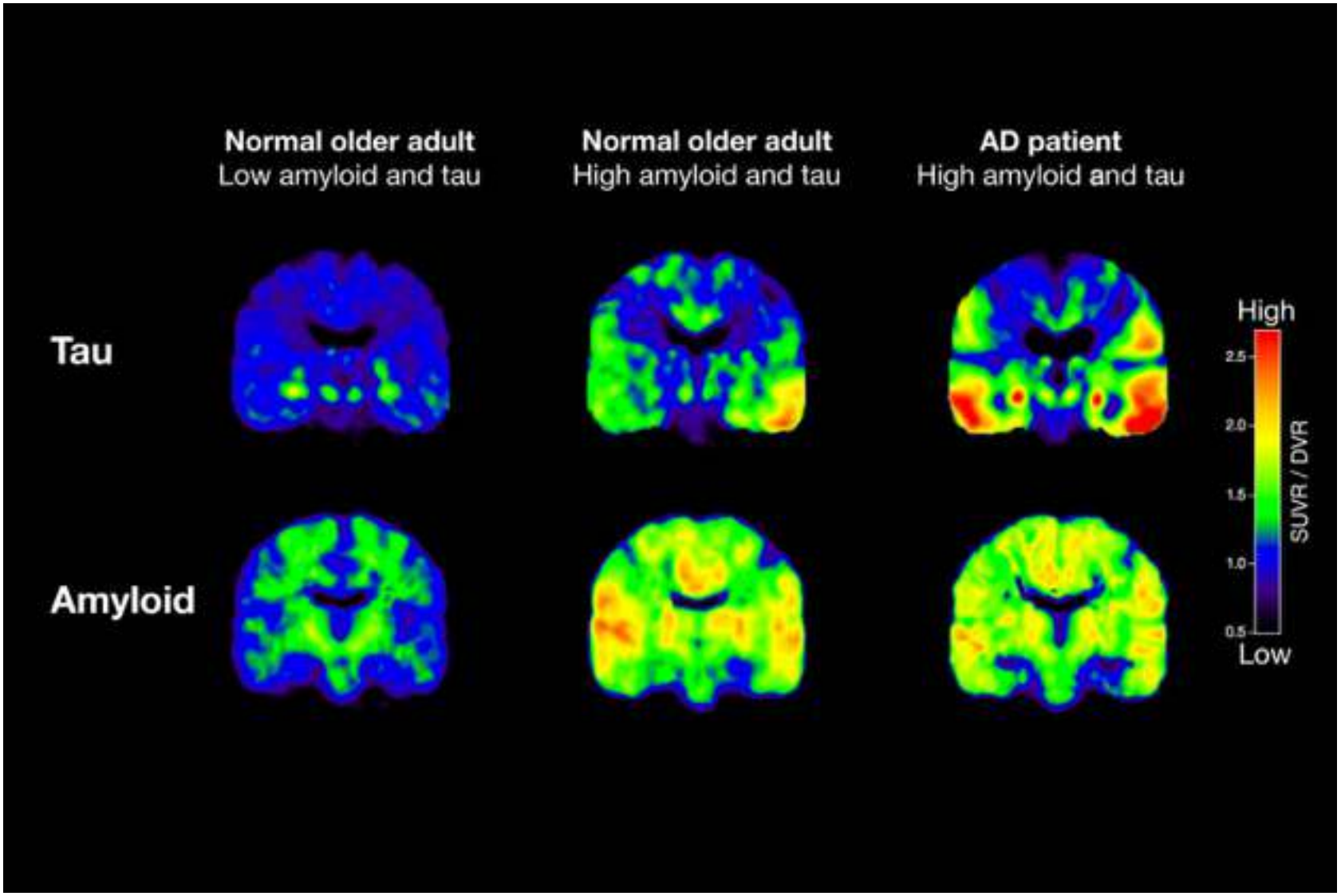


Understand the difference



Statistical power
Computational tools

Neuroimaging

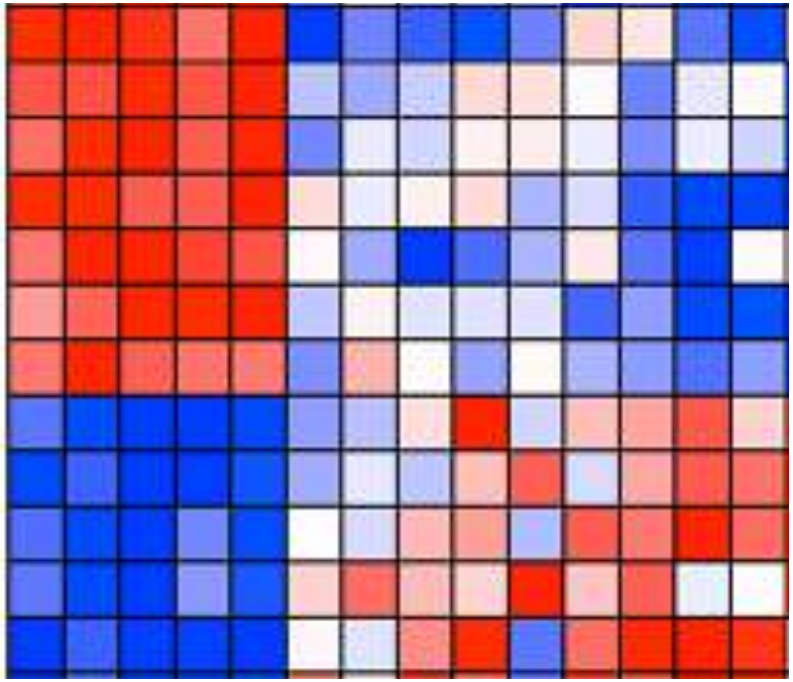


Important genes

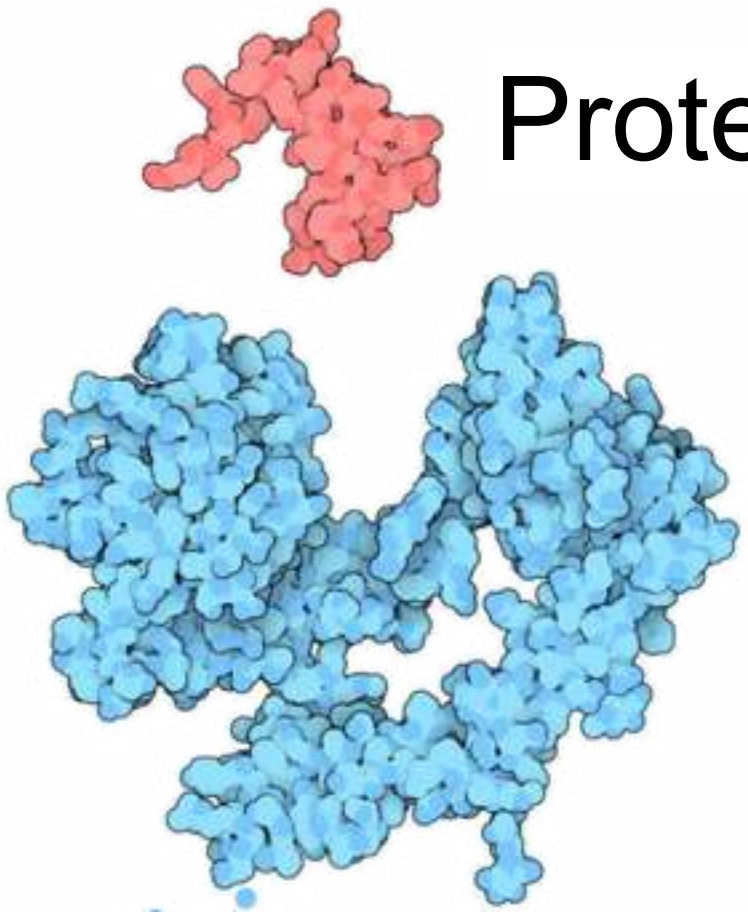
Gene 1

⋮

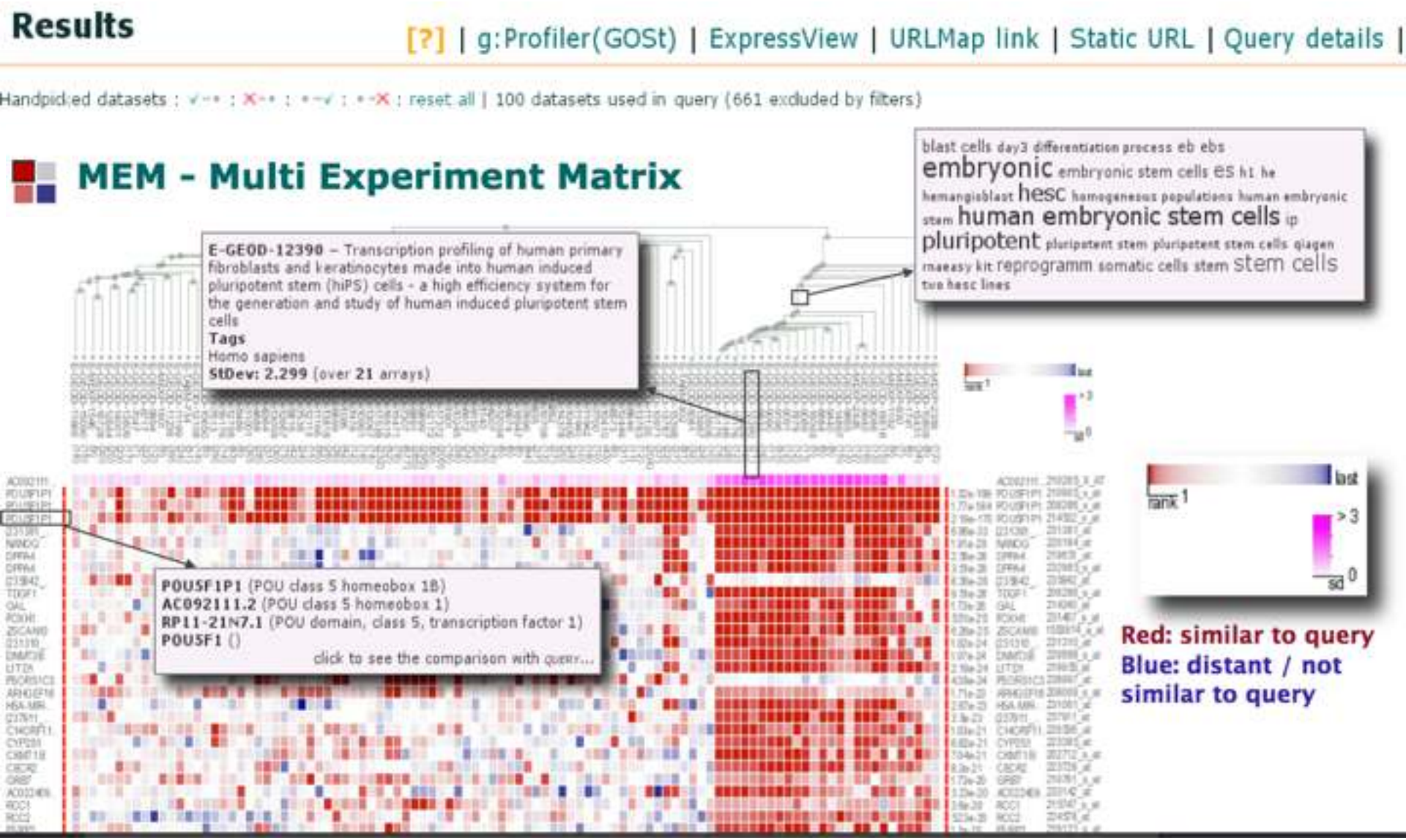
Gene n



Protein-protein interactions

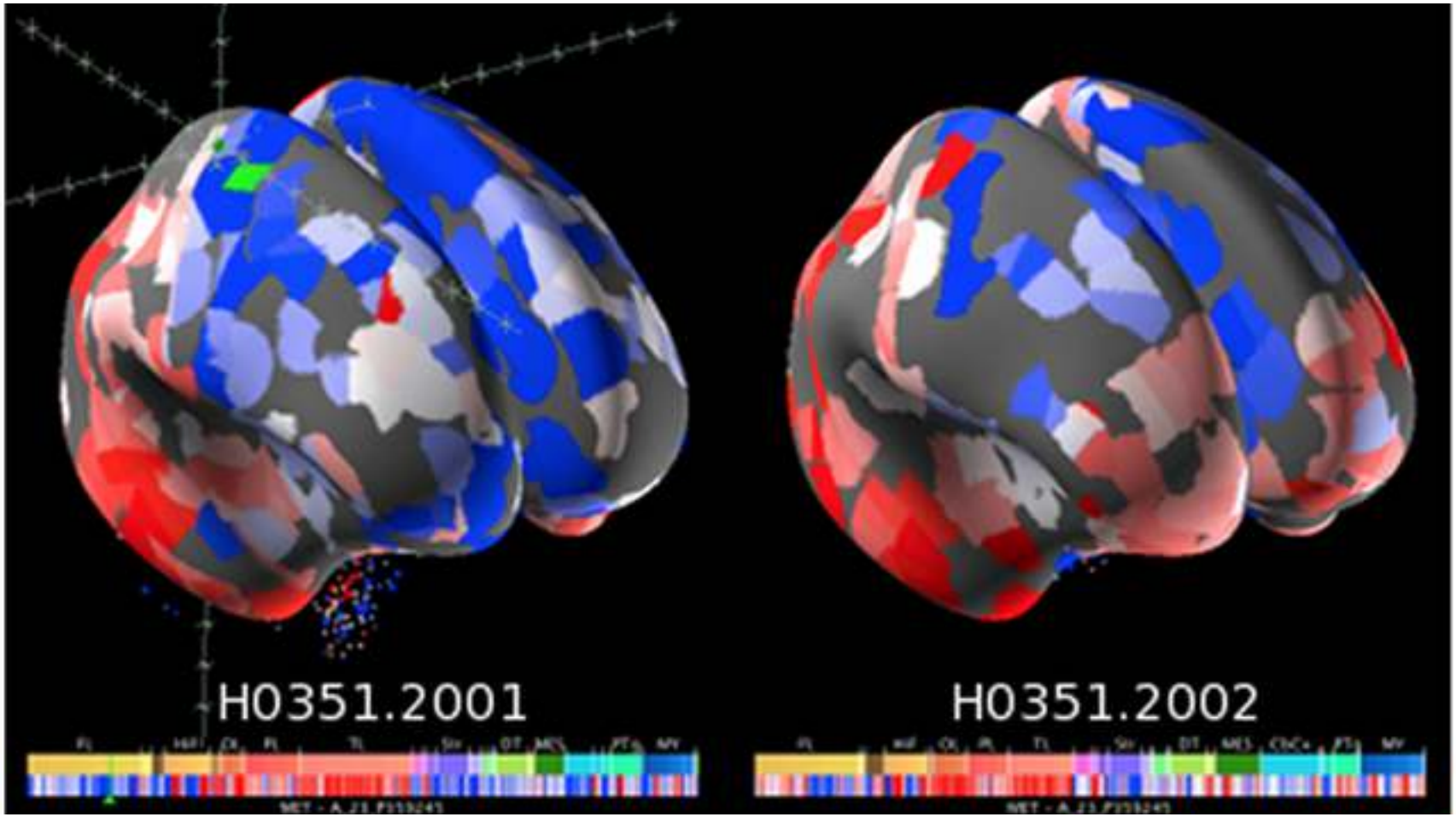


