IL CERVELLO CHE CAMBIA 9

Disordini cognitivi e demenze: Recenti avanzamenti e frontiere di ricerca

Neuroimaging: neuroradiologia

Luca Roccatagliata
Dipartimento di Scienze della Salute (DISSAL)
Università degli Studi di Genova
U.O.C. Neuroradiologia
IRCCS Ospedale Policlinico San Martino Genova

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

DiSSal

UNIVERSITÀ DEGLI STUDI DI GENOVA

ARTICLES

Is dementia incidence declining?

Trends in dementia incidence since 1990 in the Rotterdam Study

E.M.C. Schrijvers, MD, PhD
B.F.J. Verhaaren, MD
P.J. Koudstaal, MD, PhD
A. Hofman, MD, PhD
M.A. Ikram, MD, PhD
M.M.B. Breteler, MD, PhD

Correspondence & reprint requests to Dr. Breteler: Monique.Breteler@dzne.de

ABSTRACT

Objective: To investigate whether dementia incidence has changed over the last 2 decades

Methods: We compared d
years from the Rotterdam
1990 (n = 5,727), the se
and followed for at maxin
the 2 subcohorts in total
compared mortality rates
Finally, we compared brai
who underwent brain ima

Results: In the 1990 subc
the 2000 subcohort (8,384 person-years), 49 persons. Age-adjusted dementia incidence rates were consistently, yet nonsignificantly, lower in the 2000 subcohort in all strata, reaching borderline significance in the overall analysis (incidence rate ratio 0.75, 95% confidence interval [CI] 0.56–1.02). Mortality rates were also lower in the 2000 subcohort (rate ratio 0.63, 95% CI 0.52–0.77). The prevalence of hypertension and obesity significantly increased between 1990 and 2000. This was paralleled by a strong increase in use of antithrombotics and lipid-lowering drugs. Participants in 2005–2006 had larger total brain volumes ($p < 0.001$) and less cerebral small vessel disease (although nonsignificant in men) than participants in 1995–1996.

Conclusions: Although the differences in dementia incidence were nonsignificant, our study suggests that dementia incidence has decreased between 1990 and 2005. *Neurology*® 2012;78: 1456-1463

Table 2 Age-adjusted dementia incidence rates and incidence rate ratios of the 2000 vs the 1990 subcohort[a]

Age stratum, y	Total	Men	Women
All			
Incidence rate 1990	6.56	6.25	6.78
Incidence rate 2000	4.92	4.48	5.20
IRR (95% CI)	0.75 (0.56-1.02)	0.72 (0.44-1.16)	0.77 (0.52-1.14)

Dementia incidence in 2000 vs 1990 declined

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Results: In the 1990 subcohort (25,696 person-years), 286 persons developed dementia, and in the 2000 subcohort (8,384 person-years), 49 persons. Age-adjusted dementia incidence rates were consistently, yet nonsignificantly, lower in the 2000 subcohort in all strata, reaching borderline significance in the overall analysis (incidence rate ratio 0.75, 95% confidence interval [CI] 0.56–1.02). Mortality rates were also lower in the 2000 subcohort (rate ratio 0.63, 95% CI 0.52–0.77). The prevalence of hypertension and obesity significantly increased between 1990 and 2000. This was paralleled by a strong increase in use of antithrombotics and lipid-lowering drugs. Participants in 2005–2006 had larger total brain volumes ($p < 0.001$) and less cerebral small vessel disease (although nonsignificant in men) than participants in 1995–1996.

Conclusions: Although the differences in dementia incidence were nonsignificant, our study suggests that dementia incidence has decreased between 1990 and 2005. *Neurology*® 2012;78: 1456-1463

Total brain volume (% of ICV), mean (SE)		
1995–1996	78.2 (0.2)	79.0 (0.2)
2005–2006	80.7 (0.1)	82.7 (0.1)
***p* Value**	<0.001	<0.001
WML volume (% of ICV), mean (SE)		
1995–1996	0.83 (0.06)	1.34 (0.08)
2005–2006	0.68 (0.05)	0.79 (0.06)
***p* Value[b]**	0.49	<0.001

Neuroimaging

Larger brain volume in 2000 cohort

Lower WMH burden in 2000 cohort

Vascular Dementia: imaging criteria

Vascular dementia caused by vascular pathology

DSM V and NINDS-AIREN criteria for diagnosis

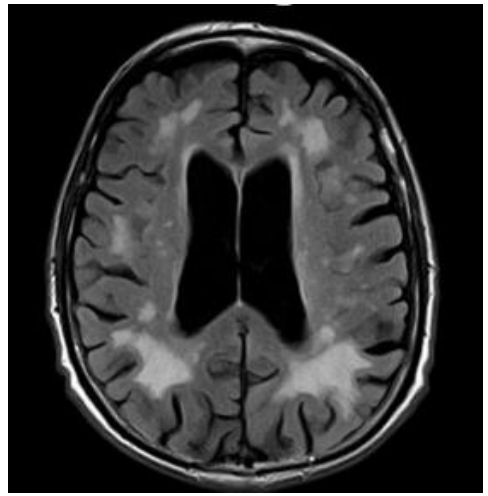
Small vessel disease:

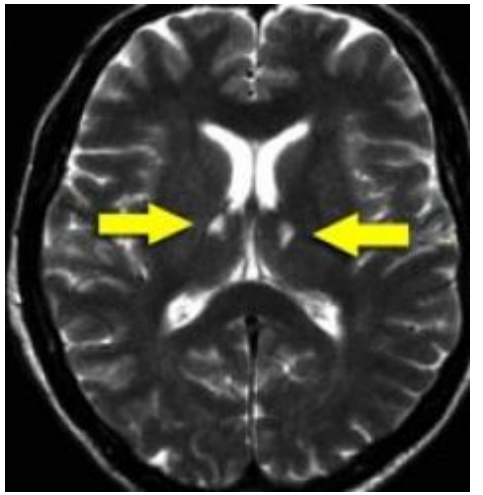
Either >25% of white matter involved

OR >=2 lacunar infarcts in basal ganglia/internal capsule

AND >=2 lacunar infarcts frontal WM

OR bilateral thalamic infarcts





Roman GC Neurology 1993

Vascular cognitive impairment (VCI)

VCI: contribution of vascular pathology to any severity of cognitive impairment, ranging from subjective cognitive decline and mild cognitive impairment to dementia

The key requirements for a diagnosis of VCI are:

(1) demonstration of a cognitive deficit by neuropsychological testing

(2) presence of cerebrovascular disease at imaging

VCI refers to all forms of cognitive deficits of vascular origin ranging from MCI to dementia. Diagnosis must be based on cognitive testing involving a minimum of 4 cognitive domains, including executive/attention, memory, language, and visuospatial functions.
Vascular dementia (VaD) requires a decline in cognitive function and a deficit in performance in ≥2 cognitive domains that are of sufficient severity to affect activities of daily living.
Vascular mild cognitive impairment (VaMCI) includes 4 subtypes: amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domain; VaMCI should be based on the assumption of a decline in cognitive function. Activities of daily living may be normal or mildly impaired.
Probable: A diagnosis of probable VaD or VaMCI requires the following:
(1) Imaging evidence of cerebrovascular disease and (a) a clear temporal relationship between a vascular event (eg, stroke) and onset of cognitive deficits or (b) a clear relationship between the severity and pattern of cognitive impairment and the presence of diffuse subcortical vascular pathology;
(2) Absence of a history of gradually progressive cognitive deficits, suggesting the presence of neurodegenerative disease.
Possible: A diagnosis of possible VaD or VaMCI requires imaging evidence of cerebrovascular disease and should be made if there is no clear relationship between vascular disease and cognitive impairment, if the criteria for probable VaD or VaMCI are not fulfilled, if aphasia precludes proper cognitive assessment, or if there is a history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.
Unstable VaMCI: subjects with probable of possible VaMCI whose symptoms revert to normal

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Unstable VaMCI: subjects with probable of possible VaMCI whose symptoms revert to normal

The key requirements for a diagnosis of VCI are:

(1) demonstration of a cognitive deficit by neuropsychological testing

(2) presence of cerebrovascular disease at imaging

Includes cases with mixed pathologies, such as mixed vascular and AD-type pathologies

Mixed pathology effects on Loss of Microstructural Integrity

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SCIENTIFIC REPORTS

OPEN

Correlations between Gray Matter and White Matter Degeneration in Pure Alzheimer's Disease, Pure Subcortical Vascular Dementia, and Mixed Dementia

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Hyemin Jang[1,4], Hunki Kwon[5], Jin-Ju Yang[5], Jinwoo Hong[5], Yeshin Kim[1,4], Ko Woon Kim[6], Jin San Lee[7], Young Kyoung Jang[1,4], Sung Tae Kim[2], Kyung Han Lee[3], Jae Hong Lee[8], Duk L. Na[1,4,9,10], Sang Won Seo[1,4,9,11], Hee Jin Kim[1,4] & Jong-Min Lee[5]

Evaluation of different patterns of correlation between gray matter (GM) and WM microstructural changes in pure ADD, pure SVaD, and mixed dementia.

