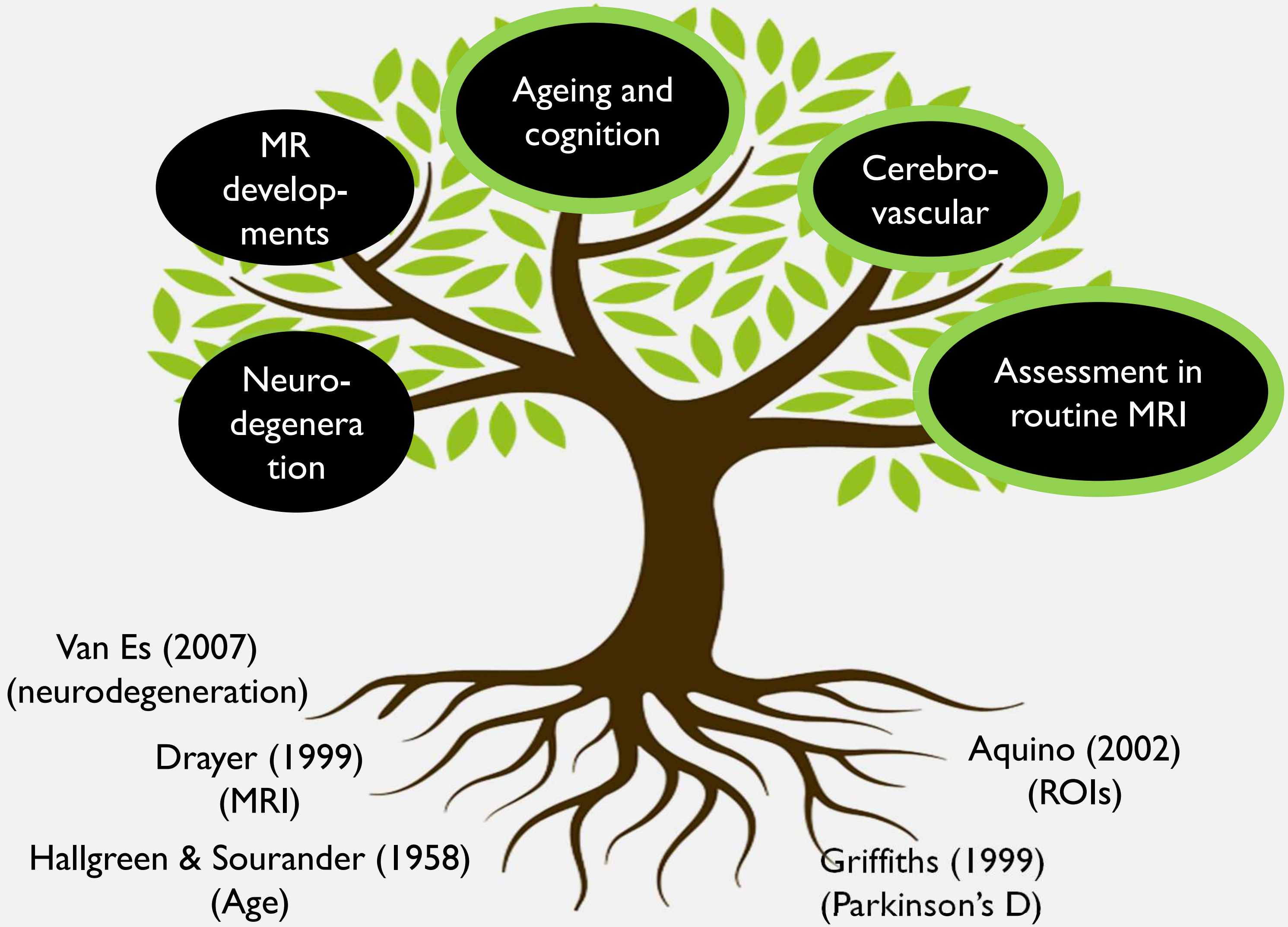
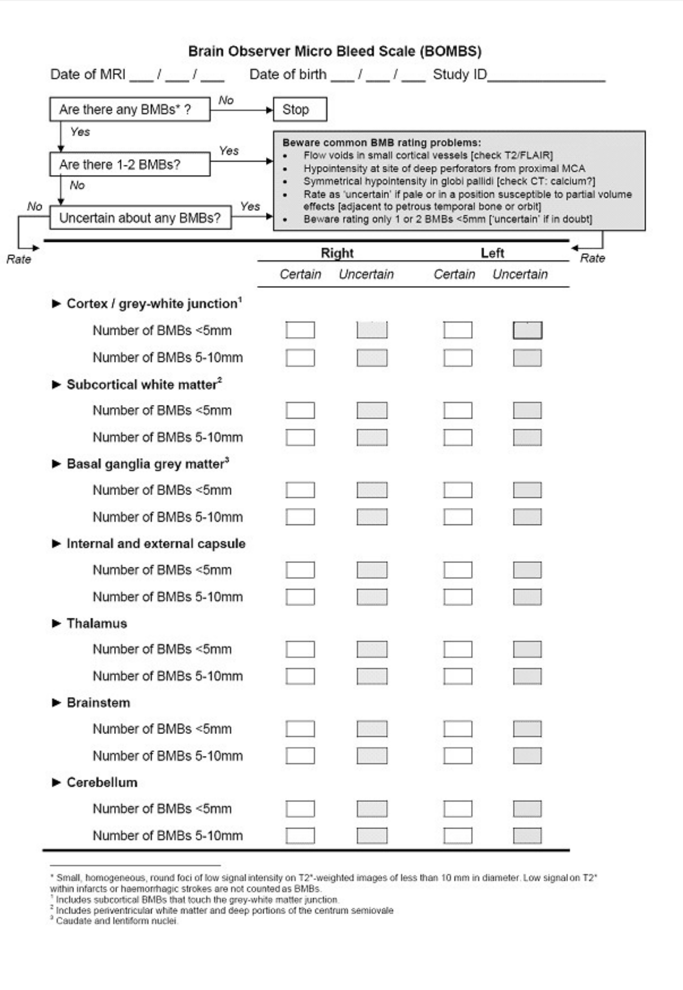
BRAIN MINERAL DEPOSITION IN PATIENTS WITH MILD STROKE, SMALL VESSEL DISEASE AND AGEING

Maria del C. Valdés Hernández

RESEARCH ON BRAIN MINERAL DEPOSITION – MAP OF OUR CONTRIBUTION



BRAIN OBSERVER MICROBLEEDS SCALE - BOMBS (CORDONNIER, SALMAN, WARDLAW)



Brain Observer Micro Bleed Scale (BOMBS)

Date of MRI ___ / ___ / ___ Date of birth ___ / ___ / ___ Study ID______________

Are there any BMBs* ? — *No* → Stop

Yes ↓

Are there 1-2 BMBs? — *Yes* → (box below)

No ↓

Uncertain about any BMBs? — *Yes* → (box below); *No* → *Rate*

Beware common BMB rating problems:
- Flow voids in small cortical vessels [check T2/FLAIR]
- Hypointensity at site of deep perforators from proximal MCA
- Symmetrical hypointensity in globi pallidi [check CT: calcium?]
- Rate as 'uncertain' if pale or in a position susceptible to partial volume effects [adjacent to petrous temporal bone or orbit]
- Beware rating only 1 or 2 BMBs <5mm ['uncertain' if in doubt]

