Vascular pathology & imaging

임 재 성
한림의대 신경과

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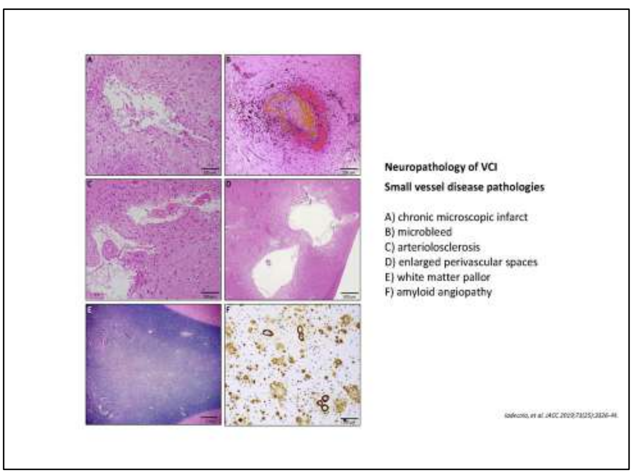
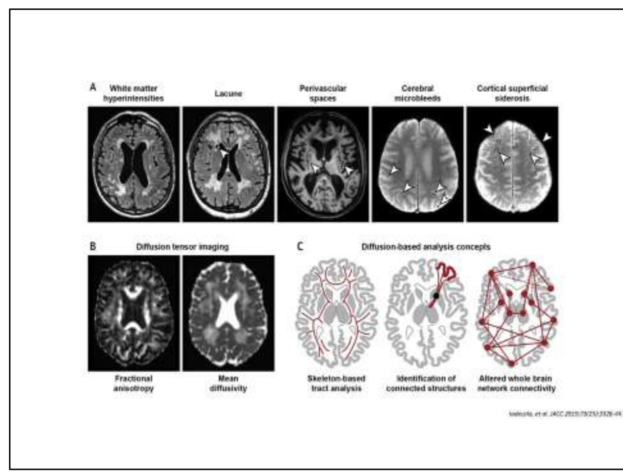
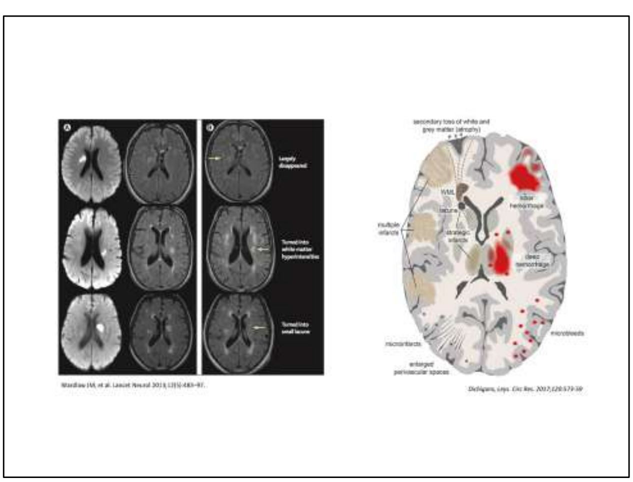
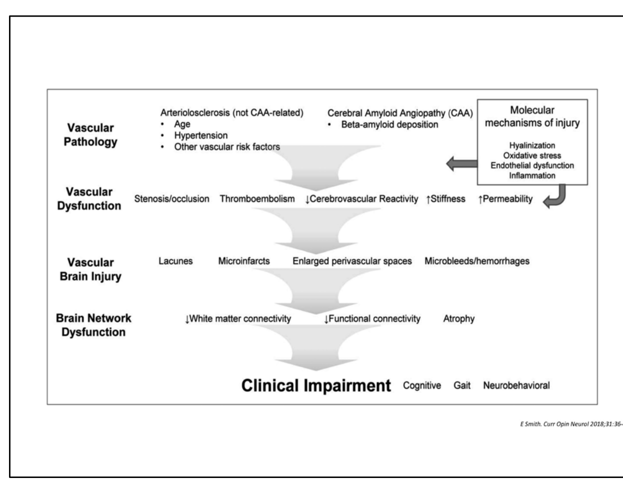
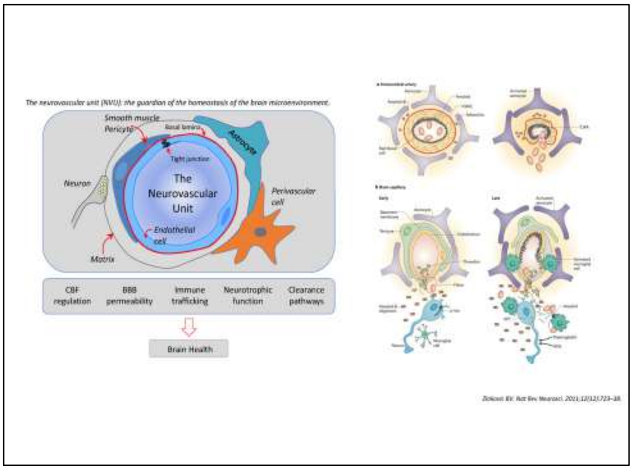
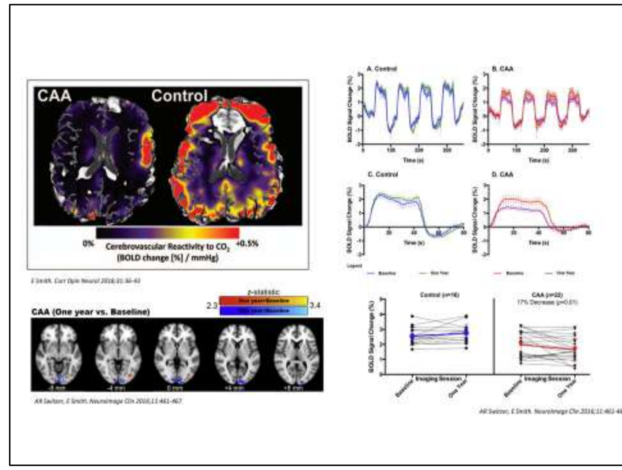


