Final Full PROGRAMME (www.vas-cog.com) Time Zone: UK BST (GMT + 1hr)

Convenors: Raj Kalaria (Newcastle), John O’Brien (Cambridge), Hugh Markus (Cambridge)

Time | Wed 8th September 2021  
Day 1
---|---
11.45-12.45  | Oral Session I

**Breakout Room 1: Biomarkers I - SVD Pathophysiology**
Chairs: Chris Chen (Singapore), Perminder Sachdev (Australia) (Talks 5 min each)

01. Association of type 2 diabetes, according to the number of risk factors within target range, with structural brain abnormalities, cognitive performance and risk of dementia - April van Gennip (The Netherlands)
02. Cerebrospinal fluid biomarkers, brain structural and cognitive performances between normotensive and hypertensive controlled, uncontrolled and untreated 70-year-old adults - Atef Badji (Sweden)
03. Perivascular fibroblasts activity precedes the onset of ALS neurodegeneration with high plasma SPP1 associated with short patient survival - Sebastian Lewandowski (Sweden)
04. CAIDE dementia risk score relates to severity and progression of cerebral small vessel disease in healthy midlife adults: the prevent-dementia - Audrey Low (UK)
05. The impact of Alzheimer biomarkers and vascular factors on cognitive decline in memory clinic patients - Veerle van Gils (The Netherlands)
06. Validation of a novel clinical neurovascular coupling biomarker - Suzanne E. van Dijk (The Netherlands)
07. Analyzing multimodal MRI at tract-level with neural networks enhances the prediction of cognitive performance in memory clinic patients with small vessel disease - Alberto De Luca (The Netherlands)
08. Network-based lesion impact score is an independent predictor of post-stroke cognitive impairment - J. Matthijs Biesbroek (The Netherlands)
<table>
<thead>
<tr>
<th>Breakout Room 2: Stroke, Cognition and Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairs: Ingmar Skoog (Sweden), Louise Allan (Exeter) (Talks 5 min each)</td>
</tr>
<tr>
<td>10. Trajectories of cognitive change following stroke: a stepwise decline towards dementia - Joao Delgado (UK)</td>
</tr>
<tr>
<td>11. Long-Term Outcomes Among Nigerian Stroke Survivors - the CogFAST-Nigeria Study - Gabriel Ogunde (Nigeria)</td>
</tr>
<tr>
<td>12. Brain regions involved in the strategic processes of verbal fluency: a mVLSM study in 337 stroke patients - Flore Dorchies (France)</td>
</tr>
<tr>
<td>13. Patterns and predictors of short-term trajectory of post-stroke cognitive function - Jess Lo (Australia)</td>
</tr>
<tr>
<td>15. Pure vascular-ischemic disease and cognitive impairment - Elisabet Englund (Sweden)</td>
</tr>
<tr>
<td>16. Association between Cerebral Small Vessel Disease and Alzheimer’s disease pathologies - Yuan Cai (China)</td>
</tr>
<tr>
<td>17. Combined associations of cognitive and motor impairments with functional outcome in covert cerebral small vessel disease - Hanna Jokinen (Finland)</td>
</tr>
<tr>
<td>18. Cerebral small vessel function in patients with CADASIL and sporadic cerebral small vessel disease: assessment of hemodynamic response function with 7T MRI - the Zoom@svds study, Hilde van den Brink (The Netherlands)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12.50-13.00</th>
<th>Welcome/ Opening (10 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenors: Raj Kalariya, John O’Brien, Hugh Markus (UK)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>13.00-13.30</th>
<th>Plenary I Clinical VCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joanna Wardlaw (UK)- 20 min 10 min discussion</td>
<td></td>
</tr>
<tr>
<td>Chair: John O’Brien (UK)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>13.30-14.45</th>
<th>Symposium I: - The importance of VRF and Heart Variability for Cognition and Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairs: Kamran Ikram &amp; Daniel Bos (The Netherlands)</td>
<td></td>
</tr>
<tr>
<td>- Orthostatic hypotension/heart failure and dementia - Frank Wolters (The Netherlands) (12 min)</td>
<td></td>
</tr>
<tr>
<td>- Heart rate variability/blood pressure variability and cognition/dementia - Yuan Ma (USA) (12 min)</td>
<td></td>
</tr>
<tr>
<td>- Cardiac dysfunction and cognition/dementia - Saima Hilal (Singapore) (12 min)</td>
<td></td>
</tr>
<tr>
<td>- Cardiac biomarkers: current state-of-the-art - Zhenyu Zhang (Belgium) (12 min)</td>
<td></td>
</tr>
<tr>
<td>2 x ECR talks (open abstracts, 5 mins each)</td>
<td></td>
</tr>
<tr>
<td>19. Visit-to-Visit Variability in Blood Pressure over 10 Years, Cognitive Decline and Incident Dementia in Three Community-Based Cohorts of Older Adults - Simin Mahinrad (USA)</td>
<td></td>
</tr>
<tr>
<td>20. Investigating the risk of cardiovascular risk factor subgroups in cognitively normal elderly on Alzheimer’s disease: a latent class approach - Myuri Ruthirakuhan (Canada)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

**14:45-15:45 Poster Blitz session I** (3 min or less each)
Chair: Adrian Wong (Hong Kong, China)

21. Prevalence of cognitive impairment and dementia in a multi-ethnic elderly cohort
the Singapore Epidemiology of Eye Diseases study (SEED)- Ting Pang (Singapore)
22. Discriminant Validity of the Progressive Forgetfulness Question in a Stepwise
Dementia Screening Approach in a Singaporean Elderly Population- Ting Pang
(Singapore)
23. Neurofilament light level correlates with brain atrophy and cognitive and motor
performance in subjects with cerebral white matter hyperintensities, Marge Kartau
(Finland)
24. Age-associated changes in the renin-angiotensin system: implications for future
clinical trials- Robert MacLachlan (UK)
25. Renin-angiotensin system gene expression and dementia pathology in Alzheimer’s
disease, vascular and mixed dementia- Hannah Tayler (UK)
26. Angiotensinogen, ACE-1 and ACE-2 in Alzheimer’s disease and vascular
dementia- Özge Güzel (UK)
27. Fibrinogen activates microglia and drives extracellular vesicle mediated
propagation of pro-inflammatory signaling- Austyn Roseborough (Canada)
28. Relationships between Myeloperoxidase and the Cognitive and Neuroimaging
Correlates of Mild Vascular Cognitive Impairment- Kritleen Bawa (Canada)
29. Modelling Alzheimer’s Disease through Environmentally Induced Neurovascular
Dysfunction within an In Vitro Cell Model- Ernesto Zarate-Aldrete (UK)
30. Endothelin-1-mediated contraction of human brain pericytes is dysregulated in the
presence of Aβ1-40- Elliott Hibbs (UK)
31. Automatic quantification of perivascular spaces in T2-weighted images at 7T MRI-
Hugo Kuijf (The Netherlands)
32. Connection Between Kidney Function and Cognition in the Elderly- Tomas
Månsson (Sweden)
33. Low carotid end diastolic velocity is associated with white matter hyperintensities
and cortical atrophy in the Swedish "Good Aging in Skane" study- Katarina
Ellström (Sweden)
34. Association of cerebral small vessel disease burden with brain structure and
cognitive and vascular risk trajectories in mid-to-late life- Michelle G. Jansen (The
Netherlands)
35. Self-reported cognitive decline, emotional symptoms, and daytime sleep after
ischemic stroke, Elisabeth Kliem (Norway)
36. Social Cognition is Associated with General Cognitive Function Post-Stroke- Elise
Gjestad (Norway)
37. Prevalence of, and risk factors for, vascular cognitive impairment in CADASIL-
Amy A Jolly (UK)

15.50-16.15 Tea Break

16.15-17.15 Symposium II: *Is Brain Inflammation relevant for VCI?*
Chairs: Frank Eric de Leeuw (Netherlands) & John O’Brien (UK)
• PET studies of microglial activation and blood brain barrier dysfunction in SVD- Hugh Markus (UK) (15 min)
• Reprogramming of the peripheral immune system in SVD- Niels Riksen (The Netherlands) (15 min)

2 x ECR talks (open abstracts, 5 mins each)

38. A cluster of blood-based biomarkers reflecting extracellular matrix organization, inflammation and signal transduction relates to cerebral blood flow in patients with cardiovascular disease- L Malin Overmars (The Netherlands)
39. Does 11C-PK11195 binding predict lesion growth at one year? - Daniel Tozer (UK)

Discussion

10:00 – 10:10 Plenary II: Brain vascular extracellular matrix and VCI
Gary Rosenberg (USA)- 20 min 10 min discussion
Chair: Eric Smith (Canada)

10:10 End of Day 1

---

**Thursday 9th September 2021**

**Day 2**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:20-08:30</td>
<td><strong>Welcome/ Opening</strong> (10 min)</td>
</tr>
<tr>
<td></td>
<td><em>Housekeeping announcements</em></td>
</tr>
<tr>
<td>08:30-09:00</td>
<td><strong>Plenary III: Genetics of Stroke and VCI- from discovery to clinical applications</strong></td>
</tr>
<tr>
<td></td>
<td>Martin Dichgans (Germany)- 20 min 10 min discussion</td>
</tr>
<tr>
<td></td>
<td>Chair: Hugh Markus (UK)</td>
</tr>
<tr>
<td>09:00-10:00</td>
<td><strong>Symposium III: Cardiovascular risk management throughout the life course to prevent/treat dementia</strong></td>
</tr>
<tr>
<td></td>
<td>Chairs: Majon Muller &amp; Edo Richard (The Netherlands)</td>
</tr>
<tr>
<td></td>
<td>• Prevention of dementia: a life-course approach- Majon Muller (The Netherlands) (5min)</td>
</tr>
<tr>
<td></td>
<td>• CVRM to prevent dementia- Edo Richard (The Netherlands) (15 min)</td>
</tr>
<tr>
<td></td>
<td>• CVRM to treat dementia- Majon Muller (The Netherlands) (10 min)</td>
</tr>
<tr>
<td></td>
<td>2 x ECR on related topics (5 mins each)</td>
</tr>
<tr>
<td></td>
<td>40. Withdrawn</td>
</tr>
<tr>
<td></td>
<td>41. A systematic review into the relationship between blood pressure variability and grey and white matter structures- Daria Gutteridge (Australia)</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
</tr>
<tr>
<td>10:00-10:10</td>
<td><strong>Viewpoint session: Aducanumab for Alzheimer’s Disease</strong>- Anders Wallin (Sweden); Response: Vincent Mok (Hong Kong, China)</td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10:10-10:30</td>
<td>Coffee Break</td>
</tr>
<tr>
<td>10:30-11:00</td>
<td>Plenary IV: <em>Risk Factors for SVD: an Asian Perspective</em></td>
</tr>
<tr>
<td></td>
<td>Chair: SangYun Kim (S Korea)</td>
</tr>
<tr>
<td>11:00-12:00</td>
<td>Poster Blitz session II (3 min or less each)</td>
</tr>
<tr>
<td></td>
<td>42. Association Between Blood Pressure Variability with Dementia and Cognitive Impairment: A Systematic Review and Meta-analysis- Philip Tully (Australia)</td>
</tr>
<tr>
<td></td>
<td>43. The Relationship of Acute Delirium with Cognitive and Psychiatric symptoms after Stroke: A longitudinal study- Vilde Nerdal (Norway)</td>
</tr>
<tr>
<td></td>
<td>44. Neuropsychiatric symptoms accelerate cognitive impairment associated with small vessel disease- Anne Arola (Finland)</td>
</tr>
<tr>
<td></td>
<td>45. Systemic endothelial function and cerebral microbleeds: a cross-sectional analysis within the Rhineland study- Gokhan Pehlivan (Germany)</td>
</tr>
<tr>
<td></td>
<td>46. The brain renin-angiotensin system is altered in age and Alzheimer’s disease- Robert MacLachlan (UK)</td>
</tr>
<tr>
<td></td>
<td>47. The relationship between cognitive reserve and change in cognition during the first three months post-stroke- Ragnhild Roaldsnes (Norway)</td>
</tr>
<tr>
<td></td>
<td>48. Metabolic syndrome is associated with poor cognition: a population-based study of 70-year-olds without dementia- Anna Marseglia (Sweden)</td>
</tr>
<tr>
<td></td>
<td>49. Small and large MRI-visible perivascular spaces in the basal ganglia of Parkinson’s disease patients- Stephanie Berberian (Canada)</td>
</tr>
<tr>
<td></td>
<td>50. Microstructural changes in the penumbras of cerebral small vessel disease lesions are associated with cognition and sleep- Joel Ramirez (Canada)</td>
</tr>
<tr>
<td></td>
<td>51. Venous Collagenosis, White Matter Hyperintensity and the Perivascular Space- David Lahna (USA)</td>
</tr>
<tr>
<td></td>
<td>52. Serum Placental Growth Factor as a Marker of Cerebrovascular Disease burden in patients with Alzheimer’s Disease, Liu-Yun Wu (Singapore)</td>
</tr>
<tr>
<td></td>
<td>53. Higher total cholesterol in APOEe4 carriers contributes to Alzheimer’s disease risk: findings from the Alzheimer’s disease Neuroimaging Initiative, Michelle Dunk (USA)</td>
</tr>
<tr>
<td></td>
<td>54. Does white matter hyperintensity location predict cognitive impairment in an elderly population? - Polly Roads (UK)</td>
</tr>
<tr>
<td></td>
<td>55. Prevalence and correlates of white matter hyperintensities in Royal Canadian Air Force pilots and Aircrew- Joel Ramirez (Canada)</td>
</tr>
<tr>
<td></td>
<td>56. Gait and Falls in Cerebral Amyloid Angiopathy- Breni Sharma (Canada)</td>
</tr>
<tr>
<td>12:05-12:35</td>
<td>Plenary V: <em>Gait as a biomarker for VCI</em></td>
</tr>
<tr>
<td></td>
<td>Chair: Suvarna Alladi (India)</td>
</tr>
<tr>
<td>12:35-13:00</td>
<td>Lunch Break</td>
</tr>
<tr>
<td>13:00-14:00</td>
<td>Early Career Researchers (ECR) Session: <em>&quot;The future of VCI research: a collaborative approach&quot;</em></td>
</tr>
<tr>
<td></td>
<td>4 x ECR talks (open abstracts, 10 min each)</td>
</tr>
</tbody>
</table>
57. Diffusion MRI harmonization enables joint-analysis of multicenter data of patients with cerebral small vessel disease – Bruno Miguel Brito Robalo (The Netherlands)
58. Effects of vascular burden on cognition are mediated by atrophy, amyloid, and glucose metabolism: a multi-centre mixed cohort of small vessel disease and Alzheimer’s pathology- Julie Ottøy (USA)
59. Risk factors for onset of post-stroke depression in diverse ethno-regional groups- Ben C.P. Lam (Australia)
60. NOTCH3 variant position is associated with vascular NOTCH3 aggregation load in CADASIL patients - Gido Gravesteijn (The Netherlands)

14.00-14.30 Plenary VI: Variation in global stroke burden and influence on clinical and brain VCI phenotypes: Implications for prevention
Sudha Seshadri (USA)- 20 min 10 min discussion
Chair: Sandra Black (Canada)

14.30-15.30 Oral Session II

**Breakout Room 1: Biomarkers I - White Matter Pathophysiology, Vascular Reactivity**
Chairs: Geert Jan Biessels (The Netherlands), Eric Smith (Canada) (Talks 5 min each)

61. Strategic white matter hyperintensity locations for cognitive impairment in memory clinic patients: a large-scaled multicenter study- Mirthe Coenen (The Netherlands)
62. Strategic white matter hyperintensity locations and cognitive functioning in community-dwelling individuals: rationale and design- Floor A.S. de Kort (The Netherlands)
63. Sex differences in white matter hyperintensities are modified by menopause: the Rhineland study, Valerie Lohner (Germany)
64. The association between cardiovascular risk factors and white matter hyperintensity MRI phenotypes- Jasmin A. Keller (The Netherlands)
65. Cilostazol in Decreasing Progression of Cerebral White Matter Hyperintensities- Bonaventure Ip (Hong Kong, China)
66. The relation between small vessel function and white matter integrity in patients with CADASIL: the zoom@svds study, Naomi Vlegels (The Netherlands)
67. Vascular reactivity is decreased in early stages of dementia; a novel MRI biomarker- Suzanne E. van Dijk (The Netherlands)
68. Cerebrovascular reactivity in cerebral amyloid angiopathy- Andrew E Beaudin (Canada)

**Breakout Room 2: Blood Brain Barrier Pathophysiology, Models and Dementias**
Chairs: Marco Duering (Germany), Stuart Allan (UK) (Talks 5 min each)

69. Uptake and replication of SARS-COV-2 in the cells of the neurovascular unit- Katherine Kellett (UK)
70. Cognitive impairment post cardiac arrest - reperfusion and hypoperfusion damage- Elisabet Englund (Sweden)
71. Phosphorylated-tau181 is a Predictor of Poststroke Cognitive Impairment: A Longitudinal Study- Li-Kai Huang (Taiwan)
72. The relationship between late-life hypertension and disease pathology in Alzheimer’s, vascular, and mixed dementia- Hannah Tayler (UK)
73. Blood-brain barrier dysfunction and reduced cerebrospinal fluid levels of soluble amyloid precursor protein-β in patients with subcortical small-vessel disease – a report from the Gothenburg Mild Cognitive Impairment study- Petronella Kettunen (Sweden)

74. Loss of hippocampal pericytes in vascular dementia, post-stroke dementia and Alzheimer’s disease- Yoshiki Hase (UK)

75. A cluster of blood-based biomarkers reflecting coagulation relates to the burden of cerebral small vessel disease- Sanne Kuipers (The Netherlands)

76. Mitochondrial mechanisms and carbonic anhydrases mediate neurovascular dysfunction in CAA models- Silvia Fossati (USA)

77. A dual potassium channelopathy underlies small vessel disease of the brain in a mouse model of Alzheimer’s disease- Harry Pritchard (UK)

15.30-15.40 Concluding Comments: VasCog Society Deb Gustafson (USA); VasCog 2023 Ingmar Skoog (Sweden)

End of day 2 and VasCog 2021 Conference
ASSOCIATION OF TYPE 2 DIABETES, ACCORDING TO THE NUMBER OF RISK FACTORS WITHIN TARGET RANGE, WITH STRUCTURAL BRAIN ABNORMALITIES, COGNITIVE PERFORMANCE AND RISK OF DEMENTIA

April van Gennip (1) / Coen Stehouwer (1) / Martin van Boxtel (2) / Frans Verhey (2) / Annemarie Koster (3) / Abraham Kroon (1) / Sebastian Köhler (2) / Marleen van Greevenbroek (1) / Anke Wesselius (4) / Simone Eussen (5) / Walter Backes (6) / Jacobus Jansen (6,7) / Miranda Schram (8) / Ronald Henry (1) / Archana Singh-Manou (9)(10) / Thomas van Sloten (1)

(1) Department of Internal Medicine, School for Cardiovascular Diseases CARIM, Maastricht University Medical Centre, the Netherlands (2) Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience MHENS, Maastricht University Medical Centre, the Netherlands (3) Department of Social Medicine, Care and Public Health Research Institute CAPHRI, Maastricht University, the Netherlands (4) Department of Genetics and Cell Biology, Complex Genetics, School of Nutrition and Translational Research in Metabolism NUTRIM, Maastricht University Medical Centre, the Netherlands (5) Department of Epidemiology, School for Cardiovascular Diseases CARIM, Maastricht University Medical Centre, the Netherlands (6) Department of Radiology and Nuclear Medicine, School for Mental Health and Neuroscience MHENS, Maastricht University Medical Centre, the Netherlands (7) Department of Electrical Engineering, Eindhoven University of Technology, the Netherlands (8) Department of Internal Medicine and department of Psychiatry and Neuropsychology, School for Cardiovascular Diseases CARIM, School for Mental Health and Neuroscience MHENS, Maastricht University Medical Centre, the Netherlands (9) Université de Paris, INSERM U1153 Epidemiology of Ageing and Neurodegenerative diseases, Paris, France (10) Department of Epidemiology and Public Health, University College London, London, UK

Background: Type 2 diabetes is associated with increased risks of cognitive dysfunction and brain abnormalities. The extent to which risk factor modification can mitigate these risks is unclear. We investigated the associations between incident dementia, cognitive performance and brain abnormalities among individuals with type 2 diabetes, according to the number of risk factors within target range, compared to controls without diabetes.

Methods: Prospective data from UK Biobank of 87,856 individuals (n=10,663 diabetes/n=77,193 controls; baseline 2006-2010; dementia follow-up until February, 2018). Analysis was replicated using data from the Netherlands (the Maastricht Study; cohort with oversampling of type 2 diabetes; examination 2010-2019; cross-sectional data). Individuals with type 2 diabetes were categorized according to the number of seven risk factors within target range (nonsmoking; guideline-recommended levels of HbA1c, blood pressure, BMI, albuminuria, physical activity, diet). Outcomes were incident dementia, domain-specific cognitive performance, white matter hyperintensity volume and total brain volume.

Results: After a mean follow-up of 9.0 years, 147 (1.4%) individuals with diabetes and 412 (0.5%) controls had incident dementia. Compared to controls, individuals with type 2 diabetes had a higher incidence of dementia (HR:1.88 (95% CI:1.55;2.27)). Among individuals with diabetes, excess dementia risk decreased stepwise for a higher number of risk factors within target range. Among individuals with type 2 diabetes who had 5-7 risk factors on target, compared to controls (incidence rate per 1,000 person-years 0.62 (95% CI:0.56;0.68)), the absolute rate difference per 1,000 person-years for dementia was 0.20 (-0.11; 0.52) and the hazard ratio for dementia was 1.32 (0.89; 1.95). Similarly, differences in processing speed, executive function, and brain volumes were progressively smaller for a higher number of risk factors within target range; these results were replicated in the Maastricht Study.

Conclusions: Among individuals with type 2 diabetes, excess dementia risk, lower cognitive performance and brain abnormalities decreased stepwise for a higher number of risk factors within target range.
CEREBROSPINAL FLUID BIOMARKERS, BRAIN STRUCTURAL AND COGNITIVE PERFORMANCES BETWEEN NORMOTENSIVE AND HYPERTENSIVE CONTROLLED, UNCONTROLLED AND UNTREATED 70-YEAR-OLD ADULTS


Karolinska Institutet, CAR, Sahlgrenska Academy

Background: The pathophysiological mechanisms underlying the relationship between Alzheimer disease (AD) and hypertension are not fully understood, but they most likely involve microvascular dysfunction and cerebrovascular pathology. No study has yet provided a comprehensive comparison of cerebrospinal fluid (CSF) biomarkers and structural brain differences between normotensive and hypertensive groups in a single and large cohort of older adults in relationship to cognitive performance.

Objective: The aim of the present work was to investigate the differences in cognitive performances, CSF biomarkers and magnetic resonance imaging (MRI) of brain structure between normotensive, controlled hypertensive, uncontrolled hypertensive, and untreated hypertensive older adults from the Gothenburg H70 Study.

Methods: As an indicator of vascular brain pathology, we measured white matter hyperintensities (WMHs), lacunes, cerebral microbleeds, enlarged perivascular space (epvs), and fractional anisotropy (FA). To assess markers of AD pathology, we measured hippocampal volume, temporal cortical thickness on MRI, and amyloid-β42, phosphorylated tau, and Neurofilament light protein (NFL) in cerebrospinal fluid. Various neuropsychological tests were used to assess performances in memory, attention/processing speed, executive function, verbal fluency, and visuospatial abilities.

Results: We found more white matter pathology in hypertensive compared to normotensive participants, with the highest vascular burden in uncontrolled participants (e.g. lower FA, more WMHs, and epvs). No significant difference was found in any MRI or CSF markers of AD pathology when comparing normotensive and hypertensive participants, nor among hypertensive groups. No significant difference was found in most cognitive functions between groups.