→ *Rate*

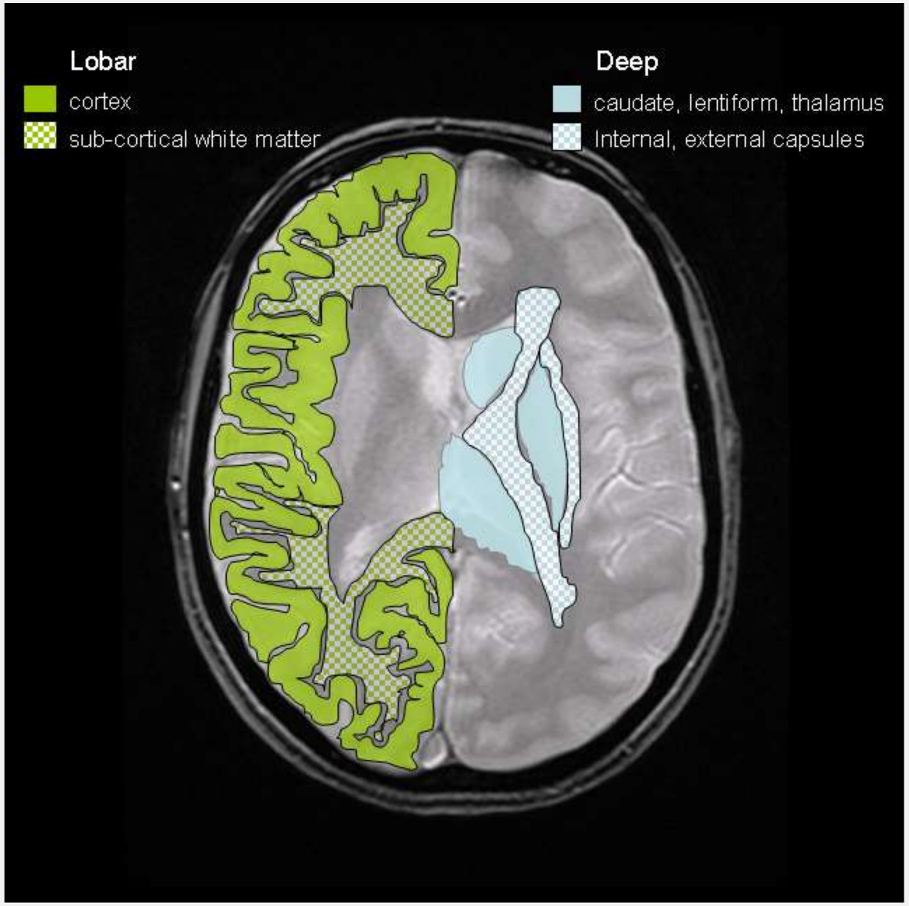
	Right		Left	
	Certain	*Uncertain*	*Certain*	*Uncertain*
► **Cortex / grey-white junction**[1]				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Subcortical white matter**[2]				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Basal ganglia grey matter**[3]				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Internal and external capsule**				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Thalamus**				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Brainstem**				
Number of BMBs <5mm				
Number of BMBs 5-10mm				
► **Cerebellum**				
Number of BMBs <5mm				
Number of BMBs 5-10mm				

* Small, homogeneous, round foci of low signal intensity on T2*-weighted images of less than 10 mm in diameter. Low signal on T2* within infarcts or haemorrhagic strokes are not counted as BMBs.

[1] Includes subcortical BMBs that touch the grey-white matter junction.

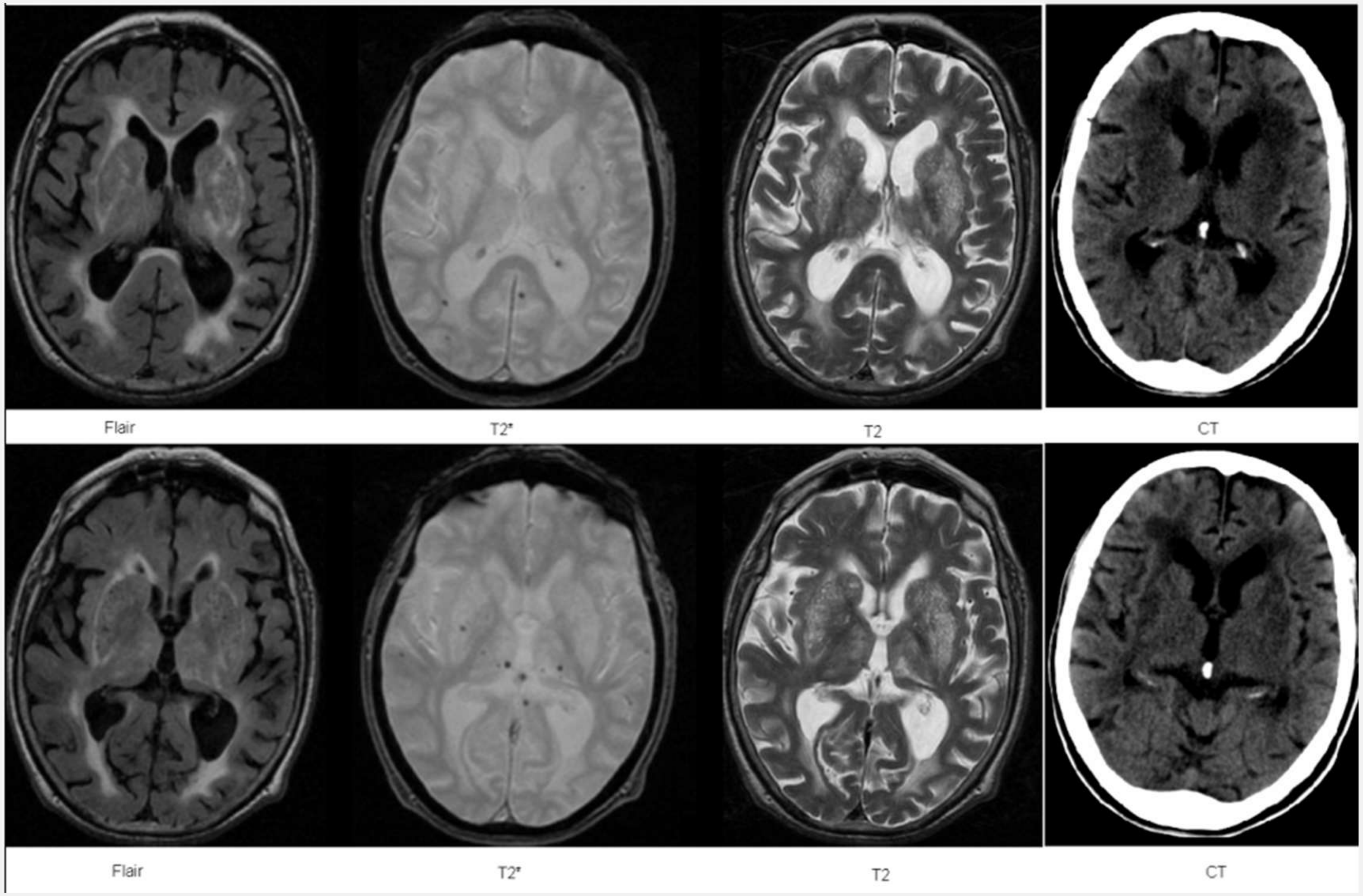
[2] Includes periventricular white matter and deep portions of the centrum semiovale

[3] Caudate and lentiform nuclei.