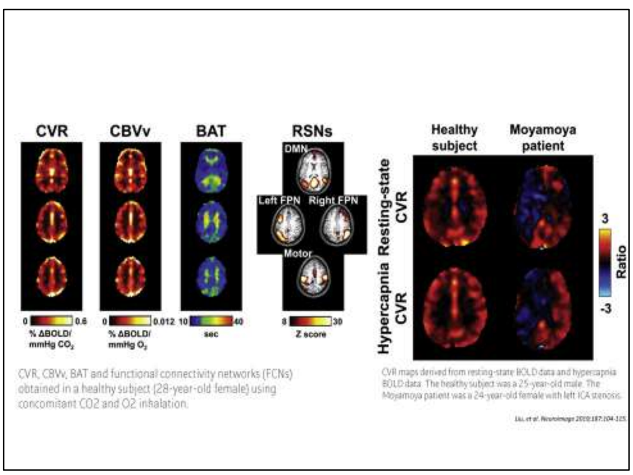


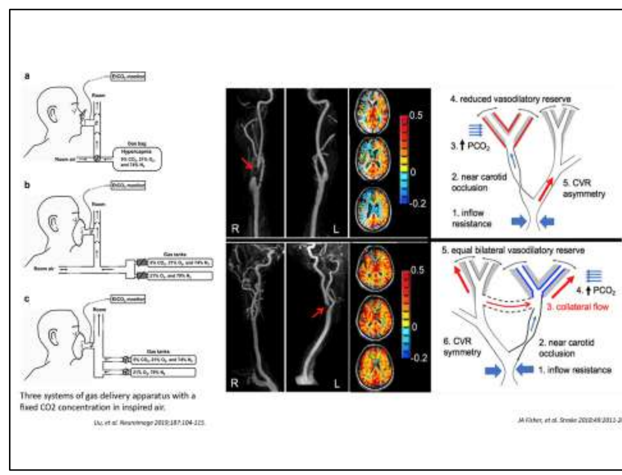


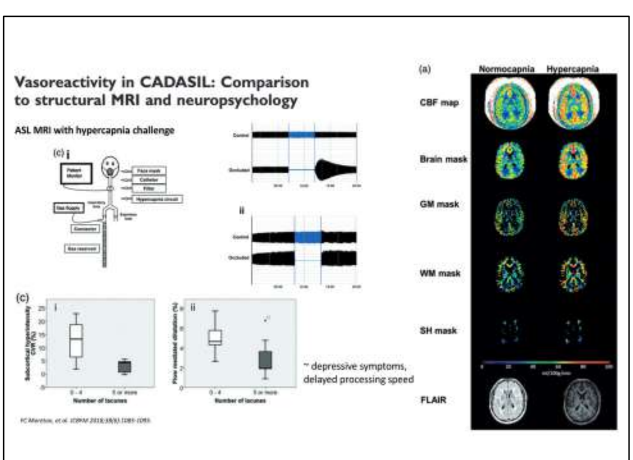


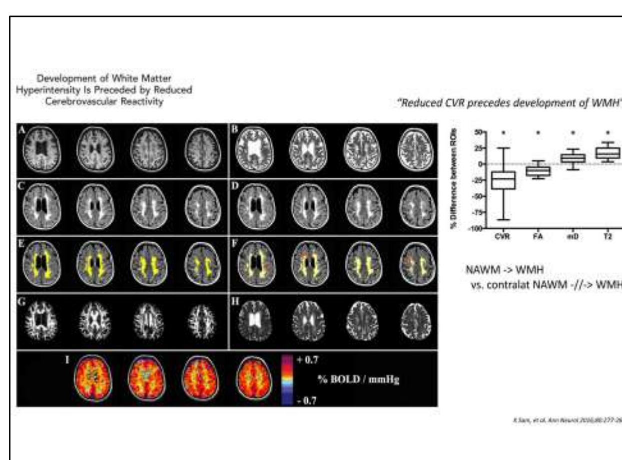

The neurovascular unit (NVU): the guardian of the homeostasis of the brain microenvironment.
Smooth muscle
Pericyte
Basal lamina
Astrocyte
Tight junction
The Neurovascular Unit
Neuron
Perivascular cell
Endothelial cell
Matrix
CBF regulation
BBB permeability
Immune trafficking
Neurotrophic function
Clearance pathways
Brain Health

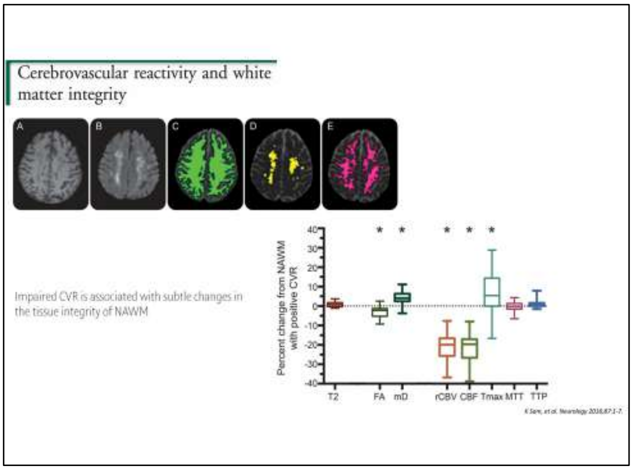

CAA
Control
0%
Cerebrovascular Reactivity to CO2
+0.5%
(BOLD change [%] / mmHg)
A. Control
B. CAA
C. Control
D. CAA
CAA (One year vs. Baseline)
Control (n=16)
CAA (n=22)

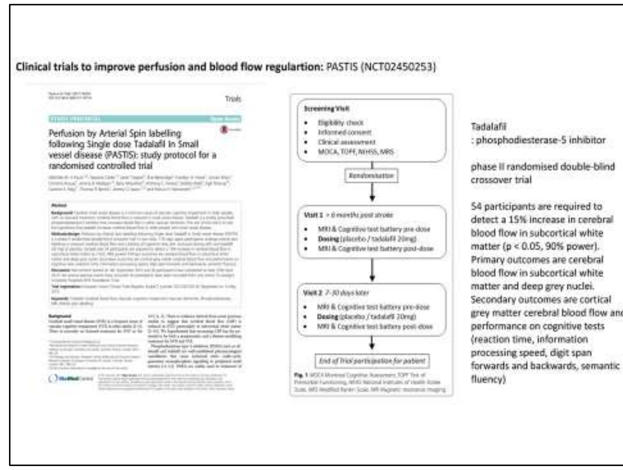

CVR
CBVv
BAT
RSNs
DMN
Left FPN
Right FPN
Motor
% ΔBOLD/ mmHg CO2
% ΔBOLD/ mmHg O2
sec
Z score
Healthy subject
Moyamoya patient
Resting-state CVR
Hypercapnia CVR
Ratio
CVR, CBVv, BAT and functional connectivity networks (FCNs) obtained in a healthy subject (28-year-old female) using concomitant CO2 and O2 inhalation.
CVR maps derived from resting-state BOLD data and hypercapnia BOLD data. The healthy subject was a 25-year-old male. The Moyamoya patient was a 24-year-old female with left ICA stenosis.

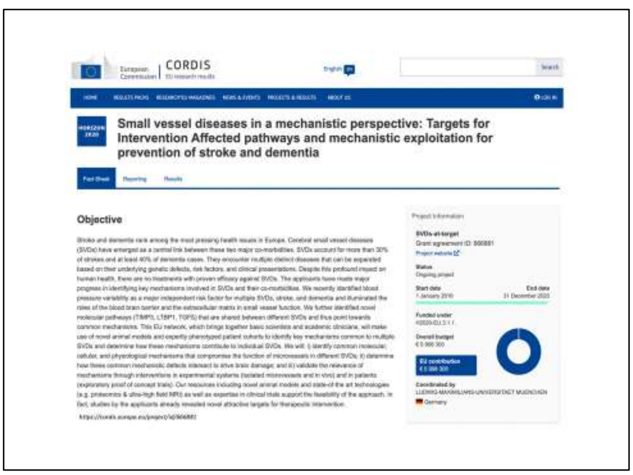

4. reduced vasodilatory reserve
3. ↑ PCO2
2. near carotid occlusion
5. CVR asymmetry
1. inflow resistance
5. equal bilateral vasodilatory reserve
4. ↑ PCO2
3. collateral flow
6. CVR symmetry
2. near carotid occlusion
1. inflow resistance
Three systems of gas delivery apparatus with a fixed CO2 concentration in inspired air.

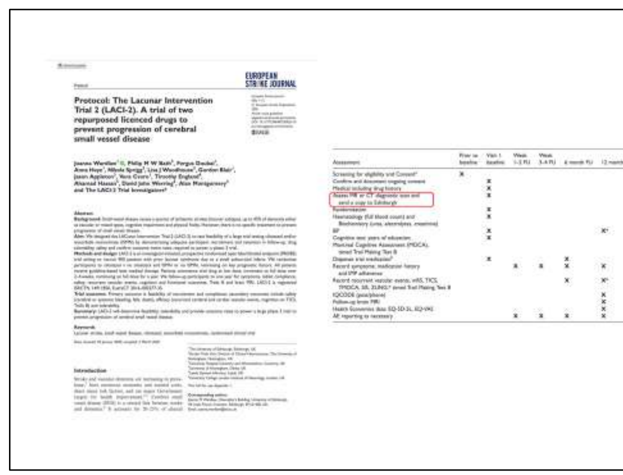

Vasoreactivity in CADASIL: Comparison to structural MRI and neuropsychology
ASL MRI with hypercapnia challenge
Normocapnia
Hypercapnia
CBF map
Brain mask
GM mask
WM mask
SH mask
FLAIR
Number of lacunes
~ depressive symptoms, delayed processing speed

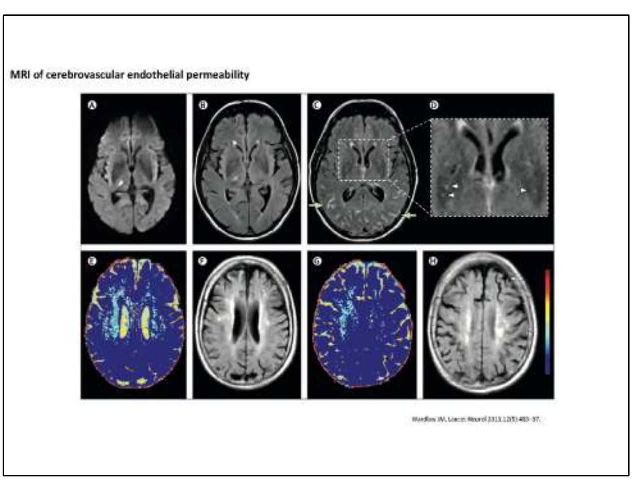

Development of White Matter Hyperintensity Is Preceded by Reduced Cerebrovascular Reactivity
"Reduced CVR precedes development of WMH"
% Difference between ROIs
CVR
FA
mD
T2
NAWM -> WMH
vs. contralat NAWM -//-> WMH
% BOLD / mmHg

