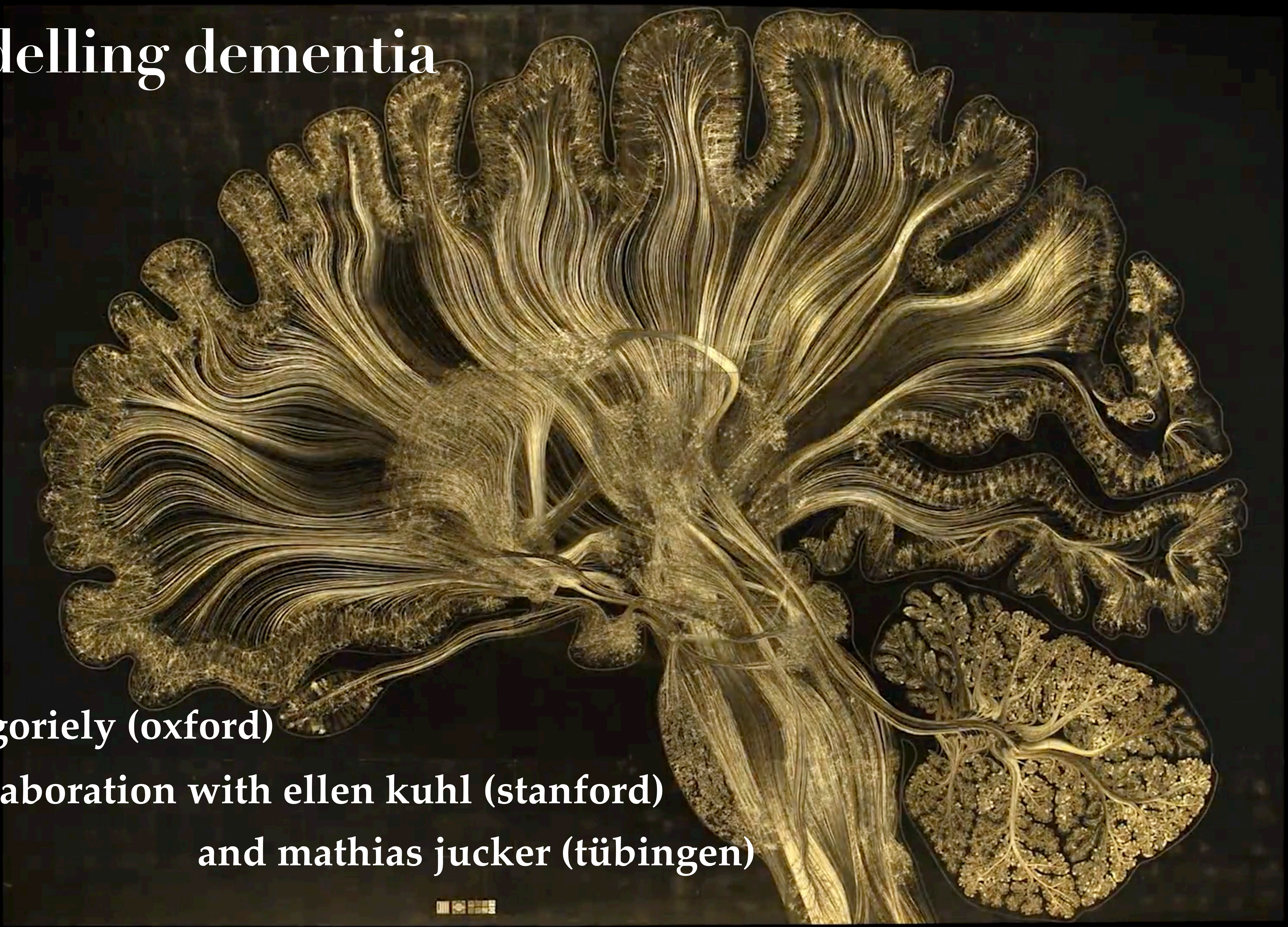
modelling dementia



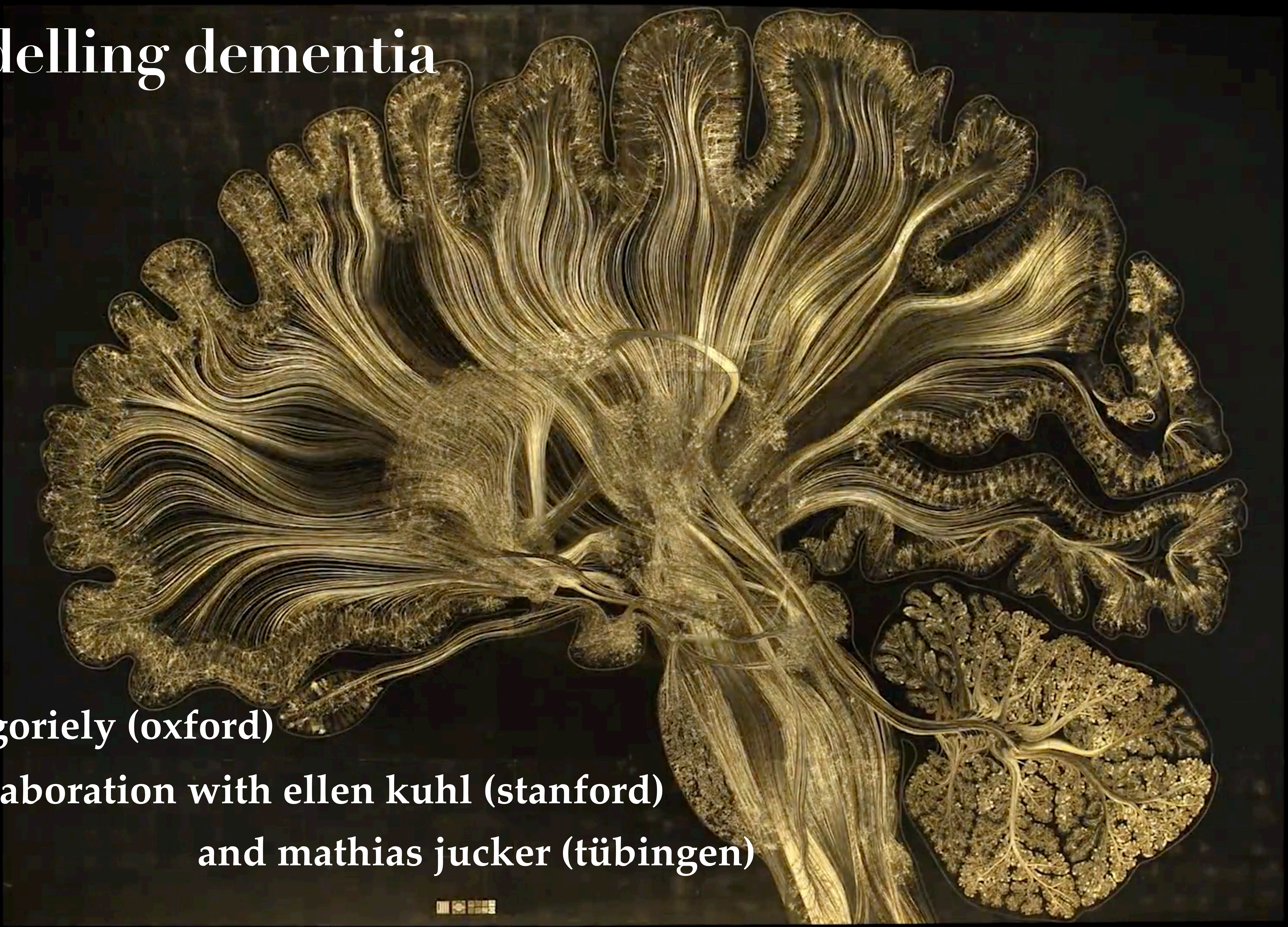
alain goriely (oxford)

in collaboration with ellen kuhl (stanford)

and mathias jucker (tübingen)

[art: g. dunn & b. edwards]

modelling dementia



alain goriely (oxford)

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[art: g. dunn & b. edwards]

1.

“ich habe mich verloren”

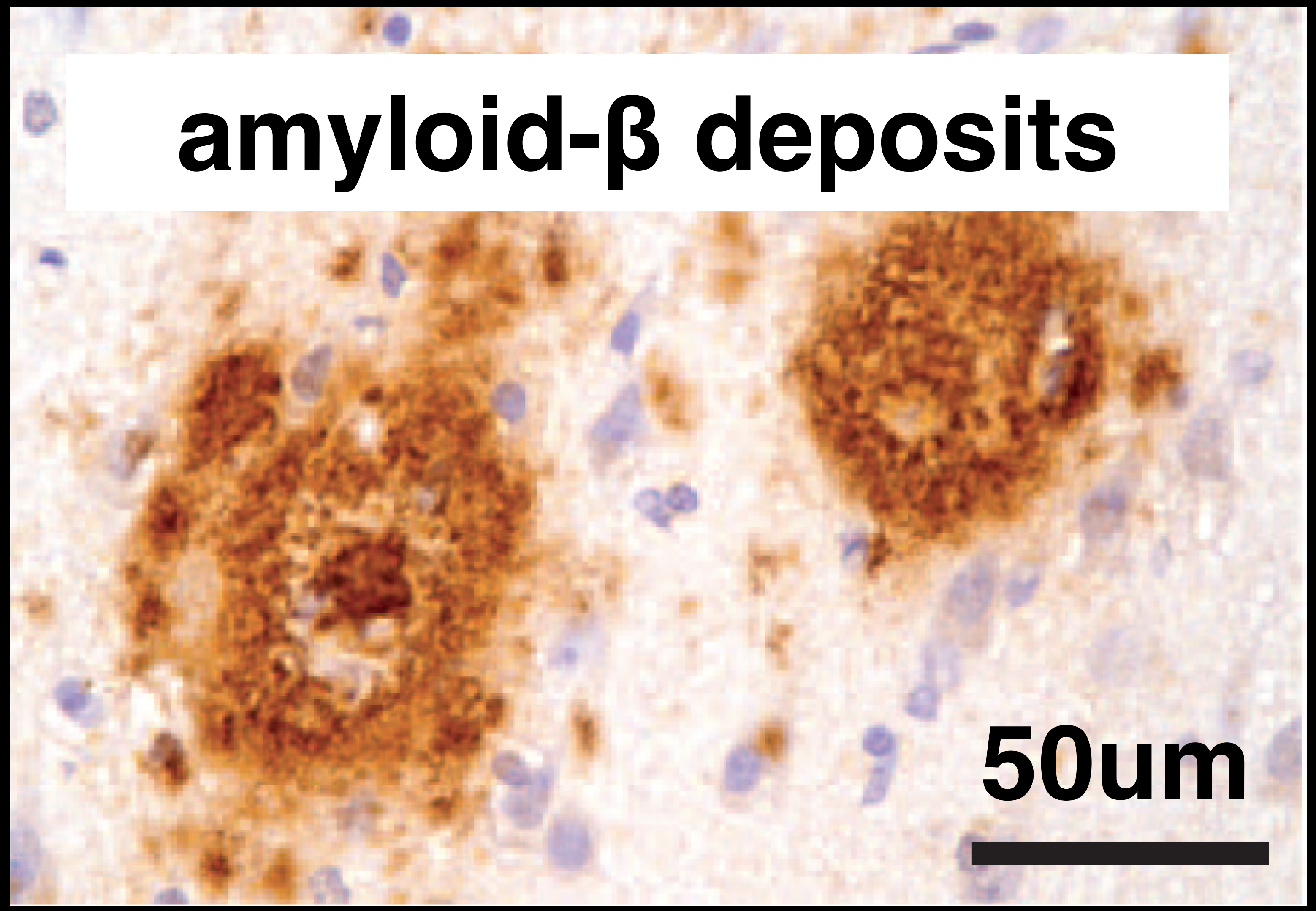
auguste deter

auguste deter
"i have lost myself”

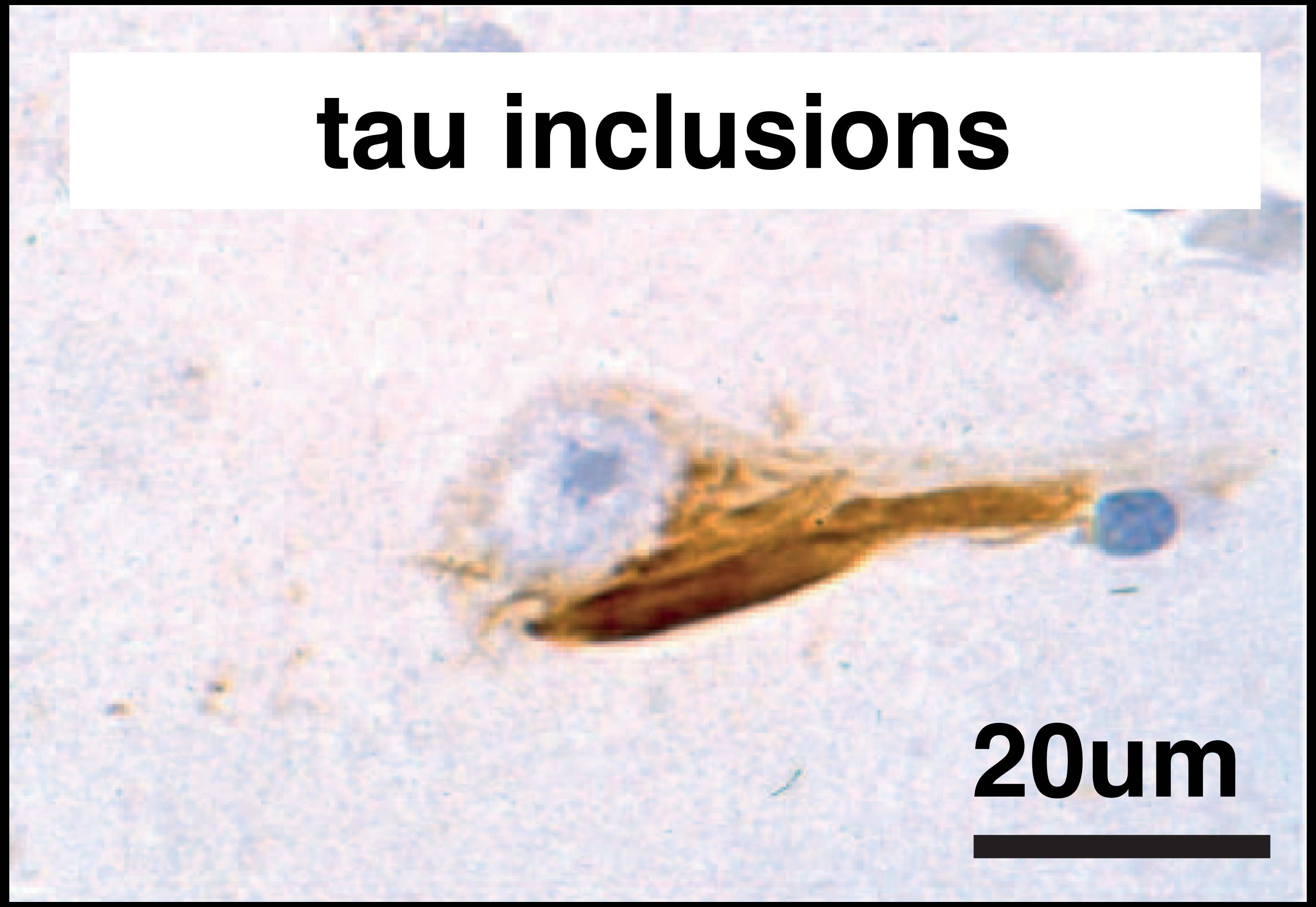
auguste deter
"i have lost myself”

alois alzheimer
“the disease of forgetfulness"

auguste deter
"i have lost myself”

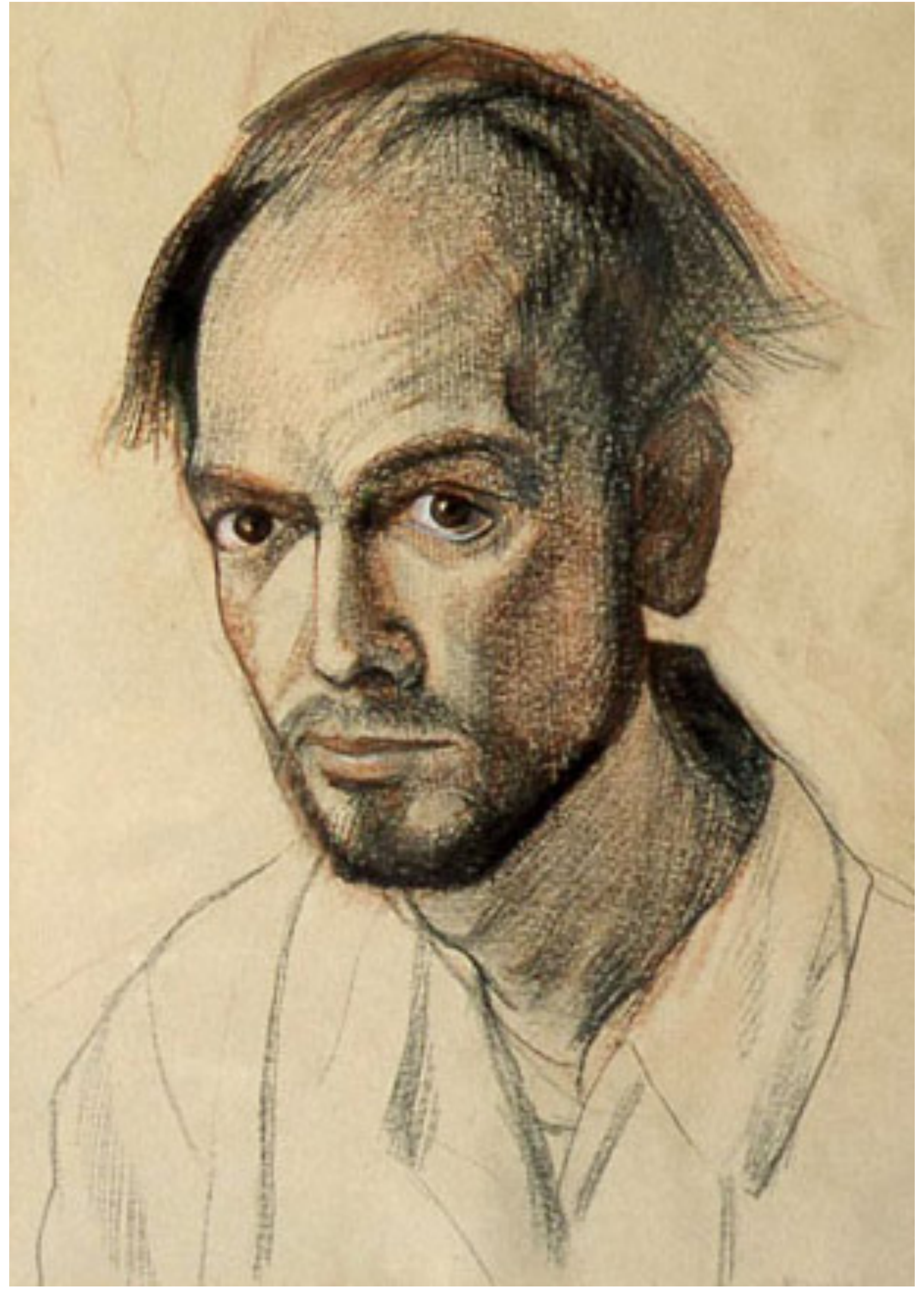


amyloid-β deposits



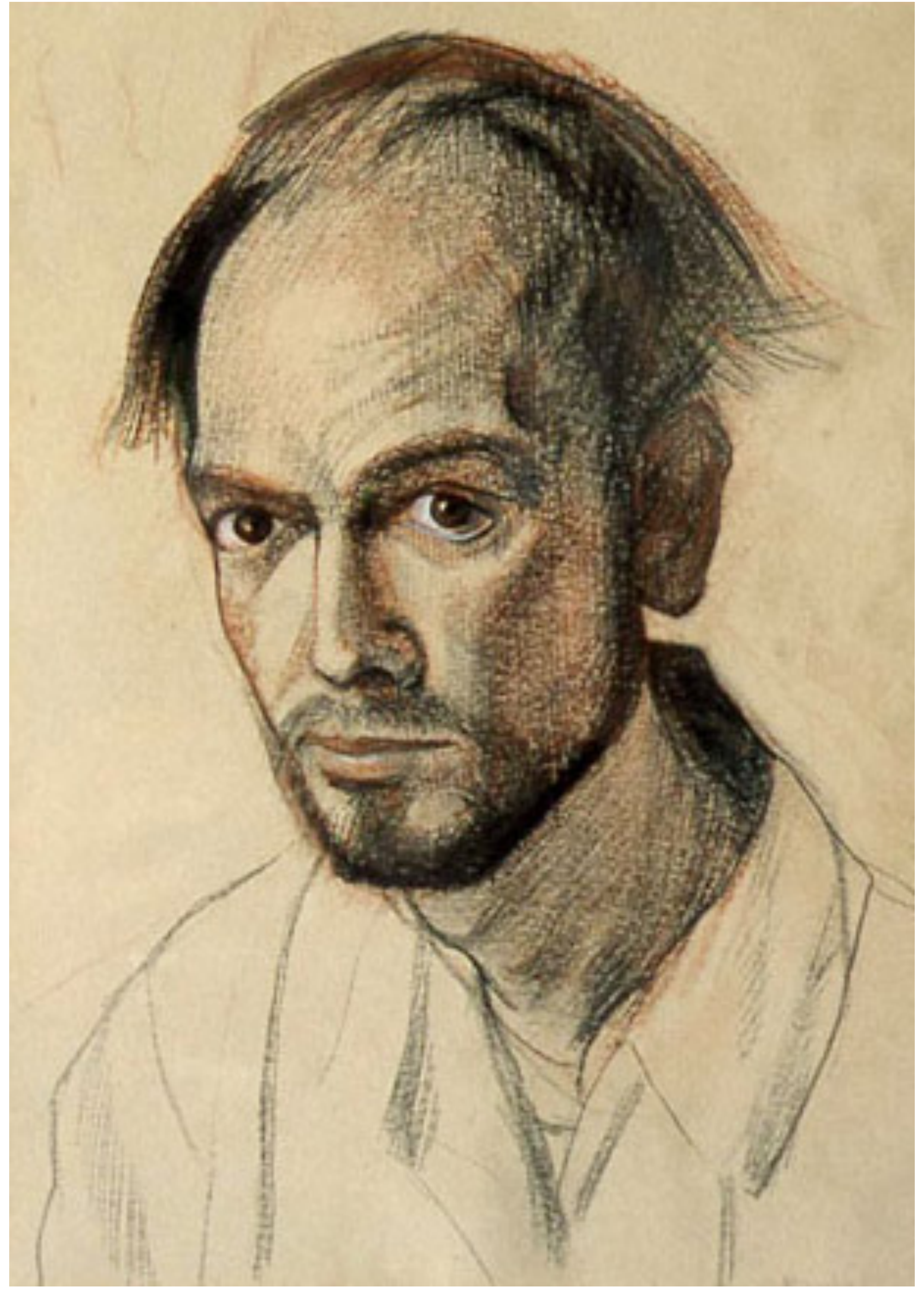
tau inclusions

william
utermohlen



’67

william utermohlen



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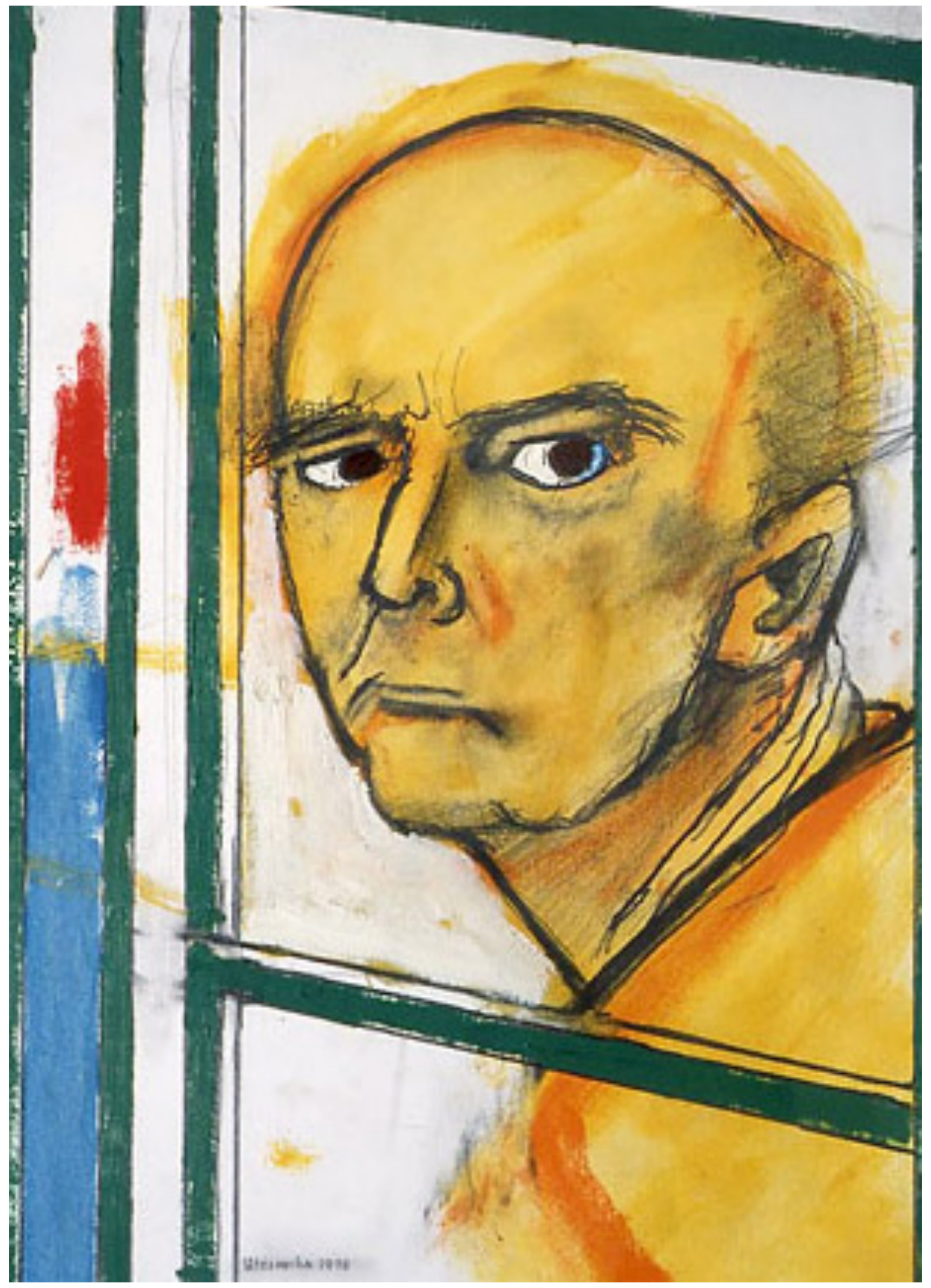

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william utermohlen

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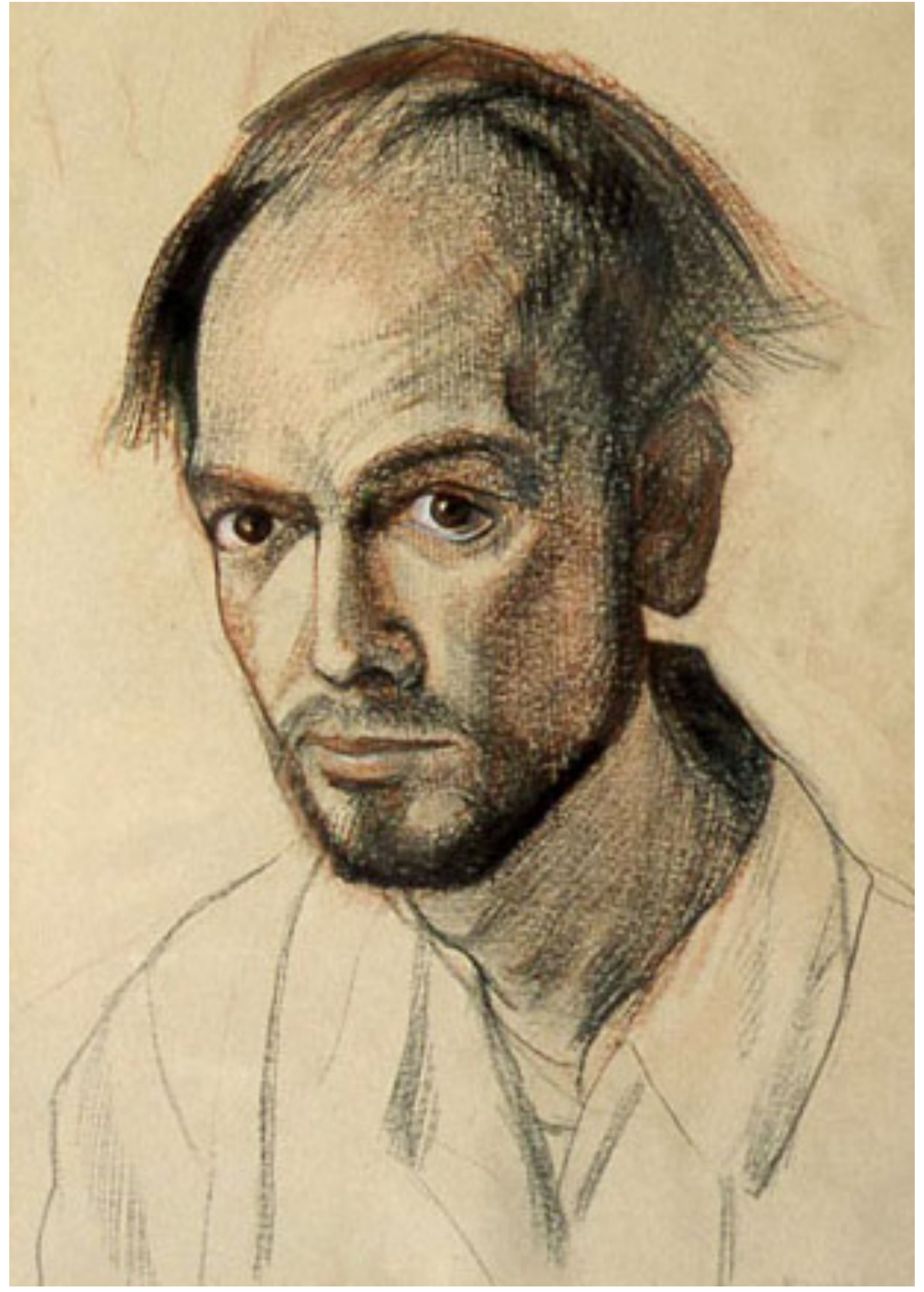

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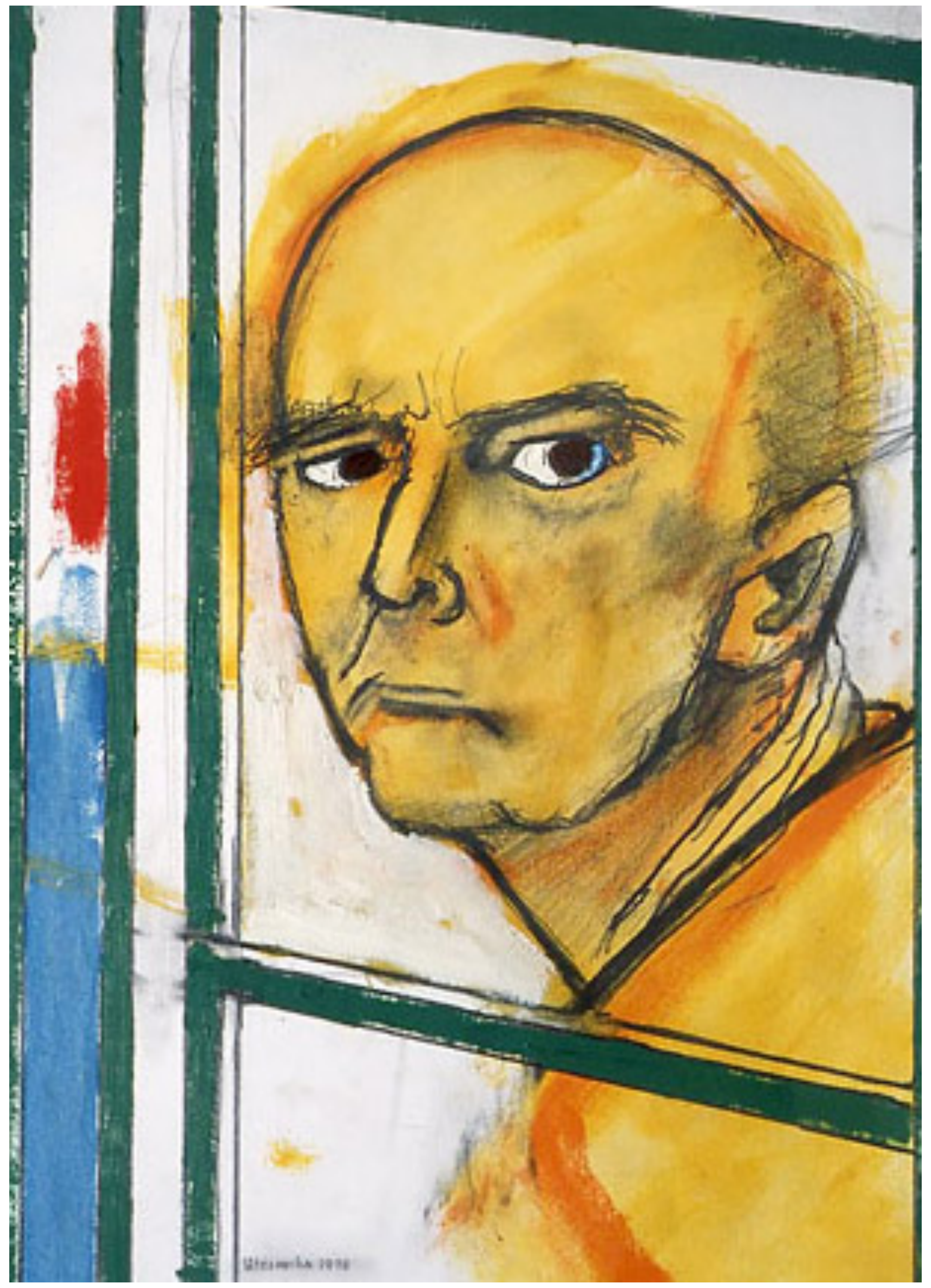

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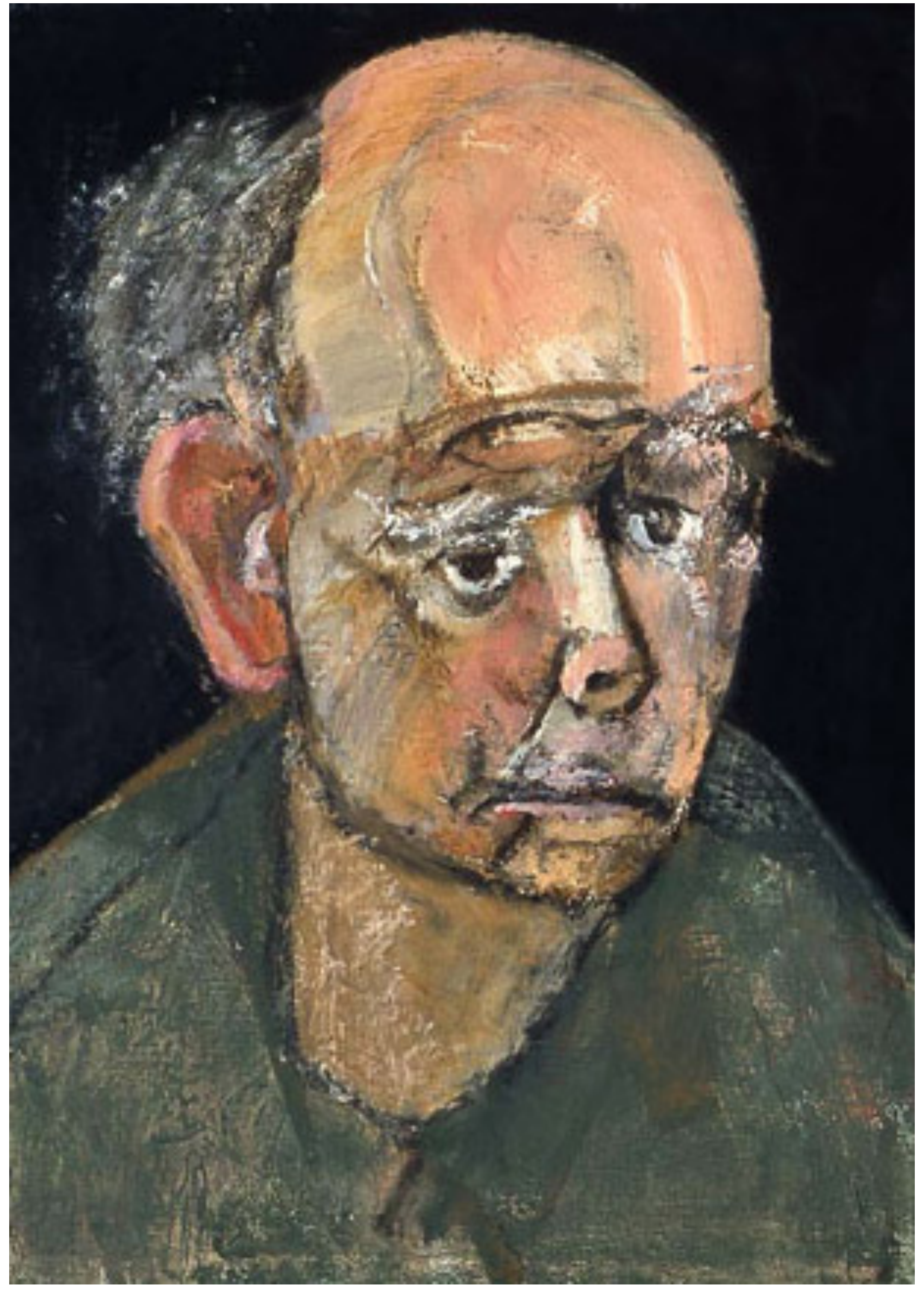
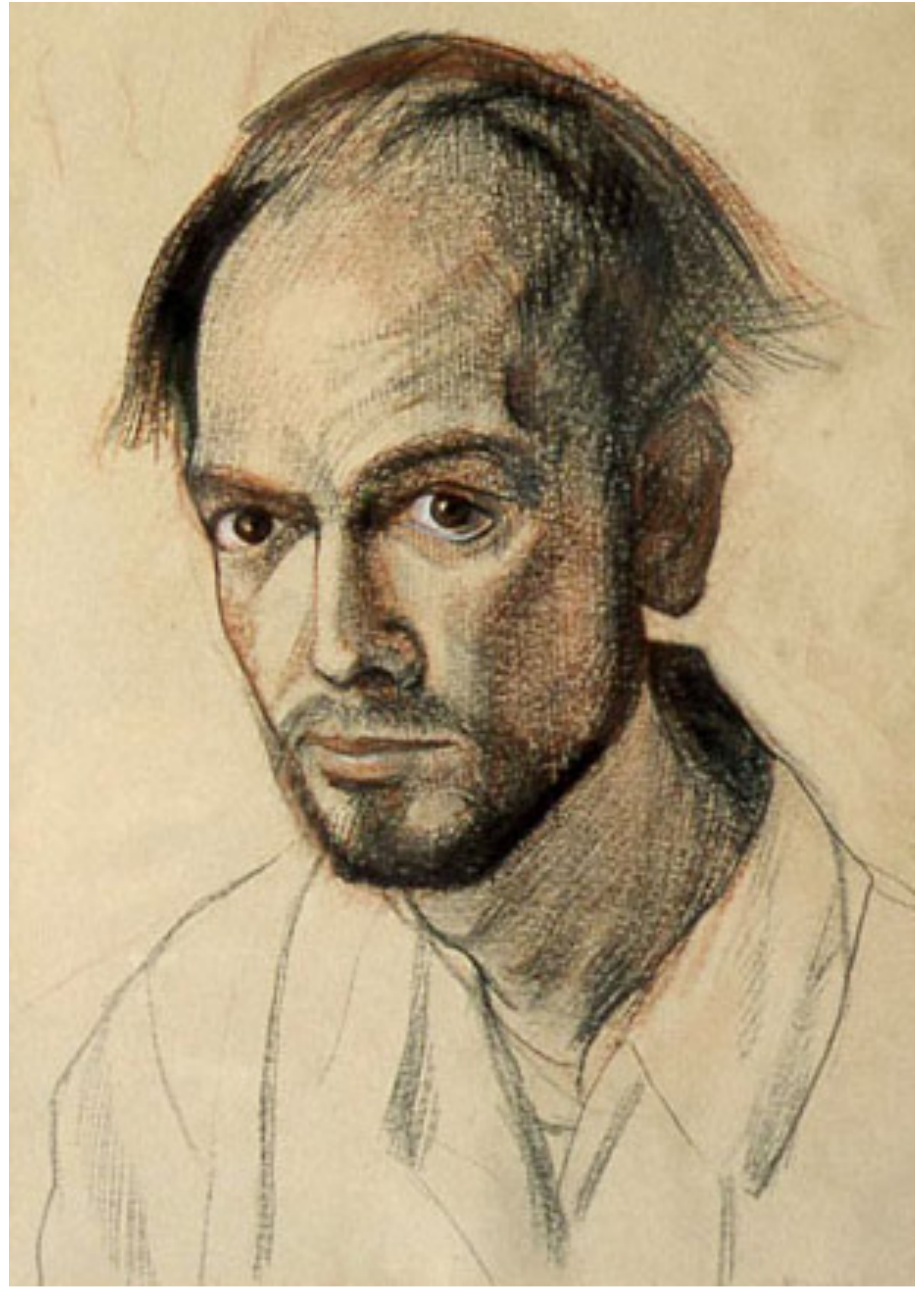


william utermohlen



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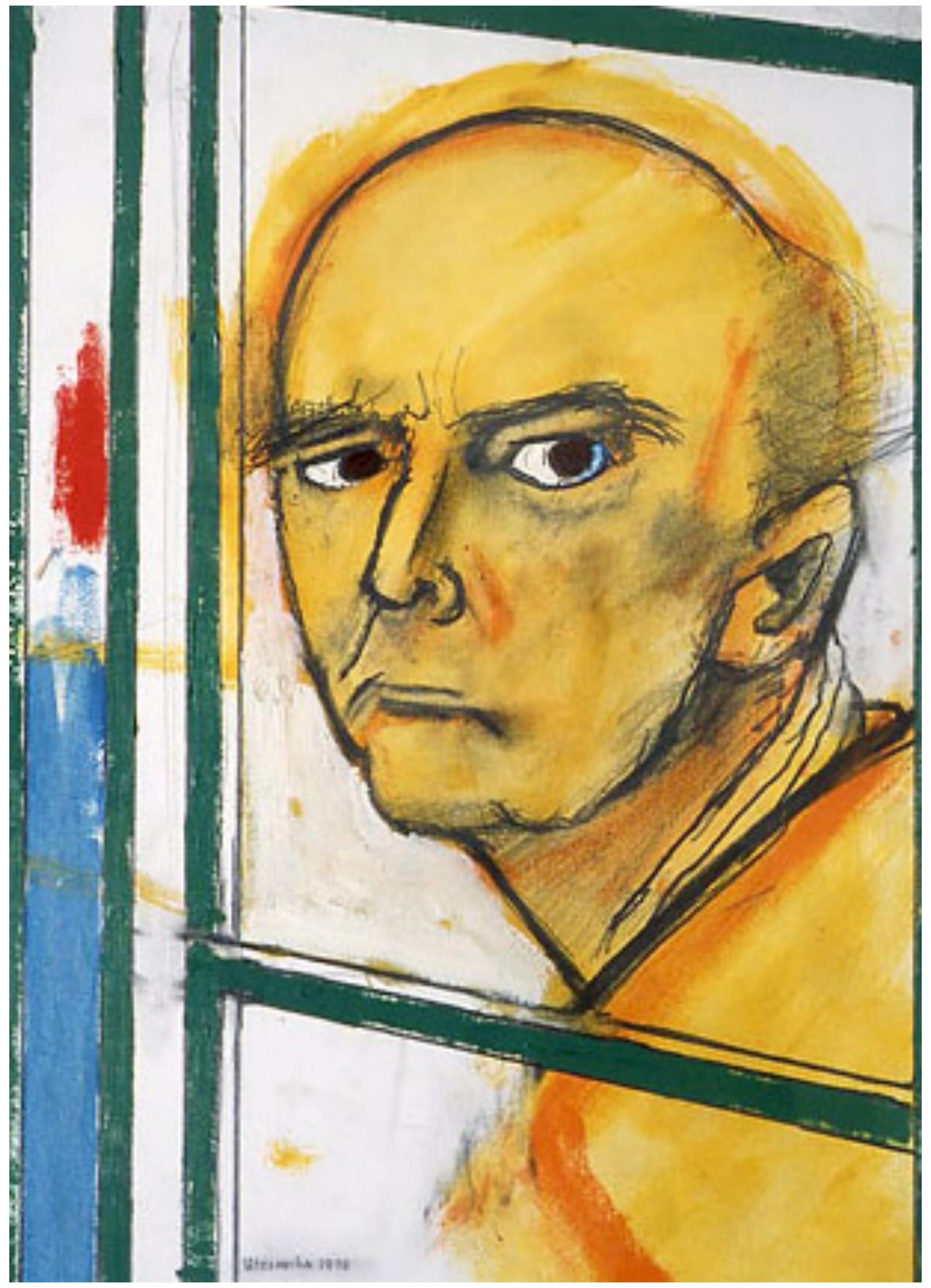

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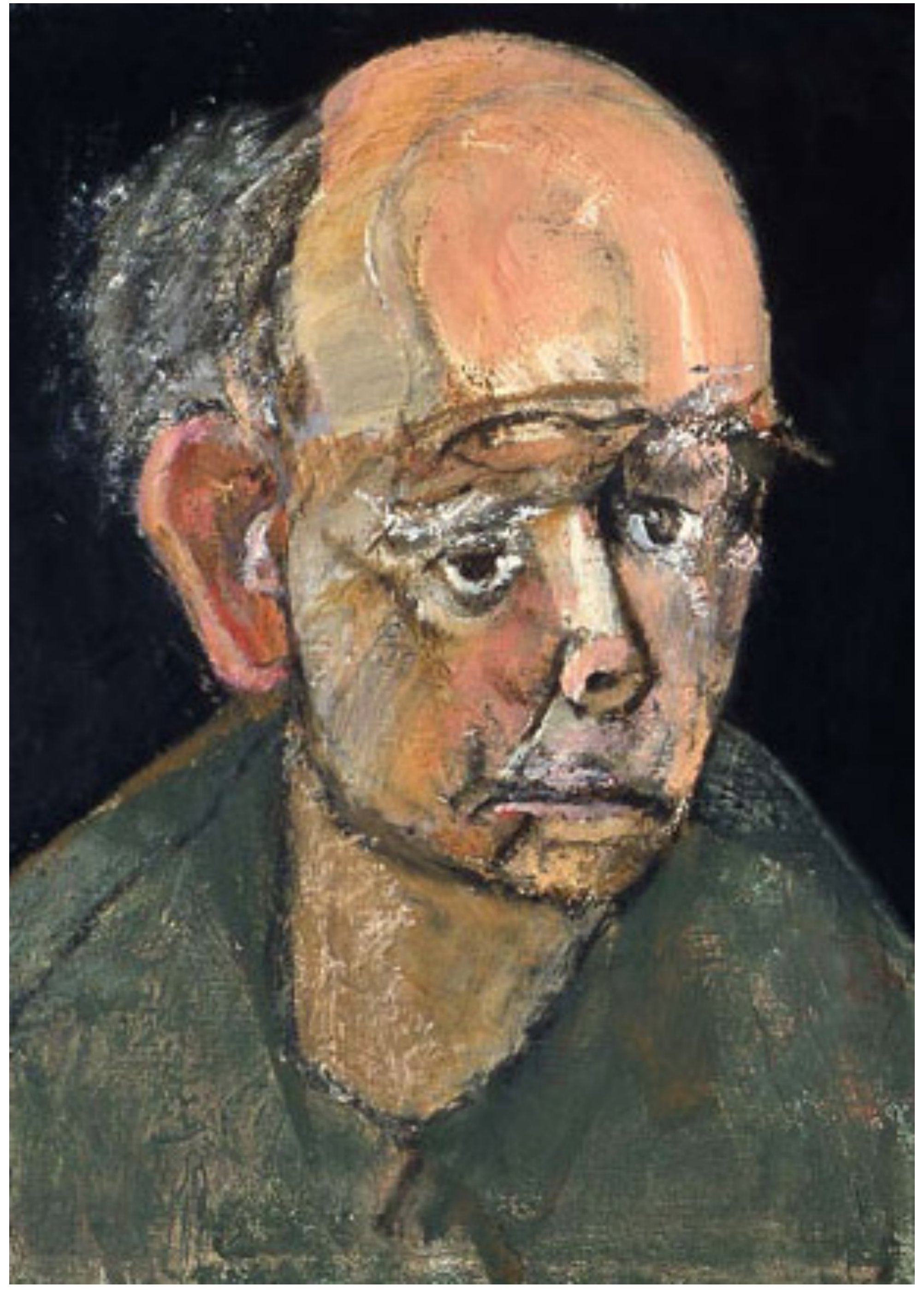

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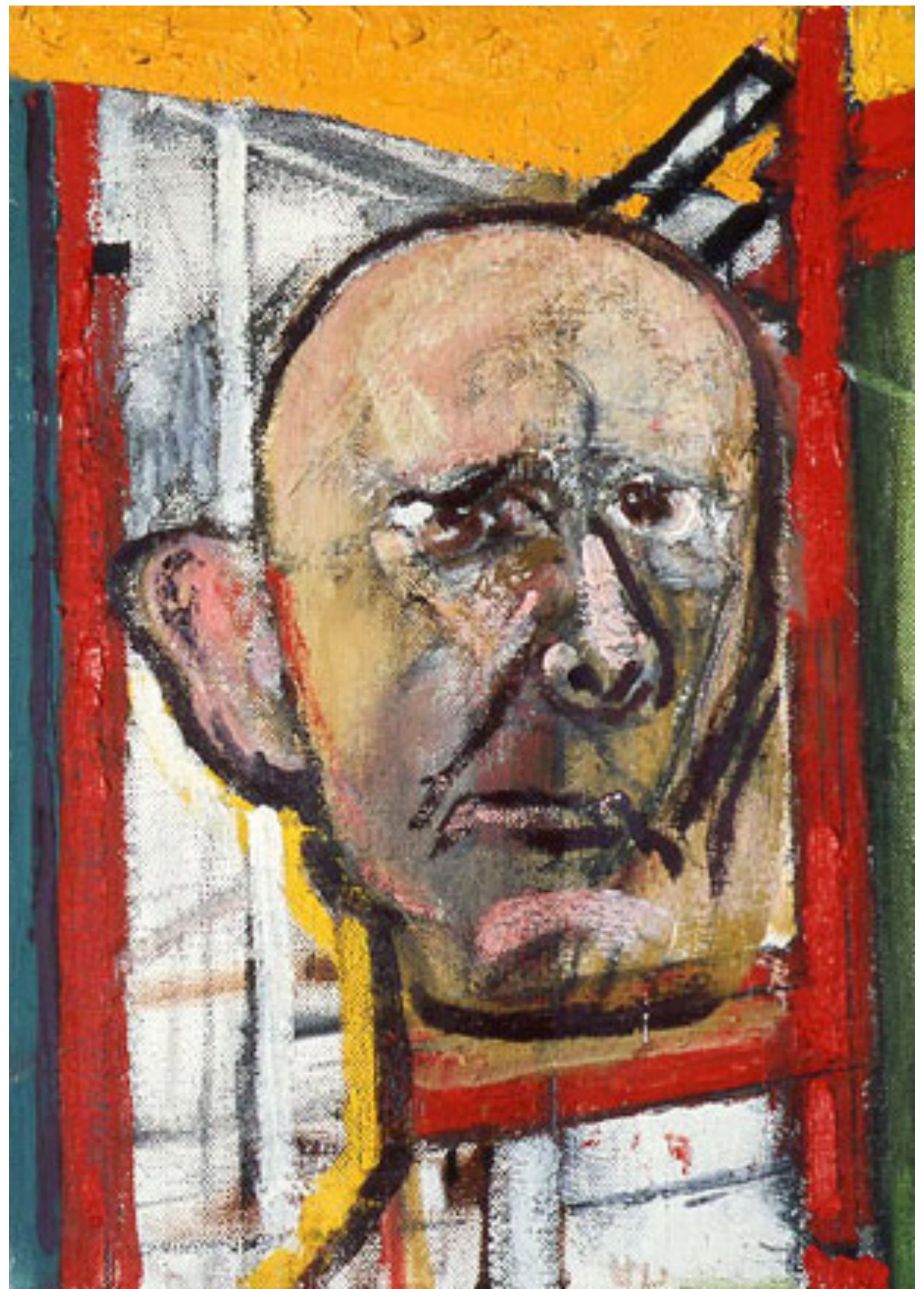

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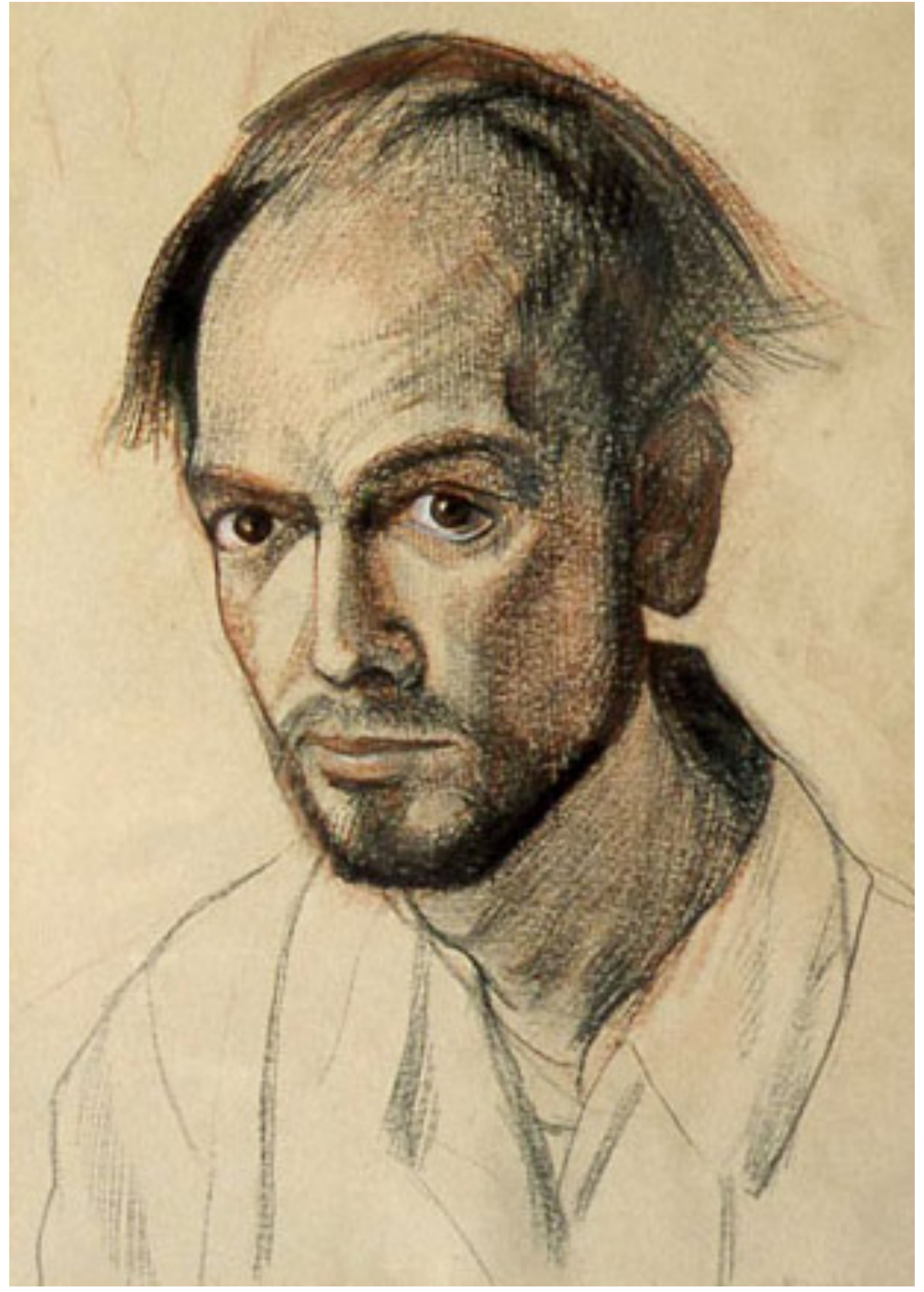
william utermohlen



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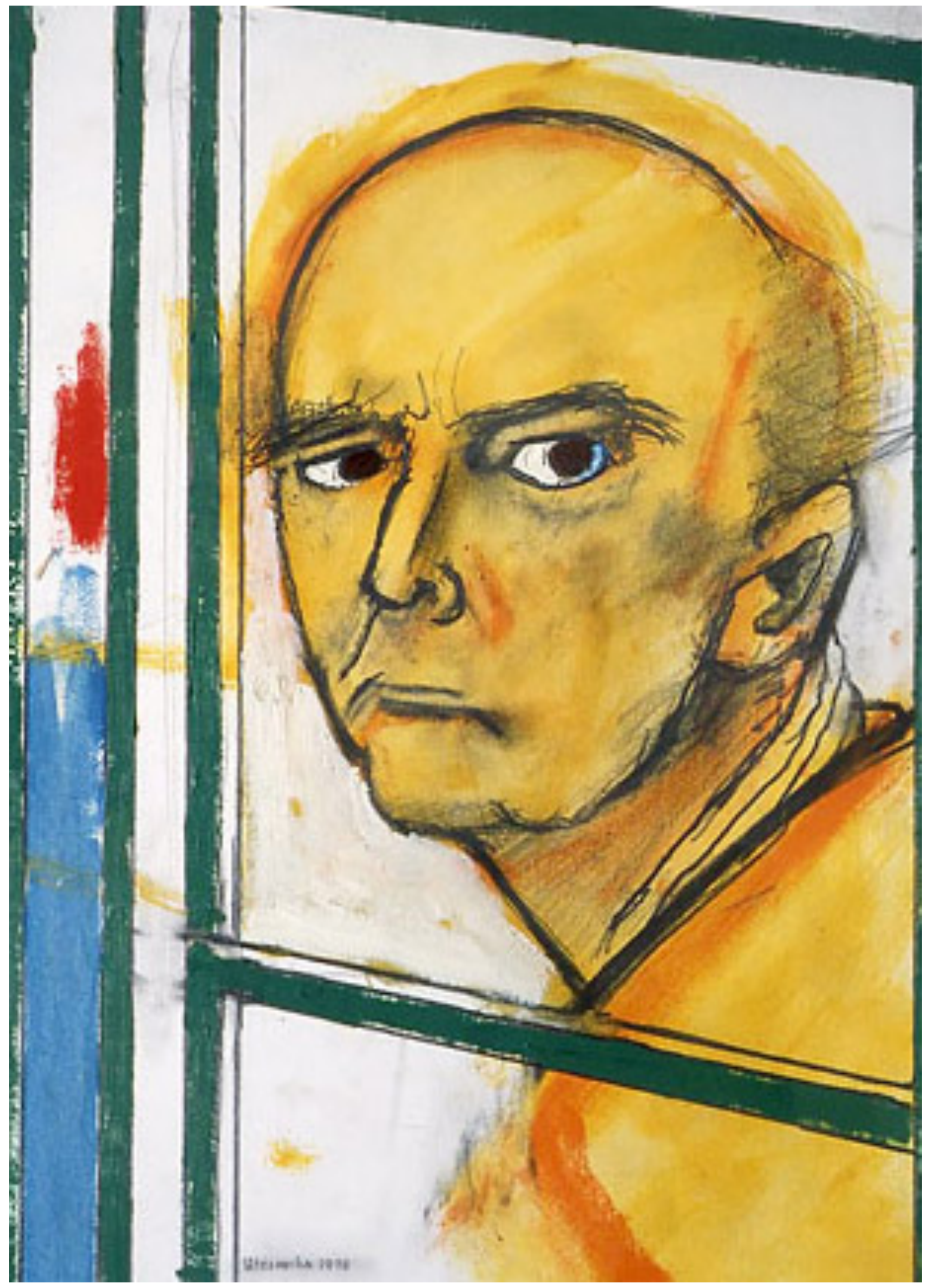

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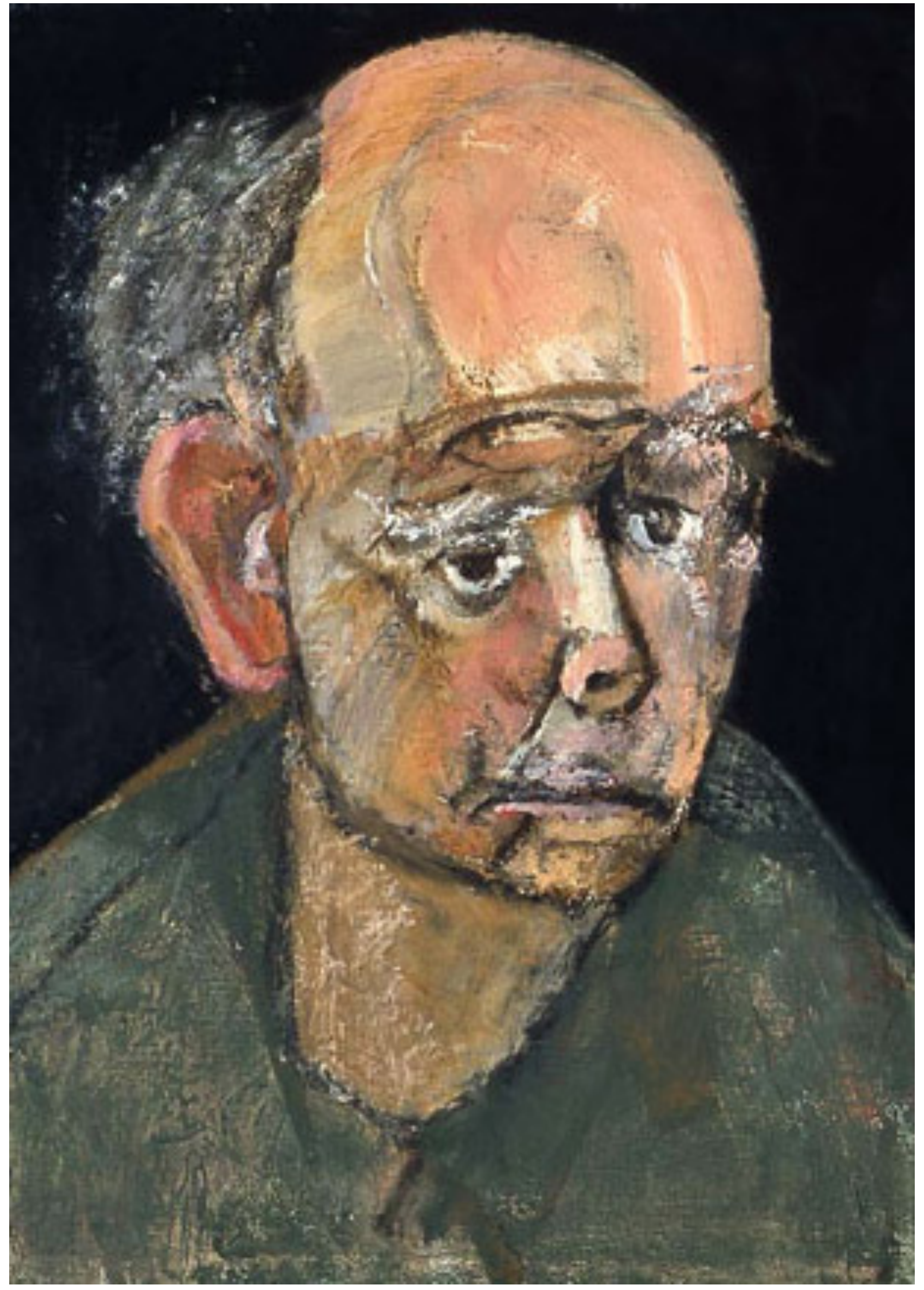

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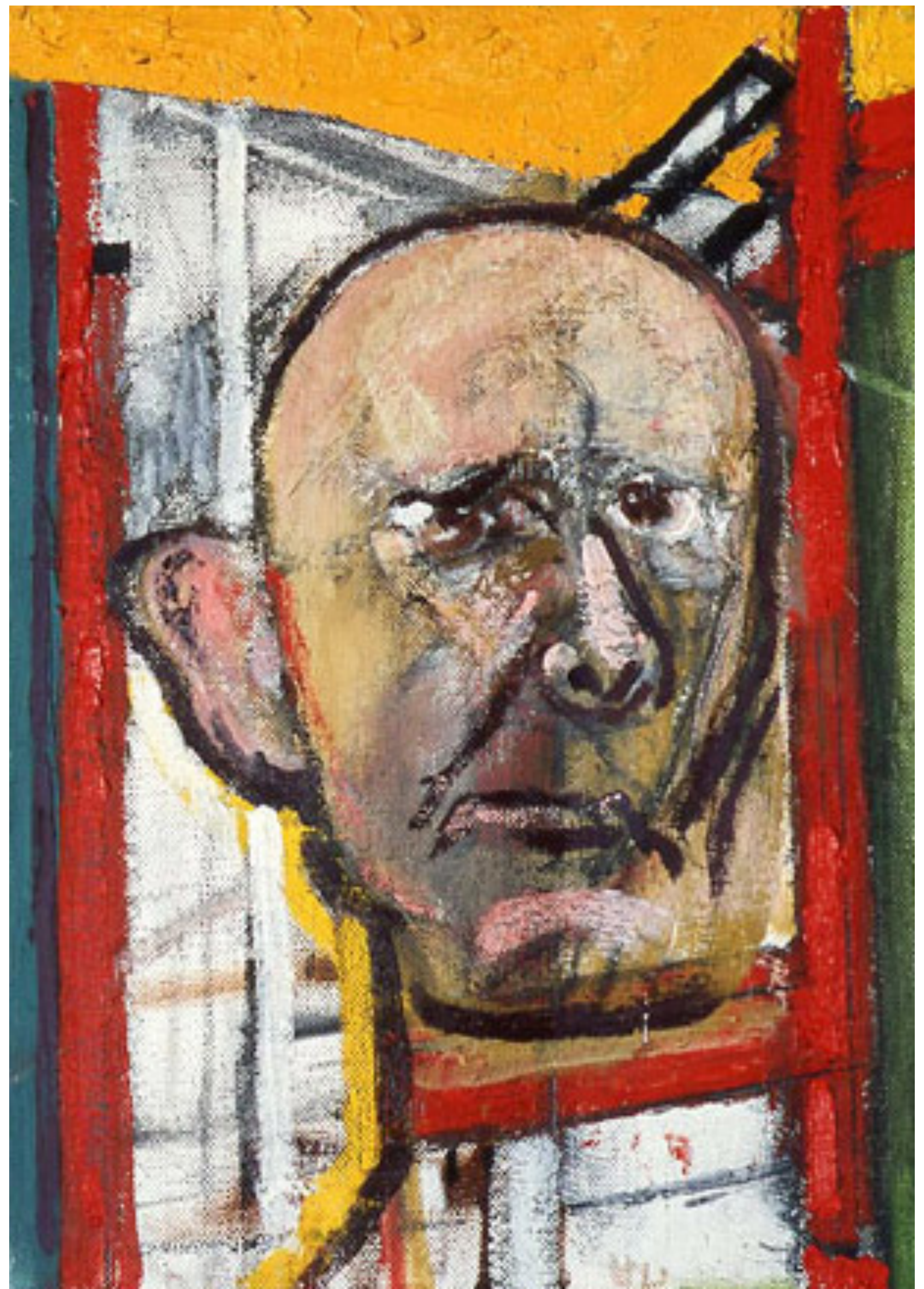

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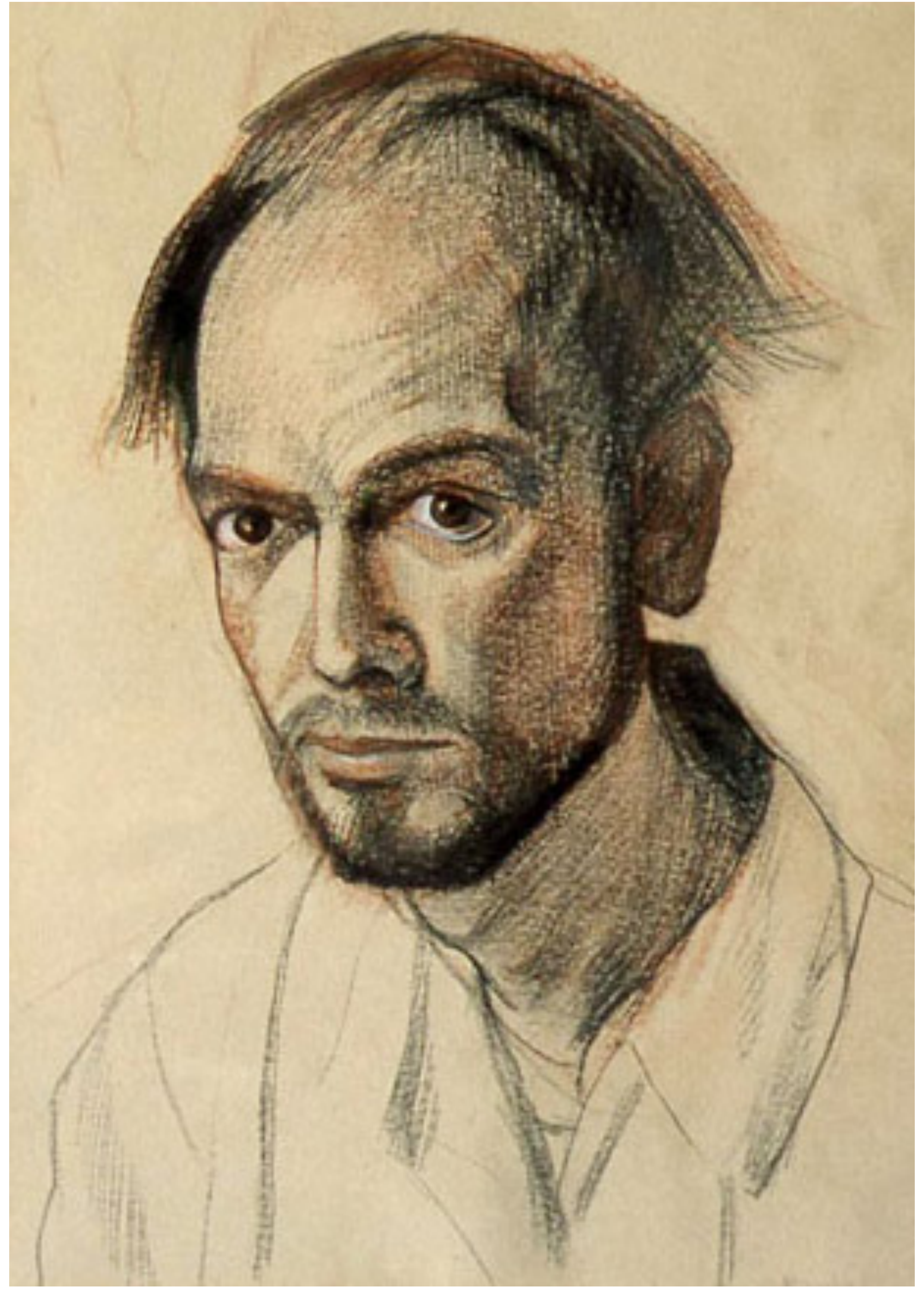
william utermohlen



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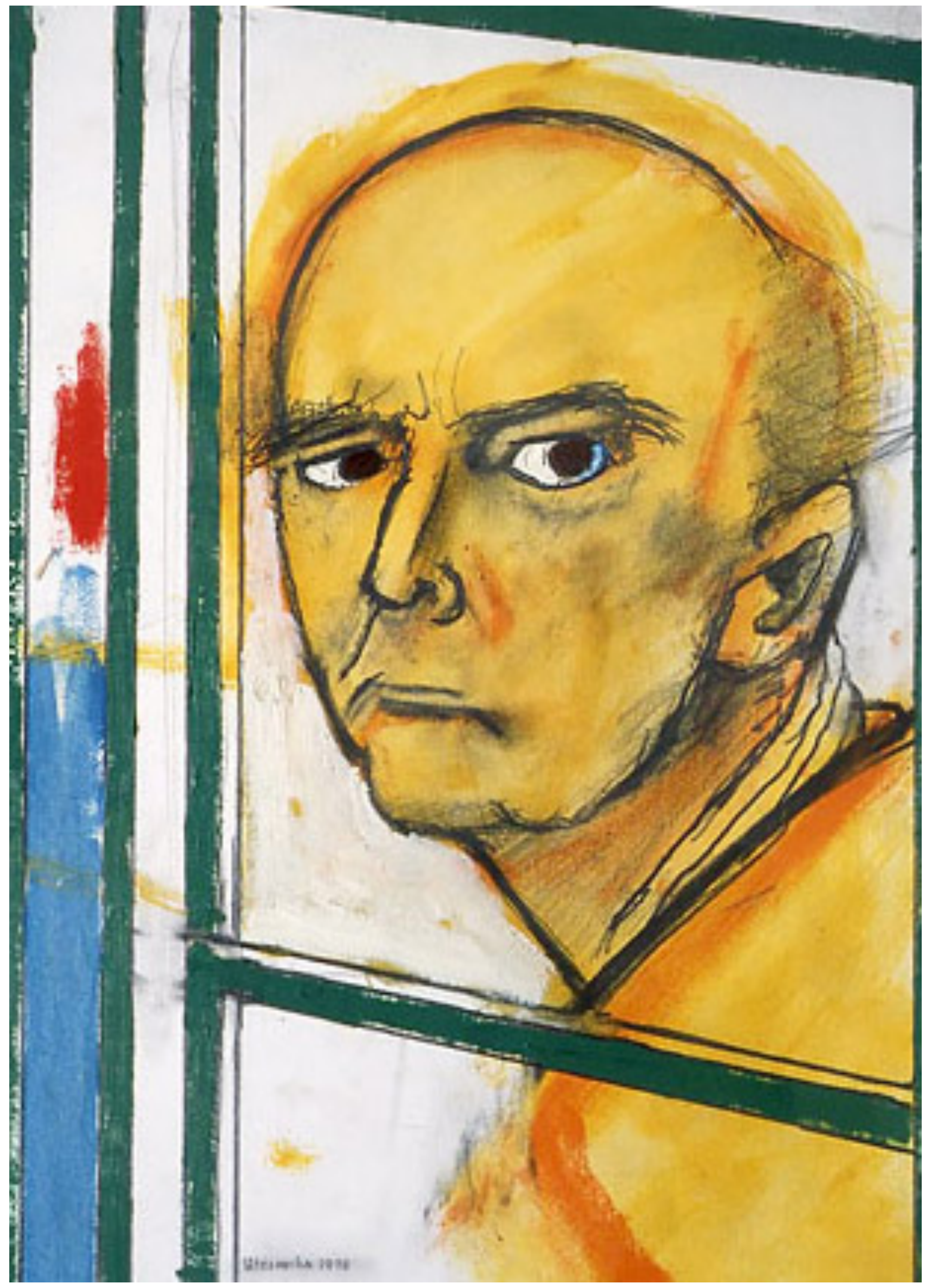

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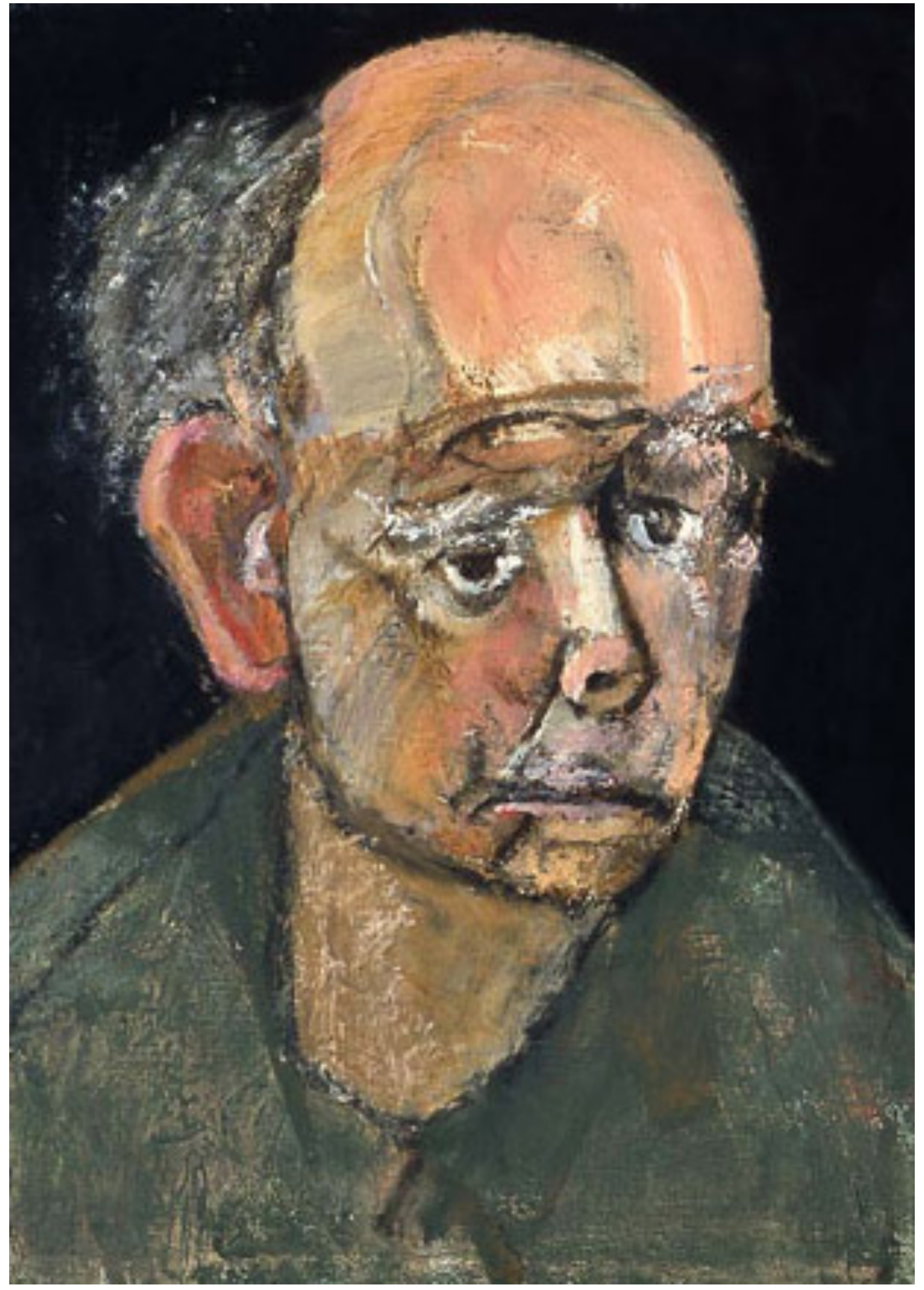

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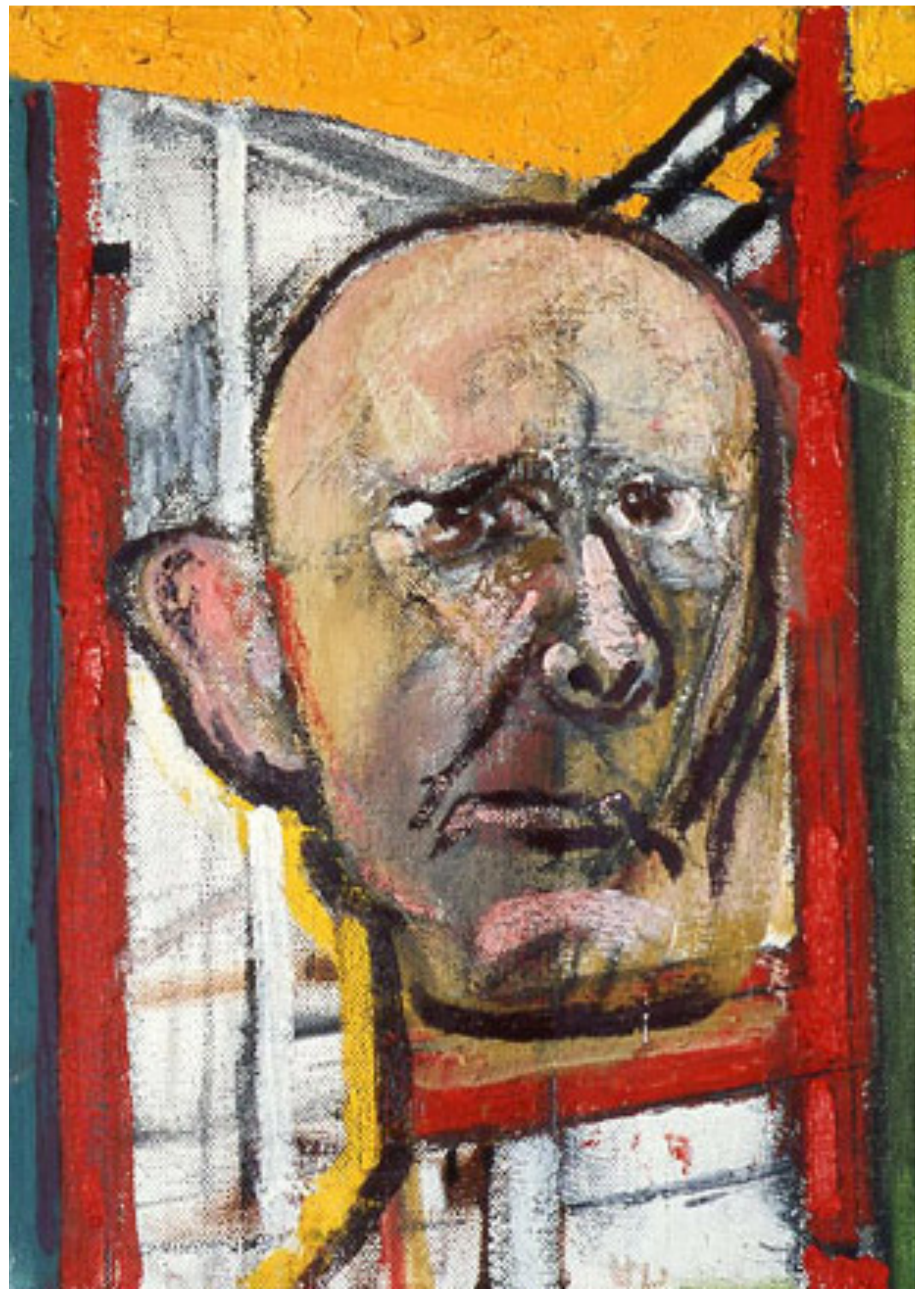

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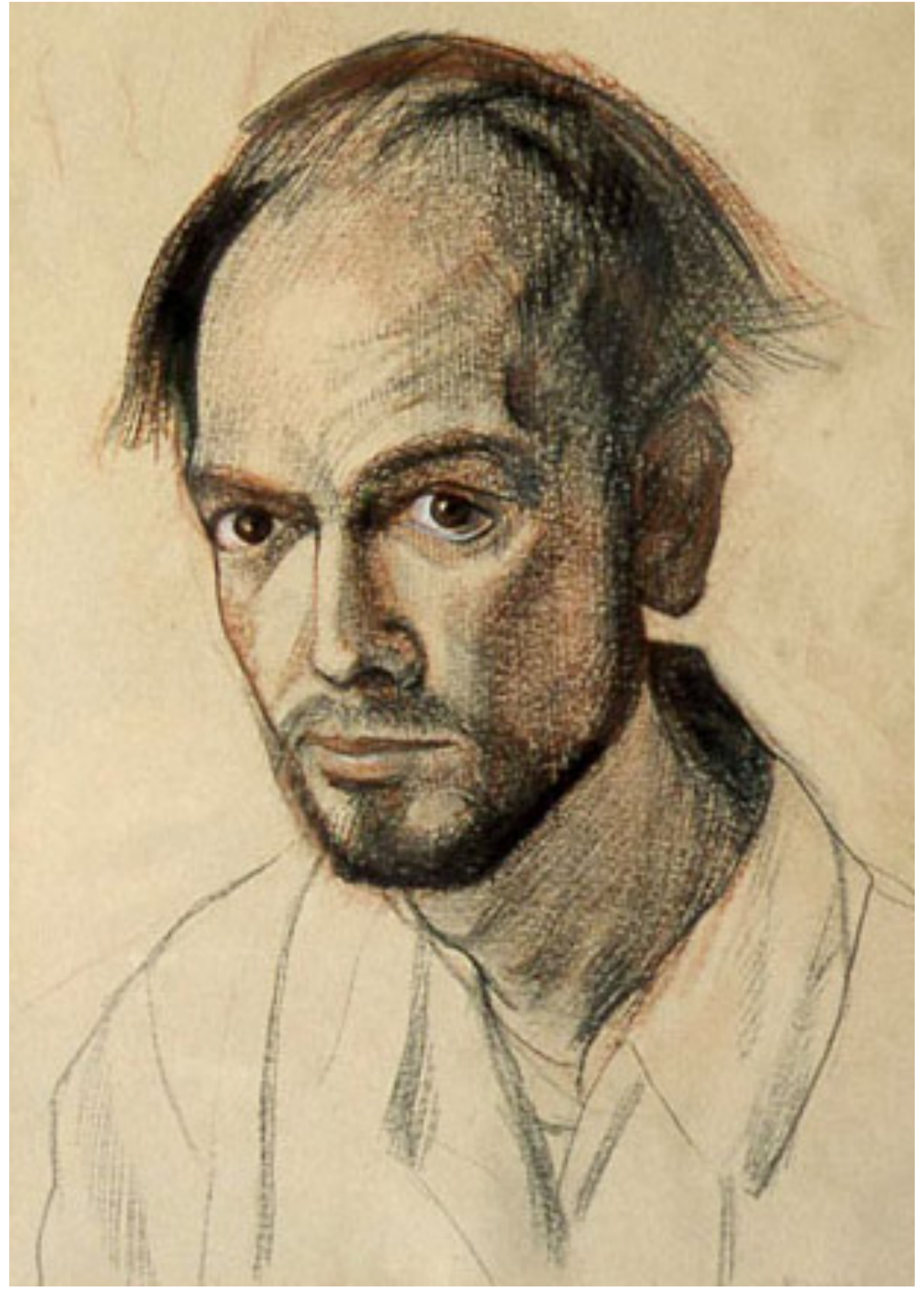
william utermohlen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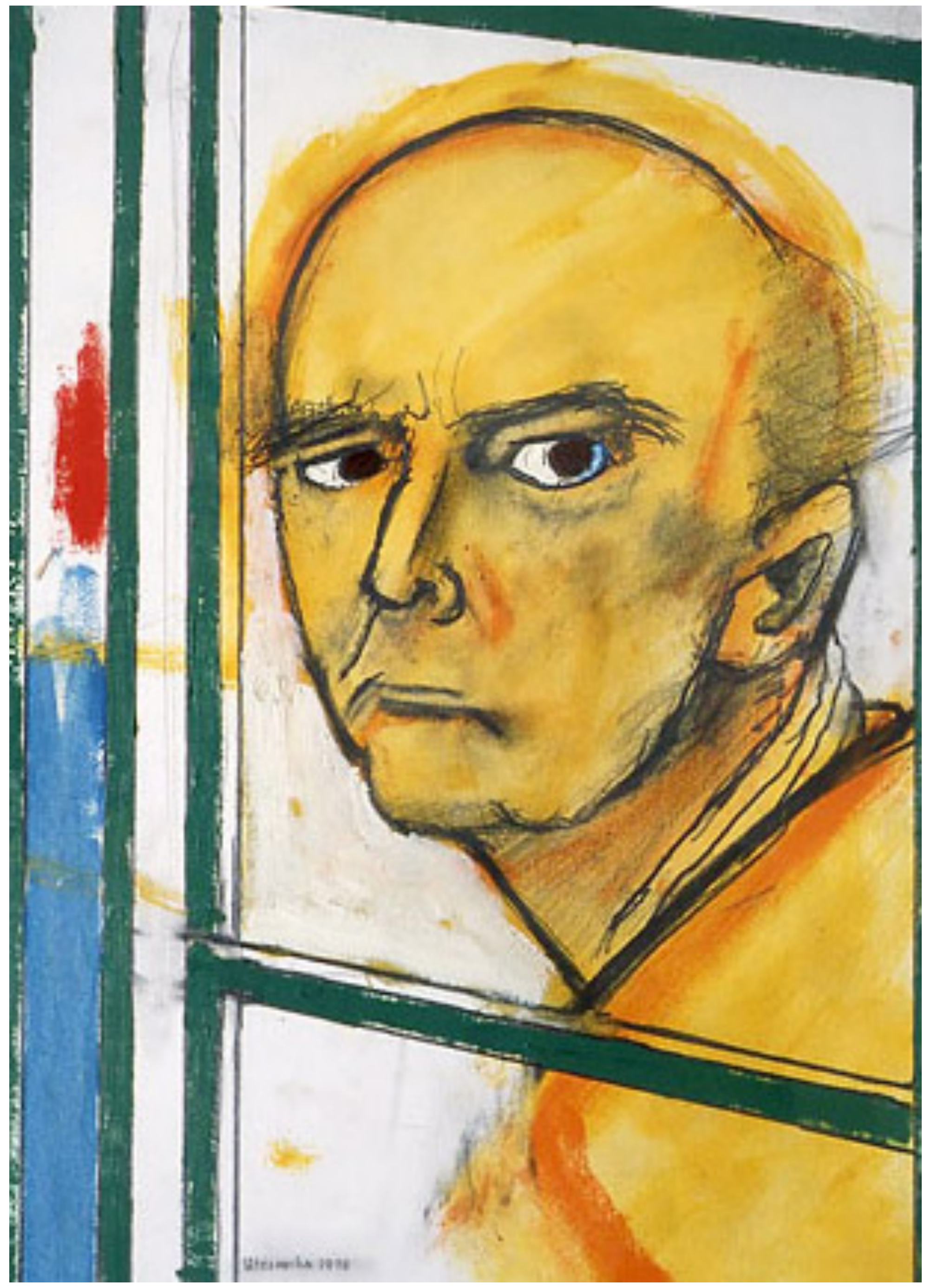
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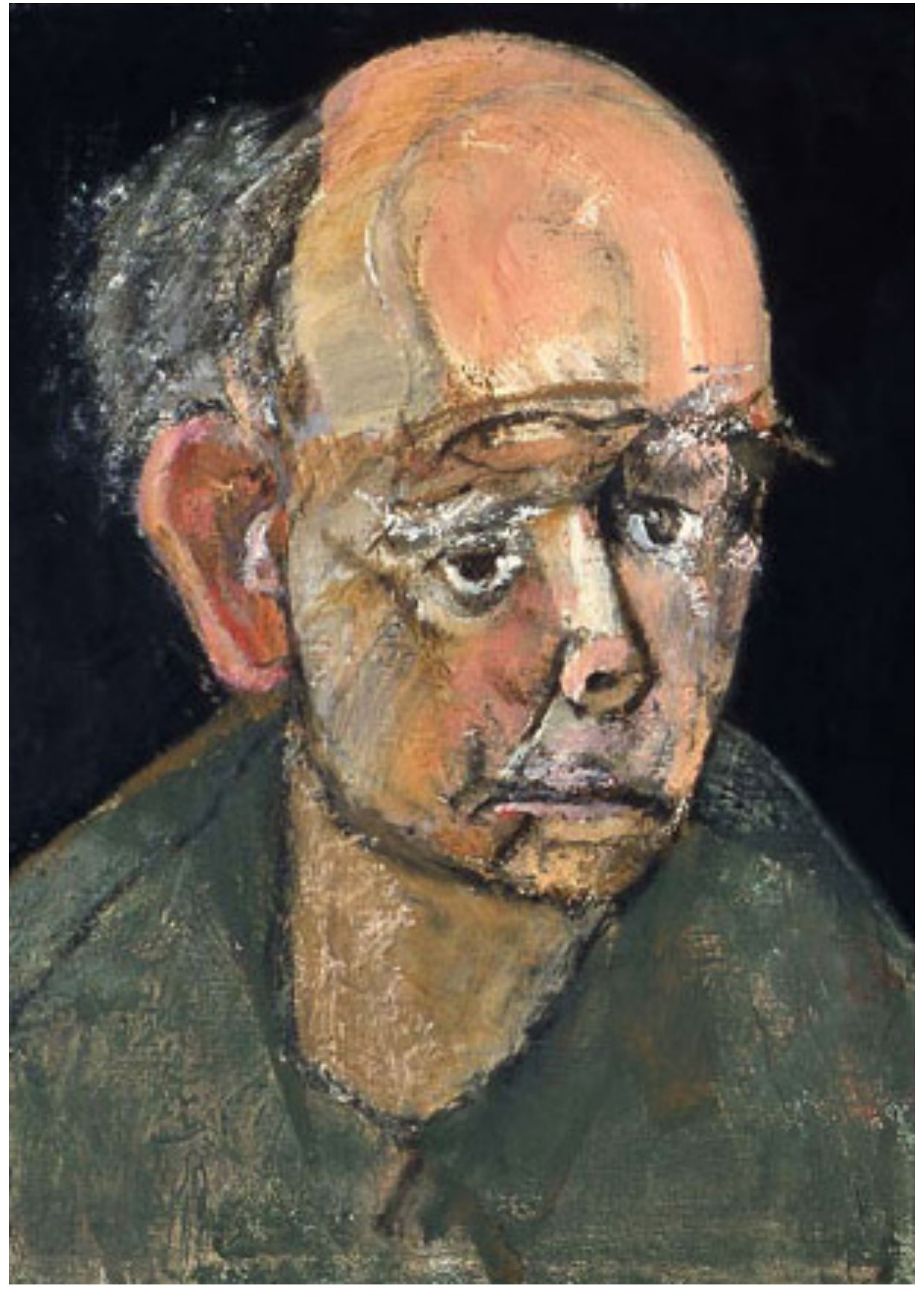
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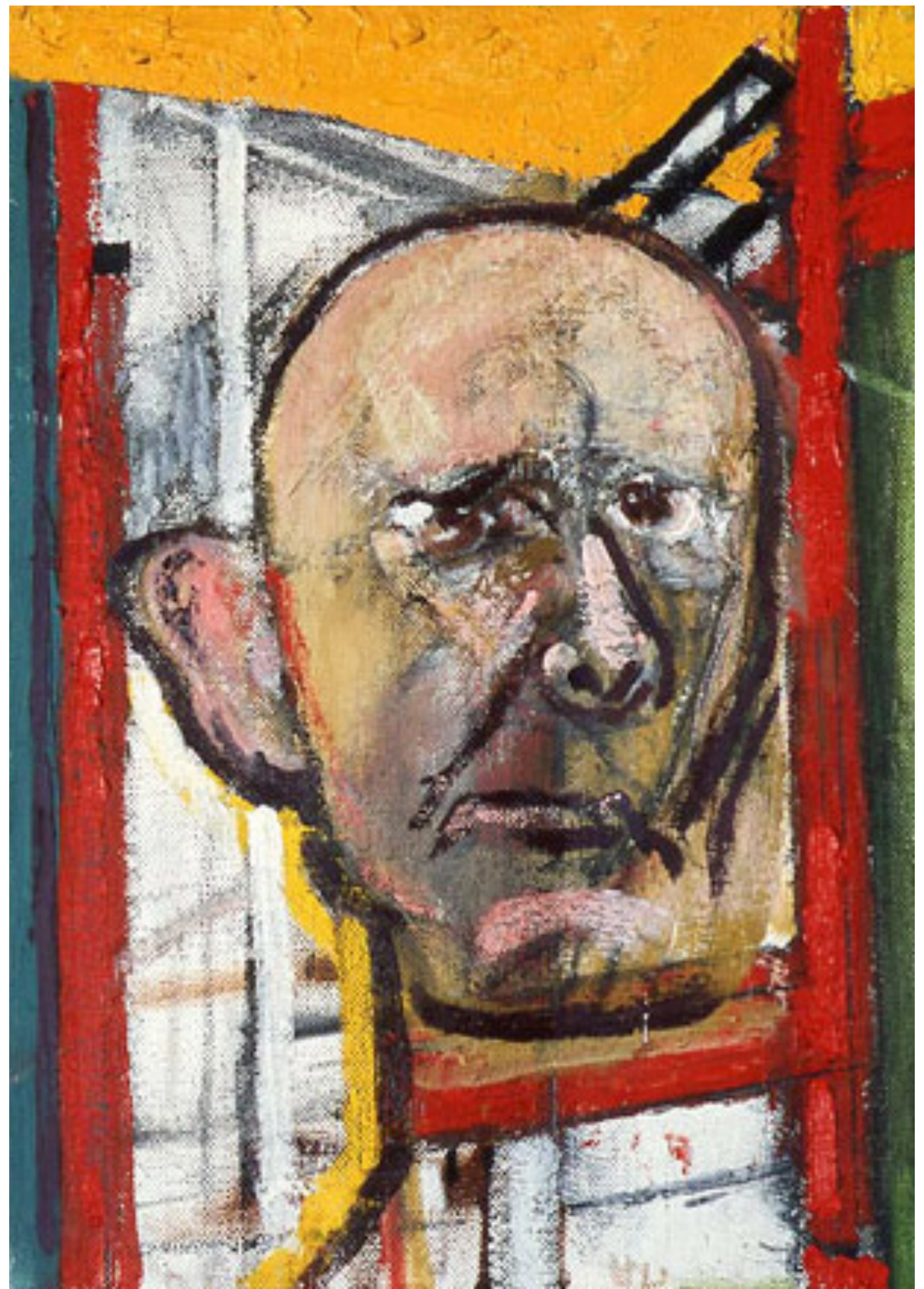
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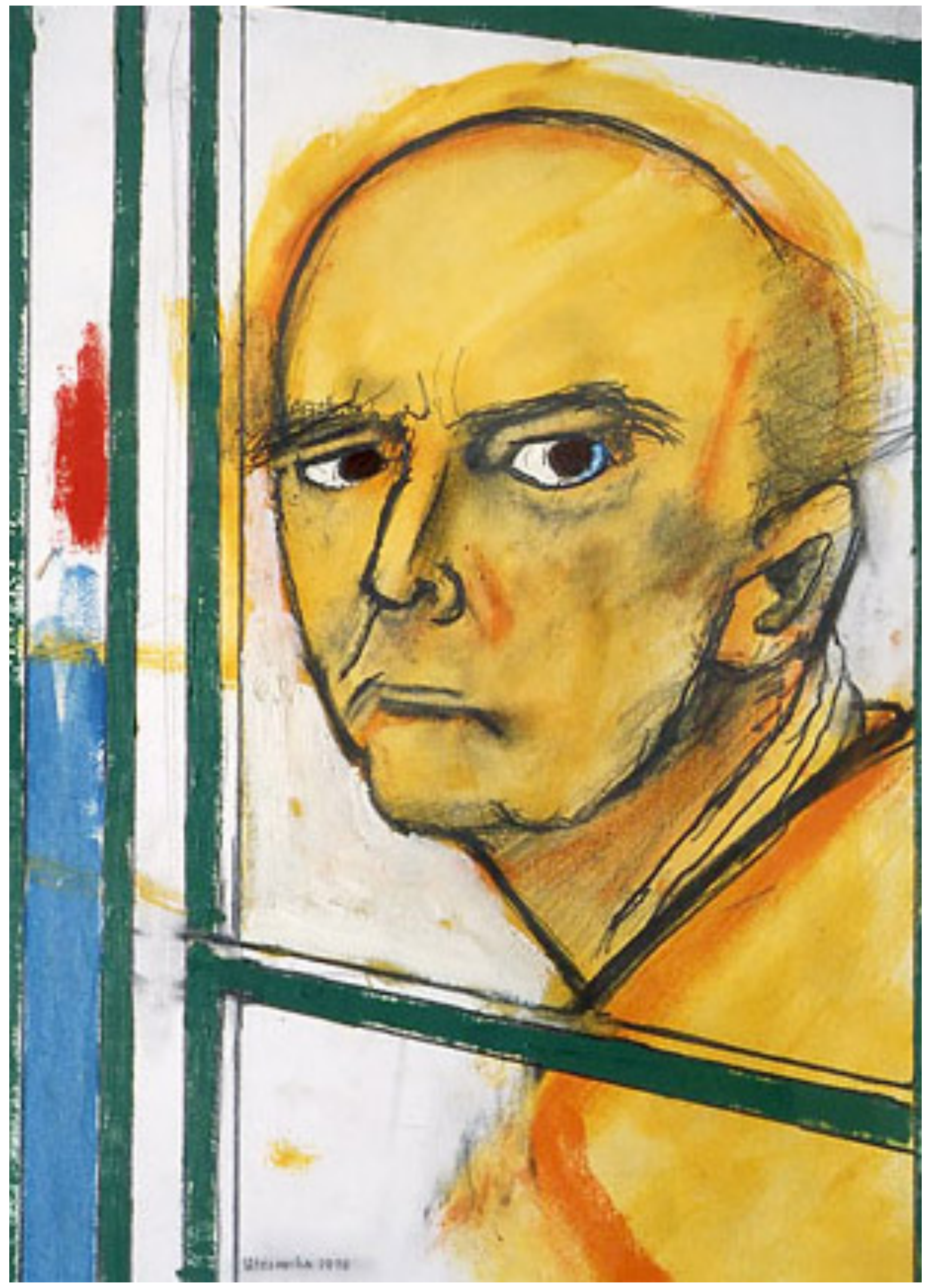
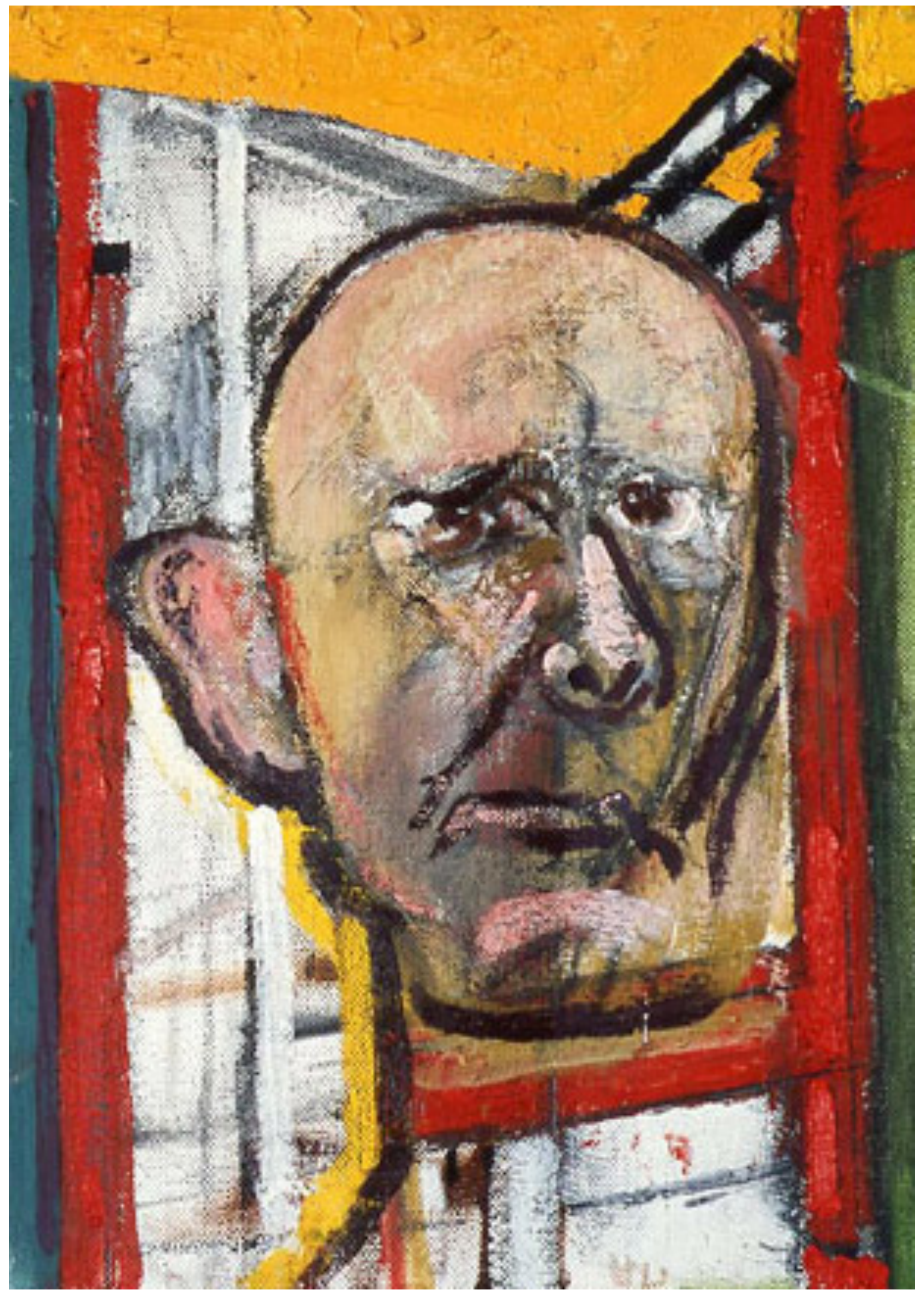
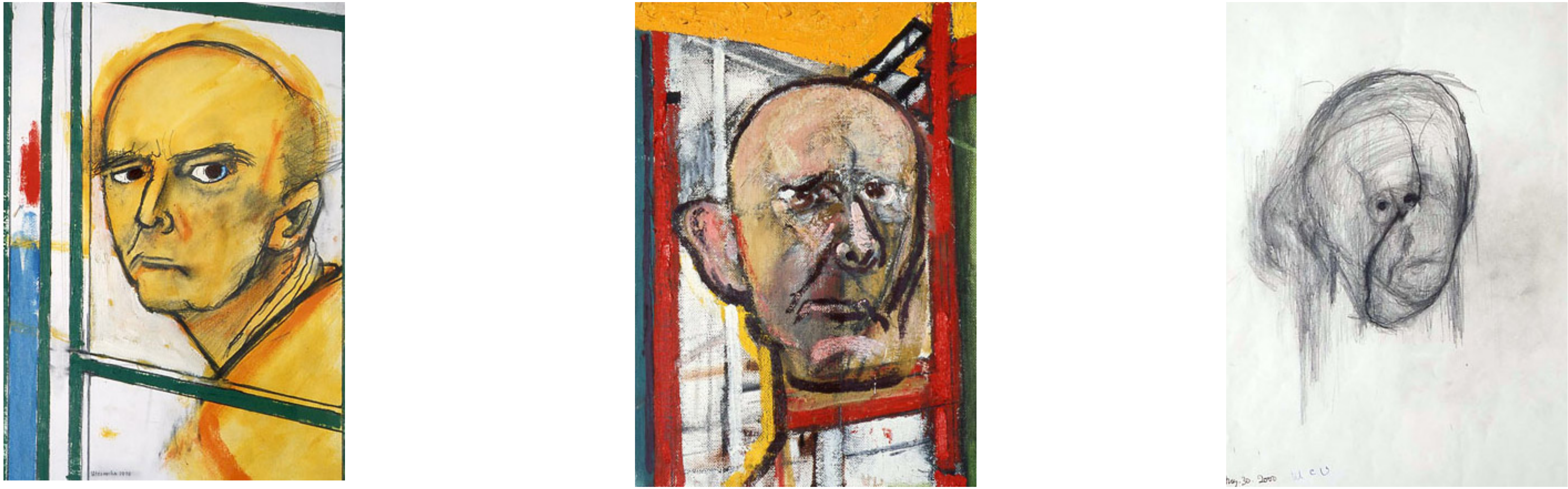