Cordonnier et al. Stroke 40, pp 94–109 (2009)

BRAIN MINERAL DEPOSITION - IDENTIFICATION



Systematic review up to July 2011 → 46/465 studies with mineral deposition confirmed in MRI/CT

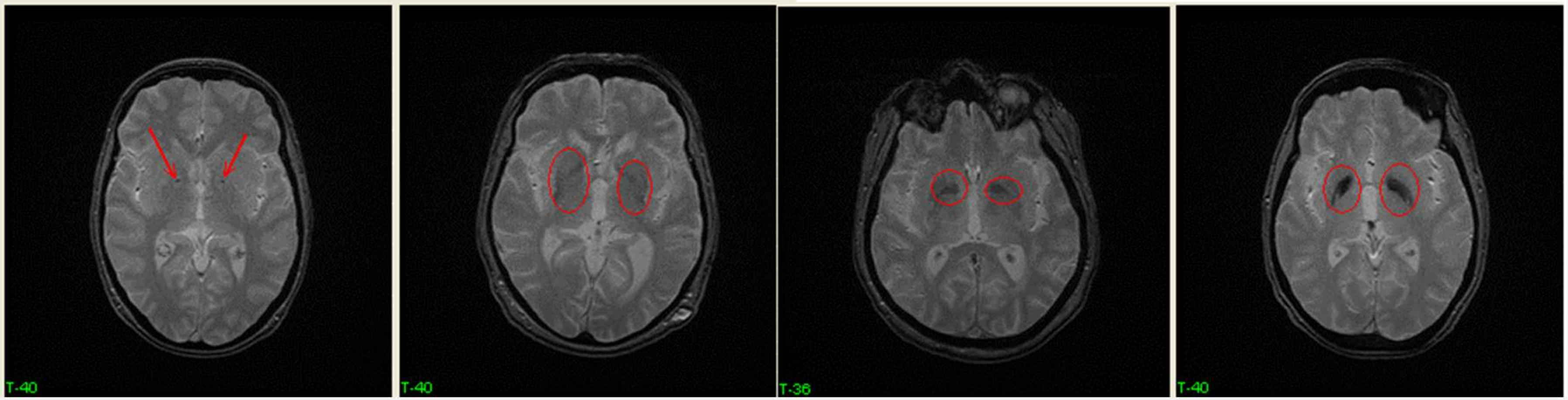
40/46 Iron (n=553), 3/46 Calcium (n=52), 1/46 Copper, 6/46 Manganese

40/46 studies confirmed findings histologically

Valdes Hernandez et al. Eur Radiol 22, pp 2371–2381(2012)

BRAIN MINERAL DEPOSITION - IDENTIFICATION

Visual rating scale



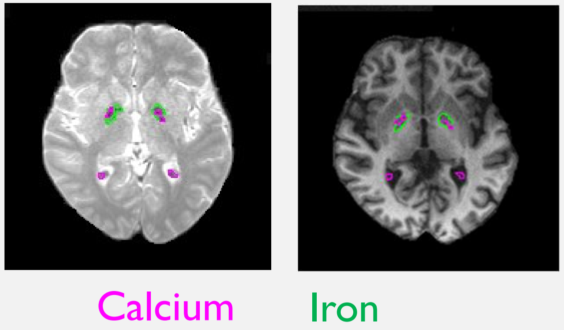
Penke et al. Neurobiol Aging 33, pp 510-517(2012)

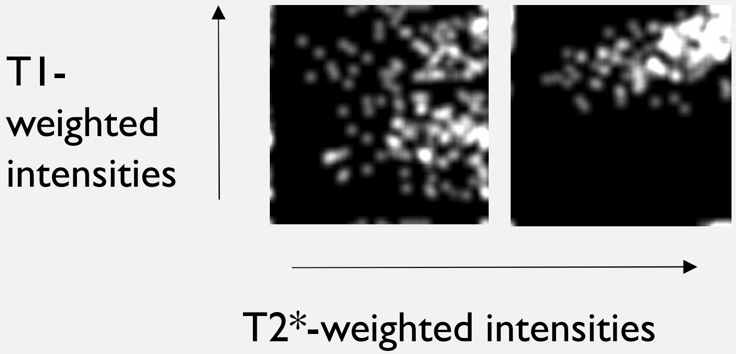
Incorporated in standard neuroradiological forms available from:
https://www.ed.ac.uk/clinical-sciences/edinburgh-imaging/research/analysis-and-processing/image-analysis-tools-downloads/all-the-edinburgh-imaging-rating-tools

BRAIN MINERAL DEPOSITION - IDENTIFICATION

Mineral	Imaging sequence/method	Appearance
Iron	T2*-weighted MRI	Hypointense
	T2-weighted	Hypointense
	CT	Hyperattenuated (i.e., white)
Calcium	T2-weighted MRI	Hypointense
	T1-weighted MRI	Hyperintense
	CT	Hyperattenuated
Copper, Manganese	T1-weighted MRI	Hyperintense

Valdes Hernandez et al. Eur Radiol 22, pp 2371–2381(2012)

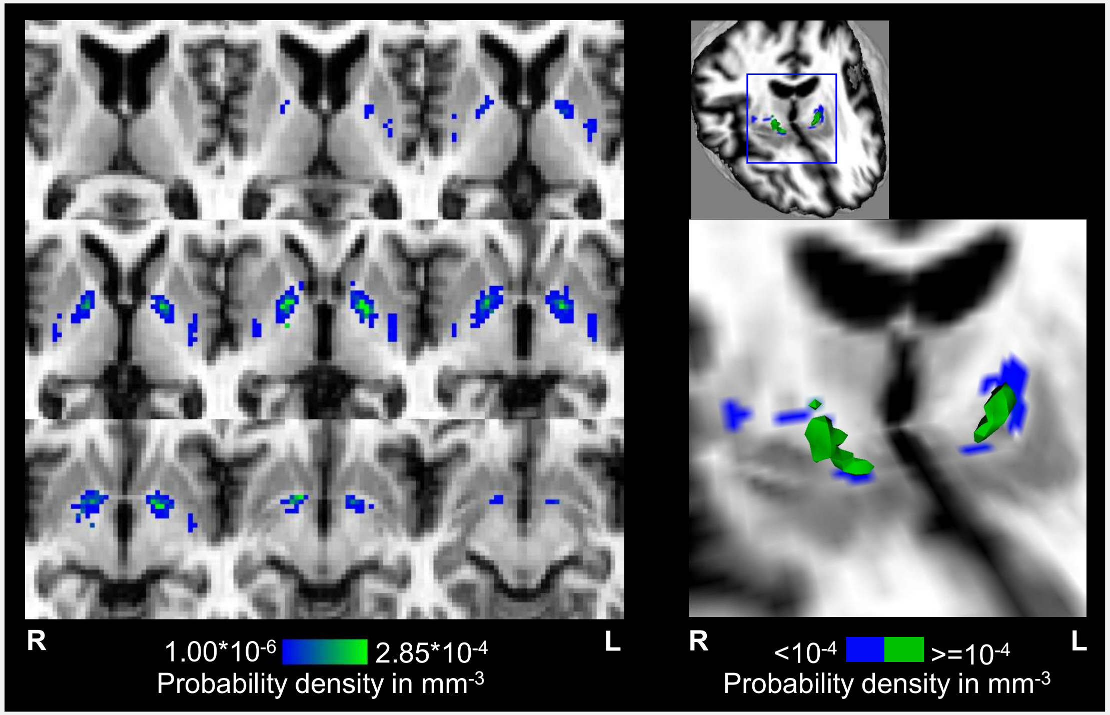


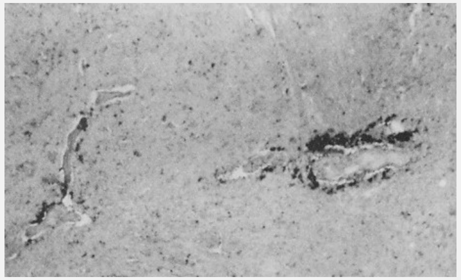


Valdes Hernandez et al. JMRI 40, pp 324–333 (2014) (doi: 10.1002/jmri.24348)