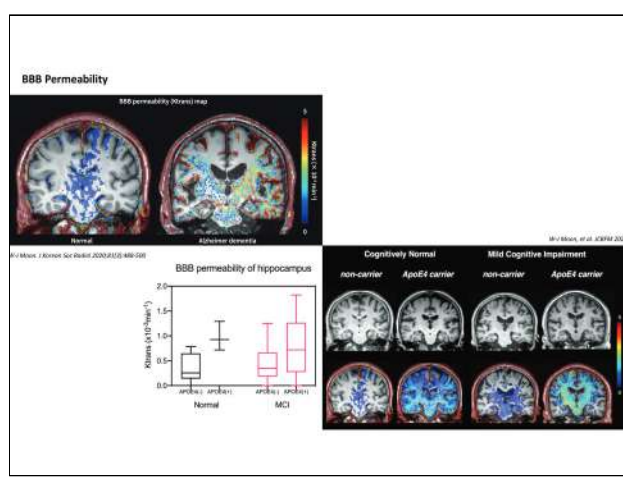

Cerebrovascular reactivity and white matter integrity
Impaired CVR is associated with subtle changes in the tissue integrity of NAWM
Percent change from NAWM with positive CVR
T2
FA
mD
rCBV
CBF
Tmax
MTT
TTP

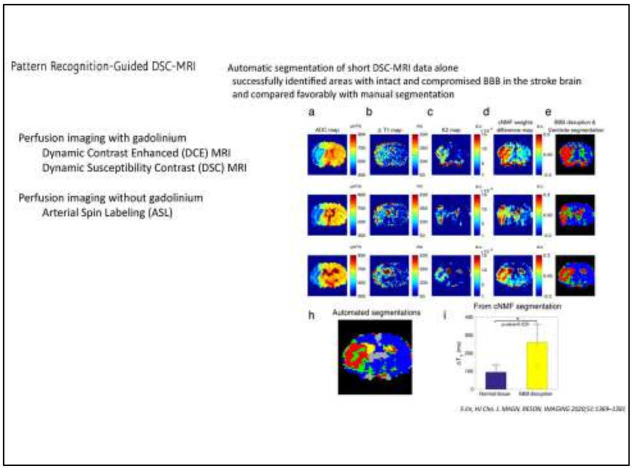

Clinical trials to improve perfusion and blood flow regulartion: PASTIS (NCT02450253)
Perfusion by Arterial Spin labelling following Single dose Tadalafil In Small vessel disease (PASTIS): study protocol for a randomised controlled trial
Tadalafil
: phosphodiesterase-5 inhibitor
phase II randomised double-blind crossover trial
54 participants are required to detect a 15% increase in cerebral blood flow in subcortical white matter (p < 0.05, 90% power).
Primary outcomes are cerebral blood flow in subcortical white matter and deep grey nuclei.
Secondary outcomes are cortical grey matter cerebral blood flow and performance on cognitive tests (reaction time, information processing speed, digit span forwards and backwards, semantic fluency)


CORDIS
Small vessel diseases in a mechanistic perspective: Targets for Intervention Affected pathways and mechanistic exploitation for prevention of stroke and dementia
Objective

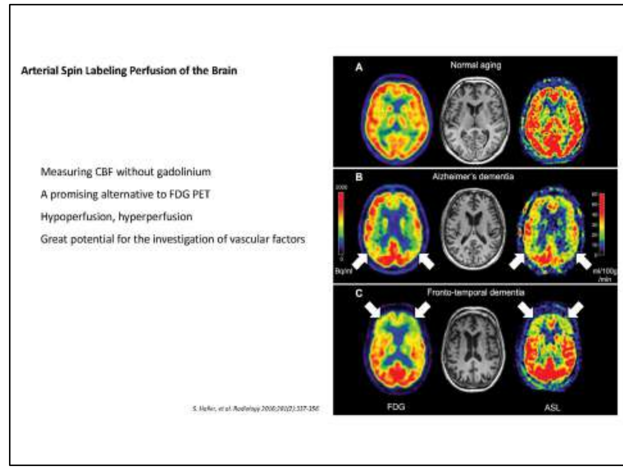

EUROPEAN STROKE JOURNAL
Protocol: The Lacunar Intervention Trial 2 (LACI-2). A trial of two repurposed licenced drugs to prevent progression of cerebral small vessel disease


MRI of cerebrovascular endothelial permeability

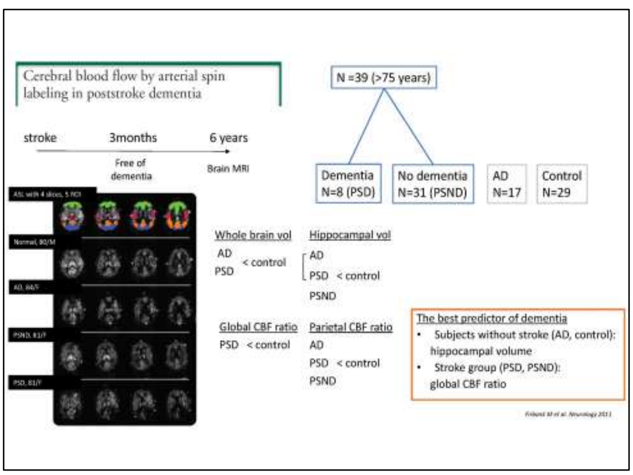

BBB Permeability
BBB permeability of hippocampus
Normal
Alzheimer dementia
Cognitively Normal
Mild Cognitive Impairment
non-carrier
ApoE4 carrier
Normal
MCI



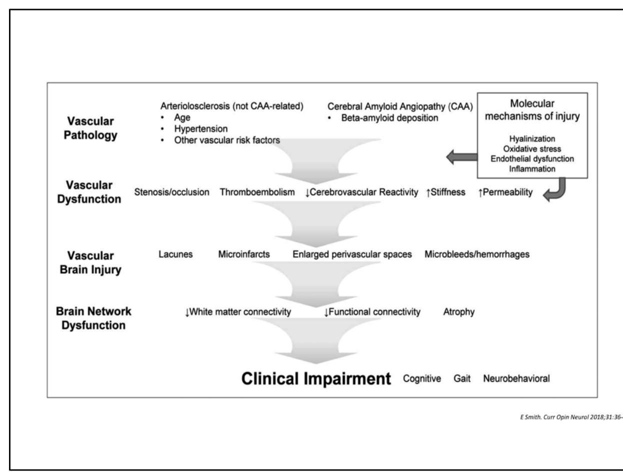
Pattern Recognition-Guided DSC-MRI
Automatic segmentation of short DSC-MRI data alone successfully identified areas with intact and compromised BBB in the stroke brain and compared favorably with manual segmentation
Perfusion imaging with gadolinium
Dynamic Contrast Enhanced (DCE) MRI
Dynamic Susceptibility Contrast (DSC) MRI
Perfusion imaging without gadolinium
Arterial Spin Labeling (ASL)
a
b
c
d
e
h
Automated segmentations
i
From cNMF segmentation



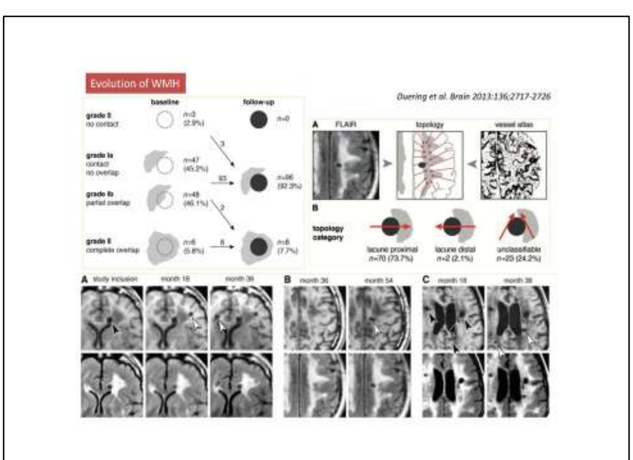
Arterial Spin Labeling Perfusion of the Brain
Measuring CBF without gadolinium
A promising alternative to FDG PET
Hypoperfusion, hyperperfusion
Great potential for the investigation of vascular factors
A
Normal aging
B
Alzheimer's dementia
C
Fronto-temporal dementia
FDG
ASL



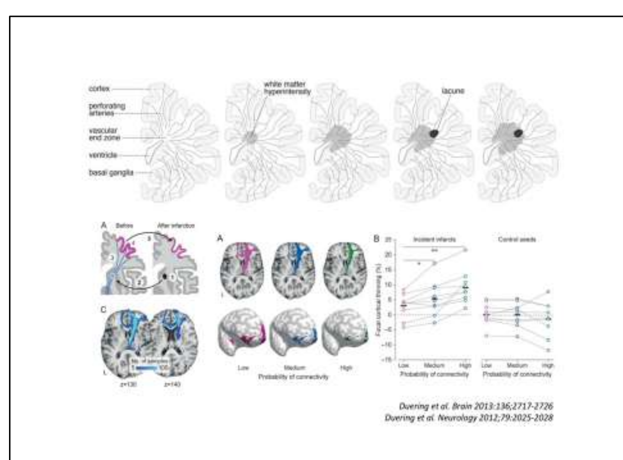
Cerebral blood flow by arterial spin labeling in poststroke dementia
stroke
3months
6 years
Free of dementia
Brain MRI
N =39 (>75 years)
Dementia N=8 (PSD)
No dementia N=31 (PSND)
AD N=17
Control N=29
Whole brain vol
AD
PSD
< control
Hippocampal vol
AD
PSD < control
PSND
Global CBF ratio
PSD < control
Parietal CBF ratio
AD
PSD < control
PSND
The best predictor of dementia
• Subjects without stroke (AD, control): hippocampal volume
• Stroke group (PSD, PSND): global CBF ratio



