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, MD

08-09-2021
Type 2 diabetes → Cognitive dysfunction → Structural brain abnormalities
Type 2 diabetes versus controls

Incident dementia in relation to risk factor control

- No to 2 risk factors on target: Hazard ratio 2.42 (1.67; 3.52)
- 3 risk factors on target: Hazard ratio 2.33 (1.73; 3.15)
- 4 risk factors on target: Hazard ratio 1.70 (1.23; 2.33)
- 5 to 7 risk factors on target: Hazard ratio 1.32 (0.89; 1.95)

Controls (Reference)

Individuals with type 2 diabetes n=10,663
Controls n=77,193
Adjusted for age, sex and education
### Domain-specific cognitive performance in relation to risk factor control

#### Executive function (SD)

<table>
<thead>
<tr>
<th>Risk Factor Status</th>
<th>B (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No to 2 risk factors on target</td>
<td>-0.28 (-0.37; -0.19)</td>
</tr>
<tr>
<td>3 risk factors on target</td>
<td>-0.12 (-0.19; -0.05)</td>
</tr>
<tr>
<td>4 risk factors on target</td>
<td>-0.12 (-0.19; -0.05)</td>
</tr>
<tr>
<td>5 to 7 risk factors on target</td>
<td>-0.09 (-0.19; 0.01)</td>
</tr>
<tr>
<td>Controls</td>
<td>Reference</td>
</tr>
</tbody>
</table>
Structural brain abnormalities in relation to risk-factor control

White matter hyperintensity volume (log-transformed ml)

- No to 2 risk factors on target: 0.35 (0.19; 0.51)
- 3 risk factors on target: 0.23 (0.10; 0.37)
- 4 risk factors on target: 0.14 (0.04; 0.24)
- 5 to 7 risk factors on target: 0.04 (-0.08; 0.15)
- Controls: Reference
Type 2 diabetes → Cognitive dysfunction → Dementia → Structural brain abnormalities
Thank you

Acknowledgments

• Thomas van Sloten, PI
• Coen Stehouwer
• Archana Singh-Manoux
• Ronald Henry
• Miranda Schram
• Jacobus Jansen
• Walter Backes
• Simone Eussen

• Abraham Kroon
• Martin van Boxtel
• Frans Verhey
• Annemarie Koster
• Sebastian Köhler
• Marleen van Greevenbroek
• Anke Wesselius
Cerebrospinal fluid biomarkers, brain structural and cognitive performances between normotensive and hypertensive controlled, uncontrolled and untreated 70-year-old adults
Hypertension

- Hypertension is an important risk factor for Alzheimer’s disease (AD)

- The pathophysiological mechanisms underlying the relationship between AD and hypertension are not fully understood

- Hypertension has been linked to the constellation of radiological manifestations of cerebrovascular pathology (cSVD markers, DTI metrics etc.)
Aim

Study the clinical, MRI and CSF differences between normotensive, controlled hypertensive, uncontrolled hypertensive and untreated hypertensive older individuals aged 70 years old.
Material and Methods

- Gothenburg H70 Birth Cohort Studies (n=523, mean age 70.5 y)
- Blood samples (LDL, HDL, glucose etc.)
- Neurocognitive assessments covering a broad range of cognitive domains
- CSF samples (P-Tau, AB42, NFL)
- Brain MRI analysis (T1w, DTI, FLAIR & VenoBOLD)

- Gray matter
  - Temporal thickness
  - Hippocampal volume

- Microstructure
  - FA cingulum
  - FA white matter

- cSVD markers
  - Microbleed, WMHs
  - epvsCS, epvsBG, Lacunes
Hypertension (HT) classification

1) Normotensive (NT)
i) No history of HT + normal BP with SBP <140 mmHg and DBP <90 mmHg
ii) Previous history of HT but not taking antihypertensive medication and SBP <140 mmHg and DBP <90 mmHg

2) Hypertensive controlled (HC)
History of hypertension, currently on anti-hypertensive treatment and SBP <140 mmHg and DBP <90 mmHg

3) Hypertensive treated uncontrolled (HTU)
History of hypertension, currently on antihypertensive medication and SBP $\geq$140 mmHg or DBP $\geq$90 mmHg

4) hypertensive untreated (HU)
i) History of hypertension, not taking antihypertensive medication and SBP $\geq$ 140 mmHg or DBP $\geq$90 mmHg
ii) No history of hypertension and either SBP $\geq$140 mmHg or DBP $\geq$90 mmHg
Results

- Higher vascular burden in uncontrolled hypertensive participants
- Uncontrolled hypertension participants has more vascular pathology than participants with untreated hypertension
- CSF and MRI markers of AD pathology did not differ between normotensive and hypertensive participants
- Cognitive function did not differ either between groups
Take home message

• Treatment of hypertension MAY not be enough to prevent further cerebrovascular pathology, good control may also be necessary.

• Hypertension MAY be associated with cognitive changes in late life through cerebrovascular pathology rather than AD related pathology

• MRI markers of vascular pathology can capture cerebrovascular changes that have not yet translated into cognitive symptoms
Thank you for your attention

QUESTIONS?
03. Perivascular fibroblasts activity precedes the onset of ALS neurodegeneration with high plasma SPP1 associated with short patient survival- Sebastian Lewandowski (Sweden)
CAIDE dementia risk score on cerebral small vessel disease progression

VasCog Conference
08 September 2021

Audrey Low
University of Cambridge
OUTLINE

Research in context

Methodology

Findings

Summary & Implications
OVERARCHING OBJECTIVE
Understanding the role of cerebrovascular disease in dementia

Pathological correlates
- How does cerebral small vessel disease relate to established markers of dementia?
- How do these pathologies interact to affect cognitive decline?