40 Pittsburgh compound B (PiB) positive ADD patients without WM hyperintensities (pure ADD)

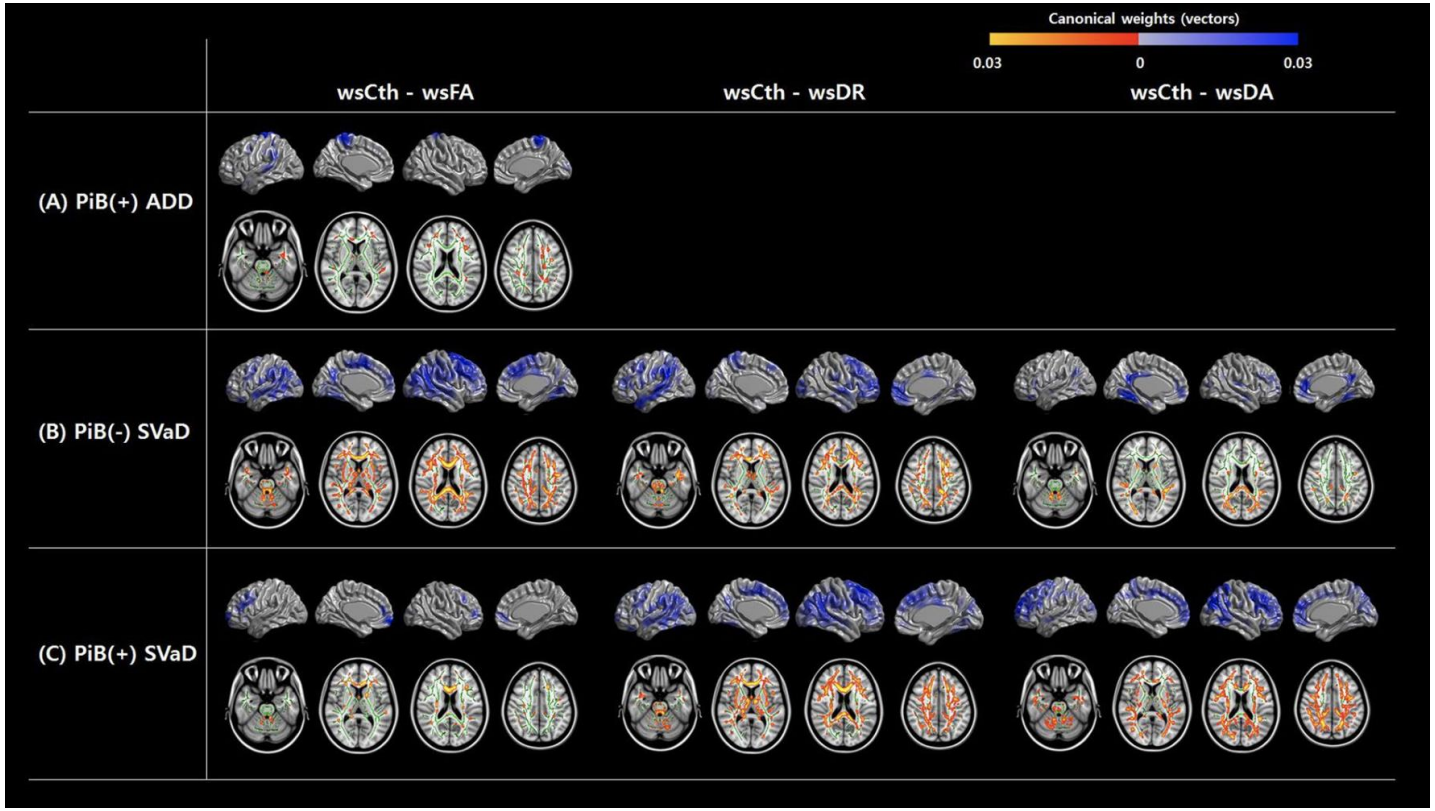
32 PiB negative SVaD patients (pure SVaD)

23 PiB positive SVaD patients (mixed dementia)

56 normal controls

WM microstructural integrity quantified by DWI using fractional anisotropy (FA), axial diffusivity (DA), and radial diffusivity (DR) value

Correlation between cortical thickness and white matter integrity



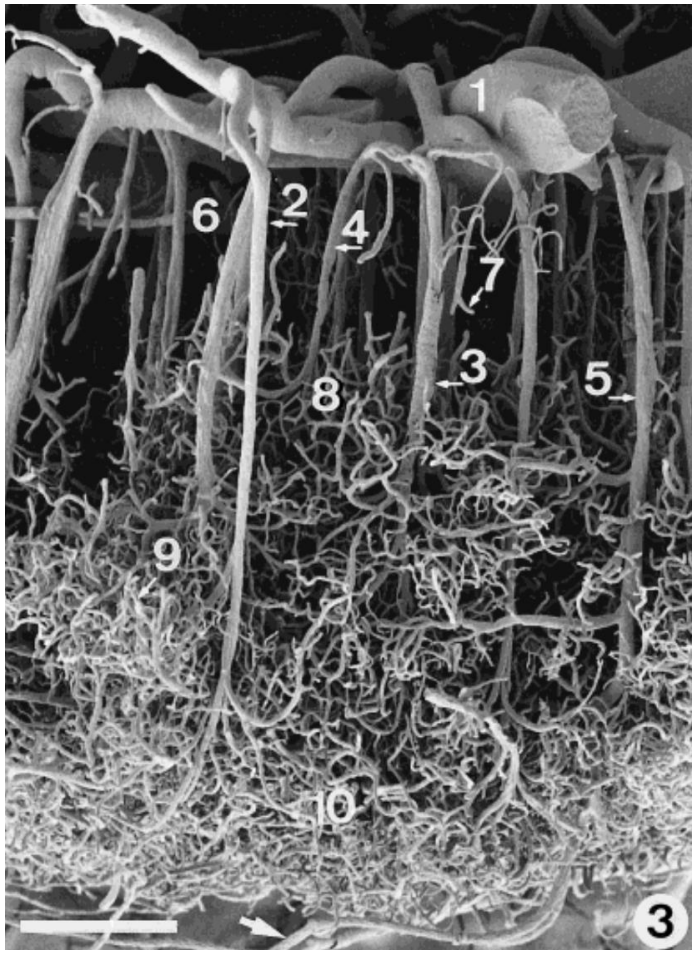
In the pure ADD group, disruption of WM integrity was minimal with lower DA in WM adjacent to the cortex

In pure SVaD and mixed dementia, there was extensive disruption of WM integrity with higher DR and overall higher DA, but lower DA in WM adjacent to the cortex

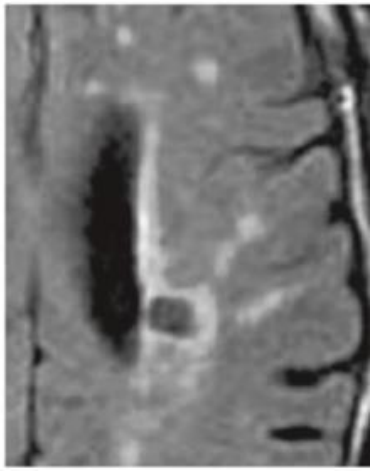
Cortical thinning in pure SVaD strongly correlated with changes in FA and DR, while cortical thinning in mixed dementia strongly correlated with changes in DR and DA

These findings suggest that the relationship between GM and WM degeneration differs according to the underlying pathobiology

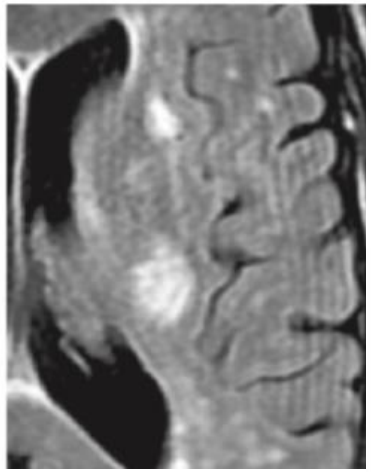
Imaging of SVD



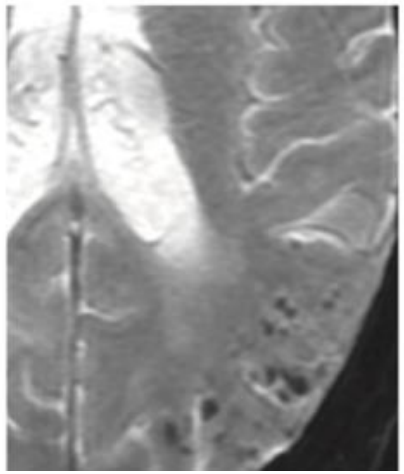
Lacune



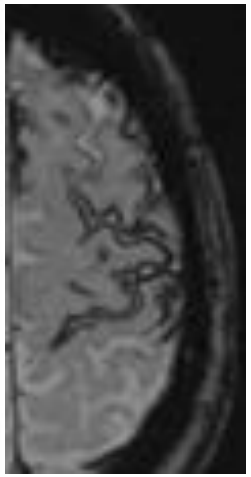
White matter hyperintensity

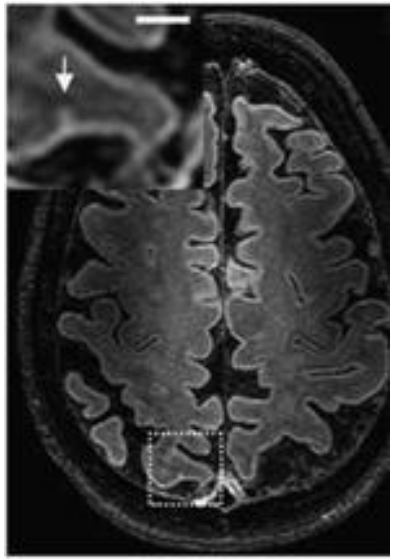


Cerebral microbleed



Superficial siderosi

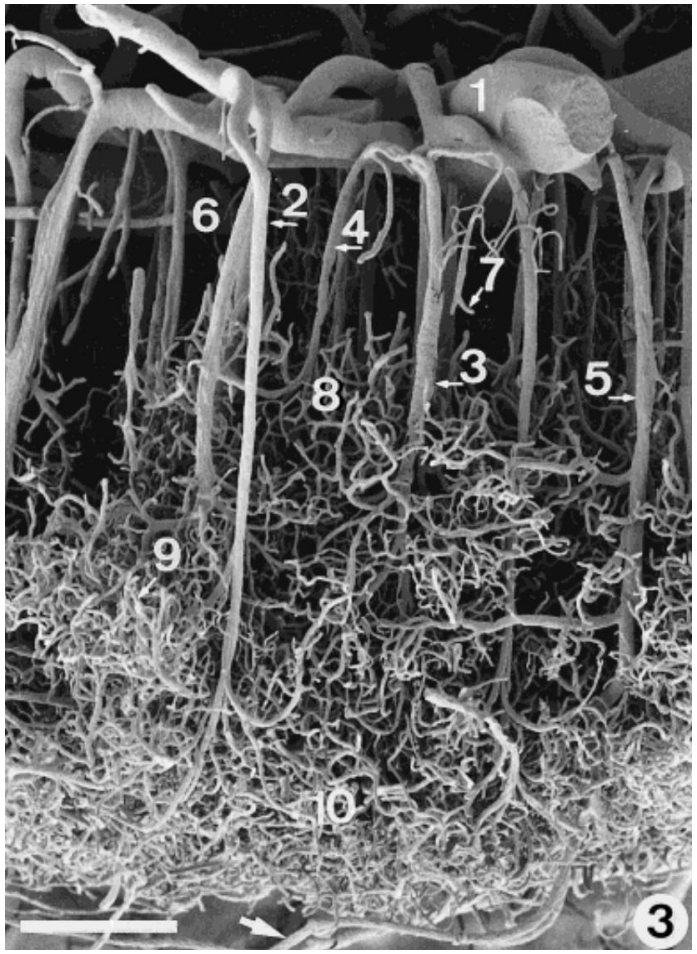


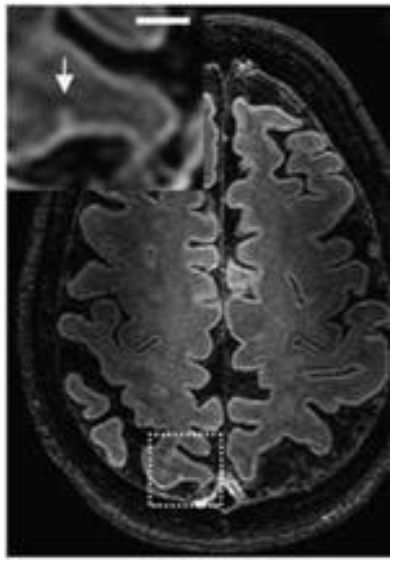


cortical cerebral microinfarcts

Brain volume loss (“atrophy”)

