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Gabriel Ziegler

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Pilot Award Summaries

1. Decision tree testing cognition-MRI associations to define and differentiate CR and BM
Lídia Vaqué-Alcázar, University of Barcelona
CR and BM are complementary constructs, but a robust differentiation between them is challenging. Therefore, we designed a unified approach incorporating measures of brain magnetic resonance imaging (MRI) data and cognitive change, which will allow us to examine the neural mechanisms by identifying crucial functional circuits underlying CR and BM. Our experimental design is based on a decision tree where at each step a residual approach between episodic memory (EM) and multimodal MRI-based measures will provide a general metric rising to distinguish between BM: when there is a correspondence between EM stability and brain structure, and CR: when we detect a discrepancy between EM stability and multimodal MRI-based measures. This proposal will use already available longitudinal data of healthy participants aged 60 or over, including the 3 key components for each subject: (1) measures of age-related changes assessed by MRI acquisitions, (2) EM performance, and (3) typical CR proxies. A strength of this study is that here, in order to categorize the individuals, we will focus on a discrepancy (or not) between the age-related brain changes (component 1) and the associated changes in cognition (component 2). Further, we have planned to study how the 'hypothetical variable' (component 3) influences the relationship between 1 and 2 (i.e., CR) or influences 1 (i.e., BM). This could provide evidence whether the component 3 (i.e., 'hypothetical variable') proposed in both CR and BM operational definitions may be contributing at the same time to reduce rates of cognitive decline in the face of age-related brain changes (i.e., CR), and also may be associated with neuroprotective mechanisms, more related to BM (or BR). Overall, we think that the present approach will overcome some limitations in terms of clarifying the conceptual boundaries between CR and BM concepts.

2. A test of the hypothesis that factors acting to protect synapse function are at the core of the biological basis of cognitive reserve
Daniel Gray, University of Arizona
This study utilizes legacy brain tissue from a large experiment designed to study the molecular mechanisms of cognitive aptitude in F344 rats across the lifespan, including young, middle-aged, and old rats. All rats underwent (1) a series of structural and diffusion-weighted MRI scans, (2) a large battery of cognitive assessments that included tests of both medial temporal lobe and frontal cortical brain function that enabled the selection of those individuals that were average-, low- or high-performing for their age groups, and (3) histological brain sections were prepared of the hippocampus and will be labelled to identify two distinct proteins that are critical for synapse health and plasticity. These include the immediate-early gene neuronal pentraxin 2 (NPTX2) and markers for a specialized extracellular matrix structure called perineuronal nets (PNNs) that provide physical and biochemical support to synapses. These data will allow us to test via multiple regression models whether the expression of proteins associated with synapse health (3) moderates the relationship between structural changes in grey and white matter as assessed by MRI (1) and levels of cognitive function (2). We anticipate that some subset of the structural brain variables (total volume, ventricle size, lipofuscin) measured will be associated with synapse health and cognitive function. If our hypothesis is correct, we expect that the expression of our markers of synapse health will be highest in the high cognitive functioning rats across the lifespan (that is, in all 3 age groups). This might indicate that synapse health at all points of the lifespan helps define the trajectory that an individual's cognitive function will take as age-associated changes in brain structure and function begin to accumulate. If we can establish this relationship, then we can design longitudinal studies to test our prediction that the slopes of cognitive decline will differ in animals that conform to our definition of these distinct cognitive statuses. This could be accomplished in future experiments by measuring cognitive status at regular intervals (in animals across the lifespan) to define the behavioral trajectories of these individuals. These animals can then be sacrificed at various points of the lifespan to assess synapse health in the context of the behavioral trajectories defined by the longitudinal cognitive testing.

3. Cognitive training to enhance cognitive reserve in aging mice
Holly Hunsberger, Columbia University
In this study cognitive reserve will be measured in the face of age-related changes. We can also include Alzheimer's disease (AD) mice, which would be included as a brain insult/disease state. These studies will be longitudinal. The intervention here is, education or training. The question is: how does education enhance CR in the face of aging and disease? We will measure short, long, and working memory at 6-8 months of age as cognitive performance. We have the option to test these mice in short or working memory as a baseline measure at 2 months. We will measure the number of senescent cells within the hippocampus (and later whole brain) as a potential measure of brain change that influences memory. We know that senescent cells are increased with age. We will tag a contextual memory to examine differences in memory trace cell activation as a potential molecular mechanism of CR. We know that memory trace cell activation is decreased with age and AD pathology but anticipate that early-life training may help preserve it. The study can also test for potential brain maintenance. In this scenario mice will naturally age without training. Sex and mouse strain could impact cell senescence and memory trace activation, thus preserving memory. Other factors that may impact CR or BM will also be considered, including exercise in the training apparatus, handling of mice, novel environment of the training apparatus.

