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The metabolic brain signature of cognitive resilience in the 80+: beyond Alzheimer pathologies

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Research into cognitive resilience imaging markers may help determine the clinical significance of Alzheimer's disease pathology among older adults over 80 years (80+). In this study, we aimed to identify a fluorodeoxyglucose (FDG)-PET based imaging marker of cognitive resilience. We identified 457 participants ⩾ 80 years old (357 cognitively unimpaired, 118 cognitively impaired at baseline, mean age of 83.5 ± 3.2 years) from the population-based Mayo Clinic Study of Aging (MCSA) with baseline MRI, Pittsburgh compound B-PET and FDG-PET scans and neuropsychological evaluation. We identified a subset of 'resilient' participants (cognitively stable 80+, $n = 192$) who maintained normal cognition for an average of 5 years (2–10 years). Global PIB ratio, FDG-PET ratio and cortical thickness from Alzheimer's disease signature regions were used as Alzheimer's disease imaging biomarker outcomes and global cognitive z-score was used as a cognitive outcome. First, using voxel-wise multiple regression analysis, we identified the metabolic areas underlying cognitive resilience in cognitively stable 80+ participants, which we call the 'resilience signature'. Second, using multivariate linear regression models, we evaluated the association of risk and protective factors with the resilience signature and its added value for predicting global cognition beyond established Alzheimer's disease imaging biomarkers in the full 80+ sample. Third, we evaluated the utility of the resilience signature in conjunction with amyloidosis in predicting longitudinal cognition using linear mixed effect models. Lastly, we assessed the utility of the resilience signature in an independent cohort using ADNI ($n = 358$, baseline mean age of 80 ± 3.8). Our main findings were: (i) FDG-PET uptake in the bilateral anterior cingulate cortex and anterior temporal pole was associated with baseline global cognition in cognitively stable 80+ (the resilience signature); (ii) established Alzheimer's disease imaging biomarkers did not predict baseline global cognition in this subset of participants; (iii) in the full MCSA 80+ and ADNI cohorts, amyloid burden and FDG-PET in the resilience signature were the stronger predictors of baseline global cognition; (iv) sex and systemic vascular health predicted FDG-PET in the resilience signature, suggesting vascular health maintenance as a potential pathway to preserve the metabolism of these areas; (v) the resilience signature provided significant information about global longitudinal cognitive change even when considering amyloid status in both the MCSA and ADNI cohorts. The FDG-PET resilience signature may be able to provide important information in conjunction with other Alzheimer's disease biomarkers for the determination of clinical prognosis. It may also facilitate identification of disease targeting modifiable risk factors such as vascular health maintenance.

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Abbreviations: CMC = cardiac metabolic chronic condition; FDG = fluorodeoxyglucose; PIB = Pittsburgh compound B

Introduction

As the Alzheimer's disease research field moves towards a biological definition of the disease (Jack *et al.*, 2018) parallel efforts are needed to define the biological basis and neural correlates of cognitive resilience. This will help clarify the clinical significance of Alzheimer's disease pathology seen by *in vivo* biomarkers and provide mechanistic insights into the development of alternative therapeutic approaches such as lifestyle interventions.

The 'cognitive resilience' paradigm stems from the observation of the disconnect between pathology and cognition, i.e. normal cognition in the presence of Alzheimer's disease pathology. This disconnect occurs in a significant proportion of the elderly, evidenced by neuropathology, PET imaging and CSF findings (Mintun *et al.*, 2006; Pike *et al.*, 2007; Aizenstein *et al.*, 2008; Price *et al.*, 2009; Rowe *et al.*, 2010). Along with the exponential increase in the prevalence of Alzheimer's disease pathology and Alzheimer's disease dementia with age (Corrada *et al.*, 2008; Jack *et al.*, 2017*a*, *b*), the pathology–cognition disconnect also becomes more marked with increasing age, such that ~50% of older adults over 80, referred to as the oldest old in the literature, show normal cognition despite significant Alzheimer's disease pathology (Crystal *et al.*, 1988; Katzman *et al.*, 1988; Price *et al.*, 2009; Balasubramanian *et al.*, 2012; Bennett *et al.*, 2012; Corrada *et al.*, 2012; Mathis *et al.*, 2013). Longitudinal imaging and neuropathology studies have reported subtle or no correlation between Alzheimer's disease pathology and cognitive trajectories in cognitively unimpaired oldest old, raising further questions about the clinical significance of Alzheimer's disease pathology in this group (Savva *et al.*, 2009; Balasubramanian *et al.*, 2012; Snitz *et al.*, 2013). Overall, these results provide the basis for research into additional factors and mechanisms that may support cognition and play a role in the clinical expression of Alzheimer's disease pathology at older ages.

Among the oldest old, those who maintain normal cognition may represent a subgroup who experience 'successful' cognitive ageing, potentially protected from dementia, and thus provide a model to identify brain mechanisms underlying cognitive resilience. Brain mechanisms underlying cognitive resilience may include: (i) varying tolerance/resilience to pathological changes; (ii) varying resistance to pathological changes; and/or (iii) maintenance or preservation of key brain regions sustaining cognition (Arenaza-Urquijo and Vemuri, 2018). Recent efforts have focused on the first two set of mechanisms using imaging and CSF biomarkers (Hohman *et al.*, 2016; Rentz *et al.*, 2017; Carvalho *et al.*, 2018). Research using surrogate markers of cognitive resilience and reserve suggests, however, that resilience mechanisms and Alzheimer's disease pathology may independently contribute to cognition (Vemuri *et al.*, 2011; Gidicsin *et al.*, 2015; Soldan *et al.*, 2017), providing support for mechanism (iii) described above. Even though regions primarily not targeted by the disease may be crucial in supporting cognition at older ages, little research has been aimed at identifying these cognitive resilience markers. Emerging evidence from neuropathology studies support synaptic markers as measures of resilience to Alzheimer's disease pathology at the cellular level (Perez-Nievas *et al.*, 2013; Boros *et al.*, 2017), and thus fluorodeoxyglucose (FDG)-PET would be a good imaging candidate for investigating and quantifying cognitive resilience.

The overall aim of the present study was to advance our knowledge about the mechanistic underpinnings of cognitive resilience in older adults 80 years and older (80+). Using FDG-PET imaging, we wanted to identify brain areas that (i) are supportive of cognition in cognitive resilient 80+ participants; (ii) are associated with protective/risk factors; and (iii) add predictive value in explaining cognitive performance beyond established Alzheimer's disease biomarkers. We posit that such brain regions may be useful candidate markers for cognitive resilience.

We conducted analyses in three broad steps: First, on the basis that old age and maintenance of normal cognitive performance is consistent with cognitive resilience and potentially successful cognitive ageing, we focused on a group of cognitively stable 80+ subjects. Here, using voxel-wise analysis of FDG-PET scans, we identified brain metabolic regions that supported cognition in this subset of participants. Then we investigated protective/risk factors as potential predictors of the metabolism of these regions and evaluated their added value to predict baseline cognition in the full 80+ sample beyond established Alzheimer's disease imaging biomarkers [Pittsburgh compound B (PIB)-PET, FDG-PET and cortical thickness]. Finally, we assessed the utility of these regions to predict longitudinal global cognitive change in conjunction with amyloidosis.