Risk factors
- What risk factors propagate the severity and longitudinal progression of SVD?

Differentiating SVD subtypes
- Hypertensive arteriopathy
- Cerebral amyloid angiopathy
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Scope of today’s presentation: CAIDE score (global burden, individual components)
OUTLINE

- Research in context
- Methodology
- Findings
- Summary & Implications
METHODS

Participants

Cohort: PREVENT-Dementia Study (cognitively healthy midlife adults)
Sample size: 185 at baseline; 158 at follow-up

Longitudinal design
Follow-up period: 2 years

Measures

Predictor
- CAIDE score¹

Cerebral small vessel disease (SVD)
- White matter hyperintensities
- Cerebral microbleeds
- Lacunes
- Enlarged perivascular spaces
- Total SVD burden

Inflammation
- C-reactive protein
- Fibrinogen

Age
Education
Sex
APOE
Systolic blood pressure
Body mass index (BMI)
High cholesterol
Physical activity

¹ Kivipelto et al., 2006, Lancet Neurology

METHODS

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(cognitively healthy midlife adults)

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Inflammation
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Global SVD burden
(Staals et al., 2014)

CAA-SVD
(Low et al., 2020, 2021)

Hypertensive arteriopathy
(Low et al., 2020, 2021)

METHODS

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(healthy midlife adults)
Sample size: 185 at baseline; 158 at follow-up

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• CAIDE score
• Cerebral small vessel disease (SVD)
• White matter hyperintensities
• Cerebral microbleeds
• Lacunes
• Enlarged perivascular spaces
• Total SVD burden

Inflammation

• C-reactive protein
• Fibrinogen


Composite scores

Global SVD burden (Staals et al., 2014)
CAA-SVD (Low et al., 2020, 2021)
Hypertensive arteriopathy (HA-SVD)

Hypertensive arteriopathy (HA-SVD) vs. cerebral amyloid angiopathy (CAA-SVD)

Staals et al., 2014; Charidimou et al., 2016, 2017; Greenberg et al., 2009; Pasi et al., 2017
CAIDE SCORE ON CEREBRAL SMALL VESSEL DISEASE

BASELINE
CAIDE score related to almost all SVD measures, global and regional

LONGITUDINAL
CAIDE score related to white matter lesion progression

CAIDE = Cardiovascular Risk Factors, Aging, and Incidence of Dementia

Low et al., under review

Strength of association with CAIDE score
All associations significant to FDR-corrected p<.001

- Total SVD score
- CAA-SVD score
- HA-SVD score
- Enlarged perivascular spaces
- White matter hyperintensities
- Lacunes
- Cerebral microbleeds

Spearman's rho
(95% Confidence Interval)
## Contribution of Individual Components

### SVD Markers

#### Contribution of Individual Components

<table>
<thead>
<tr>
<th></th>
<th>White matter hyperintensities</th>
<th>Lacunes</th>
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<th>Composite SVD scores</th>
<th>Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total PVH Deep Frontal Temporal Parietal Occipital</td>
<td>Global Lobar Deep Global Lobar Deep</td>
<td>CSO BG Total SVD HA SVD CAA SVD CRP Fib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>0.92 1.11 0.86 -0.29 1.78 1.96</td>
<td>2.83** -0.68 -0.85 0.51</td>
<td>1.33 2.21* -1.24</td>
<td>0.46 0.60</td>
<td>0.99 0.32 0.60</td>
<td>-1.29 -1.49</td>
</tr>
<tr>
<td>Older age</td>
<td>2.28* 2.69** 1.59 2.89** 1.73</td>
<td>2.22* 0.46</td>
<td>-1.17 -0.78 0.11</td>
<td>1.22 1.81 -0.77</td>
<td>3.26** 3.53***</td>
<td>1.34 1.39 2.09* 0.67 2.35*</td>
</tr>
<tr>
<td>Lower education</td>
<td>-0.64 -0.41 -0.92 -0.50 0.03</td>
<td>-0.85 -0.37</td>
<td>1.93 2.51* 3.05**</td>
<td>1.10 1.33 -0.53</td>
<td>0.22 0.06</td>
<td>1.05 0.49 0.99</td>
</tr>
<tr>
<td>APOE4+</td>
<td>0.77 0.27 0.15 0.18 -0.07 -0.01</td>
<td>1.05 0.81 0.83</td>
<td>1.57 1.13 0.76</td>
<td>1.91 -0.31</td>
<td>1.23 0.47 1.58</td>
<td>-1.33 -0.78</td>
</tr>
<tr>
<td>Hypertension+</td>
<td>-0.83 -0.33 -0.53 -0.29 -1.48</td>
<td>3.69*** 3.54*** -0.11 -0.13 -0.51</td>
<td>0.34 0.35 0.04</td>
<td>1.66 0.31 1.16</td>
<td>4.09*** 2.34*</td>
<td></td>
</tr>
<tr>
<td>Hypercho+</td>
<td>0.40 1.80</td>
<td>0.07 -0.15 -0.48</td>
<td>0.68 1.26 -1.27</td>
<td>-1.30 0.31</td>
<td>1.37 0.45 0.95</td>
<td>-1.60 -0.98</td>
</tr>
<tr>
<td>Higher BMI</td>
<td>-0.75 -0.09 -0.85 -0.53 -0.29</td>
<td>-1.41 -1.37 -0.64</td>
<td>2.15* 1.86 0.46</td>
<td>-1.25 -0.13</td>
<td>1.11 0.11 0.12</td>
<td>0.51 -0.31</td>
</tr>
<tr>
<td>Low physical activity</td>
<td>0.089 0.119 0.065 0.129 0.063</td>
<td>0.105 0.087</td>
<td>0.230 0.176 0.170</td>
<td>0.102 0.108 0.064</td>
<td>0.088 0.126</td>
<td>0.218 0.156 0.147</td>
</tr>
</tbody>
</table>