BRAIN MINERAL DEPOSITION - QUANTIFICATION

- Trained analyst manually segmented BGIDs in 73 LBC1936 participants (Glatz et al., Neuroimage 82, pp 470-480 (2013))
- Spatial probability map confirmed suggestion (Feekes J.A., Brain 2006) that BGIDs may be associated with penetrating arteries supplying the globus pallidus

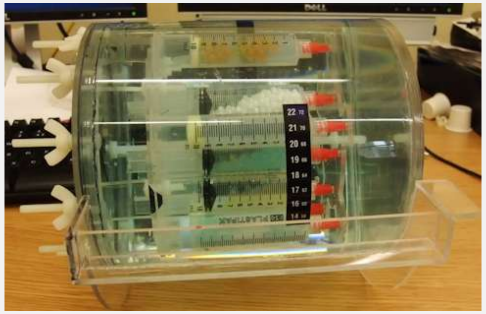


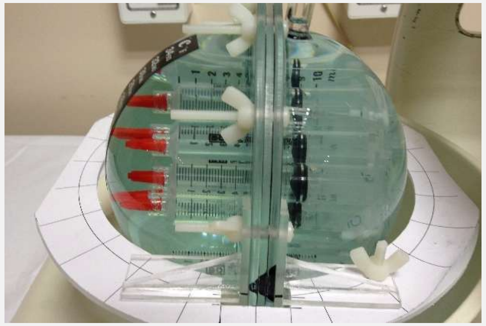


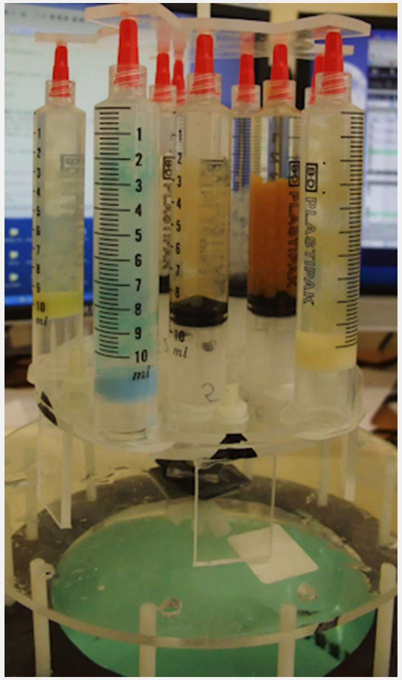
Iron encrustations around lenticulostriate arteries of the globus pallidus

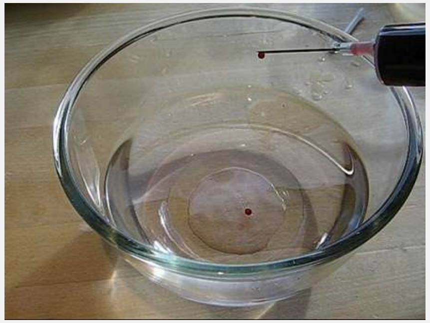
Morris C.M., Acta Anat (Basel)(1992)

BRAIN MINERAL DEPOSITION - MRI PHANTOM WORK (A. GLATZ)



