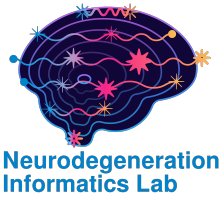


Multimodal imaging for clinical research

Timothy Rittman

University of Cambridge

Cambridge University Hospitals NHS Trust

September 2024

Outline

Clinical biomarkers

Combining imaging biomarkers

Combining imaging and neuropathology

Modelling disease

Clinical biomarkers

A clinical case

76 year old lady

- 2 years of change in behaviour
- diagnosis of Alzheimer's disease and fronotemporal dementia
- poor balance, abnormal eye movements
- swallowing problems

Dementia diagnosis rate

The dementia diagnosis rate in **England** was **65.2%** in July 2024.

65.2% of people aged 65 or over who are estimated to have dementia, had a recorded diagnosis of dementia on 31st July. This is an increase from 65% on 30th June.

ALZHEIMER'S RESEARCH UK FOR A CURE

A clinical case

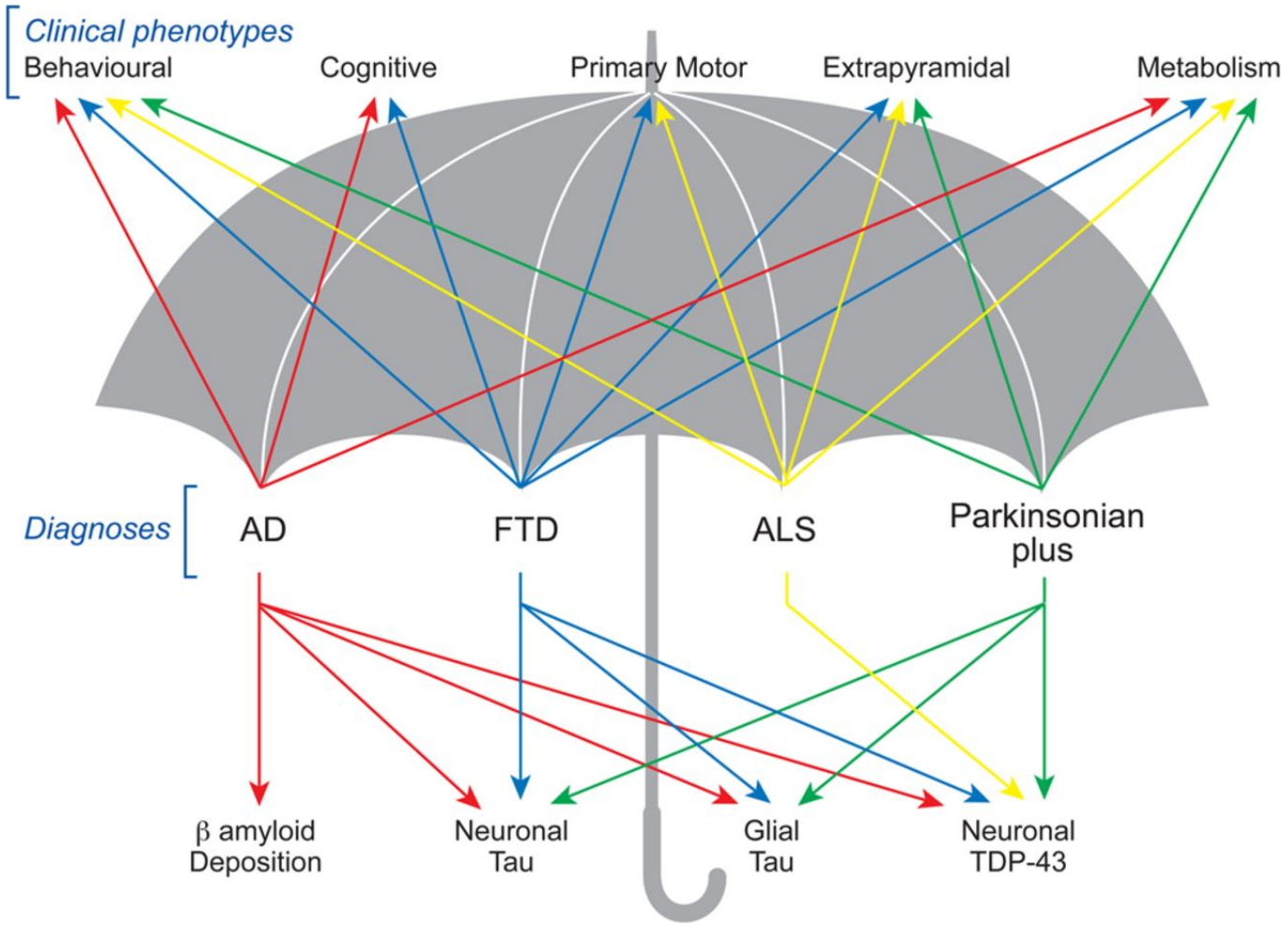
76 year old lady

- 2 years of change in behaviour
- diagnosis of Alzheimer's disease and fronotemporal dementia
- poor balance, abnormal eye movements
- swallowing problems

Diagnosis

- Clinical diagnosis
- Research criteria diagnosis
- Pathological diagnosis

Dementia - proteins to syndromes



Ahmed et al JNNP 2016 87:1234

A clinical case

76 year old lady

- 2 years of change in behaviour
- diagnosis of Alzheimer's disease and fronotemporal dementia
- poor balance, abnormal eye movements
- swallowing problems
- steps backwards on pull test
- flat emotional affect, impulsive

Diagnosis

- Clinical diagnosis
  - Frontotemporal Dementia/Progressive Supranuclear Palsy
- Research criteria diagnosis
  - Progressive Supranuclear Palsy - frontal variant (O1, O2, O3, P3, A2, C2)
- Pathological diagnosis
  - Unknown, but >90% Primary tauopathy of Progressive Supranuclear Palsy

A clinical case

76 year old lady

- 2 years of change in behaviour
- diagnosis of Alzheimer's disease and fronotemporal dementia
- poor balance, abnormal eye movements
- swallowing problems

Prognosis

- Rapid progression over the past 6 months
- "We need to plan financially"
- Time to:
  - additional care
  - hospital admission
  - death
  - carer burnout

A clinical case

76 year old lady

- 2 years of change in behaviour
- diagnosis of Alzheimer's disease and fronotemporal dementia
- poor balance, abnormal eye movements
- swallowing problems

Response to medications

- Beneficial effect?
- Side-effects?