#### Contribution of Individual CAIDE Components

### Cross-Sectional

|                          | Total PVH Deep Frontal Temporal Parietal Occipital | Global Lobar Deep Global Lobar Deep | CSO BG Total SVD HA SVD CAA SVD CRP Fib |
|--------------------------|-------------------------------|---------|----------------------|-------------------------------|----------------------|--------------|
| Male sex                | 0.65 1.52 -1.07 1.94 -0.06 | 0.27 -1.12 | na na na | 0.67 0.22 0.00 | 0.52 -1.08 | -0.99 0.72 -0.59 | -0.03 0.57 |
| Older age                | 2.98** 2.36* 2.20* 2.46* | 1.08 0.92 1.15 | na na na | 0.98 1.25 0.78 | -0.71 0.75 | -0.17 0.19 -0.36 | -0.11 0.79 |
| Lower education          | 0.12 -0.51 1.86 -0.28 0.62 | -1.24 1.40 | na na na | -0.01 0.00 0.00 | -0.10 0.15 | -0.39 0.13 -0.46 | 6.05*** 2.19* |
| APOE4+                   | 3.05** 1.77 3.49*** 1.11 | 3.28** 1.46 2.76* | na na na | 1.84 0.00 0.24 | 0.31 0.38 | -0.14 0.01 0.54 | 0.15 0.24 |
| Hypertension+            | 0.46 -0.06 0.45 -0.15 0.56 | 0.03 0.10 | na na na | -0.12 -0.29 0.00 | -0.47 -0.14 | 1.80 -0.71 1.85 | -1.91 -0.65 |
| Hypercho+                | -0.11 0.09 0.16 0.78 -0.60 | 0.33 -0.89 | na na na | -0.01 0.00 0.00 | -0.74 -0.68 | -1.48 0.06 -1.24 | 1.41 1.76 |
| Higher BMI               | 0.40 0.87 -0.05 0.23 -1.45 | 1.02 0.80 | na na na | -0.02 1.28 0.00 | 1.35 -0.45 | 1.09 -0.60 1.39 | 0.23 -0.29 |
| Low physical activity    | 0.07 0.99 -1.53 0.13 0.09 | 0.61 -0.44 | na na na | 1.46 0.74 0.00 | -1.42 -1.35 | -1.52 -0.34 -0.64 | 1.47 0.93 |

### Longitudinal

|                          | Total PVH Deep Frontal Temporal Parietal Occipital | Global Lobar Deep Global Lobar Deep | CSO BG Total SVD HA SVD CAA SVD CRP Fib |
|--------------------------|-------------------------------|---------|----------------------|-------------------------------|----------------------|--------------|
| Male sex                | 0.92 1.11 0.86 -0.29 1.78 1.96 | 2.83** -0.68 -0.85 0.51 | 1.33 2.21* -1.24 | 0.46 0.60 | 0.99 0.32 0.60 | -1.29 -1.49 |
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| APOE4+                   | 0.77 0.27 0.15 0.18 -0.07 -0.01 | 1.05 0.81 0.83 | 1.57 1.13 0.76 | 1.91 -0.31 | 1.23 0.47 1.58 | -1.33 -0.78 |
| Hypertension+            | -0.83 -0.33 -0.53 -0.29 -1.48 | 3.69*** 3.54*** -0.11 -0.13 -0.51 | 0.34 0.35 0.04 | 1.66 0.31 1.16 | 4.09*** 2.34* |
| Hypercho+                | 0.40 1.80 | 0.07 -0.15 -0.48 | 0.68 1.26 -1.27 | -1.30 0.31 | 1.37 0.45 0.95 | -1.60 -0.98 |
| Higher BMI               | -0.75 -0.09 -0.85 -0.53 -0.29 | -1.41 -1.37 -0.64 | 2.15* 1.86 0.46 | -1.25 -0.13 | 1.11 0.11 0.12 | 0.51 -0.31 |
| Low physical activity    | 0.089 0.119 0.065 0.129 0.063 | 0.105 0.087 | 0.230 0.176 0.170 | 0.102 0.108 0.064 | 0.088 0.126 | 0.218 0.156 0.147 | 0.166 0.116 |

### Highlighted Cells

Highlighted cells = significant association

STRENGTH OF ASSOCIATION
(Darker = stronger association)
Strongest contributors to baseline SVD burden were older age and hypertension

**Older age** related to diffuse SVD lesions (WMH, EPVS) and CAA

**Hypertension** was associated with focal lesions and hypertensive arteriopathy, rather than CAA

**Obesity** was related to greater prevalence of lacunes and higher levels of blood inflammatory markers

---

**BASELINE ASSOCIATIONS**

<table>
<thead>
<tr>
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<th>White matter hyperintensities</th>
<th>Lacunes</th>
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<td>-0.75</td>
<td>-0.97</td>
<td>-0.10</td>
<td>-0.65</td>
<td>-0.53</td>
<td>-0.29</td>
</tr>
<tr>
<td>R²</td>
<td>0.098</td>
<td>0.119</td>
<td>0.065</td>
<td>0.129</td>
<td>0.063</td>
<td>0.105</td>
</tr>
</tbody>
</table>
Older age and APOE4 predicted WMH progression over 2 years, but not the progression of other SVD markers.