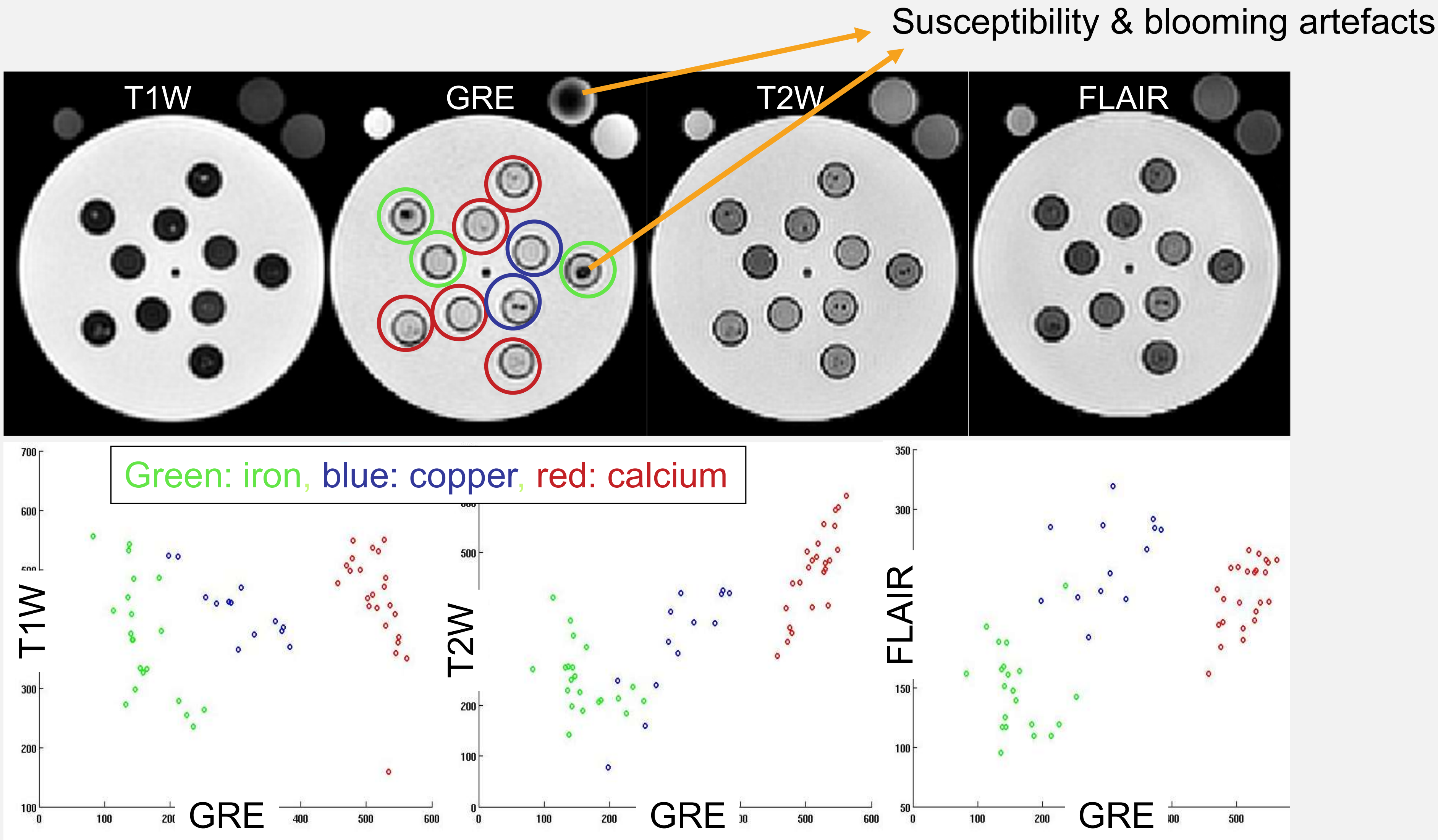






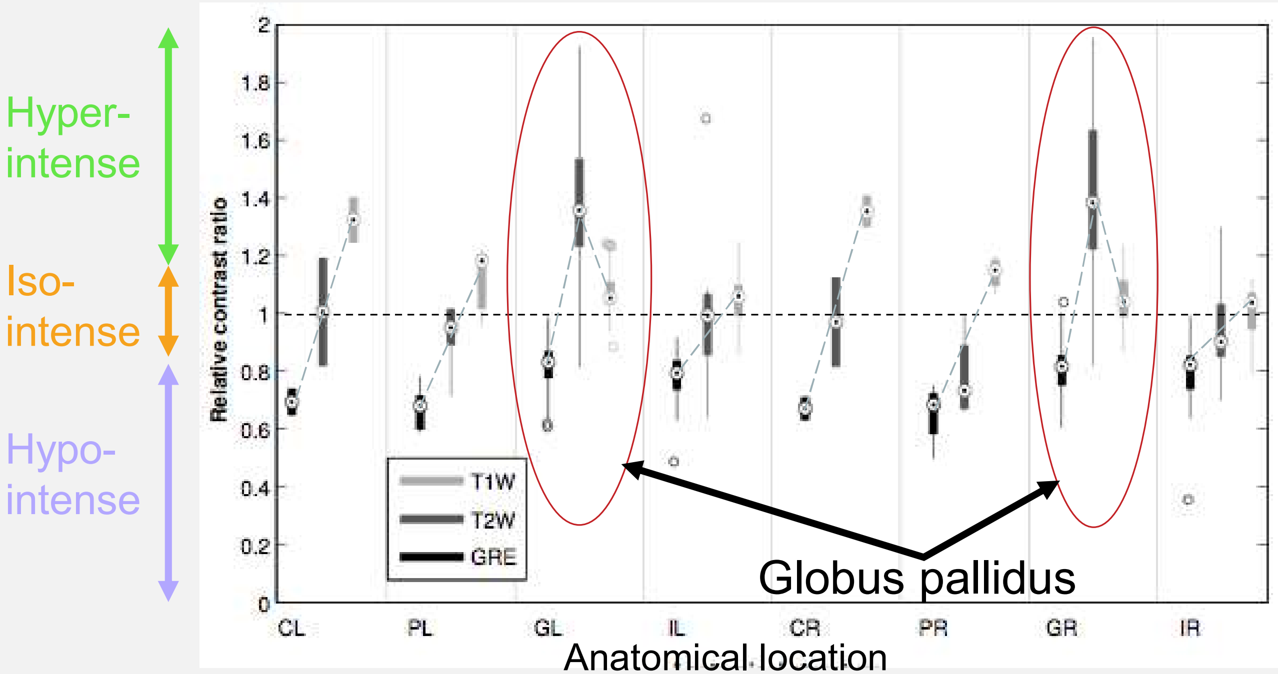
Andreas Glatz PhD Thesis University of Edinburgh
https://ethos.bl.uk/OrderDetails.do?uin=uk.bl.ethos.721183

BRAIN MINERAL DEPOSITION - MRI PHANTOM WORK (A. GLATZ)



BRAIN MINERAL DEPOSITION - QUANTIFICATION

- Comparison of contrast ratios (CRs): ratio between GRE, T2W and T1W signal intensities of BGIDs and normal-appearing tissue (Analysis in MRI from manually segmented ROIs in 73 LBC1936 participants)
- Contrast Ratio is significantly different in globus pallidus on T2W (longer T2) → Multi-modality approach only to use T1 and T2* - weighted images



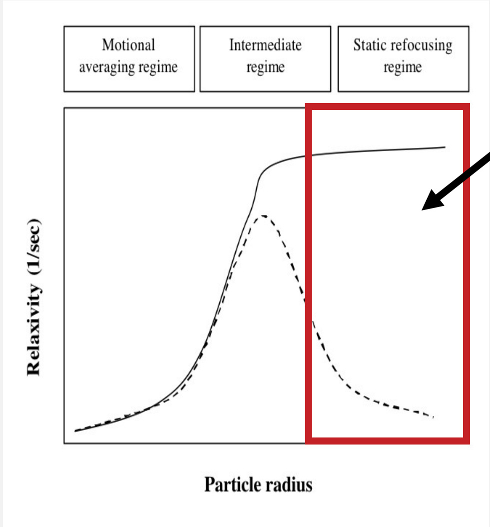


Figure 1.8: Effect of particle size on R2* (solid curve) and R2 (dashed curve)

Haque, T.L., Eur J Radiol, 2003

Large disparity Between R2 (1/T2) and R2* (1/T2*)

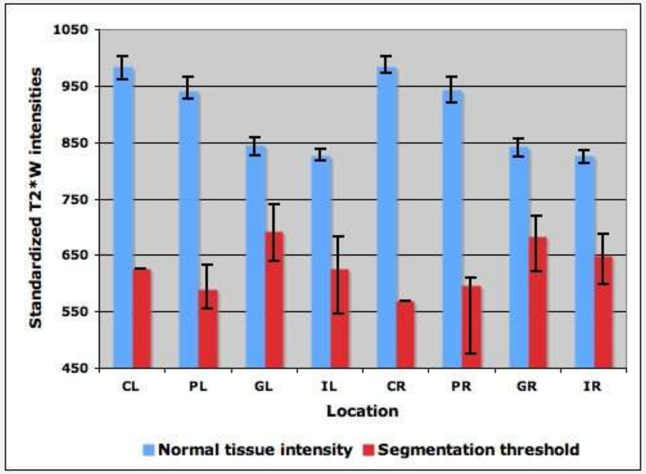
Possible causes:
-Aggregation
-Higher susceptibility
-Lower diffusion

Andreas Glatz PhD Thesis University of Edinburgh
https://ethos.bl.uk/OrderDetails.do?uin=uk.bl.ethos.721183

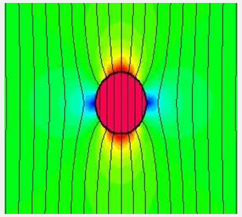
BRAIN MINERAL DEPOSITION – QUANTIFICATION CHALLENGES

- Detection of BGIDs is challenging on GRE:
  - Normal iron accumulation in the BG
  - Confounding features (vessel)
  - Blooming and partial volume artefacts

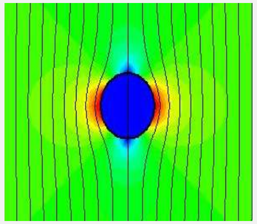
Thresholds and normal tissue intensities do not correlate.
Could explain why less IDs are detected in putamen.



- Magnetic susceptibility easily differentiable using phase images or qMRI but not blood-relevant sequences in clinical protocols

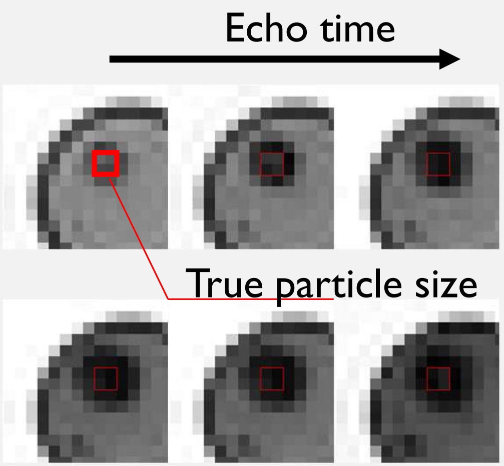


Paramagnetic particle
(e.g. iron)



Diamagnetic particle
(e.g. calcium)

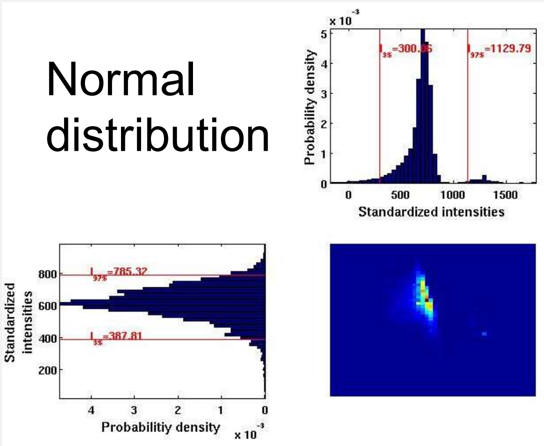
- Appearance highly dependent on imaging protocols