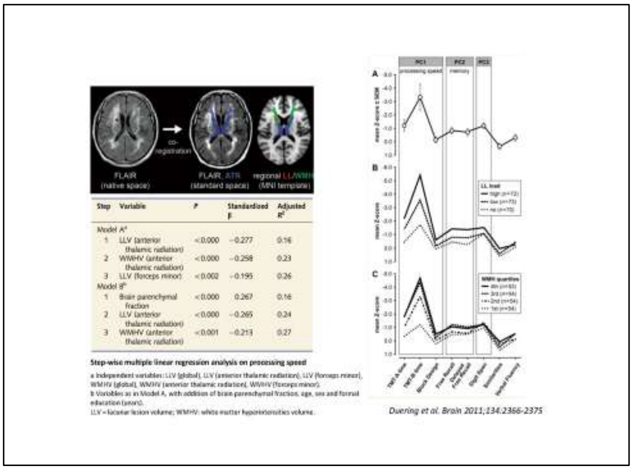
Vascular Pathology
Arteriolosclerosis (not CAA-related)
• Age
• Hypertension
• Other vascular risk factors
Cerebral Amyloid Angiopathy (CAA)
• Beta-amyloid deposition
Molecular mechanisms of injury
Hyalinization
Oxidative stress
Endothelial dysfunction
Inflammation
Vascular Dysfunction
Stenosis/occlusion
Thromboembolism
↓Cerebrovascular Reactivity
↑Stiffness
↑Permeability
Vascular Brain Injury
Lacunes
Microinfarcts
Enlarged perivascular spaces
Microbleeds/hemorrhages
Brain Network Dysfunction
↓White matter connectivity
↓Functional connectivity
Atrophy
Clinical Impairment
Cognitive
Gait
Neurobehavioral
E Smith. Curr Opin Neurol 2018;31:36-43



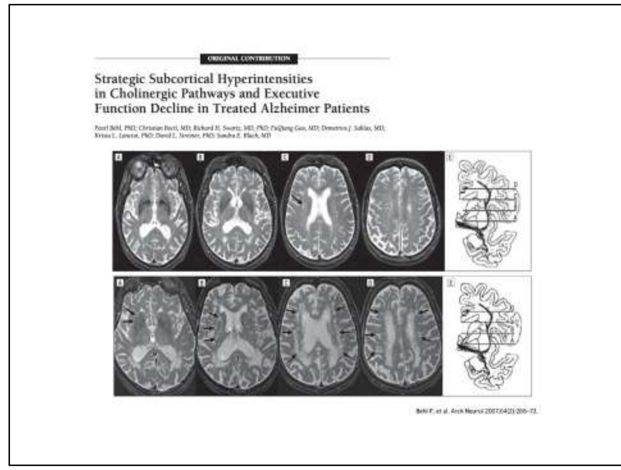
Evolution of WMH
Duering et al. Brain 2013;136;2717-2726
baseline
follow-up
FLAIR
topology
vessel atlas



cortex
white matter hyperintensity
lacune
Duering et al. Brain 2013:136;2717-2726
Duering et al. Neurology 2012;79:2025-2028



Step	Variable	P	Standardized β	Adjusted R^2
Model A[a]				
1	LLV (anterior thalamic radiation)	<0.000	−0.277	0.16
2	WMHV (anterior thalamic radiation)	<0.000	−0.258	0.23
3	LLV (forceps minor)	<0.002	−0.195	0.26
Model B[b]				
1	Brain parenchymal fraction	<0.000	0.267	0.16
2	LLV (anterior thalamic radiation)	<0.000	−0.265	0.24
3	WMHV (anterior thalamic radiation)	<0.001	−0.213	0.27



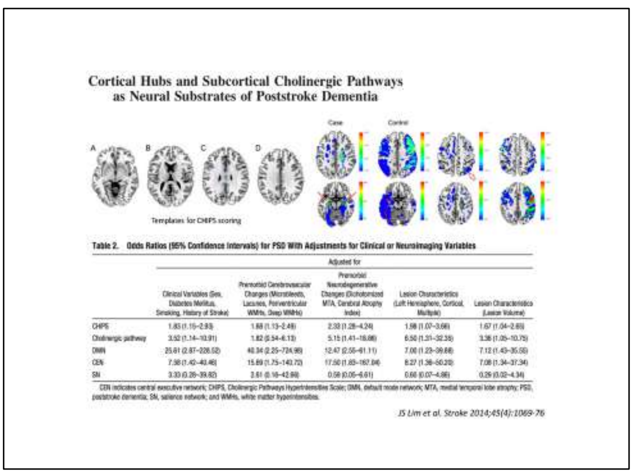
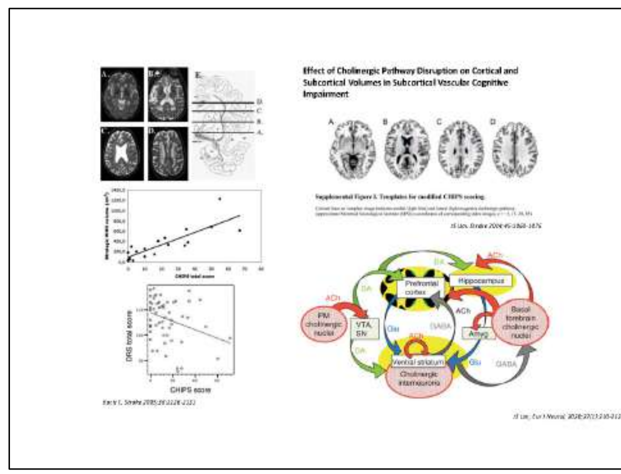
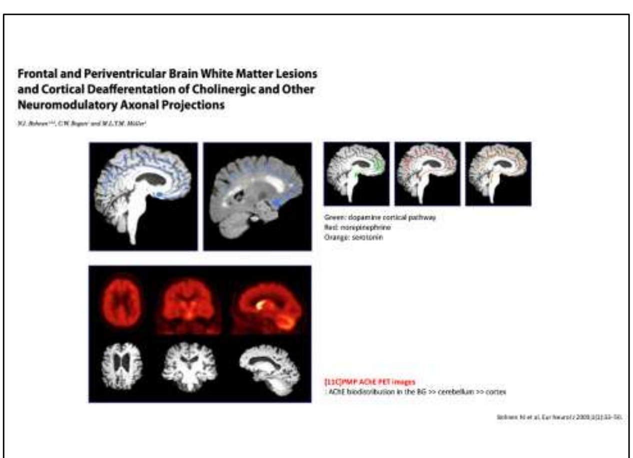


Table 2. Odds Ratios (95% Confidence Intervals) for PSD With Adjustments for Clinical or Neuroimaging Variables

	Adjusted for				
	Clinical Variables (Sex, Diabetes Mellitus, Smoking, History of Stroke)	Premorbid Cerebrovascular Changes (Microbleeds, Lacunes, Periventricular WMHs, Deep WMHs)	Premorbid Neurodegenerative Changes (Dichotomized MTA, Cerebral Atrophy Index)	Lesion Characteristics (Left Hemisphere, Cortical, Multiple)	Lesion Characteristics (Lesion Volume)
CHIPS	1.83 (1.15–2.93)	1.68 (1.13–2.48)	2.32 (1.28–4.24)	1.98 (1.07–3.66)	1.67 (1.04–2.65)
Cholinergic pathway	3.52 (1.14–10.91)	1.82 (0.54–6.13)	5.15 (1.41–18.88)	6.50 (1.31–32.38)	3.38 (1.05–10.75)
DMN	25.61 (2.87–228.52)	40.34 (2.25–724.98)	12.47 (2.55–61.11)	7.00 (1.23–39.88)	7.12 (1.43–35.55)
CEN	7.58 (1.42–40.46)	15.89 (1.75–140.72)	17.50 (1.83–167.04)	8.27 (1.36–50.20)	7.08 (1.34–37.34)
SN	3.33 (0.28–39.82)	2.61 (0.16–42.89)	0.58 (0.05–6.61)	0.60 (0.07–4.86)	0.29 (0.02–4.34)

CEN indicates central executive network; CHIPS, Cholinergic Pathways Hyperintensities Scale; DMN, default mode network; MTA, medial temporal lobe atrophy; PSD, poststroke dementia; SN, salience network; and WMHs, white matter hyperintensities.





