

Stepwise connectivity patterns along the gradients of brain organization in Alzheimer's disease



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Background

Introduction

Alzheimer's disease (AD) is characterized by the accumulation of amyloid- β (A β) plaques and neurofibrillary tau tangles, and gradual cognitive decline. **tau accumulates** through both **structural** (trans-neuronal spread model¹) and **functional** connections (nodal stress model^{2,3}).

The **entorhinal cortex (EC)** is one of the **earliest sites of tau pathology**⁴, before accumulating in **limbic** regions and the **neocortex**⁵. Both **direct** and **indirect connections** to the EC can undergo **abnormal or compensatory reorganizations** resulting in the characteristic **loss of small-worldness topology** in AD⁶.

Existing work

- Stepwise connectivity⁷ has been applied to functional, **but not structural** connectomic data
- **No quantitative integration** of stepwise connectivity in **gradient space**⁸

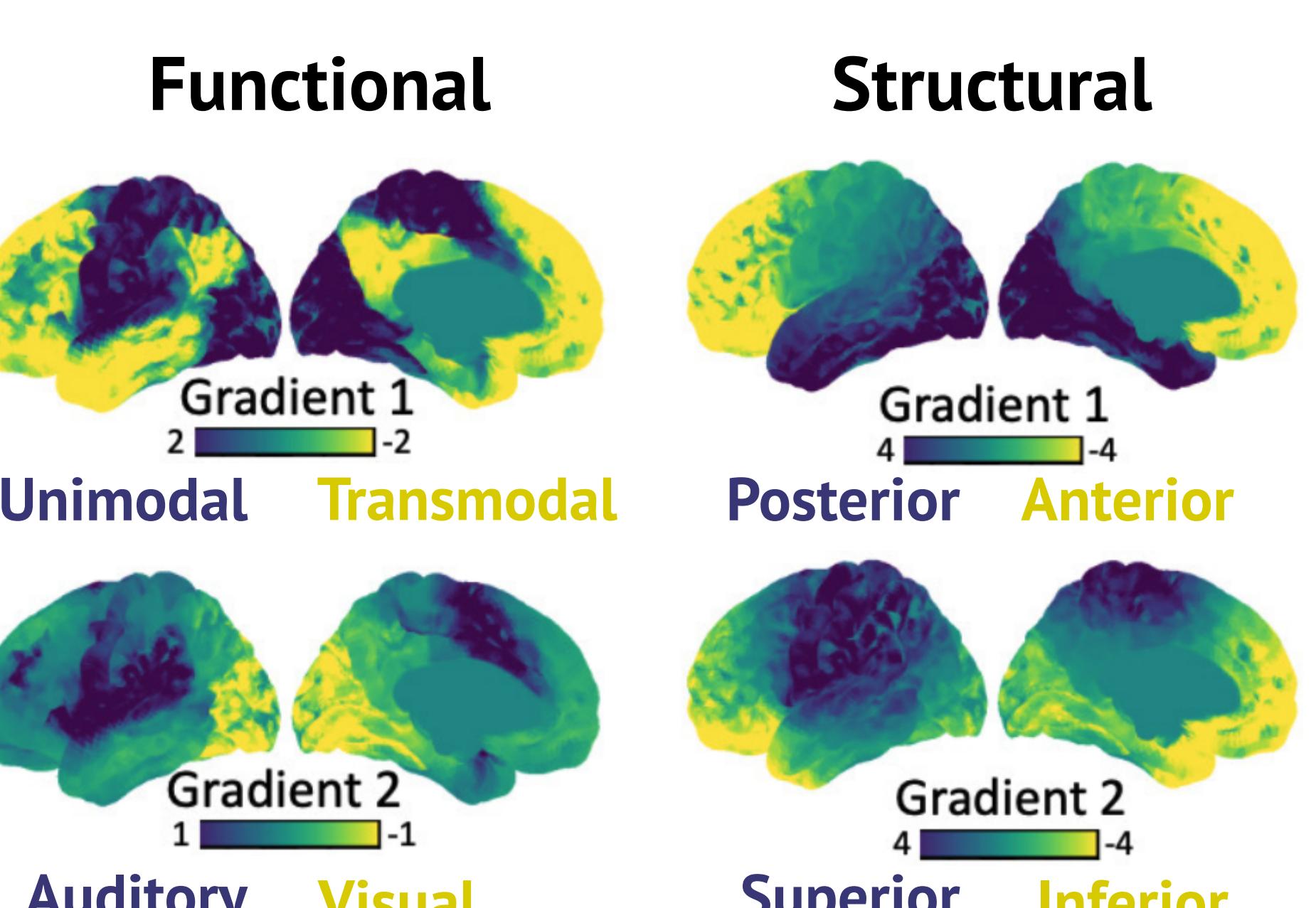
Aim

Characterize the direct and indirect connectivity changes to the entorhinal cortex to understand network reorganization in AD.

