LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

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FÜR PSYCHIATRIE UND PSYCHOTHERAPIE

Marion von Tessin Memory-Zentrum

2ND INTERNATIONAL CONFERENCE ON COGNITIVE RESERVE IN DEMENTIA AND OTHER DISORDERS

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Dear Colleagues and Friends,

After the big success of the 1st International Conference on Cognitive Reserve in the Dementias and other Disorders (ResDem) in 2017, it is my great pleasure to invite you to the 2nd ResDem in Munich on 15-16 November 2019.

The traditional definition of healthy aging as years lived free from disease is replaced by a concept focussing on a process that allows individuals to maintain their normal function as they age. This is in stark contrast to the usual healthcare and public health approaches, which mostly aim at identifying and treating acute illnesses rather than maintaining the intrinsic capacities throughout the life course. This paradigm shift in the definition of healthy aging will have to be followed by a process of redesigning our health care approaches with a stronger focus on preserving function.

The concept of reserve was established to account for the observation that a given degree of brain pathology may result in different degrees of symptoms in different individuals. There is a large amount of evidence on epidemiological risk and protective factors for neurodegenerative diseases and dementia, but the biological mechanisms that underpin the protective effects of certain lifestyle and physiological variables are not yet understood, which limits the development of more effective preventive and treatment strategies.

ResDem aims to establish a forum for the global cognitive reserve scientific community, focusing on the interface between basic, clinical and epidemiological research and on factors and mechanisms that may promote individual brain health and prevent or delay the onset of dementia. We want to promote exchange of innovative ideas between the leading scientists and to train a new generation of young researchers.

There will be plenty of opportunity to network.

We cordially invite you to join us in beautiful Munich!

Prof. Dr. Robert Perneczky
Conference Chair

Prof. Dr. Norbert Müller
Conference Co-Chair

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Yaakov Stern, Columbia University New York

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10.20-10.40 PET imaging in anti-amyloid treatment trials
Timo Grimmer, TU Munich

10.40-11.00 Brain metabolism and cognitive reserve
Matteo Bauckneht, University of Genoa

11.00-11.20 The fronto-parietal control network and its' role in reserve & resilience
Nicolai Franzmeier, LMU Munich

11.20-11.40 Dynamic connectivity changes in preclinical frontotemporal dementia
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11.40-12.00 Protective effects of CSF sTREM2 on cognitive performance
Michael Ewers, LMU Munich

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Chinedu Udeh-Momoh, Imperial College London

13.50-14.10 BACE1 inhibition and dendritic spines
Jochen Herms, LMU Munich

14.10-14.30 Aβ deposition and microglial response in Alzheimer's mouse models
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14.30-14.50 Folding mechanisms of alpha-synuclein in vivo
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16.30-16.40 Motor reserve moderates the detrimental effect of dopamine transporter loss on motor function in Parkinson's disease
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16.50-17.00 Association of TDP-43 proteinopathy, cerebral amyloid angiopathy, and Lewy bodies with cognitive impairment in individuals with or without Alzheimer's disease neuropathology
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17.00-17.10 Increased Neuroanatomic Risk for Alzheimer's Disease Associated with Fine Particle Exposure: Exploring the Role of Cognitive Reserve
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17.10-17.20 The relationship between tau pathology and microglial activation in PSP-Richardson's syndrome
Maura Malpetti, University of Cambridge

SESSION 4. DEBATE: CAN WE TEST COGNITIVE RESERVE IN ANIMAL MODELS? (17.20-18.00)
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17.20-17.35 Pro: Appropriate animal models are available
Oliver Wirths, University of Göttingen

17.35-17.50 Con: Better animal models must be developed
Amos Korczyn, Tel Aviv University

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Closure Day 1

DAY 2 SATURDAY, 16TH NOVEMBER 2019

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Robert Perneczky, Norbert Müller, LMU Munich/ Marion v. Tessin Center

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Norbert Müller, LMU Munich & Marion v. Tessin Center

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Robert Perneczky, LMU Munich

09.35-09.55 Astroglial imaging in early Alzheimer's disease
Paul Edison, Imperial College London

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Michael Heneka, University of Bonn

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Richard Lathe, University of Edinburgh

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14.20-14.40 Challenging neural plasticity in schizophrenia
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14.40-15.00 The metabolic brain signature of cognitive resilience
Eider Arenaza-Urquijo, Barcelonabeta Brain Research Center

15.00-15.20 Effects of a 3-Year Multi-Domain Intervention on cognitive performance in older adults with increased dementia risk
Pierre-Jean Ousset, University of Toulouse

15.20-15.40 Functional and structural connectivity changes and their association with lifestyle factors in the DELCODE study
Boris-Stephan Rauchmann, LMU Munich

15.40-16.00 Closing words and awards presentation
Robert Perneczky, Norbert Müller, LMU Munich/ Marion v. Tessin Center

16.00-16.45 Farewell coffee

Conference closure

Opportunities and challenges of reserve research

Yaakov Stern

Columbia University New York

I will give a brief history of the concepts underlying reserve, including brain reserve, cognitive reserve and brain maintenance. The research approaches to understanding the neural basis of these concepts will be discussed. I will then describe the progress of a program designed to come to consensus on operational definitions for terms related to reserve and resilience among human and animal researchers. I will also share some new data exploring the neural implementation of cognitive reserve.

SESSION 1: NEUROBIOLOGY OF RESERVE

PET imaging in anti-amyloid treatment trials

Timo Grimmer

TU Munich

The clinical course of AD differs substantially from patient to patient as well as clinical response to treatment. This is probably partly explained by differences in cognitive reserve.

Therefore, biomarkers becoming increasingly important to objectively measure the course of the underlying AD pathophysiology. In particular, imaging biomarkers showing the cumulative AD pathology are frequently used to measure the effects of new therapeutic approaches aimed at modifying disease progression.

In particular, amyloid PET provides valuable information on the efficacy of anti-amyloid treatment strategies as compared to high variability in clinical response.

The usefulness of amyloid PET are demonstrated by examples from current anti-amyloid drug trials.

PET imaging allows the treatment response in clinical trials to be detected earlier and in smaller samples than with clinical measures.

Brain metabolism and cognitive reserve

Matteo Bauckneht

University of Genoa

FDG-PET has historically demonstrated that Alzheimer's Disease (AD) patients with higher education have since the early stages more severe and extended "posterior" AD-typical cortical hypometabolism with respect to poorly educated patients expressing the same level of cognitive symptoms. Given its unique capability to evaluate in vivo glucose consumption thus capturing synaptic function and dysfunction, FDG-PET can be used to run the so-called metabolic connectivity analysis. In fact, by calculating correlation coefficients -or pattern of intercorrelations- between values of FDG uptake, it is possible to estimate the functional association between cerebral areas. The talk will cover studies that have investigated metabolic networks underlying CR. In particular, it was demonstrated that although AD-typical damage is more prominent in highly educated AD patients, these patients have a relatively higher metabolic level with respect to poorly educated patients in the right frontolateral dorsal cortex (DLFC). Thanks to metabolic connectivity studies it was demonstrated that DLFC is involved in a wide bilateral frontal-limbic and temporal network in highly educated AD while it is basically only autocorrelated in poorly educated AD. Moreover, as this large bilateral frontotemporal-limbic metabolic network was highlighted also in highly educated elderly controls in topographically overlapping but less extended cortical regions, it seems to correspond to both neural reserve and neural compensation mechanisms. Finally, the potential role of FDG-PET in the evaluation of cognitive reserve in non-AD neurodegenerative diseases will be also covered.

The fronto-parietal control network and its' role in reserve & resilience

Nicolai Franzmeier

LMU Munich

Background

Alzheimer's disease (AD) patients vary in their ability to maintain cognition in the face of brain pathology. A major question is, which brain differences support higher reserve, i.e. attenuated cognitive decline despite AD pathology. Previous cross-sectional fMRI studies have shown that the left frontal cortex (LFC), i.e. a key hub of the fronto-parietal control network, may support reserve: Specifically, higher global LFC connectivity has been associated with relatively preserved cognition in both autosomal dominant and sporadic AD. An important open question is, however, whether higher global LFC connectivity actually attenuates the future rate of cognitive decline, i.e. a core prediction of the reserve model.

Methods

We obtained baseline resting-state fMRI in 51 autosomal dominant AD (ADAD) cases and 68 non-carrier controls from the DIAN cohort with on average 3-years of longitudinal cognitive follow-up data. Subject-specific global LFC-connectivity was obtained by seed-based resting-state connectivity analysis. As a proxy of disease severity, we used estimated years from symptom onset (EYO). Using linear mixed models, we tested the interaction effect (global LFC-connectivity x EYO) on longitudinal changes in a global cognitive composite.

Results

ADAD-patients showed significantly stronger global cognitive decline than non-carrier controls (interaction EYO x mutation-status, $p<0.001$). Most importantly, higher global LFC connectivity was associated with significantly attenuated longitudinal global cognitive decline in ADAD patients (interaction EYO x global LFC connectivity, $p<0.001$, Figure 1).

Conclusion

Our findings suggest that higher global LFC connectivity attenuates future cognitive decline in ADAD, further supporting its' role as a neural substrate of reserve in AD.

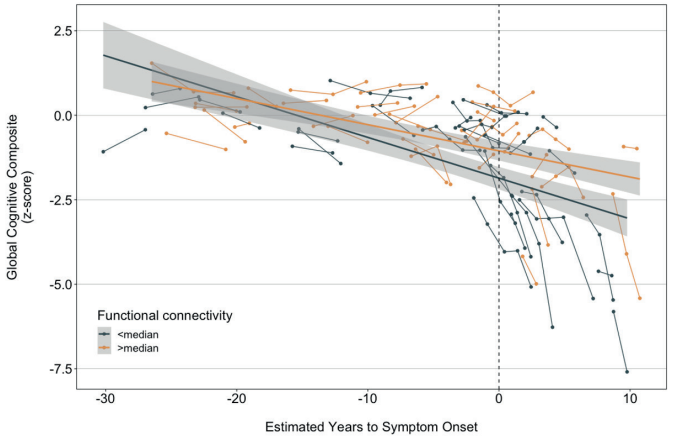

Figure 1:

Association between EYO and longitudinal changes in the global cognitive composite, stratified by high vs. low global LFC connectivity. Note that splitting the sample in high vs. low global LFC connectivity is for illustrational purposes only, the underlying model was computed based on interactions between continuous global connectivity values and EYO.

Dynamic connectivity changes in preclinical frontotemporal dementia

Enrico Premi

University of Brescia

Frontotemporal Dementia (FTD) is preceded by a long period of subtle brain changes, occurring in the absence of overt cognitive symptoms, that need to be still fully characterized. Dynamic network analysis based on resting-state magnetic resonance imaging (rs-fMRI) is a potentially powerful tool for the study of preclinical FTD.

In the present study, we employed a "chronnectome" approach (recurring, time-varying patterns of connectivity) to evaluate measures of dynamic connectivity in 472 at-risk FTD subjects from the Genetic Frontotemporal dementia research Initiative (GENFI) cohort.

We considered 249 subjects with FTD-related pathogenetic mutations and 223 mutation non-carriers (HC). Dynamic connectivity was evaluated using independent component analysis and sliding-time window correlation to rs-fMRI data, and meta-state measures of global brain flexibility were extracted.