A clinical case

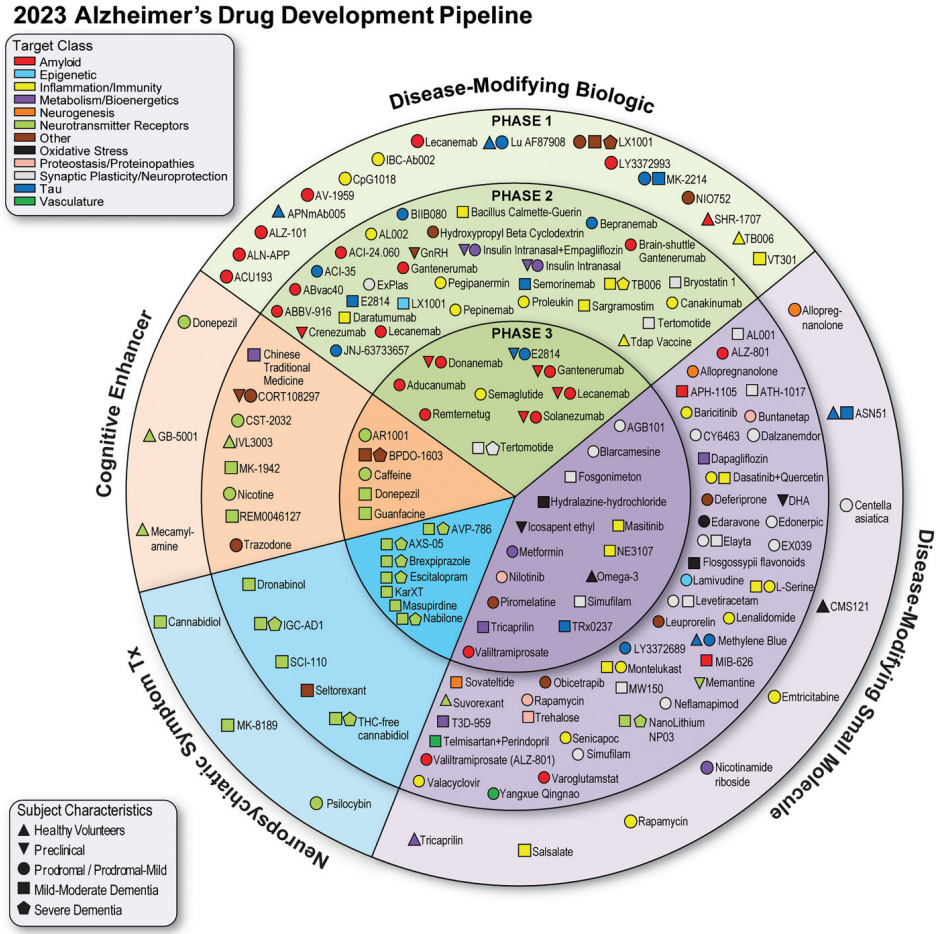
76 year old lady

- 2 years of change in behaviour
- diagnosis of Alzheimer's disease and fronotemporal dementia
- poor balance, abnormal eye movements
- swallowing problems

Understanding disease mechanisms

- Tau accumulation
- Inflammation
- Synapse loss
- Cell loss

Treatment development



A clinical case

76 year old lady

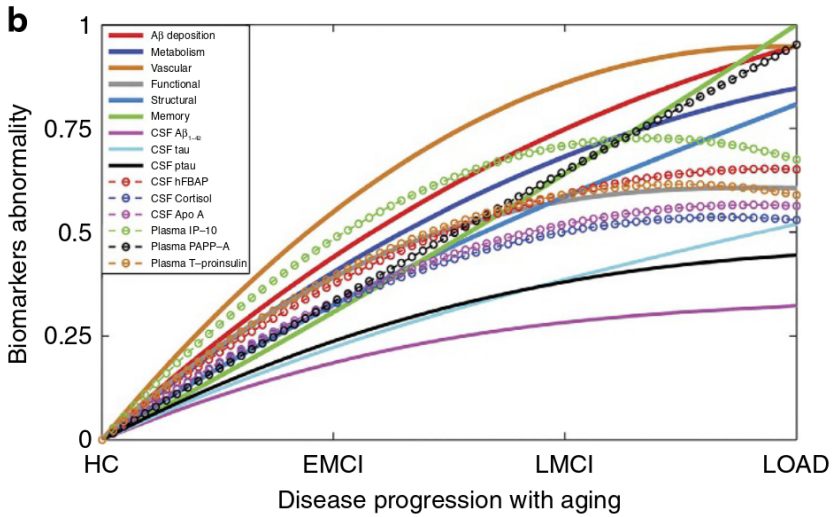
- 2 years of change in behaviour
- diagnosis of Alzheimer's disease and fronotemporal dementia
- poor balance, abnormal eye movements
- swallowing problems

Understanding the brain

- What does dysfunction tell us about normal brain function?

Combining imaging biomarkers

Alzheimer's disease mechanisms



Investigating disease mechanisms with imaging

- Ascribe mechanisms to imaging modalities
- Dynamic multifactorial direct interaction network

Conclusions

- No unique disease mechanism
- Early vascular disease

Iturria-Medina et al. Neuroimage 2017

Clinical question

What is the underlying cause of executive dysfunction in Progressive Supranuclear Palsy?

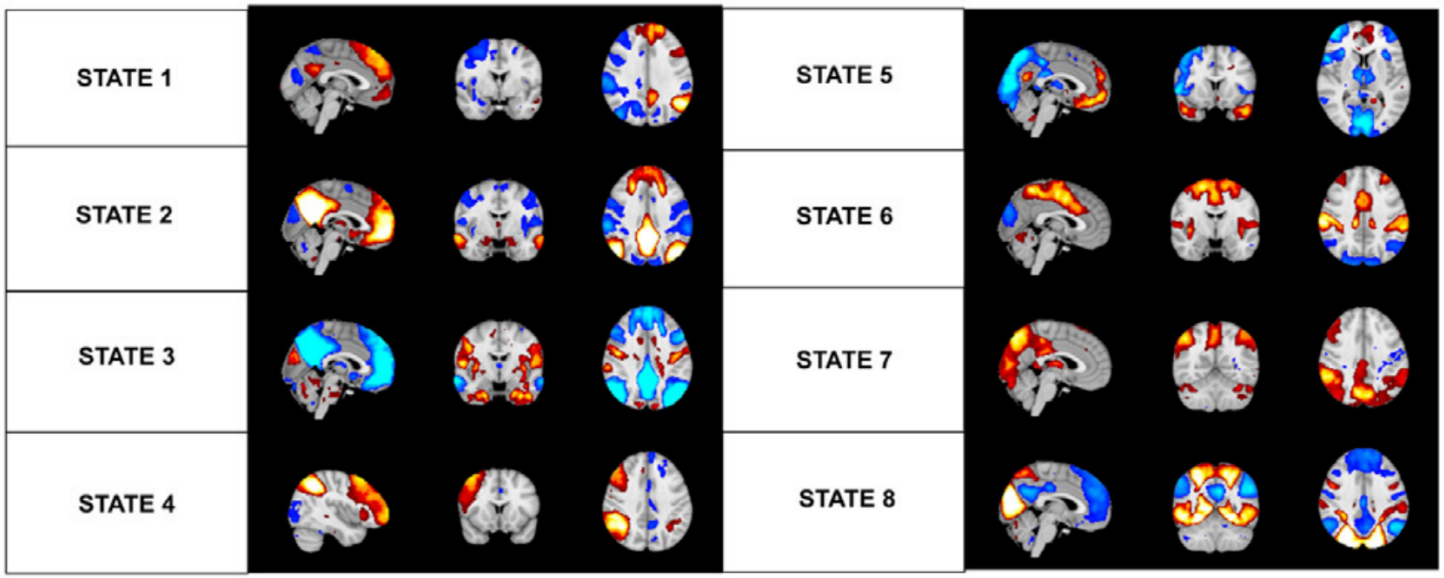
- "Frontal" symptoms without significant frontal atrophy