Lower education was related to longitudinal increase in levels of inflammation.
AGE x CAIDE ON CEREBRAL SMALL VESSEL DISEASE

MAIN EFFECT
As expected, age was related to all markers of cerebral small vessel disease

INTERACTION EFFECT
High CAIDE score amplified the effect of age on increasing white matter lesion severity

CAIDE = Cardiovascular Risk Factors, Aging, and Incidence of Dementia

Low et al., under review
Age and hypertension were the strongest contributors to SVD:
- **AGE** was more closely related to diffuse SVD pathology (WMH/EPVS) and CAA
- **HYPERTENSION** was more closely related to focal SVD lesions (lacunes, CMB) and hypertensive arteriopathy

Global CAIDE risk amplified the effect of age on SVD burden

---

**SUMMARY & IMPLICATIONS**

Highlights importance of examining multiple SVD markers together

Risk factors influence cerebrovascular health via different pathways

Highlights importance of distinguishing between different SVD subtypes

Heightened susceptibility to vascular alterations?

Effect of age on CVD could possibly be lessened through management of modifiable risk factors (e.g., exercise, obesity)
Thank you

Audrey Low

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@audreylow

John T. O’Brien (Supervisor)
Hugh S. Markus (Supervisor)
Craig W. Ritchie
Karen Ritchie
Li Su

Graciela Muniz-Terrera
Maria-Eleni Dounavi
Elijah Mak
James Stefaniak
Maria Prats-Sedano
Elizabeth McKiernan
Stephen Carter

PREVENT-Dementia Study
Cambridge Old Age Psychiatry

NIHR
National Institute for Health Research

TRIBEKA

EPAD
European Platform for Alzheimer’s Drug Accelerator

alzheimer's association

Profile @ ResearchGate
Supplementary slides
PARTICIPANT SELECTION FLOWCHART

PREVENT cohort
Recruited at baseline n=210

With baseline MRI n=193

Excluded: incidental MR findings (5 meningioma, 1 brain tumour) n=6

n=187

Excluded: no APOE data n=2

FINAL SAMPLE (BASELINE) n=185

No follow-up MRI n=27

FINAL SAMPLE (FOLLOW-UP) n=158
# Imaging Markers of Cerebral Small Vessel Disease

<table>
<thead>
<tr>
<th>What are they?</th>
<th>White matter hyperintensities</th>
<th>Lacunes</th>
<th>Enlarged perivascular spaces</th>
<th>Cerebral microbleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchy or diffuse lesions thought to represent axonal loss and demyelination</td>
<td>Focal subcortical infarcts caused by occlusion of perforating arteries</td>
<td>Microscopic fluid-filled spaces surrounding perforating vessels of the brain that become visible when dilated. Also referred to as Virchow-Robin spaces</td>
<td>Small foci of chronic accumulation of blood products in brain tissue. Also referred to as microhaemorrhages</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRI sequence and appearance</th>
<th>FLAIR (+)</th>
<th>T1-weighted (−)</th>
<th>T2-weighted (+)</th>
<th>FLAIR (−)</th>
<th>SWI (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical size</td>
<td>Variable</td>
<td>3-15 mm</td>
<td>&lt;3 mm</td>
<td>2.5 mm Up to 10 mm</td>
<td></td>
</tr>
<tr>
<td>Shape</td>
<td>Irregular Punctate/Confluent</td>
<td>Round / Ovoid</td>
<td>[Axial view] In centrum semiovale: rounded / linear In basal ganglia: round/ovoid, cyst-like</td>
<td>Round / Ovoid</td>
<td></td>
</tr>
<tr>
<td>Method of quantification</td>
<td>Semi-automated quantification of volumes + Fazekas rating</td>
<td>Manual identification with cross-verification in T1, T2 and FLAIR scans</td>
<td>EPVS rating scale (range from 0-4)</td>
<td>Manual identification according to Microbleed Anatomical Rating Scale (MARS)</td>
<td></td>
</tr>
</tbody>
</table>
THE PREVENT-DEMENTIA STUDY

- Multi-site longitudinal study

- Cognitively healthy mid-life adults (aged 40-59)

- Overall aim: To identify the earliest signs of dementia, which may occur in the brain decades before symptoms appear


https://preventdementia.co.uk/
DEVELOPMENT OF COMPOSITE SVD SCORES

Existing evidence of regional differences between SVD subtypes
(Staals et al., 2014; Charidimou et al., 2016, 2017; Greenberg et al., 2009; Pasi et al., 2017)

Established global SVD rating scale
(Staals et al., 2014)

<table>
<thead>
<tr>
<th>White matter hyperintensities</th>
<th>Global SVD</th>
</tr>
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<tbody>
<tr>
<td>PVH = 3 and/or</td>
<td></td>
</tr>
<tr>
<td>DWMH = 2 or 3</td>
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<table>
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<tr>
<th>Hypertensive arteriopathy SVD</th>
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<tbody>
<tr>
<td>DWMH = 2 or 3</td>
<td>PVH = 3 and/or</td>
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<td></td>
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<table>
<thead>
<tr>
<th>Enlarged perivascular spaces</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EPVS in basal ganglia ≥ 2</td>
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<table>
<thead>
<tr>
<th>Cerebral microbleeds</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CMB present</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lacunes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunes present</td>
<td></td>
</tr>
</tbody>
</table>

Composite scoring system for SVD subtypes (Low et al., 2020)

<table>
<thead>
<tr>
<th>HA-SVD and CAA-SVD scoring published in: Low et al, JNNP, 2020; Low et al., Neurobiol Aging, 2021; Low et al., under review</th>
</tr>
</thead>
</table>