Results show that presymptomatic FTD exhibits diminished dynamic fluidity, visiting less meta-states, shifting less often across them, and travelling through a narrowed meta-state distance, as compared to HC. Dynamic connectivity changes characterize preclinical FTD, arguing for the desynchronization of the inner fluctuations of the brain. These changes antedate clinical symptoms and might represent an early signature of FTD to be used as a biomarker in clinical trials.

Protective effects of CSF sTREM2 on cognitive performance

Michael Ewers

LMU Munich

Background

Microglia activation is the brain's major response for removing pathogens and inducing repair processes in disease. TREM2 is a key molecular that triggers disease-associated microglia activation, where loss-of-function mutations in the TREM2 gene are associated with a dramatically increased risk in AD. Whether higher protein levels of TREM2 in AD are associated with higher maintenance of cognitive abilities in the presence of AD pathology is however unclear. Here we measured soluble TREM2 (sTREM2) in the cerebrospinal fluid (CSF) to test whether TREM2 is predictive of slower rates of cognitive decline within the spectrum of AD.

Methods

sTREM2 was measured via ELISA in the CSF from 385 subjects including cognitive normal controls, mild cognitive impairment (MCI) and AD dementia patients recruited within the Alzheimer's disease neuroimaging initiative (ADNI). Hippocampus volume was assessed via Freesurfer. Composite score of episodic memory and global cognition were assessed annually for up to 11.5 years (median = 4 years, range = 1.5 – 11.5 years).

Results

In mixed effects regression analyses in subjects with biomarker-evidence of Aβ and pathologic tau (N = 285), higher CSF sTREM2 at baseline predicted slower rate of worsening in episodic memory and global cognition. Furthermore higher CSF sTREM2 was associated with slower hippocampus volume loss. The regression analyses were all controlled for CSF $Aß_{1-42}$, CSF p-tau_{181}, age, gender, education and clinical diagnosis. Cox-regression showed higher CSF sTREM2 to be associated with slower rate of clinical progression to MCI or AD dementia.

Conclusions

Higher levels of sTREM2 at a given level of primary AD pathology including Aβ and tau show protective effects on cognitive changes in AD, and may thus enhance cognitive resilience against AD pathology.

Glucocorticoids and cognitive function in preclinical AD

Chinedu Udeh-Momoh

Imperial College London

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) system is thought to contribute to Alzheimer's disease (AD) pathogenesis, as well as clinical symptom development (De Leon et al., 1988, Notarianni, 2013). Indeed hyper-secretion and aberrant signalling actions of the axis's end-effector molecule, glucocorticoid (GC) is reported to impede normal amyloid-beta and tau processing (i.e. the key histo-pathological hallmarks of the condition), promote neurodegeneration, synaptic dysfunction, and importantly facilitate AD-related cognitive deficits (De Leon et al., 1988, Baglietto-Vargas et al., 2013). Furthermore, recent evidence in cognitively healthy elderly individuals posits abnormal GC secretion as a predictive marker for rapid cognitive decline in individuals at high risk for AD (Pietrzak et al., 2017).

Focusing on time points prior to the onset of AD symptoms, I will present data from a detailed exploration of the HPA axis biological signature, where we describe fully the intracellular signalling actions of the glucocorticoid hormone at the preclinical stage. Unlike existing studies evaluating HPA axis actions in AD where animal models utilised have not featured robust pathological hallmarks of the disease or investigated the prodromal stage; our study comprehensively phenotypes the molecular characteristics of the abnormal HPA axis response in an animal model (3X-Tg-AD) that recapitulates key pathological features in human AD [namely amyloid deposition and neurofibrillary tangle formation (Oddo et al.,2003)] at the pre-pathology and pre-symptomatic stage. Extensive circadian abnormalities in this particular model has been reported, an occurrence that precedes the manifestation of AD pathological features (Sterniczuk et al., 2010), and thought to contribute to symptoms including cognitive deficits, even in humans (Nusiek et al., 2015, Tranah et al., 2011).

Novel findings depicting the molecular mechanisms that contribute to the notable circadian rhythm disturbances at the pre-pathology and pre-symptomatic stage will be described (Udeh-Momoh et al., manuscript in preparation).

Additionally, data obtained from the Alzheimer's disease Neuroimaging initiative (ADNI) featuring the first evidence for the pro-cognate effects of brain and cognitive reserve indices in pre-symptomatic individuals at high risk for clinical progression as a result of an aberrant HPA axis and cerebral amyloid profile will be presented (Udeh-Momoh et al., 2019).

BACE1 inhibition and dendritic spines

Jochen Herms

LMU Munich

Objectives

Mutations within the β-cleavage site of APP confer protection against cognitive decline in the elderly and BACE1 gene ablation abrogates β-amyloid pathology in Alzheimer mice strongly supporting BACE1 as a valid target to diminish Aβ related toxicity. However, despite the development of potent and selective small-molecule BACE1 inhibitors, so far all human clinical trials have failed to rescue the cognitive decline in AD patients.
Methods: We investigated the impact of early BACE1 inhibition on the dynamics of amyloid, axonal and presynaptic pathology in APPPS1 mice using time-lapse in vivo two-photon imaging

Results

In APPPS1 mice pharmacological treatment with the potent, small-molecule BACE1 inhibitor NB-360 fails to revert but significantly reduces the progressive amyloid deposition and mitigates presynaptic pathology. BACE inhibition was most potent to block the formation of new plaques close to existing plaques.

Conclusion

The results strongly imply presymptomatic application of BACE1 inhibitors before amyloid deposition has reached an asymptote of accumulation to achieve optimum efficacy. Since our data indicates that BACE1 accumulation around plaques significantly contributes to further Aβ deposition, targeting plaque-associated axonal damage could emerge as a suitable strategy not only in treating synapse loss but also to target Aβ accumulation itself.

Aβ deposition and microglial response in Alzheimer's mouse models

Matthias Brendel

LMU Munich

Amyloid mouse models are frequently used to study molecular mechanisms of Alzheimer's disease. This talk highlights the opportunities of in vivo Positron-Emission-Tomography (PET) imaging of amyloidosis and microglia in different amyloid mouse models. In vivo therapy monitoring by PET facilitates to account for the heterogeneous amount of neuropathology at baseline and allows to study predictors of therapy response. A special focus is placed on asymmetric distribution of neuropathology in these models.

Folding mechanisms of alpha-synuclein in vivo

Tim Bartels

University College London

Neuronal aggregates of alpha-synuclein (αSyn) (Lewy bodies and neurites) are a pathological hallmark of Dementia with Lewy Bodies (DLB) and Parkinson's disease (PD). We recently discovered that αSyn, a neuronal protein of unclear physiological function, normally exists in cells and brain tissue principally as a α-helically folded tetramer that resists pathological aggregation. We show here that the tetrameric form is not only resistant to time-dependent self-aggregation but also shows increased resistance to misfolding initiated by tiny amounts of fibrillar material, i.e., "seeded aggregation". Based on our new findings, it is important to identify factors that could trigger the denaturation of folded αSyn and allow its abnormal aggregation in neurons. We can demonstrate that DLB and sPD patients exhibit a region-specific reduction of αSyn multimers in brain tissue according to the classical Braak staging scheme, indicating their destabilization in the course of the disease. The results indicate the vulnerability of early affected brain regions, the importance of a balance of aSYN multimers and monomers and the functional reserve of different brain regions. A factor governing the stabilization of multimers seems to be lipid composition of the cell specific membranes since transient lipid contact acts as a catalyst for multimer formation, meaning that lipid vesicles might act as a "liposomal chaperone" capable of conferring aggregation resistance to the large cytosolic pool of αSyn.

BACE1 in neurobiology and Alzheimer's disease

Stefan Lichtenthaler

TU Munich

The aspartyl protease BACE1 has fundamental functions in the nervous system and is a key drug target in Alzheimer's disease (AD). BACE1 is functionally also linked to schizophrenia and epilepsy. This talk will present the latest discoveries on the function of BACE1 and its substrates, the use of BACE1 substrates as potential companion diagnostics for therapeutic BACE1-targeted inhibitors and of the chances and challenges of BACE1 as an AD drug target.

SESSION 3 - FREE COMMUNICATIONS SESSION

Cerebrospinal fluid biomarkers and cognitive reserve

Panagiotis Alexopoulos

University of Patras

The talk will provide an overview of the influence of cognitive brain reserve on the complex interplay between demographic characteristics, cerebrospinal fluid biomarker levels, longitudinal biomarker changes and clinical symptoms in neurocognitive disorder due to Alzheimer's disease.

Physiological effectiveness of different transcranial stimulation methods (tDCS vs tRNS) in relation to duration of stimulation

Jan Häckert

LMU Munich

With this trial we compared the physiological effectiveness of transcranial direct current stimulation (tDCS) and transcranial random noise stimulation (tRNS) in relation to the duration of stimulation. Both stimulation protocols should induce long-term potentiation (LTP), each protocol was applied for 7, 13 and 20 minutes respectively and the after effects were recorded for one hour after the stimulation. We were able to demonstrate long-term potentiation only with tRNS stimulation and a duration of 7 minutes that began 20 minutes and persisted up to 60 minutes after the stimulation and with a duration of 20 minutes for only one time bin at 50 minutes after the stimulation. The other stimulation protocols did not induce significant LTP after the stimulation.

Motor reserve moderates the detrimental effect of dopamine transporter loss on motor function in Parkinson's disease

Verena Dzialas[1], Merle C. Hoenig[1,2]*, Gérard N. Bischof[1,3], Alexander Drzezga[1,2,4], Thilo van Eimeren[1,4,5]*

[1] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Nuclear Medicine, Cologne, Germany
[2] Molecular Organization of the Brain, Institute for Neuroscience and Medicine II, Research Center Juelich, Juelich, Germany
[3] University of Cologne, Faculty of Mathematics and Natural Sciences, Cologne, Germany
[4] German Center for Neurodegenerative Diseases, Bonn/Cologne, Germany
[5] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Neurology, Cologne, Germany

**both authors contributed equally to this work*

Background
As measure of cognitive reserve, the residual approach considers the variance in cognition not being explained by demographic and neuroimaging predictors. Here, we employed this approach to determine motor reserve (MR) in patients with Parkinson's disease (PD) based on the variance in motor performance not being explained by dopamine transporter loss in the putamen.

Methods
We included 152 PD patients (M(age)= 58.66 ± 4.49, M(UPDRS-III)= 20.44 ± 8.41) for whom a MRI, DaT SPECT, and clinical information were available at the PPMI database. After image pre-processing using SPM12, grey matter (GM) maps were extracted using the CAT12 toolbox. Additionally, the physical activity score for the elderly (PASE) was computed. We derived the MR residuals using linear regression including putaminal DaT SPECT signal as predictor and UPDRS-III as dependent variable, controlling for age and sex. Afterwards, a correlation analysis was performed between the residuals and PASE, followed by voxel-wise group comparison based on the GM maps between groups with high and low MR. Finally, a graph-theoretical network analysis was conducted to determine structural differences between the low and high MR group.

Results
High MR was associated with greater physical activity. PD patients with high MR showed greater GM-volume in motor-associated regions when compared to individuals with low MR. Additionally, the high MR group presented different regional network structure, in particular in motor-associated hubs, than the low MR group.

Conclusion
The residual approach proves as sensitive measure of MR. Higher MR is likely maintained by structural differences of underlying neuronal networks.