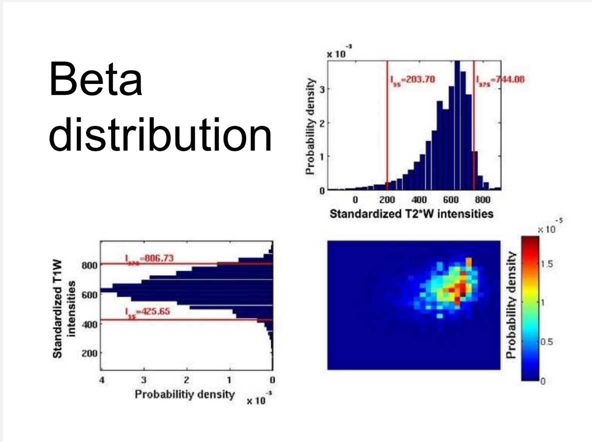


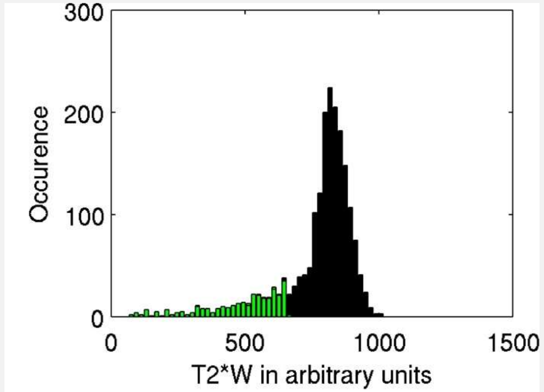
BRAIN MINERAL DEPOSITION - QUANTIFICATION

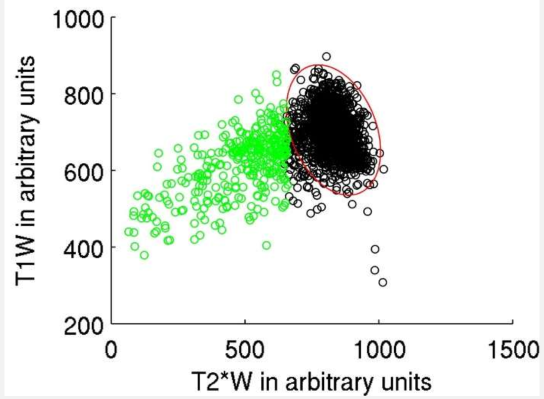
- Requires combination of multi-modal signal intensities
  - Highest contrast on GRE / SWI / SWAN
  - Differentiation of iron deposits and calcification with T1W (in absence of phase image)
- BGID intensities treated as outlier signal intensities
  - Generally not normally distributed

Glatz et al., NeuroImage 105, pp 332-346 (2015)

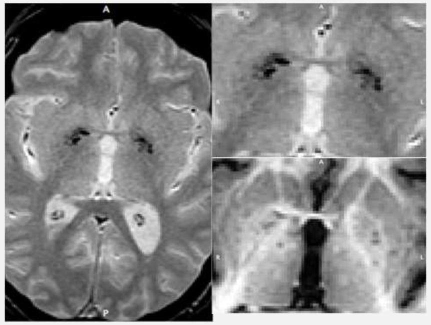




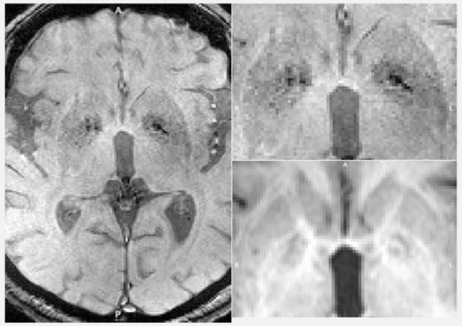




AUTOMATED DETECTION OF IRON DEPOSITS ON CLINICAL MRI VOLUMES



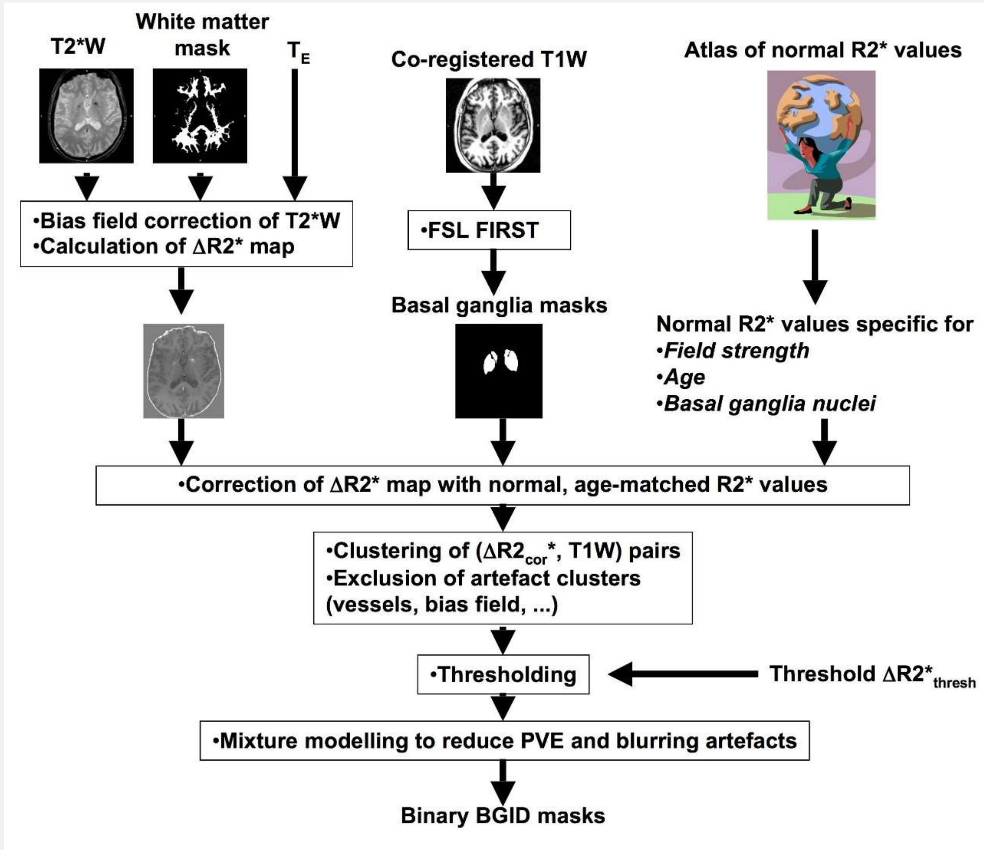
Lothian Birth Cohort 1936
1.5T GE (T2*w GRASS/FISP, T1w)



Austrian Stroke Prevention study
3T Siemens (T2*w SPGR/FLASH, T1w)