Scoring informed by: Staals et al., 2015; Charidimou et al., 2016, 2017; Greenberg et al., 2009; Pasi et al., 2017, Pantoni, 2010
## PARTICIPANT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% females</td>
<td>69.7%</td>
<td>69.0%</td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>51.9 (5.5)</td>
<td>54.2 (5.4)</td>
</tr>
<tr>
<td><strong>Education in years</strong></td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.9 (3.4)</td>
<td>16.1 (3.4)</td>
</tr>
<tr>
<td><strong>CAIDE score (range 0 to 18)</strong></td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.8 (2.9)</td>
<td>5.9 (2.9)</td>
</tr>
<tr>
<td><strong>APOE4</strong></td>
<td>% carriers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37.3%</td>
<td>38.0%</td>
</tr>
<tr>
<td><strong>APOE2</strong></td>
<td>% carriers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.7%</td>
<td>8.2%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>% positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.1%</td>
<td>15.1%</td>
</tr>
<tr>
<td><strong>Hyperlipidaemia</strong></td>
<td>% positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.3%</td>
<td>19.2%</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td>% positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.2%</td>
<td>3.5%</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>% on medication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.6%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Antihyperlipidaemic medication</td>
<td>% on medication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.3%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Antidiabetic medication</td>
<td>% on medication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td><strong>SVD markers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH volume (% of TIV)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.10 (0.14)</td>
<td>0.12 (0.19)</td>
</tr>
<tr>
<td>Lacunes (present/absent)</td>
<td>% present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.8%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Cerebral microbleeds (present/absent)</td>
<td>% present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.4%</td>
<td>24.0%</td>
</tr>
<tr>
<td>Enlarged perivascular spaces (range 0-4)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.72 (0.54)</td>
<td>0.72 (0.55)</td>
</tr>
<tr>
<td><strong>Composite SVD scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global SVD (range 0-4)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.39 (0.65)</td>
<td>0.44 (0.66)</td>
</tr>
<tr>
<td>CAA (range 0-4)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.45 (0.67)</td>
<td>0.47 (0.70)</td>
</tr>
<tr>
<td>Hypertensive arteriopathy (range 0-4)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.18 (0.47)</td>
<td>0.20 (0.48)</td>
</tr>
<tr>
<td><strong>Inflammatory markers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.14 (2.72)</td>
<td>3.20 (3.98)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.05 (0.69)</td>
<td>3.03 (0.72)</td>
</tr>
</tbody>
</table>
ASSOCIATION WITH CAIDE DEMENTIA RISK SCORE
CAIDE score was associated with nearly all markers (global and regional)

Spearman's rho (95% Confidence Interval)
### Longitudinal Association with CAIDE Dementia Risk Score

<table>
<thead>
<tr>
<th></th>
<th>Statistics</th>
<th>p value</th>
<th>FDR-corrected p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White matter hyperintensities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$t = 3.44$</td>
<td>$&lt;0.001^{***}$</td>
<td>0.004**</td>
</tr>
<tr>
<td>Periventricular</td>
<td>$t = 3.72$</td>
<td>$&lt;0.001^{***}$</td>
<td>0.004**</td>
</tr>
<tr>
<td>Deep</td>
<td>$t = 2.55$</td>
<td>0.012*</td>
<td>0.043*</td>
</tr>
<tr>
<td>Frontal</td>
<td>$t = 3.52$</td>
<td>$&lt;0.001^{***}$</td>
<td>0.004**</td>
</tr>
<tr>
<td>Temporal</td>
<td>$t = 0.51$</td>
<td>0.609</td>
<td>0.760</td>
</tr>
<tr>
<td>Parietal</td>
<td>$t = 2.52$</td>
<td>0.013*</td>
<td>0.043*</td>
</tr>
<tr>
<td>Occipital</td>
<td>$t = 1.75$</td>
<td>0.082</td>
<td>0.164</td>
</tr>
<tr>
<td><strong>Cerebral microbleeds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole brain</td>
<td>$r_s = 0.14$</td>
<td>0.087</td>
<td>0.164</td>
</tr>
<tr>
<td>Lobar</td>
<td>$r_s = 0.13$</td>
<td>0.113</td>
<td>0.193</td>
</tr>
<tr>
<td>Deep</td>
<td>$r_s = 0.06$</td>
<td>0.458</td>
<td>0.649</td>
</tr>
<tr>
<td><strong>Enlarged perivascular spaces</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>$t = -0.41$</td>
<td>0.679</td>
<td>0.760</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>$t = -0.37$</td>
<td>0.715</td>
<td>0.760</td>
</tr>
<tr>
<td><strong>Composite SVD scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global SVD</td>
<td>$t = 0.49$</td>
<td>0.625</td>
<td>0.759</td>
</tr>
<tr>
<td>HA-SVD</td>
<td>$t = -0.07$</td>
<td>0.947</td>
<td>0.947</td>
</tr>
<tr>
<td>CAA-SVD</td>
<td>$t = 0.95$</td>
<td>0.344</td>
<td>0.531</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>$t = 2.41$</td>
<td>0.017*</td>
<td>0.049*</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>$t = 1.79$</td>
<td>0.076</td>
<td>0.164</td>
</tr>
</tbody>
</table>
The impact of Alzheimer biomarkers and vascular factors on cognitive decline in memory clinic patients

Veerle van Gils

08-09-2021
Background

- AD biomarkers are associated with cognitive decline
- Vascular brain damage and risk have also shown to be related to cognitive decline
- Vascular brain damage and risk factors are common in AD