Conclusion: Our results suggest that good blood pressure control may be key to prevent cerebrovascular pathology. In addition, hypertension may contribute to cognitive decline through its effect on cerebrovascular pathology rather than AD-related pathology. These findings suggest that hypertension is associated with MRI markers of vascular pathology in the absence of a significant decline in cognitive functions.
PERIVASCULAR FIBROBLASTS ACTIVITY PRECEDES THE ONSET OF ALS NEURODEGENERATION WITH HIGH PLASMA SPP1 ASSOCIATED WITH SHORT PATIENT SURVIVAL

Anna Månberg (1) / Nathan Skene (2) / Folkert Sanders (3) / Anna Szczepinska (3) / Julia Remnestål (1) / Joke De Vocht (4) / Jasper Anink (5) / Hermienke Vergunst-Bosch (6) / Elena Rodriguez-Vieitez (7) / Jonathan Gilthorpe (8) / Robert Harris (3) / Eleonora Aronica (5) / Philip Van Damme (4) / Albert Ludolph (9) / Jan Veldink (6) / Caroline Ingre (10) / Peter Nilsson KTH (11) / Sebastian Lewandowski (3)

Apart from the well-defined neuron-centric factors, few reports consider that variability of sporadic ALS progression can depend on the less-defined contributions from non-neuronal cell types including glia and blood vessels. Nonetheless, inaccurate survival prognosis continues to confound clinical trial design and effective treatments will likely remain elusive unless we better understand how non-neuronal cells contribute to ALS aetiology. Here we report that perivascular fibroblast cell gene activity during presymptomatic disease stage remodels blood vessel matrix and provides distinct plasma protein biomarker that can independently predict short ALS patient survival at diagnosis. We inferred cell activity in ALS spinal cord transcriptomes using single-cell guided profiling. We determined that sporadic ALS patients present cellular changes consistent with two mouse models in which gene expression patterns from vascular cells precede the blood-brain barrier dysfunction and microglial response. Notably, perivascular fibroblast cells elicited the strongest pre-onset gene enrichments and their marker proteins SPP1 and COL6A1 accumulated in enlarged perivascular spaces in sporadic ALS patients. Moreover, in 574 ALS patients from four independent cohorts, increased plasma levels of SPP1 at disease diagnosis repeatedly predicted shorter survival with a stronger effect than established indications of bulbar onset or neurofilament levels in cerebrospinal fluid. We propose that the activity of the recently-discovered perivascular fibroblast can predict ALS patient survival and provide a novel conceptual framework to re-evaluate definitions of ALS aetiology.
CAIDE DEMENTIA RISK SCORE RELATES TO SEVERITY AND PROGRESSION OF CEREBRAL SMALL VESSEL DISEASE IN HEALTHY MIDLIFE ADULTS: THE PREVENT-DEMNETIA

Audrey Low (1) / Maria A Prats-Sedano (1) / James D Stefaniak (1) / Elizabeth McKiernan (1) / Stephen F Carter (1) / Maria-Eleni Dounavi (1) / Elijah Mak (1) / Li Su (1) / Olivia Stupart (1) / Graciela Muniz-Terrera (2) / Karen Ritchie (2)(3) / Craig W Ritchie (2) / Hugh S Markus (4) / John T O'Brien (1)

(1) Department of Psychiatry, School of Clinical Medicine, University of Cambridge, UK (2) Centre for Dementia Prevention, University of Edinburgh, Edinburgh, UK (3) INSERM, Montpellier, France (4) Department of Clinical Neurosciences, University of Cambridge, UK

Background: Markers of cerebrovascular disease are common in dementia, and may be present before dementia onset. However, their clinical relevance in midlife adults at risk of future dementia remains unclear. Therefore, we examined whether the CAIDE dementia risk score, and its individual components, were associated with markers of cerebral small vessel disease (SVD), and if they predicted future progression of SVD. We also determined their relationship to systemic inflammation, which has been additionally implicated in dementia and SVD.

Methods: Cognitively-healthy midlife participants were assessed at baseline (n=185) and two-year follow-up (n=158). To assess SVD, we quantified white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), microbleeds, and lacunes. We derived composite scores of SVD burden, and subtypes of hypertensive arteriopathy and cerebral amyloid angiopathy (CAA). Inflammation was quantified using serum C-reactive protein (CRP) and fibrinogen.

Results: At baseline, higher CAIDE scores were associated with all markers of SVD and inflammation (Figure 1). Longitudinally, CAIDE scores predicted greater total (p<.001), periventricular (p<.001) and deep (p=.012) WMH progression, and increased CRP (p=.017). Assessment of individual CAIDE components suggested that markers were driven by different risk factors (Figure 2): Cross-sectionally, WMH and EPVS were driven by age/hypertension, while lacunes/deep microbleeds were driven by hypertension/obesity; longitudinally, older age and APOE4 were the main contributors to WMH progression. Interaction analyses demonstrated that higher CAIDE scores amplified the effect of age on both inflammation and SVD (Figure 3) – WMH (p=.017), CAA (p=.007), but not hypertensive arteriopathy (p=.646) – and the effect of WMH on poorer memory (p=.004).

Conclusion: Higher CAIDE scores, indicating greater risk of dementia, predicts future progression of both WMH and systemic inflammation. Findings highlight the CAIDE score’s potential as both a prognostic and predictive marker in the context of cerebrovascular disease, identifying at-risk individuals who might benefit most from managing modifiable risk.
THE IMPACT OF ALZHEIMER BIOMARKERS AND VASCULAR FACTORS ON COGNITIVE DECLINE IN MEMORY CLINIC PATIENTS

Veerle van Gils (1) / Willemijn J. Jansen (2) / Domantė Kučikienė (3) / Ana Sofia Costa (3) / Jörg B. Schulz (3) / Frans Verhey (4) / Kathrin Reetz (3) / Stephanie J. B. Vos (5)

(1) Maastricht University, Alzheimer Center Limburg / Inez Ramakers Maastricht University, University Hospital RWTH Aachen (2) Maastricht University, Alzheimer Center Limburg / Leonie Banning Maastricht University, Alzheimer Center Limburg (3) University Hospital RWTH Aachen

Background: Alzheimer’s disease (AD) biomarkers of amyloid and tau pathology have shown to be associated with cognitive decline. This study aims to explore if comorbid vascular risk or burden contributes to cognitive decline in a memory clinic population.

Methods: A total of 294 patients were included from the Maastricht and Aachen university memory clinics (Table 1). AD pathology was defined as cerebrospinal fluid (CSF) amyloid beta(Aβ)42 or Aβ42/40 abnormality and/or tau (p-tau) abnormality, using local cut-offs. Vascular pathology was defined differently in separate analyses, i.e. as cerebrovascular burden and vascular risk. Presence of cerebrovascular burden was defined with a composite score ≥2 (range 0-12) of white matter hyperintensities (Fazekas), cerebral microbleeds, infarcts and haemorrhages on MRI. Presence of vascular risk was defined as having hypertension, dyslipidaemia or diabetes mellitus (any type) from medical history diagnosis or medication use. Participants were divided into four groups: no pathology, vascular pathology, AD pathology, and mixed pathology. Outcome measures were memory, attention, executive functioning and verbal fluency z-scores, and global cognition (MMSE) up to 5 years after baseline. Linear mixed models were used to assess differences in cognitive function and decline across groups, adjusted for age, gender, education, and site.

Results: The mixed and AD pathology groups consistently showed faster cognitive decline compared to the no pathology and vascular groups on attention, verbal fluency and MMSE. This was found for both vascular pathology definitions (Figure 1 & 2). When vascular pathology was defined by vascular risk, all groups showed greater decline compared to the no pathology group on executive functioning, and the AD group showed a greater decrease in MMSE scores over time compared to the mixed group.

Conclusion: AD and mixed pathologies are similarly associated with cognitive decline in a memory clinic population, although the definition of vascular pathology may have implications for the cognitive trajectory.
VALIDATION OF A NOVEL CLINICAL NEUROVASCULAR COUPLING BIOMARKER

Suzanne E. van Dijk / Jessie Lak / Anne Hafkemeijer / Jeroen van der Grond / Sanneke van Rooden

Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

In the last decade, the role of vascular aspects in dementia has become more recognized. Usually, vascular damage is documented by observing secondary vascular cerebral damage such as microbleeds, (lacunar) infarcts, white matter hyperintensities and hemorrhagic lesions on MRI or CT. Recently, a new non-invasive approach to establish the neurovascular coupling in the brain was proposed using functional MRI. In this method, the changes in the blood oxygen level dependent (BOLD) response in the occipital lobe after a visual stimulus was studied, showing overt changes in patients with hereditary cerebral amyloid angiopathy (Dutch type-CAA). Dutch type-CAA mutation carriers develop symptoms early in life, usually between 50 and 60 years of age. Nevertheless, to expand the use of this BOLD/checkerboard approach to more common types of dementia – Alzheimer’s disease and vascular dementia, more measurement characteristics need to be established. Most importantly, it is expected that in elderly populations there will be an age-effect on parameters of neurovascular coupling in response to visual stimulation, since the vessel wall tends to stiffen during the ageing process. To study the ageing effect on the BOLD/checkerboard (figure 1) parameters: BOLD amplitude, Time-To-Peak, and Time-To-Baseline (figure 2), were analyzed in 87 healthy adults between the age of 20 – 86 years. We found a significant correlation between age and BOLD amplitude (p=0.004). No significant correlation between age and time to peak, and between age and time to baseline were found. Our data show a clear effect of ageing on the BOLD amplitude which directly can be related to a diminished flexibility of the vessel wall at older age. Our results imply that studies using the BOLD/checkerboard approach to study the neurovascular status, should always be age controlled.
ANALYZING MULTIMODAL MRI AT TRACT-LEVEL WITH NEURAL NETWORKS ENHANCES THE PREDICTION OF COGNITIVE PERFORMANCE IN MEMORY CLINIC PATIENTS WITH SMALL VESSEL DISEASE

Alberto De Luca (1) / Hugo Kuijf (2) / Lieza Exalto (1) / Geert-Jan Biessels (1)

(1) Neurology Department, UMC Brain Center, University Medical Center Utrecht, the Netherlands (2) Image Sciences Institute, University Medical Center Utrecht, the Netherlands

Objectives: To investigate whether combining diffusion MRI (dMRI) metrics of the main white matter (WM) bundles with conventional MRI markers in a neural network (NN) analysis improves the prediction of concurrent cognitive performance in patients with small vessel disease (SVD).

Methods: We retrospectively selected 102 patients (73.7±10.2 years old, 53 females) from the Utrecht memory clinic cohort with MRI-visible SVD for which a 3T session including dMRI and conventional MRI was available in addition to cognitive evaluation. MRI was processed with in-house pipelines based on CAT12, ExploreDTI and MRIToolkit to derive the imaging features described in Figure 1. Next, 73 major WM bundles were reconstructed with CSD deterministic tractography and automated clustering. Multivariate linear models (MVLM) and a 2-layers feed-forward NN with 20 nodes were applied to predict cognitive performance (processing speed, memory) of individual patients using a leave-one-out paradigm. Input features for the NN were selected by repeating 10-times the procedure shown in Figure 1 on 50% of the subjects.

Results: MVLM selected WMHV, BPF and MD(WM) in addition to demographics (age, sex, years of education) as best predictors of processing speed, achieving R2=0.38 as compared to R2=0.26 with demographics only. Conversely, with MVLM no imaging metric improved the prediction of memory as compared to demographics only (R2=0.27). With NN, the feature selection resulted in 13 tract-specific metrics and 5 whole brain metrics for processing speed, and 28 tract-specific metrics and 4 whole brain metrics for memory, as shown in Figure 2. Leave-one-out prediction (Figure 3) with all selected features as well as with an optimal subset remarkably improved the prediction performance up to R2=0.49 and R2=0.41 for processing speed and memory, respectively.

Conclusions: We propose a framework to integrate multimodal MRI metrics based on neural networks that considerably improved the prediction of cognitive performance as compared to conventional methods.
NETWORK-BASED LESION IMPACT SCORE IS AN INDEPENDENT PREDICTOR OF POST-STROKE COGNITIVE IMPAIRMENT


(1) Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, Utrecht, the Netherlands (2) Department of Neurology, Elisabeth Tweesteden Hospital, Tilburg, the Netherlands (3) Image Sciences Institute, University Medical Center Utrecht, Utrecht, the Netherlands (4) Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Hong Kong SAR, China (5) Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea (6) Department of Neurology, Amiens University Hospital, Laboratory of Functional Neurosciences (UR UPJV 4599) (7) Jules Verne Picardy University, 80054 Amiens Cedex, France (8) Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, Russell Square House, 10 - 12 Russell Square, London WC1B 5EH, United Kingdom (8) Université Lille, Inserm, CHU Lille, U1172 - LiNCog - Lille Neuroscience & Cognition, F-59000, France (9) Department of Neurology, University of Edinburgh, Edinburgh, United Kingdom (10) UK Dementia Research Institute at the University of Edinburgh, Edinburgh, United Kingdom (11) Department of Pharmacology, National University of Singapore, Singapore, Singapore (12) Memory, Aging and Cognition Center, National University Health System, Singapore, Singapore (13) Department of Neurology, Erasmus Medical Center, Rotterdam, the Netherlands (15) Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore (16) Experimental Psychology, Helmholtz Institute, Utrecht University, the Netherlands (17) Department of Psychology, Hallym University, Chuncheon, Republic of Korea (18) Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands (19) Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China (20) Therese Pei Fong Chow Research Centre for Prevention of Dementia, Margaret Kam Ling Cheung Research Centre for Management of Parkinsonism, Gerald Choa Neuroscience Centre, The Chinese University of Hong Kong, Hong Kong SAR, China (21) Department of Neurology, Hallym University Sacred Hospital, Hallym Neurological Institute, Hallym University College of Medicine, Anyang, Republic of Korea (22) Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom (23) Department of Neurology, Maastricht University Medical Center, Maastricht, the Netherlands (24) BrainNow Research Institute, Shenzhen, Guangdong Province, China (25) Raffles Neuroscience Centre, Raffles Hospital, Singapore, Singapore

Background: Post-stroke cognitive impairment (PSCI) is a common consequence of stroke. Accurate PSCI risk prediction remains challenging. The recently developed network impact score (see DOI:10.1161/STROKEAHA.119.025637), which integrates information on infarct location and size with brain network topology, may improve PSCI risk prediction.

Aims: To determine if the network impact score is an independent predictor of PSCI at pre-specified timepoints during follow-up, and of cognitive recovery or cognitive decline.

Methods: We pooled data from patients with acute ischemic stroke from 12 cohorts through the Meta VCI Map consortium. PSCI was defined as impairment in ≥1 cognitive domain on neuropsychological examination, or abnormal Montreal Cognitive Assessment. Cognitive recovery was defined as conversion from PSCI < 3 months post-stroke to no PSCI at follow-up, and cognitive decline as conversion from no PSCI < 3 months to PSCI. Generalized Estimating Equations (GEE) models were used to relate the network impact score to repeated measures of PSCI and logistic regression to relate the score to PSCI stratified according to post-stroke interval (< 3, 3-12, 12-24, > 24 months), cognitive recovery, and cognitive decline. Models were adjusted for age, sex, education, clinical history of stroke, and infarct volume.

Results: We included 2488 patients with 4941 cognitive assessments (see flowchart; patient characteristics provided in Table 1). The lesion impact score (range -3.07 to 2.46) predicted PSCI in the GEE model (odds ratio [OR] per 1-point increase: univariable 1.47 [95%CI 1.33-1.63], multivariable 1.25 [95%CI 1.12-1.40], and logistic regression models for all post-stroke intervals with comparable ORs (Table 2). The network impact score was not significantly associated with either cognitive recovery or
decline. The results were unchanged after excluding patients (n=152) from the PROCRAS cohort in which the network impact score was developed.

Conclusion: The network impact score is an independent predictor of PSCI at timepoints up to and beyond 24 months after ischemic stroke.
RELATIONSHIP BETWEEN CEREBROVASCULAR PATHOLOGY AND RESTING-STATE FUNCTIONAL CONNECTIVITY: A SYSTEMATIC REVIEW

Natasha Clarke (1) / Désirée Lussier (1) / Flavie Detcheverry (1) / Eric Smith (2) / Sridar Narayanan (3) / AmanPreet Badhwar (1)

(1) Centre de Recherche de l’Institut Universitaire de Gériatrie de Montréal (2) Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary (3) McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University

Introduction: Cerebrovascular pathology can disrupt resting-state functional connectivity (rsFC), a measure of correlated activity in spatially disparate brain regions derived using MRI. White matter hyperintensities (WMHs), the most common MRI-detected feature of cerebral small vessel disease (SVD), are also prevalent in Alzheimer’s disease (AD). We conducted a systematic review to better understand the association between cerebrovascular pathology and rsFC, in patients a) along the AD continuum with evidence of WMHs, or b) with genetically defined SVD (e.g. CADASIL).

Methods: A PRISMA-guided systematic search was performed in PubMed/Embase/PsycInfo for articles published until February 2021. Articles were assessed by three authors using Rayyan (www.rayyan.ai). Included studies evaluated the association between rsFC and an index of cerebrovascular pathology in a) AD or its prodrome Mild Cognitive Impairment (MCI) or b) CADASIL/CARASIL. Duplicates, case reports, reviews, non-human and non-English articles were excluded.

Results: 12 of 508 papers met inclusion criteria (Figure1), indicating a knowledge gap. AD/MCI studies (N=8) suggested an association between WMH load and rsFC. The default mode network (DMN) was most investigated. In the majority of studies, increased global WMH load was associated with increased DMN rsFC in the MCI group, while no such association was found in the AD dementia group. CADASIL studies (N=4; none in CARASIL) reported decreased rsFC in the DMN, which was mostly associated with worse cognitive performance.

Discussion: Studies of rsFC in CADASIL suggest that cerebrovascular pathology has a detrimental impact on rsFC. Along the AD continuum, there may be a compensatory mechanism in response to WMH load in the MCI, but not dementia stage. Analysis of results from sporadic SVD are underway and will be presented. Emerging evidence suggests that differences in rsFC could act as a potential biomarker to aid in differential diagnosis or disease staging.
TRAJECTORIES OF COGNITIVE CHANGE FOLLOWING STROKE: A STEPWISE DECLINE TOWARDS DEMENTIA

Joao Delgado (1) / Louise Allan (1) / Rajesh Kalaria (2)

(1) University of Exeter Medical School (2) Newcastle University

Stroke survivors are at an increased risk of developing dementia. However, the direct effects of stroke in global cognition, and on incident dementia remain unknown. We investigated post-stroke changes to cognition, while accounting for time to dementia diagnosis, and identified risk factors for early onset of dementia following stroke.

A prospective cohort of 355 stroke survivors, aged ≥75 years, followed for up to 12 years. CAMCOG-R and MMSE indices measured global cognition at annual visitations. Risk factors were recorded at baseline. Mixed effect models characterised trajectories of cognitive change, and logistic models tested associations between early onset of dementia and risk factors, adjusted for age and gender. Statistical significance was set at p=0.05.

91 of the 355 participants (25.6%) developed dementia during follow-up. This group showed a steeper decline in CAMCOG-R (Coef=-1.91, CI=-2.23:-1.59,p<0.01) compared to the no dementia group.

The dementia group, stratified into groups of 3 years of follow-up, showed a period of cognitive stability after stroke, lasting 3 years for the 4-6Y, 4 years for the 7-9Y; and 6 years for the 10-12Y, but followed by a steep decline in the 3 years before a dementia diagnosis. The 1-3Y group displayed cognitive decline after stroke. Similar results were identified for MMSE.

Risk factors for early onset of dementia include repeat stroke (OR=3.99, CI=1.30:12.25,p=0.016), number of cardiovascular risk factors (OR=2.02, CI=1.26:3.25,p=0.004), and <80 baseline CAMCOG-R score (OR=3.50 CI=1.29:9.49,p=0.014).

We showed two stages of cognitive change in stroke survivors, a period of cognitive stability followed by a steep decline 3 years before a dementia diagnosis. This suggests a stroke predisposes for dementia, possibly by diminishing cognitive reserve but with a smaller impact on cognition. Cognitive decline may be precipitated later by subsequent events, e.g. subsequent stroke. These findings support the assertion that the development of vascular dementia can be stepwise.
LONG-TERM OUTCOMES AMONG NIGERIAN STROKE SURVIVORS - DATA FROM THE COGFAST-NIGERIA STUDY

Gabriel Ogunde (1)(2) / Joshua Akinyemi (2) / Adesola Ogguniyi (1)(3) / Rajesh N. Kalaria (1)(4) / Rufus Akinyemi (1)(3)(4)

(1) Neuroscience and Ageing Research Unit, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, Nigeria (2) Department of Epidemiology and Medical Statistics, Faculty of Public Health, College of Medicine, University of Ibadan, Nigeria (3) Department of Neurology, University College Hospital, Ibadan, Nigeria (4) Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom

Background: Africa faces a rising burden of stroke with rising incidence and prevalence but little is known about the profile and trajectory of long-term outcomes including cognition, depression, functional dependency, health-related quality of life and mortality. The aim of this study was to explore the profile, trajectory and determinants of long-term outcomes up to four years among a cohort of stroke survivors recruited into the CogFAST-Nigeria study.

Methods of Study: The data analysed were collected in a longitudinal study of stroke survivors who were prospectively recruited from the Federal Medical Centre, Abeokuta and University College Hospital, Ibadan Nigeria. Subjects with subarachnoid haemorrhage, co-morbid psychiatric or neurologic illness, or any systemic disease that could impair cognition were excluded from the study. Cognitive function was assessed using the vascular neuropsychological battery, depression was evaluated by the Geriatric Depression Scale-short form, functional dependency through the Barthel Index and quality of life through the Health-Related Quality of Life in Stroke Patients (HRQOLISP) tool. Baseline enrolment was done three months after stroke (2010-2011) and the stroke survivors were followed up for a period of four years after the baseline enrolment (2014-2015).

Results: Of the 253 stroke survivors recruited into the study, 157 (62.6%) were males. The mean age was 60.2 (±9.8) years. The mean number of years of formal education was 10.21 (±5.3). Among the stroke survivors, the proportions of those with cognitive impairment were 53.2% at six months follow-up, 56.9%, 58.7%, 60.9%, and 66.7% at 1, 2, 3 and 4 years respectively, while the proportion of those with depression were 39.3% at 3 months post-stroke, 35.2%, 35.5%, 26.7%, and 36.1% at 1, 2, 3 and 4 years respectively after enrolment into the study. The proportion of those with functional impairment were 12.5%, 13.3%, 15.4%, 22.2%, and 23.3% at six months, 1, 2, 3, and 4 years respectively. The case fatality rate was 7.5% (95% C.I = 4.82-11.4) at six months post-stroke, 24.8% (95% CI = 19.93-30.6), 39.4% (95% CI=3.65-45.7) and 45.3% (95% CI=39.42-51.6) at 1, 3 and 4 years follow-up respectively. Factors associated with mortality at 10% significance level include professional occupation (OR= 0.49; 90% CI=0.27-0.92; p-value=0.063) and those living with spouse/living with spouse and children (OR=0.57; 90%CI=0.35-0.93 p-value=0.058) while previous stroke was associated with functional dependency (OR=2.17; 95% C.I = 1.19-3.95, p-value 0.011) among the stroke survivors. Meanwhile, older age (>70 yrs) (OR=23.47; 95%C.I=2.71-203.44, p-value=0.004), higher education (OR=0.17 95%C.I=0.04-0.69, p-value=0.013), professional occupation (OR=13.25; 95%C.I=1.04-168.55; p-value=0.046), previous stroke (OR=7.03 95%C.I=1.30-37.96, p-value=0.023), and caregiver burden (OR=3.51; 95% C.I=1.53-8.05, p-value=0.003) were predictors of cognitive impairment among the stroke survivors.

Conclusion: Impairment (both in the cognitive function and functional dependency) increased among the stroke survivors over time. There is a need to improve stroke rehabilitation among stroke survivors including particular attention on those with recurrent stroke.
BRAIN REGIONS INVOLVED IN THE STRATEGIC PROCESSES OF VERBAL FLUENCY: A MVLSM STUDY IN 337 STROKE PATIENTS

Flore Dorchies / Martine Roussel / Olivier Godefroy

Department of Neurology and Laboratory of Functional Neurosciences, Amiens University Hospital, France

Context: Several studies in verbal fluency have shown the potential of using additional indexes to the number of correct responses in order to determine more precisely the origin of the deficit. On the other hand, studies conducted in functional imaging and pathology report the difficulties in clearly defining the neuroanatomical correlates of these additional indexes.

Objective: To examine the patterns of verbal fluency deficits in stroke patients and identify their lesion determinants using the multivariate Voxel-based lesion symptom mapping (mVSLM) method.

Method: 337 patients and 851 controls executed the literal and semantic verbal fluency tests analyzed using global and strategic indices (clustering, switching, lexical frequency). Performance profiles were compared between groups and the relationships between verbal fluency, processing speed and naming were studied. mVLSM analyses were performed to identify lesion patterns associated with worse verbal fluency performance.

Results: Strategic indexes differed between patients and controls and reflected different processes than those involved in the processing speed and naming tasks. In addition, these indexes correlated with partly distinct left hemisphere brain networks. The mVLSM analyses selected the fronto-striatal tract (FST) and uncinate fasciculus (UF) for clustering, anterior thalamic projections (ATP) for switching and lexical frequency, and the superior temporal pole (TP) for lexical frequency only.

