



Precision medicine for dementia: thinking large and thinking small

Professor James B Rowe FMedSci

In honour of Professor AJS McFadzean



- Gave patients hopes of recovery
- Inspired generations of physicians
- Understood the scientific basis of health and disease as the foundation of medical education and research

A high-angle, wide shot of a bustling street market. The street is filled with a dense crowd of people of various ages and ethnicities. On the left, there are several market stalls with colorful awnings in shades of yellow, green, and blue. Some stalls have signs, including one for 'Alpha' with a logo and contact information. On the right, there are shops and buildings with various signs, including 'A1 Retail', 'TO LET', 'Perfect PIZZA Company', and 'JUST EAT'. Traffic lights are visible on both sides of the street, showing green lights. The overall atmosphere is busy and vibrant.

Dementia 1 in 3

Number 1 cause of death

Dementia



50,000,000 x3

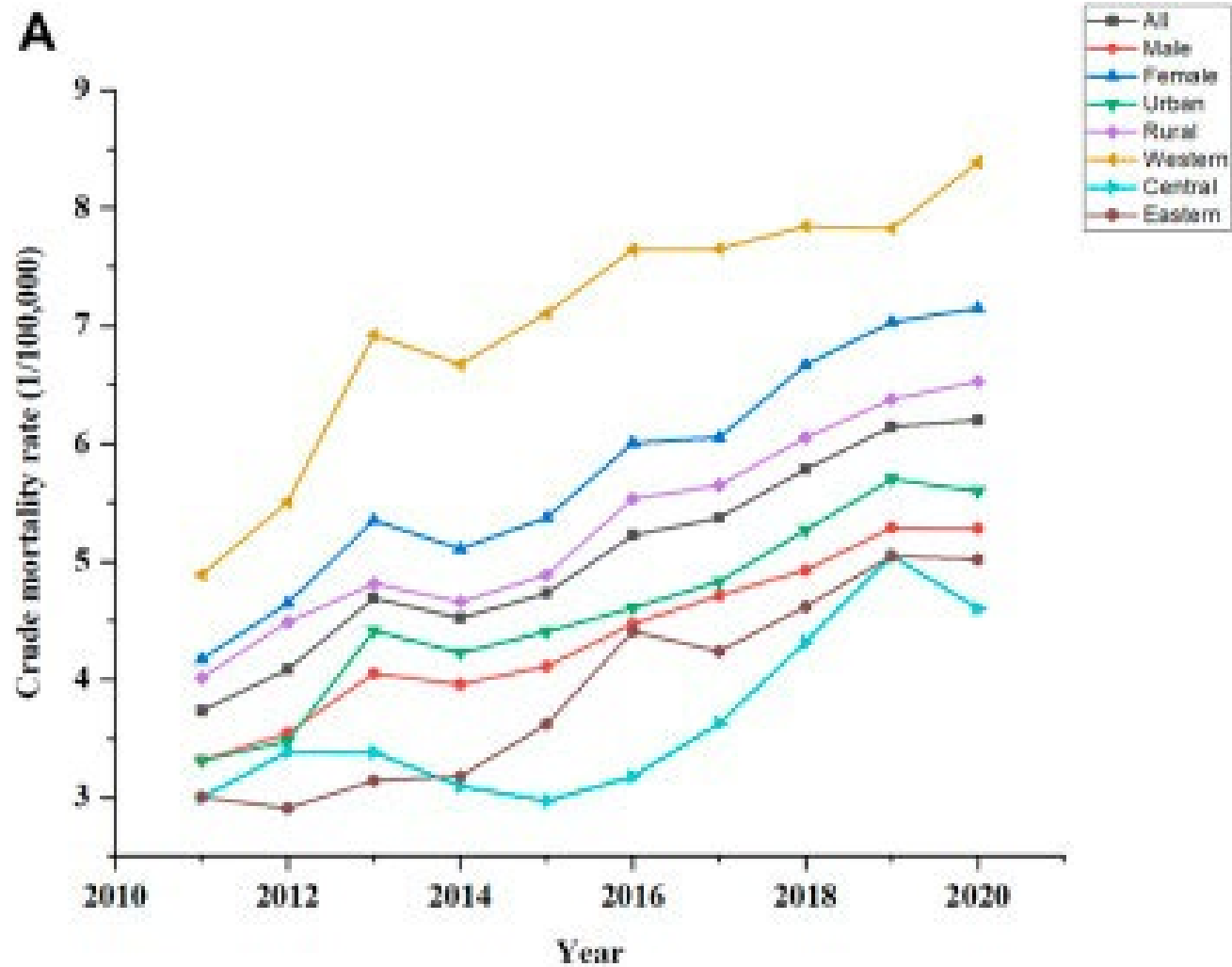


\$1000,000,000,000



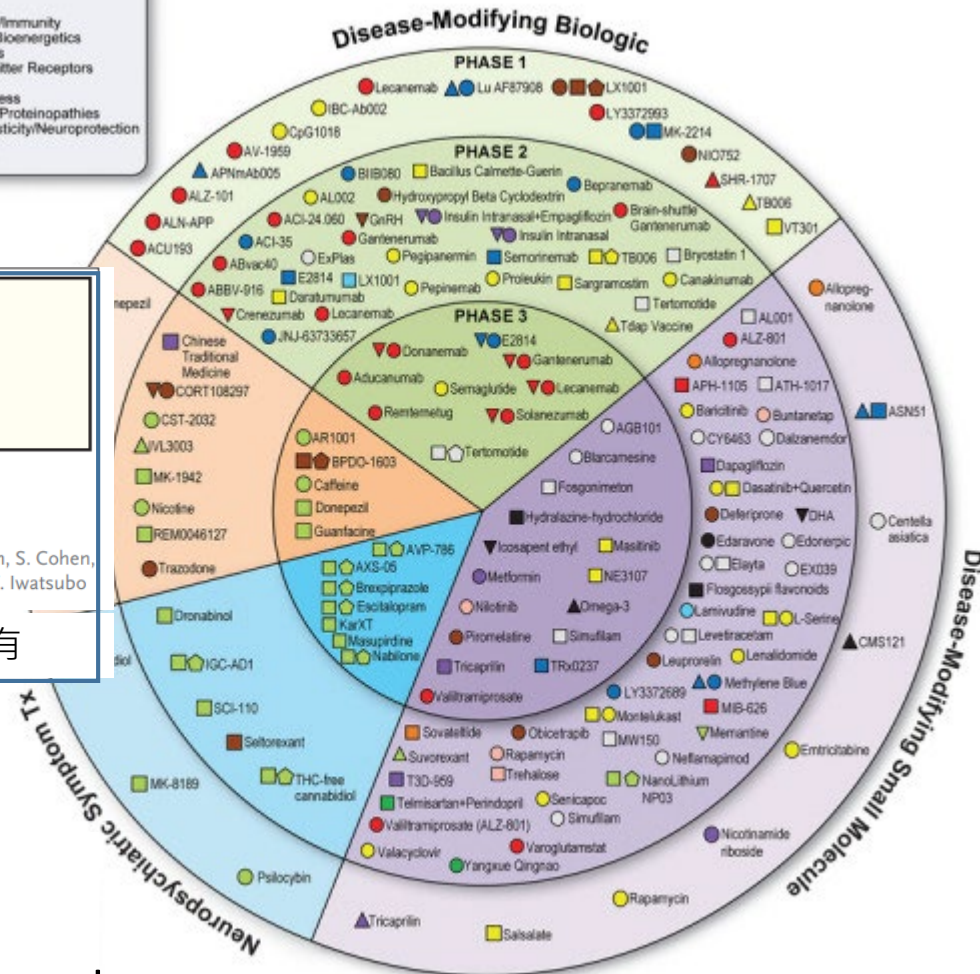
\$1,000,000,000

Mortality from Dementia in China



Hope

2023 Alzheimer's Drug Development Pipeline (Cummings 2023)



The NEW ENGLAND JOURNAL of MEDICINE

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Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

仑卡奈单抗治疗早期阿尔茨海默病著作权归作者所有

But none likely to work uniformly
→ Precision medicine, to get the right treatment to the right patient at the right time (and the right tools to show it works)

Precision medicine

Phenotype

How do we get beyond diagnosis, to quantify the unique version of illness expressed by each individual patient?

Mechanism

Can we get cellular and neurochemical precision in living patients, that we take for granted in preclinical (animal) models?

The Bruce Willis Effect

March 2022

March 2023

NEWS Menu
World | Africa | Asia | Australia | Europe | Latin .

NEWS Menu
Entertainment & Arts

Bruce Willis gives up acting due to brain disorder aphasia

© 30 March 2022



Bruce Willis has dementia, his family announces

🕒 4 days ago



So what does he have?
aphasia?
dementia?
two disorders?
One dynamic disease?