Co-expression



http://biit.cs.ut.ee/mem/

Expression in brain regions

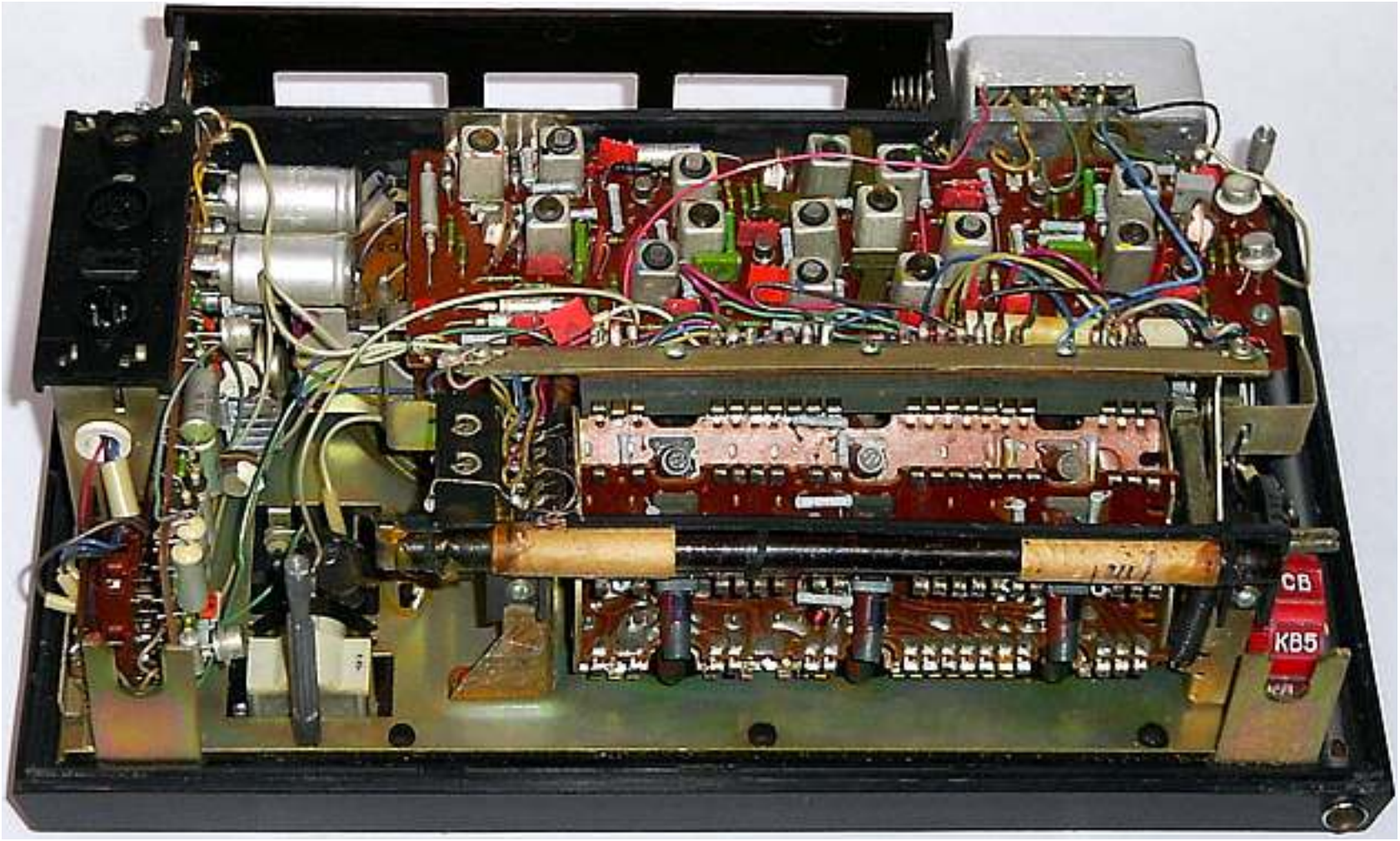


http://human.brain-map.org/static/brainexplorer

We solved it! Right?

How does it work?

How does work?

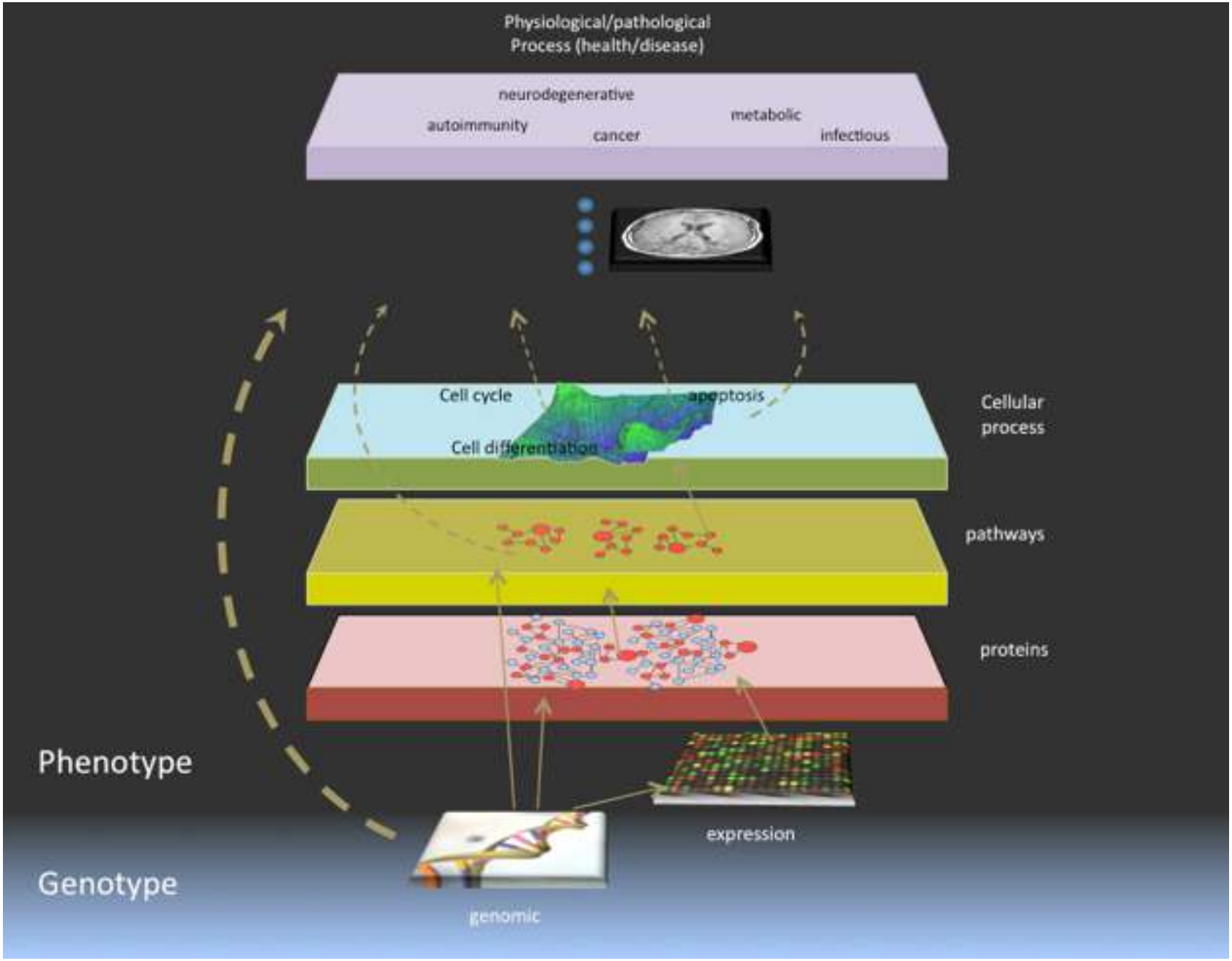


How does it work?

Lazebnik, Y. (2002). Can a biologist fix a radio?—Or, what I learned while studying apoptosis. Cancer cell