Materials and methods

Selection of participants

Participants for this study were selected from the Mayo Clinic Study of Aging (MCSA), a population based study started in

2004 among Olmsted County, Minnesota residents aged 70–89. The Olmsted County population was enumerated using the Rochester Epidemiology medical records linkage system (Rocca *et al.*, 2012; Sauver *et al.*, 2012). Details about study design and clinical diagnostic criteria are discussed elsewhere (Roberts *et al.*, 2008; Petersen *et al.*, 2010). For the present study, we included all participants 80 years and older who had a baseline amyloid and FDG-PET scan, had completed the full neuropsychological battery and were in the Alzheimer's disease cognitive spectrum (cognitively unimpaired, mild cognitive impairment or probable Alzheimer's disease).

Defining cognitive resilience as stable normal cognition in the 80+ population

In this study, we define 'cognitive resilience' as maintaining normal cognition or cognitively unimpaired status at very old age. We refer to this group of participants as cognitively stable 80+ (see the selection chart in Fig. 1). As compared to resilience to Alzheimer's disease pathology, the definition of cognitive resilience here does not rely on Alzheimer's disease biomarkers but relies on the notion of cognitive stability in the face of 'risk', age in this case (Kaup *et al.*, 2015; Arenaza-Urquijo and Vemuri, 2018). Given the high prevalence and incidence of dementia in the 80+ population, a longitudinal criterion for 'cognitive stability' seems necessary to exclude individuals with higher probabilities to progress to mild cognitive impairment and dementia. The importance of including longitudinal approaches to investigate successful cognitive ageing has been previously highlighted (Fiocco and Yaffe, 2010).

A study participant was considered cognitively stable when they presented a stable cognitively unimpaired diagnosis during follow-up visits, i.e. no progression to mild cognitive impairment or dementia. We only considered participants with a minimum clinical follow-up of two visits after the baseline visit. Cognitively stable 80+ participants had remained cognitively normal for 5 years as an average, ranging from 2 to 10 years. The current approach has an advantage of including a resilient group of participants who do not develop cognitive impairment during follow-up visits in the study. A disadvantage is that we do know whether a participant will develop cognitive impairment beyond the clinical follow-up. See Supplementary Fig. 1 for further details.

The full sample of 80+ cognitively unimpaired and impaired at baseline participants were used for subsequent analyses aiming (i) to evaluate the robustness of the imaging findings with increasing sample size and inclusion of cognitively unimpaired at baseline 80+ participants; and (ii) to assess the utility of the imaging marker in the full 80+ sample. The demographic characteristics of the full 80+ group and cognitively stable 80+ subsample are provided in Table 1.

Standard protocol approvals, registrations and patient consent

The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards and informed consent was obtained from all participants or their surrogates.

FDG-PET scan preprocessing

FDG-PET images were preprocessed using our in-house automated image processing pipeline (Jack *et al.*, 2008). In brief, FDG-PET scans were scaled by the signal in the pons to create standardized uptake value ratio (SUVR) images and spatially normalized using SPM12 to the in-house template (Schwarz *et al.*, 2017) via their co-registered MRI scan. These FDG-PET maps were then smoothed at 6 mm full-width at half-maximum and entered as dependent variables into voxel-wise multiple regression models using SPM12, as described below.

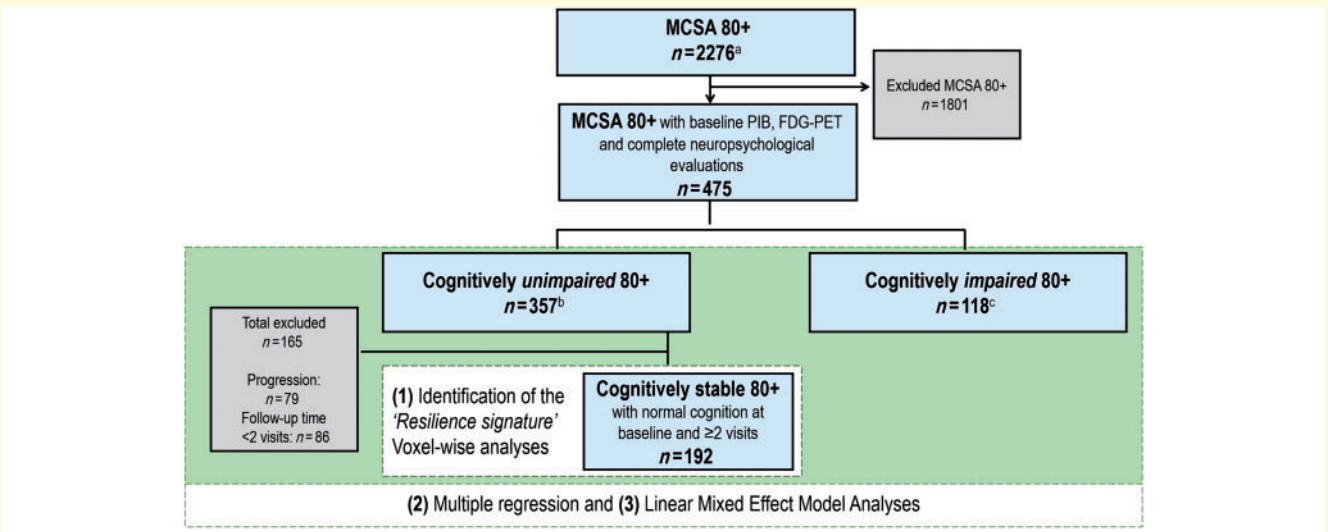

Figure 1 Selection and analyses chart. [a]MCSA imaging visit during time period 1 May 2006–31 July 2017. [b,c]Forty-eight cognitively unimpaired and impaired participants did not have follow-up visits and were not considered for the linear mixed effect model. Thus the mixed effect model included $n = 427$ and 1586 observations. Labels 1–3 indicate the statistical analyses performed.

Table 1 Demographic characteristics of the 80+ sample

	Full 80+ sample ($n = 475$)[a] Mean (SD)	Cognitively stable 80+ ($n = 192$) Mean (SD)
Age	83.5 (3.21)	82.7 (2.8)
Sex, % male	58	53
Education, years	14.4 (2.99)	14.8 (2.81)
Vascular risk (CMC)	2.74 (1.5)	2.7 (1.5)
Global cognition z-score	−0.74 (1.2)	−0.007 (0.79)
Amyloid positive, %	59	47
APOE4 positive, %	27.2	20

Characteristics of the cognitively stable subset of participants are provided separately.
[a]Of the full sample, 25% were cognitively impaired.
CMC = cardiac metabolic chronic conditions score.