4. Defining a biological marker of cognitive reserve with deep learning from structural MRI
Anna Marseglia, PhD, Karolinska Institute
The overall aim of this study is to investigate whether a biological marker of cognitive reserve can modify the associations between measure(s) of brain pathology and changes in cognitive function. Age-related brain pathology measures include of Alzheimer's disease (AD) neurodegeneration as assessed with a cortical thickness pattern and of vascular damage based on markers of SVD. Cognition is measured using a composite measure of global cognition (G-score), generated by averaging the Z-scores a battery of tests. Our biological measure of cognitive reserve will be based on differences between predicted brain age (PBA) and the person's chronological age (CA) was developed given the same level of cognition, based on a deep learning model. Differences between PBA and CA are computed and categorized into 4 quartiles, with Q1 indicating younger-appearing brain (thus more reserve) to Q4 indicating older-appearing brain (less reserve). Then, within the Gothenburg H70 Birth Cohort Study-Birth cohort 1944 (including septuagenarians without dementia, cognitive impairment, or other neuro-psychiatric disorders, followed up after 5 yrs. from baseline [2014-2016]), we will investigate cross sectionally and longitudinally the potential modifying effect of the biological marker of cognitive reserve on the relationship between age-related brain pathology and changes in global cognitive function.

5. Improving the moderation and independent effect criteria of cognitive reserve
Rory Boyle, Trinity College Dublin
One criteria for candidate neuroimaging measure of CR is that it must be associated with cognition independently of brain structure (i.e. should display an 'independent' effect on cognition). The overall aim of this study is to assess imaging-based correlates of CR. We will first create a residual variable representing CR from the regression of global cognition on grey matter volume, hippocampal volume, mean cortical thickness, age, and sex. The residual from this regression reflects the degree to which an individual's cognition is better or worse than expected given their brain structure, age, and sex. We will then develop a functional connectivity-based measure of CR (network-strength predicted CR) by applying connectome-based predictive modelling to predict the CR residual from functional connectivity data. We will test the validity of network-strength predicted CR by assessing whether it a) explains variation in longitudinal cognitive function above and beyond the effects of Alzheimer's disease (AD) signature cortical thickness (brain change) and/or b) moderates the relationship between AD-signature cortical thickness and longitudinal cognitive function. If either of these criteria are satisfied, we will operationalize CR as network-strength predicted CR. If neither criteria is satisfied,

we will operationalize CR as the CR residual. We will operationalize BM using the brain-predicted age difference, a robust machine learning residual, which compares an individual's structural brain health, reflected by their voxel-wise grey matter density, to the state typically expected at that individual's age. We have previously shown that larger brain-predicted age differences, reflecting worse BM, are associated with lower cognitive function. This previous study included the two required components for elucidating BM: 1) measure of age-related brain change = (cross-sectional) brain-predicted age difference; 2) measures of associated change in cognition = (cross-sectional) cognitive function. We will assess whether the operationalized measures of BM and CR, separately, are independently associated with longitudinal cognitive function after accounting for physiological and clinical health covariates. We hypothesize that CR, but not BM, will remain independently associated with longitudinal cognitive function.