- Each dataset can be considered as a layer
- Combinations of different layers brings us to new knowledge

Picture by H.Peterson



http://baranzinilab.ucsf.edu/integration-large-scale-omics-data-sets

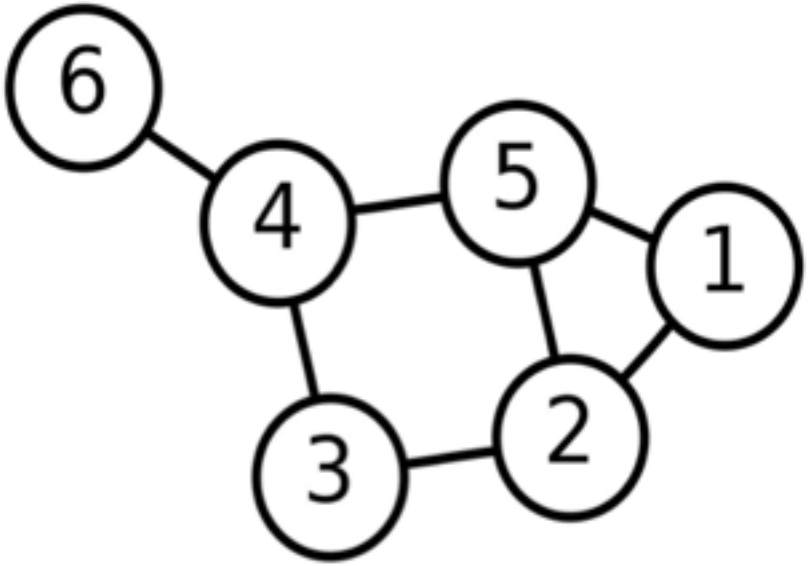
Q:

How to combine such heterogeneous information and to make sense of it?