Do vascular factors influence the impact of AD biomarkers on cognitive decline in a memory clinic population?
Methods

247 patients from Maastricht and Aachen memory clinics

Baseline data

**AD biomarker**
Amyloid (CSF Aβ-42)

**Vascular burden**
1. MRI vascular damage
   - White matter hyperintensities (WMH)
   - Microbleeds
   - Infarct/hemorrhage
2. Vascular risk factors
   - Hypertension
   - Dyslipidemia
   - Diabetes

No pathology

Only vascular

Only AD

Vascular + AD

Cognition (up to 5 years)
- MMSE
- Neuropsychological assessment
  - Memory
  - Attention
  - Executive functioning
  - Language / fluency

Linear mixed models
adjusted for cohort, age, education, gender & cognitive status
### Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Frequency / mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>247</td>
<td>66.8 (9.3)</td>
</tr>
<tr>
<td><strong>Gender, male %</strong></td>
<td>247</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Education (years)</strong></td>
<td>247</td>
<td>11.8 (3.4)</td>
</tr>
<tr>
<td><strong>Diagnostic group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Subjective Cognitive Decline</td>
<td>247</td>
<td>24%</td>
</tr>
<tr>
<td>o Mild Cognitive Impairment</td>
<td></td>
<td>53%</td>
</tr>
<tr>
<td>o Dementia</td>
<td></td>
<td>22%</td>
</tr>
<tr>
<td><strong>Groups – MRI vascular damage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o No pathology</td>
<td>235</td>
<td>29%</td>
</tr>
<tr>
<td>o Only MRI vascular damage</td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>o Only AD</td>
<td></td>
<td>39%</td>
</tr>
<tr>
<td>o MRI vascular burden + AD</td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td><strong>Groups – vascular risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o No pathology</td>
<td>245</td>
<td>16%</td>
</tr>
<tr>
<td>o Only vascular risk</td>
<td></td>
<td>22%</td>
</tr>
<tr>
<td>o Only AD</td>
<td></td>
<td>22%</td>
</tr>
<tr>
<td>o Vascular risk + AD</td>
<td></td>
<td>41%</td>
</tr>
</tbody>
</table>
Results - MMSE

**Decrease in MMSE score for the AD and mixed groups, while the no pathology and vascular groups remain stable over time**
Results - Memory

**AD & MRI vascular damage**

- No pathology
- Only AD
- Only vascular
- Vascular + AD

**AD & vascular risk factors**

Lower memory (Z-score) for the AD and mixed groups at baseline compared to the no pathology and vascular groups.
Conclusions

- Cognitive decline was mainly driven by AD.
- Vascular burden was not associated with cognitive decline and did not add to the prognosis in persons with AD.
- Different definitions of vascular burden did not have clear implications for the cognitive trajectory of patients.
Acknowledgements

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RWTH Aachen
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Ana Sofia Costa
Domante Kučikienė
Jörg Schulz

Funding sources

Contact: v.vangils@maastrichtuniversity.nl
VALIDATION OF A NOVEL CLINICAL NEUROVASCULAR COUPLING MARKER

Suzanne E. van Dijk, MSc; Jessie Lak, MSc; Anne Hafkemeijer, PhD;
Jeroen van der Grond, PhD; Sanneke van Rooden, PhD

Suzanne E. van Dijk
Department of radiology
LUMC
Aim: assess effects of aging, SVD and cardiovascular risk factors on BOLD/checkboard parameters in group of healthy adults and determine reproducibility and test-retest reliability

Adapted from Arthurs & Boniface (2002), Trends Neurosci
Methods

- N=87 (healthy adults, age 20 – 86)
- 3T (f)MRI including checkerboard task
Small vessel disease markers:
• Microbleeds (deep and lobar)
• Lacunar infarcts
• Perivascular spaces (Centrum Semiovale and Basal Ganglia)
• White matter hyperintensities
• Gray matter volume

Cardiovascular risk factors
• Hypertension
• Hyperlipidemia
• Diabetes Mellitus
Associations between age, SVD, cardiovascular risk factors and BOLD/checkerboard parameters

Age*
- Association between age and BOLD amplitude (p=0.004)
- No association between age and Time to Peak or Time to Baseline

Small vessel disease markers**
- No associations between SVD markers and BOLD/checkerboard parameters

Cardiovascular risk factors**
- No associations between cardiovascular risk factors and BOLD/checkerboard parameters

* Linear regression model, adjusted for sex and study group
** Linear regression model, adjusted for age, sex and study group
Reproducibility and test-retest reliability

- N=12 (age 42.6 ± 12.1)
- Checkerboard task
  - Reproducibility: 3-week interval
  - Test-retest: 3 consecutive measurements

<table>
<thead>
<tr>
<th>Reproducibility</th>
<th>BOLD amplitude</th>
<th>Time to Peak</th>
<th>Time to baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson correlation</td>
<td>0.836 (p=0.001)</td>
<td>0.738 (p=0.009)</td>
<td>0.493</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test-retest reliability</th>
<th>BOLD amplitude</th>
<th>Time to peak</th>
<th>Time to baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICC (2-way mixed)</td>
<td>0.928</td>
<td>0.801</td>
<td>0.473</td>
</tr>
</tbody>
</table>
Conclusions

• Studies using the BOLD/checkerboard task to study the neurovascular coupling should always be age controlled

• No association between SVD or cardiovascular risk factors and BOLD/checkerboard parameters in group of healthy adults

