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Background

- Brain atrophy in frontotemporal dementia (FTD)** has been shown to follow the topology of large-scale brain networks^{1,2} and partially co-localize with neurotransmitter receptor distributions.³

Methods

- MRI data** from bvFTD, nfvPPA, and svPPA patients (Table 1) were used to derive atrophy maps (Fig. 2) by group-averaging W-scores of brain volumes relative to controls. Data were obtained from the Frontotemporal Lobar Degeneration Neuroimaging Initiative.
- PET-derived neurotransmitter receptor density maps**⁷ (Fig. 3) were incorporated into **weighted models** as regional modulators of pathology production or spread.
- Models tested **amplifying** or **protective effects** of receptor densities on pathology accumulation or propagation.

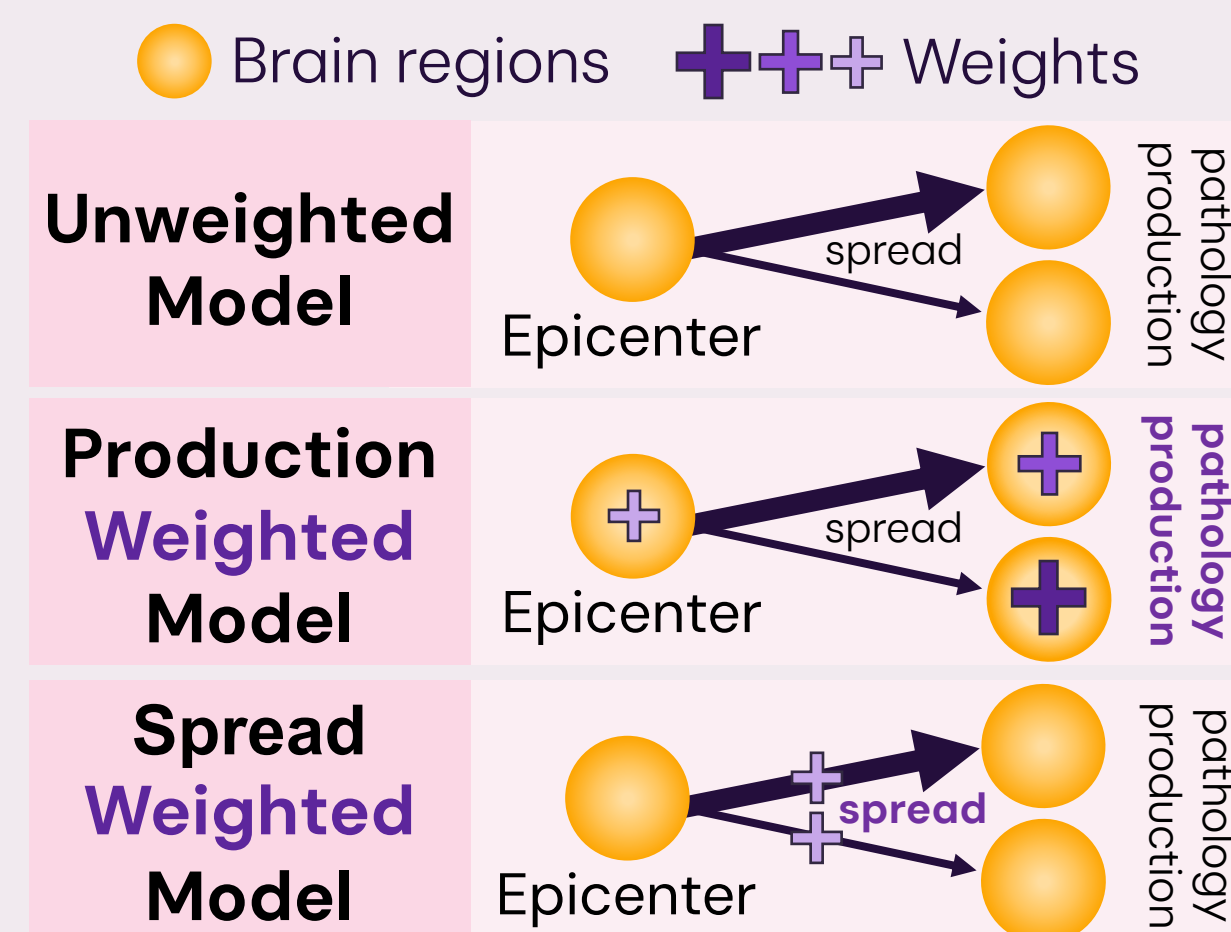


Figure 1. Network spreading models

	Control	bvFTD	nfvPPA	svPPA
Individuals, n	70	22	11	20
Sex, (F/M)	45 / 25	8 / 14	5 / 6	9 / 11
Age, mean (SD)	63.1 (7.5)	62.5 (5.6)	67.1 (8.7)	62.5 (6.8)
CDR[®] plus NACC FTLTD global score, (0.5 / 1 / 2)	–	3 / 10 / 9	5 / 6 / –	6 / 12 / 2