Molecular precision is not enough

C9orf72
mutation

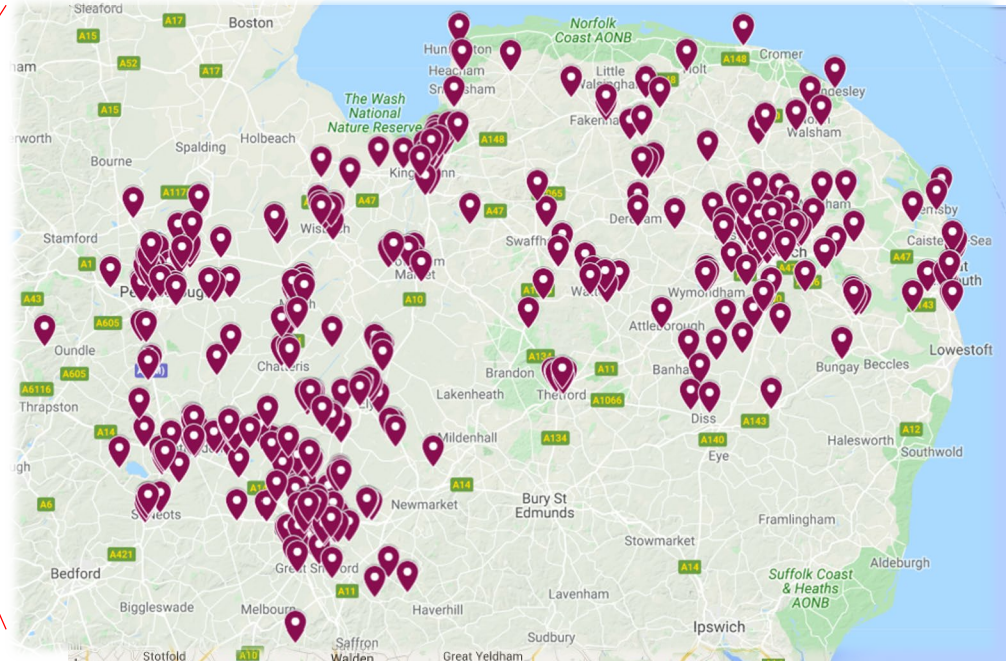
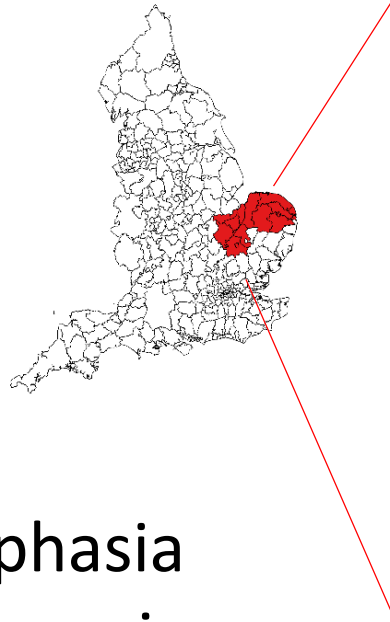


Frontotemporal Dementia
Aphasia
Parkinsonism
Motor neuron disease
Psychosis
Ataxia
In any combination !

The logo for WAVE Life Sciences features a stylized blue wave graphic above the word 'WAVE' in a bold, black, sans-serif font. Below 'WAVE', the words 'LIFE SCIENCES' are written in a smaller, black, sans-serif font. Below the logo, the text 'FOCUS-C9 ASO Therapy' is written in a black, sans-serif font.

FOCUS-C9 ASO Therapy

PiPPIN: Pick's disease and Progressive Supranuclear Palsy prevalence and incidence study (2013-2022)



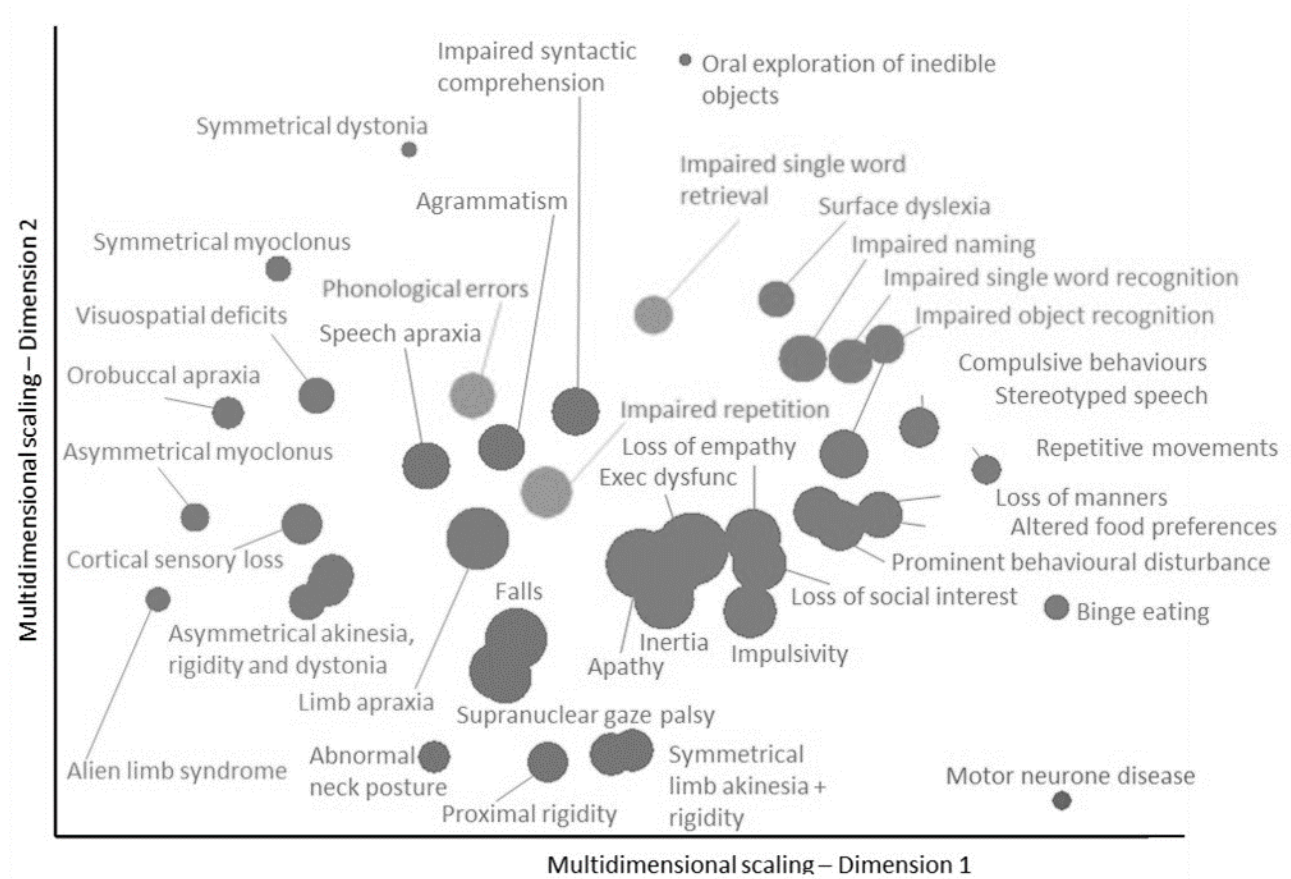
Progressive Aphasia
Atypical Parkinsonism
Frontotemporal Dementia

*60 clinical, cognitive,
behavioural, measurements.*

Coyle-Gilchrist et al Neurology 2016
Lansdall et al Brain, 2018
Murley et al, Brain 2020

PiPPIN: Pick's disease and Progressive Supranuclear Palsy prevalence and incidence study (2013-2022)