A:

Networks!

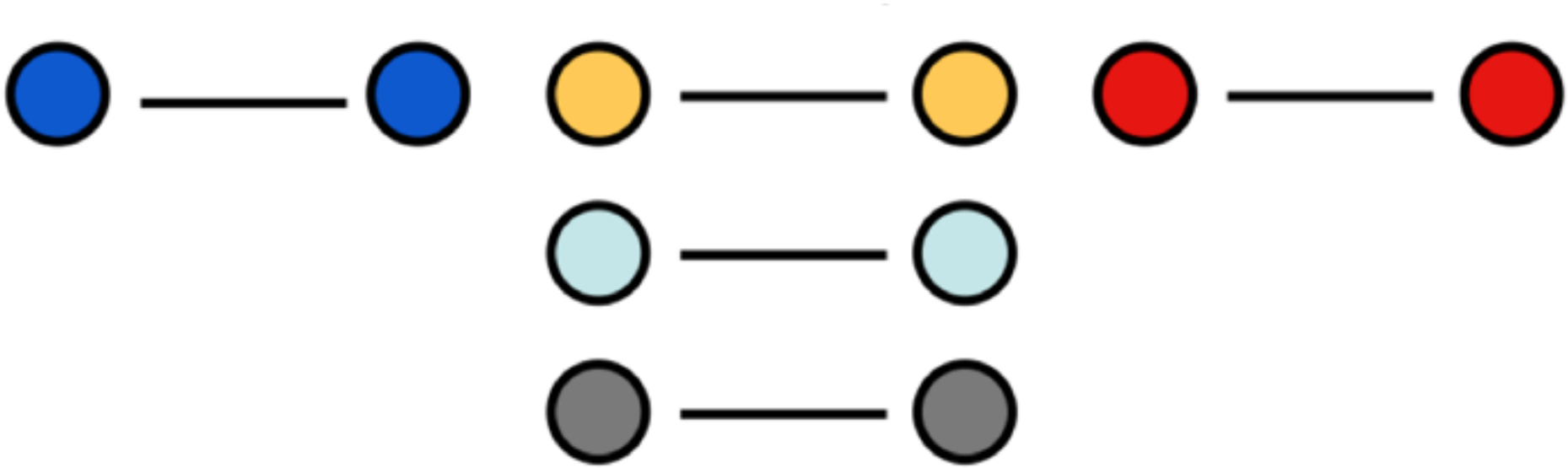
Nodes



- Genes
- Proteins
- Metabolites
- Enzymes
- etc.