Table 1. Participant characteristics

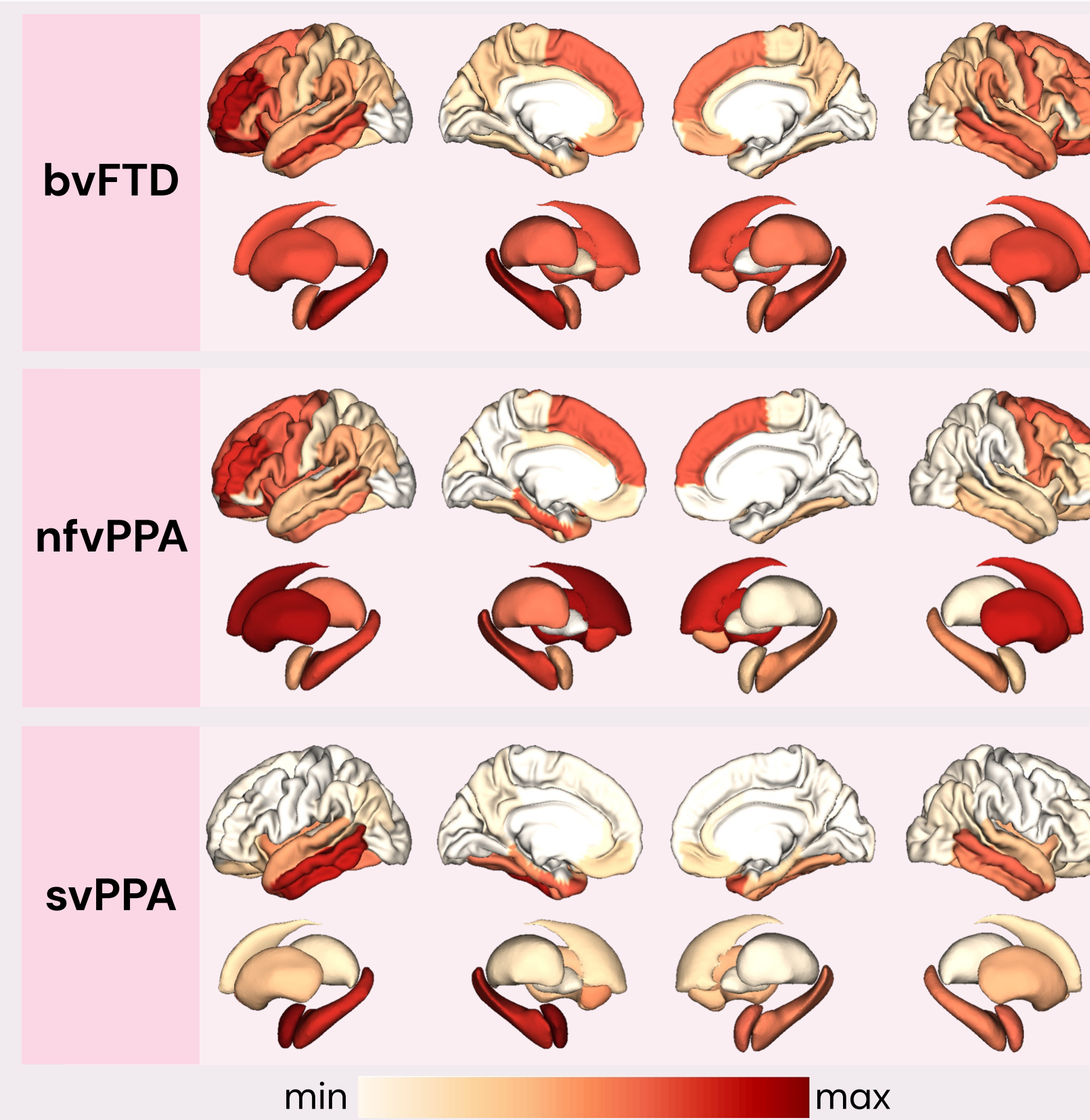


Figure 2. Group-averaged atrophy maps across clinical syndromes

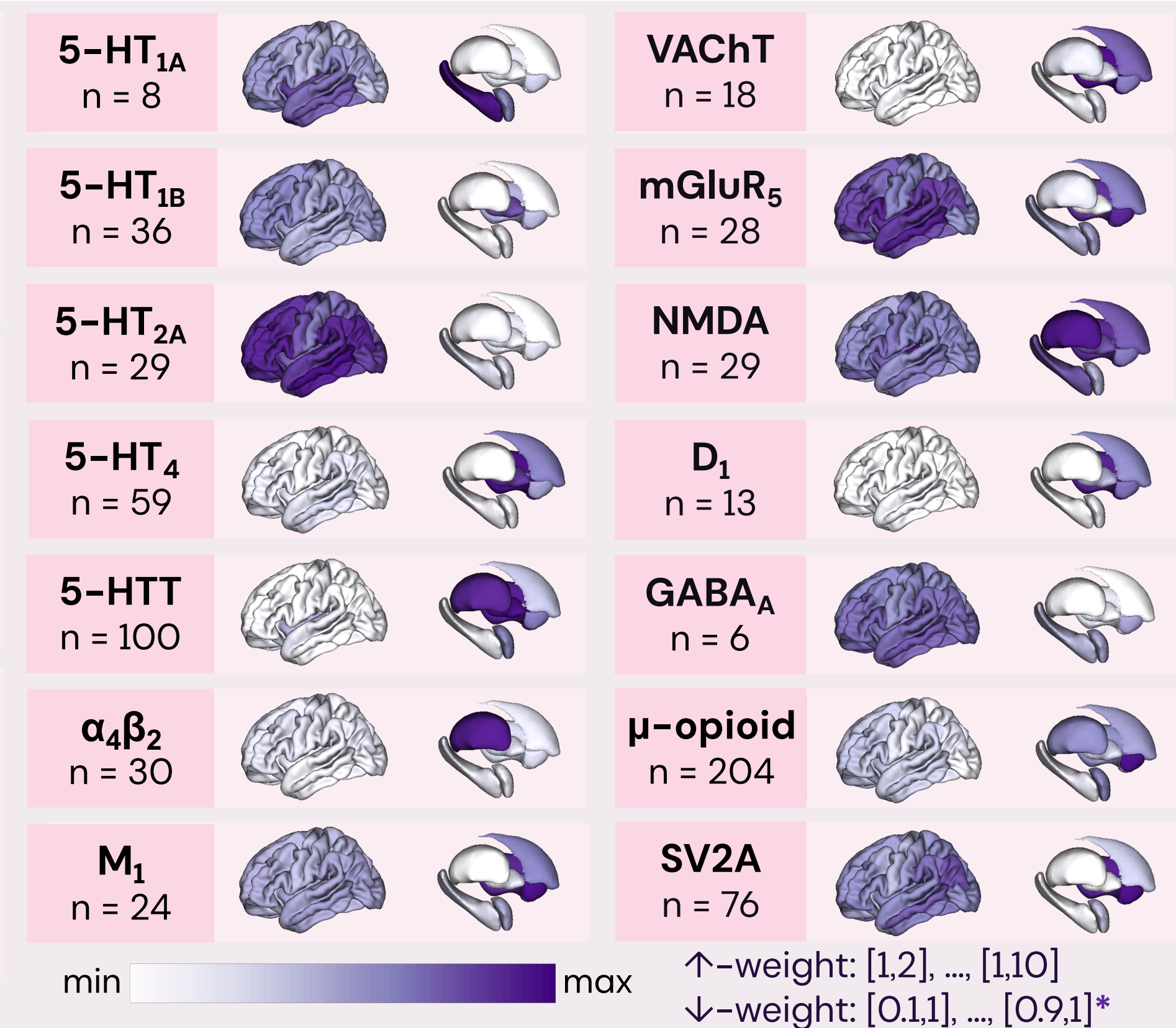


Figure 3. Regional neurotransmitter receptor density maps
*Densities were inverted (–density) before scaling

Results

bvFTD & nfvPPA:

Best models had local production down-weighted by **5-HT_{1B}**.

svPPA:

The **unweighted model** predicted regional atrophy well. The best weighted model provided minimal improvement.

	Model	Weighting	Epicenter	<i>r</i>	SSE	Akaike weight
bvFTD	Unweighted	–	Putamen	0.515	3.554	0.001
	Best Weighted	Production ↓ by 5-HT_{1B} [0.2,1]	Pars opercularis	0.622	2.972	0.675
nfvPPA	Unweighted	–	L. Pallidum	0.475	5.344	<0.001
	Best Weighted	Production ↓ by 5-HT_{1B} [0.1,1]	L. Caudal middle frontal	0.666	3.834	0.895
svPPA	Unweighted	–	Temporal pole	0.859	1.404	0.057
	Best Weighted	Spread ↓ by VACHT [0.1,1]	Temporal pole	0.863	1.310	0.326

Table 2. Model fit results. Comparison between the unweighted and best weighted model for each clinical syndrome.

Conclusions

- svPPA** atrophy pattern is explained well by **connectivity-driven pathology spread** alone.
- Using **5-HT_{1B}** densities to **down-weight production** improved model performance in predicting atrophy patterns in **bvFTD & nfvPPA**.
- Neurotransmitter receptor densities may **differentially modulate regional pathology accumulation** across clinical FTD phenotypes.

References

- Shafiei *et al.*, *Brain*, 2022; 2. Agosta *et al.*, *Brain*, 2024;
- Premi *et al.*, *Neurobiol. Dis.*, 2023; 4. Raj *et al.*, *Neuron*, 2012;
- Weickenmeier *et al.*, *Phys Rev Lett*, 2018;
- He *et al.* *MICCAI*, 2023; 7. Hansen *et al.*, *Nat Neurosci*, 2022