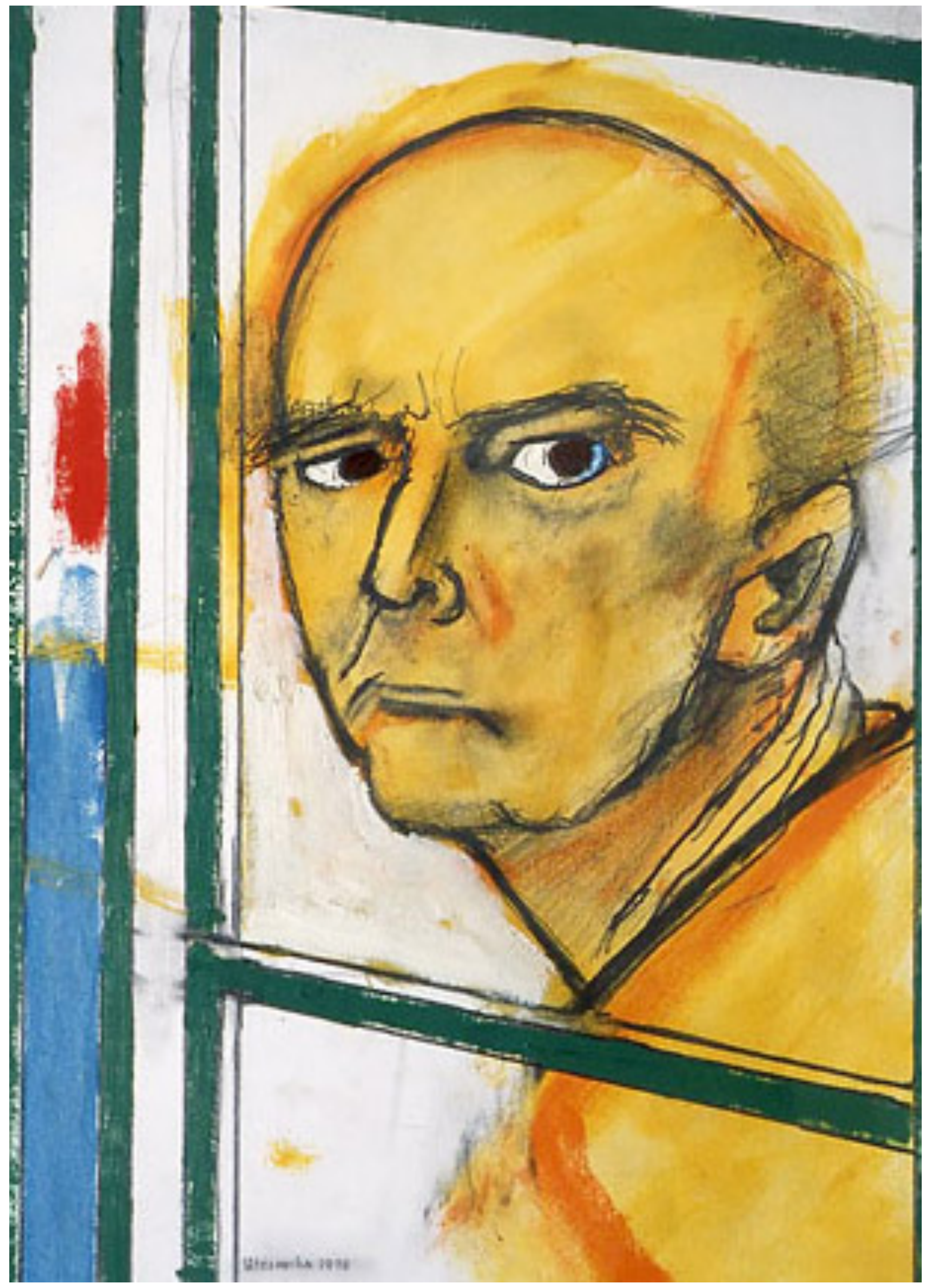


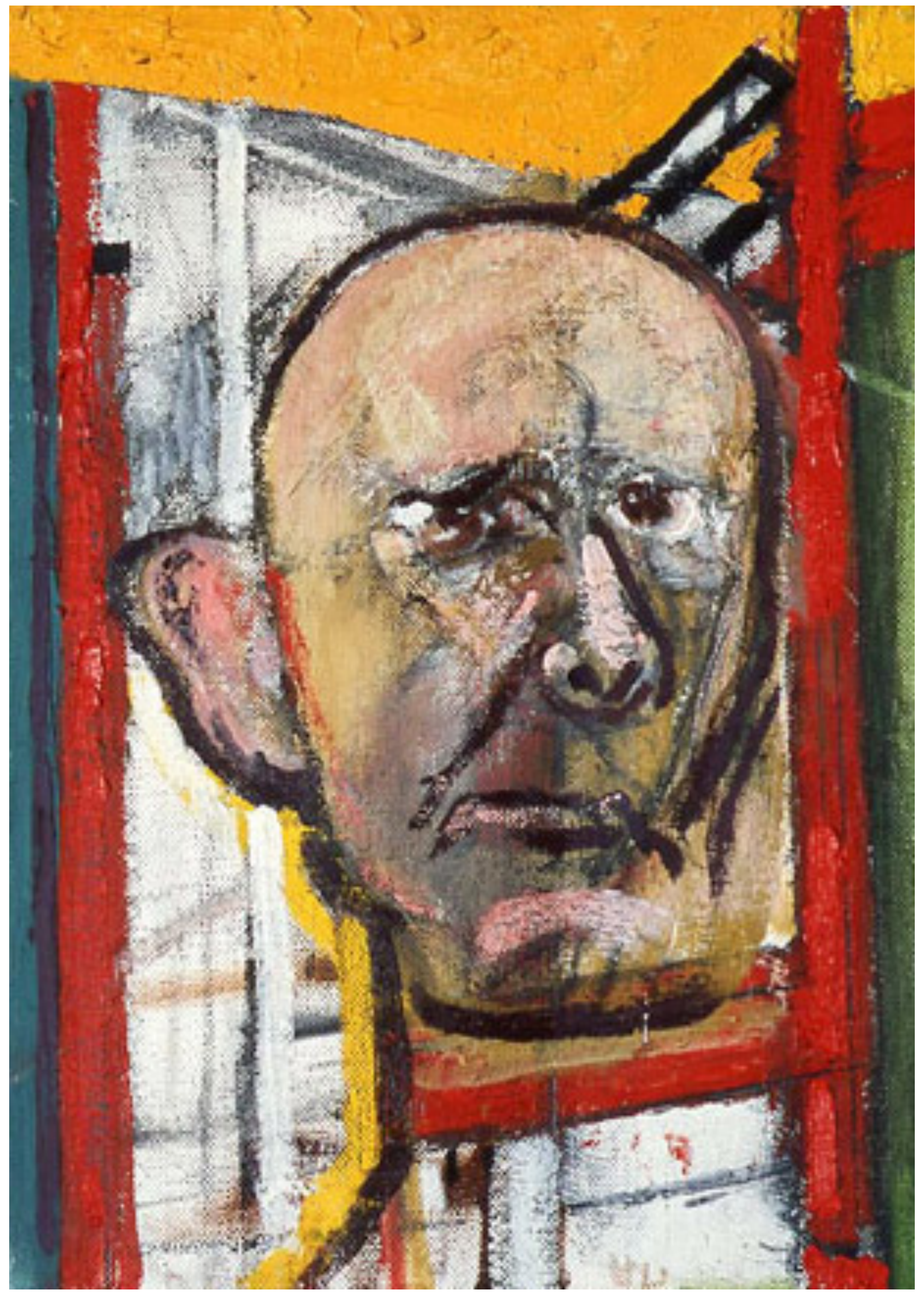
Stage I-II



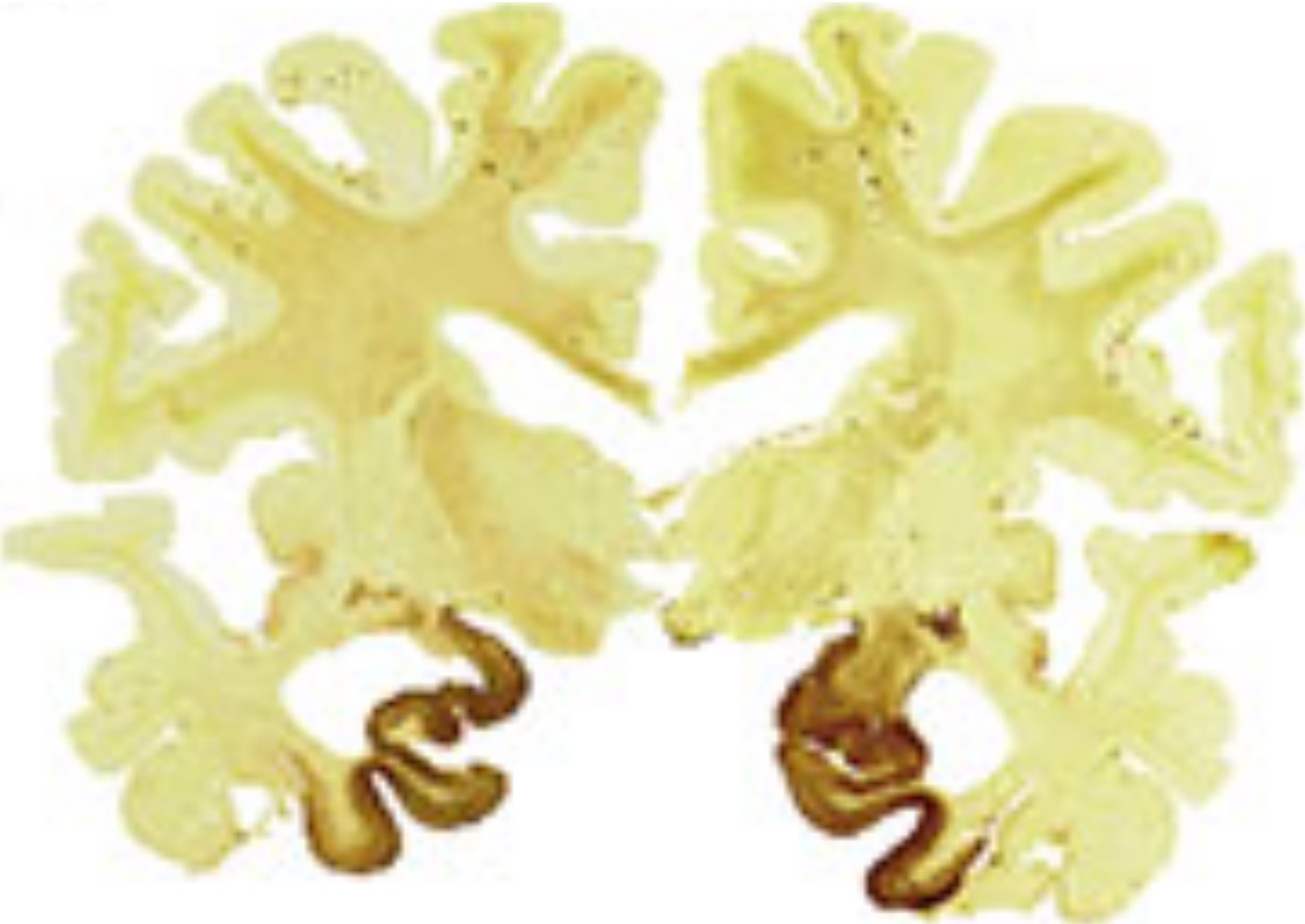
Stage I-II

Stage III-IV



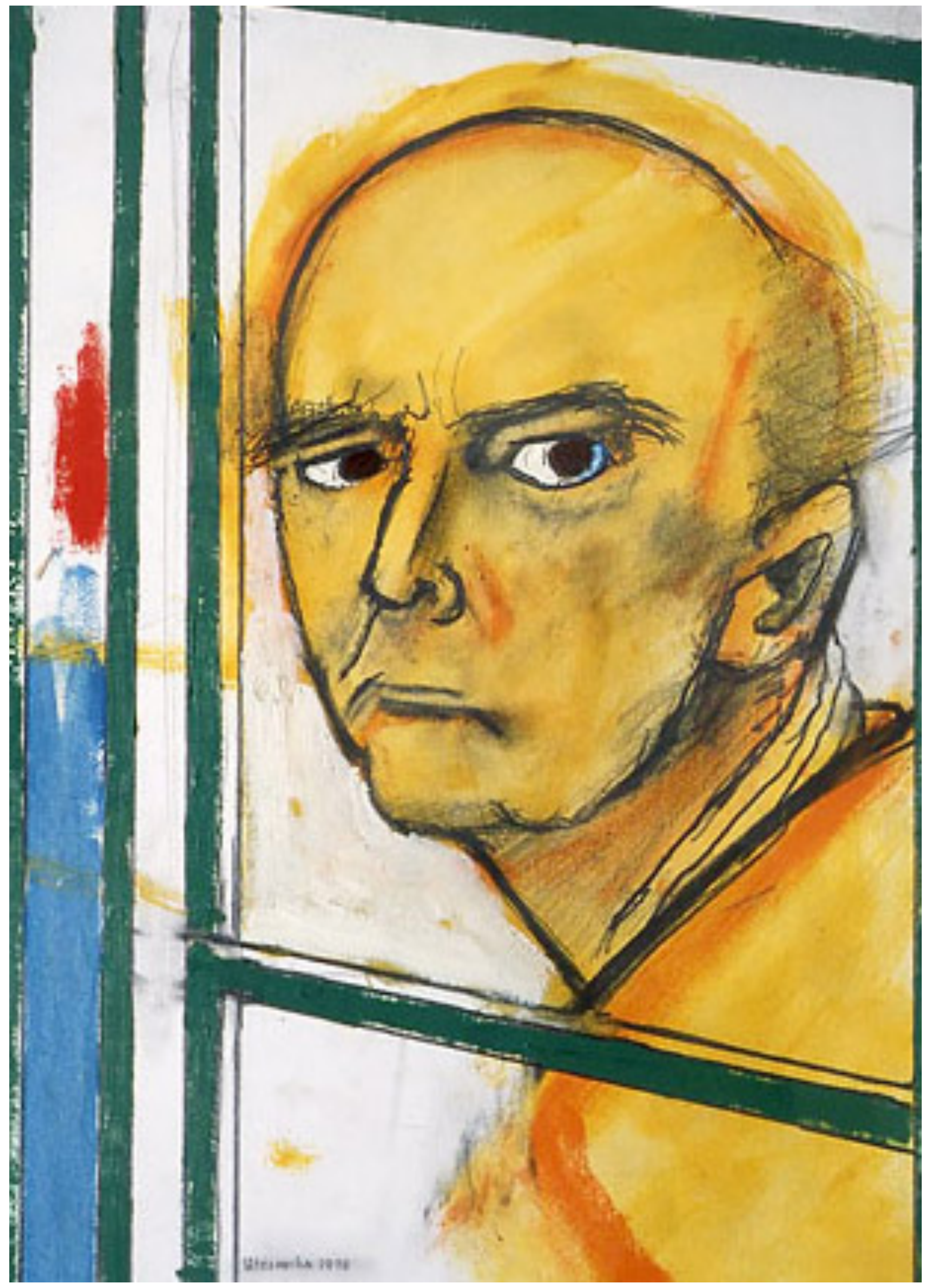


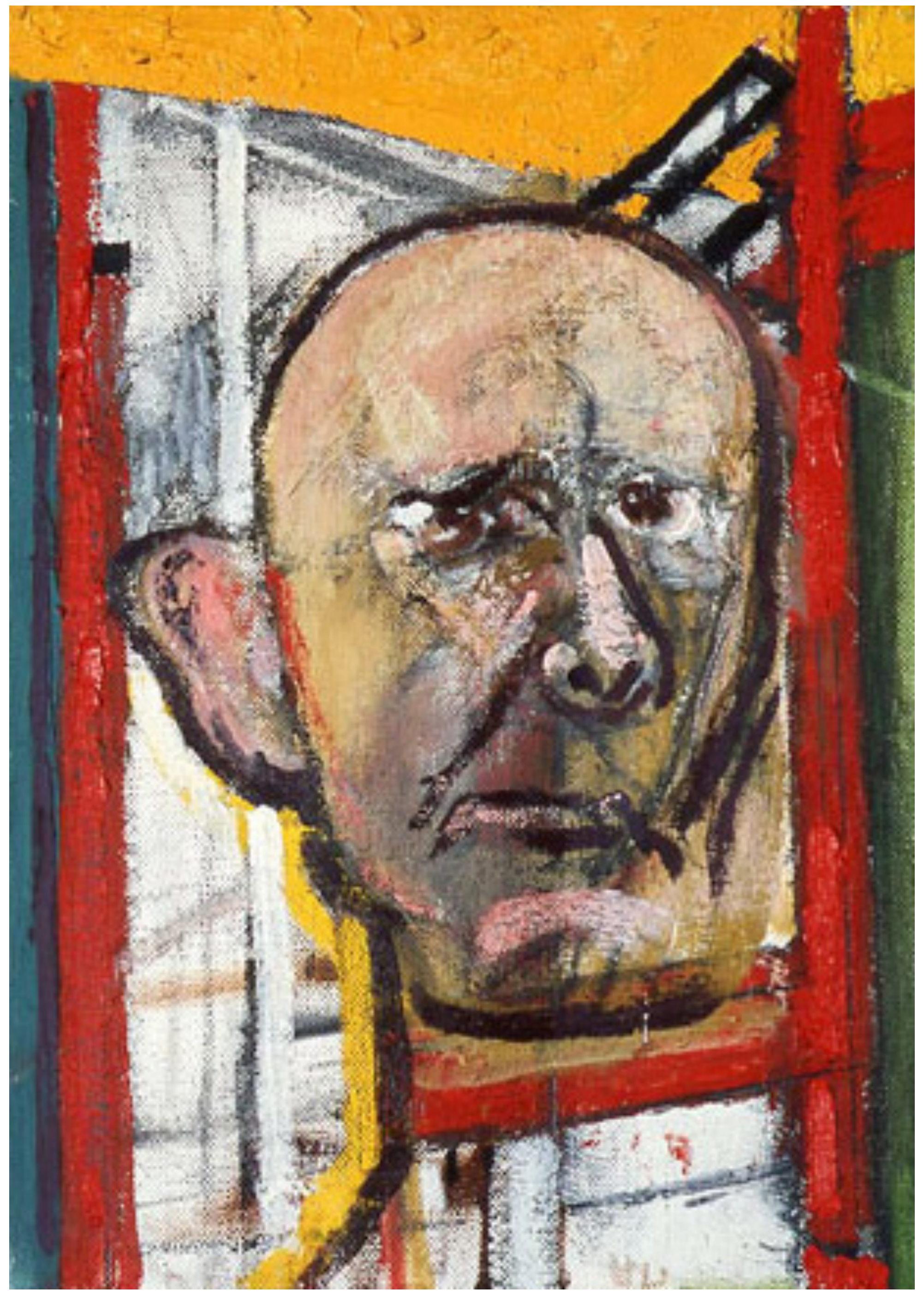
Stage I-II

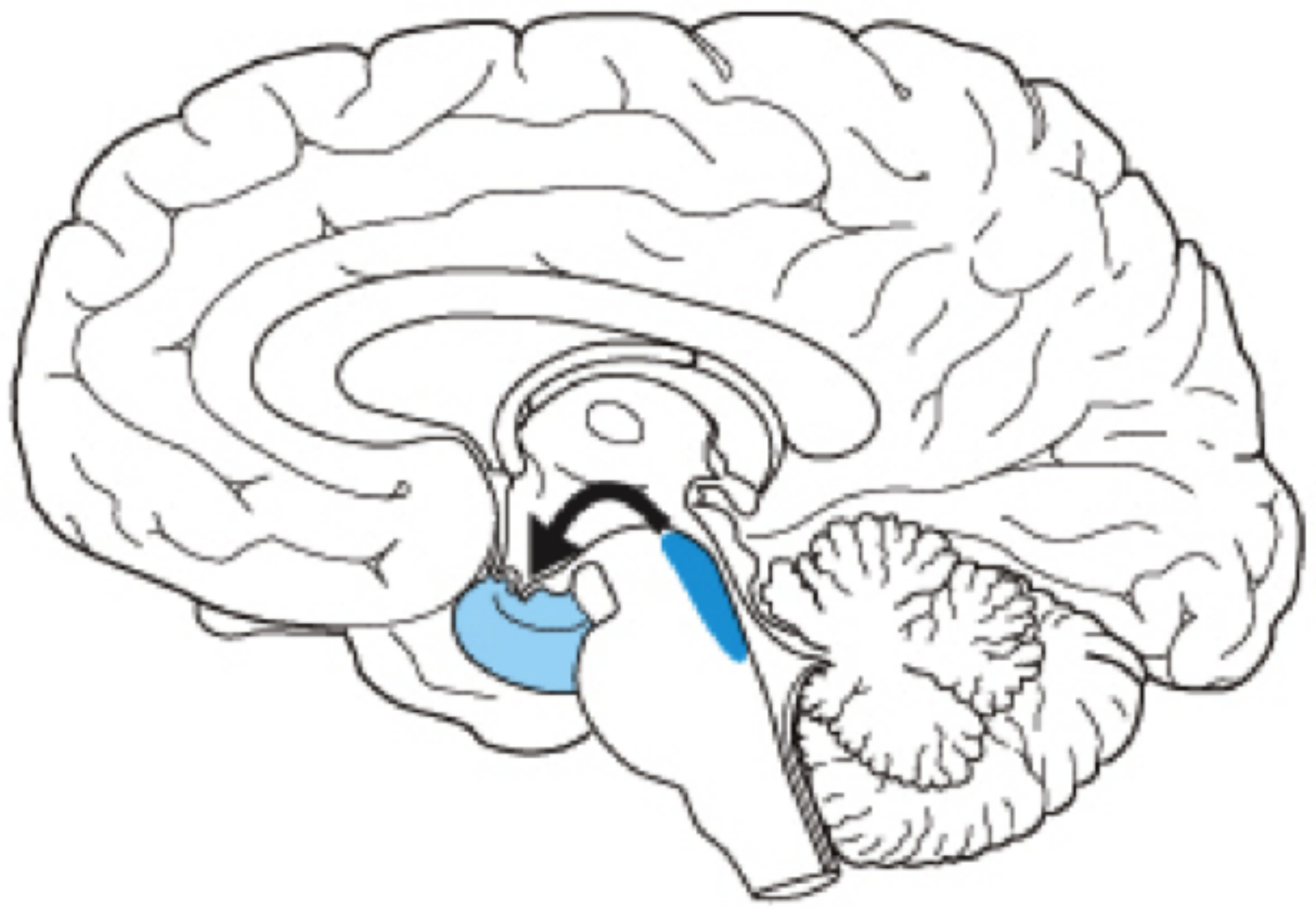


Stage III-IV

Stage IV-V







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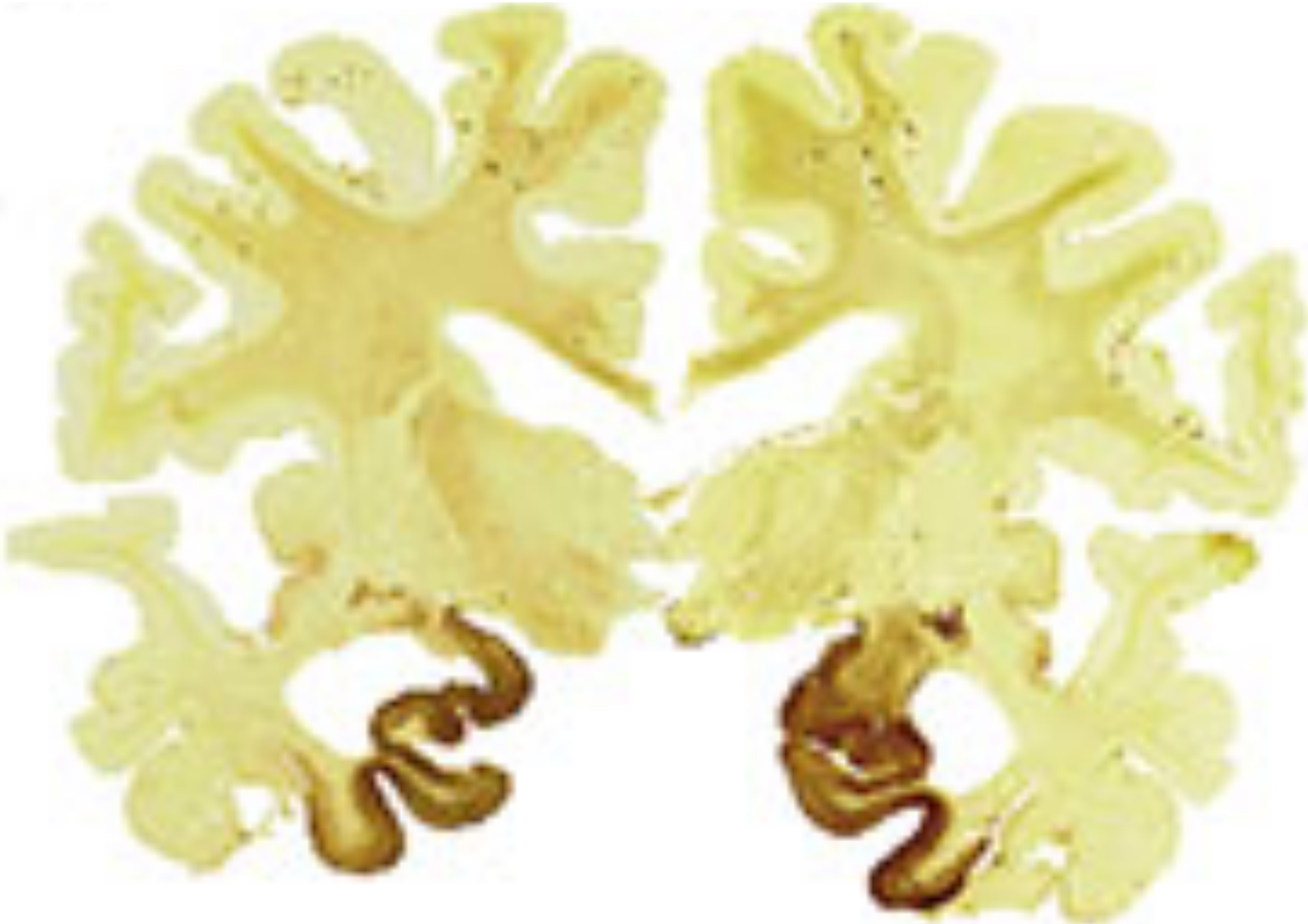
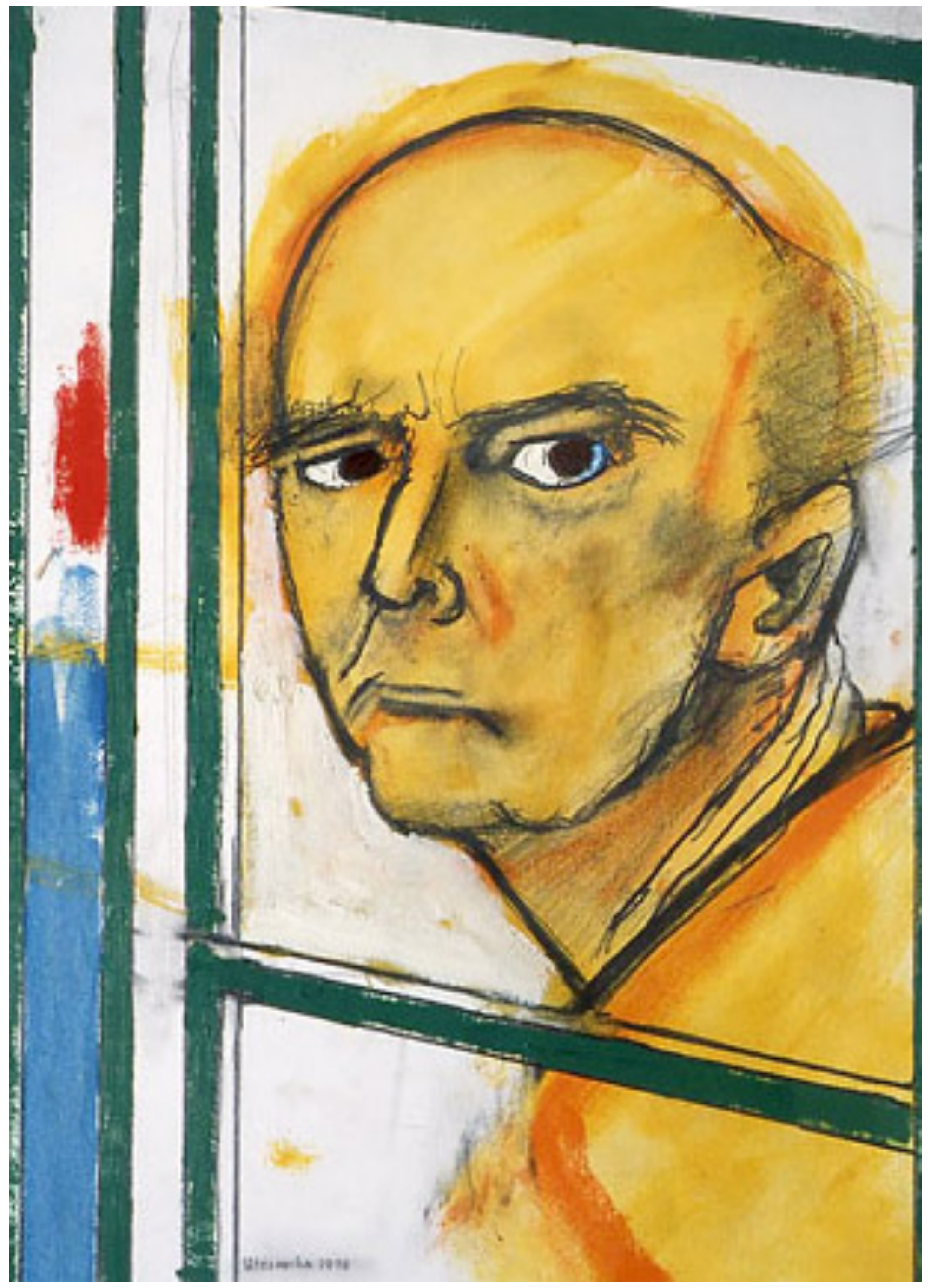
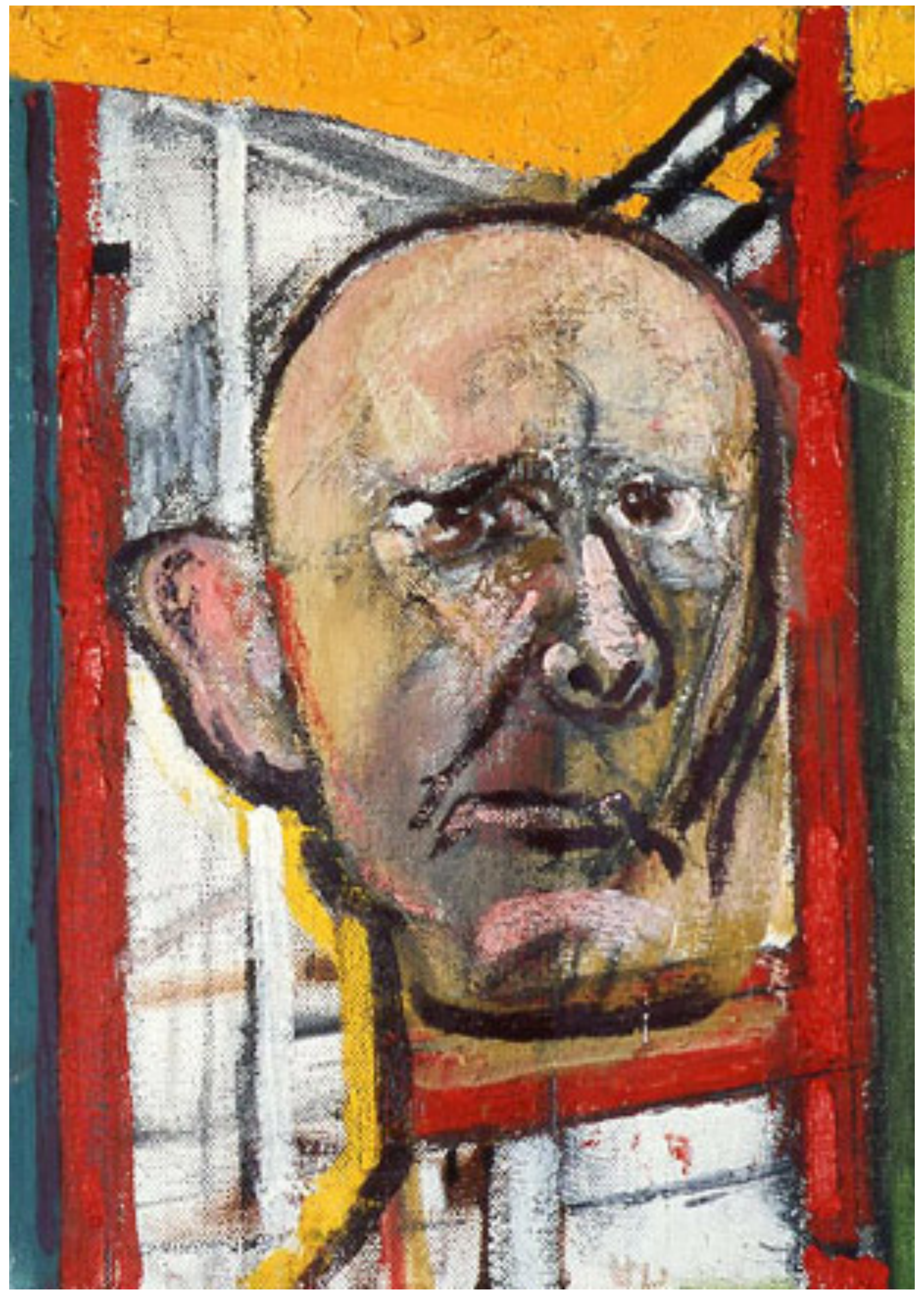
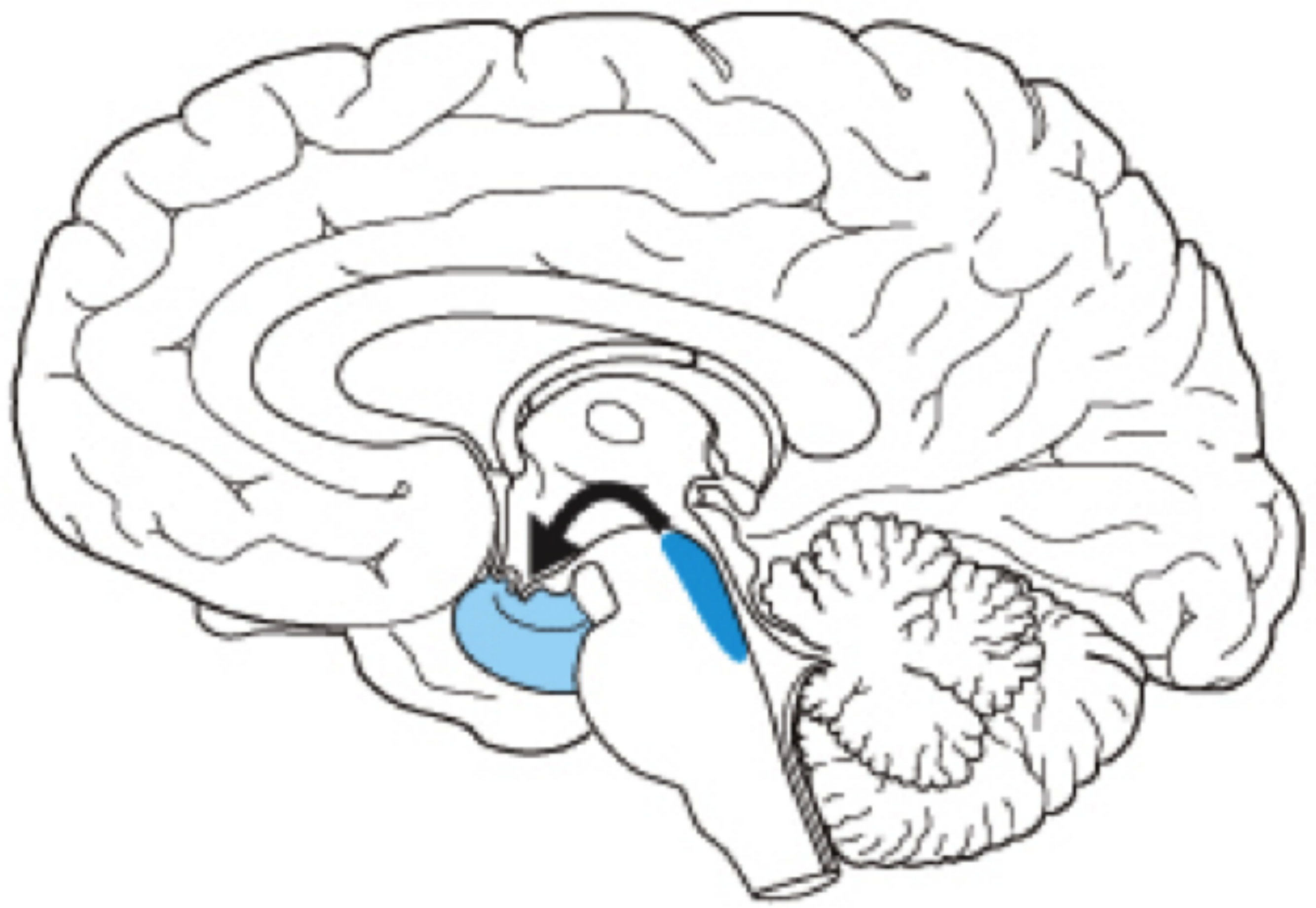


