# Cortex gradient mapping shows heightened network hierarchy in presymptomatic Frontotemporal Dementia

**Bouzigues A.**[1,2], Le Du V.[1], Joulot M.[1,] Russell L.L.[2], Rowe J.B.[3], Borroni B.[4], Galimberti D.[5,6], Tiraboschi P.[7], Masellis M.[8], Tartaglia M.C.[9], Finger E.[10], van Swieten J.C.[11], Seelaar H.[11], Jiskoot L.C.[11], Sorbi S.[12,13], Butler C.[14], Graff C.[15,16], Gerhard A.[17,18], Langheinrich T.[17,19], Laforce R.[20], Sanchez-Valle R.[21], de Mendonça A.[22], Moreno F.[23,24], Synofzik M.[25,26], Vandenberghe R.[27,28,29], Ducharme S.[30,31,32], Levin J.[33,34,35], Otto M.[36], Pasquier F.[37,38,39], Santana I.[40,41,42], Schroeter M.L.[43,44], Le Ber I.[1,45], Margulies D.[46,47], Rohrer J.D.[2] and Migliaccio R.[1,45], **on behalf of the GENetic Frontotemporal dementia Initiative (GENFI)**

## INTRODUCTION

A brain **network hierarchy** is thought to emerge during neurodevelopment. It is assumed this organisation allows information encoding and integration, **from sensation to cognition** (Mesulam, 1998).

Recent work has applied a **novel decomposition framework** to represent connectomes in low-dimensional space; **gradient mapping**. The principal gradient, which explains the most variance in connectivity, **separates immediate environment sensory processes from transmodal integration processes** (Fig 2).

**Yeo 7 functional networks**

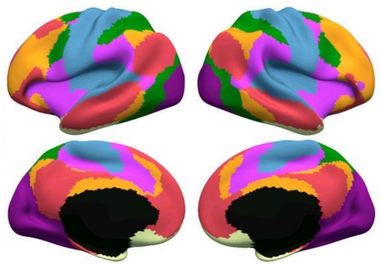


Fig 1 Yeo et al., 2011

**Canonical cortical networks**

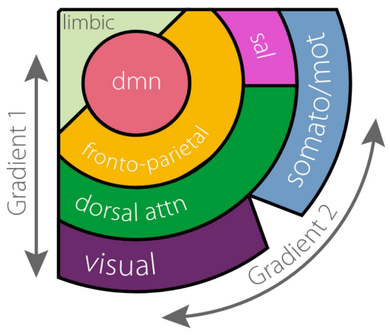



Fig 2 Margulies et al., 2016

**→This project investigated connectome gradients in microtubule-associated protein tau (MAPT) mutation carriers, at presymptomatic (PS) and symptomatic (Symp) Frontotemporal Dementia (FTD) stages**

## METHODS

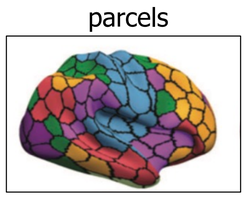
Sample demographic details

| | N | Age | Sex | EYO | MMSE |
|---|---|---|---|---|---|
| **Controls** | 110 | 42.3±11.8 | 60:50 | - | 29.4±1.0 |
| **PS MAPT** | 66 | 39.5±11.4 | 38:28 | 13.1±11.9 | 29.5±1.0 |
| **Symp MAPT** | 36 | 55.2±9.8 | 12:24 | - | 25.0±4.6 |

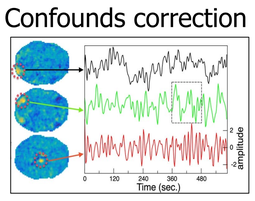
**Age, EYO, MMSE:** group mean ± SD; **Sex:** (females:males).

### Whole-brain connectome gradient mapping pipeline

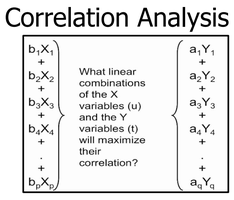
**Step 1:**
Cortical parcellation
Schaefer atlas – 400 parcels



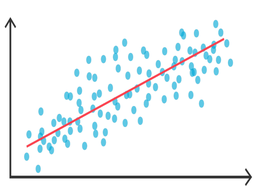
**Step 2:**
resting-state fMRI timeseries extraction
Confounds correction