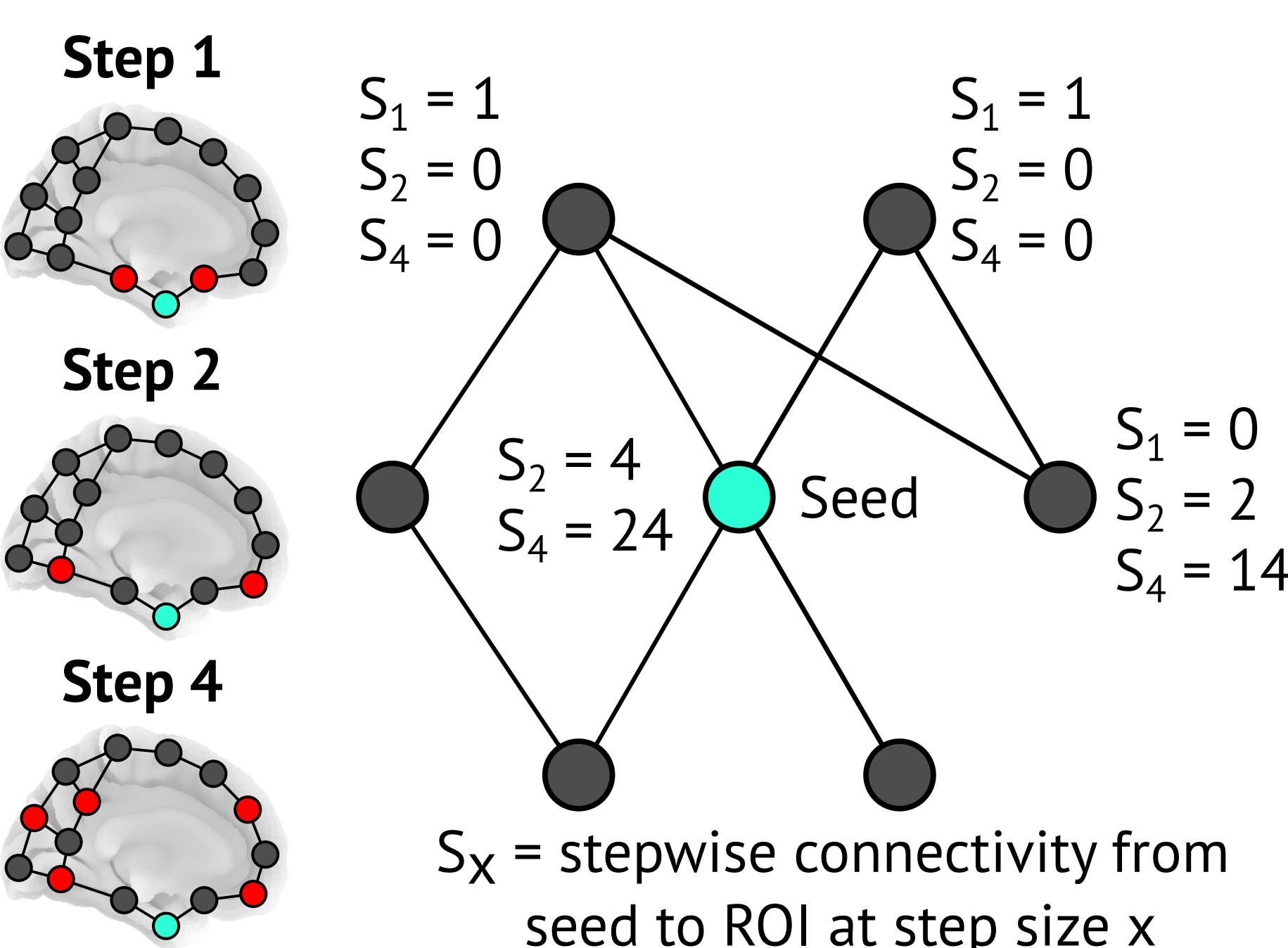
Methods

Connectomic gradients

Gradients⁹ capture the **smooth spatial transitions** in connectivity variation unlike **conventional parcellations** which assume **discrete network boundaries** and **homogeneity within ROIs**.



Conventional connectomics focuses on **direct seed-to-target** connections between regions. **Stepwise functional/structural connectivity (SFC/SSC)**⁷ also considers **indirect** connections through other nodes connecting seed to target.