6. Reserve and Maintenance in AD: Effects on Individual Cognitive Trajectories (REMIND-ICT)
Colin Groot, VU University Medical Center Amsterdam
We will investigate the concepts of cognitive reserve, brain reserve and brain maintenance by evaluating individual cognitive trajectories, as assessed by Bayesian change point analyses. The first analysis will include longitudinal data from initially nondemented individuals with known AD pathology who then receive an AD diagnosis. The analysis looks at the initial level of performance, the time to the change point where cognitive decline begins, and the time to dementia. CR, as represented by the proxy education would be related to both the higher level of initial premorbid function and to the delay in inflection point. We hypothesize that brain reserve (as assessed with structural measures: gray matter atrophy and white matter hyperintensities) will be more strongly associated with higher initial performance (higher inflection points). However the time to the point of infection more driven to a greater degree by brain maintenance as measured by differential change in build-up of structural measures and AD pathology (CSF amyloid and tau).
The second analysis will focus on amyloid positive individuals diagnosed with AD. It will assess the relative effects of brain reserve and brain maintenance on cognitive trajectories after cognitive decline sets in. It will longitudinally assess the interplay of rates of structural degeneration and AD pathology build-up after a diagnosis of dementia. Cognitive reserve would be reflected by more rapid decline in individuals with higher education, since the pathology is more advanced at the time of diagnosis. However, we will also evaluate the rate of increase in AD pathology, since more rapid decline could be accounted for differential loss of brain maintenance which would result in the more rapid increase in AD pathology.

7. Exploring multivariate metrics to benchmark functional brain maintenance
Gabriel Ziegler, University College London
In this project brain maintenance is based on a multivariate index which primarily measures youthlike appearance of distributed activity patterns in the FADE fMRI task in old age. For that purpose, a model of fMRI activity patterns (during performance of the same task) is learned in a healthy young reference cohort (n=100). The trained model accounts for multi-voxel correlations and heterogeneity within this group. This one-class classification (or novelty detection) approach then enables defining a similarity index (called FADE score) for new unseen subjects (which have performed the FADE task) which will be assessed in old age, e.g., in participants at risk of dementia (DELCODE DZNE cohort, n=543, 59-89 yo, characterized using biomarkers, WMH, longitudinal MRI and cognition). The proposed FADE score is cross-sectionally defined using individual differences at baseline rather than within-subject changes as required by the current definition of BM. However, it might play the role of a hypothetical variable predicting age- and/or pathology related brain changes, which are tied to cognitive decline on an individual level. More specifically, we use hippocampal (or AD-) network atrophy rates as measures of age-related brain changes, insults or disease that theoretically impact cognitive outcomes. The latter are assessed using clinical PACC score over follow-up measurements. First, we establish whether there is an association of hippocampal network and cognitive changes over follow-ups. Second, we test if FADE differences can predict these shared individual differences of brain-behavioral changes. The latter would support the role of FADE score as an important baseline predictor for BM (over

time). Finally, the project aims to test whether the proposed FADE score (as a fMRI-based BM index) might play the role of a CR variable in participants facing ageing-related pathology. More specifically, the project implements the CR definitions by testing if effects of hippocampal network atrophy rates (as a longitudinal measure of aging-related brain pathology) on rates of cognitive decline (over follow-ups) are moderated by the FADE score.

8. Functional activation patterns to explain cognitive performance beyond brain structure and age
Christian Habeck, Columbia University Vagelos College of Physicians and Surgeons
We propose to operationalize Cognitive Reserve is as an fMRI activation pattern that (1) accounts for cognitive performance and (2) is uncorrelated with brain structure and age. This is accord with the suggested operational definition for CR in that it includes: brain changes associated with cognition: multimodal characterization of brain structure changes, using regional cortical volume, regional cortical thickness, tract integrity, 2: change task performance, and 3 a putative measure of cognitive reserve: an fMRI activation, or functional-connectivity, pattern. In order to derive that CR pattern, we will Orthogonalize fMRI data and cognitive outcome with respect to brain structure and age. We will then use PCA-regression (Scaled Subprofile Modeling; SSM) to derive a residual activation pattern that accounts for residual cognitive performance; the pattern score will now be orthogonal to brain structure and age by design. We can then test the associations of pattern score with traditional CR proxies like education and verbal intelligence using standard Pearson correlation. We will also forward apply the derived patterns(s) to held-out data and test whether the resulting pattern score accounts for cognitive performance beyond age and brain structure. For genuine replication in de-novo data sets, we will use fMRI activation data from several other tasks collected in our laboratory, a verbal Working-Memory task, a set-switching task.