Stage III-IV

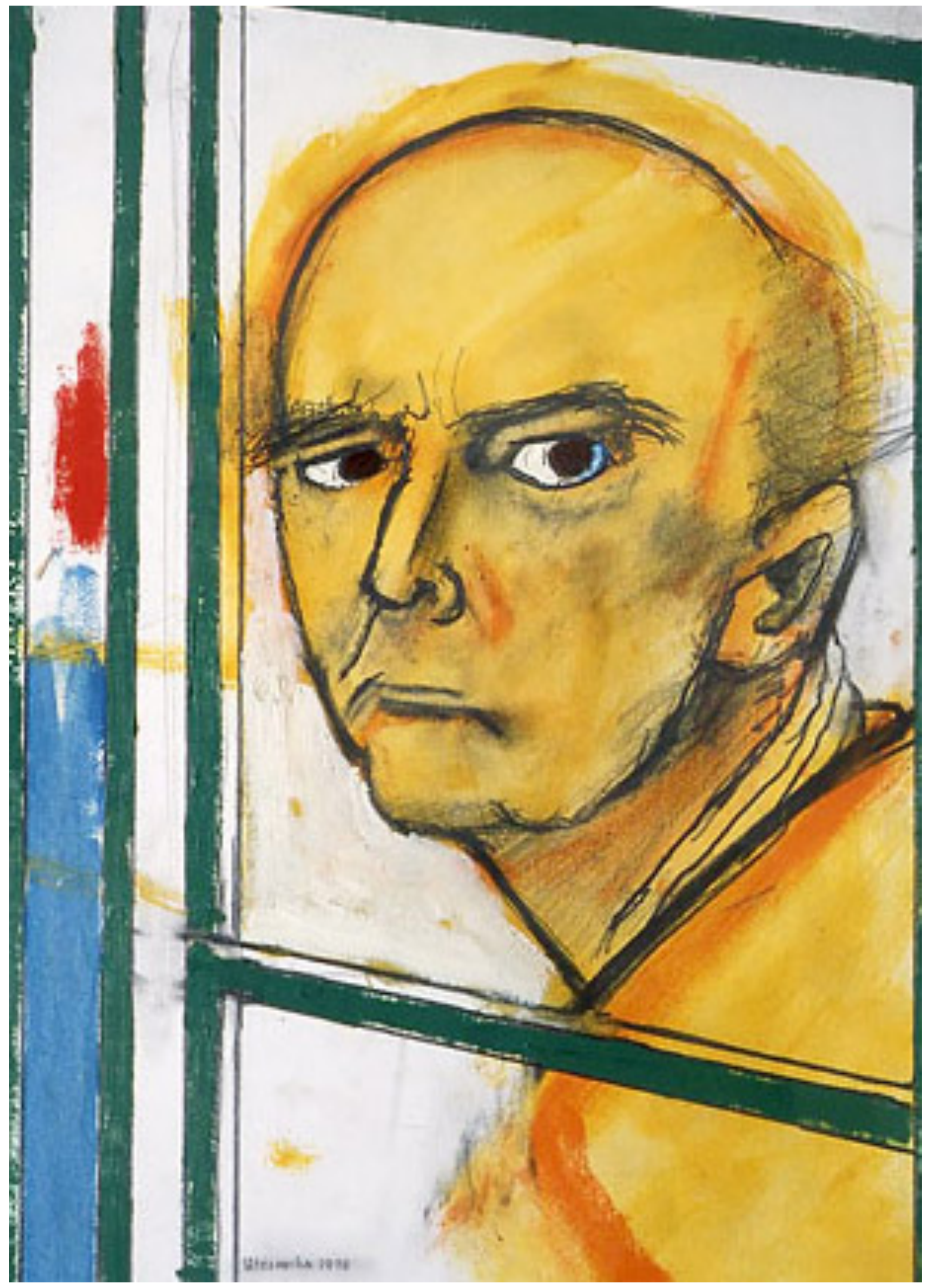
Stage IV-V

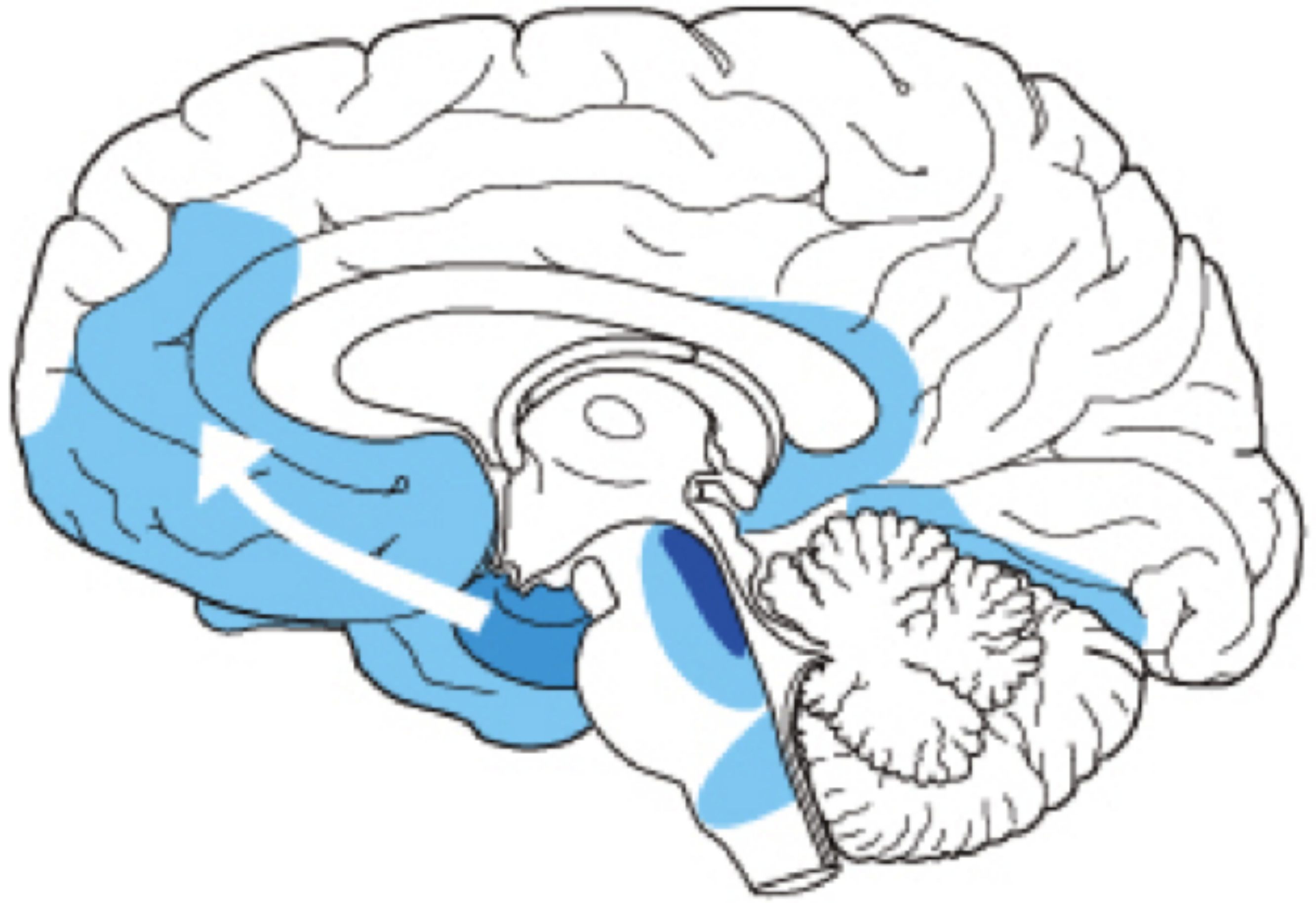




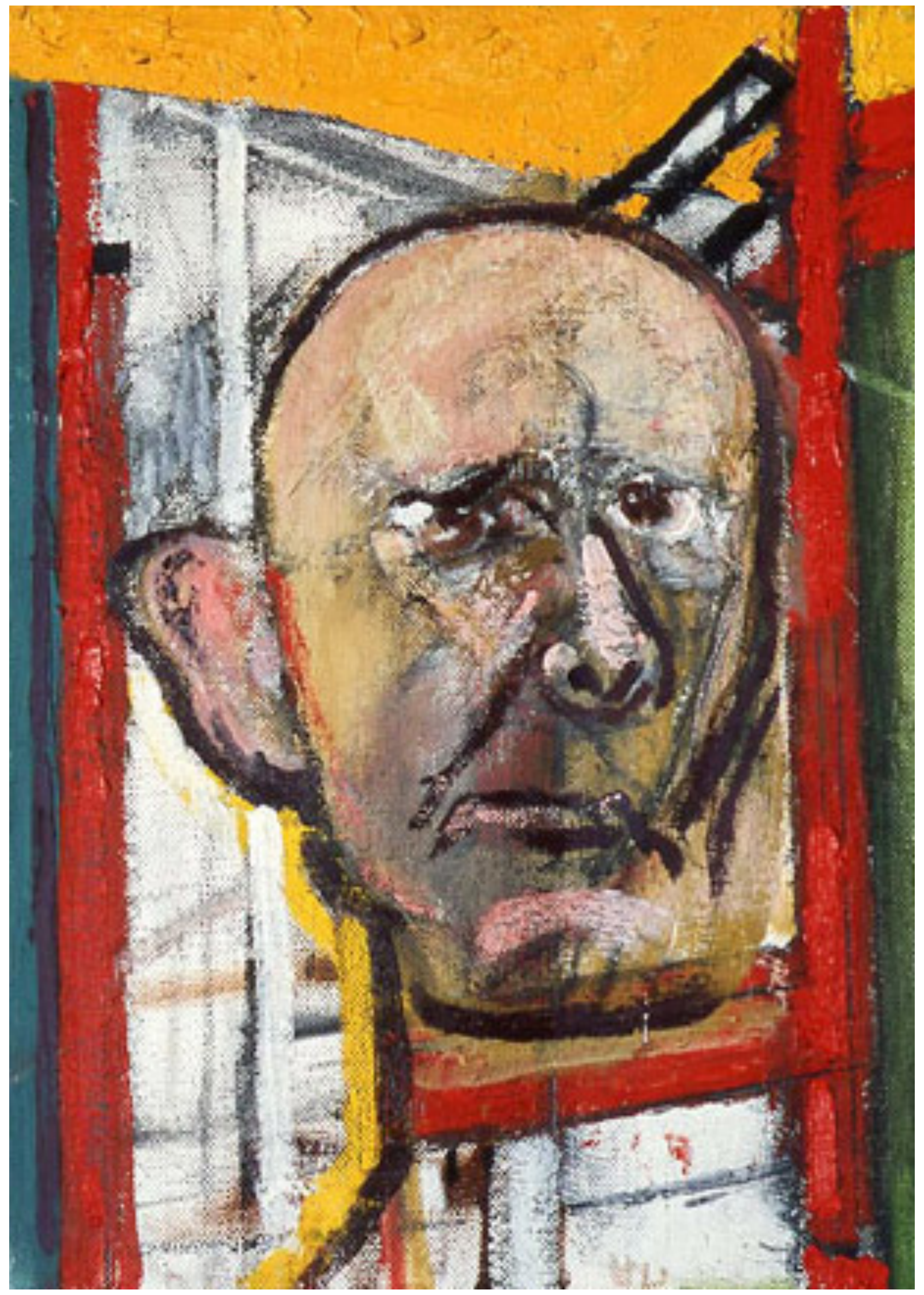


Stage I-II

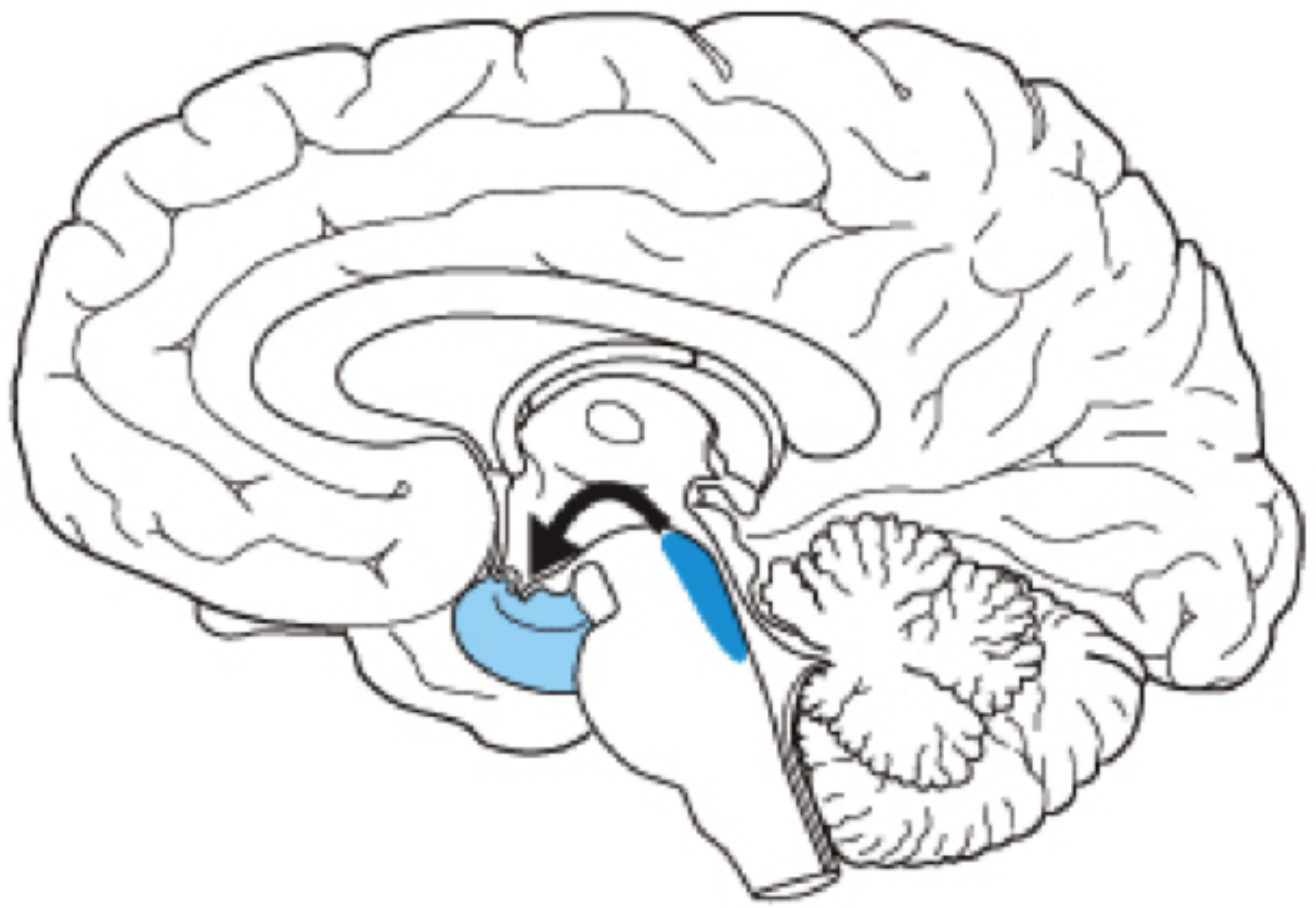




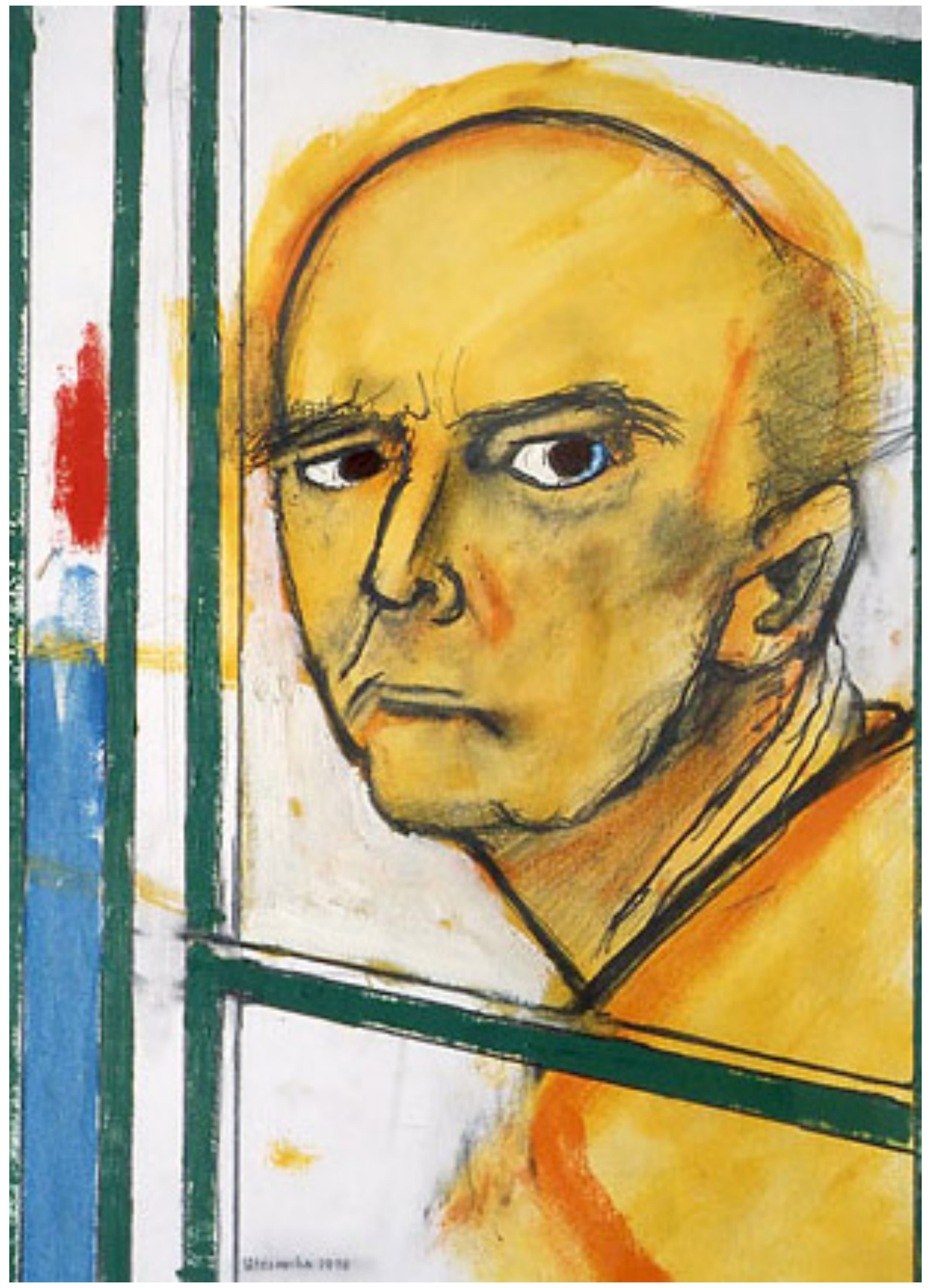
Stage III-IV

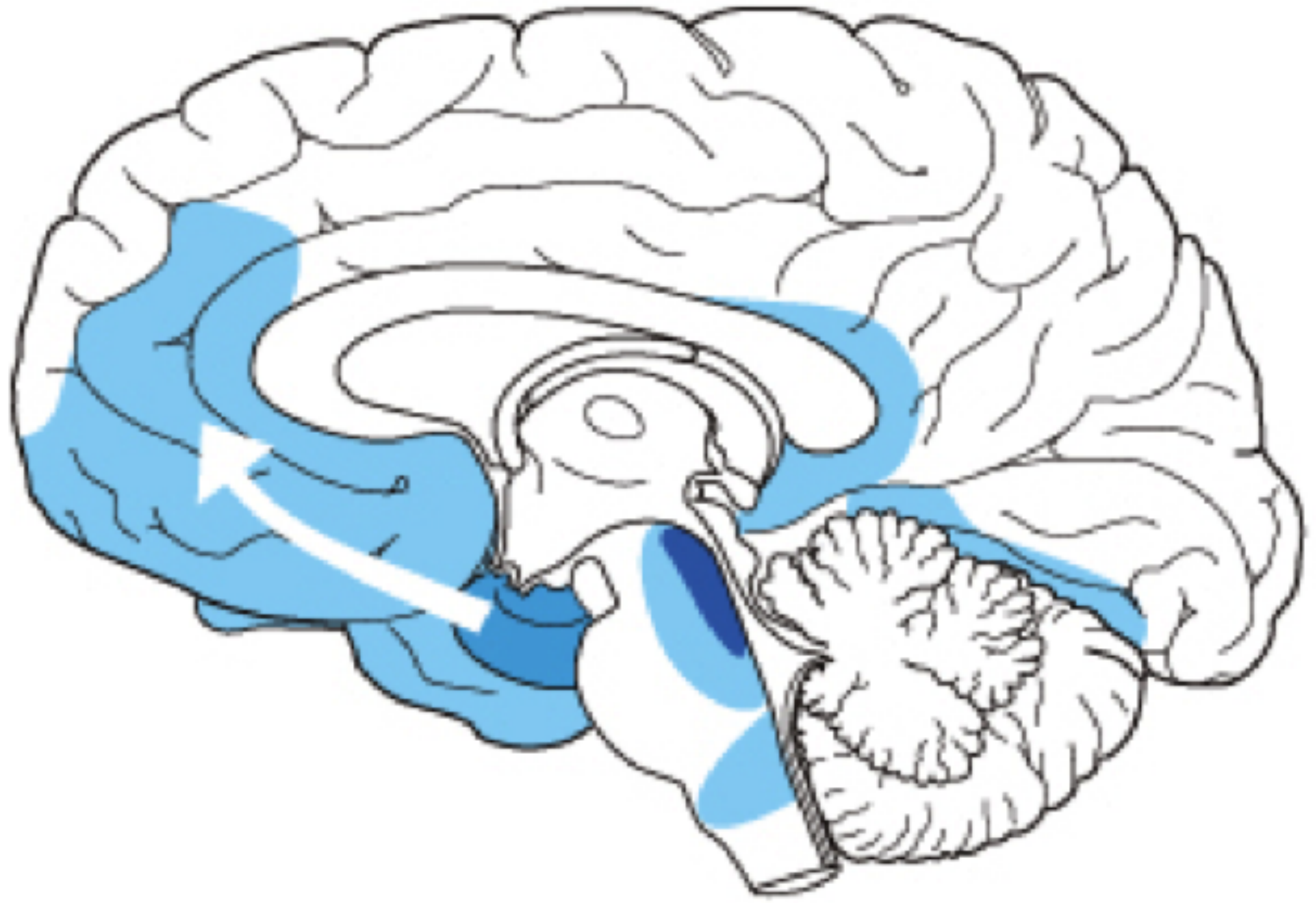


Stage IV-V

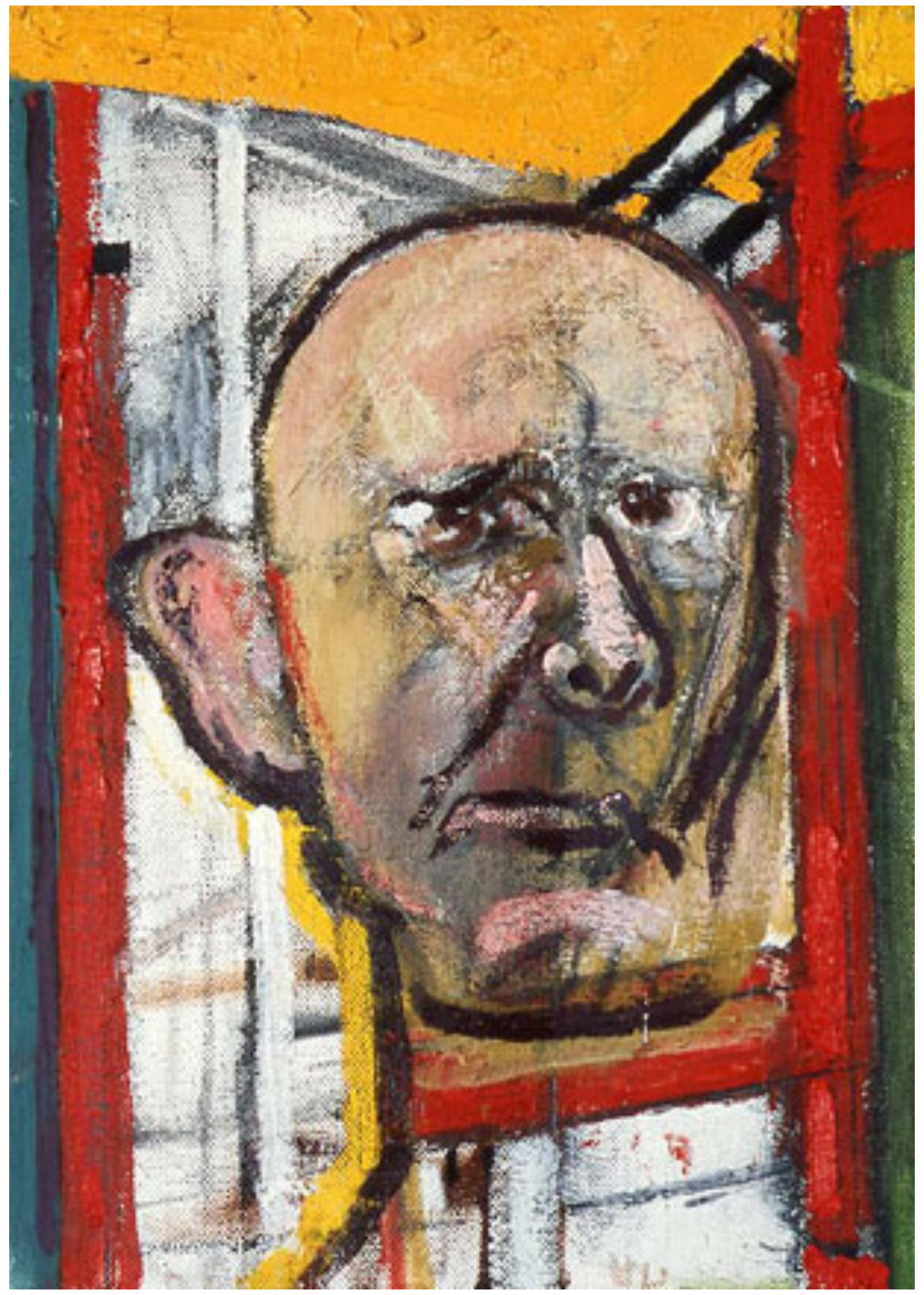


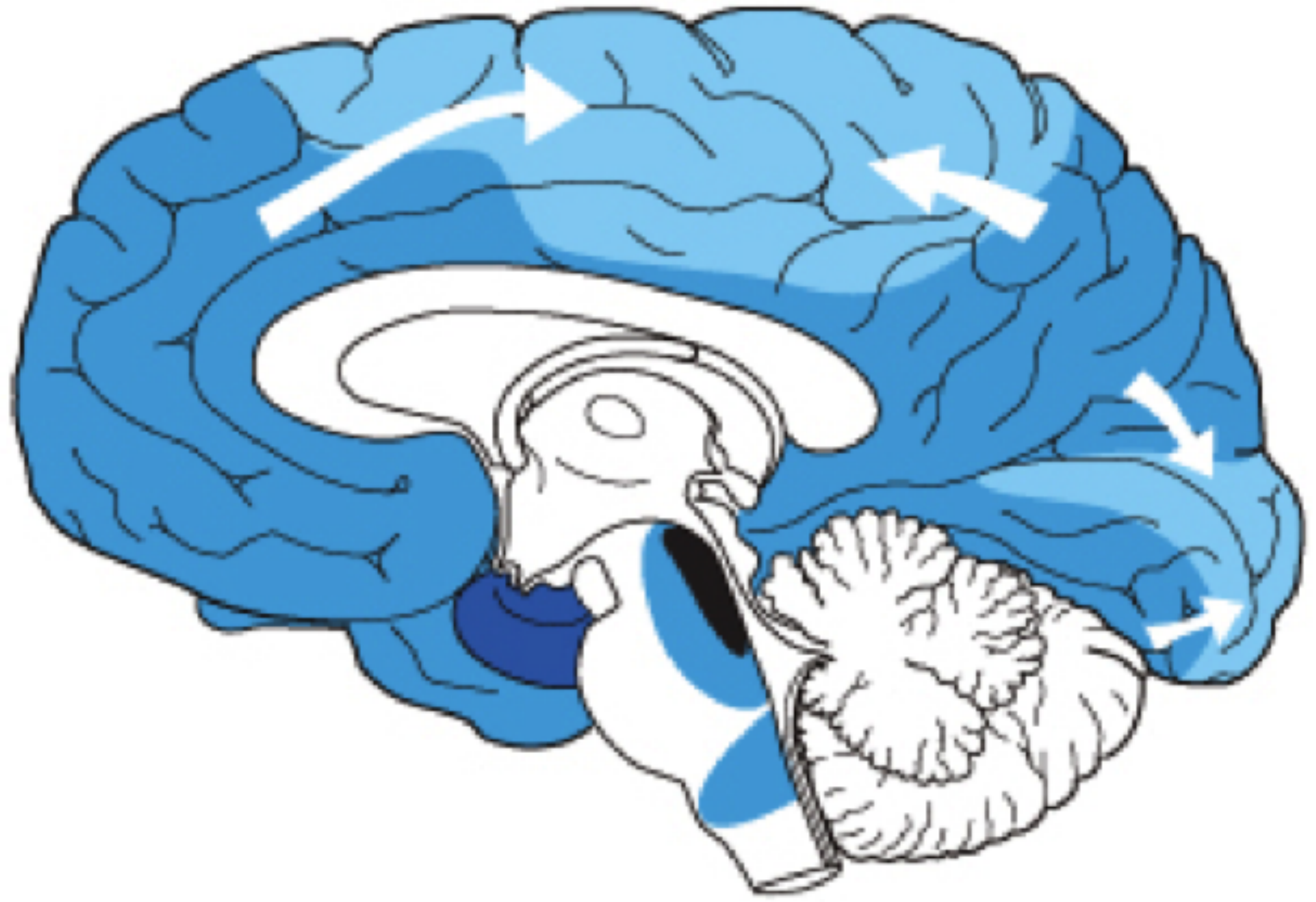
Stage I-II





Stage III-IV

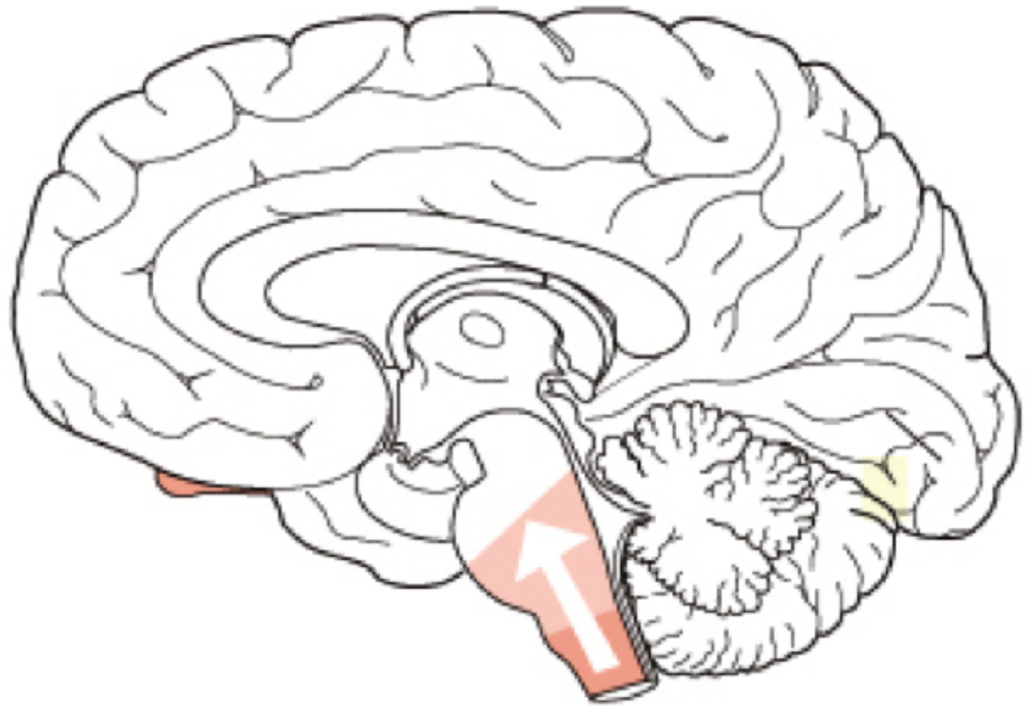




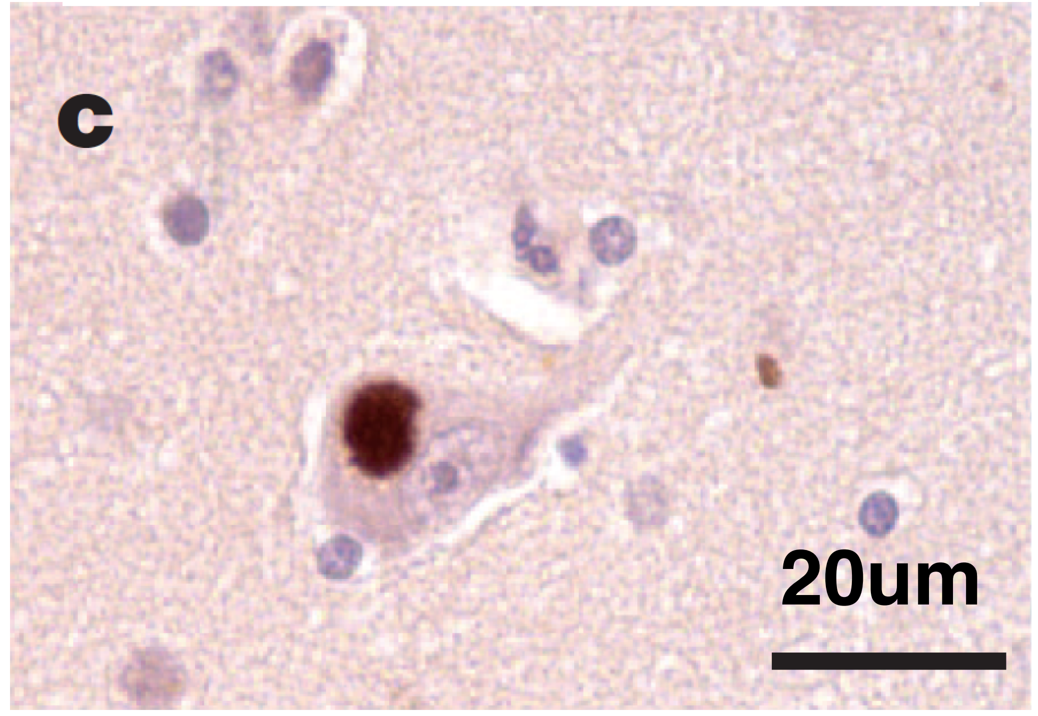
Stage IV-V

other neurodegenerative diseases

parkinson's disease

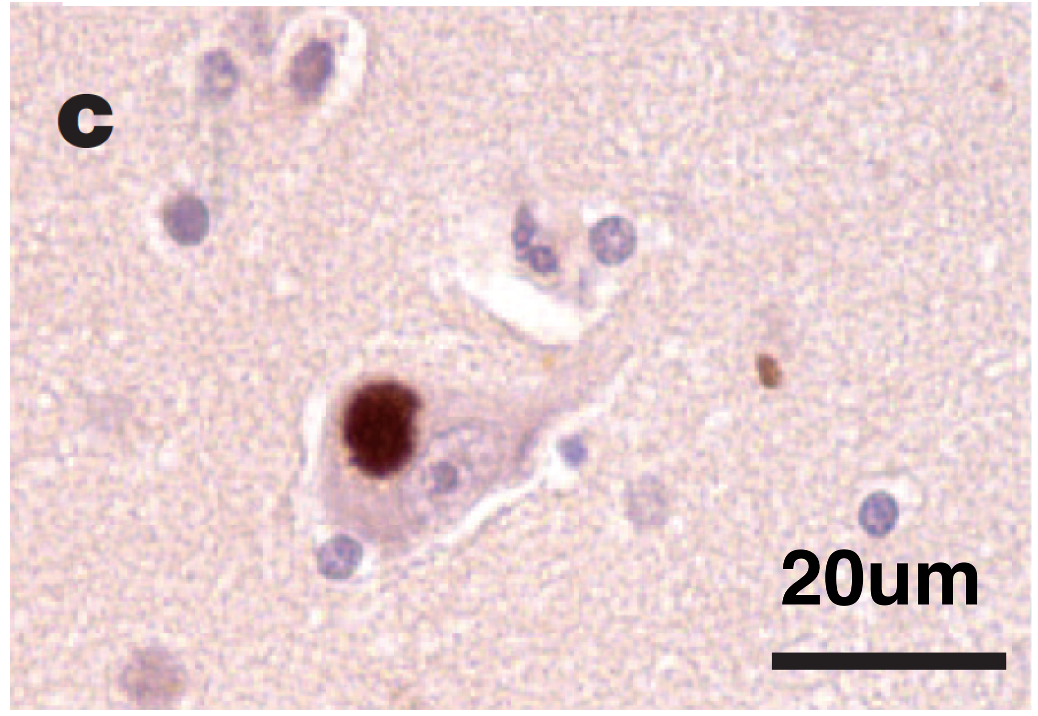


α-synuclein inclusions



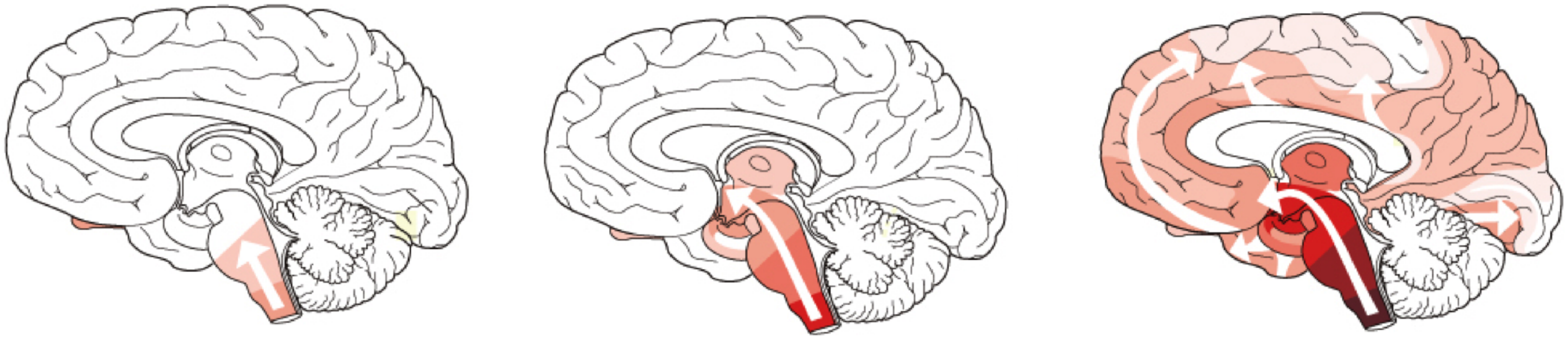
other neurodegenerative diseases

parkinson’s disease

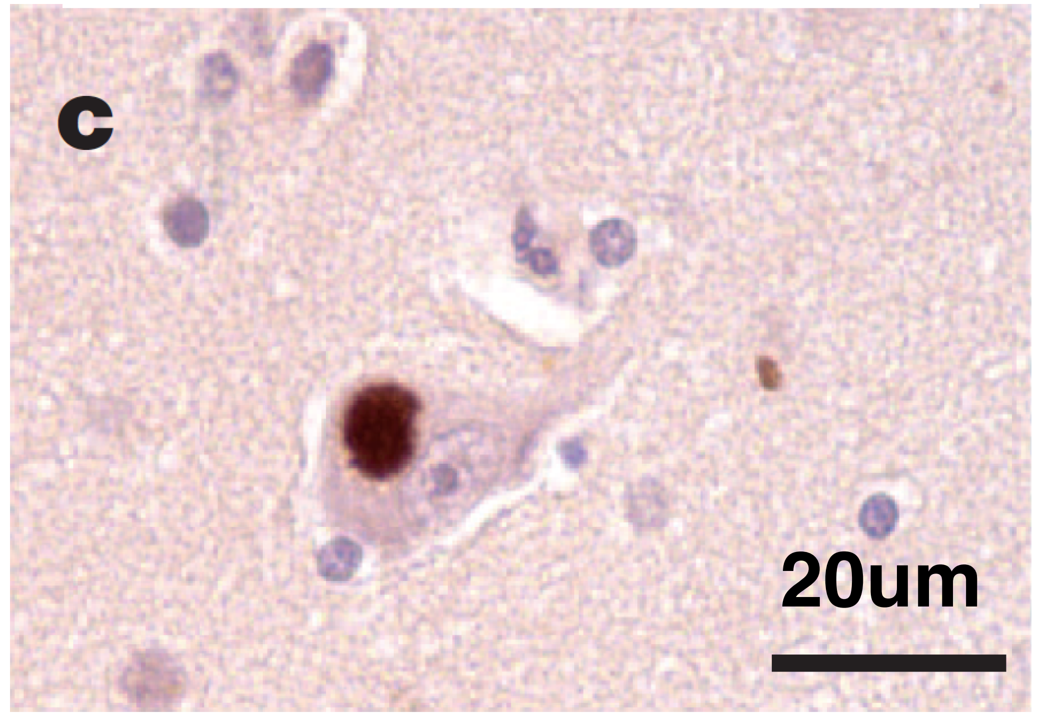

α-synuclein inclusions

other neurodegenerative diseases

parkinson's disease

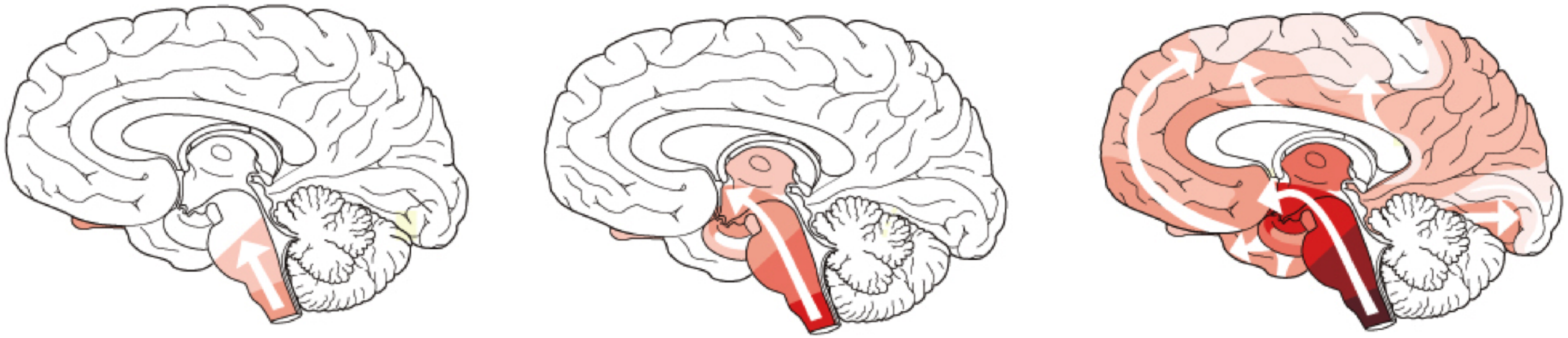


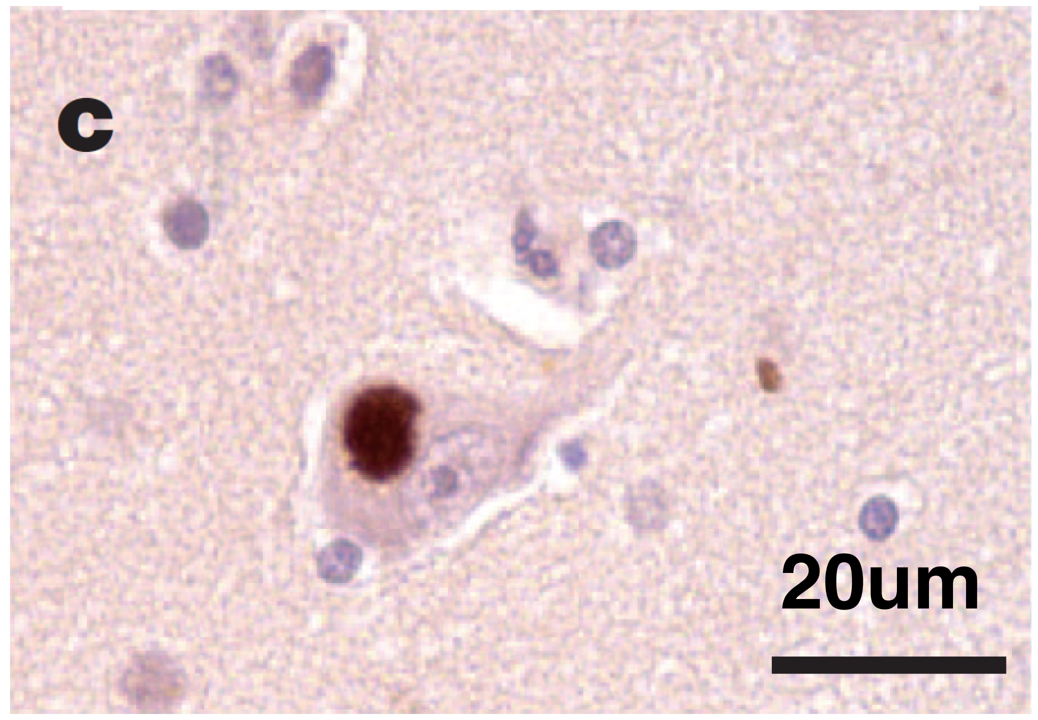
α-synuclein inclusions



other neurodegenerative diseases

parkinson’s disease



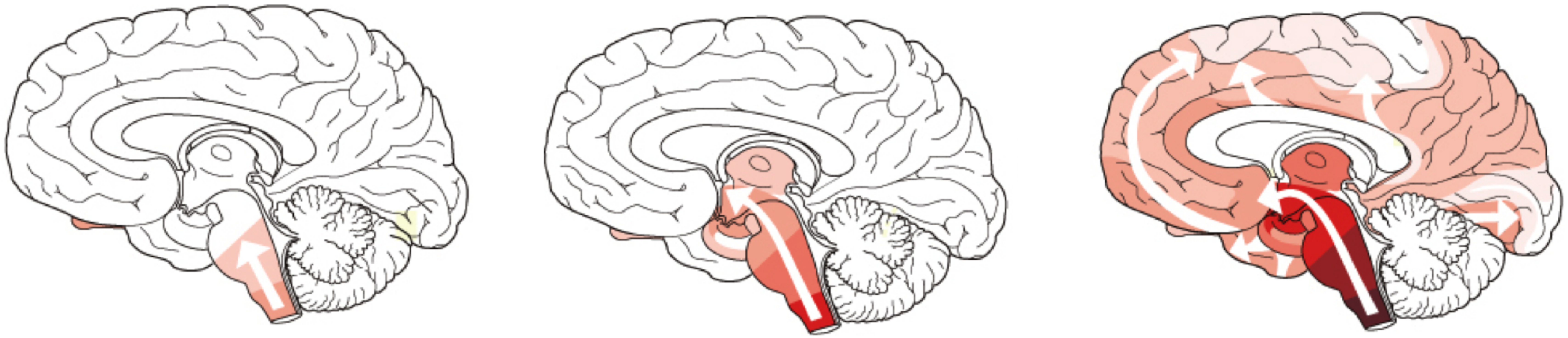


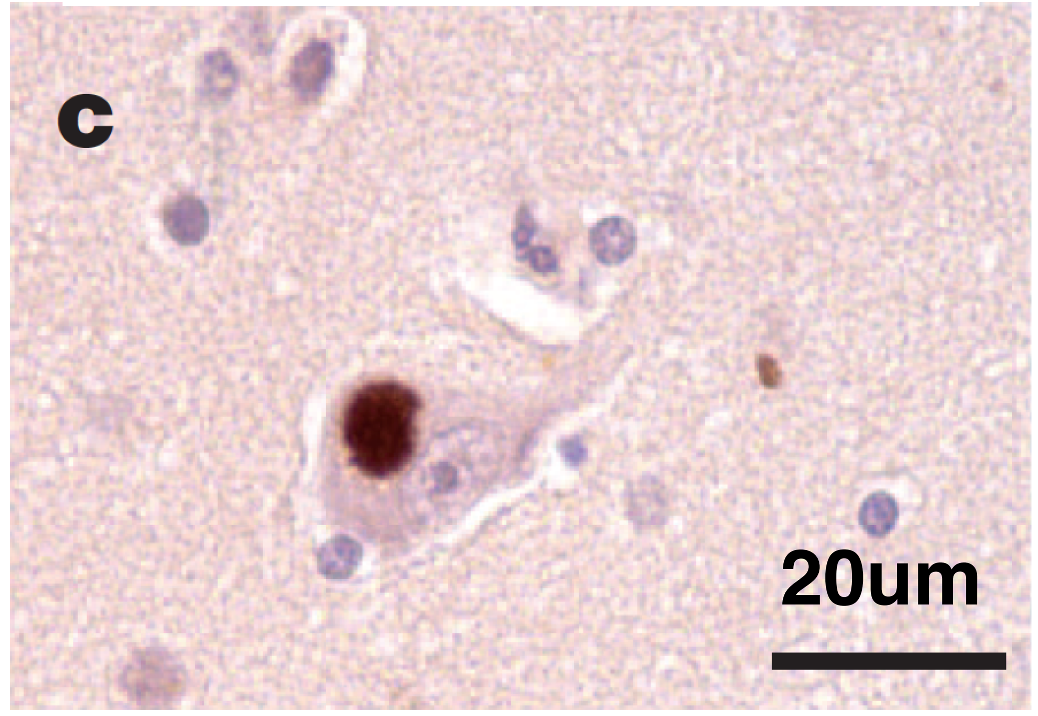
α-synuclein inclusions

amyotrophic lateral sclerosis

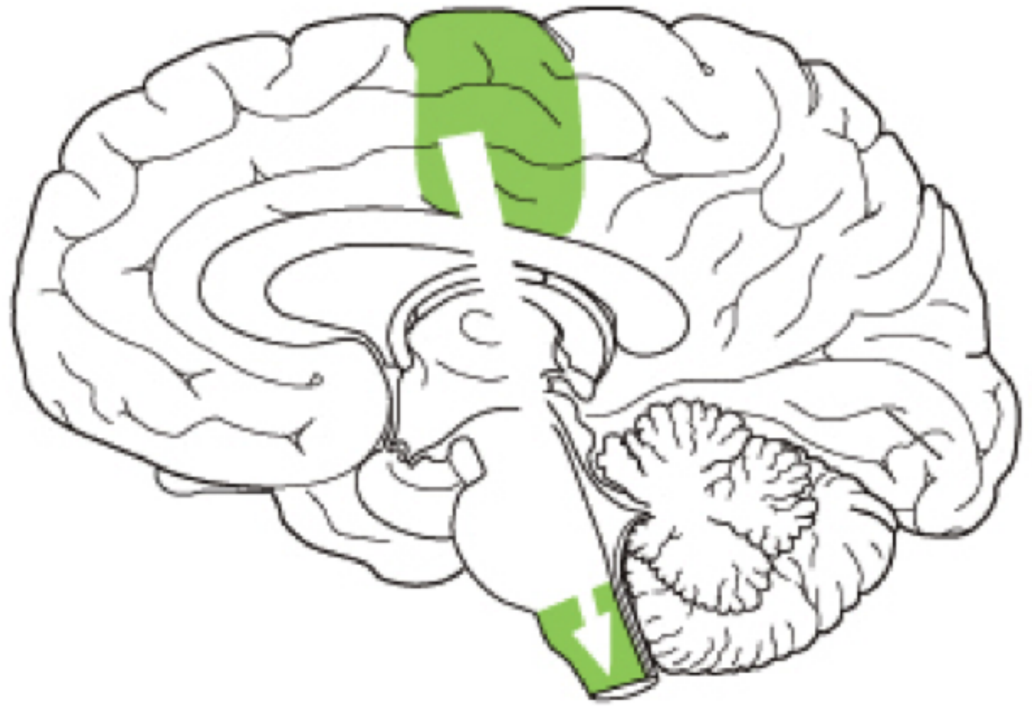
other neurodegenerative diseases

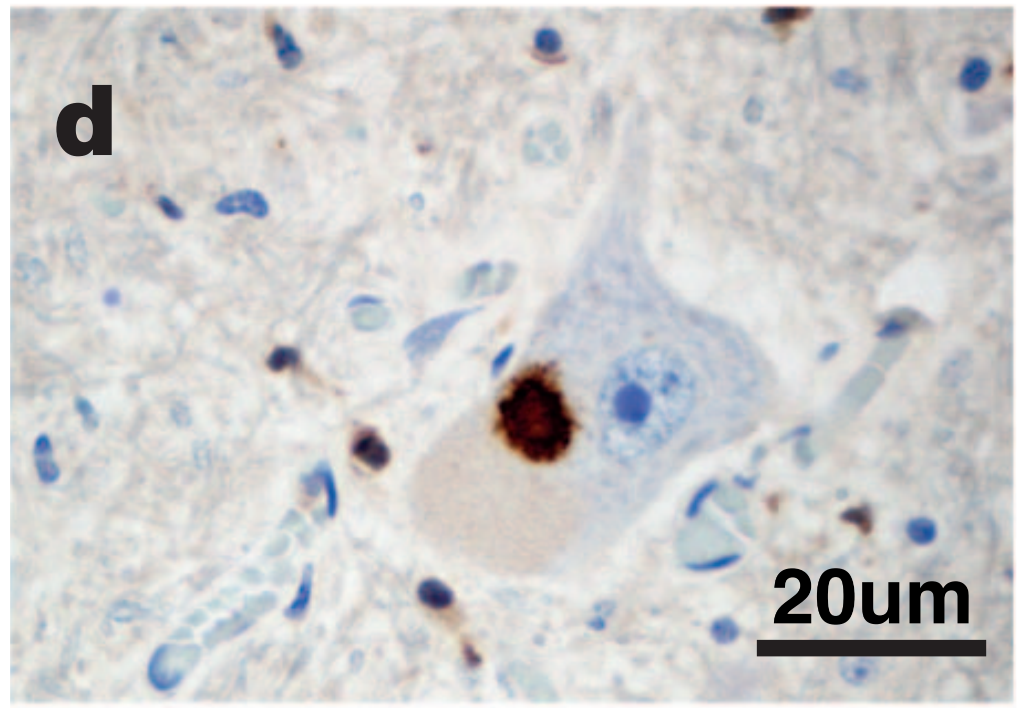
parkinson's disease




α-synuclein inclusions

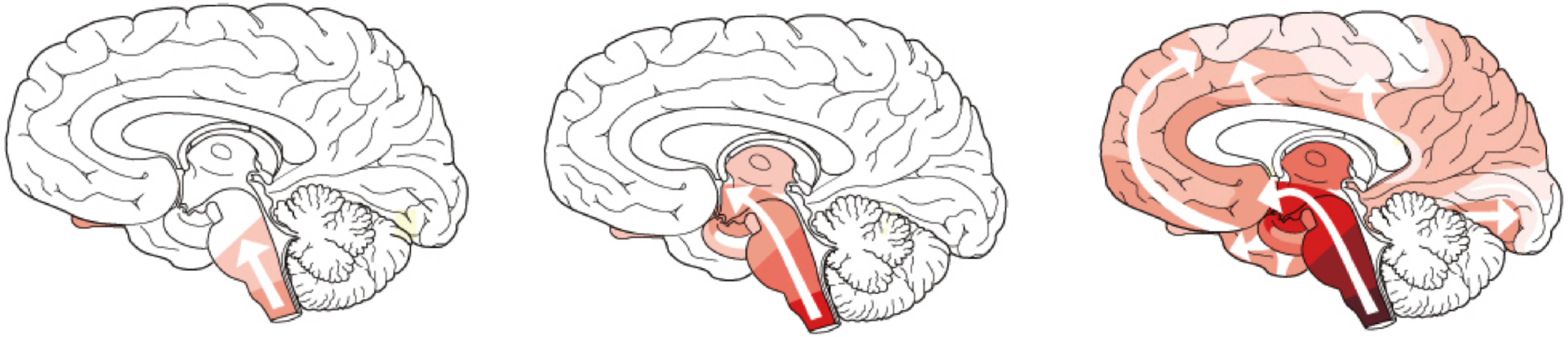
amyotrophic lateral sclerosis

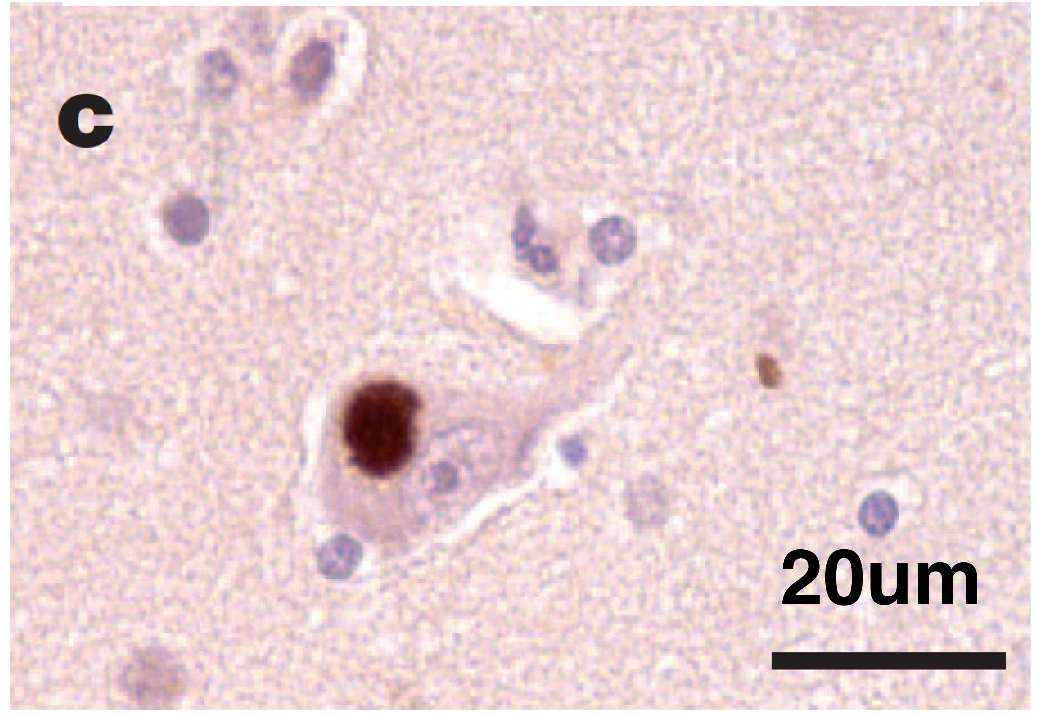



TDP-43 inclusions

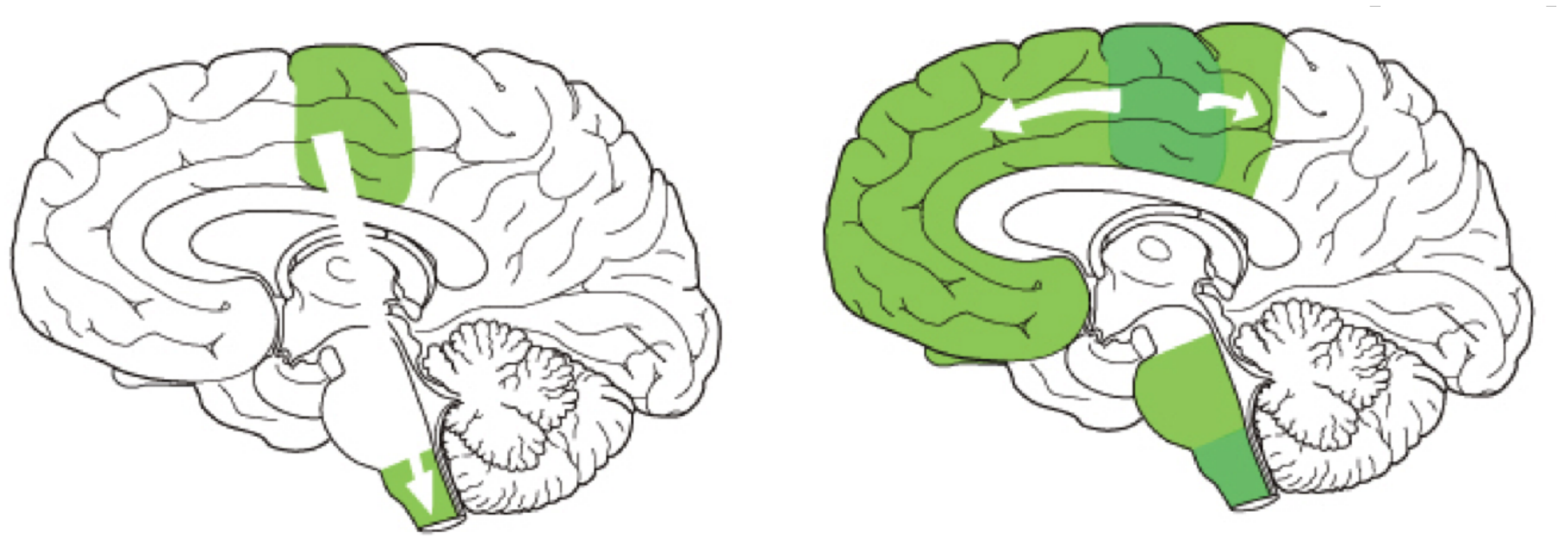
other neurodegenerative diseases

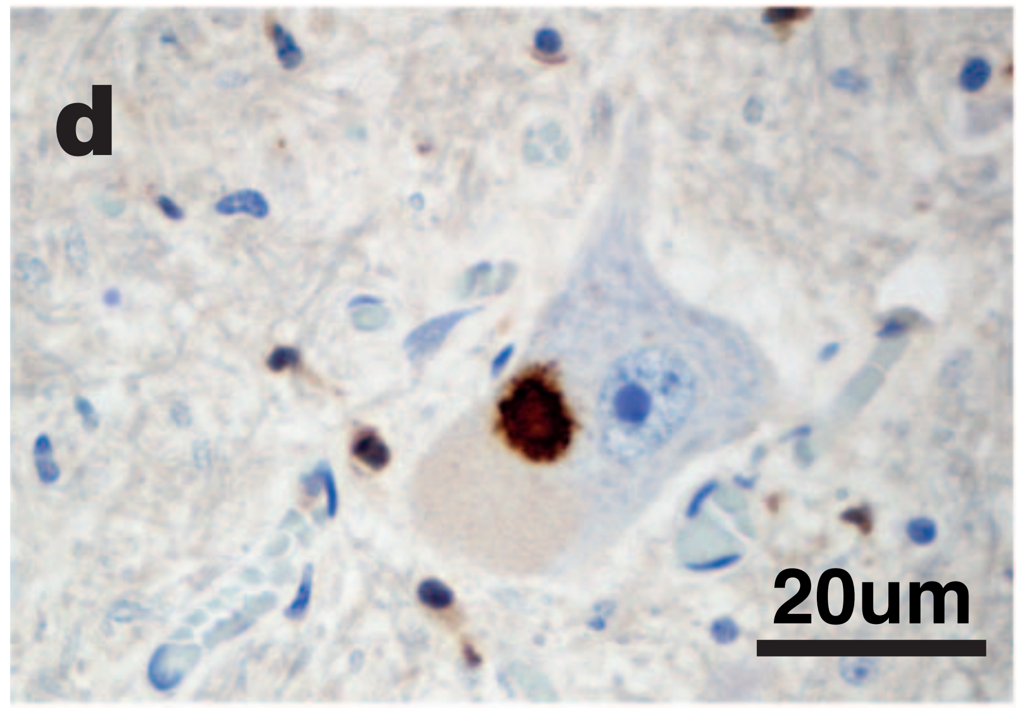
parkinson’s disease




α-synuclein inclusions

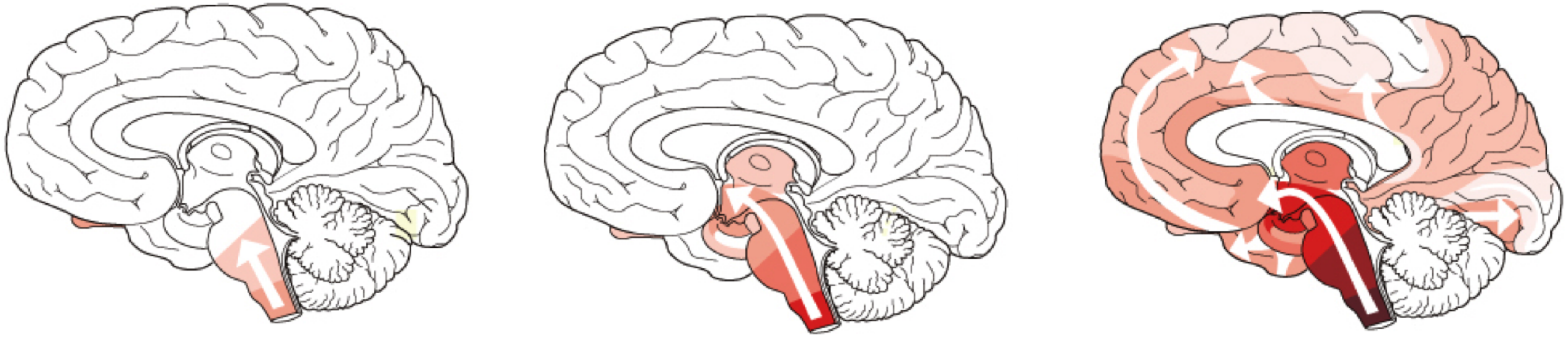
amyotrophic lateral sclerosis



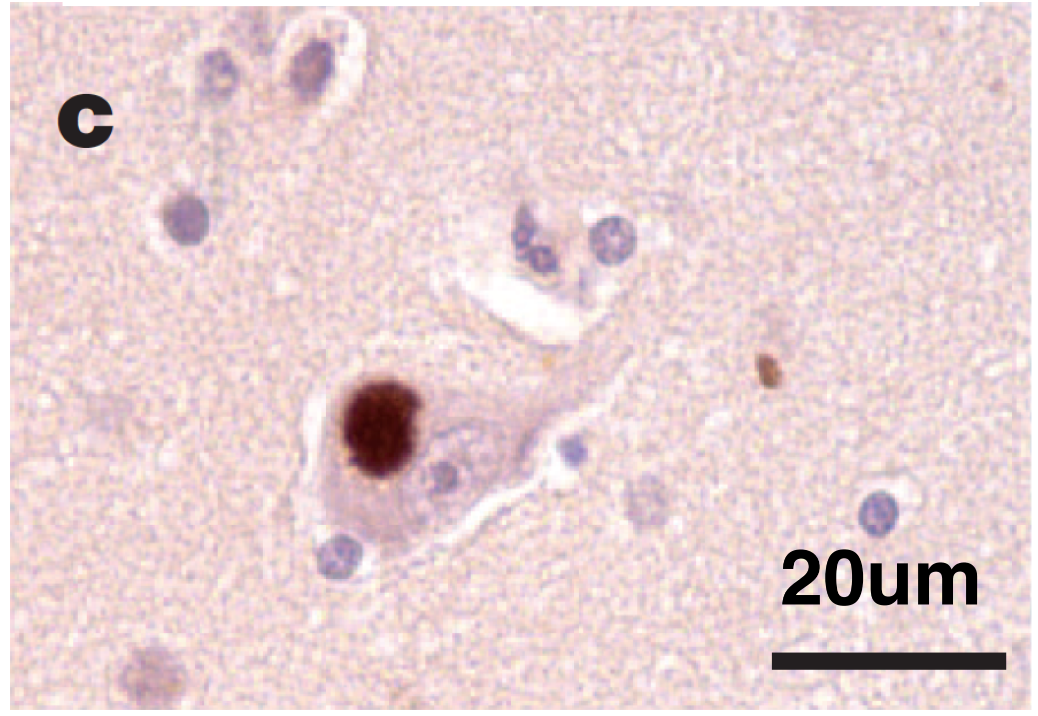

TDP-43 inclusions

other neurodegenerative diseases

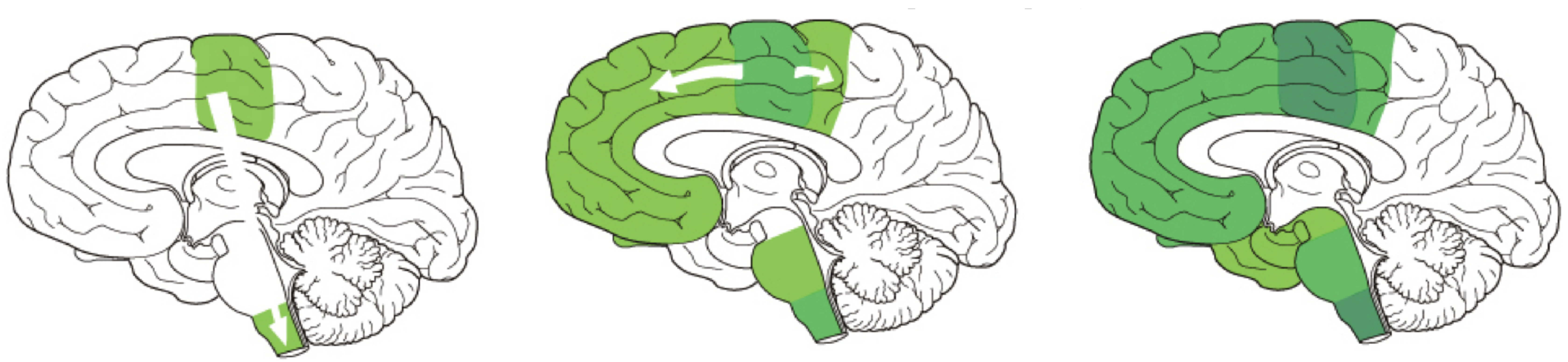
parkinson's disease



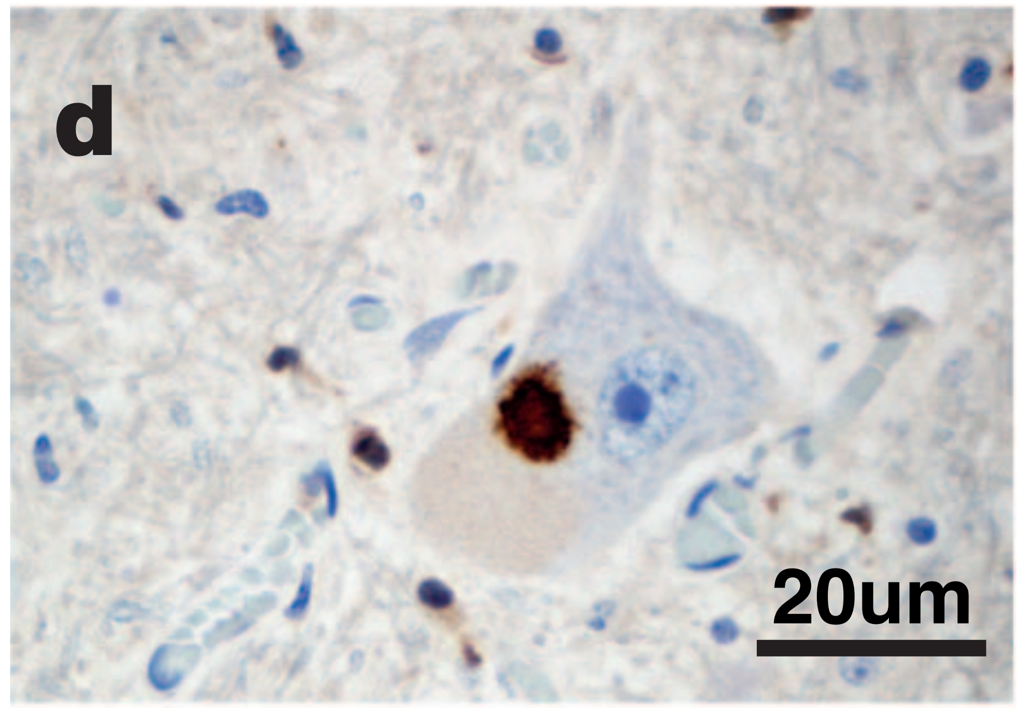
α-synuclein inclusions



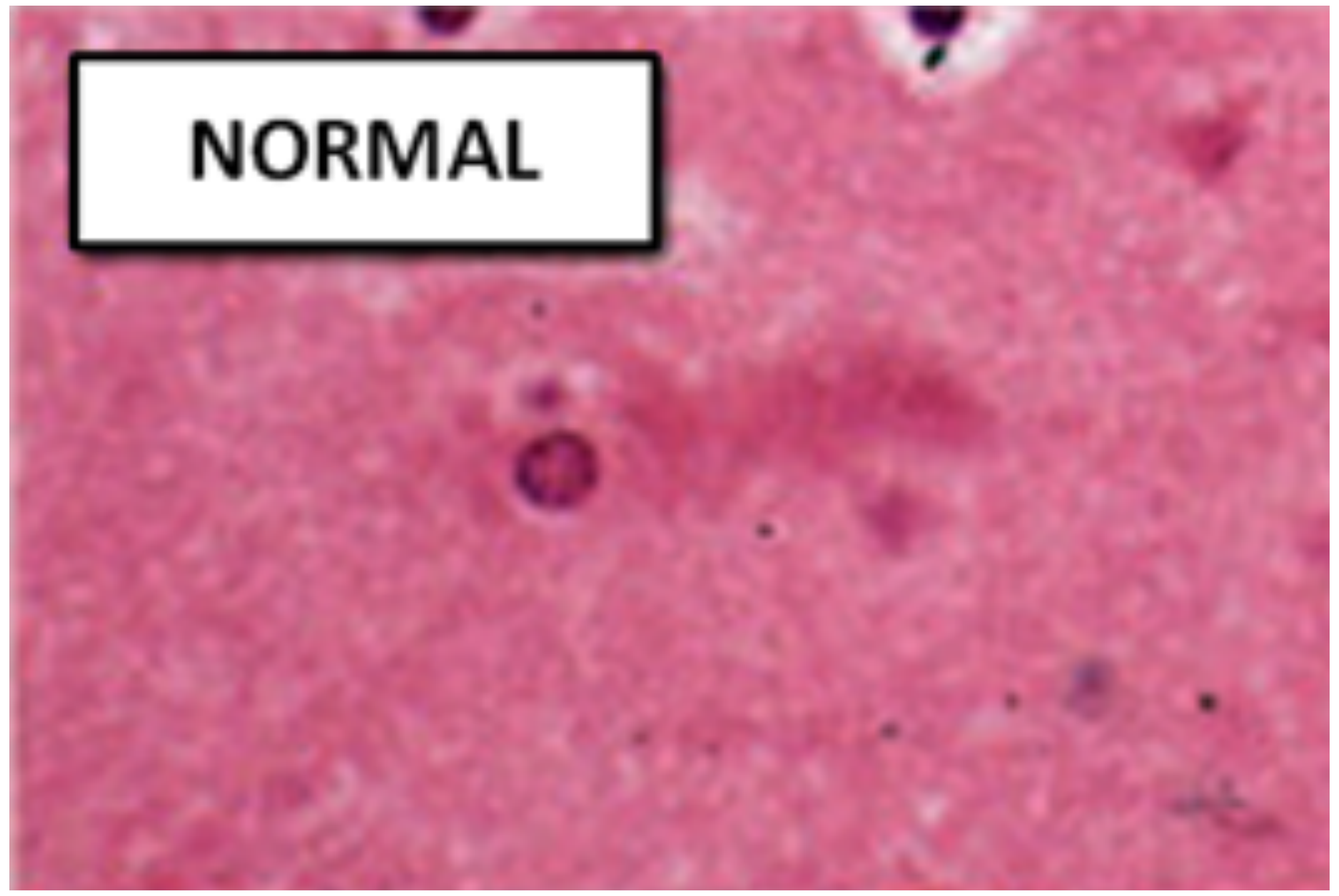
amyotrophic lateral sclerosis

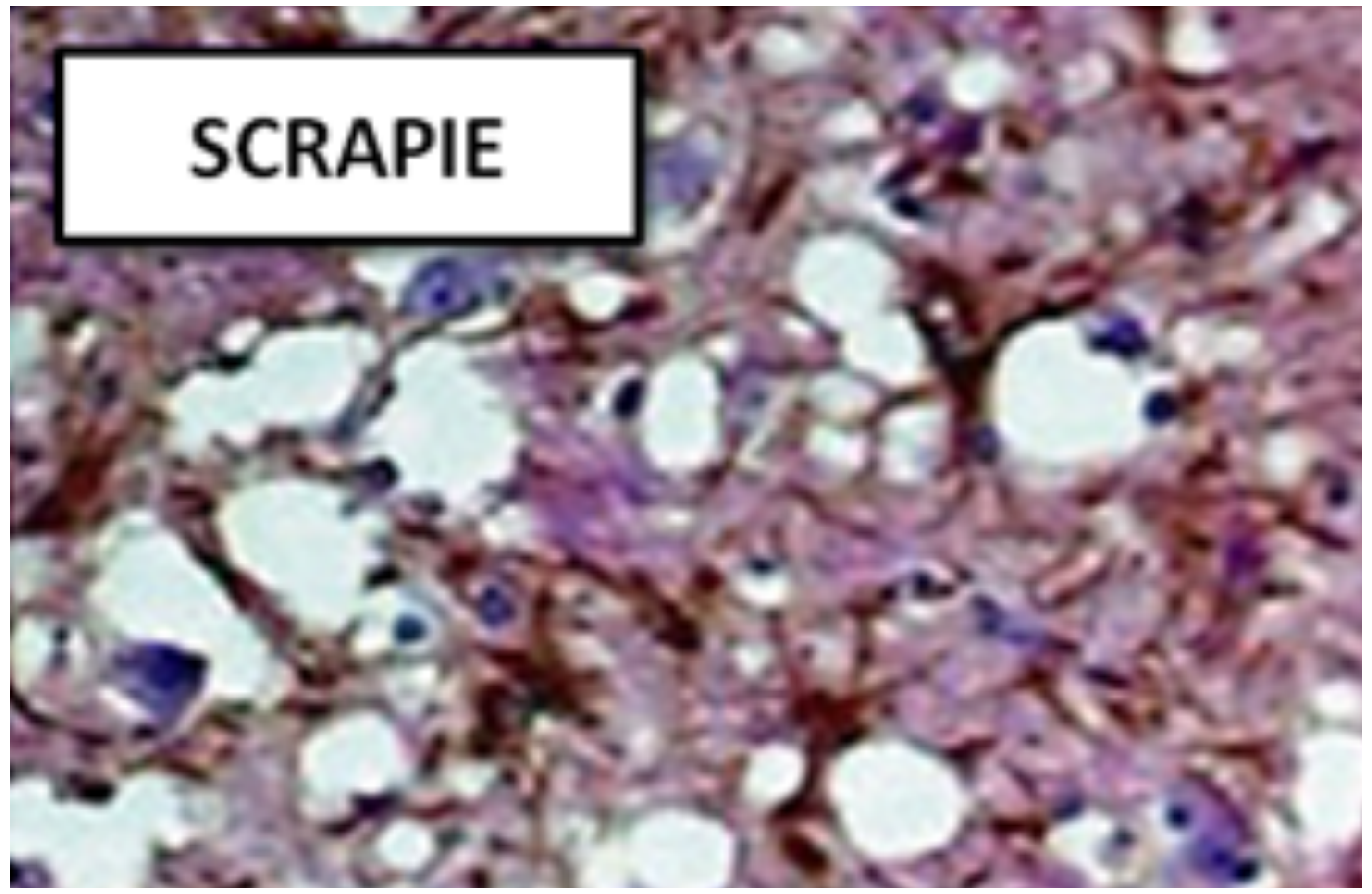


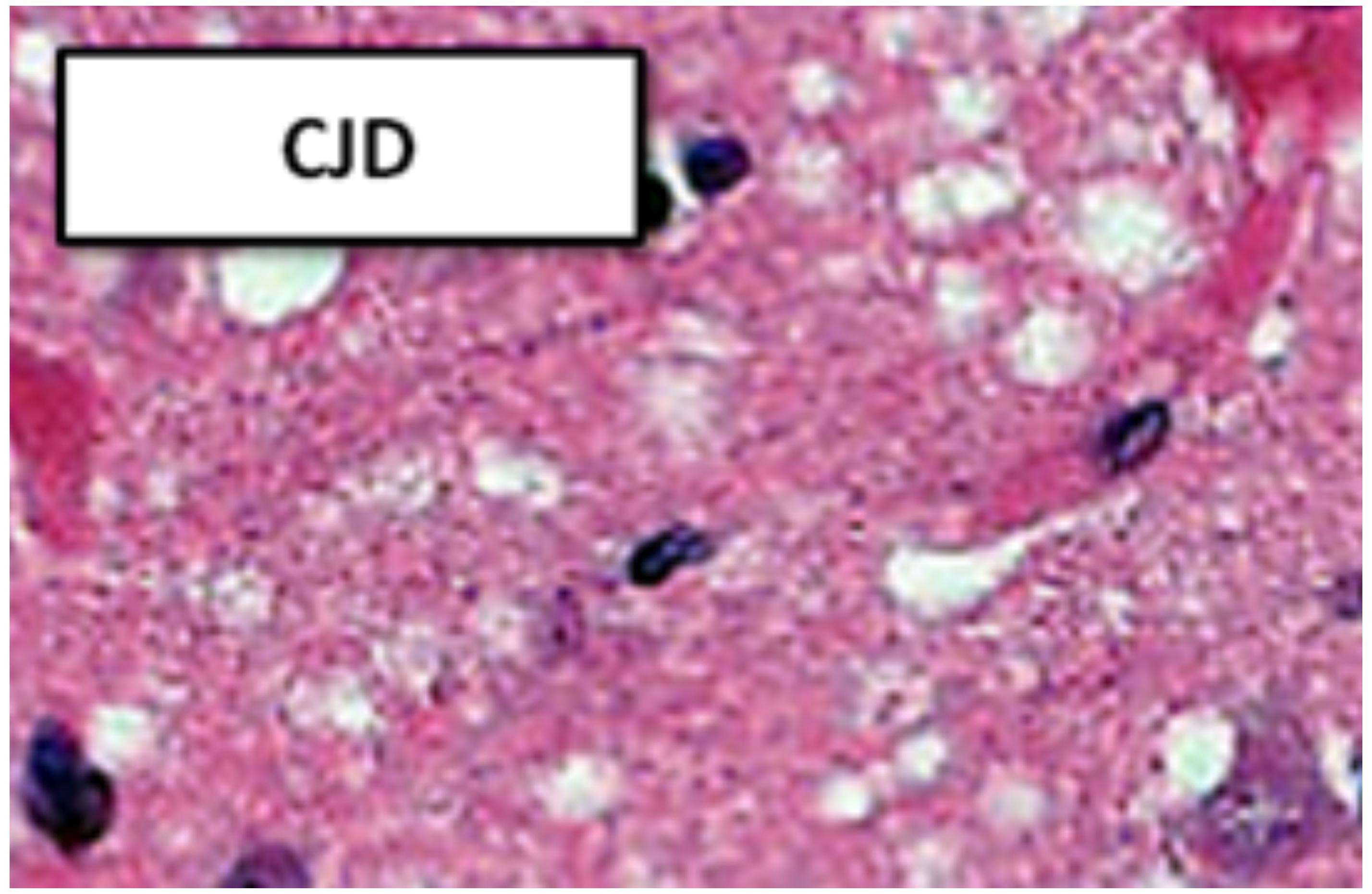
TDP-43 inclusions

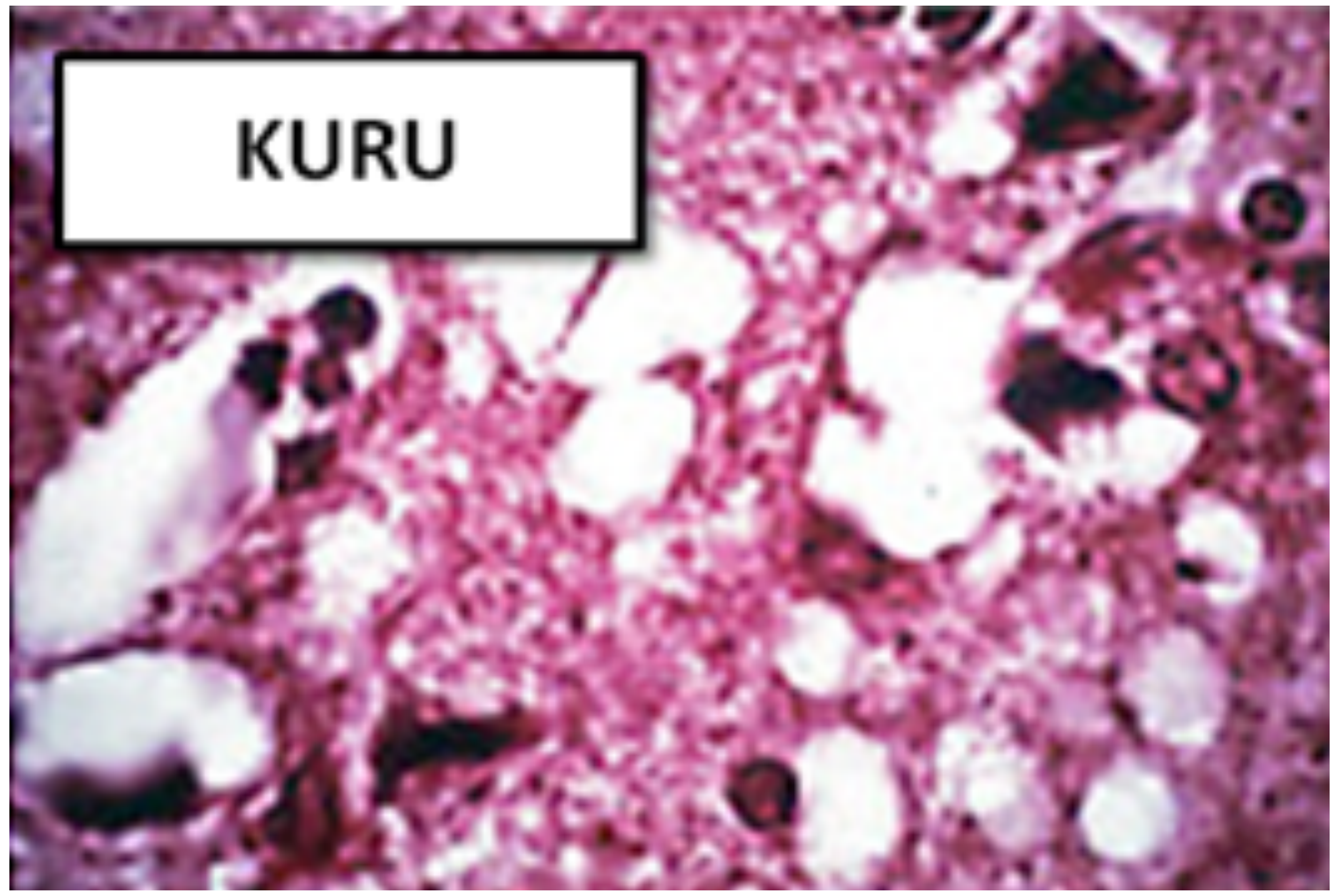


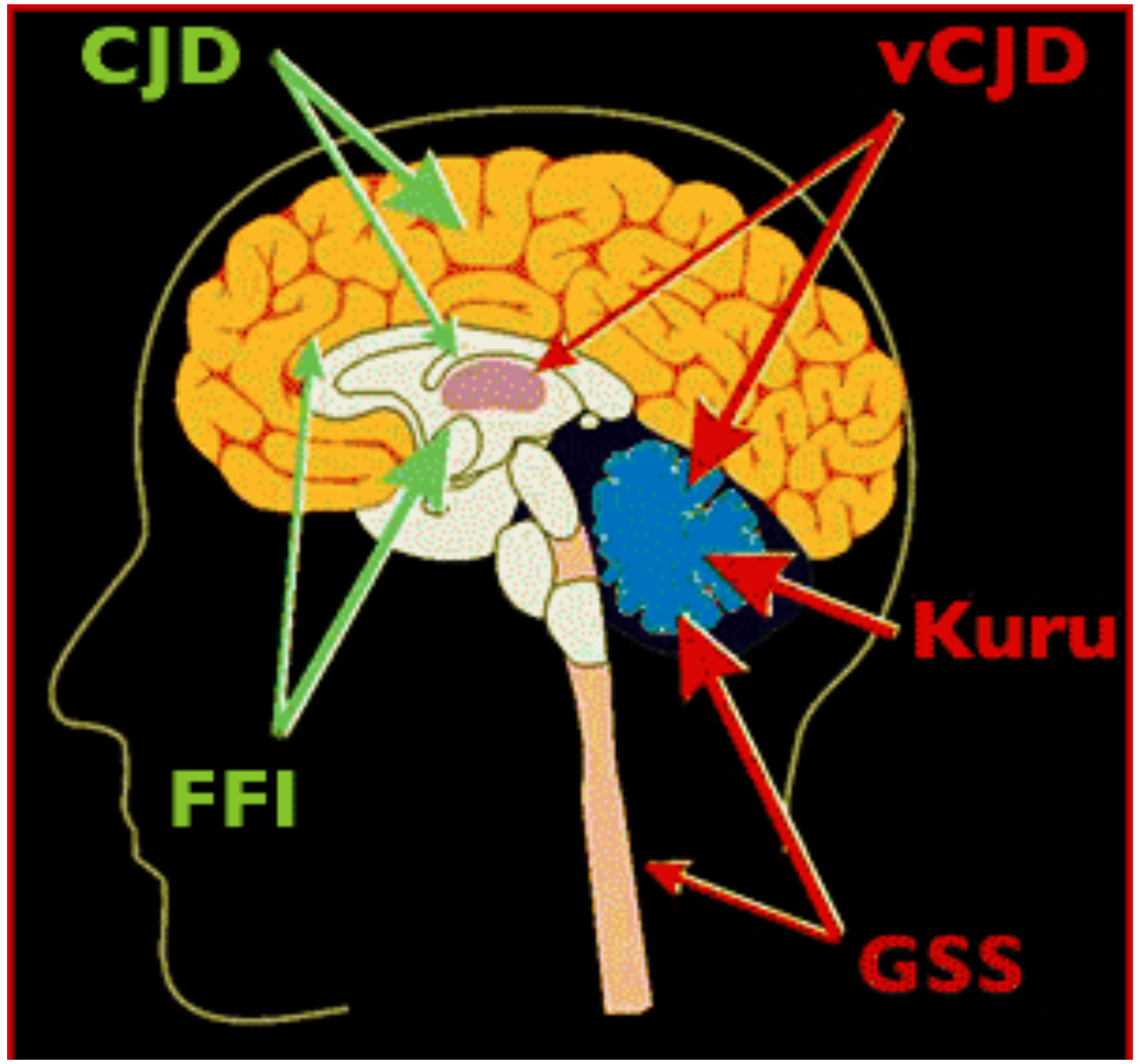
prion diseases

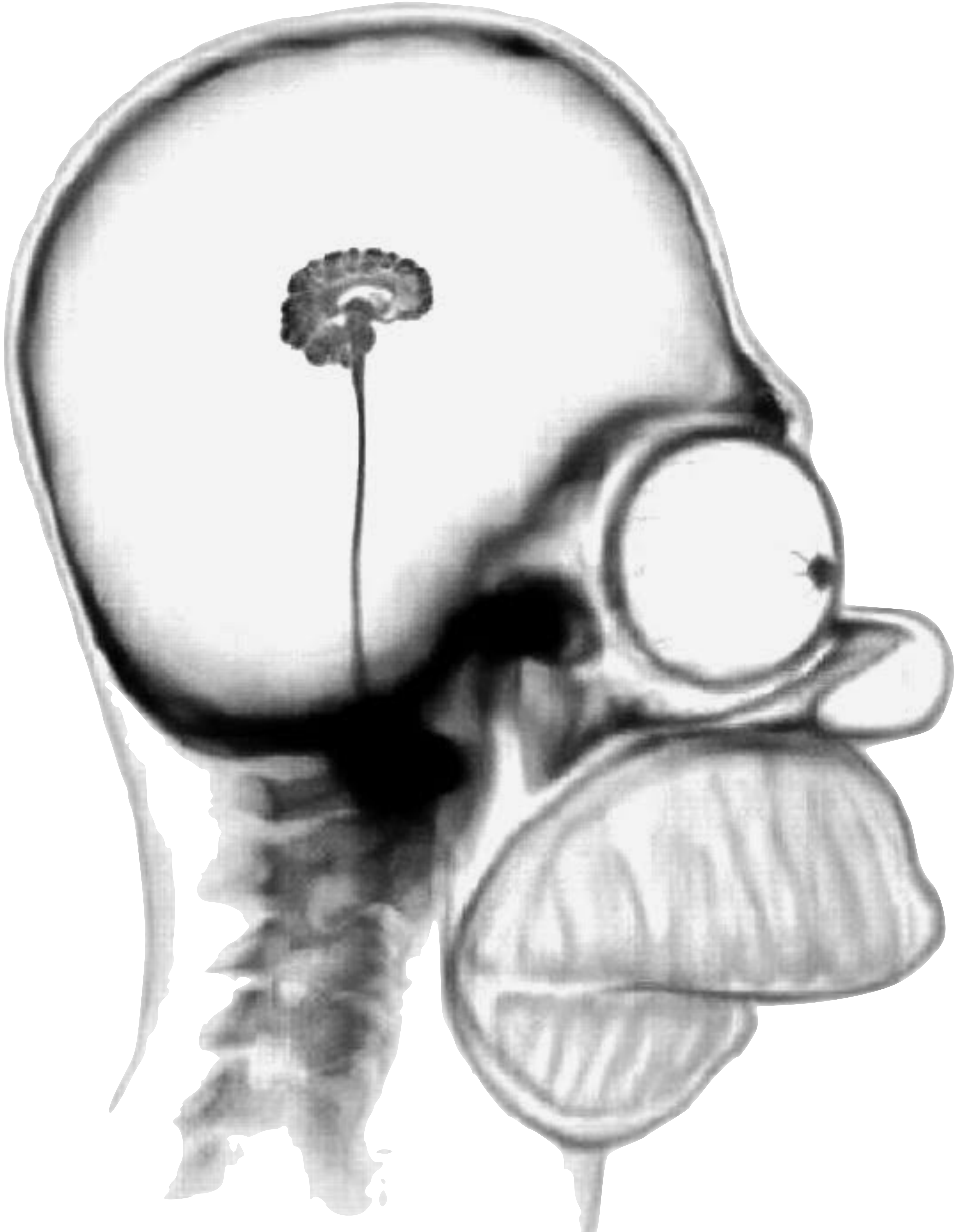




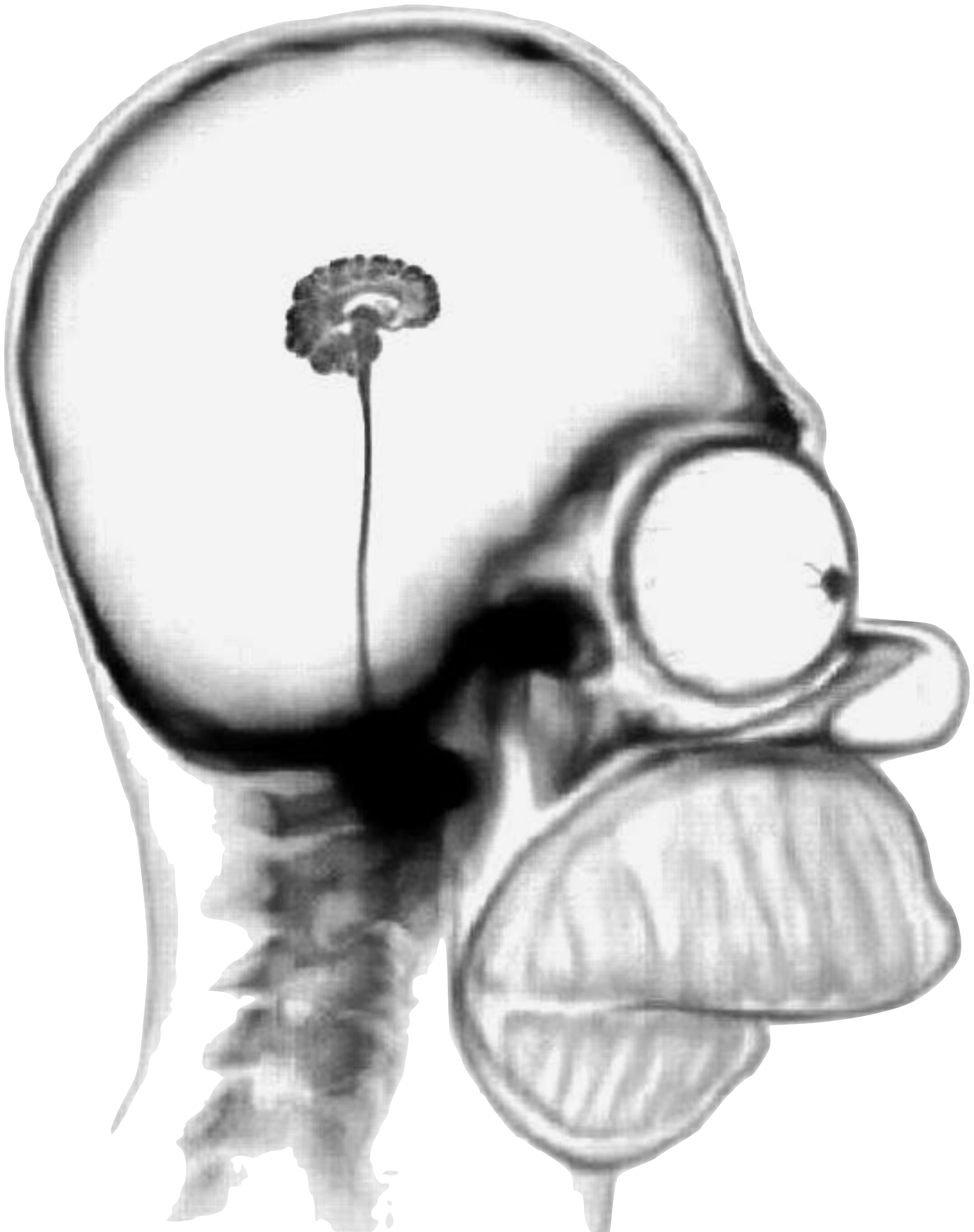




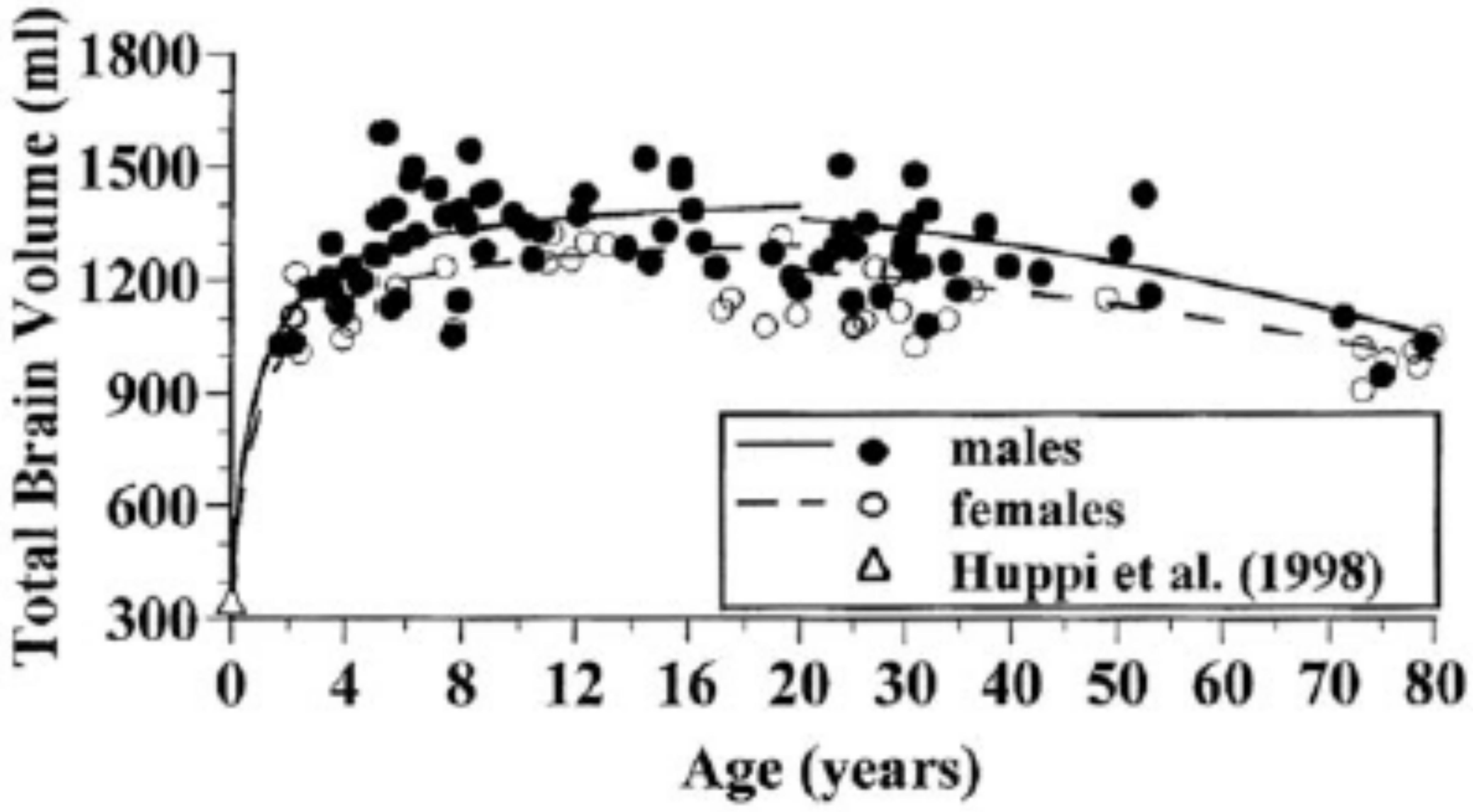




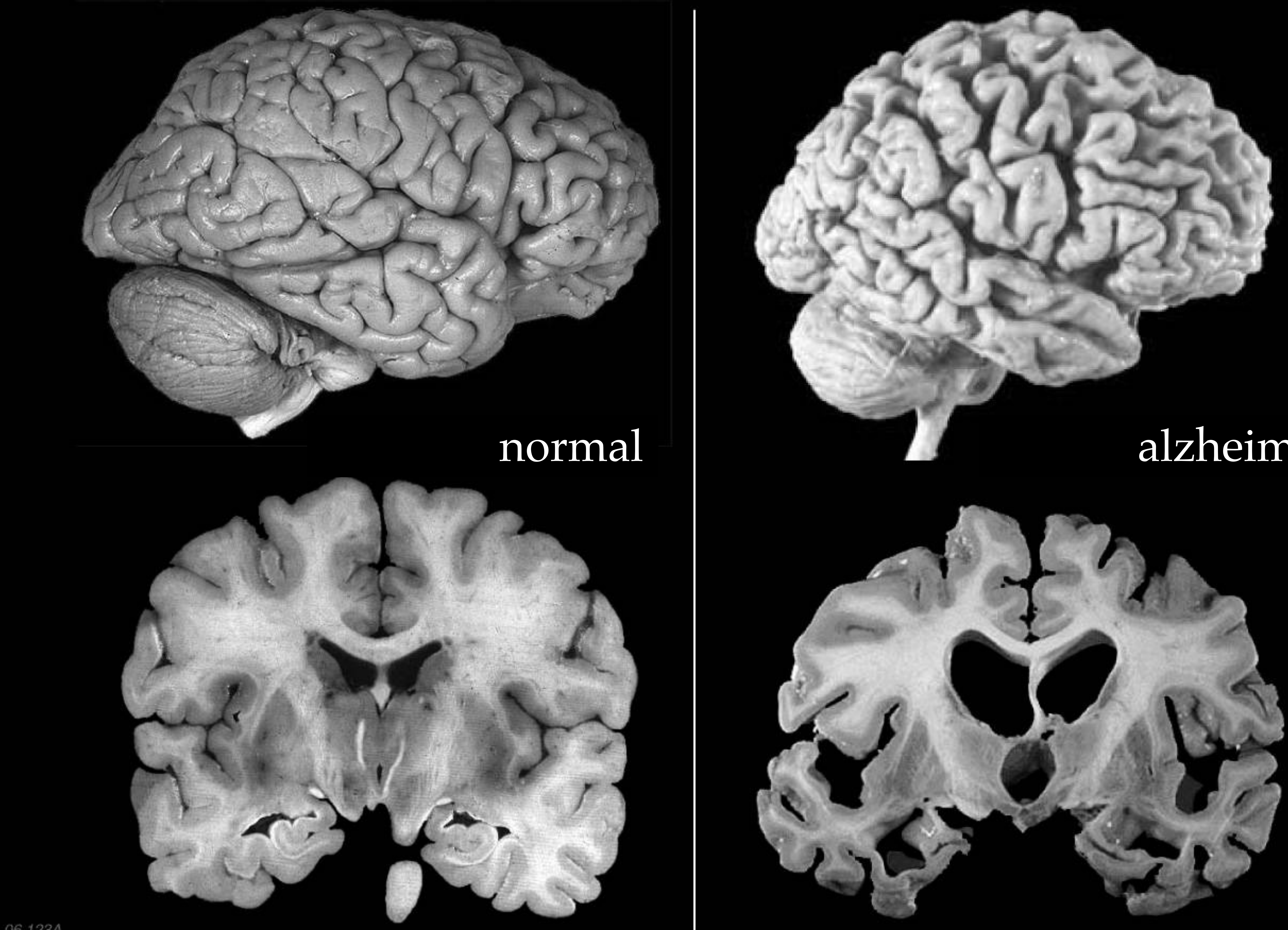
brain atrophy



brain atrophy



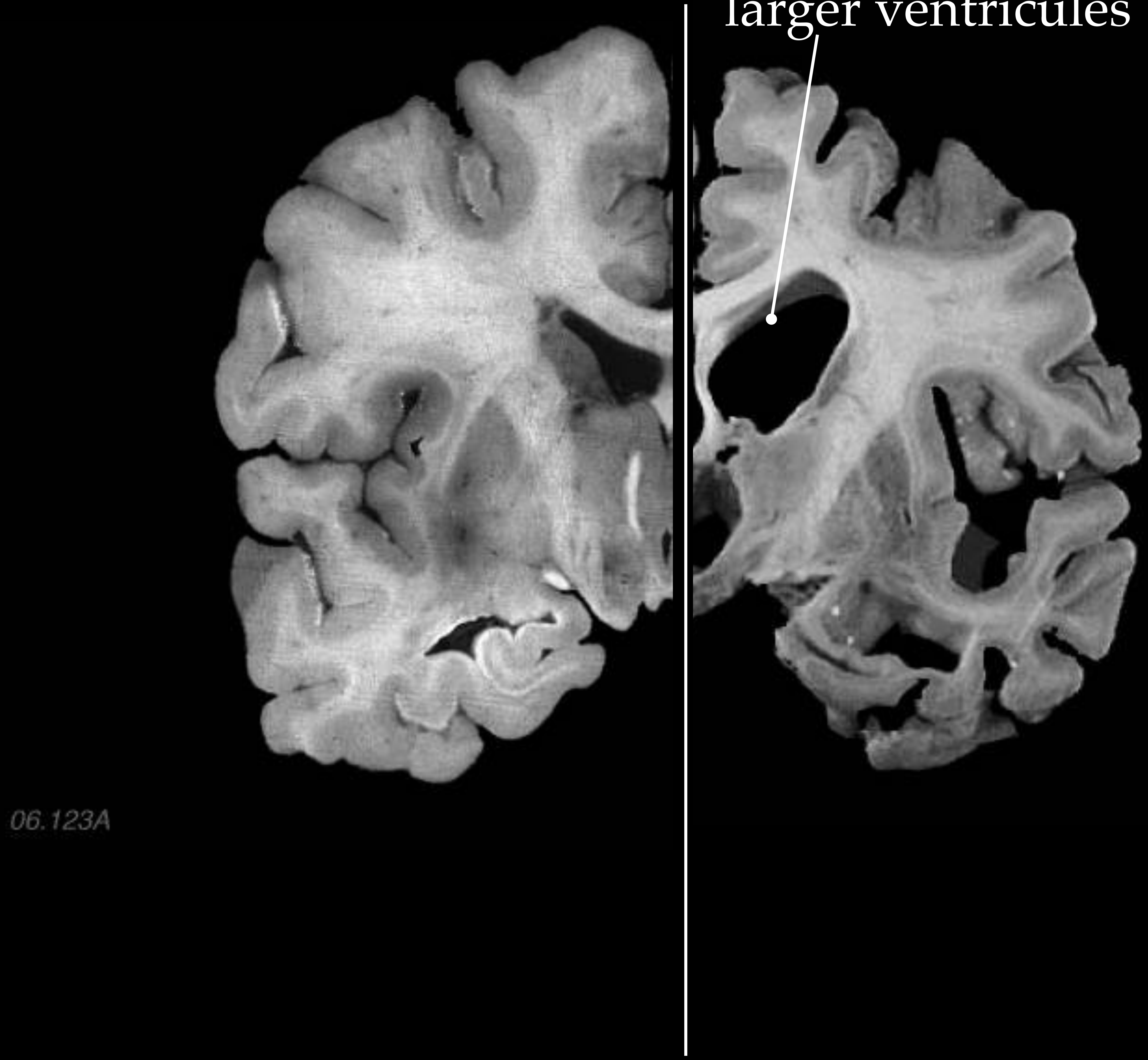
[courchesne et al. 2000]



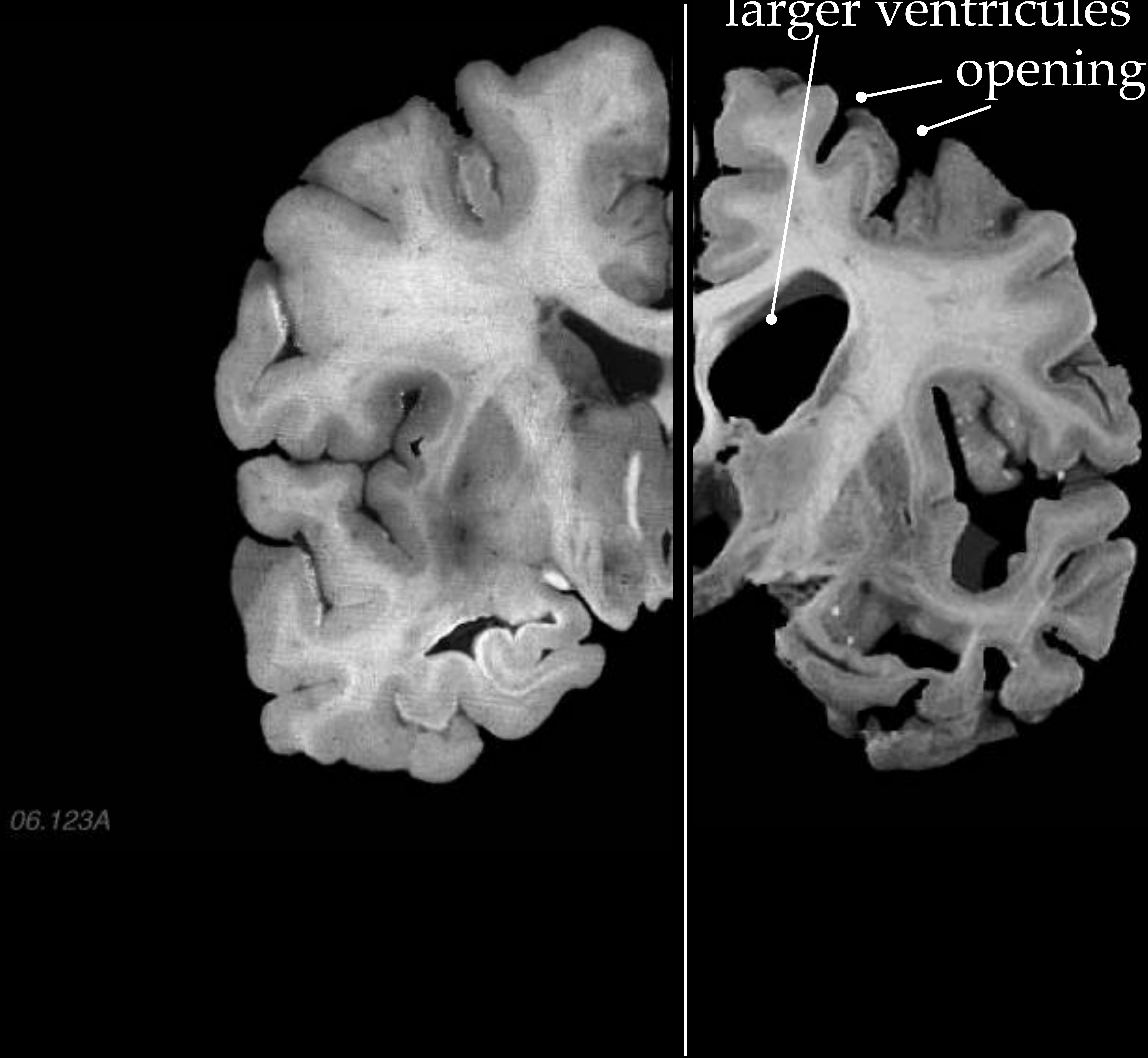
normal

alzheimer disease

06.123A

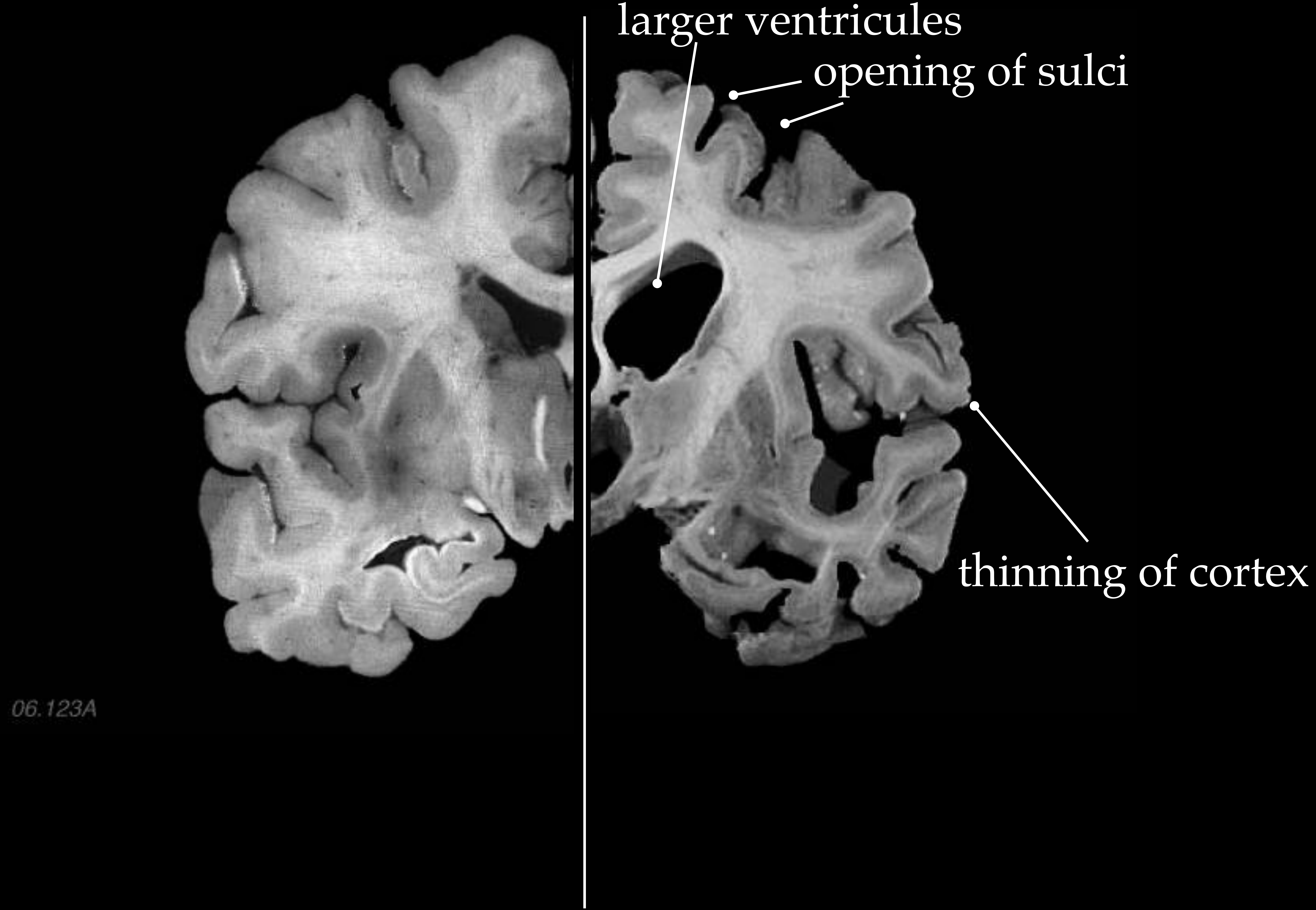


larger ventricules

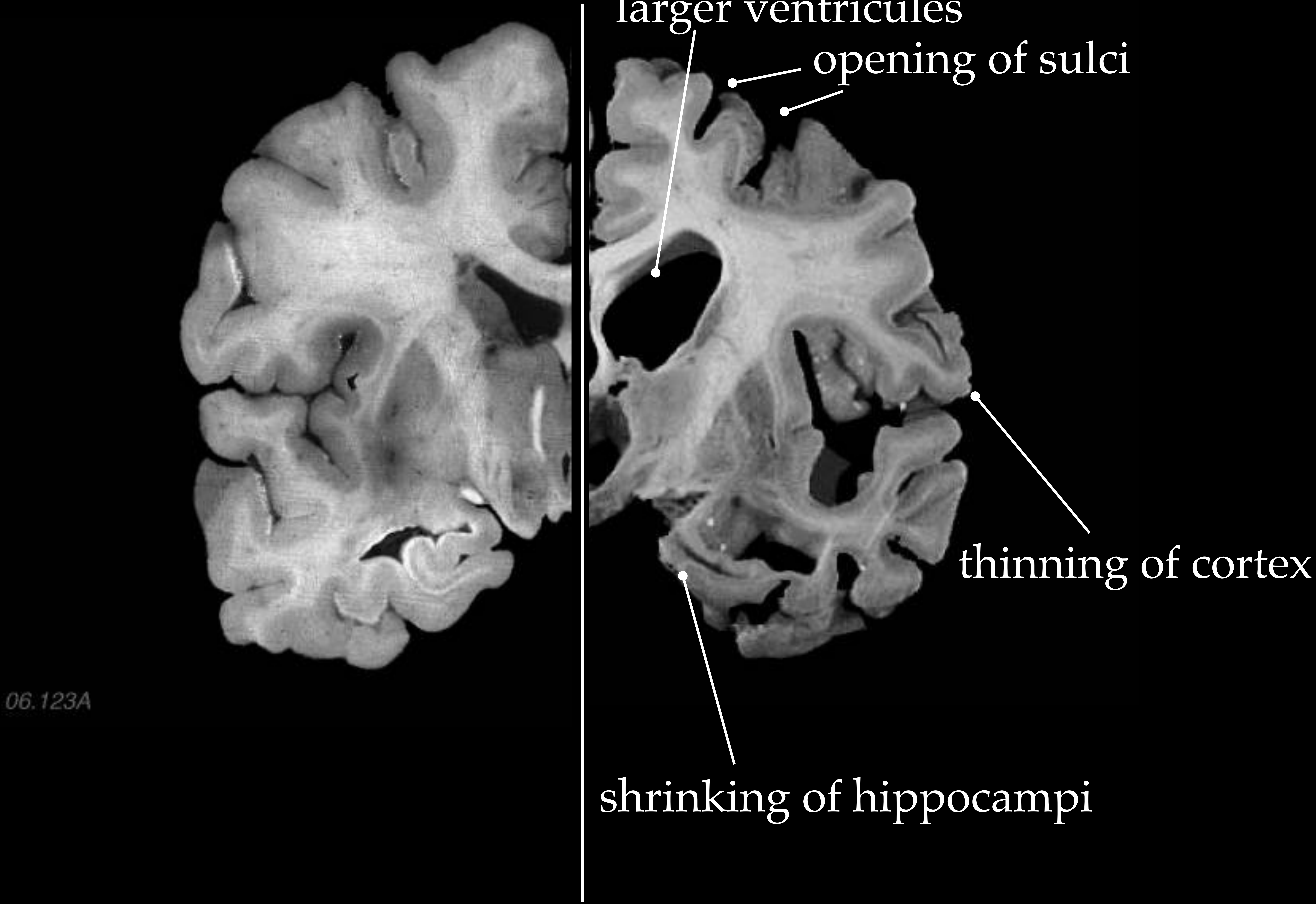


larger ventricules

opening of sulci



larger ventricules
opening of sulci
thinning of cortex
06.123A



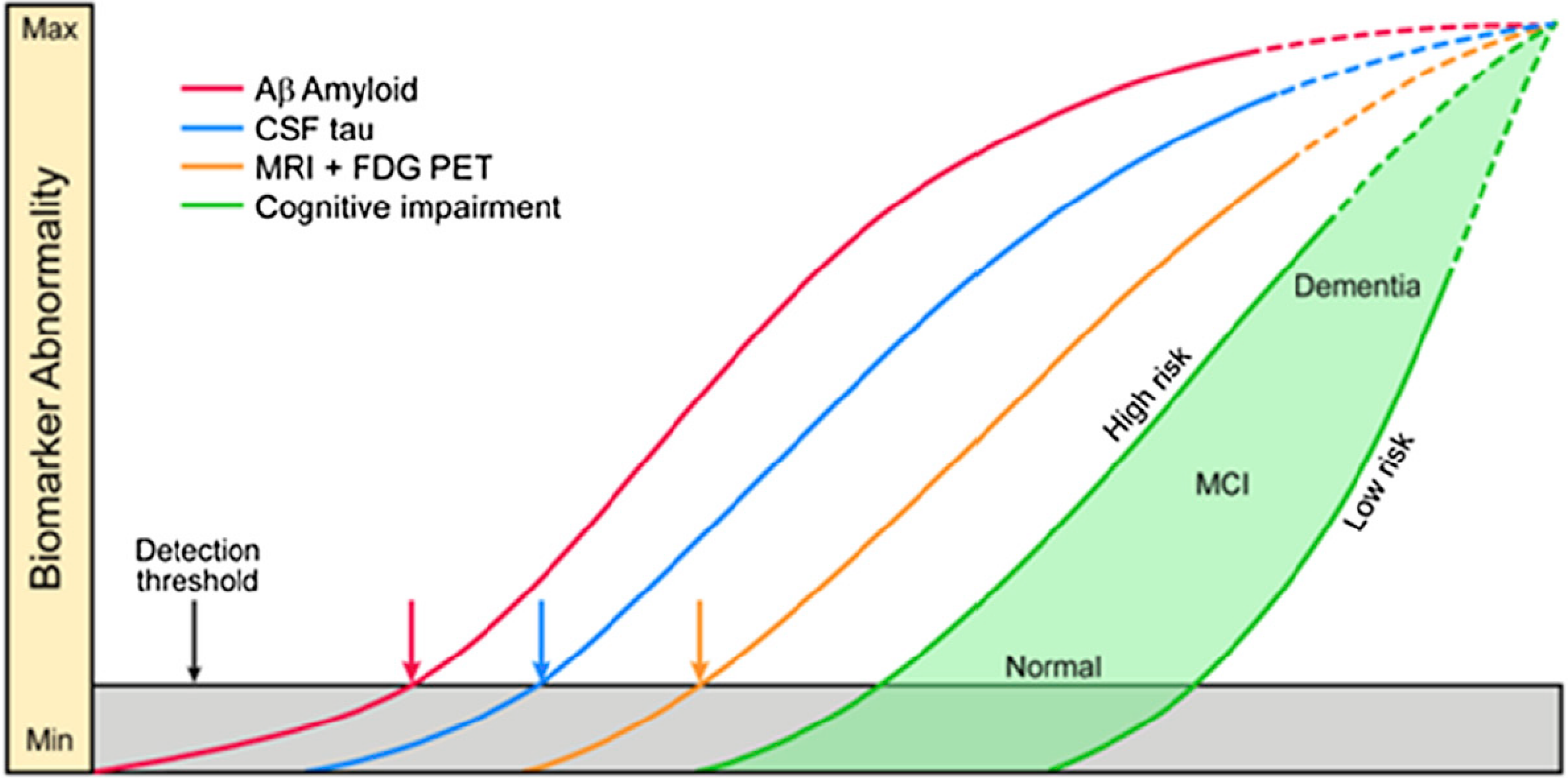
larger ventricules

opening of sulci

thinning of cortex

shrinking of hippocampi

jack's curves (2013)



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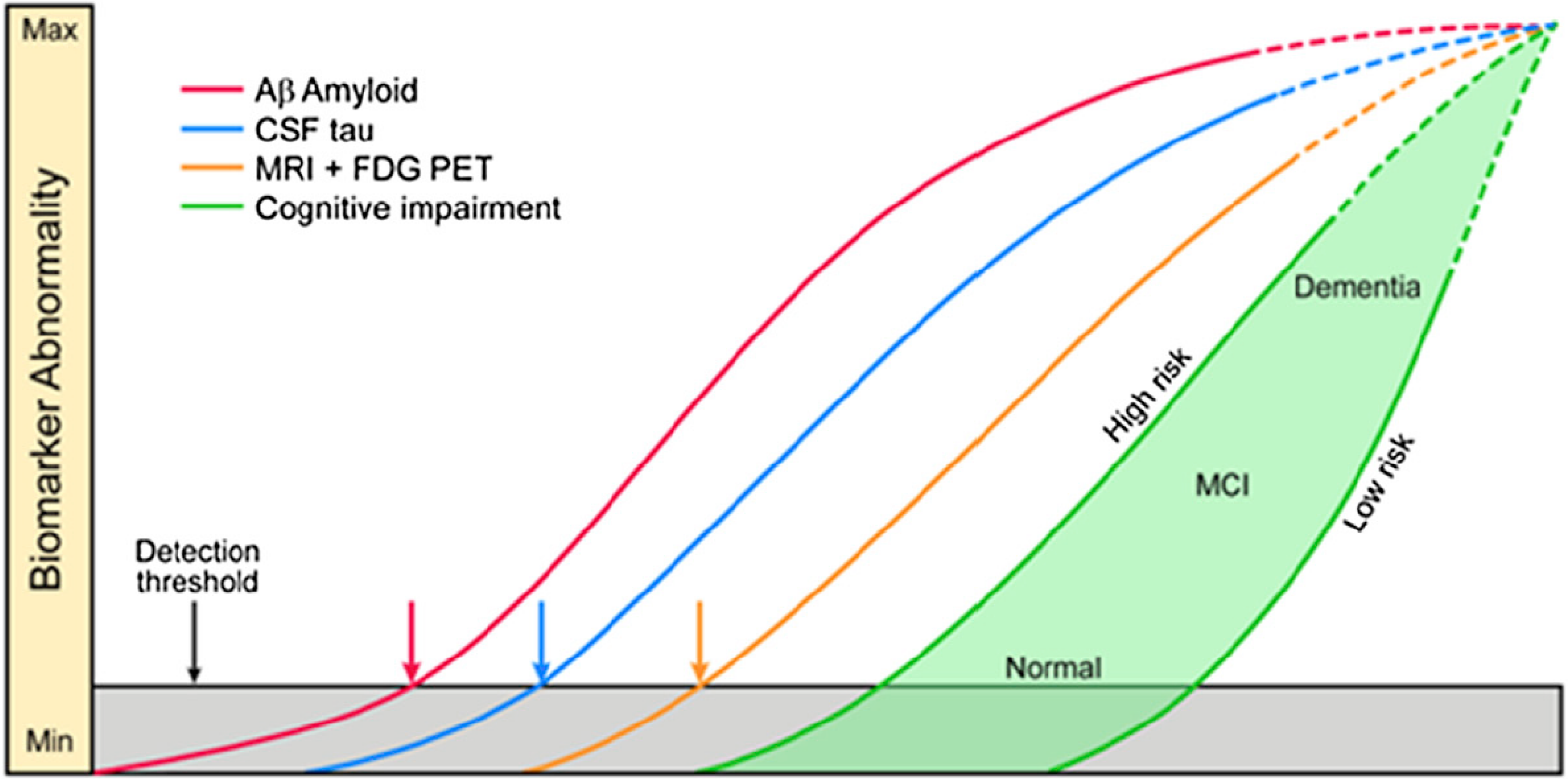

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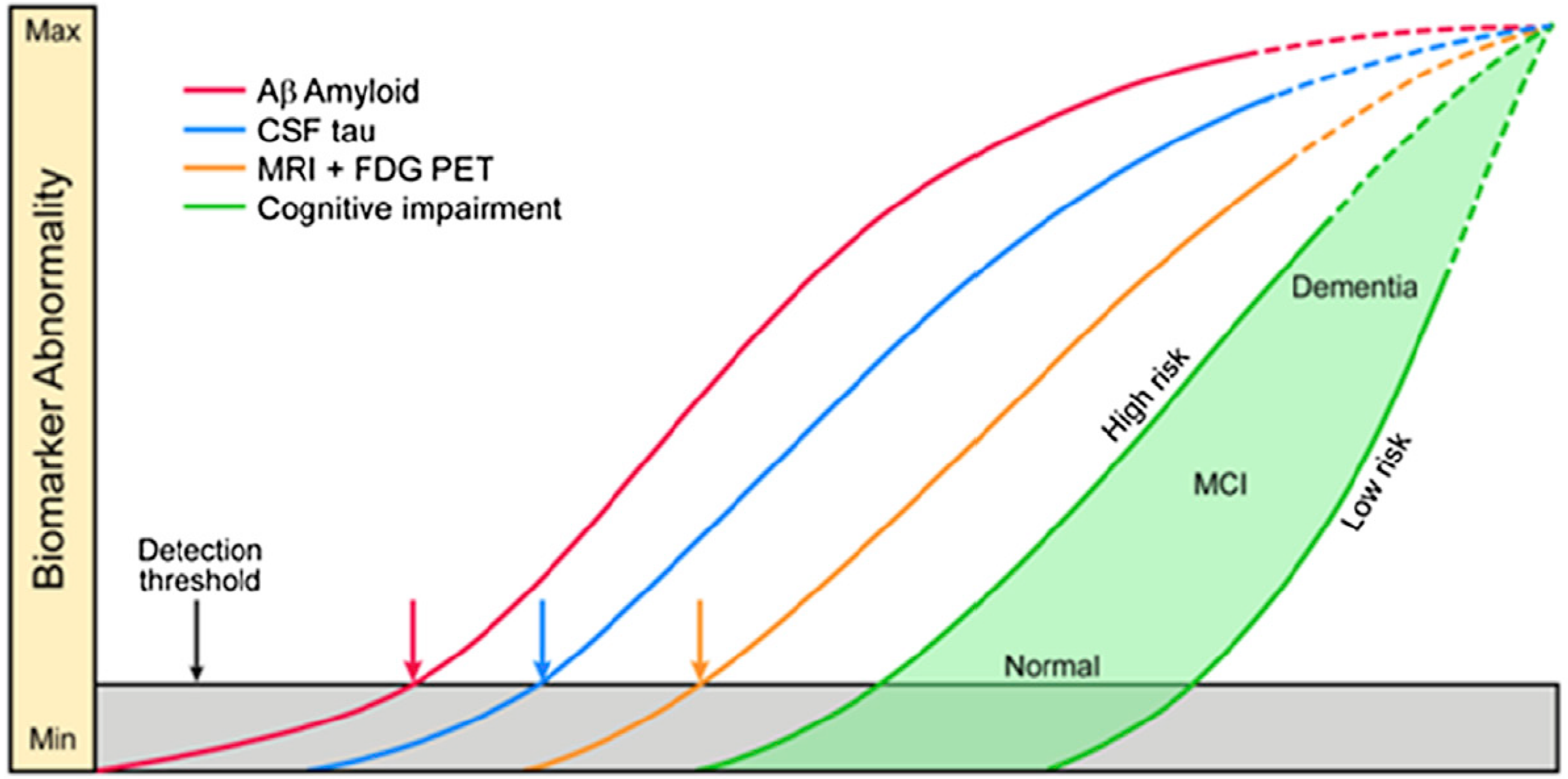

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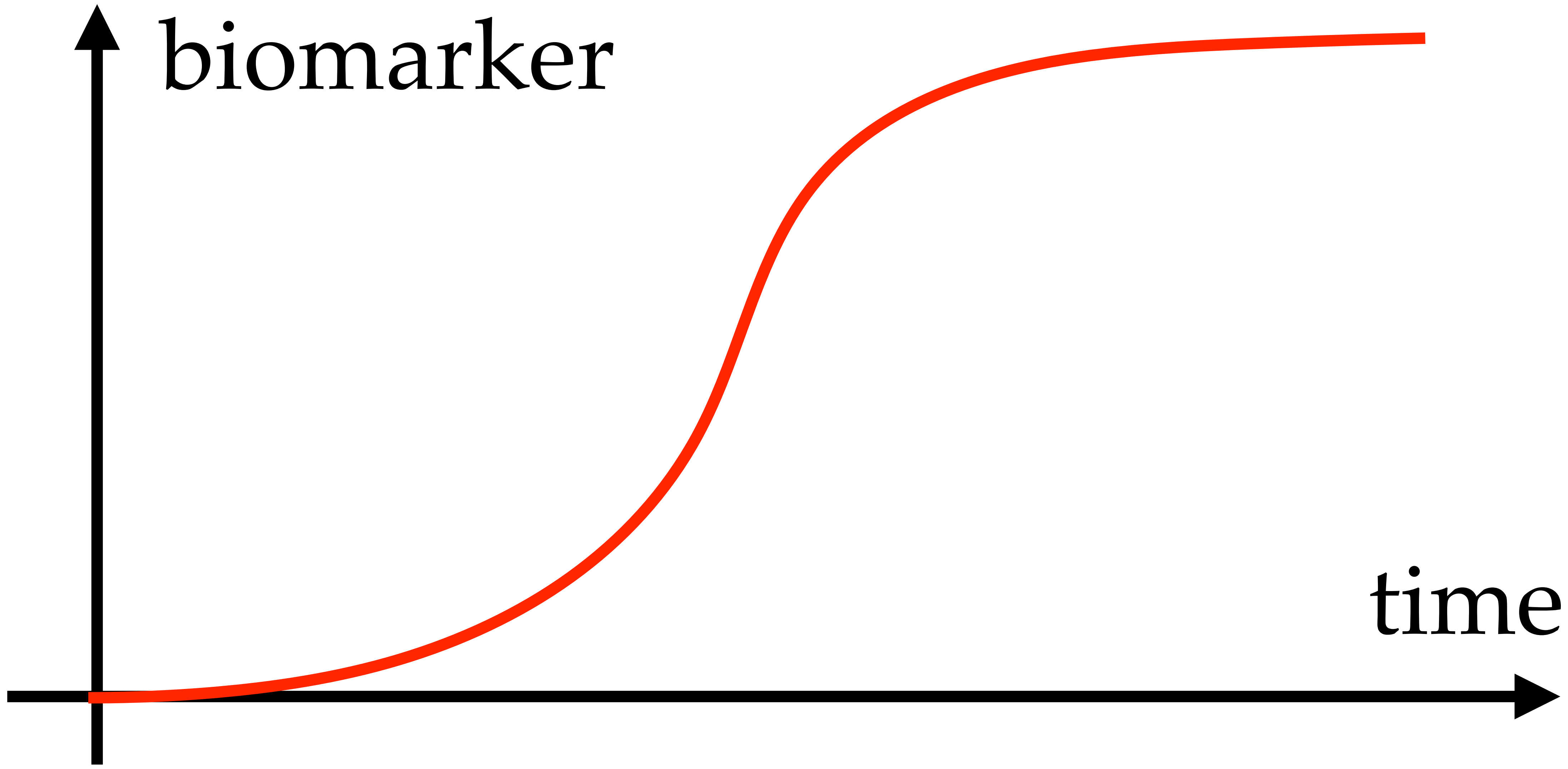

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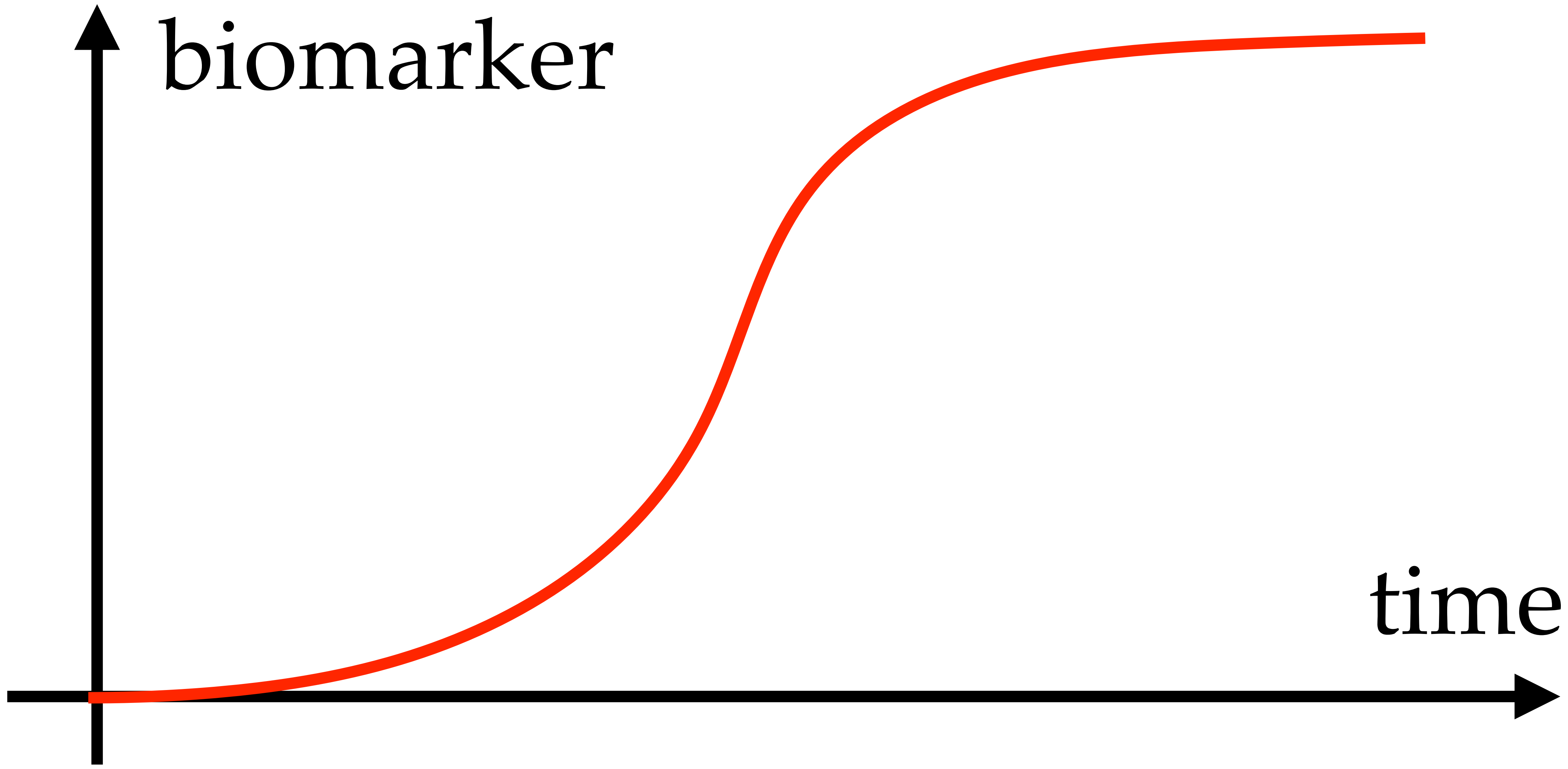