Loss in microstructural integrity of the white matter

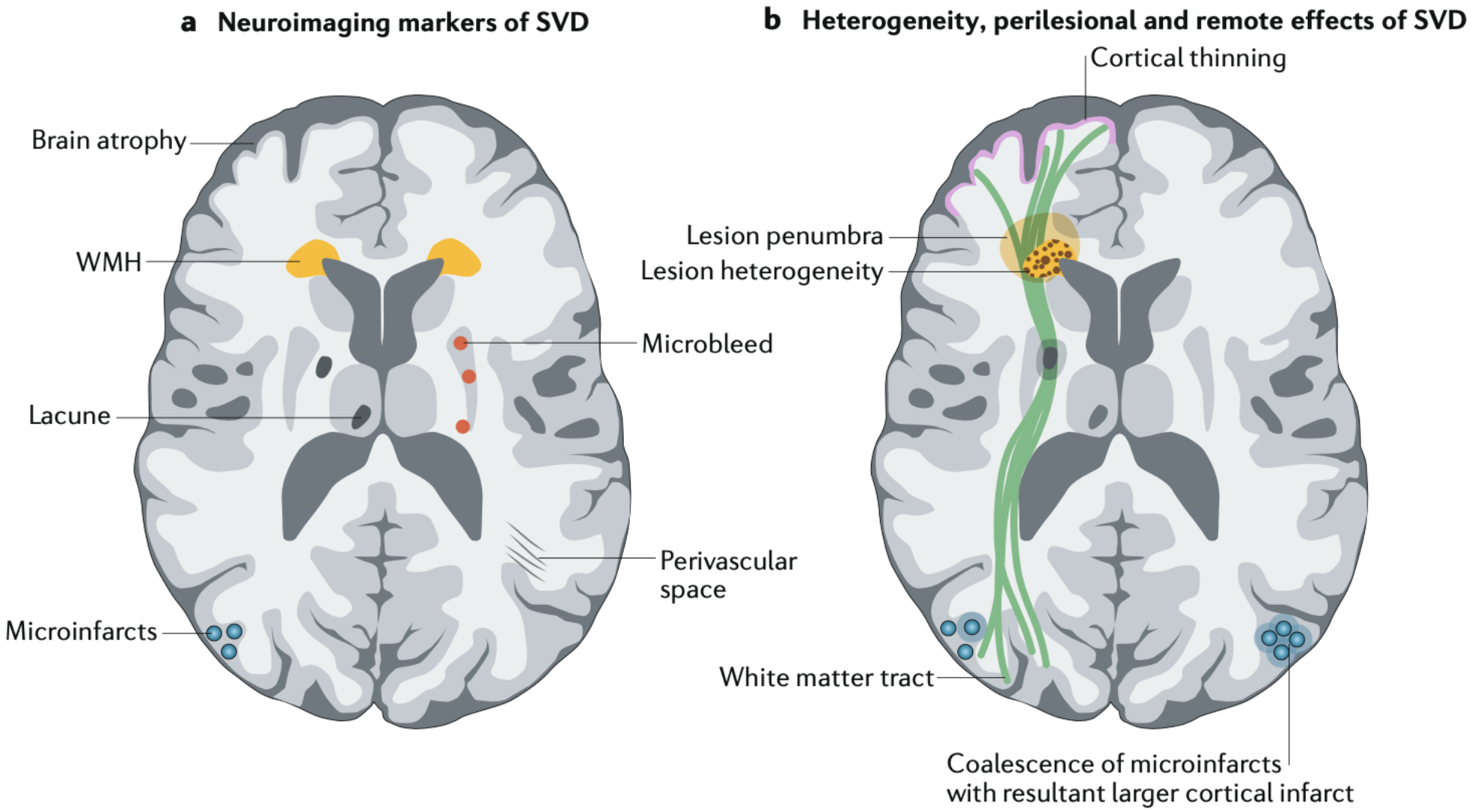




cortical cerebral microinfarcts

Loss in microstructural integrity of the white matter

Connectivity studies: Loss in microstructural integrity of the white matter



From: tertelgte et al. Nature reviews Neurology 2018

ARTICLES

Structural network efficiency is associated with cognitive impairment in small-vessel disease

OPEN

Andrew J. Lawrence, PhD
Ai Wern Chung, PhD
Robin G. Morris, PhD
Hugh S. Markus, FRCP*
Thomas R. Barrick, PhD*

Correspondence to
Dr. Lawrence:
alawrenc@sgul.ac.uk

ABSTRACT

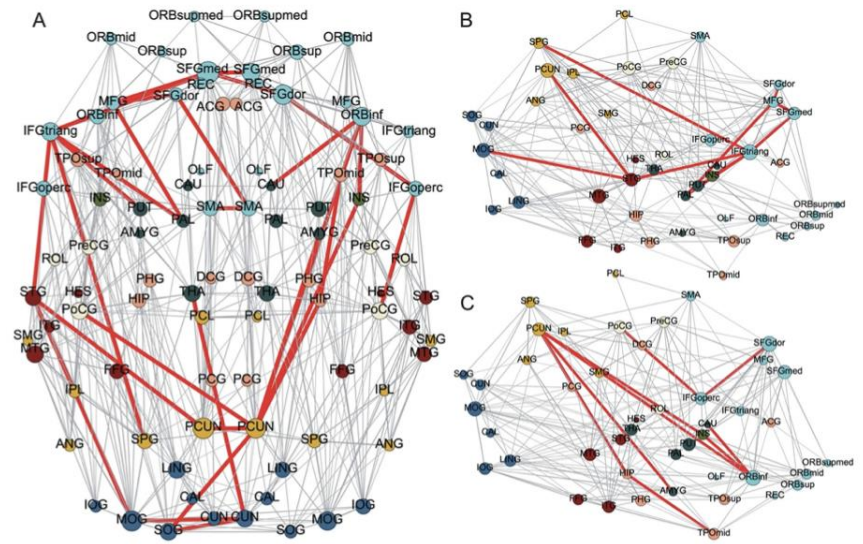
Objective: To characterize brain network connectivity impairment in cerebral small-vessel disease (SVD) and its relationship with MRI disease markers and cognitive impairment.

Methods: A cross-sectional design applied graph-based efficiency analysis to deterministic diffusion tensor tractography data from 115 patients with lacunar infarction and leukoaraiosis and 50 healthy individuals. Structural connectivity was estimated between 90 cortical and subcortical brain regions and efficiency measures of resulting graphs were analyzed. Networks were compared between SVD and control groups, and associations between efficiency measures, conventional MRI disease markers, and cognitive function were tested.

Results: Brain diffusion tensor tractography network connectivity was significantly reduced in SVD: networks were less dense, connection weights were lower, and measures of network efficiency were significantly disrupted. The degree of brain network disruption was associated with MRI measures of disease severity and cognitive function. In multiple regression models controlling for confounding variables, associations with cognition were stronger for network measures than other MRI measures including conventional diffusion tensor imaging measures. A total mediation effect was observed for the association between fractional anisotropy and mean diffusivity measures and executive function and processing speed.

Conclusions: Brain network connectivity in SVD is disturbed, this disturbance is related to disease severity, and within a mediation framework fully or partly explains previously observed associations between MRI measures and SVD-related cognitive dysfunction. These cross-sectional results highlight the importance of network disruption in SVD and provide support for network measures as a disease marker in treatment studies. *Neurology*® 2014;83:304–311

Figure 1 Subnetwork identified as impaired in patients with small-vessel disease relative to controls



Contents lists available at ScienceDirect

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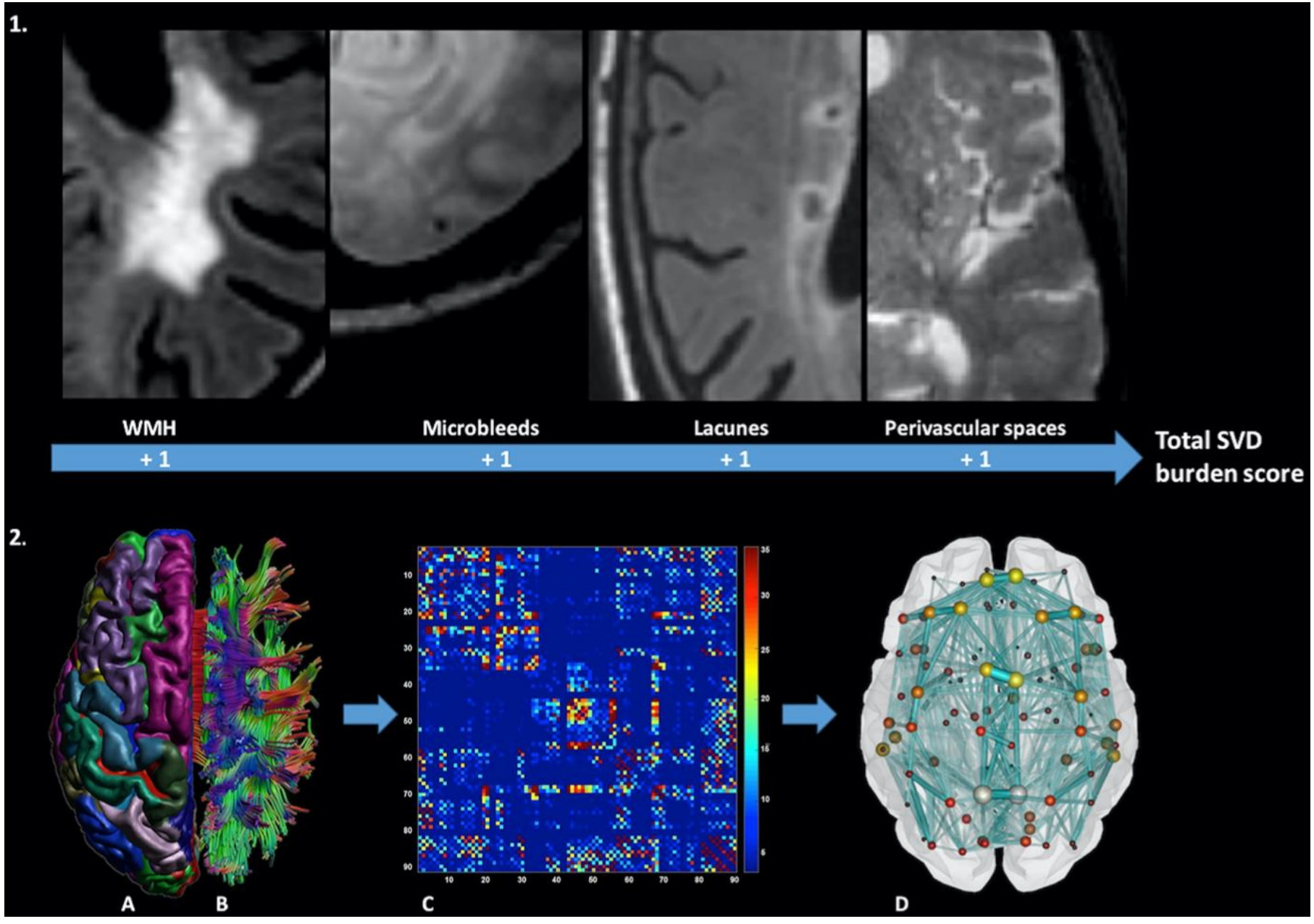
journal homepage: www.elsevier.com/locate/ynicl