Multidimensional scaling of signs and symptoms

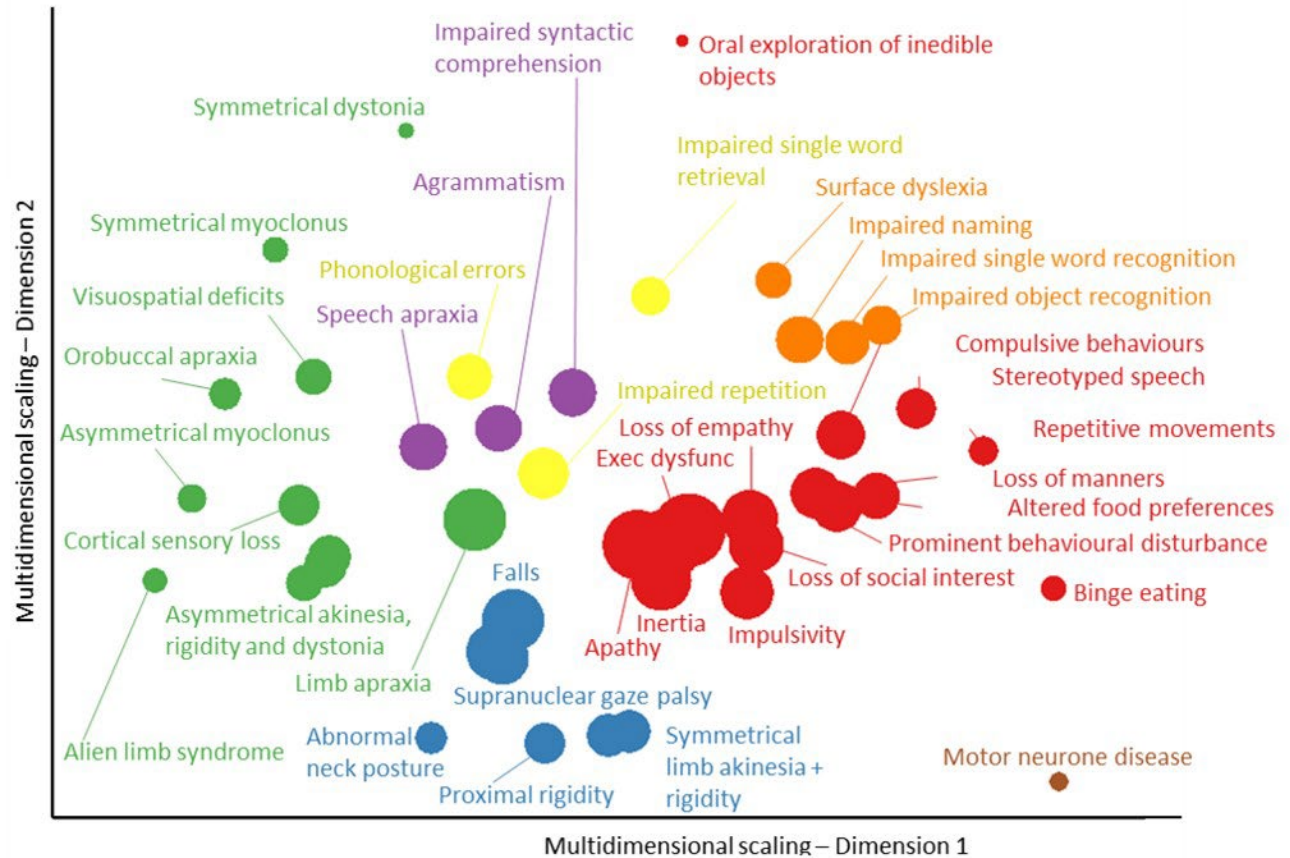


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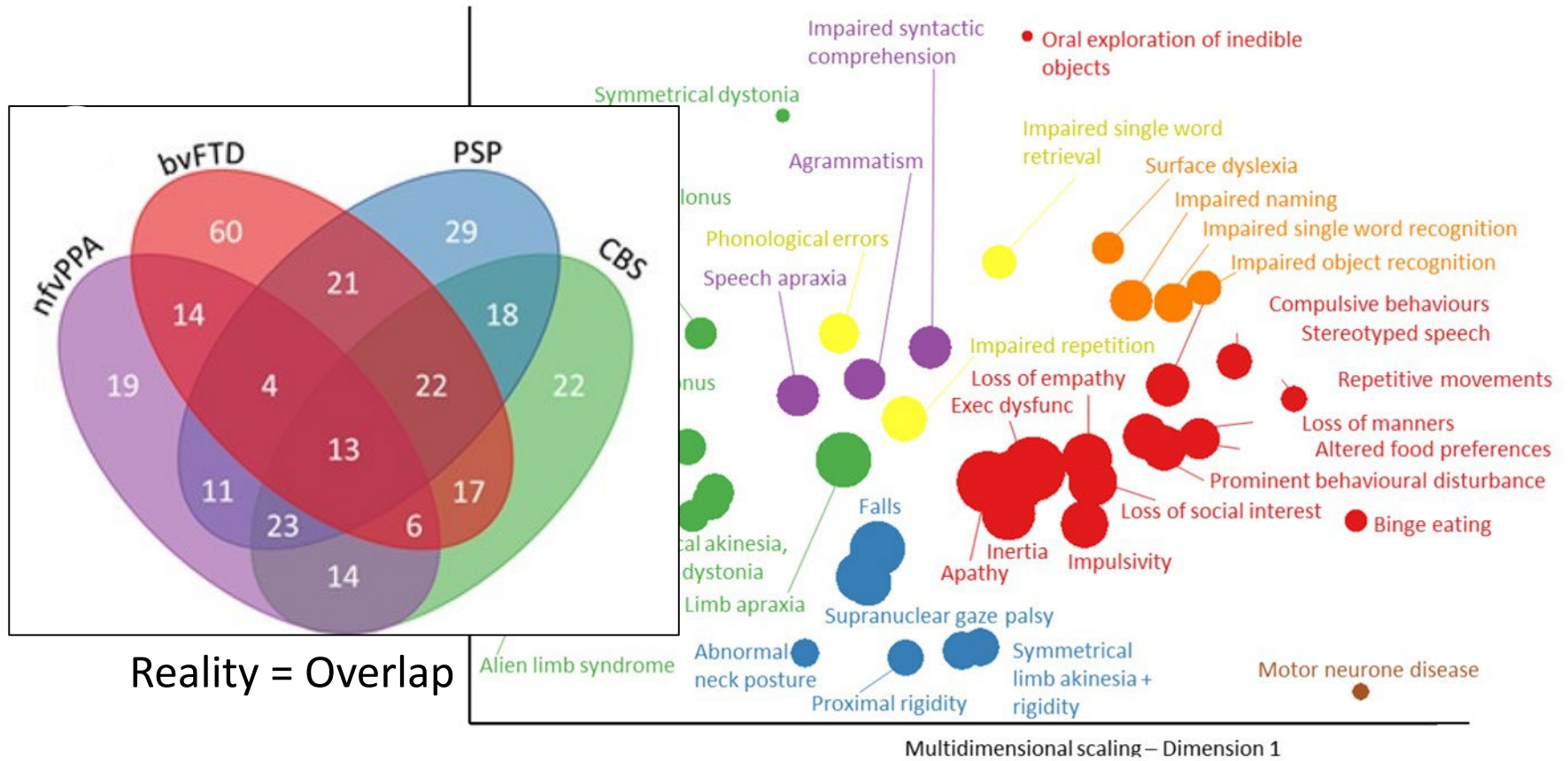


Classic diagnostic "Groups"



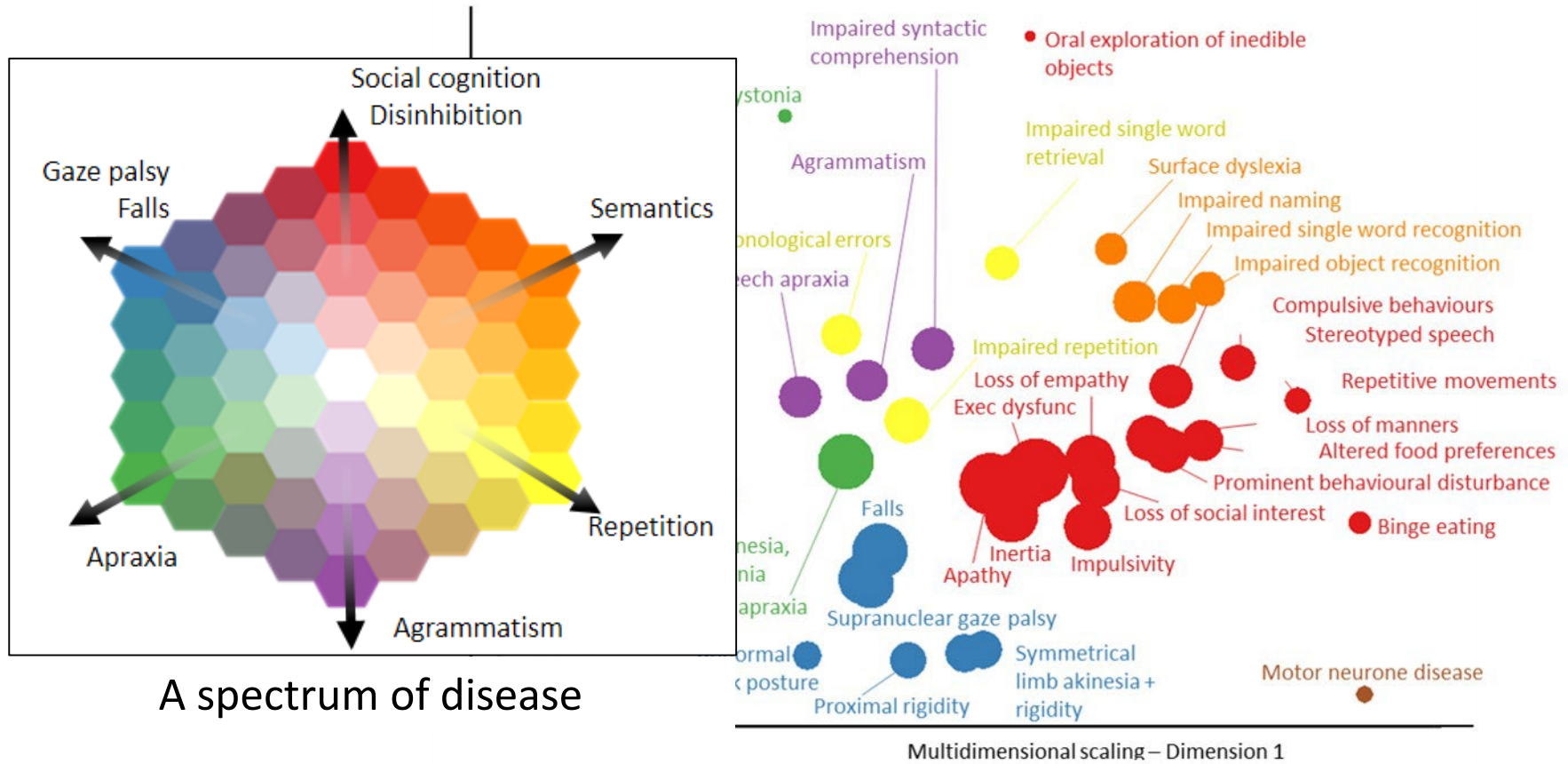
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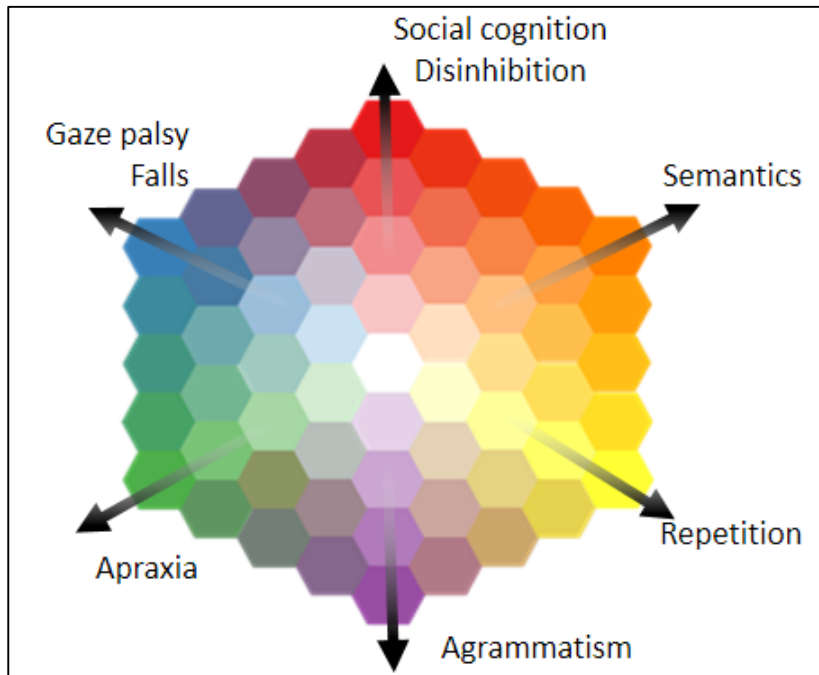


