A LONGITUDINAL STUDY OF THE TASK-RELATED ACTIVATION TRAJECTORY IN PEOPLE WITH MILD COGNITIVE IMPAIRMENT AND SUBJECTIVE COGNITIVE DECLINE

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INTRODUCTION

- Brain hyperactivation - defined as higher level of activation compared to controls - was suggested as a very early signature of prodromal Alzheimer's disease (AD). Hyperactivation would gradually decrease as the patient progresses to dementia.
- Thus, task-related activation follows a non-linear inverse U-shape trajectory as the disease progresses (Clément and Belleville, 2010, 2012; Corriveau-Lecavalier et al., 2021).
- However, prior studies have mostly relied on a cross-sectional design and focused on the study of mild cognitive impairment (MCI), or AD.
- Studying adults with subjective cognitive decline (SCD) provides an opportunity to explore brain changes at an earlier stage of the disease, while symptoms are very subtle.
- **Longitudinal studies** in people with MCI, but also with SCD, can be used to capture the temporal dynamics and inter-individual differences of these very early activation changes.

OBJECTIVE: Identify the temporal trajectory of task-related activation in participants with SCD and MCI from the CIMA-Q cohort, where data has been collected at two or more time points.

Participant Characteristics:

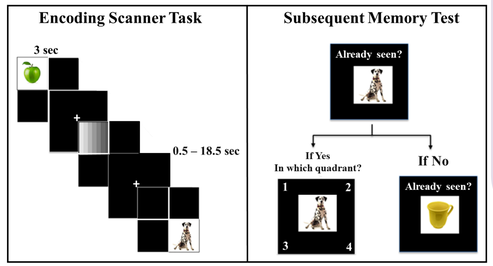
	Baseline N=53	Follow-up 2 years N=50	Follow-up 4 years N=22
Age (years)	72,6 (4,4)	74,8 (4,4)	77,6 (4,6)
Education (years)	15,6 (3,6)	15,4 (3,6)	15,9 (2,6)
Diagnosis (SCD/MCI)	40/13	39/11	14/8
Sex (female/male)	36/17	35/15	22/9
MoCA (/30)	26,9 (2,1)	27,1 (2,5)	26,6 (2,4)
MMSE (/30)	24,8 (1,1)	24,5 (1,7)	24,0 (1,7)
fMRI Associative Memory Score	0,6 (0,1)	0,6 (0,2)	0,7 (0,2)

Note:
SCD: subjective cognitive decline.
MCI: mild cognitive impairment.
MoCA: Montreal Cognitive Assessment.
MMSE: The Mini-Mental State Examination.
Means and standard deviations are reported for continuous variables.

METHODS

Neuroimaging Data Acquisition:

- **Data collection:** Every two years (2-3 time-points; baseline, 2-year and 4-year follow-up).
  - ✓ *Average follow-up:* 3.2 years.
- **Brain imaging**: Anatomical 3D-T1-W and task-related fMRI:
  - ✓ Hippocampal volume was measured with FreeSurfer 5.3.
  - ✓ fMRI data collected during encoding was analyzed in a rapid event-related design with SPM12. Beta values were extracted using the MarsBar toolbox
- **fMRI contrast:**
  correct source > control
- **Associative memory score:**
  - CS/(Hit+FA)



- **Correct Source (CS):** Item and its position were correctly identified.
- **Wrong Source (WS):** Item was recognized but not its position.
- **Correct Recognition (Hit):** Items correctly identified (CS+ WS)
- **False Alarm (FA):** A new item was falsely recognized

Statistical Analyses:

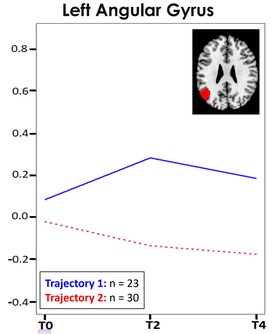
A group-based trajectory model (a specialized application of finite mixture modeling designed to identify clusters of individuals who follow similar trajectories) was estimated to identify groups of participants based on their common activation trajectories in the hippocampus and in specific cortical areas known to be affected by AD.

ApoE4 status, baseline cognition and hippocampal volume were then compared in groups defined by their activation trajectories (independent t-tests for continuous variables and chi-squares for categorical variables).

RESULTS

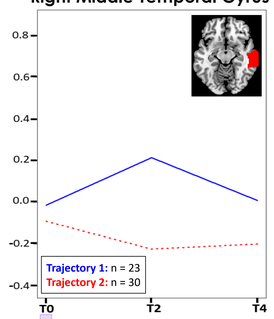
Two different trajectories of activation were identified, which evolve in opposite directions over time:
Trajectory 1: characterized by an inverted U-shape trajectory with **an initial increase in activation leading to hyperactivation at T2, followed by a decrease** over time.
Trajectory 2: characterized by a **lower overall activation level**, which remains stable over time or decreases slightly.

Left Angular Gyrus



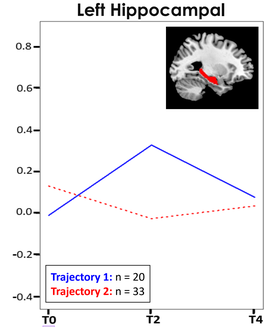
Participants in **trajectory 1** have a smaller hippocampal volume (HV) than participants in **trajectory 2**
(HV trajectory 1: -0.38 < HV trajectory 2: 0.04;$t_{(50)} = -2.5$, $p < 0.015$)

Right Middle Temporal Gyrus



There is larger proportion of ApoE4 carriers in **trajectory 1** than **trajectory 2**.
(X2: 5.006, p = 0.025)

Left Hippocampal



There is larger proportion of ApoE4 carriers in **trajectory 2** than **trajectory 1**
(X^2: 5.759, $p = 0.029$)

CONCLUSIONS

An inverted U-shape trajectory was found with high activation followed by a gradual decrease in activation in AD-signature regions. This trajectory in the medial temporal lobe and angular gyrus was associated with a smaller hippocampal volume and/or the presence of the ApoE4 allele, both of which are biomarkers that increase the likelihood of developing AD. In turn, the ApoE4 allele was associated with a slowly decreasing activation in the hippocampus, perhaps reflecting the descending portion of the inverse U-shape in this region.

This finding supports the hypothesis that the inverted U-shape trajectory of hyperactivation could be an index of prodromal AD

References

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