The cumulative effect of small vessel disease lesions is reflected in structural brain networks of memory clinic patients

Rutger Heinen[a,1], Naomi Vlegels[a,*,1], Jeroen de Bresser[b,c], Alexander Leemans[d], Geert Jan Biessels[a], Yael D. Reijmer[a], On behalf of the Utrecht Vascular Cognitive Impairment study group

Methods: 173 patients from the memory clinic of the University Medical Center Utrecht underwent a 3 T brain MRI scan (including diffusion MRI sequences) and neuropsychological testing. MRI markers for SVD were rated and compiled in a previously developed total SVD score. Structural brain networks were reconstructed using fiber tractography followed by graph theoretical analysis. The relationship between total SVD burden score, global network efficiency and cognition was assessed using multiple linear regression analyses.

The cumulative effect of small vessel disease lesions is reflected in structural brain networks of memory clinic patients



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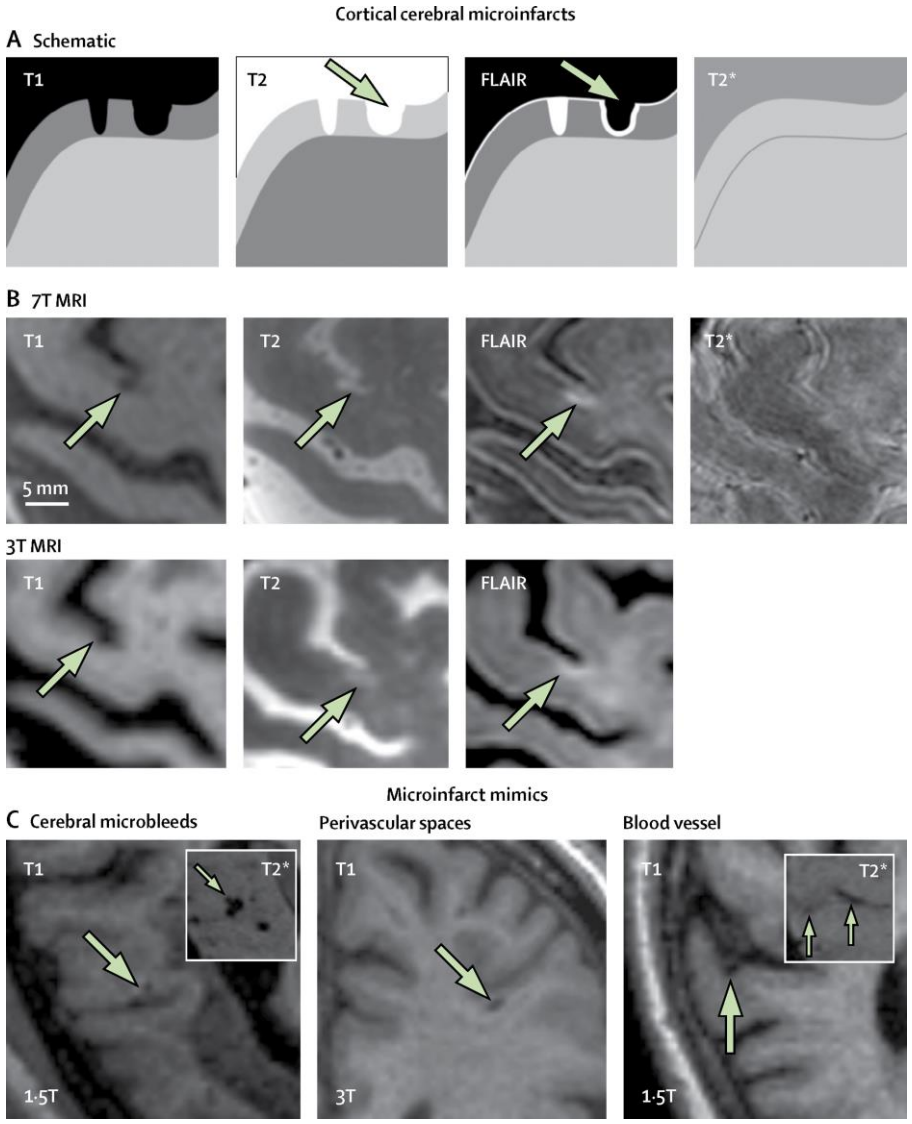
Results: Each point increase on the SVD burden score was associated with 0.260 [−0.404 - -0.117] SD units decrease of global brain network efficiency ($p < .001$). Global network efficiency was associated with information processing speed (standardized $B = -0.210$, $p = .004$) and attention and executive functioning ($B = 0.164$, $p = .042$), and mediated the relationship between SVD burden and information processing speed ($p = .027$) but not with executive functioning ($p = .12$).

Conclusion: Global network efficiency is sensitive to the cumulative effect of multiple manifestations of SVD on brain connectivity. Global network efficiency may therefore serve as a useful marker for functionally relevant SVD-related brain injury in clinical trials.

Imaging biomarkers of SVD: new players



Cortical cerebral micro-infarcts

Used to be “invisible lesions”

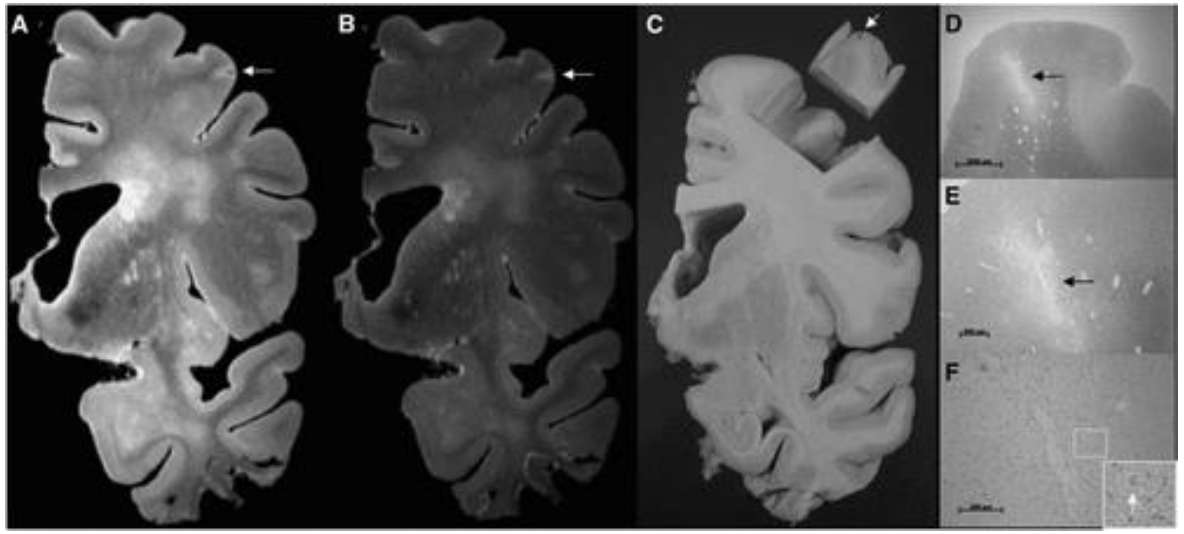
< 1-2 mm in size

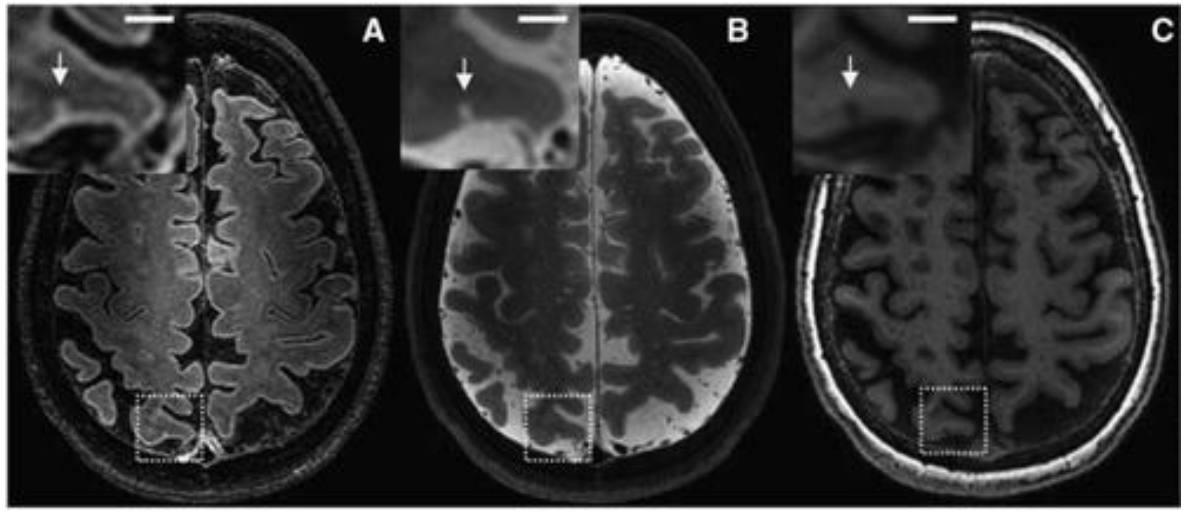
Neuropathology: 24% in non-demented

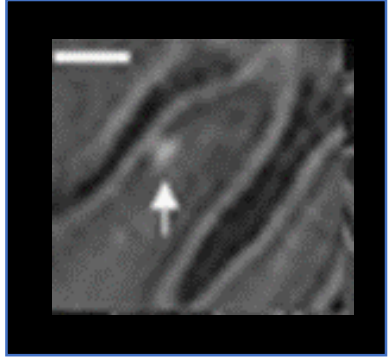
7 tesla > 3 Tesla

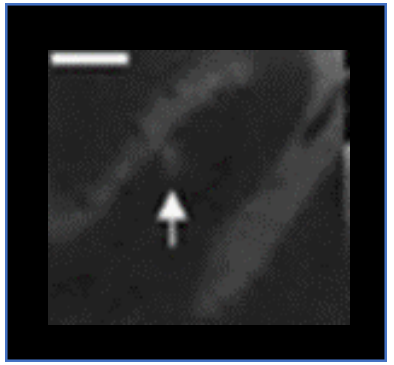
Independent relation to dementia and cognitive impairment