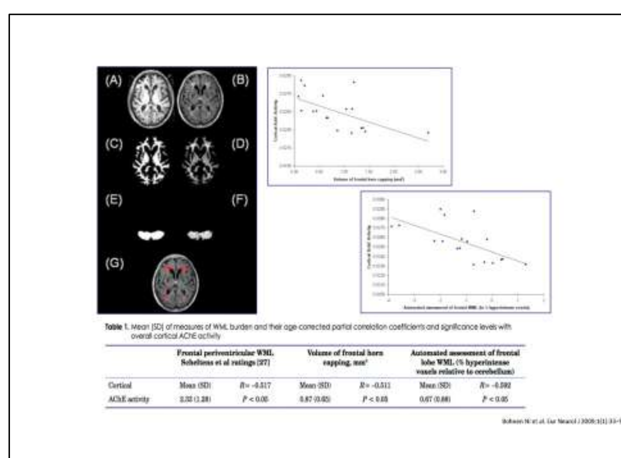
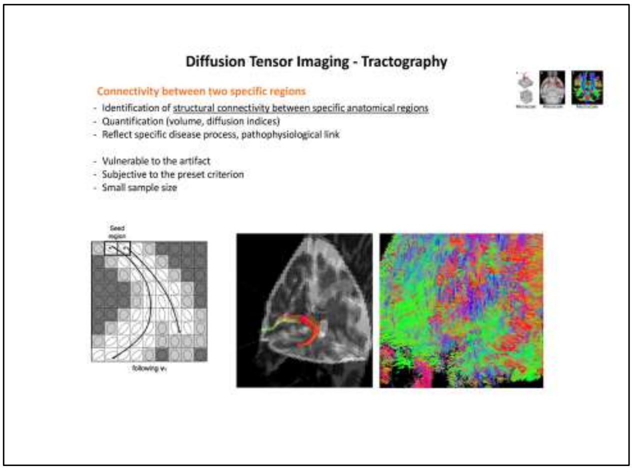
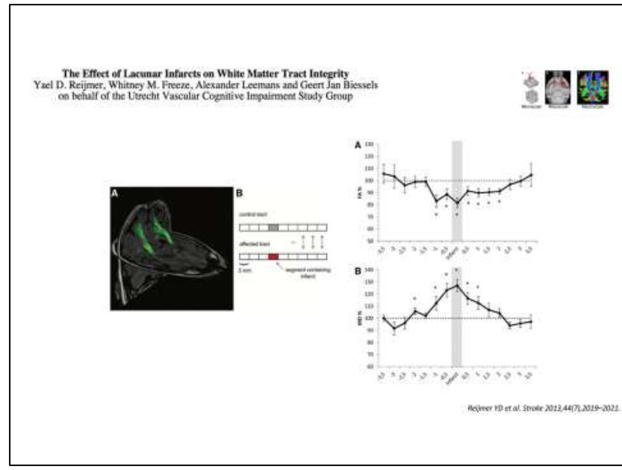
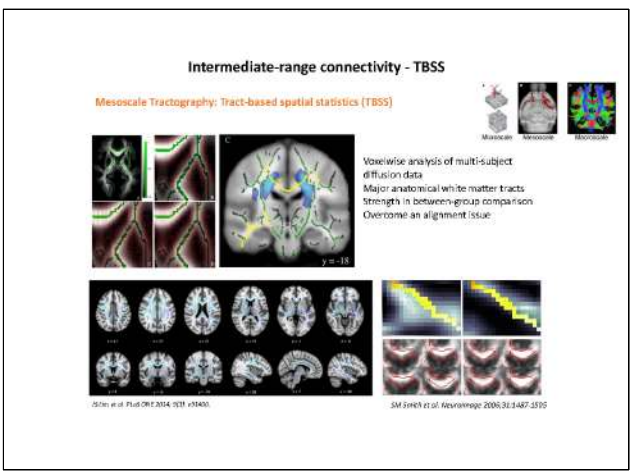


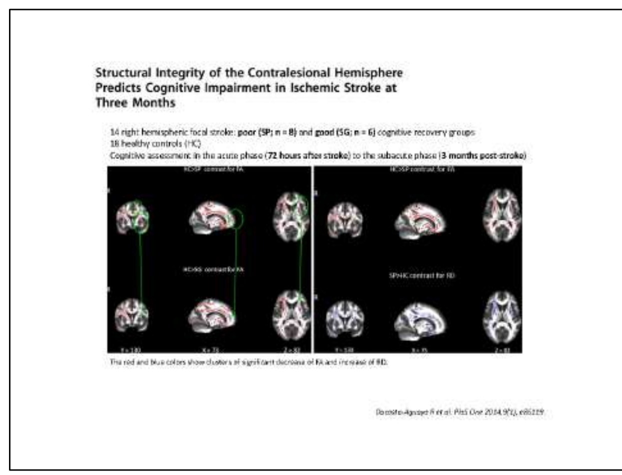
Table 1. Mean (SD) of measures of WML burden and their age-corrected partial correlation coefficients and significance levels with overall cortical AChE activity

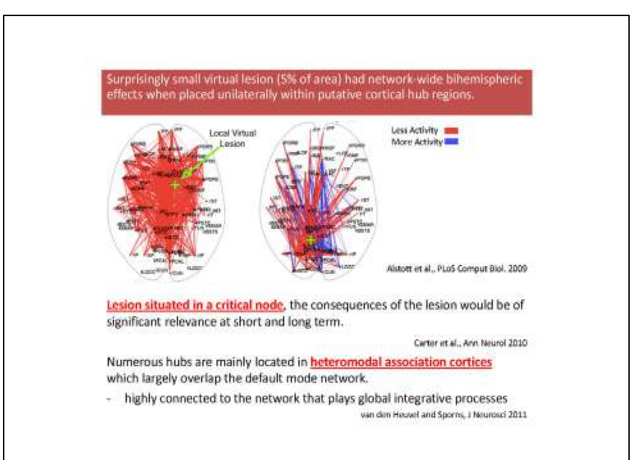
	Frontal periventricular WML Scheltens et al ratings [27]		Volume of frontal horn capping, mm³		Automated assessment of frontal lobe WML (% hyperintense vessels relative to cerebellum)	
Cortical AChE activity	Mean (SD) 2.32 (1.28)	R= −0.517 P < 0.05	Mean (SD) 0.87 (0.65)	R= −0.511 P < 0.05	Mean (SD) 0.67 (0.88)	R= −0.592 P < 0.05

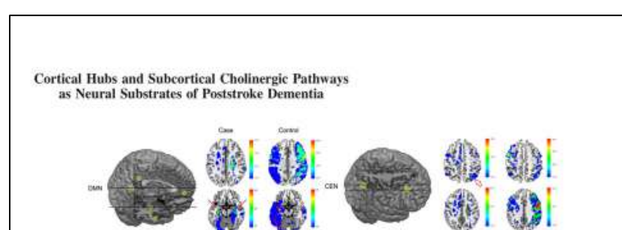












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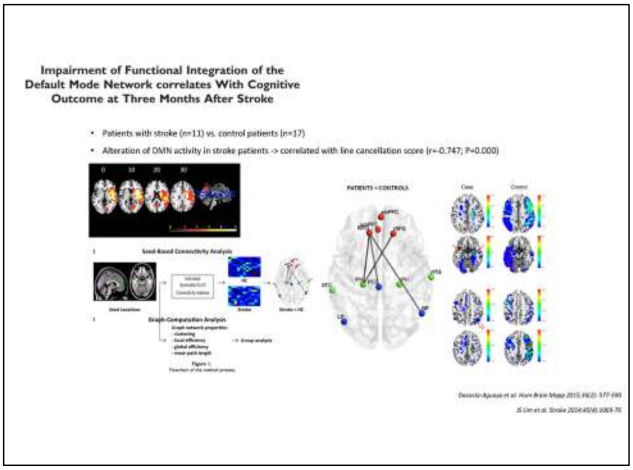
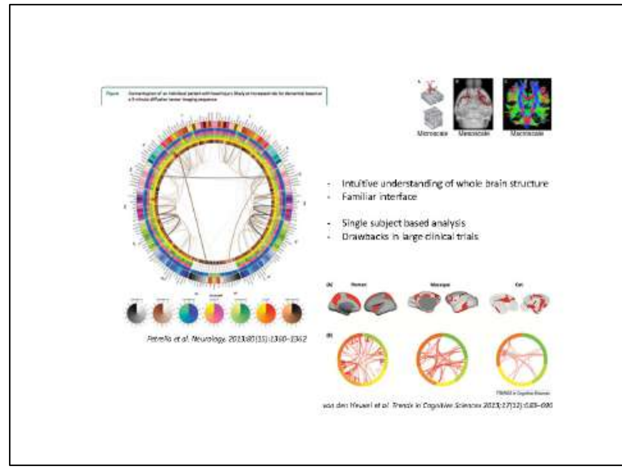
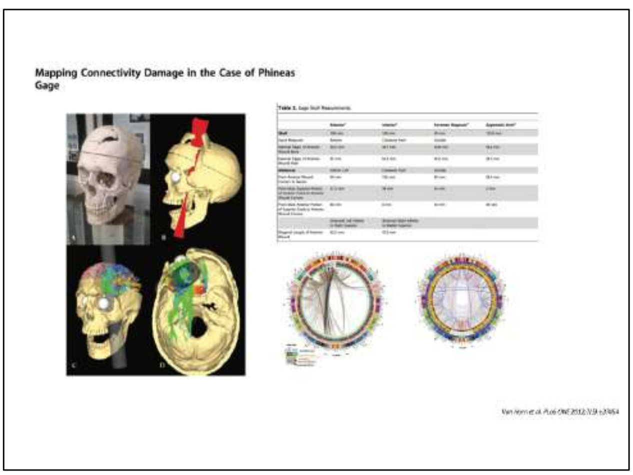
SN	3.33 (0.28–39.62)	2.81 (0.16–42.68)	0.59 (0.05–6.61)	0.60 (0.07–4.86)	0.29 (0.02–4.34)