Quantification of Alzheimer's disease biomarkers

Details of the acquisition, processing and summary measure for Alzheimer's disease signatures for amyloid PET, FDG-PET and MRI computed on the MCSA study participants are discussed previously (Lowe *et al.*, 2009; Jack *et al.*, 2017*a*, *b*).

Global cortical PIB-PET retention ratio

A global cortical PIB-PET retention ratio was computed by calculating the median uptake over voxels in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest for each subject and dividing this by the median uptake over voxels in the cerebellar grey matter region of interest of the atlas (Lopresti *et al.*, 2005) and was used as an amyloid biomarker. We classified subjects as being on the amyloid pathway (amyloid-β-positive or Alzheimer's disease pathophysiology) if their global cortical PIB-PET SUVR was $\geqslant 1.42$.

Global FDG-PET ratio measure

A global FDG-PET ratio measure was computed for each individual scan by averaging the left and right angular gyri, bilateral posterior cingulate and left middle/interior temporal gyrus pons-normalized SUVR values for each participant as described previously (Landau *et al.*, 2011) and was used as an FDG-based Alzheimer's disease biomarker.

Global cortical thickness measure

A global cortical thickness measure was computed using FreeSurfer (v.5.3)-derived temporal lobe cortical thickness composite reporter region of interest of entorhinal, inferior temporal, middle temporal, and fusiform regions of interest (Jack *et al.*, 2017*a*, *b*) from 3 T MPRAGE scans and was used as an MRI-based Alzheimer's disease biomarker.

Global cognition variable

All study participants underwent a neuropsychological evaluation designed for the MCSA study, as described previously (Roberts *et al.*, 2008; Petersen *et al.*, 2010). For the present analyses we used a global cognitive z-score as a cognitive outcome variable which is a z-transformation of the average of nine tests covering four domain z-scores (executive function, language, memory, and visuospatial performance) (Vemuri *et al.*, 2014).

Risk and protective factors: intellectual enrichment and vascular health

We assessed intellectual enrichment and systemic vascular health indicators as potential predictors of the resilience signature. Intellectual enrichment was measured using years of education and midlife cognitive activities. We ascertained systemic vascular health by computing a score for cardiac metabolic chronic conditions (CMC) based on electronic health records of the Rochester Epidemiology Project (REP) (Rocca *et al.*, 2012) as a summation of the presence or absence of hypertension, hyperlipidaemia, cardiac-arrhythmias, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke. Here, we dichotomized it based on the median score of 2 (Vemuri *et al.*, 2017*a*).

Statistical analyses

The statistical analyses were conducted using Statistical Parametric Mapping (SPM 12), IBM Statistical Package for Social Science (SPSS) and R packages.

Identifying the brain areas associated with global cognition in the cognitively stable 80+: the resilience signature

In the first set of analyses, we focused on cross-sectional FDG-PET data from cognitively stable 80+ participants to identify specific areas associated with global cognition and evaluated protective and risk factors associated with these areas.

To identify the resilience signature regions supporting global cognition in this group, we performed a voxel-wise multiple regression analysis in SPM 12 with smoothed and normalized FDG-PET maps and z-global cognition scores as the variable of interest. A study-specific grey matter mask was used as an explicit mask for the voxel-wise analysis. The segmented and normalized grey matter maps of the study participants were averaged and thresholded to include voxels with a grey matter probability >0.2. Voxel-wise results were considered significant when false discovery rate (FDR) $P < 0.05$ and a cluster extend of $K > 1500$ mm^3. Anatomical grey matter labels were determined with reference to the Mayo Clinic Adult Lifespan Template (MCALT, Schwarz *et al.*, 2017).

To show the specificity of these results to the cognitively stable 80+ group, we carried out the same analyses in all cognitively unimpaired at baseline 80+ participants. We also ran a complementary two-sample *t*-test voxel-wise analysis to identify brain metabolic areas that differed between participants who developed cognitive impairment during follow-up visits (progressors) and those that remained stable. The objective of the two analyses was to assess the overlap between these areas and areas detected in our primary analyses.

Table 2 Results of the linear multiple regression models to predict global cognition in the cognitively stable subset of participants and the full 80+ sample

Model	Cognitively stable 80+				Full sample 80+			
	R^2 0.23	Beta	CI	*P*	R^2 0.38	Beta	CI	*P*
Intercept[a]		−0.93	−5.5 to 3.6	0.686		−2.3	−6.34 to 0.32	0.077
Demographic variables								
Age[a]		−0.04	−0.08 to 0.002	0.063		**−0.06**	−0.09 to 0.04	**<0.001**
Sex[a]		−1.34	−0.35 to 0.09	0.231		−0.08	−0.26 to 0.11	0.425
Education, years[a]		**0.09**	0.06 to 0.13	**<0.001**		**0.13**	0.11 to 0.17	**<0.001**
APOE4 status[a]		−0.11	−0.38 to 0.17	0.447		−0.04	−0.25 to 0.17	0.728
Imaging variables								
'Resilience signature' FDG-PET[b]		**0.32**	1.32 to 4.05	**<0.001**		**0.20**	1.32 to 3.79	**<0.001**
'Alzheimer's disease signature' FDG-PET[b]		−0.04	−0.87 to 0.47	0.494		**0.11**	0.07 to 1.66	**0.033**
PIB ratio[b]		−0.06	−0.36 to 0.20	0.545		**−0.20**	−0.68 to −0.29	**<0.001**
'Alzheimer's disease signature' cortical thickness[b]		<0.001	−0.95 to 0.95	0.998		**0.11**	0.23 to 1.64	**0.009**

The table allows assessment of the robustness of the results with increasing sample size and inclusion of cognitively impaired 80+. Unadjusted R square, beta coefficients, confidence intervals (CI) for unstandardized betas and *P*-values are provided.
[a]Unstandardized Beta coefficient.
[b]Standardized Beta coefficient.

Demographic and risk or protective factor predictors of the resilience signature

The association between the resilience signature, demographic variables, amyloid status (amyloid-β-positive or -negative) *APOE* E4 genotype, vascular risk (CMC) and intellectual enrichment was assessed. For this statistical analysis and the analyses described below, we extracted a FDG-PET uptake value in the 'resilience signature' for each individual subject in the study, using the subject's normalized and smoothed FDG-PET maps.

Evaluating the added value of the resilience signature for predicting baseline cognition

In the second set of analyses, we assessed and compared the strength of the effect of the resilience signature to the effect of Alzheimer's disease imaging biomarkers to explain baseline global cognition. As pointed out above, with this analysis we aimed to assess the robustness of the results with increasing sample size and including cognitively impaired 80+. We thus fitted a multiple regression model for predicting baseline global cognition including demographic variables (age, sex, education), *APOE* E4 status and imaging variables (resilience signature, PIB ratio, FDG-PET and cortical thickness from the Alzheimer's disease signature) in the subset of cognitively stable 80+ and the full 80+ sample. To allow assessment of the specificity of the results to the cognitively stable group, the same model was fitted in cognitively unimpaired at baseline 80+ participants and is presented in the Supplementary material.