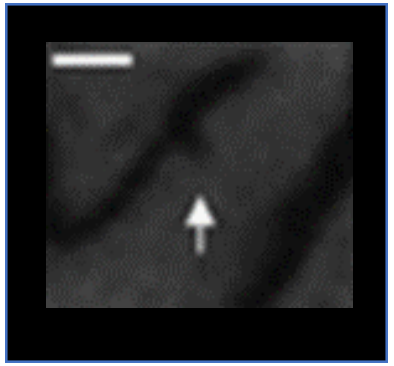
The invisible lesions:
cortical cerebral microinfarcts

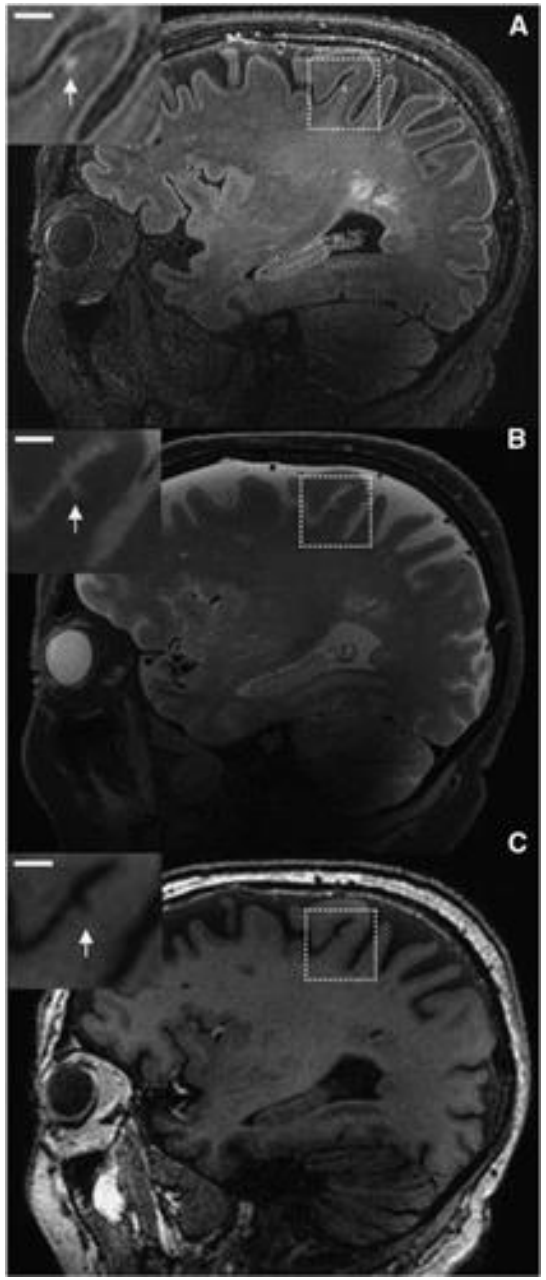












van Veluw SJ et al In Vivo Detection of Cerebral Cortical Microinfarcts with High-Resolution 7T MRI JCBFM

Original Article

JCBFM

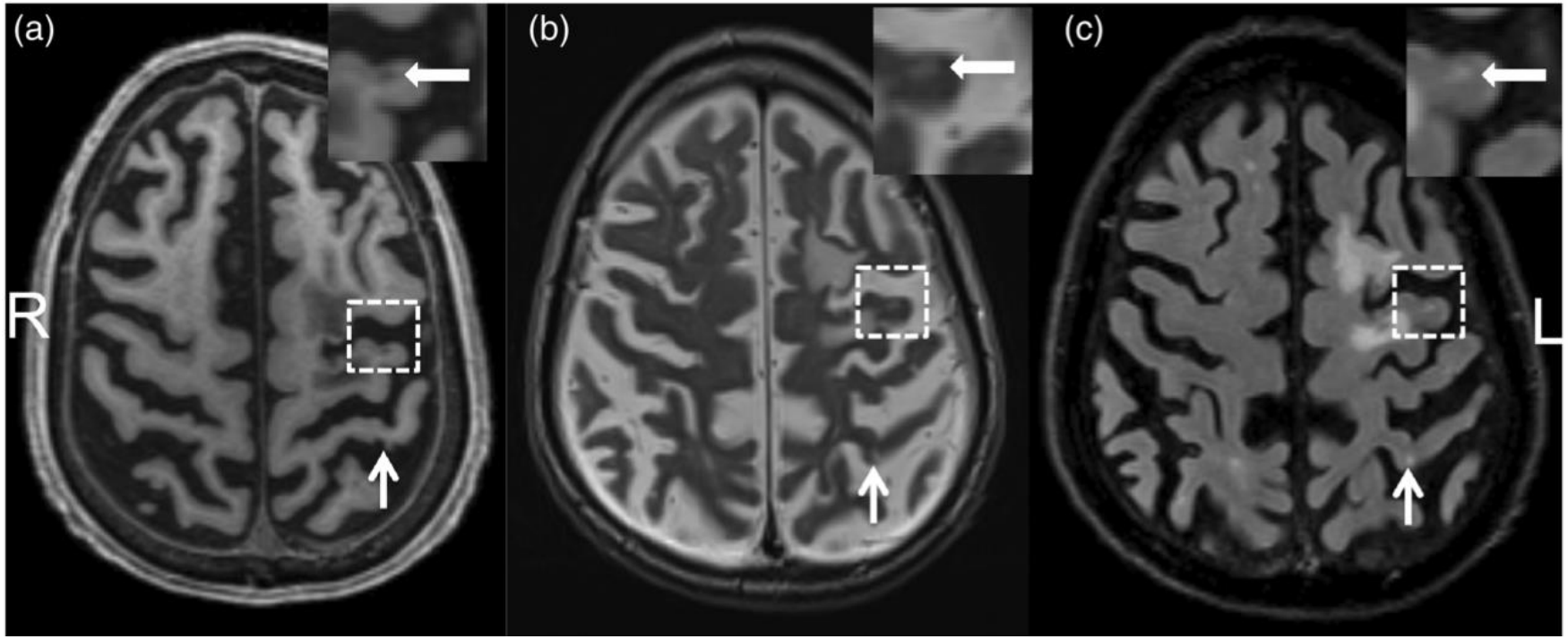
Journal of Cerebral Blood Flow & Metabolism
0(0) 1–10

DOI: 10.1177/0271678X19835565
journals.sagepub.com/home/jcbfm

SAGE

Cortical cerebral microinfarcts predict cognitive decline in memory clinic patients

Saima Hilal[1,2,3], Chuen Seng Tan[4], Susanne J van Veluw[5,6], Xin Xu[1,2], Henri Vrooman[7], Boon Y Tan[8], Narayanaswamy Venketasubramanian[9], Geert J Biessels[6] and Christopher Chen[1,2,10]



313 patients with baseline 3T MRI scans

At least two neuropsychological assessments

Cortical CMIs graded on baseline MRI

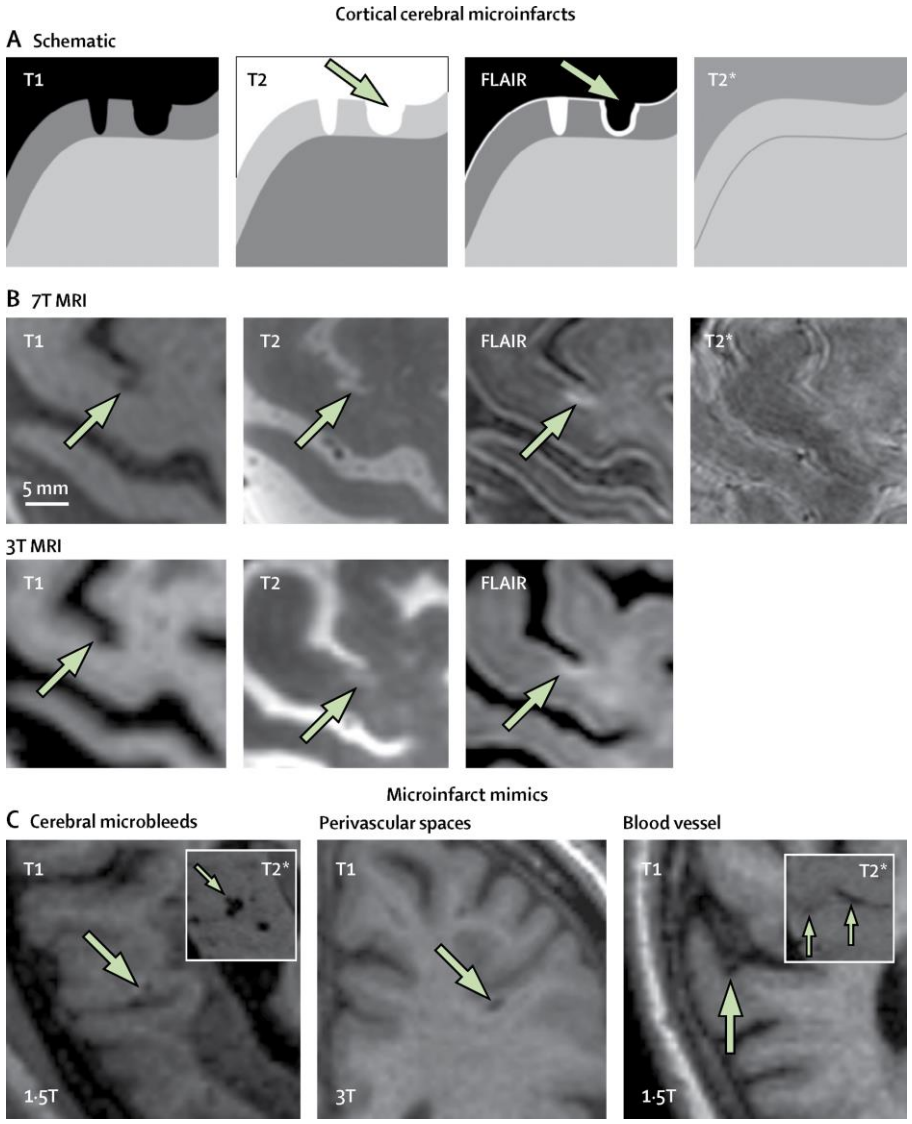
The Montreal Cognitive Assessment (MoCA) and a neuropsychological battery to assess cognition