Markers of vitamin B12 status in relation to CSF biomarkers and cognitive performance

Babak Hooshmand

Background
The association between markers of vitamin B12 status (vitamin B12, holotranscobalamin (HoloTC), homocysteine (tHcy), and methylmalonic acid (MMA)) and cerebrospinal fluid (CSF) biomarkers of Alzheimer's type dementia which precede cognitive impairment has been investigated by only a few small studies and the results have been inconsistent. Our objective was to investigate the relationship between B12-related biomarkers with CSF total tau, Amyloid-β 42 (Aβ42) and cognitive performance.

Methods
Data included 462 patients aged 40-94 years referred to the Memory Clinic at the Ulm University Hospital, Ulm, Germany between 12.2009 and 08.2015. CERAD battery was used to examine the cognitive status, and different domains were derived. Regression models were used to investigate the associations.

Results
After adjusting for age, sex, creatinine levels and APOEβ4 status, higher values of B12 and lower values of MMA were associated with lower concentrations of CSF total-tau: the odds ratios (ORs) (95% confidence intervals (CI)) were 0.39 (0.15-0.99) and 5.60 (1.93-16.26) for the highest quartile of B12 and MMA compared to the lowest, respectively. Furthermore, HoloTC, MMA, and tHcy were associated with several cognitive domains such as episodic memory and executive functioning. No relationships were found with Aβ42.

Conclusions
Vitamin B12 may be independent predictors of CSF biomarkers of Alzheimer's disease and cognitive status. Randomized controlled trials are needed to determine the importance of B12 supplementation on slowing structural brain changes and cognitive decline.

Association of TDP-43 proteinopathy, cerebral amyloid angiopathy, and Lewy bodies with cognitive impairment in individuals with or without Alzheimer's disease neuropathology

Sumali Bajaj

While it is widely known that AD is a multifactorial disease and that patients frequently have pathologies other than ß-amyloid (Aß) plaques and neurofibrillary (Tau) tangles in the brain, the extent to which these co-occurring neuropathologies (TDP-43, CAA and Lewy Body) can affect cognitive decline is poorly understood at present. We developed a statistical model describing the association of the three co-occurring pathologies in patients with AD and non-AD pathology on the progression of cognitive scores (MMSE; CDR-SB) over time. Longitudinal scores were modelled within a Bayesian framework using a hierarchical regression model with random intercepts and slopes, as well as beta regression for our sensitivity analysis. Having TDP-43 pathology, even without AD, was associated with a substantially fast annual rate of cognitive decline (ß = -1.19; 95% CI: -1.71, -0.69 and 0.70; 95% CI: 0.35, 1.06 for MMSE and CDR-SB respectively). 63% in our data had TDP-43 or CAA along with AD pathology. These results suggest that even if a drug completely removed all parenchymal Aβ and Tau neuropathology within a well-defined AD population, a high proportion of individuals may continue to cognitively decline, potentially being another possible explanation for the failure of clinical trials solely target ß Amyloid. As a next step we hope to incorporate cognitive reserve in our model to understand the true relation between neuropathologies and cognitive decline.

Increased Neuroanatomic Risk for Alzheimer's Disease Associated with Fine Particle Exposure: Exploring the Role of Cognitive Reserve

Diana Younan[1], Andrew J. Petkus, PhD[2], Xinhui Wang, PhD[2], Ramon Casanova[3], Ryan Barnard[3], Sarah A. Gaussoin[3], Santiago Saldana[3], Susan M. Resnick, PhD[4], Marc Serre, PhD[5], William Vizuete, PhD[5], Victor W. Henderson, MD[6], Bonnie C. Sachs, PhD[7], Daniel P. Beavers, PhD[3], Joel A. Salinas, MD[8], Sally A. Shumaker, PhD[9], JoAnn E. Manson, MD, DrPH[10], Margaret Gatz, PhD[11], Stephen R. Rapp, PhD[12], Helena C. Chui, MD[2], Mark A. Espeland, PhD[3], Jiu-Chiuan Chen, MD[1]

[1] Department of Preventive Medicine, University of Southern California, Los Angeles, CA | [2] Department of Neurology, University of Southern California, Los Angeles, CA | [3] Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC | [4] Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, MD | [5] Department of Environmental Sciences and Engineering, University of North Carolina, Chapel Hill, NC | [6] Departments of Epidemiology & Population Health and of Neurology and Neurological Sciences, Stanford University, Stanford, CA | [7] Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC | [8] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA | [9] Department of Social Sciences & Health Policy, Wake Forest School of Medicine, Winston-Salem, NC | [10] Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA | [11] Center for Economic and Social Research, University of Southern California, Los Angeles, CA | [12] Department of Psychiatry and Behavioral Medicine, Wake Forest School of Medicine, Winston-Salem, NC

Individuals with high cognitive reserve (CR) may better cope with PM2.5 neurotoxicity on brain aging. We investigated whether CR modifies the association between PM2.5 and brain atrophy predictive of Alzheimer's disease (AD). Community-dwelling participants (aged 70-87) from the Women's Health Initiative (WHI) Study of Cognitive Aging and the WHI Memory Study of Magnetic Resonance Imaging were assigned AD pattern similarity (AD-PS) scores, a biomarker capturing gray matter atrophy in brain areas vulnerable to AD1. Residential three-year average PM2.5 exposure preceding MRI-1 were aggregated from daily 1999-2010 estimates from nationwide spatiotemporal modeling. CR was derived by a: 1) Multiple Indicator, Multiple Cause (MIMIC) framework2 (Fig.1) to measure general reserve; 2) Variance Decomposition approach3 (Fig.2) to measure general and domain-specific (attention; verbal memory; figural memory; language; visuospatial) reserve; 3) measure of vocabulary. We examined whether reserve (median-split) modified the association between PM2.5 and AD-PS scores (5-year standardized difference) using generalized linear models. Among 469 women, PM2.5 (per 2.05 μg/m3 increase) was associated with increased AD-PS scores (β=0.011; p=0.141). Adverse effects of PM2.5 were greater among women with low (β=0.032; p=0.004) vs. high (β=-0.009; p=0.367) attention reserve (pinteraction=0.005) and women with low (β=0.029; p=0.010) vs. high (β=-0.0033; p=0.746) vocabulary (pinteraction=0.027). There was no effect modification by general (via MIMIC or variance decomposition) or other domain-specific reserve. Our novel findings suggest high reserve attenuates PM2.5 neurotoxicity on brain aging in the preclinical stage. Distinctive neuropsychological processes, possibly reflecting different neuropathological underpinnings of CR measures, may impart differential susceptibility to the air pollution neurotoxicity continuum.

Modified Mini-Mental State (3MS) scores, education, and social engagement included as reflective indicators and physical activity and occupational attainment as formative latent variables of CR. Note: Social engagement was defined as participating in meetings of clubs, lodges, or parent groups or attending religious services or church during the past month. Physical activity defined as MET-hours per week from walking (WALKEXP), hard exercise (HARDEXP; e.g., aerobics, jogging, tennis, swimming laps), moderate exercise (MODEXP; e.g., biking outdoors, calisthenics, easy swimming, folk dancing), and mild exercise (MILDEXP; e.g. slow dancing, bowling, golf). Occupation was defined using dummy variables for managerial/professional (MANGR; e.g., teacher, guidance counselor, doctor, registered nurse, lawyer, accountant, architect, computer/systems analyst, personnel/sales manager), technical/sales/admin support (TECH; e.g. computer programmer/operator, dental assistant, laboratory technician, sales clerk, cashier, receptionist), and service (SERV; policewoman, teaching assistant, child care attendant, maid, cook, waitress, seamstress), with homemaker as the reference group.

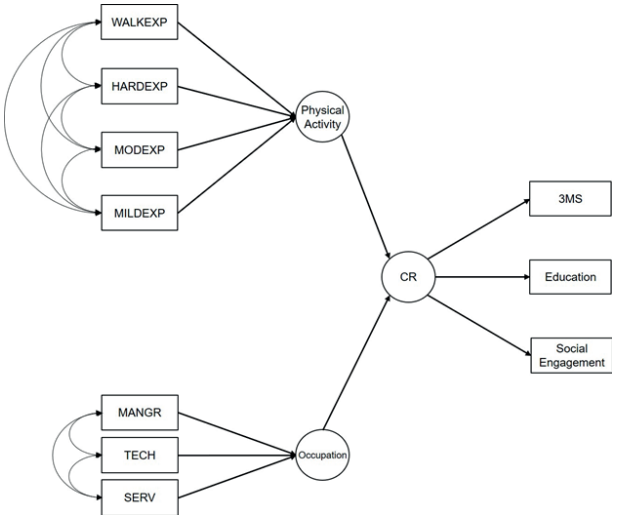

Figure 1. Multiple indicators, multiple causes (MIMIC) model

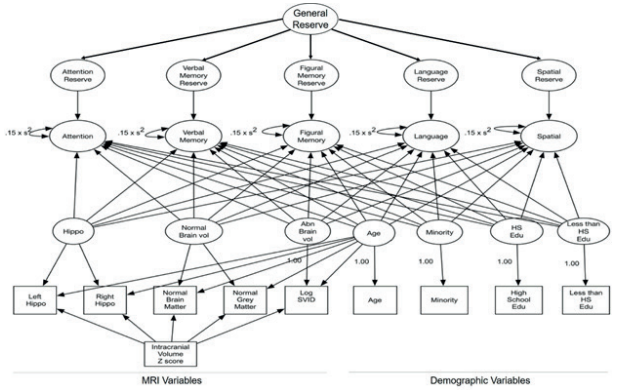

Figure 2. Variance decomposition approach

Diagram of the variance decomposition approach depicting the higher-order multivariate reserve model. Note: Left Hippo represents left hippocampal volume, Right Hippo represents right hippocampal volume, Log SVID represents log transformed small vessel ischemic disease. All MRI variables had residual variance constrained to .15 times the variance in order to account for error in measurement.

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The relationship between tau pathology and microglial activation in PSP-Richardson's syndrome

Maura Malpetti

Despite the undoubted importance of tau pathology in Progressive Supranuclear Palsy (PSP), neuroinflammation has also been recognized as another key aspect in the pathophysiology of PSP. However, it remains unclear whether these pathogenic processes are related in vivo.

We examined the relationship between tau pathology and microglial activation using [18F]AV-1451 (indexing tau burden) and [11C]PK11195 (microglial activation) PET in 17 patients with PSP-Richardson's syndrome.

Non-displaceable binding potential (BPND) for each ligand was quantified from 83 brain regions of interest (ROIs) based on a modified Hammers Atlas with brainstem parcellation. First, [18F]AV-1451 and [11C]PK11195 BPND values were correlated across all ROIs. Second, the anatomical patterns of [18F]AV-1451 and [11C]PK11195 binding co-localization was determined across sets of regions derived from tracer-specific principal component analyses (PCAs). Finally, PCA-derived brain patterns of tau pathology and neuroinflammation were correlated to clinical severity.

[18F]AV-1451 and [11C]PK11195 binding were positively related across all brain ROIs ($r=0.577$, $p<0.0001$). PCAs identified four components for each ligand, reflecting the relative expression of tau pathology or neuroinflammation in distinct groups of brain regions. Positive associations between [18F]AV-1451 and [11C]PK11195 components were found in sub-cortical ($r=0.769$, $p<0.0001$) and cortical components ($r=0.836$, $p<0.0001$). PCA-derived components reflecting tau burden ($r=0.599$, $p=0.011$) and neuroinflammation ($r=0.713$, $p=0.001$) in sub-cortical areas related to disease severity.