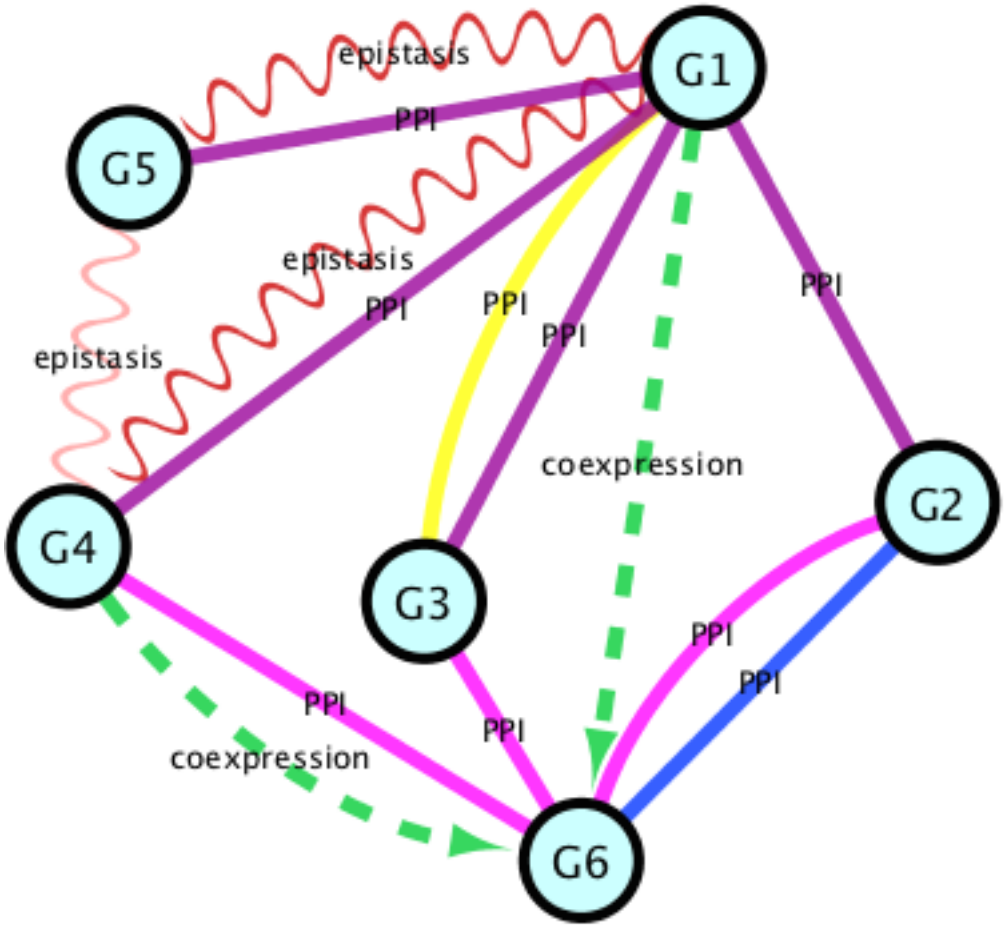
Edges

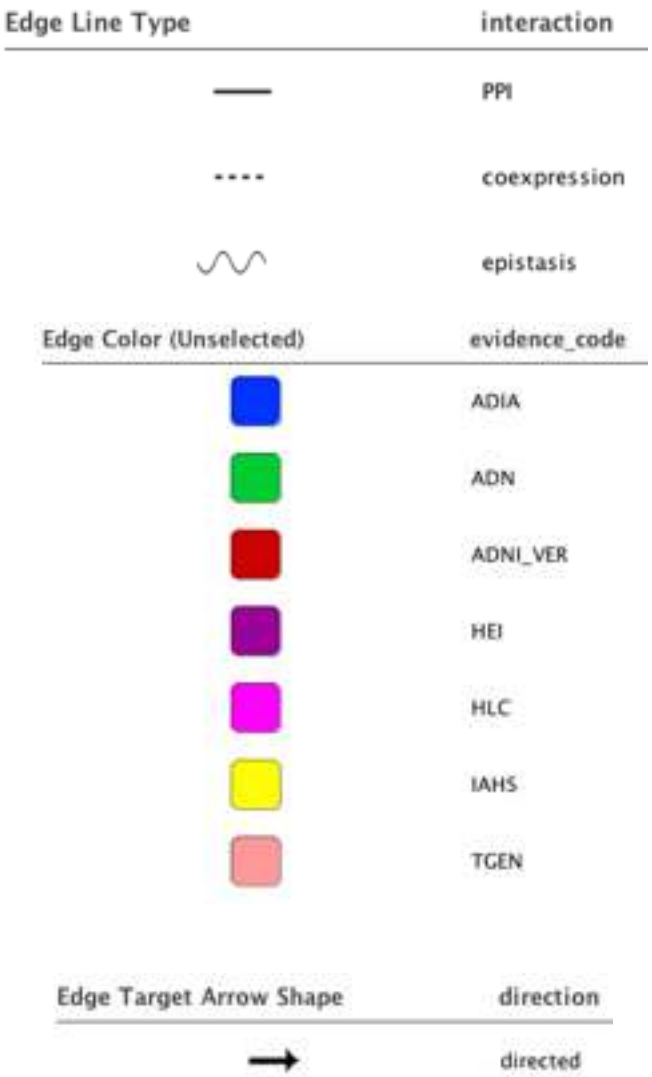
Co-expression PPI Epistasis



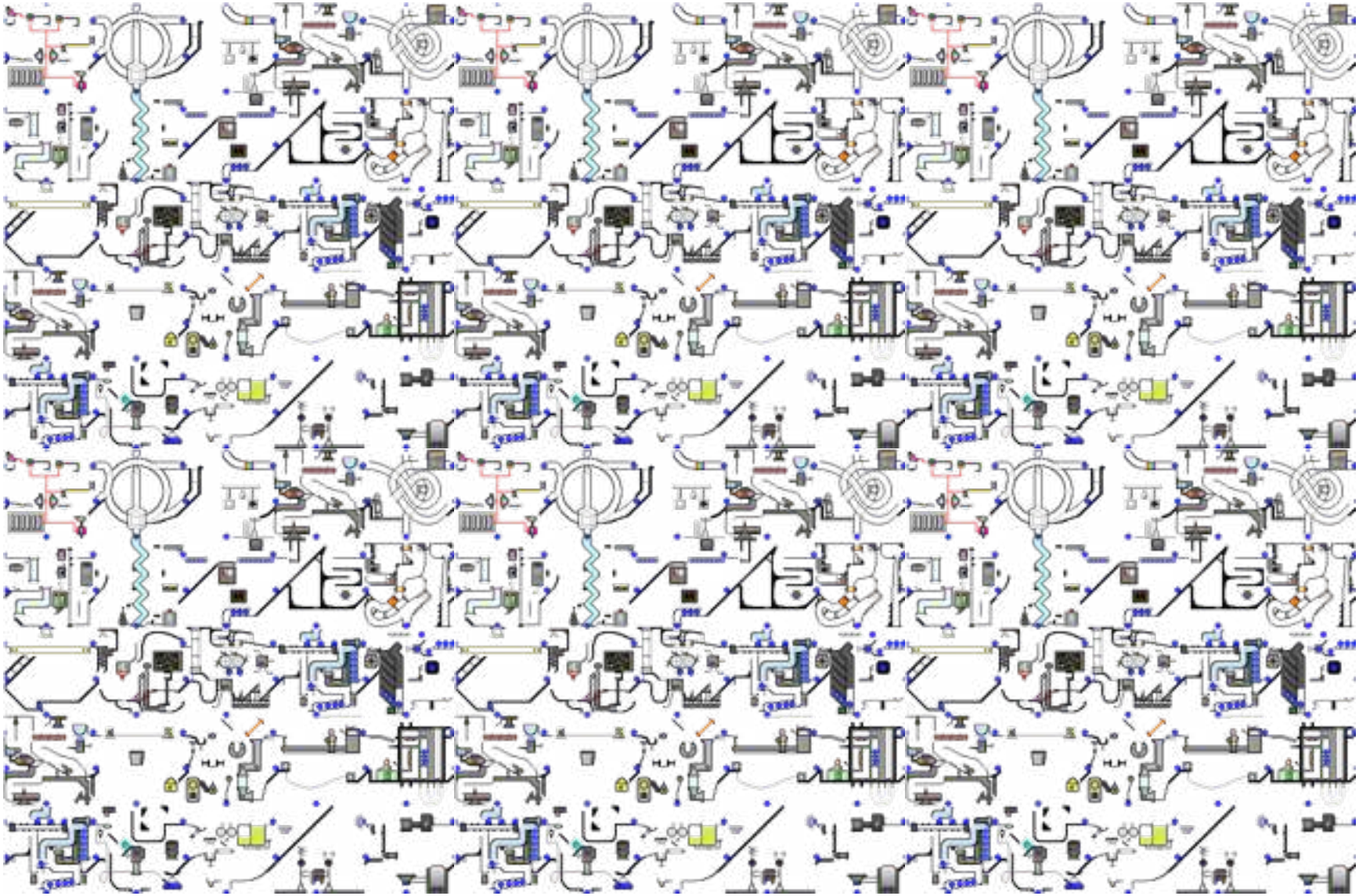
Biological relationships, interactions, regulations, reactions, transformations, activations, inhibitions, etc.

Edges in the network

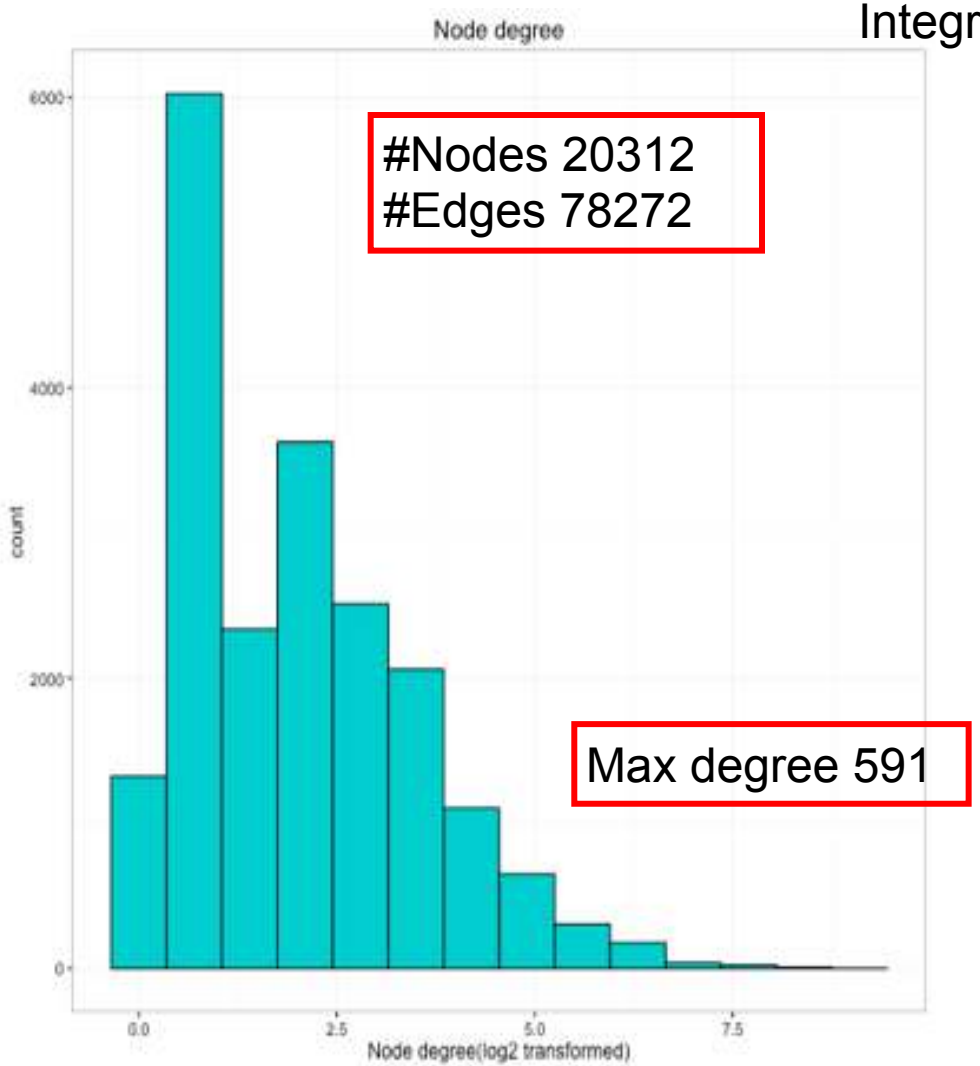




Simple representation of the integrated data



Network analysis. Node degree.



Integrated dataset is represented as graph

Gene name	Degree
LRRK2	278
APP	192
MAPT	76
KHDRBS1	74
CLU	63
FYN	52
BIN1	41
RIN3	38
EPHA1	38
APOE	32
CD2AP	31
CASS4	30
INPP5D	22
MACF1	22