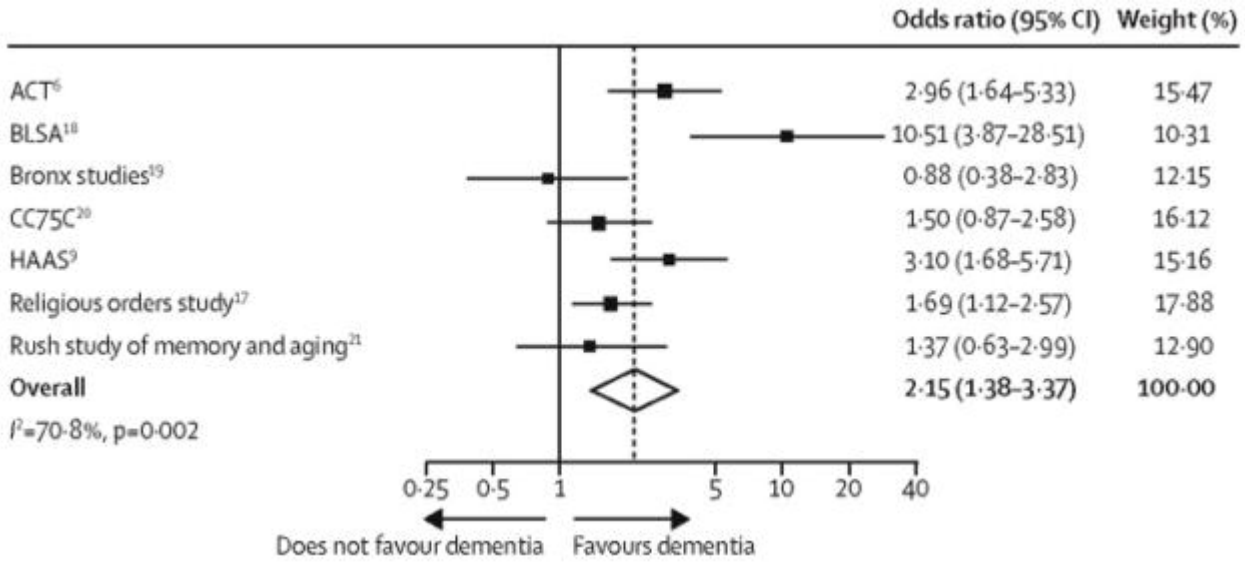
Patients with increased cortical CMIs showed greater decline in MoCA and global cognition per year

Patients with > 2 cortical CMIs decline on average by 2 scores on MoCA and 0.5 on global cognition at year two

Furthermore, cortical CMIs at baseline were associated with accelerated decline in memory and language domains

Imaging biomarkers of SVD: new players



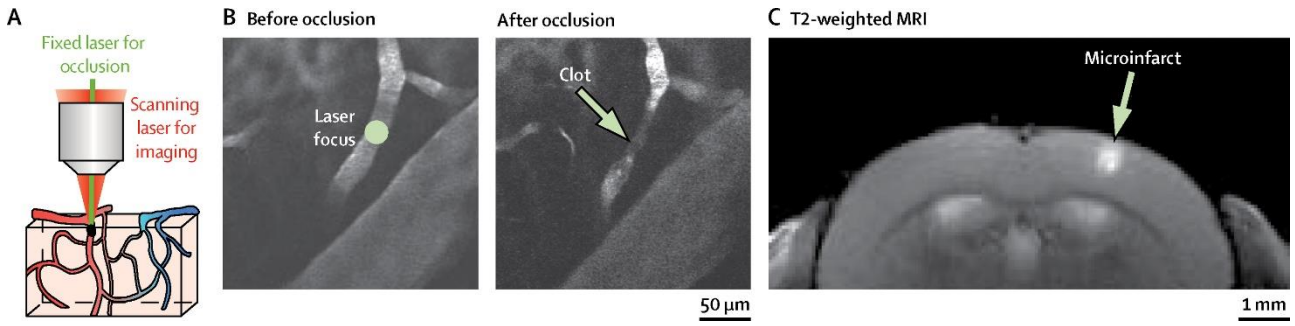


Pooled Odds of Dementia in Persons with cortical microinfarcts

Causes of cerebral microinfarcts (CM)

CM have multiple underlying causes, which can coexist in a single patient:

1) Cerebral small vessel disease (eg, cerebral amyloid angiopathy, arteriolosclerosis)
2) Microemboli
3) Hypoperfusion



Cerebral microinfarcts have been successfully modelled in the brains of rodents by occluding penetrating arterioles

Penetrating arterioles are a key locus for occlusion, because unlike the interconnected pial and capillary systems, blood flow through a penetrating arteriole cannot be efficiently re-routed around a localised clot

Cortical Microinfarcts and White Matter Connectivity in Memory Clinic Patients

Doeschka Ferro[1†], Rutger Heinen[1†], Bruno de Brito Robalo[1], Hugo Kuijf[2], Geert Jan Biessels[1], and Yael Reijmer[1] On behalf of the Utrecht VCI study group*

[1] Brain Center, University Medical Center Utrecht, Department of Neurology, University Medical Center Utrecht, University Utrecht, Utrecht, Netherlands, [2] Image Sciences Institute, University Medical Center Utrecht, University Utrecht, Utrecht, Netherlands

- 164 memory clinic patients
- Mean age of 72 ± 11 years
- 3 tesla MRI with DWI
- Cortical CMIs were rated by visual inspection (hypointense on T1-weighted imaging, hyper- or isointense on FLAIR or T2-weighted imaging and isointense on T2*-weighted imaging)
- Lesions had to be strictly intracortical

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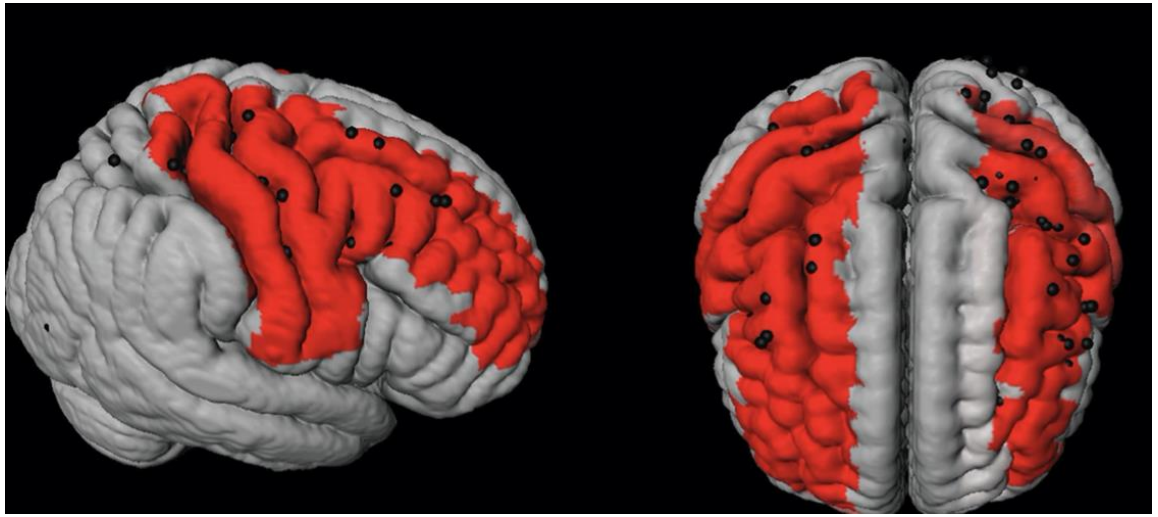
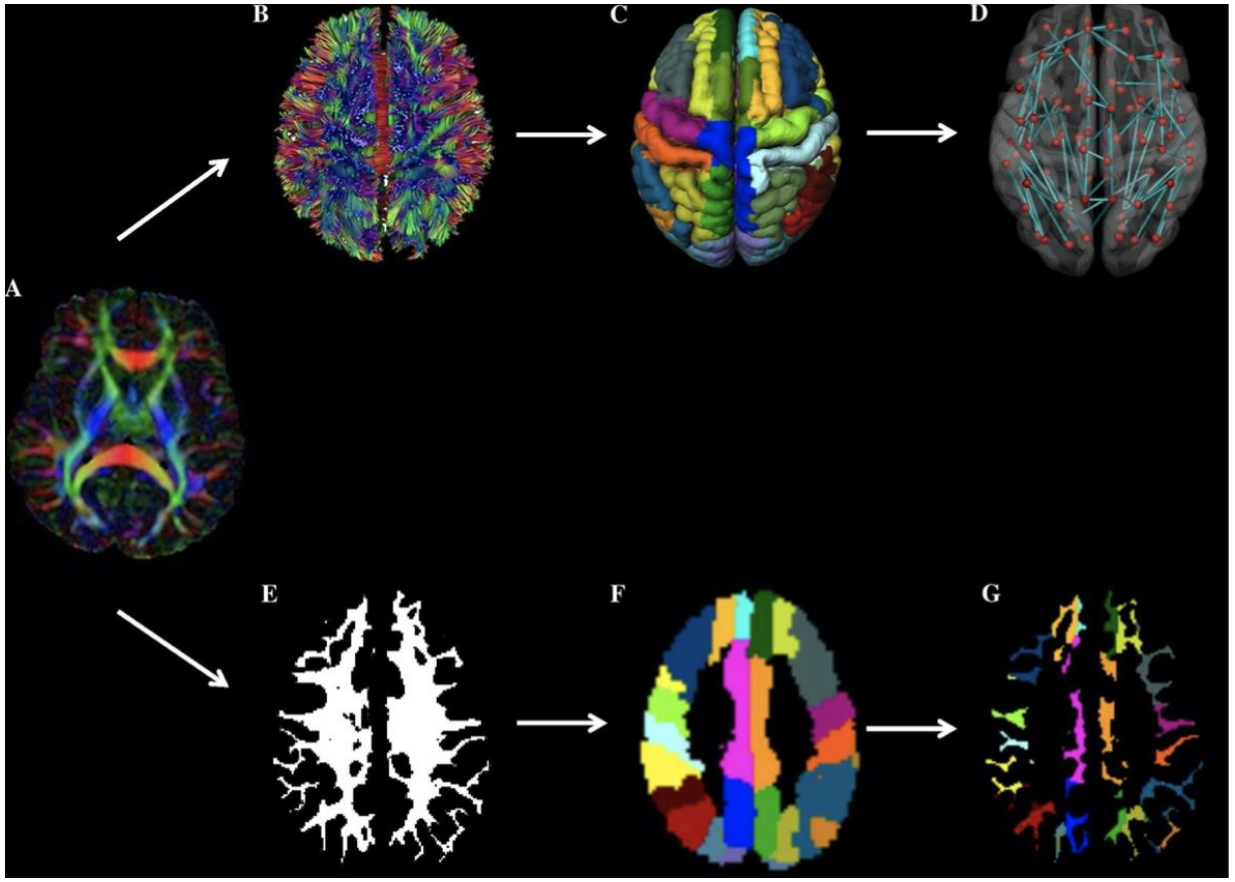




Cortical CMIs display a strong spatial clustering, as more than 70% of the cortical CMIs were located in frontal, precentral, and postcentral brain regions covering only 16% of the cortical surface.