Conclusion: These results suggest (i) a discriminative ability of strategic indexes reflecting clustering, switching and lexico-phonological or lexico-semantic retrieval processes, (ii) an independence of these indexes to processing speed and naming abilities in cerebrovascular disease, and (iii) a specific involvement of certain brain networks depending on the processes considered.
PATTERNS AND PREDICTORS OF SHORT-TERM TRAJECTORY OF POST-STROKE COGNITIVE FUNCTION

Jessica Lo / John Crawford / Perminder Sachdev / Stroke and Cognition Consortium (STROKOG) / UNSW

Introduction: Existing literature on the course of post-stroke cognitive function have so far focused on the average rate of cognitive change. Finer modelling of individual variations that identify several typical trajectories would benefit our understanding of poststroke cognitive outcomes and their predictors. This project utilizes data from the Stroke and Cognition consortium (STROKOG) and focuses on the initial post-stroke period. We aim to 1) identify several typical trajectories of post-stroke cognitive function, 2) examine the predictors of the cognitive trajectories, and 3) estimate their risk of dementia.

Methods: Latent class growth analysis was used to examine patterns of trajectory of cognitive function (harmonised global cognition z-scores) between the first visit (2-6 months) and the second visit (about 1 year up to 15 months). Generalised linear mixed models were used to examine the associations between risk factors and cognitive function, and survival analysis was used to estimate the risk of dementia.

Results: Nine international studies with 1,745 patients were included and 1,381 patients were followed up. Latent class growth analysis identified four distinct groups: 8.7% experienced decline; 32% remained stable, 42% experienced moderate improvement, and 17% experienced large improvement. Patients who had worse baseline global cognition z-scores (mean -3.9 SD) had the largest decline, while those who had better baseline scores (mean 0.09 SD) experienced cognitive improvement. Mixed model identified the follow predictors of cognitive decline: age, lower education, a history of diabetes, prior stroke, stroke severity, and large vessel strokes compared to small vessel strokes. Patients who experienced cognitive decline had much greater risk of dementia compared to those who had stable cognitive trajectories.

Conclusion: The pattern of cognitive change from 2-6 months to 15 months after stroke varied and was associated with baseline cognitive performance and with age, education, stroke characteristics and diabetes.
VISUOSPATIAL DYSFUNCTION IN VASCULAR COGNITIVE IMPAIRMENT SUBTYPES- A COMPARATIVE STUDY FROM A TERTIARY CARE CENTER IN KOLKATA.

Atanu Biswas Bangur

Institute of Neurosciences, IPGME&R and SSKM hospital, Kolkata, West Bengal, India

Introduction: Conventional teachings have predominantly emphasised on the role of cortical structures in the genesis of visuospatial dysfunction. However, the role of subcortical structures and white matter pathways in causing visuospatial dysfunction cannot be neglected. Although visuospatial dysfunction has been described in cortical dementias including Alzheimer’s disease and Frontotemporal dementia, it is an important feature of Vascular Cognitive impairment.

Methods: In this observational cross-sectional study, we recruited 76 patients of Vascular Cognitive impairment with a score of 4 or more on the modified Hachinski ischemic scale. The patients were then classified into large vessel and small vessel Vascular dementia based on the NINDS-AIREN criteria. Visuospatial function was assessed using the Kolkata cognitive battery and tests from Adenbrooke’s cognitive examination which was validated for Bengali language. The Frontal Assessment battery was used to test the executive function in these patients while the dementia severity was assessed using the Clinical Dementia Rating scale.

Results: We found that visuospatial dysfunction was more prominent in large vessel Vascular Cognitive impairment (35.7%) compared to small vessel Vascular Cognitive impairment (16.7%). In large vessel disease, the visuospatial dysfunction was present more for the right sided lesions. In small vessel disease, the visuospatial dysfunction was present at higher white matter hyper-intensity scores. Moreover, in small vessel disease Executive dysfunction was present in the majority of patients with visuospatial dysfunction.

Conclusion: Visuospatial dysfunction is an important feature of Vascular Cognitive impairment - both large and small vessel disease. Thus, not only lesions of the cortical structures but those of the subcortical structures and pathways are responsible for visuospatial dysfunction in Vascular Cognitive impairment.
Mixed pathologies are common in the brains of the elderly with cognitive impairment – the given prevalence data indicating a highly variable number of cases of both mixed and “clean” pathologies, the latter decreasing with age (1). It has been proposed that indeed the majority of old age neuropathology associated with cognitive decline is of mixed type and that only few “pure” cases of vascular-ischemic pathology occur (2). In a clinicopathological study from Brazil (3), however, the prevalence of pure vascular dementia (VaD) was 21.2%, judged to be particularly high because of poor management of cardiovascular risks in the country.

In our experience, the number of cerebrovascular - ischemic disease (CVD) compatible with vascular cognitive impairment and VaD is high also in Sweden, not only as part of mixed disease but also as pure CVD. Within the Department of Neuropathology in Lund, Sweden, 40 of 65-70 full brain investigations per year are performed for diagnostics of disease compatible with cognitive impairment. We evaluated the number of cases burdened with solely vascular-ischemic pathology in individuals (> 70 years), clinically diagnosed with cognitive decline/dementia during a 5-year period (2016-2020), regardless of the given clinical diagnosis of disease type.

Among 200 cases with clinically diagnosed cognitive disorder, pure CVD was found in 24% of the cases. Mixed vascular and neurodegenerative disease of any kind formed a similarly large group, but did not exceed the number of pure CVD cases. It appears that a relatively high prevalence of pure CVD may be seen in many types of societies, also where cardiovascular risk awareness and management is considered to be high.

References
2) McAleese K et al. BMC Medicine (2016) 14:129
ASSOCIATION BETWEEN CEREBRAL SMALL VESSEL DISEASE AND ALZHEIMER’S DISEASE PATHOLOGIES

Yuan Cai (1) / Wanting Liu (1) / Xiang Fan (1) / Lin Shi (2) / Lisa Wing Chi Au (1) / Bonnie Yin Ka Lam (1) / Jill Abrigo (2) / Vincent Chung Tong Mok (1)

(1) Division of Neurology, Department of Medicine and Therapeutics, Therespe Per Fong Chow Research Centre for Prevention of Dementia, The Chinese University of Hong Kong, Hong Kong SAR, China (2) Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR, China

Background: Controversy exists with respect to the etiological role of cerebral small vessel disease (CSVD) in Alzheimer's disease (AD). We thus evaluated the association between white matter hyperintensity (WMH), a MRI marker of CSVD, with brain Aβ/tau burden among subjects with varying severity levels of cognitive impairment.

Methods: A total of 84 stroke-free subjects (healthy controls [HC]=10; subjective cognitive decline [SCD]=32; mild cognitive impairment [MCI]=26; dementia =16) were included. All patients underwent structural MRI, 11C-PIB, and 18F-T807 PET to measure WMH volume, Aβ deposition (A+) and pathologic tau (T+), respectively. WMH volume was quantified by automatic segmentation using AccuBrain® IV 1.1 (BrainNow Medical Technology Company Ltd.). Levels of plasma Aβ40, Aβ42, t-tau, p-tau181 and NfL were tested by Single molecule array (SiMoA) among 71 subjects.

Results: No significant association was found between WMH volume and global 11C-PIB or 18F-T807 SUVR on PET, and between WMH volume with subjects who were A+T+ in the overall population. There was also no significant association found within different cognitive subgroups except in those with dementia, where we found that increasing global 11C- PIB SUVR correlated with lower WMH volume (B=-1.76 ;95% CI, -2.92- -0.59; p=0.007). We found that increasing WMH volume correlated with higher plasma p-tau 181 level (B =0.10 ;95% CI, 0.012-0.188; p=0.03) and there was no association between WMH volume and plasma Aβ40, Aβ42, t-tau and NfL levels.

Conclusion: We found no association between brain Aβ or tau burden and WMH volume, except an inverse association was noted between Aβ and WMH in dementia patients. The WMH volume was associated with plasma p-tau level. Our results suggest that CSVD may be associated mainly with an increase in tau burden.
COMBINED ASSOCIATIONS OF COGNITIVE AND MOTOR IMPAIRMENTS WITH FUNCTIONAL OUTCOME IN COVERT CEREBRAL SMALL VESSEL DISEASE

Hanna Jokinen (1)(2) / Hanna M. Laakso (1)(2) / Matti Ahlström (3) / Anne Arola (4) / Juha Lempiäinen (3) / Johanna Pitkänen (3) / Teemu Paajanen (5) / Sietske A. M. Sikkes (6) / Juha Koikkalainen (7) / Jyrki Lötiönen (7) / Antti Korvenoja (8) / Timo Erkinjuntti (3) / Susanna Melkas (3)

(1) Division of Neuropsychology, HUS Neurocenter, Helsinki University Hospital (2) University of Helsinki; Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Finland (3) Department of Neurology, Helsinki University Hospital and University of Helsinki, Finland (4) Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Finland (5) Research and Service Centre, Finnish Institute of Occupational Health, Finland (6) Department of Clinical, Neuro and Developmental Psychology, VU University; Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam UMC, The Netherlands (7) Combinotics Ltd; Faculty of Health Sciences, University of Eastern Finland, Finland (8) Department of Radiology, HUS Diagnostic Center, Helsinki University Hospital and University of Helsinki, Finland

Objective: Cognitive and motor impairments are the key clinical manifestations of cerebral small vessel disease (SVD), but their combined effects on functional outcome have not been elucidated. We investigated the interactions and mediating effects of cognitive and motor functions on instrumental activities of daily living (IADL) and quality of life in older individuals with various degrees of white matter hyperintensities (WMH).

Methods: Participants of the Helsinki Small Vessel Disease Study (n=152) were assessed according to an extensive clinical, neuropsychological and MRI protocol. Cognitive composite scores for global cognition, processing speed, executive functions and memory were constructed from multiple tests within each domain. Physical examination included measures of gait speed, balance (single-leg-stance) and functional mobility (timed-up-and-go test). IADL was evaluated with a proxy-based Amsterdam IADL questionnaire and quality of life with a self-report EUROHIS-Qol index. Volumes of WMH and gray matter (GM) were obtained with automated segmentation.

Results: Domain-specific cognitive and motor functions had strong interrelations with each other, and they were significantly associated with IADL, quality of life as well as WMH and GM volumes. A consistent pattern on significant interactions between cognitive and motor functions was found on IADL, but not on quality of life. In particular, low cognitive scores together with decline in the timed-up-and-go test and gait speed were strongly related to impaired IADL. The association of WMH volume with IADL was mediated by global cognition, whereas the association of GM volume with IADL was mediated by global cognition and timed up-and-go performance.

Conclusion: The results highlight the complex interplay and synergism between motor and cognitive abilities on functional outcome in SVD. The combined effect of motor and cognitive disturbances on IADL is likely to be greater than their individual effects. WMH and brain atrophy contribute to disability through cognitive and motor impairment.
CEREBRAL SMALL VESSEL FUNCTION IN PATIENTS WITH CADASIL AND SPORADIC CEREBRAL SMALL VESSEL DISEASE: ASSESSMENT OF HEMODYNAMIC RESPONSE FUNCTION WITH 7T MRI – THE ZOOM@SVDs STUDY

Hilde van den Brink (1) / Jeroen Siero (2) / Anna Kopczak (3) / Tine Arts (2) / Benno Gesierich (3) / Jaco Zwanenburg (2) / Marco Duering (3) / Martin Dichgans (3) / Geert Jan Biessels (1)

(1) Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands (2) Department of Radiology, Center for Image Sciences, University Medical Center Utrecht, Utrecht, the Netherlands (3) Institute for Stroke and Dementia Research, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany

Background: Neuropathology studies in cerebral small vessel diseases (SVDs) show small vessel alterations that likely impact small vessel function. We investigated in vivo cerebral small vessel reactivity with 7T MRI in patients with CADASIL, sporadic SVDs and controls. Reactivity was compared between patients and controls, and was related with white matter hyperintensities (WMHs) as a proxy of disease severity.

Methods: We included 19 patients with CADASIL (age 50.8±10.8 years, 53% women) with 10 controls (age 45.1±11.4, 40% women) and 35 patients with sporadic SVDs (age 64.7±9.4, 40% women) with 20 controls (age 63.2±6.9, 40% women) from the ZOOM@SVDs study. Small vessel reactivity was assessed with blood oxygenation level-dependent (BOLD) MRI acquired on 7T during a visual stimulation experiment. We compared the fits of the average hemodynamic response function (HRF) in the visual cortex between patients and their respective controls. Within patients, we related the affected HRF-characteristics with WMH volume.

Results: In patients with CADASIL, the amplitude (BOLD % change) of the HRF fit in response to the visual stimulus was lower than in controls, whereas patients with sporadic SVDs showed a similar amplitude, but a more narrow reactivity response (full-width-at-half-maximum) compared to their controls (Figure 1, Table 1). Lower amplitude in CADASIL did not significantly relate with WMH volume (rs= -0.32, p=.18), but the narrow reactivity response in sporadic SVDs related with higher WMH volume (rs= -0.45, p=.006, Figure 2).

Conclusion: Small vessel reactivity in the visual cortex was decreased both in patients with CADASIL and sporadic SVDs, but in dissimilar ways in both groups. Abnormal reactivity could be a new dynamic marker of SVDs that can help provide insight into underlying disease mechanisms.
VISIT-TO-VISIT VARIABILITY IN BLOOD PRESSURE OVER 10 YEARS, COGNITIVE DECLINE AND INCIDENT DEMENTIA IN THREE COMMUNITY-BASED COHORTS OF OLDER ADULTS

Simin Mahinrad / Lisa Barnes / David Bennett / Farzaneh Sorond / Philip Gorelick

Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Background: BP variability (BPV) has emerged as a novel marker for cognitive decline among older adults. However, the link between BPV and risk of dementia subtypes remains incompletely understood.

Aim: In this study, we assessed the relationship of long-term visit-to-visit BPV with cognitive decline and risk of Alzheimer's disease (AD) and mild cognitive impairment (MCI) among community-dwelling older adults.

Methods: We used longitudinal data (between 1994 and 2019) from three community-based cohort studies: the Religious Orders Study, Rush Memory and Aging Project and Minority Aging Research Study. A total of 2403 dementia-free participants ≥65 years of age (76% female, 78% white) were followed for a median of 9 years (interquartile range 6-13). Visit-to-visit BPV was quantified from annual BP measurements (Table1 legend). Several domains of cognition were assessed annually. Risk of AD and MCI were defined as conversion from normal cognition to AD and MCI clinical diagnosis, respectively.

Results: Using linear mixed-effect models adjusted for demographics, vascular risk factors, and medications, larger visit-to-visit systolic and diastolic BPV were associated with steeper decline in all cognitive domains except for perceptual speed (all p-values< 0.05, Table1). During follow-up, 502 and 1193 participants developed incident AD and MCI, respectively. In multivariate adjusted Cox proportional hazard models, participants in the highest tertile of SBPV had 1.69 fold (95% CI=1.34, 2.14) higher risk of AD and 1.20 fold (1.03, 1.39) higher risk of MCI (Figure1). Participants in the highest tertile of DBPV had 1.27 fold (1.09, 1.48) higher risk of AD and 1.20 fold (1.04, 1.39) higher risk of MCI (Figure1).

Conclusion: Higher BPV is associated with accelerated cognitive decline and higher risk of AD and MCI in community-dwelling older adults, independent of other vascular risk factors and medication use. Therefore, reducing BPV may represent an important therapeutic target to preserve cognition in old age.
INVESTIGATING THE RISK OF CARDIOVASCULAR RISK FACTOR SUBGROUPS IN COGNITIVELY NORMAL ELDERLY ON ALZHEIMER’S DISEASE: A LATENT CLASS APPROACH

Myuri Ruthirakuan (1) / Hugo Cogo-Moreira (2) / Walter Swardfager (1) / Nathan Herrmann (1) / Krista Lanctot (1) / Sandra Black (1)

(1) Sunnybrook Research Institute (2) Federal University of São Paulo

BACKGROUND: Individual cardiovascular risk factors (CVRFs) have been associated with neurodegenerative processes. However, CVRFs often co-occur with one another and little is known regarding the extent of their clustering, and effect on progression to Alzheimer’s disease (AD). We identify classes of CVRFs in cognitively normal (CN) individuals, and investigate between-group differences in incident AD.

METHODS: CN individuals were recruited from the National Alzheimer’s Coordinator Center dataset. A latent class analysis (LCA) was conducted with five vascular (hypertension, hypercholesterolemia, heart condition, stroke, and smoking history), and two metabolic (diabetes, and high body mass index (BMI)) indicators. Incidence of AD was compared between CVRF classes. As mortality may be a competing event, post-hoc analyses investigated between-group differences in incidence of death, death without an AD diagnosis, and AD while remaining alive throughout follow-up.

RESULTS: This study included 12,412 CN individuals (age:70.9±10.5, male:35%, 6% progressed to AD). Three classes of CVRFs were identified (Figure 1). One group had low probabilities of CVRFs (N=5398(43%)) (reference). The second group had higher probabilities of hypertension and hypercholesterolemia (vascular-dominant class)(N=5721(46%)). The third group had higher probabilities of hypertension, hypercholesterolemia, diabetes, and high BMI (vascular/metabolic class)(N=1293(10%)). Compared to the reference group, only the vascular-dominant class had a significantly greater incidence of AD (OR:1.30, 95%CI:.94-1.80, p< .001). Post-hoc analyses demonstrated that compared to the reference group, the vascular-dominant (OR:3.26, 95%CI:2.40-4.43, p< .001), and vascular/metabolic classes (OR:1.84, 95% CI:1.13-3.00, p=.02) had a greater incidence of death. The incidence of death without an AD diagnosis was significantly greater in the vascular-dominant (OR: 3.31, 95%CI: 2.45-4.74, p< .001) and vascular/metabolic classes (OR: 3.12, 95%CI: 2.35-4.14, p< .001), compared to the reference group. The incidence of AD in those who were alive throughout follow-up was significantly greater in the vascular-dominant (OR: 1.54, 95%CI: 1.09-2.12, p=.02) and vascular/metabolic classes (OR: 1.46, 95%CI: 1.01-2.11, p=.04), compared to the reference group.

CONCLUSION: Three phenotypes of CVRFs were identified in CN elderly; a group with low probabilities of CVRFs, a vascular-dominant class, and a vascular/metabolic class. Only the vascular-dominant class was associated with a greater incidence of AD. However, selective mortality is a likely contributor to the attenuated association between the vascular/metabolic class and incident AD.
PREVALENCE OF COGNITIVE IMPAIRMENT AND DEMENTIA IN A MULTI-ETHNIC ELDERLY COHORT THE SINGAPORE EPIDEMIOLOGY OF EYE DISEASES STUDY (SEED)

Ting Pang (1) / Xuhao Zhao (1) / Xin Xu 1 (1)(2)

(1) School of Public Health & the 2nd Affiliated Hospital of School of Medicine, Zhejiang University, China (2) Memory, Ageing and Cognition Centre (MACC), Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Background: Singapore is a multi-ethnic country and the burden of dementia is increasingly severer due to the rapid aging population. The various risks of dementia by ethnicity lead to an urgent need to update the prevalence of dementia by different ethnic groups.

Objective: To estimate the prevalence of cognitive impairment and dementia and compare the results by different ethnic and age groups.

Methods: Epidemiology of Dementia in Singapore (EDIS) was a 2-phase community-based study. Subjects who screened as cognitive vulnerability through the validated Abbreviated Mental Test (AMT) and the Progressive Forgetting Self-Report (PFQ) at phase 1 were examined by comprehensive clinical evaluation for cognitive impairment and dementia at phase 2.

Results: Among 3780 subjects (aged ≥60 years) at phase 1, 957 were entered into phase 2. Results from phase 2 showed 669 (17.7%) with cognitive impairment, 307 with cognitive impairment with no dementia (CIND)-Mild, 316 with CIND-Moderate and 46 with dementia. The overall age and race standardized prevalence was 2.51%(95%CI=[2.0%-3.1%]) for dementia, 6.32%(95%CI=[5.5%-7.2%]) for CIND-Mild and 8.12%(95%CI=[7.2%-9.1%]) for CIND-Moderate. With increasing age, the prevalence of dementia increased from 0.07% (65-69) to 37.5% (≥85). Prevalence of dementia were 2.45%, 2.34% and 1.32% among Chinese, Malay and Indians respectively.

Conclusion: The prevalence of dementia remains high, suggesting the importance of long-term dementia monitoring and intervention. Noting the various prevalence of dementia between the three ethnic groups, further study should explore possible demographic and clinical indicators associated with the different risks.
DISCRIMINANT VALIDITY OF THE PROGRESSIVE FORGETFULNESS QUESTION IN A STEPWISE DEMENTIA SCREENING APPROACH IN A SINGAPOREAN ELDERLY POPULATION

Ting Pang (1) / Xuhao Zhao (1) / Cheuk Ni Kan (2) / Changzheng Yuan (1) / Xin Xu (1)(2)

(1) School of Public Health & the 2nd Affiliated Hospital of School of Medicine, Zhejiang University, China (2) Memory, Ageing and Cognition Centre, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Objective: To investigate the diagnostic utility of a self-reported assessment of progressively forgetfulness question (PFQ), as compared to other commonly used screening tools, in detecting dementia or cognitive impairment (CI) in an elderly community in Singapore.

Methods: This is a two-phased community-based study among elderly Singaporeans (age≥60). Participants who were screened as positive at phase I by the validated Abbreviated Mental Test (AMT) and PFQ entered phase II. During phase II, participants were administered the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and a formal neuropsychological battery. No Cognitive Impairment (NCI), Cognitive Impairment-No Dementia (CIND), were diagnosed by the results of a locally validated neuropsychological battery. Dementia was diagnosed by DSM-IV criteria. All discriminatory indices were calculated to determine the diagnostic utility of the PFQ against and in combination of the MMSE, MoCA and AMT.

Results: A total of 918 participants were included in the analysis. The PFQ showed good sensitivity (75.1%) and excellent NPV (95.4%) for ruling out healthy elderly at the phase I. At the phase II, the PFQ had excellent sensitivity but poor specificity in detecting CI (sensitivity=96.9%, specificity=3.3%), high risk (sensitivity=96.3%, specificity=3.2%) and dementia (sensitivity=93.3%, specificity=3.2%). The AUCs for MoCA(0.95), MMSE(0.94) and AMT(0.93) is greater than among participants who reported PFQ=yes than those who reported PFQ=no (MoCA=0.87, MMSE=0.83 and AMT=0.74).

Conclusion: Asking for the PFQ can facilitate case finding of dementia on the scale of a large population. Additionally, a stepwise way using the PFQ is recommended when detecting dementia among the elderly.
Background: The usefulness of neurofilament light (NfL) as a biomarker for small vessel disease (SVD) has not yet been established. We examined the relationship between NfL level, neuroimaging changes, and clinical findings in subjects with varying degrees of white matter hyperintensities (WMH).

Methods: A subgroup of participants (n=35) in the Helsinki SVD Study underwent an analysis of NfL in cerebrospinal fluid (CSF) and plasma as well as a brain MRI and neuropsychological and motor performance assessments. Evaluation of WMH and structural brain volumes were obtained with automatic segmentation.

Results: CSF NfL did not correlate significantly with total WMH volume (r=0.278, p=0.105). However, strong correlations were observed between CSF NfL level and volumes of cerebral grey matter (r=-0.569, p<0.001), cerebral cortex (r=-0.563, p<0.001), and hippocampi (r=-0.492, p=0.003). CSF NfL was also consistently associated with performance in global cognition (r=-0.403, p=0.016), executive functions (r=-0.402, p=0.017), memory (r=-0.463, p=0.005), and processing speed (r=-0.386, p=0.022). In motor skills tests, CSF NfL was correlated with Timed Up and Go test results (r=0.531, p=0.001), and gait speed (r=-0.450, p=0.007), but not with results in single-leg stance test. Plasma NfL level showed the same correlations but somewhat weaker.

Conclusions: NfL level was strongly related to global gray matter and hippocampal atrophy, but not with WMH severity. NfL was also consistently associated with cognitive and motor performance. Our results suggest that NfL generally reflects frailty in the central nervous system (CNS).
AGE-ASSOCIATED CHANGES IN THE RENIN-ANGIOTENSIN SYSTEM: IMPLICATIONS FOR FUTURE CLINICAL TRIALS

Robert MacLachlan / Scott Miners / Patrick Kehoe

University of Bristol

The renin-angiotensin system (RAS) is a hormonal system that primarily regulates systemic blood pressure and water balance within the body, however, the RAS is also localised and functions independently within organs including the brain. Overactivation of brain RAS is associated with cognitive impairment and disease pathology in Alzheimer’s disease. RAS-targeting agents, commonly prescribed for hypertension, have been shown to slow the progression and delay the onset of dementia. The aim of my PhD is to characterise age-related changes in brain RAS pathways in animal models of AD and in human post-mortem brain tissue to inform when the timing of intervention would provide the most beneficial effects.

Angiotensin-converting enzyme-1 (ACE-1) is responsible for angiotensin-II synthesis. Angiotensin-II is the main effector protein of RAS and is responsible for causing vasoconstriction. Angiotensin-converting enzyme-2 (ACE-2) is responsible for angiotensin 1-7 synthesis. Angiotensin 1-7 is an effector protein responsible for eliciting vasodilation.