Our results confirm the relevance of neuroinflammation to PSP-Richardson's syndrome and a close association with tau pathology in the core regions for this disease. This encourages the application of [18F]AV-1451 and [11C]PK11195 PET as markers of co-localised pathological mechanisms in PSP.

Pro: Appropriate animal models are available

Oliver Wirths

Dept. of Psychiatry, University Medical Center Göttingen

In mouse models of Alzheimer's disease (AD), impaired neurogenesis has been repeatedly reported to be associated with further AD-typical hallmarks such as extracellular plaque deposition, neuroinflammation or behavioral deficits. Hippocampal neurogenesis plays a necessary role in the maintenance of learning and memory abilities, depending on proper function of the hippocampal circuitry. As treatment approaches targeting Abeta peptides were so far not successful in clinical trials, alternative strategies aiming on disease prevention become more important. There is ample evidence from epidemiological, as well as preclinical studies, that more general interventions, such as increased physical activity or caffeine intake, might contribute to a reduced AD risk. Accordingly, numerous studies have shown that in particular continuous exercise can successfully counteract or prevent pathological changes in AD in transgenic mouse models. Although many studies demonstrated that increased physical activity results in significantly increased neurogenesis rates in adult rodent brains, there is also data showing no beneficial effects, in particular in more aggressive transgenic AD mouse models.

Con: Better animal models must be developed

Amos Korczyn

Tel-Aviv University Medical School

Cognitive reserve is a hypothetical term. It basically refers to the observation in humans that people who have achieved higher intellectual attainments develop less cognitive decline in aging than expected from the pathological changes in their brain, eg beta-amyloid load.

This observation by itself is problematic. Since we believe that cognition resides in the brain (rather than in the mind), there should be a correlation between cognitive loss in aging and some anatomical changes. If amyloid or tau do not show a sufficient strong correlation, other parameters (synapses?) must be searched for.

Once such a correlation is found, the relevant question will be whether any intervention, such as schooling, will affect the cognitive status and the anatomical changes similarly; and why would this effect be only seen in old age.

Cognitive reserve has so far only been demonstrated in elderly people. It is however not easy to show such decline in experimental animals and therefore any attempt to affect "cognitive reserve" through "intellectual stimulation " at young age is fraught with insurmountable difficulties.

Clinical aspects of neuroinflammation in Alzheimer's disease

Norbert Müller

Marion v. Tessin Center

The pathogenetic mechanisms of Alzheimer's disease (AD) are up to now only partly understood. There is no doubt that 'immunosenescence', the aging of the (healthy) immune system, leads to impaired immune function and that aging is the main risk factor for AD. Also beyond doubt is that neuroinflammation plays a key role in the pathophysiology of the disease. However, whether inflammation is an underlying cause or a resulting condition in AD remains unresolved. At higher ages, communication in the peripheral and CNS immune systems, including both the initiation of the immune process and the down-regulation of inflammation, are impaired; this impaired communication might be one of the main factors contributing to the immune pathology of AD. The innate (monocytes, macrophages) and adaptive immune systems (T- and B-cells) have been shown to be upregulated in aging and AD. Mounting evidence indicates that microglia activation contributes to neuronal damage in neurodegenerative diseases, but beneficial aspects of microglia activation have also been identified. The possible role of C-reactive protein as inflammation marker is discussed. In this regard, we discuss the limitations and advantages of the protective effects of non-steroidal anti-inflammatory drugs (NSAIDs) and anti-inflammatory treatment options and identify possible future implications for AD therapy that might result from this underlying neuroinflammation.

In vivo imaging of glial activation

Magdalena Sastre

Imperial College London

Inflammatory changes have been firmly linked with deficits in neuronal function and synaptic plasticity in Alzheimer's disease (AD), especially in brain areas controlling memory and cognition. Progress has been hampered by the inability to follow the development of glial activation longitudinally in live animals, which has the major advantage of allowing changes in imaging measures to be correlated with changes in behaviour and cognition.

A technique that may enable such longitudinal in vivo investigations is positron emission tomography (PET), a medical imaging technique that is able to measure the distribution and concentration of sub-pharmacological doses of radiolabelled compounds within the body over time. A new generation of radiotracers targeting TSPO, such as the [11C]-PBR28 have been developed to measure activated microglia.

Our data show that the binding of PBR28 in the 5XFAD model of AD shows an increase compared with wild-type mice and coincides with the positive staining of the microglial marker Iba-1 in the same brain areas, providing support for the suitability of [11C]PBR28 as a tool for in vivo monitoring of microglial activation.

In addition, we have been investigating the use of the imidazoline tracer [3H]BU99008 for in vitro autoradiography, as marker of astrocytes. [3H]BU99008 binding in the healthy rodent brain was low and appeared to be increased in severe animal models that include gliosis.

Neuroinflammation in Alzheimer's disease: the ActiGliA study

Robert Perneczky

LMU Munich

The accumulation of pathologic proteins such as amyloid-β (Aβ) and tau in the brain characterise Alzheimer's disease (AD), but other changes including the degeneration of brain networks and a response of the immune system also play key roles. Brain structural and functional connectivity become impaired increasingly as AD progresses. Alterations of the intrinsic connectivity of brain resting state networks and fibre tracts correlate with disease severity and can be measured in vivo using BOLD functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) respectively. The role of glial activation in the neuropathology of AD has also been widely recognised both as a consequence and as a contributing factor for the formation of Aβ and tau aggregation. Immune surveillance in the brain is mainly due to astroglial and microglial cells and microglial activation can be measured reliably by TSPO positron emission tomography (PET). To understand better important associations between network degeneration and immune response in AD, we initiated the ActiGliA prospective cohort study in 2018. Here we present initial results of the first ≈100 patients, including baseline clinical and biomarker characteristics of the cohort and topographical associations between disease-stage dependent microglial activation and resting state connectivity changes. In line with previous findings, we confirm that brain functional and structural connectivity are disrupted and microglial activity is elevated in AD; however, we also show that significant inter-subject heterogeneity exists, warranting more detailed correlation with individual characteristics including symptom severity and Aβ and tau status.

Astroglial activation in cognitively impaired subjects in vivo using novel 11C-BU99008 PET and its relationship with amyloid load

Running Title: Amyloid and astroglial activation in AD/MCI

Paul Edison[1], Valeria Calsolaro[1], Paul M Matthews[1,2], Jim F M Myers[1], Zhen Fan[1], Robin J Tyacke[1], Ashwin V Venkataraman[1], Grazia D Femminella[1], Robert Perneczky[3,4,5,6], Roger N Gunn[1,7], Eugenii A Rabiner[7,10], Steve Gentleman[1], Christine A Parker[1,8], Philip S Murphy[8], Paul B Wren[8], Rainer Hinz[9], David J Nutt[1]

[1] *Imperial College London, London, United Kingdom*
[2] *UK Dementia Research Institute at Imperial College London*
[3] *Department of Psychiatry and Psychiatry, University Hospital, LMU Munich, Munich, Germany*
[4] *German Center for Neurodegenerative Disorders (DZNE) Munich, Munich, Germany*
[5] *Munich Cluster for Systems Neurology (SyNergy), Munich, Germany*
[6] *Ageing Epidemiology Research Unit (AGE), School of Public Health, Imperial College London, London, UK*
[7] *Invicro, London, United Kingdom*
[8] *GlaxoSmithKline, Stevenage, United Kingdom*
[9] *Wolfson Molecular Imaging Centre, University of Manchester, UK*
[10] *King's College London, London, United Kingdom*

Background
Glial activation plays a significant role in cognitive impairment. ^{11}C-BU99008 is a novel PET tracer selective for Imidazoline I_2 binding sites distributed on glial cells. The aim of this study was to evaluate ^{11}C-BU99008 uptake in cognitively impaired amyloid positive and amyloid negative subjects evaluated using ^{18}F-florbetaben PET.

Methods
11 cognitively impaired patients and 10 healthy controls [HC]) underwent 3T MRI, ^{11}C-BU99008 PET with arterial blood sampling and ^{18}F-florbetaben PET. ^{11}C-BU99008 PET was analysed quantitatively using arterial plasma input function while ^{18}F-florbetaben uptake was used to define amyloid-positivity.

Results
Six cognitively impaired subjects were amyloid-positive. They showed significantly higher tracer uptake relative to the HC in the frontal, temporal, medial temporal, parietal and occipital lobes, along with posterior cingulate and the cerebellum. All six amyloid positive subjects showed cortical clusters of significant ^{11}C-BU99008 uptake along with a positive voxel-wise correlation between ^{11}C-BU99008 and ^{18}F-florbetaben uptake.

Conclusion
Our results demonstrated increased I_2-BSs in cognitively impaired amyloid positive subjects using ^{11}C-BU99008 reflecting astroglial activation providing a potential new tool for longitudinal assessment astroglial activation in mechanistic and intervention studies.

Innate Immunity in Alzheimer's disease

Michael Heneka

University of Bonn

The accumulation of neurotoxic amyloid beta peptides and/or neurofibrillary tangle formation are key pathological hallmarks of Alzheimer's disease. The brain has been considered as an immune-privileged organ, however, increasing evidence from translational, genetic, and pathological studies suggests that activation of distinct innate immune pathways are a third important disease hallmark.

Microglia play a pivotal role in this immune response and are activated by binding of aggregated proteins or aberrant nucleic acids to pattern recognition receptors. This immune activation leads to the release of inflammatory mediators, but also distracts microglia cells from their physiological functions and tasks, including debris clearance and trophic factor support. NLRP3 inflammasome activation and release of ASC specks contribute to spreading of pathology and impair microglia clearance mechanisms, and together contribute to neuronal spine loss, neuronal degeneration, and ultimately to spatial memory deficits. In keeping with this immune hypothesis of neurodegeneration, inhibition of this and other immune pathways protect from neurodegeneration in cellular and murine models of neurodegenerative disease. Modulation of the microglia driven innate immune response at key signaling steps might therefore be protective and alter disease progression.

The Infectious Etiology of Alzheimer Disease and the Antimicrobial Protection Hypothesis

Richard Lathe

Division of Infection Medicine, University of Edinburgh Medical School, Edinburgh, UK

Alzheimer disease (AD) is characterized by the deposition in brain of β-amyloid (Aβ), but is Aβ a cause of disease or a defense mechanism? Removal of Aβ by antibody therapies has no beneficial effect in AD. Evidence now argues that Aβ protects the brain against microbial infection. Diverse infectious agents, including herpes viruses, are upregulated in AD brain: Aβ is induced by infection, and has direct antimicrobial action, leading to the antimicrobial protection hypothesis. Antiviral therapy may potentially prevent later onset of AD. Unsolved questions include which specific microbes proliferate in AD brain, whether antimicrobial therapy can indeed slow AD progression, and what is different about AD individuals that precipitates neurodegeneration.

The contribution of mid-life activities to late-life cognitive reserve

Richard Henson

University of Cambridge

I will describe data from the Cambridge Centre for Ageing Neuroscience (CamCAN; www.cam-can.org) in which we related cognitive health (using the Cattell test of Fluid Intelligence) in retired people over 65 to measures of their lifetime experience (using the Lifetime of Experiences Questionnaire). Apart from education, mid-life non-specific activities (physical, social and intellectual activities outside occupation) made a unique contribution to predicting current (late-life) cognitive health. Moreover, mid-life non-specific activities moderated the relationship between cognitive health and brain health, as defined by total gray-matter volume estimated from T1 MRI images: greater mid-life activities were associated with a weaker relationship between cognitive and brain health, satisfying a common definition of cognitive reserve.