Phantom work

https://github.com/aglatz/mineral-deposit-segmentation-pipeline

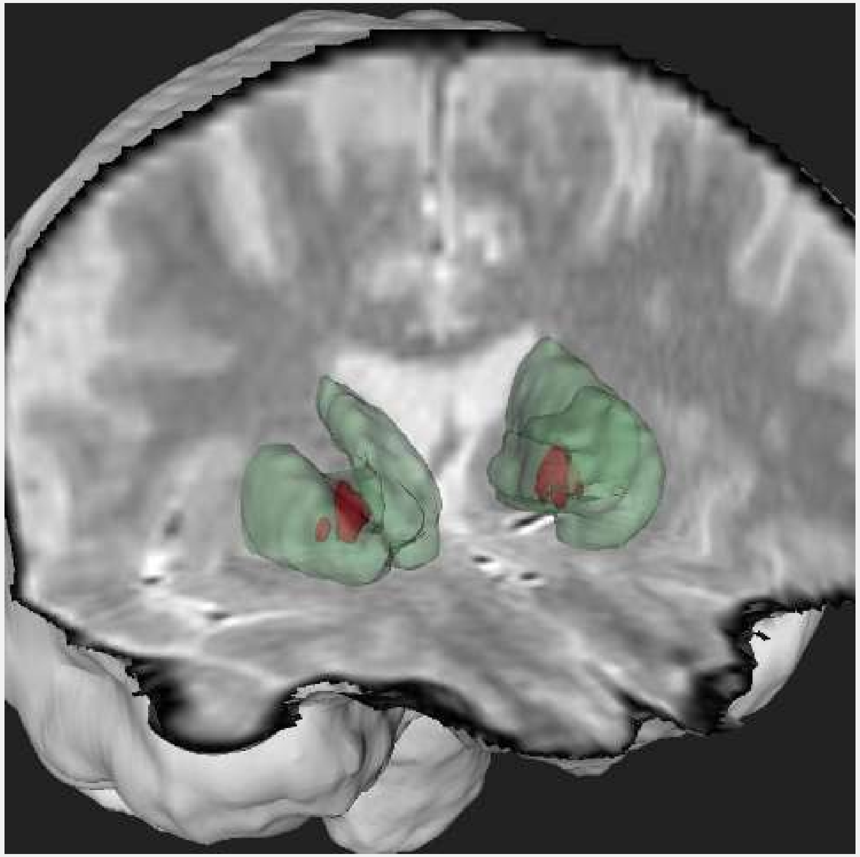


Glatz et al., NeuroImage 105, pp 332-346 (2015)
https://doi.org/10.1016/j.neuroimage.2014.10.001

BRAIN IRON DEPOSITION AT AGE 72 – FINDINGS IN THE LOTHIAN BIRTH COHORT 1936

(N = 143)

- More iron at age 72 associated with lower general cognitive ability at age 11 and 72, explaining 4% to 9% of the variance
- The relationship with age 72 cognitive ability remained significant after controlling for childhood cognition
- IDs are a biomarker of age-related cognitive decline

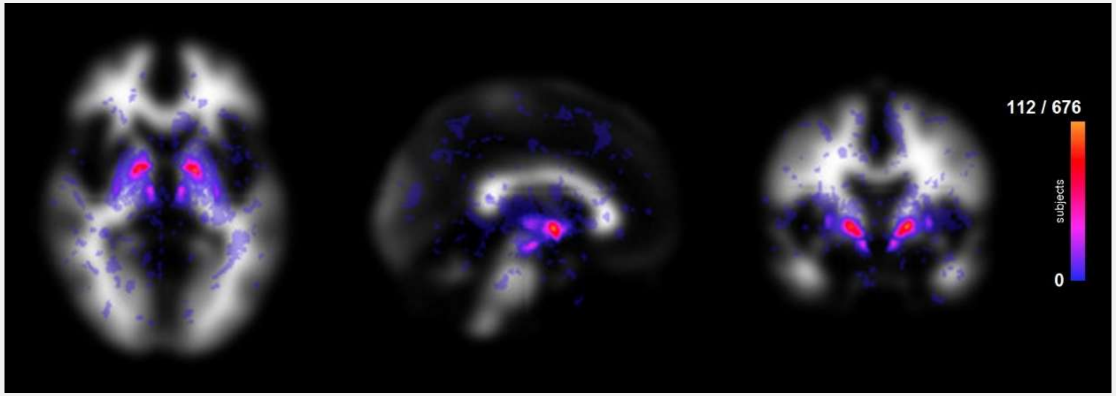


Penke et al. Neurobiol Aging 33, pp 510-517(2012)

BRAIN IRON DEPOSITION AT AGE 72 – FINDINGS IN THE LOTHIAN BIRTH COHORT 1936

(N = 676)

- Cognitive ability was significantly related to ID volume even after control for all health (including vascular risk) factors (mean $\beta=-0.119$) and childhood IQ.
- After multivariate control, the only health factor that was consistently related to ID volume was previous history of stroke
- IDs were relevant to later-life cognitive ability, and not simply related to pre-existing cognitive ability from childhood

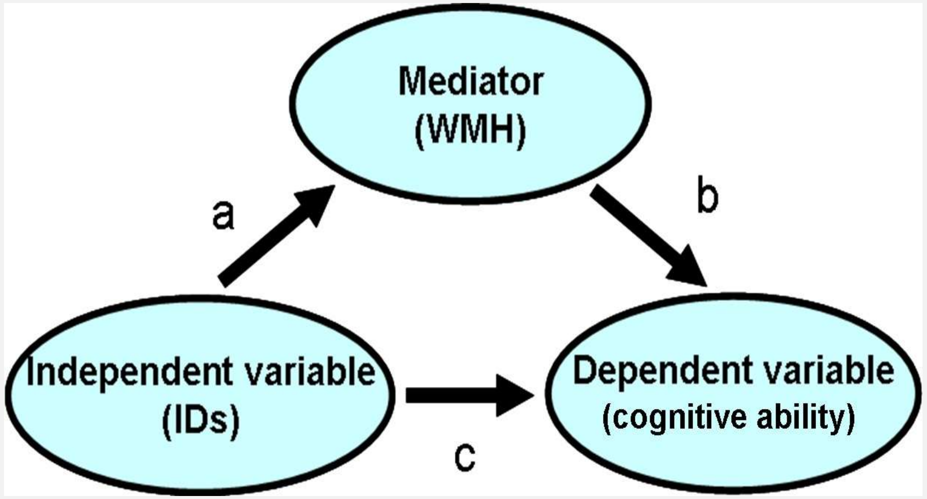


Valdés Hernandez et al. AGE (2015) 37:100

BRAIN IRON DEPOSITION AT AGE 72 – FINDINGS IN THE LOTHIAN BIRTH COHORT 1936

(N = 676)

- WMH volume had a significant negative association with general cognitive function, independent of IDs (std β=-0.13, $p<0.01$).
- The association between cognition and IDs in the brain stem (and minimally the total brain iron load), was partially and significantly mediated by WMH volume ($p=0.03$).
- IDs might be an indicator of small vessel disease that predisposes to white matter damage, affecting the neuronal networks underlying higher cognitive functioning.

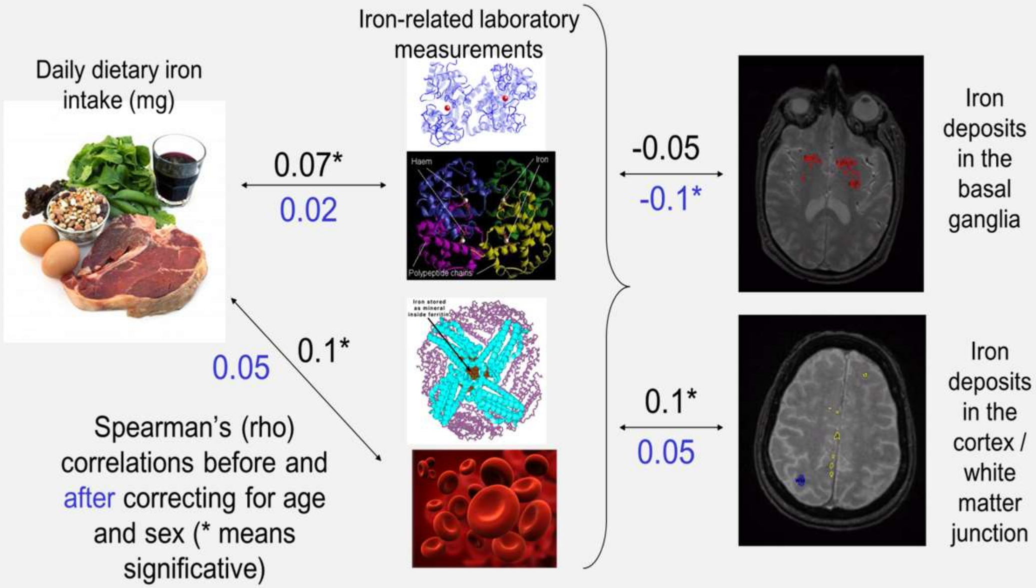


Valdes Hernandez et al. Eur J Neurol (2016)
doi:10.1111/ene.13006

BRAIN IRON DEPOSITION AT AGE 72 – FINDINGS IN THE LOTHIAN BIRTH COHORT 1936

(N = 676)