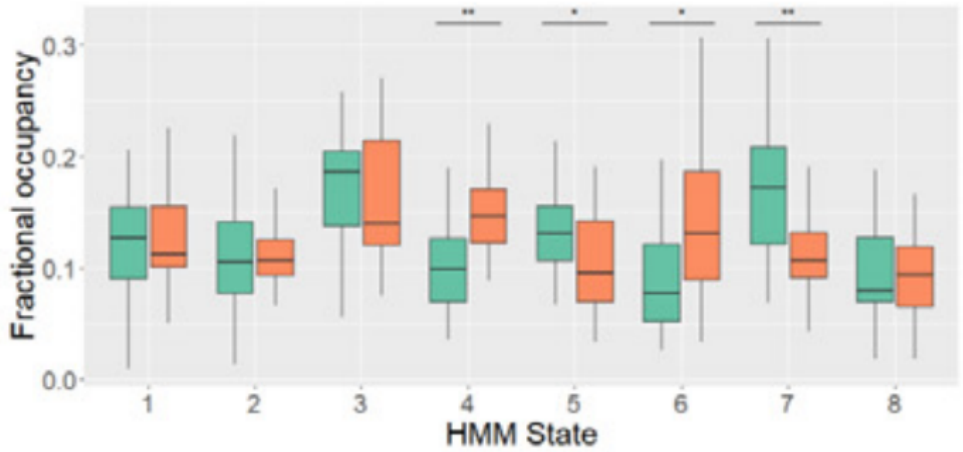
Patient groups

	CCPP: Control	**CCPP: PSP**	**PROSPECT: Control**	**PROSPECT: PSP**
Number	22	24	36	42
Age (years)	64.9 (9.9)	70.1 (6.5)	67.3 (7.1)	71.1 (7.3)
Gender (F/M)	14/8	11/13	26/10	15/27
PSP clinical phenotype (n)		PSP-RS = 16 PSP-subcortical= 0 PSP-cortical=8		PSP-RS = 25 PSP-subcortical= 11 PSP-cortical=6
ACE		82 (11.4)	95.7 (3.4)	81.3 (11.6)
PSPRS		34.9 (12.5)		33.9 (14.2)