The level and activity of RAS proteins were measured within the brain homogenates of a mouse cohort with two transgenic models and corresponding wild-type mice at various ages. This provided an insight into how ageing and disease affect protein expression and activity. Protein levels for angiotensin II and angiotensin 1-7 were measured by ELISA and protein activity for ACE-1 and ACE-2 were measured by activity assays.

A significant reduction was observed in ACE-2 activity with increasing age in the wild-type mice whereas a significant increase in angiotensin 1-7 level was also observed with increasing age. This increase in angiotensin 1-7 levels was unexpected and will require further investigation to elucidate how it is increased. We hypothesise that either angiotensin 1-7 ACE-2-independent synthesis is increased with age or there is a reduction in angiotensin 1-7 degradation.
RENIN-ANGIOTENSIN SYSTEM GENE EXPRESSION AND DEMENTIA PATHOLOGY IN ALZHEIMER’S DISEASE, VASCULAR AND MIXED DEMENTIA

Hannah M. Tayler / Olivia A. Skrobot / Özge Güzel / J. Scott Miners / Patrick G. Kehoe

University of Bristol

Background: The brain renin-angiotensin system (RAS) has roles in both vasoactivity and memory, with levels and expression of its components altered in neurodegeneration. Ang-II type 1 receptor (AGTR1) facilitates the main cardiovascular effects of Ang-II and is linked to pathological processes. By contrast, activation of Ang-II type 2 receptor (AGTR2) counteracts the damaging effects of AGTR1. Upstream, renin (REN) produces Ang-I which binds to the prorenin/renin receptor (ATP6AP2). Regulatory RAS receptors, IRAP (LNPEP) is involved in memory formation, while MAS (MAS1) inhibits neurodegeneration and inflammation. Relative expression of the corresponding genes for these RAS targets in Alzheimer’s disease (AD), vascular dementia (VaD), and comorbid mixed dementia cases was investigated.

Methods: AD (n=50), mixed AD/VaD (n=24), VaD (n=21) and control (n=50) frontal cortex post-mortem samples from the South-West Dementia Brain Bank were examined. RAS target gene expression was measured by qPCR TaqMan assays for; AGTR1, AGTR2, LNPEP, MAS1, REN, and ATP6AP2, standard reference genes (SRG) (RPL13, UBE2D2), and cell-type specific (astrocytic, GFAP and neuronal, Rbfox3) reference genes. Relative changes in gene expression were calculated using the 2-ΔΔCT method.

Results: Expression of AGTR1 was elevated in mixed cases only in relation to Rbfox3 and SRG. AGTR2 was upregulated in relation to SRG in AD cases. LNPEP was downregulated in AD in relation to GFAP, however, upregulated in relation to SRG in both mixed and VaD cases. MAS1 was downregulated in relation to Rbfox3 and GFAP in both AD and mixed groups. REN expression was lower in all groups and ATP6AP2 in AD and mixed cases. Expression levels examined in relation to pathological markers of neurodegeneration will be presented.

Conclusion: RAS gene expression in AD was not reflected in VaD, suggesting RAS signalling may be differentially altered in these dementia subtypes.
ANGIOTENSINOGEN, ACE-1 AND ACE-2 IN ALZHEIMER’S DISEASE AND VASCULAR DEMENTIA

Özge Güzel / Hannah Mary Tayler / Olivia Anna Skrobot / James Scott Miners / Patrick Gavin Kehoe

Dementia Research Group, Faculty of Translational Health Sciences, Bristol Medical School, University of Bristol, UK

Background: Alteration of the renin angiotensin system (RAS) within the brain potentially contributes to the pathogenesis of Alzheimer’s disease (AD). ACE1 encodes angiotensin II converting enzyme-1 (ACE1), a rate-limiting enzyme in the classical renin-angiotensin system (cRAS) responsible for the conversion of Ang-I (generated from angiotensinogen) to Ang-II. ACE-2 is the central enzyme in the generation of Ang (1-7) from Ang II and is a central mediator of the counterregulatory RAS (rRAS) arm. In this study, we investigated the mRNA expression of ACE1, ACE2 and AGT, and protein levels of ACE1 and AGT in the frontal cortex in AD and examined their associations with the ACE1 variant (rs4343) (a proxy marker for the more commonly studied indel polymorphism) which is an established risk factor for AD.

Methods: We studied 95 dementia cases including AD, Mixed, and VaD, and 50 control brains from the South West Dementia Brain Bank, University of Bristol. The mRNA expression levels of ACE1, ACE2 and AGT were quantified with TaqMan™ real-time RT-PCR. ACE-1 and AGT levels were measured by sandwich ELISA in frontal cortex in dementia and control samples in a larger cohort (n=251) for which we have previously obtained data on ACE1 (rs4343) polymorphism by PCR.

Results: AGT and ACE2 mRNA were expressed at significantly lower levels in the frontal cortex in AD (relative to GFAP, an astrocytic calibrator gene) (p=0.002 and 0.03, respectively). ACE1 mRNA expression and ACE-1 protein levels were unchanged in AD. The reduction of AGT mRNA level was most pronounced in heterozygous (I/D) individuals compared to homozygous (D/D) individuals (p=0.04).

Conclusion: These results suggest that altered expression of ACE2 and AGT may contribute to the progression of AD. Further work is underway to determine the cell-specific distribution of RAS in the brain.
Aging and cerebral small vessel disease (SVD) have deleterious effects on the white matter of the brain including an increase in pro-inflammatory microglia and blood-brain barrier dysfunction, evidenced by upregulation of NFkB and NLRP3 inflammasome signaling pathways and extravasation of serum fibrinogen, respectively. Despite the importance of these two features of aging and SVD, the interactions between blood-brain barrier dysfunction and microglia activity remains unclear. In this study we investigate whether exposure to low doses of fibrinogen can induce persistent activation of microglia cells. We further investigate a potential role for extracellular vesicles (EVs) in the propagation of pro-inflammatory signaling between microglia. For dose determination acute exposure experiments, BV2-microglia were exposed to a range of fibrinogen doses (0.01-4 mg/ml) for three hours. EVs were collected and isolated from fibrinogen exposed cells for cargo analysis and applied to naïve cells (2k-12k EVs/cell). To model persistent fibrinogen exposure, cells were treated with either fibrinogen or fibrinogen EVs every 3 hours for 9 hours. RNA was collected after 3, 6, and 9 and 12 hours and pro-inflammatory transcript expression was measured. Microglia acutely upregulated transcription of pro-inflammatory signaling molecules IL-6, IL1β, iNOS and NLRP3 in a dose-dependent manner following exposure to fibrinogen. Furthermore, EVs-derived from fibrinogen exposed microglia transported fibrinogen and upregulated levels of IL1β, IL-6 and NLRP3 in naïve cells. Repeated exposure to either fibrinogen or fibrinogen-derived EVs resulted in increased and sustained upregulation of pro-inflammatory transcript levels. Fibrinogen induced robust microglia activation at concentrations 20-fold lower than circulating-plasma levels, suggesting that leakage through the blood brain barrier is sufficient for the induction of pro-inflammatory microglia. EV-mediated signaling may represent a novel mechanism enhancing fibrinogen-induced microglial activity. Future work investigating EV-mediated propagation in vivo will improve our understanding of blood-brain barrier dysfunction and microglia activation in the context of aging and SVD.
RELATIONSHIPS BETWEEN MYELOPEROXIDASE AND THE COGNITIVE AND NEUROIMAGING CORRELATES OF MILD VASCULAR COGNITIVE IMPAIRMENT

Kritleen Bawa (1) / Nathan Herrmann (2) / Damien Gallagher (2) / Sandra Black (2) / Joel Ramirez (2) / Simon Graham (2) / Pei-shan Wei (2) / Paul Oh (2) / Ana Andreazza (2) / Alex Kiss (2) / Walter Swardfager (2) / Krista Lanctôt (2)

(1) University of Toronto (2) Sunnybrook Research Institute

Mild vascular cognitive impairment (mVCI) presents with both cognitive impairment and vascular dysfunction, but the underlying disease pathophysiology is not well understood. Recent studies suggest a role of innate immune activity, including neutrophils, in cognitive decline. Myeloperoxidase (MPO), an enzyme found in neutrophils, has been shown to play a role in vascular and cognitive dysfunction. This study explores the associations of MPO with disease markers of mVCI, specifically verbal memory and neural white matter damage. Patients were recruited during intake from a cardiac rehabilitation program. Clinical history of vascular disease, and the core criteria for Subcortical Ischemic MCI, described in Gorelick et al. 2011, including cognitive deficits and neuroimaging results were used to make the diagnosis of mVCI. Verbal memory, a cognitive domain affected in mVCI populations, was assessed using the Hopkins Verbal Learning Test - Revised (HVLT-R). Plasma MPO concentration was measured using enzyme-linked immunosorbent assay in fasting blood and white matter hyperintensity (WMH) volumes were measured using a 3T MRI scanner. Multiple linear regression models were used for the statistical analyses, while controlling for the following covariates: body mass index (BMI) and education for verbal memory outcomes; and age and resting systolic blood pressure (RSBP) for WMH volume outcomes. In n= 27 patients (age= 67.2 ± 7.5, male%= 74%, BMI= 29.4 ± 5.3), plasma MPO was negatively associated with verbal memory (β= -2.28, p=0.04), particularly word recognition (β= -3.51, p=0.01), after controlling for education and BMI. Elevated MPO was associated with higher periventricular WMH volumes (β= 0.74, p=0.03), before controlling for age and RSBP, but not with deep WMH volume. The results of this study suggest that neutrophils, specifically MPO, may be involved in the pathophysiology of mVCI and may be facilitating its effects on cognition via affecting the neuroimaging correlates of the disease.
Exposure to urban particulate matter has detrimental effects on cerebrovascular integrity associated with Alzheimer’s disease (AD) risk. Fine particles < 2.5 μm (PM2.5) continually bioaccumulate within the neurovascular parenchyma, exacerbating oxidative stress, inflammation and misfolded protein accumulation observed in the early stages of AD. Considering astroglia undergo activation of molecular programs in response to pathological stimuli, initiation of reactive reprogramming induced by PM2.5 may elucidate disease-specific reactive phenotypes. The aim of this study is to assess the effects of PM2.5-induced astroglial reactivity on neurovascular communication as an early indicator of neurodegeneration and AD-like pathology using a human cell model. Primary astrocytes were characterized for their functional and physiological properties including reactive capacity as measured through cytokine release. Neurovascular intercellular communication between astrocytes and brain microvascular endothelial cells (BMECs) was evaluated by measuring transendothelial electrical resistance (TEER), indicating barrier functionality over time within a transwell-type neurovascular unit model. Short-term exposure to PM2.5 led to an increased astroglial release of proinflammatory cytokine IL-6, similar to the acute response measured from prolonged treatment with cytokines IL-1β and TNF-α. Co-culture of untreated astrocytes and BMECs led to significantly higher TEER values when compared with monocultures. These data suggest a distinct molecular response from primary astrocytes in relation to physiologically accurate concentrations of PM2.5. Given the effect of astrocytes on endothelial barrier maintenance, expanding on these findings to address the effect of this reactive state on adjacent neurovascular cell types will procure a robust understanding of the wider cerebrovascular effects of environmental pollution.
ENDOTHELIN-1-MEDIATED CONTRACTION OF HUMAN BRAIN PERICYTES IS DYSREGULATED IN THE PRESENCE OF Aβ1-40

Elliott Hibbs / Seth Love / Scott Miners

University of Bristol

Vascular dysfunction and brain ischemia are defining pathologies of vascular dementia, and are increasingly recognised as underestimated contributors to cognitive decline and disease pathology in Alzheimer’s disease (AD). Pericytes are critical for dynamic regulation of cerebral blood flow, and are damaged and degenerate in AD. Vascular abnormalities in AD correlate with elevated levels of the potent vasoconstrictor peptide endothelin-1 (EDN1). We hypothesise that dysregulated EDN1-mediated pericyte contraction is a major contributor to cerebral hypoperfusion in AD.

This study aimed to characterise EDN1-mediated contraction of foetal and adult human brain-derived pericytes and determine whether Aβ modifies the contractile response. An electrical impedance assay was used to assess pericyte contraction in response to EDN1. We used BQ123 and BQ788, to characterise the role of EDN1 type-A and type-B receptors respectively and monitored the effects of pre-exposure of pericytes to Aβ peptides for 1 and 24 h. Change in calculated cell index was used to reflect rates of contraction (acute response < 30 mins) and proliferation (chronic response 48 hours).

EDN1 treatment caused a dose-dependent contraction of foetal pericytes at 1nM (p=0.0283), 0.01µM (p=0.0035), 0.1µM (p=0.0022) and 1µM (p=0.0003) EDN1. Adult pericytes were less sensitive to EDN1 and contracted at 0.1µM (p=0.0008) and 1µM (p< 0.0001) EDN1 only. Pre-treatment with BQ123, but not BQ788, prevented the contraction of foetal and adult pericytes. Exposure to Aβ1-40 for 24 hours significantly impaired EDN1-mediated contraction of foetal pericytes (p=0.0249).

These data indicate that EDN1-mediated pericyte contraction occurs via EDNRA and that pre-exposure to Aβ1-40 impairs pericyte contraction. Studies are underway to determine how Aβ peptides regulate EDN1-mediated pericyte contractility and to explore differences between foetal and adult-derived cells.
AUTOMATIC QUANTIFICATION OF PERIVASCULAR SPACES IN T2-WEIGHTED IMAGES AT 7T MRI

Jolanda Spijkerman / Jaco Zwanenburg / Willem Bouvy / Mirjam Geerlings / Geert Jan Biessels / Jeroen Hendrikse / Peter Luijten / Hugo Kuijf

UMC Utrecht

Introduction Perivascular spaces (PVS) are believed to be involved in brain waste disposal. PVS are associated with cerebral small vessel disease. At higher field strengths more PVS can be observed, which is challenging for manual PVS assessment. We developed a method to automatically detect and quantify PVS.

Methods A machine learning approach identified possible PVS in an automatically positioned ROI in the centrum semiovale (CSO), based on signal intensities in high-resolution T2-weighted TSE scans, and Frangi’s vesselness values (Figure 1). Next, 3D PVS tracking was performed in 50 persons (mean age 62.9 years (range 27 – 78), 19 male), and quantitative measures were extracted. Maps of PVS density, length, and tortuosity were created. Manual PVS annotations were available to train and validate the automatic method.

Results Good correlation was found between the automatic and manual PVS count: intraclass correlation coefficient (ICC; absolute/consistency) is 0.64/0.75, and Dice similarity coefficient (DSC) is 0.61. The automatic method counts fewer PVS than the manual count, because it ignores the smallest PVS (length < 2 mm). For 20 persons manual PVS annotations of a second observer were available. Compared with the correlation between the automatic and manual PVS, higher inter-observer ICC was observed (0.85/0.88), but DSC was lower (0.49 in 4 persons). Longer PVS can be observed (Figure 2) posterior in the CSO compared with anterior in the CSO. Higher PVS tortuosity can be observed (Figure 3) in the center of the CSO compared with the periphery of the CSO.

Conclusion Our fully automatic method can detect PVS in a 2D slab in the CSO, and extract quantitative PVS parameters by performing 3D tracking. This method enables automated quantitative analysis of PVS in health and disease.
CONNECTION BETWEEN KIDNEY FUNCTION AND COGNITION IN THE ELDERLY

Tomas Månsson / Sölve Elmståhl / Aldana Rosso / Marieclaire Overton / Mats Pihlsgård

Medical faculty, Lund university

Introduction: Impaired kidney function, cardiovascular disease and cognitive dysfunction are common in the elderly population [1, 2]. Cardiovascular risk factors are strongly associated with both impaired kidney function [3], and cognitive dysfunction [4, 5]. Cerebrovascular disease is associated with cognitive dysfunction [6], and cerebrovascular disease is common in the presence of kidney dysfunction [7]. Therefore, a connection between impaired kidney function and cognitive dysfunction on a vascular basis is possible.

Methods: All data is obtained from the general population cohort study “Good aging in Skåne” (GÅS). Impaired kidney function is defined as eGFR < 60 ml/min/1.73m² [3]. A cognitive test battery including 11 tests is used to assess the cognitive domains learning and memory, language, complex attention, executive function, perceptual-motor, meta-memory, as well as global cognitive function.

Results: In a first cross-sectional study, a relationship between impaired eGFR and impairment in the cognitive domains learning and memory, language, complex attention, executive function and global cognitive function, but not meta-memory, was found [8]. To the authors knowledge, no one has previously investigated a connection between kidney function and meta-memory.

In a follow up longitudinal study, moderately impaired kidney function preceded impairment in processing speed, but did not predict dementia or minimal cognitive impairment (MCI) [9]. Processing speed is sensitive to cerebrovascular disease [6, 10], suggesting our findings could represent early vascular implications on cognition.

Conclusion: Moderately impaired eGFR preceded cognitive impairment, suggesting that overview of cardiovascular risk factors is indicated even at moderately impaired kidney function, to prevent future cognitive impairment.

References

LOW CAROTID END DIASTOLIC VELOCITY IS ASSOCIATED WITH WHITE MATTER HYPERINTENSITIES AND CORTICAL ATROPHY IN THE SWEDISH "GOOD AGING IN SKÅNE" STUDY

Katarina Ellström (1) / Kasim Abul-Kasim (2) / Arkadiusz Siennicki-Lantz (1) / Sölve Elmståhl (1)

(1) Division of Geriatric Medicine, Malmö, Sweden (2) Division of Diagnostic Radiology, Lund, Sweden

AIM: The relationship between hemodynamic properties of the larger arteries and cerebral small vessel disease (CSVD) is not yet fully understood. Our aim was to study the prevalence and interrelations between magnetic resonance (MR) markers of CSVD and specific brain atrophies, and their association to carotid artery duplex flow parameters.

METHOD: We investigated a population based randomised cohort of older adults (n=391) aged 70-87, in the Swedish Good Aging in Skåne (GÅS) Study. Exclusion criteria was Peak Systolic Velocity ≥ 120 cm/s. Peak Systolic Velocity (PSV) and End Diastolic Velocity (EDV) were assessed by carotid duplex, and resistivity index (RI) and Pulsatibility Index (PI) were calculated using the Pourcelot and Goslin formula. Nine radiological findings were investigated by visual rating scales: white matter changes (WMC) using Fazekas’ scale, pontine white matter changes (PMC), microbleeds (< 2-5 mm) (MB), lacunar infarctions (< 10mm) (LAC), medial temporal lobe atrophy (MTA) according to Schelten’s scale, global cortical atrophy (GCA) according to Pasquier’s scale, parietal atrophy (KPA) according to Koedam’s scale, precuneus atrophy (PA) and central atrophy (CA). Hierarchical cluster analysis was performed to investigate CSVD covariance, and regression models were used to test for associations to carotid flow parameters.

RESULTS: Pathologies were found in 80% of subjects and distribution of CSVD was heterogenic. EDV in common carotid arteries (CCA) was associated with “moderate/severe WMC” (OR:0.92; p=0.004), KPA (OR:0.94; p=0.022), PA (OR:0.94; p=0.022), GCA (OR:0.90; p=0.013), “number of MRI pathologies” (β-0.07; p< 0.001) and “total MRI-burden score” (β-0.11; p< 0.001), adjusted for age and sex. The latter three were associated with pulsatility and resistivity indexes.

CONCLUSION: Low mean EDV, proposed as a marker of arteriosclerosis, was associated with signs of CSVD and patterns of brain atrophy, indicating a vascular component in the process of brain aging.
ASSOCIATION OF CEREBRAL SMALL VESSEL DISEASE BURDEN WITH BRAIN STRUCTURE AND COGNITIVE AND VASCULAR RISK TRAJECTORIES IN MID-TO-LATE LIFE

Michelle G. Jansen (1)(2) / Ludovica Griffanti (3)(4) / Clare E. Mackay (3)(4) / Melis Anatürk (3)(5) / Luca Melazzini (4)(6) / Ann-Marie G. de Lange (3)(7) / Nicola Filippini (3)(4) / Enikő Zsoldos (3)(4) / Kim Wiegertjes (2) / Frank-Erik de Leeuw (2) / Archana Singh-Manoux (8)(9) / Mika Kivimäki (8) / Klaus P. Ebmeier (3) / Sana Suri (3)(4)

(1) Donders Centre for Cognition, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands (2) Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, the Netherlands (3) Department of Psychiatry, University of Oxford, United Kingdom (4) Wellcome Centre for Integrative Neuroimaging (Oxford Centres for Functional MRI of the Brain & Human Brain Activity) Nuffield Department of Clinical Neurosciences & Psychiatry, University of Oxford, United Kingdom (5) Centre for Medical Image Computing, Department of Computer Science, University College London, United Kingdom (6) Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy (7) Department of Psychology, University of Oslo, Norway (8) Department of Epidemiology and Public Health, University College London, United Kingdom (9) Université de Paris, INSERM, U1153, Epidemiology of Ageing and Neurogenerative diseases, Paris, France

Objective: To characterize the longitudinal lifestyle, cognitive and brain structural determinants of total cerebral small vessel disease (SVD) burden in older ages.

Methods: Participants were 623 community-dwelling adults (mean age 69.96 SD 5.18, 79% men) from the Whitehall II Imaging Sub-study with multi-modal MRI acquired between 2012-2016. We used linear mixed effect models to investigate associations of SVD burden with up to 25-year retrospective trajectories of vascular risk and cognitive performance, assessed at 5-year intervals between 1991-2016. General linear modelling was used to investigate concurrent associations with (1) retrospective trajectories of vascular risk factors and cognitive decline, (2) concurrent grey matter (GM) density and white matter (WM) microstructure, and (3) whether these associations were modified by cognitive status (Montreal Cognitive Assessment, MoCA).

Results: Severe SVD burden was associated with higher mean arterial pressure throughout midlife (β 3.36, 95% CI [0.42-6.30]), and faster cognitive decline in phonemic fluency (β -0.07, 95% CI [-0.13—0.01]), and verbal reasoning (β -0.05, 95% CI [-0.11—-0.001]). Moreover, SVD burden was related to reduced GM volumes in 9.7% of total GM, and widespread WM microstructural decline (FWE-corrected p< 0.05). Notably, the latter association was most pronounced in individuals who showed cognitive impairments on MoCA (F3,608 = 2.14, p = 0.007).

Conclusion: Total SVD burden in older age is associated with higher midlife blood pressure, faster cognitive decline, and poorer indicators of cerebral GM density and WM microstructure. These findings highlight the importance of managing midlife vascular health to preserve brain structure and cognitive functions.
SELF-REPORTED COGNITIVE DECLINE, EMOTIONAL SYMPTOMS, AND DAYTIME SLEEP AFTER ISCHEMIC STROKE

Elisabeth Kliem (1)(2) / Angela Labberton (3) / Mathias Barra (2)(4) / Elise Gjestad (1)(5) / Bent Indredavik (6)(7) / Ramune Grambaite (1)(2)

(1) Department of Psychology, Norwegian University of Science and Technology, Trondheim, Norway (2) The Health Services Research Unit – HØKH, Akershus University Hospital HF, Lørenskog, Norway (3) Division for Health Services, Norwegian Institute of Public Health, Norway (4) BCEPS, University of Bergen, Bergen, Norway (5) Clinic of Medicine, St. Olavs Hospital, Trondheim University Hospital, Norway (6) Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, Norwegian University of Science and Technology, Trondheim, Norway (7) Department of Medicine, Stroke Unit, St Olavs Hospital, Trondheim University Hospital, Norway

Introduction: After stroke, emotional symptoms (such as depression or anxiety), cognitive decline and increased daytime sleep are common. However, the relationship between these sequelae remains unclear. We aimed to study if (1) self-reported cognitive decline and emotional symptoms 3 months after hospital discharge predict increased self-reported daytime sleep at 1 year, and if (2) increased daytime sleep at 3 months predicts emotional symptoms and cognitive decline at 1 year.

Method: Data of ischemic stroke patients without previous history of dementia or depression were collected 3 months and 1 year after hospital discharge using postal surveys. Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). Self-reported increase in daytime sleep and decline in concentration and memory were each assessed with one dichotomous item. Multiple linear and binary logistic regression was used to estimate the relationship of daytime sleep with cognitive decline and emotional symptoms, controlling for age, sex and stroke severity (NIH Stroke Scale, NIHSS).

Results: In 140 patients (baseline-NIHSS mean and standard deviation (M±SD)=3.6±4.3; MMSE 25.2±4.9; age 73.2±10.9) 27.7% reported increased daytime sleep at 3 months, and 37.1% at 1 year. Self-reported decline in memory and concentration and in concentration and memory were each assessed with one dichotomous item. Multiple linear and binary logistic regression was used to estimate the relationship of daytime sleep with cognitive decline and emotional symptoms, controlling for age, sex and stroke severity (NIH Stroke Scale, NIHSS).