Topological network analysis

GraphWeb

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public web server for graph-based analysis of biological networks

http://biit.cs.ut.ee/graphweb/index.cgi

1. Extract the largest connected component.

2. Markov Cluster Algorithm

3. Hub-based Modules

#Nodes 11322
#Edges 34244

Markov Cluster Algorithm

GraphWeb

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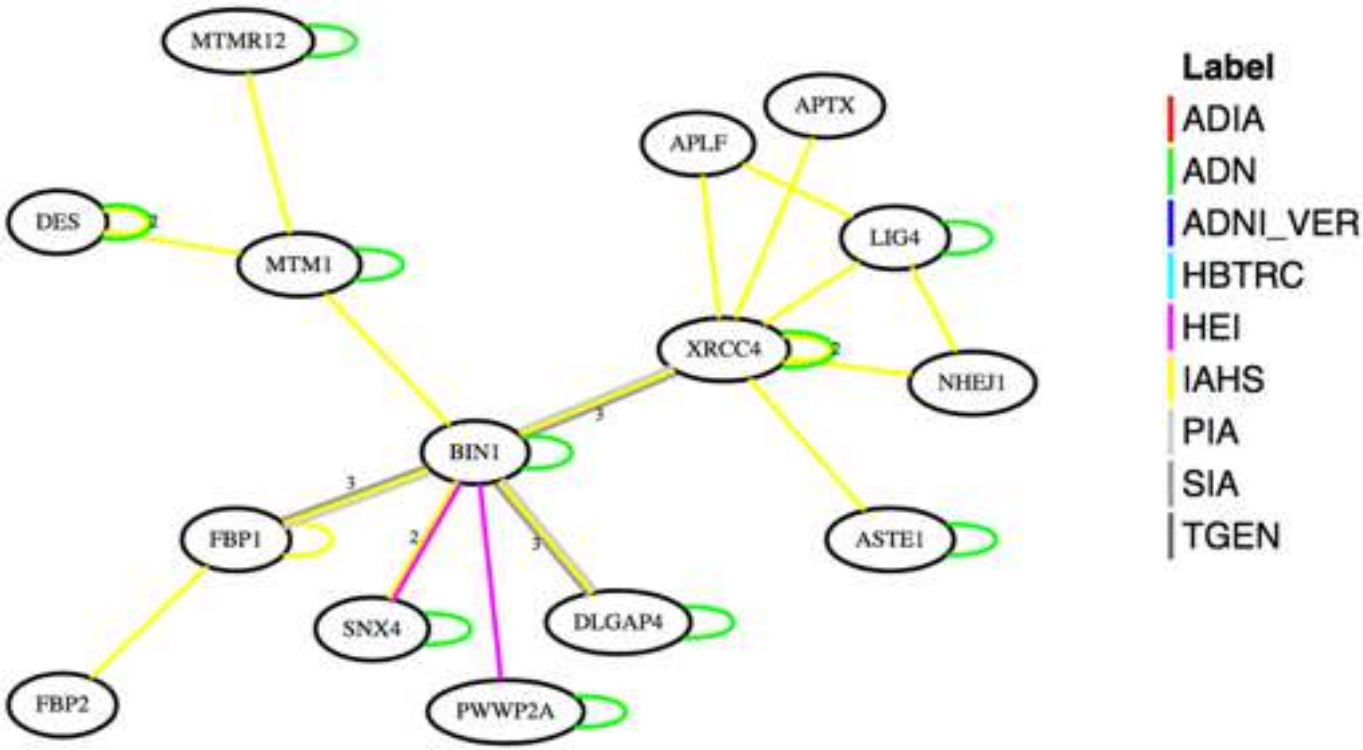
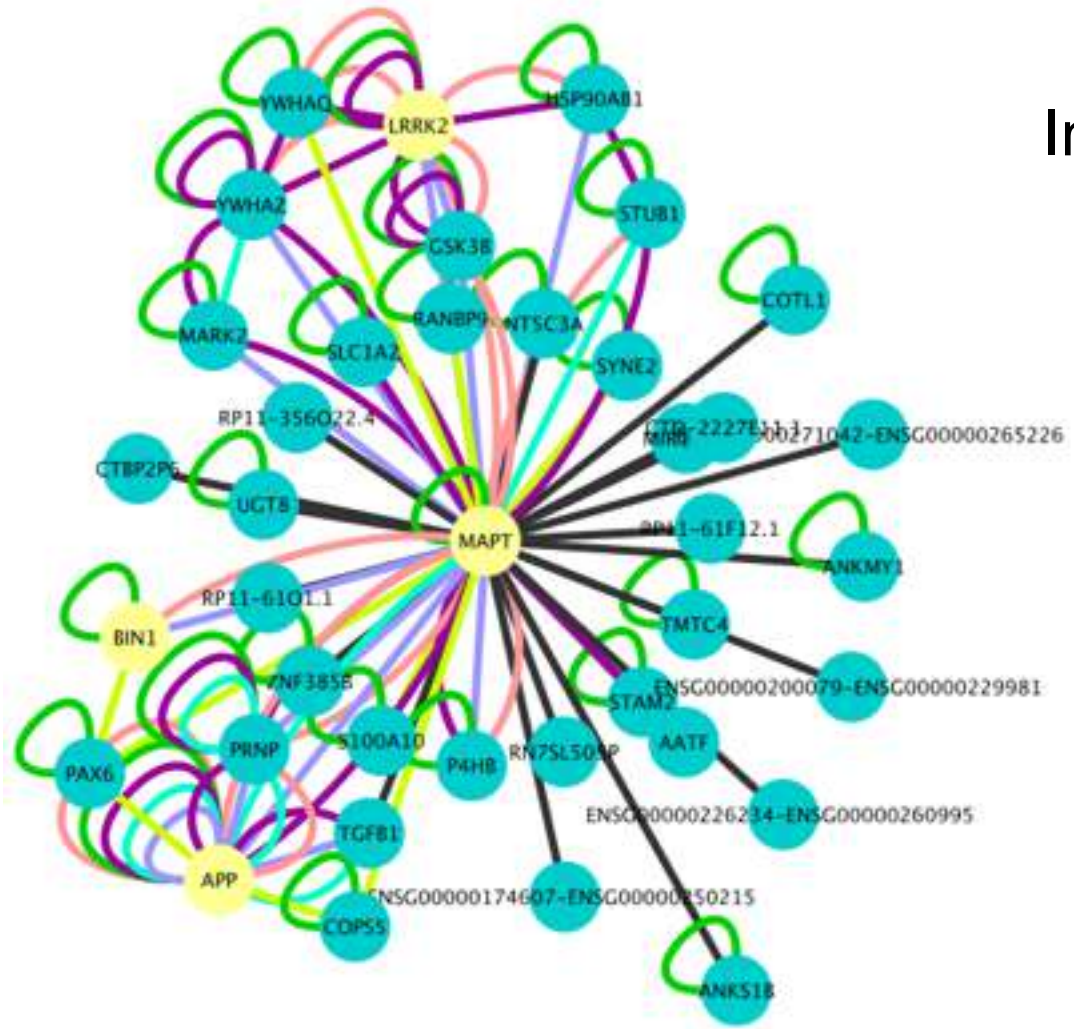
2175 modules found



Hub-based modules



Individual datasets

g:Profiler toolset
http://biit.cs.ut.ee/gprofiler

J. Reimand, M. Kull, H. Peterson, J. Hansen, J. Vilo: *g:Profiler - a web-based toolset for functional profiling of gene lists from large-scale experiments* (2007) NAR 35 W193-W200
Jüri Reimand, Tambet Arak, Priit Adler, Liis Kolberg, Sulev Reisberg, Hedi Peterson, Jaak Vilo: *g:Profiler -- a web server for functional interpretation of gene lists (2016 update)* Nucleic Acids Research 2016; doi: 10.1093/nar/gkw199

g:GOSt

Tool for functional profiling of gene lists from **large-scale** experiments

PLXDC1
TM4SF5
ACSL6
SLC47A1
FGF1
VLDLR
XKR5
GDF15
AIM2
AMPD3
MAP7D2
PGC
MYO1G
APOD
CPN1
CLGN
PLCD3
D11WSU47E
FBXO27
ESYT3

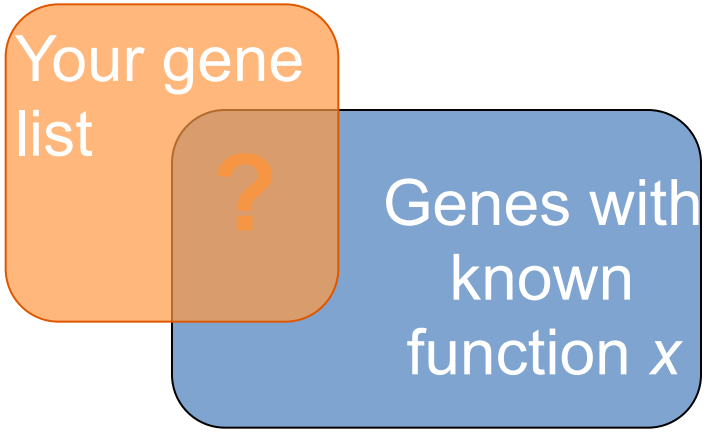
Gene Ontology
Cellular component
Molecular function
Biological process