Whiteside et al Neurobiology of Aging 2021 107:109

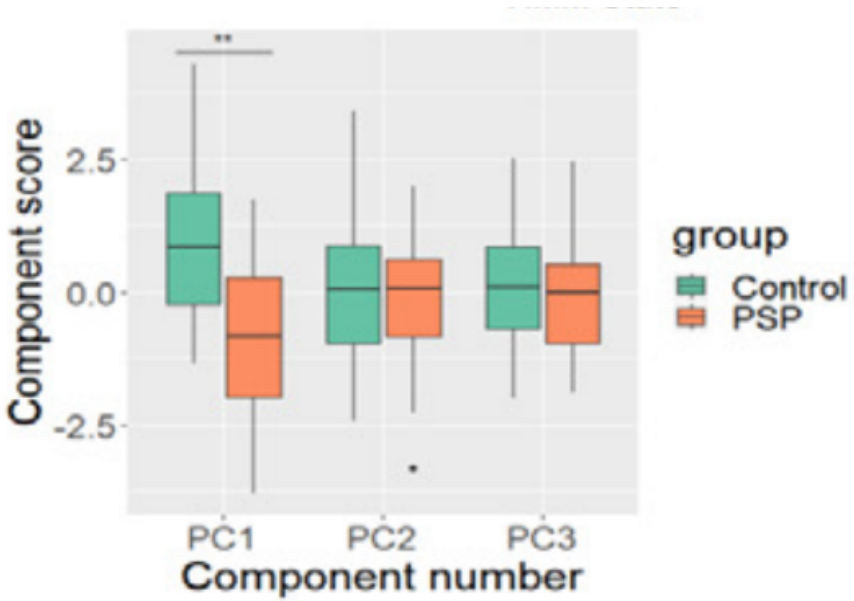
Functional Hidden Markov Model states

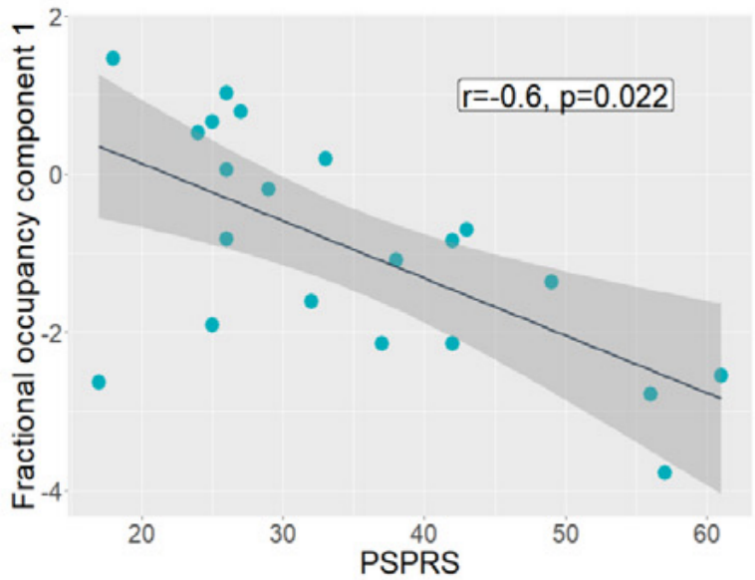




Whiteside et al Neurobiology of Aging 2021 107:109

Functional network dynamics - state components



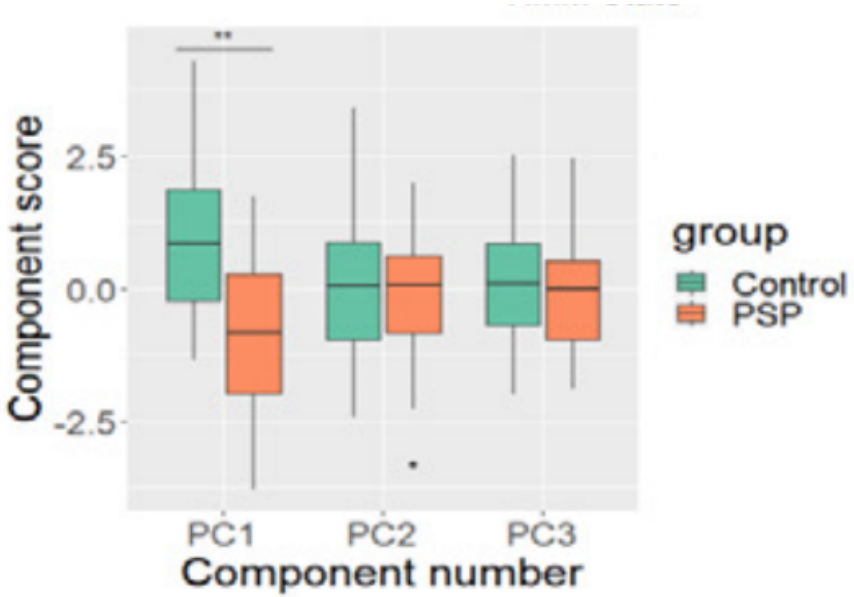


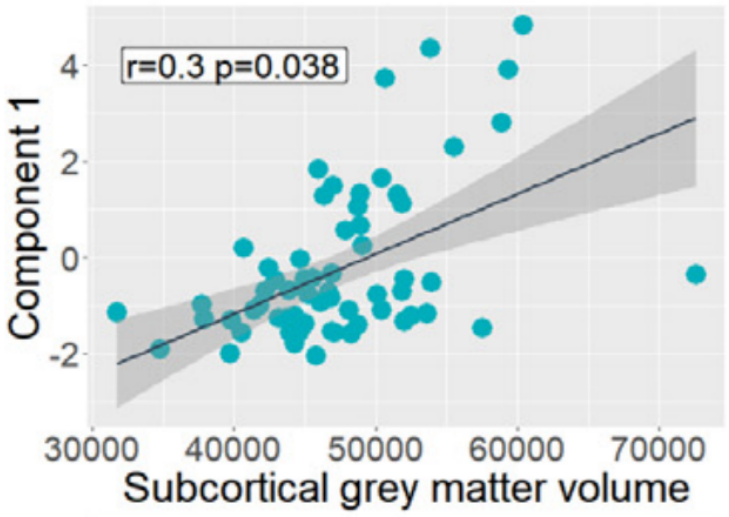
Inefficient network dynamics

- More time spent in frontal/executive networks
- Associated with worse disease severity

Whiteside et al Neurobiology of Aging 2021 107:109

Functional network dynamics - state components





Inefficient network dynamics

- More time spent in frontal/executive networks
- Associated with worse disease severity
- Related to subcortical atrophy

Whiteside et al Neurobiology of Aging 2021 107:109

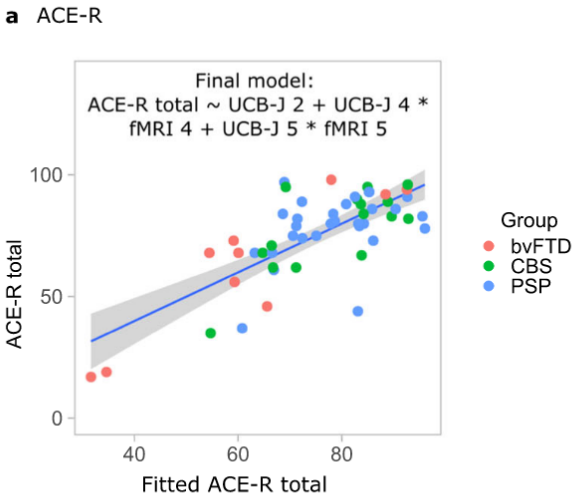
PET and MRI in Frontotemporal Dementia

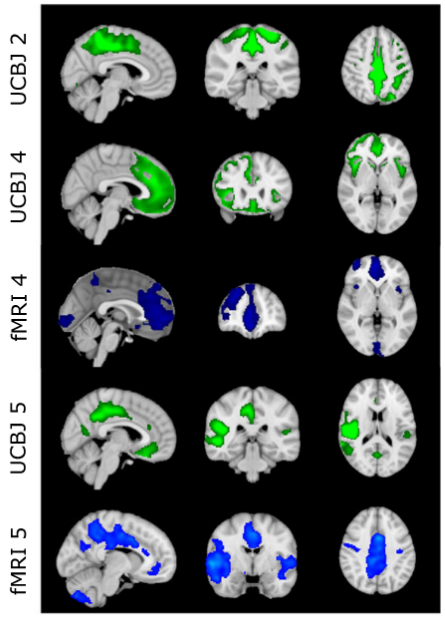
Could synaptic loss be underlying the changes in connectivity and severity?

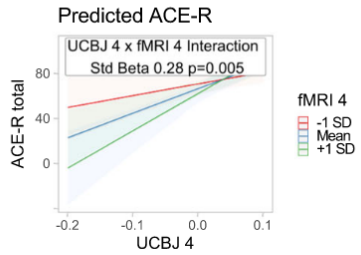
PET and MRI in Frontotemporal Dementia

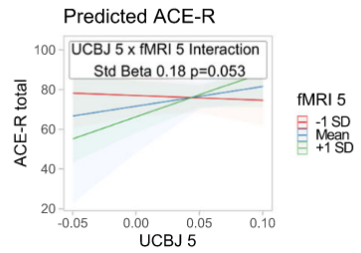
	Control	PSP	CBS	bvFTD
N	24	29	16	10
Age at fMRI	70.0 (8.4)	70.8 (8.4)	67.1 (5.7)	65.0 (9.1)
Sex (M/F)	16/8	15/14	7/9	8/2
Mean DVARS	5.0 (0.4)	5.2 (0.6)	4.9 (0.4)	5.9 (0.8)
ACE-R	95.8 (2.6)	78.6 (13.4)	77.8 (16.9)	63.1 (29.0)
PSPRS	–	34.0 (11.1)	27.2 (11.1)	17.6 (11.2)
CBI-R	–	53.2 (34.3)	37.7 (19.8)	86.9 (34.5)