Assessing the utility of the resilience signature in conjunction with amyloidosis

Finally, we evaluated whether FDG-PET uptake in the resilience signature predicted longitudinal change in global cognition in the full 80+ sample, i.e. the full Alzheimer's disease cognitive spectrum, taking into account amyloid status. We fitted a linear mixed effect model with global cognition as a dependent variable and time (age at visit), PIB status, sex, years of education, *APOE* status, and number of visits as fixed effects (predictors). The model included all main effects as well as interactions with time, including our interaction of interest, i.e. the resilience signature FDG-PET uptake by time (age at visit), but also the interactions between PIB, *APOE*, education, sex and time, that we wanted to test and/or control. Random effects for intercept and slopes were included to account for initial differences and different trajectories across participants. A significant interaction of a predictor with time would indicate that the rate of change of global cognition over time differs according to the value of the predictor variable, i.e. according to FDG-PET uptake of the resilience signature. As illustrated in the chart (Fig. 1), the mixed effect model included 333 cognitively unimpaired at baseline 80+ subjcets, 94 cognitively impaired 80+ subjects and a total of 1586 observations.

Assessing the utility of the resilience signature in the ADNI cohort

We performed sensitivity analyses in participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) ($n = 358$). As in the analyses described above, we evaluated whether the FDG-PET resilience signature predicted (i) cross-sectional global cognition over and above Alzheimer's disease biomarkers using multiple linear regression models; and (ii) longitudinal cognitive change after accounting for amyloid status using mixed effect models. See Supplementary material and Supplementary Table 1 for the description of the participants and methods.

Data availability

MCSA data used in this study are not publically available for download.

Results

Established Alzheimer's disease imaging biomarkers do not predict baseline cognition in cognitively stable 80+ participants

As shown in Table 1, 47% and 20% of the cognitively stable 80+ participants were amyloid-positive and *APOE* E4-positive, respectively. Compared to the cognitively stable 80+ participants the percentage of amyloid-β-positive (Pearson chi-square = 11.46, $P = 0.001$) was significantly lower than in the rest of cognitively unimpaired at baseline 80+ while the percentage of APOE4 carriers did not differ (Pearson chi square = 1.07, $P = 0.32$). These results suggest that cognitive stability is possible even with amyloid and *APOE* E4 positivity in the 80+ population.

Among the cognitively stable 80+, education was significantly associated with baseline global cognition and PIB ratio. FDG ratio or cortical thickness from Alzheimer's disease signature regions did not predict baseline cognition. These results support our hypothesis that other regions may be fundamental to sustain global cognition in this subset of 80+ participants defined as 'cognitively resilient'.

The resilience signature: bilateral anterior-mid cingulate, medial prefrontal and anterior temporal lobes

Voxel-wise multiple regression analyses showed that global cognition was positively associated with FDG-PET uptake in the bilateral anterior-mid cingulate gyrus (dorsal and ventral sections of the anterior cingulate) extending to the medial prefrontal cortex (rostral and medial sections), and the bilateral anterior temporal lobes (Fig. 2). Peak coordinates are provided in Supplementary Table 2. The most significant peaks were located in the left temporal pole and left anterior cingulate gyrus. The peak coordinates and cluster size of the significant results are provided in Table 3. Of note, the cognitively stable 80+ group did not show any association between global cognition and the Alzheimer's disease signature regions which supports the multiple regression analyses presented in the previous section.

The two additional analyses outlined in the methods provided support for the specificity of the results detected in the cognitively stable 80+ group. The sensitivity analysis in the cognitively unimpaired at baseline 80+ group showed a widespread association between global cognition and FDG-PET uptake including the Alzheimer's disease signature regions (Supplementary Fig. 2). In the complementary analyses (Supplementary Fig. 3), only posterior cingulate cortex was observed when cognitively stable 80+ subjects were compared to progressors.

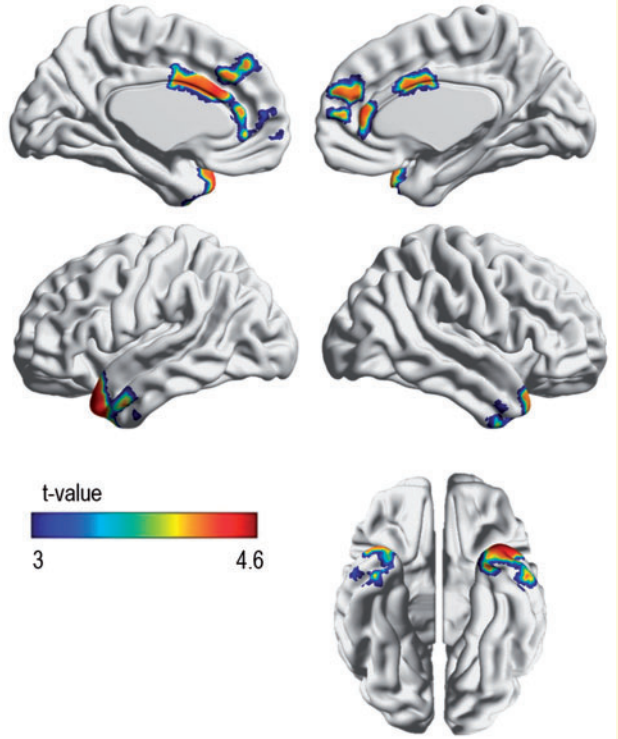

Figure 2 Results from the voxel-wise multiple regression analysis between global cognition and FDG-PET uptake in cognitively stable 80+ participants. Maps were thresholded at FDR $P < 0.05$ and $K > 1500$ mm^3. Note the lack of association between cognition and FDG in Alzheimer's disease signature regions.

Table 3 Results of the mixed effect model to predict global cognitive change in the 80+ sample

	Beta	CI	*P*
Intercept	18.70	7.16 to 30.24	0.002
Time, age at visit	−0.29	−0.40 to −0.16	<0.001
Sex	−2.06	−3.79 to −0.33	0.02
Education, years	0.21	−0.06 to 0.49	0.13
APOE4 status	0.91	−1.22 to 3.04	0.28
'Resilience signature' FDG-PET	−11.58	−20.92 to −2.24	0.015
PIB status	6.91	5.21 to 8.61	<0.001
Number of visits	0.03	−0.001 to 0.06	0.057
Sex × time	0.02	0.003 to 0.043	**0.027**
Education, years × time	−0.001	−0.06 to 0.49	0.50
APOE4 status × time	−0.01	−0.03 to 0.011	0.28
'Resilience signature' FDG-PET × time	0.17	0.07 to 0.28	**0.002**
PIB status × time	−0.08	−0.10 to −0.07	**<0.001**

Beta coefficients, confidence intervals (CI) for unstandardized Betas and *P*-values are provided.