9. Cross-sectional and longitudinal modelling of brain and cognitive age to study cognitive reserve and maintenance
Melis Anturek, University College London
Our study aims to use machine learning to estimate brain age based on MRI (i.e., T1-weighted, diffusion-weighted and FLAIR images) and cognitive age, based on neuropsychological measures. This will enable us to estimate the brain age gap (BAG) and cognitive age gap (CAG), which quantify how much an individual's apparent brain/cognitive age deviates from healthy aging patterns. Our study then examines the heritability of cross-sectional estimates of BAG and CAG and their genomic correlations, as well as how traditional markers of cognitive reserve (i.e., premorbid IQ, education) and a composite lifestyle measure relate to changes in these metrics over time. The proposed project will address these research objectives by conducting a secondary analysis of three datasets: the UK Biobank study, Lothian Birth Cohort 1936 and Insight 46.

The cross-sectional analyses in our study premise that individual differences in BAG at a given time point reflect, at least partially, interindividual variation in age-related brain changes. However, a cross-sectional approach cannot truly disentangle whether the observed differences in BAG are due to pre-existing differences in brain structure or differences in the rate of brain ageing between individuals. Therefore, our study will also take longitudinal data into account, by estimating BAG at all available time points. This will allow us to statistically model changes in BAG and CAG, over time. In this way, stability in BAG over time could be indicative of brain maintenance while stable CAG trajectories combined with concurrent changes in BAG could indicate cognitive reserve. Overall, our study integrates the components of brain maintenance as (1) BAG potentially captures age-related brain changes, (2) will be investigated alongside cognitive trajectories and (3) examined in relation to lifestyle factors. Additionally, our study operationalizes cognitive reserve as CAG, after adjusting for BAG. In this way, we take into account age-related changes in brain structure (component 1) and in cognitive function (component 2). We also regress premorbid IQ, education and a lifestyle marker onto CAG, after adjusting for BAG (component 3).

10. Molecular markers to operationally define cognitive reserve
Thomas C, Foster, University of Florida
Utilizing a public functional genomics data repository, Gene Expression Omnibus, we identified cross-sectional transcriptional data from the CA1 region of male rats. Using the water maze, aged animals were characterized as cognitively impaired (AI) or unimpaired (AU; i.e., component 2 from the consensus document). From 5 initial studies, we identified genes representing possible age-related brain changes (i.e., component 1 from the consensus document), defined as genes that were significantly ($p<0.05$) different (increasing or decreasing) between all aged animals and young. This set of potential aging genes was then tested against other data sets that examined gene expression in the whole hippocampus of rats and mice to evaluate reliability of these age-related genes. To determine possible mechanisms for cognitive reserve (i.e., component 3 from the consensus document), genes were identified that were significantly ($p<0.025$) different between AU and young, and these same genes were not different ($p>0.1$) from young and AI rats. In addition, we defined brain maintenance genes as those that were not different ($p>0.1$) between young and AU rats, and these same genes were significantly ($p<0.025$) different between AI and young. Finally, we examined the relationship between expression of activity dependent immediate early genes (IEG) in region CA1 and the medial prefrontal cortex (mPFC) of animals characterized on two different tasks, water maze and attentional set-shift. Shifts in network engagement, exhibited as efficiency (less activation of immediate early genes, which are associated with preserved cognition) and compensation (greater activation of immediate early genes which are associated with preserved cognition), were evaluated between young, AU, and AI rats. To ascertain shifts in regional recruitment as compensatory or debilitative, IEG activation in the CA1 and mPFC were correlated between the three groups.

11. Disentangling the role of CR proxies in a longitudinal age-homogenous study incorporating multiple measures of brain health and cognitive change
Sara James, University College London
Exposures associated with CR may in some cases not only moderate the expression of age-related brain changes, insults or disease (cognitive reserve), but could also contribute to the development of age-related brain changes, insults or disease (brain maintenance) Using a longitudinal age-homogenous population-based study we aim to investigate: 1: Which typical CR proxy exposures are directly associated with the development and change of a range of measures indexing age-related brain changes, insults or disease; and to what extent the associated brain health measures mediate the relationship between the CR proxy exposures and cognition and cognitive decline. 2. Which, and to what extent, a range of typical CR proxy exposures moderate the subtle cognitive expression (cognition and cognitive decline) of a range of measures indexing age-related brain changes, insults or disease. We will explore the unique contributions of a range of CR proxy exposures given that they could have differential effects. The CR proxy exposures of interest have been chosen based on prior evidence that they predict later-life cognition and include early social circumstances; childhood IQ; own educational attainment; occupational attainment; and crystallized ability. We will explore the effects from a range of pathological markers, characterizing overall brain health. Pathology markers include Aβ status (indicative of AD pathology); white matter hyperintensity volume (indicative of cerebral small vessel disease); hippocampal and brain volume, and cortical thickness (indicative of atrophy).