PET and MRI in Frontotemporal Dementia









Combining imaging and neuropathology

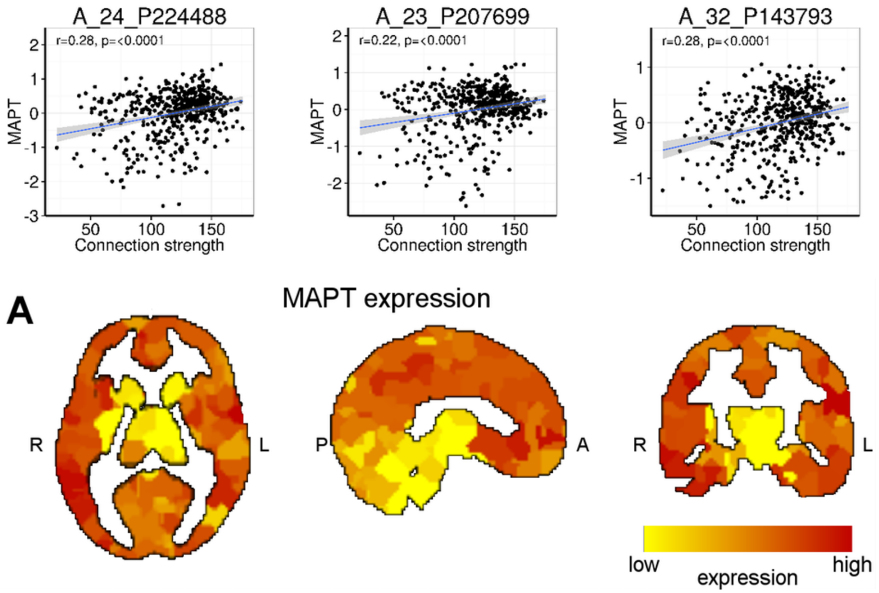
Combining imaging and neuropathology

Do functional neuroimaging changes reflect tau pathology?

Functional organisation reflects genetic expression

Connectivity vs MAPT expression

- Allen human brain atlas
- PSP and Parkinson's disease
- Connectivity reflects MAPT expression
- Connectivity correlates with verbal fluency

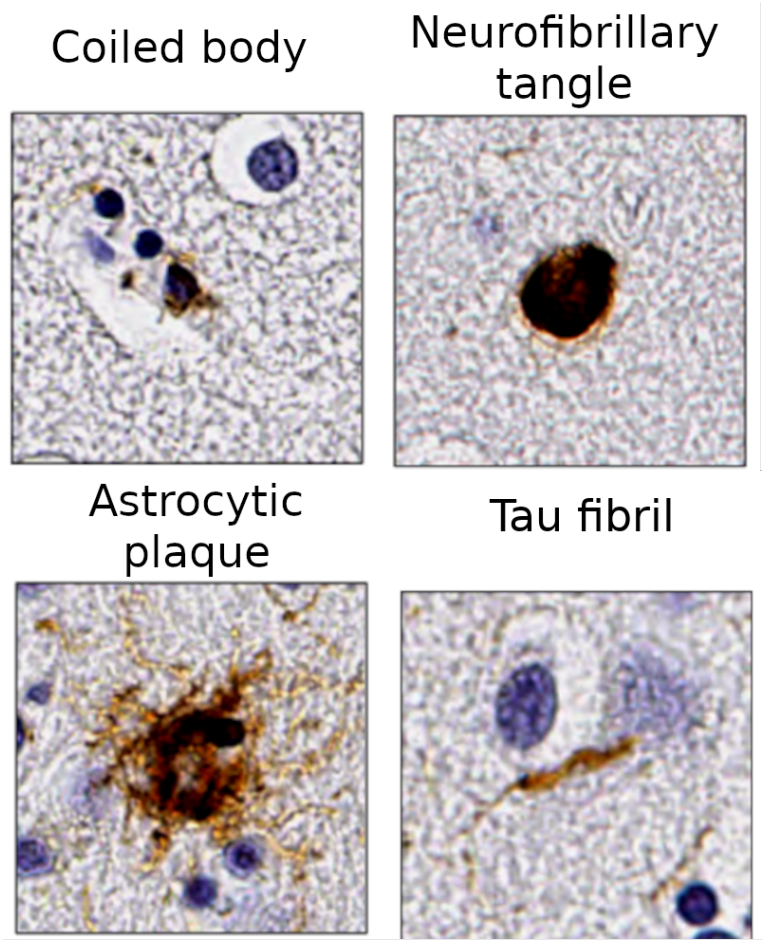


Rittman et al 2016 Neurobiol. Ageing

Combining imaging and neuropathology

Do functional neuroimaging changes reflect tau pathology?