PiPPIN: Pick's disease and Progressive Supranuclear Palsy prevalence and incidence study (2013-2022)

Multidimensional scaling of signs and symptoms



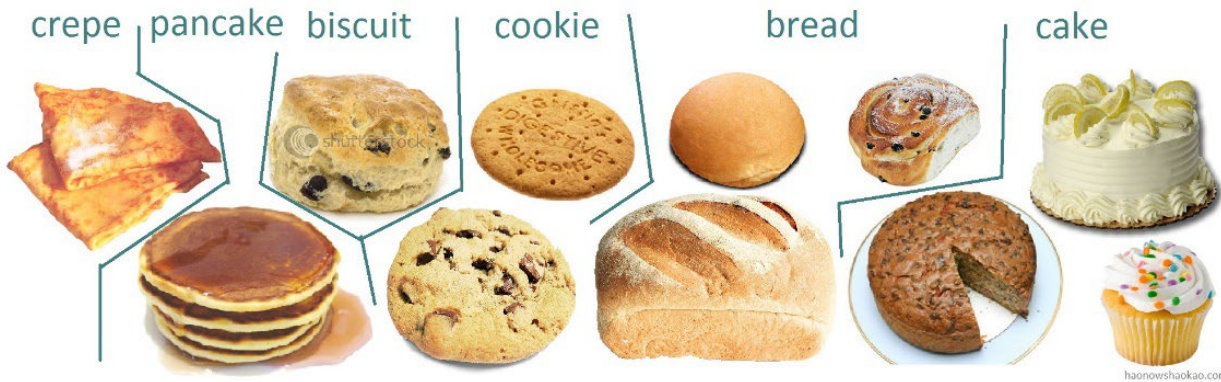
PiPPIN: Pick's disease and Progressive Supranuclear Palsy prevalence and incidence study (2013-2022)



Patients can be placed precisely in this multidimensional space.

Each dimension (not diagnosis) becomes the target of therapy.

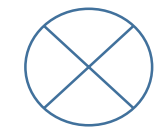
Understanding disease dimensions



Eggs ...



Butter



Sugar

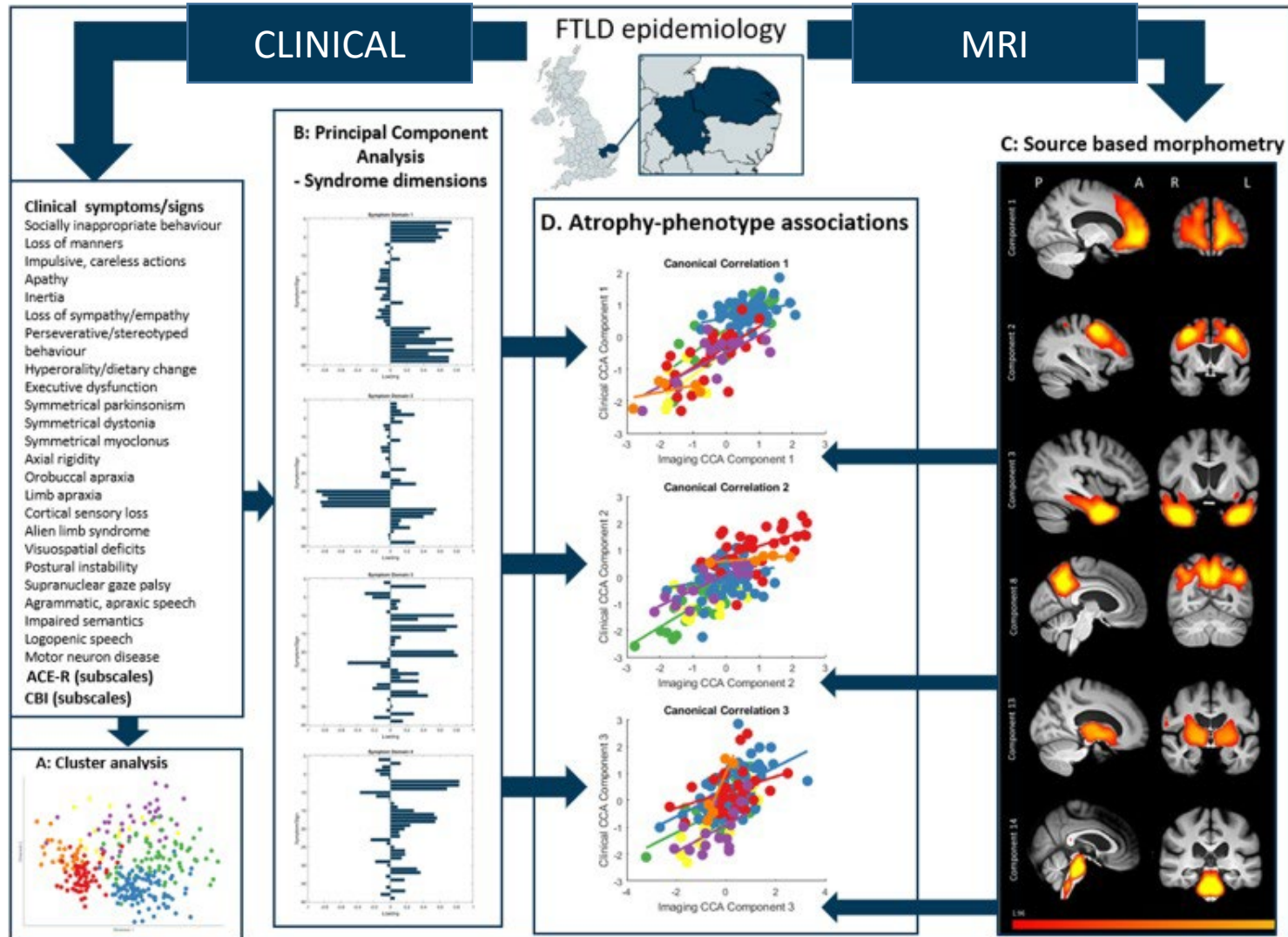


Flour





Understanding disease dimensions

500 people, 60 measures, 6 diseases → 3 simple relationships



Mapping the multidimensional geometric landscape of graded phenotypic variation and progression in neurodegenerative syndromes