Conclusion: Patients with higher levels of emotional symptoms and self-reported cognitive decline at 3 months are at a higher risk for increased daytime sleep at 1 year. Interventions targeting emotional symptoms and cognitive decline may prevent excessive daytime sleep and secure patients’ engagement in rehabilitation and successful recovery.
SOCIAL COGNITION IS ASSOCIATED WITH GENERAL COGNITIVE FUNCTION POST-STROKE

Elise Gjestad (1)(2) / Anja Vaskinn (3)(4) / Elisabeth Kliem (1) / Ingvild Saltvedt (5)(6) / Ramune Grambaite (1)(2)(7)

(1) Department of Psychology, Norwegian Institute of Science and Technology, Trondheim, Norway (2) Clinic of Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway (3) Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, Oslo, Norway (4) Norwegian Centre for Mental Disorders Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway (5) Department of Neuromedicine and Movement Science, Norwegian Institute of Science and Technology, Trondheim, Norway (6) Department of Geriatrics, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway (7) Health Services Research Unit (HØKH), Akershus University Hospital, Lørenskog, Norway

Objective: The DSM-5 introduces social cognition as one of six cognitive domains that may be impaired in post-stroke neurocognitive disorder. Social cognition refers to processing of information about other people’s thoughts and emotions, which may be affected in many clinical populations. However, how it presents in the stroke population has not yet been sufficiently described. Impairment in abilities such as emotion recognition and theory of mind (understanding and considering the mental state of another) may have far-reaching consequences for rehabilitation, returning to society, and relating to others. The aim of this study was to examine the association between social cognition and general cognitive function post-stroke.

Method: 29 patients (76% male, mean age 67.8, SD=10.5) diagnosed with stroke three years ago were included. All patients were part of the longitudinal multicentre Nor-COAST cohort study and had been followed up with regular intervals since the acute phase. A neuropsychological test battery was administered as part of an additional follow-up. General cognitive function was measured by the Mini Mental State Examination (MMSE), while social cognition was measured using the Hinting Task (theory of mind) and Pictures of Facial Affect (emotion recognition). Regression analysis was then used to examine the association between general cognitive function and performance on the social cognition tests. The results were controlled for age as well as sex, due to the higher percentage of men in the sample.

Results: A better performance on MMSE was associated with better performance in emotion recognition \( p=.02, R^2=.30, \beta=.42 \). No significant association was found between MMSE and the theory of mind task \( p>.05 \).

Conclusion: Results support the hypothesis that there is a relationship between general cognitive function and ability to identify emotions in others 3 years post-stroke. Further exploration of this association is warranted.
Objective: CADASIL is the most common monogenic form of stroke and is also associated with early onset dementia. We determined the prevalence of vascular cognitive impairment (VCI) in a cohort of CADASIL patients and which factors were associated with VCI risk.

Methods: Cognition was assessed in genetically confirmed CADASIL patients (n = 176) and healthy controls (n = 265) using the Brief Memory and Executive Test (BMET) and Montreal Cognitive Assessment (MoCA). We determined the prevalence of VCI and its associations with clinical risk factors, mutation location (EGFr 1-6 versus EGFr 7-34), and MRI markers (lacunes, white matter hyperintensity volume, brain volume and cerebral microbleeds).

Results: CADASIL patients (Mean (SD) age 50.95 (11.3)) had significantly worse performance across all domains of the BMET than controls (Mean (SD) age 52.37 (7.93)), with worst performance on the letter sequencing task (figure 1). VCI, defined using the BMET, was present in 39.8% of the CADASIL group and 10.2% of controls. VCI, defined using the MoCA, was present in 48.9% of the CADASIL group and 21.1% of controls.

While controlling for age and sex, history of stroke was associated with increased VCI on the BMET (OR 2.10, 95% CI [1.06, 4.17] p = 0.03) and on the MoCA (OR 2.55, 95% CI [1.24, 5.24] p = 0.01). There was no relationship of VCI to sex, cardiovascular risk factors or mutation site. Lacune count was the only MRI parameter independently associated with VCI on the BMET, after controlling for other MRI parameters, (OR: 1.67, 95% CI [1.14, 2.44], p = 0.008).

Conclusions: VCI is present in 40-50% of CADASIL patients with a mean age of 50 years. Reductions were seen across all cognitive domains including memory. Stroke and lacune count on MRI were both independent predictors of VCI on the BMET. No association was found with mutation site.
A CLUSTER OF BLOOD-BASED BIOMARKERS REFLECTING EXTRACELLULAR MATRIX ORGANIZATION, INFLAMMATION AND SIGNAL TRANSDUCTION RELATES TO CEREBRAL BLOOD FLOW IN PATIENTS WITH CARDIOVASCULAR DISEASE

L Malin Overmars (1) / Sanne Kuipers (2) / Bram van Es (1) / Esther Bron (3) / Imo Hoefer (1) / L Jaap Kappelle (2) / Matthias van Osch (4) / Charlotte Teunissen (5) / Saskia Haitjema (1) / Geert Jan Biessels (2) / Heart-Brain Connection Consortium

Cardiovascular disease can negatively impact the brain, among others through decreased cerebral blood flow (CBF), and may contribute to vascular cognitive impairment. Decreased CBF has been attributed to oxidative stress, inflammation and endothelial dysfunction, but exact biological processes underlying decreased CBF in this context are largely unknown. We hypothesized that identification of clusters of blood-based biomarkers that are related to variation in CBF in patients with vascular disease may provide leads on biological processes involved.

In 428 participants (mean age 67.2±8.6 years; 37% female; 74% cardiovascular diseases/26% reference participants) we assessed the relation between 92 protein blood-based biomarkers from the OLINK cardiovascular III panel and partial volume corrected whole brain normal-appearing gray matter CBF (measured with 3T pseudo-continuous arterial spin labeling), with cluster-based analyses. The existence of clusters was substantiated with both prior knowledge and data-driven cluster analyses.

Fifteen biomarkers correlated with CBF. Six biomarkers positively correlated with CBF (r range 0.10-0.19; Benjamini-Hochberg corrected p-values < 0.05) but formed no cluster. Nine biomarkers negatively correlated with CBF (r range: -0.10 to -0.19 Benjamini-Hochberg corrected p-values < 0.05) and formed one cluster according to both prior knowledge and data-driven analyses (figure 1). A calculated biomarker compound score based on the identified cluster showed a significant negative correlation with CBF (r -0.23, p< 0.05) (figure 2). The relation between this cluster and CBF was independent of age. Pathway analysis showed that the biomarkers forming the cluster predominantly reflect extracellular matrix organization, inflammation and signal transduction processes.

In conclusion, we identified a cluster of blood-based biomarkers reflecting extracellular matrix organization, inflammation and signal transduction processes, that is negatively related to CBF in patients with cardiovascular disease. If validated in future studies, these processes might be therapeutic targets for preserving CBF and improving cognitive outcomes in people with cardiovascular disease.
DOES $^{11}$C-PK11195 BINDING PREDICT LESION GROWTH AT ONE YEAR?

Daniel Tozer (1) / Robin Brown (1) / Jesscia Walsh (1) / Tim Fryer (2) / Young Hong (2) / Martin Graves (3) / Hugh Markus (1)

(1) Stroke research Group, Department of Clinical Neurosciences, University of Cambridge (2) Wolfson Brain Imaging Centre, Department of Clinical Neurosciences, University of Cambridge (3) Department of Radiology, University of Cambridge

It has been suggested that a pathway of inflammation, and blood-brain barrier permeability is related to SVD damage such as white matter hyperintensities (WMH). We have previously found hot spots of increased microglial density in SVD subjects compared to controls, indicative of ongoing damage. This study tested whether microglial density at baseline, as measured using $^{11}$C-PK11195 PET, is increased in new WMH voxels measured one year later.

For 19 subjects with sporadic SVD, 14 with CADASIL and 19 controls, we acquired FLAIR, T1-weighted and DTI MR images, from which fractional anisotropy (FA) and mean diffusivity (MD) maps were calculated, and PET data for 75 minutes post-injection to produce maps of binding potential (BP; a metric of binding site density). MRI was repeated at one year.

Baseline and follow-up FLAIR images were registered and subtracted to create maps of new lesion voxels. Whole brain NAWM was delineated using the T1 images segmented with SIENAX, and MR and PET images were registered to a common space. Mean $^{11}$C-PK11195 BP, baseline FA and MD were then determined for the new lesion voxels and NAWM.

Across the cohort it was found that new lesion voxels had lower $^{11}$C-PK11195 BP than NAWM (-0.133 vs. -0.045, p=0.0005, Fig1). This result was also seen in the three subject groups when analysed separately. In new lesion voxels compared to NAWM, FA (0.29 vs. 0.36) and MD (1045 vs. 900 x10^-6 mm^2/s) both showed increased abnormality (both p=0.0005).

The lower $^{11}$C-PK11195 binding in new lesion voxels suggests that this tissue has evolved beyond the point that inflammation is occurring. When coupled with the abnormal diffusion parameters seen in new lesion tissue, it would appear that up to one year prior to lesion formation the tissue is already damaged and well on the pathway to lesion formation.
PULSATILITY INDEX OUTPERFORMS CONVENTIONAL IMAGING MARKERS IN THE ASSOCIATION WITH COGNITION IN COMMUNITY ELDERLY

Bonnie Yin Ka Lam / Maggie Lam / Brian Yiu / Adrian Wong / Shi Lin / Jill Abrigo / Vincent Mok

The Chinese University of Hong Kong

Increase in pulsatility index (PI), measured by the transcranial Doppler (TCD), correlates with cognitive impairment and is associated with progression of non-demented patients into Alzheimer’s disease (AD) with dementia, suggesting that increase in small vessel resistance is a critical marker of cognitive decline. No study compared PI and MRI markers for small vessel disease or AD that have been shown to be associated with worse cognitive functions. The objectives of this study include: (i) compare PI against conventional MRI markers in its association with cognition, and (ii) investigate the association of PI and cognition in the presence of vascular risk factors.

We measured clinical data and PI in the middle cerebral artery in 331 stroke- and dementia-free community subjects. General cognition was assessed using Hong Kong-Montreal Cognitive Assessment. Conventional imaging markers (including lacunes, white matter hyperintensities (WMH), brain parenchymal fraction (BPF), cerebral microbleeds, Alzheimer’s Disease Resemblance Atrophy Index (ADRAI)) were assessed by MRI. Linear regression models were used to compare the sensitivity of PI against conventional MRI markers (including WMH, BPF, ADRAI, lacune and cerebral microbleeds count), with age and years of education entered as covariates. PI was negatively associated with cognition (standardised $b=-0.122$, $p=0.01$). PI outperformed (standardised $b=-0.118$, $p=0.012$) other imaging markers and contributes to 1.1% change in the variance. PI was associated with higher systolic blood pressure (standardised $b=0.122$, $p=0.028$), and level of triglyceride (standardised $b = 0.126$, $p = 0.021$).

To conclude, PI is associated with cognition, higher levels of blood pressure and triglycerides, suggesting the importance of cerebral small vessel dysfunction in causing cognitive decline among older people. PI outperforms conventional MRI markers in the association with cognition in community subjects without dementia.
A SYSTEMATIC REVIEW INTO THE RELATIONSHIP BETWEEN BLOOD PRESSURE VARIABILITY AND GREY AND WHITE MATTER STRUCTURES

Daria Gutteridge

University of South Australia

Blood pressure variability (BPV) has, independent of the mean BP, been linked with cognitive impairment and dementia. However, the pathophysiological mechanisms by which BPV affects cognition is unclear. This systematic review assessed the relationship between different BPV measures and white and grey matter structures. The following databases were last searched in January 2021; EMBASE, MEDLINE, EMCARE, and SCOPUS. Peer-reviewed studies that reported on the relationship between within-subject BPV (short-, medium- or long-term variability) or a circadian blood pressure measurement and MRI assessed brain structures were included. Overall, twenty studies met the criteria and were included, of which eleven studies looked at short-term BPV, eight articles investigated visit-to-visit BPV, and one study looked at a compositional BPV measurement. Due to heterogeneity in study samples, meta-analysis was not possible. Across the included studies, associations between MRI indices and BP dipping patterns were mixed but higher long-term systolic BPV and higher sleep systolic BPV was found to be associated with lower whole brain volume and hippocampal volume. This review highlights the adverse effect that increased BPV has upon the brain and helps to better understand the biological mechanisms of how BPV is linked with cognitive decline, including dementia, in late life.
ASSOCIATION BETWEEN BLOOD PRESSURE VARIABILITY WITH DEMENTIA AND COGNITIVE IMPAIRMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

Rianne de Heus (1) / Christophe Tzourio (2) / Emily Lee (3) / Melissa Opoza (3) / Andrew Vincent (3) / Kaarin Anstey (4) / Albert Hofman (5) / Kazuomi Kario (6) / Simona Lattanzi (7) / Lenore Launer (8) / Yuan Ma (5) / Rajiv Mahajan (9) / Simon Mooijaart (10) / Michiaki Nagai (11) / Ruth Peters (12) / Deborah Turnbull (3) / Yuichiro Yano (13) / Jurgen Claassen (14) / Jurgen Claassen (14) / Phillip Tully (3)

(1) Radboud university medical center, Nijmegen, The Netherlands (2) Bordeaux Population Health, Univ. Bordeaux (3) Freemasons Centre for Male Health and Wellbeing, Adelaide Medical School, The University of Adelaide, Australia (4) School of Psychology, University of New South Wales, Sydney, Australia (5) Department of Epidemiology, Harvard T H Chan School of Public Health, Boston, MA, USA (6) Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine (7) Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy (8) Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA (9) University of Adelaide, Lyell McEwin Hospital, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia (10) Department of Gerontology and Geriatrics, Leiden University Medical Center, Institute for Evidence-Based Medicine in Old Age, Leiden, The Netherlands (11) Department of Cardiology, Hiroshima City Asa Hospital, 2-1-1, Kabeminami, Aasakita-ku, Hiroshima, Japan (12) The University of New South Wales, Neuroscience Research Australia, Sydney, Australia; Imperial College London, London, UK (13) Yokohama City University Center for Novel and Exploratory Clinical Trials, Yokohama City University Hospital, Yokohama, Japan (14) Radboud university medical center, Donders Institute for Brain Cognition and Behaviour, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Nijmegen, The Netherlands

Background: Research consistently links high blood pressure variability (BPV) with stroke and cerebrovascular disease as well as adverse cardiovascular outcomes. However, the association between BPV with dementia and cognitive impairment is inconsistent. Moreover, it remains uncertain whether BPV holds more significance in understanding vascular contributions to cognitive impairment by comparison to the more established risk factor of mean blood pressure.

Methods: A systematic search of PubMed, Embase, PsycINFO and Scopus was performed until May 2021 for studies that quantified the association between resting BPV with dementia or cognitive impairment in adults. A multilevel meta-analysis was employed, which included effect sizes for both BPV and mean BP, with a combined end-point of dementia or cognitive impairment as primary outcome. Secondary outcomes were dementia subtypes, cognitive impairment, cognitive decline, as well as domain-specific cognitive function (both r and d family effect sizes).

Results: The primary analysis included 54 effect sizes extracted from 20 studies in primarily older adults, with a total analytical sample of n=7,899,697. Multilevel meta-analysis showed that higher systolic BPV (OR=1.25 [95% CI, 1.16-1.35]), mean systolic pressure (OR=1.12 [95% CI, 1.02-1.29]), diastolic BPV (OR=1.20 [95% CI, 1.12-1.29]) and mean diastolic pressure (OR=1.16 [95% CI, 1.04-1.29]) were associated with the primary outcome of dementia and cognitive impairment. A direct comparison of effect sizes showed that mean BP effect sizes were less strong than BPV effect sizes (OR=0.92 [95% CI, 0.87-0.97], p< 0.01), indicating that the relative contribution of BPV exceeded that of mean BP. However, methodological and statistical heterogeneity was high. Secondary analyses were less consistent as to whether BPV and mean BP were differentially associated with dementia sub-types and cognitive domains.

Conclusion: The available evidence indicated that BPV was more strongly associated with dementia and cognitive impairment than mean blood pressure in primarily older adult samples.
THE RELATIONSHIP OF ACUTE DELIRIUM WITH COGNITIVE AND PSYCHIATRIC SYMPTOMS AFTER STROKE: A LONGITUDINAL STUDY

Vilde Nerdal (1) / Elise Gjestad (1)(2) / Ragnhild Munthe-Kaas (3)(4) / Ingvild Saltvedt (5)(6) / Stian Lydersen (7) / Ramune Grambaite (1)(2)(8)

(1) Department of Psychology, Norwegian Institute of Science and Technology, Trondheim, Norway (2) Clinic of Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway (3) Department of Medicine, Rørvik Hospital, Norway (4) Department of Clinical Medicine, University of Oslo, Norway (5) Department of Neuromedicine and Movement Science, Norwegian Institute of Science and Technology, Trondheim, Norway (6) Department of Geriatrics, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway (7) Department of Mental Health Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway (8) Health Services Research Unit (HØKH), Akershus University Hospital, Lørenskog, Norway

Objectives: Delirium is a common complication in the acute phase of cerebrovascular events. The condition is often overlooked, and the long-term consequences poorly understood. This study aims to examine whether acute delirium in stroke predicts more severe cognitive and emotional symptoms over the course of three years.

Method: 169 stroke-survivors (48.5% women, mean (SD) age: 72.4 (13.0); National Institutes of Health Stroke Scale (NIHSS): 3.61 (5.0)) were screened for delirium by the Confusion Assessment Method (CAM) during the first two days of hospital stay. All procedures were part of the longitudinal multicenter Nor-COAST study. Global cognition was measured by the Montreal Cognitive Assessment Test (MoCA) and emotional symptoms were measured using the Hospital Anxiety and Depression Scale (HADS) at 3, 18, and 36 months. Mixed-model linear regression was applied with MoCA and HADS scores as dependent variables. Independent variables were delirium, time, and their interaction. The analyses were adjusted for age, gender, education, NIHSS-score, and premorbid dementia.

Results: 24 patients met the criteria for delirium (Age: 79.0 (7.7); NIHSS: 5.3 (5.7)), while 145 were non-delirious (Age: 71.3 (13.4); NIHSS: 3.1 (4.0)). Delirium was associated with poorer global cognition (MoCA) at 18 (p = .017) and 36 months (p = .024). HADS scores were higher for patients with delirium at 18 (p = .001) and 36 months (p = .003). The group differences in mean scores were highest at 36 months for MoCA (21.97 (1.2) vs. 24.86 (.38)) and at 18 months for HADS (13.36 (1.73) vs. 7.11 (.57)).

Conclusion: The results suggest that delirium predicts poorer long-term outcomes after stroke, both for general cognition and emotional symptoms. Focus on prevention and adequate assessment, as well as treatment and long-term follow up can be important contributions for decreasing the burden of post-stroke disability.
NEUROPSYCHIATRIC SYMPTOMS ACCELERATE COGNITIVE IMPAIRMENT ASSOCIATED WITH SMALL VESSEL DISEASE

Anne Arola (1)(2) / Tuuli Levänen (1) / Hanna M. Laakso (1)(2) / Johanna Pitkänen (3) / Juha Lempiäinen (3) / Matti Ahlström (3) / Juha Koikkalainen (4)(5) / Jyrki Lötjönen (4)(6) / Antti Korvenoja (7) / Timo Erkinjuntti (3) / Susanna Melkas (3) / Hanna Jokinen (1)(2)

(1) HUS Neurocenter, Division of Neuropsychology, Helsinki University Hospital and University of Helsinki (2) Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki (3) Department of Neurology, Helsinki University Hospital and University of Helsinki (4) Combinotics Ltd, Tampere (5) Faculty of Health Sciences, University of Eastern Finland, Kuopio (6) Department of Neuroscience and Biomedical Engineering, School of Science, Aalto University, Espoo, Finland (7) HUS Diagnostic Center, Radiology, Helsinki University Hospital and University of Helsinki

Background: Neuropsychiatric symptoms are related to disease progression and cognitive decline over time in cerebral small vessel disease (SVD) characterised by white matter hyperintensities (WMH). How neuropsychiatric symptoms relate to cognitive functioning in the presence of WMH is less well understood. We investigated the occurrence of neuropsychiatric symptoms and their relationship between cognitive performance and functional abilities in subjects with varying degrees of WMH.

Methods: The Helsinki Small Vessel Disease Study recruited 152 subjects, who underwent brain MRI, comprehensive neuropsychological evaluations, and assessment of neuropsychiatric symptoms using the Neuropsychiatric Inventory Questionnaire (NPI-Q) filled in by an informant (n=134). Functional abilities were assessed using the Amsterdam Instrumental Activities of Daily Living (A-IADL) questionnaire.

Results: NPI-Q total score correlated significantly with WMH volume (rs=0.20, p=0.019) and inversely with A-IADL score (rs=-0.41, p< 0.001), but it was not related to age, education or sex. In total, 34% of the subjects had one or more informant evaluated neuropsychiatric symptoms. The most common symptoms were depression (19%), irritability (16%), apathy (9%), night time disruptive behaviours (11%) and changes in appetite (9%). Linear regressions adjusted for age and education revealed no significant main effects between neuropsychiatric symptoms and cognitive performance. However, significant interactions were found between neuropsychiatric symptoms and WMH on cognitive composite scores for global cognition, processing speed, executive functions and memory as shown in Figure 1. Linear regressions adjusted for age and education also showed significant main effects between neuropsychiatric symptoms and A-IADL as well as WMH and A-IADL.

Conclusions: Neuropsychiatric symptoms associate with stronger impact of WMH on cognitive impairment. Furthermore, the presence of neuropsychiatric symptoms is related to worse functional abilities. Neuropsychiatric symptoms should be routinely assessed in SVD as they are related to worse cognitive and functional outcomes.
SYSTEMIC ENDOTHELIAL FUNCTION AND CEREBRAL MICROBLEEDS: A CROSS-SECTIONAL ANALYSIS WITHIN THE RHINELAND STUDY

Gokhan Pehlivan (1) / Valerie Lohner (1) / Monique M.B. Breteler (1)(2)

(1) Population Health Sciences, German Center for Neurodegenerative diseases (DZNE), Bonn, Germany (2) Institute for Medical Biometry, Informatics and Epidemiology (IMBIE), Faculty of Medicine, University of Bonn, Germany

Background: Emerging evidence from animal studies suggests that impairment of endothelial function leads to cerebral microbleeds (CMB). However, data on the association between endothelial function and CMB in humans is scarce. Thus, we aimed to investigate the association of systemic endothelial function with CMB in a population-based study.

Methods: Our analysis is based on the first participants of the Rhineland Study, who underwent 3T brain MR imaging. The presence and count of CMB were visually assessed on susceptibility-weighted images. We assessed systemic endothelial function as reactive skin hyperemia (RSH, %) using laser-Doppler flowmetry with a local thermal provocation test. We examined the association between RSH and CMB using hurdle models. We adjusted for age and sex, and, in a second model additionally for body mass index, systolic blood pressure, antihypertensive medication use, total brain volume, smoking, diabetes and prevalent cardiovascular diseases. RSH was very skewed and therefore ln-transformed. CMBs were categorized based on count (as 0, 1, 2, 3-5, >5 CMBs) and the median of the CMB count in each category was used in the analysis.

Results: The final analysis included 2457 participants (women: 1420, 57.8%) with a mean age of 53.8 (SD=13.7) years. Median of RSH was 380.6% (interquartile range: 203.1–671.2 %). CMB were seen in 306 (12.5 %) participants. Of those, 170 (55%) were women, 75% had 1 CMB, and the highest number of CMB present in one person was 59. Overall, RSH did not differ between participants with or without CMB. However, among persons with CMB, better systemic endothelial function was associated with a lower odds of having more CMB, even after adjustment for covariates (OR (95% Confidence interval): Model-1: 0.76 (0.59–0.99); Model-2: 0.70 (0.52–0.94)).

Conclusion: Our finding suggests that systemic endothelial function may be causally related to cerebral microbleeds independent of traditional vascular risk factors.
THE BRAIN RENIN-ANGIOTENSIN SYSTEM IS ALTERED IN AGE AND ALZHEIMER’S DISEASE

Robert MacLachlan / Patrick Kehoe / Scott Miners

University of Bristol

The renin-angiotensin system (RAS) regulates systemic blood pressure but functions independently within organs including the brain. Although systemic RAS is downregulated with age, localised organ-specific RAS becomes overactivated with age and may predispose to the onset of disease. In Alzheimer’s disease (AD), a shift in the balance of RAS towards classical RAS (cRAS) activation and loss of protective counter-regulatory (rRAS) have been reported. In this study, we have explored age- and disease-related changes in brain RAS, specifically the expression and enzyme activities of ACE-1 and ACE-2 (central mediators of the cRAS and rRAS pathways respectively).