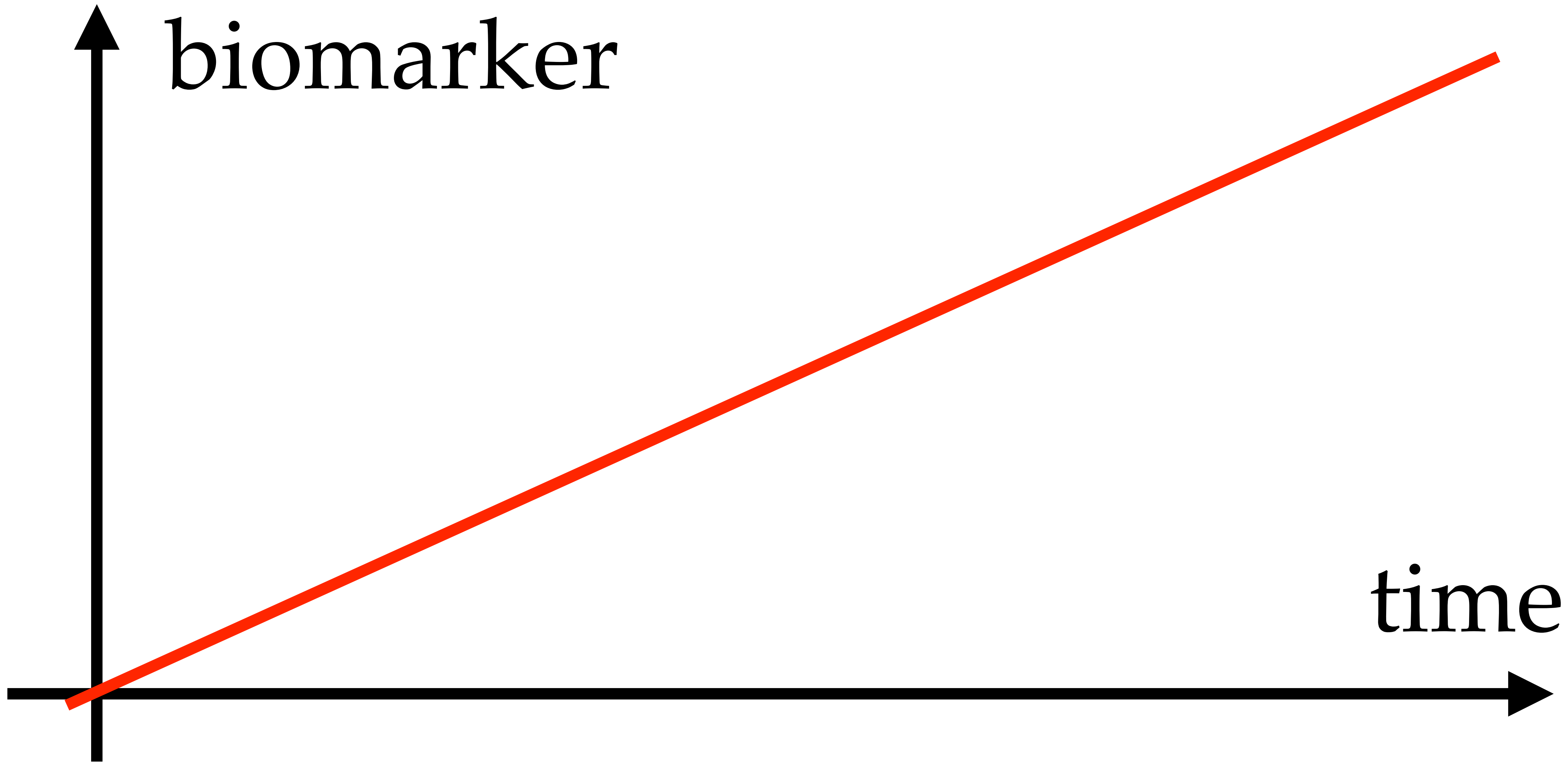

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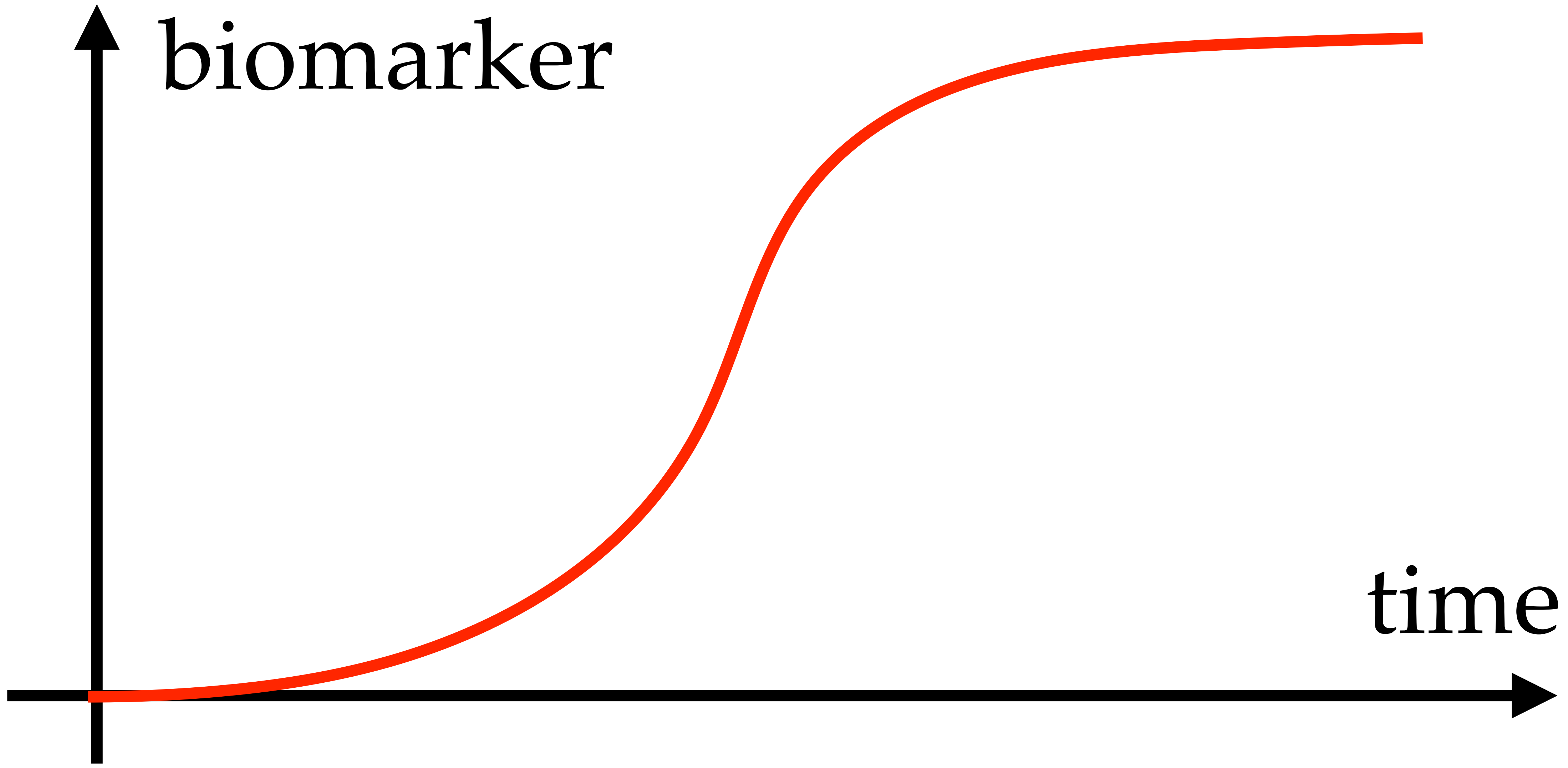

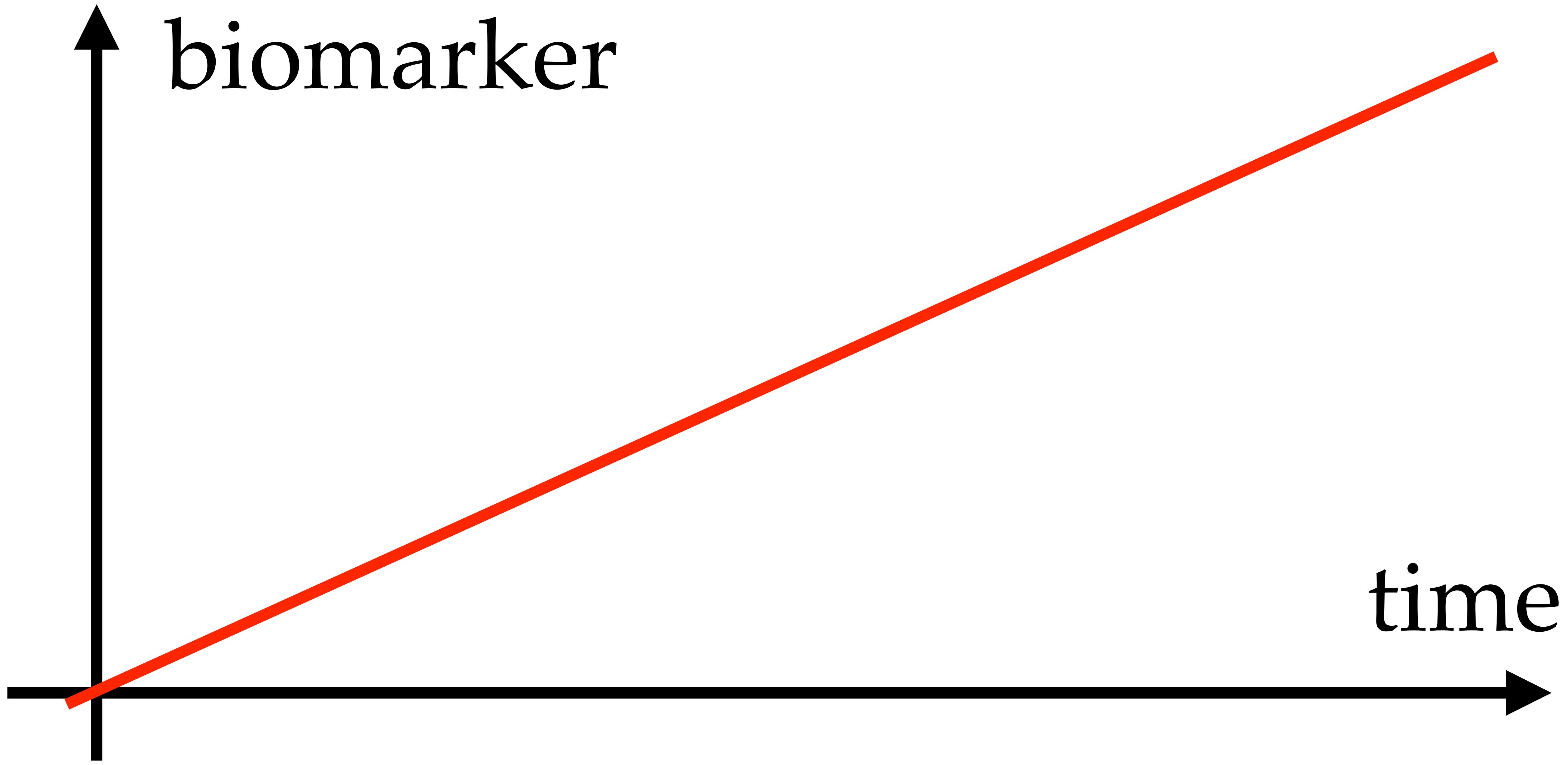

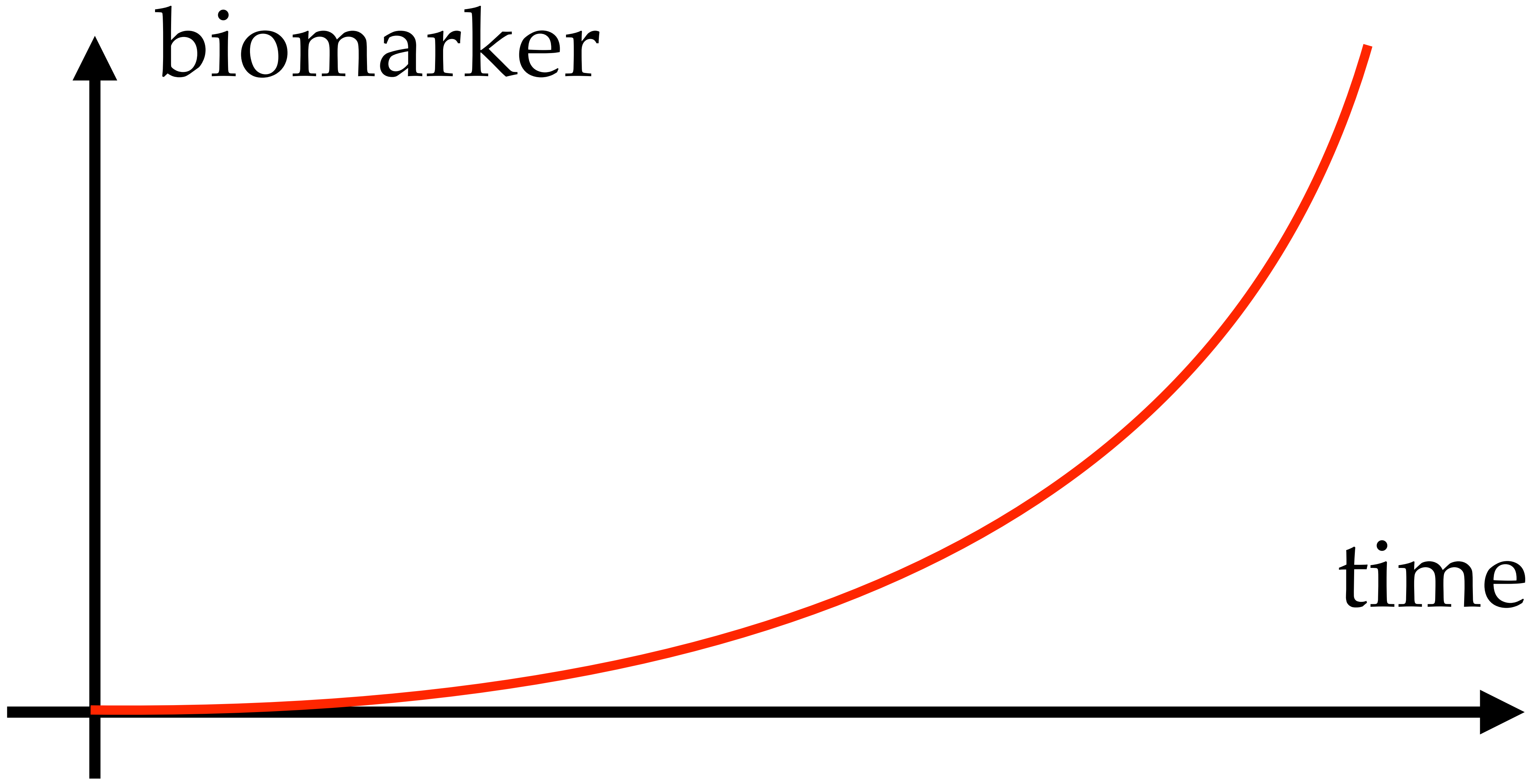

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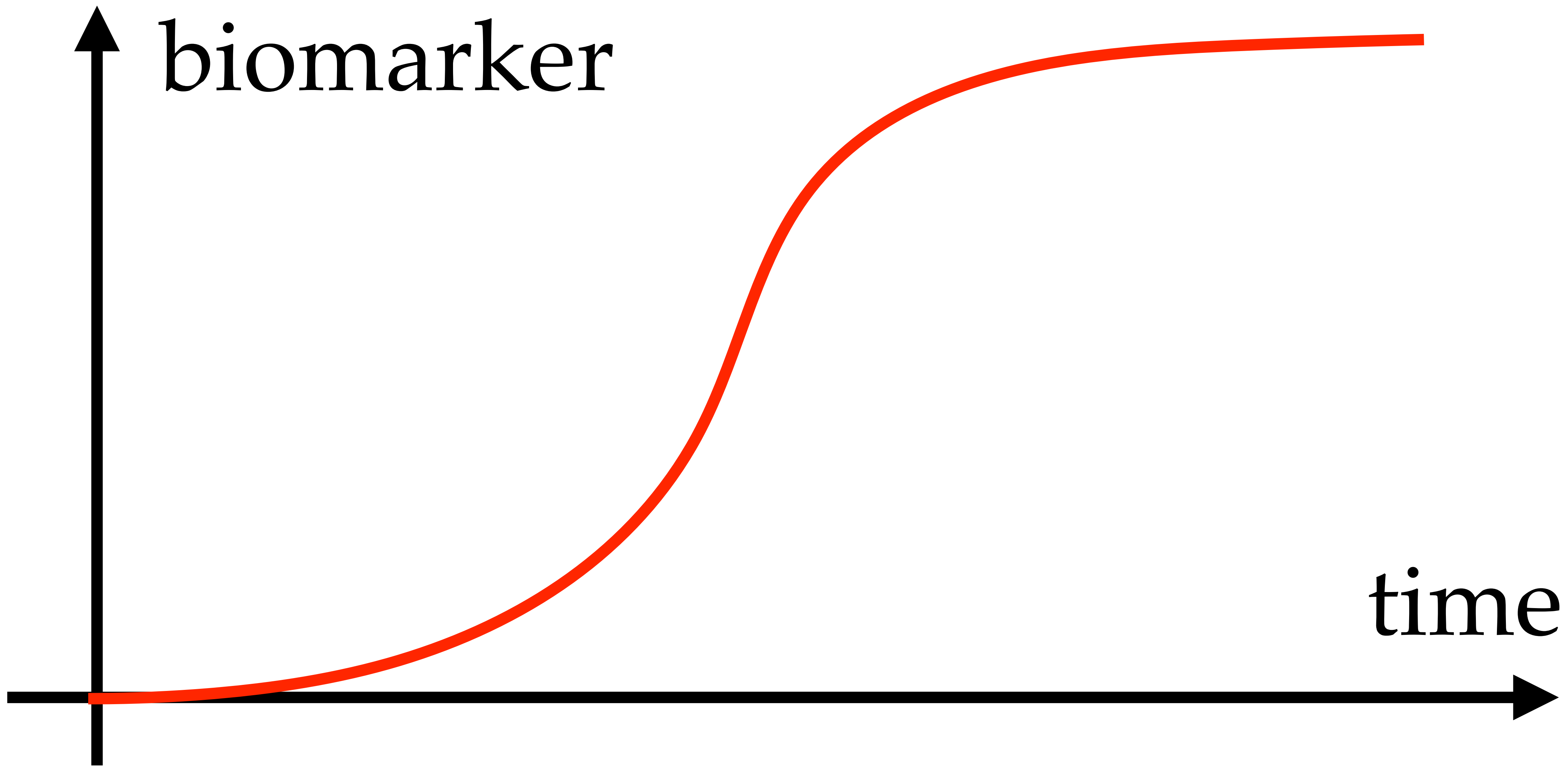

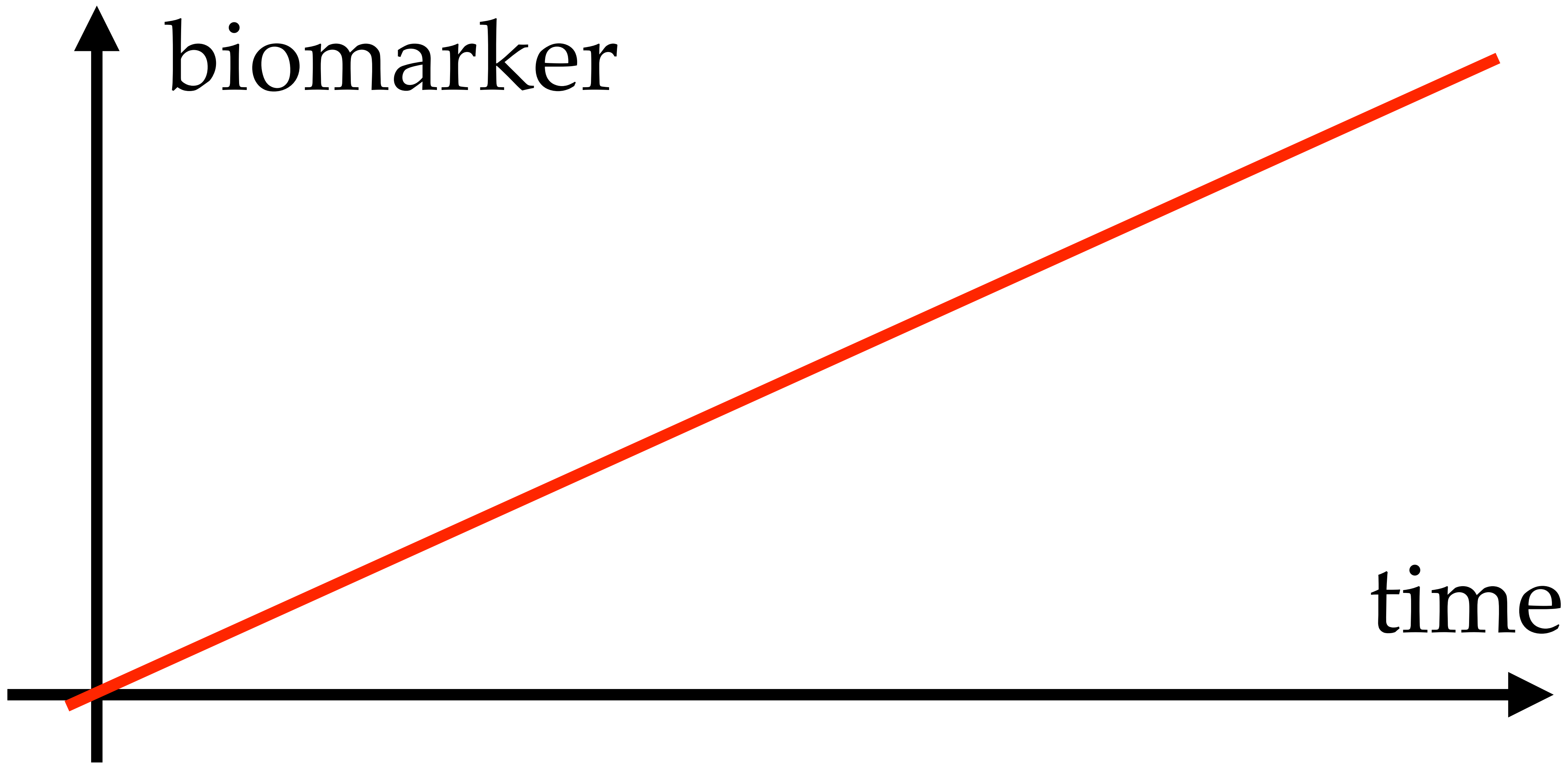

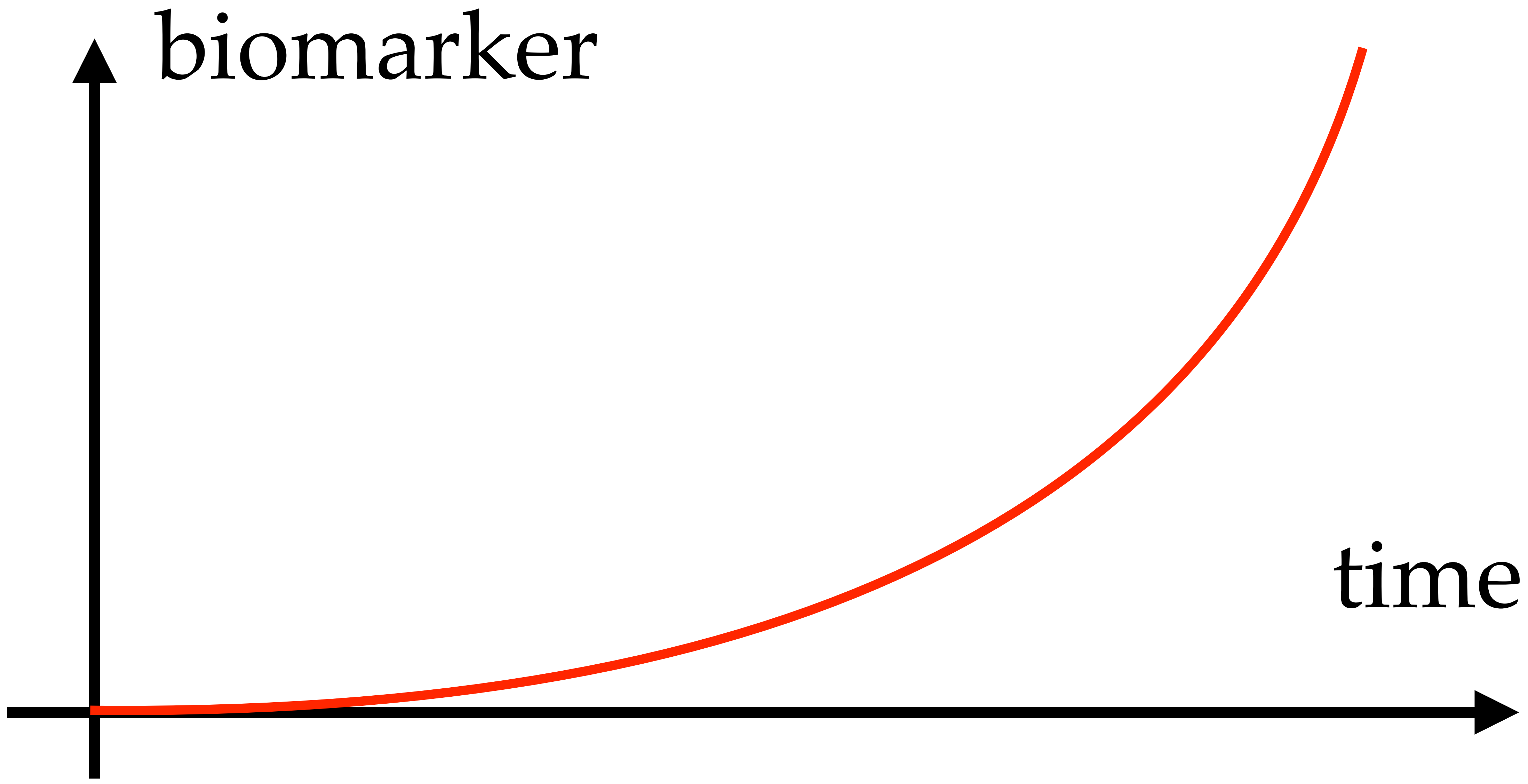

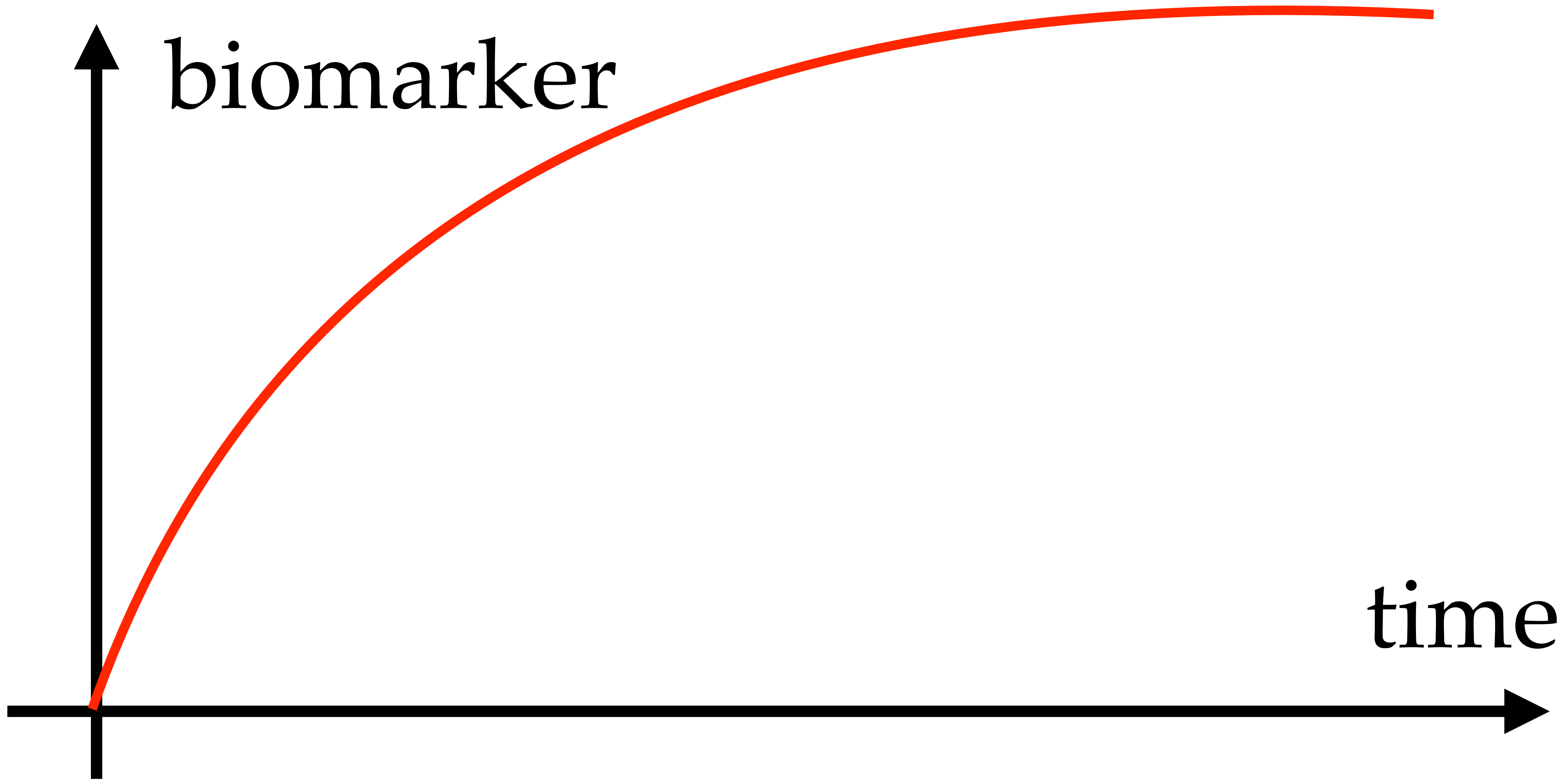

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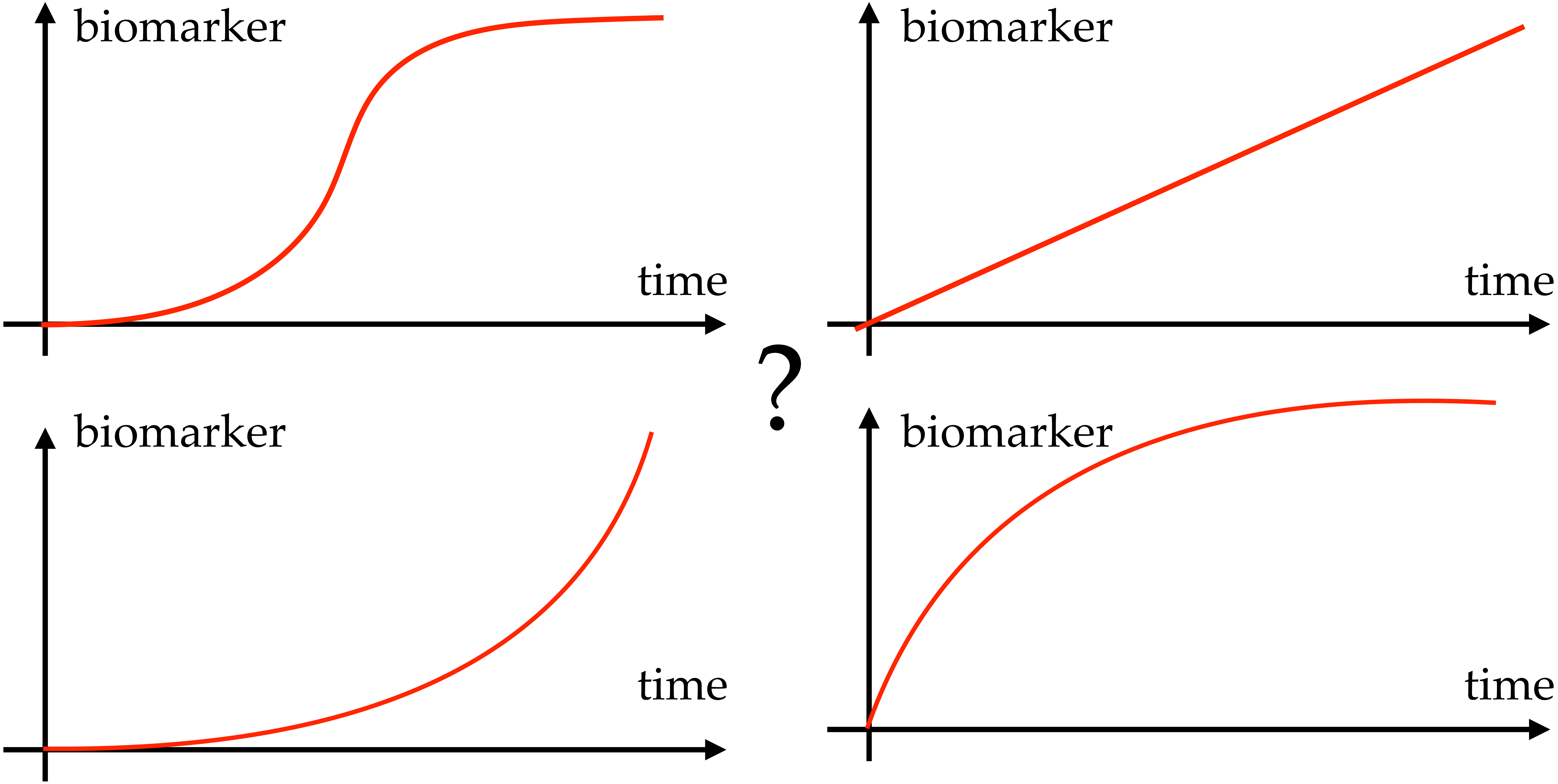
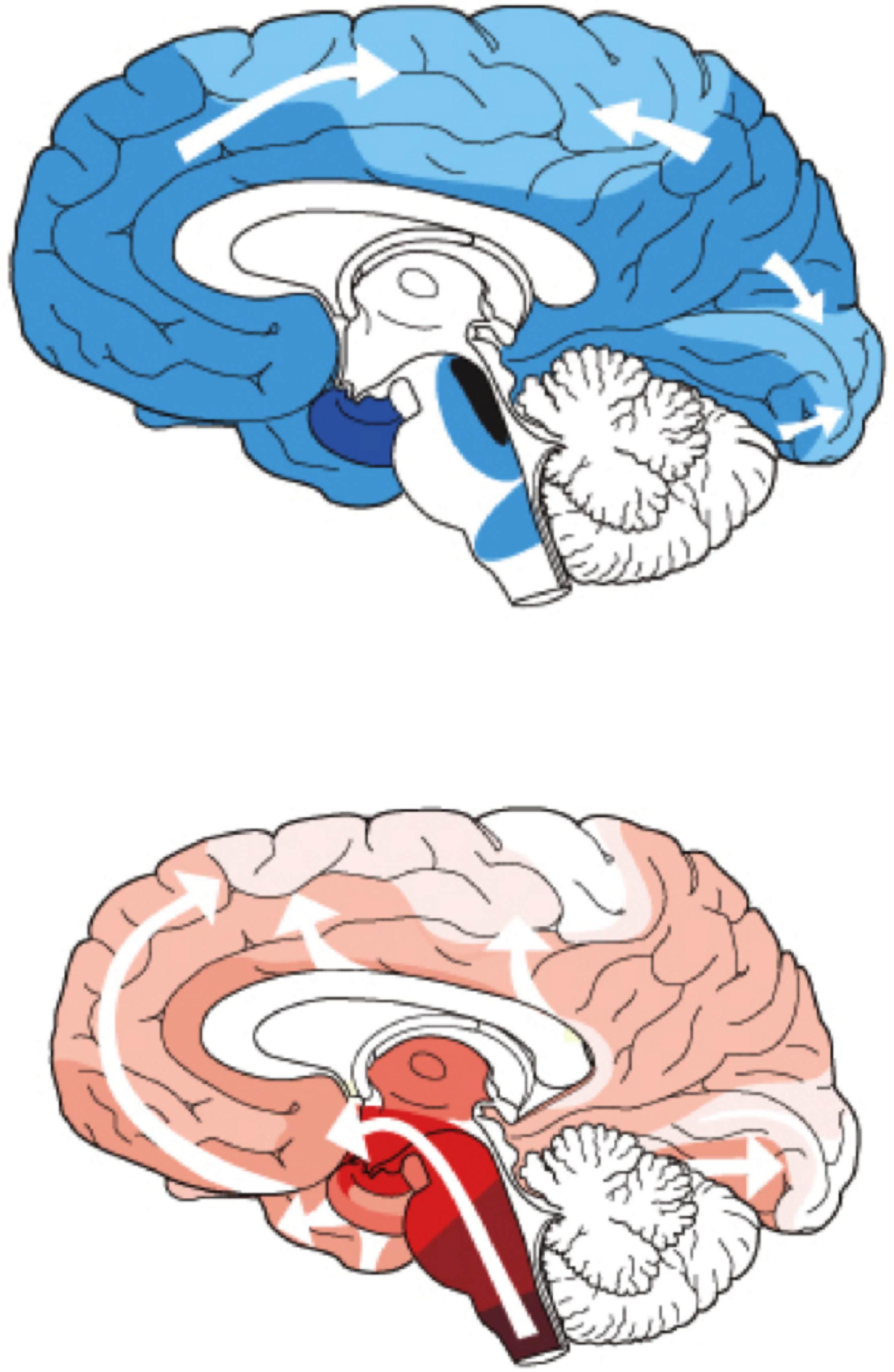


challenges for a model

🧠 spatial progression

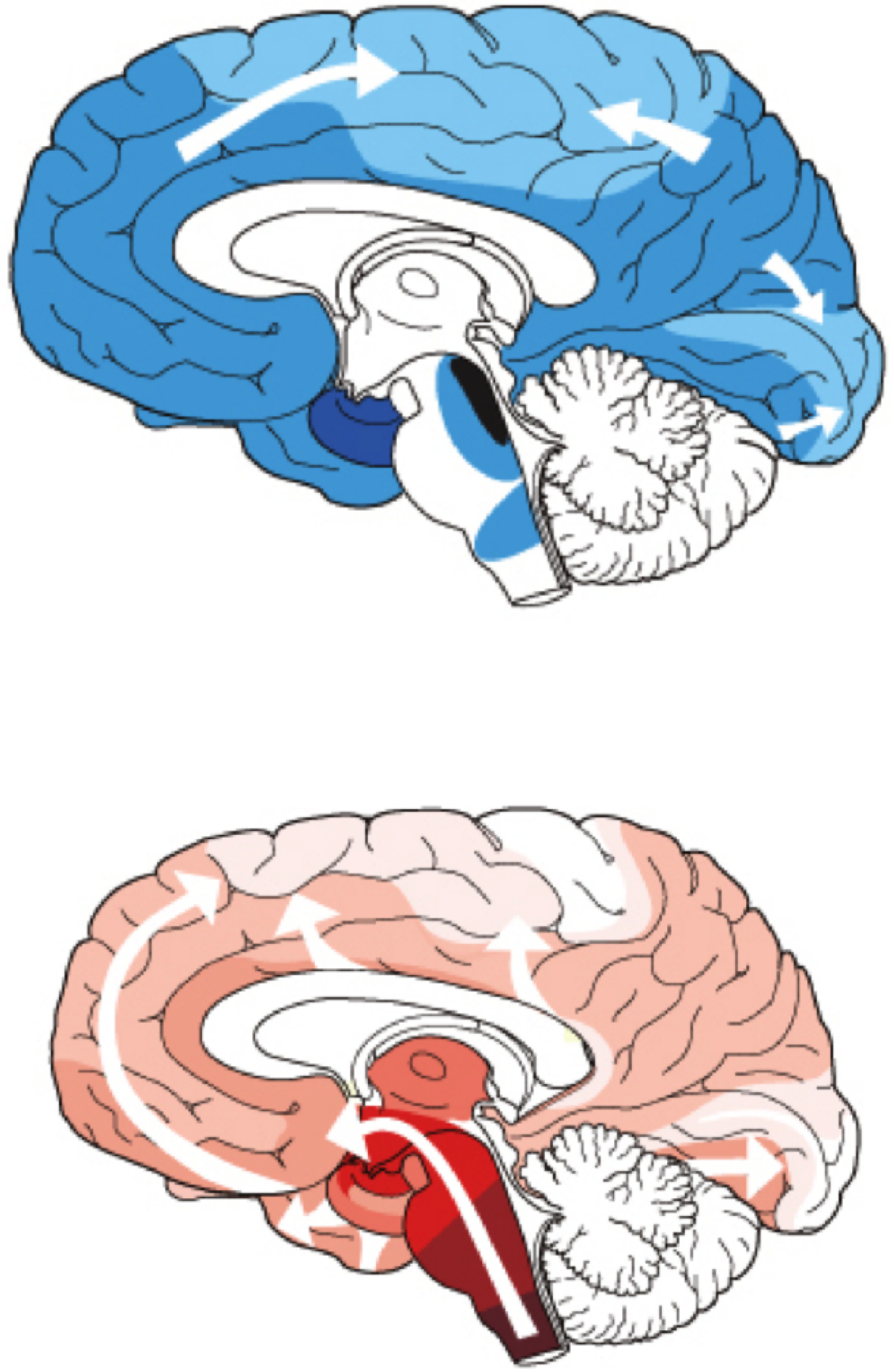
challenges for a model

- spatial progression

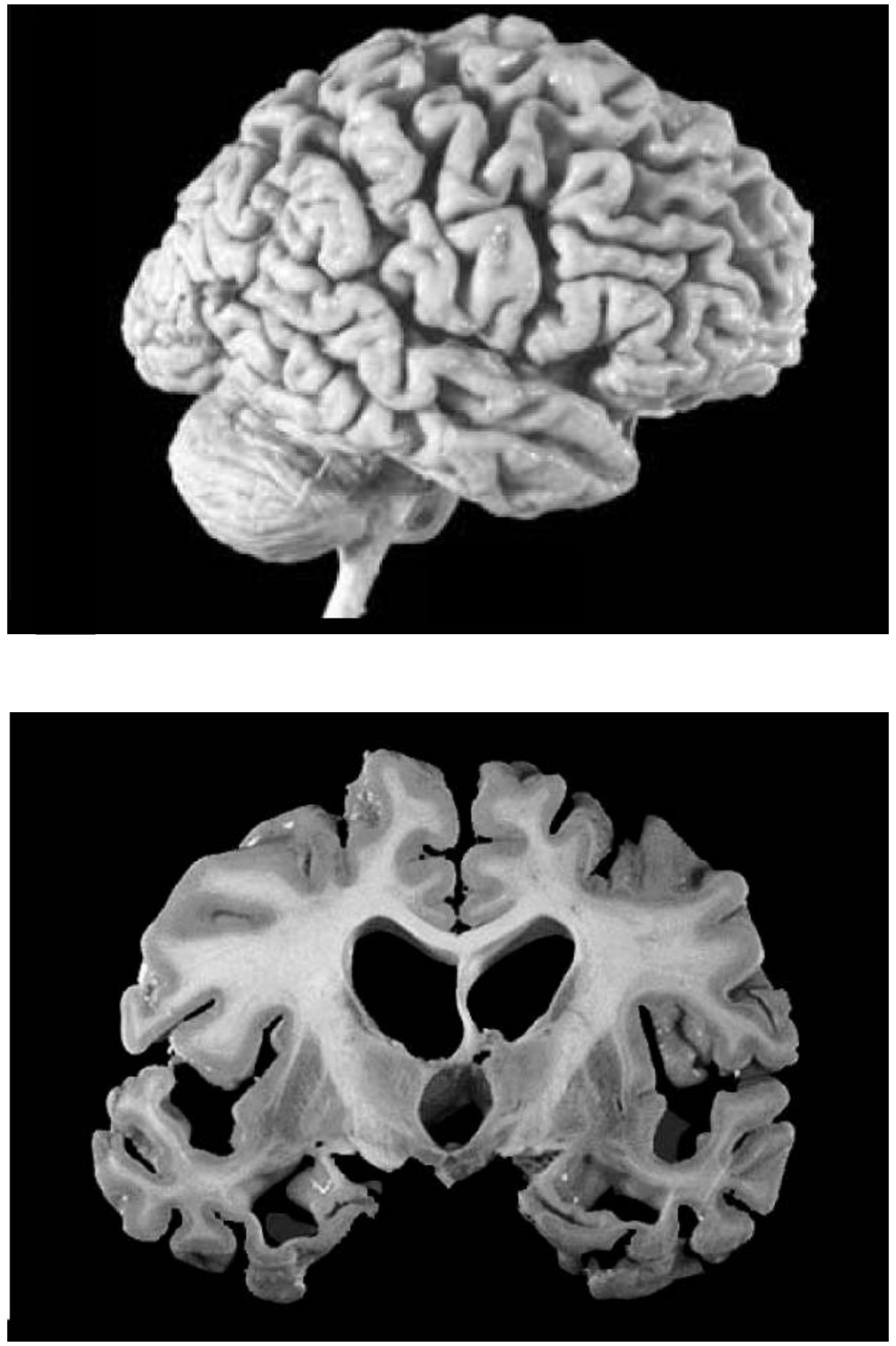


challenges for a model

- spatial progression

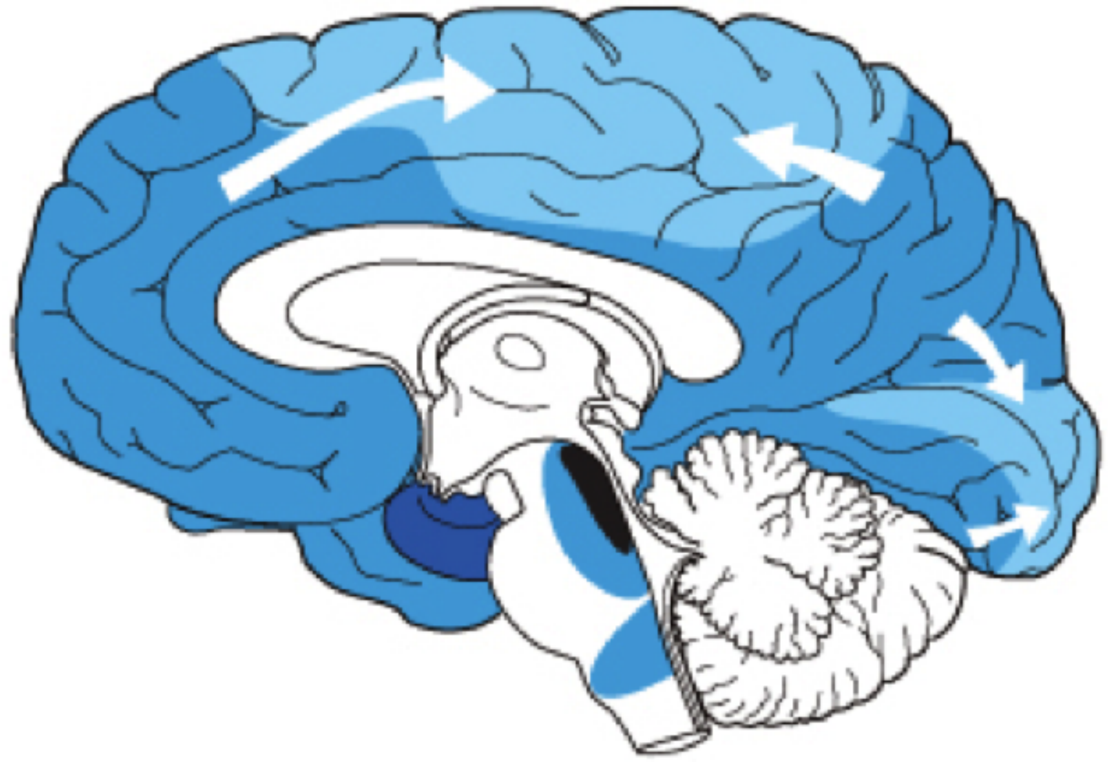


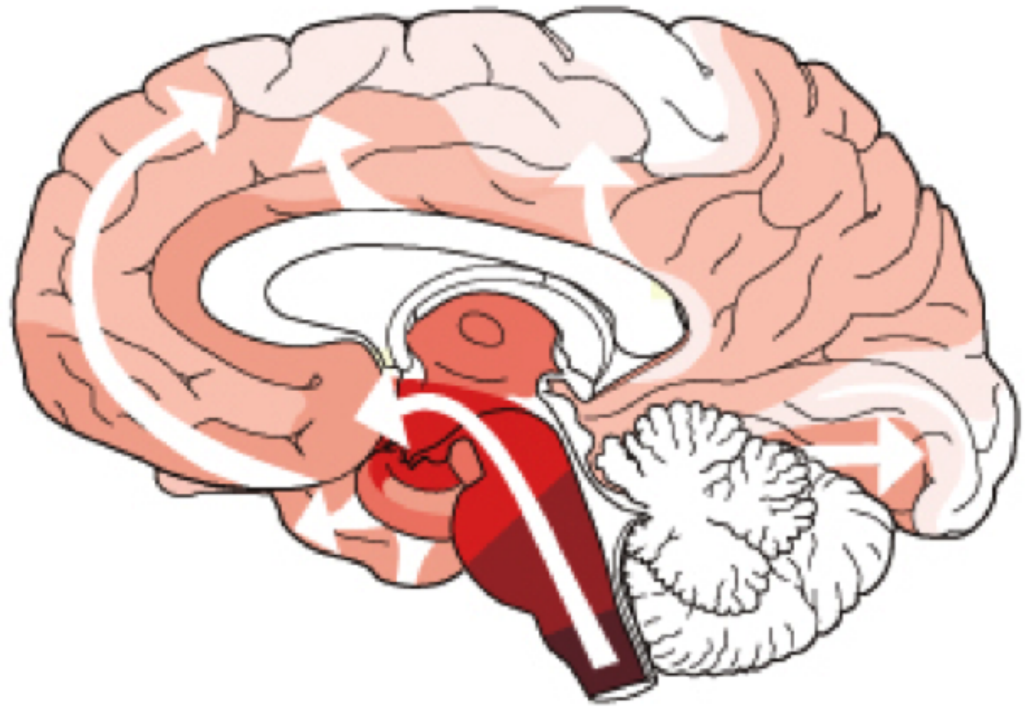
- atrophy pattern



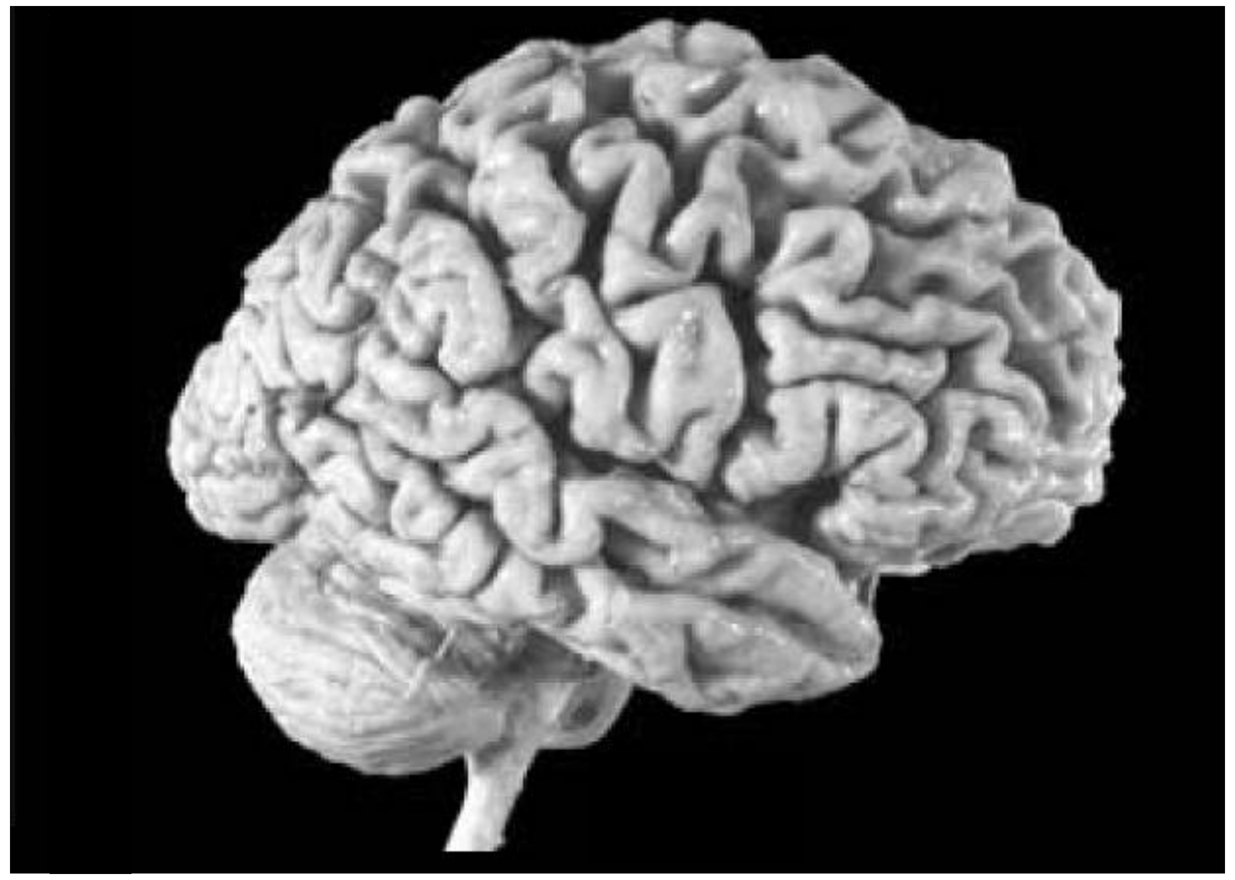
challenges for a model

spatial progression

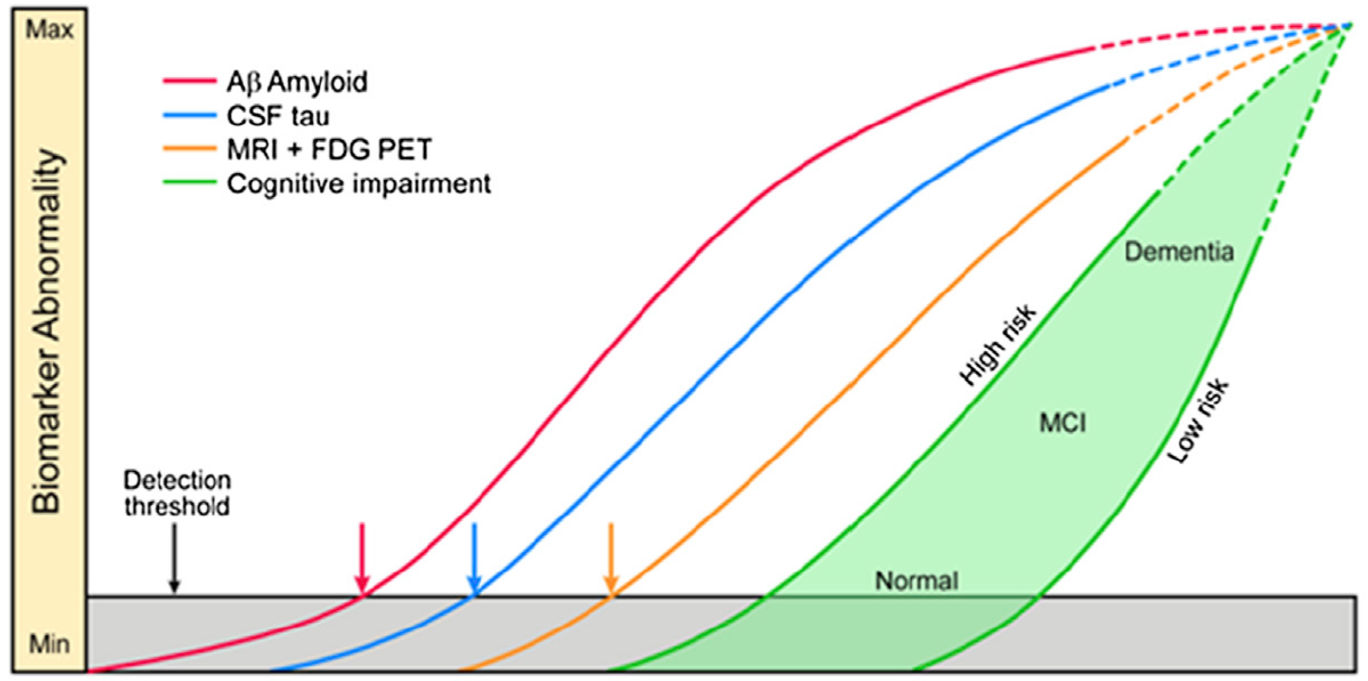




atrophy pattern

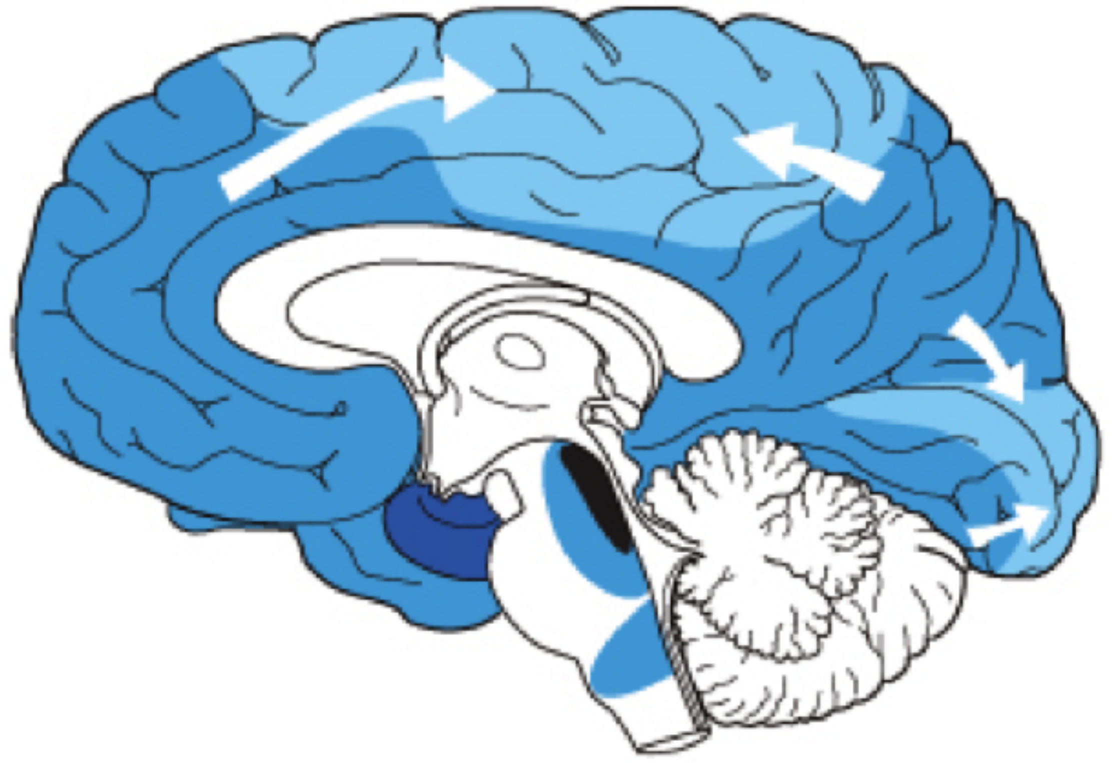


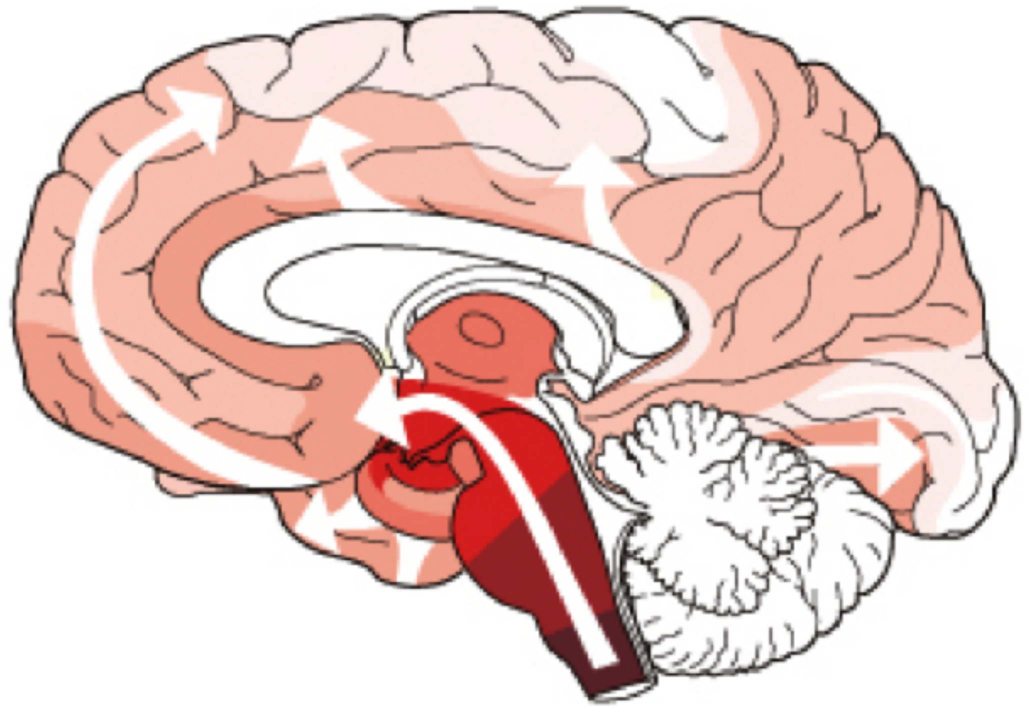
biomarker evolution



challenges for a model

spatial progression





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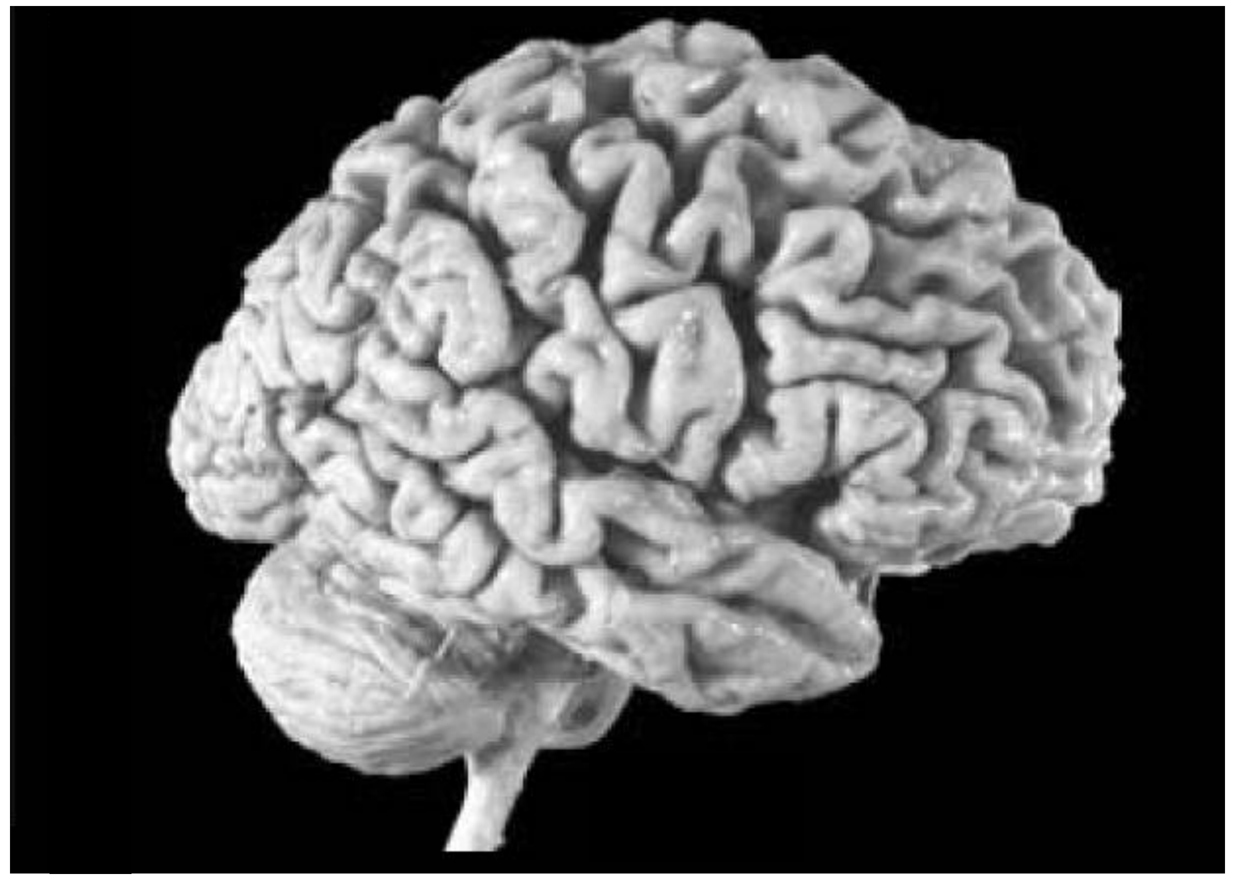
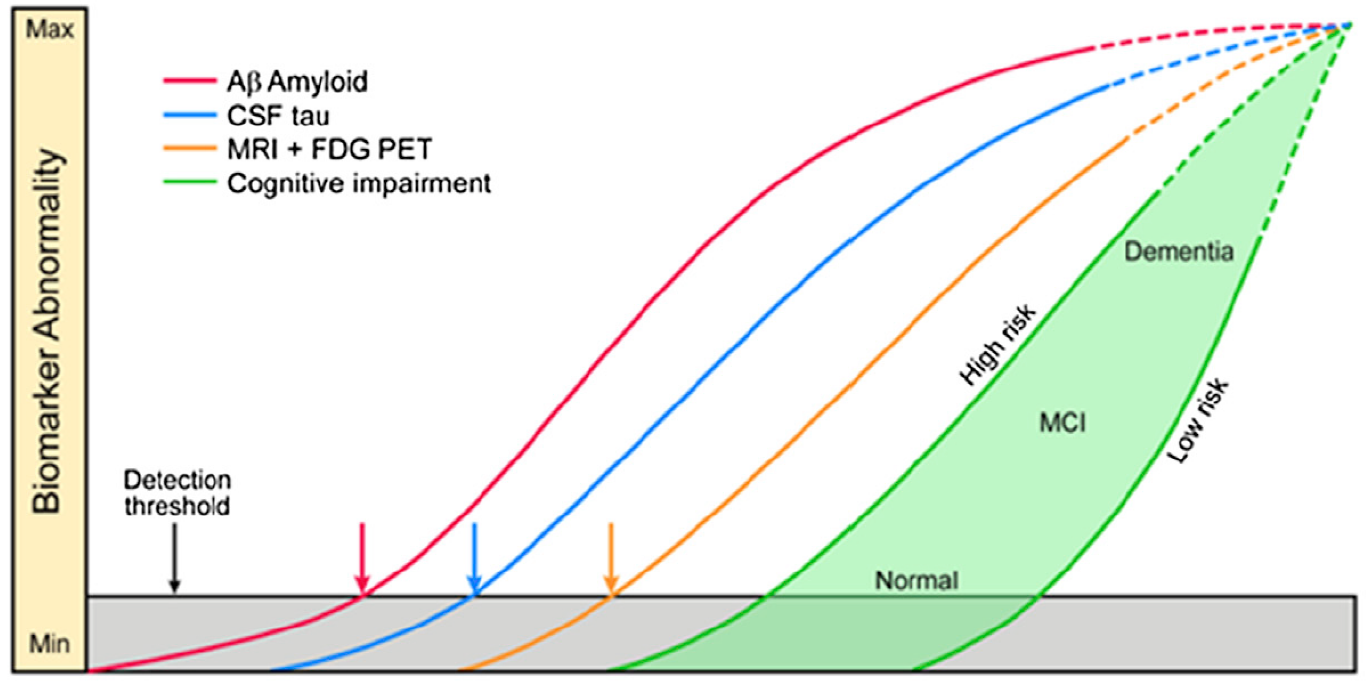


biomarker evolution



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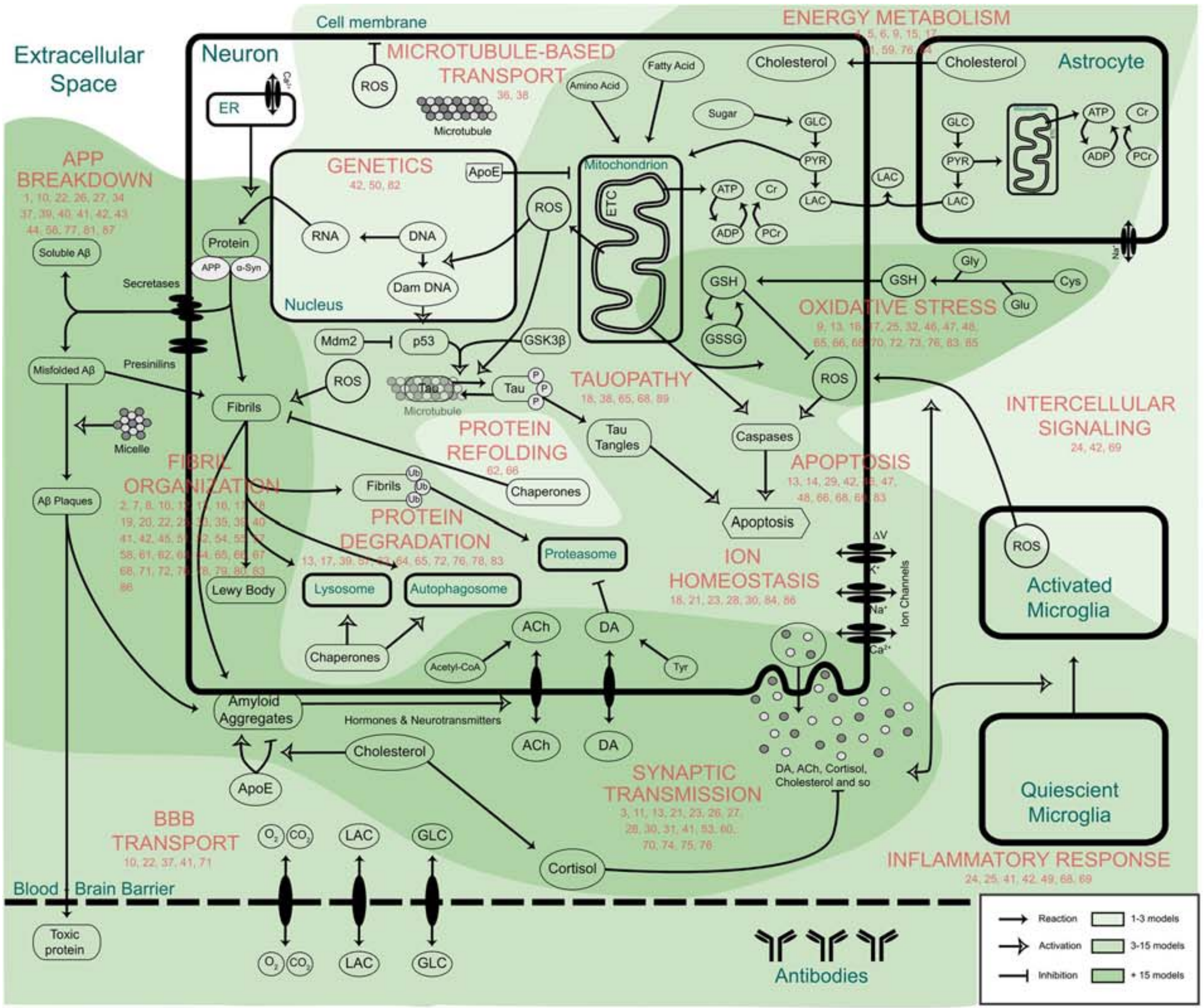

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89. **Yuraszeck2010 [17]**

Models in BioModels (Curated Branch)

Models in BioModels (Non-curated Branch)

Models not in BioModels

[Lloret-Villa et al. 2017]

2.

“un peu d’analyse et de calcul”

daniel bernoulli

why math?

why math?

daniel bernoulli 1760

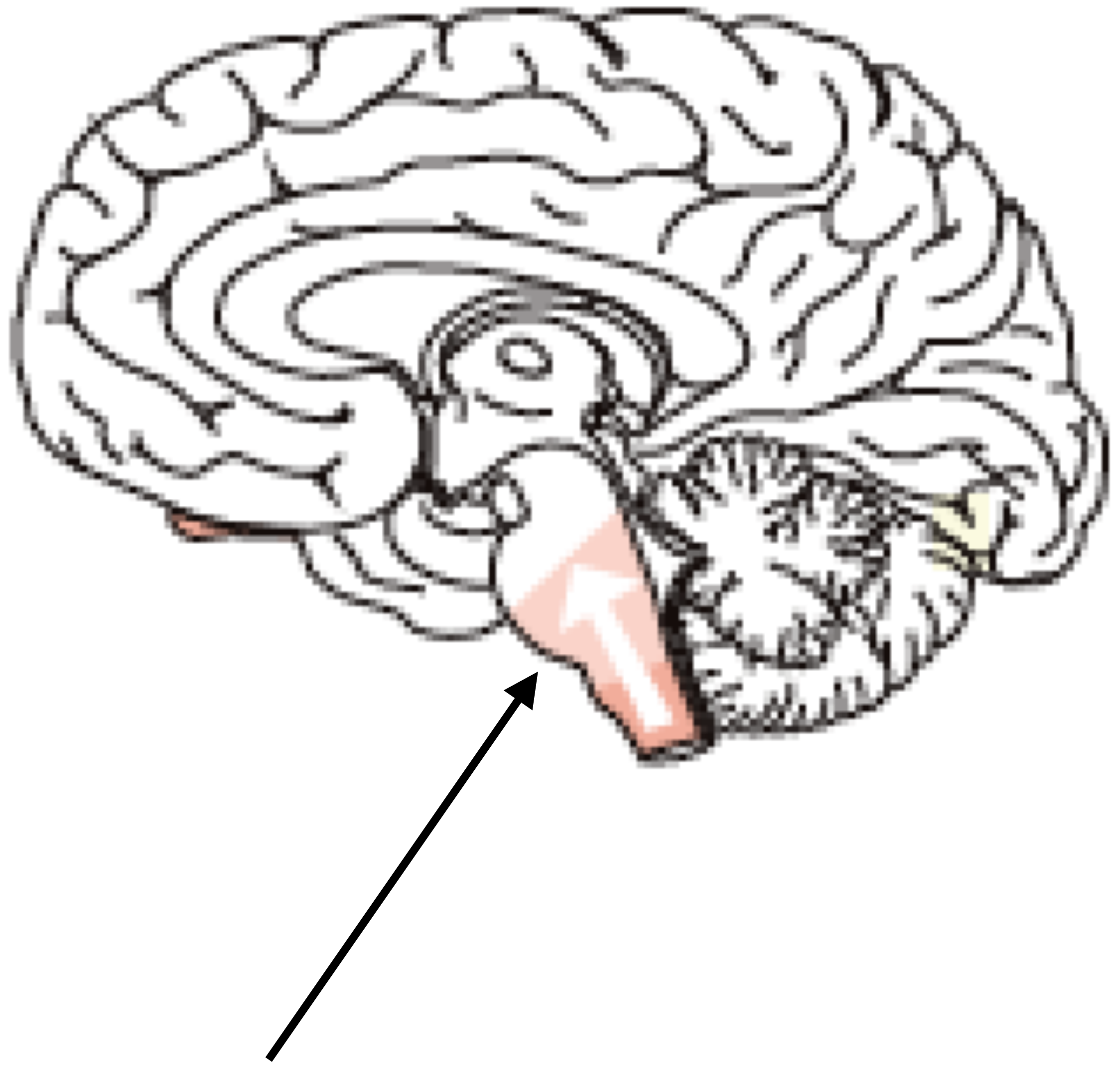
why math?

daniel bernoulli 1760

“i simply wish that, in a matter which so closely concerns the wellbeing of the human race, no decision shall be made without all the knowledge which a little analysis and calculation can provide.”

a first model:
network diffusion

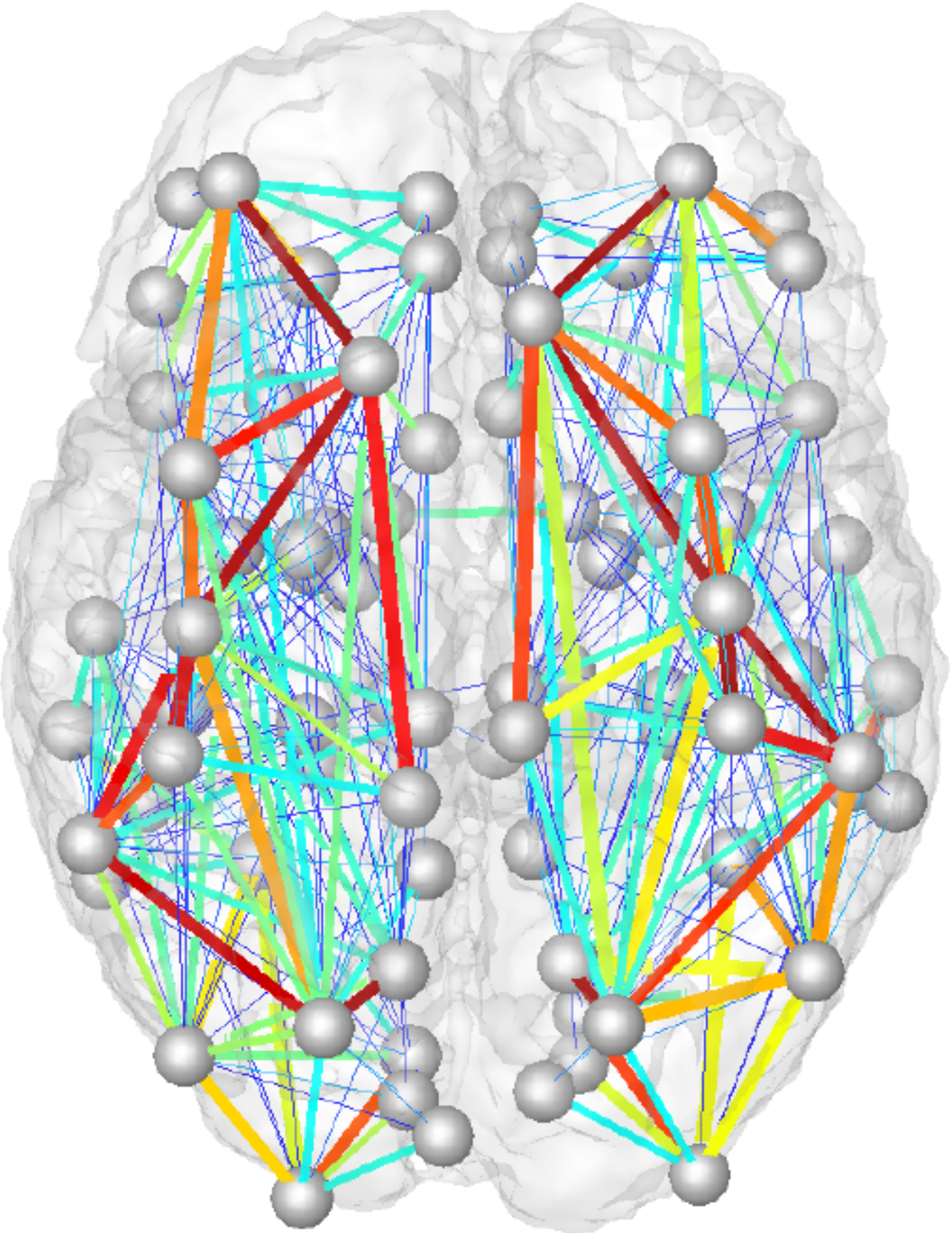
transport of toxic proteins

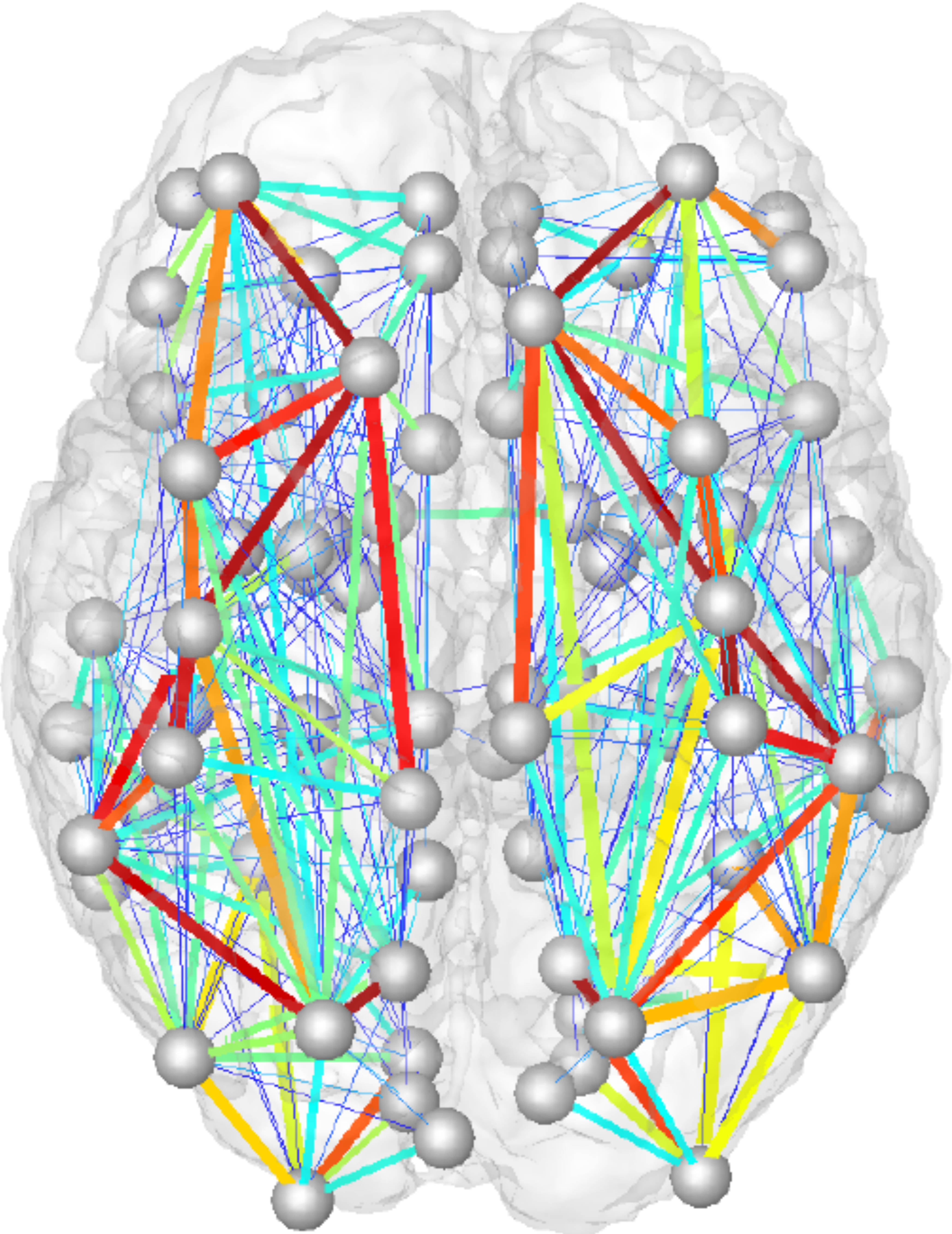


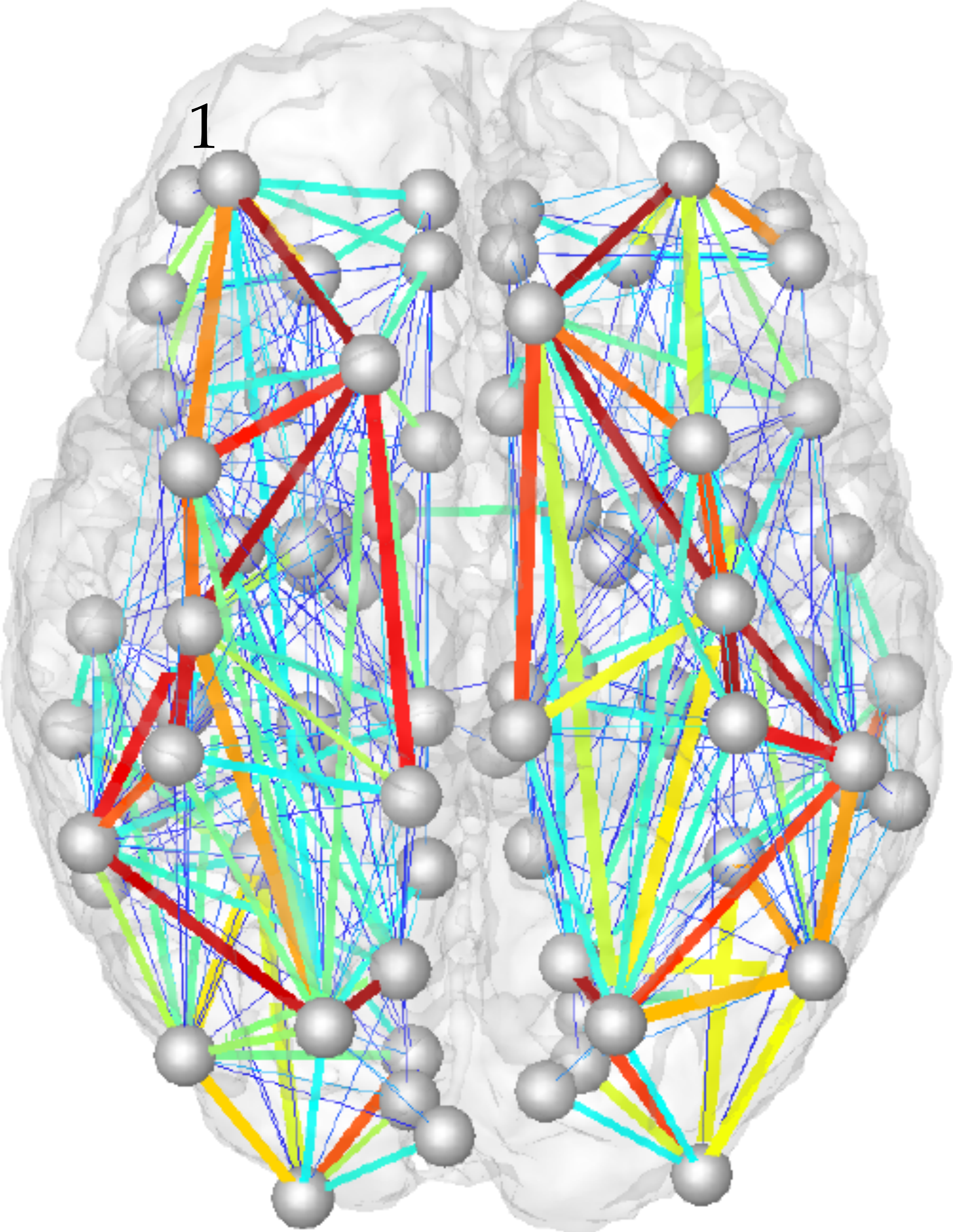
intial seeding

α–synuclein in parkinson's

- idea: toxic proteins diffuse along axonal pathways
- model: look at diffusion on the structural network



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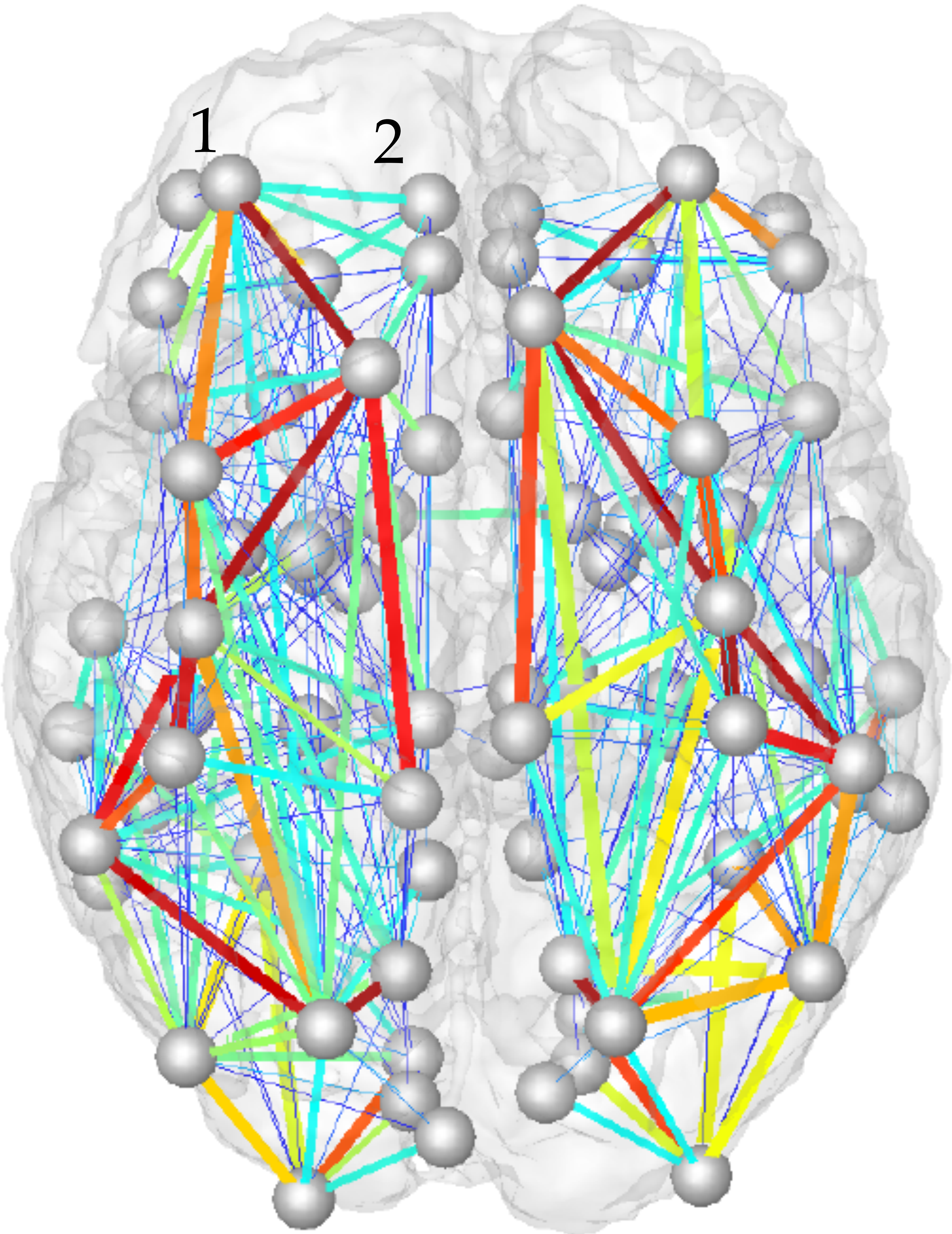
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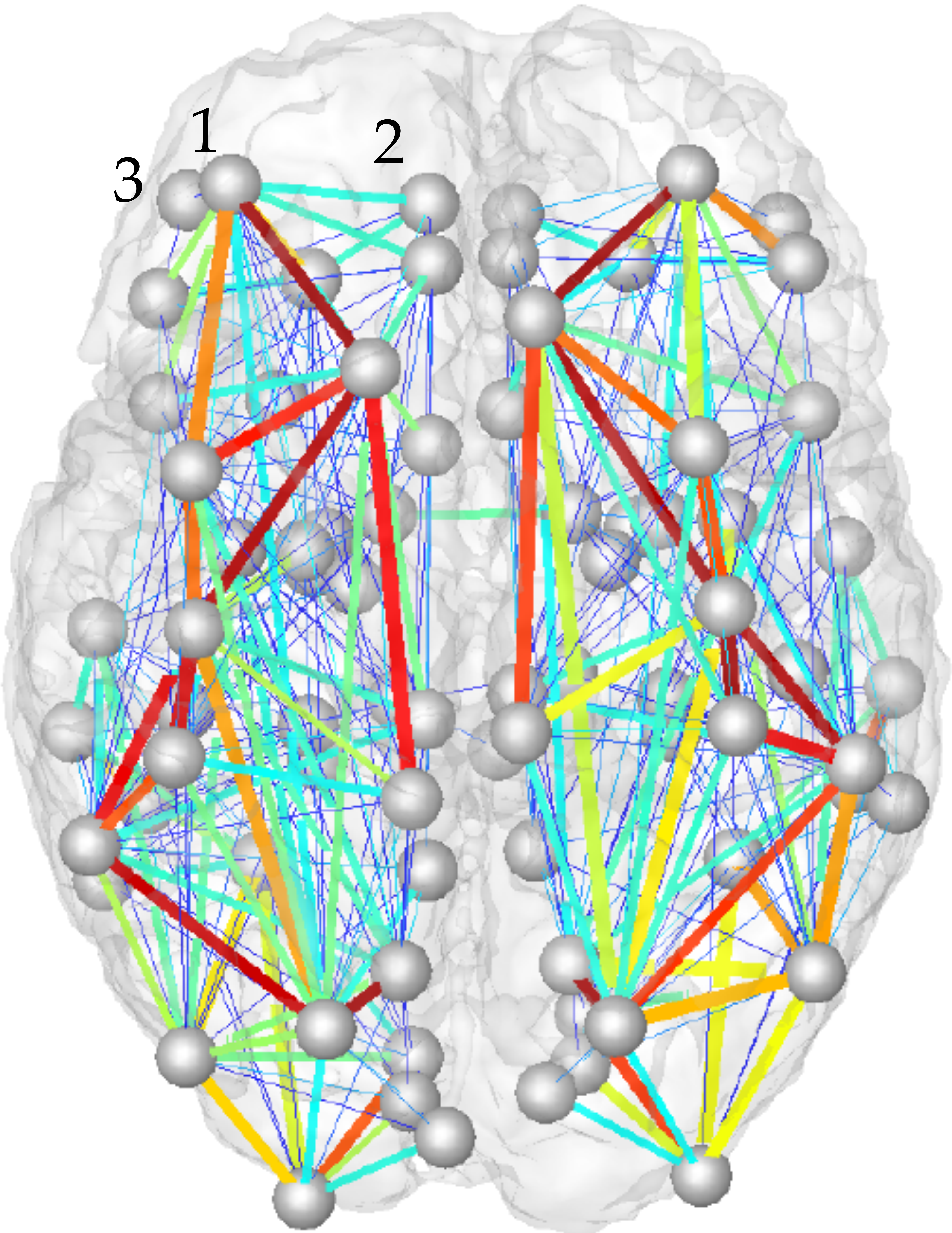
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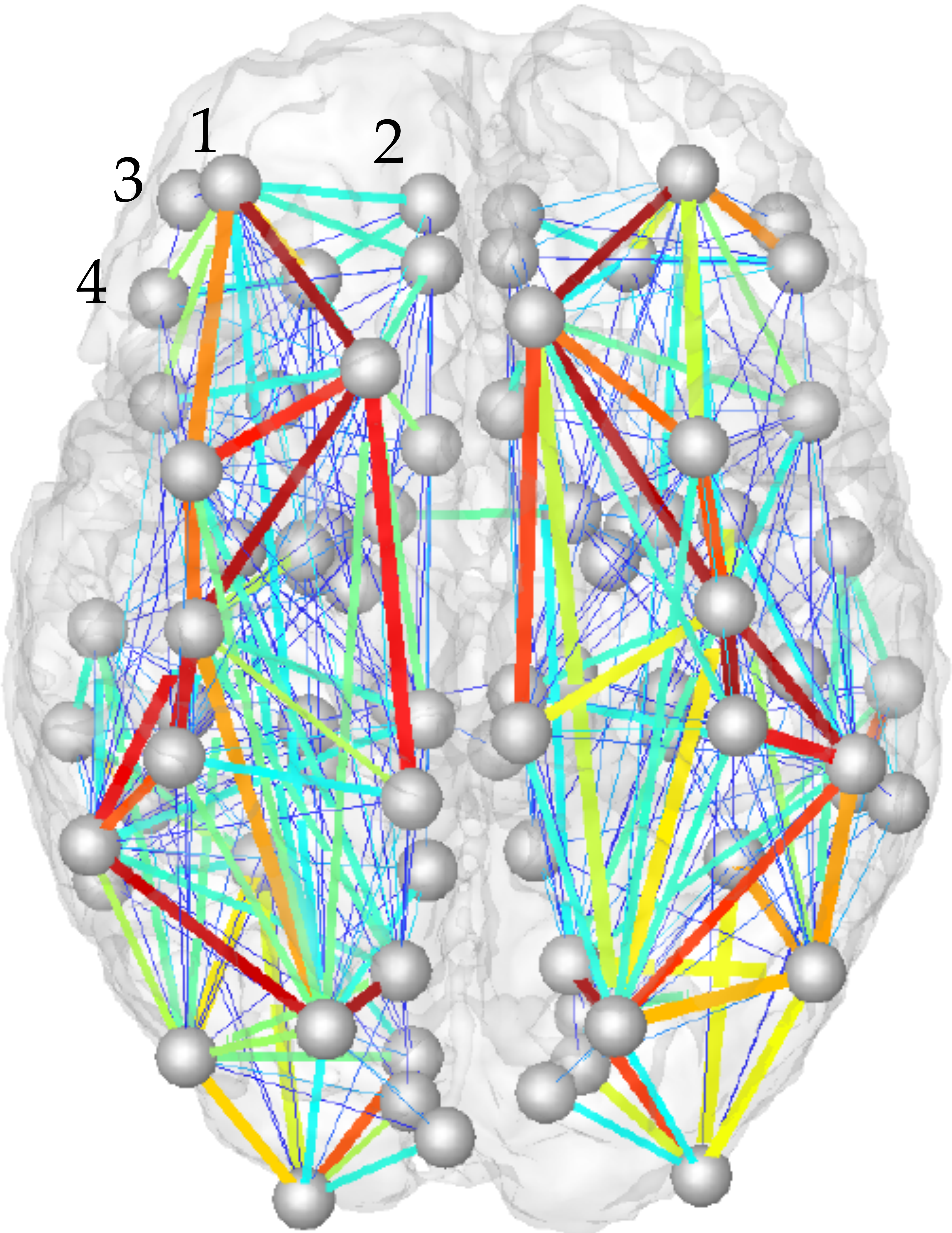
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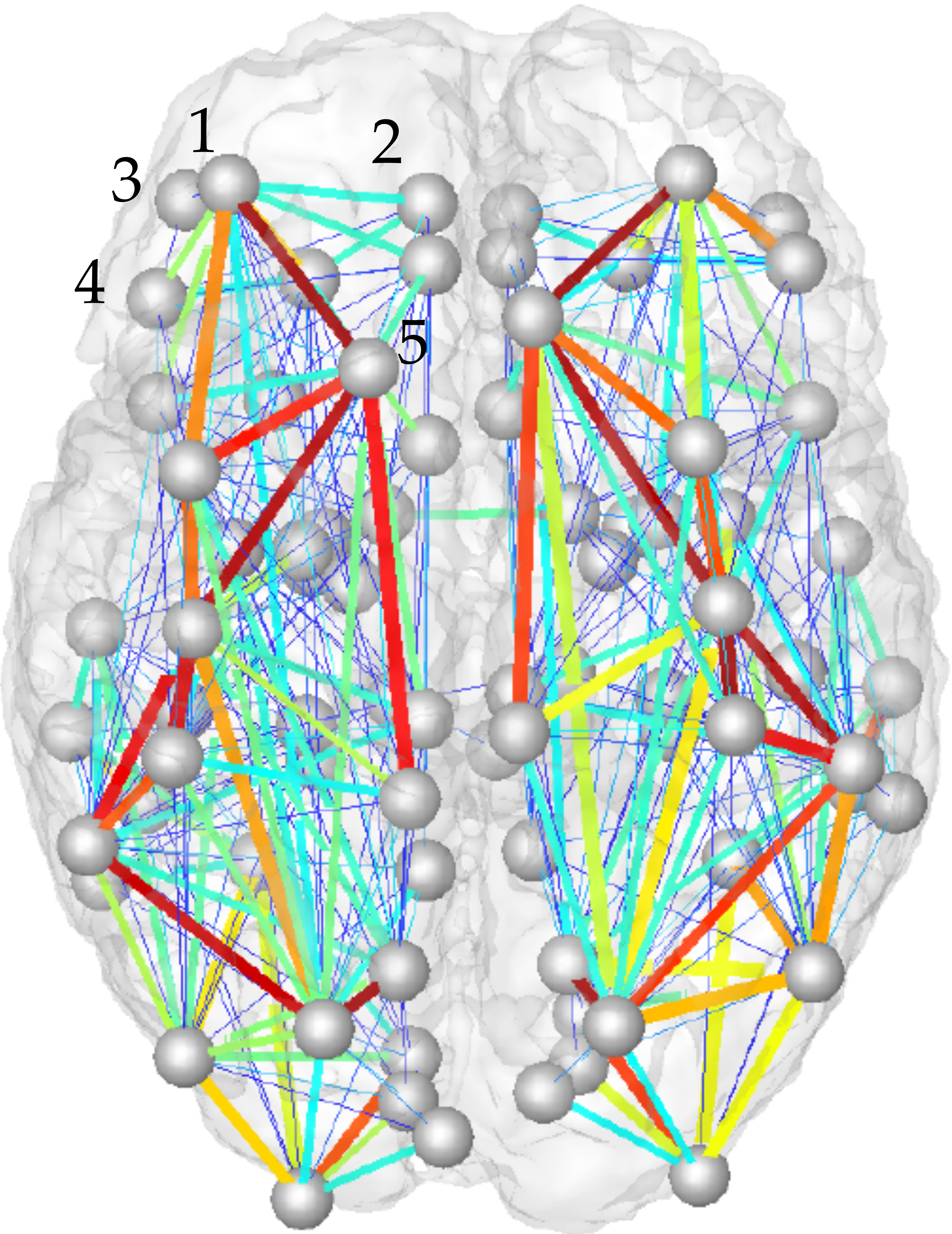
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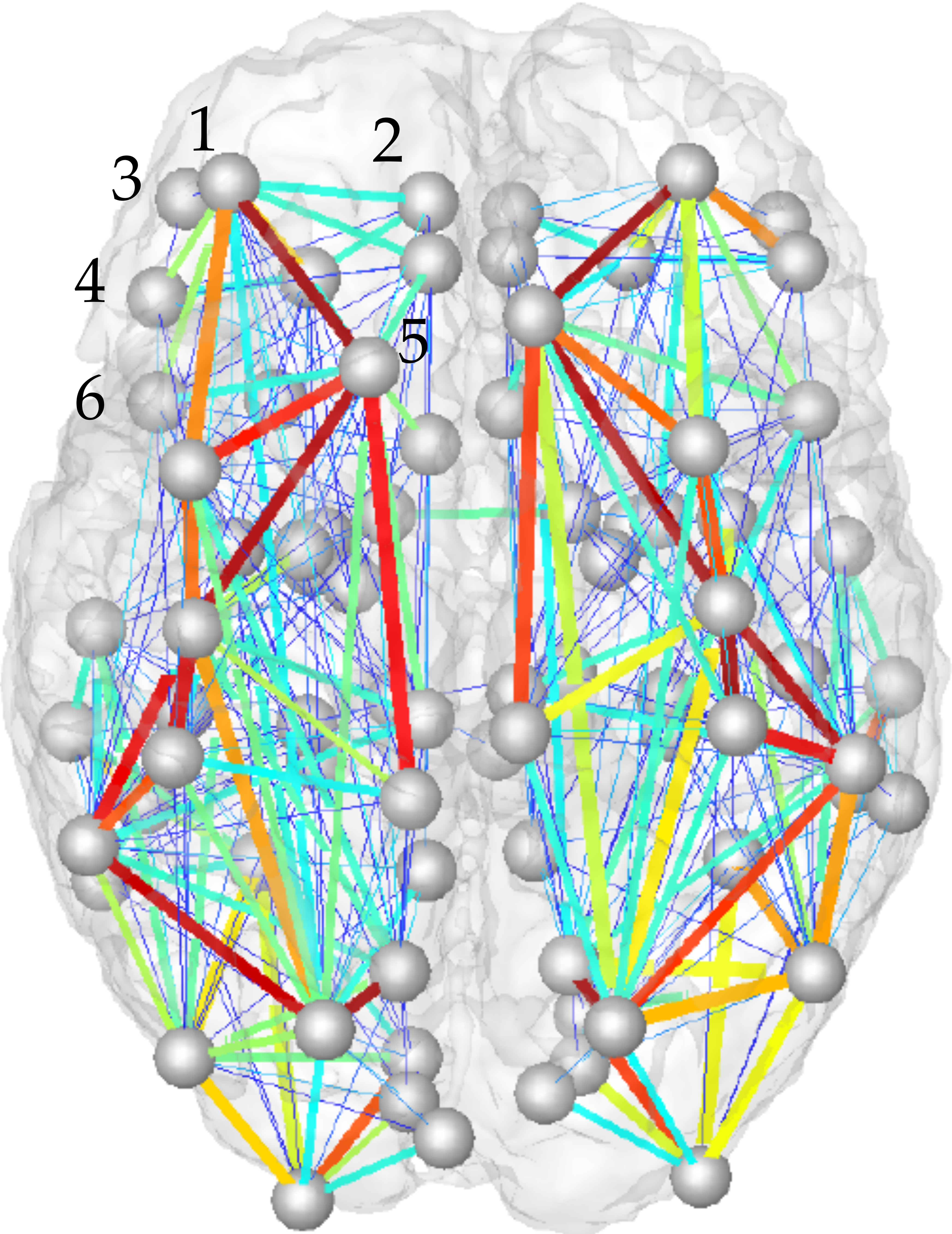
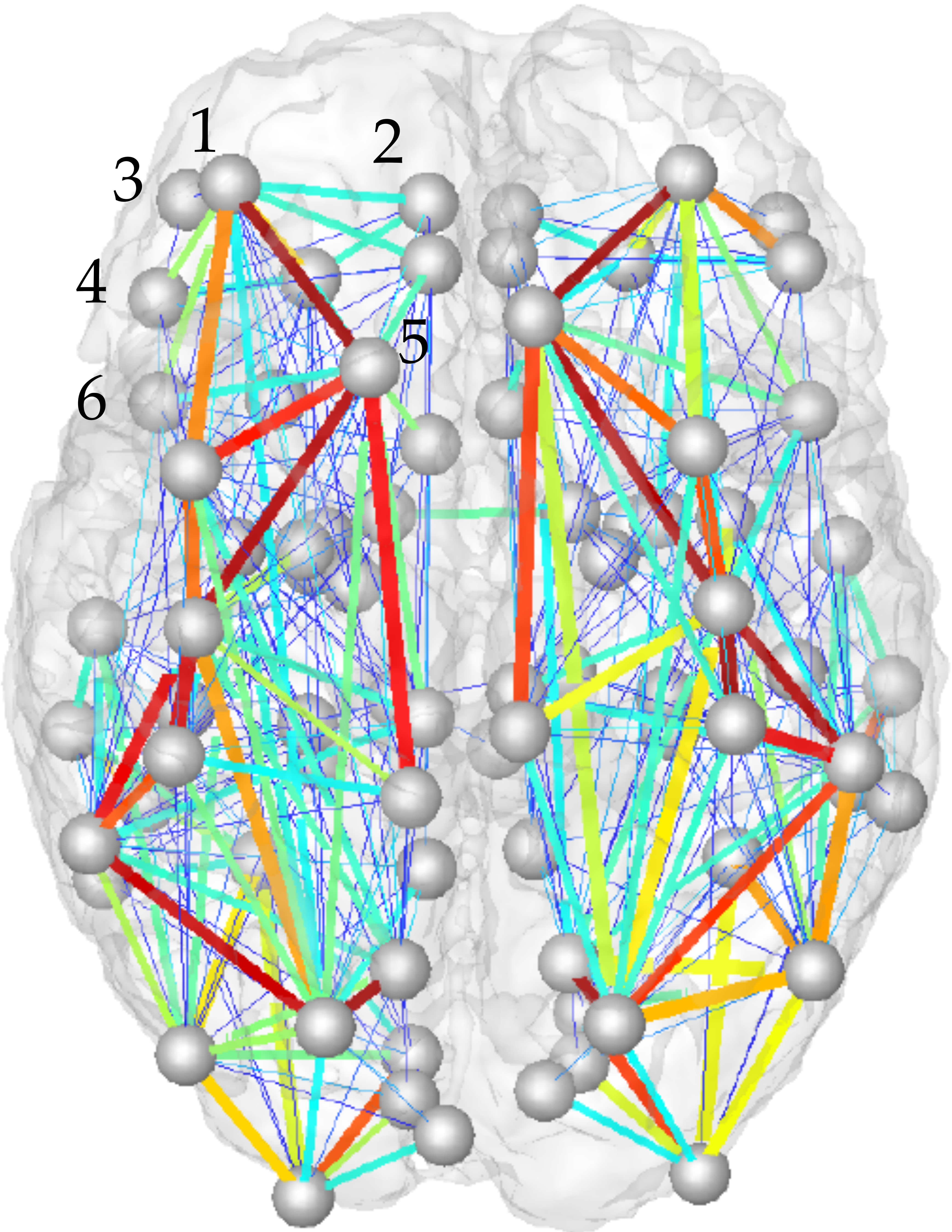
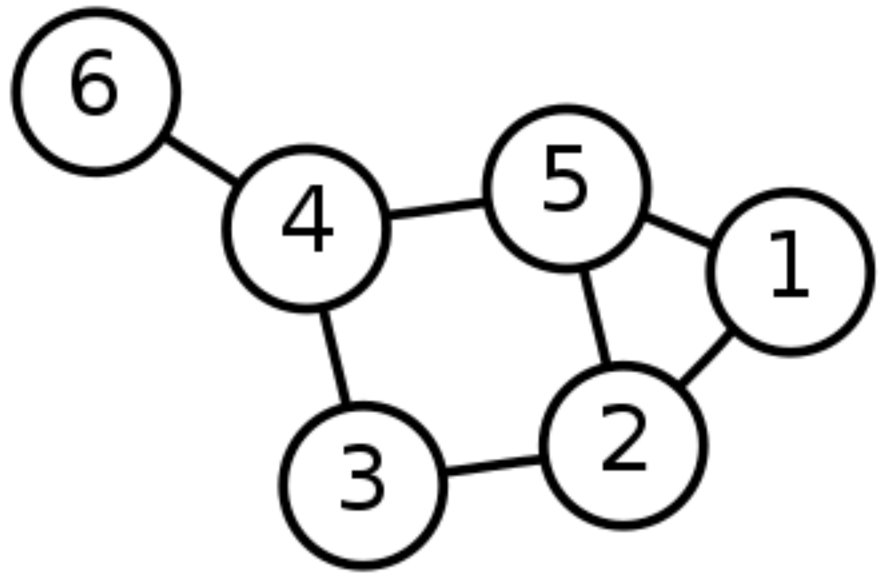

