Hippocampal intrinsic connectivity supports cognitive reserve in amyloid-positive cognitively normal subjects and Alzheimer's disease patients

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Background

Cognitive reserve (CR) accounts for the adaptation of cognitive processes in the phase of brain pathology [1]. CR can be estimated by means of surrogate measures such as years of education or occupation. Recently, the residual approach was introduced as a more direct and dynamic measure of CR. This approach considers the variance in cognition not being explained by demographic and neuroimaging predictors as CR measure (Figure 1) [2]

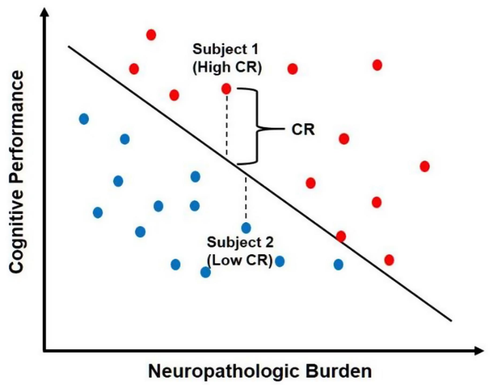


Figure 1 – Example of residuals relating to a subject with high CR (red) and low CR (blue). Lee et al., 2018

Aim

To determine a functional neuronal correlate of CR from resting-state functional MRI (rs-fMRI) using the residual approach on amyloid PET imaging and demographic data?

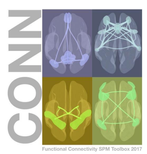
Participants & Data Processing

	AmyNeg CN (n= 46)	AmyPos CN (n=57)	Early AD (n=31)
Age	71.20 (6.3)	72.67 (5.6)	75.32 (7.1)
Sex (M/F)	24/22	20/37	16/15
MMSE	28.76 (1.4)	28.81 (1.2)	25.77 (2.7)
Education	15.67 (2.8)	15.93 (2.6)	13.97 (3.2)
[18F]AV45	1.01 (.02)	1.40 (.33)	1.71 (.29)

Table 1 – Demographics (Mean, SD). Data from OASIS 3 for subjects with baseline & follow-up fMRI, [18F]AV45 scan & neuropsycho. data. AmyNeg/Pos = amyloid negative/ positive, CN =cognitively normal, AV45 = Florbetapir (SUVr)

Functional MRI:

- fMRI images were normalized to MNI space using SPM12
- Intrinsinc connectivity (IC) maps were derived using the Conn toolbox
- Beta images were submitted to SPM analysis



Positron Emision Tomography (PET):

- Preprocessed [18F]AV45 were extracted
- SUVr values for global cortical amyloid load were computed based on Freesurfer ROIs

Methods

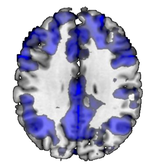
Residual Approach:

Cognition estimated =

$$\beta 0 + \beta 1_{A\beta\_global} + \beta 2_{Age} + \beta 3_{Sex} + \beta 4_{ApoE4}$$

Cognition Residuals =

$$\text{Cognition}_{observed} - \text{Cognition}_{estimated} / SD$$



Statistical Analysis:

- Whole-brain voxel-wise regression analysis with IC maps in amyloid-positive group and residuals
- Subgroup analysis: AmyPos CN vs. Early AD
- Correlation between education and residuals

Results

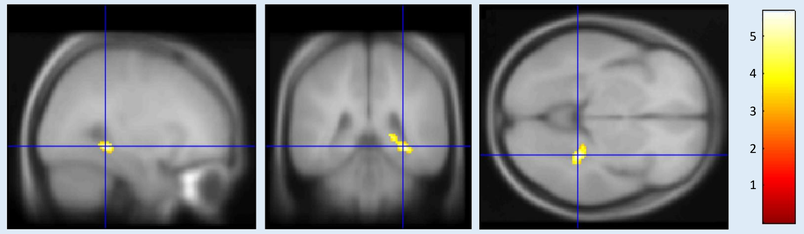
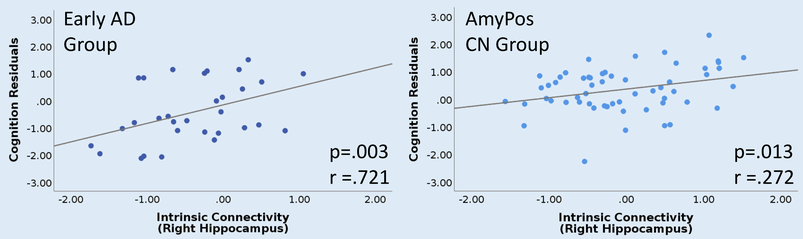


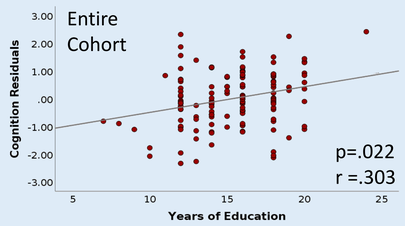
Figure 2 – Positive association between residuals of the early AD group and intrinsic connectivity in the right hippocampus

Increased intrinsic connectivity of the right hippocampus associated with higher CR (i.e., cognition residuals) in amyloid- positive, but not in amyloid-negative subjects

Stronger association in early AD group than amyloid-positive cognitively normal subjects



Years of education positively related with cognition residuals



Conclusion

- ✓ **Intrinsic hippocampal connectivity might contribute to CR seen in both preclinical and clinical phases of AD with greater contribution in clinical cases of AD**
- ✓ **The residual approach proves to be sensitive to compensatory effects of intrinsic connectivity in the face of AD-pathology and is associated with level of education**

Academic partners | SMEs | Industrial partners | Patient organisation

References

1. Stern et al. *Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance.* Alzheimer's Dementia, 2018
2. Lee et al. *Neural substrates of cognitive reserve in Alzheimer's disease spectrum and normal aging.* NeuroImage, 2019

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Acknowledgement: This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115952. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.