Modulation of genetic risk by lifestyle factors

Arfan Ikram

Erasmus Medical Center Rotterdam

Dementia has a considerable component of genetic heritability with recent genome-wide association studies (GWAS) identifying several genetic variants related to risk of dementia. Additionally, several GWAS have also identified risk variants linked to endophenotypes of reserve. Individually, these genetic variants have a very modest effect, but collectively the genetic burden can be considerable and can even be used for risk stratification purposes.

The question remains though to what extent this genetic risk is amenable by lifestyle interventions. This information is important not only for individual management of people worried about their dementia risk, but it can also provide leads to develop preventive strategies that effectively target high-risk persons.

This talk will discuss important work in this area and provide directions for future research. Recent findings from the UK Biobank and the Rotterdam Study will be highlighted.

Cardiovascular health and dementia risk

Cecilia Samieri

University of Bordeaux

Dementia results from a dynamical cascade of neuropathological processes involving two major components: a lesional component, made of different types of brain lesions accumulated over many years, and a compensatory component, defined by reserve and resilience mechanisms. Cardiometabolic risk factors are among the strongest risk factors for dementia, and have the potential to modulate both lesional and compensatory components. This presentation will provide an overview of current knowledge on the heart-brain connection, with a lifecourse epidemiological perspective. We will use examples of research conducted in cohorts with very long follow-up, such as the Three-City study, to illustrate the links between cardiometabolic heath and dementia. We will show how trajectories of cardiometabolic factors differ years before diagnosis in individuals that went on to develop dementia, and how optimal cardiovascular health levels is linearly associated with a decreasing risk of dementia. The ultimate goal is to better understand how, and in which time windows over the lifecourse, cardiometabolic health modulates both neuropathology and reserve/resilience mechanisms to prevent dementia.

Physical activity, apolipoprotein-ε4 and multi-domain cognition among healthy older adults

Catherine Robb[a]; Chinedu Udeh-Momoh[a]; Petra A. Warka[c]; Lefkos Middleton[a]; Robert Perneczky[a,b]

[a] *Neuroepidemiology and Ageing Research Unit, School of Public Health, Imperial College London;*
[b] *Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-Universität München, Munich, Germany;*
[c] *Centre for Innovative Research Across the Life Course, Faculty of Health and Life Sciences, Coventry University*

Introduction
Physical activity (PA) engagement is consistently associated with preserved cognition and lower risk of cognitive decline among older adults. Whether PA mitigates enhanced risk for dementia via APOEε4 allele carriage and amyloid status is less understood. This study aimed to evaluate the longitudinal relationship between PA, peripheral amyloid-beta levels and cognition among cognitively healthy older adults, and whether these associations varied as a function of APOEε4 carrier status.

Methods
Data of 901 cognitively healthy older adults (60-85 years; mean age = 68.7 ± 3.9) from the CHARIOT: PRO Main Study were utilised. The mean follow-up period was 18.5 months (SD 1.7), ranging from baseline to 30-months. Mixed-models regression analyses explored the associations between PA and cognition over time, including effect modification by APOEε4 carrier status and peripheral amyloid-beta levels. All analyses were controlled for a priori selected health and demographic factors.

Results
Being physically active was positively associated with longitudinal multi-domain cognitive performance. The positive association between PA and delayed memory trajectories were augmented among APOEε4 carriers, when compared to non-carriers. There was an inverse association between amyloid-beta plasma levels and global cognition and attention index scores, which were modified by late-life PA.

Conclusion
This study highlights the benefits of PA in mitigating cognitive decline in older age, especially among certain risk groups. Elucidating the complex interrelations between modifiable and non-modifiable risk factors for AD will aid in promoting lifestyle intervention as a viable preventative strategy for public health recommendations.

Sleep disturbance and dementia risk

Shireen Sindi

Karolinska Institute Stockholm

Introduction
Sleep disturbances commonly follow the onset of dementia. However, few longitudinal studies have assessed whether sleep disturbances are associated with dementia risk. The current study examines the associations between sleep disturbances and dementia using population-based data.

Methods
Sleep disturbances were assessed in three population-based studies (H70 study and Kungsholmen Project (KP) (Sweden); Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study (Finland)). Late-life baseline analyses (3-10 years follow-up) used all three studies (N=1446). Baseline ages≈70 (CAIDE, H70), and ≈84 (KP). Midlife baseline (age≈50) analyses used CAIDE (21 and 32 years follow-up) (N=1407).

Results
Midlife insomnia (fully adjusted hazard ratio (HR) = 1.24, 95% confidence interval (95% CI) = 1.02 -1.50) and late-life terminal insomnia (fully adjusted odds ratio (OR) = 1.94, 95% CI = 1.08 – 3.49) were associated with a higher dementia risk. Late-life long sleep duration (> 9 hours) was also associated with an increased dementia risk (adjusted OR = 3.98, 95% CI = 1.87 – 8.48).

Discussion
Midlife insomnia and late-life terminal insomnia or long sleep duration were associated with a higher late-life dementia risk. These results indicate that different stages in the life course are sensitive to specific sleep disturbances and warrant clinical attention.

SESSION 7 - PREVENTION AND INTERVENTION STRATEGIES

Biomarkers and response to a multi-modal lifestyle intervention: The FINGER study

Alina Solomon

University of Eastern Finland, Institute of Clinical Medicine/Neurology, Kuopio, Finland
Karolinska Institutet, Department of Clinical Geriatrics, Center for Alzheimer Research, Stockholm, Sweden

Several modifiable vascular and lifestyle related risk factors throughout the life course have been linked to the risk of cognitive impairment and dementia. Randomized controlled trials (RCTs) targeting these factors are much needed. Given the multifactorial etiology of dementia, multi-domain interventions targeting several risk factors and disease mechanisms simultaneously are most likely to be effective.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a pioneering trial providing the first evidence from a large RCT that a multi-domain lifestyle intervention may prevent cognitive and functional impairment. FINGER includes several exploratory sub-studies investigating intervention effects on various biomarkers, as well as potential heterogeneity of intervention effects on cognition according to baseline biomarkers. New results from the trial will be presented, with focus on e.g. structural brain MRI, amyloid-PET, genetic markers (APOE, telomere length).

FINGER represents a pragmatic model, which is now being tested in diverse populations and settings worldwide. To promote synergy across these trials and optimize efforts towards dementia prevention, we recently launched the World-Wide FINGERS Initiative. WW-FINGERS is an interdisciplinary network, to share experiences and data, and plan joint initiatives focusing on dementia prevention. WW-FINGERS will facilitate synergistic use of data from several countries, creating a unique opportunity for rapid implementation of knowledge and definition of effective and feasible prevention programs for diverse populations.

Challenging neural plasticity in schizophrenia

Alkomiet Hasan

LMU Munich

Schizophrenia is a disorder associated with impaired neural plasticity and cognitive dysfunctions. These cognitive dysfunctions are only to a limited extent responsive to antipsychotic treatment or cognitive trainings. In the recent years, non-invasive brain stimulation techniques have been introduced as plasticity-modulating techniques in the fields of schizophrenia research and treatments. The talk will give a short introduction into the concept of impaired plasticity and cognitive dysfunctions in schizophrenia and will display results of how non-invasive brain stimulation improves plasticity in schizophrenia.

The metabolic brain signature of cognitive resilience

Eider Arenaza-Urquijo, PhD

Barcelonabeta Brain Research Center

The goal of the study was to identify a fluorodeoxyglucose (FDG)-PET based imaging marker of cognitive resilience. The study included 457 participants 80 years or older (80+) 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). First, we identified the metabolic areas underlying cognitive resilience in cognitively stable 80 + participants, which we call the 'resilience signature'. Second, we evaluated the association of risk and protective factors with the resilience signature and its added value for predicting global cognition beyond established AD imaging biomarkers in the full 80 + sample. Third, we evaluated the utility of the resilience signature in conjunction with amyloidosis in predicting longitudinal cognition. 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) in the full MCSA 80 +, amyloid burden and FDG-PET in the resilience signature were the stronger predictors of baseline global cognition; (iii) sex and systemic vascular health predicted FDG-PET in the resilience signature; (iv) the resilience signature provided significant information about global longitudinal cognitive change even when considering amyloid status. The FDG-PET resilience signature may be able to provide important information for the determination of clinical prognosis.

Effects of a 3-Year Multi-Domain Intervention on cognitive performance in older adults with increased dementia risk

Pierre-Jean Ousset

University of Toulouse

Summary

Few published trials have investigated the efficacy of an intervention combining a specific compound and lifestyle interventions compared with placebo for the prevention of cognitive decline. The Multidomain Alzheimer Preventive Trial (MAPT) tested the effect of omega 3 polyunsaturated fatty acid supplementation and a multidomain intervention (physical activity, cognitive training, and nutritional advice), alone or in combination, compared with placebo, on cognitive decline.

Methods

MAPT was a 3-year, multicentre, randomised, placebo-controlled trial with four parallel groups conducted at 14 memory centres in France. Participants were nondemented, 70 years or older, presenting either a spontaneous memory complaint, limitations in one instrumental activity of daily living, or slow gait speed. They were randomized to either the multidomain intervention plus omega 3 polyunsaturated fatty acids, multidomain intervention plus placebo, omega 3 polyunsaturated fatty acids alone, or placebo alone. The primary outcome was change from baseline to 36 months on a composite Z score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding test, ten Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test). The trial was registered with ClinicalTrials. gov (NCT00672685).

Results

1680 participants were enrolled between May 30, 2008, and Feb 24, 2011. In the modified intention-to-treat population (n=1525), there were no significant differences in 3-year cognitive decline between any of the three intervention groups and the placebo group. Between-group differences compared with placebo were 0·093 (95% CI 0·001 to 0·184; adjusted p=0·142) for the combined intervention group, 0·079 (–0·012 to 0·170; 0·179) for the multidomain intervention plus placebo group, and 0·011 (–0·081 to 0·103; 0·812) for the omega 3 polyunsaturated fatty acids group. The interventions did not raise any safety concerns and there were no differences between groups in serious or other adverse events.

Discussion and conclusion

The multidomain intervention and polyunsaturated fatty acids, either alone or in combination, had no significant effects on cognitive decline over 3 years in elderly people with memory complaints. However, analyses in subgroups and ancillary studies suggest an effect in targeted populations: participants with low omega 3 fatty acid index or subjects presenting an amyloid proven pathology. This should be confirmed in further studies targeting these specific groups of at-risk individual.

Amyloid β species dependent neuronal hyperactivation in hippocampal mouse slices

Manuel M. Simon[1], Benedikt Zott[1], Wei Hong[2], Matthew P. Frosch[3], Dominic M. Walsh[2], Arthur Konnerth[1]

[1]Institute of Neuroscience and the Munich Cluster for Systems Neurology, Technical University of Munich, 80802 Munich, Germany.
[2]Laboratory for Neurodegenerative Research, Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA 02115, USA.
[3]C.S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital, Boston, MA 02114, USA.

The occurrence of neuronal hyperactivation in early stages of Alzheimer´s disease (AD) is a well characterized phenomenon. In the past, we could demonstrate that neuronal hyperactivity can even be triggered in wildtype mice by the application of soluble Aβ in vivo. Here, we report the development of an in vitro assay using two-photon calcium imaging in the hippocampal CA1 area. We found that the induction of hyperactivity is Aβ species dependent and requires a 'threshold' level of preexisting neuronal baseline activity.