12. Aging and Memory – Origins of heterogeneity in cognitive trajectories study
Eero Vuoksimaa, PhD, University of Helsinki
We will use longitudinal cognitive and brain imaging data from the Vietnam Era Twin Study of Aging to investigate if brain maintenance and/or cognitive reserve explain heterogeneity in episodic memory trajectories from late middle age to early old age. A composite score of three episodic memory tests from three time points (at mean ages of 56y, 62y, 68y) will be used to indicate cognitive change (outcome / dependent variable). Predictors (independent variables) of cognitive change are changes in relative cortical

surface area and thickness in regions implicated in Alzheimer's disease (brain maintenance model). We will test whether young adult – at a mean age of 20y – general cognitive ability and lifetime years of education impact brain maintenance, cognitive reserve or both. For BM we will test if these exposures are associated with less brain change, resulting in better preserved cognition. For CR, we will test if these proxy measures of cognitive reserve moderate the effects of cortical surface area / thickness change on cognitive trajectories: cognitive reserve interaction model with three components to test if those with higher cognitive ability can tolerate brain changes better than those with lower cognitive ability.

Table: Pilot project summary

Investigator	Human/ Nonhuman	Cognitive Reserve (CR)				Brain Maintenance (BM)			
		Brain Change	**Cognitive change**	**Factor associated with CR**	**CR Hypothesis**	**Brain Change**	**Cognitive change**	**Factor promoting BM**	**BM hypothesis**
Lídia Vaqué-Alcázar	H	Structural MRI measures of age-related change	Episodic memory measures at least two timepoints	years of education and lifestyle associated measures	Factors associated with CR will moderate the relationship between change in multimodal MRI-based measures and change in episodic memory	Structural MRI measures of age-related change	Episodic memory measures at least two timepoints	years of education and lifestyle associated measures	Factor promoting BM will be related to age-related structural and/or functional brain change, resulting in preservation of episodic memory
Daniel Gray	N	structural and diffusion-weighted MRI scans	cognitive assessment to identify high-, average-, and low-performing rats for an age group	2 proteins critical for synapse health and plasticity: neuronal pentraxin 2 (NPTX2) and perineuronal nets (proteoglycans)	Expression of proteins associated with synapse health will moderate the relationship between structural changes and levels of cognitive function				
Holly Hunsberger	N	senescent cells	contextual memory and memory trace	repeated acquisition training at early age	Early life training will be associated with more preserved memory trace cell activation and memory in the presence of senescent cells	senescent cells	contextual memory and memory trace	mouse strain or sex	Mouse strain or sex be associated with more preserved senescent cells, resulting in more preserved memory trace and contextual memory
Anna Marseglia	H	AD neurodegeneration and vascular changes (SVD)	global cognition	differences between predicted brain age and chronological age given the same level of cognition	The CR measure will moderate the relationship between AD/SVD and cognition				
Rory Boyle	H	AD neurodegeneration measured by a cortical thickness pattern and brain structure (WM hyperintensities, WM integrity, vascular health)	cognitive function	expression of a functional network that is correlated with a residual score. The residual score reflects the degree to which cognition is better or worse than expected given brain structure, age, and sex	The CR functional network will (a) be associated with longitudinal cognitive function above and beyond the effects of AD signature cortical thickness or (b) moderate the impact of the change in AD signature cortical thickness on longitudinal cognitive function. Both effects ((a) or (b)) will remain statistically significant after accounting for brain structure measures.	AD neurodegeneration and brain structure	cognitive function	Life exposures	A brain-predicted age difference residual reflecting the deviation of an individual's MRI brain measures from healthy aging patterns will be associated with longitudinal cognitive function.
Colin Groot	H	Structural measures and AD pathology (CSF amyloid and tau)	cognitive change in: Study 1 nondemented individuals with AD pathology; Study 2: individuals with diagnosed AD	Education	Study 1: CR will be represented by higher initial performance. CR will moderate AD pathology resulting in a longer time until the beginning of cognitive decline. Study 2: there will be more rapid decline in individuals with higher education, driven by pathology being be more advanced at the time of diagnosis.	Structural measures and AD pathology (CSF amyloid and tau)	cognitive change in: Study 1 nondemented individuals with AD pathology; Study 2: individuals with diagnosed AD	Education	Study 1: differential rate of structural measures decline and AD pathology increase time influence the time to develop AD. Study 2: Differences in the rate of increase in AD pathology will account for differences in rate of cognitive decline. In both cases education could account for differences in BM
Gabriel Ziegler	H	hippocampal network atrophy, as a longitudinal	Cognitive battery	FADE score: A model of the degree to which older people show	The impact of change in hippocampal network atrophy on rates of cognitive decline will be moderated by the FADE score.	hippocampal network atrophy	Cognitive battery	FADE score: A model of the degree to which	The FADE score will change with hippocampal atrophy. Both will correlate with change in cognitive performance