 Siddharth Ramanan, Danyal Akarca, Shalom K. Henderson, Matthew A. Rouse, Kieren Allinson, Karalyn Patterson,  James B. Rowe, Matthew A. Lambon Ralph

doi: <https://doi.org/10.1101/2023.10.11.23296861>

National Alzheimer's Coordinating Center

39 measures of

Cognition & behaviour

Functional activities

Neuropsychiatric

Motor functions

Depression

Language

Longitudinal

Alzheimer's disease



behavioural variant

frontotemporal dementia

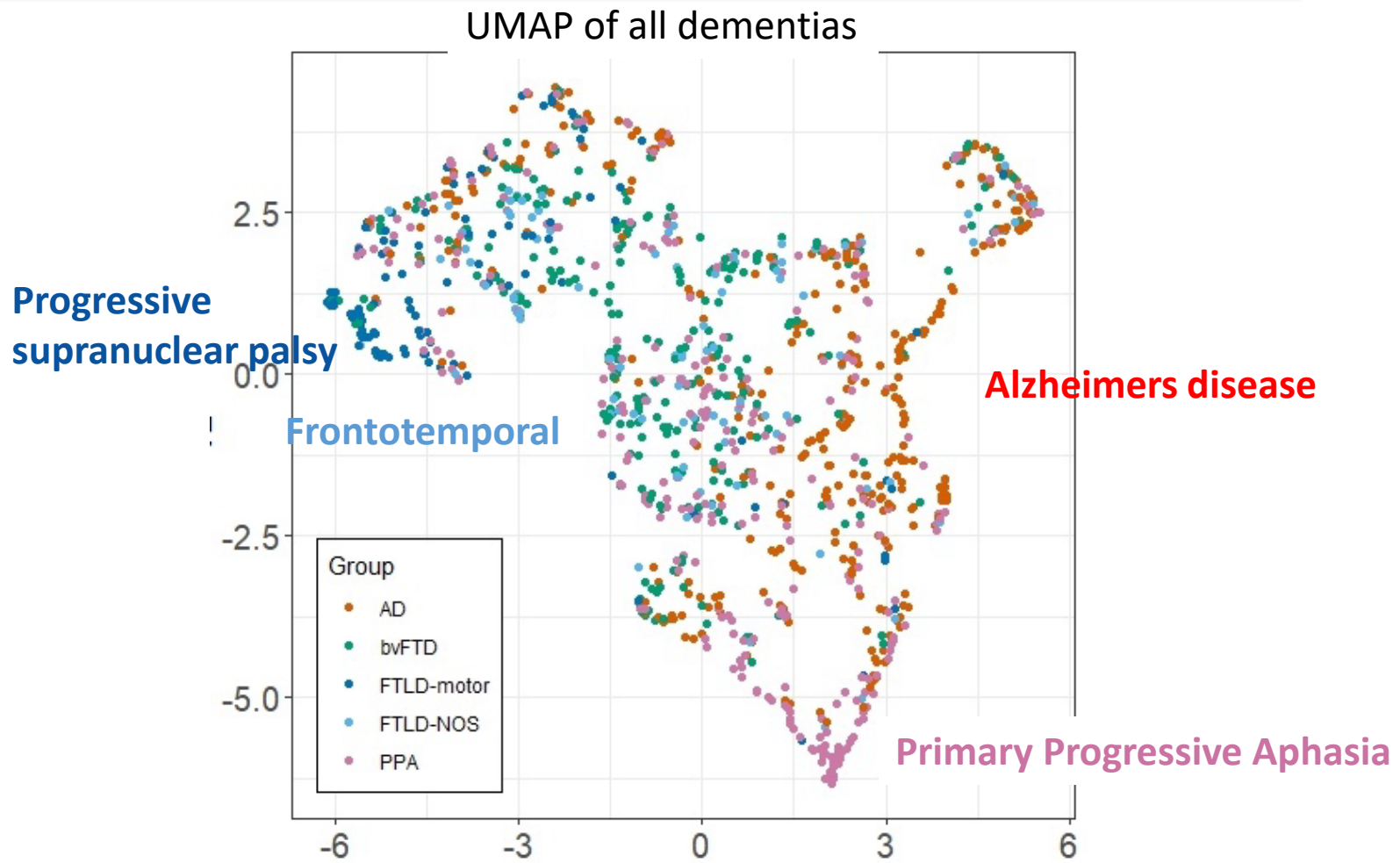
Corticobasal Syndrome &
Progressive Supranuclear Palsy

Primary Progressive Aphasia



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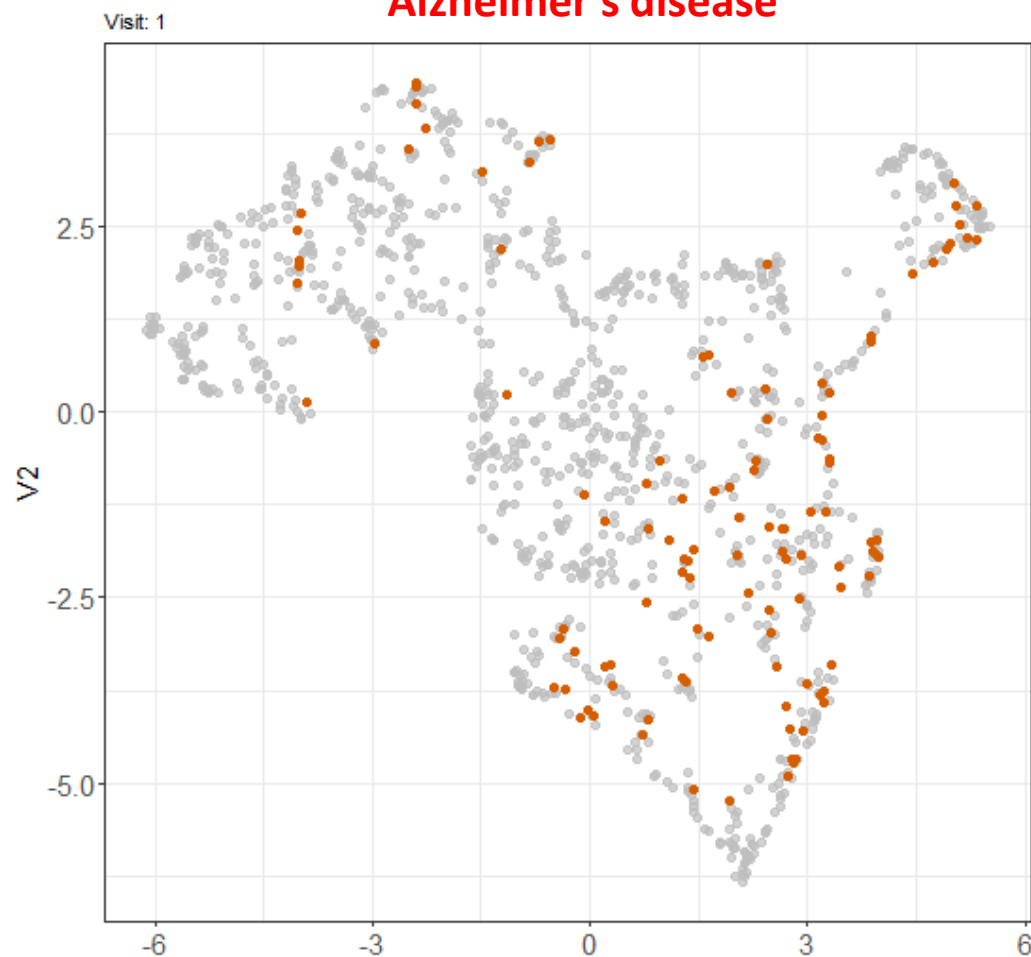


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Alzheimer's disease

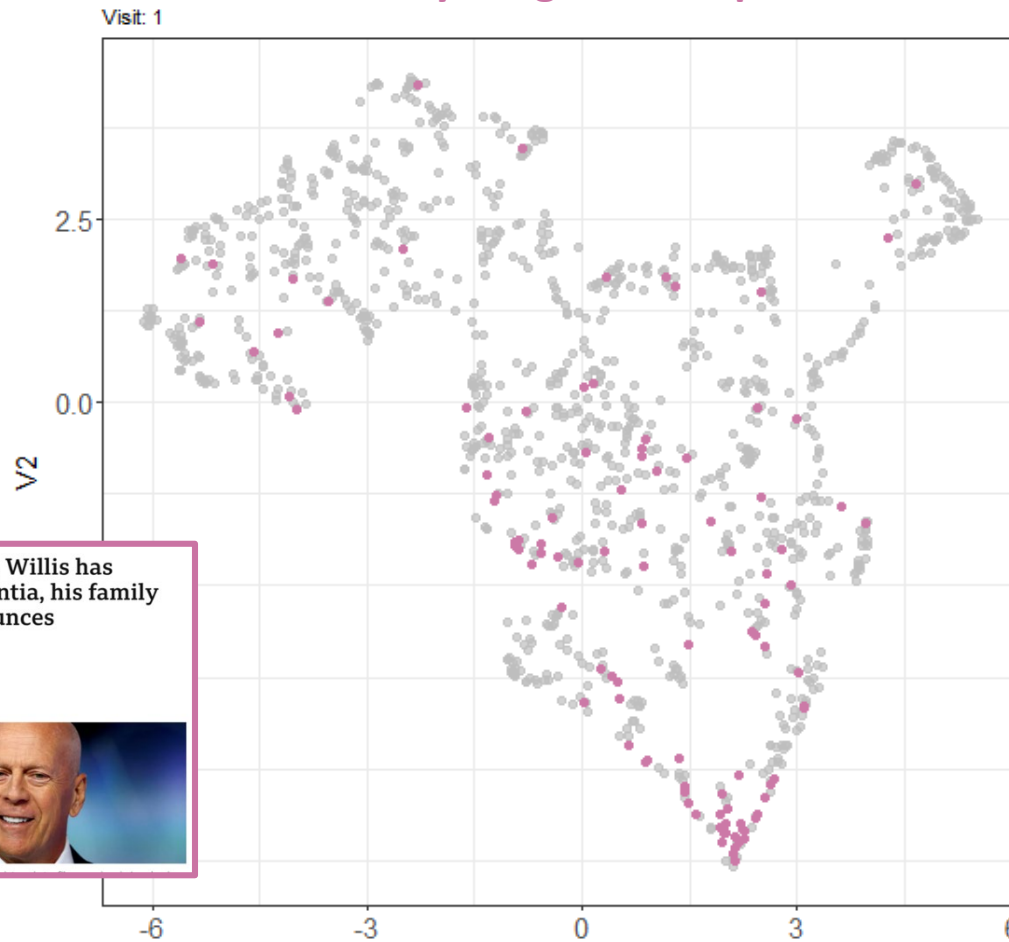


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Primary Progressive Aphasia



Bruce Willis gives up acting due to brain disorder aphasia

© 30 March 2022



GETTY IMAGES

Bruce Willis has dementia, his family announces

© 4 days ago



REUTERS

Precision medicine

How do we get beyond diagnosis, to quantify the unique version of illness expressed by each individual patient?