Regulation
miRBase miRNAs
TRANSFAC TF targets

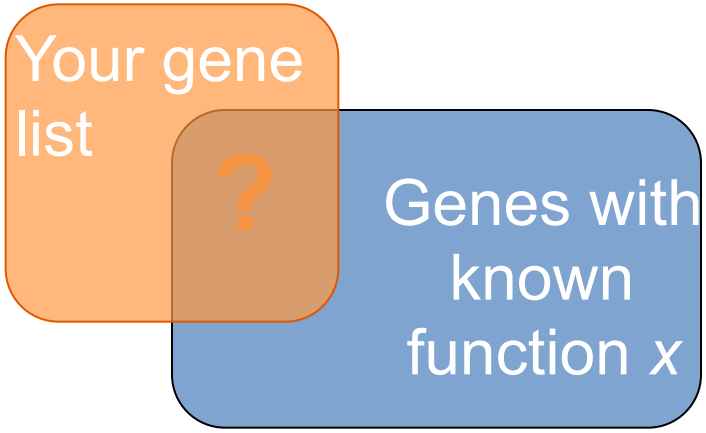
Pathways
KEGG
Reactome

Varia
Biogrid PPIs
CORUM protein complexes
Human Phenotype Ontology

Functional enrichment statistics

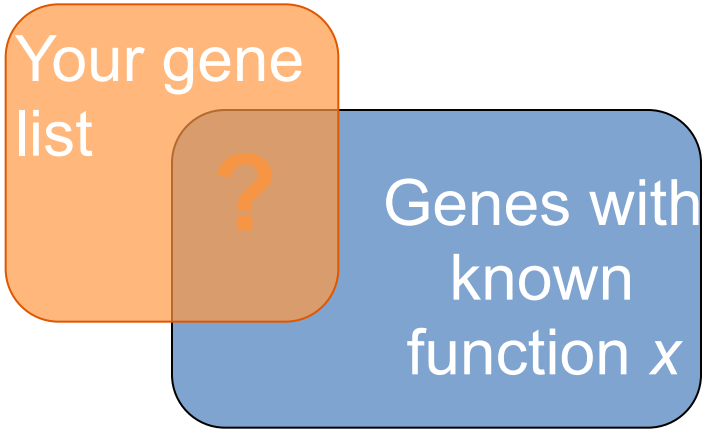


Functional enrichment statistics



Does your gene list includes **more** genes with function *x* than expected by random chance?

Functional enrichment statistics



Does your gene list includes **more** genes with function *x* than expected by random chance?

$$p = \sum_{i=k_\pi}^{min(n,K_\pi)} \frac{\binom{K_\pi}{i}\binom{N-K_\pi}{n-i}}{\binom{N}{n}}$$

Reading the output

Statistics

source	term name Gene Ontology (Biological process)	term ID	n. of term genes	n. of query genes	n. of common genes	corrected p-value
BP	ncRNA metabolic process	GO:0034660	475	50	10	8.05e-04
BP	tRNA metabolic process	GO:0006399	199	50	6	3.02e-02

Your genes
50

10

GO:0034660
ncRNA metabolic process
475 genes

Markov Cluster Algorithm

GraphWeb

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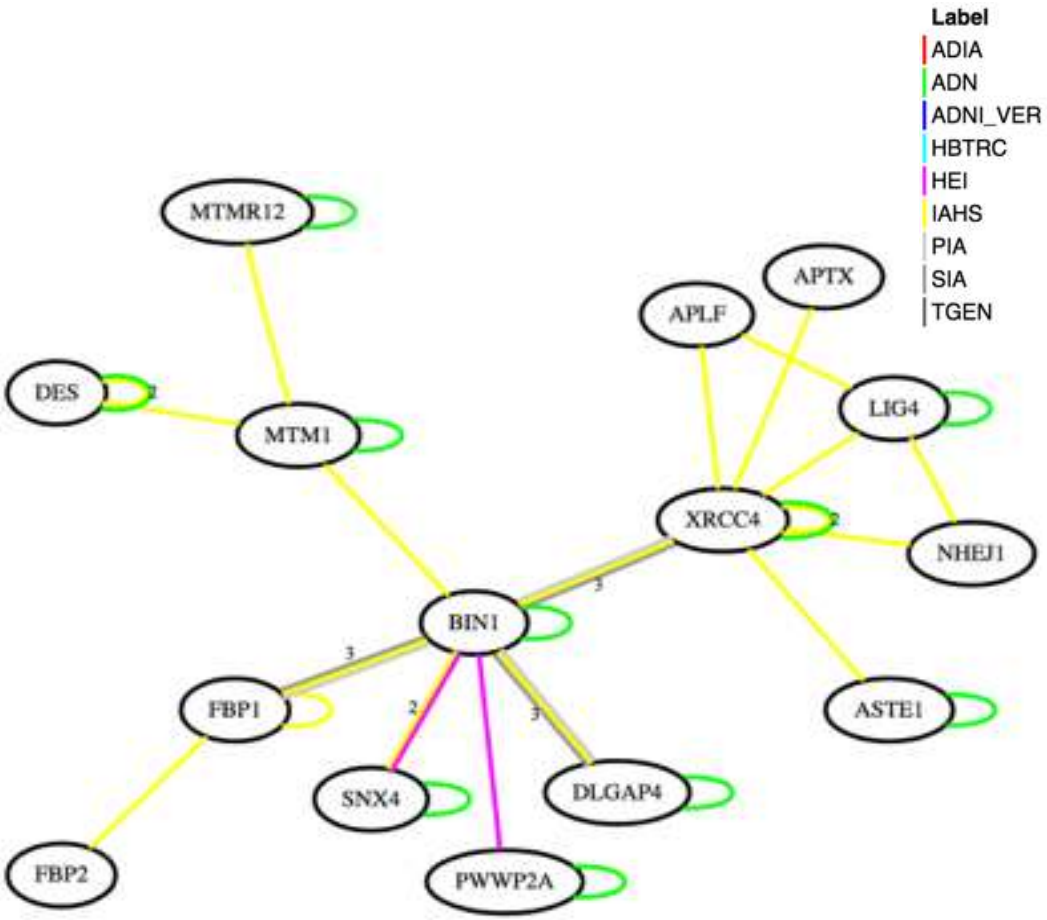
2175 modules found

