Evidence for Functional Connectivity Pattern Changes in Frontotemporal Dementia Patients using Connectome Gradient Mapping

Bouzigues, A[1,2]., Le Du, V.[1], Godefroy, V.[1], Russell, L.L.[2], Batrancourt, B.[1], Levy, R.[1,3], Margulies., D.S.[4,5], Rohrer, J.D.[2], Migliaccio, R.L.[1,3]

[1] Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
[2] Dementia Research Centre, Queen Square Institute of Neurology, University College London, London, United Kingdom
[3] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Neurology, IM2A, Paris, France
[4] Université de Paris, CNRS, Integrative Neuroscience and Cognition Center, Paris, France
[5] Wellcome Centre for Integrative Neuroimaging, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

Background

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 principle gradient, which explains the most variance in connectivity, **separates immediate environment sensory processes from transmodal integration processes** (Figure 1).

This project applied gradient mapping to 3 subtypes of frontotemporal dementia patients; **behavioural variant (n=38), semantic variant (n=17) and non-fluent variant (n=18)**, compared with **controls (n=54)**.

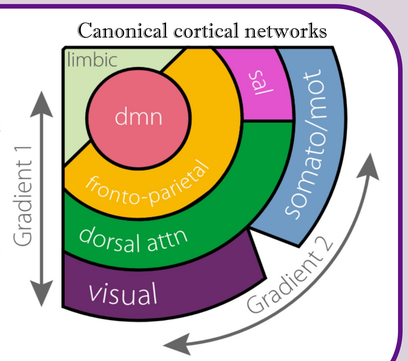
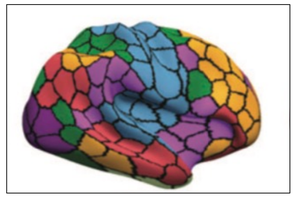


Figure 1 from Margulies et al., 2016

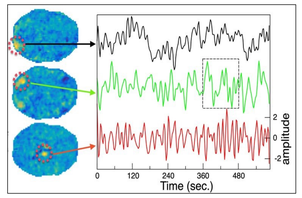
Methods

Whole-brain connectome gradient mapping pipeline

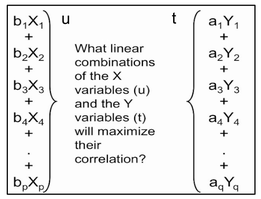
Step 1:
Cortical parcellation
Schaefer atlas – 400 parcels



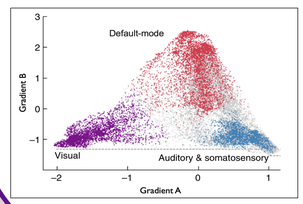
Step 2:
resting-state fMRI timeseries extraction
Confounds correction



Step 3:
Generalised Canonical Correlation Analysis

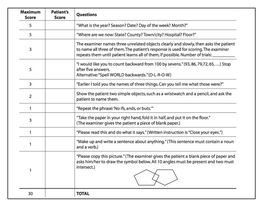


Step 4:
Gradient embedding values in continuous connectivity space



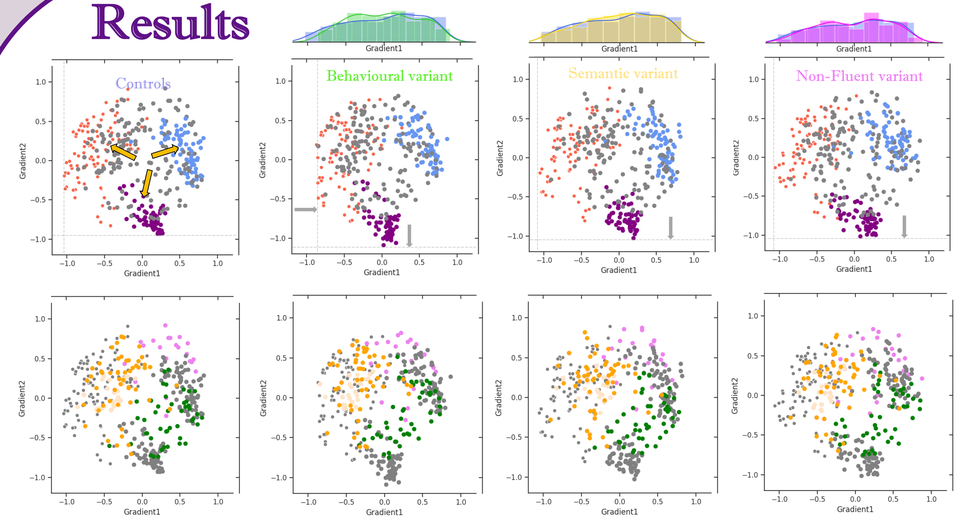
Step 5:
Parcelwise group comparisons
Linear regressions - FDR corr