Systemic vascular health is associated with the resilience signature

Early or midlife intellectual enrichment variables were not significantly associated with FDG-PET uptake in the resilience

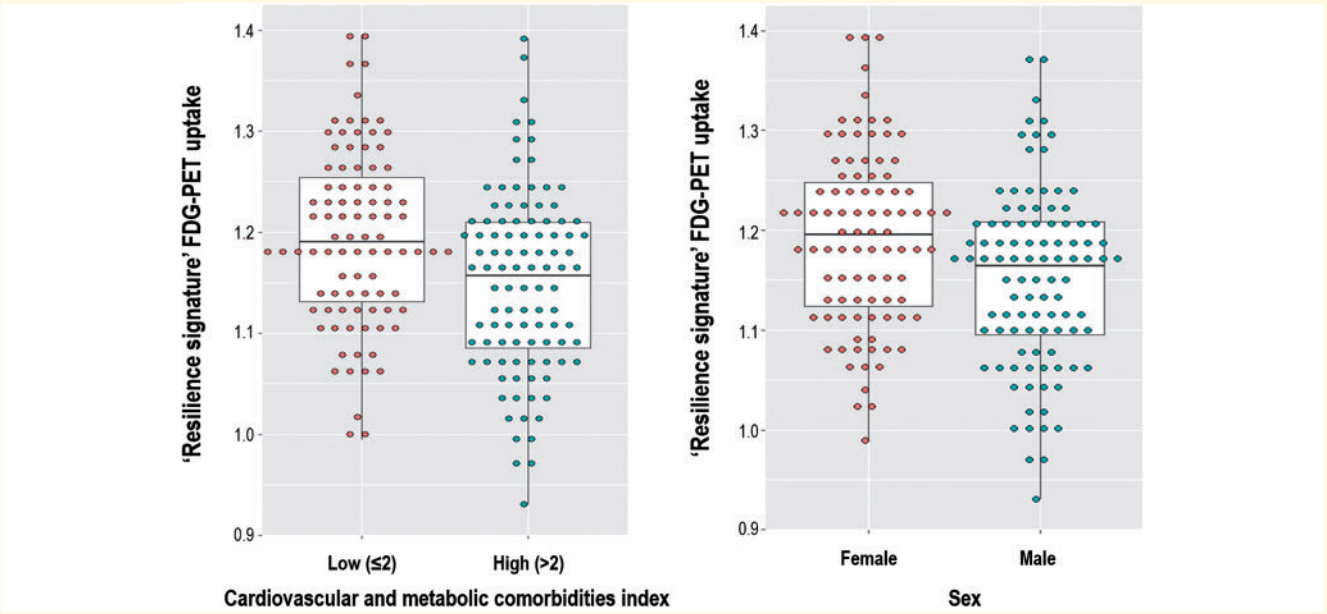

Figure 3 Vascular health and sex effects on the resilience signature. Box plots showing the effect of CMC (high versus low; *left*) and sex (*right*) on the resilience signature.

signature (years of education: t = 0.48, $P = 0.64$; midlife cognitive activity: t = −0.30; $P = 0.76$). However, lower vascular risk (CMC high versus low) was associated with higher FDG-PET uptake in the resilience signature (t = 2.61; $P = 0.02$). Examining demographic variables, women had greater metabolism in this area (t = −2.33; $P = 0.02$) but there was only a marginal effect of age (t = 1.8; $P = 0.07$) (Fig. 3). Further analyses with high ($n = 101$) versus low ($n = 91$) CMC groups showed that the CMC groups differed in sex and years of education such that the lower CMC group had more years of education (high CMC = 14.33 years ± 2.79; low CMC = 15.35 years ± 2.76; t = −2.55; $P = 0.01$) and included a lower proportion of males (high CMC = 66 males/101; low CMC 34 males/91; Pearson chi-square = 15.02; $P < 0.001$).

Neither amyloid nor the presence of an *APOE* E4 allele was associated with metabolism in this area and voxel-wise analyses adjusting for these two covariates showed that the association between FDG-PET in the resilience signature and global cognition was similar in each group (Figs 4–6 and Supplementary Table 3). Further, FDG-PET uptake in the resilience signature was higher in the cognitively stable 80+ as compared to the rest of cognitively unimpaired at baseline 80+ (t = 3.7, $P < .001$), suggesting that these areas were more preserved.

The resilience signature and amyloid are the stronger predictors of baseline global cognition in all 80+ participants

Table 2 below summarizes results in the subsets of cognitively stable as well as in the full 80+ sample. While the resilience signature was the only brain imaging marker associated with global cognition in the cognitively stable 80+ group, both FDG-PET from the Alzheimer's disease-signature and the resilience signature significantly contributed to explain global cognition ($P < 0.001$) in cognitively unimpaired at baseline 80+ (Supplementary Table 4). Standardized beta coefficients from the multiple regression analyses in the full 80+ sample indicated that FDG-PET uptake in the resilience signature had one of the strongest effects on baseline global cognition, only comparable to the effect of PIB. The models considering demographic variables, *APOE* E4 status and imaging markers explained up to 38% of the variance in global cognitive performance.

In summary, PIB ratio and FDG-PET in the resilience signature were the most strongly associated with baseline global cognition across analyses.

The resilience signature predicts longitudinal global cognitive change in all 80+ participants accounting for amyloid effects

Using mixed effect models, we identified a significant interaction between the resilience signature and time, indicating that participants with greater FDG-PET in the resilience signature performed better over time. Among the other predictors, sex and PIB status also significantly interacted with time, indicating greater cognitive decline in participants with higher baseline PIB ratio and in males (Fig. 4 and Supplementary Table 4).