Initially, we were puzzled by the fact that synthetic Aβ dimer application could not induce hyperactivity in untreated hippocampal slices. We discovered that in in vitro preparations the level of spontaneous baseline activity is much lower than in vivo. After raising the neuronal activity pharmacologically, we were able to observe Aβ-induced neuronal hyperactivation. Furthermore, we demonstrated that the application of brain extract from an AD patient provoked the same hyperactivity. Immunodepletion of Aβ prevented the effect. Finally, we injected human Aβ dimers which potently induced hyperactivation whereas human Aβ monomers were largely ineffective.

In summary, we demonstrated the hyperactivity-inducing effect of human and synthetic Aβ in hippocampal slices with pharmacologically increased neuronal activity. Notably, the application of all Aβ species was ineffective in functionally silent untreated slices, suggesting an activity-dependent mechanism of Aβ dependent hyperactivation.

Long-term trajectories of body weight, diet and physical activity from midlife through late-life and subsequent cognitive decline in women

Maude Wagner, Francine Grodstein, Cecile Proust-Lima, Cecilia Samieri**

**these authors contributed equally*

Background
Healthy lifestyle has been associated with a lower risk of cognitive decline and dementia. However, there have been inconsistencies in the literature on the age range at which lifestyle factors critically impact subsequent cognitive aging. Our objective was to examine trajectories of lifestyle factors from mid- through later-life in relation to subsequent cognitive decline in a large prospective cohort of women, the Nurses' Health Study (NHS).

Methods
We conducted a nested case-control study within the NHS, of women aged 70 years who were administered 4 repeated cognitive interviews from 1995-2001 and who provided extensive data on lifestyle from 1976. Among 14,956 women free of cognitive impairment at initial interview, cases (n=l,496) were defined as those with the 10% worst slopes of cognitive decline and controls (n=7,478) as those with slopes better than the median. We compared trajectories of body mass index (BMI), alternate Mediterranean diet (A-MeDi) score and physical activity between cases and controls, using data collected from 1976 for BMI, from 1984 for diet and from 1986 for activity, and continuing through 1 year prior to the first cognitive interview.

Results
At baseline assessment of lifestyle in midlife, women who subsequently became cases of cognitive decline had higher BMI, lower physical activity levels and worse A-MeDi score. From mid- through later life, we found a deceleration of weight gain and a decrease of physical activity among cases (P<.001 for difference in trajectories between groups) versus controls; one year preceding ascertainment of cognitive decline, BMI of cases was similar to controls and physical activity levels were markedly lower. A-MeDi scores of cases remained worse than of controls consistently over follow-up (P=.87 for difference in trajectories).

Conclusions
In conclusion, maintaining healthy lifestyle since midlife (BMI, diet and physical activity) may help reduce cognitive decline in aging. At older ages, both deceleration of weight gain and decrease in physical activity levels may reflect early signs of cognitive impairment. These patterns suggest that studies focusing on later-life risk factors for cognitive aging may be subject to reverse causation bias.

Joint Modeling of Time-Varying Exposure History and Health Outcomes: Identification of Critical Windows

Maude Wagner, Francine Grodstein, Cecilia Samieri, Cecile Proust-Lima*.*

** these authors contributed equally*

Context
Life-long exposures constitute a primary focus of research on the etiology of many chronic diseases. Yet, identifying the critical windows when risk factors mostly impact the risk of disease remains an open statistical question. Some methods have already been proposed to assess the effect of a time-varying exposure history. However, research mostly focused on a continuously observed error-free exposure, a binary or time-to-event outcome and a concomitant evaluation of exposure and outcome.

Objective
We propose a joint modelling approach to estimate the dynamics of association between a time-varying exposure history and a subsequent longitudinal health outcome.

Method
We jointly model the trajectory of the exposure over time and its weighted cumulative effect on the subsequent trajectory of the outcome. As we consider separate time windows for the exposure and the outcome, inference can be obtained with a two-stage approach. Subject-specific predictions of exposure are computed from a flexible mixed model in stage 1, thus handling missing data and error in exposure measurement. In stage 2, weighed time-dependent effects (modelled by splines) of these predicted exposures are included in the mixed model for the outcome. The method, which was evaluated in simulations, can be easily implemented in standard statistical software.

Results
We studied the association between body mass index (BMI) history (collected from midlife) and cognition (evaluated after age 70) in the Nurses' Health Study cohort. In a sample of 19,415 women, the method identified two major critical windows of association. Long before the first cognitive evaluation (roughly 24 to 12 years), higher levels of BMI were associated with poorer cognition. In contrast, adjusted for the whole history, higher levels of BMI became associated with better cognition in the last years prior to the first cognitive interview, thus reflecting reverse causation (changes in exposure due to underlying disease).

Conclusions
The proposed joint modelling approach provides a flexible tool to evaluate the trajectory of effect of a time-varying exposure on a subsequent longitudinal outcome. It is particularly useful to explore complex dynamic relationships, as illustrated with BMI and cognition, and address for various clinical questions by identifying critical windows of lifelong exposures.

The effect of frailty on the association of cognitive and brain reserve with 5-year mortality: The Rotterdam Study

J.L. Zijlmans[1], S. Lamballais[1], L. Lahousse[1,2], M.W. Vernooij[1,3], M.K. Ikram[1,4], M.A. Ikram[1], A.I. Luik[1]

[1] Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium
[3] Department of Radiology, Erasmus University Medical Center, Rotterdam, the Netherlands
[4] Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands

Background
A lower cognitive and brain reserve may increase mortality risk. It is unclear if this increased mortality risk is driven by the brain or by a general age related loss of physical fitness, defined by increased frailty. Therefore, we investigated the associations of cognitive and brain reserve with mortality and the role of physical frailty in these associations.

Methods
We followed 1,490 dementia-free participants from the Rotterdam study (mean age 74±5.5 years) for an average of 5.3±1.4 years. Cognitive reserve (CR) at baseline was estimated through variance decomposition using structural equation modeling. Brain reserve (BR) at baseline was defined as the proportion of brain volume of the total intracranial volume measured on a 1.5T MRI scanner. Frailty was operationalized using the Fried physical frailty phenotype. We used cox-proportional hazard models with reserve-frailty interaction terms to estimate hazard ratios for mortality.

Results
A higher CR (HR 0.80, 95% CI 0.68-0.93) was associated with a lower risk of mortality but a higher BR (HR 0.86, 95%CI 0.73-1.03) was not significantly associated with a lower risk of mortality when frailty status was included in the model. The CR*frailty interaction term (HR 1.45, 95% CI 1.08-1.93) was significantly associated with mortality. The BR*frailty interaction term (HR 0.91, 95%CI 0.67-1.24) was not associated with mortality.

Conclusion
A higher cognitive reserve protects against the risk of early mortality, particularly in intermediate frail to frail participants. This study suggests that it is important to consider both cognitive reserve and frailty status in future risk adjustment measures and preventive strategies.

Tau pathology, neuroinflammation and longitudinal cognitive changes in Alzheimer's disease

Maura Malpetti

Tau pathology, neuroinflammation, and neurodegeneration are key aspects of Alzheimer's disease (AD). We studied how baseline assessments of in vivo tau pathology ([18F]AV-1451 PET), neuroinflammation ([11C]PK11195 PET) and brain atrophy (structural MRI) predict longitudinal cognitive changes in AD.

Twenty-six patients (12 AD and 14 with amyloid-positive MCI) and 29 controls underwent baseline assessment with [18F]AV-1451 PET, [11C]PK11195 PET, and structural MRI. Cognition was examined annually over 3 years using the revised Addenbrooke's Cognitive Examination. Regional grey-matter volumes, [18F]AV-1451 and [11C]PK11195 binding were derived from temporo-parietal AD-specific regions. To reduce data dimensionality, we used a Principal Component Analysis (PCA) on each imaging modality separately. A Latent Growth Curve model was applied on longitudinal cognitive scores to estimate the rate of annual decline in each participant. We regressed the estimated slopes on the neuroimaging components, examining univariable models with single-modality predictors, and a multi-modality regression model.

PCA identified a single MRI component, and two components for each PET ligand: one in anterior temporal regions, and another in posterior temporo-parietal regions. In single-modality models, cognitive decline correlated to the first component of each modality. In patients, multiple linear and Bayesian linear regression converged to indicate an optimal predictive model with both [18F]AV-1451 components and the anterior [11C]PK11195 component, excluding the MRI component.

Our results suggest that although temporo-parietal atrophy predicts cognitive decline in AD if considered in isolation, there is better prediction from regional tau burden and neuroinflammation. This supports the use of PET imaging for prognostication and stratification in clinical trials.

Sculpting the brain: a dynamic functional connectivity (Chronnectome) study in chess players.

Enrico Premi[1], Stefano Gazzina[2], Matteo Diano[3], Andrea Girelli[4], Vince D. Calhoun[5], Armin Iraji[5], Qiyong Gong[6], Kaiming Li[6], Franco Cauda[7,8], Roberto Gasparotti[9], Alessandro Padovani[10], Barbara Borroni[10], Mauro Magoni[1]*

[1] Stroke Unit, Azienda Socio Sanitaria Territoriale Spedali Civili, Spedali Civili Hospital, Brescia, Italy [2] Neurophysiopathology Unit, Azienda Socio Sanitaria Territoriale Spedali Civili, Spedali Civili Hospital, Brescia, Italy | [3] Department of Psychology, University of Turin, Turin, Italy | [4] TakeAppWay, Manerbio, Italy | [5] The Mind Research Network, Albuquerque, USA; Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, USA | [6] Huaxi MR Research Center, Section of Neuroradiology, Department of Radiology, West China Hospital of Sichuan University, China | [7] GCS fMRI, Koelliker Hospital and University of Turin, Turin, Italy | [8] Focus Lab, Department of Psychology, University of Turin, Turin, Italy | [9] Neuroradiology Unit, University of Brescia, Italy | [10] Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

Background

Multidisciplinary approaches have demonstrated that the brain is potentially modulable by the long-term acquisition and practice of specific skills. In fact, chess playing can be considered as a prototype for "sculpting the brain" with evident complex interactions among brain networks boosting the specific cognitive processes required. Dynamic network analysis based on resting-state magnetic resonance imaging (rs-fMRI) can be useful to further explore this modulating effect, studying the whole-brain fluidity/dynamism (the chronnectome) of chess players.

Methods

Dynamic connectivity parameters of 18 professional chess players and 20 chess novices were evaluated using independent component analysis, sliding-time window correlation and k-means approach to rs-fMRI data. Four indexes of meta-state dynamic fluidity were studied: i) the number of distinct meta-states a subject pass through, ii) the number of switches from one meta-state to another, iii) the span of the realized meta-states (as the largest distance between two meta-states that subjects occupied), and iv) the total distance traveled in the state space.

Results

Chess players exhibited an increased dynamic fluidity, as they occupied a higher number of meta-states (meta-state numbers, 75.8±7.9 vs 68.8±12.0, p=0.043 FDR-corrected) and changed from one meta-state to another more often (meta-state changes, 77.1±7.3 vs 71.2±11.0, p=0.043 FDR-corrected) than chess novices. Furthermore, chess players operated over an increased dynamic range with increased meta-state total distance, as they travelled more overall distance, between successive meta-states, through the state space than chess novices (meta-state total distance, 131.7±17.8 vs 108.7±19.7, p=0.0004 FDR-corrected).