1
2
3
4
5
6

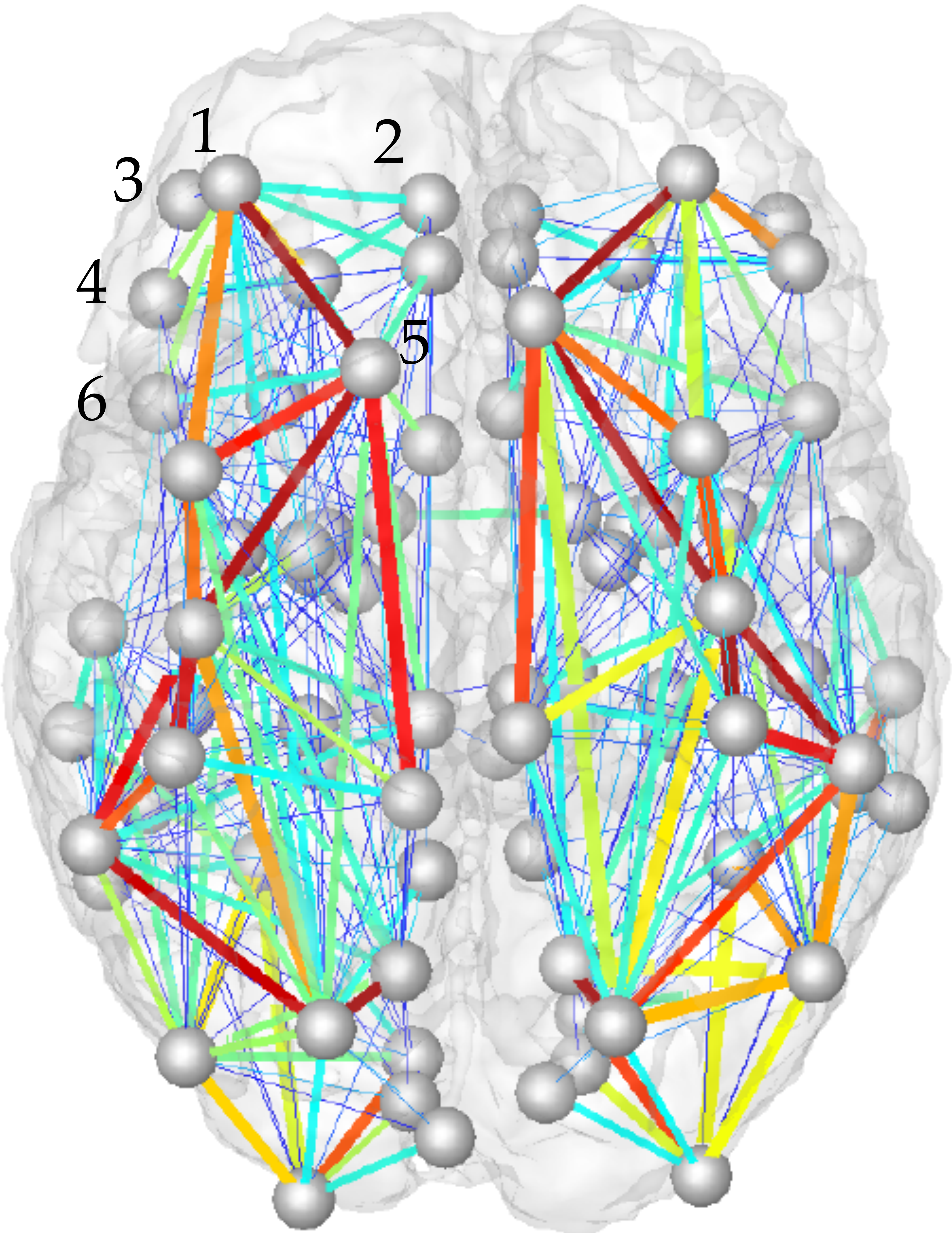
create a matrix from the graph



create a matrix from the graph

example:

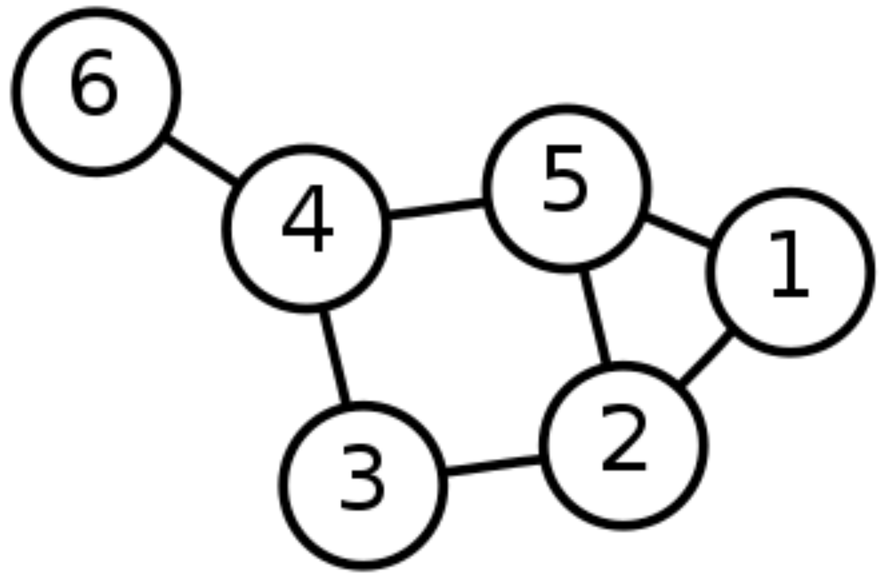




create a matrix from the graph

rules: start with node 1

example:

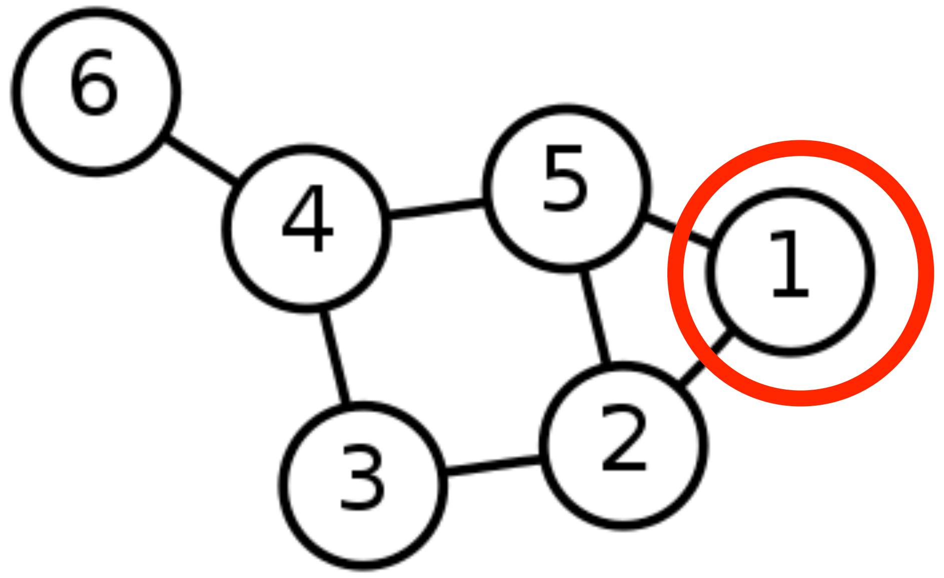


$$L = \begin{pmatrix} 2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

create a matrix from the graph

rules: start with node 1

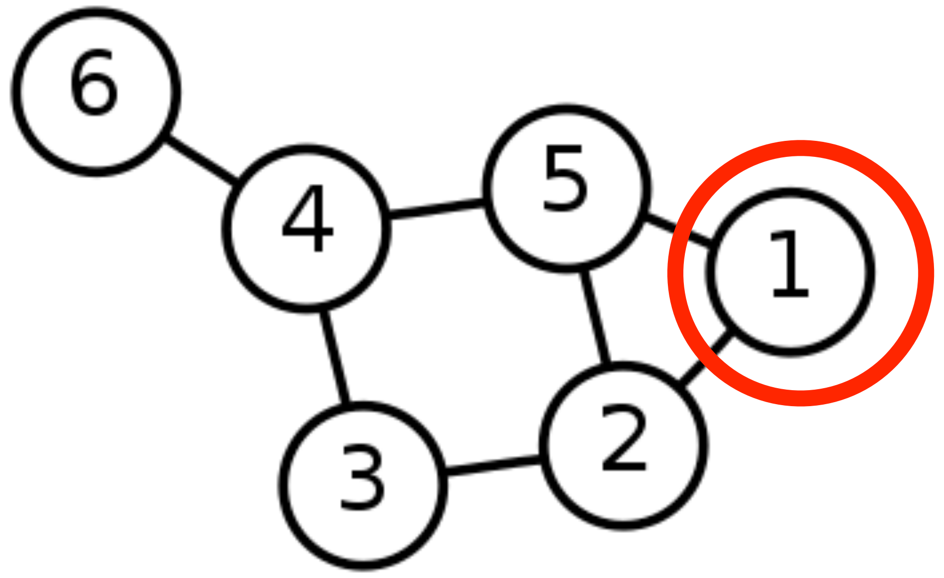
example:



$$L = \begin{pmatrix} 2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

create a matrix from the graph

example:



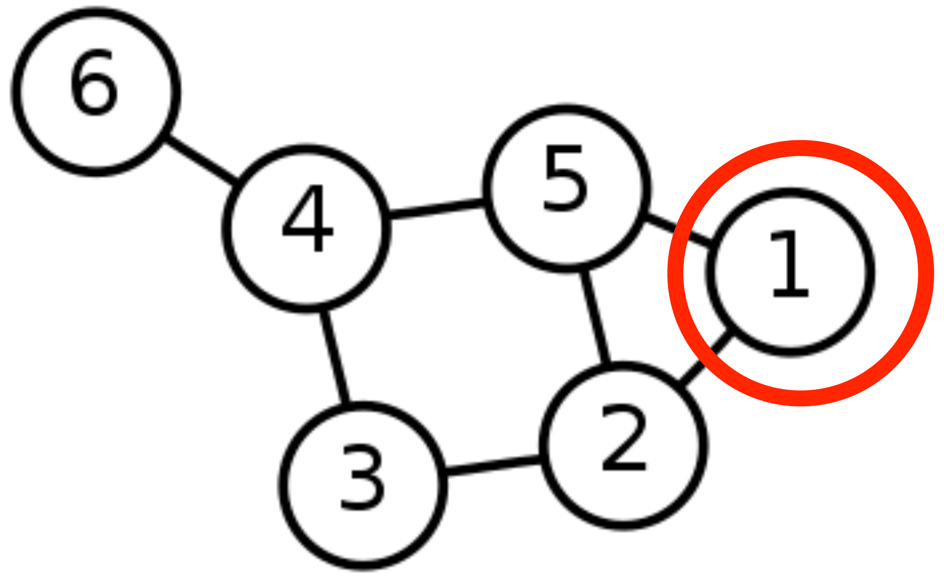
$$L = \begin{pmatrix} 2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

rules: start with node 1

-node 1 connected to 2 nodes.
place a 2 in line 1 column 1

create a matrix from the graph

example:



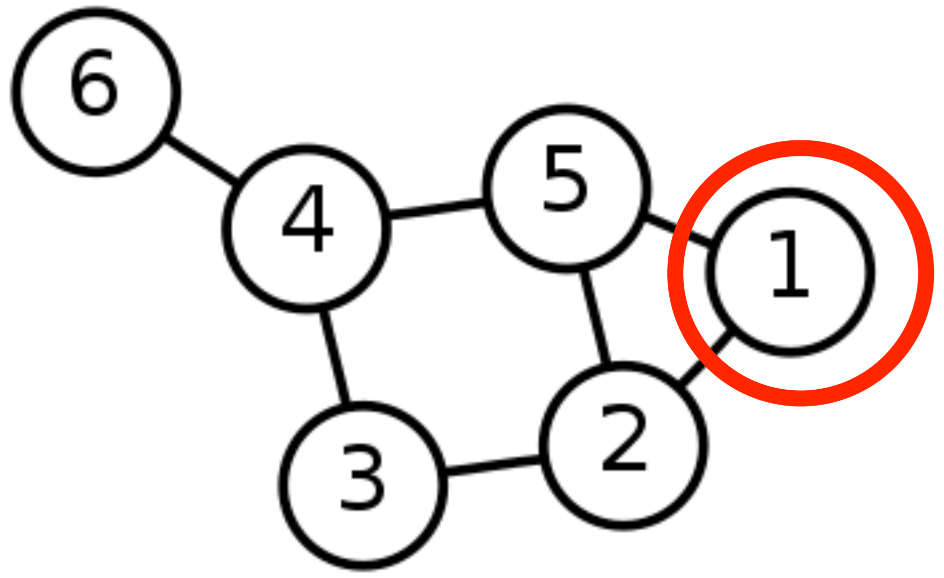
rules: start with node 1

-node 1 connected to 2 nodes.
place a 2 in line 1 column 1

$$L = \begin{pmatrix} \boxed{2} & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

create a matrix from the graph

example:



$$L = \begin{pmatrix} \boxed{2} & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

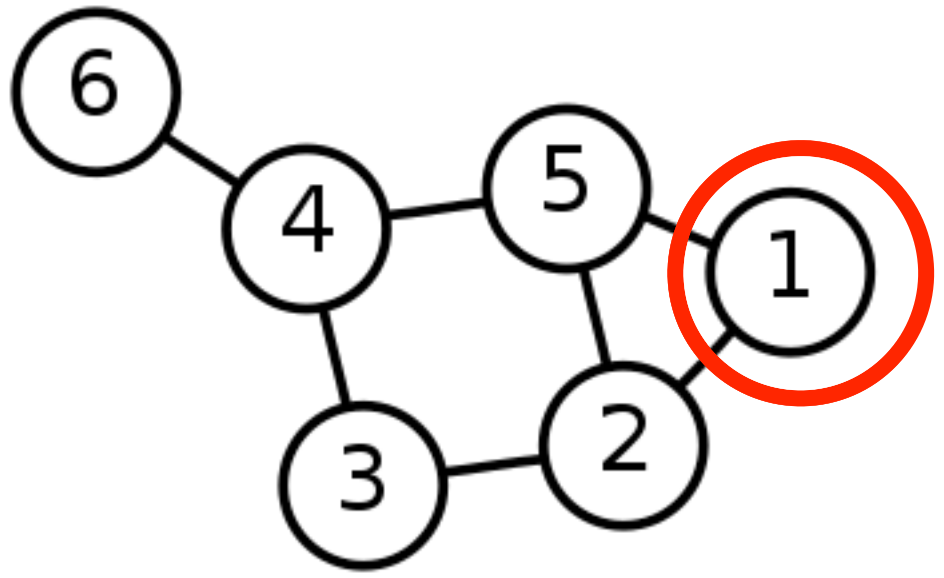
rules: start with node 1

-node 1 connected to 2 nodes.
place a 2 in line 1 column 1

-place a -1 in line 1 column 2 and 5

create a matrix from the graph

example:



$$L = \begin{pmatrix} \boxed{2} & \boxed{-1} & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

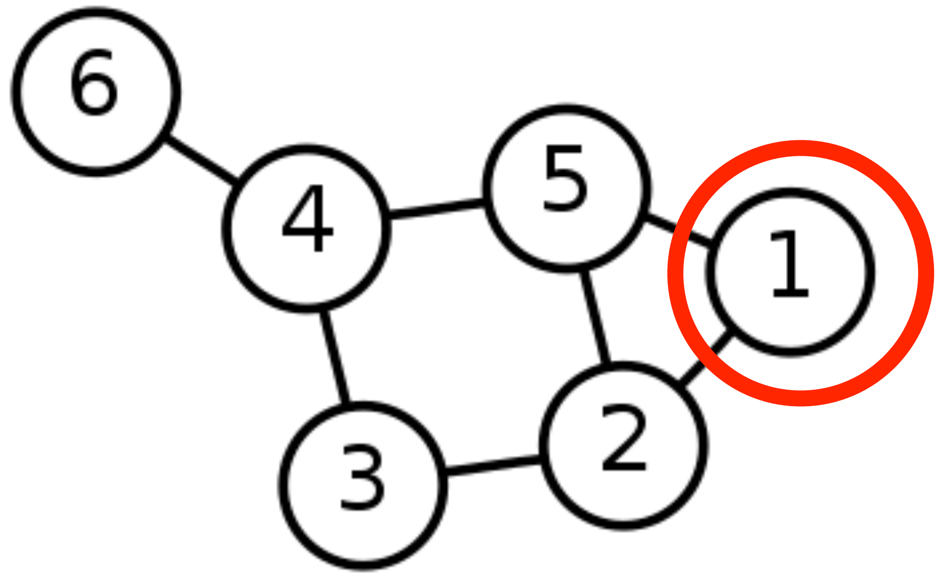
rules: start with node 1

-node 1 connected to 2 nodes.
place a 2 in line 1 column 1

-place a -1 in line 1 column 2 and 5

create a matrix from the graph

example:



$$L = \begin{pmatrix} \boxed{2} & \boxed{-1} & 0 & 0 & \boxed{-1} & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

rules: start with node 1

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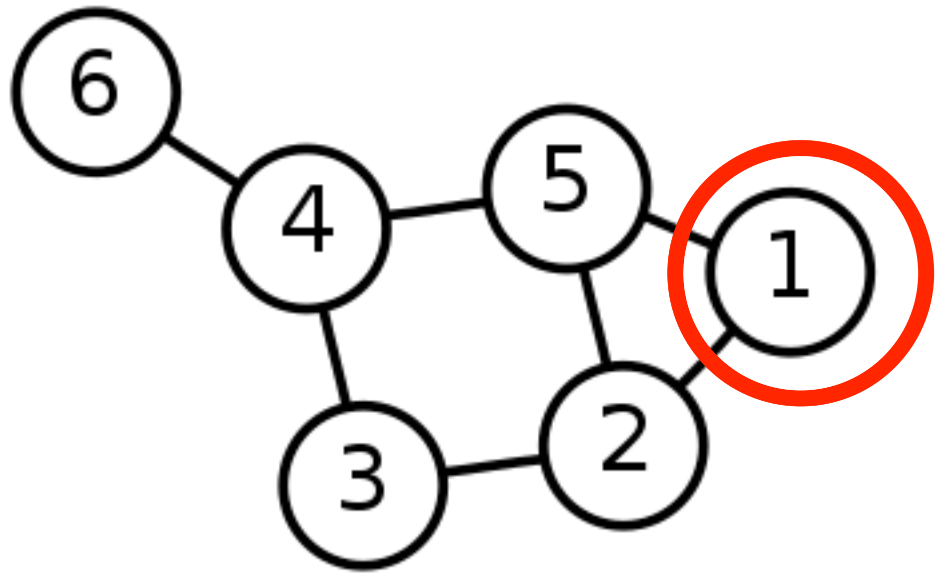

$$L = \begin{pmatrix} 2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

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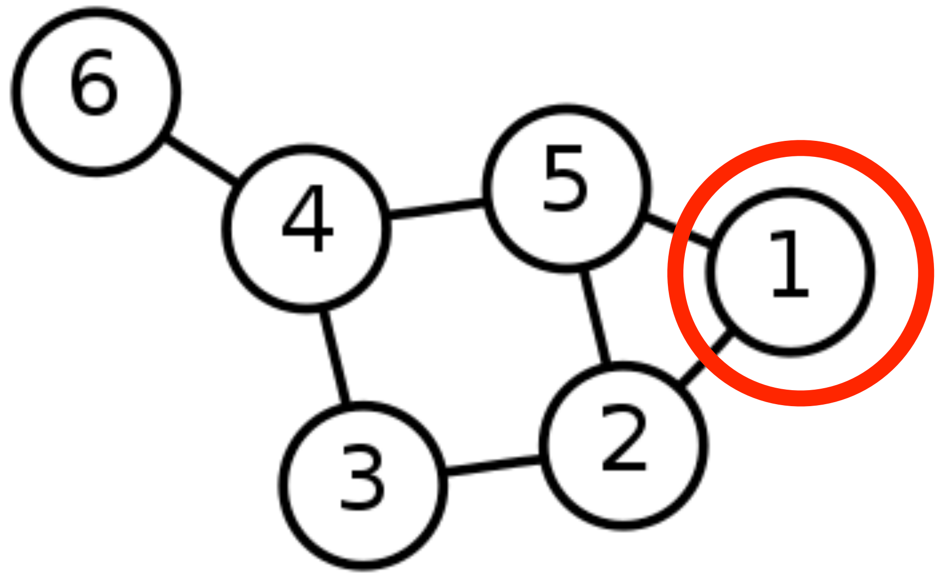

$$L = \begin{pmatrix} \textcolor{blue}{\bigcirc}\!\!\!\!2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

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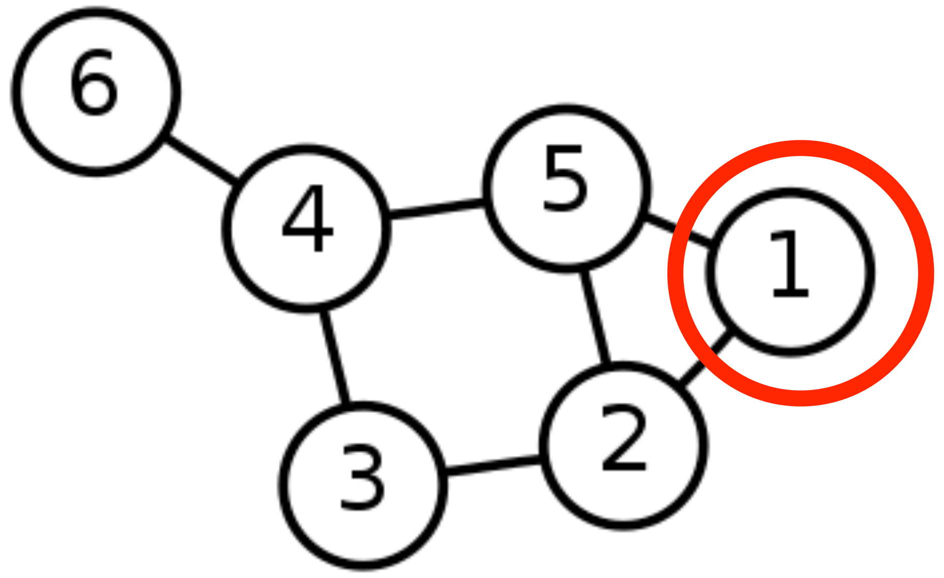

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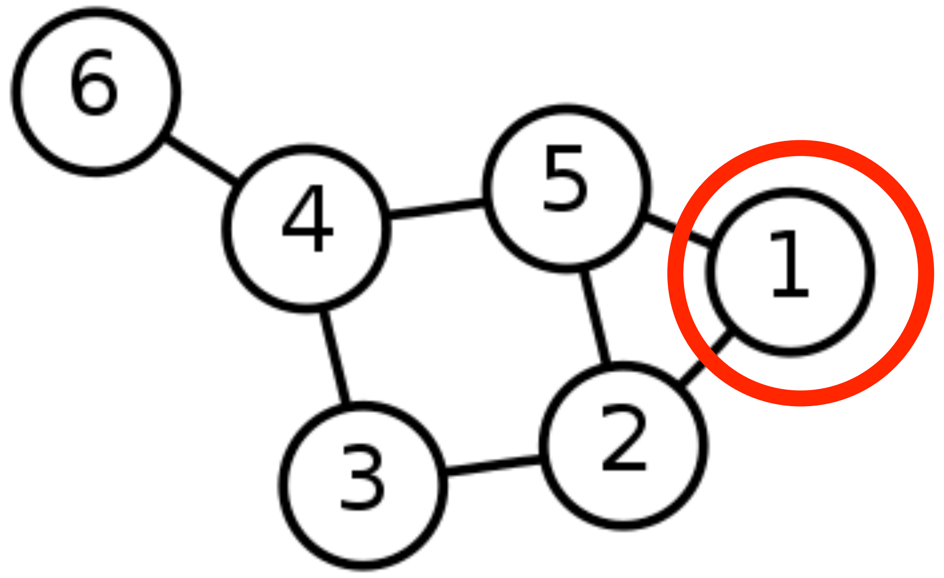

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rules: start with node 1

-node 1 connected to 2 nodes.
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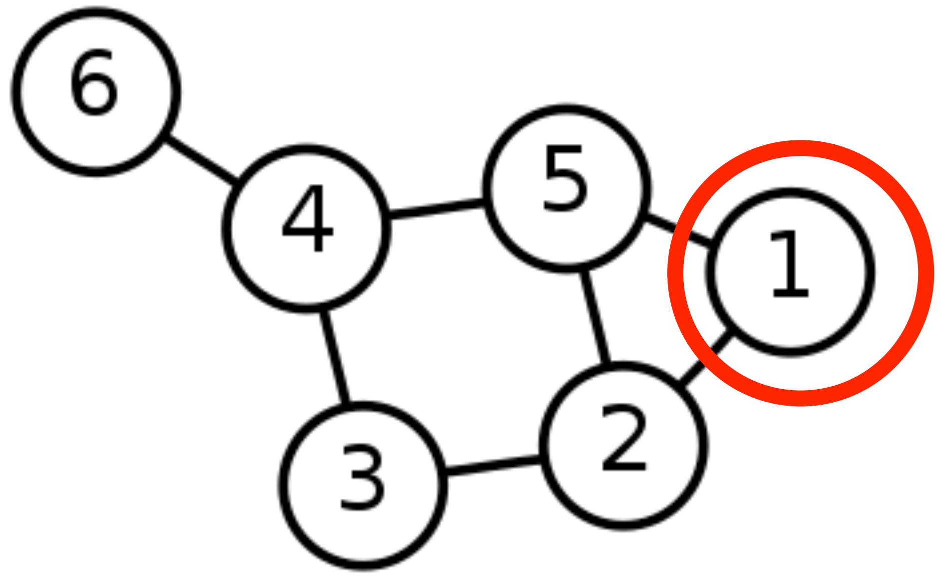
-place a -1 in column 1 line 2 and 5

-repeat with nodes 2,…,6

create a matrix from the graph

example:



$$L = \begin{pmatrix} 2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

graph laplacian

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-repeat with nodes 2,…,6

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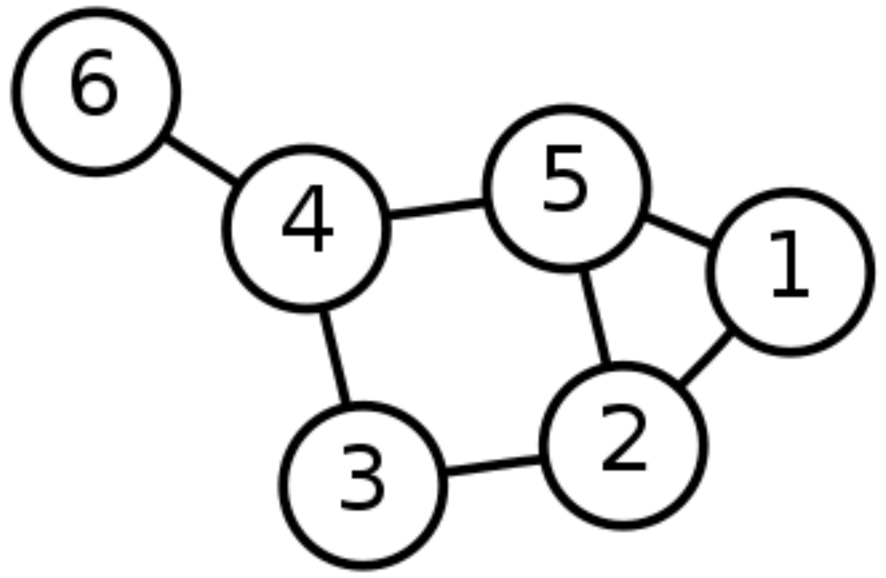
example:



next find the eigenmodes

$$L\mathbf{v} = \lambda\mathbf{v}$$

$$L = \begin{pmatrix} 2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

graph laplacian

create a matrix from the graph

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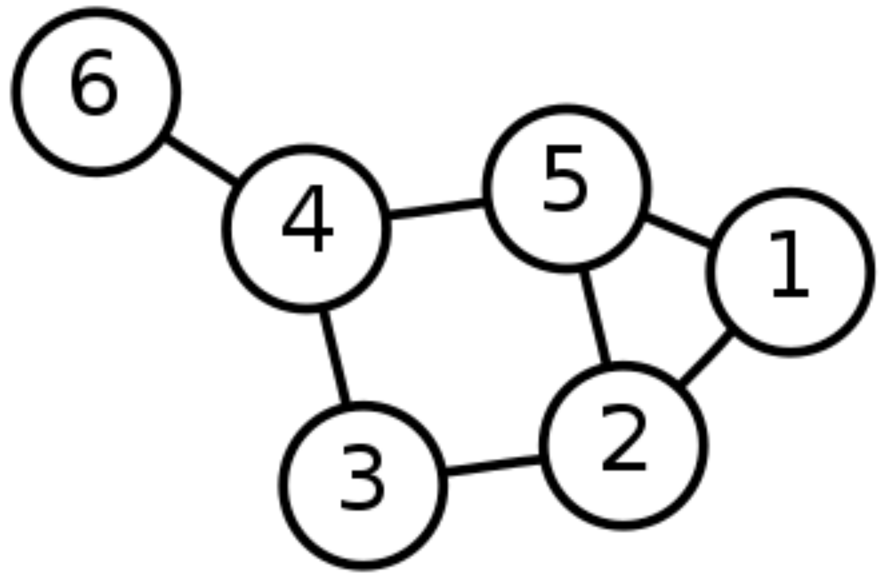

$$L = \begin{pmatrix} 2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

graph laplacian

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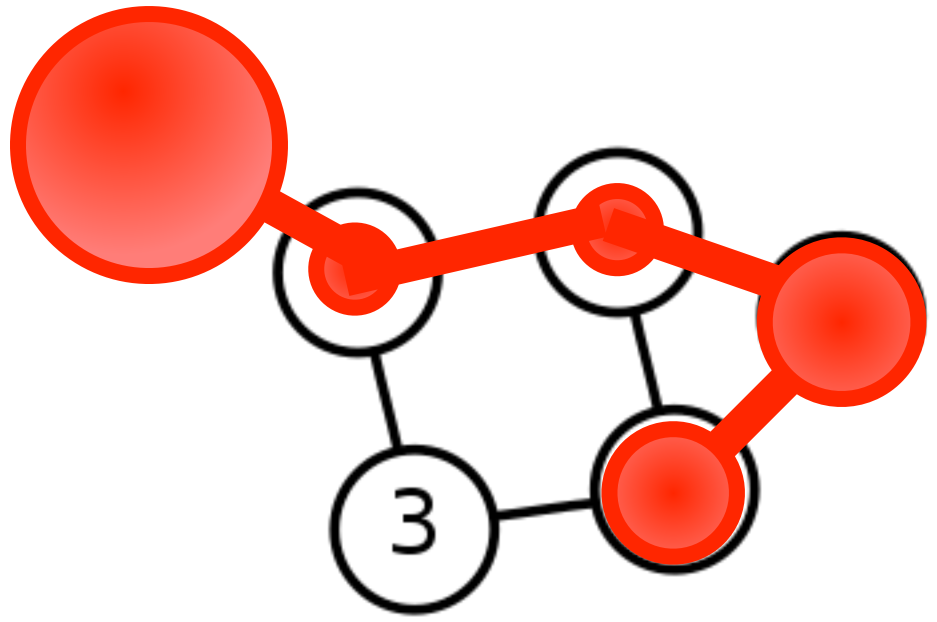
solution with second smallest λ:

$$\lambda = 0.7 \quad \text{and} \quad \mathbf{v} = \begin{pmatrix} -5.2 \\ -3.8 \\ 0.9 \\ 2.7 \\ -2.7 \\ 10 \end{pmatrix}$$

create a matrix from the graph

example:



$$L = \begin{pmatrix} 2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$$

graph laplacian

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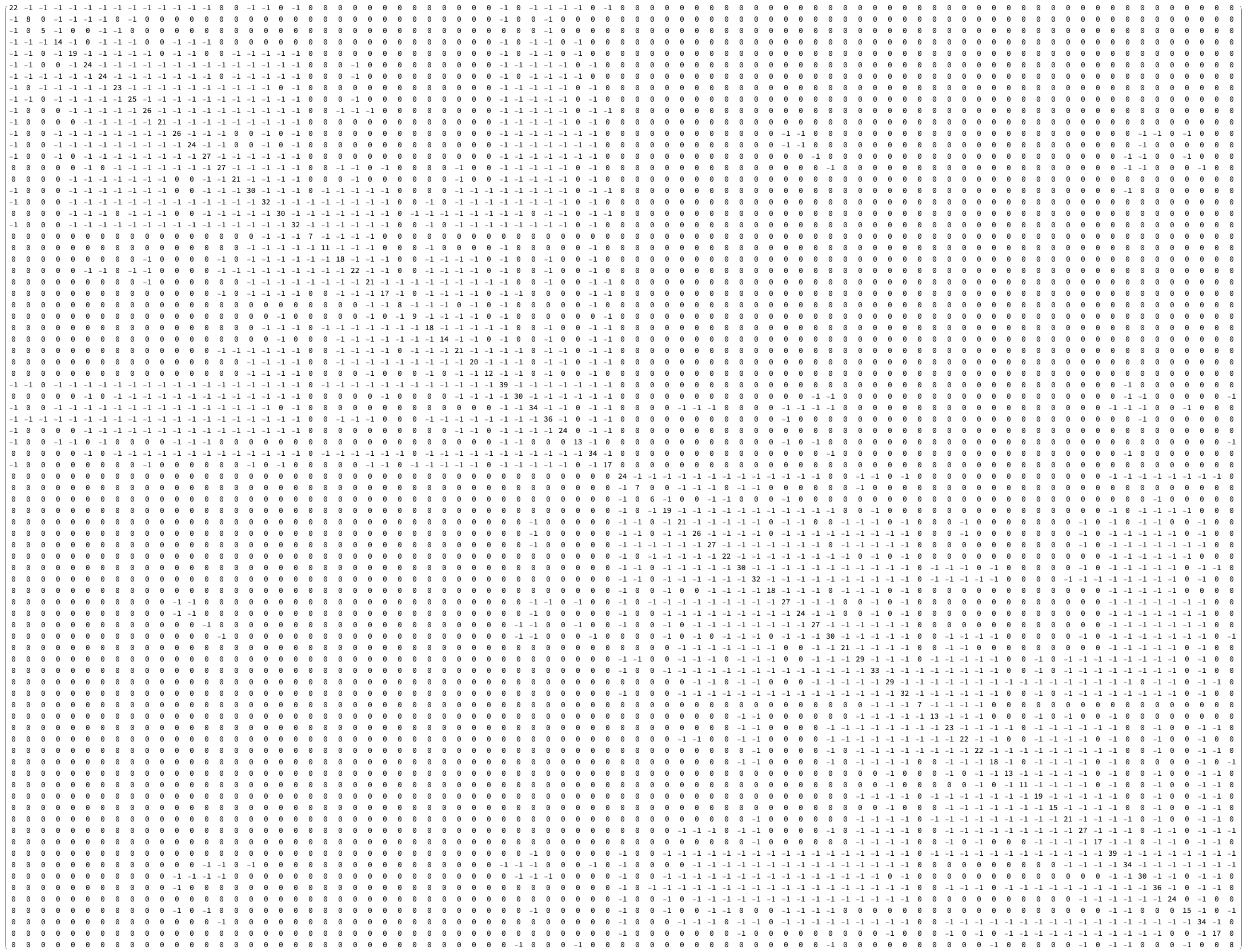
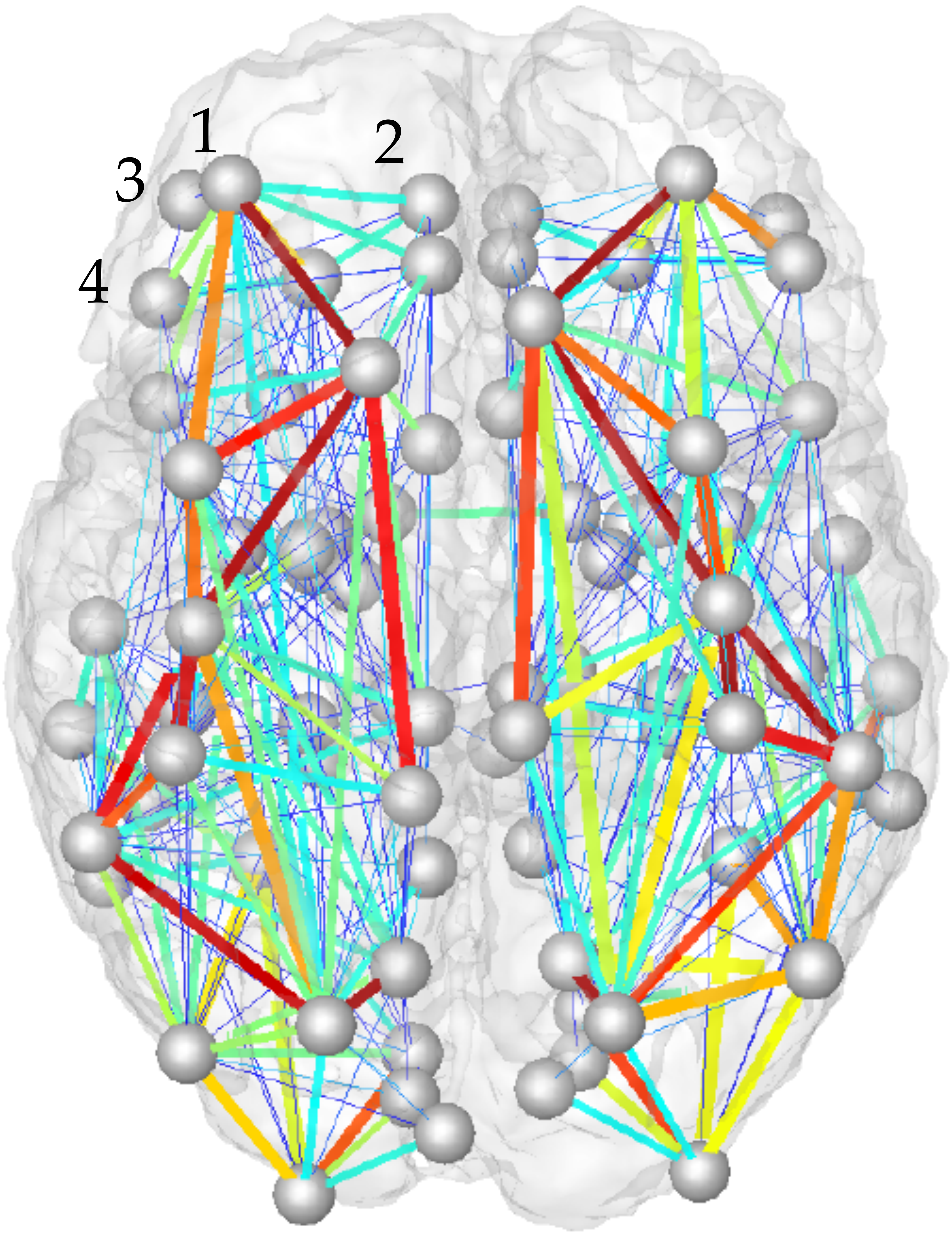
back to the brain

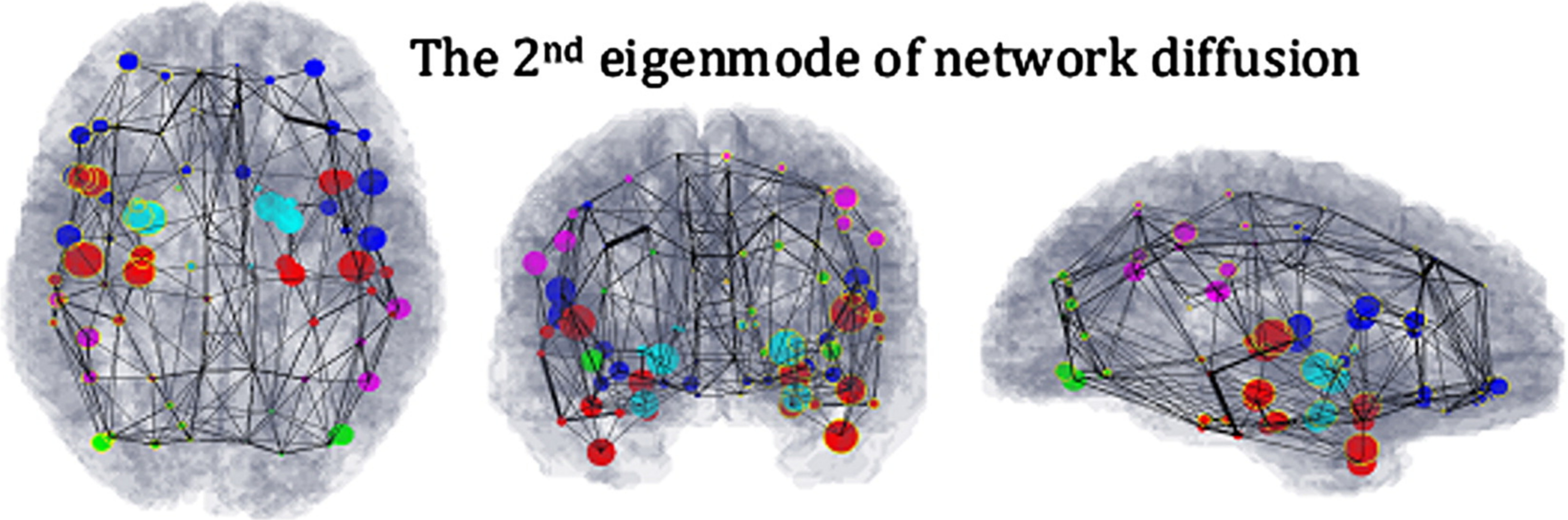
$L =$





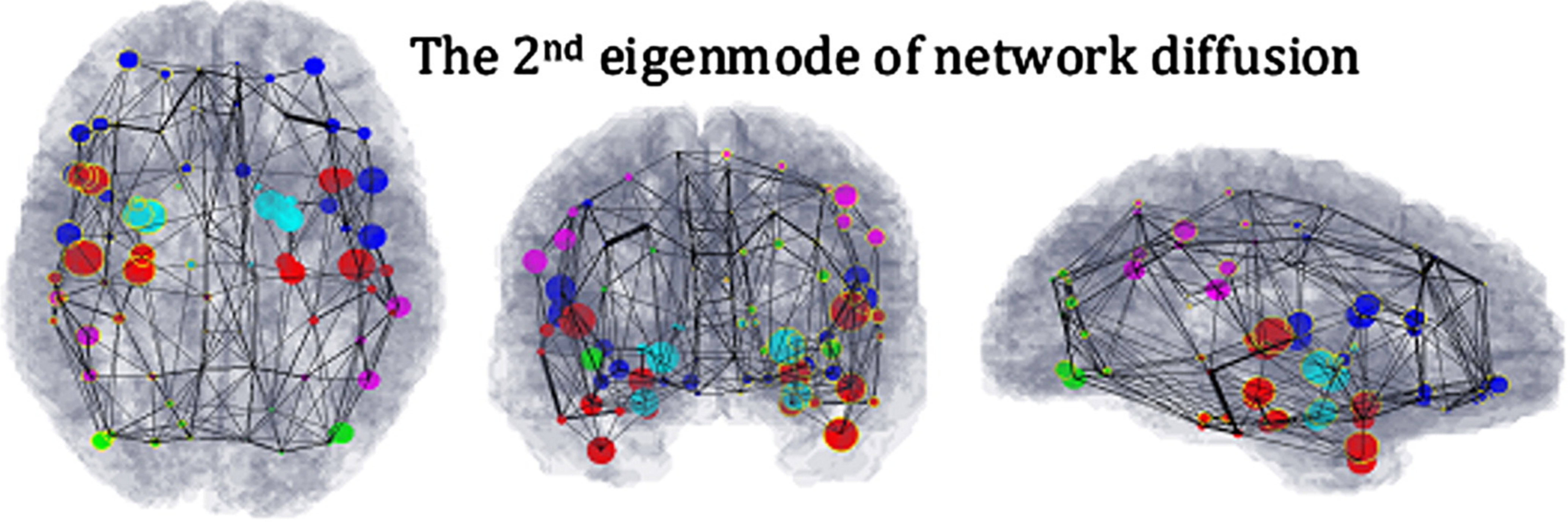
$$\left(\begin{matrix}
22 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & -1 & -1 & 0 & -1 & 0 & 0 & 0 \\
-1 & 8 & 0 & -1 & -1 & -1 & -1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-1 & 0 & 5 & -1 & 0 & 0 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-1 & -1 & -1 & 14 & -1 & 0 & -1 & -1 & -1 & 0 & 0 & -1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-1 & -1 & 0 & -1 & 19 & -1 & -1 & -1 & -1 & -1 & 0 & -1 & -1 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & 0 \\
-1 & -1 & 0 & 0 & -1 & 24 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & 0 \\
-1 & -1 & -1 & -1 & -1 & -1 & 24 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & 0 \\
-1 & 0 & -1 & -1 & -1 & -1 & -1 & 23 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & -1 & 0 & 0 & 0 \\
-1 & -1 & 0 & -1 & -1 & -1 & -1 & -1 & 25 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & 0 \\
-1 & 0 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & 26 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & -1 \\
-1 & 0 & 0 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & 21 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & 0 \\
-1 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 26 & -1 & -1 & -1 & 0 & 0 & -1 & 0 & -1 & 0 & 0 & 0 \\
-1 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 24 & -1 & -1 & 0 & 0 & -1 & 0 & -1 & 0 & 0 & 0 \\
-1 & 0 & 0 & -1 & 0 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 27 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -1 & 0 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 27 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & -1 \\
0 & 0 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & -1 & -1 & 21 & -1 & -1 & -1 & -1 & 0 & 0 & 0 \\
-1 & 0 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 & -1 & -1 & -1 & 30 & -1 & -1 & -1 & 0 & -1 & -1 \\
-1 & 0 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 32 & -1 & -1 & -1 & -1 & -1 \\
0 & 0 & 0 & 0 & -1 & -1 & -1 & 0 & -1 & -1 & -1 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & 30 & -1 & -1 & -1 & -1 \\
-1 & 0 & 0 & 0 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & -1 & 32 & -1 & -1 & -1
\end{matrix}\right.$$

The 2nd eigenmode of network diffusion

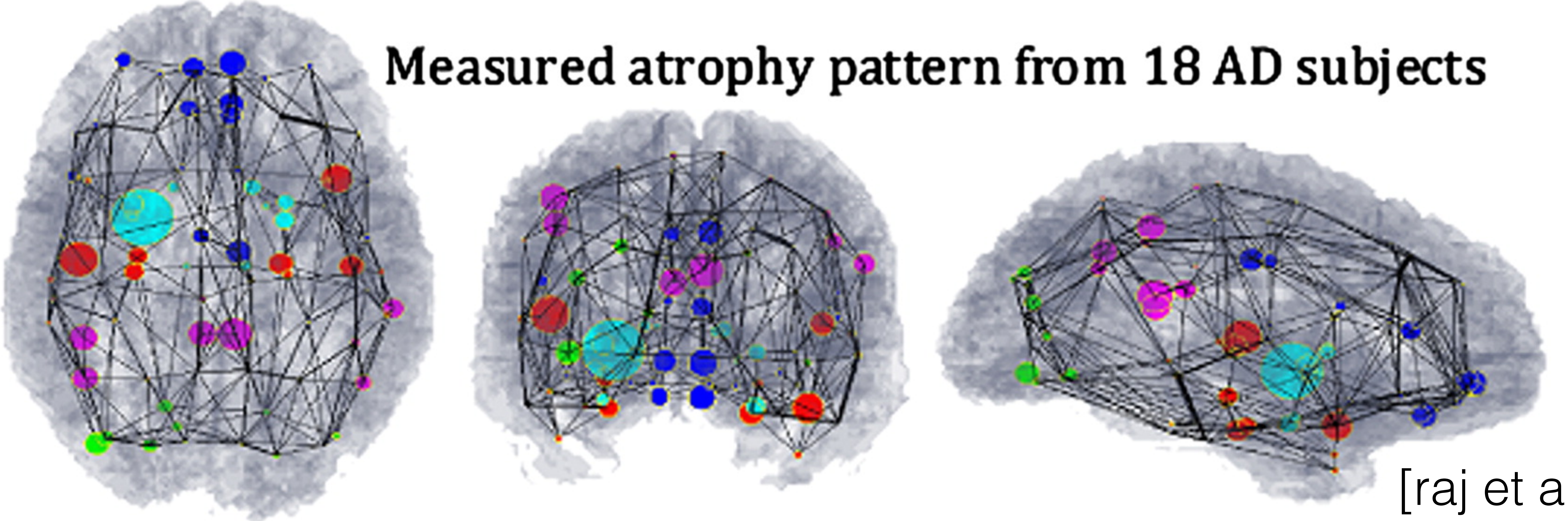


[raj et al. 2012]

The 2nd eigenmode of network diffusion



Measured atrophy pattern from 18 AD subjects



[raj et al. 2012]

3.

“they violate most of biology's sacred rules”

jonah lehrer proust

prion-like mechanism

healthy

[from walker and jucker 2015]

prion-like mechanism

misfolding

healthy

[from walker and jucker 2015]

prion-like mechanism

misfolding

healthy toxic

[from walker and jucker 2015]

prion-like mechanism

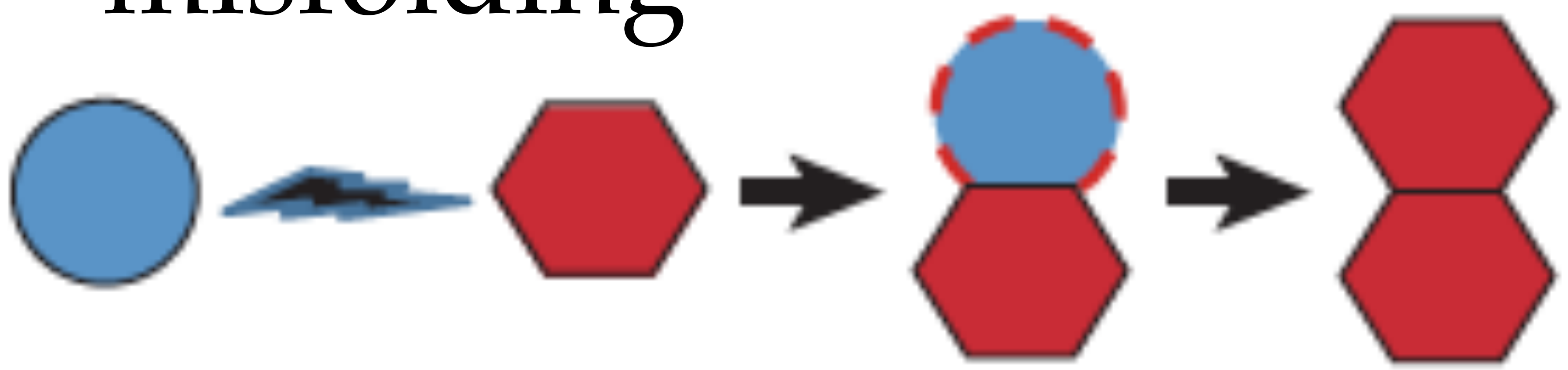
templating
aggregation

misfolding

healthy toxic

[from walker and jucker 2015]

prion-like mechanism



misfolding

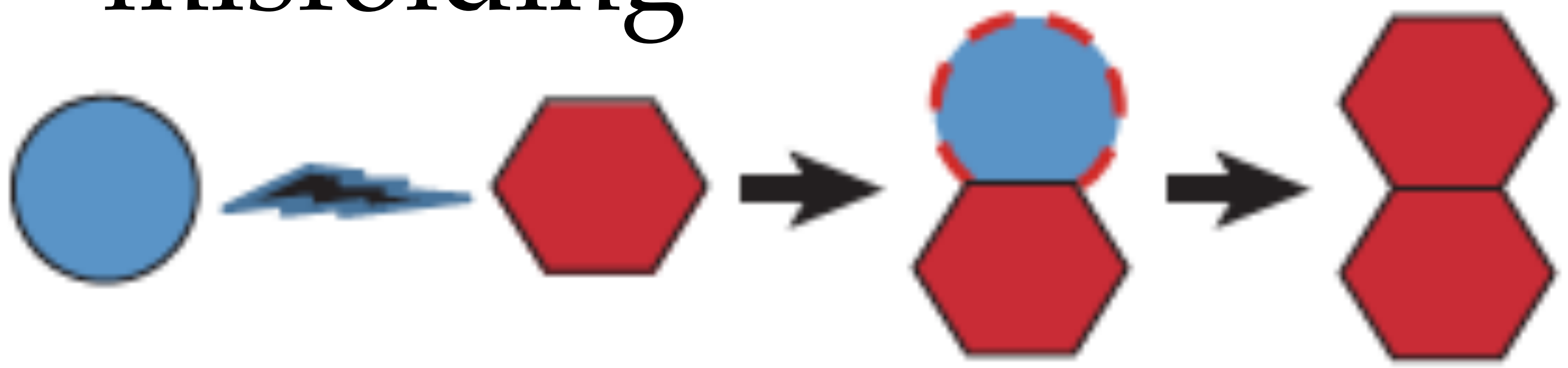
templating
aggregation

healthy

toxic

[from walker and jucker 2015]

prion-like mechanism



growth
aggregation

templating
aggregation

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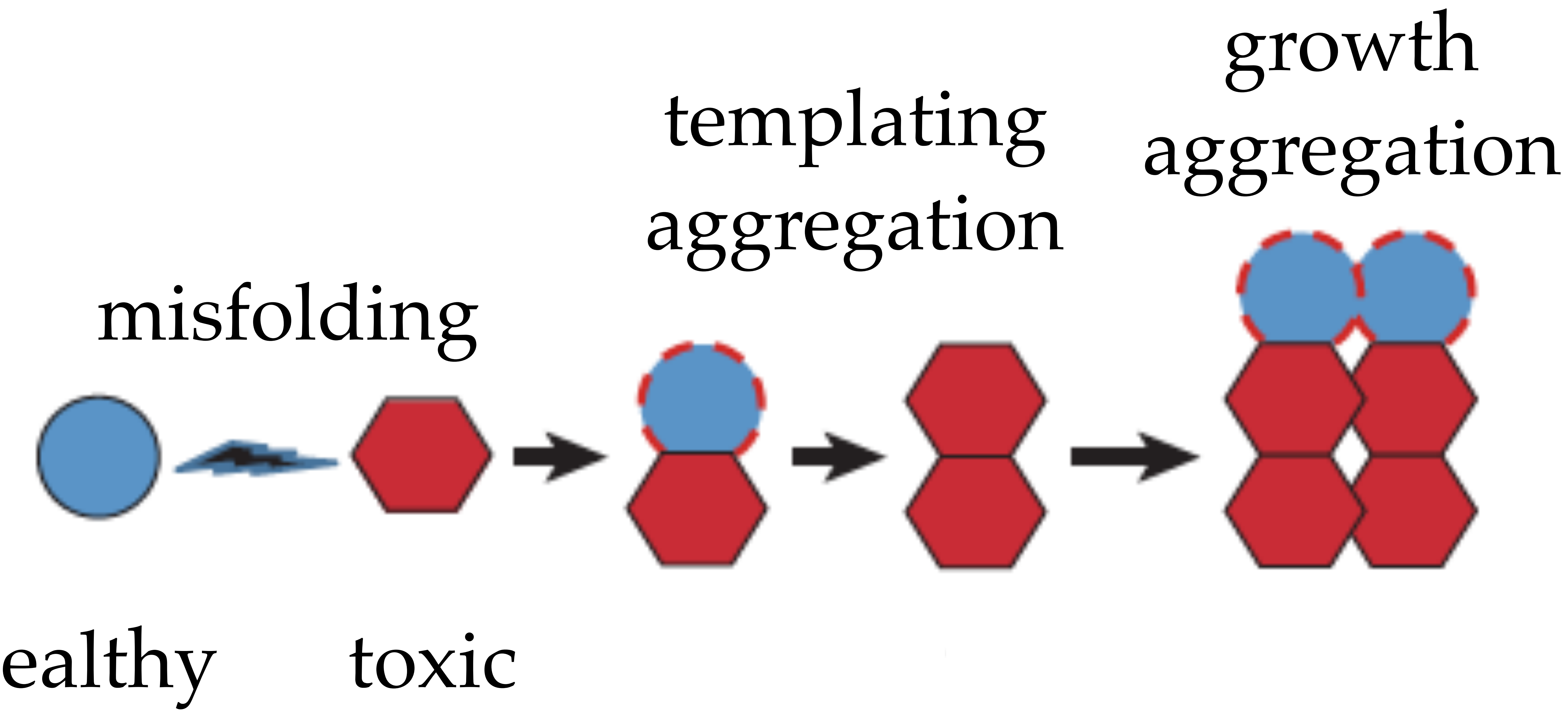
[from walker and jucker 2015]

prion-like mechanism


misfolding

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growth aggregation

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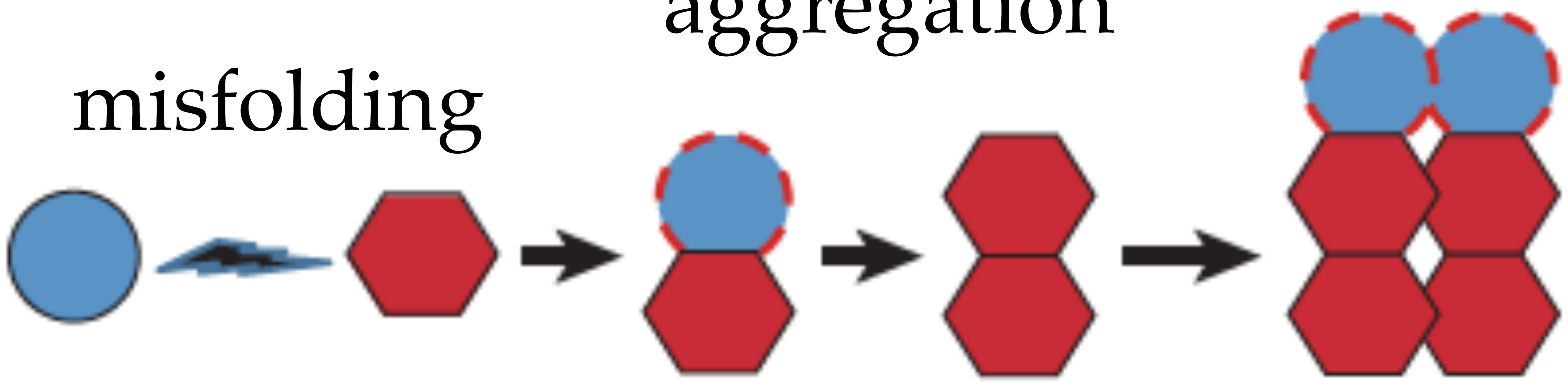


growth aggregation

templating aggregation

misfolding

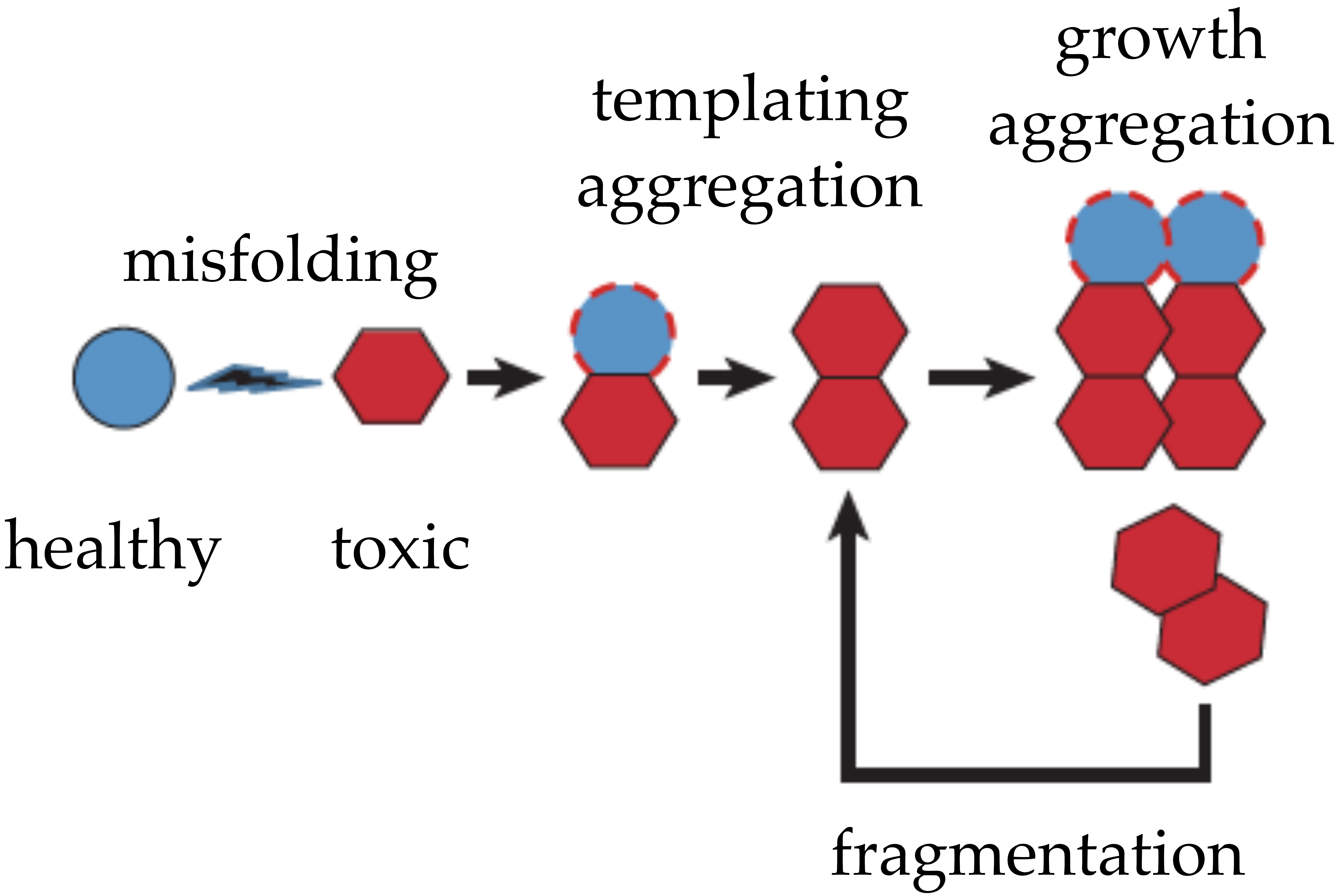
healthy

toxic

fragmentation

[from walker and jucker 2015]

prion-like mechanism



growth aggregation

templating aggregation

misfolding

healthy

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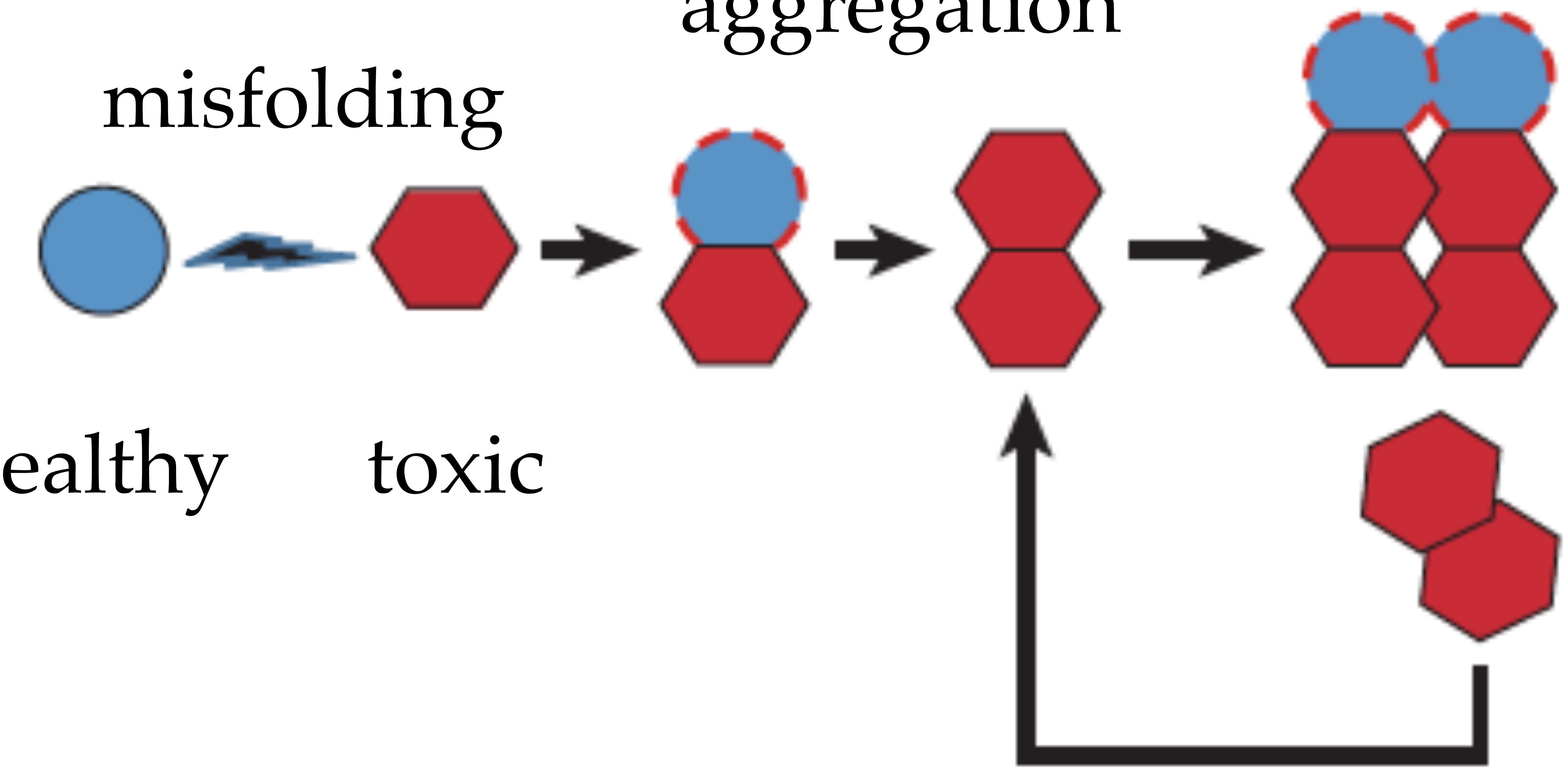
[from walker and jucker 2015]

prion-like mechanism

protofibrils



misfolding

templating
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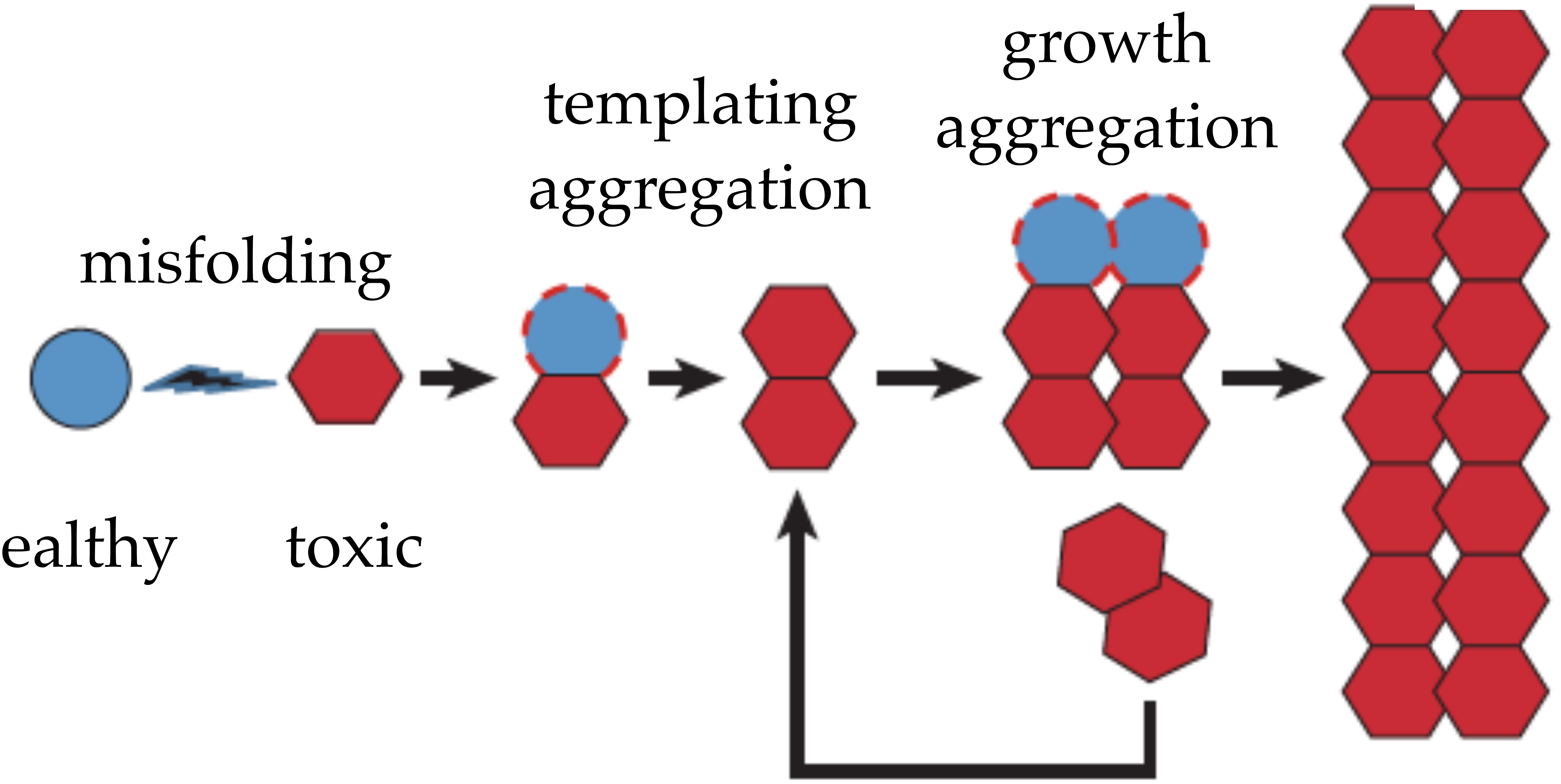
[from walker and jucker 2015]

prion-like mechanism



misfolding

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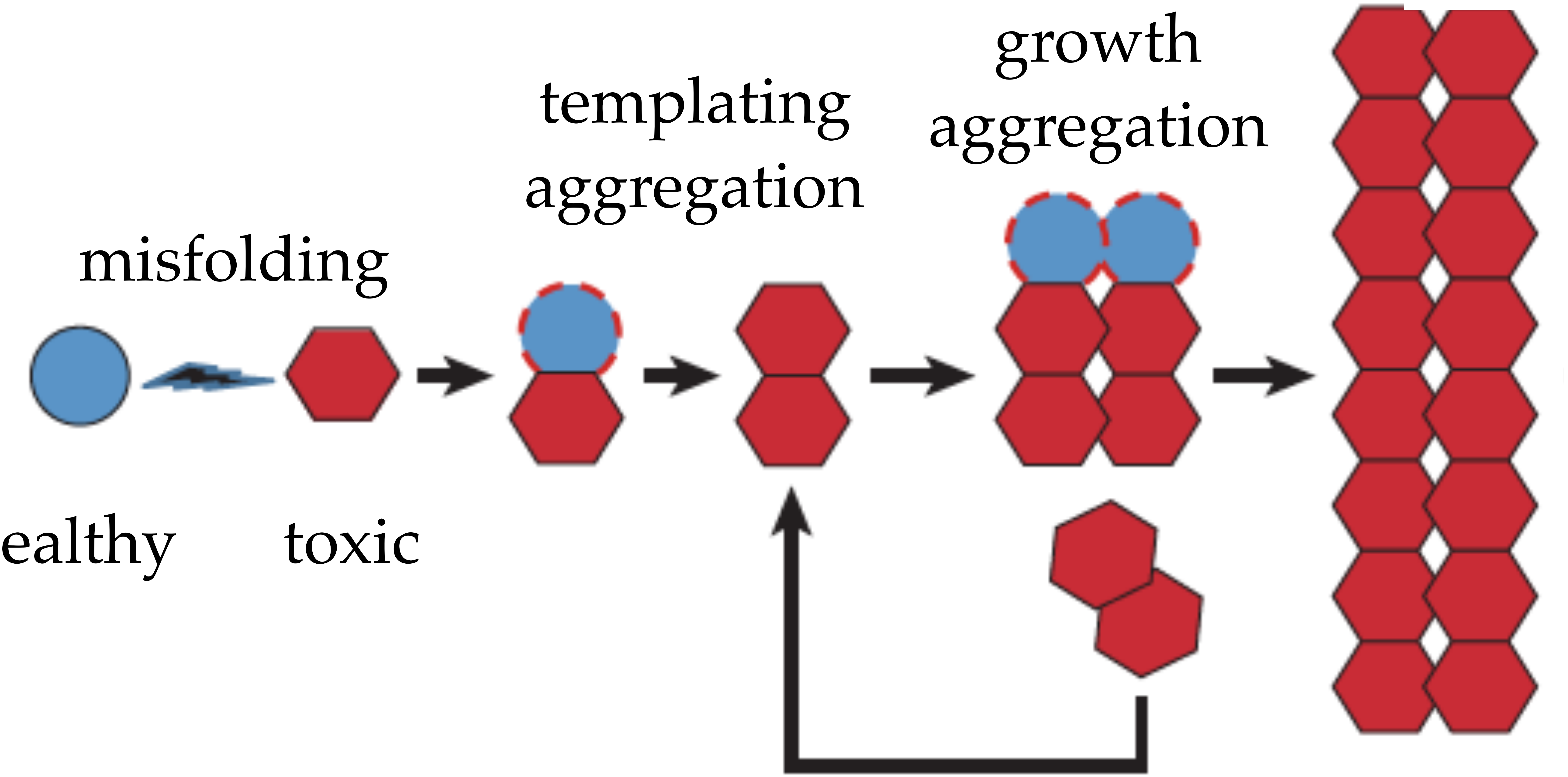

protofibrils

fibrils

growth aggregation

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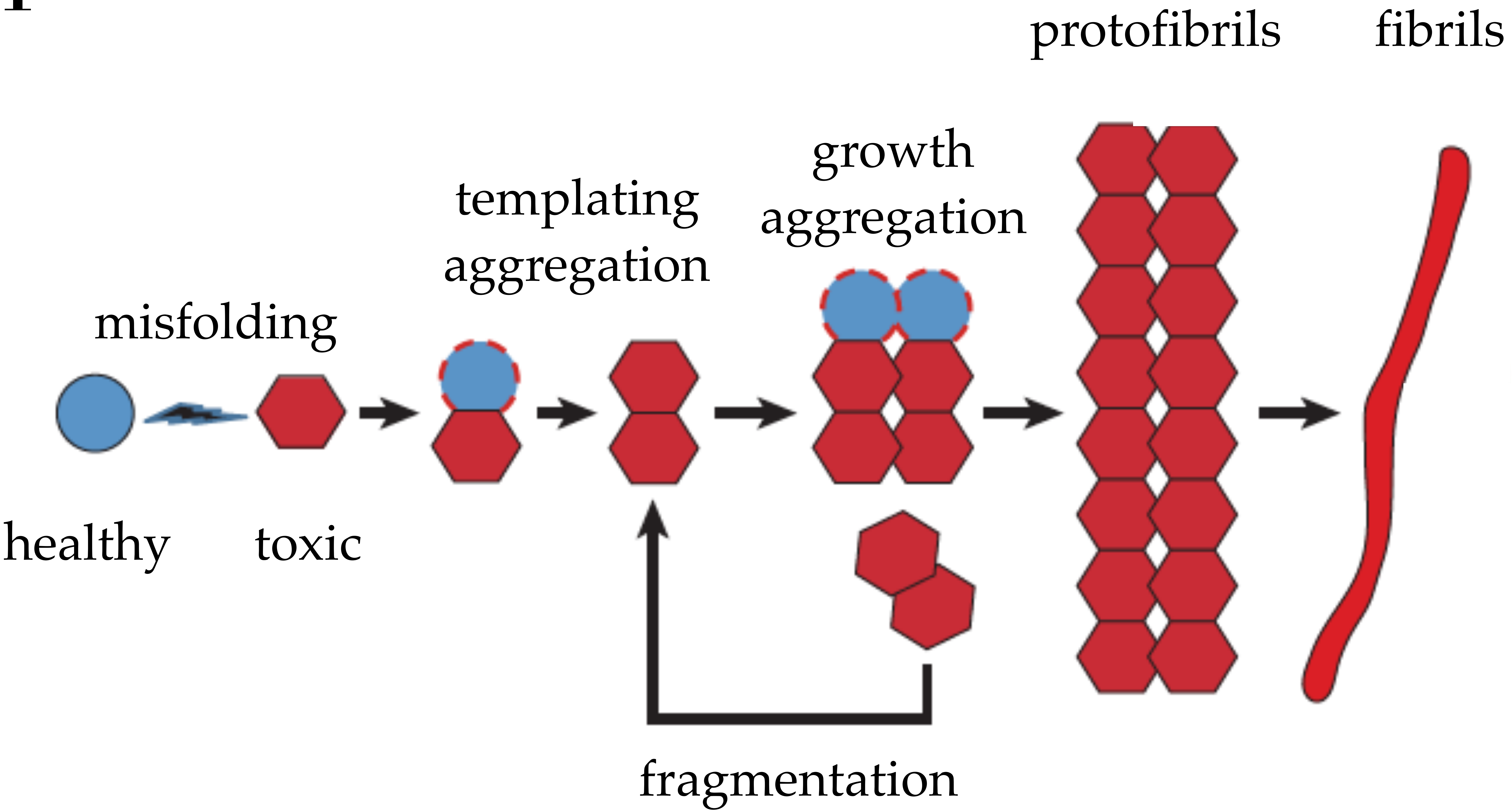
[from walker and jucker 2015]

prion-like mechanism



[from walker and jucker 2015]

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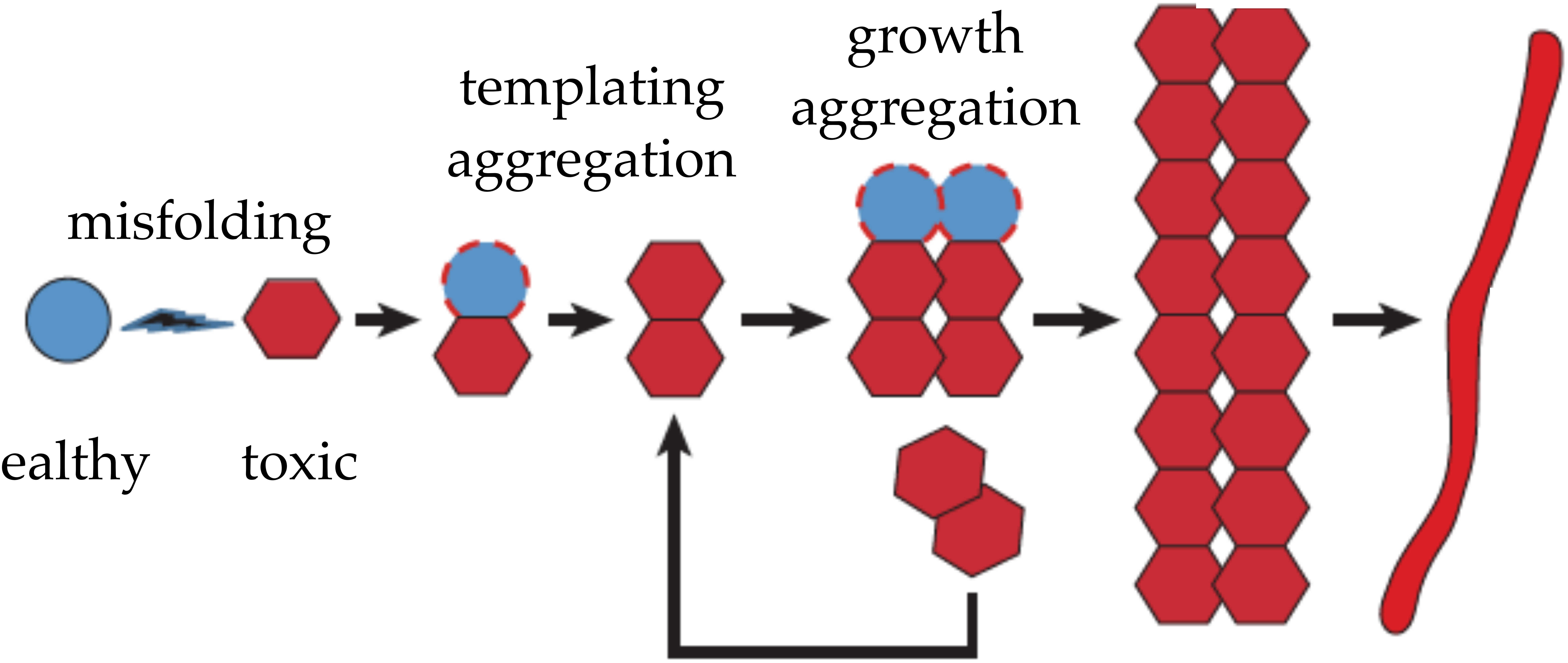

misfolding

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fibrils

NFT

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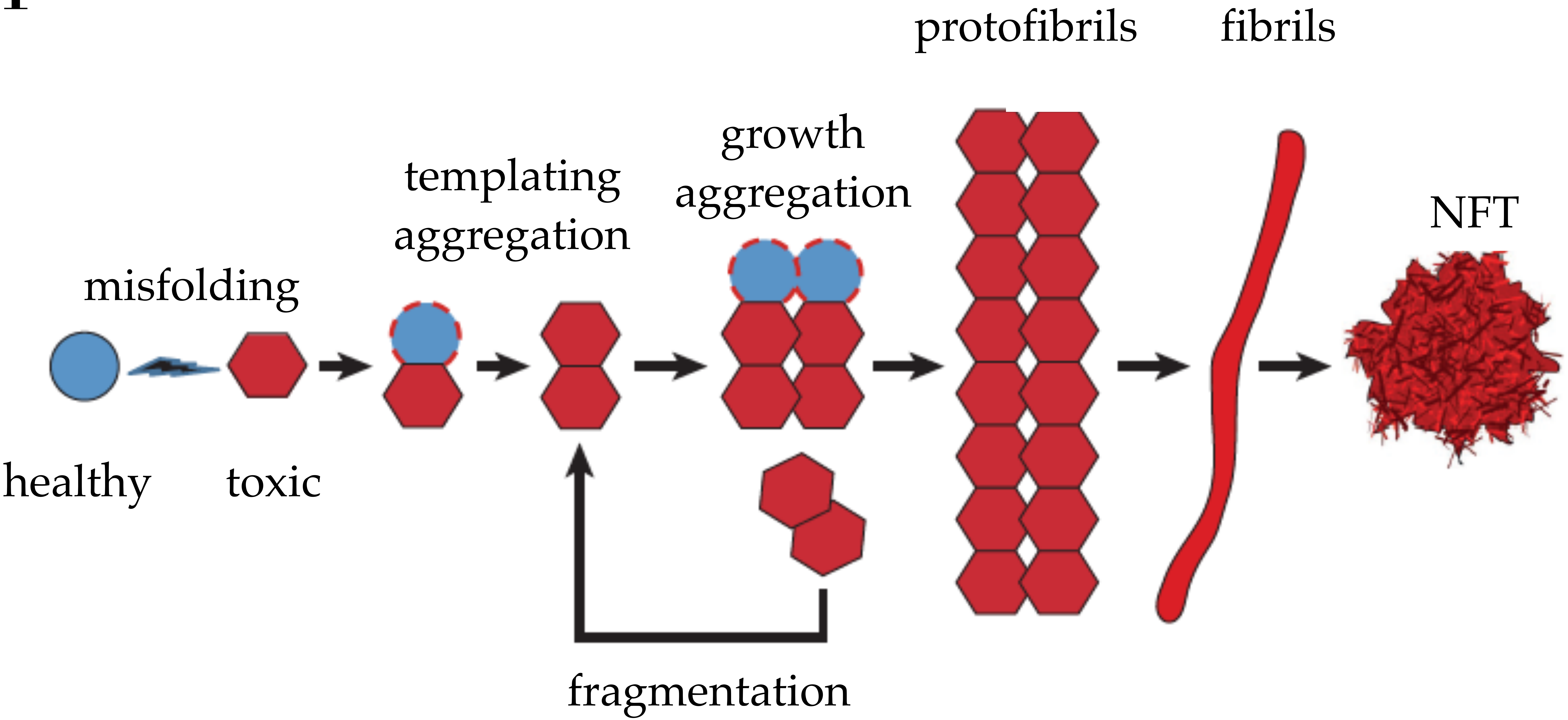