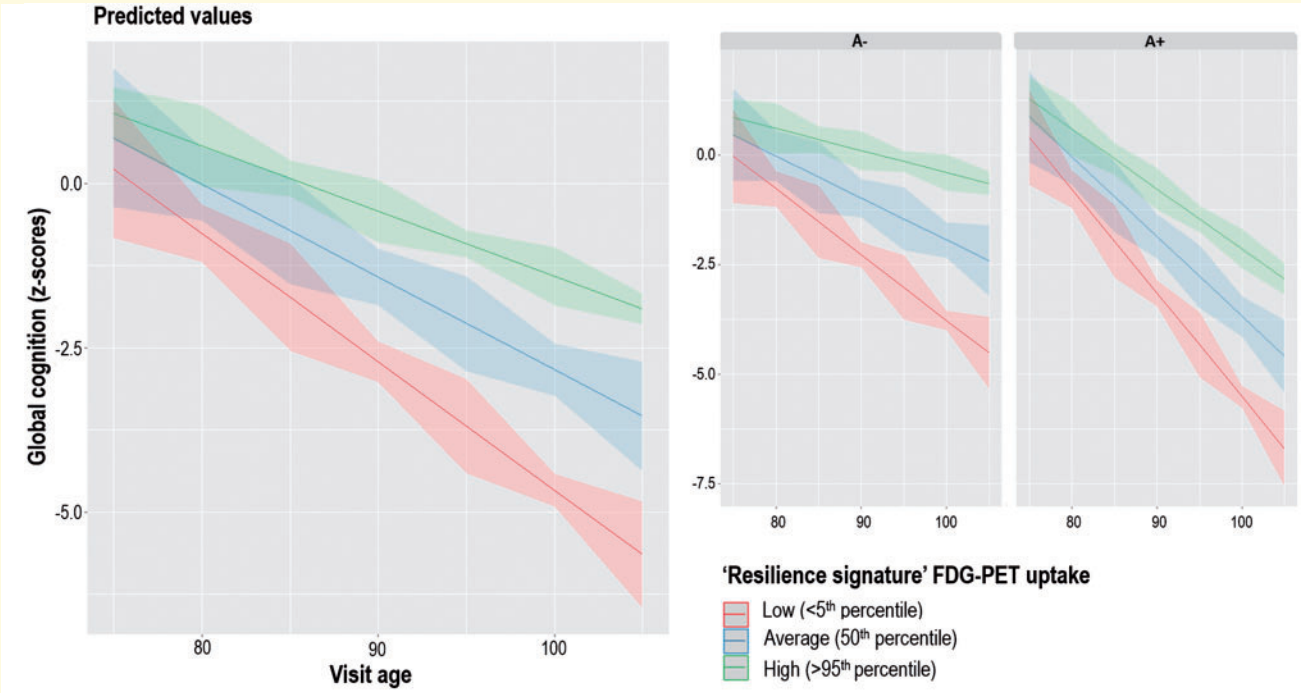

Figure 4 Predicted cognitive trajectories. *Left*: Trajectories for an 80+ participant with low, average or high FDG-PET uptake in the resilience signature. *Right*: Trajectories for an 80+ participant with low, average or high FDG-PET uptake in the resilience signature with normal versus abnormal amyloid status (A−, A+).

The resilience signature predicts cross-sectional global cognition and longitudinal global cognitive change in the ADNI cohort

In cross-sectional analyses, FDG-PET in the resilience signature, but not in Alzheimer's disease regions, predicted global cognition. Using mixed effect models, we identified a significant interaction between the resilience signature and time, indicating that participants with greater FDG-PET in the resilience signature showed less cognitive decline over time accounting for amyloid status (Supplementary Table 5 and 6).

Discussion

Recently, the Alzheimer's disease research field has shifted towards a biological definition of the disease (Jack *et al.*, 2018). The biomarker-based definition of Alzheimer's disease makes a distinction between Alzheimer's disease neuropathological changes and clinical symptoms and brings forward interest to understanding the dissociation between these two entities. Investigating factors that provide cognitive resilience will allow us to understand how individuals are able to maintain normal cognition in the setting of risk exposure, for example, very old age or *APOE* E4 carriage (see clarification of definitions and terminologies in Arenaza-Urquijo and Vemuri, 2018). We operationalized a 'cognitively resilient' or cognitively stable group (as ⩾80 years with a stable cognitively unimpaired status during 5 years as average) and found that in this group (i) established Alzheimer's disease imaging biomarkers (including PIB ratio) were not associated with baseline global cognition; (ii) increased FDG-PET uptake in the bilateral anterior cingulate and anterior temporal poles was associated with better baseline global cognition (the resilience signature); and (iii) better systemic vascular health was associated with greater metabolism in the resilience signature. In the full 80+ sample, we found that (iv) FDG-PET uptake in the resilience signature and amyloid were the stronger risk factors associated with baseline global cognition; and (v) the resilience signature significantly predicted longitudinal cognitive change, independently of amyloid status.

Defining cognitive resilience in the 80+ population

Imaging-focused studies have commonly approached the concept of successful cognitive ageing on the basis of 'exceptionality' instead of stability or maintenance of normal cognition over time (e.g. exceptional memory ability after 60s, 70s or 80s compared to younger individuals or age matched peers; Harrison *et al.*, 2012, 2018; Rogalski *et al.*, 2013; Sun *et al.*, 2016; Dekhtyar *et al.*, 2017; Lin *et al.*, 2017*a*; for exceptions see Pudas *et al.*, 2013; Rosano *et al.*, 2012; Lin *et al.*, 2017*b*). Another difference across studies is the selected cognitive domains to investigate successful cognitive ageing, for example, a single domain, usually memory, or a global cognitive score (see Negash *et al.*,

2011 for an assessment of different operationalizations). The different approaches may capture different aspects of successful ageing and, as highlighted below, there are common but also specific mechanisms identified using varying approaches. The definitions used may have implications for the identified underlying mechanisms, generalization of mechanisms, and described biomarker and cognitive trajectories in the defined subset. There is a need for consensus definitions that may help researchers interpret results from a common ground and integrate them in a general framework of successful cognitive ageing.

Cognitively stable 80+: amyloid and *APOE* status

Although cognitively stable 80+ participants were selected as maintaining normal cognition after 80 (5 years on average), almost half of them were amyloid positive (i.e. in the Alzheimer's disease continuum) and 20% were *APOE* E4 carriers. These results suggest that stability of normal cognition occurs in the presence of Alzheimer's disease pathology and genetic risk profiles in a significant proportion of the cognitively unimpaired older individuals. Previous imaging studies among the non-demented oldest old (including mild cognitive impairment participants) have reported the presence of amyloid pathology to be common in this population (Zhao *et al.*, 2018). Studies focusing on successful agers, however, have suggested lower amyloid deposition (Harrison *et al.*, 2018), reduced Alzheimer's disease pathology at autopsy (Gefen *et al.*, 2015) and a lower percentage of *APOE* E4 carriers (Rogalski *et al.*, 2013). The main difference between those studies and the present one, as pointed out above, is the definition of successful cognitive agers or resilient participants. Although previous studies suggest that exceptional memory abilities might be incompatible with high Alzheimer's disease pathology and *APOE* E4 carriage, our results suggest that a stable cognitively unimpaired diagnosis after age 80 might be possible even in the presence of Alzheimer's disease pathology and in *APOE* E4 carriers.

Established Alzheimer's disease biomarkers do not predict cross-sectional global cognition in cognitively stable 80+

Our results showed that established Alzheimer's disease biomarkers, i.e. PIB-PET, FDG-PET and cortical thickness in Alzheimer's disease signature regions, were not cross-sectionally associated with global cognition among cognitively stable 80+. It is important to note that this result was specific to this subset of participants because established Alzheimer's disease imaging markers were associated with global cognition among the cognitively unimpaired at baseline 80+ subset of participants in supplementary analyses. This finding is congruent with reports suggesting that the relationship between amyloid burden and global cognition among cognitively unimpaired adults may be weak (Hedden *et al.*, 2013; Mormino, 2014), which would be expected to be even weaker in *a priori* selected cognitively stable participants. However, neither FDG-PET and cortical thickness in Alzheimer's disease signature regions predicted cognition (Wirth *et al.*, 2013*a*, *b*; Mormino, 2014). Overall, we interpret these results as reinforcing our hypothesis that regions different from the Alzheimer's disease signature regions may be key to sustaining cognitive performance in this subset of participants.