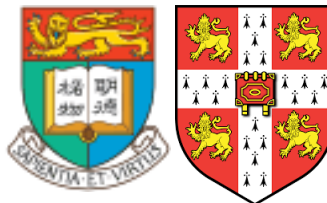


BOLD Experiments: N=500,000



**Dementias
Platform** ^{UK}

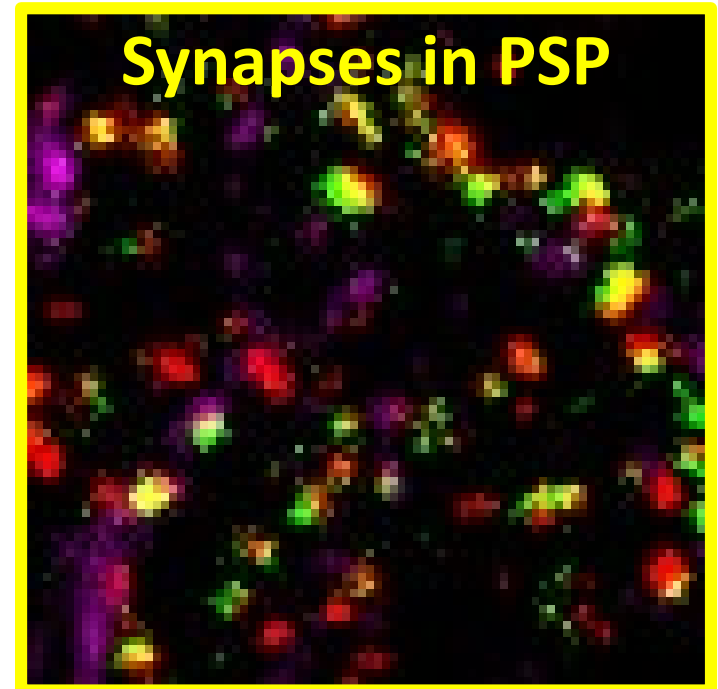
Secure Data Sharing: N=3.5 million



Cross-disciplinary AI expertise

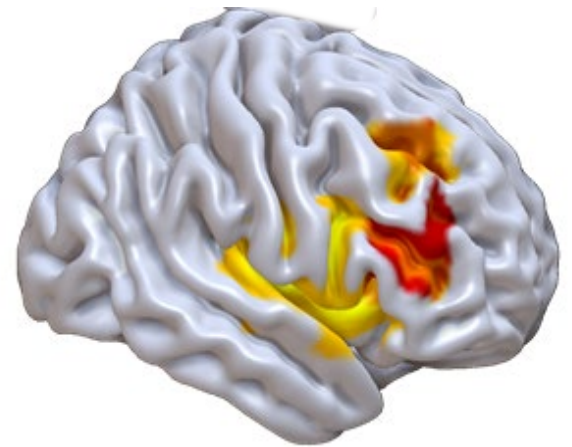
Precision medicine - of disease mechanism

Can we get cellular and neurochemical precision in living patients, that we take for granted in preclinical or post mortem studies?



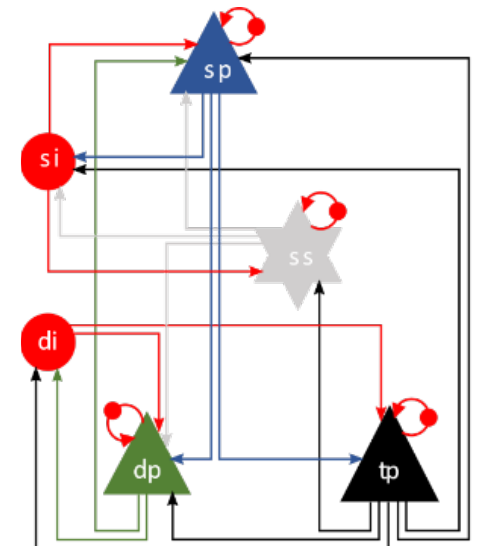
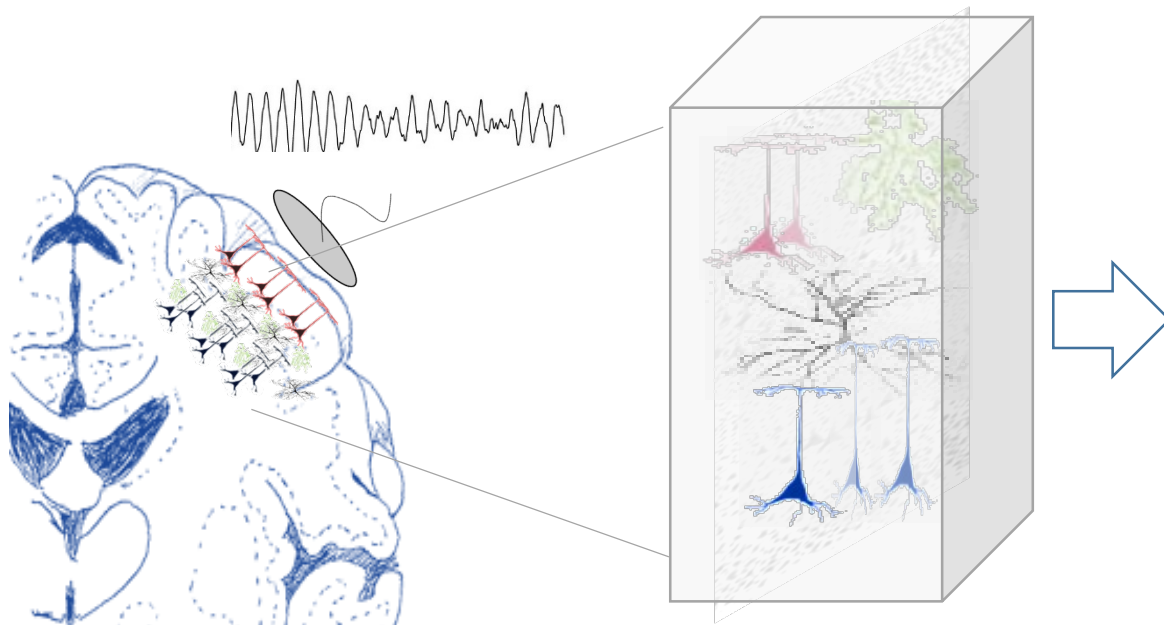
63x DAPI MAP2 HOMER BASSOON
Grey Matter of PSP patient

Magnetoencephalography (MEG) to study patho*physiology* of dementia



MEG: Safe and well tolerated in dementia
Excellent to distinguish dementias and enhance drug trials

Biophysical models of human cognitive physiology



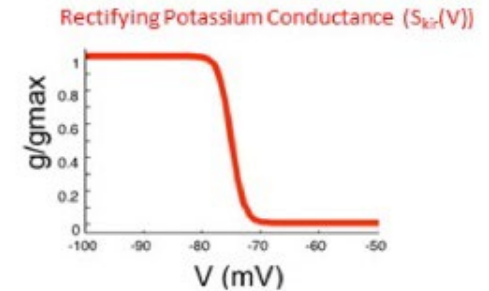
$$C \frac{dV}{dt} = \alpha_{Na} g_{AMPA} \cdot (V_{Na} - V) + \alpha_{Cl} g_{GABA} \cdot (V_{Cl} - V)$$

$$+ \alpha_{Ca/Na} S_{Mg}(V) \cdot g_{NMDA} (V_{Na/Ca} - V) + \alpha_{KL} \cdot (V_K - V)$$