Human post-mortem brain tissue with no neurodegenerative clinical diagnosis was used to investigate the effect of age (n=132; 19-80y) and tissue with known Braak stage was used to investigate the effect of AD (n=120). ACE-1 and ACE-2 protein levels were measured by ELISA and enzyme activities were measured by fluorogenic peptide activity assays. Ang-II levels were measured by an in-house direct ELISA.

In normal ageing, ACE-1 and Ang-II levels increased with age (p=0.0001, p< 0.0001, respectively) and correlated against each other (r=0.2986, p=0.0065). In contrast, ACE-1 enzyme activity was reduced with age (p< 0.0001), particularly after the age of 65, and was negatively correlated with Ang-II (r=-0.3913, p=0.0002). ACE-2 level and activity were unaltered in the ageing cohort. In AD, ACE-1 enzyme activity was increased (p=0.0281), specifically in Braak tangle stage III-IV i.e. at an intermediate stage. ACE-1 and Ang-II protein level were unchanged; as was ACE-2 level and activity.

We have shown that brain RAS is altered with normal ageing and in the early stages of AD. We suggest that a protective feedback mechanism, mediated by Ang-II, prevents overactivation of the ACE-1 enzyme and is dysregulated in the early stages of AD. These findings provide further insight into the potential role of RAS in AD.
THE RELATIONSHIP BETWEEN COGNITIVE RESERVE AND CHANGE IN COGNITION DURING THE FIRST THREE MONTHS POST-STROKE

Ragnhild Roaldsnes (1) / Elisabeth Kliem (1)(2) / Ramune Grambaite (1)(2)

(1) Department of Psychology, Norwegian University of Science and Technology, Trondheim, Norway (2) The Health Services Research Unit – HØKH, Akershus University Hospital HF, Lørenskog, Norway

Background: Reduced memory and executive function (EF) are commonly seen post-stroke. Cognitive reserve (CR), the brain’s ability to adapt from damage and degeneration, has been suggested to protect cognitive function. However, these relationships are not sufficiently studied post-stroke. This study examined the association between CR and cognitive function one-week to three-months post-stroke. Additionally, we wanted to see if higher CR is associated with more improvement in memory and executive domains.

Method: 79 patients with ischemic stroke (MMSE > 23) were assessed with a battery of neuropsychological tests within one-week and followed up at three-months post-stroke. Composite variables for memory (using subtests from WAIS-III, WMS-III and the Rey Auditory Verbal Learning Test) and EF (using subtests from WAIS-III, D-KEFS and Halstead-Reitan test batteries) were calculated for both timepoints, then variables measuring change in memory and EF respectively. Years of education, occupation (using ISCO-88) and IQ (using the National Adult Reading Test and two subtests from WASI) were used as CR proxies. Multiple linear regression was used to estimate the relationship of CR proxies with cognitive change, controlling for age and sex.

Results: The patients’ mean (M) age was 64.42 (SD=8.97), day one NIHSS M=3.56 (3.25), three-months NIHSS M=0.66 (1.59) and education M=11.01 (2.95). 34% of patients were female. IQ was significantly (p< .001) associated with memory and EF at one-week (β =.48, and β=.63) and at three-months (β =.67 and β =.68). Occupation and education were not significantly associated with memory and EF at one-week or three-months. Changes in memory and EF were not significantly associated with IQ, education or occupation.

Conclusion: Out of the CR proxies used only IQ was shown to be significantly associated with cognitive function post-stroke. None of the CR proxies were significantly related to changes in cognition, indicating that CR may not promote improvement of cognitive function during the first three months post-stroke.
METABOLIC SYNDROME IS ASSOCIATED WITH POOR COGNITION: A POPULATION-BASED STUDY OF 70-YEAR-OLDS WITHOUT DEMENTIA

Anna Marseglia (1) / Alexander Darin-Matsson (2) / Johan Skoog (3) / Lina Rydén (3) / Timothy Hadarsson-Bodin (3) / Silke Kern (3) / Therese Rydberg Sterner (3) / Ying Shang (2) / Anna Zettergren (3) / Eric Westman (1) / Ingmar Skoog (3)

(1) Division of Clinical Geriatrics, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden (2) Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden (3) Centre for Ageing and Health (AgeCap) at the University of Gothenburg, Sweden

Background: Individual conditions of metabolic syndrome (MetS) have been related to dementia, however, their combined impact on the preclinical stage is unknown. We investigated the associations between MetS and domain-specific cognitive function as well as the role of sociodemographic, cardiovascular, and genetic factors.

Methods: Within the Gothenburg H70 Birth Cohort Study-Birth cohort 1944, 1131 dementia-free participants (aged 70 years) were examined during 2014-2016. MetS (central obesity plus at least two factors [reduced HDL-cholesterol, elevated triglycerides, blood pressure, or blood glucose]) was identified according to the International Diabetes Federation criteria. Five cognitive domains (memory, attention/perceptual speed, executive function, verbal fluency, visuospatial abilities) were generated after z-standardizing raw scores from ten neuropsychological tests. Education, heart disease, claudication (indicating peripheral atherosclerosis), and apolipoprotein (APOE) genotype were ascertained by trained staff. Data were analyzed with linear regression models.

Results: Overall, 618 participants (55%) had MetS. In multi-adjusted linear regressions, MetS was related to poorer performance in attention/perceptual speed ($\beta$ -0.14 [95% CI -0.25, -0.02]), executive function ($\beta$ -0.12 [95% CI -0.23, -0.01]), and verbal fluency ($\beta$ -0.19 [95% CI -0.30, -0.08]). These associations were present only among individuals who did not carry any APOE-ε4 allele or were highly educated. However, among those with MetS, high education was related to better cognitive performance. MetS together with comorbid heart disease or claudication was associated with even worse cognitive performance than each alone.

Conclusions: MetS is associated with poor attention/perceptual speed, executive function, and verbal fluency performance. Education, APOE-ε4 allele, and comorbid cardiovascular disease influenced the observed associations.
SMALL AND LARGE MRI-VISIBLE PERIVASCULAR SPACES IN THE BASAL GANGLIA OF PARKINSON’S DISEASE PATIENTS

Stephanie Berberian (1) / Joel Ramirez (1) / David P. Breen (2) / Anne Rowling (3) / Tiago A. Mestre (4) / Connie Marras (5) / Donna Kwan (6) / Sean Symons (7) / Mario Masellis (8) / Sandra E. Black (8) / Anthony E. Lang (5)

Background: MRI-visible perivascular spaces in the basal ganglia (BG-PVS) are typically considered to be asymptomatic; however, there is evidence to suggest that they may be a marker of motor disability in Parkinson’s disease (PD). Additionally, recent studies suggest a difference in the pathogenesis and risk profile between small (≤3 mm in diameter) and large (> 3 mm in diameter) PVS.

Purpose: To examine small and large BG-PVS and their association with disease severity in PD patients.

Methods: Patients were recruited from the Ontario Neurodegenerative Disease Research Initiative (ONDRI). MRI-based measures included BG-PVS, lacunes, periventricular and deep white matter hyperintensities (p/dWMH). Summary scores from Parts I-IV of the Movement Disorders Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) were used to assess disease severity. Partial Spearman’s correlation and negative binomial regression models adjusted for multiple comparisons using the Benjamin-Hochberg false discovery rate were applied to the data. All analyses accounted for age, sex, education, HbA1C, cholesterol, systolic BP, smoking, lacunes, and WMH.

Results: PD patients with only small BG-PVS demonstrated an association with Part I (p<0.01, 95% C.I.: 0.005, 0.023) and Part II (p<0.01, 95% C.I.: 0.004, 0.023) of the MDS-UPDRS, whereas patients with large BG-PVS demonstrated an association with Part III (p<0.0001, 95% C.I.: 0.012, 0.027) and Part IV (p<0.001, 95% C.I.: 0.015, 0.05). Additionally, only small BG-PVS were correlated with pWMH (rho=0.26, p=0.015), no other significant correlations were found.

Conclusions: These findings suggest that small BG-PVS are more likely to impact PD-related motor and non-motor aspects of experiences in daily living (assessed by MDS-UPDRS Parts I-II), while large BG-PVS are more likely to impact the motor signs and treatment-related motor complications (Parts III-IV). Additionally, the small BG-PVS may be more of an indicator of global small vessel disease severity, given its independent correlation with pWMH that was not demonstrated with large BG-PVS.
MICROSTRUCTURAL CHANGES IN THE PENUMBRA LAYERS OF CEREBRAL SMALL VESSEL DISEASE LESIONS ARE ASSOCIATED WITH COGNITION AND SLEEP

Joel Ramirez (1) / Kirstin Walker (1) / Melissa McSweeney (1) / Hassan Akhavein (1) / Melissa F. Holmes (1) / Miracle Ozzoude (1) / Christopher JM Scott (1) / Fuqiang Gao (1) / Seyed MH Haddad (2) / Paula McLaughlin (3) / Brian Levine (4) / Donna Kwan (5) / Manuel Montero-Odasso (6) / Elizabeth Finger (7) / William E McIlroy (8) / Anthony E. Lang (9) / Maria C. Tartaglia (10) / Jennifer Mandzia (7) / Bradley J MacIntosh (11) / Morris Freedman (4) / Jennifer Rabin (11) / Stephen C. Strother (4) / Mario Masellis (13) / Sean Symons (14) / Robert Bartha (15) / Andrew Lim (13) / Richard H Swartz (16) / Sandra E Black (13) / Maged Goubran (11)

Objective: To investigate microstructural changes of the penumbra layers surrounding different cerebrovascular disease lesion sub-types and associations with cognition and sleep quality.

Methods: We examined 146 participants with cerebrovascular disease from the Ontario Neurodegenerative Disease Research Initiative. Periventricular and deep white matter hyperintensities (p/dWMH), lacunes, and perivascular spaces (PVS) were segmented from structural MRI. Using diffusion MRI, fractional anisotropy (FA) and mean diffusivity (MD) were estimated from the penumbra layers surrounding each lesion sub-type. Linear regression models were used to examine diffusion metrics within each lesion type (central), outermost penumbra layer (distal), across the penumbra gradients (slope), and for all normal appearing WM (global). Associations with Processing Speed, Executive Function, Memory, Visuospatial Reasoning and sleep quality (PSQI) were examined, controlling for demographics, vascular risk factors, sleep medications and sleep apnea.

Results: FA and MD were significantly different between penumbra layers of all lesion sub-types (all p<0.0001). Central: Linear regressions revealed FA within pWMH was associated with memory (β=-0.19, p=0.04); MD within dWMH with processing speed (β=-0.23, p=0.03), and memory (β=-0.2, p=0.05). Sleep analysis revealed MD within dWMH was associated with PSQI (β=-1.22, p<0.001). Distal: FA in the outermost NAWM layer of BG-PVS was associated with visuospatial (β=0.31, p=0.04), processing speed (β=0.4, p=0.004), and executive function (β=0.29, p=0.02); and FA in the outermost NAWM layer of lacunes was associated with executive function (β=0.52, p=0.005). Slope: FA slope of pWMH penumbra was associated with memory (β=0.22, p=0.02) and executive function (β=0.19, p=0.02); and, MD slope of dWMH was associated with processing speed (β=0.26, p=0.01), and executive function (β=0.18, p=0.04). Sleep analysis revealed the MD slope of dWMH was associated with PSQI (β=1.13, p<0.001).

Interpretation: These findings suggest that white matter alterations that extend beyond the vascular lesions demarcated on standard structural MRI may be associated with poor sleep quality and cognitive dysfunction.
VENOUS COLLAGENOSIS, WHITE MATTER HYPERINTENSITY AND THE PERIVASCULAR SPACE

David Lahna (1) / Daniel Schwartz (1) / Randy Woltjer (1) / Sandra Black (2) / Natalie Roese (1) / Hiroko Dodge (1) / Erin Boespflug (1) / Julia Keith (2) / Fuqiang Gao (2) / Joel Ramirez (2) / Lisa Silbert (1)

(1) OHSU (2) Sunnybrook

Background: Periventricular white matter hyperintensities (pvWMH) are commonly observed on MRI in older individuals and are associated with cognitive and motor decline. The etiology of pvWMH remains unknown. Venous collagenosis has been implicated, which may also interfere with perivascular fluid flow leading to dilation of perivascular spaces (PVS). Here we examine relationships between in vivo pvWMH volume and ex vivo morphological quantification of collagenosis and the perivascular space in veins and arteries.

Method: Brain tissue from 25 Oregon Alzheimer’s Disease Center subjects was selected based on availability of in vivo 1.5 Tesla MRI (Table 1), used to quantify whole brain WMH burden. Three Paraffin embedded 6μm thick coronal blocks of tissue from anterior, middle and posterior white matter abutting the ventricle were stained with Masson’s Trichrome and smooth muscle actin. Slides were digitized and an automated hue based algorithm identified 547 vessels and segmented each into collagenenized vessel walls, lumen and perivascular space. The area of each compartment was used to calculate lumen diameter, collagen width and PVS width (Figure 1).

Pearson’s correlation coefficients between collagenosis and PVS width were calculated in both veins and arteries. Multiple linear regressions for veins and arteries with pvWMH volume as the dependent variable and either collagen thickness or perivascular space width were performed which included covariates of vessel diameter, age at death, sex, and time interval between MRI and death.

Results: PVS width and collagen thickness were significantly correlated in both arteries (r=0.21, p=0.001) and veins (r=0.23, p=0.001). Increased venous collagen (p=.017) was a significant predictor of higher pvWMH burden while arterial collagen was not (p=.128). Neither PVS width in arteries (p=.937) nor veins (p=.133) predicted pvWMH burden.

Conclusion: These findings are consistent with a model in which venous collagenosis mediates the relationship between cardiovascular risk factors and pvWMH. While collagenosis and PVS dilation may both be consequences of increased pulse pressure due to arteriosclerosis, only venous collagenosis appears to predict pvWMH burden.
SERUM PLACENTAL GROWTH FACTOR AS A MARKER OF CEREBROVASCULAR DISEASE BURDEN IN PATIENTS WITH ALZHEIMER’S DISEASE

Liu-Yun Wu (1)(2) / Joyce Chong (1)(2) / Bibek Gyanwali (2)(3) / Saima Hilal (2)(4)(5) / Christopher Chen (1)(2) / Mitchell Lai (1)(2)

(1) Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Kent Ridge, Singapore (2) Memory Aging and Cognition Centre, National University Health System, Kent Ridge, Singapore (3) Department of Biochemistry, National University of Singapore, Singapore (4) Saw Swee Hock School of Public Health, National University of Singapore, Singapore (5) Departments of Epidemiology and Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

Background: Cerebrovascular diseases (CeVD) have been identified as an important determinant of the progression of Alzheimer’s disease (AD). Development of robust blood-based biomarkers provide critical tools to assess studies on diagnosis and treatments of AD with concomitant CeVD. Here, we investigated the potential of circulating placental growth factor (PlGF), a potent pro-angiogenic factor that has been related to endothelial dysfunction and vascular inflammation, in preclinical stages of cognitive impairment and in AD, as well as its associations with MRI markers of CeVD in an Asian memory clinic cohort.

Methods: 109 patients with AD, 76 with cognitively impaired no dementia (CIND), and 56 non-cognitively impaired (NCI) were included in this cross-sectional study. All subjects underwent 3T brain MRI to assess markers of CeVD; white matter hyperintensities (WMHs, measured by ARWMC scores), lacunes, cortical infarcts, and cerebral microbleeds (CMBs). Serum PlGF concentrations were measured by electrochemiluminescence immunoassays and normalized by log 2 transformation. Information on demographical characteristics and vascular risk factors were collected.

Results: PlGF was significantly elevated in AD compared to NCI controls (p=0.044), but not in CIND. Stratified analysis showed that higher concentrations of PlGF were associated with AD only in the presence of significant CeVD (odds ratio [OR] 6.20; 95% confidence interval [CI] 1.46 – 26.37, p=0.014), after adjustment for covariates. Among the MRI markers of CeVD assessed, PlGF levels were significantly higher in subjects with Subsequent multivariate regression analyses showed that PlGF was significantly associated with WMHs independent of vascular risk factors and other relevant CeVD markers (mean difference [β] 2.69, 95% CI 0.95 – 4.4, p=0.003) in AD, while its association with CMBs was attenuated after adjustment for WMHs (p=0.122).

Conclusions: Serum PlGF has potential clinical utility as a biomarker for the presence of CeVD such as WMH in AD. Future longitudinal studies are needed to assess the utility of PlGF as a prognostic marker of AD with concomitant CeVD.
HIGHER TOTAL CHOLESTEROL IN APOE4 CARRIERS CONTRIBUTES TO ALZHEIMER’S DISEASE RISK: FINDINGS FROM THE ALZHEIMER’S DISEASE NEUROIMAGING INITIATIVE

Michelle Dunk / Ira Driscoll

University of Wisconsin - Milwaukee

APOE ε4 allele is the greatest genetic risk factor for Alzheimer’s disease (AD), yet mechanisms underlying its risk conferral are not well understood. APOE is involved in blood lipid metabolism. While the literature suggests relationships between high total cholesterol (TC), APOE ε4 allele, and AD, reports of TC in relation to AD are conflicting and obviate the need for further investigation. We analyzed data from 1,534 Alzheimer’s Disease Neuroimaging Initiative (ADNI) participants to examine the relationship between TC and APOE risk for AD. Participants were grouped by APOE status as either APOE2+ (ε2/ε2 and ε2/ε3 genotypes), APOE3 (ε3/ε3 genotype), or APOE4+ (ε4/ε4 and ε4/ε3 genotypes). Diagnostic groups included cognitively normal (N = 404), mild cognitive impairment due to AD (MCI; N = 833), AD (N = 297), and composite dementia (CD; AD or MCI, N = 1,130). Generalized linear modeling was used to compare TC levels across APOE and diagnostic groups. Mendelian randomization was performed to assess whether APOE’s relationship with AD is mediated by TC. APOE4+ carriers had higher TC compared to APOE3 (p = 0.002) and APOE2+ (p = 0.04) carriers. TC levels were also higher in AD (p< 0.001), MCI (p< 0.01), and CD (p< 0.01) compared to CN. Mendelian randomization revealed that APOE4+ carriers had higher log odds ratios (LOR) per mg/dL increase in TC for MCI (LOR 0.10, 95% confidence interval (CI) 0.04-1.99), AD (LOR 0.19, 95% CI 0.09-3.99), and CD (LOR 0.12, 95% CI 0.06-2.45) compared to APOE3 carriers. Our results suggest that higher TC combined with lesser ability of APOE4+ carriers to metabolize it may, at least in part, underlie AD risk. Our findings highlight a possible mechanism by which APOE confers AD risk and suggest a potential for AD risk modification through maintenance of healthy TC levels.

Funding: Michelle Dunk was partially supported by the Summer Graduate Research Fellowship through the University of Wisconsin – Milwaukee. ADNI data collection and sharing were funded by the National Institutes of Health Grant U01 AG024904 and Department of Defense award number W81XWH-12-2-0012.
DOES WHITE MATTER HYPERINTENSITY LOCATION PREDICT COGNITIVE IMPAIRMENT IN AN ELDERLY POPULATION?

Polly Roads / Polina Emeliyanova / Laura Parkes
University of Manchester

Cerebral small vessel disease is associated with lacunar stroke and is responsible for up to 45% of dementias. A key neuroimaging feature of the disease is white matter hyperintensities (WMH). Increasing WMH volume predicts poorer cognition, but the association is inconsistent. The location of the lesions may be important. This study used ADNI data from elderly participants (n=599, mean age 72.1±7.2 years) with mixed cognition (191 cognitively normal, 408 cognitively impaired). WMH volume was quantified from T2-weighted FLAIR and T1-weighted images with the lesion segmentation toolbox, creating lesion binary maps. These were used to assess the relationship between strategic WMH location and cognition in both voxel-based and tract-based analyses. The average binary maps for both cognitive groups were remarkably similar (Figure 1). In the voxel-based analysis, participant MoCA score (standardised as a z-score against the cognitively normal mean score) was multiplied with their binary lesion map so that each voxel represented a WMH-weighted z-score. The mean weighted z-score for each voxel was then calculated to produce a cognitive risk map (Figure 2). Clusters of voxels, located mainly in the anterior and superior corona radiata, were associated with worse cognition (Figure 2). In the tract-based analysis, only the cognitively impaired participants were included to identify tracts most strongly associated with cognitive impairment. Multiple linear regression of tracts against MoCA scores (Figure 3) found that the WMH in the superior longitudinal fasciculus was significantly negatively associated with MoCA score (R2= -0.393, p=0.035), whereas global WMH volume did not correlate with cognition (R2= 0.159, p=0.256). The association of the anterior corona radiata and the superior longitudinal fasciculus with cognition, particularly executive function as assessed by MoCA, expands on previous literature, whilst the lack of the association with global WMH suggests that tract-specific WMH volume is more closely associated with cognitive impairment.
PREVALENCE AND CORRELATES OF WHITE MATTER HYPERINTENSITIES
IN ROYAL CANADIAN AIRFORCE PILOTS AND AIRCREW

Joel Ramirez (1) / Oshin Vartanian (2) / Melissa F. Holmes (1) / Miriam Palmer (1) / Christopher J.M. Scott (1) / Shawn G. Rhind (2) / Gary Gray (3) / Sandra E. Black (4) / Joan Saary (3)

(1) Dr. Sandra Black Centre for Brain Resilience and Recovery, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, University of Toronto (2) Defence Research and Development Canada, Toronto Research Centre; University of Toronto (3) Canadian Forces Environmental Medicine Establishment, Department of National Defence, Government of Canada, University of Toronto (4) Black Department of Medicine (Neurology), Sunnybrook Health Sciences Centre and University of Toronto

Background: White matter hyperintensities (WMH) of presumed vascular origin are commonly observed on MRI in older adults and patients with neurodegenerative and neurovascular disease. A recent series of studies examining WMH in United States Air Force U-2 pilots found higher WMH burden was associated with lower cognitive performance in otherwise healthy, high-functioning individuals.

Purpose: To present preliminary findings for a study that will examine the prevalence and correlates of WMH in Royal Canadian Airforce (RCAF) Pilots and aircrew.

Methods: Our goal is to enroll N=50 study participants from the RCAF with anticipated exposure to low ambient pressures (including fast jet pilots, parachutists involved in high altitude parachute operations, and aviation physiology technicians). The comprehensive test protocol includes a battery of cognitive measures, standard laboratory tests, cardiac bubble agitated saline contrast echo study, blood proteomic multiplex array analysis, and MRI. Quantification of WMH will be performed using a standardized and validated neuroimaging pipeline. The following preliminary partial correlation results between head-size corrected WMH volumes and cognitive performance are based on the currently acquired sub-sample of the total target study participants (N=30, 60%).

Results: A negative correlation was demonstrated between WMH volumes and N-back test performance (1-back D prime: rho=-0.552, p=0.006), delayed-matching-to-sample test performance (DMTS % accuracy: rho=-0.439, p=0.036), and the Shipley-2 vocabulary crystallized IQ (standard score: rho=-0.424, p=0.044), after controlling for Framingham risk, depression (~BDI), metabolic syndromes (BP, glucose, HDL, etc.), inflammation (hs-CRP), and mild traumatic brain injury.

Conclusions: These preliminary results suggest that increases in WMH volume, potentially due to occupational exposure to low ambient pressures from high altitude operations, may be associated with subtle cognitive impairment. In order to further elucidate the potential pathological mechanisms involved, future results will include analyses of the cardiac bubble saline contrast echo, blood proteomics, and relative comparisons with the NATO working group.
GAIT AND FALLS IN CEREBRAL AMYLOID ANGIOPATHY

Breni Sharma (1) / Myrlene Gee (2) / Angela Zwiers (1) / Krista Nelles (2) / Emily Cox (1) / Zahinoor Ismail (1) / Richard Camicioli (2) / Eric E. Smith (1)

(1) University of Calgary (2) University of Alberta

Background: Cerebral amyloid angiopathy (CAA) is characterized by vascular amyloid deposition. Little is known about the gait profile of CAA. We sought to determine whether gait was impaired in CAA, and whether it was related to falls or fear of falling.

Methods: Participants (29 CAA, 47 normal controls [NC], 24 mild cognitive impairment [MCI], and 16 Alzheimer’s disease with dementia [AD]; Table 1) completed gait assessments using the ProtoKinetics Zeno Walkway, consisting of three passes at a preferred pace and three dual task walks (counting backwards, naming animals, and serial sevens). Gait parameters were subdivided into four domains: rhythm (cadence, stride time, and swing time), pace (speed, stride length, and double support), postural control (stride width and stride width variability), and variability (variability of stride time, stride length, and double support percent). Models were adjusted for age, sex, and height. Participants completed the Falls and Balance questionnaire, in which they provided the number of falls in the last year and a score on a scale of 0-10 of their fear of falling.

Results: Rhythm and pace were impaired in CAA during preferred pace and dual task conditions, to a similar degree as in AD (Table 2). Gait parameters were not associated with number of falls (Table 3). However, in both CAA participants and all participants combined, better scores on pace and variability were associated with less fear of falling (Table 3).