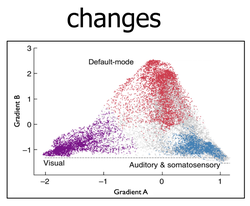

**Step 3:**
Dimension reduction – Generalised Canonical Correlation Analysis



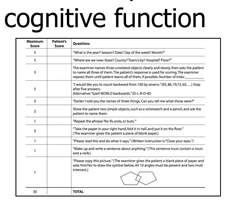

**Step 5:**
Parcelwise group comparisons – Linear regressions



**Step 4:**
From parcels to resting-state canonical network changes



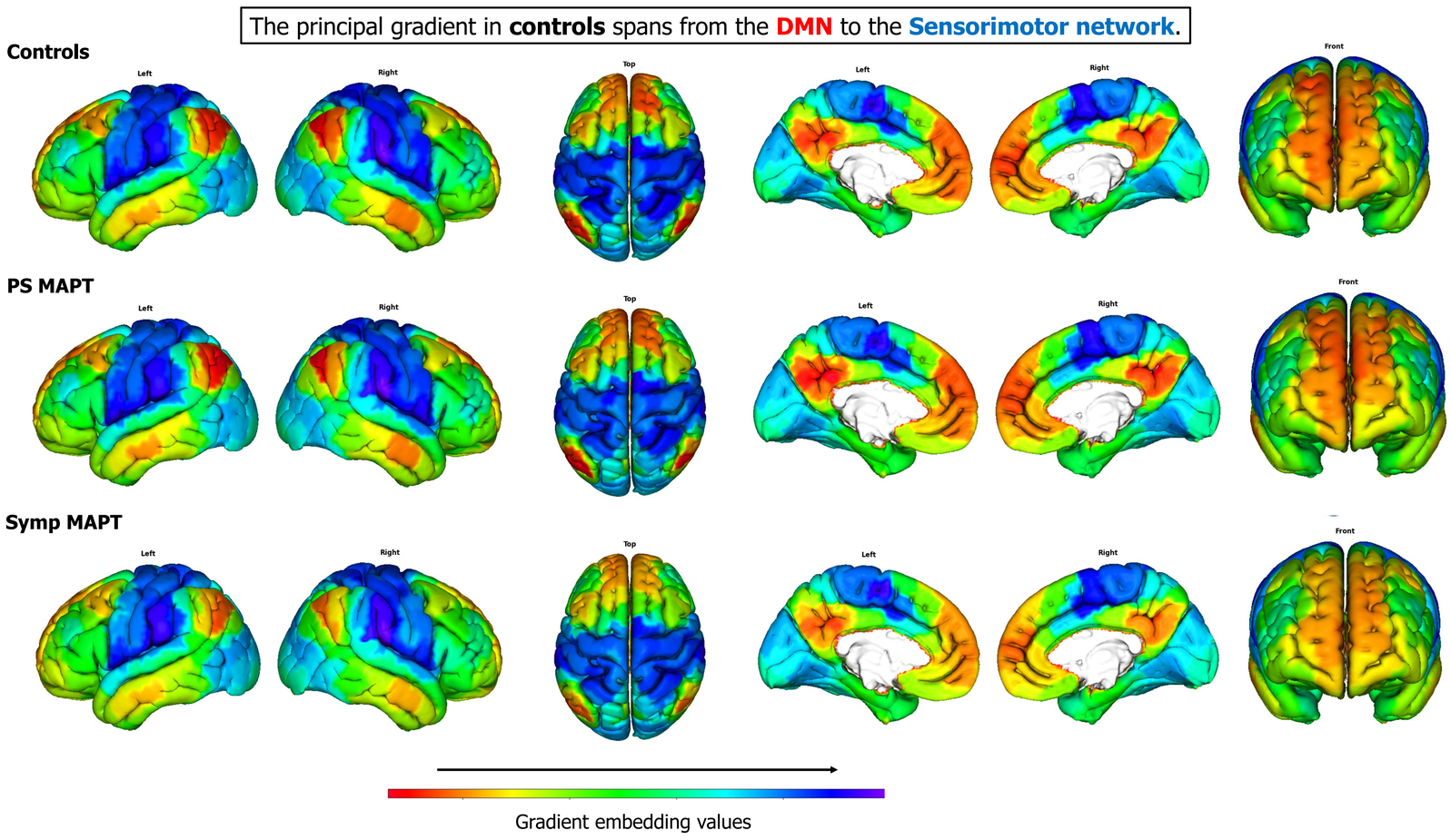

**Step 6:**
Principal gradient's relationship with cognitive function



## RESULTS

### 1. Principal gradient

The principal gradient in **controls** spans from the **DMN** to the **Sensorimotor network**.