Conclusions

Chess playing provided a complex and multi-level modulation of brain activity. Beyond the known involvement of specific brain hubs/networks, our findings suggested that the whole-brain activity is deeply involved, potentially modulating the spontaneous and time-varying fluctuation of whole-brain signal. The enhanced global brain dynamic fluidity of chess players could provide an effective in vivo surrogate marker for clinical trials on non-pharmacological interventions in the clinical and preclinical phases of neurodegenerative diseases.

Revisiting cognitive reserve hypothesis in Frontotemporal dementia: education modulates brain synchronization.

Enrico Premi[1,2], Viviana Cristillo[1], Stefano Gazzina[1,3], Alberto Benussi[1], Antonella Alberici[1], Maria Sofia Cotelli[4], Vince D. Calhoun[5], Armin Iraji[5], Mauro Magoni[2], Maria Cotelli[6], Anna Micheli[7], Roberto Gasparotti[8], Alessandro Padovani[1], Barbara Borroni[1]

[1] Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy | [2] Stroke Unit, Azienda Socio Sanitaria Territoriale Spedali Civili, Spedali Civili Hospital, Brescia, Italy | [3] Neurophysiopathology Unit, Azienda Socio Sanitaria Territoriale Spedali Civili, Spedali Civili Hospital, Brescia, Italy | [4] Neurology Unit, Vallecamonica Hospital, Esine, Brescia, Italy | [5] the Mind Research Network, Albuquerque USA; Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, USA | [6] Istituto di Ricovero e Cura a Carattere Scientifico Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy | [7] Casa di Cura S. Francesco, Bergamo, Italy | [8] Neuroradiology Unit, University of Brescia, Italy

Objective

To investigate the cognitive reserve (CR) effect on dynamical properties of time-varying whole-brain network connectivity (the chronnectome) in Frontotemporal dementia (FTD).

Methods

Resting-state functional magnetic resonance imaging (rs-fMRI) data were collected from 128 FTD, namely 81 behavioural variant FTD and 47 Primary Progressive Aphasia patients. Dynamic connectivity parameters were evaluated using independent component analysis, sliding-time window correlation and k-means approach to rs-fMRI data. We evaluated the relationship between education, a proxy measure of CR, and four indexes of meta-state dynamic fluidity: i) the number of distinct meta-states a subject pass through, ii) the number of switches from one meta-state to another, iii) the span of the realized meta-states (as the largest distance between two meta-states that subjects occupied), and iv) the total distance traveled in the state space.

Results

We found a significant inverse correlation between years of education and the number of distinct meta-states (Pearson's correlation, r=-0.246, p=0.01 False Discovery Rate FDR-corrected), the number of switches from one meta-state to another (r=-0.288, p=0.01 FDR-corrected), the meta-state span (r=-0.202, p=0.03 FDR-corrected), and the total distance in the state space (r=-0.309, p=0.01 FDR-corrected).

Conclusions

This study suggests that in a focal dementia, as FTD is, the whole brain is engaged in CR mechanisms, and, in turns, this acts as a compensatory effect on whole brain synchronization. The potential modulation of the global inner rhythms of the brain could represent a novel target of intervention in FTD, regardless of the pathological involvement of specific brain regions. or the presence of a defined proteinopathy.

Activated PPARγ abrogates misprocessing of amyloid precursor protein, Tau missorting and synaptotoxicity

Susanne Moosecker[1], Patrícia Gomes[2,3], Chrysoula Dioli[2,3], Shuang Yu[1], Ioannis Sotiropoulos[2,3],, Osborne F.X. Almeida[1],***

[1]Max Planck Institute of Psychiatry, Munich, Germany
[2]Life and Health Sciences Research Institute (ICVS), University of Minho, Braga, Portugal
[3]ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal

Type 2 diabetes increases the risk for dementia, including Alzheimer's disease (AD). Pioglitazone (Pio), a pharmacological agonist of the peroxisome proliferator–activated receptor γ (PPARγ), improves insulin sensitivity and has been suggested to have potential in the management of AD symptoms, albeit through mostly unknown mechanisms. We here investigated the potential of Pio to counter synaptic malfunction and loss, a characteristic of AD pathology and its accompanying cognitive deficits. Results from experiments on primary mouse neuronal cultures and a human neural cell line (SH-SY5Y) show that Pio treatment attenuates amyloid β (Aβ)–triggered the pathological (mis–)processing of amyloid precursor protein (APP) and inhibits Aβ–induced accumulation and hyperphosphorylation of Tau. Further, Pio treatment blocks Aβ–triggered missorting of hyperphosphorylated Tau to synapses and the subsequent loss of PSD95–positive synapses. These latter effects of Pio are PPARγ–mediated since they are blocked in the presence of GW9662, a selective PPARγ inhibitor. Collectively, these data show that activated PPARγ buffer neurons against APP misprocessing, Tau hyperphosphorylation and its missorting to synapses and subsequently, synaptic loss. These first insights into the mechanisms through which PPARγ influences synaptic loss make a case for further exploration of the potential of PPARγ agonists in the prevention and treatment of synaptic AD pathology.

Repurposing anti-inflammatory drugs for Alzheimer's disease: a retrospective cohort study in UK Clinical Practice Research Datalink

Bowen Su

Background
Alzheimer's disease (AD) affects more than 50 million people worldwide, with a global health cost rising to one trillion US dollars in 2018. However, there is currently no effective disease-modifying treatment for this condition. Increasing evidence suggests that AD pathogenesis includes strong interactions with immunological mechanisms in the brain. Non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) are typical treatments for inflammatory diseases, such as rheumatoid arthritis (RA). Thus, the aim of this study is to investigate the associations between the prescriptions of common anti-inflammatory drugs and AD.

Methods
This is a retrospective cohort study. We used the UK Clinical Practice Research Datalink (CPRD) data dated from 1987 to 2018 to compare anti-inflammatory drugs and assessed their comparative effectiveness in reducing the risk of development of dementia. Participants aged over 50 at their first anti-inflammatory drug prescription and with at least two prescriptions for the treatment of RA during an initial 12-month treatment assessment period, dated at least one year after the patient registration date to ensure new drug taker status were included in the analysis. Dementia incidence was defined by the presence of at least one of the following: medical code for dementia diagnosis or dementia-specific drug prescription. Conventional Cox regression models were used to test the effects of classical DMARDs on the development of dementia, with the adjustment of covariates using propensity score weighting (PSW) method. Multiple imputation was used to account for missing values.

Results
A total of 6,879 dementia cases were observed in the RA cohort (N=17,853) after eight years of follow up, with an onset age ranging from 56 to 100 years old. Our analysis showed a protective effect of methotrexate use compared to sulfasalazine use on risk of dementia Hazard Ratio (HR) 0.94 (95%CI: 0.87- 0.98, P=0.002) after adjustment for relevant covariates. This finding was qualitatively similar with propensity score weighting and with further adjustment for covariates and imputation of missing data. There was no evidence for an association between use of NSAIDs and other DMRADs drugs in relation to dementia onset.

Conclusion
Our results suggest a possible protective effort of methotrexate among RA patients for dementia. Future analysis are needed to confirm this finding and investigate dose response of drug exposure time as well as the effects of combination therapies.

A data-driven framework for validating composite measures of cognitive reserve

Rory Boyle

Most cognitive reserve (CR) measures do not consider the full range of CR indicators. Composite measures of CR proxies allow all indicators to be considered and display consistent positive relationships with cognitive function (Opdebeeck et al., 2016). The present study presents a data-driven framework which enables each CR proxy, and all possible composite measures, to be tested and validated as measures of CR.

487 participants (mean age = 68.6 years) provided data. Cognitive function was measured using a composite of standardised scores from the MMSE, Animals task, Colour Trails Task A and B, Immediate and Delayed Recall. Brain structure was measured using grey matter to intracranial volume ratio (GMV). CR proxies were educational attainment, occupational complexity, literacy/intelligence, social engagement, cognitively stimulating activities, leisure activities, and physical activity.

For each composite, a three-step hierarchical-multiple regression was performed to predict cognitive function. In step 1, the IV was GMV. In step 2, the CR composite was added as an IV. In step 3, the interaction term (GMV*CR proxy) was added as an IV. CR composites with significant interaction terms were ranked based on R-squared changed magnitude from step 2 to step 3.

Results using this framework will be presented. This framework will enable identification of the proxy/composite with the biggest moderation effect on the brain structure-cognition relationship. These results will serve as a test of which proxies/composites display construct validity as a measure of CR and can guide researchers in their approach to measuring CR.

Holistic rehabilitative games to engage and stimulate seniors to prevent decline

Cassandra Ei Lyn Seah

One person develops dementia every 3 seconds. The cost of dementia is expected to become a trillion-dollar disease this year and it is one of the biggest global public health challenge with an estimated number of 50 million people affected worldwide with nearly 10 million new cases every year (World Health Organisation, 2019). As our population ages it is crucial for us to develop interventions to aid rehabilitation.

The exploration and creation of the holistic rehabilitative games provides occupational therapists and caregivers with an additional means to engage and stimulate a senior to prevent decline with a greater emphasis on holistic stimulation with analysis (motor, sensory, cognitive, social and track these skills). It can be used to train visual and tactile skills, precision, eye-hand coordination, and evoke memories and emotions. These products can be customized with varying levels of gameplay based on the patient's needs as a person's condition fluctuates on a daily basis. Current products like sensory blankets, reminiscence therapy, puzzle games and higher tech items like snoozelen or mindpalace incorporates a range of multi-sensory stimulation, cognitive skills or nostalgia. They however lack further stimulation and structured way to analyse results.

Users, their families and governments might potentially benefit from improved mood, better relaxation and other benefits with regard to quality of life, that would translate to easier caretaking for persons with Dementia. This may possibly allow them to spend lesser direct and indirect resources on health and social care.

An Alzheimer's disease polygenic risk score to predict clinical diagnosis in a community-based cohort

Hannah Stocker

The strongest genetic risk factor for Alzheimer's disease (AD) is APOE4 and recent genome-wide association (GWA) meta-analyses have confirmed additional associated genetic loci. The aim of this study was to investigate the ability of an AD polygenic risk score (PRS) and APOE status to predict clinical diagnosis of AD, vascular dementia (VD) and all-cause dementia and secondarily across age, sex and education strata in a community-based cohort followed over 14 years. A PRS encompassing genetic variants reaching genome-wide significant associations to AD (excluding APOE) was calculated and APOE status was determined in 3,728 participants. During follow-up, 74, 65, and 221 participants were diagnosed with AD, VD and all-cause dementia, respectively. Prediction ability of AD, VD and all-cause dementia by the PRS and APOE was assessed by multiple logistic regression and receiver operating characteristic curve analyses. The PRS per standard deviation increase in score and APOE4 (≥1e4 allele) positivity were significantly associated with greater odds of AD (PRS OR, 95% CI: 1.65, 1.33-2.05; APOE4 OR, 95% CI: 3.14, 1.96-5.04) and AD prediction accuracy was improved when adding the PRS to a base model of age, sex and education (ASE) (c-statistics: ASE, 0.775; ASE+PRS, 0.813), with lesser accuracy for VD and all-cause dementia. Increased education appeared to attenuate association to AD diagnosis among those with increased AD genetic risk. The PRS enriched the ability of APOE4 status to discern AD with stronger associations than to VD or all-cause dementia in a prospective community-based cohort.