Combining imaging and neuropathology

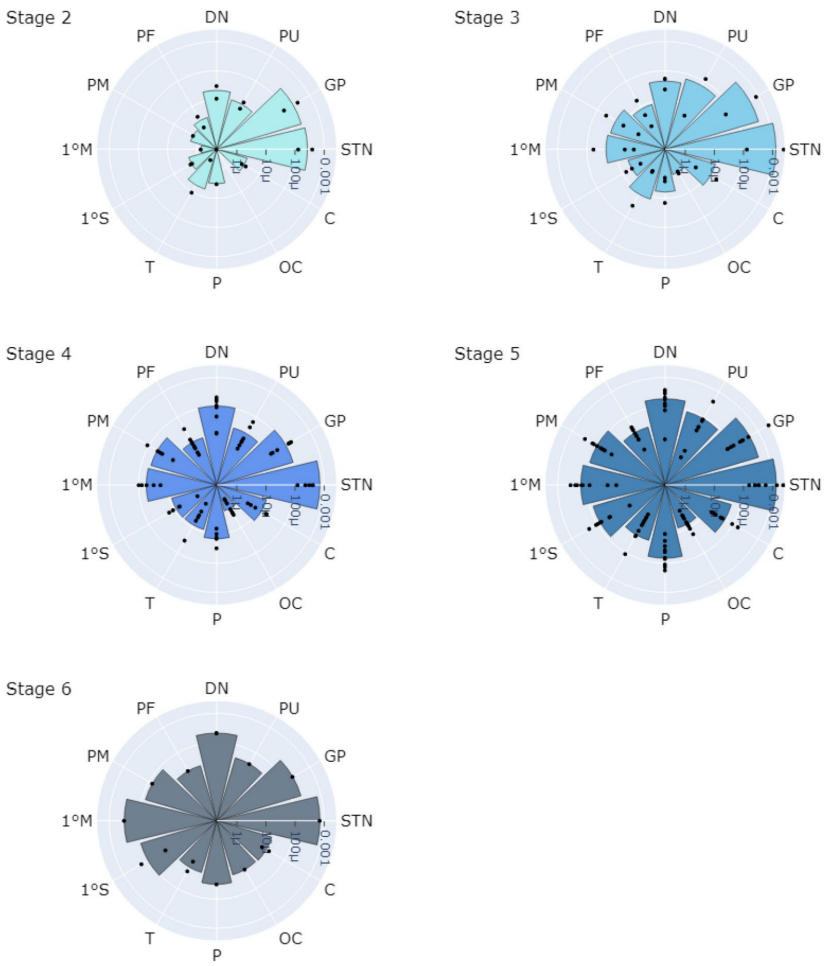


Pansuwan et al. 2023 Acta Neuropath Comms

Combining imaging and neuropathology

Automated tau quanitification

- Quantification reflects PSP staging

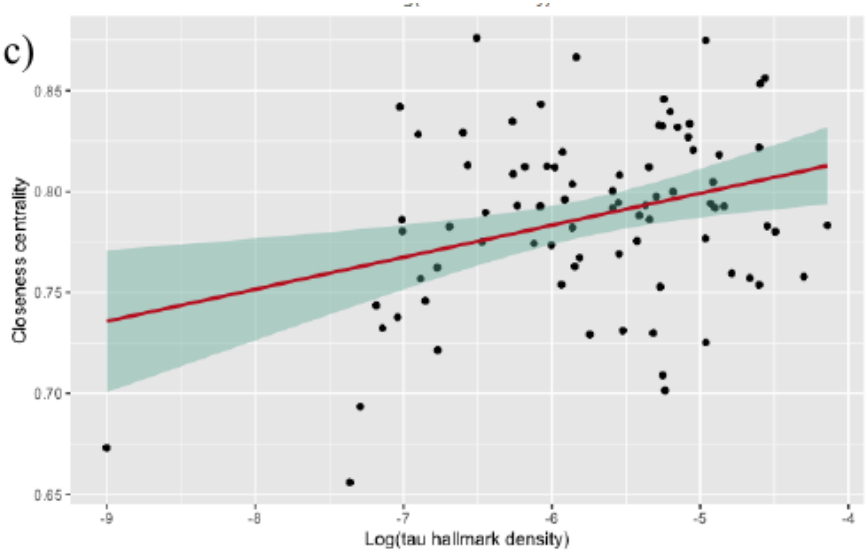


Pansuwan et al. 2023 Acta Neuropath Comms

Combining imaging and neuropathology

Automated tau quanitification

- Quantification reflects PSP staging
- Tau accumulation correlates with loss of functional network efficiency



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Modelling disease

Modelling atrophy from genetics

Do genetics influence the development of atrophy in PSP?