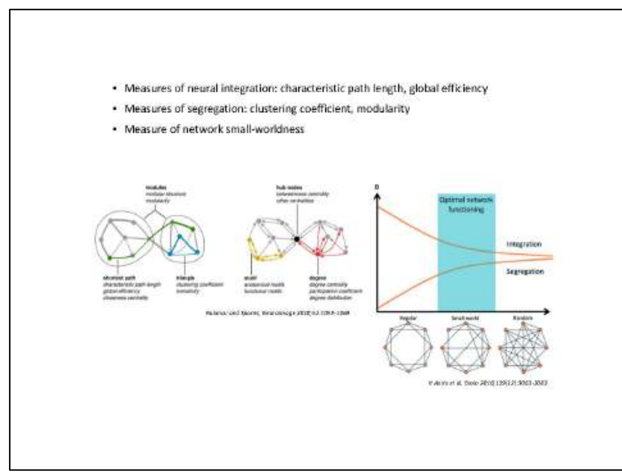
CEN indicates central executive network; CHIPS, Cholinergic Pathways Hyperintensities Scale; DMN, default mode network; MTA, medial temporal lobe atrophy; PSD, poststroke dementia; SN, salience network; and WMHs, white matter hyperintensities.

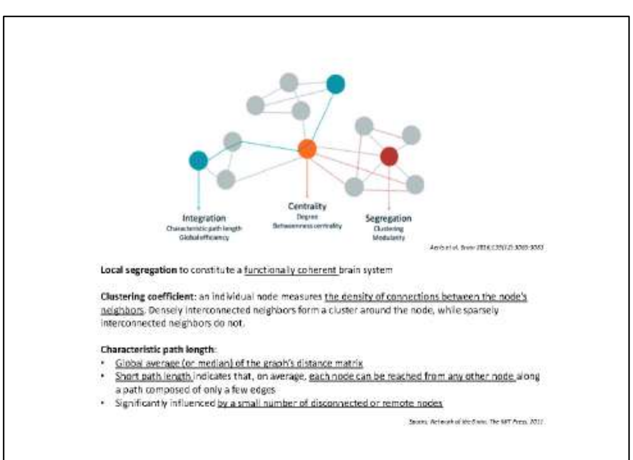
JS Lim et al. Stroke 2014;45(4):1069-76

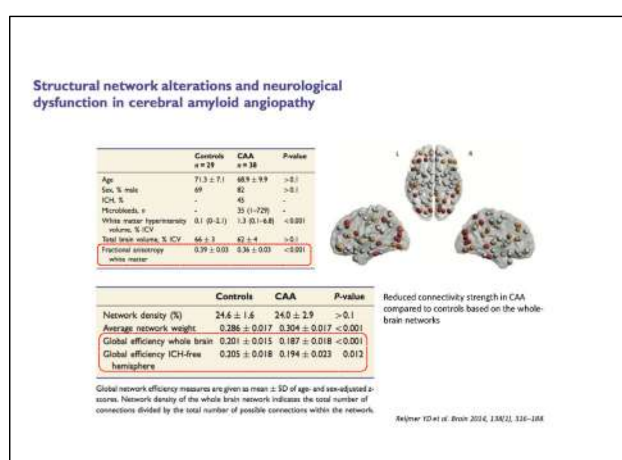






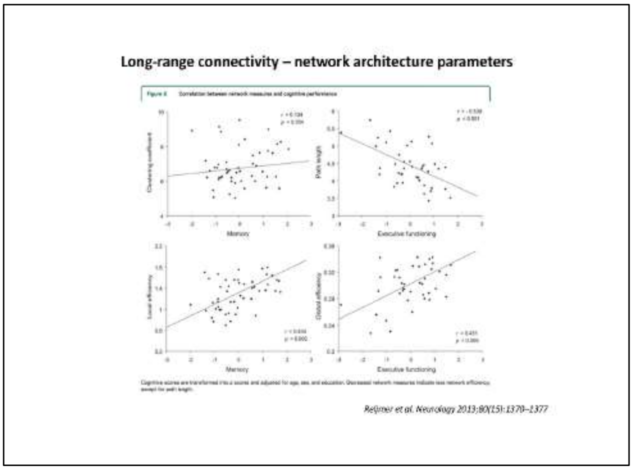


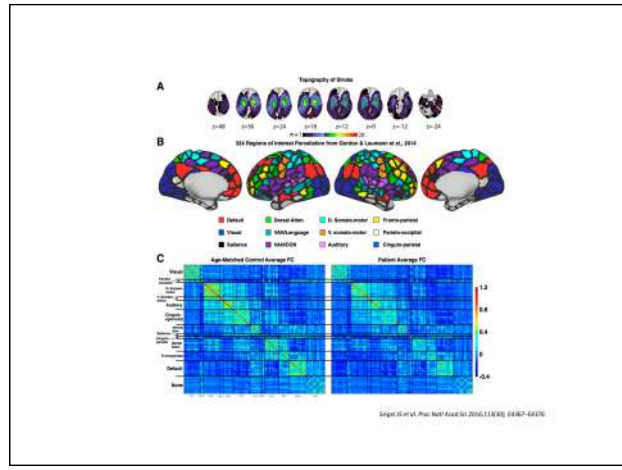


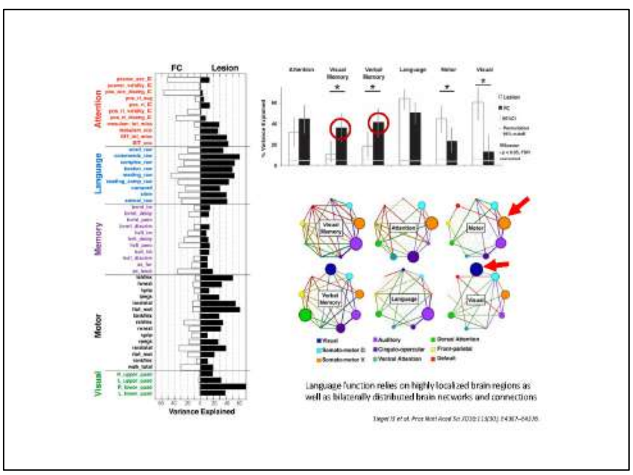


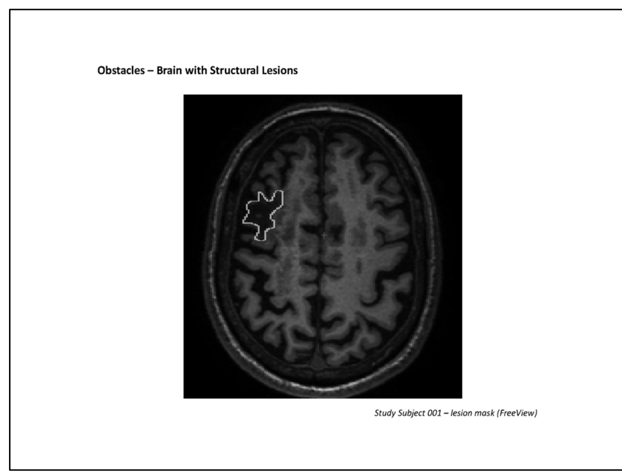
	Controls n = 29	CAA n = 38	P-value
Age	71.3 ± 7.1	68.9 ± 9.9	>0.1
Sex, % male	69	82	>0.1
ICH, %	-	45	-
Microbleeds, n	-	35 (1–729)	-
White matter hyperintensity volume, % ICV	0.1 (0–2.1)	1.3 (0.1–6.8)	<0.001
Total brain volume, % ICV	66 ± 3	62 ± 4	>0.1
Fractional anisotropy white matter	0.39 ± 0.03	0.36 ± 0.03	<0.001