Results

Demographics

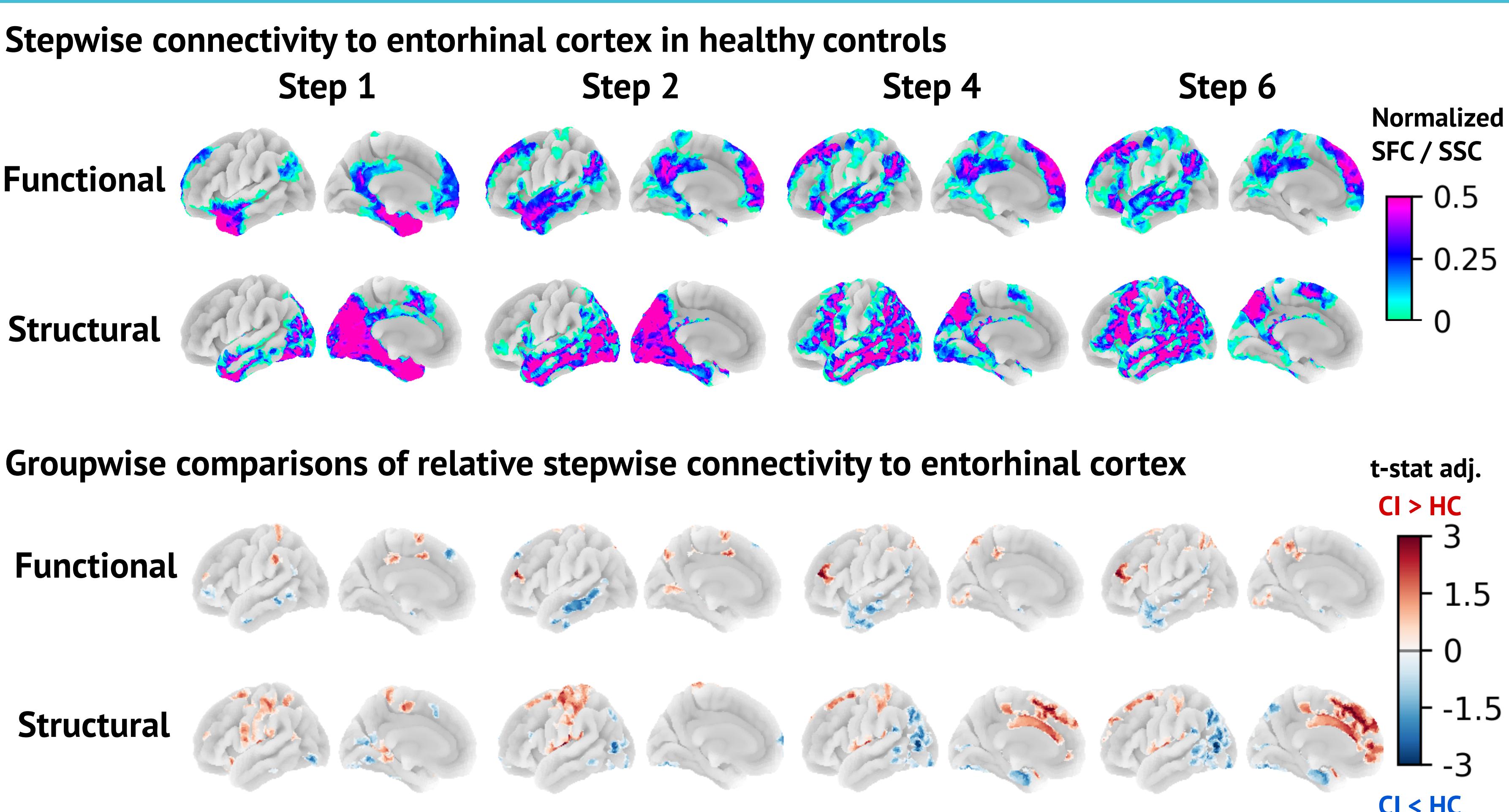
TRIAD cohort						
	Overall n = 213	HC n = 103	CN A+ n = 35	CI n = 75	P-value*	
Diagnosis, n (%)						
HC	138 (64.8)	103 (100)	35 (100)	41 (54.7)		
MCI	41 (19.2)			34 (45.3)		
AD	34 (16)					
Sex	F	129	63 (61.2)	24 (68.6)	42 (56)	0.447
Age, mean (SD)		69.3 (9.2)	68.6 (9.7)	73.5 (7.8)	68.3 (8.8)	0.012*
APOE-e4, n (%)	Carriers	77 (36.8)	27 (26.5)	9 (25.7)	41 (56.9)	< 0.001