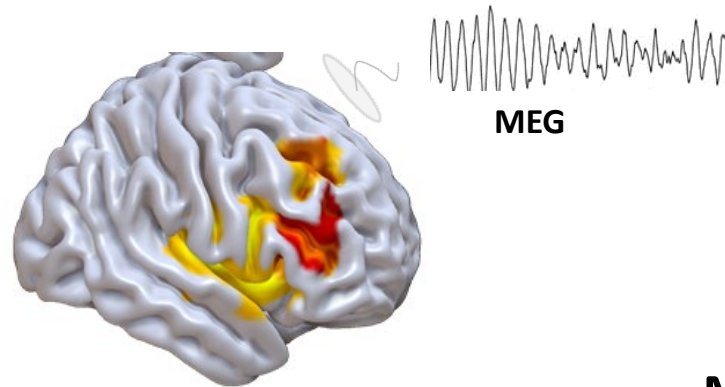
$$+ \alpha_{Kir} S_{Kir}(V) \cdot g_{Kir} (V_K - V)$$

$$\frac{dg}{dt} = \frac{1}{\tau} \cdot [H(V_{pre} - V_{thresh}, \omega) - g]$$

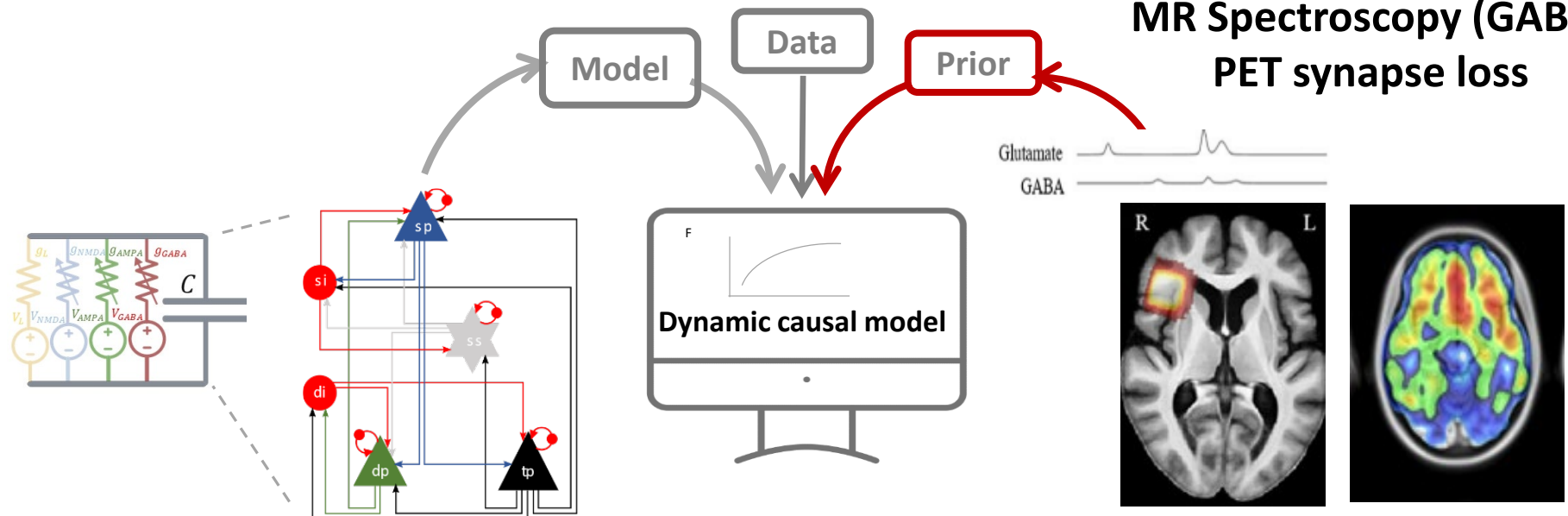
Per population



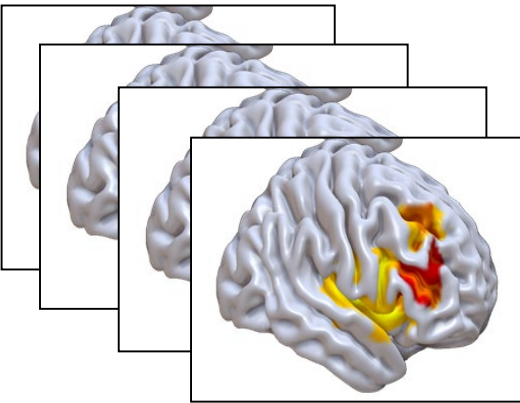
Biophysical models reveal *hidden causes* of pathophysiology



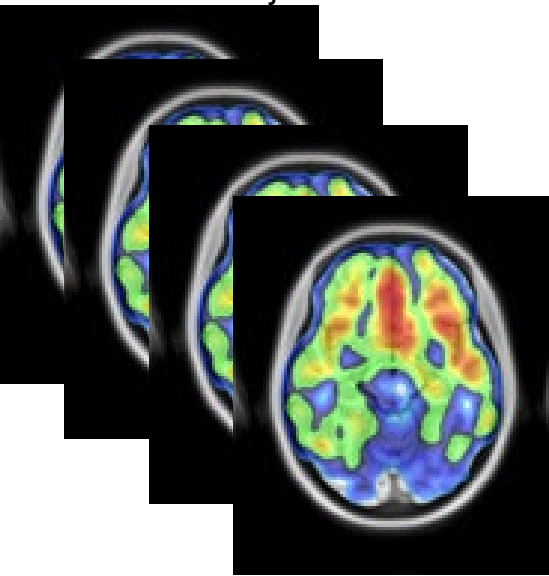
Multimodal markers
MR Spectroscopy (GABA)
PET synapse loss



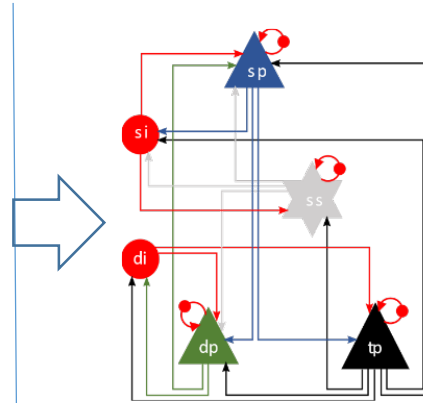
Biophysical models reveal *hidden causes* of pathophysiology



Multi-subject MEG

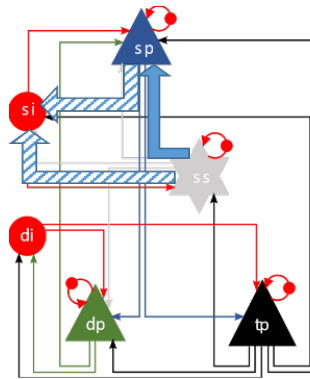


UCBJ Synaptic PET scan



“**where in the cortical microcircuit** (which neuron class, which neurotransmitter) does prior knowledge of an **individual’s synapse loss (PET)** improve the model evidence (improve generative model to reproduce the observed MEG data)”

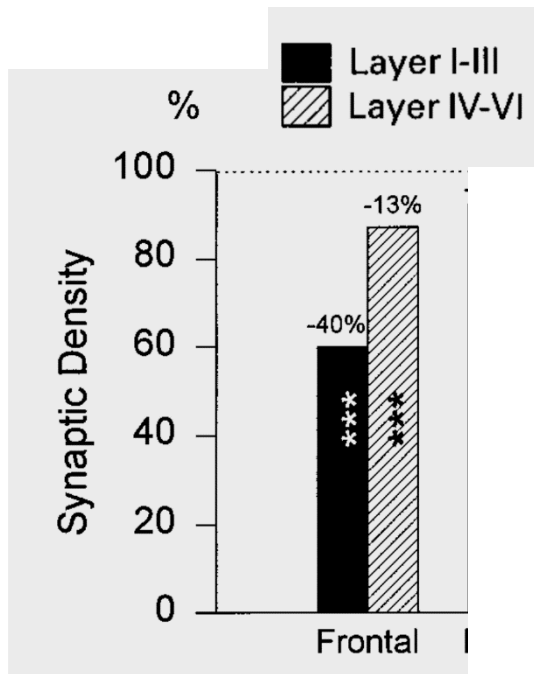
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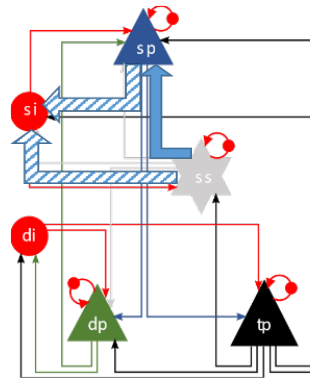
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RESULT: loss of synapses (UCBJ PET) affects the MEG generators (DCM) at the level of superficial pyramidal cells