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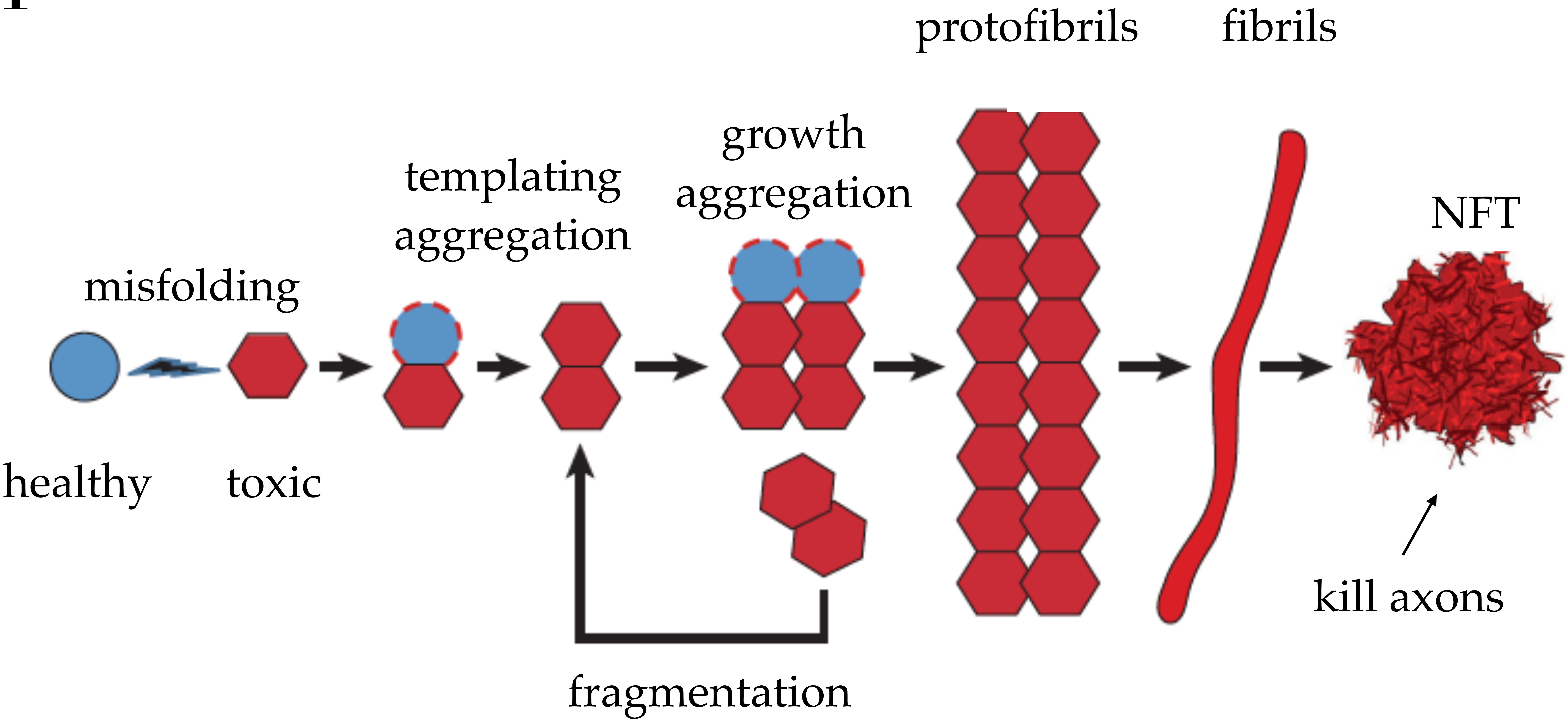
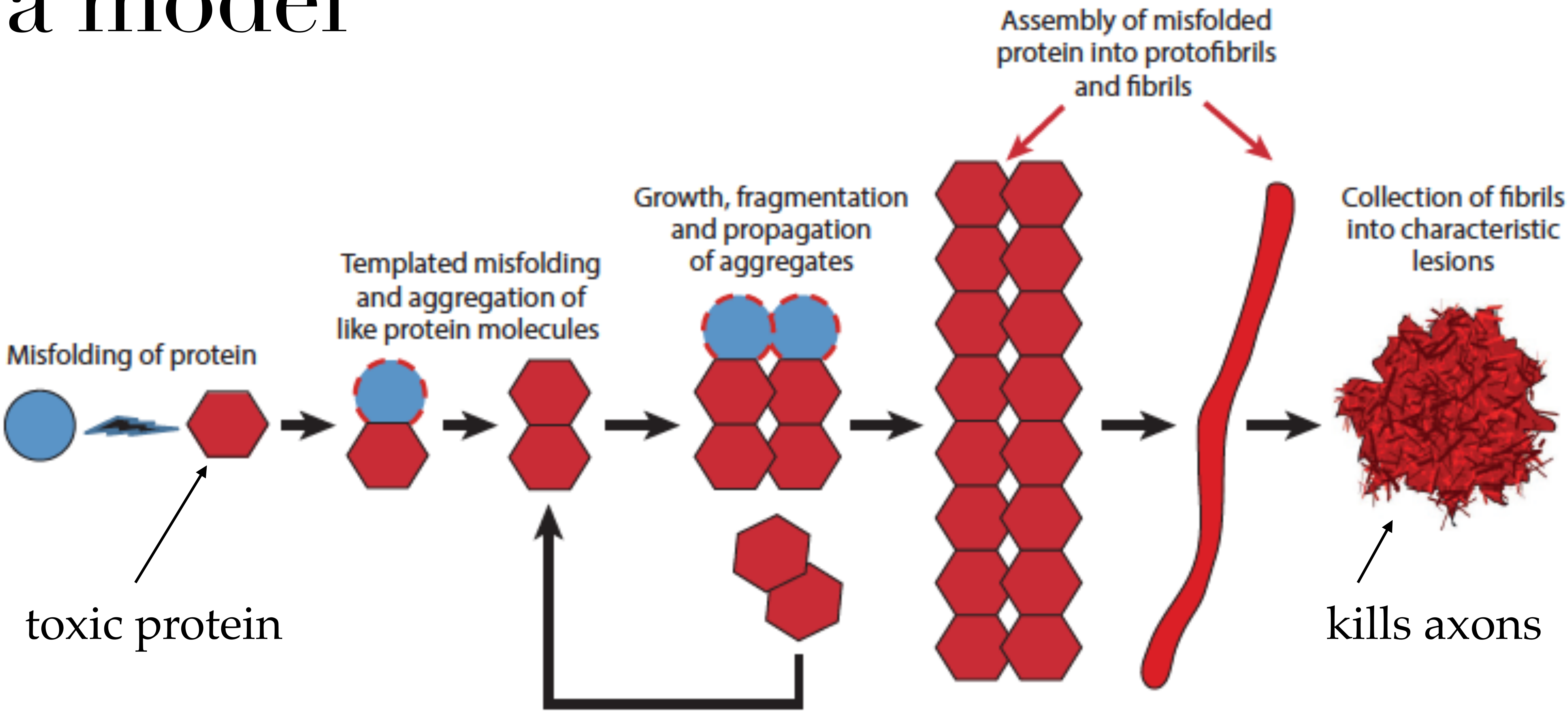


[from walker and jucker 2015]

a model

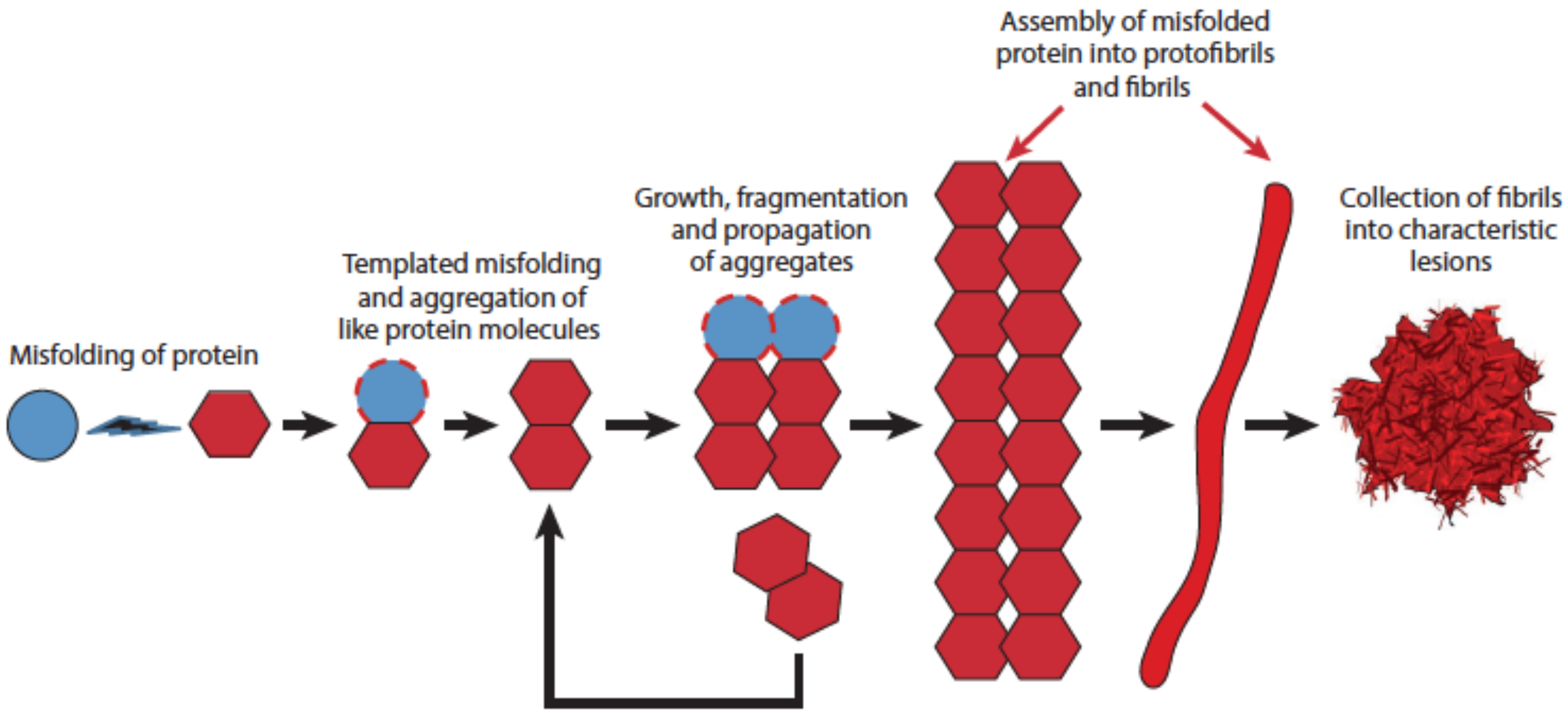


toxic protein

kills axons

[from walker and jucker 2015]

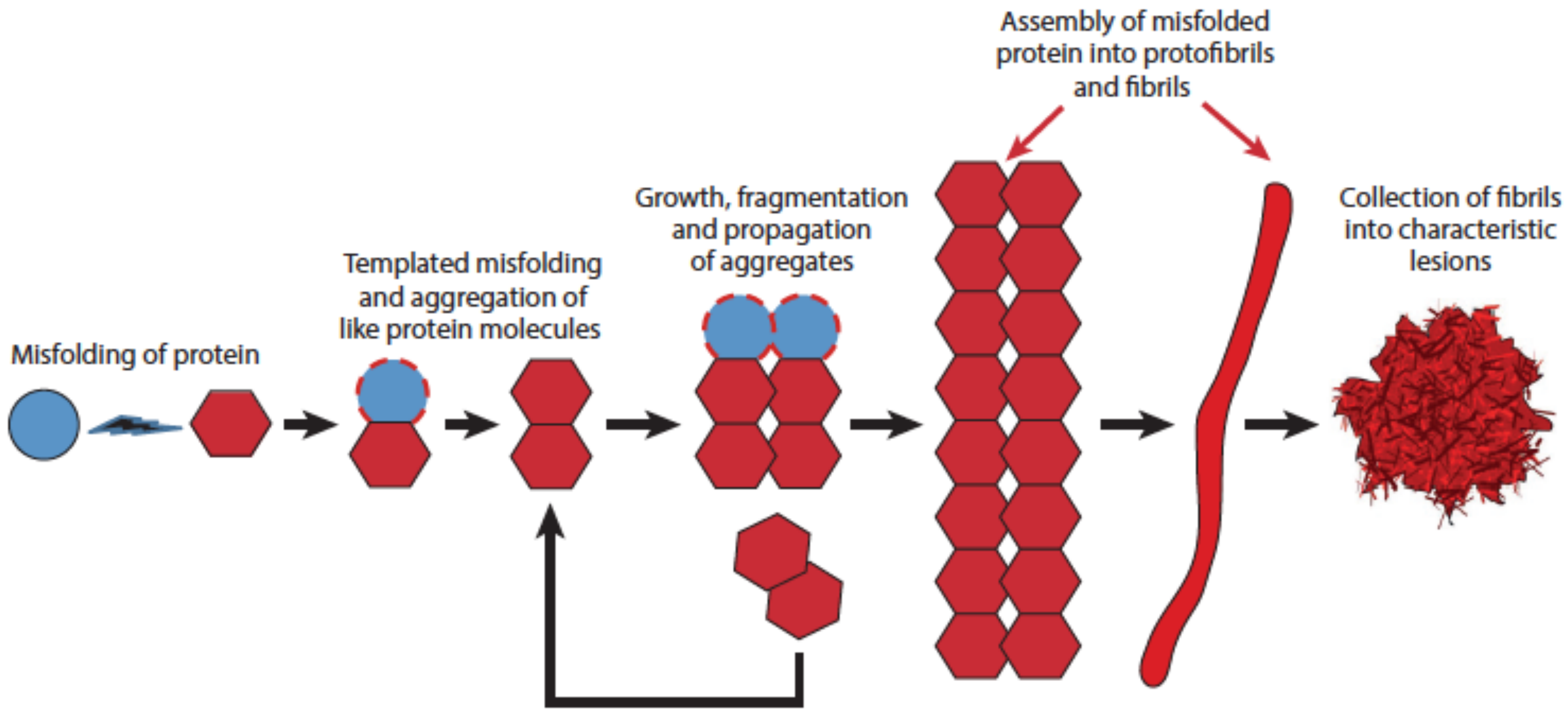
a model



[from walker and jucker 2015]

a model

- follow concentrations of good and toxic proteins in space and time



[from walker and jucker 2015]

a model

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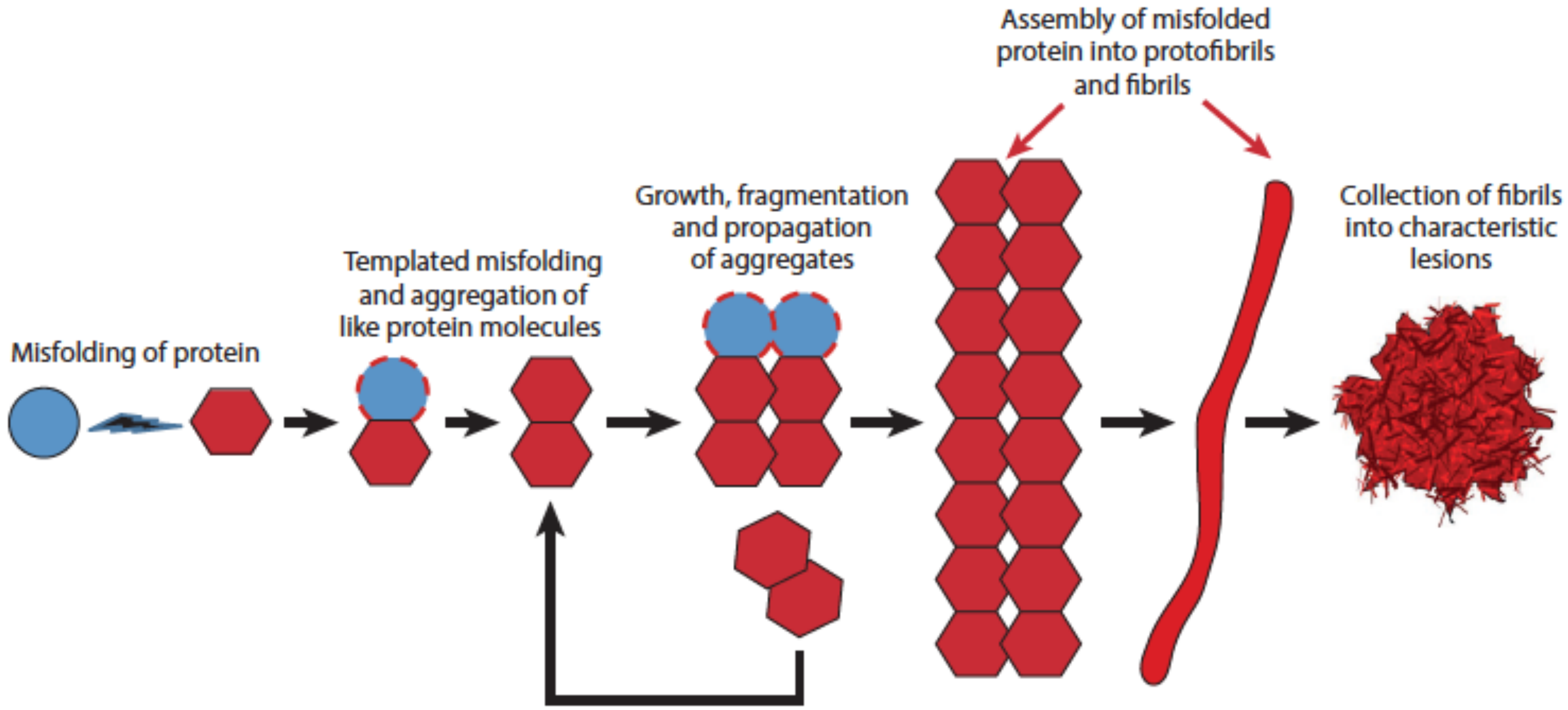
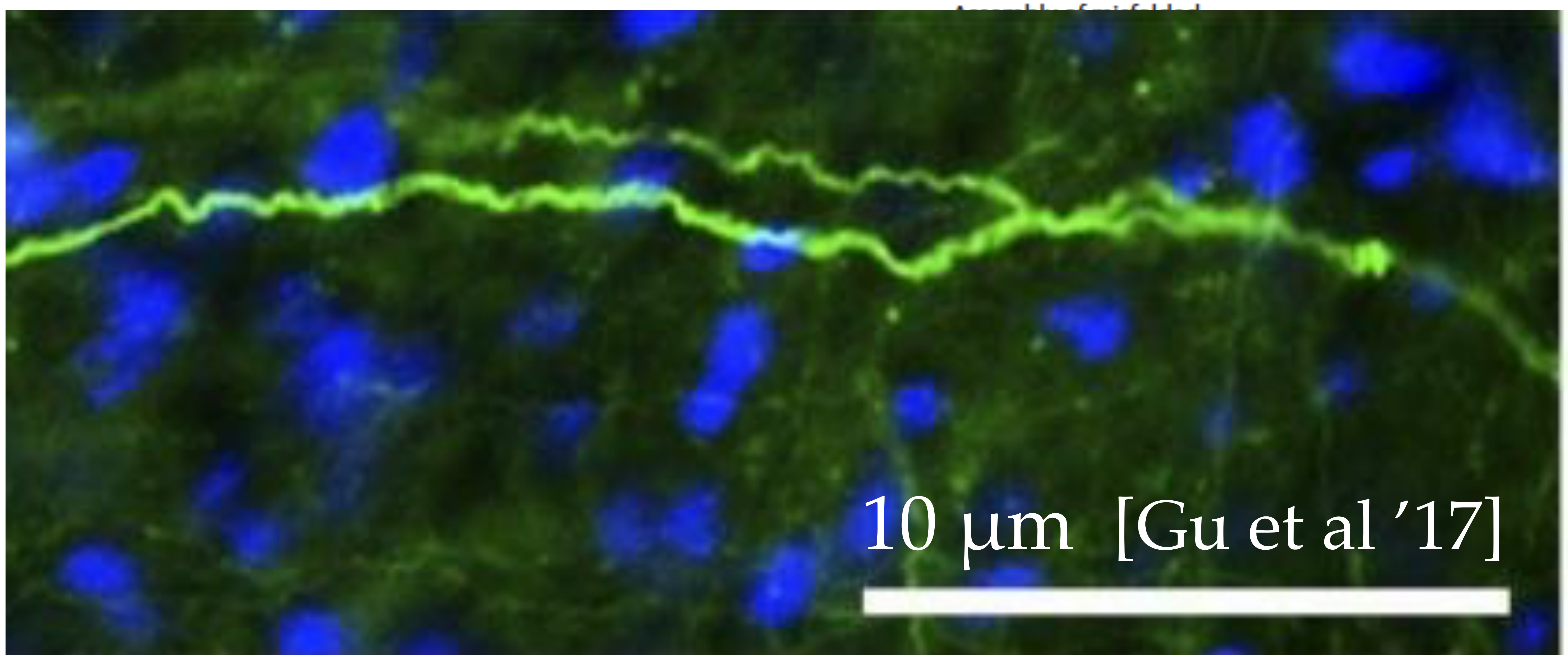


- rate equations for possible aggregation and fragmentation

[from walker and jucker 2015]

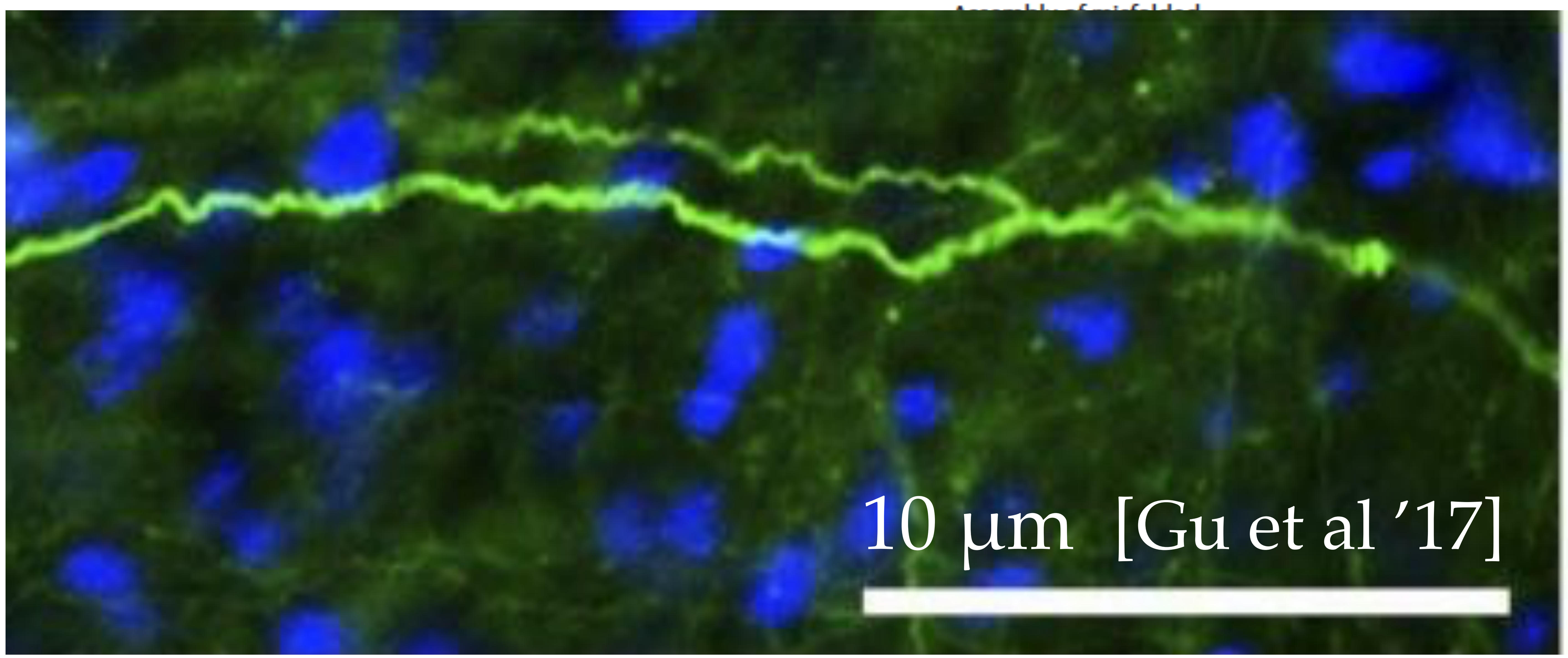
a model



- follow concentrations of good and toxic proteins in space and time
- rate equations for possible aggregation and fragmentation
- fast transport along axons, slow transport in the tissue

[from walker and jucker 2015]

a model



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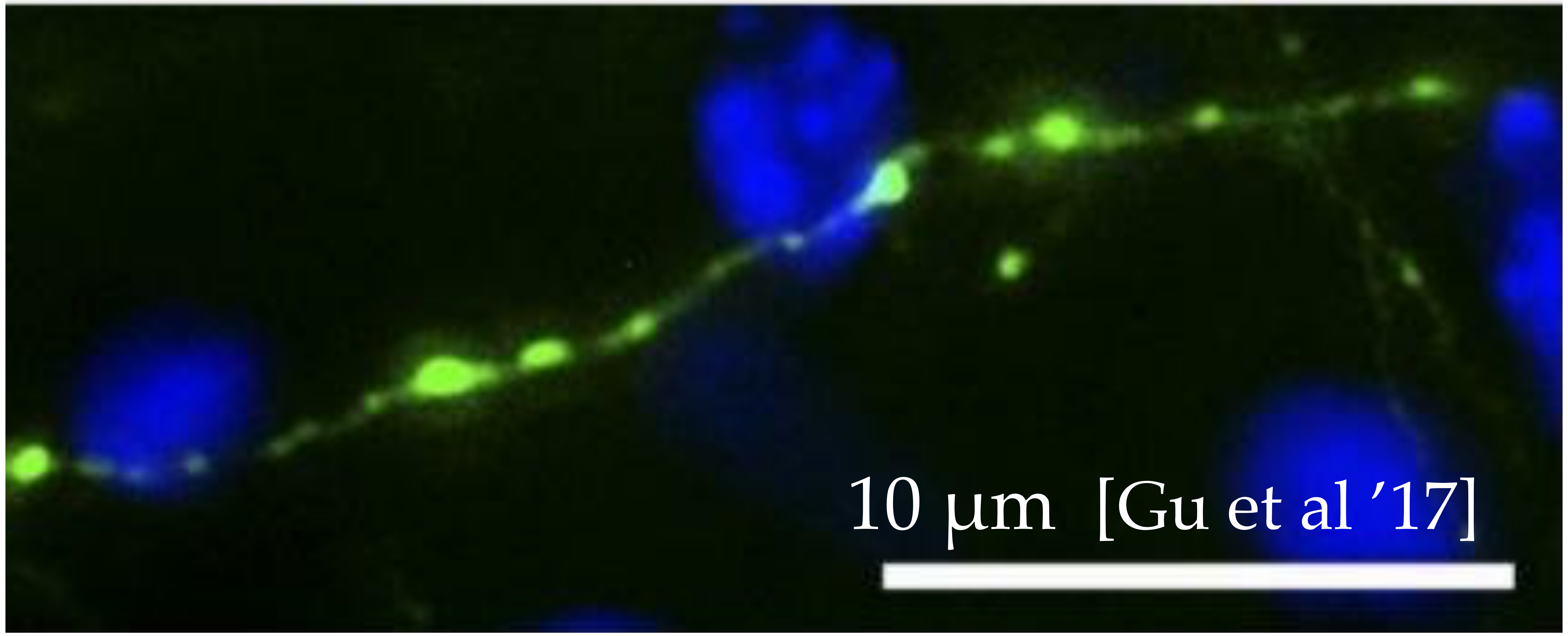

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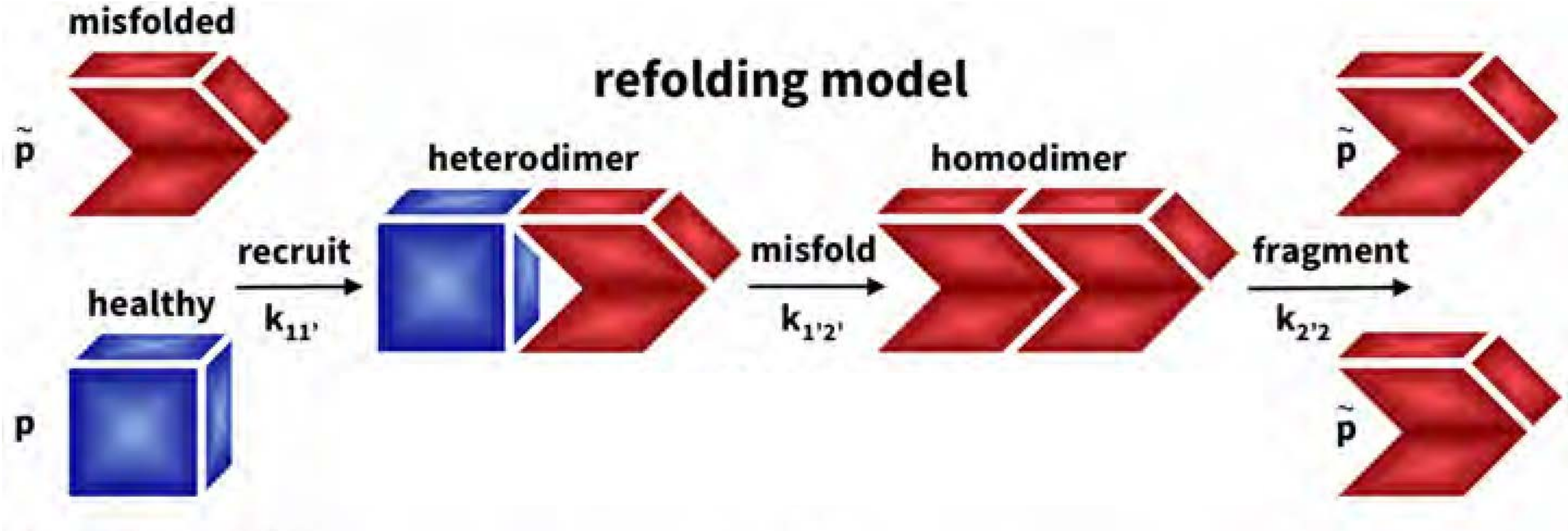
[from walker and jucker 2015]

kinetic model

- we assume two populations of healthy and toxic (misfolded) proteins.



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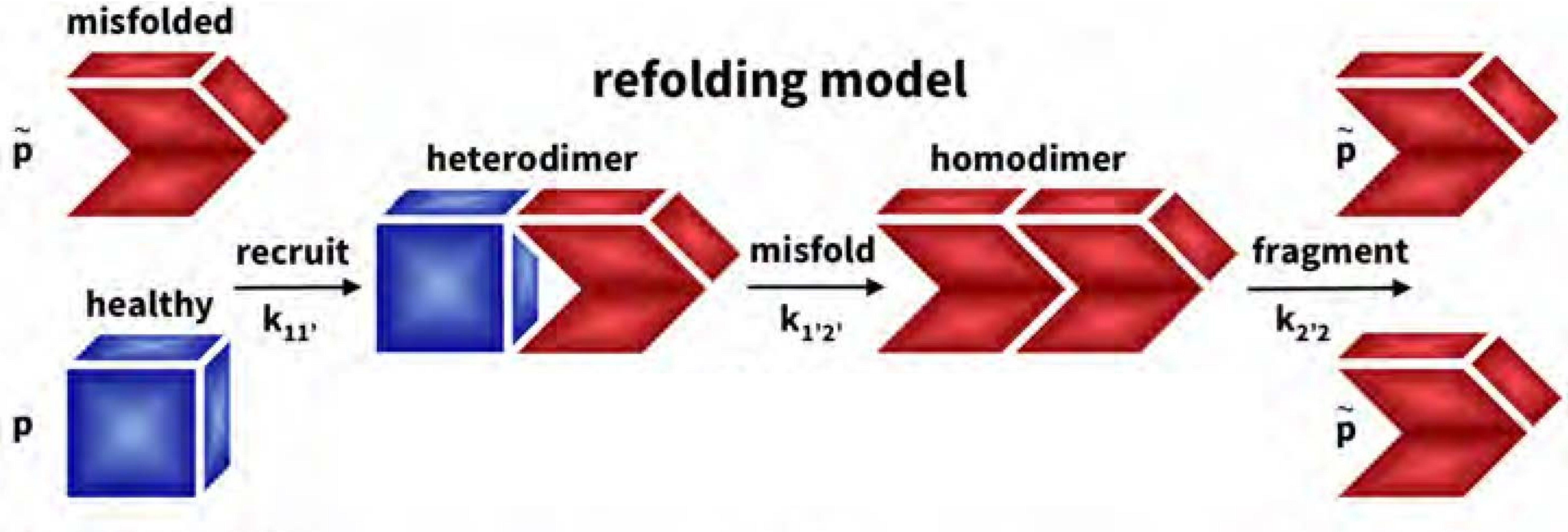
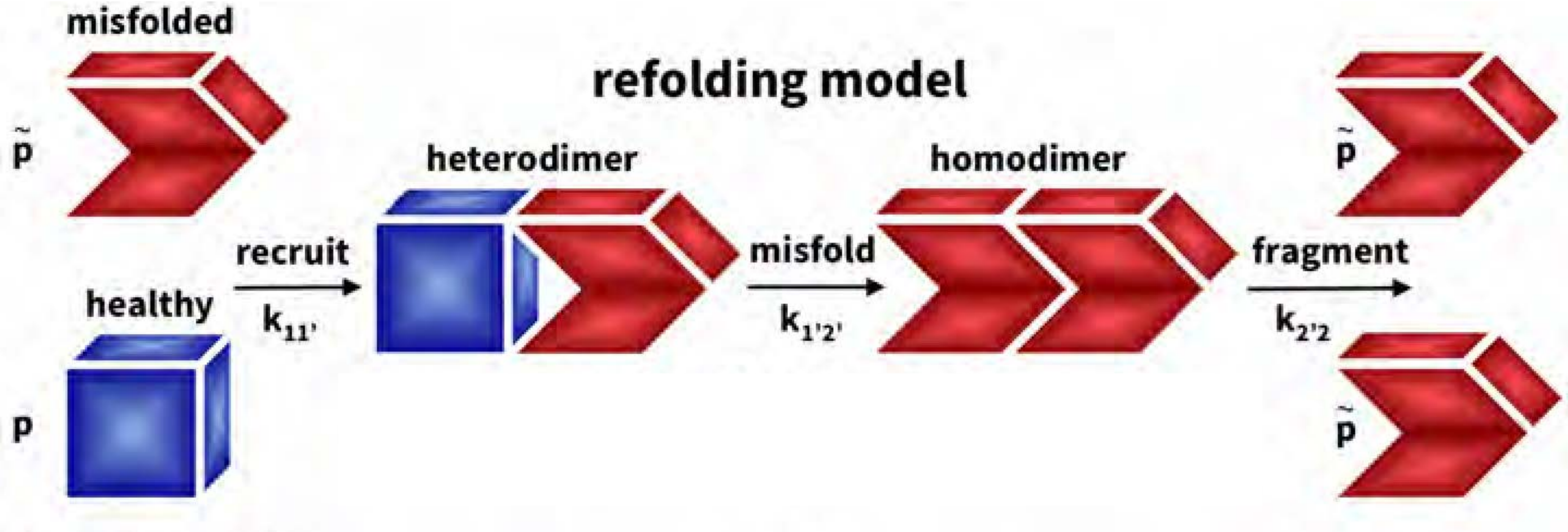


$$p + \widetilde{p} \xrightarrow{k_{11'}} p\widetilde{p}$$

kinetic model

- we assume two populations of healthy and toxic (misfolded) proteins.



$$p + \widetilde{p} \xrightarrow{k_{11'}} p\widetilde{p}$$

$$p + \widetilde{p} \xrightarrow{k_{1'2'}} \widetilde{p}\widetilde{p}$$

kinetic model

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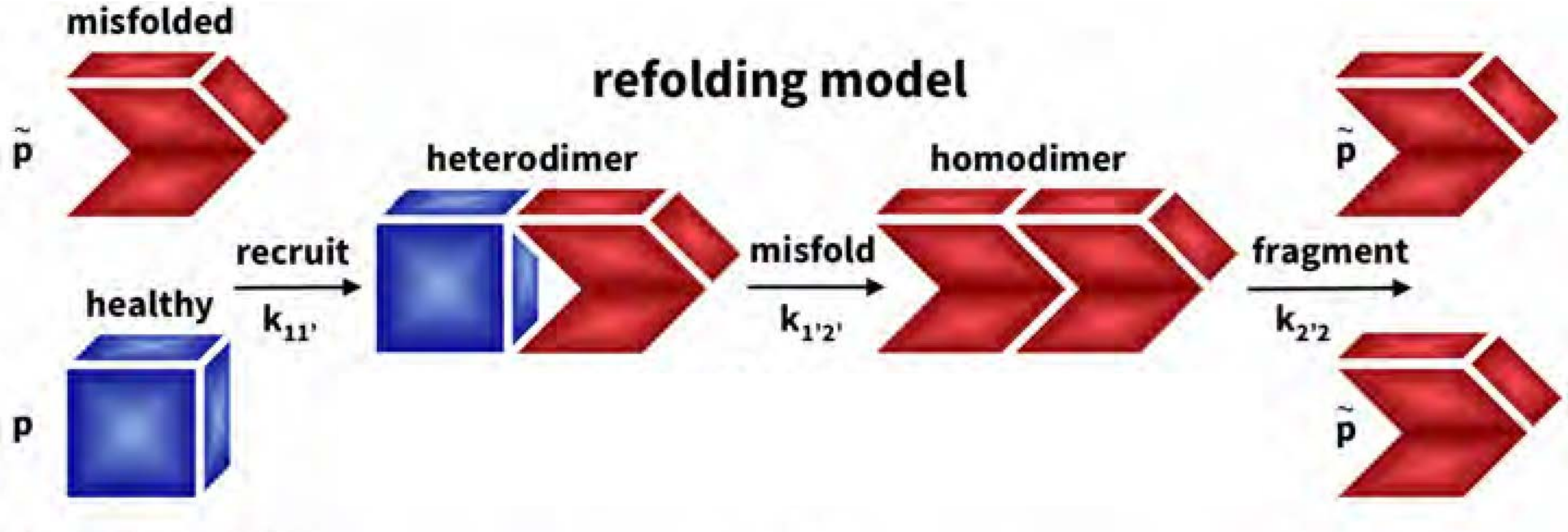

$$p + \widetilde{p} \xrightarrow{k_{11'}} p\widetilde{p} \qquad p + \widetilde{p} \xrightarrow{k_{1'2'}} \widetilde{p}\widetilde{p} \qquad \widetilde{p}\widetilde{p} \xrightarrow{k_{2'2'}} \widetilde{p} + \widetilde{p}$$

kinetic model

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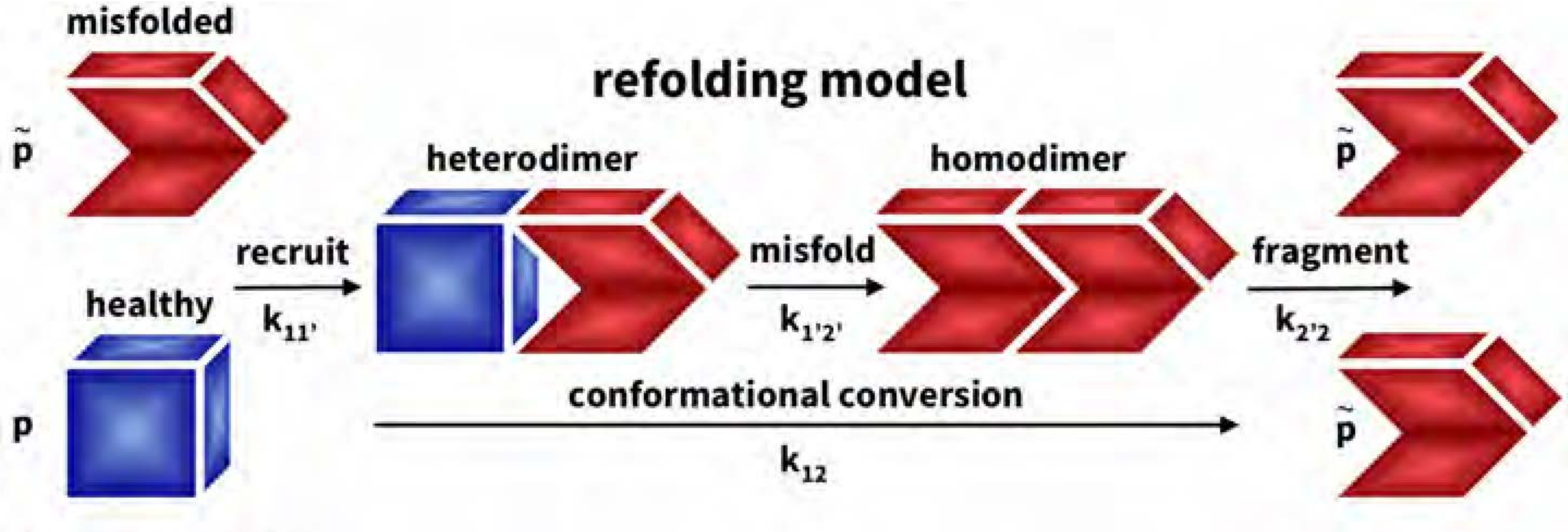
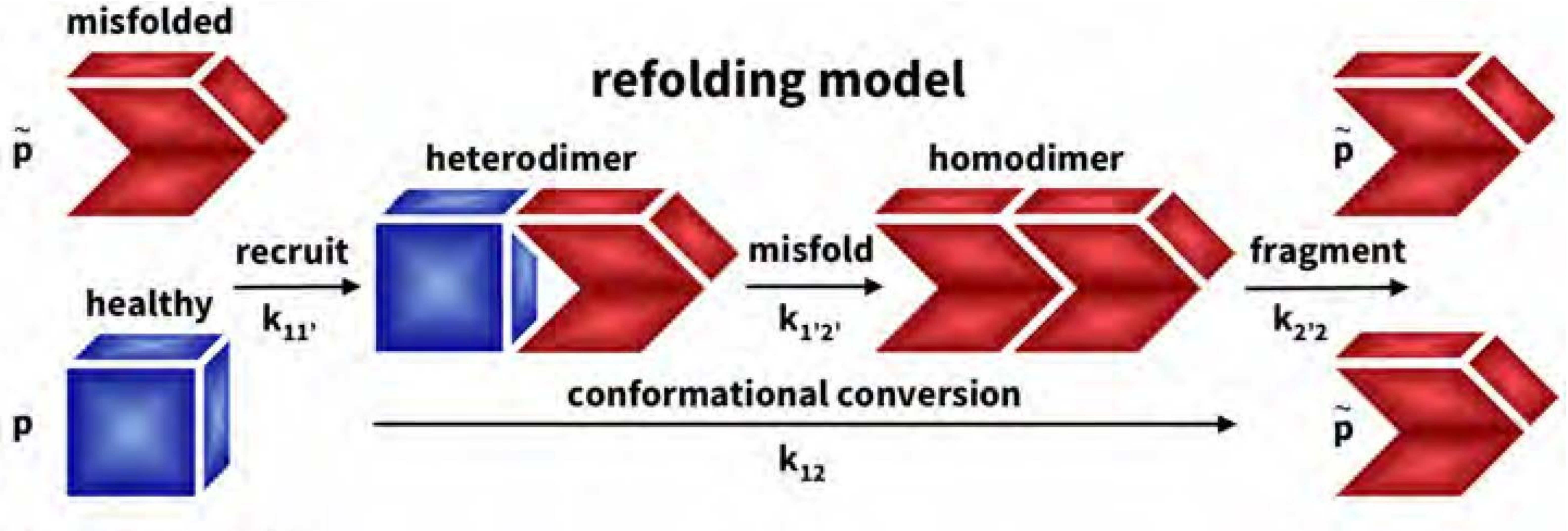


$$p + \widetilde{p} \xrightarrow{k_{11'}} p\widetilde{p} \qquad p + \widetilde{p} \xrightarrow{k_{1'2'}} \widetilde{p}\widetilde{p} \qquad \widetilde{p}\widetilde{p} \xrightarrow{k_{2'2'}} \widetilde{p} + \widetilde{p}$$

kinetic model

- we assume two populations of healthy and toxic (misfolded) proteins.



$$p + \widetilde{p} \xrightarrow{k_{11'}} p\widetilde{p} \qquad p + \widetilde{p} \xrightarrow{k_{1'2'}} \widetilde{p}\widetilde{p} \qquad \widetilde{p}\widetilde{p} \xrightarrow{k_{2'2'}} \widetilde{p} + \widetilde{p}$$

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

kinetic model

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

kinetic model

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + k_0 - k_1 p - k_{12} p \widetilde{p}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) \qquad - \widetilde{k}_1 \widetilde{p} + k_{12} p \widetilde{p}$$

kinetic model

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + \overset{\textbf{production}}{\boxed{k_0}} - k_1 p - k_{12} p \widetilde{p}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) \qquad - \widetilde{k}_1 \widetilde{p} + k_{12} p \widetilde{p}$$

kinetic model

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + \overset{\text{production}}{k_0} - \overset{\text{clearance}}{k_1 p} - k_{12} p \widetilde{p}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) - \widetilde{k}_1 \widetilde{p} + k_{12} p \widetilde{p}$$

kinetic model

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + \overbrace{k_0}^{\text{production}} - \overbrace{k_1 p}^{\text{clearance}} - k_{12} p \widetilde{p}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) - \underbrace{\widetilde{k}_1 \widetilde{p}}_{\text{clearance}} + k_{12} p \widetilde{p}$$

kinetic model

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + \overset{\text{production}}{\boxed{k_0}} - \overset{\text{clearance}}{\boxed{k_1 p}} - \overset{\text{conversion}}{\boxed{k_{12} p \widetilde{p}}}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) - \underset{\text{clearance}}{\boxed{\widetilde{k}_1 \widetilde{p}}} + k_{12} p \widetilde{p}$$

kinetic model

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + \overbrace{k_0}^{\text{production}} - \overbrace{k_1 p}^{\text{clearance}} - \overbrace{k_{12} p \widetilde{p}}^{\text{conversion}}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) \qquad - \underbrace{\widetilde{k}_1 \widetilde{p}}_{\text{clearance}} + \underbrace{k_{12} p \widetilde{p}}_{\text{conversion}}$$

kinetic model

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + \overbrace{k_0}^{\textbf{production}} - \overbrace{k_1 p}^{\textbf{clearance}} - \overbrace{k_{12} p \widetilde{p}}^{\textbf{conversion}}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) - \underbrace{\widetilde{k}_1 \widetilde{p}}_{\textbf{clearance}} + \underbrace{k_{12} p \widetilde{p}}_{\textbf{conversion}}$$

for $p \gg \widetilde{p}$ and p at equilibrium we have

kinetic model

$$p + \widetilde{p} \xrightarrow{k_{12}} \widetilde{p} + \widetilde{p}$$

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + \overbrace{k_0}^{\text{production}} - \overbrace{k_1 p}^{\text{clearance}} - \overbrace{k_{12} p \widetilde{p}}^{\text{conversion}}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) - \underbrace{\widetilde{k}_1 \widetilde{p}}_{\text{clearance}} + \underbrace{k_{12} p \widetilde{p}}_{\text{conversion}}$$

for $p \gg \widetilde{p}$ and p at equilibrium we have

$$\boxed{\frac{\partial c}{\partial t} = \mathrm{Div}(\mathbf{D} \cdot \nabla c) + \alpha c(1 - c)}$$

kinetic model

$$p + \tilde{p} \xrightarrow{k_{12}} \tilde{p} + \tilde{p}$$

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + \overset{\text{production}}{k_0} - \overset{\text{clearance}}{k_1 p} - \overset{\text{conversion}}{k_{12} p \tilde{p}}$$

$$\frac{\partial \tilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\tilde{p}} \cdot \nabla \tilde{p}) - \underset{\text{clearance}}{\tilde{k}_1 \tilde{p}} + \underset{\text{conversion}}{k_{12} p \tilde{p}}$$

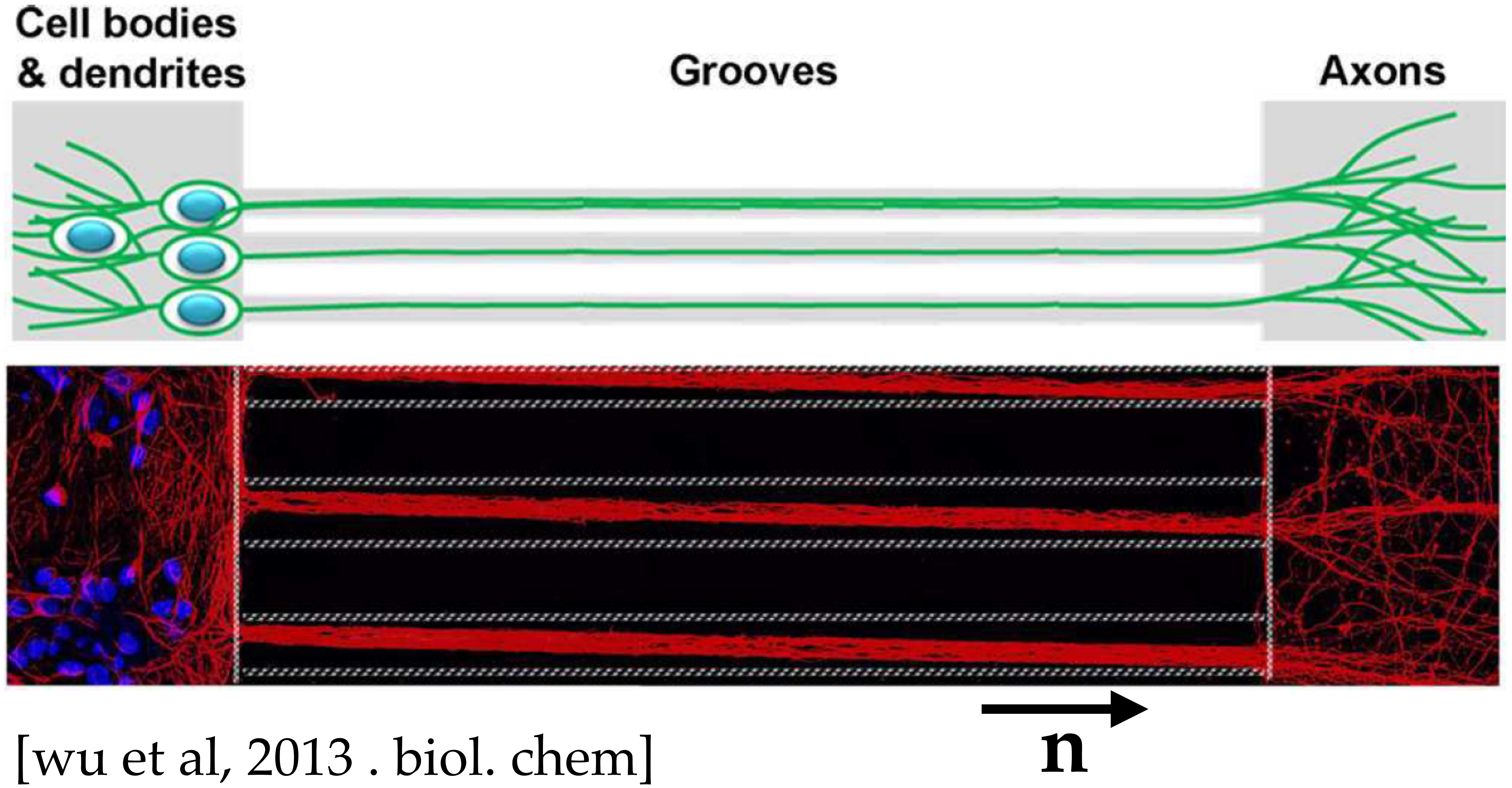
for $p \gg \tilde{p}$ and p at equilibrium we have

$$\boxed{\frac{\partial c}{\partial t} = \mathrm{Div}(\mathbf{D} \cdot \nabla c) + \alpha c(1 - c)}$$

anisotropic fisher equation (1937)

anisotropic diffusion

$$\boxed{\frac{\partial c}{\partial t} = \mathrm{Div}(\mathbf{D} \cdot \nabla c) + \alpha c(1 - c)}$$



[wu et al, 2013 . biol. chem]

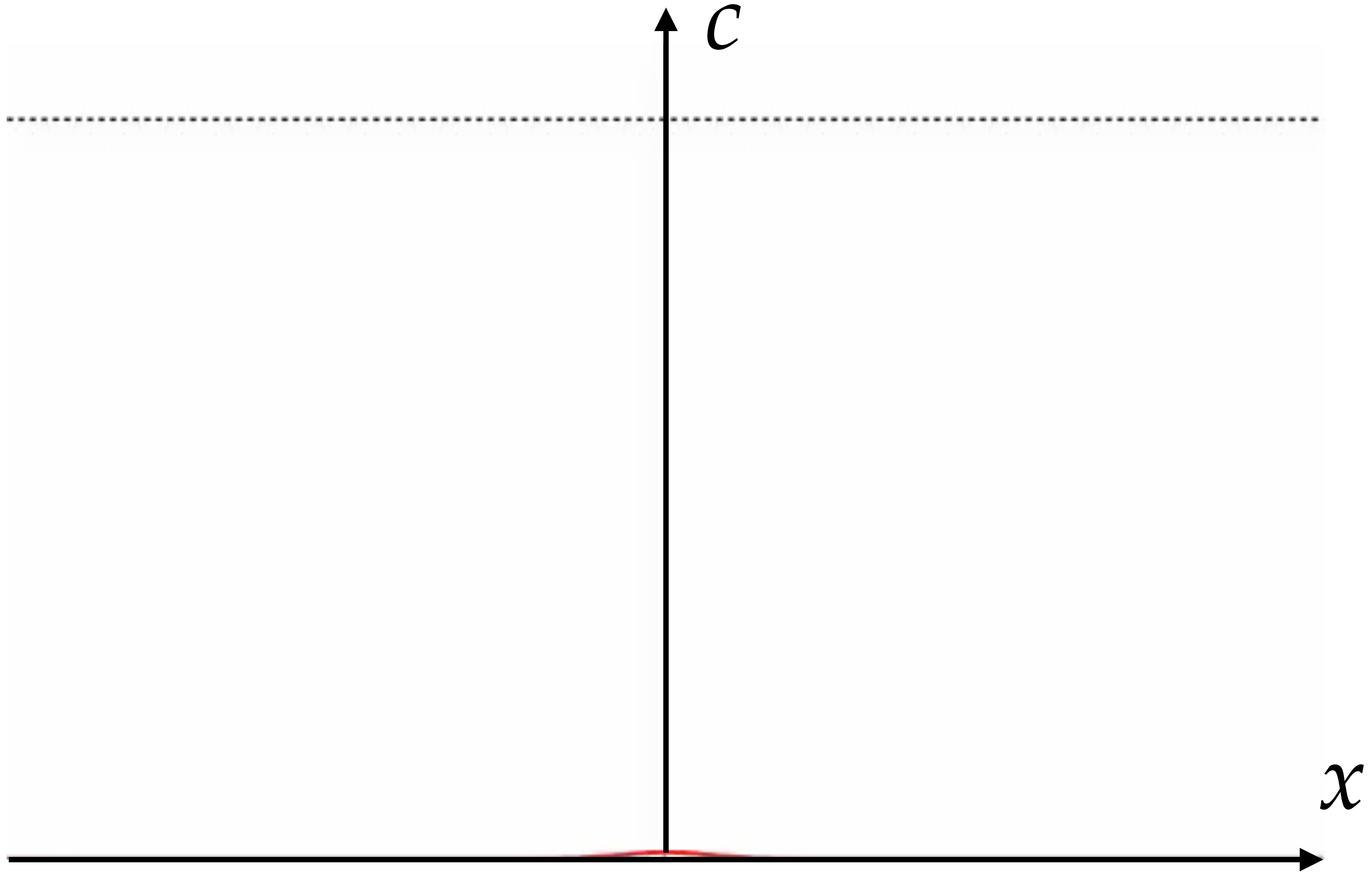
fast axonal transport d
along **n**

slow extracellular diffusion δ
perpendicular to **n**

anisotropic diffusion

$$\boxed{\frac{\partial c}{\partial t} = \mathrm{Div}(\mathbf{D} \cdot \nabla c) + \alpha c(1 - c)}$$

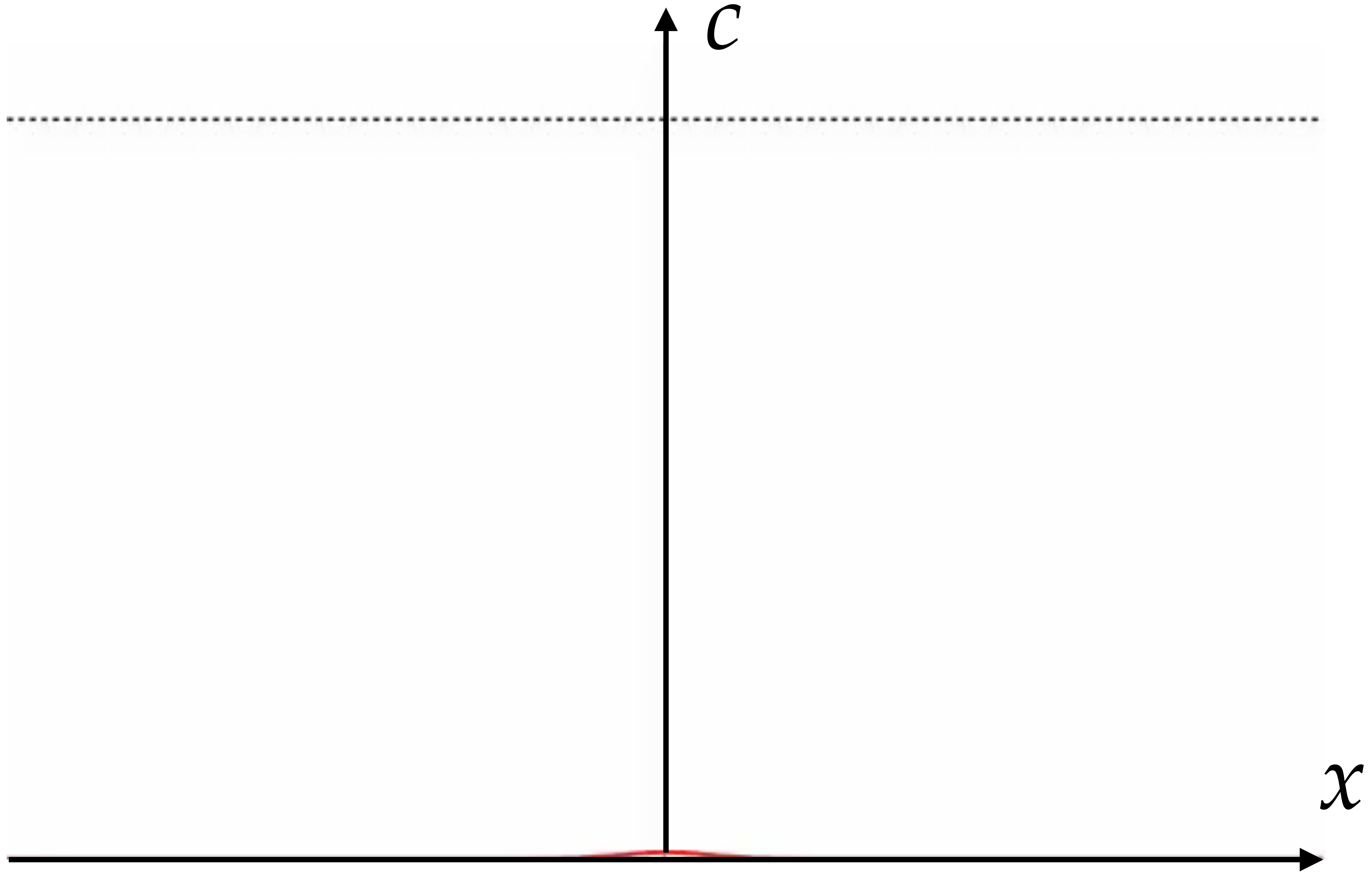
in one dimension:



anisotropic diffusion

$$\boxed{\frac{\partial c}{\partial t} = \mathrm{Div}(\mathbf{D} \cdot \nabla c) + \alpha c(1 - c)}$$

in one dimension:



anisotropic diffusion

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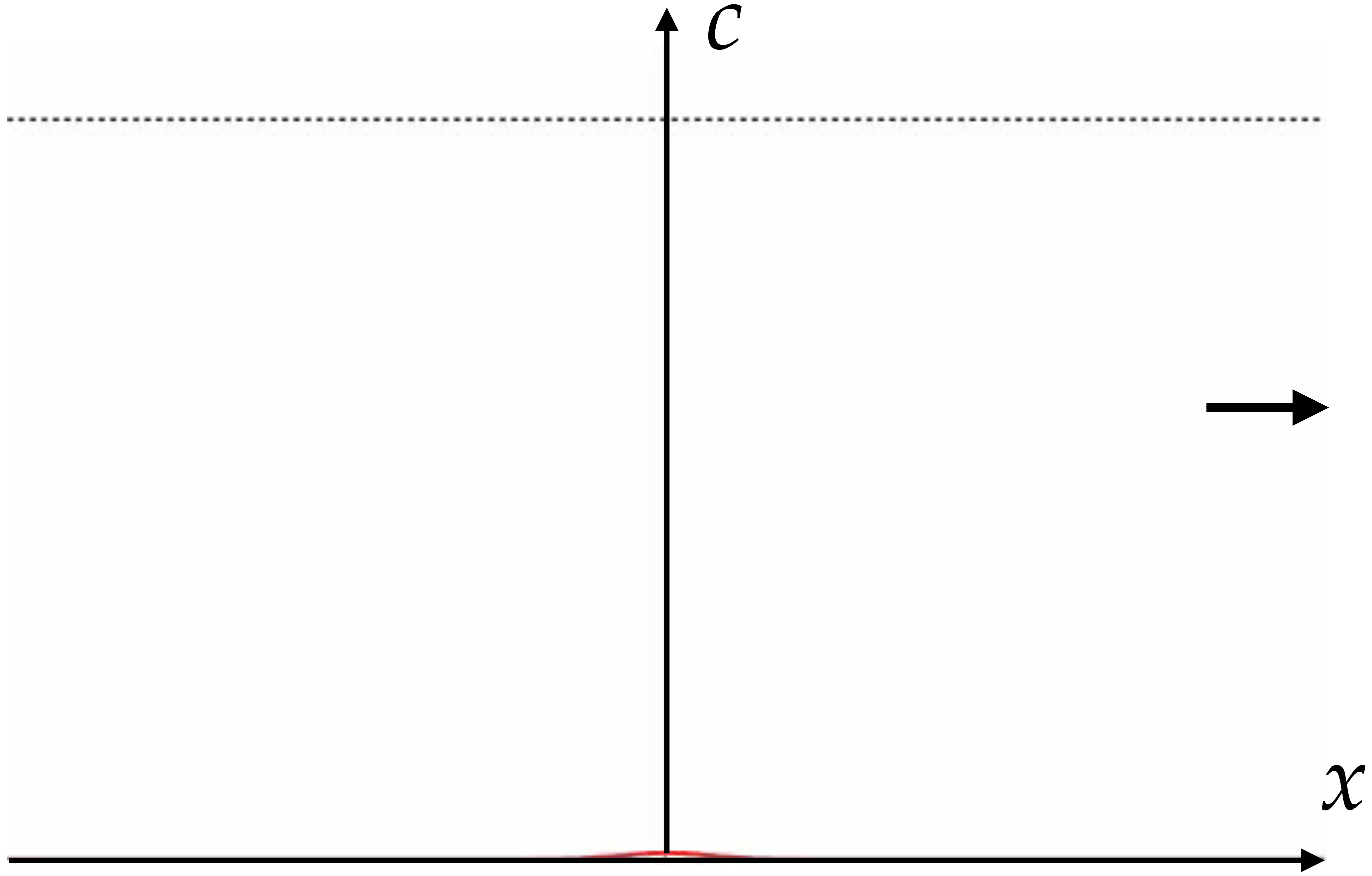
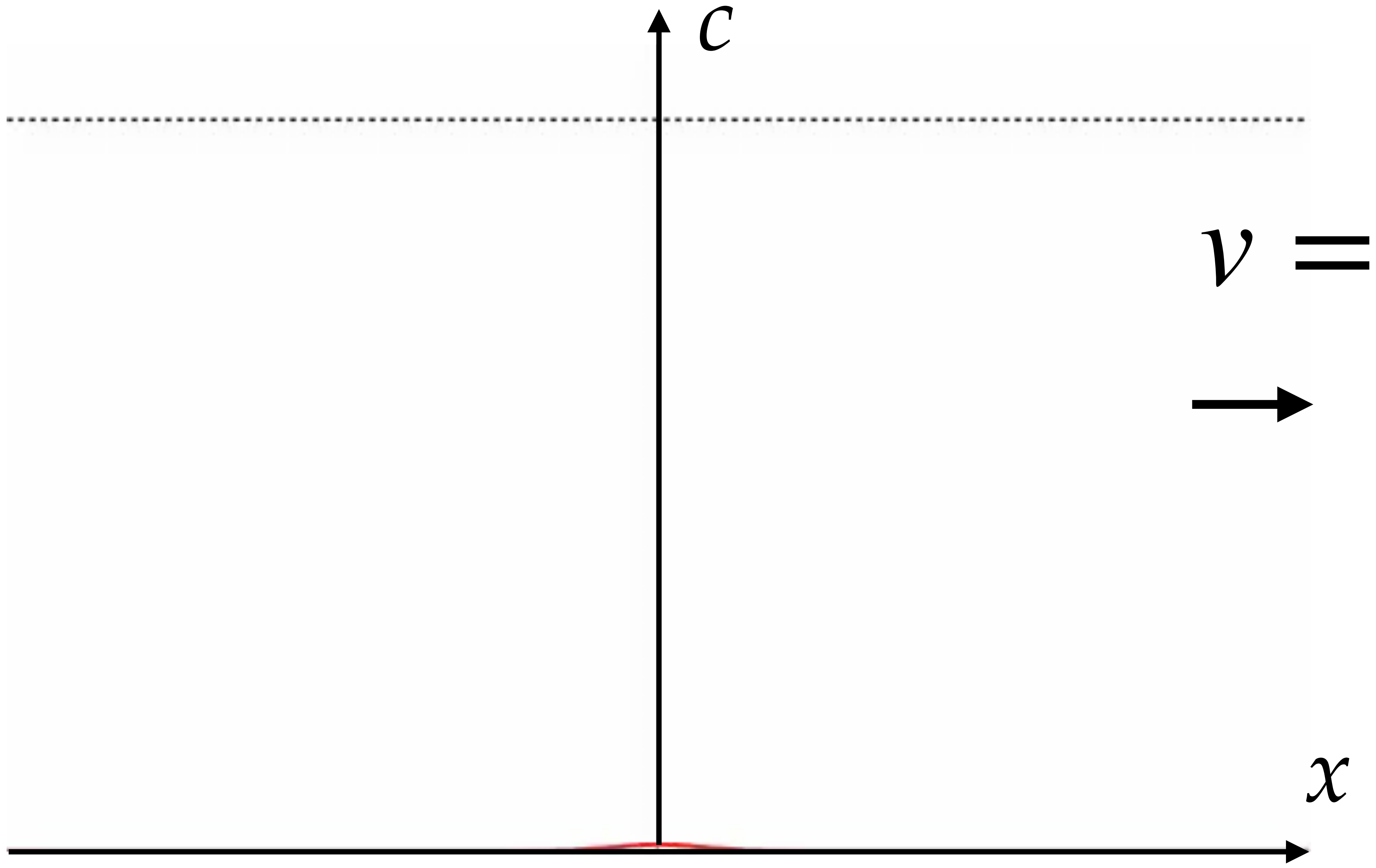
in one dimension:



anisotropic diffusion

$$\boxed{\frac{\partial c}{\partial t} = \mathrm{Div}(\mathbf{D} \cdot \nabla c) + \alpha c(1 - c)}$$

in one dimension:

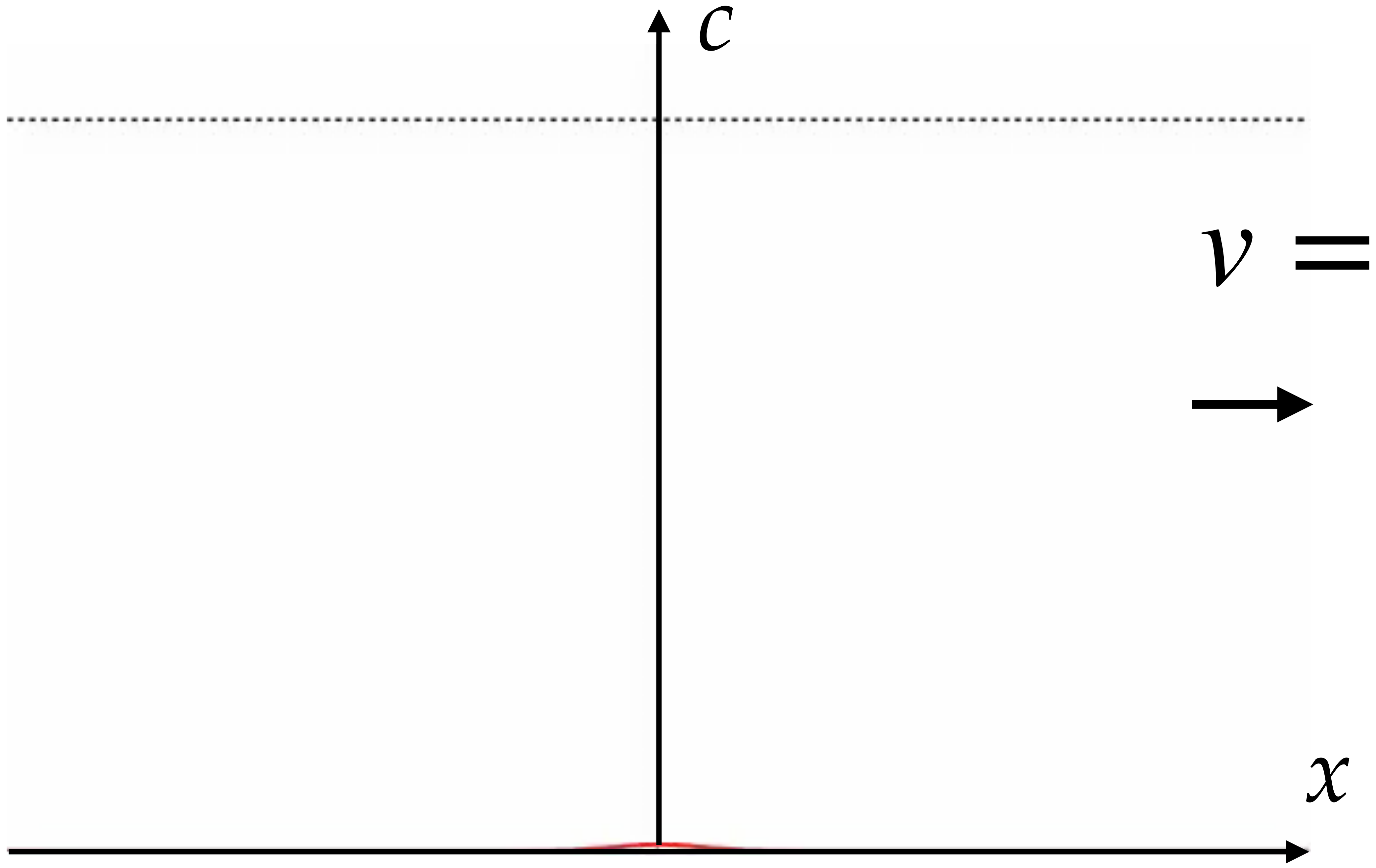


$$v = 2\sqrt{\alpha d}$$

anisotropic diffusion

$$\boxed{\frac{\partial c}{\partial t} = \mathrm{Div}(\mathbf{D} \cdot \nabla c) + \alpha c(1 - c)}$$

in one dimension:

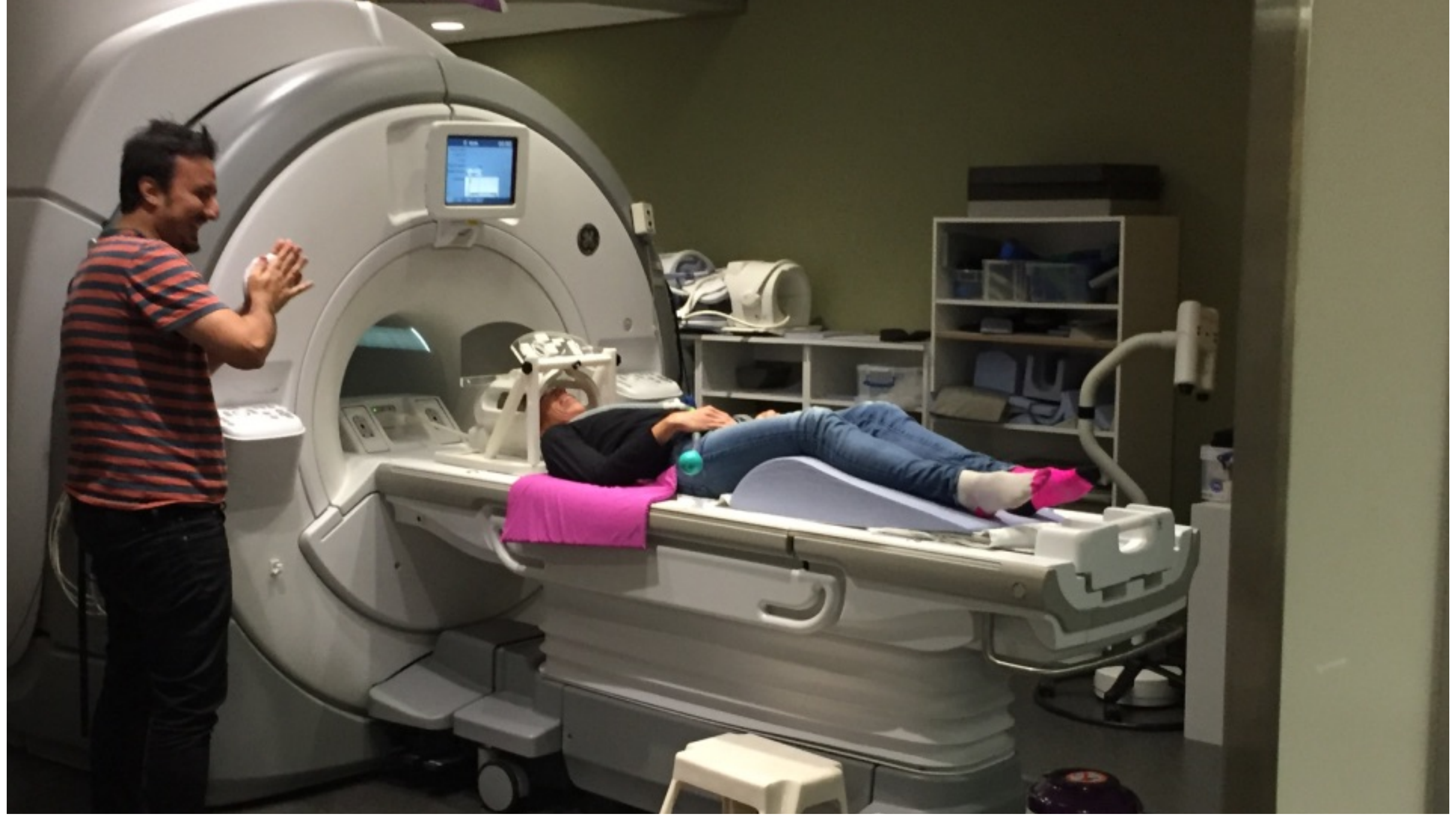


$$v = 2\sqrt{\alpha d}$$

→

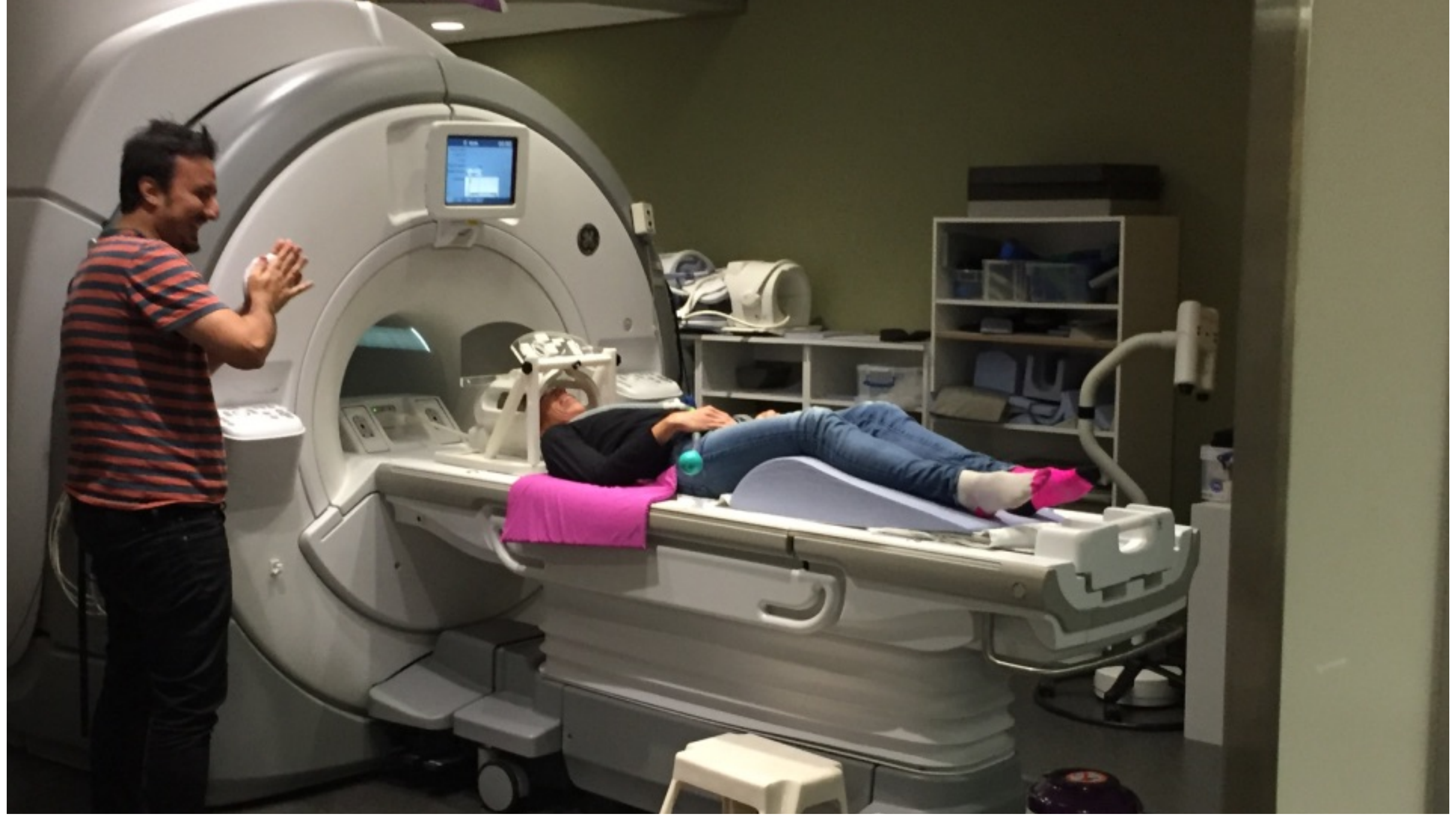
$$C(t) = \frac{1}{V}\int_{\Omega} c(\mathbf{x}, t)\,\mathrm{d}\mathbf{x}$$

biomarker abnormality



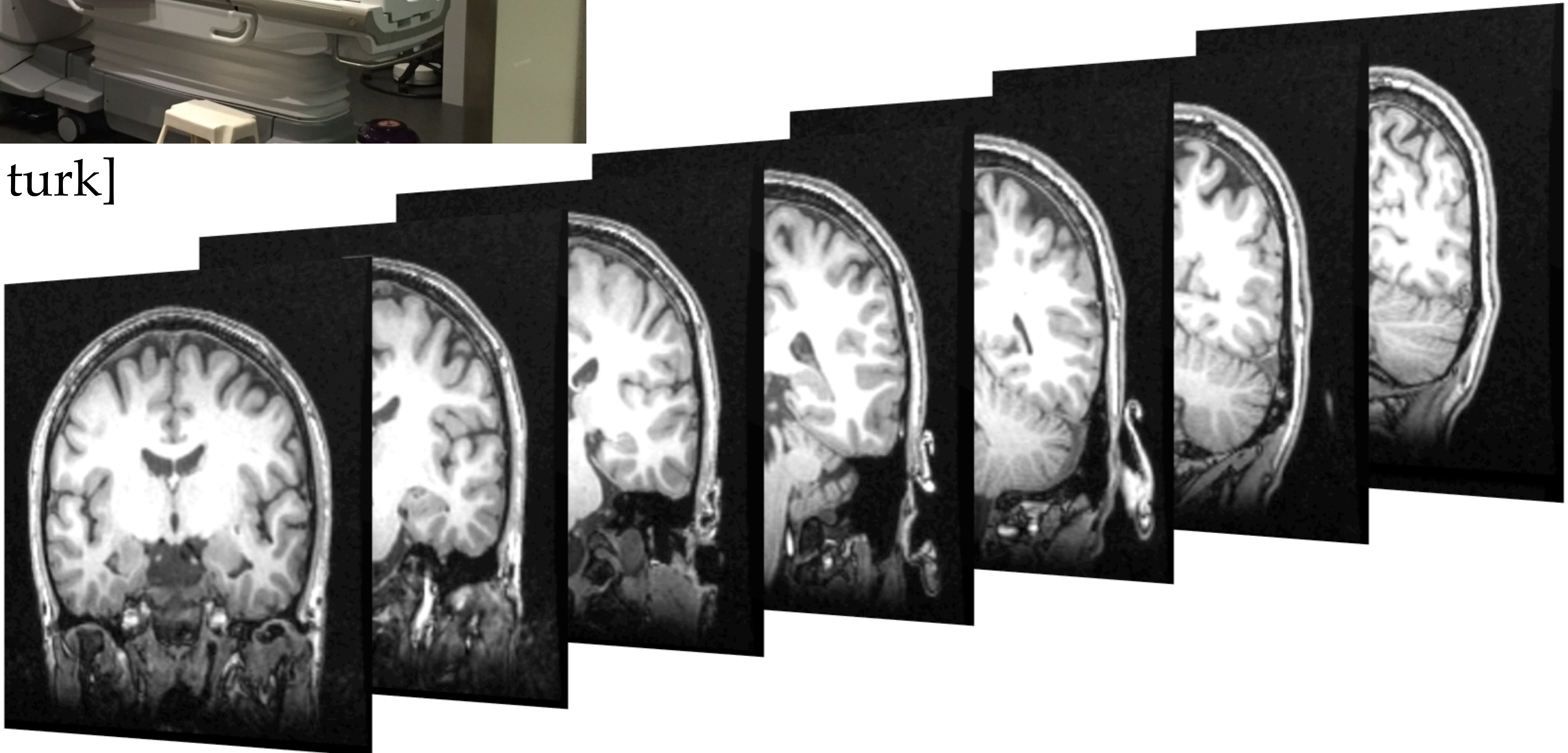
[with m. turk]

1. data acquisition



[with m. turk]

1. data acquisition



2. segmentation

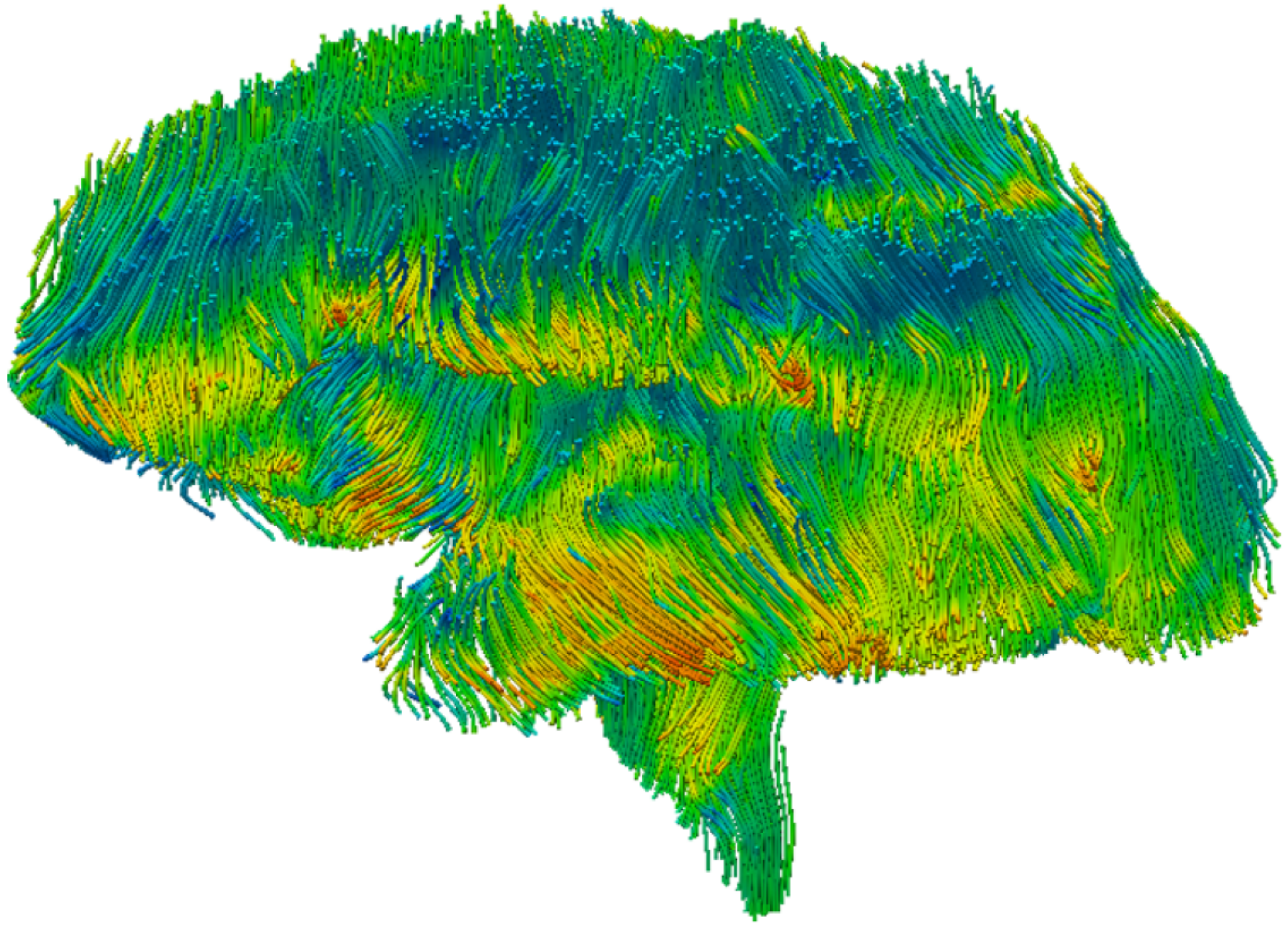
sagittal slices

coronal slices

transverse slices

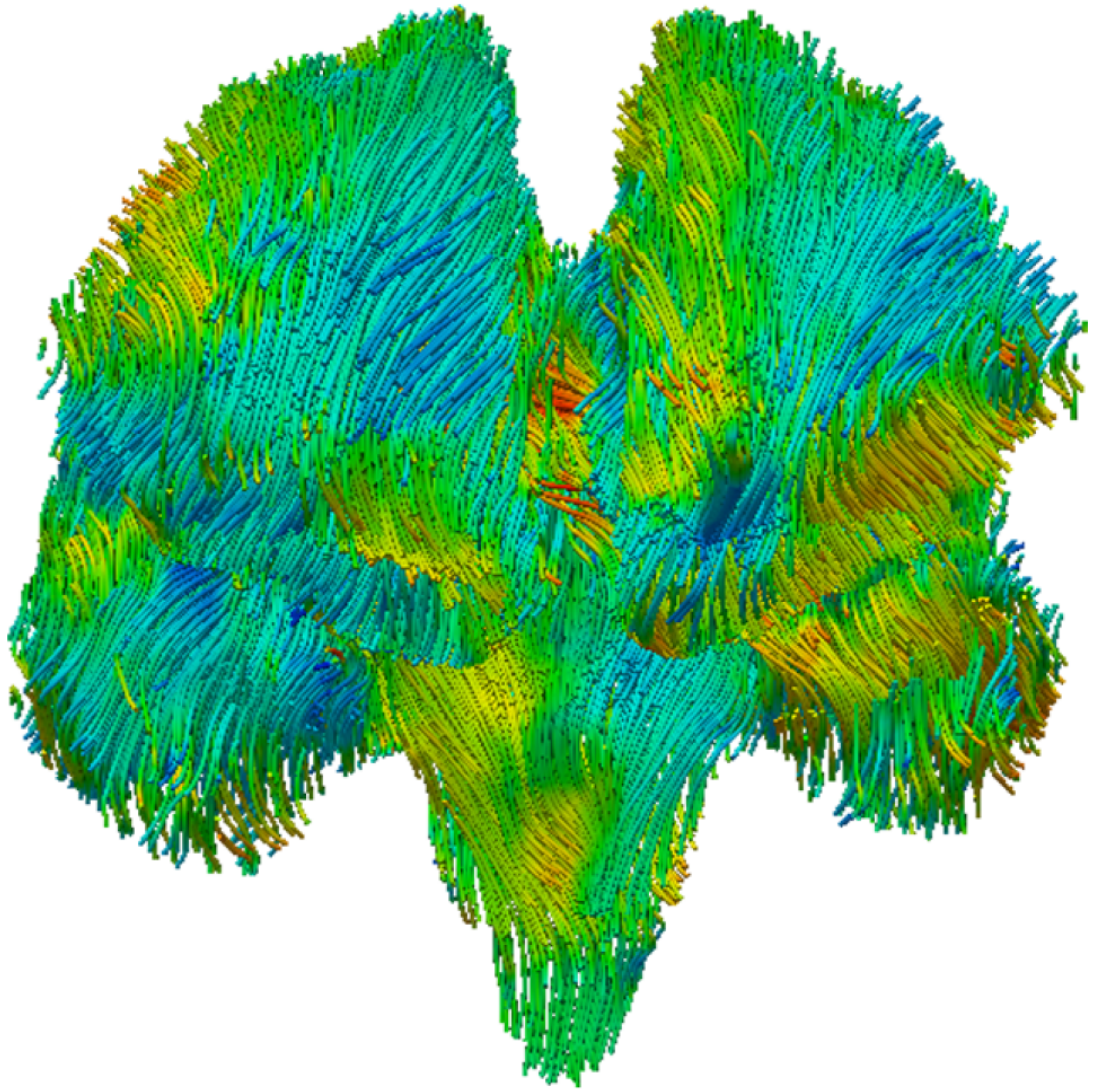
3. information on axonal direction

sagittal view



whole brain

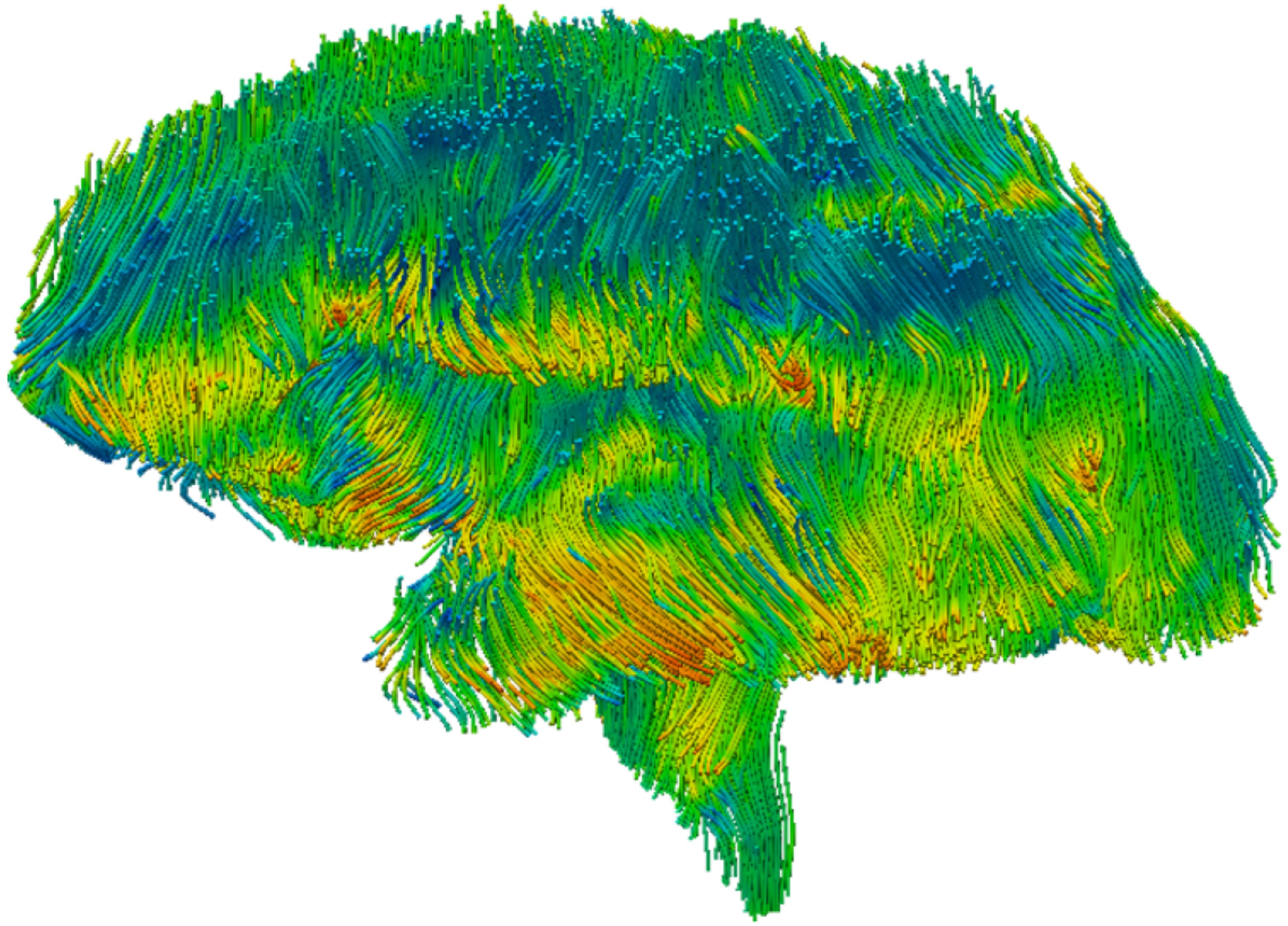
coronal view



[weickenmeier, jucker, ag, kuhl 2018]

3. information on axonal direction

sagittal view



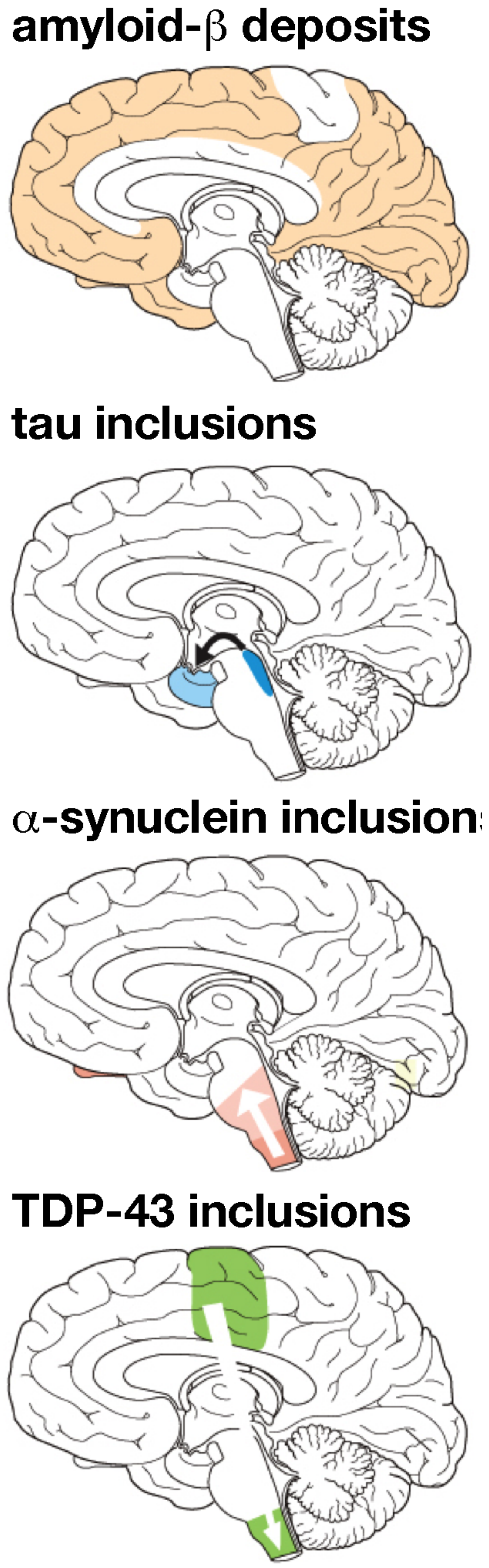
whole brain

coronal view

[weickenmeier, jucker, ag, kuhl 2018]