TABLE 2 | Association between cortical CMI presence and whole brain and regional FA- and MD-weighted WM connectivity in high and low CMI burden regions.

	Cortical CMI absent ($N = 134$)	Cortical CMI present ($N = 30$)	Model 1			Model 2		
			Beta [95% CI]	*t*-value	*p*	Beta [95% CI]	*t*-value	*p*
WHOLE BRAIN								
FA	0.294 ± 0.017	0.290 ± 0.017	−0.093 [−0.256;0.070]	−1.19	0.234	−0.052 [−0.234;0.104]	−0.69	0.490
MD[a]	0.979 ± 0.057	0.993 ± 0.061	0.087 [−0.047;0.228]	1.27	0.208	0.018 [−0.108;0.138]	0.26	0.795
HIGH CORTICAL CMI BURDEN REGIONS								
FA	0.301 ± 0.020	0.296 ± 0.021	−0.109 [−0.254;0.036]	−1.40	0.165	−0.059 [−0.216;0.098]	−0.78	0.440
MD[a]	0.936 ± 0.057	0.958 ± 0.066	0.136 [−0.013;0.285]	1.82	0.071	0.030 [−0.102;0.162]	0.41	0.683
LOW CORTICAL CMI BURDEN REGIONS								
FA	0.294 ± 0.016	0.290 ± 0.016	−0.091 [−0.228;0.068]	−1.16	0.247	−0.051 [−0.204;0.102]	−0.67	0.501
MD[a]	0.983 ± 0.058	1.000 ± 0.063	0.082 [−0.050;0.208]	1.20	0.231	0.017 [−0.102;0.130]	0.24	0.808

CMI, Cerebral microinfarct; FA, Fractional anisotropy-weighted WM connectivity; MD, Mean diffusivity-weighted WM connectivity. Lower FA and higher MD indicated impaired WM connectivity.

[a]MD values $\times 10^{-3}$ mm^2/s.

Model 1: Covariates age and sex (degrees of freedom = 160).

Model 2: Covariates sex, age, WMH Fazekas grade 3, presence of lacunar and non-lacunar infarct (degrees of freedom = 157).

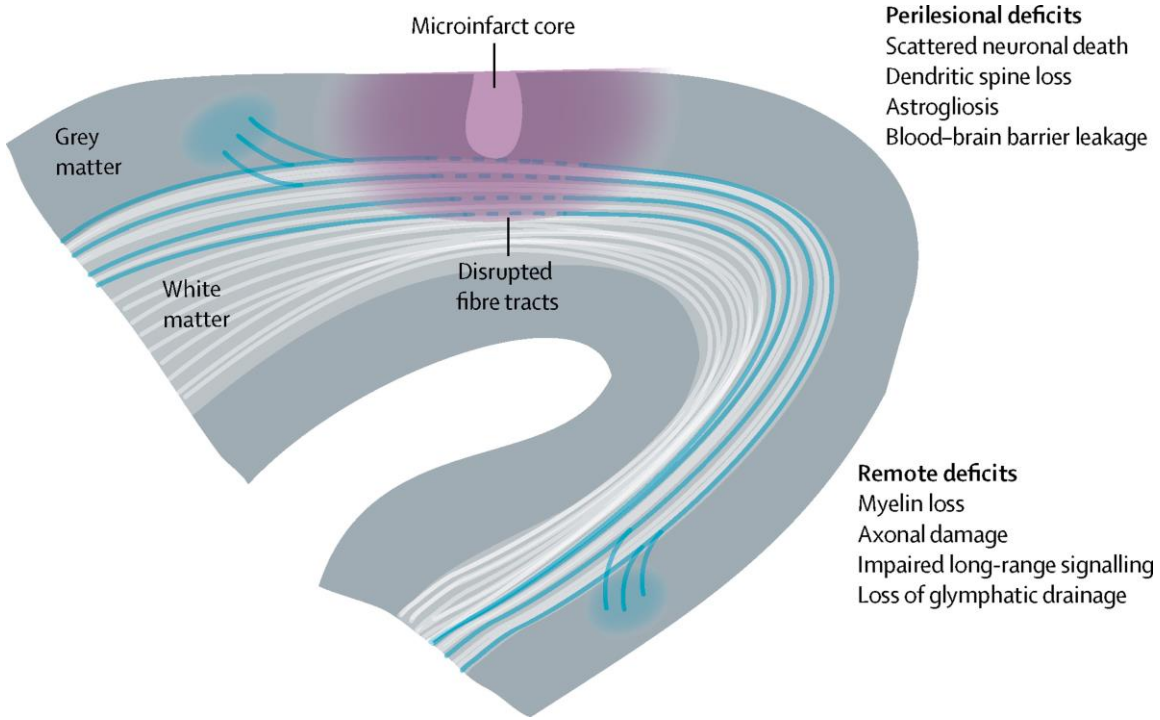
no evidence that the actual presence of cortical CMIs was related to disruption of WM connections to either the high CMI burden regions or within the whole brain.

Effects of cerebral microinfarcts (CM)

CM can have physio-pathological effects that extend beyond the non-viable core observed by MRI or in neuropathological studies

Neuronal dysfunction might involve diaschisis, whereby death of neurons within the CM core disables the cortical and subcortical circuits to which they were previously integrated

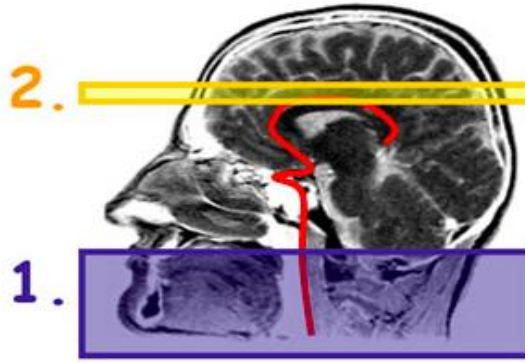
CM affecting white matter tracts are likely to disrupt communication between brain regions by damaging axonal structures

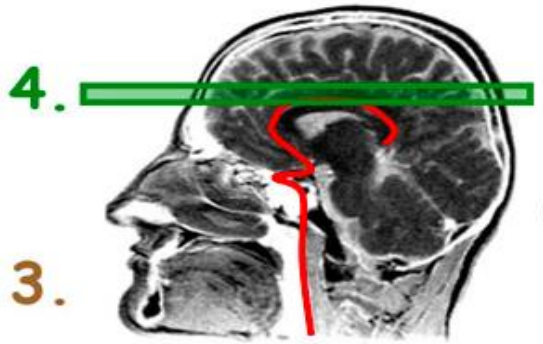


Future directions

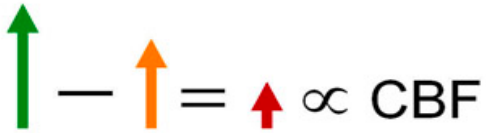
Imaging di perfusione - ASL

1. Tag inflowing arterial blood by magnetic inversion
2. Acquire the **Tag Image**





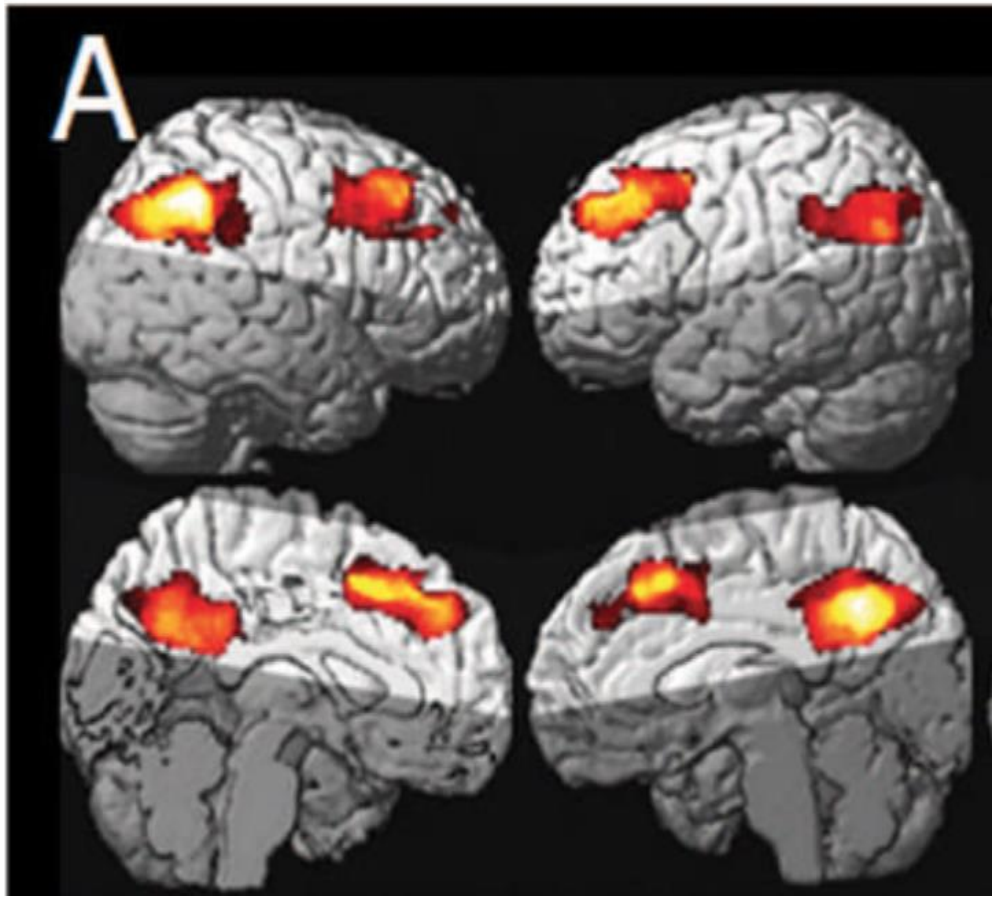
3. Repeat experiment without tag
4. Acquire the **Control Image**
5. Subtract: **Control Image** - **Tag Image**



The **Difference** in magnetization between control and tag conditions is proportional to regional cerebral blood flow.