Biophysical models reveal *hidden causes* of pathophysiology



Synaptophysin reduced
in superficial layers
frontal cortex in FTD
At post mortem



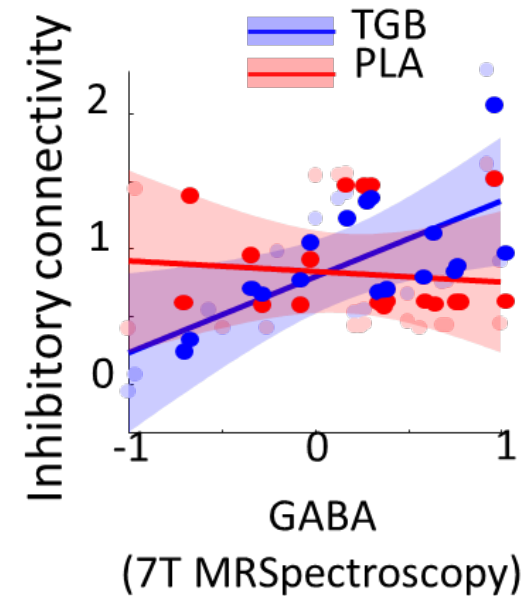
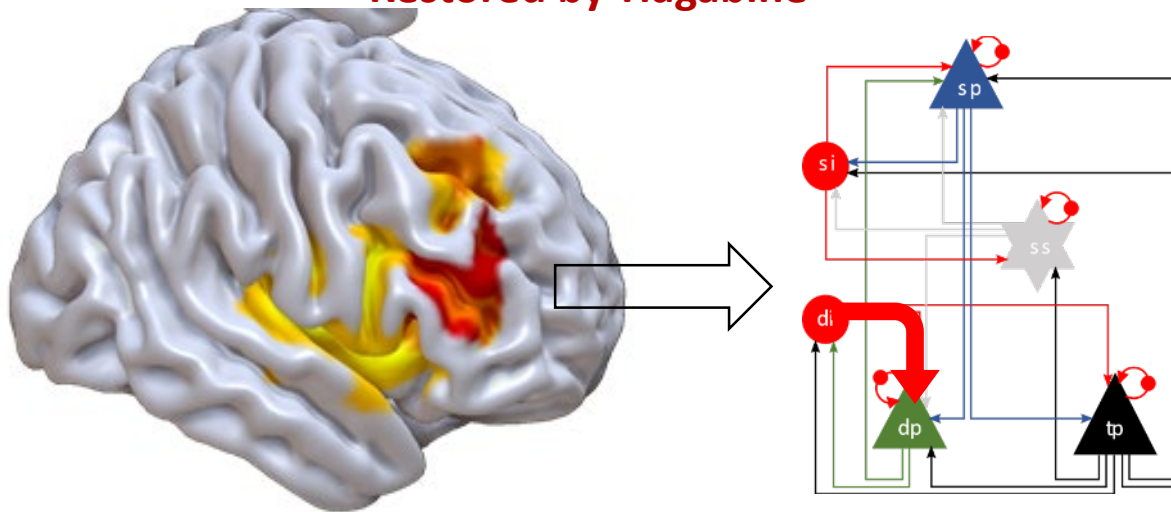
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RESULT: loss of synapses (UCBJ PET) affects the MEG generators (DCM) at the level of superficial pyramidal cells

How does a drug work, and for whom? (individual Tiagabine response predicted by 7T MRS)

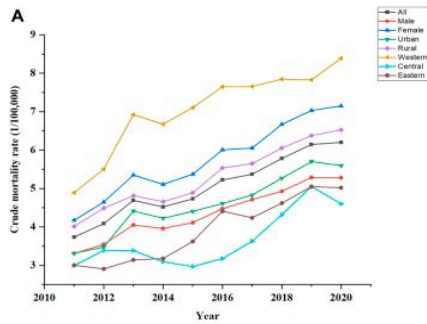
Reduced by frontotemporal dementia

Restored by Tiagabine



*The effect of a GABA-ergic reuptake inhibitor (Tiagabine)
To restore frontal lobe cognitive physiology
Depends on deep GABA-ergic interneurons
As a function of individual GABA levels
→ Precision of pharmacology and phenotype*

Conclusions



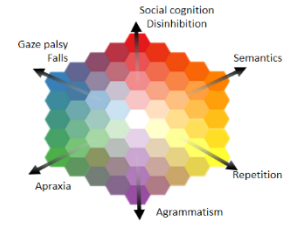
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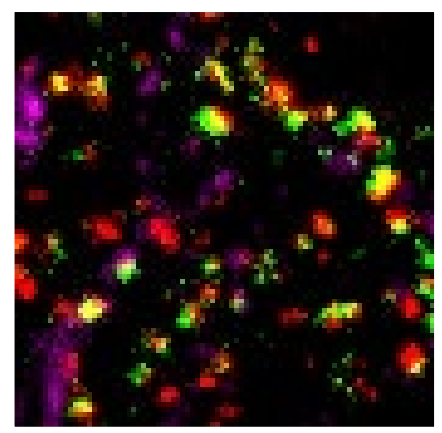
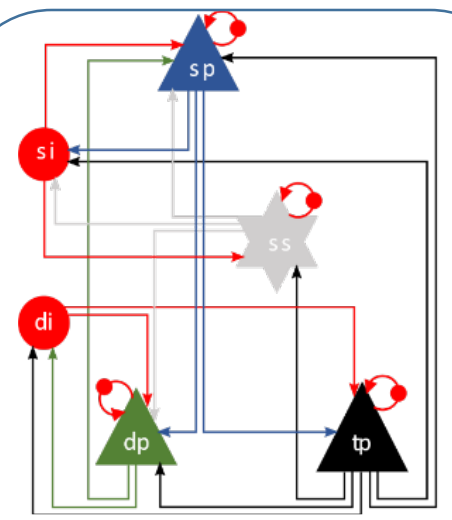
Challenge and Hope



Dimensions of disease



Data, Sharing, Analysis



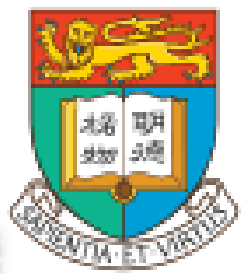
Biophysical models

Professor McFadzean



- ✓ Gave patients hopes of recovery
 - New hope for people with dementia
- ✓ Inspired generations of physicians
 - Optimism and rapid progress
- ✓ Understood the scientific basis of health and disease as the foundation of medical education and research

Thank you - and thanks to my great team at the Cambridge Centre for Frontotemporal Dementia and Dementias Platform UK



Tallie Adams
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Michelle Naessens
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Alex Shaw (CUBRIC)
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Michael Perkington (AZ)
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And many others

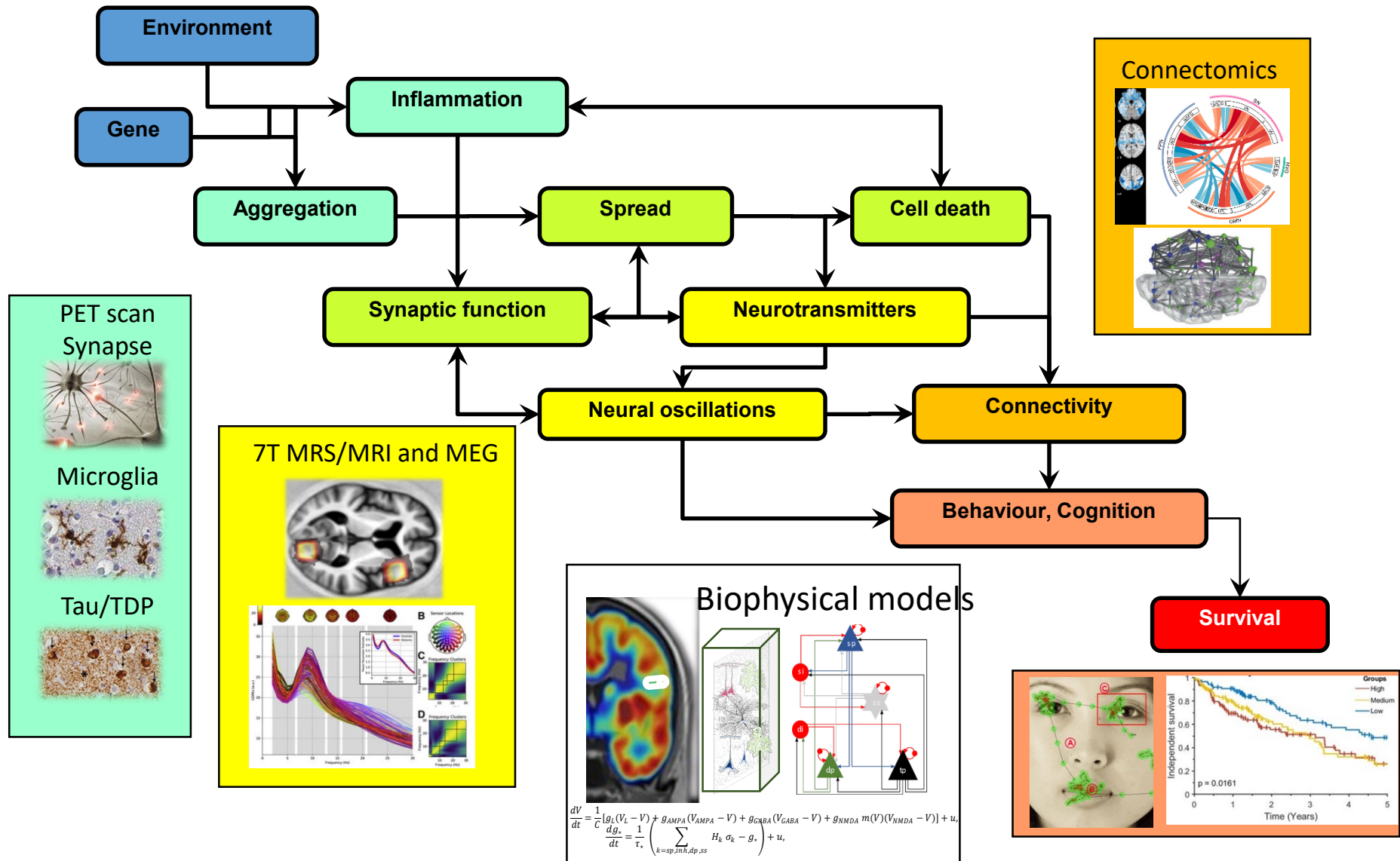
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Neurobiology of disease dimensions



The pathogenic cascade of Dementia offers multiple targets for therapy