### 2. Principal gradient network-level group differences

**Mixed model** comparing parcel principal gradient values in PS and Symp MAPT groups to controls within each network, adjusted **for age, sex and mutation type.**

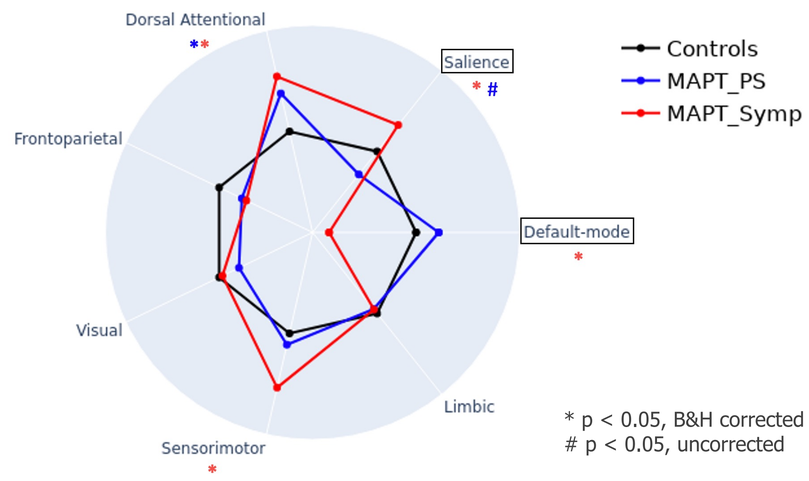


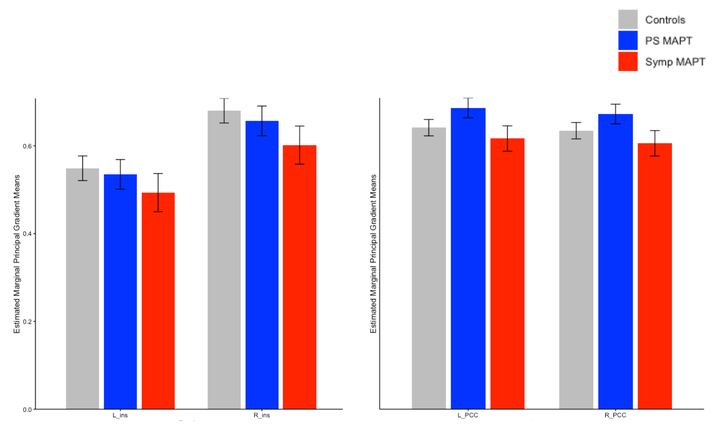

Diagram showing mean z-score principal gradient values for each network in PS and Symp MAPT groups based on control group.

- Symp MAPT show significantly different principal gradient values compared to controls within Dorsal Attentional, Salience, Default-mode and Sensorimotor networks (p<0.044, B&H corrected).
- PS MAPT show early significant changes in the Dorsal Attentional network in the direction of changes found in Symp MAPT (p=0.015, B&H corrected).
- PS MAPT show an opposite pattern of early changes compared to Symp MAPT for the Salience (p=0.024, uncorrected) and Default-mode (p=non-sig) networks.

### 3. Principal gradient parcel group differences

Principal gradient values of parcels within core hubs of Salience (bilateral insula) and Default-mode (bilateral precuneus/posterior cingulate cortex) networks were averaged.

**Mixed model** comparing PS and Symp MAPT groups to controls for each of these core hubs, adjusted for age, sex and mutation type.




Mean principal gradient values for each hub across groups.

- None of the group comparisons reached statistical significance but trends can be observed.
- On average, neither the left or right insular is the hub causing PS MAPT to show a reverse Salience pattern change compared to Symp MAPT.
- On average, the precuneus/posterior cingulate cortex hub does suggest involvement in the overall DMN pattern reversal in PS MAPT compared to Symp MAPT.

## CONCLUSIONS

**Segregation** of unimodal and transmodal networks is essential for **cognitive function** and is overall well maintained even in disease.

**Disrupted network hierarchy** found in **Symp MAPT**
→ significant shift of extreme end networks (Sensorimotor & DMN) towards the centre, consistent with previous findings of a constriction of connectivity space in other clinical populations
→ significant changes of middle networks (Salience & Frontoparietal) showing changes within the hierarchy

**PS MAPT** showed **early significant changes** compared to controls in **Dorsal Attentional network**
→ this is a new finding which has not been previously reported
→ gradient mapping identifies network changes in both groups which other frameworks have not put forward before

**PS MAPT** mutation carriers **didn't always show network changes in the direction of Symp MAPT** (Salience & DMN)
→ the core DMN hub involving the precuneus/posterior cingulate cortex may drive such findings suggesting a heightened network hierarchy which could be a compensatory mechanism prior to symptom onset

## PERSPECTIVES

Our findings in PS MAPT may result from neurodevelopmental effects rather than compensatory mechanisms: PS MAPT < 30 years old have been found to show **higher TIV & cognition** (Finger et al., 2022).

**Potential for early disease identification and predicting treatment outcomes** in **therapeutic studies** requires further investigation: longitudinal, larger samples and in other genetic groups.

Investigating **between different mutations is needed** as MAPT carriers have been found to show mutation-specific progression patterns (Young et al., 2021).

Get in touch to discuss further!

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## ACKNOWLEDGMENTS

FONDATION RECHERCHE ALZHEIMER
FRANCE ALZHEIMER & MALADIES APPARENTÉES
SORBONNE UNIVERSITÉ