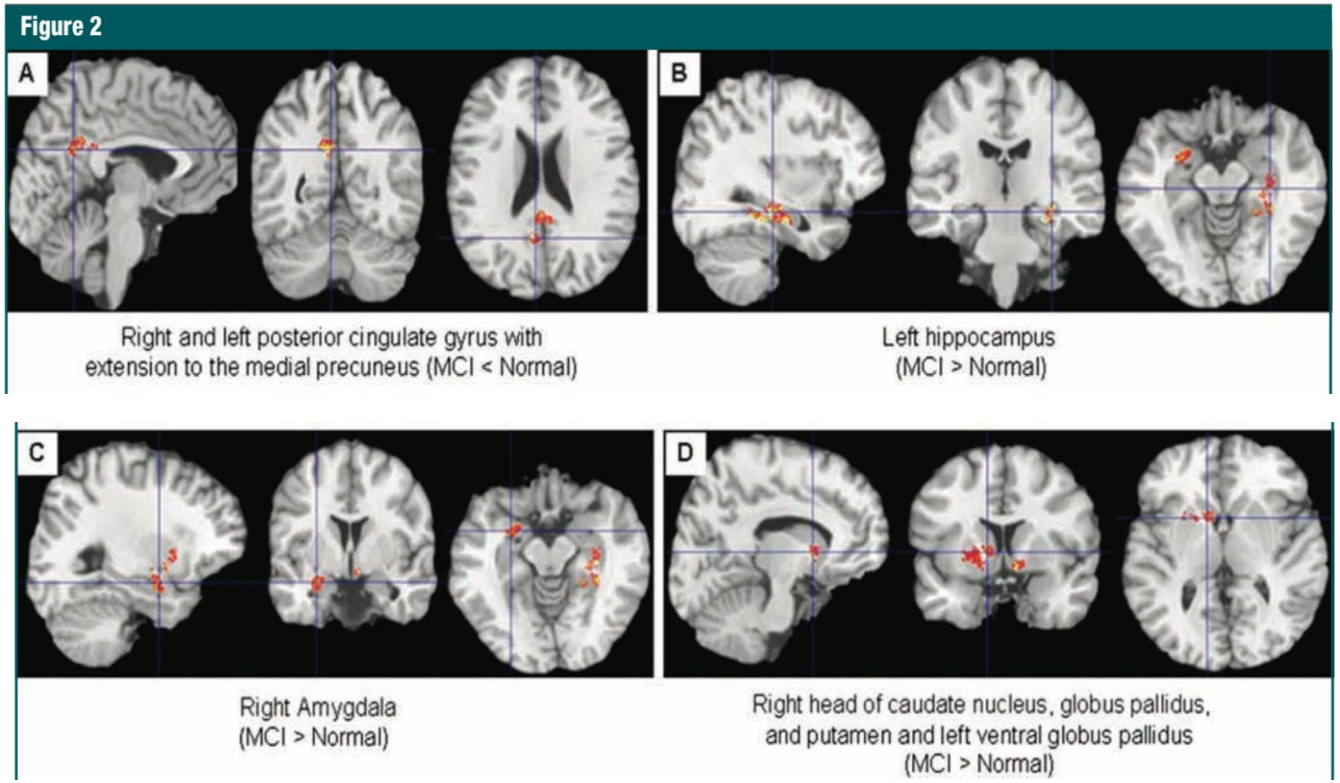
- L'iperperfusione puo' riflettere un aumento di attivita' di natura compensatoria in una popolazione neuronale minimamente coinvolta dal processo neurodegenerativo
- L'ipoperfusione puo' segnalare una riduzione dell'attivita' neuronale prima che le alterazioni strutturali siano diventate evidenti

Imaging di perfusione - AD



Johnson et al., Radiology 2005

- In pazienti AD, il pattern di ipoperfusione comprende le aree parietali e frontali bilateralmente.



Dai et al., Radiology 2009

- L'imaging di perfusione e' in grado di mostrare aree di aumentata attivita' neuronale in pazienti MCI.

Imaging di perfusione - FTD

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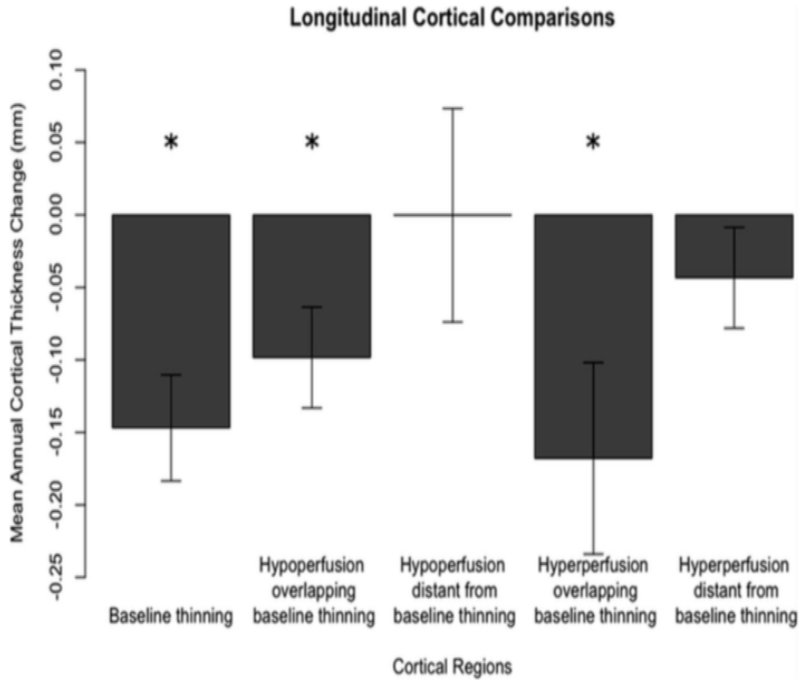
ARTERIAL SPIN LABELING PERFUSION PREDICTS LONGITUDINAL DECLINE IN SEMANTIC VARIANT PRIMARY PROGRESSIVE APHASIA

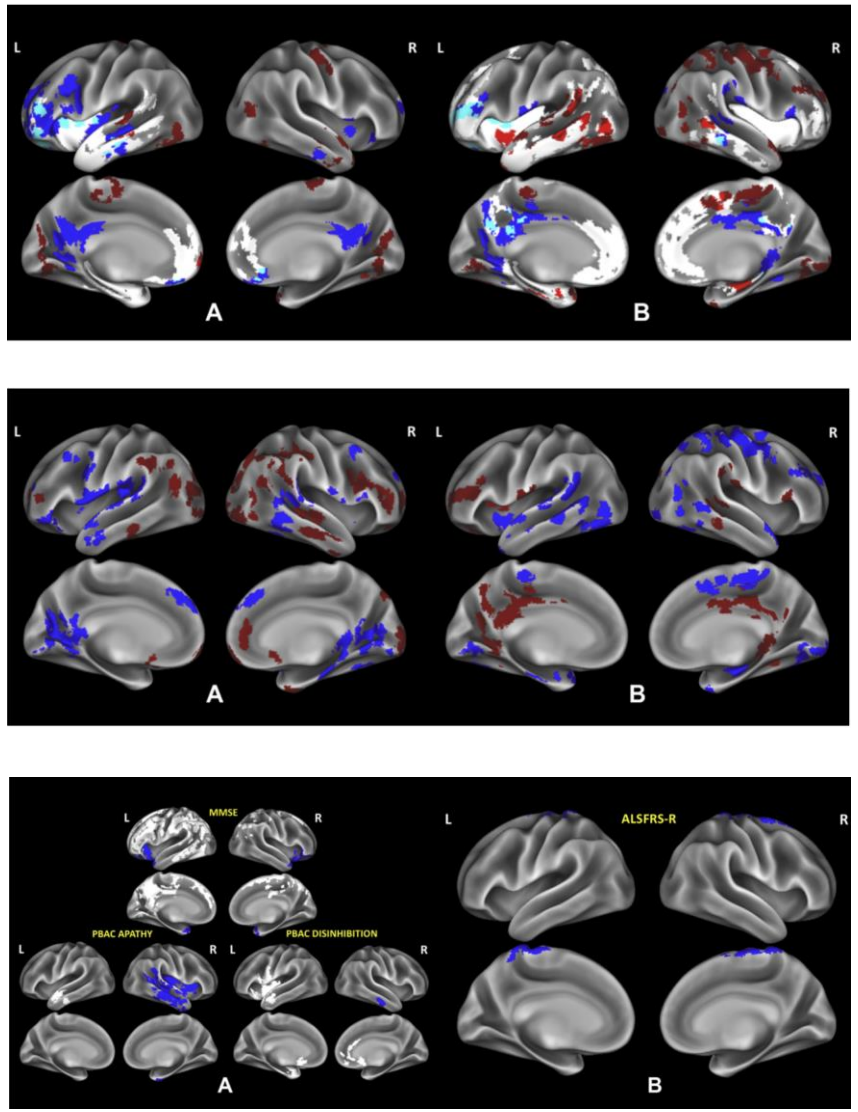
Christopher A. Olm, MA[1], Benjamin M. Kandel, BA[2], Brain B. Avants, PhD[2], John A. Detre, MD[3], James C. Gee, PhD[2], Murray Grossman, MD, EdD[1], and Corey T. McMillan, PhD[1,*]

[1]Penn Frontotemporal Degeneration Center, Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

[2]Penn Image Computing and Science Lab, Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA

[3]Departments of Neurology and Radiology, University of Pennsylvania, Philadelphia, PA, USA





Ferraro et al., 2018

- L'ipoperfusione marca regioni cerebrali coinvolte nei primi stadi di patologia, mentre l'iperperfusione caratterizza regioni a coinvolgimento patologico piu' tardivo in SLA e bvFTD.
- L'ipoperfusione correla con i sintomi clinici in SLA e bvFTD.

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