4. 3d model

seeding of toxic proteins

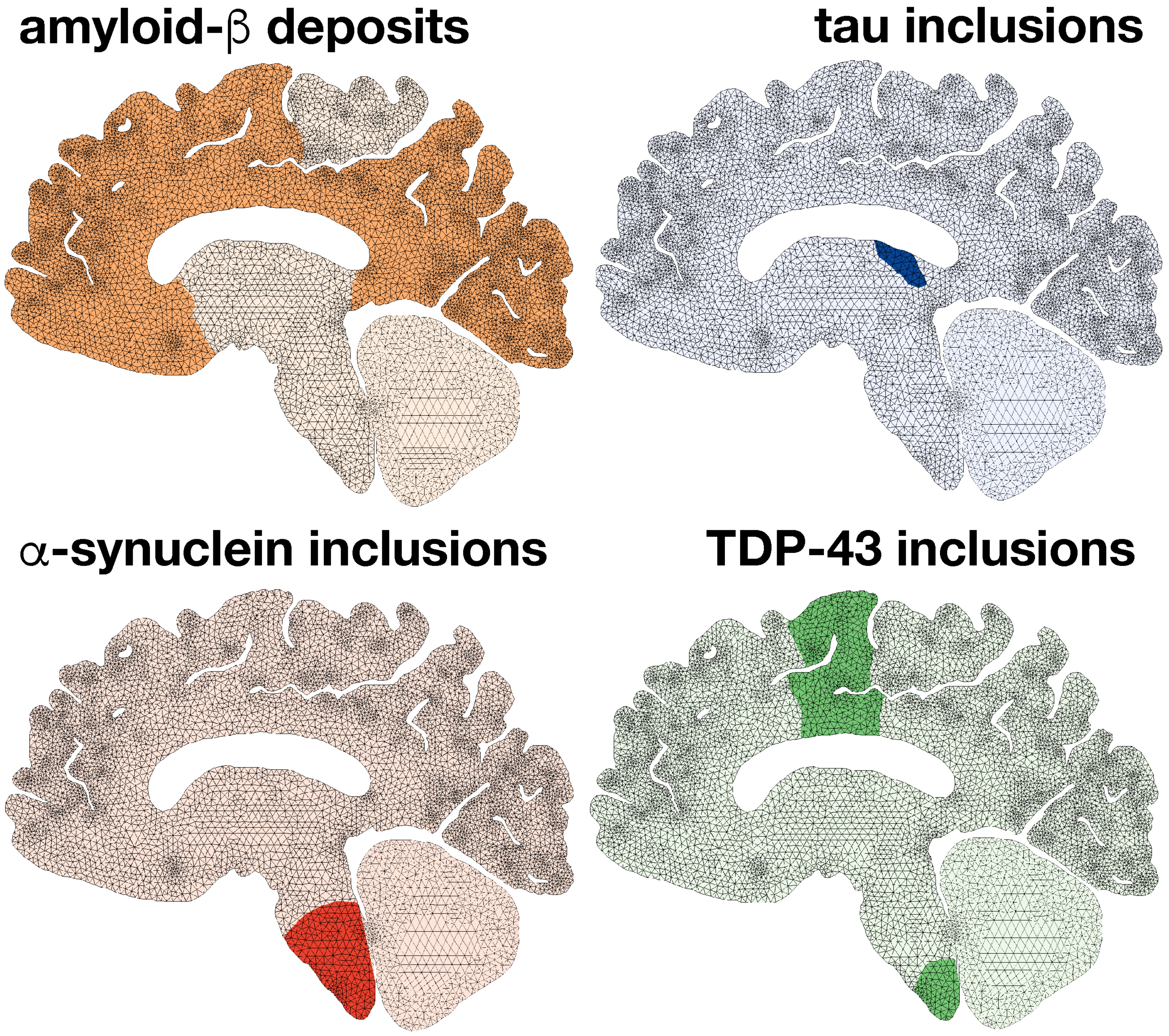


amyloid-β deposits

tau inclusions

α-synuclein inclusion

TDP-43 inclusions



amyloid-β deposits

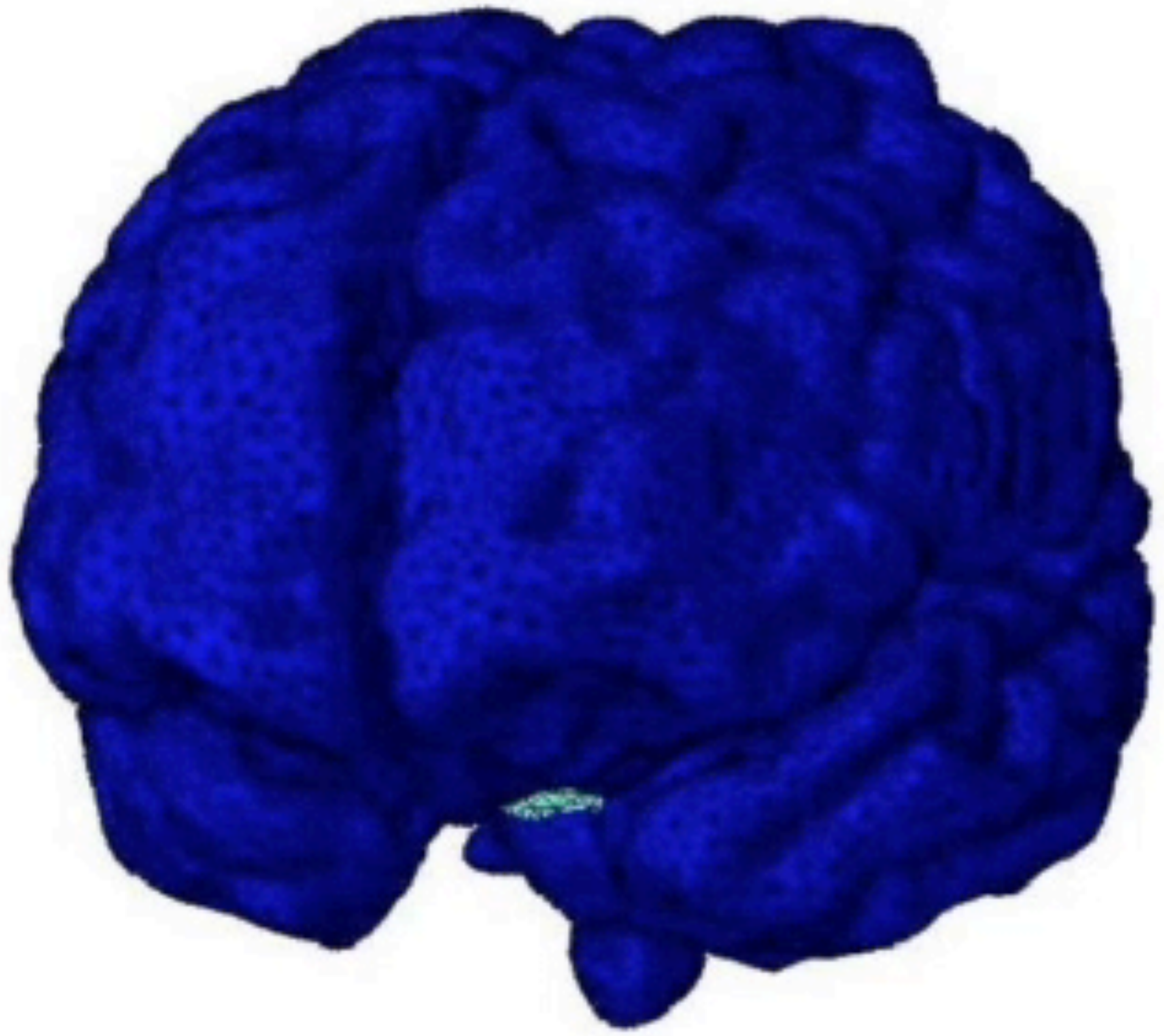
tau inclusions

α-synuclein inclusions

TDP-43 inclusions

[jucker, walker, 2013],

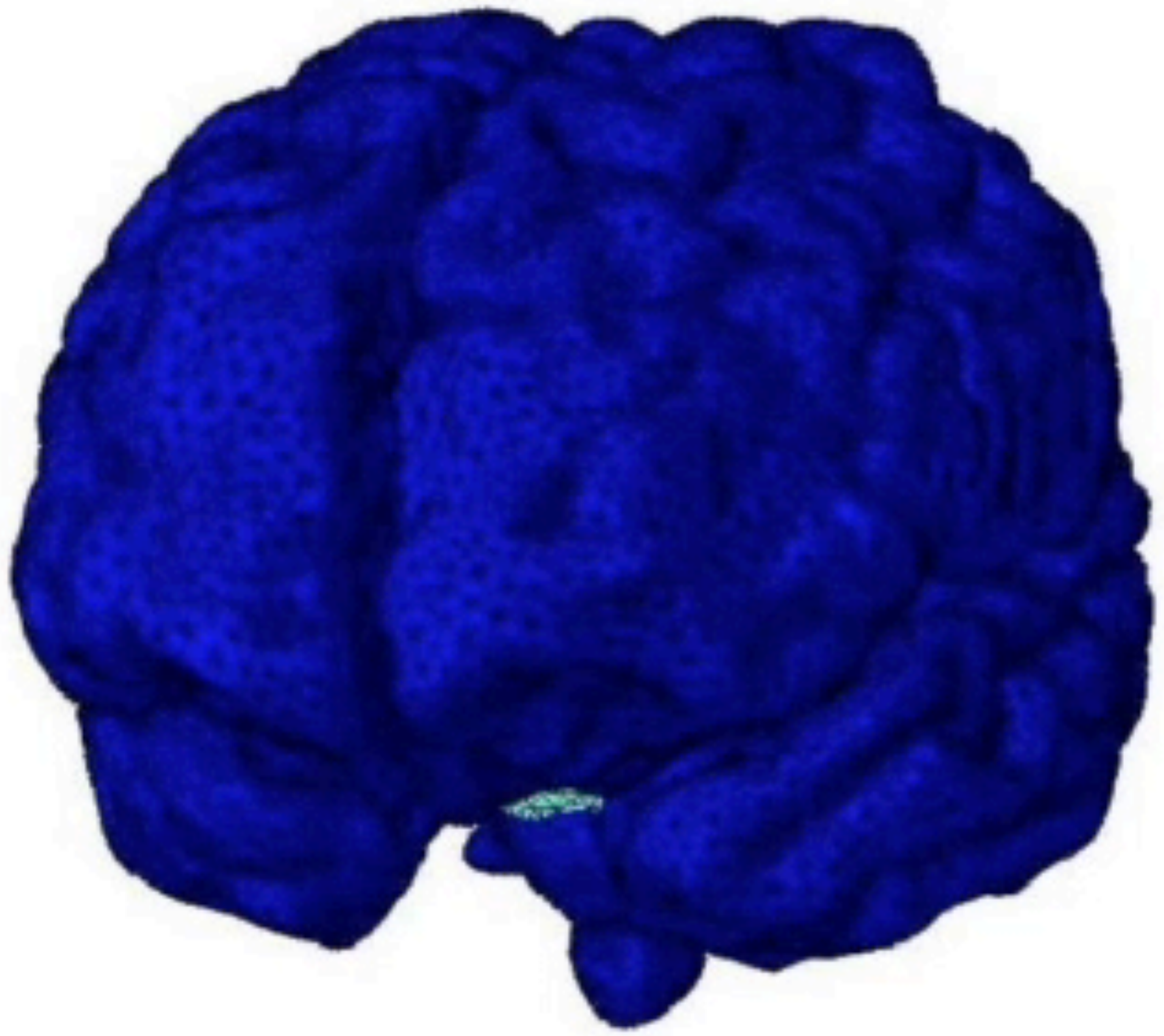
[weickenmeier, jucker, ag, kuhl 2018]



tau propagation in Alzheimer's disease

onset ● late-stage

tau infestation mid-stage



tau propagation in Alzheimer's disease

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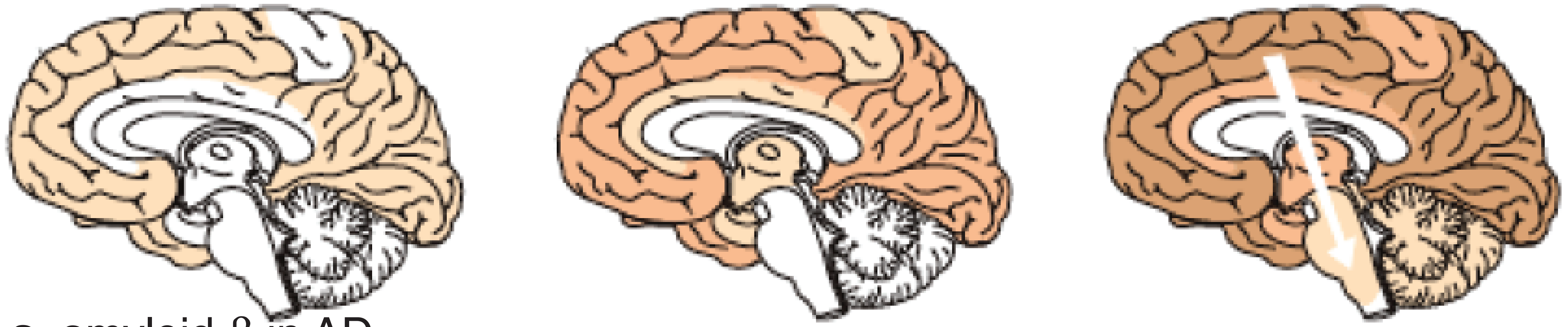
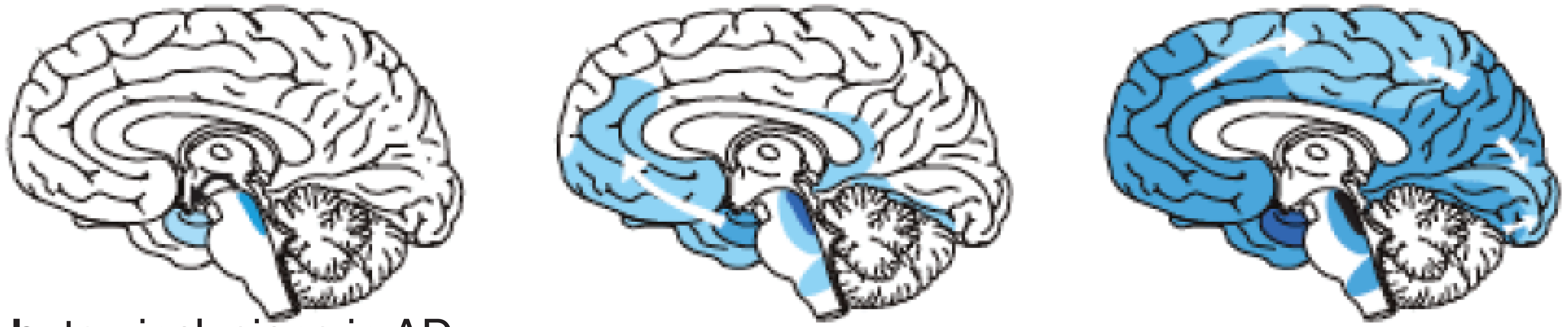
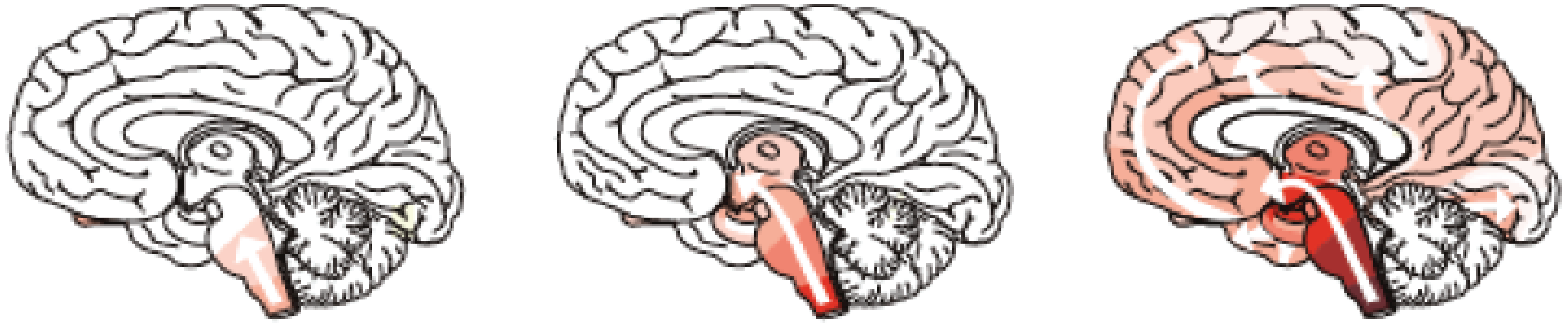
tau infestation mid-stage



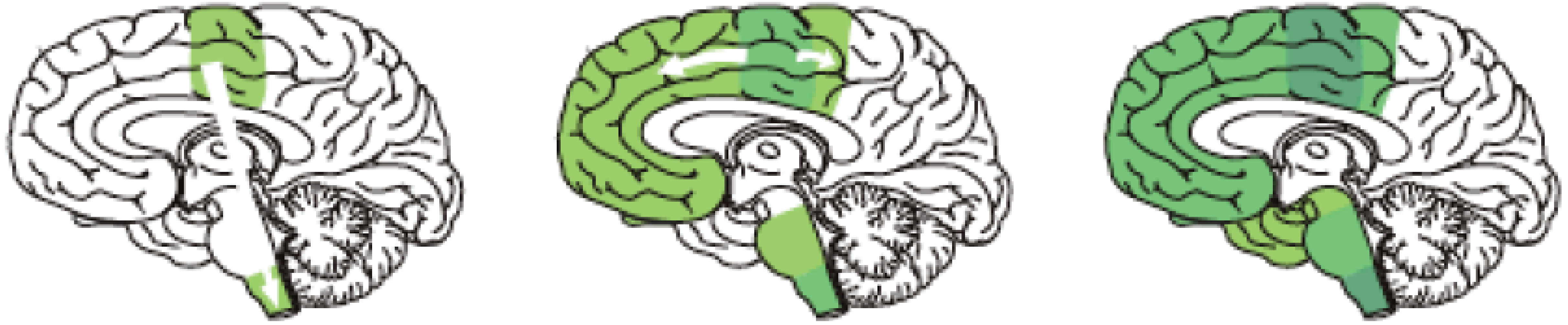
a. amyloid-β in AD



b. tau inclusions in AD

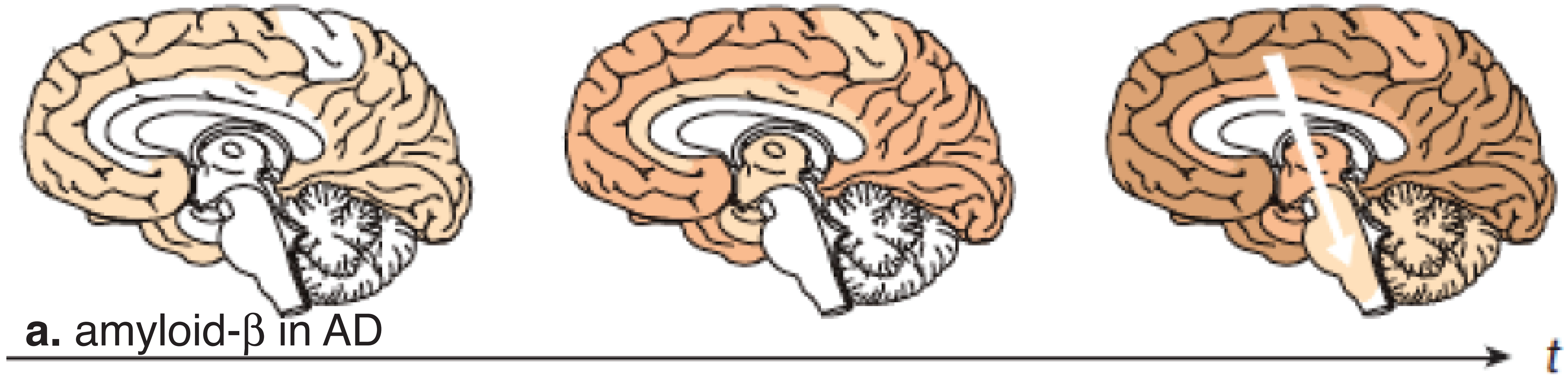


c. α–synuclein inclusions in PD

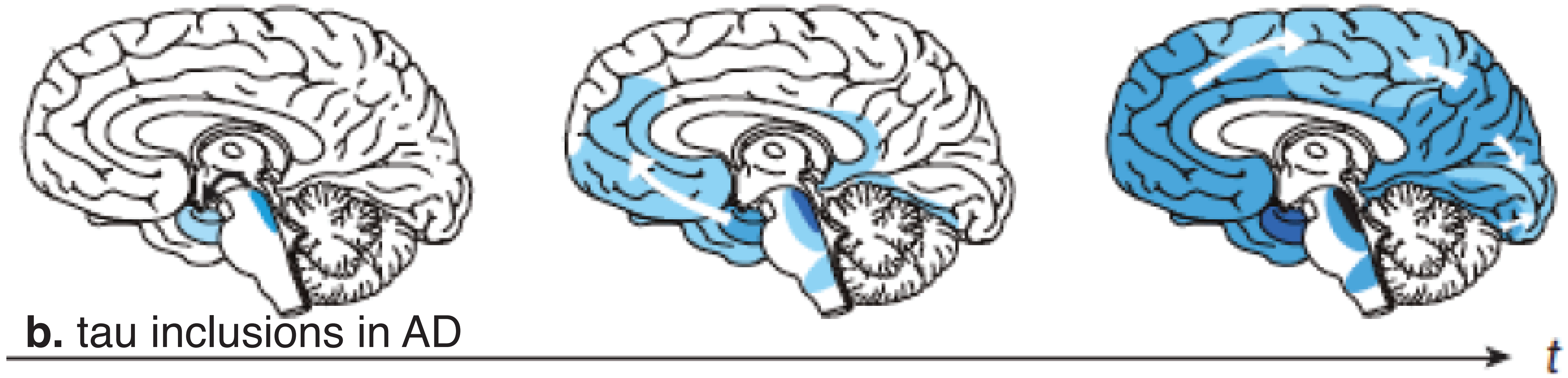


d. TPD-43 inclusion in amyotrophic lateral sclerosis

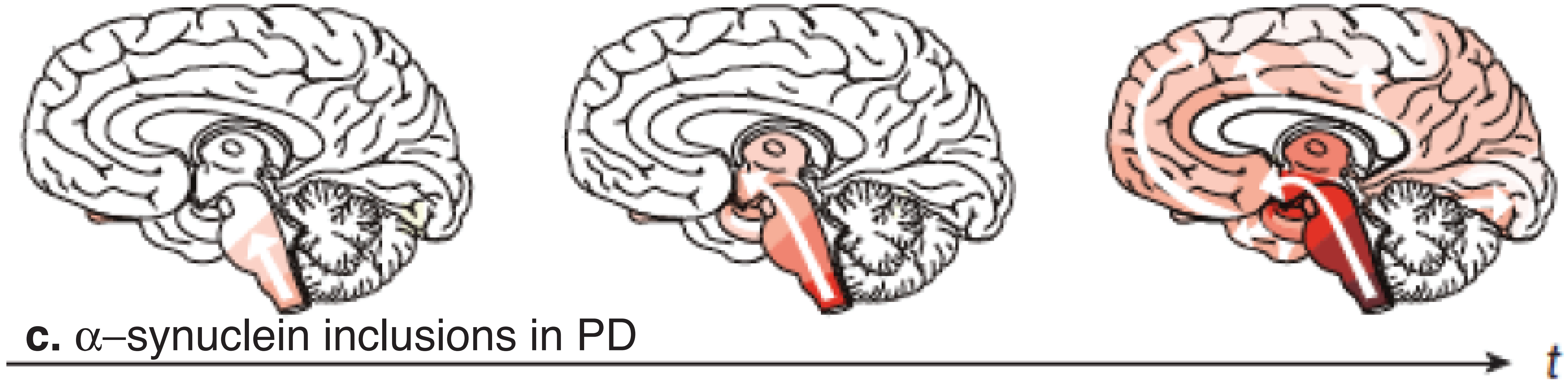
[weickenmeier, ag, kuhl, 2018]



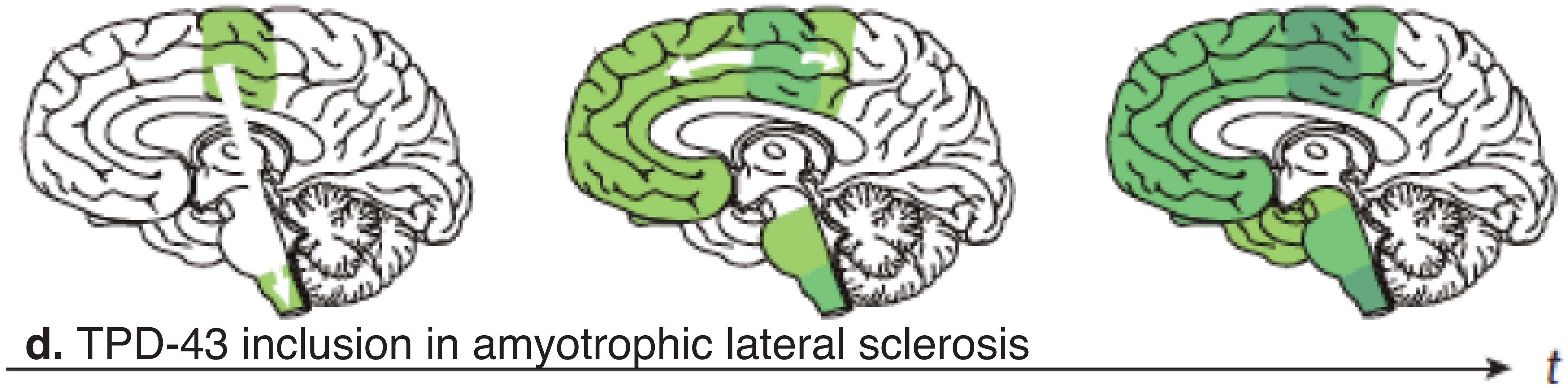
a. amyloid-β in AD



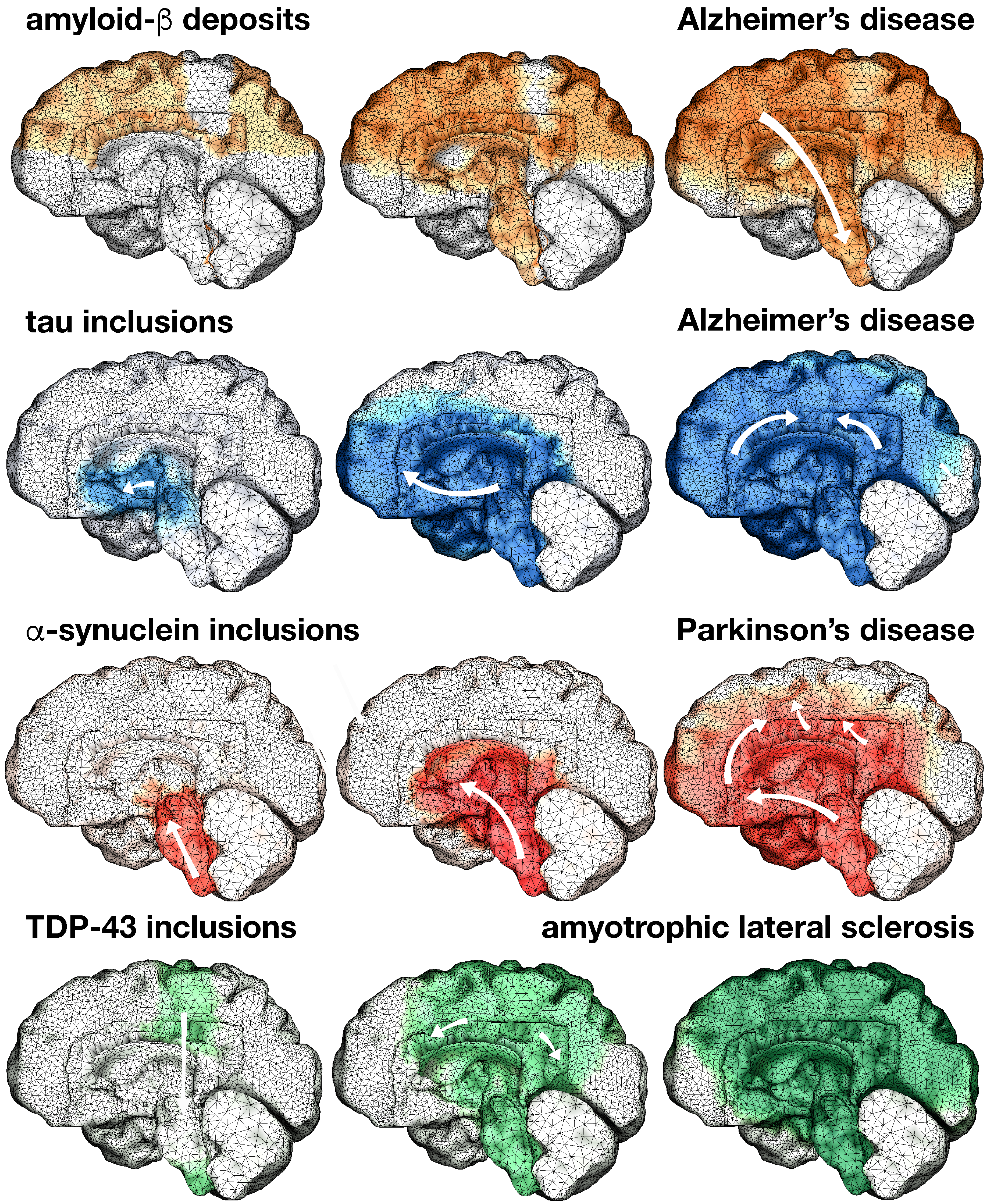
b. tau inclusions in AD



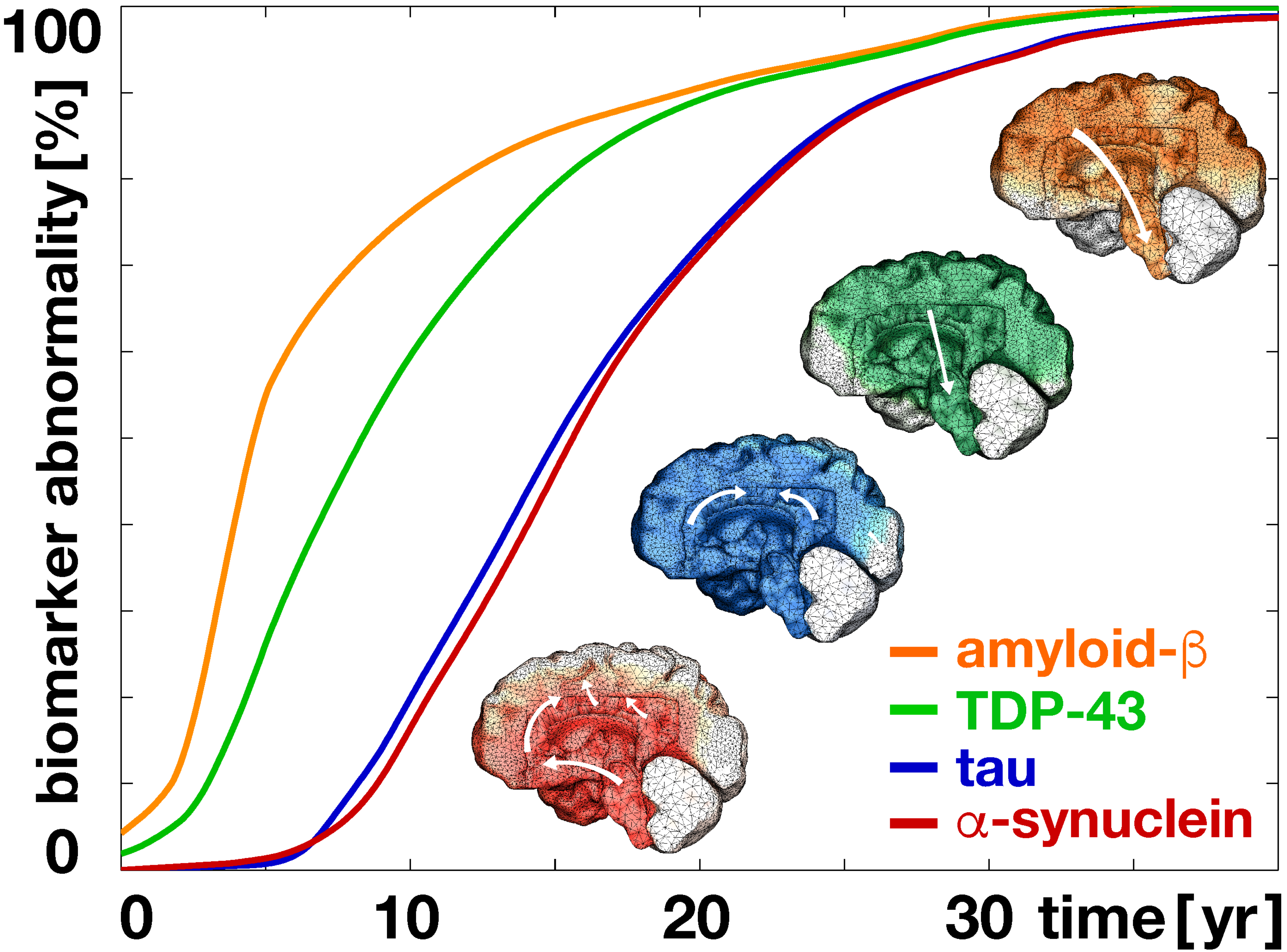
c. α–synuclein inclusions in PD

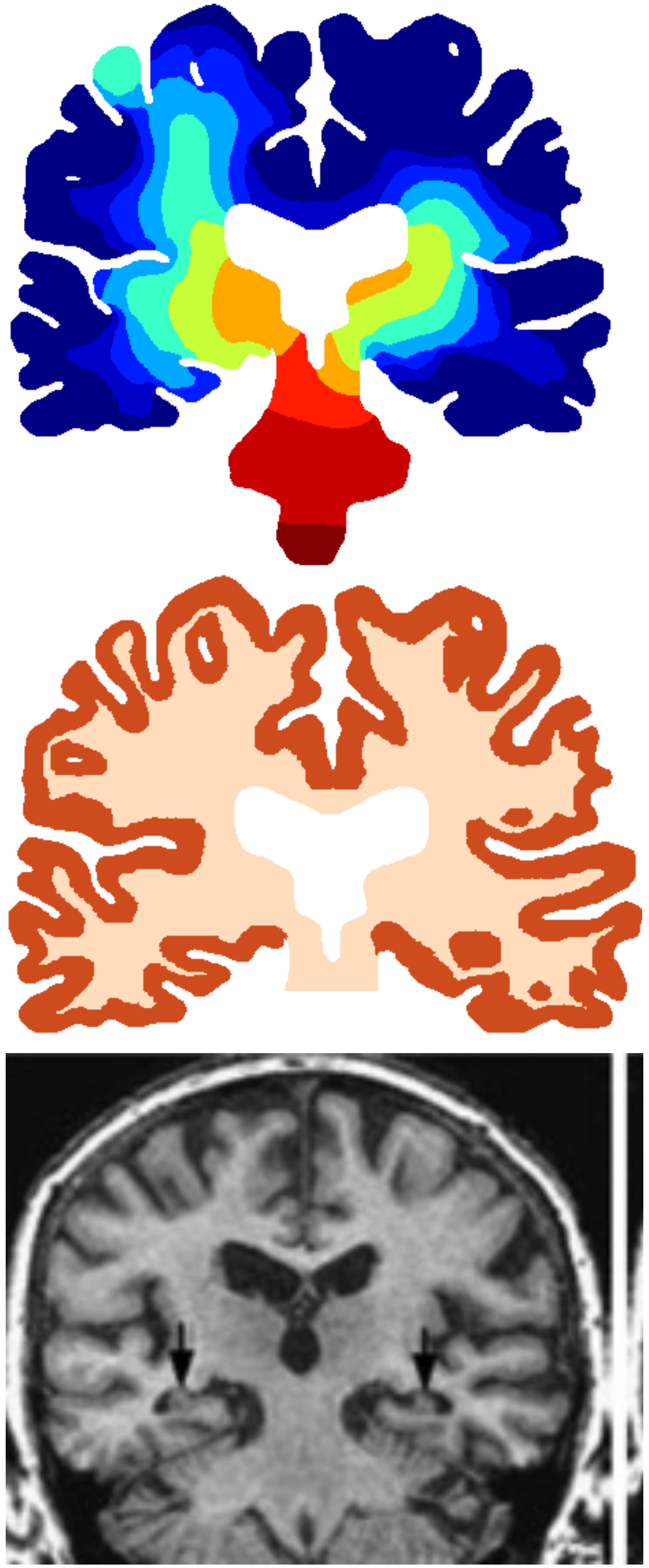


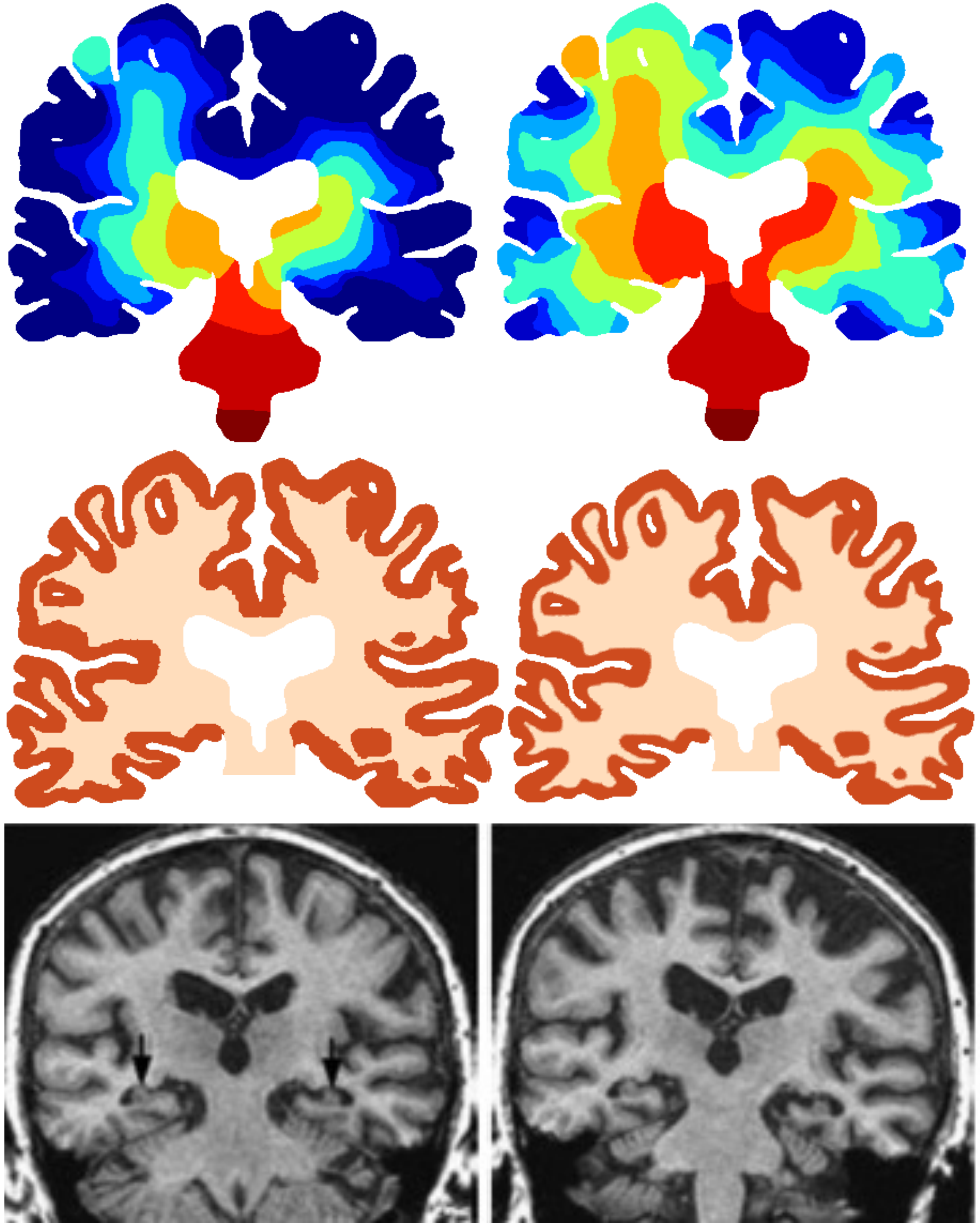
d. TPD-43 inclusion in amyotrophic lateral sclerosis

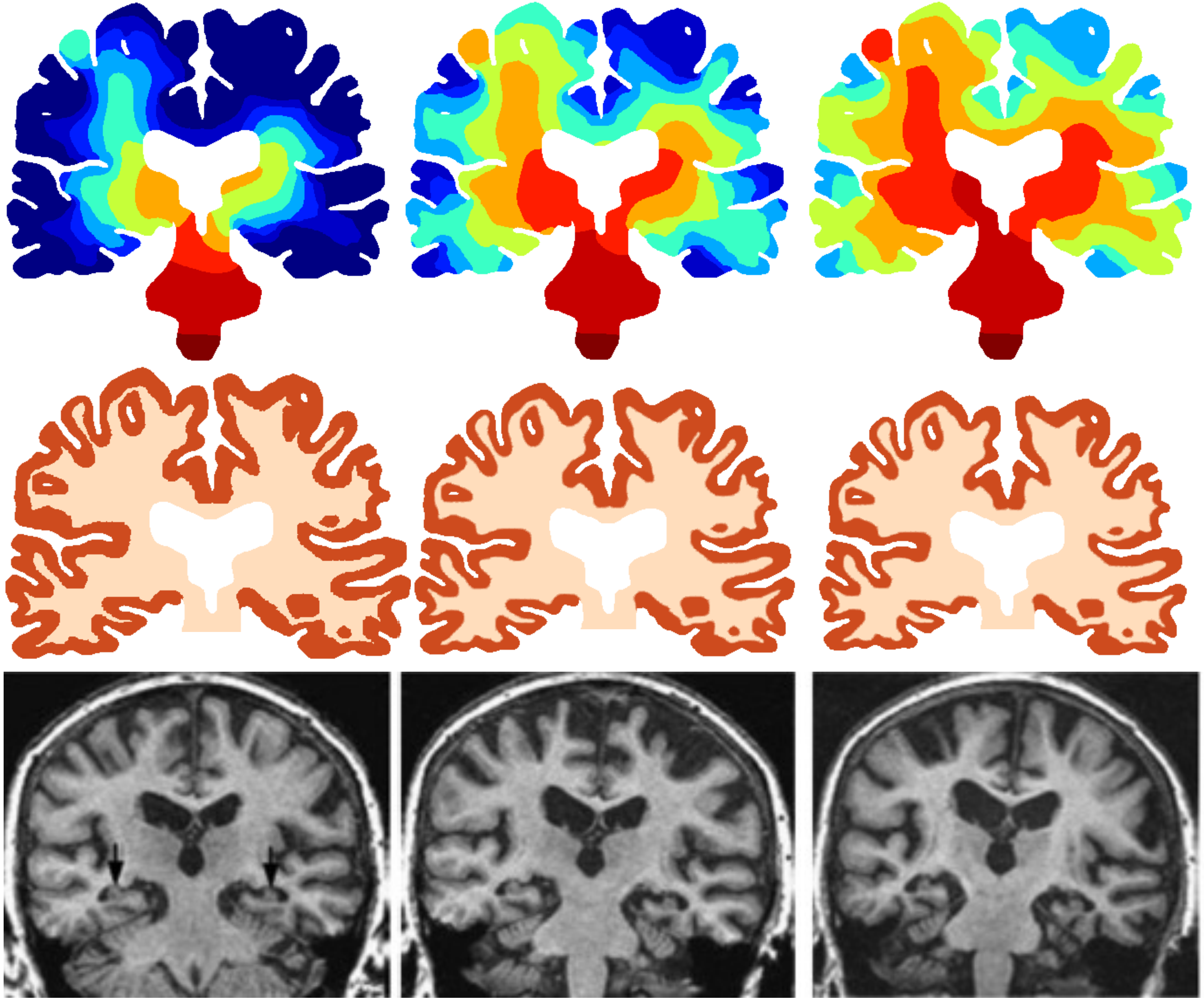


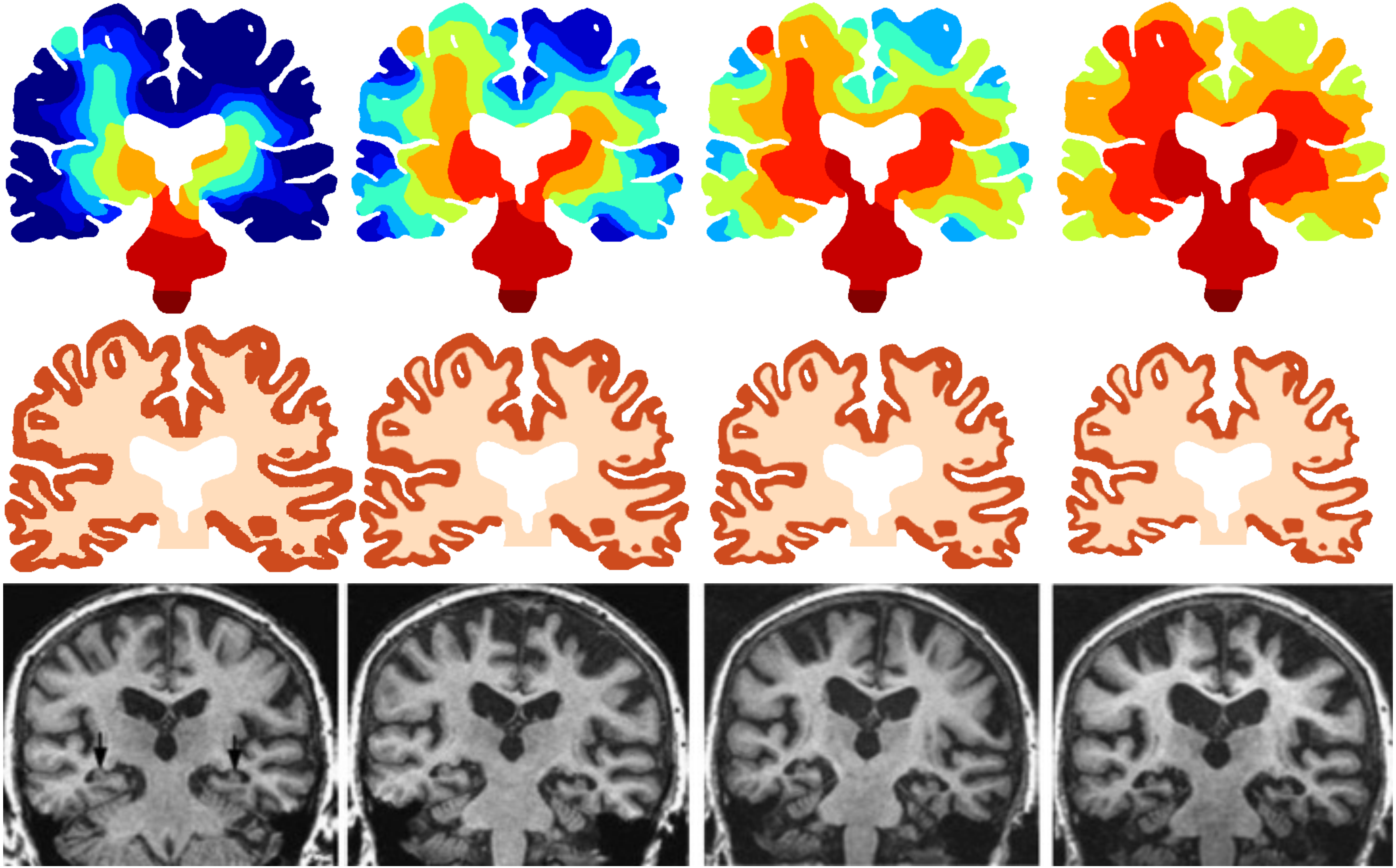
[weickenmeier, ag, kuhl, 2018]

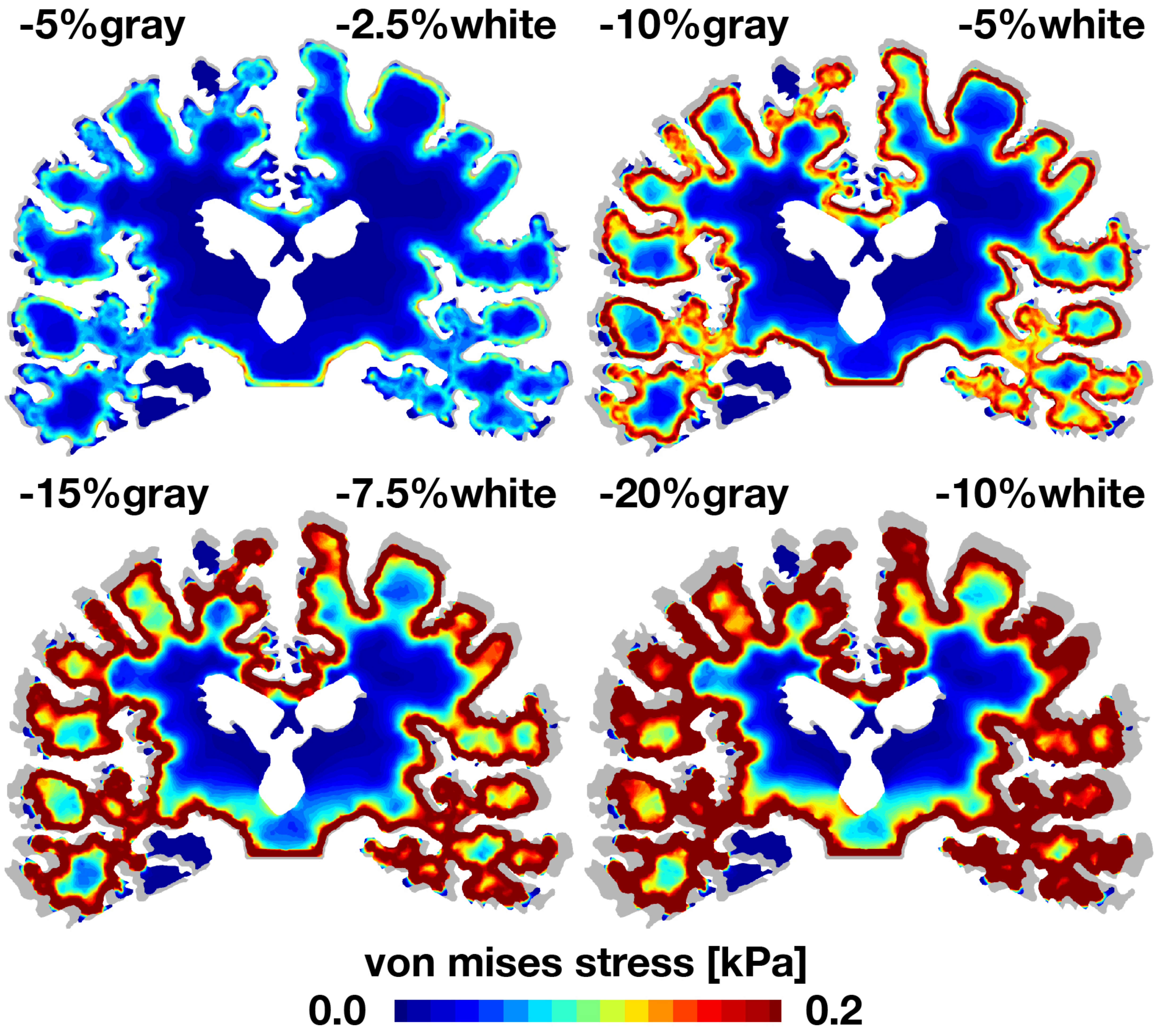

100
0
biomarker abnormality [%]
0
10
20
30
time [yr]
amyloid-β
TDP-43
tau
α-synuclein

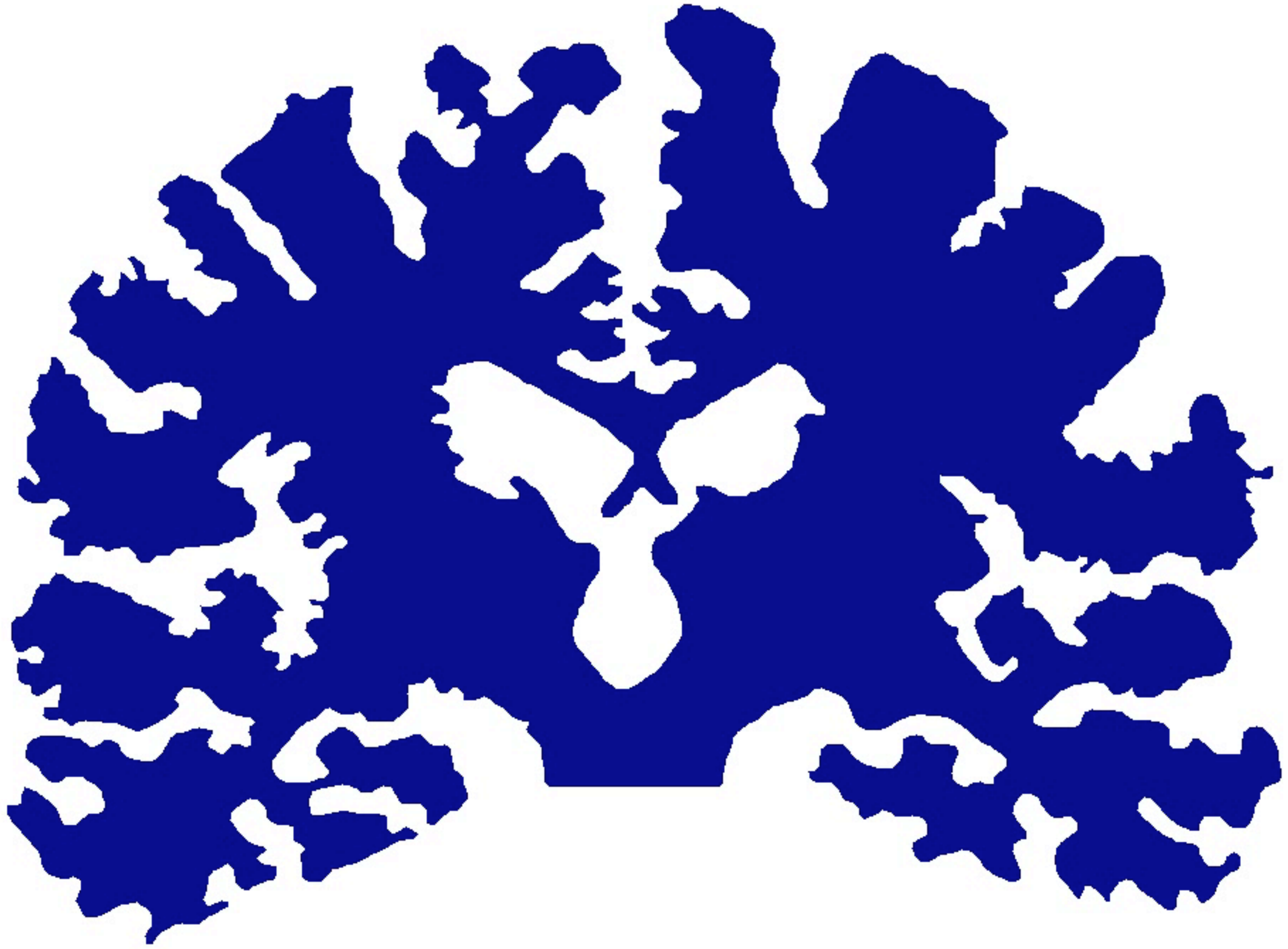




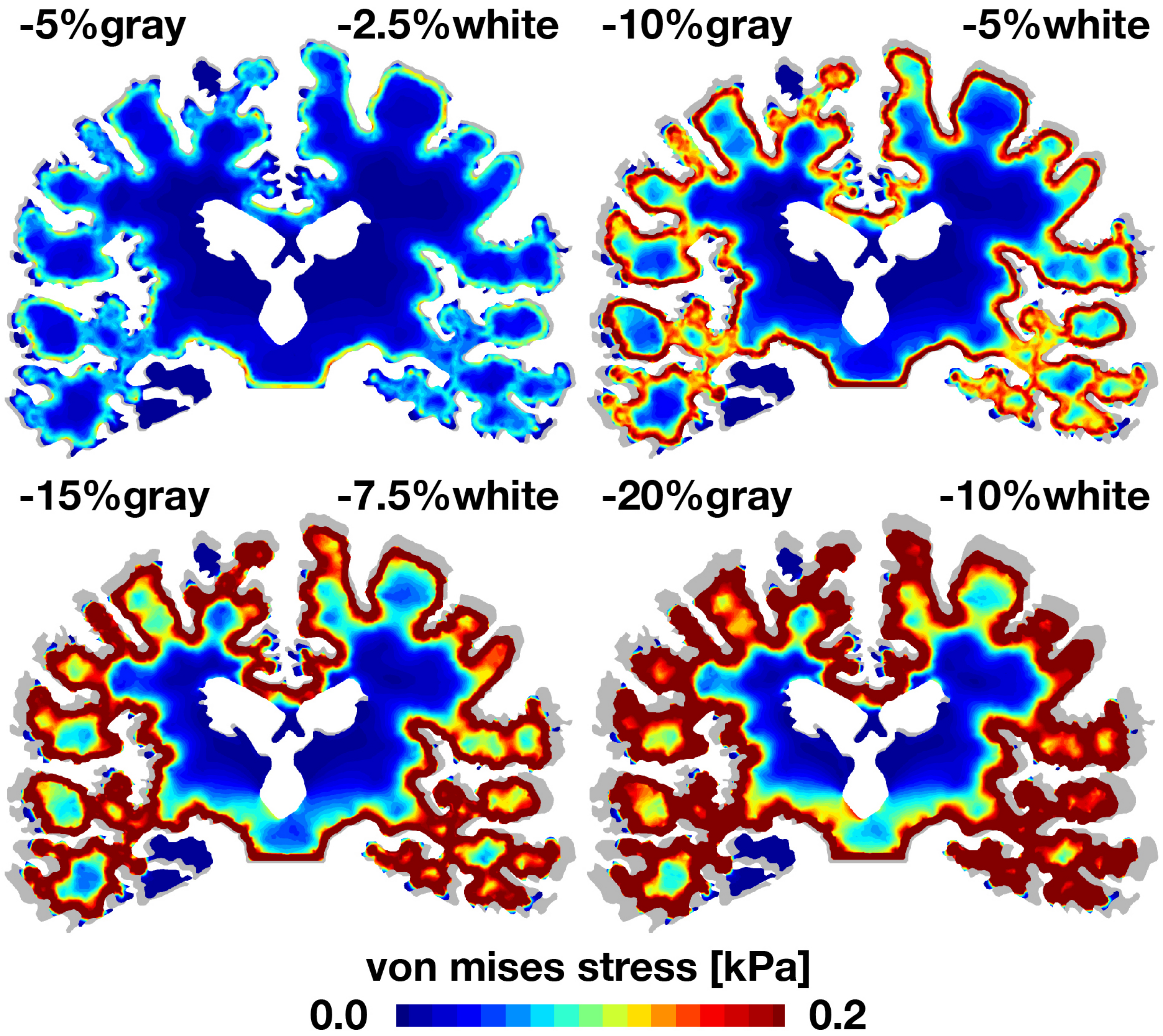


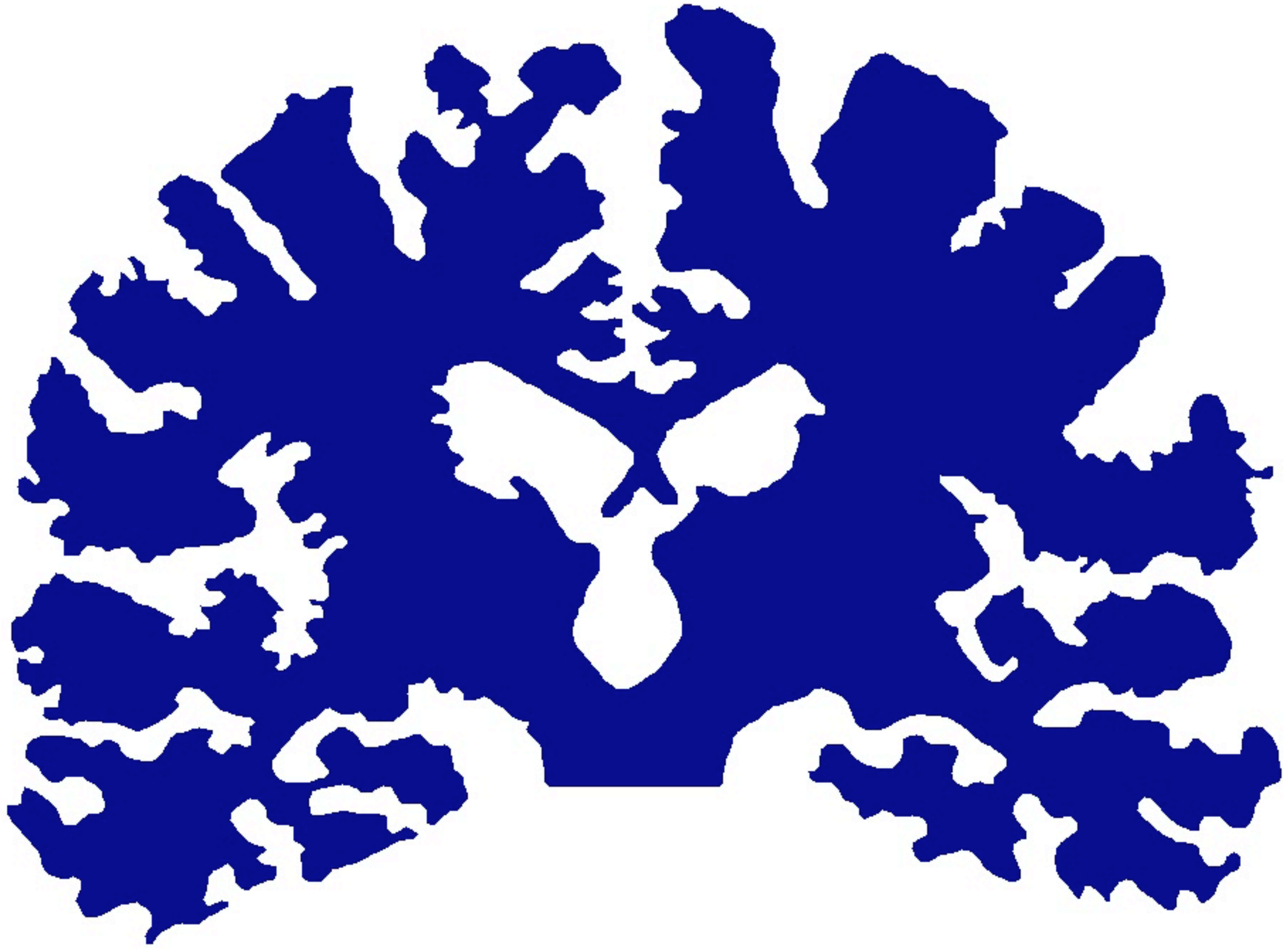






[harris, de rooij, kuhl 2018]





[harris, de rooij, kuhl 2018]

4.
“the struggle of whether we connect more”

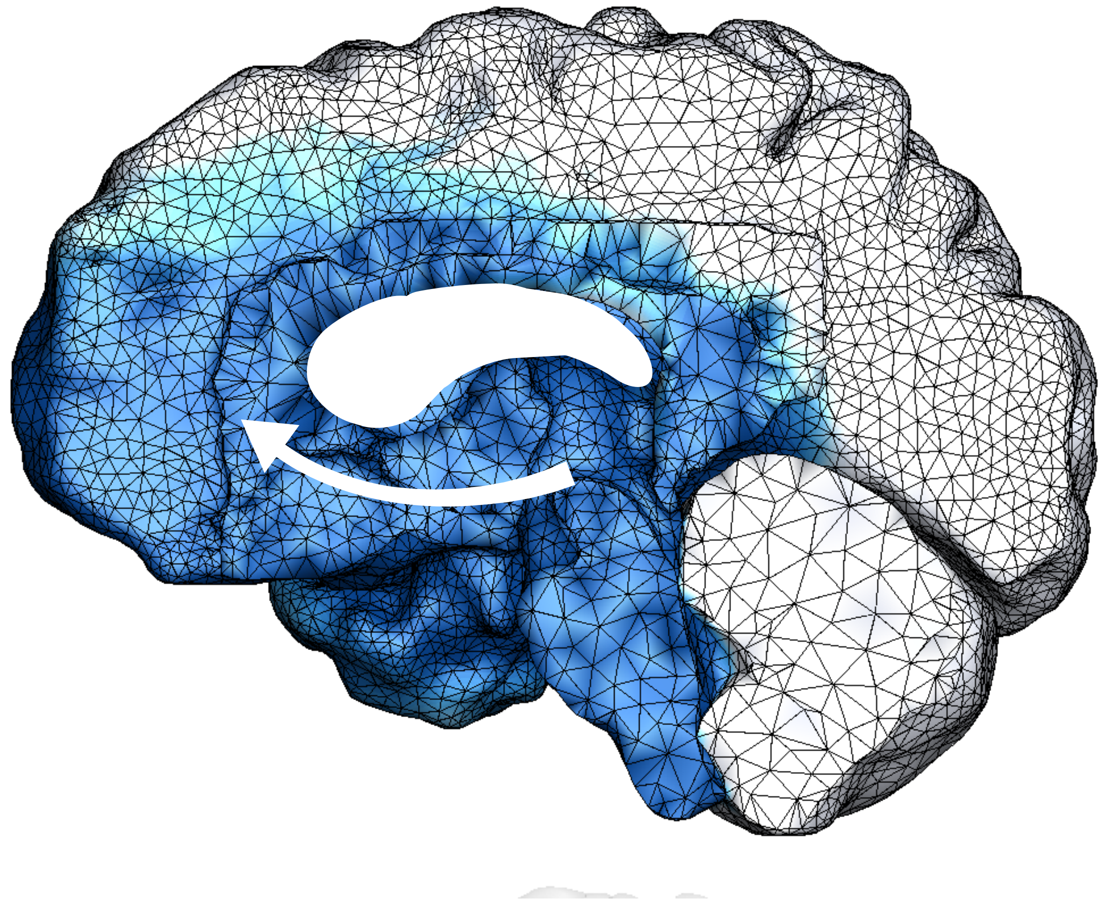
4.

“the struggle of whether we connect more”

marck zuckerberg

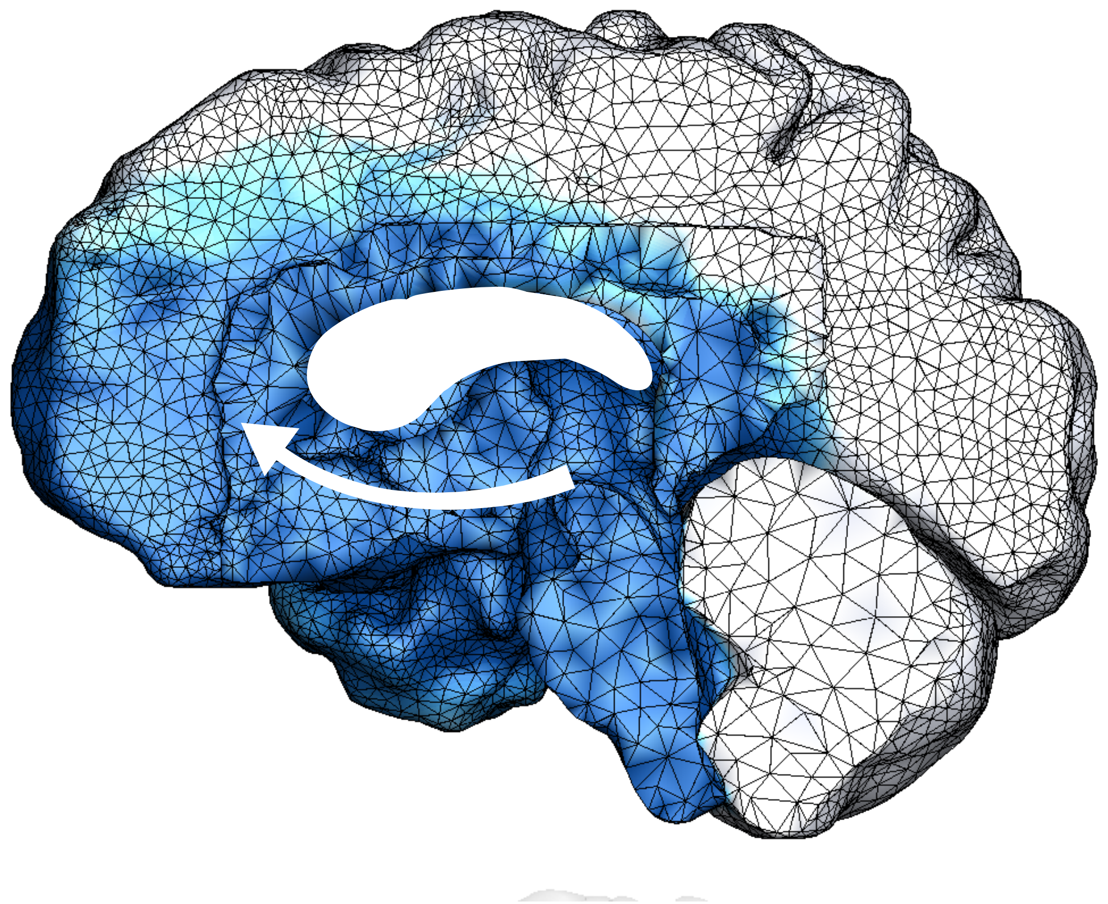
continuum model

discrete model



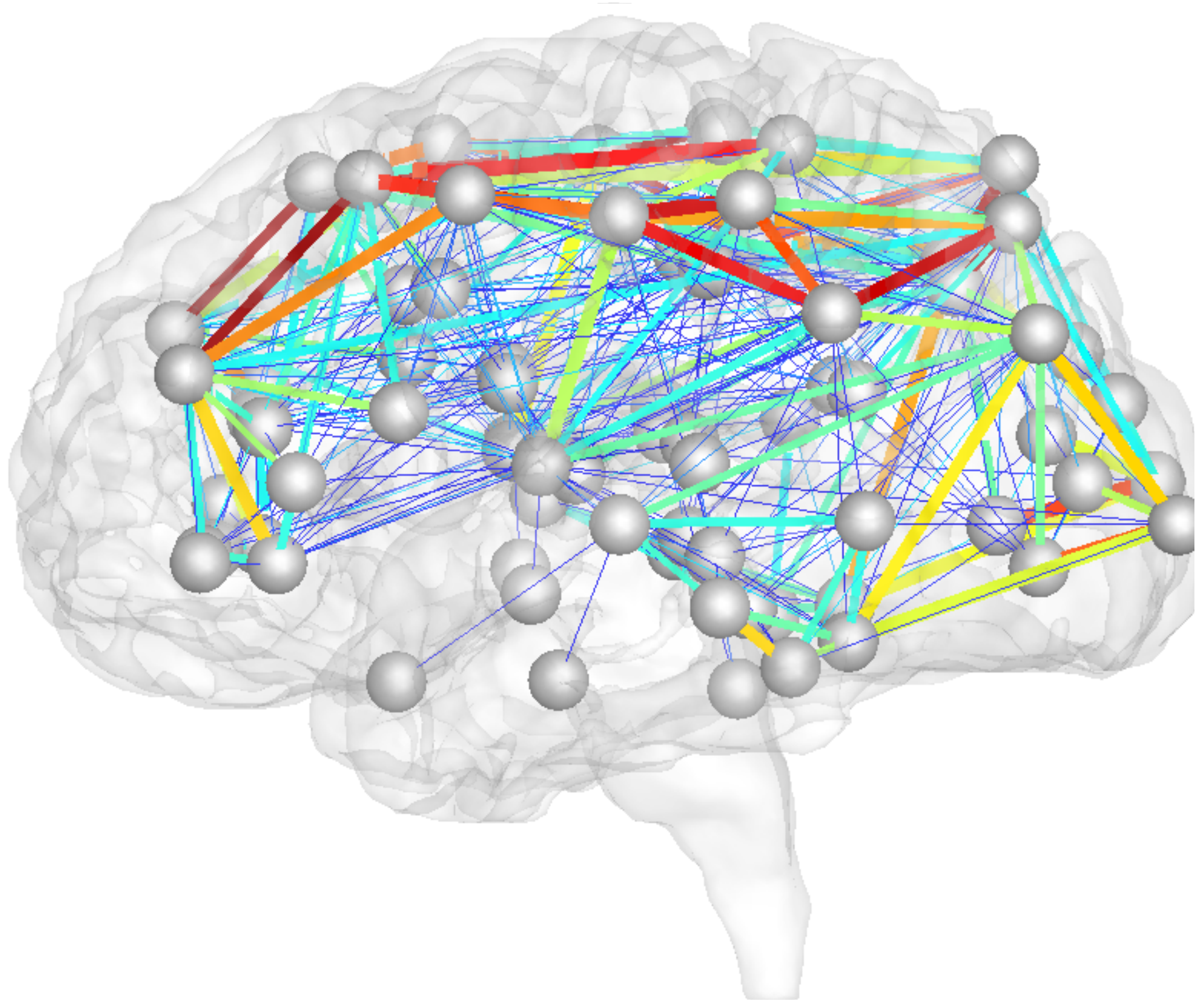
define p and $\widetilde{p}$ at all points

continuum model



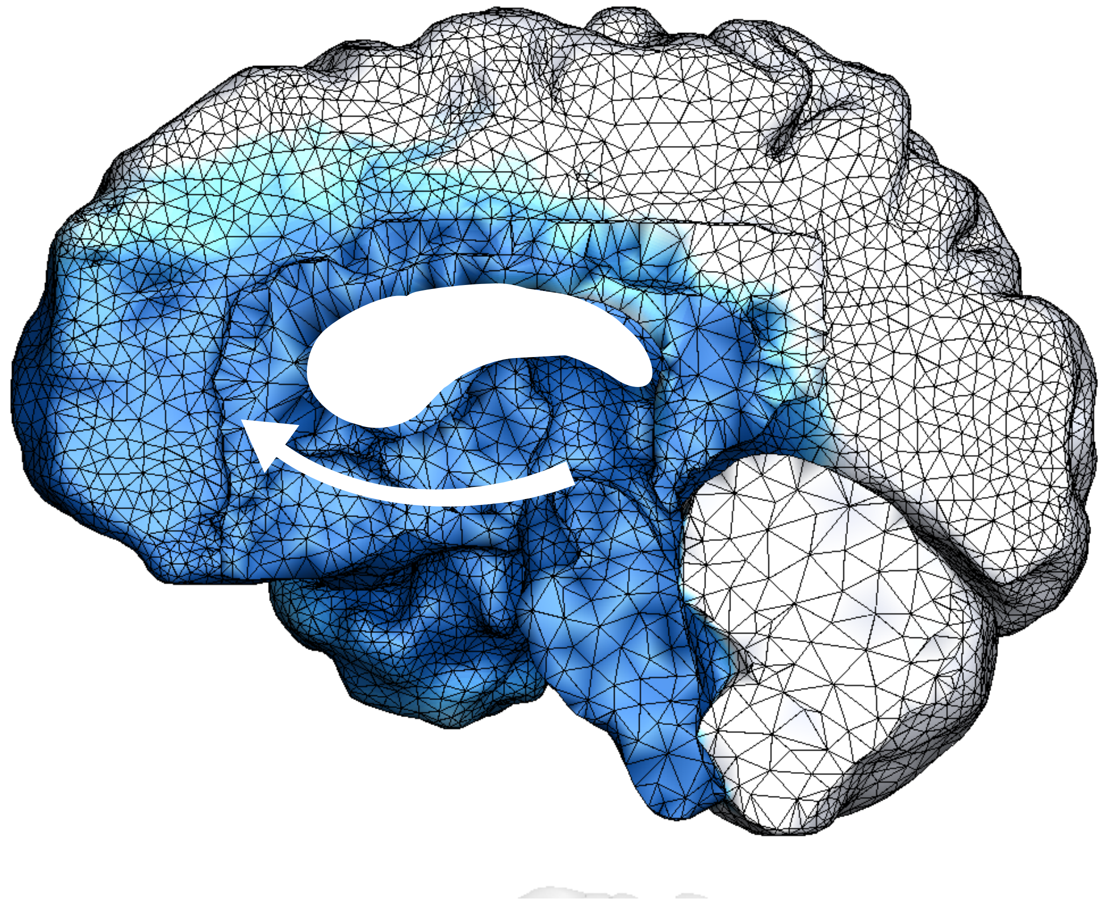
define p and $\widetilde{p}$ at all points

discrete model



define p_i and $\widetilde{p}_i$ at each node i

continuum model

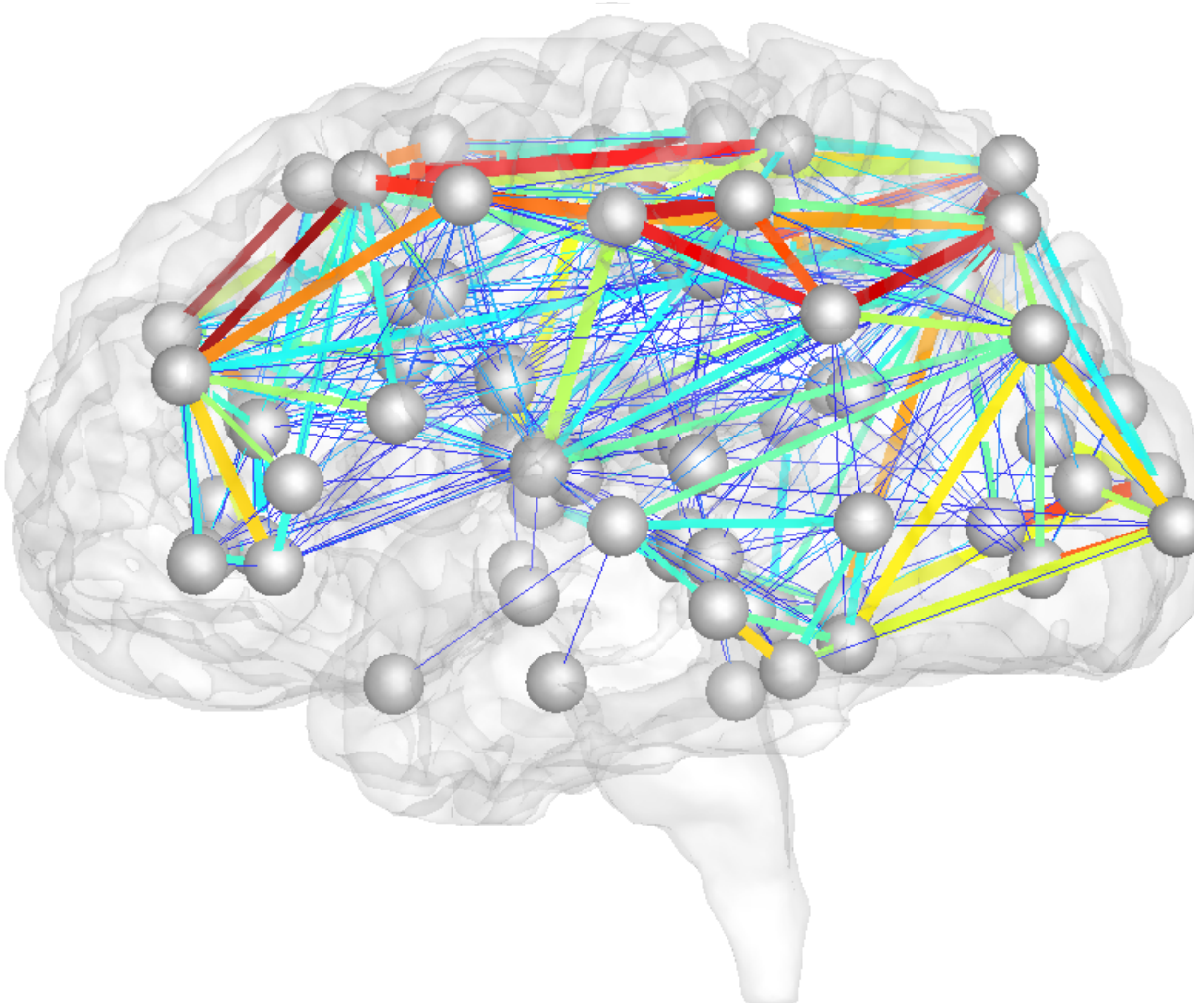


define p and $\widetilde{p}$ at all points

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + k_0 - k_1 p - k_{12} p \widetilde{p}$$

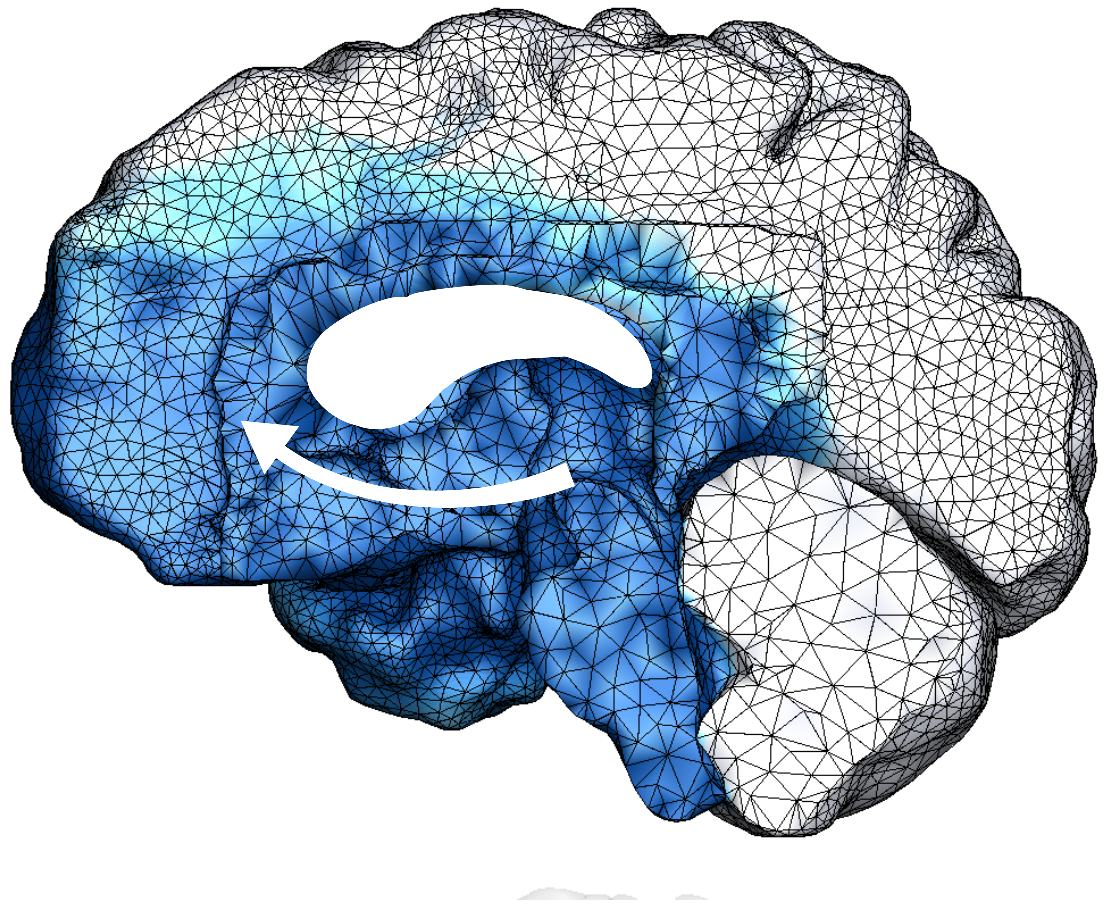
$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) \qquad - \widetilde{k}_1 \widetilde{p} + k_{12} p \widetilde{p}$$

discrete model



define p_i and $\widetilde{p}_i$ at each node i

continuum model

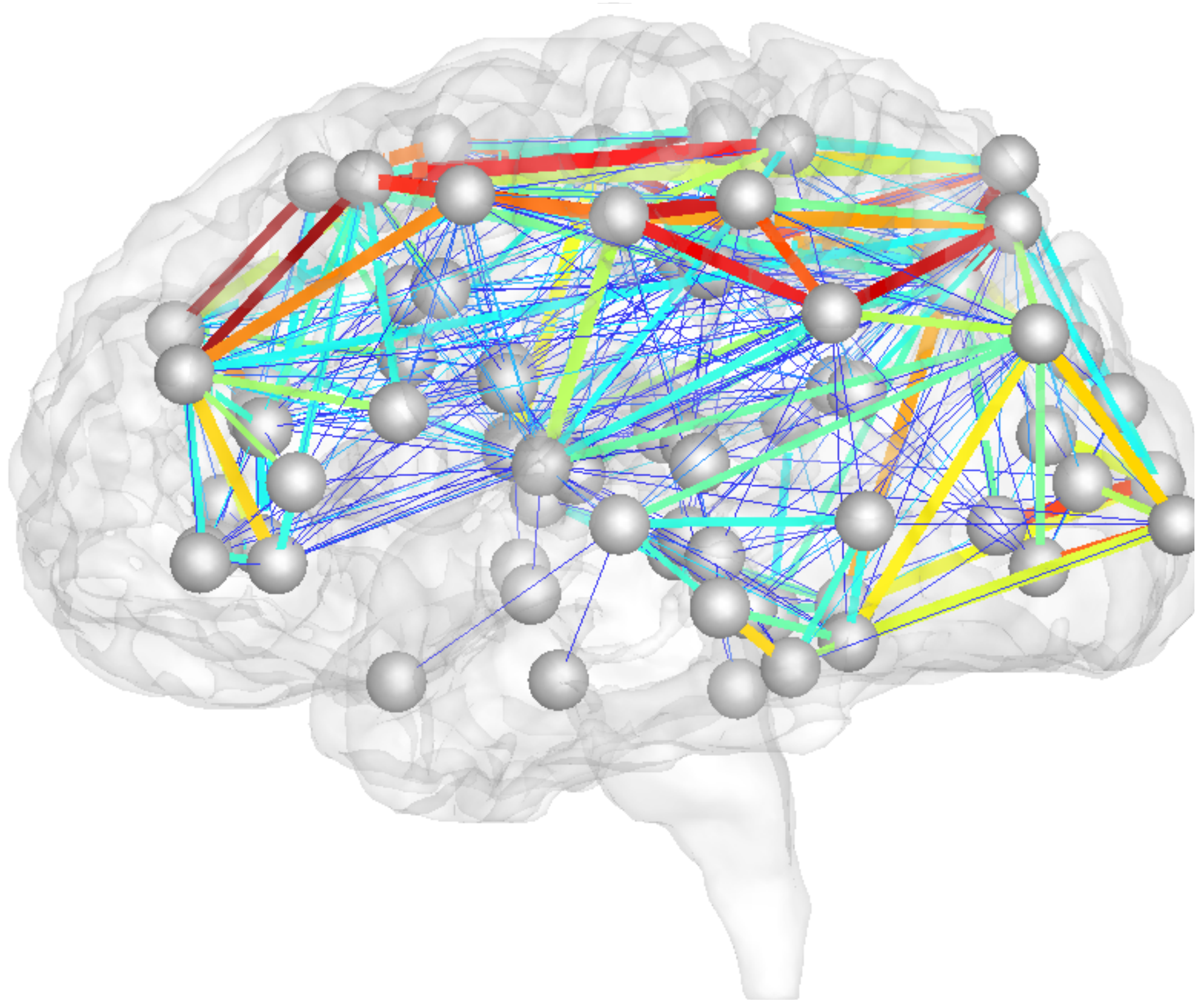


define p and $\widetilde{p}$ at all points

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + k_0 - k_1 p - k_{12} p \widetilde{p}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) \qquad - \widetilde{k}_1 \widetilde{p} + k_{12} p \widetilde{p}$$

discrete model

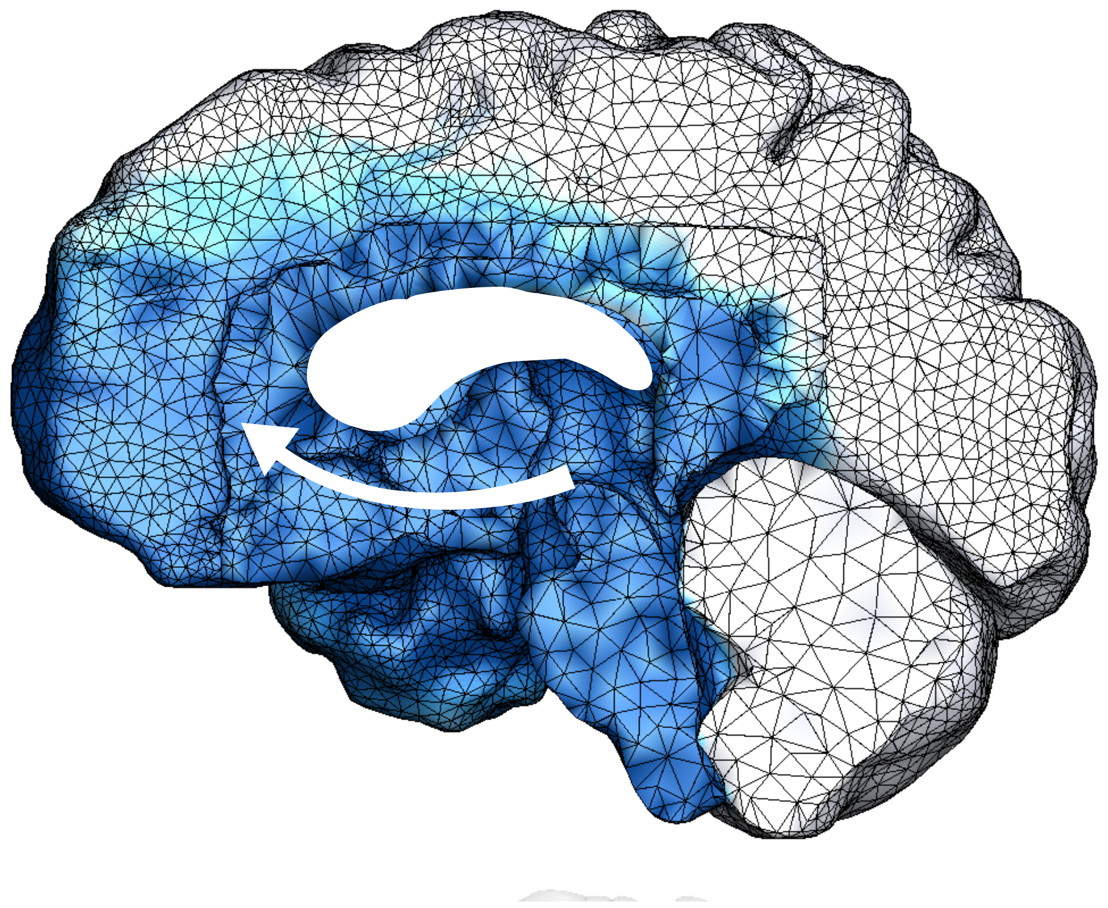


define p_i and $\widetilde{p}_i$ at each node i

$$\frac{dp_i}{dt} = - \sum_{j=1}^{n} L_{ij} p_j + k_0 - k_1 p_i - k_{12} p_i \widetilde{p}_i$$

$$\frac{d\widetilde{p}_i}{dt} = - \sum_{j=1}^{n} L_{ij} \widetilde{p}_j \qquad - \tilde{k}_1 p_i - k_{12} p_i \widetilde{p}_i$$

continuum model



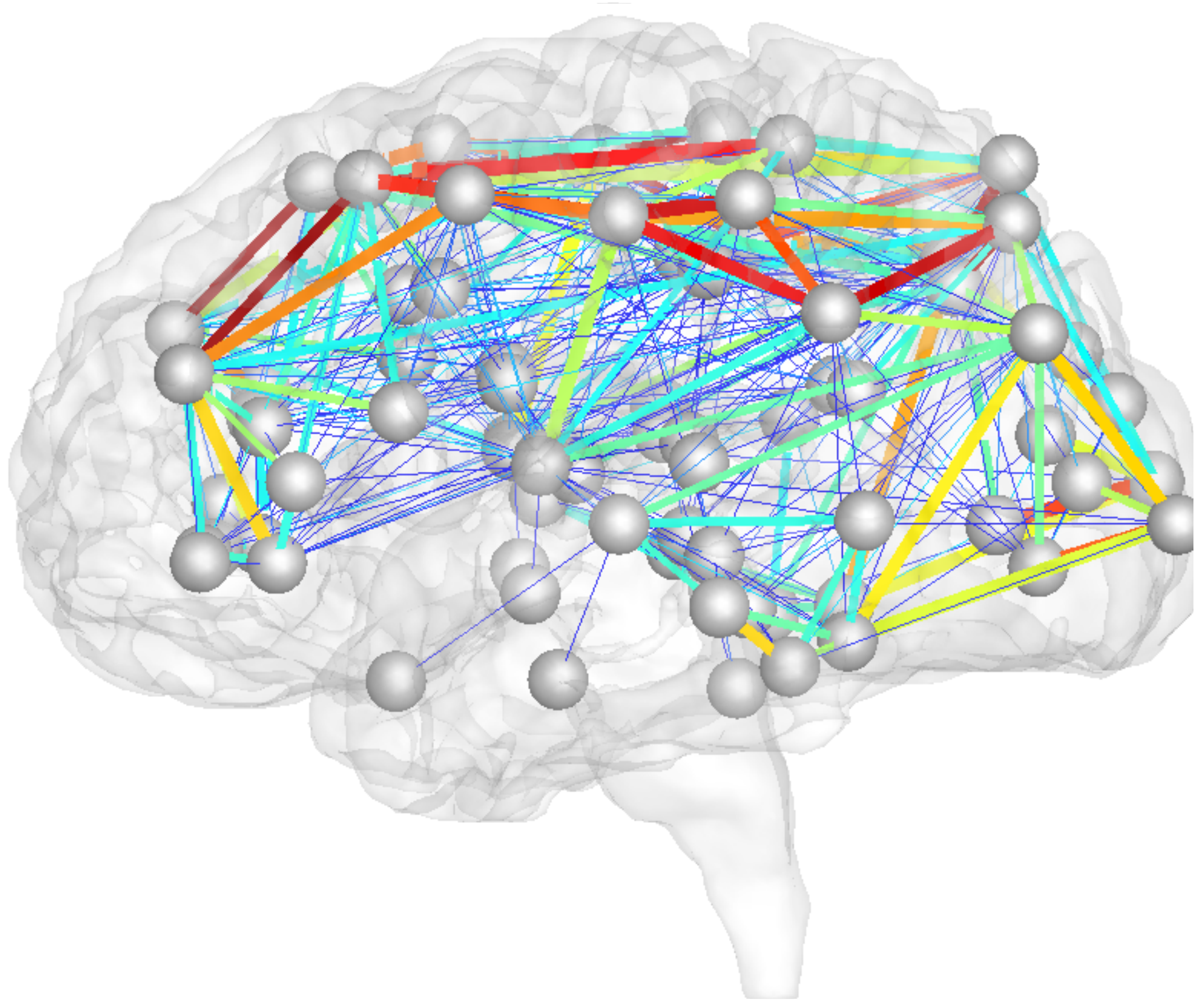
define p and $\widetilde{p}$ at all points