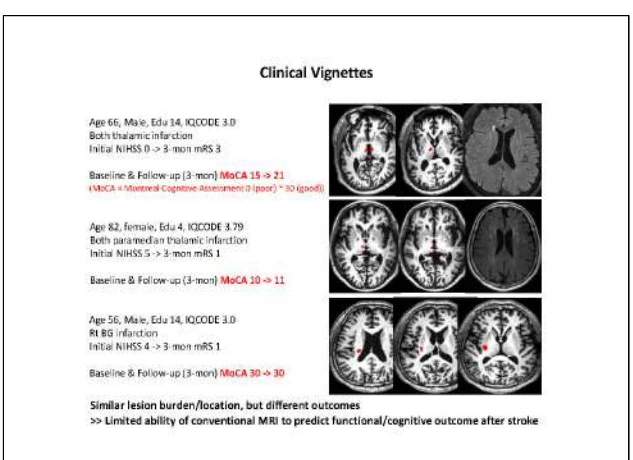
	Controls	CAA	P-value
Network density (%)	24.6 ± 1.6	24.0 ± 2.9	>0.1
Average network weight	0.286 ± 0.017	0.304 ± 0.017	<0.001
Global efficiency whole brain	0.201 ± 0.015	0.187 ± 0.018	<0.001
Global efficiency ICH-free hemisphere	0.205 ± 0.018	0.194 ± 0.023	0.012

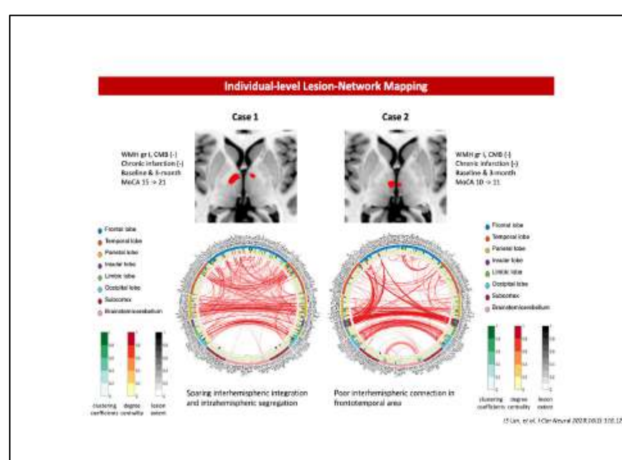

Long-range connectivity – network architecture parameters
Memory
Executive functioning
Reijmer et al. Neurology 2013;80(15):1370–1377

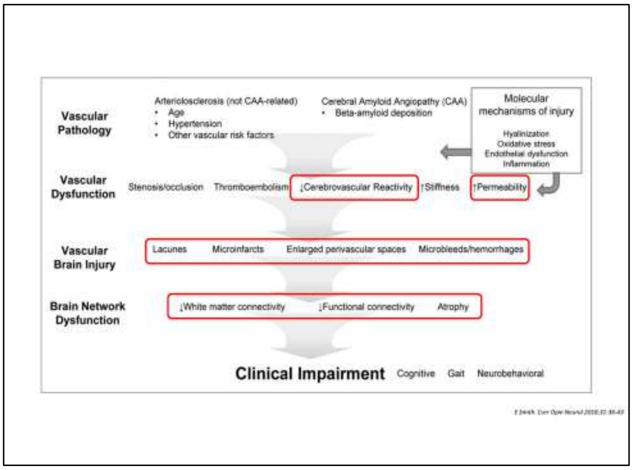

A
Topography of Stroke
B
C
Age-Matched Control Average FC
Patient Average FC


FC
Lesion
Attention
Language
Memory
Motor
Visual
Variance Explained
Language function relies on highly localized brain regions as well as bilaterally distributed brain networks and connections

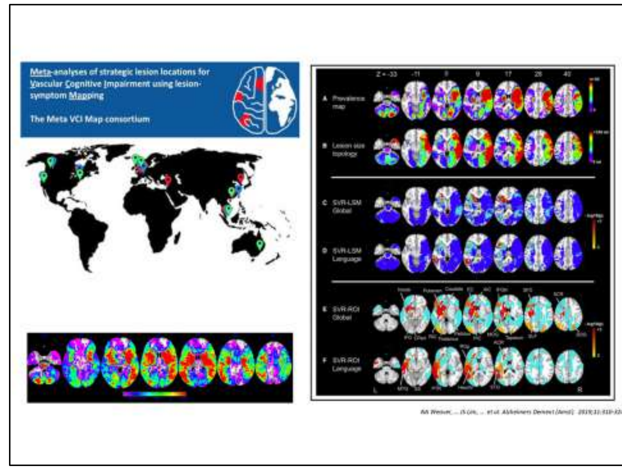

Obstacles – Brain with Structural Lesions
Study Subject 001 – lesion mask (FreeView)


Clinical Vignettes
Age 66, Male, Edu 14, IQCODE 3.0
Both thalamic infarction
Initial NIHSS 0 -> 3-mon mRS 3
Baseline & Follow-up (3-mon) MoCA 15 -> 21
Age 82, female, Edu 4, IQCODE 3.79
Both paramedian thalamic infarction
Initial NIHSS 5 -> 3-mon mRS 1
Baseline & Follow-up (3-mon) MoCA 10 -> 11
Age 56, Male, Edu 14, IQCODE 3.0
Rt BG infarction
Initial NIHSS 4 -> 3-mon mRS 1
Baseline & Follow-up (3-mon) MoCA 30 -> 30
Similar lesion burden/location, but different outcomes
>> Limited ability of conventional MRI to predict functional/cognitive outcome after stroke

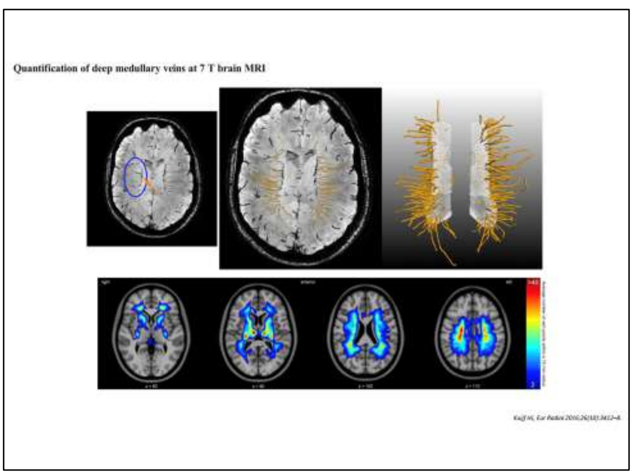

Individual-level Lesion-Network Mapping
Case 1
Case 2
Sparing interhemispheric integration and intrahemispheric segregation
Poor interhemispheric connection in frontotemporal area



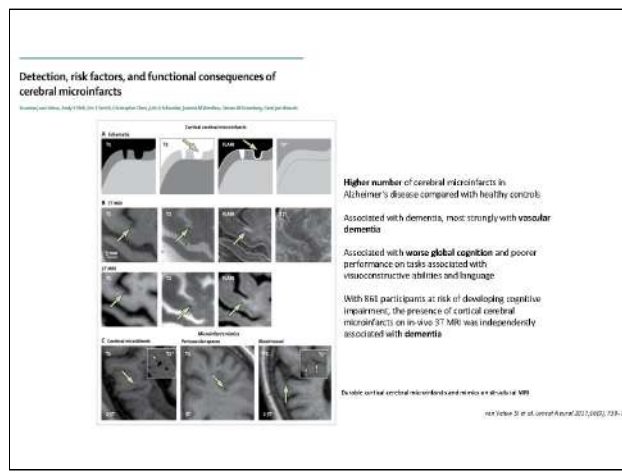
Vascular Pathology
Arteriolosclerosis (not CAA-related)
• Age
• Hypertension
• Other vascular risk factors
Cerebral Amyloid Angiopathy (CAA)
• Beta-amyloid deposition
Molecular mechanisms of injury
Hyalinization
Oxidative stress
Endothelial dysfunction
Inflammation
Vascular Dysfunction
Stenosis/occlusion
Thromboembolism
↓Cerebrovascular Reactivity
↑Stiffness
↑Permeability
Vascular Brain Injury
Lacunes
Microinfarcts
Enlarged perivascular spaces
Microbleeds/hemorrhages
Brain Network Dysfunction
↓White matter connectivity
↓Functional connectivity
Atrophy
Clinical Impairment
Cognitive
Gait
Neurobehavioral