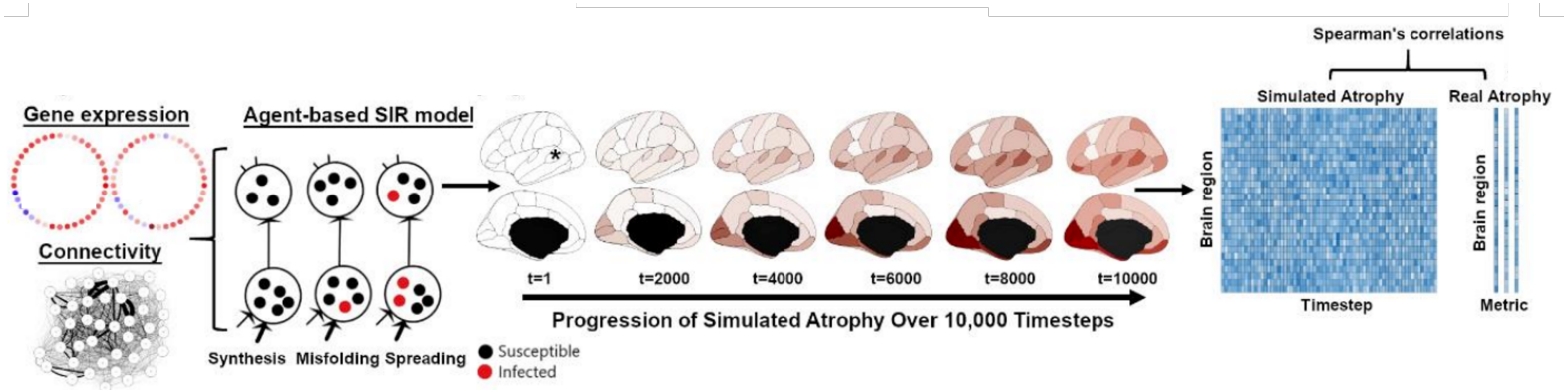
Modelling atrophy from genetics

Disorders

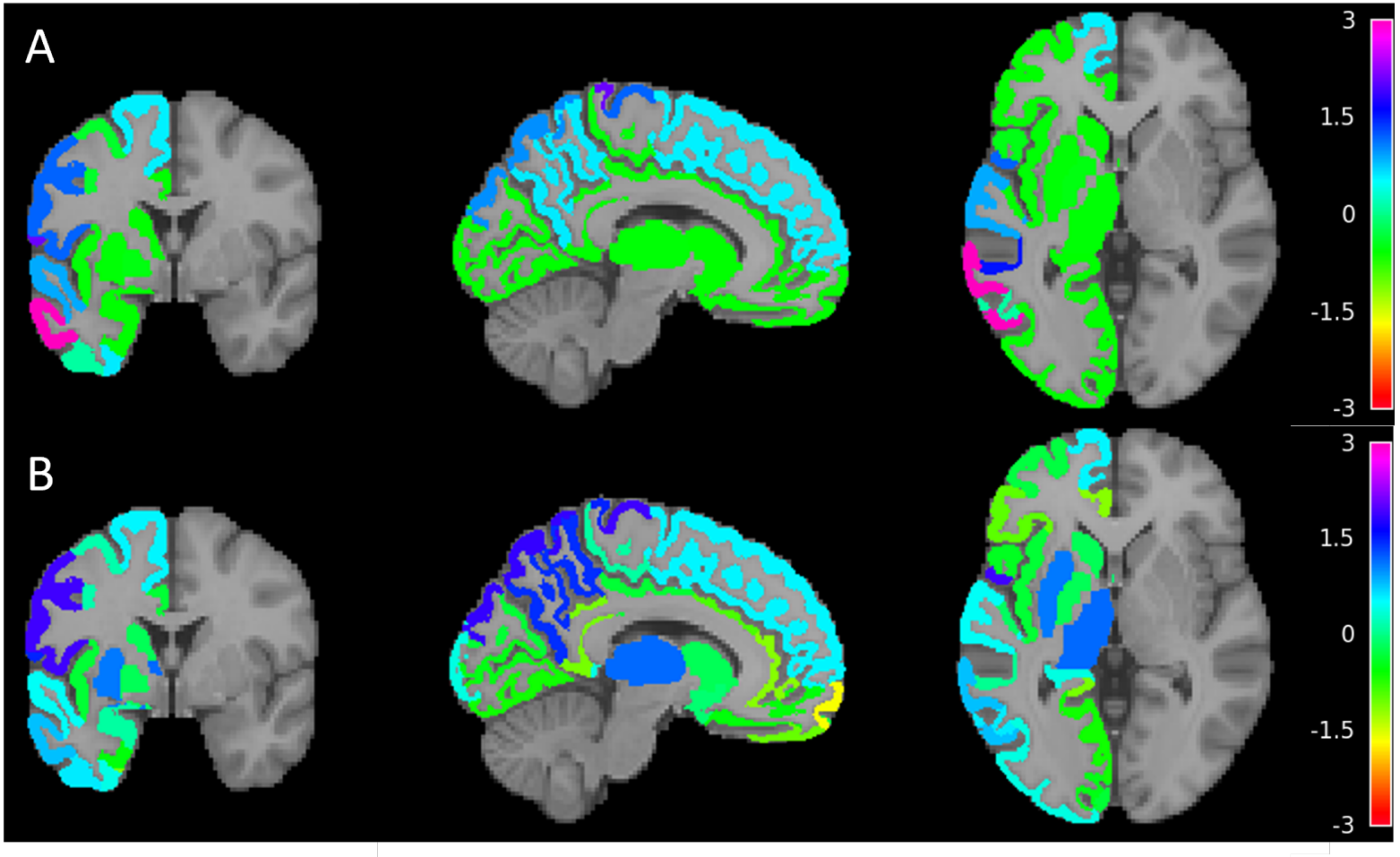
- Progressive Supranuclear Palsy

Genes

APOE, BSN, C9orf72, CXCR4, DCTN1, DUSP10, EIF2AK3, GRN, MAPT, MOBP, NPC1, PRNP, RUNX2, SLCO1A2, STX6, TRIM11,



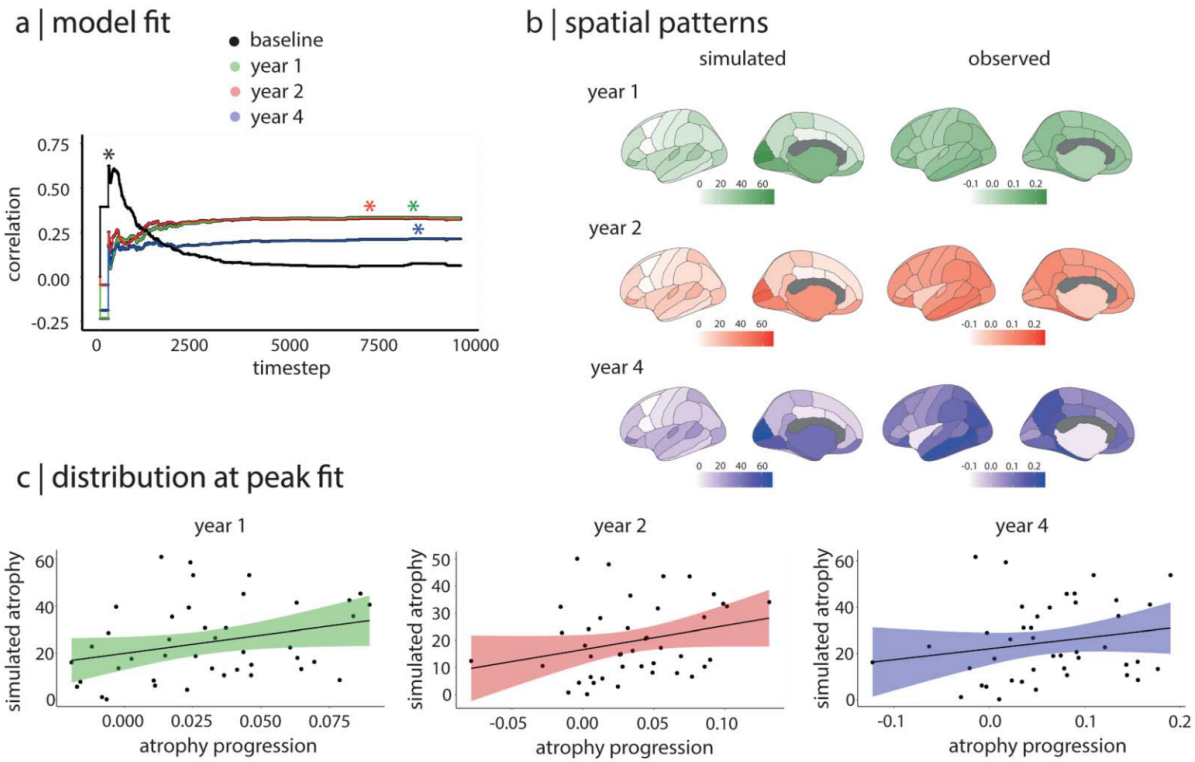
Modelling atrophy from genetics



A = Modelled atrophy

B = Observed atrophy

Modelling atrophy from genetics - Parkinson's disease

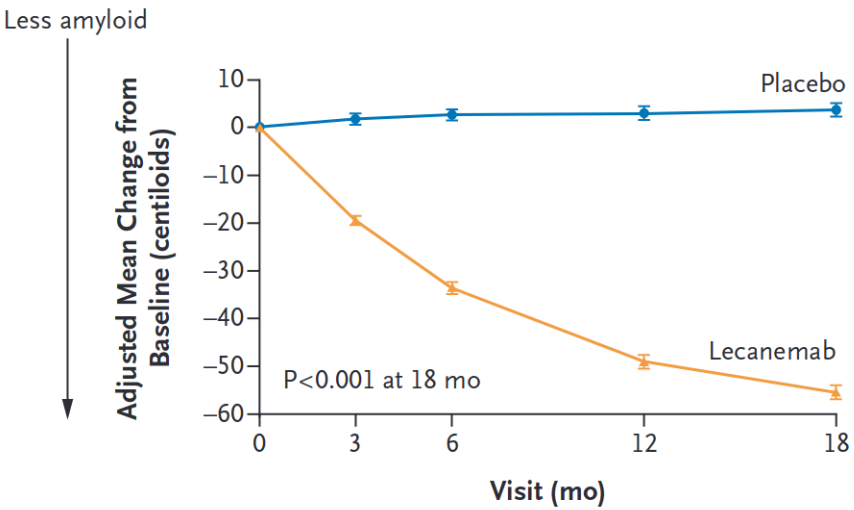


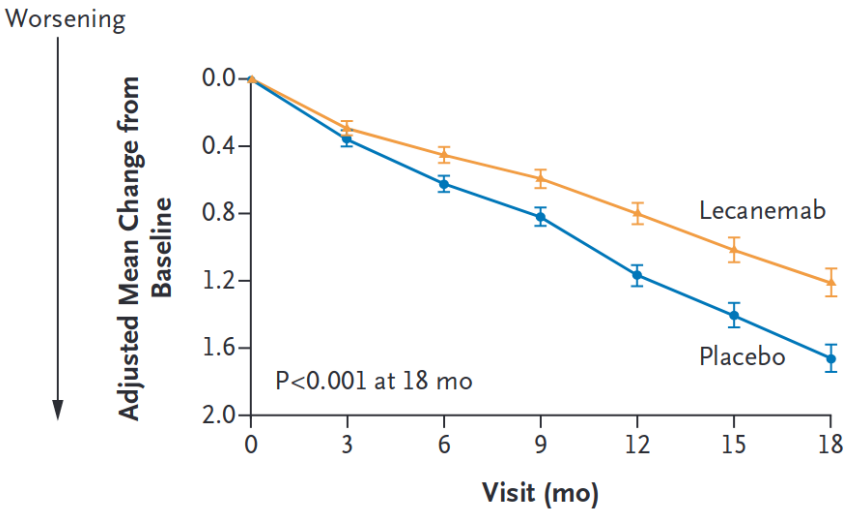
Bratislav Misic: https://netneurolab.github.io/