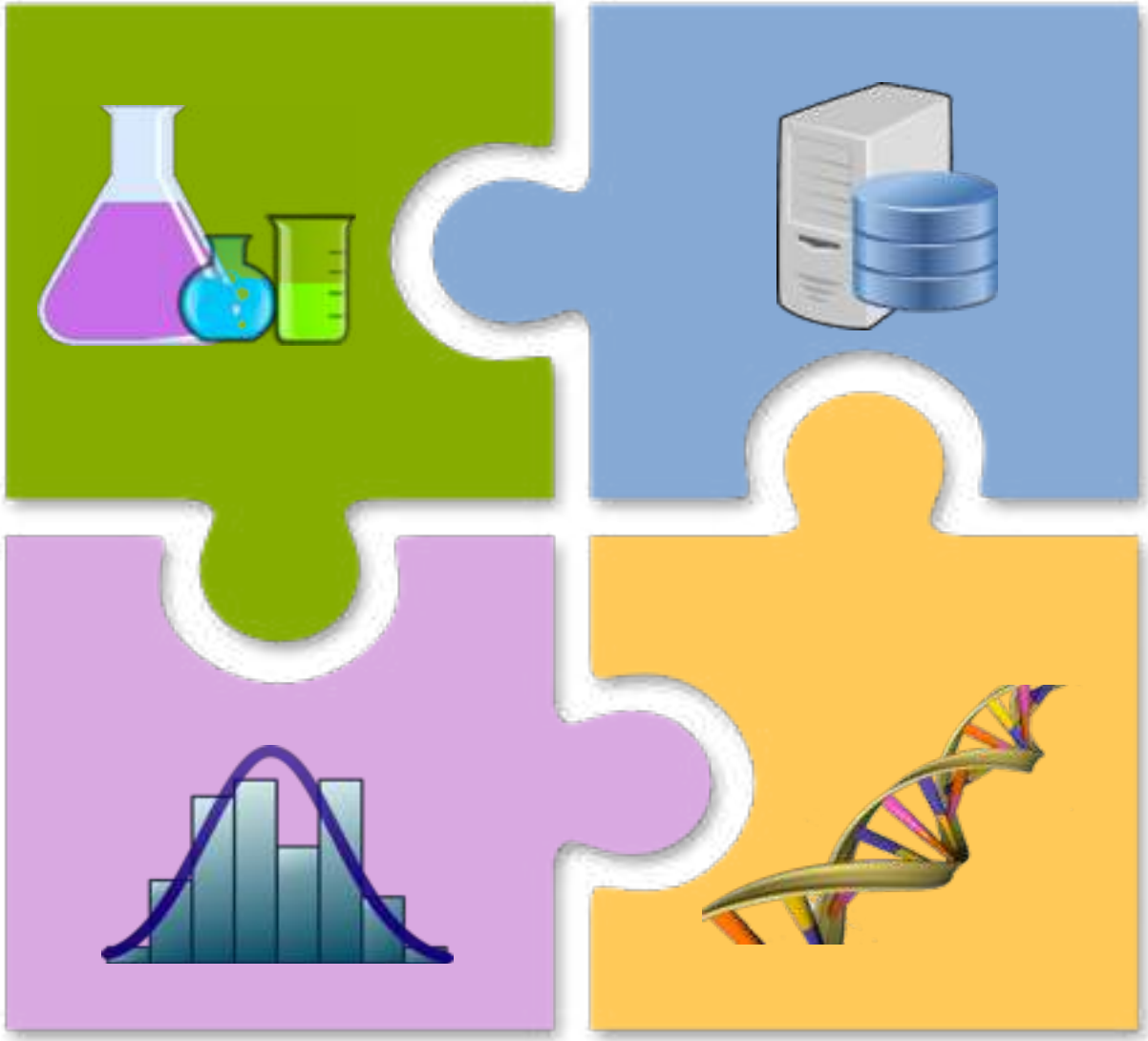
Enrichment results for example module

4.33e-07	GO:BP	DNA ligation
2.40e-05	GO:CC	nonhomologous end joining complex ...
1.00e-03	GO:MF	fructose 1,6-bisphosphate ...
4.68e-08		DNA ligase IV-XRCC4-XLF complex ...
8.75e-06	KEGG	Non-homologous end-joining
1.86e-03	REACTOME	Nonhomologous End-joining ...

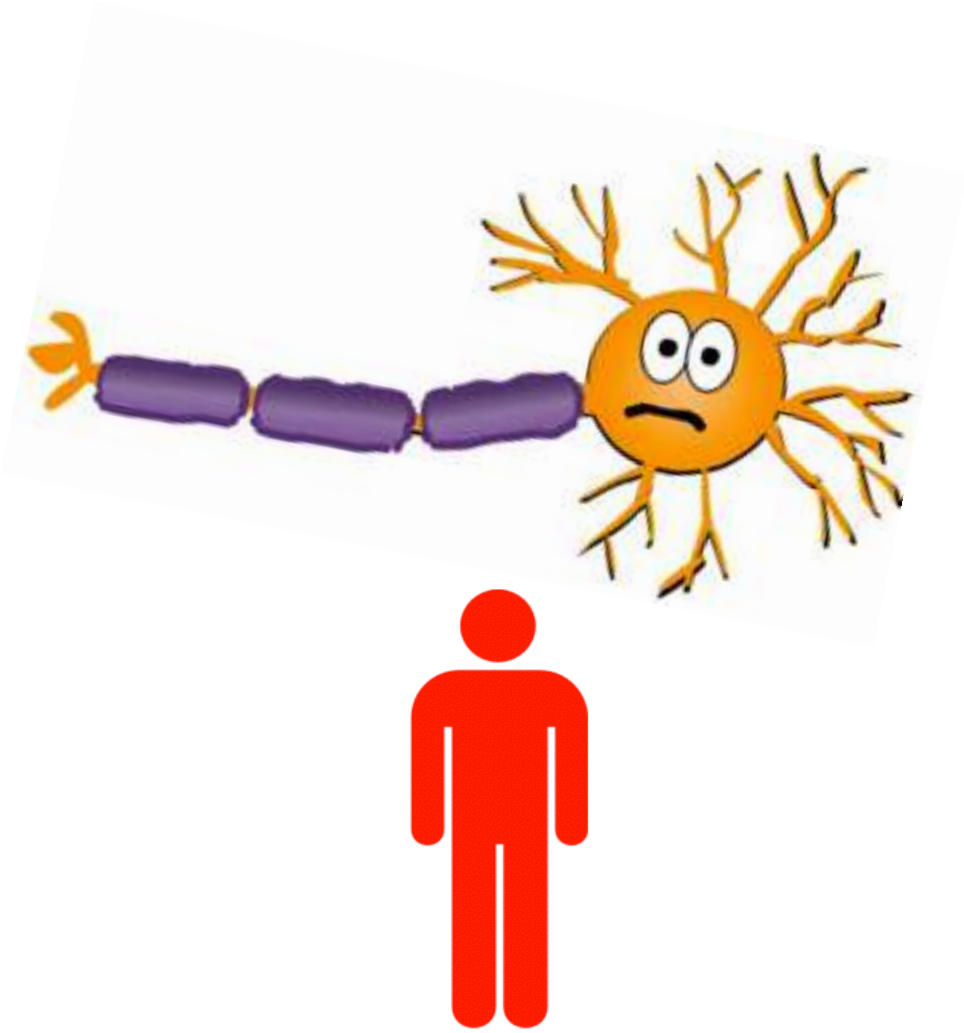


Sharing with the community

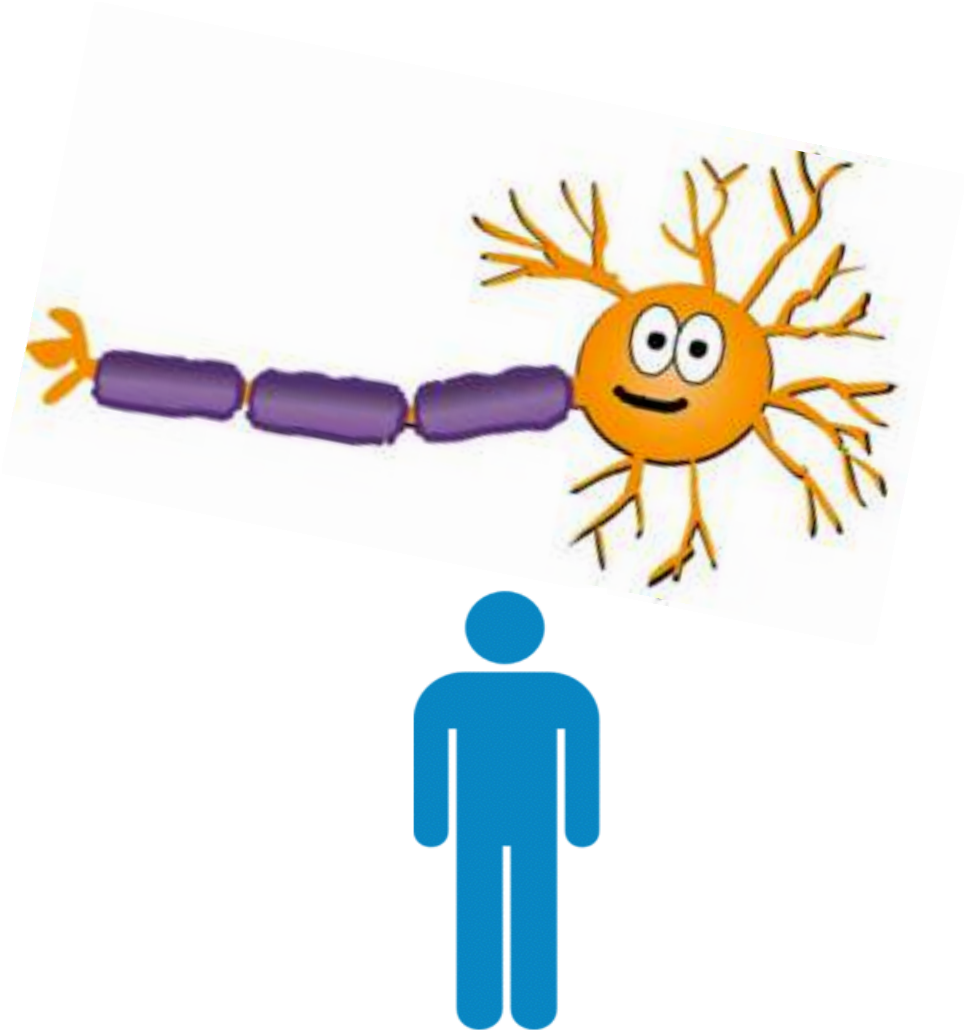
Data integration = understanding the disease better



Make unhappy neurons



Make neurons happy



I will study human brain
I will study human brain
I will study human brain
I will study human brain
I will study human brain
I will study human brain
I will study human brain
I will study human brain

“The brain is a commodity used to fertilize ideas.”

Elbert Hubbard

THANK YOU!

Questions