KCNH2 effect on brain activity in healthy controls and schizophrenia patients

Mar Farjó-Vilas Mestre

Background
Variability in neural excitability genes, such KCNH2, has been associated with impaired neural and cognitive function in schizophrenia. However, few is known about KCNH2 effect on brain activity, we studied healthy controls (HC) and SZ patients' neural correlates during an fMRI protocol.

Methods
We studied the effect of KCNH2-rs38007789 on whole brain activity (GE 1.5-T scanner) while 79 HC and 79 SZ patients performed a working memory task (n-back) with two difficulty levels (1-back and 2-back). We analysed the diagnosis x genotype interaction on the performance of each difficulty level (ANOVA using SPSS) and on brain activity (2-back vs 1-back) (regression using FEAT-FSL) controlling for age, sex and premorbid-IQ.

Results
SZ patients obtained poorer performance scores than HC (p<0.001), but no interaction was detected. Regarding brain activity (2-back vs 1-back), a significant interaction was found in clusters comprising: the middle occipital left (1166 voxels at MNI [-24,-100,6], p=0.000623) and frontal medial regions bilaterally (left: 678 voxels at MNI [-4,72,2], p=0.02; right: 614 voxels at MNI [40,56,-12], p=0.0331). Activity scores revealed that these clusters were activated in HC while SZ patients with AA genotype showed de-activation patterns.

Discussion
Our results suggest a link between KCNH2 and brain activity alterations associated with SZ, but not with cognitive performance. These findings are in line with previous studies which showed the effect of this gene on brain activity in HC (fMRI ROI-based) and its association with inefficient modulation (EEG-based). Therefore, the putative pathophysiological relevance of this locus in SZ is highlighted.

A systematic review of dementia diagnosis in primary care database in the UK

Sujin Kang

Background
Many epidemiological questions need to be answered regarding dementia, including the causes, prognosis, comorbidities, and treatment of the condition and complications. A routine electronic primary care dataset provides a way of investigating some of the complicated factors with rich information. However, there has been concern regarding whether dementia is recorded well enough.

Methods
This study has therefore explored this by conducting a systematic review to understand how dementia has been identified previously in primary care databases in the UK, and added to this by exploring additional terms and symptoms, and medications that might be helpful in identifying people with dementia.

The study estimated the prevalence and incidence rates of dementia in The Health Improvement Network (THIN) database and compared with other longitudinal studies using the comprehensive list of diagnostic codes.

Results
The estimated incidence rates per 1,000 person-years for the 60+ age group who had any of the first diagnosis among the Quality Outcomes Framework (QOF) defined codes, Other diagnoses, Dementia symptoms and Prescribed medications were 2.5, 4.7, and 15.9 in 1995, 2004, and 2015 respectively. The estimated prevalence were 2.8, 3.2, and 10.2 in 1995, 2004, and 2015 respectively.

Conclusions
The codes related to dementia symptoms (represented by mini-mental state examination, the six item cognitive impairment test, referral to memory clinic and behaviour assessment) seem to cover a broad definition of dementia or pre-existing dementia population in the UK primary care records.

At least, using of the Other diagnoses (represented by dementia annual review, senile/presenile dementia and dementia monitoring) in addition to the QOF defined codes, and Prescribed medications were evidenced that will not missing out a number of people with dementia.

Heterogeneity in the Increased Risk for Alzheimer's Disease and Related Dementias Associated with Fine Particle Exposure: Exploring the Role of Cognitive Reserve

Diana Younan[1], Andrew J. Petkus, PhD[2], Xinhui Wang, PhD[2], Susan M. Resnick, PhD[4], Marc Serre, PhD[5], William Vizuete, PhD[5], Victor W. Henderson, MD[6], Bonnie C. Sachs, PhD[7], Daniel P. Beavers, PhD[3], Joel A. Salinas, MD[8], Sally A. Shumaker, PhD[9], JoAnn E. Manson, MD, DrPH[10], Margaret Gatz, PhD[11], Stephen R. Rapp, PhD[12], Helena C. Chui, MD[2], Mark A. Espeland, PhD[3], Jiu-Chiuan Chen, MD[1]

[1] Department of Preventive Medicine, University of Southern California, Los Angeles, CA | [2] Department of Neurology, University of Southern California, Los Angeles, CA | [3] Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC | [4] Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, MD | [5] Department of Environmental Sciences and Engineering, University of North Carolina, Chapel Hill, NC | [6] Departments of Epidemiology & Population Health and of Neurology and Neurological Sciences, Stanford University, Stanford, CA | [7] Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC | [8] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA | [9] Department of Social Sciences & Health Policy, Wake Forest School of Medicine, Winston-Salem, NC | [10] Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA | [11] Center for Economic and Social Research, University of Southern California, Los Angeles, CA | [12] Department of Psychiatry and Behavioral Medicine, Wake Forest School of Medicine, Winston-Salem, NC

Background

Cognitive reserve (CR) may explain discrepancies between neuropathology severity and cognitive performance. We investigated whether a statistically-defined measure of CR modifies the association between exposure to neurotoxic particulate pollutants (PM2.5) and Alzheimer's disease and related dementias (ADRD).

Methods

Community-dwelling participants (aged 65-79) from the Women's Health Initiative Memory Study participants were followed annually (1996-2010) to identify incident ADRD cases (DSM-IV criteria). Three-year moving average PM2.5 residential exposures were aggregated from daily 1999-2010 estimates from nationwide spatiotemporal modeling. CR was derived following a Multiple Indicator, Multiple Cause (MIMIC) framework1 to incorporate cognitive scores, educational attainment, social engagement, physical activity and occupational attainment. We examined whether CR (median-split) modified ADRD risk associated with residing in locations exceeding the EPA standard (>12 vs. ≤12 μg/m3) with proportional hazards regression.

Results

272 incident ADRD cases were identified in 6125 women. Residing in locations with high PM2.5 was associated with increased ADRD risk (hazard ratio [HR]=1.70; 95% CI [1.31, 2.22]), adjusting for geographic region, age, socioeconomic characteristics, lifestyle, clinical characteristics, and hormone therapy. Low CR was associated with increased ADRD risk (HR=1.24; [0.91, 1.70]). The adverse PM2.5 effect was much greater (interaction p=0.04) among women with low CR (HR=2.08; [1.48, 2.93]) than among women with high CR (HR=1.24; [0.85, 1.83]). Sensitivity analyses showed no single MIMIC factor dominated the moderation of the observed PM2.5 neurotoxicity.

Conclusions

Our novel findings support the hypothesis that high CR may benefit the aging brain by attenuating the dementia risk imparted by long-term exposure to high particulate pollutants.

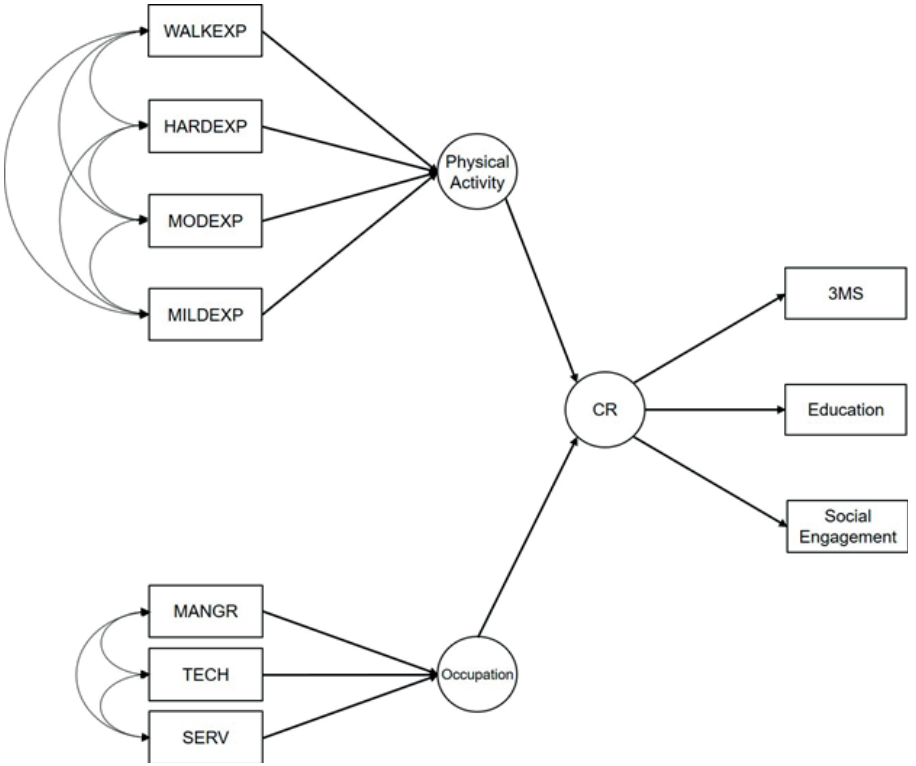

Figure 1. Multiple indicators, multiple causes (MIMIC) model

Modified Mini-Mental State (3MS) scores, education, and social engagement included as reflective indicators and physical activity and occupational attainment as formative latent variables of CR. Note: Social engagement was defined as participating in meetings of clubs, lodges, or parent groups or attending religious services or church during the past month. Physical activity defined as MET-hours per week from walking (WALKEXP), hard exercise (HARDEXP; e.g., aerobics, jogging, tennis, swimming laps), moderate exercise (MODEXP; e.g., biking outdoors, calisthenics, easy swimming, folk dancing), and mild exercise (MILDEXP; e.g. slow dancing, bowling, golf). Occupation was defined using dummy variables for managerial/professional (MANGR; e.g., teacher, guidance counselor, doctor, registered nurse, lawyer, accountant, architect, computer/systems analyst, personnel/sales manager), technical/sales/admin support (TECH; e.g. computer programmer/operator, dental assistant, laboratory technician, sales clerk, cashier, receptionist), and service (SERV; policewoman, teaching assistant, child care attendant, maid, cook, waitress, seamstress), with homemaker as the reference group.

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Learning-induced transcription factor Egr1 as a potential molecular target for gene therapy in Alzheimer's disease

S. Uyaniker, B. Hobo, L. De Vries, S.J.F. Van Der Spek, F. De Winter, K. Bossers, A.B. Smit, D.F. Swaab, H.W. Kessels, J. Verhaagen

A major hallmark of Alzheimer's disease (AD) is dysfunction and loss of synapses due to an excess of amyloid beta (Aβ). Interestingly, individual susceptibility to Aβ synaptotoxicity seems to exist. In particular, mental exercise is thought to delay the onset of AD. Our data from the human AD brain suggest that the learning-induced transcription factor Egr1 may play an instrumental role in protecting neurons against Aβ. We found that Egr1, and many synaptic genes that are potentially regulated by Egr1, are increased in the earliest stages of AD, when Aβ already accumulates but memory is largely intact (Braak 0-II). In later stages of AD, there is a significant decline in Egr1 expression and its potential target genes (Braak III-VI). To directly assess the effects of Egr1 on synaptic function in neurons, we used viral vectors to simultaneously overexpress Egr1 and APP-CT100 (the precursor to Aβ) in cultured hippocampal slices. We measured synaptic transmission using whole-cell patch clamp recordings, and dendritic spine densities using two-photon microscopy. Furthermore, we studied the effects of viral vector-mediated hippocampal Egr1 overexpression on the transcriptome, synaptic proteome and discrimination and reversal learning behavior in an APP/PS1 mouse model. Our results suggest a potential future application for Egr1 as a molecular target for gene therapy in AD.

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