Step 6:
Gradients and cognitive function relationship - MMSE



Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: ____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)
30		TOTAL

Results



Default-mode
Somatomotor
Visual

Scatter plots of the first two cortical connectome gradients' embedding values in each of the 3 patient groups compared with controls.

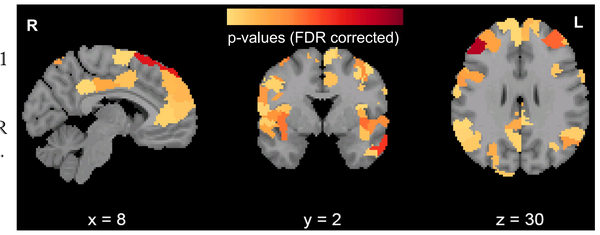
The 400 points represent 400 cortical regions, colour-coded according to the Yeo et al., 2011 canonical networks.

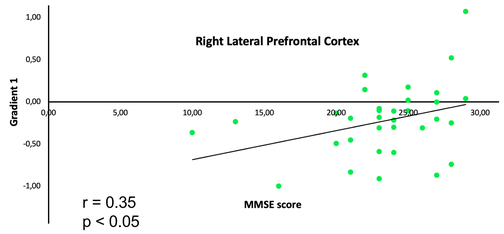
Maximal segregation of default-mode from visual /somatomotor networks can be observed.

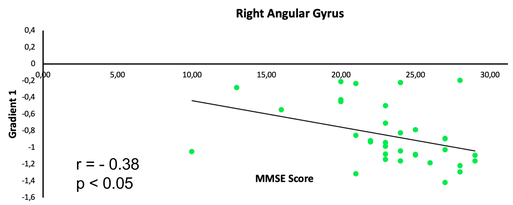
Frontoparietal
Dorsal attentional
Salience
Limbic

Parcels with a significantly different embedding value along gradient 1 in behavioural variant patients compared with controls.

Regression models were adjusted for age and sex. P-values were FDR corrected using Benjamini & Hochberg method (adjusted $p < 0.0029$).







Cortical regions found to correlate with MMSE scores in behavioural variant patients using Pearson's correlations.

Conclusions

Patients with frontotemporal dementia show evidence of **network hierarchy changes.**

Though previous work finds an extension of the **principle gradient** in clinical groups, we find it to be **contracted in our behavioural variant patients**. Moreover, the **second gradient was extended in all our patient groups.**

Such changes in behavourial variant patients were related to **cognitive function**. More work is needed to confirm which cognitive subdomains are mostly related to these functional connectivity changes.

Future directions will involve investigating whether **presymptomatic individuals** show early cortical hierarchy changes and how these evolve with time.

References

Margulies, D.S., Ghosh, S.S., Goulas, A., Falkiewicz, M., Huntenburg, J.M., Langs, G., Bezgin, G., Eickhoff, S.B., Castellanos, F.X., Petrides, M. and Jefferies, E., 2016. Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proceedings of the National Academy of Sciences*, *113*(44), pp.12574-1257.

Mesulam, M.M., 1998. From sensation to cognition. *Brain: a journal of neurology*, *121*(6), pp.1013-1052.

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R. and Fischl, B., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of neurophysiology*.

Scan this for my contact details:

Thank you to my PhD funders:

FONDATION RECHERCHE ALZHEIMER
RECONNUE D'UTILITÉ PUBLIQUE