		measure of aging-related brain pathology		youth-like fMRI activity patterns				older people show youth like fMRI activity patterns	
Christian Habeck	H	aggregate of age related changes in regional cortical volume, regional cortical thickness, tract integrity	cognitive summary scores	an fMRI pattern that correlates with task performance and is uncorrelated with brain structure	Expression of the CR fMRI pattern will be correlated with CR -related variable such as education, IQ, and life exposures. In external data, the CR fMRI pattern will account for cognitive performance beyond age and brain structure.				
Melis Anatürk	H	Brain age gap (BAG): a machine learning estimate of how much each individual's MRI brain measures deviate from healthy aging patterns	Cognitive age gap (CAG): machine learning metric of how much each individual's cognition deviates from healthy aging patterns	premorbid IQ, education and a lifestyle marker (composite measure of smoking status, physical activity and alcohol intake)	Changes in BAG on CAG trajectories will be moderated by factors associated with CR	Brain age gap (BAG)	Cognitive age gap (CAG):	premorbid IQ, education and a lifestyle marker	Less change in BAG will be associated less decline in CAG. BM promoting factors will be associated with lower BAG
Tom Foster	N	Senescence-related genes identified in this study	Spatial memory: Performance in watermaze	potential resilience genes defined as 1. expressed differently between unimpaired aged and young rats, but are not differently from young and aged impaired rats, genes associated with network efficiency or compensation	The identified potential resilience genes or networks will moderate the effect of senescence genes on spatial memory	Senescence-related genes identified in this study	Spatial memory: Performance in watermaze	potential maintenance-related genes: those that ae most different between young and aged impaired rats	The identified maintenance-related genes will delay the expression of senescence-related genes, thus preserving spatial memory
Sara James	H/N	Multiple MRI measures, as well as molecular and cellular measures	Cognitive test or incidence of MCI/dementia	Human: Early age IQ, Early life circumstance, education, occupation, leisure activity, physical activity, social networks, vascular health, crystalized ability, personality/mental health/psychological constructs and fMRI networks. Non-human: Behavioral training, Environmental enrichment, Social housing, Diet	Some measures associated with CR will modify the impact of age-related brain changes, insults or disease on cognition and cognitive decline of a range of measures indexing	Multiple MRI measures, as well as molecular and cellular measures	Cognitive test or incidence of MCI/dementia	The same as factors associated with CR	Some exposures will be directly associated with the development and change of a range of measures indexing age-related brain changes, insults or disease. These brain changes will be directly associated with cognition and cognitive decline.

Eero Vuoksimaa	H	changes in relative cortical surface area and thickness in regions implicated in Alzheimer's disease	episodic memory tests from three time points (at ages 56y, 62y, 68y)	general cognitive ability at age 20 and lifetime years of education	Factors associated with CR will moderate the effects of cortical surface area / thickness change on cognitive trajectories	changes in relative cortical surface area and thickness in regions implicated in Alzheimer's disease	episodic memory tests from three time points (at ages 56y, 62y, 68y)	general cognitive ability at age 20 and lifetime years of education	Factors promoting BM will be associated with less brain change, resulting in better preserved cognition