Abdelgawad et al. 2023 Network Neuroscience

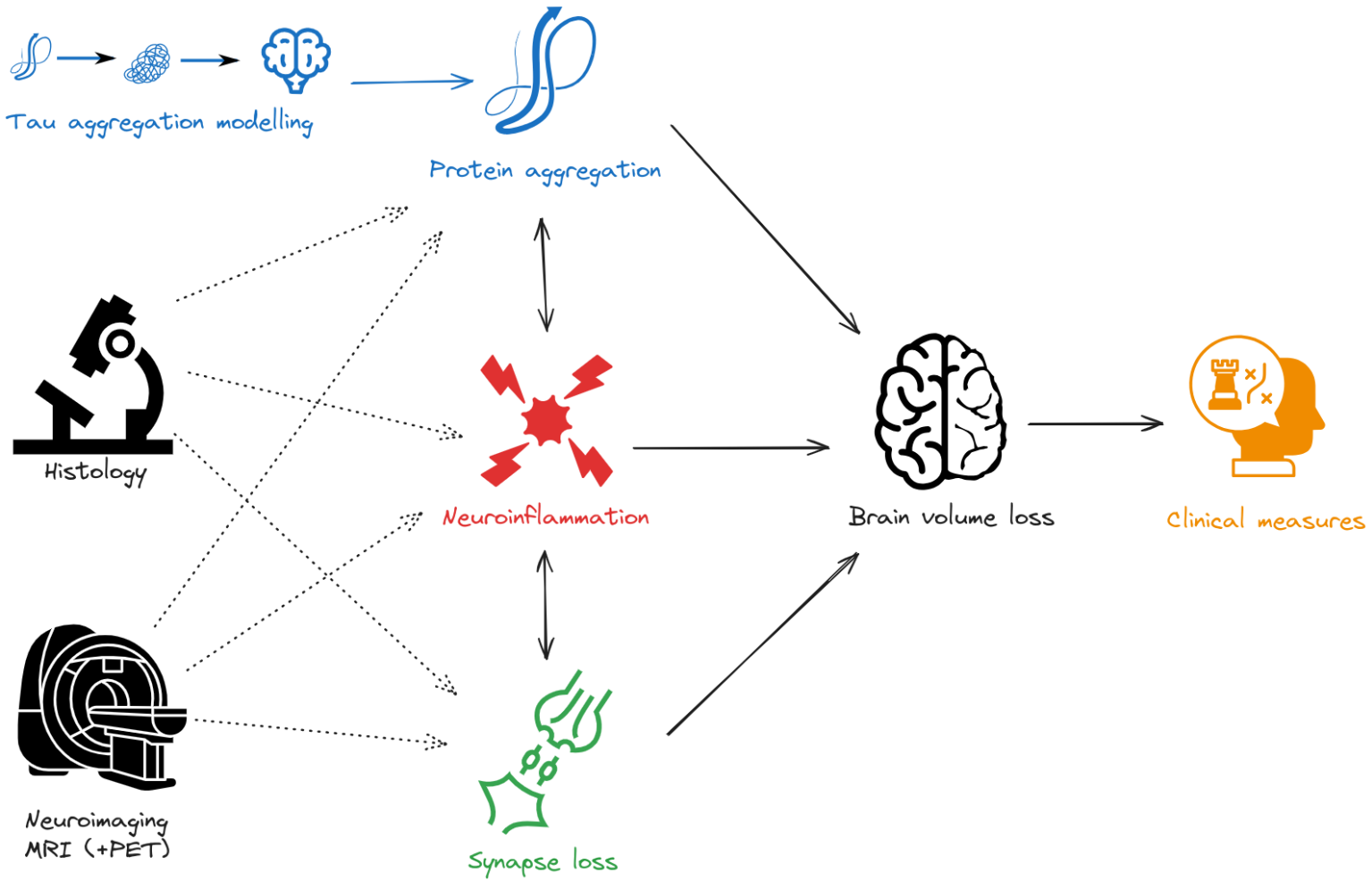
How do multiple disease mechanisms interact?

Lecanemab

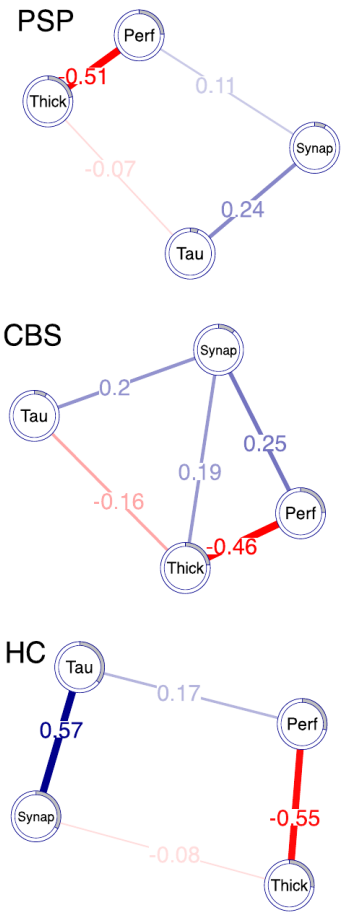

Less amyloid
Adjusted Mean Change from Baseline (centiloids)
10
0
−10
−20
−30
−40
−50
−60
Placebo
Lecanemab
P<0.001 at 18 mo
0
3
6
12
18
Visit (mo)


Worsening
Adjusted Mean Change from Baseline
0.0
0.4
0.8
1.2
1.6
2.0
Lecanemab
Placebo
P<0.001 at 18 mo
0
3
6
9
12
15
18
Visit (mo)

Modelling disease



Modelling disease



Relation between mechanisms

- Tau accumulation - AV1451 PET
- Synapse loss - UCBJ PET
- Perfusion - R1 PET
- Thickness - T1 MRI

Challenges

- Data size
- Data quality
- Missing data

Multimodal imaging for clinical utility

Conclusions

- Why?
- Consider data limitations
  - size
  - quality
  - generalisability
- Think mechanisms
  - strong a priori hypothesis

Thanks

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Collaborators
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Qinyuan Zhao
Maura Malpetti
Negin Holland

wellcome

MRC Medical Research Council

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