HC: healthy controls
CN A+: cognitively normal, amyloid positive
CI: cognitively impaired, amyloid positive
* Based on ANOVA with Bonferroni correction and Tukey's post-hoc testing

HC or CI vs A+ CN: p=0.02

More details at: <https://triad.tnl-mcgill.com/>

Whole-brain stepwise connectivity to entorhinal cortex seed



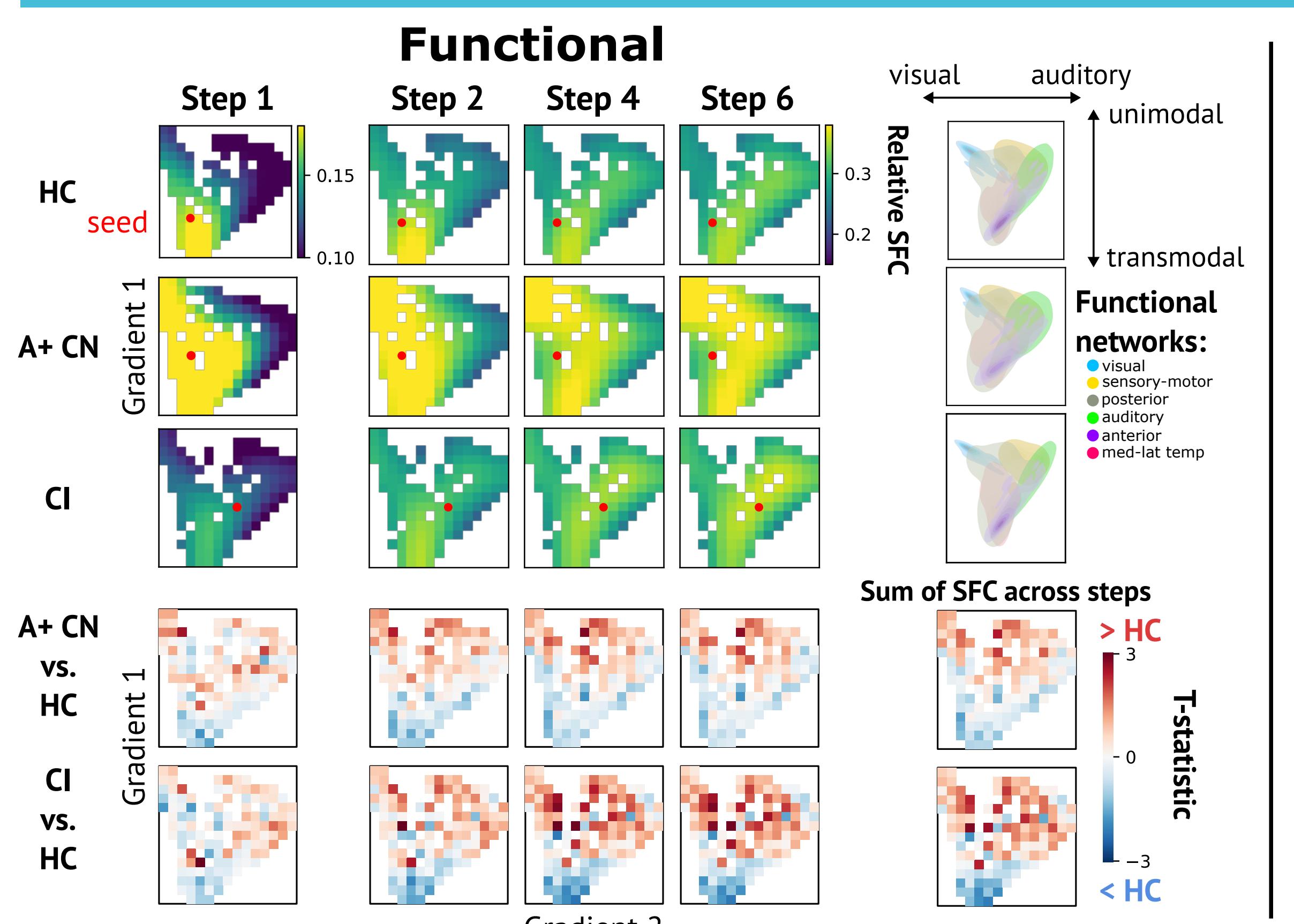
SFC (stepwise functional connectivity) highest **near seed** (step 1) and propagated to **default-mode network** (step 2) before reaching **sensorimotor regions** (steps 3-7).

SSC (stepwise structural connectivity) propagates from **posterior** (steps 1-2) to **anterior** (steps 3-7) regions.

In CI (cognitively impaired, A+):