Conclusions: Gait is impaired in CAA compared to NC and to a similar extent in AD and is associated with greater fear of falling. Further research is needed to establish the underlying causes and other consequences of gait impairment in CAA.
DIFFUSION MRI HARMONIZATION ENABLES JOINT-ANALYSIS OF MULTICENTRE DATA OF PATIENTS WITH CEREBRAL SMALL VESSEL DISEASE

Bruno Miguel de Brito Robalo (1) / Geert Jan Biessels (1) / Christopher Chen (2) / Anna Dewenter (3) / Marco Duering (3)(4) / Saima Hilal (2) / Huiberdi L. Koek (5) / Anna Kopczak (3) / Bonnie Lam (6) / Alexander Leemans (7) / Vincent Mok (6) / Laurien P. Onkenhout (1) / Hilde van den Brink (1) / Alberto de Luca (1)(7)

(1) Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands (2) Memory, Aging and Cognition Center, Department of Pharmacology, National University of Singapore, Singapore (3) Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany (4) Medical Image Analysis Center (MIAC AG) and Department of Biomedical Engineering, University of Basel, Basel, Switzerland (5) Department of Geriatric Medicine, University Medical Center Utrecht, Utrecht, The Netherlands (6) Division of Neurology, Department of Medicine and Therapeutics, Gerald Choa Neuroscience Centre, Faculty of Medicine, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China (7) Image Sciences Institute, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Objectives: Acquisition-related differences in diffusion measurements hampers joint-analysis of multicentre diffusion magnetic resonance imaging (dMRI). The purpose of this study was to establish if harmonization of the raw dMRI signal effectively removes acquisition-related differences in multicentre dMRI of elderly subjects with cerebral small vessel disease (SVD), while preserving sensitivity to disease-effects.

Methods: Five cohorts of patients with SVD (N=397) and elderly controls (N=175) were included. To establish effectiveness of harmonization, harmonization was trained with data of 13 to 15 age and sex-matched controls from each site. Fractional anisotropy (FA) and mean diffusivity (MD) were compared in matched controls between sites with tract-based spatial statistics (TBSS) and voxel-wise analysis, before and after harmonization. To assess sensitivity to disease-effects, the contrast (effect sizes of FA and MD and peak width of skeletonized MD - PSMD) between patients and controls were examined within each site. Finally, we evaluated association between white matter hyperintensity (WMH) burden FA, MD and PSMD with linear regression analyses within individual cohorts and with pooled scans, before and after harmonization.

Results: Before harmonization, significant differences in FA and MD were observed between matched controls of different sites, which were removed after harmonization (p< 0.05, Figure 1). Within sites, harmonization did not alter effect sizes of FA, MD and PSMD between patients and controls (relative change in Cohen’s d=4%, Figure 2) nor their association with WMH volume (relative change in R²=2.8%, Fig.3, A). After harmonization, data of all sites could be aggregated in a single analysis to infer the association between WMH volume and FA (R²=0.62), MD (R²=0.64), and PSMD (R² = 0.60) (Figure 3B).

Conclusions: We demonstrated that harmonization effectively removes acquisition-related differences in dMRI while preserving sensitivity to SVD-related effects. This study provides proof of concept for future multicentre SVD studies with pooled datasets.
Early Career Researchers (ECR) Session: 58

EFFECTS OF VASCULAR BURDEN ON COGNITION ARE MEDIATED BY ATROPHY, AMYLOID, AND GLUCOSE METABOLISM: A MULTI-CENTRE MIXED COHORT OF SMALL VESSEL DISEASE AND ALZHEIMER’S PATHOLOGY

Julie Ottoy LC Campbell (1) / Miracle Ozzoude LC Campbell (1) / Katherine Zukotynski LC Campbell (1)(2) / Sabrina Adamo LC Campbell (1) / Christopher Scott LC Campbell (1) / Vincent Gaudet (3) / Joel Ramirez LC Campbell (1) / Walter Swardfager (4) / Hugo Cogo-Moreira LC Campbell (1) / Benjamin Lam LC Campbell (1) / Aparna Bhan LC Campbell (1) / Parisa Mojiri LC Campbell (1) / Min Su Kang (5) / Jennifer Rabin LC Campbell (1)(2) / Alex Kiss (6) / Stephen Strother (7) / Christian Bocti (8) / Michael Borrie (9) / Howard Chertkow (10) / Richard Frayne (11) / Robin Hsiung (12) / Robert Jr. Laforce (13)/ Michael D. Noseworthy (14) / Frank S. Prato (9) / Demetrios J. Sahlas (15) / Eric E. Smith (16) / Phillip H. Kuo (17) / Vesna Sossi (12) / Alexander Thiel (10) / Jean-Paul Soucy (5) / Jean-Claude Tardif (18) / Sandra E. Black LC Campbell (1)(19); (shared last author) / Maged Goubran LC Campbell (1) (20) (shared last author)

(1) Cognitive Neurology Unit, Hôpital général Access, Université de Sherbrooke, Sherbrooke, QC, Canada
(2) Département de neurologie, Université de Sherbrooke, Sherbrooke, QC, Canada
(3) Department of Physics and Astronomy, University of British Columbia, Vancouver, BC, Canada
(4) Clinical Neurosciences, University of Calgary, Calgary, AB, Canada
(5) Department of Pharmacology & Toxicology, University of Toronto, ON, Canada
(6) Département de médecine, Université de Sherbrooke, Sherbrooke, QC, Canada
(7) Neurological Institute, Université de Montréal, Montréal, QC, Canada
(8) Département de médecine, Université de Sherbrooke, Sherbrooke, QC, Canada
(9) Jewish General Hospital, McGill University, Montreal, QC, Canada
(10) Montreal Neurological Institute, McGill University, Montreal, QC, Canada
(11) Montreal Neurological Institute, McGill University, Montreal, QC, Canada
(12) Psychiatry Department and DM Center for Brain Health, University of British Columbia, Vancouver, BC, Canada
(13) Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada
(14) Department of Electrical and Computer Engineering, University of Toronto, Toronto, ON, Canada
(15) Department of Physical Therapy, University of Toronto, Toronto, ON, Canada
(16) Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
(17) Department of Medical Imaging, Medicine, and Biomedical Engineering, University of Arizona, Tucson, AZ, USA
(18) Neurological Institute, Université de Montréal, Montréal, QC, Canada
(19) Department of Medicine (Division of Neurology), University of Toronto, Toronto, ON, Canada
(20) Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

Background: Small vessel disease (SVD) frequently co-exists with Alzheimer’s disease (AD) pathology, influencing and likely exacerbating AD progression. However, large-cohort studies in AD often exclude patients with moderate-to-severe SVD pathology as mixed disease. As such, potential contributions of SVD to cognitive impairment are not well addressed in these “clean” cases of probable AD. Here, we investigated the relationship between SVD and cognition in subjects with low-to-severe SVD and amyloid pathology. Second, we investigated the mediating roles of amyloid, glucose metabolism, and cortical atrophy in the SVD-cognition relationship.

Methods: Sixty subjects were recruited in a multi-site study (MITNEC-C6) from dementia and SVD-stroke clinics (48% amyloid-positive). They had severe SVD as quantified by white matter hyperintensity volumes [WMH; median(IQR): 30.51(22.14)cm³] and Fazekas-score≥2. In addition, we included sixty cognitively normal/MCI subjects from ADNI (22% amyloid-positive) with low-to-moderate WMH [median(IQR): 5.82(9.29)cm³]. First, regression analyses were performed between WMH volumes and cognition, including processing speed (Trails-A), executive function (Trails-B), and semantic fluency (animal-naming). Second, serial path analyses investigated if these relationships were mediated by amyloid burden (18F-florbetapir-SUVRcerebellum), glucose metabolism (18F-FDG-SUVRpons), and/or cortical thickness in AD-signature regions. All models were adjusted for age, sex, education, and bias-corrected bootstrapping with 5,000 replications.

Results: Increased WMH volumes were associated with poorer semantic fluency (β=-0.35±0.09, p=0.0004), executive function (β=+0.25±0.08, p=0.003), and speed (β=+0.22±0.08, p=0.013). Path analysis for semantic fluency and executive function showed that this relationship was mediated through cortical atrophy and to a lesser extent through amyloid and glucose metabolism (Figure 1). Vertex-wise regression analysis of WMH volume with cortical thickness and amyloid (Figure 2) highlighted the involvement of the temporal lobe.
Conclusion: Our study suggests a significant amyloid-independent pathway in which vascular burden affects cognitive impairment through cortical atrophy. This may support the idea of combinational therapeutic approaches where SVD factors are targeted alongside amyloid-beta to halt neurodegeneration and cognitive decline.
RISK FACTORS FOR ONSET OF POST-STROKE DEPRESSION IN DIVERSE ETHNO-REGIONAL GROUPS

Ben C. P. Lam (1) / Jessica W. Lo (1) / Louise Mewton (1) / Simone Reppermund (1) / Lena Oestreich (2) / Michael O’Sullivan (2) / John D. Crawford (1) / Henry Brodaty (1) / Perminder S. Sachdev (1)

(1) University of New South Wales (2) University of Queensland

Depression is common among stroke patients. Post-stroke depression (PSD) has various adverse effects on stroke recovery, and hence it is important to better understand the development of PSD and its risk factors. This research analysed the individual participant data from the Stroke and Cognition Consortium (STROKOG), an international consortium of cohort studies of stroke patients, to examine the risk factors for PSD onset in a diverse sample of stroke patients. A total of 1,867 stroke patients from 9 international hospital-based cohorts, covering four continents (Asia, North America, Europe, and Australia), were included in the analysis (see Table 1). About 35% of the participants developed PSD during the average follow-up period of 2 years. Among those who experienced PSD, the median time for first onset was about 5 months after the index stroke (Mean = 8.62 months, SD = 10.46 months; Interquartile range = 6.35 months). Mixed-effects Cox regression was conducted to examine risk factors for PSD onset. History of depression, past history of stroke, severity of stroke, functional impairment and global cognitive impairment were significant risk factors when examined individually after controlling for age, sex, and education, while cardiovascular risk factors, cardiovascular diseases, stroke laterality, and stroke subtype were not. When the significant risk factors were entered in the same Cox regression model, history of depression, functional and global cognitive impairment, together with female sex and lower education, remained as significant risk factors (see Table 2). The effects did not vary across samples from Asian and non-Asian countries. These findings highlight the major predictors of PSD, with important implications for early detection and prevention of PSD among stroke patients in diverse ethno-regional groups.
NOTCH3 VARIANT POSITION IS ASSOCIATED WITH VASCULAR NOTCH3 AGGREGATION LOAD IN CADASIL PATIENTS

Gido Gravesteijn (1) / Remco J. Hack (1) / Aat A. Mulder (2) / Minne N. Cerfontaine (1) / Remco van Doorn (3) / Ingrid M. Hegeman (4) / Carolina R. Jost (2) / Julie W. Rutten (1) / Saskia A.J. Lesnik Oberstein (1)

(1) Department of Clinical Genetics, Leiden University Medical Center (2) Department of Cell and Chemical Biology, Leiden University Medical Center (3) Department of Dermatology, Leiden University Medical Center (4) Department of Pathology, Leiden University Medical Center

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is the most prevalent hereditary cerebral small vessel disease, caused by cysteine altering variants in NOTCH3 (NOTCH3cys). CADASIL vessel wall pathology is characterized by NOTCH3 protein aggregation and ultrastructural GOM deposition. We recently discovered the first known genotype-phenotype correlation in CADASIL, showing that NOTCH3cys variants located in the six proximal epidermal growth factor-repeat domains (EGFr 1-6) of the NOTCH3 protein are associated with a more severe phenotype than NOTCH3cys variants in the distal EGFr domains (EGFr 7-34). The molecular mechanisms underlying this genotype-phenotype correlation are unknown, but we hypothesized that NOTCH3cys EGFr 7-34 variants have less propensity to aggregate compared to EGFr 1-6 variants.

To test this, we quantified vascular NOTCH3 protein aggregation in skin biopsies (n=25) and brain tissue (n=6) of CADASIL patients with NOTCH3cys EGFr 1-6 and NOTCH3cys EGFr 7-34 variants, using NOTCH3 immunohistochemistry and electron microscopy. Disease severity was assessed using clinical and neuroimaging measures (disability (mRS), lacune count and white matter hyperintensity volume).

Patients with NOTCH3cys variants located in EGFr 7-34 had less NOTCH3 aggregation in skin vessels than patients with NOTCH3cys EGFr 1-6 variants (median 5.2% [IQR 11.1] versus 48.6% [48.2] P=1.3·10⁻⁵). Also, patients with EGFr 7-34 variants had less GOM deposits than patients with EGFr 1-6 variants (median 0.0 GOM/1000µm [IQR 1.6] versus 9.8 GOM/1000µm [15.2], P=8.2·10⁻⁵). In brain vessels, a similar trend was observed. Within the EGFr 7-34 group, there was an association between NOTCH3 aggregation levels and lacune count and white matter hyperintensity volume, but not with disability.

In conclusion, NOTCH3cys variant position is associated with vascular NOTCH3 aggregation propensity, and may be one of the factors underlying the difference in disease severity between NOTCH3cys EGFr 1-6 and 7-34 variants.
Strategic white matter hyperintensity locations for cognitive impairment in memory clinic patients: a large-scaled multicenter study

Mirthe Coenen / Matthijs Biesbroek

On behalf of the META VCI Map Consortium UMC Utrecht, Utrecht, The Netherlands

Background: White matter hyperintensities (WMH) are a common manifestation of cerebral small vessel disease and a major cause of cognitive decline and dementia. Though a dose-dependent relation between WMH and cognitive decline has been established, its usefulness for explaining clinical symptoms in individual patients is limited by considerable intersubject variability. Lesion-symptom mapping studies have shown that location is an important determinant of the cognitive impact of WMH. However, these studies were hampered by incomplete brain lesion coverage (i.e. a large part of the white matter was not included in the analyses) due to modest sample sizes. In this large-scaled multicenter study, we aim to obtain WMH coverage in nearly the entire brain white matter to identify strategic WMH locations for cognitive impairment in memory clinic patients.

Methods: We collected and harmonized imaging and neuropsychological data from 11 memory clinic cohorts recruited through the META VCI Map consortium (www.metavcimap.org). Patients with any degree of cognitive symptom severity (i.e. subjective cognitive decline, mild cognitive impairment, dementia), and available neuropsychological assessment and brain MRI were included. Patients with both vascular and neurodegenerative etiology were eligible for inclusion. WMH lesion maps were registered to the Montreal Neurological Institute (MNI)-152 brain template for spatial normalization.

Results: Data collection, harmonization and pre-processing procedures were successfully completed. Pooling of individual patient data from 11 cohorts resulted in a total sample of 3525 patients. Baseline characteristics are shown in Table 1. Figure 1 shows that the combined sample provides nearly complete lesion coverage in the supratentorial white matter.

Conclusion: In this multicenter study, we established unprecedented high WMH coverage which enables inclusion of previously unstudied WMH locations and provides increased statistical power for determining the cognitive impact of WMH location. The next steps will be to perform lesion-symptom mapping to identify strategic WMH locations for cognitive impairment.
Strategic white matter hyperintensity locations and cognitive functioning in community-dwelling individuals: rationale and design

Floor A.S. de Kort / J. Matthijs Biesbroek / On behalf of the Meta VCI Map consortium

Department of Neurology and Neurosurgery, University Medical Centre (UMC) Utrecht Brain Center, Utrecht, The Netherlands

Rationale: White matter hyperintensities (WMH) are a common manifestation of cerebral small vessel disease and a major cause of cognitive decline and dementia. Despite the well-established relation between total WMH burden and cognitive impairment at a group level, there is a marked inter-subject variability in this relation. Location of WMH likely is a stronger determinant for cognitive decline than total WMH burden, and may therefore help to explain this inter-subject variability. However, a comprehensive map of strategic WMH locations and patterns, and corresponding normative data is currently lacking.

Objectives: To identify strategic white matter regions where WMH are most strongly associated with cognitive performance in community-dwelling individuals and obtain normative data for total and tract-specific WMH volumes per decade.

Design and methods: In this large-scale multicohort lesion-symptom mapping study, we will harmonize and pool individual patient data, currently from 16 population-based cohorts (Table 1) through the Meta VCI Map consortium (www.metavcimap.org). The identified cohorts comprise an estimated total of more than 20,000 community-dwelling individuals with available brain imaging and data on cognitive functioning. Participants with dementia will be excluded. Neuropsychological tests will be allocated to specific cognitive domains to calculate domain specific- and global cognitive functioning. WMH maps are registered to the MNI-152 template. Analyses will include support vector regression to perform voxel-based and region of interest-based analyses to relate WMH location to cognition. We will also establish normative data on (total and tract-specific) WMH volumes per decade.

Outcomes: The project will result in the identification of strategic WMH regions for cognitive dysfunction and normative data for total and tract-specific WMH volumes. With this information patients with excessive WMH in critical white matter regions can be identified. This will enable an individualized approach to interpreting WMH burden and location in relation to cognitive complaints in clinical practice.
SEX DIFFERENCES IN WHITE MATTER HYPERINTENSITIES ARE MODIFIED BY MENOPAUSE: THE RHINELAND STUDY

Valerie Lohner (1) / Gokhan Pehlivan (1) / Gerard Sanroma-Guell (1) / Anne Miloschewski (2) / Markus D. Schirmer (1)(3)(4) / Tony Stoecker (5)(6) / Martin Reuter (7)(8)(9) / Monique M.B. Breteler (1)(10)

(1) Population Health Sciences, German Center for Neurodegenerative diseases (DZNE), Bonn, Germany (2) Statistics and Machine Learning, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany (3) J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston (4) Clinic for Neuroradiology, University Hospital Bonn, Germany (5) MR Physics, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany (6) Department of Physics and Astronomy, University of Bonn, Bonn, Germany (7) Image Analysis, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany (8) A.A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, Massachusetts (9) Department of Radiology, Harvard Medical School, Boston, Massachusetts, USA (10) Institute for Medical Biometry, Informatics and Epidemiology (IMBIE), Faculty of Medicine, University of Bonn, Germany

Background and objective: Previous studies have consistently reported that with increasing age women have more white matter hyperintensities (WMH) than men. Whereas it has been suggested that there might be a link of these findings with menopause, previous studies were underpowered with respect to premenopausal women to explore this. Here, we investigate sex differences in and the effects of menopause on WMH across the adult life span.

Methods: This cross-sectional analysis was based on participants of the population-based Rhineland Study (30–95 years) who underwent brain MRI. We quantified WMH load automatically. Menopause status was self-reported. We examined overall associations of sex with logit-transformed WMH load using linear regression, while adjusting for age, age2, and vascular risk factors. We then checked for an age*sex interaction and stratified for menopausal status comparing men with premenopausal women (persons aged ≤56 years), men with postmenopausal women (persons aged ≥45 years), and pre- with postmenopausal women (age range 45-56 years).

Results: Of 2659 participants with a mean age of 54.0 (standard deviation: 13.8) years, 58.3% were women, of which 57.8% were postmenopausal. Overall, we found an age*sex interaction for WMH. Stratification revealed that premenopausal women and men of similar age did not differ in WMH load, but postmenopausal women had more WMH than men of similar age (b=0.26 [CI: 0.16–0.36]). Additionally, postmenopausal women had more WMH compared to premenopausal women of similar age (b=0.32 [CI: 0.05–0.59]).

Discussion: Before menopausal onset, we found no sex differences in WMH load between men and women. After menopause, however, women displayed a higher burden of WMH. Further studies are needed to investigate whether this is due to a protective effect of oestrogen in the brain or other menopause-related physiological changes, clarification of which could translate into novel therapeutic and prevention strategies.
THE ASSOCIATION BETWEEN CARDIOVASCULAR RISK FACTORS AND WHITE MATTER HYPERINTENSITY MRI PHENOTYPES

Jasmin A. Keller (1) / Ilse M. J. Kant (2) / Arjen J. C. Slooter (3) / Simone J. T. van Montfort (3) / Mark A. van Buchem (1) / Matthias J. P. van Osch (1) / Jeroen Hendrikse (4) / Jeroen de Bresser (1)

Background and Purpose: Cardiovascular risk factors are associated with white matter hyperintensity volume on brain MRI, but the exact underlying structural correlates of this association are unknown. Studying novel advanced WMH markers such as WMH shape could lead to an improved understanding of the underlying mechanisms of these associations. Therefore, we investigated the association between cardiovascular risk factors and different advanced WMH markers.

Methods: A total of 155 non-demented older adults (mean age: 71±5 years) were scanned on a 3T MRI. The association between different cardiovascular risk factors (hypertension, diabetes, body mass index and hyperlipidemia) and quantitative MRI-based WMH shape and volume markers were examined using linear regression analysis, adjusted for age and sex; and additionally for intracranial volume in the case of WMH volume.

Results: Presence of hypertension was associated with a more irregular shape of periventricular/confluent WMH (convexity: B (95% CI): -0.12 (-0.22—0.03), p=0.01; concavity index: 0.06 (0.02–0.11), p<0.01), but not with total WMH volume (0.22 (-0.15–0.59); p=0.24). Presence of diabetes was associated with deep WMH volume (0.89 (0.15–1.63); p=0.02). Body mass index and hyperlipidemia showed no association with WMH markers.

Conclusion: We showed that different cardiovascular risk factors seem to be related to a distinct pattern of WMH shape markers in non-demented older adults. These findings may suggest that different underlying cardiovascular pathological mechanisms lead to different WMH MRI phenotypes and may be valuable for early detection of dementia and for personalized treatment.
Background: White matter hyperintensities (WMH) on magnetic resonance imaging (MRI) portends the risk of cognitive decline and dementia despite traditional vascular risk factors control therapy. Cilostazol, an anti-platelet agent with vasodilating property, may reveal a treatment option in preventing WMH progression in dementia-free patients harboring confluent WMH. Methodology: In this single-center, randomized, double-blind, placebo-controlled study, we randomly assigned stroke- and dementia-free patients with confluent WMH to receive either cilostazol 100mg BD or placebo for a duration of 2 years. The primary outcome was the decrease in WMH volume over 2 years in an intention-to-treat analysis. Secondary outcomes were changes in fractional anisotrophy (FA) and mean diffusivity (MD) on MRI, and cognition as assessed by Montreal Cognitive Assessment (MoCA) and Symbol Digit Modality test (SDMT). Results: From 27th October 2014 to 21st January 2019, 120 patients were enrolled and randomized, 60 to cilostazol and 60 to placebo. Primary analysis included 51 patients in the cilostazol group and 53 patients in the control group. At 2 years, WMH volume increased by 3.6±3.2 in the cilostazol group, as compared to 2.4±3.7 in the control group (p=0.077). Secondary analyses showed that cilostazol treatment was associated with more pronounced deterioration in MoCA (-1.5±3.3 vs 0.0±3.2, p=0.021), SDMT (-1.9±4.6 vs 0.9±5.9, p=0.014), FA (-0.6±1.0 vs -0.1±0.9, p=0.024), and MD (0.4±1.3 vs -0.2±1.6, p=0.029), compared to the placebo group. Conclusion: In this trial with stroke- and dementia-free patients with confluent WMH, cilostazol did not prevent WMH progression and was associated with cognitive deterioration and loss of white matter integrity at 2 years. Further studies are required to elucidate the reasons explaining such observations associated with cilostazol.
THE RELATION BETWEEN SMALL VESSEL FUNCTION AND WHITE MATTER INTEGRITY IN PATIENTS WITH CADASIL: THE ZOOM@SVDs STUDY

Hilde van den Brink (1) / Naomi Vlegels (1) / Anna Kopczak (2) / Tine Arts (3) / Jeroen Siero (3) / Benno Gesierich (2) / Alberto de Luca (1) / Marco Duering (2) / Jaco Zwanenburg (3) / Martin Dichgans (2) / Geert Jan Biessels (1)

(1) Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands (2) Institute for Stroke and Dementia Research, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany (3) Department of Radiology, Center for Image Sciences, University Medical Center Utrecht, Utrecht, the Netherlands

Background: We recently found that cerebral small vessel function, assessed with novel techniques on 7T MRI, is abnormal in patients with CADASIL. The question is how these small vessel function alterations relate with structural brain damage. Currently, the most sensitive measure of structural brain damage in CADASIL is white matter integrity on diffusion-weighted MRI. In this project we study the association between small vessel function and white matter integrity in patients with CADASIL.

Methods: 23 patients (age 51.1±10.1 years, 52% women) with CADASIL and 13 reference participants (age 46.1±12.6, 46% women) were included from the ZOOM@SVDs study. The associations between small vessel function (1. blood flow velocity and pulsatility in perforating arteries in the semi-oval centre and basal ganglia, 2. vascular reactivity measured as the BOLD response in the visual cortex after visual stimulation, and 3. whole-brain vascular reactivity to hypercapnia assessed with BOLD) and white matter integrity (whole brain peak width of skeletonized mean diffusivity; PSMD) were tested with linear regression analyses.