• Measurements of BOLD amplitude and time to peak demonstrate excellent reproducibility and test-retest reliability
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 Luca1,2, PhD, Hugo Kuijf2, PhD, Lieza Exalto1, MD, PhD, Geert-Jan Biessels1, MD, PhD, also On behalf of the Utrecht VCI study group

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

a.deluca-2@umcutrecht.nl - @alb_dl (Twitter)
Background
Background

Microstructural metrics explain more variation in cognition than lesions

Baykara et al. 2016 Annals of Neurology
Background

White matter tracts support specific functions
Research question

Can we improve the prediction of cognitive performance in memory clinic patients with SVD-related brain injury by considering white matter tract-specific metrics?
### Study data

N=102 patients from Trace-VCI* with MRI-visible signs of vascular injury

<table>
<thead>
<tr>
<th>Study data</th>
<th>Trace-VCI N=860</th>
<th>Utrecht cohort N=196</th>
<th>MRI visible SVD N=148</th>
<th>No large ischemic lesions N=116</th>
<th>Good MRI and cognitive assessment N=102</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Fazekas ≥ 2 or small (sub)cortical infarct</strong></th>
<th>Infarct or hemorrhagic volume &lt; 4.2mL No accidental findings</th>
</tr>
</thead>
</table>

| **Memory clinic patients with SVD and no other MR visible lesion** |

**Table 1: demographic characteristics and vascular risk factors**

<table>
<thead>
<tr>
<th>Included patients n = 102</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Demographics</strong></th>
<th>Gender, % men</th>
<th>59 (58%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>73.7 ± 10.2</td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td>5 (4 - 7)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Vascular risk factors</strong></th>
<th>Hypertension</th>
<th>97 (96%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>63 (62%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>15 (15%)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>20 (20%)</td>
<td></td>
</tr>
<tr>
<td>History of reported stroke</td>
<td>17 (17%)</td>
<td></td>
</tr>
<tr>
<td>Vascular event other than stroke</td>
<td>15 (15%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Clinical diagnosis</strong></th>
<th>No objective cognitive impairment</th>
<th>18 (18%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>31 (30%)</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>53 (52%)</td>
<td></td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>6 (6%)</td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>41 (40%)</td>
<td></td>
</tr>
<tr>
<td>Other neurodegenerative etiology</td>
<td>5 (5%)</td>
<td></td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

*Boomsma et al. 2017 JMIR Res Prot.*
Automated image analysis pipeline

Considered metrics

Structural MRI
- T1-weighted
- FLAIR

Diffusion MRI
- $b = 1200\text{s/mm}^2$
- 45 directions

Conventional MRI markers
- WMHV
- BPF
- ICH [y/n]
- CTH

dMRI metrics
- FA
- MD
- PSMD
- PWD
- RESIDUALS

CAT12

MRIToolkit

ExploreDTI

https://github.com/delucaal/MRIToolkit
Automated image analysis pipeline

Features extraction

**Diffusion MRI**
\[ b = 1200\text{s/mm}^2 \]
45 directions

**MRIToolkit**
ExploreDTI

**CSD**
White Matter Analysis*

*Tracts of interest (N=73)*
Arcuate
Corpus callosum
SLF

**Whole brain level**

*Zhang et al. 2018 (NeuroImage)*
Feed-forward neural network

Input imaging markers (features)

2 layers, 20 nodes, ReLU activation
(30% dropout)

Cognitive prediction
Training and prediction

Leave 1 out (L1O) regression

Dataset N=102

Features selection

Training set N=101
10% validation

Test set (N=1)

Trained classifier

Individual prediction ($R^2$, MAE)

Repeat $N = 30$
Results

Features selected by the neural network to predict memory performance

FA
- Right Sup-PT
- Left ILF
- Right SLF-II
- Right Sup-T
- Left CB

MD
- Left CB
- Left Sup-PT
- Left ILF
- Left Sup-T
- Left Sup-OT

CTH
- Right Sup-P
- CC1
- Right TF
- Left SLF-II

WB features
- PWD (GM)*
- RESIDUALS (GM)
- MD (GM)
- FA (GM)

PWD
- Right SLF-II
- Left Sup-PT
- Right Sup-PT
- Left Sup-T
- Right CB
- Left TF

RESIDUALS
- Right Sup-P
- CC2
- Right Sup-OT
- Left/Right MdLF

WMHV
- Left TF
- CC1
- Right SLF-III
- Right Sup-OT
Results

Optimized prediction of processing speed performance (leave-one-out)

Best multivariate prediction

Neural network prediction with optimized features

Neural network prediction with best subset of features

Estimated processing speed [Z-score]

Measured processing speed [Z-score]

R² = 0.38

R² = 0.44

R² = 0.49
Results

Optimized prediction of memory performance (leave-one-out)

Best multivariate prediction

Neural network prediction with optimized features

Neural network prediction with best subset of features

R² = 0.27

R² = 0.37

R² = 0.41
Conclusions

✔ Tract-specific metrics improve the prediction of cognitive performance
  ● Proof of concept that should be validated in an external cohort

✔ Flexible framework to indentify metrics of interest
  ● More metrics can be seamlessly included
  ● Features selection opens window on interpretation
Thank you for listening!
Questions?
Network impact score is an independent predictor of post-stroke cognitive impairment

Matthijs Biesbroek, MD PhD
On behalf of the Meta VCI Map consortium
September 8th 2021
• Prediction of post-stroke cognitive impairment (PSCI) is challenging

• Recently published network impact score integrates information on infarct location and size, with a brain network atlas

• Aim: determine if the score predicts PSCI, and cognitive recovery or decline
Methods