The resilience signature: bilateral anterior cingulate and temporal lobes metabolism

The metabolism of the anterior cingulate and anterior temporal lobes was associated with global cognitive performance among cognitively stable 80+ participants. The metabolism in these areas was preserved (as compared to the rest of cognitively unimpaired 80+) and showed only a marginal effect of age in cognitively stable 80+ participants, which provides further support to the idea of preservation. The association did not vary as a function of *APOE* E4 and PIB status, suggesting these areas are fundamental to maintain global cognition in all cognitively stable 80+ participants.

Although definitions and methodologies vary among studies, a remarkable consistent finding is that the anterior cingulate has emerged as a fundamental neural correlate of successful cognitive ageing (Harrison *et al.*, 2012, 2018; Rosano *et al.*, 2012; Rogalski *et al.*, 2013; Gefen *et al.*, 2015). The microstructure of the anterior cingulate was reported to be preserved in older adults that maintained global cognitive performances over a 10-year period (Rosano *et al.*, 2012). The anterior cingulate was significantly thicker as compared to elderly and/or middle-age controls in independent studies and samples (Harrison *et al.*, 2012, 2018; Sun *et al.*, 2016), showed stronger functional connectivity with areas such as the hippocampus (Lin *et al.*, 2017*a*) and preserved neural integrity (Wang *et al.*, 2017) in older adults with exceptional memory abilities. The temporal lobes as well as prefrontal cortices have also emerged in previous studies (Rosano *et al.*, 2012; Sun *et al.*, 2016). This is, however, the first study showing that metabolic activity within these regions is associated with cognitive resilience. In complementary analyses, we assessed whether cortical thickness in the resilience signature provided similar explanatory power as metabolism in these areas. Interestingly, cortical thickness in the resilience signature was predictive of global cognition in the cognitively stable 80+ but not in the full sample, although metabolism showed a stronger effect (Supplementary Table 7). FDG-PET may provide a broader and more general measure of both structure and function thus showing a higher predictive value. Overall, our study findings taken together with previous studies suggests that the topography that we discovered here could

serve as the basis for refinement and development of robust resilience measures in the population.

Of note, our results suggest a dissociation between Alzheimer's disease-related pathological changes and resilience processes. As seen in the supplementary analysis the posterior cingulate metabolism was important to differentiate cognitively stable 80+ participants from progressors; however, preserved metabolism of the anterior cingulate and anterior temporal lobes (but not of the posterior cingulate) was associated with better cognition. This suggests that resilience processes may be, at least partly, independent of the pathological process. A biological explanation to these findings is the presence of Von Economo neurons or spindle neurons in the anterior cingulate, supporting faster transmission of information between brain regions, may underlie cognitive resilience (Nimchinsky *et al.*, 1999). These neurons have been reported to be more frequent in older adults with exceptional memory abilities (Gefen *et al.*, 2015). Moreover, the anterior cingulate is considered a critical site of transmodal integration related to episodic memory, spatial attention, cognitive and emotional control, motivational modulation, error recognition and adaptation to changes (Mesulam, 1998, 2009; Bush *et al.*, 2000; Allman *et al.*, 2001).

A testable hypothesis about the role of these regions in maintenance of normal cognition is that they may represent hub regions to sustain cognition and potentially compensation. Both the anterior cingulate and the temporal poles have been identified as hub regions for semantic memory and executive control (Zhao *et al.*, 2017). The dorsal anterior cingulate and anterior temporal lobes (together with the cerebellum) were part of a 'task invariant network' described by Stern *et al.* (2018): a network common across multiple tasks that influenced overall task performance and was associated with IQ. Furthermore, a majority of studies report responses in the frontal and temporal cortices associated with better cognitive performances among older adults (Eyler *et al.*, 2011). The specific metabolic profile of associations with cognition involving medial prefrontal regions in cognitively stable 80+ participants as compared to cognitively unimpaired at baseline 80+ participants is coherent with a model where increased frontal engagement underlies the maintenance of normal cognitive performance at older age [the Posterior Anterior Shift in Ageing (PASA) model] (Davis *et al.*, 2008). From a network-based perspective, we should highlight that our signature maps into the anterior dorsal/ventral default mode network and, according to recent theories, the connectivity of the anterior default mode network may be key along the Alzheimer's disease continuum (Jones *et al.*, 2016). Whether the metabolism of these areas sustains higher functional responses needs further investigation. Finally, it is important to note that a series of studies have suggested the left frontal cortex as a hub supporting higher resilience (Franzmeier *et al.*, 2017, 2018). The data-driven approach used in this study is unique in comparison to the hypothesis driven approaches used in the literature.

An important non-exclusive and testable hypothesis for future studies regarding the aetiology of the resilience signature is that it may reflect the absence or lower amount of pathologies or limited impact of pathologies on these areas. This is supported by the lack of association between amyloid and FDG-PET uptake in the resilience signature in the cognitively stable 80+ participants. Further work will clarify whether these areas are affected by neurofibrillary tangles (Delacourte *et al.*, 1999) or other pathologies in cognitively resilient older adults. In the elderly, non-Alzheimer's disease pathologies are increasingly common including cerebrovascular disease, hippocampal sclerosis and TDP-43 pathology, ageing-related tau astrogliopathy (ARTAG), and Lewy body pathology. Interestingly, recent data suggest that the anterior temporal pole is the most commonly involved cortical region with TDP-43 (Nag *et al.*, 2018). In a 90+ study, cognitive resilient participants showed lower non-Alzheimer's disease pathologies including cerebrovascular disease, hippocampal sclerosis, TDP-43, ARGAT and Lewy body pathology (Robinson *et al.*, 2018). Whether the FDG-PET resilience signature reflects absence of one of these pathologies requires additional evaluation.

Finally, it is important to note that, as discussed below, these areas were predictive of global cognition in the full 80+ sample, suggesting that they are fundamental regions for cognition, instead of a specific feature of a subset of successful agers or a consequence of higher IQ or general cognitive abilities. Thus it becomes necessary to understand how these brain areas may be preserved over the ageing process and how they relate to risk and protective factors.

Associations between the resilience signature and risk and protective factors

We found the metabolism of the resilience signature to be associated with better vascular health, which is in line with previous reports suggesting an association between exceptional brain ageing without Alzheimer's disease pathologies and vascular health (Vemuri *et al.*, 2017*b*). This finding is important because it emphasizes the relevance of vascular health to maintaining brain health and potentially achieving successful cognitive ageing (Vemuri, 2018).

We also found that females had greater metabolism in this region. This observation is consistent with previous findings suggesting a greater effect of age on the frontal cortex (specially anterior cingulate) in men than women and a greater effect of cognitive reserve proxies in the anterior cingulate in females than in males (Malpetti *et al.*, 2017). To the best of our knowledge previous studies did not report similar effects in relation to the density of Von Economo neurons and thus the biological underpinning of these effects needs further research.