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + k_0 - k_1 p - k_{12} p \widetilde{p}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) \qquad - \widetilde{k}_1 \widetilde{p} + k_{12} p \widetilde{p}$$

partial differential equations

discrete model

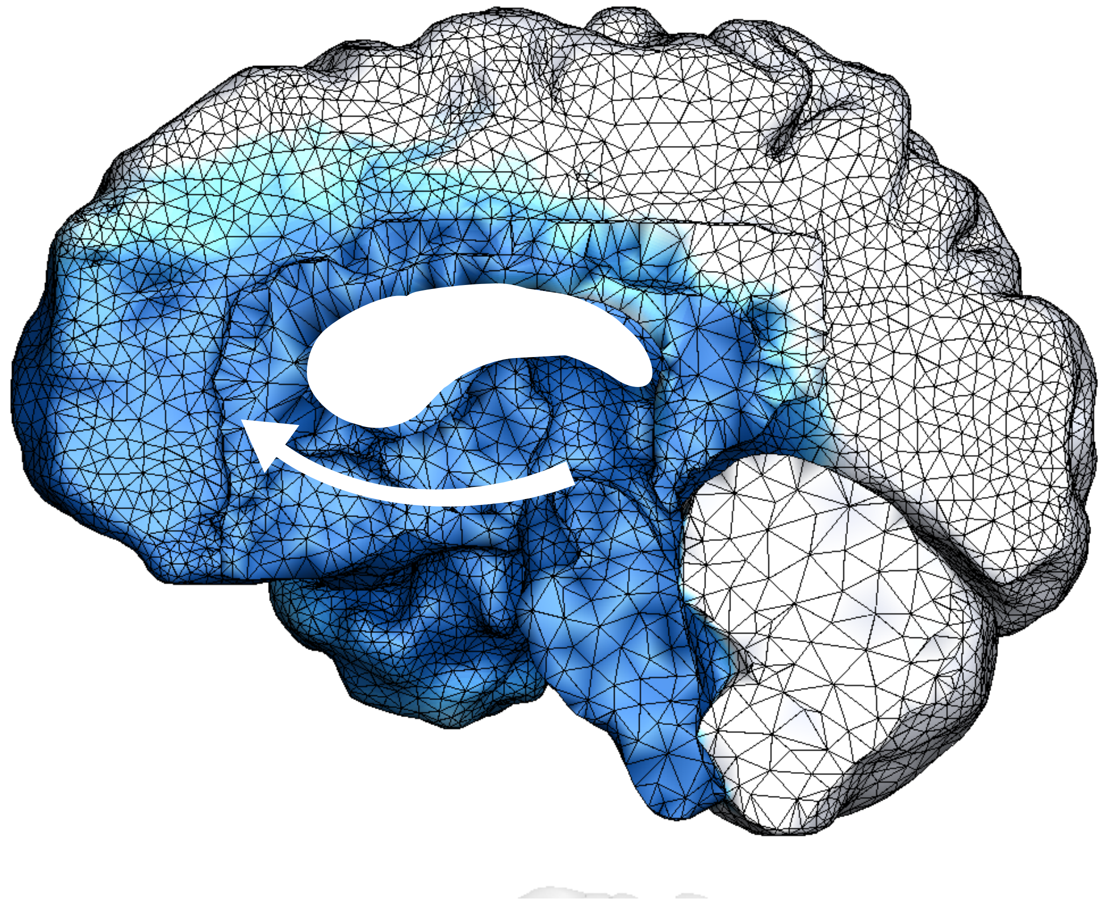


define p_i and $\widetilde{p}_i$ at each node i

$$\frac{dp_i}{dt} = -\sum_{j=1}^{n} L_{ij} p_j + k_0 - k_1 p_i - k_{12} p_i \widetilde{p}_i$$

$$\frac{d\widetilde{p}_i}{dt} = -\sum_{j=1}^{n} L_{ij} \widetilde{p}_j \qquad - \tilde{k}_1 p_i - k_{12} p_i \widetilde{p}_i$$

continuum model



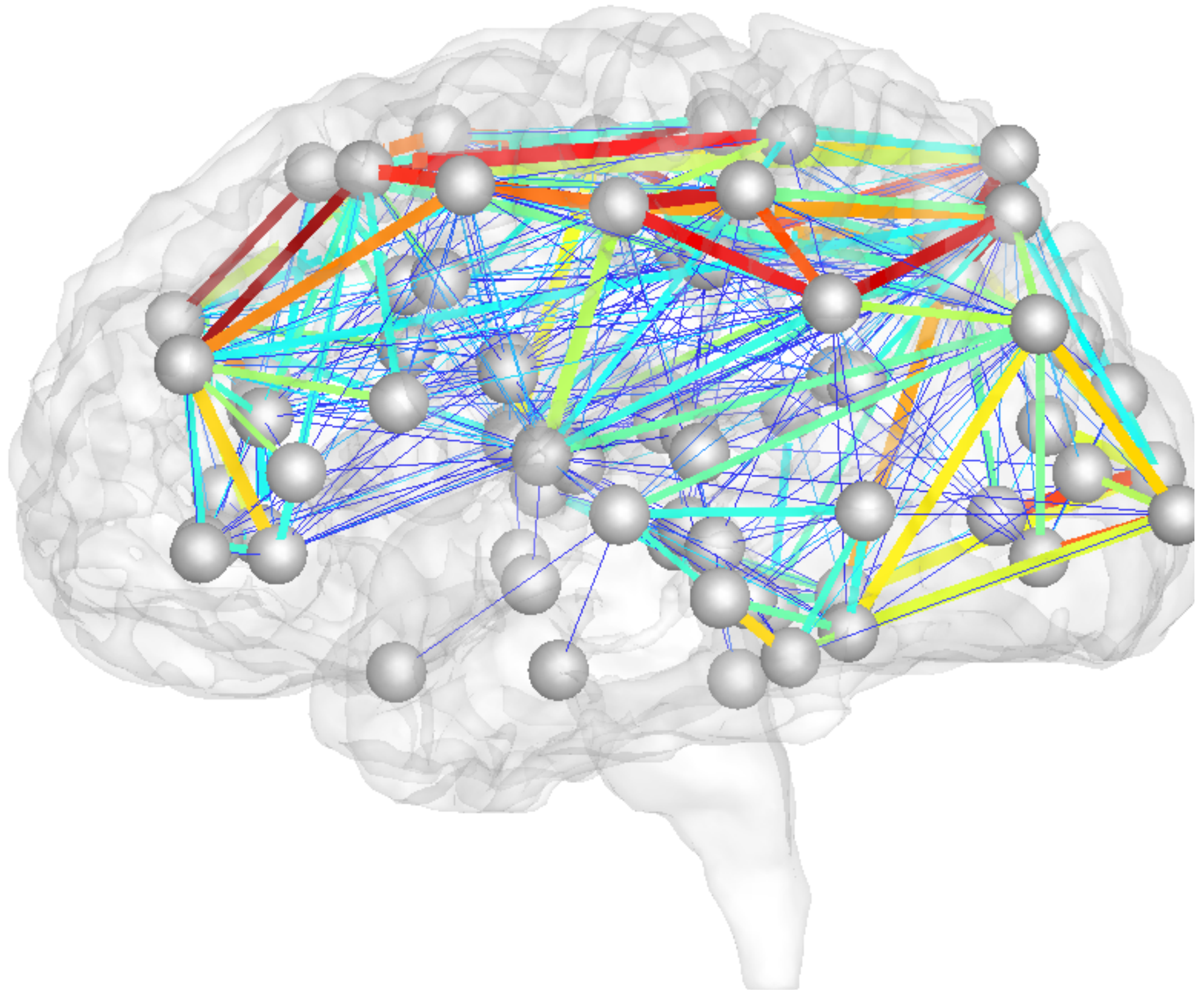
define p and $\widetilde{p}$ at all points

$$\frac{\partial p}{\partial t} = \mathrm{Div}(\mathbf{D}_p \cdot \nabla p) + k_0 - k_1 p - k_{12} p \widetilde{p}$$

$$\frac{\partial \widetilde{p}}{\partial t} = \mathrm{Div}(\mathbf{D}_{\widetilde{p}} \cdot \nabla \widetilde{p}) \qquad - \widetilde{k}_1 \widetilde{p} + k_{12} p \widetilde{p}$$

partial differential equations

discrete model

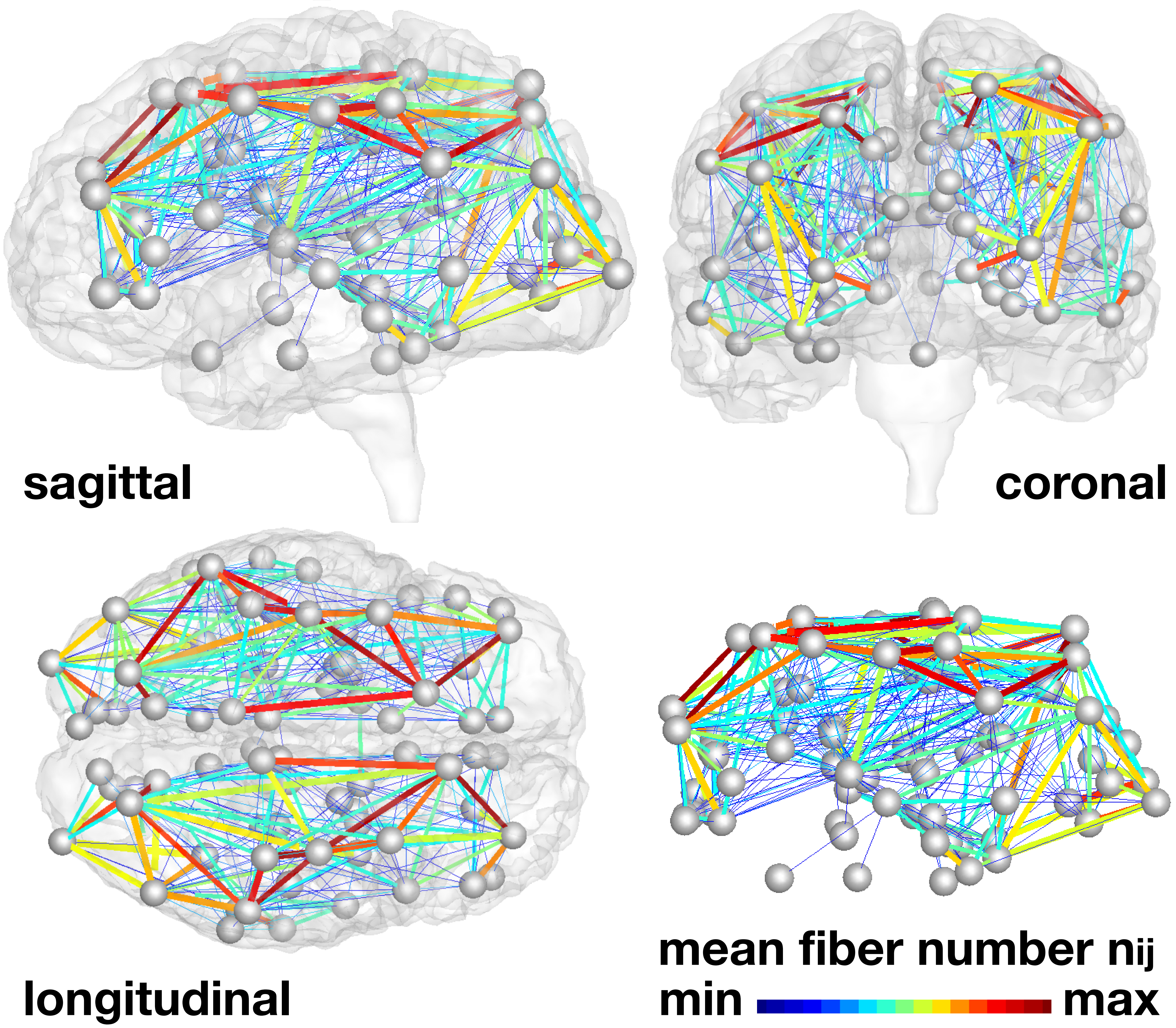


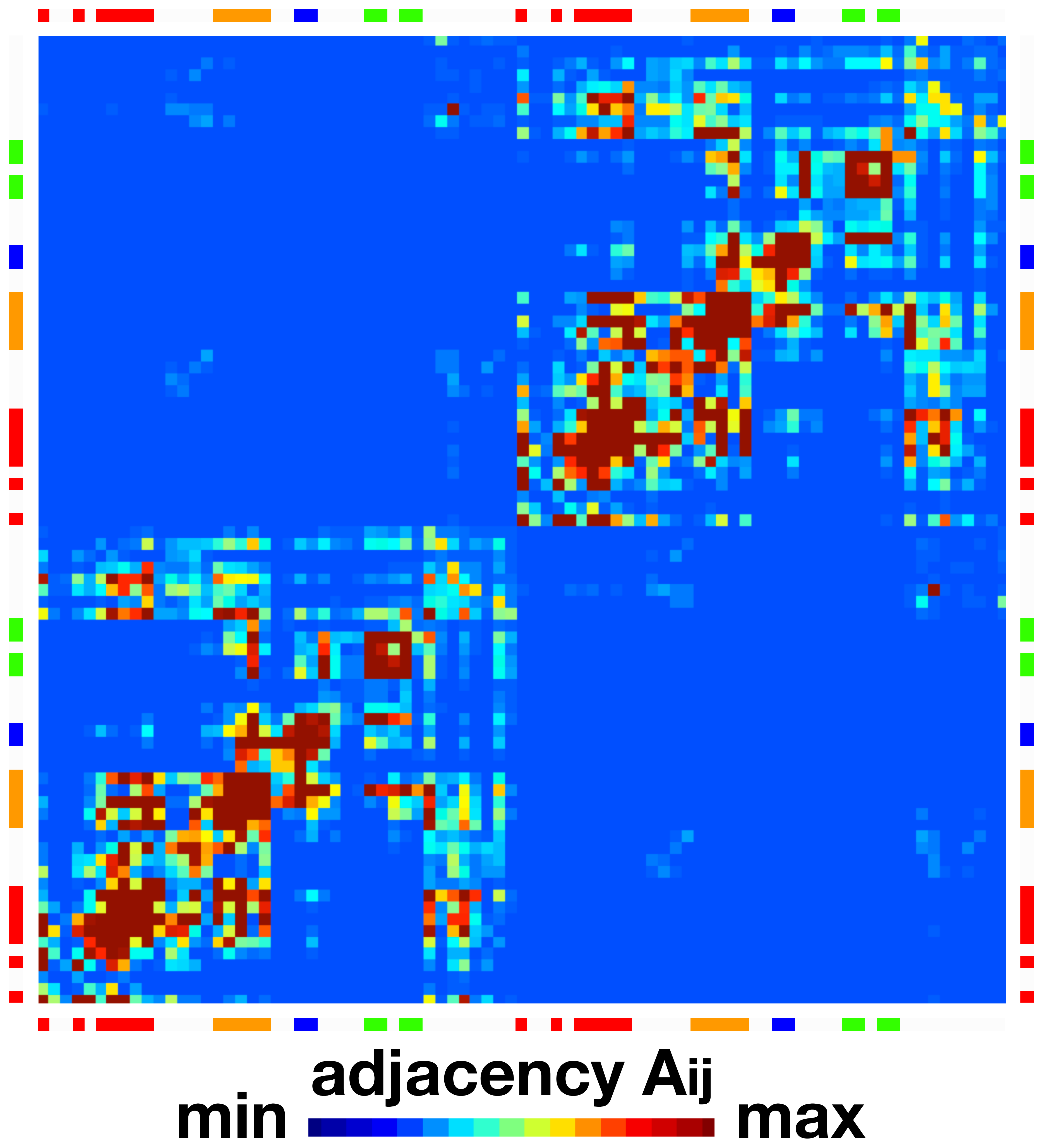
define p_i and $\widetilde{p}_i$ at each node i

$$\frac{dp_i}{dt} = - \sum_{j=1}^{n} L_{ij} p_j + k_0 - k_1 p_i - k_{12} p_i \widetilde{p}_i$$

$$\frac{d\widetilde{p}_i}{dt} = - \sum_{j=1}^{n} L_{ij} \widetilde{p}_j \qquad - \tilde{k}_1 p_i - k_{12} p_i \widetilde{p}_i$$

ordinary differential equations

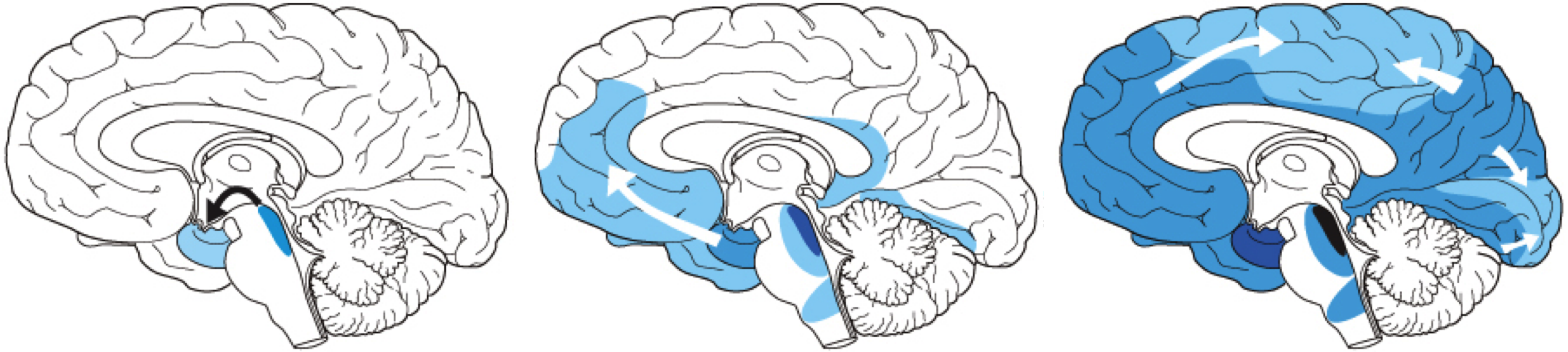




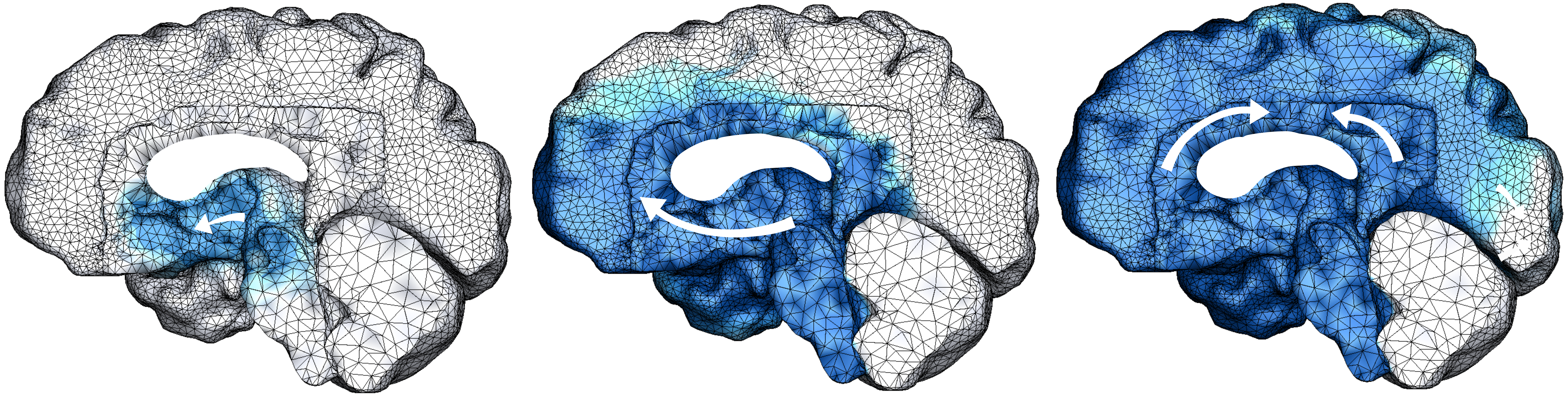
weighted graph Laplacian

$$L_{ij} = D_{ij} - A_{ij} \quad \text{with} \quad A_{ij} = \frac{n_{ij}}{l_{ij}}$$

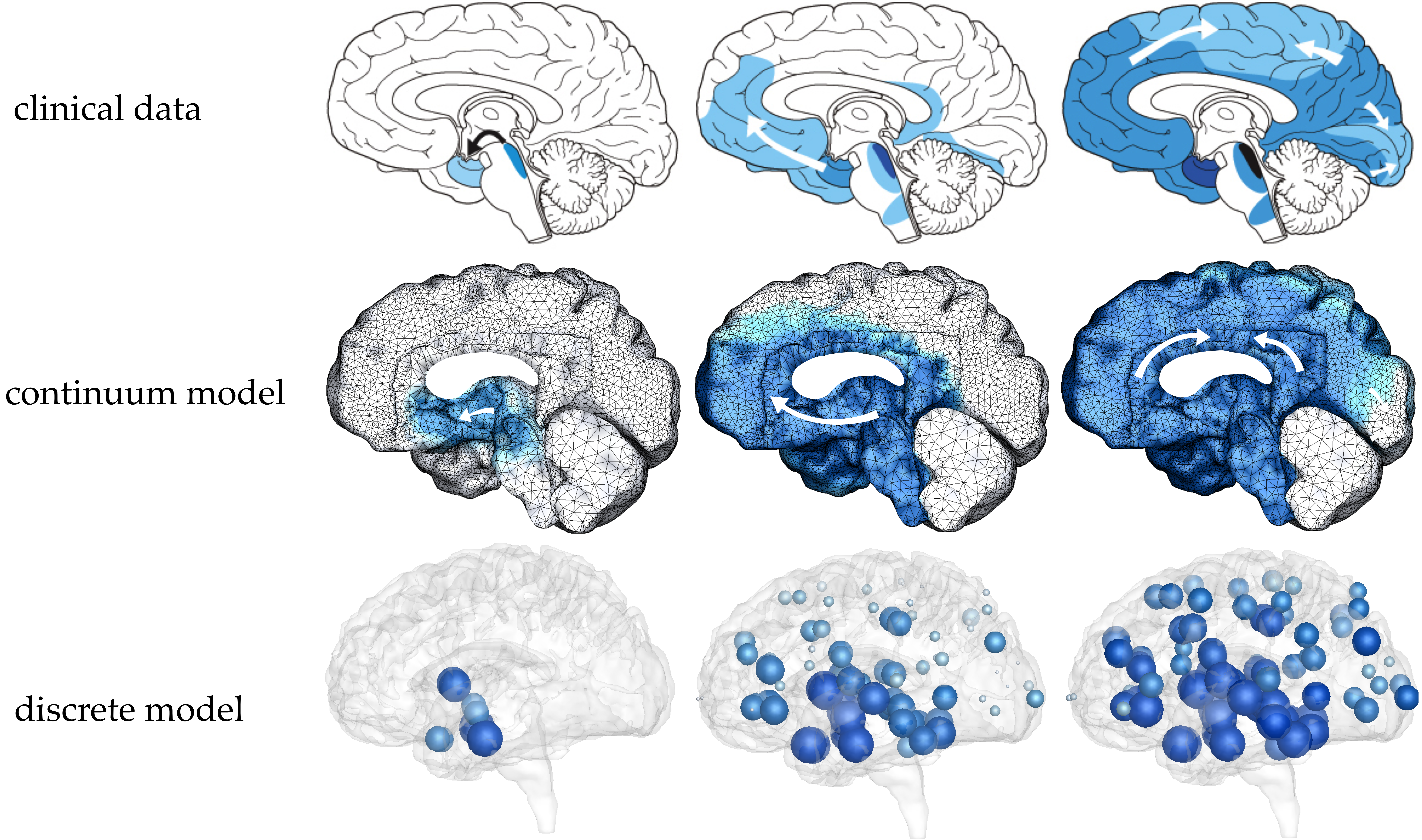
clinical data

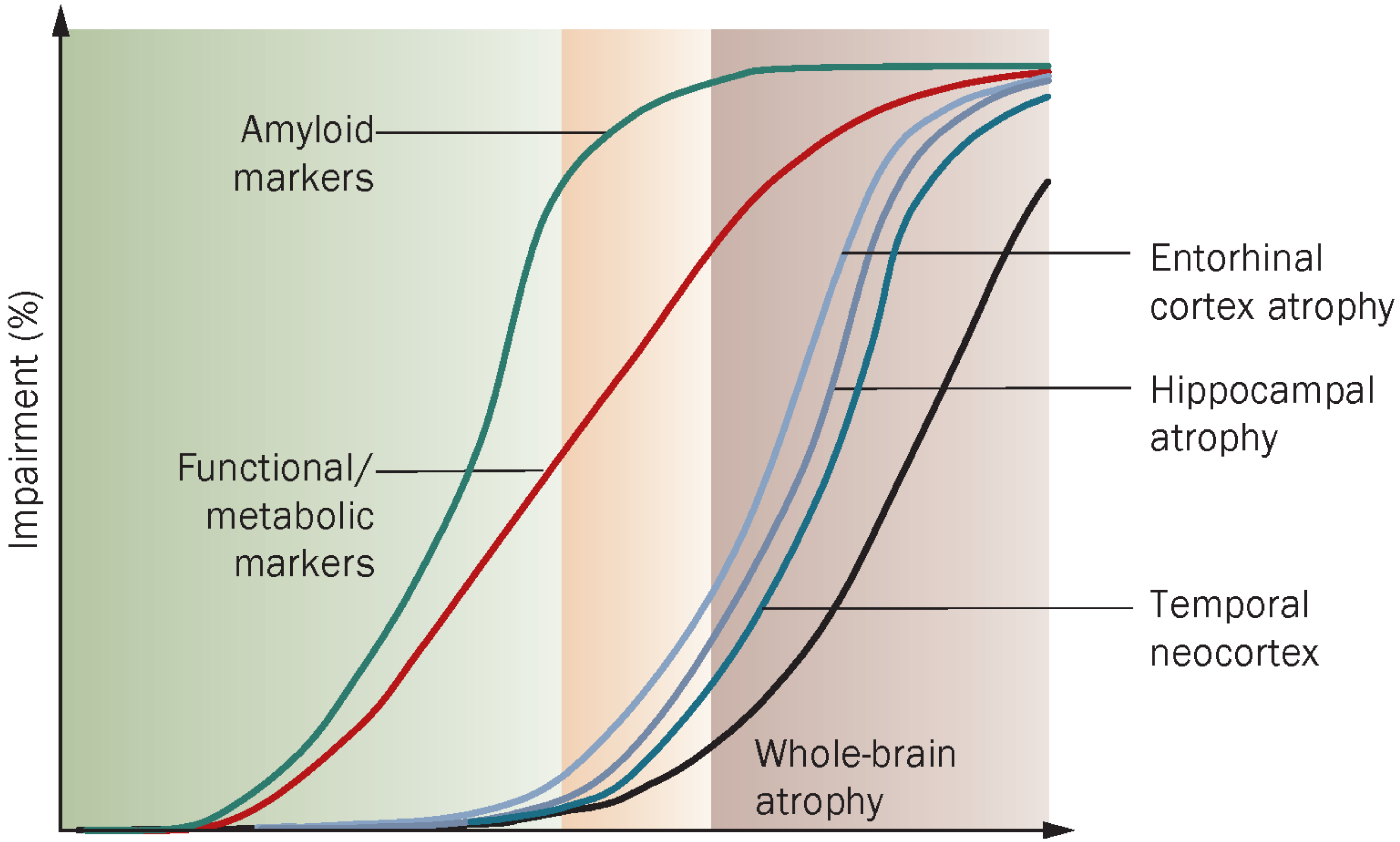


continuum model

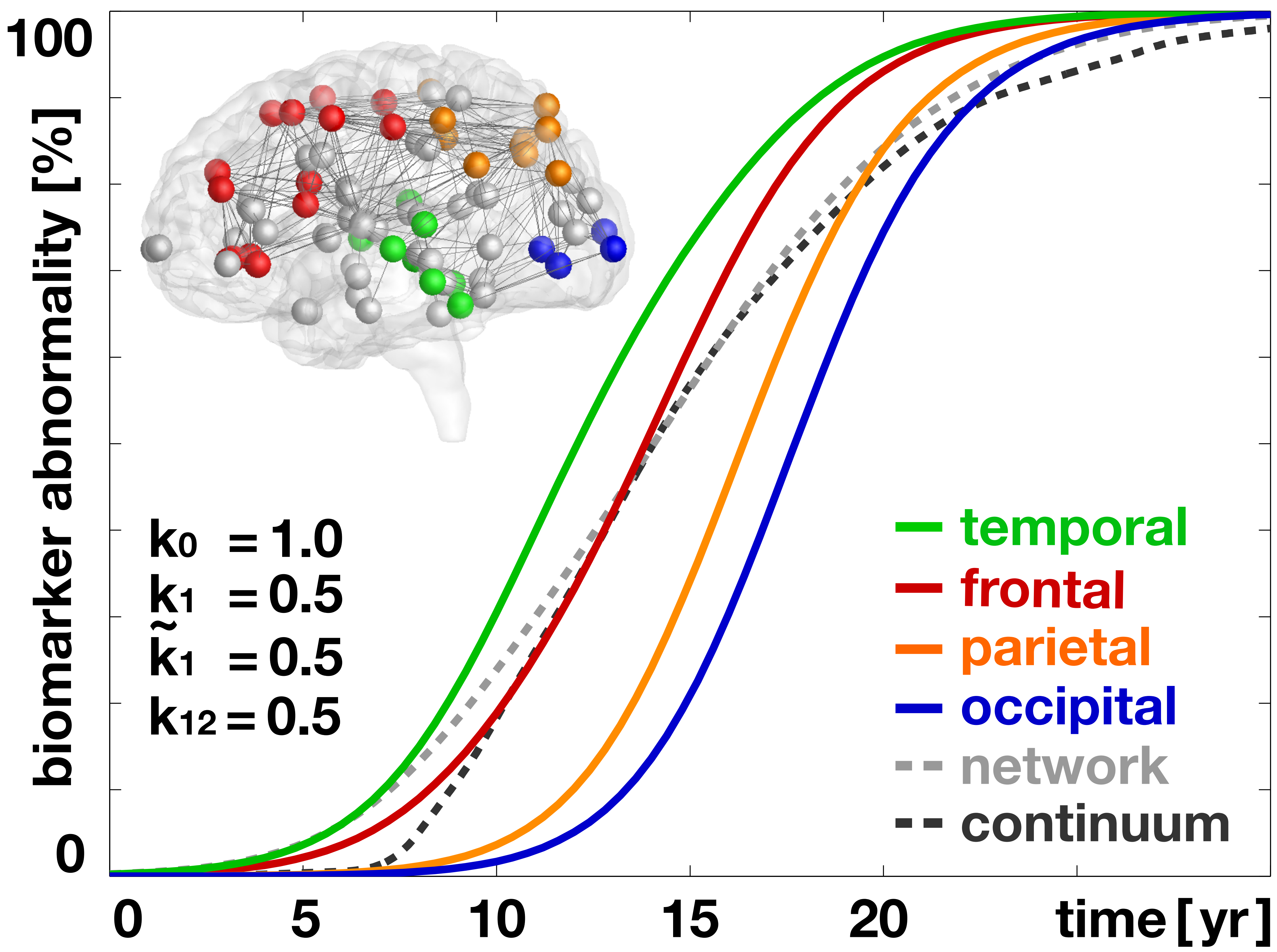


discrete model

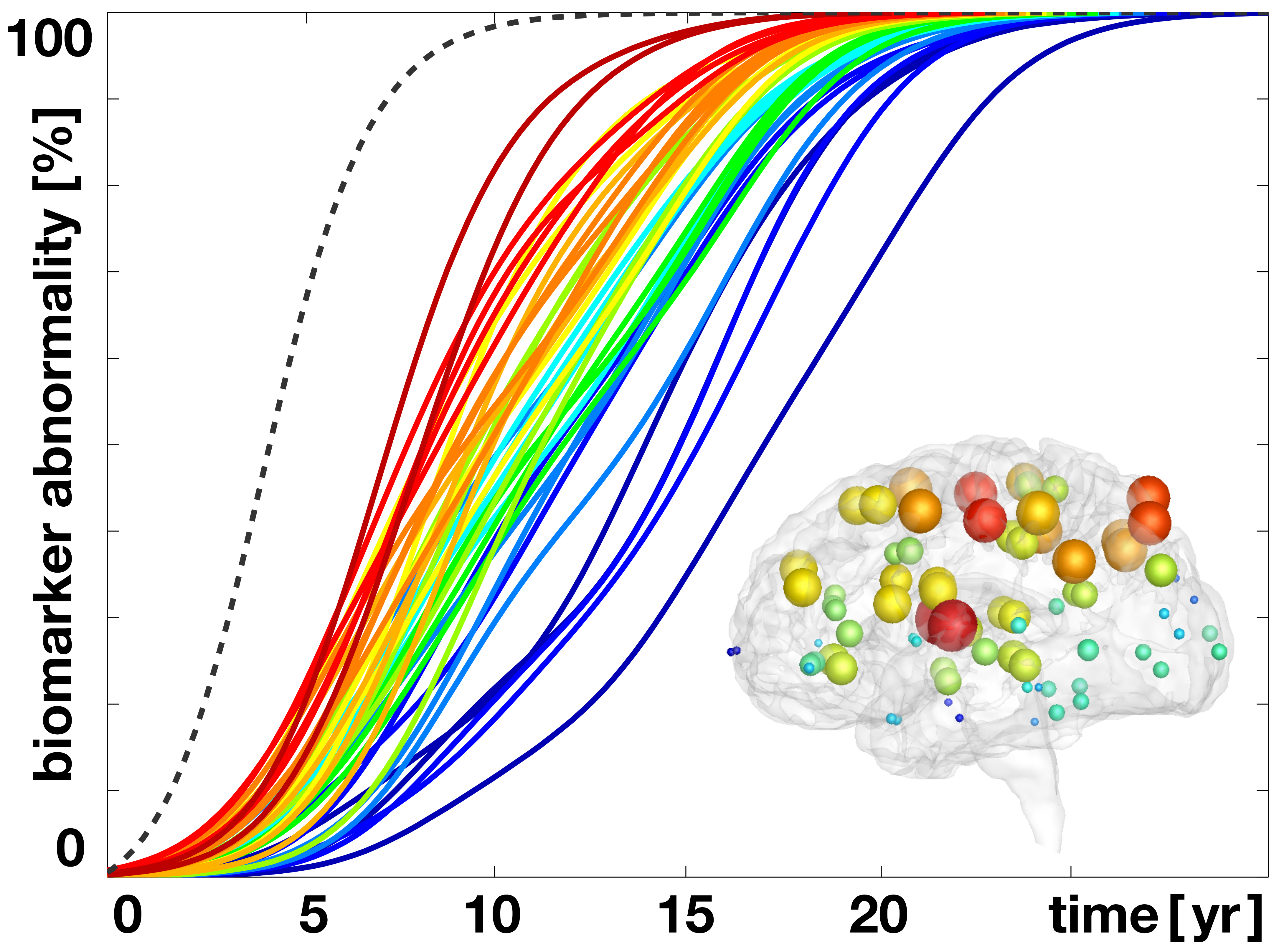

clinical data
continuum model
discrete model

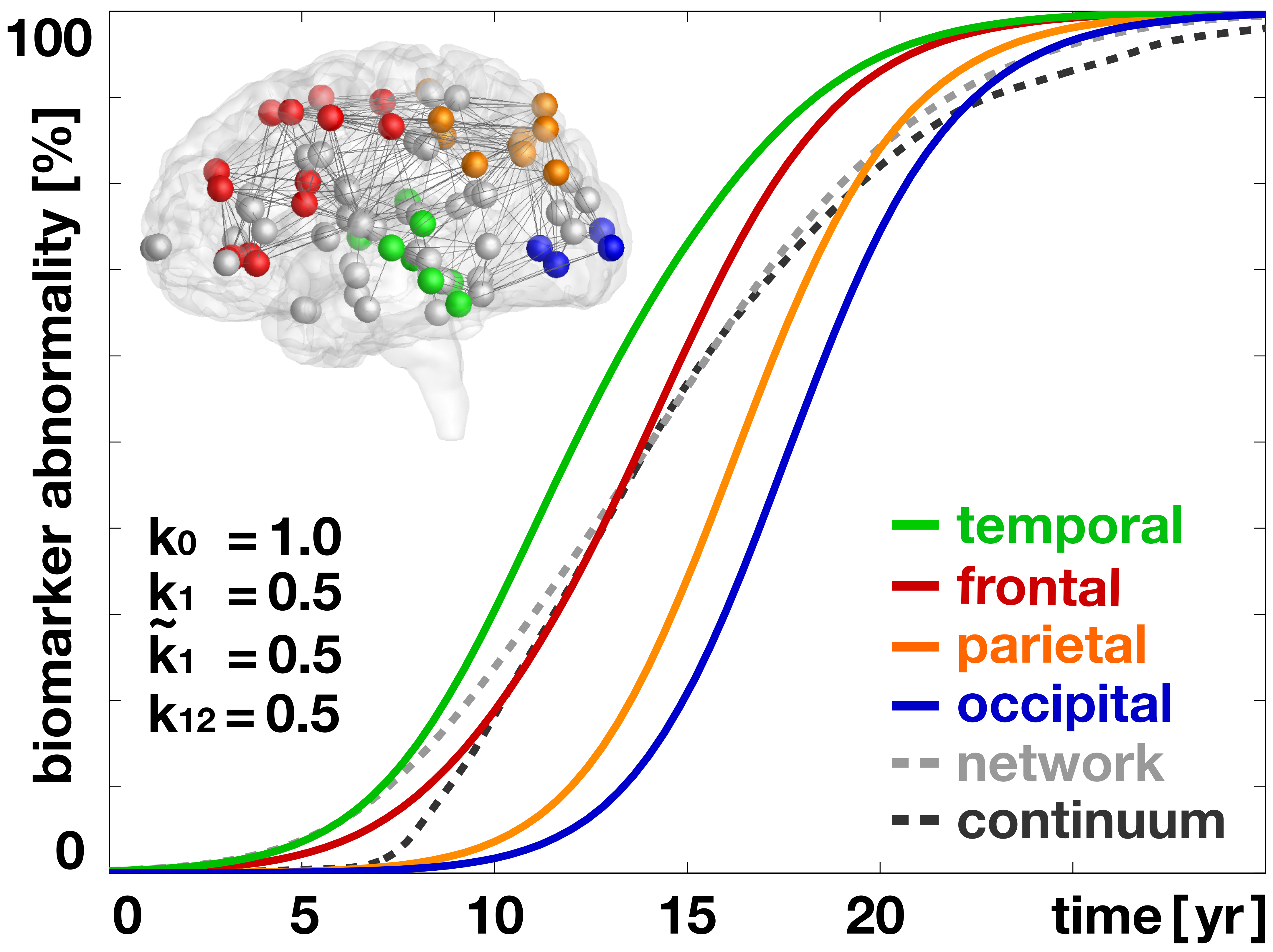


[frisoni, fox, jack, scheltens, thompson 2010]



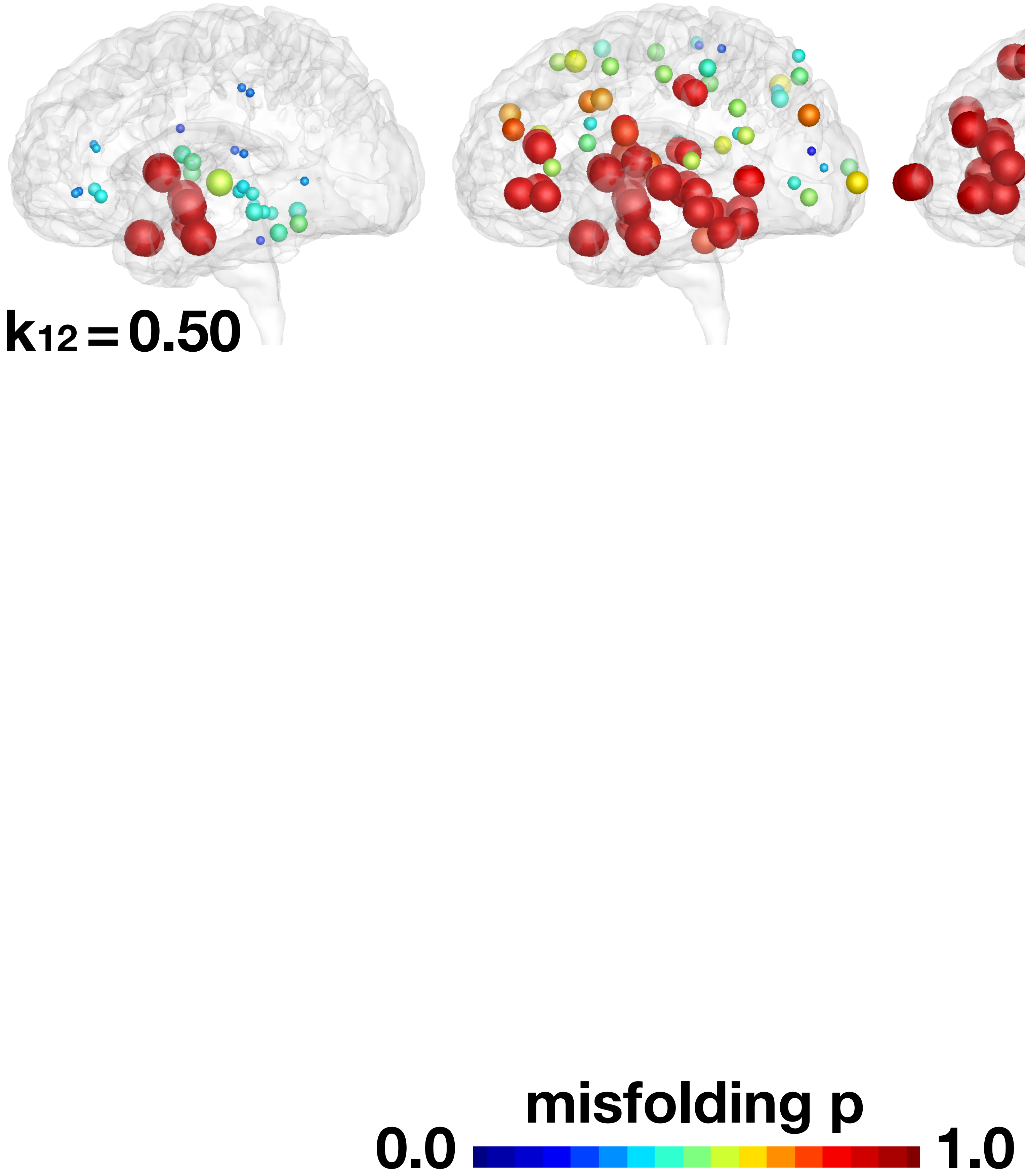
[fornari, schafer, jucker, ag, kuhl, 2019]



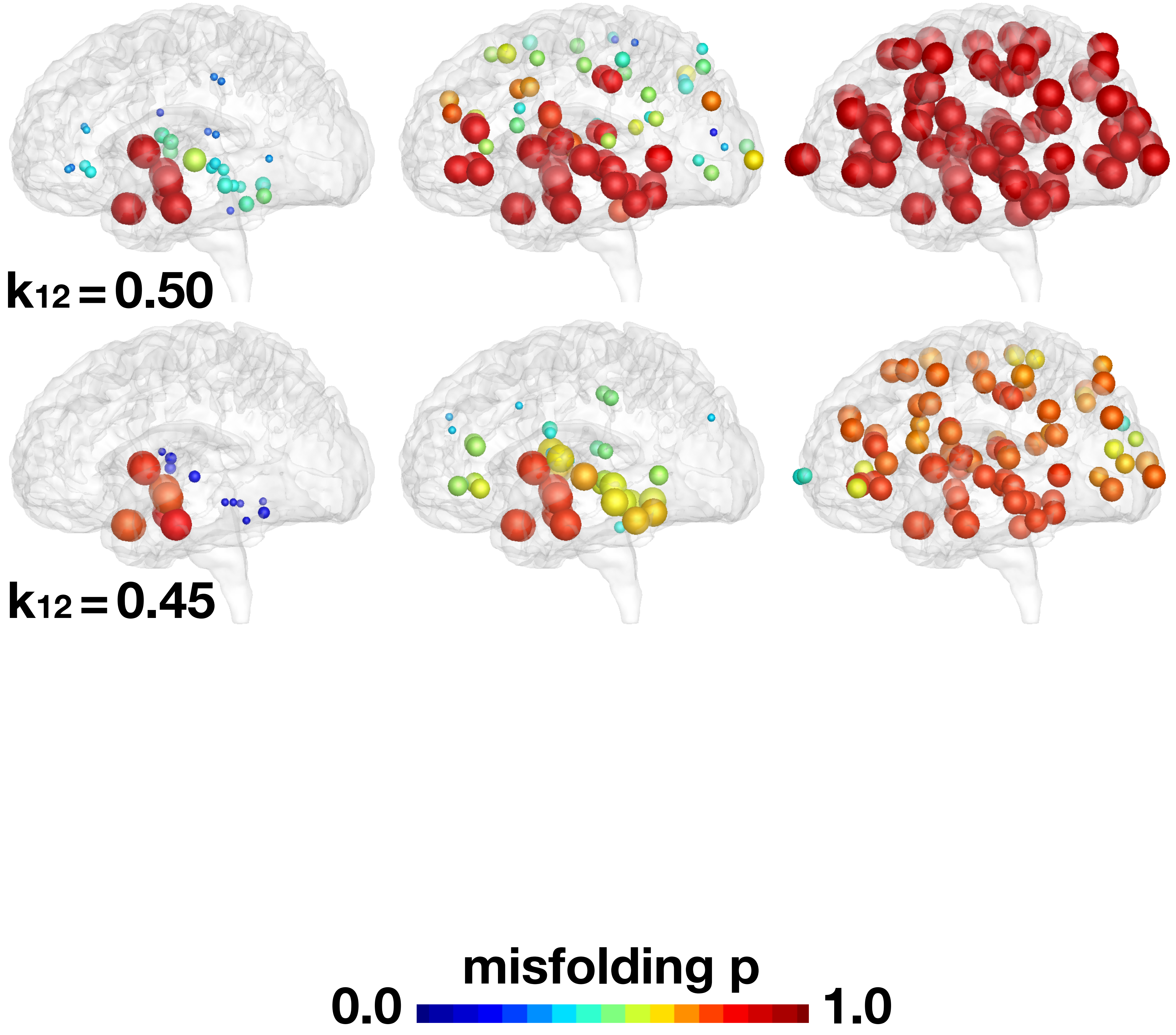


[fornari, schafer, jucker, ag, kuhl, 2019]

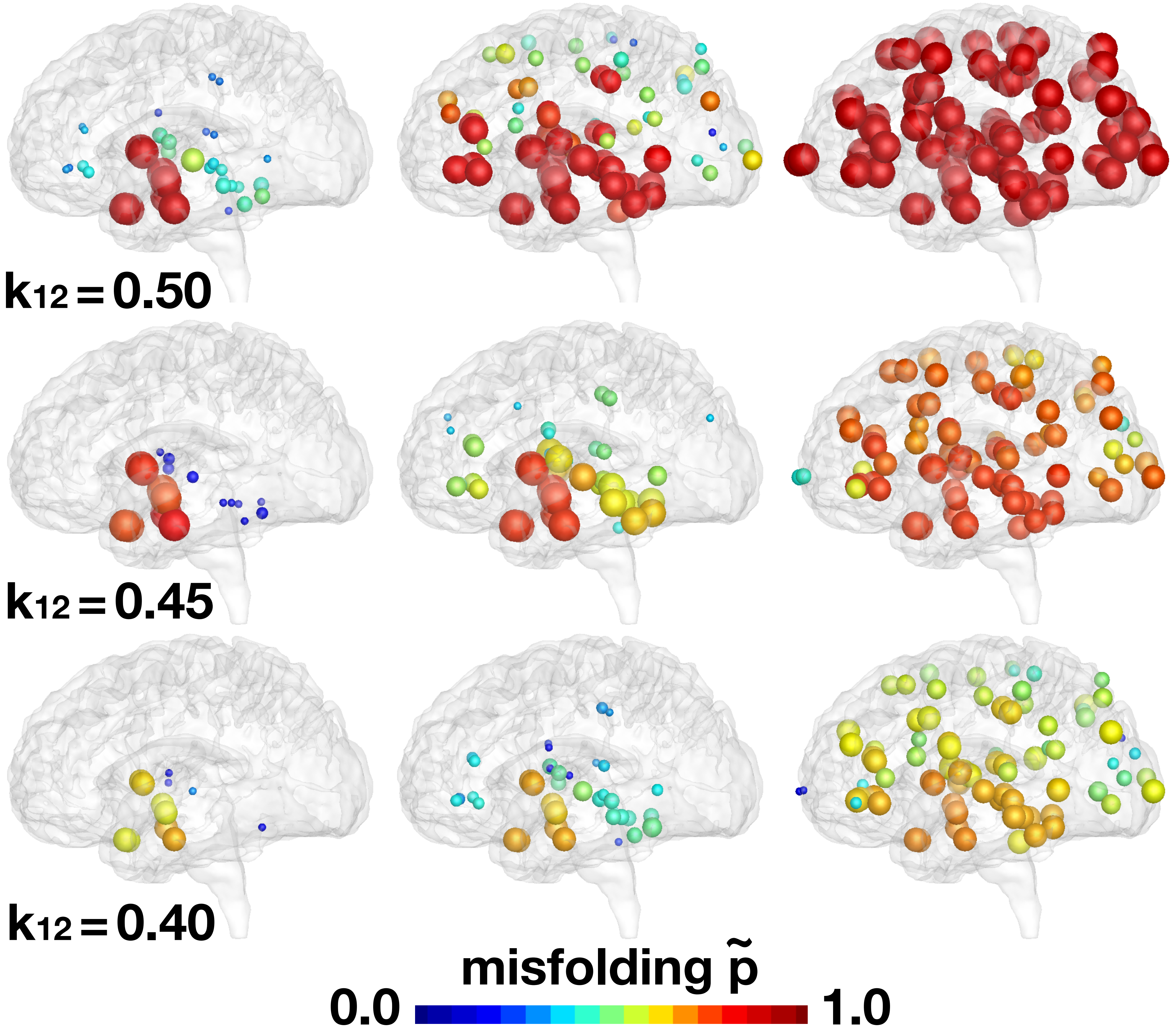
reducing production



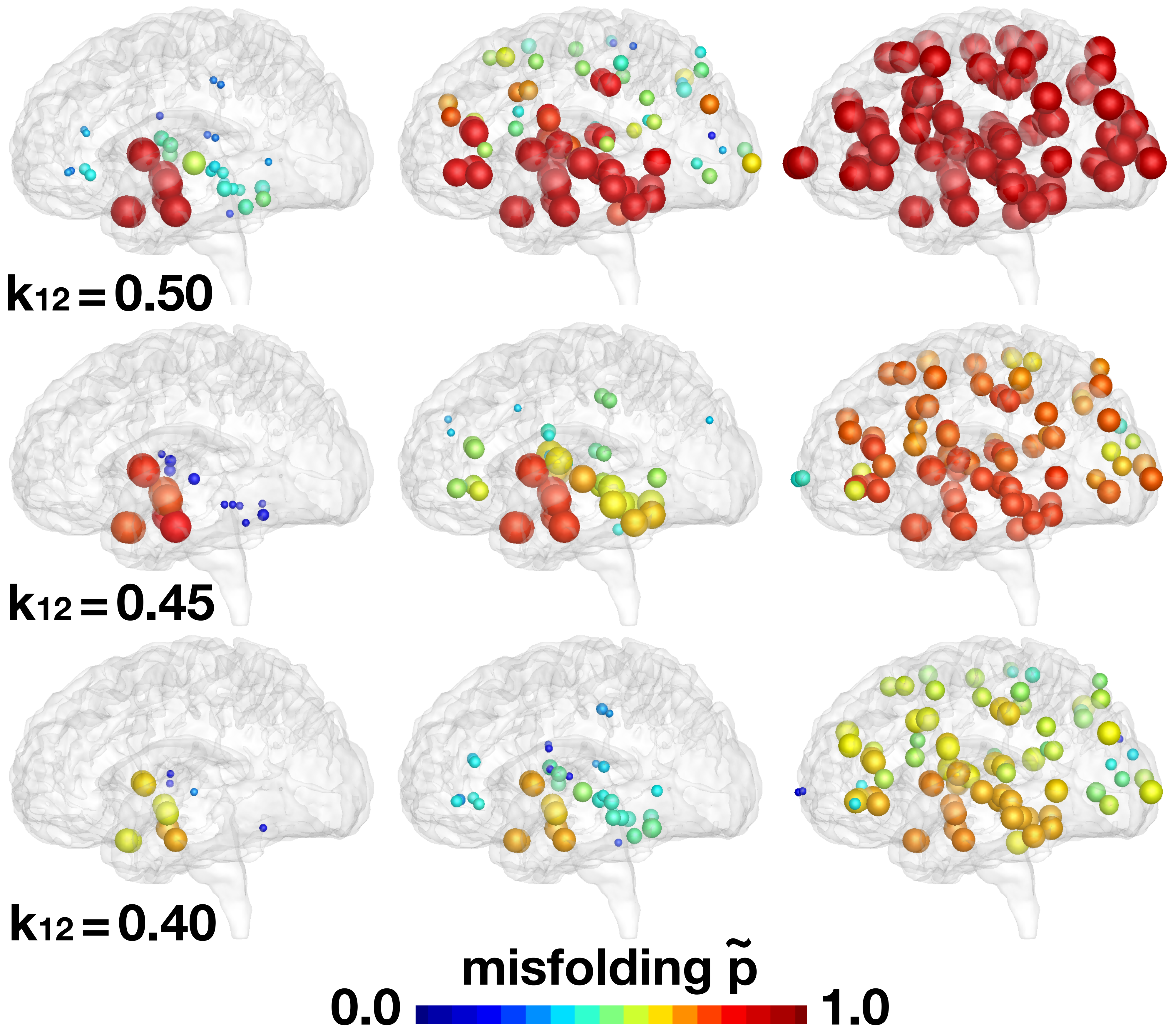
reducing production



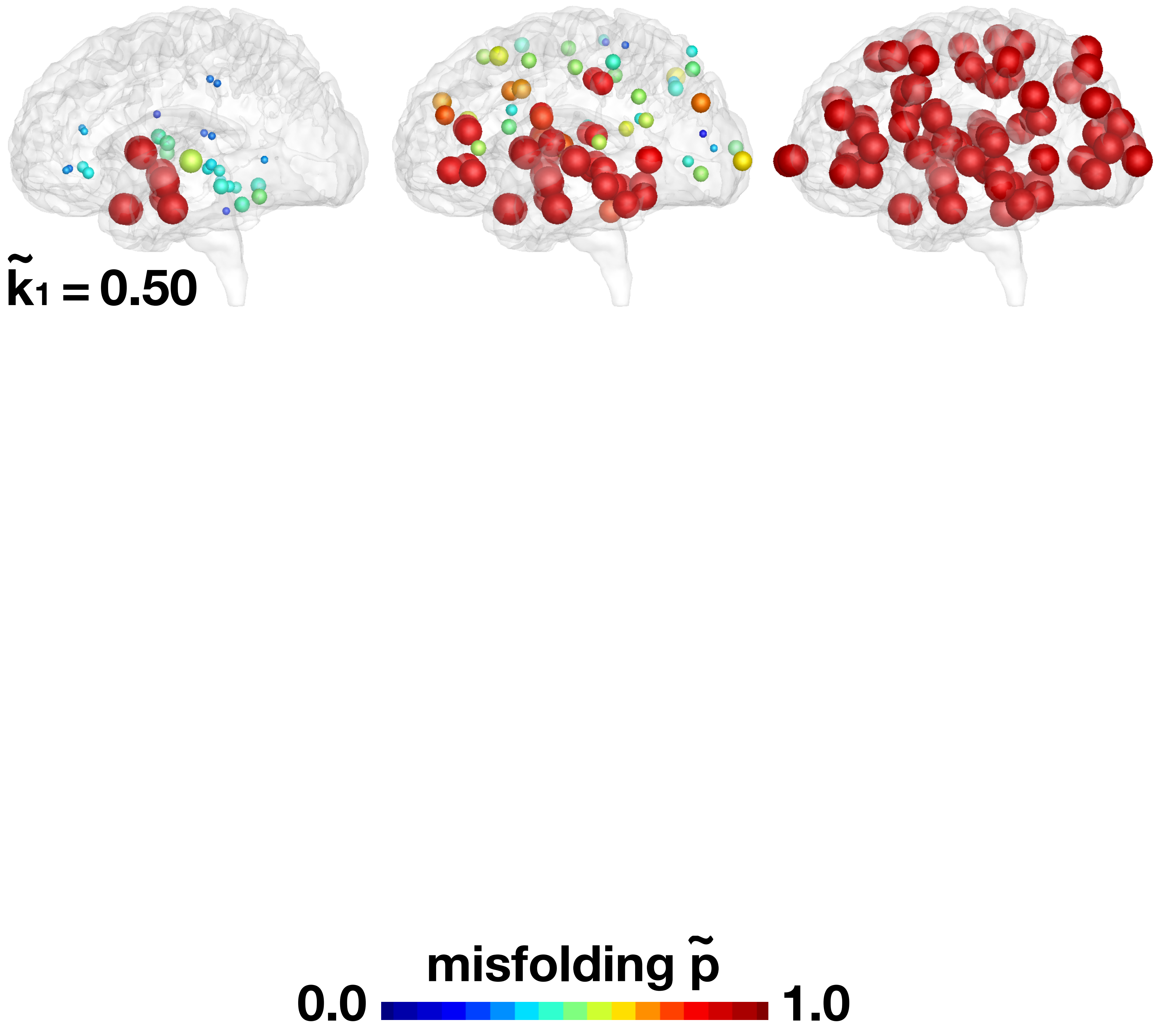
reducing production



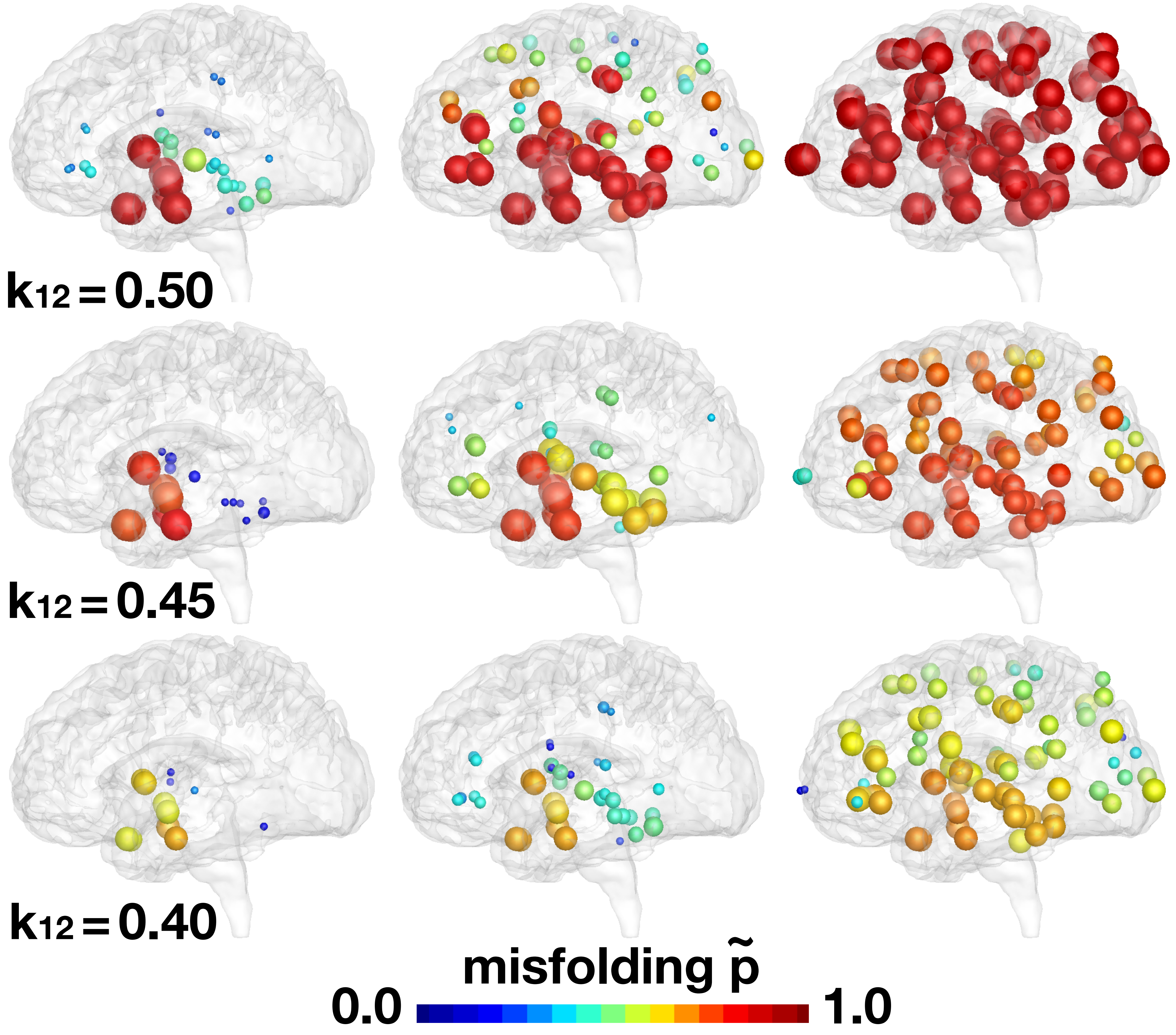
reducing production



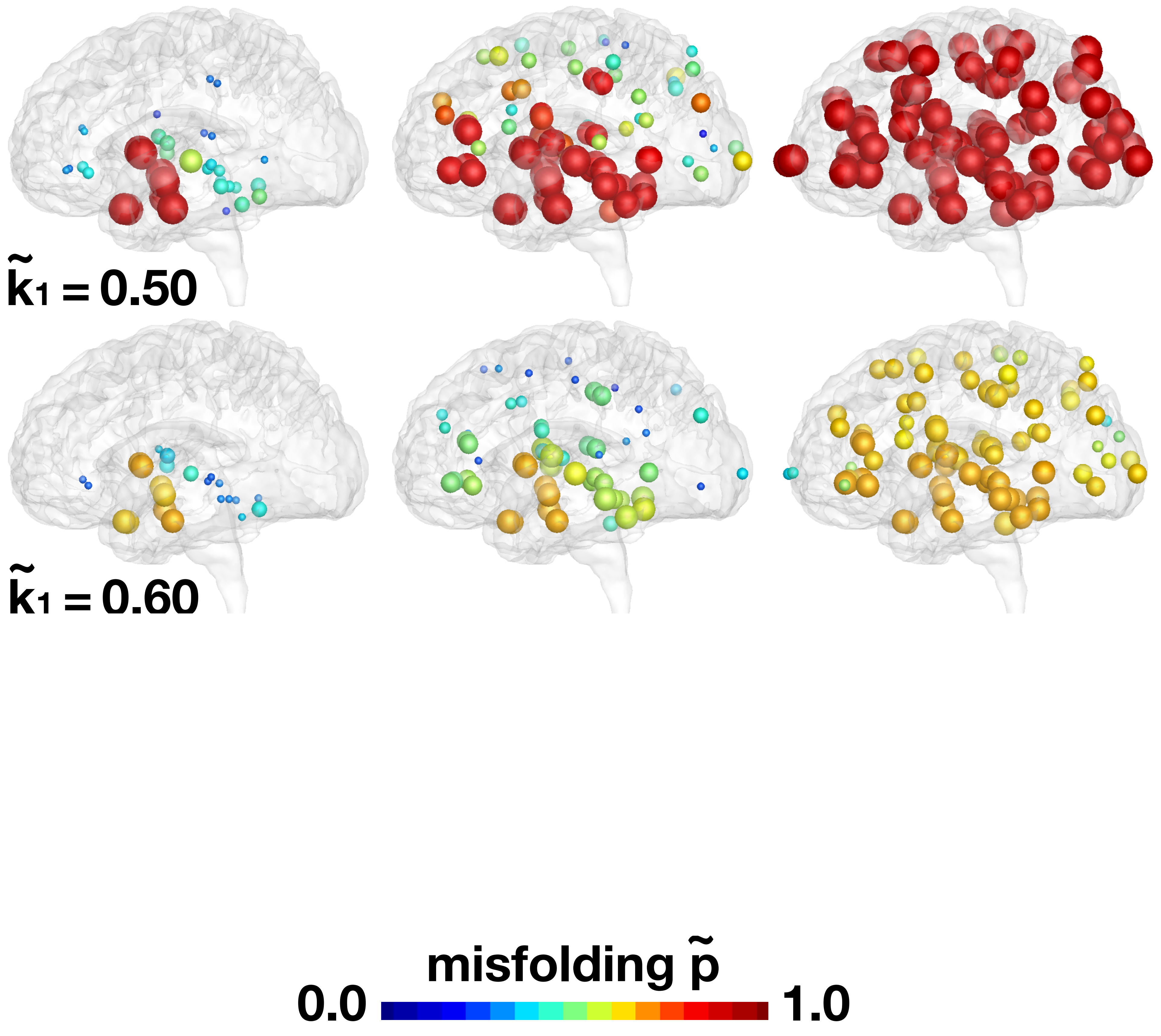
increasing clearance



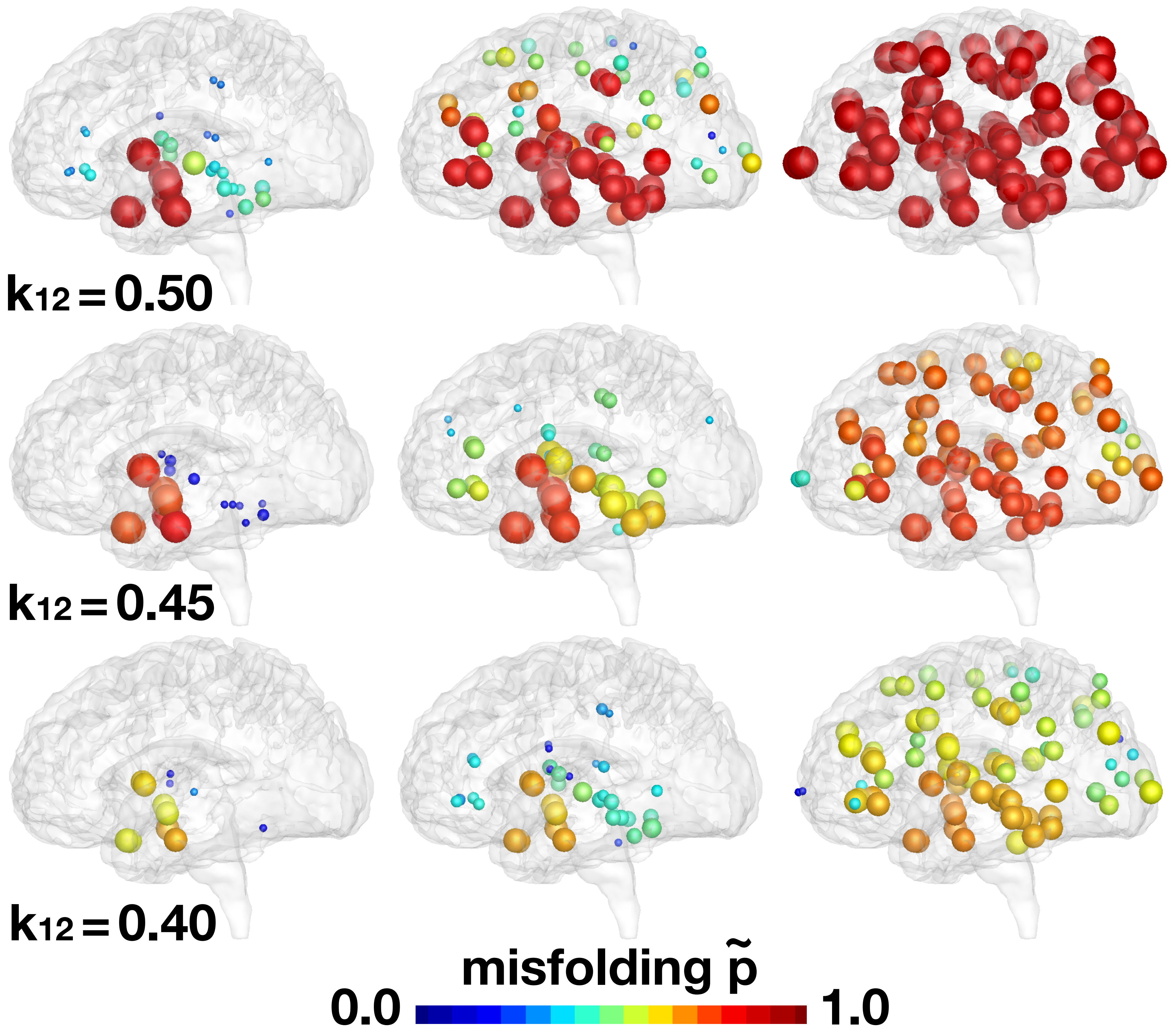
reducing production



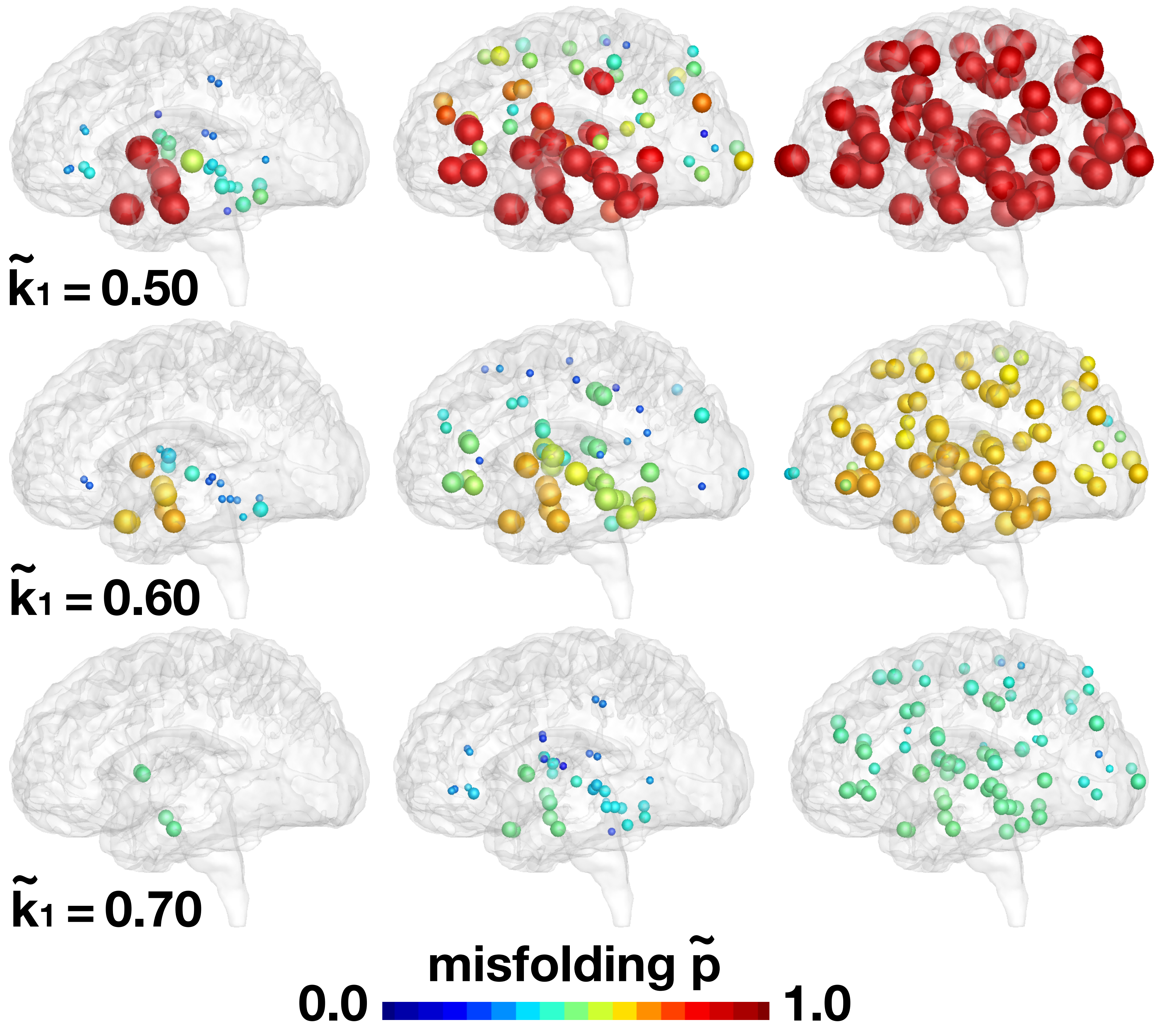
increasing clearance



reducing production



increasing clearance



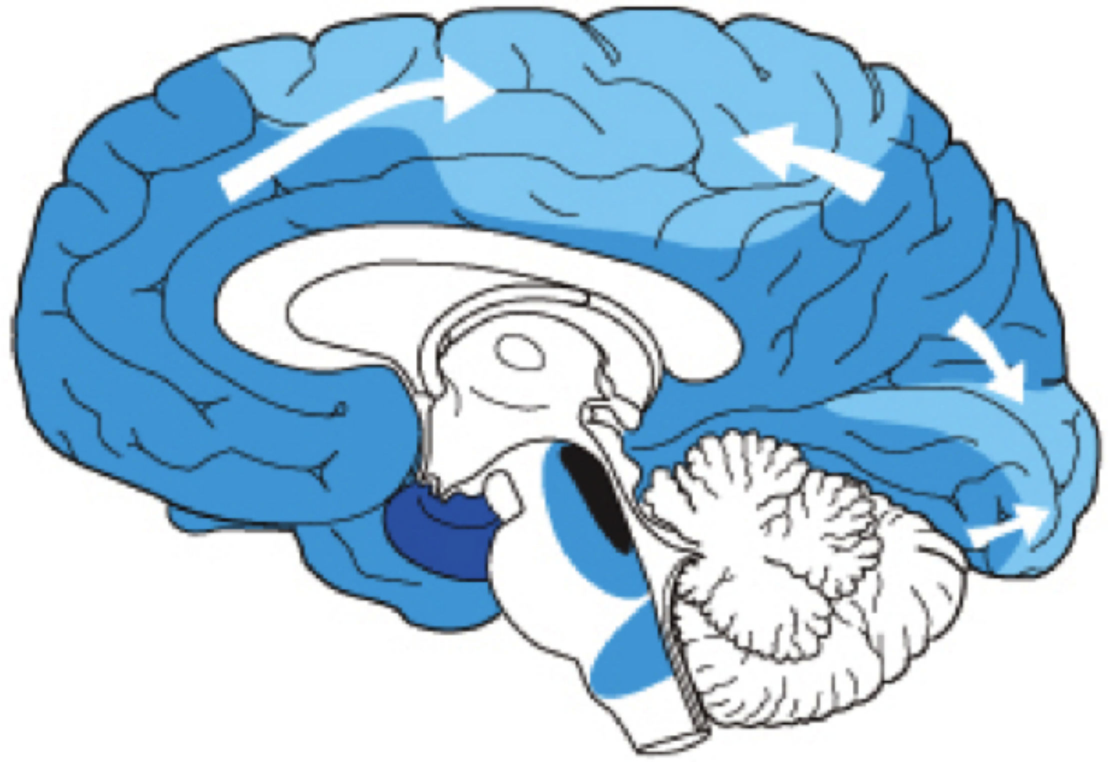
epilogue

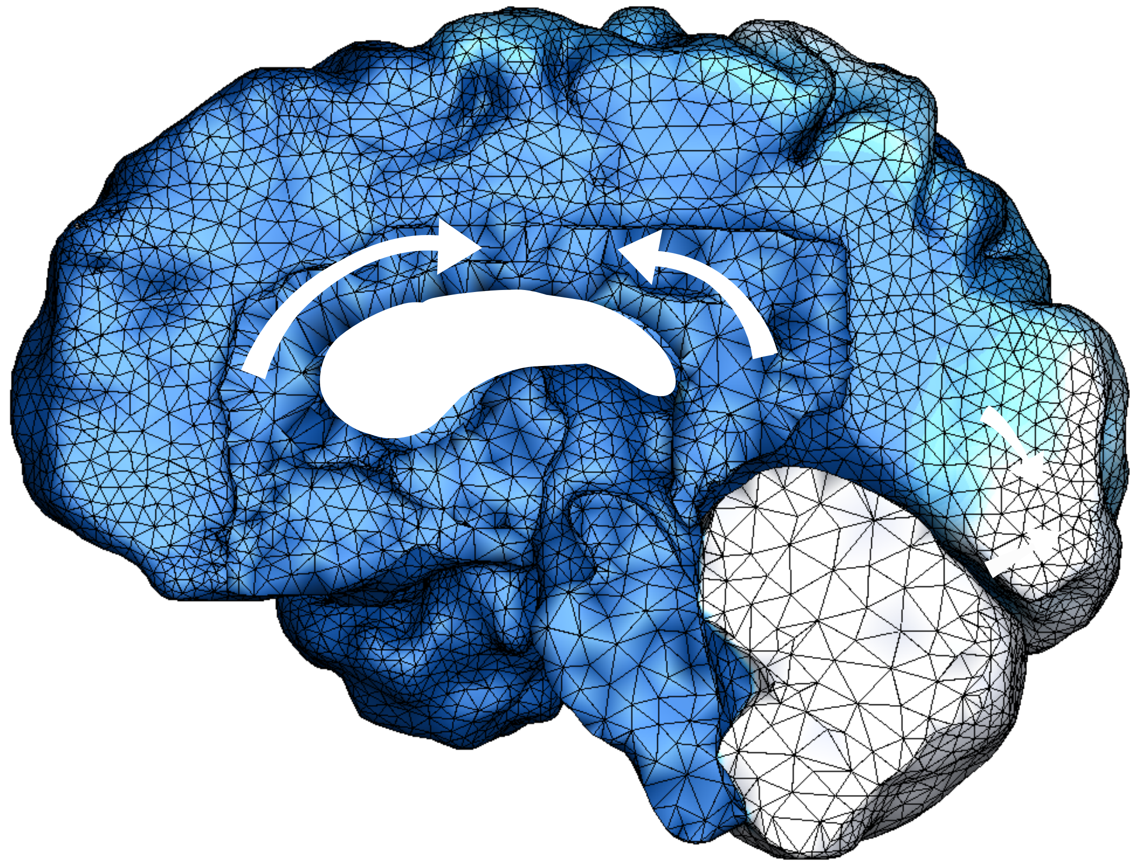
“c’est la première loi de la nature”

voltaire

what did we learn?

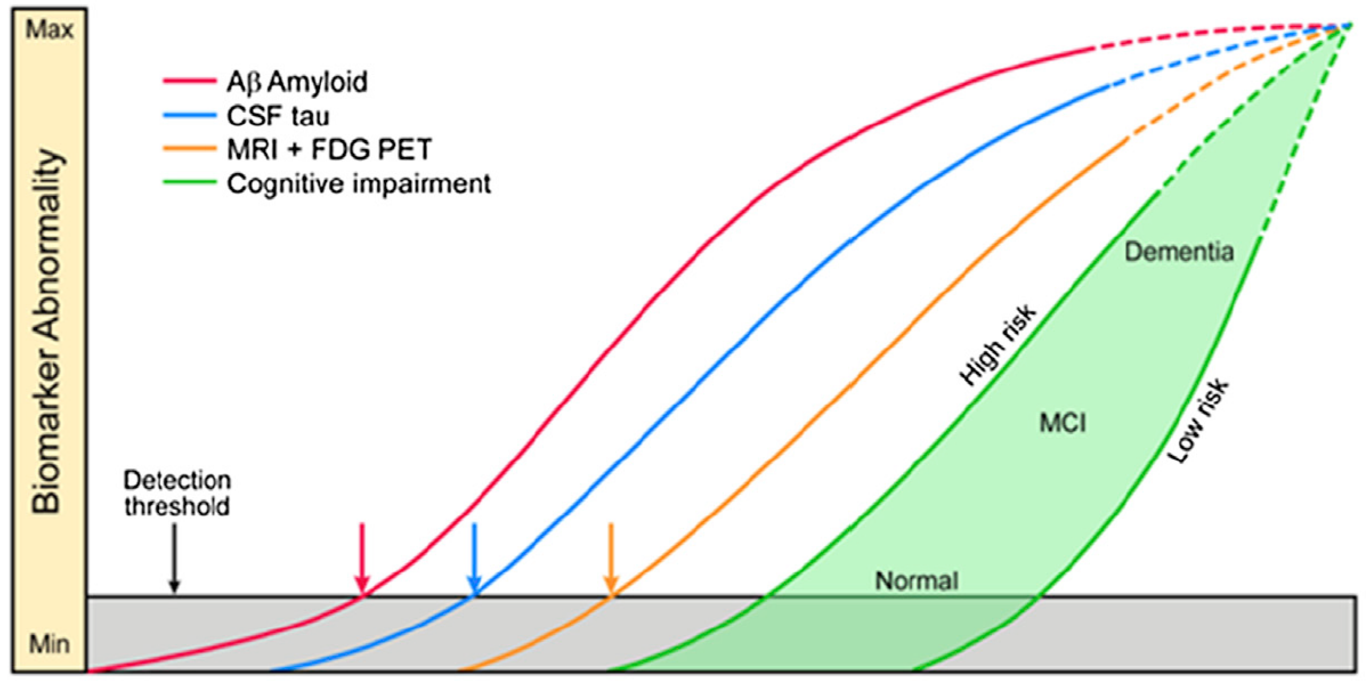
spatial progression

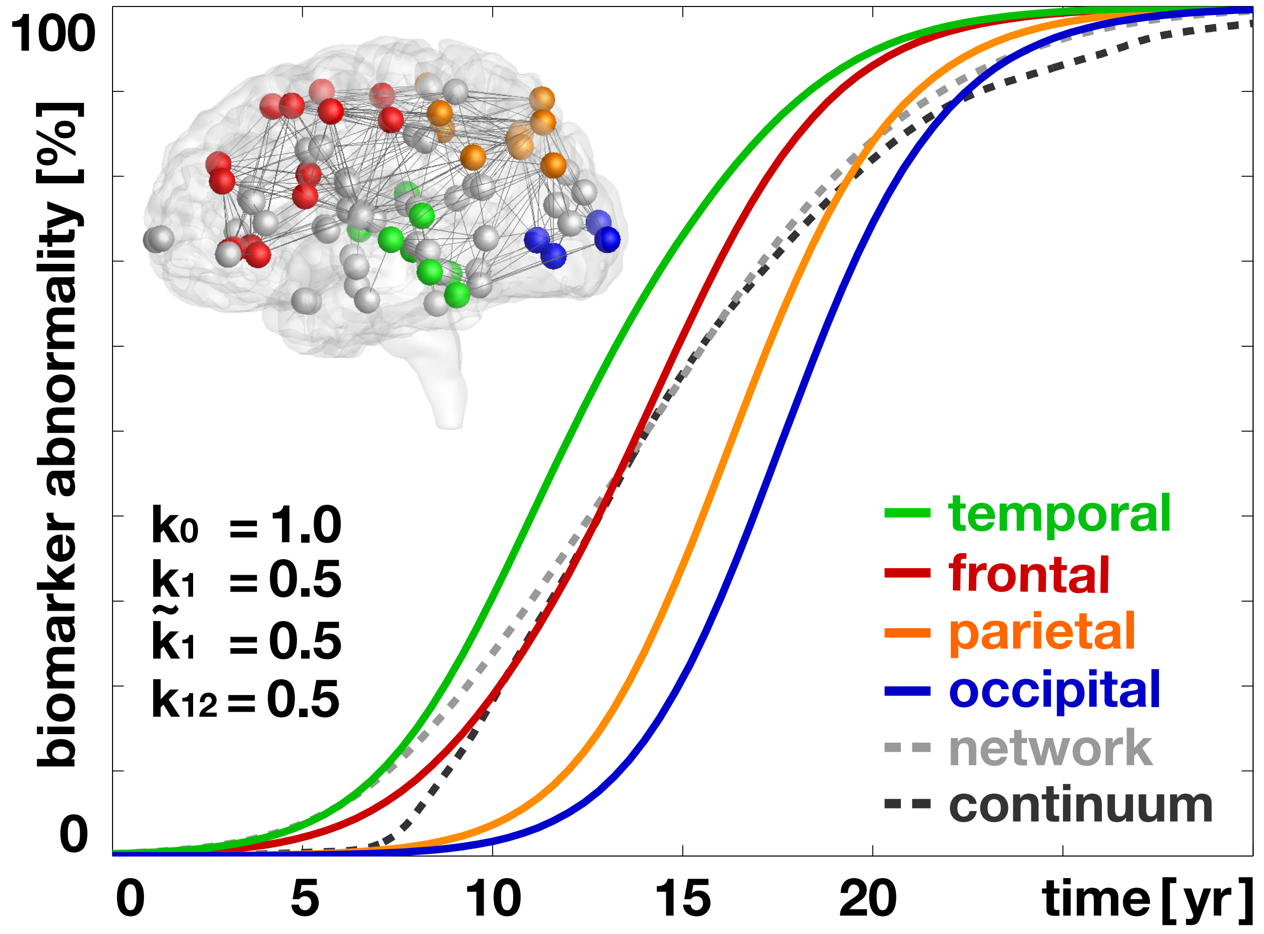




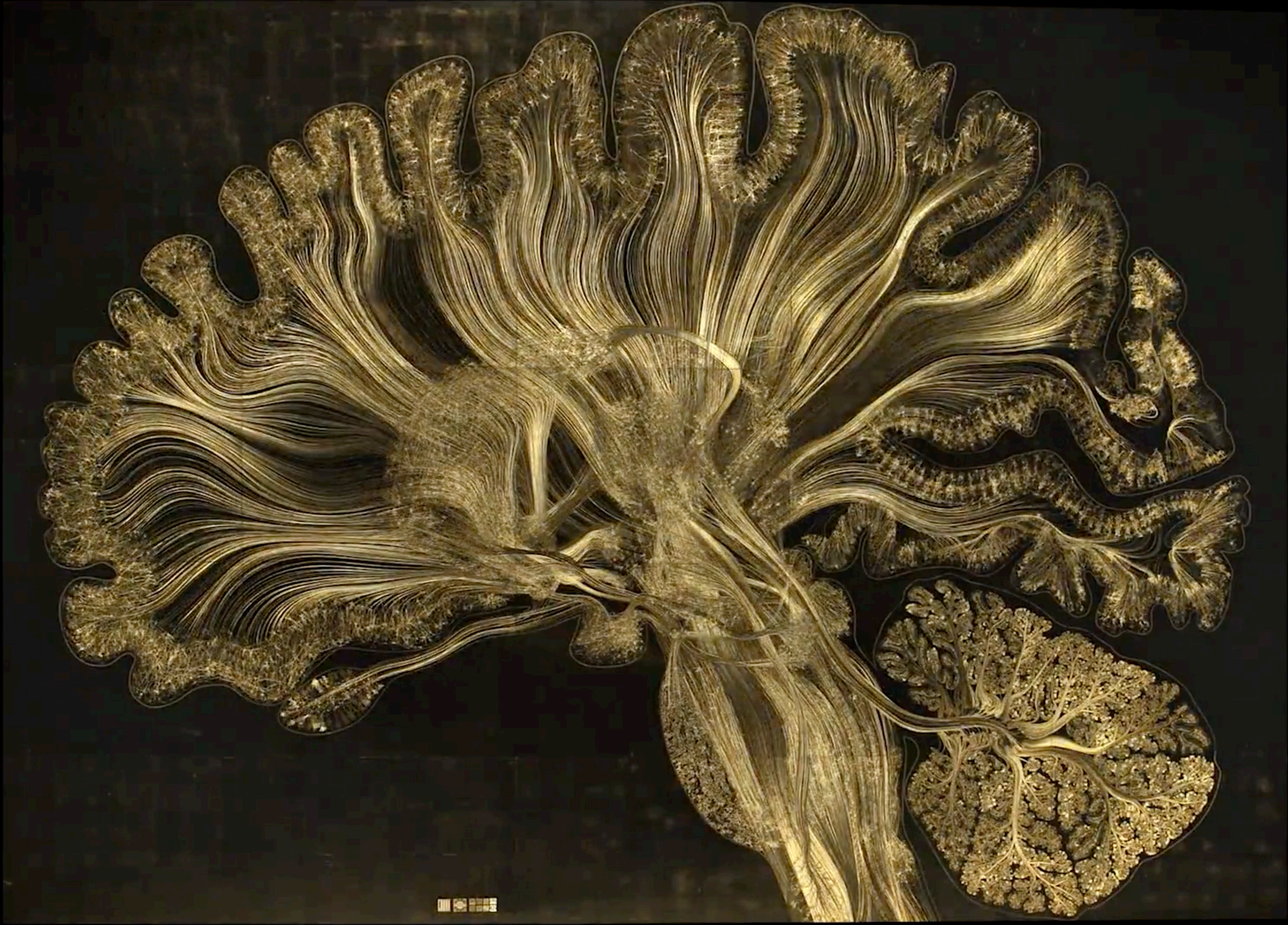
atrophy pattern

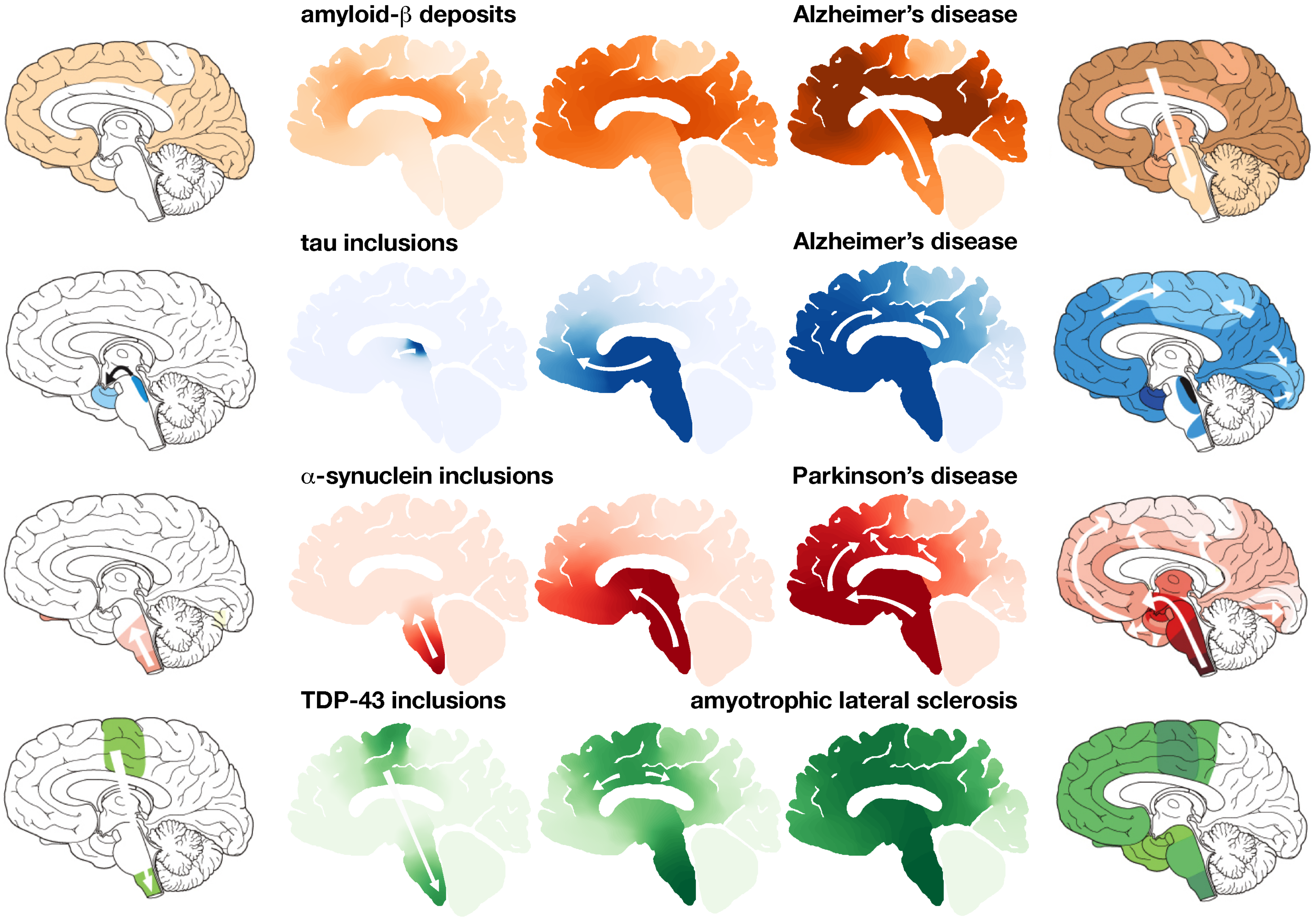
biomarker evolution



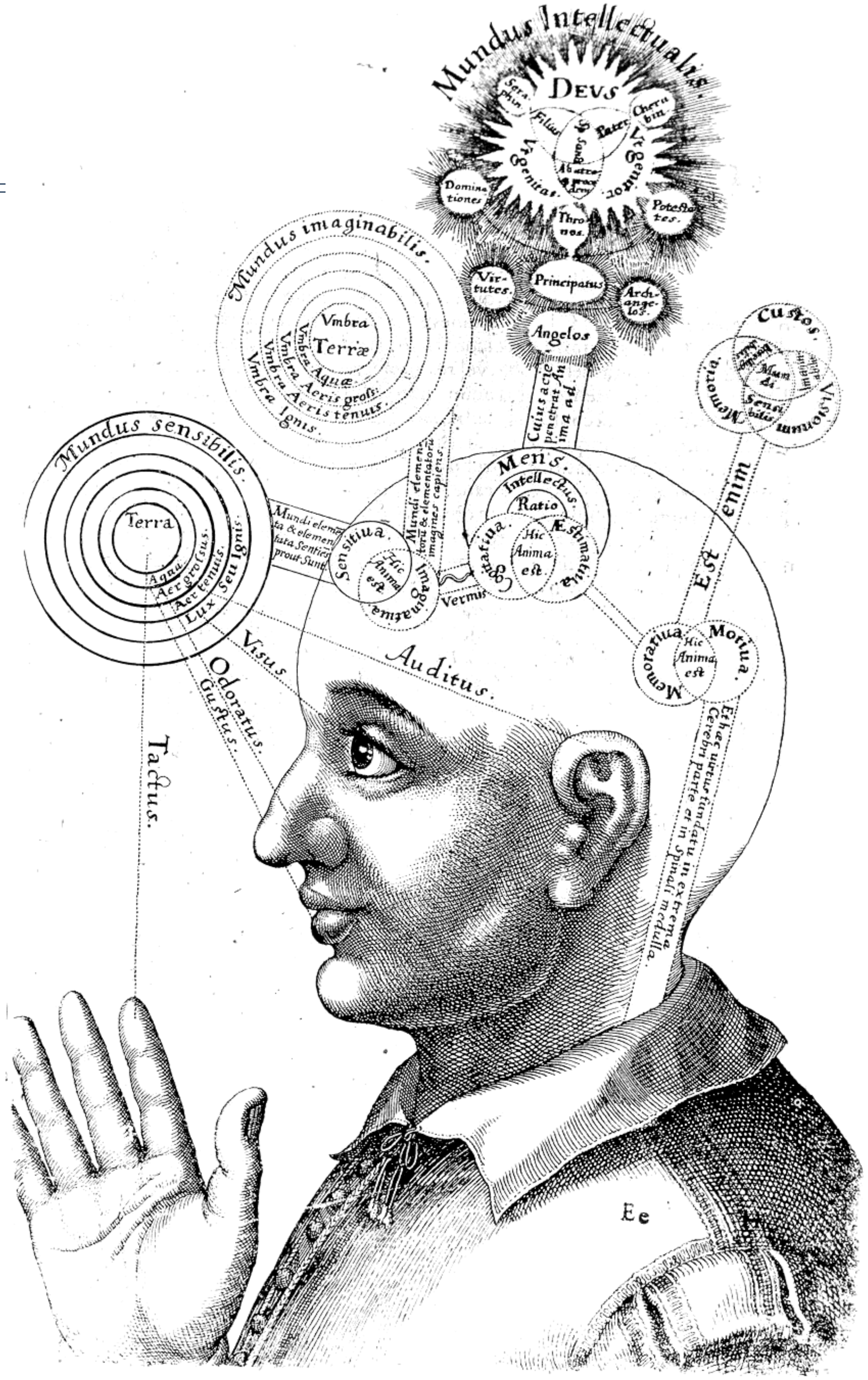


[art: g. dunn & b. edwards]




amyloid-β deposits
Alzheimer's disease
tau inclusions
Alzheimer's disease
α-synuclein inclusions
Parkinson's disease
TDP-43 inclusions
amyotrophic lateral sclerosis

What did we learn?



[Robert Fludd]