• Inclusion criteria
  – Patients with ischemic stroke, excluding isolated infratentorial or white matter infarcts

• 12 cohorts, 2488 patients, 4941 cognitive evaluations

• PSCI definition
  – <5<sup>th</sup> percentile norm-corrected performance in ≥1 cognitive domain
  – OR <5<sup>th</sup> percentile norm-corrected MoCA

Meta VCI Map: an international collaborative platform for lesion-symptom mapping studies

Weaver et al. Lancet Neurology 2021
Network impact score calculation

Step 1
infarct segmentation
Results

12 cohorts, 2488 patients, 4941 cognitive evaluations

- Mean age: 66.7 years (SD 11.7)
- 60% male
- Timing of cognitive assessment: median 263 days after stroke, range 0-4311

<table>
<thead>
<tr>
<th>Network impact score (range -3.07 to 2.46)</th>
<th>OR (95%CI) for PSCI</th>
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<td>Univariable GEE model</td>
<td>1.47 (95%CI 1.33-1.63)</td>
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- Same results in stratified analyses for PSCI <3 months, 3-12, 12-24, and >24 months
- No association with cognitive recovery or decline
Conclusion

• Network impact score is independent predictor of PSCI

• The score does not predict recovery or decline

• Online tool at www.metavcimap.org/features/software-tools

• Future steps: implement other lesion types for PSCI prediction
Thank you for your attention!

On behalf of the Meta VCI Map consortium

Contact details

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Relationship between cerebrovascular pathology and resting-state functional connectivity: a systematic review

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Resting-state functional connectivity (FC)

Posterior cingulate cortex

Time course of BOLD fluctuations

Spatially-distributed Default Mode Network

MIST Atlas

7 network templates used
- default mode (DMN)
- cerebellar (CER)
- limbic (LIM)
- visual (VIS)
- motor (MOT)
- fronto-parietal (FPN)
- salience (SAL)

Urchs et al., MNI Open Research 2017
**AD continuum FC profiles (meta-analysis)**

**Decreased** connectivity in the DMN in AD dementia

![Bar chart showing decreased connectivity in the DMN and LIM in AD dementia]

**Increased** connectivity in the DMN & LIM in AD prodrome (or MCI)

![Bar chart showing increased connectivity in the DMN and LIM in AD prodrome]

*FDR corrected q<0.05

*Badhwar et al. Alzheimers Dement, 2017*
**AD continuum FC profiles** (meta-analysis)

**Decreased** connectivity in the DMN in AD dementia

*FDR corrected q<0.05*

**Increased** connectivity in the DMN & LIM in AD prodrome (or MCI)

*Sweeney et al. Alzheimers Dement, 2019

*Badhwar et al. Alzheimers Dement, 2017*
Understand the association between cerebrovascular pathology and FC:

I. In patients with cognitive impairment due to AD (clinical diagnosis +/- biomarker evidence) with/without cerebrovascular pathology e.g. small vessel disease (SVD)

II. In patients with a diagnosis of vascular contributions to cognitive impairment and dementia (VCID) or CADASIL
   - **CADASIL**: autosomal dominant mutation in NOTCH3 gene
     - a model of FC changes due specifically to cerebrovascular pathology
     - free from confounding factors such as age
Systematic search (in accordance with PRISMA guidelines)

- Keywords: cerebrovascular terms - Wardlaw et al. (2013), FC terms - Badhwar et al. (2017)
- PubMed, Embase & PsycInfo databases searched
- Unique articles screened by 4 blinded authors using Rayyan platform
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![Flowchart showing search and screening process]

- 522 Unique Articles (database searching)
- 525 Articles screened
- 426 Articles excluded
- 98 Full-text articles assessed for eligibility
- 50 Full-text articles excluded
- 48 Articles reviewed

MRI-detected severe WMH

- 8 AD
- 24 VCID
- 4 CADASIL
- 6 AD vs. VCID
Results – AD continuum

**Default Mode Network**
AD/MCI+SVD frontal perturbations

AD/MC-SVD posterior perturbations - *in-line with Badhwar et al. (2017)*

**Executive Control Network**
AD/MCI+SVD increased in frontal regions compared to AD/MCI-SVD & CU
### Results – AD continuum

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- Higher global WMH load associated with higher FC strength, regardless of the direction of perturbed connectivity relative to CU
- Tract-specific WMHs may be associated with lower FC in networks served by those tracts
- Altered FC may mediate relationship between WMH & cognition
Results – VCID

• DMN most studied, followed by the fronto-parietal network

• Early disease (SVD-MCI) most studied

• FC perturbations between VCID & CU

• FC differences related to VCID severity (pre-symptomatic to dementia)
Results – CADASIL

- DMN regions were investigated by all 4 studies

- Compared to CU, both ↑ and ↓ in DMN FC

- Within the CADASIL group
  a) higher cerebrovascular disease burden associated with lower DMN FC
  b) increased FC strength associated with better cognitive performance

  \[ \text{-> does FC alter the impact of cerebrovascular damage on cognition?} \]
Conclusions & clinical implications

• Divergent FC changes
  a) between AD with and without SVD
  b) along the VCID spectrum of severity
  c) have been used as features in machine learning studies

  -> Outstanding question: are these changes compensatory, or a reflection of damage?

• Altered FC appears to be associated with cognition in all disease groups

• Implications for treatment stratification, particularly in AD/MCI+SVD, as SVD likely unresponsive to drugs targeting amyloid and tau

More studies - particularly longitudinal - are needed to confirm
Thank you!

Dr AmanPreet Badhwar & co-authors

Natasha Clarke, PhD
CRIUGM
VasCog 2021