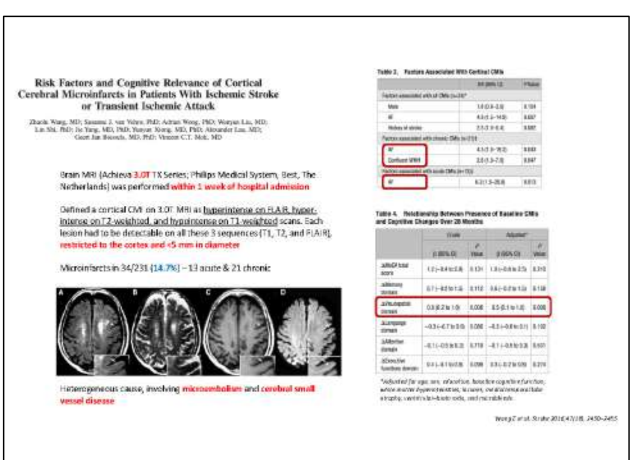
Meta-analyses of strategic lesion locations for Vascular Cognitive Impairment using lesion-symptom Mapping
The Meta VCI Map consortium



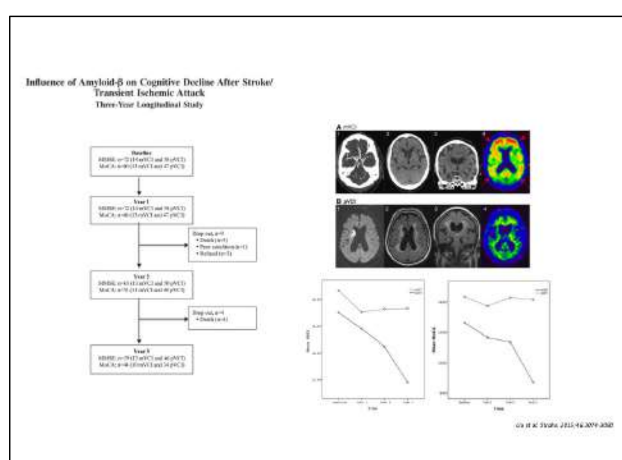
Quantification of deep medullary veins at 7 T brain MRI



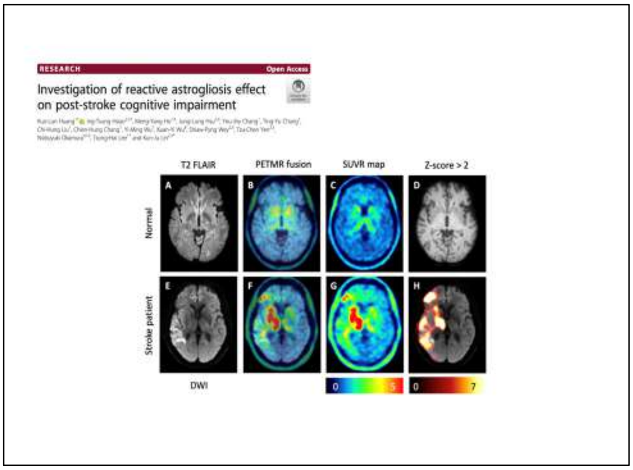
Detection, risk factors, and functional consequences of cerebral microinfarcts
Higher number of cerebral microinfarcts in Alzheimer's disease compared with healthy controls
Associated with dementia, most strongly with vascular dementia
Associated with worse global cognition and poorer performance on tasks associated with visuoconstructive abilities and language
With 861 participants at risk of developing cognitive impairment, the presence of cortical cerebral microinfarcts on in-vivo 3T MRI was independently associated with dementia

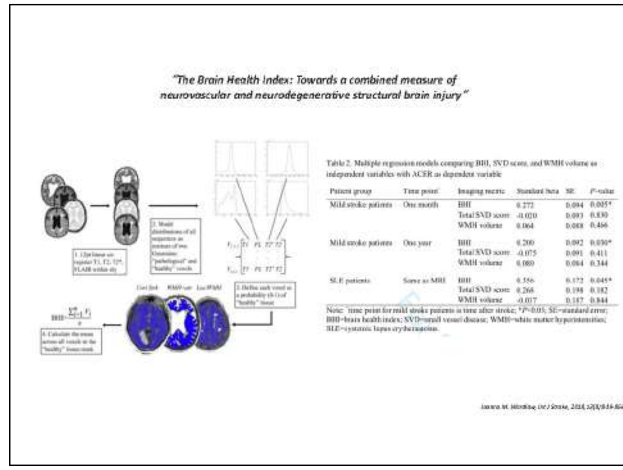


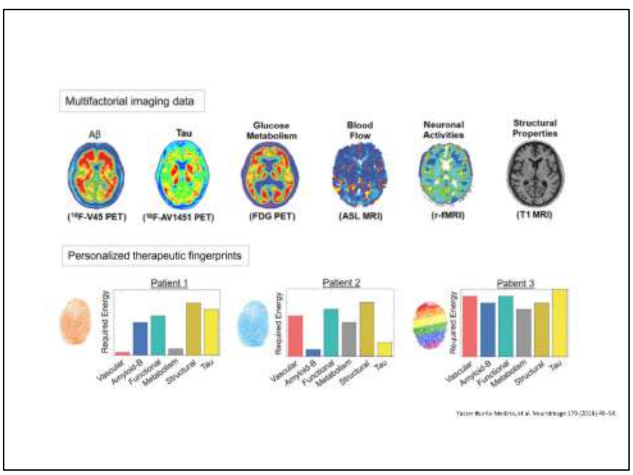
Risk Factors and Cognitive Relevance of Cortical Cerebral Microinfarcts in Patients With Ischemic Stroke or Transient Ischemic Attack
Brain MRI (Achieva 3.0T TX Series; Philips Medical System, Best, The Netherlands) was performed within 1 week of hospital admission
Defined a cortical CMI on 3.0T MRI as hyperintense on FLAIR, hyperintense on T2-weighted, and hypointense on T1-weighted scans. Each lesion had to be detectable on all these 3 sequences (T1, T2, and FLAIR), restricted to the cortex and <5 mm in diameter
Microinfarcts in 34/231 (14.7%) – 13 acute & 21 chronic
Heterogeneous cause, involving microembolism and cerebral small vessel disease

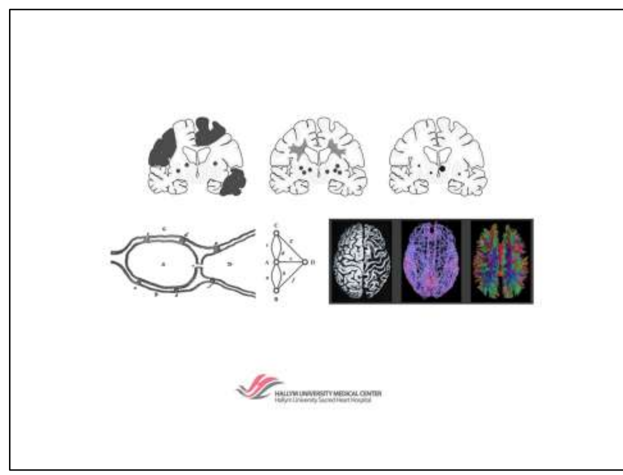


Influence of Amyloid-β on Cognitive Decline After Stroke/Transient Ischemic Attack
Three-Year Longitudinal Study


RESEARCH
Open Access
Investigation of reactive astrogliosis effect on post-stroke cognitive impairment
T2 FLAIR
PETMR fusion
SUVR map
Z-score > 2
Normal
Stroke patient
DWI


"The Brain Health Index: Towards a combined measure of neurovascular and neurodegenerative structural brain injury"
Table 2. Multiple regression models comparing BHI, SVD score, and WMH volume as independent variables with ACER as dependent variable
Patient group | Time point | Imaging metric | Standard beta | SE | P-value
Mild stroke patients | One month | BHI | 0.272 | 0.094 | 0.005*
Total SVD score | -0.020 | 0.093 | 0.830
WMH volume | 0.064 | 0.088 | 0.466
Mild stroke patients | One year | BHI | 0.200 | 0.092 | 0.030*
Total SVD score | -0.075 | 0.091 | 0.411
WMH volume | 0.080 | 0.084 | 0.344
SLE patients | Same as MRI | BHI | 0.356 | 0.172 | 0.045*
Total SVD score | 0.268 | 0.198 | 0.182
WMH volume | -0.037 | 0.187 | 0.844


Multifactorial imaging data
Aβ
Tau
Glucose Metabolism
Blood Flow
Neuronal Activities
Structural Properties
(18F-V45 PET)
(18F-AV1451 PET)
(FDG PET)
(ASL MRI)
(r-fMRI)
(T1 MRI)
Personalized therapeutic fingerprints
Patient 1
Patient 2
Patient 3
Required Energy
Vascular
Amyloid-B
Functional
Metabolism
Structural
Tau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