Results: Both small vessel function and white matter integrity were abnormal in patients as compared to the reference group (Table 1). In patients, lower blood flow velocity in perforating arteries in the semi-oval centre and lower vascular reactivity to hypercapnia in the cortical grey matter were associated with a higher PSMD (standardized Beta (B) = -0.42, p = 0.038, and B = -0.6, p = 0.021 respectively, Figure 1). The other measures of small vessel function were not significantly related to white matter integrity.

Conclusion: We observed a relationship between impaired small vessel function and decreased white matter integrity in patients with CADASIL. Whether small vessel dysfunction is an actual cause of white matter injury or even a potential treatment target warrants further investigation.
VASCULAR REACTIVITY IS DECREASED IN EARLY STAGES OF DEMENTIA; A NOVEL MRI BIOMARKER

Suzanne E. van Dijk / Jessie Lak / Jessy Kauffman / Anne Hafkemeijer / Jeroen van der Grond / Sanneke van Rooden

Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

Alzheimer’s disease (AD) is a neurodegenerative disease typically associated with memory disorders and other cognitive problems. AD is often accompanied by comorbid issues, including vascular damage. The clinical vascular markers currently used in AD research mainly focus on injury secondary to damage in the vessel wall – i.e. global and focal damage in the cerebral white matter. Recently, decreased vascular reactivity has been put forward as an early marker for vascular damage in cerebral amyloid angiopathy (CAA), which is a frequently found co-morbidity at autopsy in patients with AD. Vascular reactivity is measured as the response of blood oxygen level dependent (BOLD) signal with MRI after a visual stimulus. Our aim is to assess vascular reactivity in a cohort of memory clinic patients ranging from subjective cognitive impairment to Alzheimer’s disease, as vascular reactivity may detect underlying vascular factors already in an early stage of dementia.

We performed 3T MRI in 43 controls, 17 SCI, 20 MCI and 12 AD patients and obtained 3D T1-weighted images, FLAIR, and visually stimulated BOLD fMRI scans. Grey matter volume, white matter hyperintensities (WMHs) and vascular reactivity parameters (BOLD amplitude, time to peak (TTP), and time to baseline (TTB)) were determined. Univariate general linear models were performed, corrected for age, gender, grey matter volume and WMHs.

Amplitude of the BOLD response shows significantly lower values in dementia patients and MCI patients, but not in SCI patients in comparison to controls, see table 1. The other vascular reactivity parameters (TTP and TTB) showed no differences between groups.

Our findings demonstrate that increasing stages of dementia associate with decreasing cerebrovascular reactivity independent of age, grey matter volume and WMHs. This shows that vascular damage is a comorbidity and plays an important role already in the early (MCI) stages of dementia.
CEREBROVASCULAR REACTIVITY IN CEREBRAL AMYLOID ANGIOPATHY

Andrew E. Beaudin (1) / Cheryl R. McCreary (2) / Erin L. Mazerolle (3) / Myrlene Gee (4) / Breni Sharma (1) / Arsenije Subotic (1) / Angela Zwiers (5) / Emily Cox (5) / Krista Nelles (4) / Anna Charlton (5) / Richard Frayne (2) / Zahinoor Ismail (6) / Christian Beaulieu (7) / Glen C. Jickling (4) / Richard Camicioli (8) / G. Bruce Pike (2) / Eric E. Smith (2)

(1) Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada (2) Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada; Seaman Family MR Research Centre, Foothills Medical Centre, Alberta Health Services, Calgary, AB, Canada (3) Department of Psychology, St. Francis Xavier University, Antigonish, NS, Canada (4) Division of Neurology and Department of Medicine, University of Alberta, Edmonton, AB, Canada (5) Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada (6) Departments of Clinical Neurosciences and Psychiatry, Hotchkiss Brain Institute and Mathison Centre for Mental Health Research & Education, University of Calgary, Calgary, AB, Canada (7) Department of Biomedical Engineering, University of Alberta, Edmonton, AB, Canada (8) Division of Neurology and Department of Medicine, Neuroscience and Mental Health Institute, University of Alberta, Edmonton, AB, Canada

Introduction: A reduced cerebrovascular reactivity (CVR) is proposed to contribute to the hemorrhagic, ischemic, and cognitive consequences of cerebral amyloid angiopathy (CAA), but it has not been measured directly. Employing a global vasodilatory stimulus (hypercapnia) this study assessed the relationships between CVR, MRI markers of CAA and cognitive function.

Design and Methods: Individuals with probable CAA (n=29; 74.7±7.7y; 9 female), mild cognitive impairment (n=19; 72.1±8.5y; 6 female), Alzheimer disease (n=12; 69.4±6.6y; 4 female) and healthy controls (n=39; 68.8±5.4y; 30 female) underwent neuropsychological testing and an MRI at 3T that included a 5% carbon dioxide (CO2) challenge. Cerebrovascular reactivity to CO2 (percent change in blood oxygen level dependent (BOLD) signal per unit increase in end-tidal partial pressure of CO2) was compared across groups controlling for age and sex. Additionally, associations between CVR and MRI markers of CAA and cognition were determined using multivariable linear regression adjusting for group, age, sex, and education.

Results: Averaged across the entire brain, grey and whiter matter CVR were lower in CAA and Alzheimer disease participants compared to healthy controls. Cerebrovascular reactivity within the primary visual cortex was lower only in CAA participants compared to healthy controls. Higher white matter hyperintensity volume was associated with lower white matter CVR; standardized coefficient [β], 95% confidence interval: -0.45, -0.88 to -0.01. Higher gray matter reactivity was associated with better global cognitive function (β: 0.19, 0.03-0.35), memory (β: 0.21, 0.07-0.35), executive function (β: 0.21, 0.02-0.40), and processing speed (β: 0.29, 0.12-0.46). Higher white matter reactivity was associated with better memory (β=0.21, 0.07-0.35) and processing speed (β=0.25, 0.08-0.41).

Conclusion: Reduced cerebrovascular reactivity is a core feature of CAA, and its assessment may provide an additional biomarker for disease severity and cognitive impairment.
Katherine Kellett / Adam Pickard / Kate Fisher / Adam Mitchell / Ross Dunne / Craig Smith / Karl Kadler / Nigel Hooper

University of Manchester

Background: Neurological symptoms are reported in a significant number of patients who are infected with SARS-CoV-2 but the mechanism of entry to the CNS is not known. It has been suggested that viral infection may exacerbate or initiate neurodegeneration but the mechanism of this is not understood. Individuals with apolipoprotein E (ApoE) ε4, a genetic risk factor for sporadic Alzheimer’s disease, are more susceptible to SARS-CoV-2 infection and have an increased risk of developing neurological complications.

Aim: The aim of this study was to establish whether the cell types that form the neurovascular unit (NVU) could be infected and support replication of SARS-CoV-2 as a possible mechanism of entry of the virus into the CNS.

Methods: Human iPSCs were differentiated into astrocytes, neurons, brain microvascular endothelial cells (bMECs) and pericytes using established protocols. Viral infectivity and replication in each cell line was determined using a modified SARS-CoV-2 virus expressing a luciferase reporter. Infectivity of cells was evaluated by immunofluorescence staining of the viral nucleocapsid protein (N-protein).

Results: Initial data suggest that astrocytes, and to a lesser extent neurons, are infected by and support replication of the SARS-CoV-2 virus, albeit at much lower levels than seen in other readily infected cell types. Astrocytes showed clear staining for viral N-protein indicating cell infection. BMECs and pericytes do not appear to be infected or support replication.

Conclusions: Astrocytes may play a key role in mediating the effects of SARS-CoV-2 in the brain. Further investigations will be carried out with the aim of establishing whether SARS-CoV-2 enters the CNS through the blood-brain barrier, whether the presence of ApoE ε4 exacerbates infection and replication, and whether viral infection promotes AD-type pathology in neurons.
Cognitive impairment post cardiac arrest - reperfusion and hypoperfusion damage

Elisabet Englund / Henric Ek Olofsson / Mattias Haglund

Lund University

In the case of resuscitated cardiac arrest – the most prominent neuropathological finding may be selective eosinophilic neuronal shrinkage and death (SEND) (1, 2) The neuronal damage may be widespread, often engaging the pyramidal cell layer of the hippocampus, the neocortex, cerebellum and the thalamus - the latter region being relatively spared in acute ischemia. In the case of longer survival after resuscitation, the hippocampus may appear atrophic.

We examined the brain from a man of 75 who died from an acute septic - embolic frontal lobe infarction and a generalized infection. The medical history included chronic obstructive lung disease and myocardial hypertrophy. Eight months prior to death, the patient was resuscitated from a cardiac arrest, with 7 minutes until return of spontaneous circulation. A change in the patient's cognitive performance was subsequently reported. During the macroscopic examination, the brain exhibited hippocampal atrophy and temporal ventricular widening as well as marked white matter thinning, in addition to a regional edema adjacent to the acute embolic infarction. Microscopically, there were eosinophilic neurons in the cortex, in the thalamus and in the hippocampus, without other, e.g. glial reactive changes. In the pyramidal cell layer the number of neurons was markedly diminished, in particular within the distal CA1 and CA2. There were widespread cortical microvascular proliferations ("raspberries"), particularly in the frontal lobes (3). The medium-sized arteries showed a mild hypertensive angiopathy. No neurodegenerative pathology was detected.

Thus, in the setting of chronic pulmonary disease, hypertension and secondary organ/vascular changes, a cardiac arrest and subsequent reperfusion may have been the cause of a documented cognitive impairment. The lack of neurodegenerative pathology but instead presence of raspberries raises the possibility that hypoperfusive states (acute or chronic) might have contributed to this condition.

References
1) Björklund E et al Resuscitation 85 (2014) 527–532
3) Ek-Olofsson H and Englund E NAN (2019), 45, 557–569
**Plasma Phosphorylated-tau181 is a Predictor of Poststroke Cognitive Impairment: A Longitudinal Study**

Li-Kai Huang (1) / Chaur-Jong Hu (2) / Yu-Chun Lo (3) / Yi-Chen Hsieh (4)

(1) Department of Neurology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan (2) Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan (3) PhD Program for Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan (4) PhD Program in Biotechnology Research and Development, College of Pharmacy, Taipei Medical University, Taipei, Taiwan

**Introduction:** Poststroke cognitive impairment (PSCI) cannot be neglected because it drastically influences the daily life of patients and their families. The present longitudinal study investigated the role of plasma biomarkers in predicting PSCI.

**Methods:** Adult patients with first-ever acute ischemic stroke were enrolled. Their cognition and function were evaluated. Furthermore, their brain-derived neurotrophic factor, plasma amyloid beta-42, total tau, and phosphorylated tau 181 (p-tau181) levels were measured. Each patient was followed up at 3 and 12 months at the outpatient department.

**Results:** Of 136 patients, 40 and 50 patients developed PSCI at 3 and 12 months after stroke, respectively. In total, 27 patients did not have PSCI at 3 months but did at 12 months. By contrast, the PSCI status of 17 patients at 3 months was reversed at 12 months. Patients with high acute plasma p-tau181 had a significantly low PSCI risk at 3 (odds ratio [OR] = 0.62, 95% confidence interval [CI] = 0.40–0.94, p = 0.0243) and 12 (OR = 0.69, 95% CI = 0.47–0.99, p = 0.0443) months after adjustment for covariates. Discrimination and reclassification statistics indicated that the p-tau181 level can improve 4.5% and 5.5% of the discrimination ability for PSCI at 3 and 12 months, respectively, based on the c-index. According to a significant trend test (p = 0.0081), the plasma p-tau181 level was the highest in individuals without PSCI followed by those with delayed-onset PSCI and early-onset PSCI with reversal, whereas the lowest plasma p-tau181 level was found among those with persistent PSCI.

**Conclusions:** Plasma p-tau181 is a potential biomarker for predicting early- and delayed-onset PSCI. Future studies should incorporate plasma p-tau181 as indicator for timely cognitive intervention in the follow-up of patients with stroke.
THE RELATIONSHIP BETWEEN LATE-LIFE HYPERTENSION AND DISEASE PATHOLOGY IN ALZHEIMER’S, VASCULAR, AND MIXED DEMENTIA

Hannah M. Tayler / Özge Güzel / Rob MacLachlan / J. Scott Miners / Seth Love

University of Bristol

Background: Hypertension is a major risk factor for vascular dementia (VaD) and may influence the risk of developing Alzheimer’s disease (AD). Hypertension in midlife is thought to increase the likelihood of AD. In later life (65+ years) the relationship is less clear; some data suggest that that late-life hypertension may protect against AD. In this study, we have investigated the effects of late-life hypertensive status, blood pressure (BP), and antihypertensive medication use on markers of AD severity (Aβ, Tau) and vascular damage, as well as biochemical markers of cerebral hypoperfusion (VEGF-A, MAG:PLP1).

Methods: Post-mortem brain tissue from donors with AD, mixed dementia, and VaD, and non-demented age-matched controls were sourced from the South-West Dementia Brain Bank (n=234). Hypertensive status, medication use, and BP measurements were obtained from clinical records. Neuropathological scores and quantitative immunohistochemical measurements of Aβ and tau were assessed in FFPE sections from the frontal and parietal lobes. Homogenates of frozen tissue samples from the contralateral hemisphere were used for biochemical measurements of disease markers and vascular damage.

Results: Hypertension was associated with a lower age of dementia onset and antihypertensive use with a higher age of onset. Late-life BP was associated with markers of vascular damage – higher small vessel disease and cerebral amyloid angiopathy (CAA) scores and elevated fibrinogen level (a marker of BBB breakdown). However, late-life diastolic BP was also associated with better cerebral perfusion – increased MAG:PLP1 ratio and lower VEGF-A, and with lower insoluble Aβ42 levels in AD and mixed dementia.

Conclusion: Our findings demonstrate a complex relationship between late-life hypertension and markers of vascular and disease pathology in dementia. Late-life hypertension may be a physiological response that maintains cerebral perfusion and Aβ homeostasis in the face of increasing cerebral vascular resistance, but that also contributes to vascular pathology.
BLOOD-BRAIN BARRIER DYSFUNCTION AND REDUCED CEREBROSPINAL FLUID LEVELS OF SOLUBLE AMYLOID PRECURSOR PROTEIN-B IN PATIENTS WITH SUBCORTICAL SMALL-VEssel DISEASE – A REPORT FROM THE GOTHENBURG MILD COGNITIVE IMPAIRMENT STUDY

Petronella Kettunen (1) / Johan Svensson (1) / Maria Bjerke (2) / Henrik Zetterberg (1) / Kaj Blennow (1) / Anders Wallin (1)

(1) University of Gothenburg (2) UZ Brussel

The subcortical small-vessel type of disease (SSVD) is the most common form of vascular cognitive impairment (VCI), and the disease affects the small vessels deep in the brain. To date, no disease-specific cerebrospinal fluid (CSF) biomarkers are available to separate SSVD from related disorders, such as Alzheimer’s disease (AD), or normal aging. This study aimed to investigate whether CSF amyloid precursor protein (APP) metabolites, including amyloid-beta (Aβ) peptides, can be used as biomarkers for SSVD. We included participants from the Gothenburg Mild Cognitive Impairment study that were stratified using the core AD biomarkers and clinically diagnosed with SSVD, AD and mixed AD/SSVD, as well as healthy controls. The levels of the CSF APP metabolites were quantified, including Aβx-38, Aβx-40, Aβx-42, as well as the soluble amyloid precursor protein-α (sAPP-α) and β (sAPP-β), employing commercially available immunoassays. Our analyses showed that sAPP-β was lower in SSVD patients than in AD patients and controls. Moreover, the CSF/serum albumin ratio was elevated in the SSVD group. Our study showed that SSVD has a biomarker profile that differs from AD and healthy controls. Specifically, sAPP-β could be an additional tool to diagnose SSVD.
LOSS OF HIPPOCAMPAL PERICYTES IN VASCULAR DEMENTIA, POST-STROKE DEMENTIA AND ALZHEIMER’S DISEASE

Yoshiki Hase / Kelvin Gotama / Luciana Maffei / Ren Ding / Raj Kalaria

Neurovascular Research Group, Translational and Clinical Research Institute, Newcastle University, United Kingdom

Background: Cerebral blood flow (CBF) is disrupted not only in vascular dementia (VaD) but also in age-related neurodegenerative dementia, contributing to cognitive dysfunction. The mural cells called ‘pericytes’ maintain blood-brain-barrier (BBB) and control local CBF. Pathological changes in the hippocampus are vital to the development of cognitive impairment in dementia. However, the role of hippocampal pericytes in dementia is largely unknown. This study investigated hippocampal pericyte changes in vascular and neurodegenerative dementia, with aim to explore novel mechanistic insights into vascular and neurodegenerative dementia.

Methods: We quantified hippocampal pericytes in 75 post-mortem brains comprising post-stroke dementia (PSD), vascular dementia (VaD), Alzheimer’s disease (AD), AD-VaD (Mixed), and post-stroke non-demented (PSND) stroke survivors as well as age-matched controls. We used collagen IV (COL4) immunohistochemistry to determine density of hippocampal pericytes in accordance with the methods we have established (Ding et al, Brain Pathol 2020). We also utilised a mouse model of vascular dementia: bilateral common carotid artery stenosis (BCAS) to validate effects of cerebral hypoperfusion in hippocampal pericytes.

Results: We observed mean (±SEM) hippocampal pericyte density in normal ageing controls as 14.1 ± 0.7 per mm capillary length. This was reduced by ~40% in VaD to 8.5 ± 3.1 per mm capillary length (P=0.001). PSD and AD showed ~25% reduction, particularly in cornu ammonis CA1 region (P=0.005 and P=0.001 respectively). In mice, cerebral hypoperfusion caused pericyte loss by ~60% compared with controls (P=0.000). Pericyte density was positively correlated with CA1 volume (r=0.54, P=0.006) and working memory scores (r=0.59, P=0.002). Notably, environmental enrichment (EE) paradigm attenuated loss of pericytes in the hippocampus.

Conclusions: Our results suggest that loss of pericytes in the hippocampus may contribute to cognitive decline in both vascular and neurodegenerative dementias. EE ameliorated cerebral hypoperfusion-induced pericyte loss, advocating pericytes could be an intervention target for vascular and age-related dementias.
A CLUSTER OF BLOOD-BASED BIOMARKERS REFLECTING COAGULATION RELATES TO THE BURDEN OF CEREBRAL SMALL VESSEL DISEASE

Sanne Kuipers (1) / L Malin Overmars (2) / Bram van Es (2) / Jeroen de Bresser (3) / Esther Bron (4) / Imo Hoefer (2) / L Jaap Kappelle (1) / Charlotte Teunissen (5) / Geert Jan Biessels (1) / Saskia Haitjema (2) / Heart-Brain Connection Consortium

(1) Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (2) Central Diagnostic Laboratory, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (3) Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands (4) Department of Radiology & Nuclear Medicine, Erasmus MC, Rotterdam, the Netherlands (5) Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam Neuroscience, Amsterdam UMC, VrijeUniversiteit Amsterdam, Amsterdam, the Netherlands

Biological processes underlying cerebral small vessel disease (cSVD) are largely unknown. We hypothesized that identification of clusters of interrelated blood-based biomarkers that are associated with the burden of cSVD provides leads on underlying biological processes.

In 494 participants (mean age 67.6±8.7 years; 36% female; 75% cardiovascular diseases/25% reference participants) we assessed the relation between 92 protein blood-based biomarkers from the OLINK cardiovascular III panel and cSVD, with cluster-based analyses. The existence of clusters was substantiated with prior knowledge as well as with data-driven cluster analyses. We focused particularly on white matter hyperintensities (WMH).

Nineteen biomarkers individually correlated with WMH volume (r range: 0.16-0.27, Bonferroni corrected p-values <0.05), of which sixteen biomarkers formed one biomarker cluster according to both prior knowledge and data-driven analyses (figure 1). A calculated biomarker compound score based on the identified cluster showed a significant positive correlation with WMH volume (r 0.3, p <0.05) (figure 2). Pathway analysis showed that this biomarker cluster predominantly reflected coagulation processes and to a lesser extent extracellular matrix organization, inflammation, and angiogenesis processes. This cluster related also significantly to other cSVD manifestations (lacunar infarcts, microbleeds, and enlarged perivascular spaces), which supports generalizability beyond WMHs. To study possible causal effects of biological processes reflected by the cluster we performed a mediation analysis that showed a mediation effect of the cluster on the relation between age and WMH volume (proportion mediated 17%), and hypertension and WMH volume (proportion mediated 21%).

In conclusion, we identified a cluster of blood-based biomarkers reflecting predominantly coagulation, that is related to manifestations of cSVD, corroborating the involvement of coagulation abnormalities in the etiology of cSVD.
MITOCHONDRIAL MECHANISMS AND CARBONIC ANHYDRASES MEDIATE NEUROVASCULAR DYSFUNCTION IN CAA MODELS

Silvia fossati
Temple University

Cerebrovascular dysfunction is one of the earliest events in Alzheimer's disease (AD) pathogenesis. Amyloid beta (Aβ) vascular deposits known as cerebral amyloid angiopathy (CAA) as well as chronic cardiovascular (CV) risk factors are known to affect endothelial cell (EC) physiology, blood brain barrier (BBB) permeability, and neurovascular (NV) health. However, the mechanisms responsible for endothelial and vascular dysfunction in AD and CAA are still poorly understood, and strategies to prevent neurovascular unit (NVU) failure are urgently needed.

Using human cerebral vascular cells in culture and mouse models of vascular amyloidosis we are clarifying cell stress mechanisms by which different amyloid species, as well as cardiovascular risk factors, affect ECs and the NVU. We tested apoptotic cell death mechanisms, mitochondrial dysfunction, BBB resistance and angiogenesis in vitro, and NV cell stress and inflammation in vivo. We also assessed the participation of carbonic anhydrases (CAs), ubiquitous enzymes catalyzing the reversible hydration of carbon dioxide and implicated in mitochondrial function, in these events, and the ability of CA inhibitors to ameliorate NV dysfunction.

Aβ peptides and aggregation species induced mitochondria and death receptor-mediated apoptotic EC death and BBB permeability. CV risk factors such as high-homocysteine or hypoxia potentiated the effects of Aβ on specific mechanisms of EC dysfunction. The deleterious effects of Aβ in ECs were counteracted by CA inhibition or silencing. Our studies in the TgSwDI mouse model of vascular amyloidosis showed that NV cell stress, neuroinflammation, vascular and immune cell-specific caspase activation, and memory impairment were all diminished by CA inhibitors.
A DUAL POTASSIUM CHANNELOPATHY UNDERLIES SMALL VESSEL DISEASE OF THE BRAIN IN A MOUSE MODEL OF ALZHEIMER’S DISEASE

Harry Pritchard (1) / Jade Taylor (1) / Katy Walsh (1) / Patrick Strangward (1) / Claire White (1) / Mariam Alakrawi (1) / Grant Hennig (2) / Mark Nelson (2) / Stuart Allan (1) / Adam Greenstein (1)

(1) University of Manchester (2) University of Vermont

Alzheimer’s disease (AD) is increasingly viewed as a small vessel disease of the brain, as reduced cerebral blood flow signifies a more severe phenotype. Blood flow into the brain is controlled by the pial arteries, which contract or dilate to ensure a consistent blood flow (autoregulation), but how this is damaged in AD is currently unknown. This study investigated the effects on amyloid beta (Aβ) in a mouse model of AD – APP23 mouse, on cerebral artery function in an ex vivo preparation, away from neuronal innervation.

18 month old, male APP23(+/−) and wild-type (Wt) littermates or 10-12 week C57/Bl6 mice were used in this study. Cerebral arteries from the APP23 mice showed an increased constriction to intraluminal pressure (60 mmHg), suggesting an underlying ion channel defect that may limit cerebral blood flow. Using a combination of pressure myography, electrophysiology and Ca²⁺ imaging techniques, we investigated K⁺ channel function in the vascular smooth muscle cells (SMCs) and endothelial cells (ECs), both which promote increased blood flow. These channels included the large-conductance Ca²⁺-activated K⁺ (BK) channel and the voltage gated K⁺ channels (Kᵥ) in the SMCs, and the intermediate/small-conductance Ca²⁺-activated K⁺ (IK/SK) channels and inward-rectifier K⁺ channel (KIR) in ECs. Our study showed an impaired BK channel function, due to the loss of Ca²⁺ events in the SMCs. Furthermore, there was an impaired KIR channel function in the ECs. To confirm the influence of Aβ on the arteries, we exposed vessels from young C57/Bl6 mice to Aβ(1-40). We confirmed a loss of BK channel function exposed to Aβ but interestingly there was no effect on the KIR channel activity.

Overall, our data provide the first detailed mechanistic explanation for the development of small vessel disease of the brain in AD and suggest exciting and novel opportunities for future intervention.