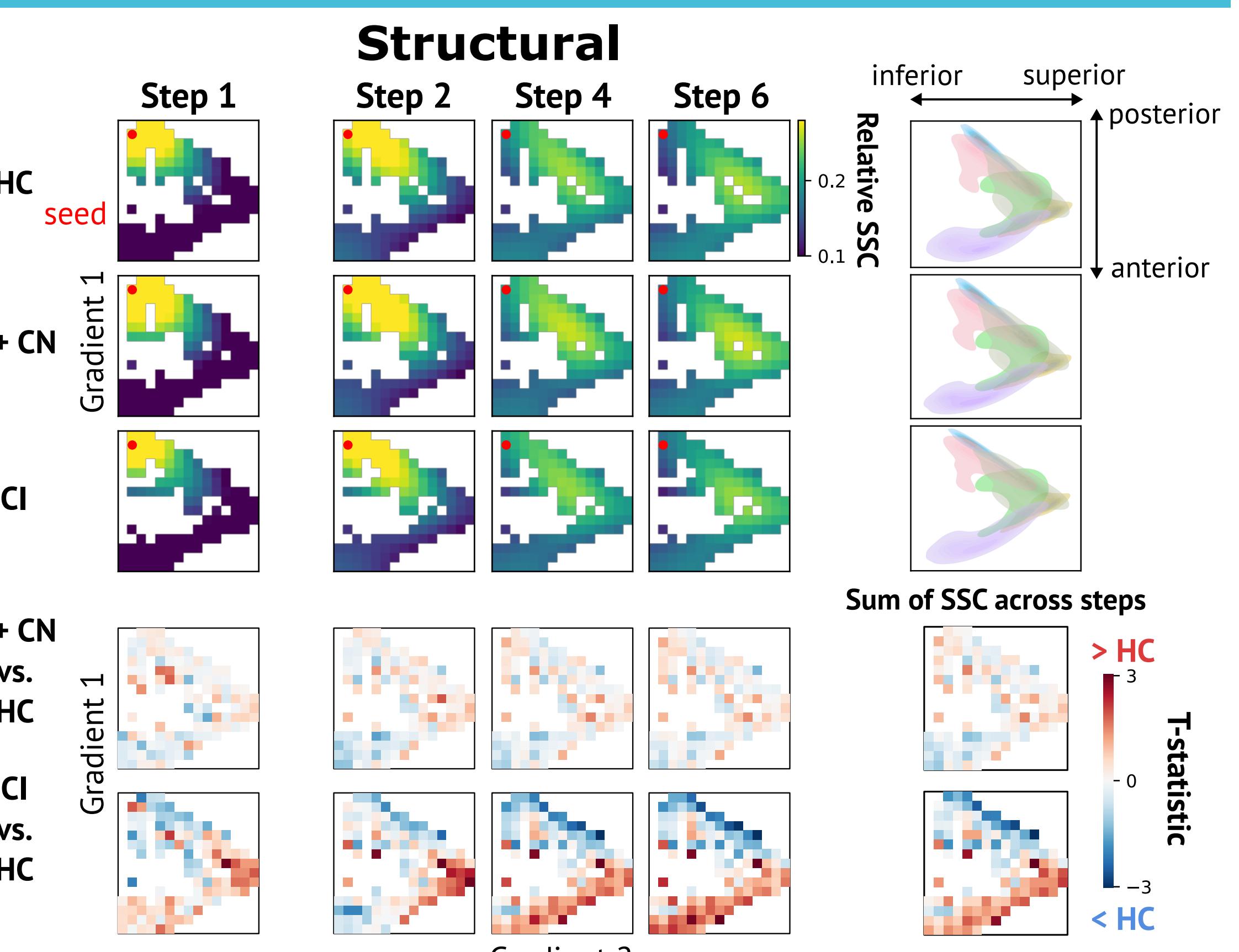
- Reduced SFC to lateral temporal subnetworks
- Increased SFC to frontoparietal, sensorimotor regions
- Reduced SSC to medial-temporal/posterior regions
- Increased SSC to medial-frontal/anterior regions

Stepwise connectivity in gradient space



A+ CN showed **accelerated SFC propagation** to the rest of the brain, which may be **compensatory connectivity in preclinical stages**.

CI showed **diminished SFC** to the default-mode at the **transmodal pole** of gradient 1 and **accelerated propagation** to the sensorimotor regions at the **unimodal pole** of gradient 1.



Propagation was **restrained in the temporal-posterior pole in CI**

There was **reduced SSC to temporal-posterior regions in CI** compared to HC while there was **increased SSC to the temporal-posterior regions in A+ CN**

Conclusion

We used a novel integration of gradients and stepwise connectivity to demonstrate widespread network reorganization in AD.

In CI patients, there is reduced direct connectivity between the EC and default and temporo-occipital cortices, but reduced indirect connectivity to lateral temporal networks and increased indirect connectivity to sensorimotor regions.

Future directions

Consider the relationship between stepwise connectivity, gradients and various neurophysiological aspects of cognition or molecular assays of AD pathology, to better translate findings into clinical implications.

References

- Zhou (2012) Neuron; 2.Vogel (2020) Nat. Commun.; 3.Ottroy (in press) Nat. Commun.; 4.Therriault (2022) Nat. Aging; 5.Braak (1991) Neuropathol; 6.Sanz-Arigita (2010) PLoS One; 7.Sepulcre (2012) J. Neurosci.; 8.Hong (2019) Nat. Commun.; 9.Margulies (2016) PNAS