There was no relationship between the resilience signature and intellectual enrichment factors. Previous studies, however, have found increased metabolism or grey matter

volume with years of education within the areas included in the signature, notably the anterior cingulate cortex (Arenaza-Urquijo *et al.*, 2013). A potential explanation for the different results is that the effects of education may be mediated by different factors including better lifestyles and better vascular health. Thus, associations between brain imaging variables and education may vary depending on the vascular risk profiles of the study sample. This explanation is consistent with the results showing that participants in the low CMC group were higher educated.

Resilience signature predicts baseline and longitudinal cognition beyond established Alzheimer's disease biomarkers

After identifying the resilience signature, we tested whether this signature accounted for additional variance in global cognition, and we compared its effect to PIB, FDG-PET and cortical thickness in Alzheimer's disease signature regions. Multiple regression analyses showed that the resilience signature and PIB were the main predictors of baseline cognition, with effects only comparable to those of education. We validated these results in ADNI cohort showing that the resilience signature and amyloid were the main predictors of baseline cognition. A linear mixed effect model for predicting longitudinal cognitive decline showed that both the resilience signature and PIB significantly interacted with time, such that the resilience signature would predict better performances over time independently of the effect of PIB. On an interesting note, education had an effect on baseline cognition but did not interact with time to predict lesser decline over time. In the ADNI cohort, the resilience signature and amyloid significantly interacted with time, such that the resilience signature would predict less cognitive decline over time independently of amyloid status.

These results suggest that applying resilience imaging markers in conjunction with Alzheimer's disease biomarkers may provide a more accurate prediction of cognitive outcomes in the 80+ population. The independent contributions of the resilience signature and PIB to explain cognition is consistent with results suggesting that resilience mechanisms might contribute to cognition independently of Alzheimer's disease pathologies (Vemuri *et al.*, 2011; Soldan *et al.*, 2017). It is important to note, however, that our longitudinal models did not include FDG-PET measurements from the Alzheimer's disease regions because metabolism in Alzheimer's disease and resilience areas were strongly associated. This may suggest that ratio measurements reflecting the discordance between Alzheimer's disease and resilience processes could better capture the full picture of ongoing brain processes.

Multiple pathways for maintaining cognitive function: resilience, resistance and maintenance or preservation

The results of the present study should not be interpreted in isolation, but rather in a framework where multiple (and probably interrelated) pathways may lead to cognitive resilience and potentially successful cognitive ageing. In Fig. 5, we integrated the results of the present study in a

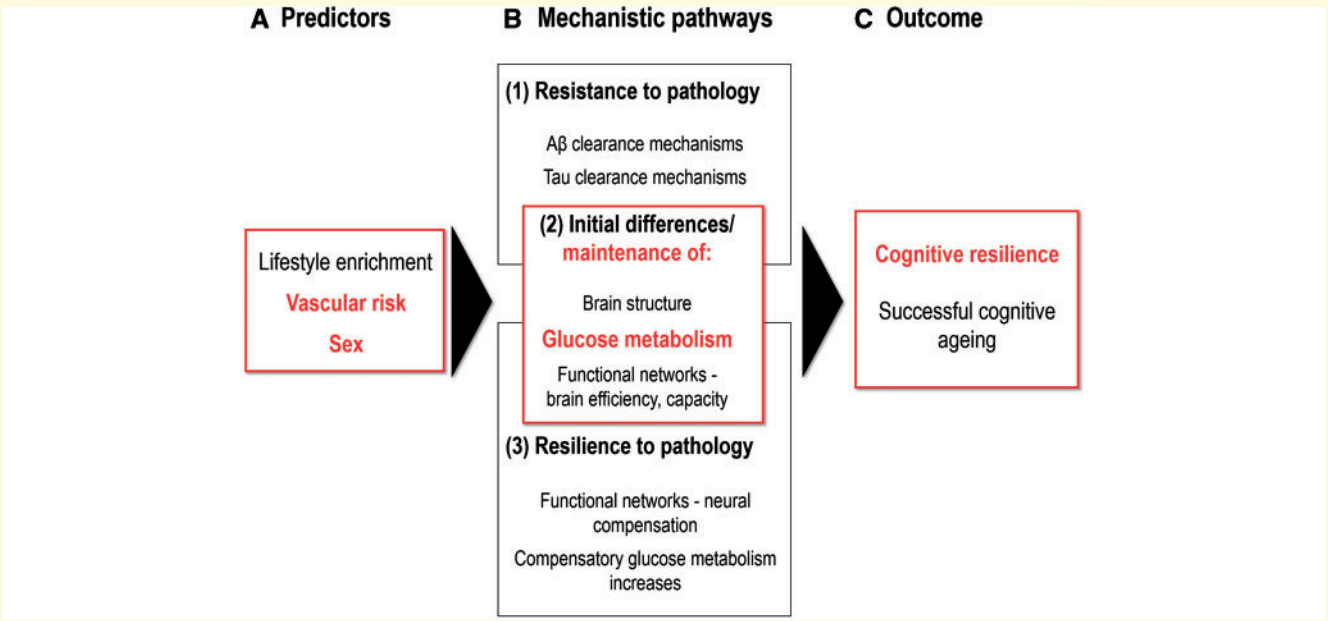

Figure 5 Paths to cognitive resilience or successful cognitive ageing. Adapted from Arenaza-Urquijo and Vemuri (2018). The predictors and potential mechanistic pathways identified in the present study are highlighted in red. Labels 1–3 indicate the statistical analyses performed. Aβ = amyloid-β.

broader framework (Arenaza-Urquijo and Vemuri, 2018) that acknowledges different pathways including resilience to pathology (Elman *et al.*, 2014), resistance to pathology (Landau *et al.*, 2012) and maintenance or preservation of key regions to sustain cognition. In the present paper we lay a foundation towards a better mechanistic understanding of a pathway that may be associated with vascular risk and sex, as well as with the maintenance or preservation of key brain areas to sustain cognitive performance at older ages. Future studies can help refine the mechanistic underpinnings of each pathway illustrated in Fig. 5.

This study has the limitation that we could not replicate the FDG-PET topography in an independent sample. However, we showed the robustness of the results by inclusion of the full 80+ sample and showed the predictive value of the resilience signature in an independent sample. Future work will need to be focused on further refining, understanding mechanisms, establishing generalizability and specificity of markers for resilience.

Overall, our results suggest that the metabolism of the anterior cingulate and anterior temporal lobes might be a good candidate marker of cognitive resilience in the 80+ population as it predicted: (i) baseline global cognition beyond (in cognitively unimpaired at baseline 80+) or equal (in all 80+) to established Alzheimer's disease imaging biomarkers including PIB; (ii) global cognitive change independently of PIB; and (iii) showed associations with vascular health, being thus potentially informative for therapeutic trials targeting modifiable risk factors. Identification of specific markers of cognitive resilience and applying them in conjunction with Alzheimer's disease biomarkers may be a pivotal step toward prevention and understanding of successful cognitive ageing, but also towards a better understanding of the factors that play a role in the transition from preclinical to symptomatic Alzheimer's disease.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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