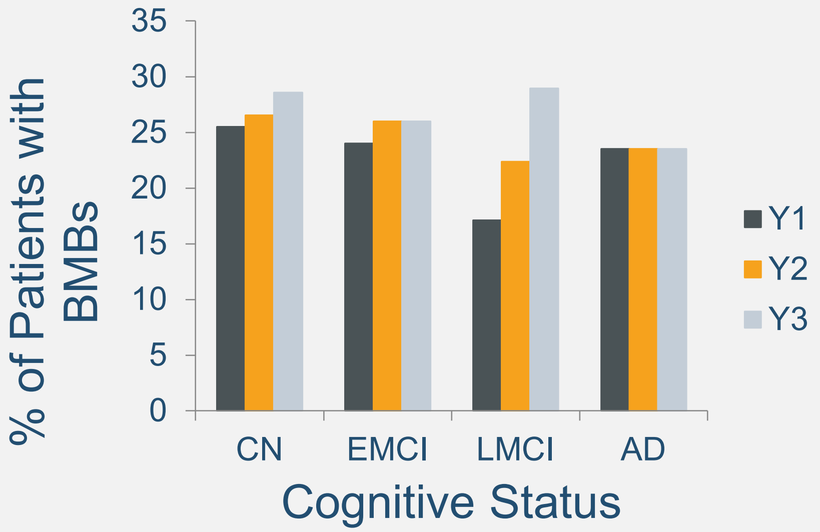
- The median daily intake of calories was 1808.5kcal (IQR=738.5), of cholesterol was 258.5mg (IQR=126.2) and of total iron was 11.7mg (IQR=5).
- Iron, calorie or cholesterol intake were not directly associated with brain IDs.
- However, caloric intake was associated with ferritin, an iron storage protein (p=0.01).
- Iron deposits in the white matter (microbleeds and minor haemorrhages) were modestly associated with cholesterol intake: 0.09, p=0.035



Valdés Hernández et al. J Nutr Health Aging 19, pp 64-69 (2015)

BRAIN MICROBLEEDS IN ADNI

(N = 291) imaged in three consecutive visits 1 year apart



No statistically significant differences in BMB prevalence between cognitive groups each year

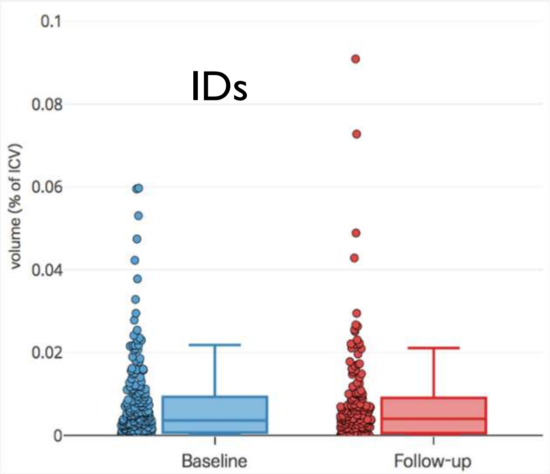
ANCOVA 1 – Biospecimen Measurements & Other	
BMBY1→BMBY2	Cholesterol (B=0.002, SE=<0.001, p=0.0097)
BMBY2→BMBY3	Number of years in Education (B=-0.029, SE=0.013, p=0.028)
BMBY1→BMBY3	Cholesterol (B=0.002, SE=<0.001, p=0.044) Family History of Dementia (B=-0.10, SE=0.046, p=0.028)
ANCOVA 2 – Brain Measurements & Other	
BMBY1→BMBY2	Family History of AD (B=0.060, SE=0.025, p=0.016)
BMBY2→BMBY3	-
BMBY1→BMBY3	-
ANCOVA 3 – Cognition & Other	
BMBY1→BMBY2	Endocrine-Metabolic Risk Factors (B=0.10, SE=0.050, p=0.044)
BMBY2→BMBY3	-
BMBY1→BMBY3	-

Statistically significant predictors for potential change in BMB count at each time point (i.e. BMB progression).

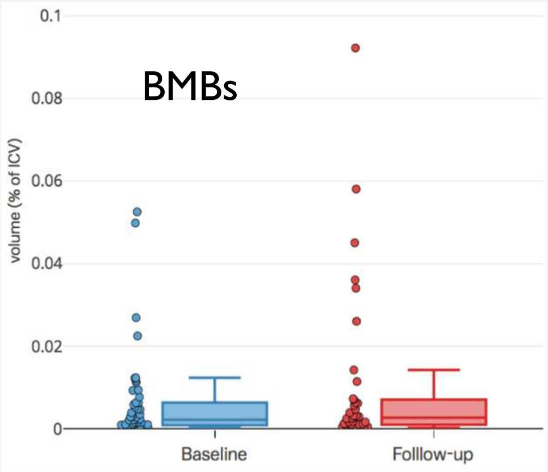
Harper et al. J Int Med Res 46, pp 3518-3538 (2018)

BRAIN IRON DEPOSITS AND MICROBLEEDS IN PATIENTS WITH MILD STROKE

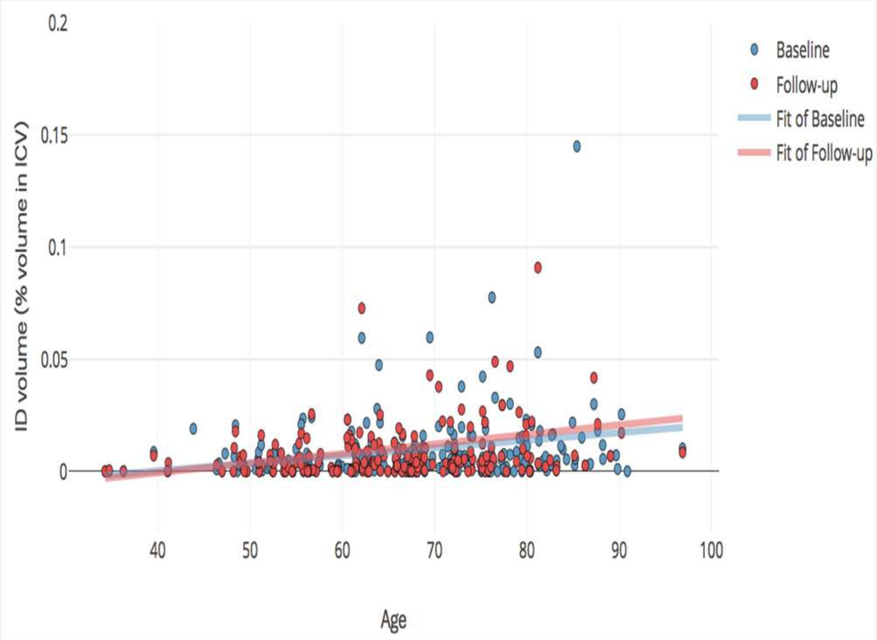
Baseline (N = 264) and 1-year post-stroke (N=190)



- ✓ In 80% of patients
- ✓ In patients who had: median[IQR]=0.09 [0.04 – 0.18] ml



- ✓ In 22% of patients
- ✓ In patients who had: median[IQR]=0.03 [0.01 – 0.07] ml



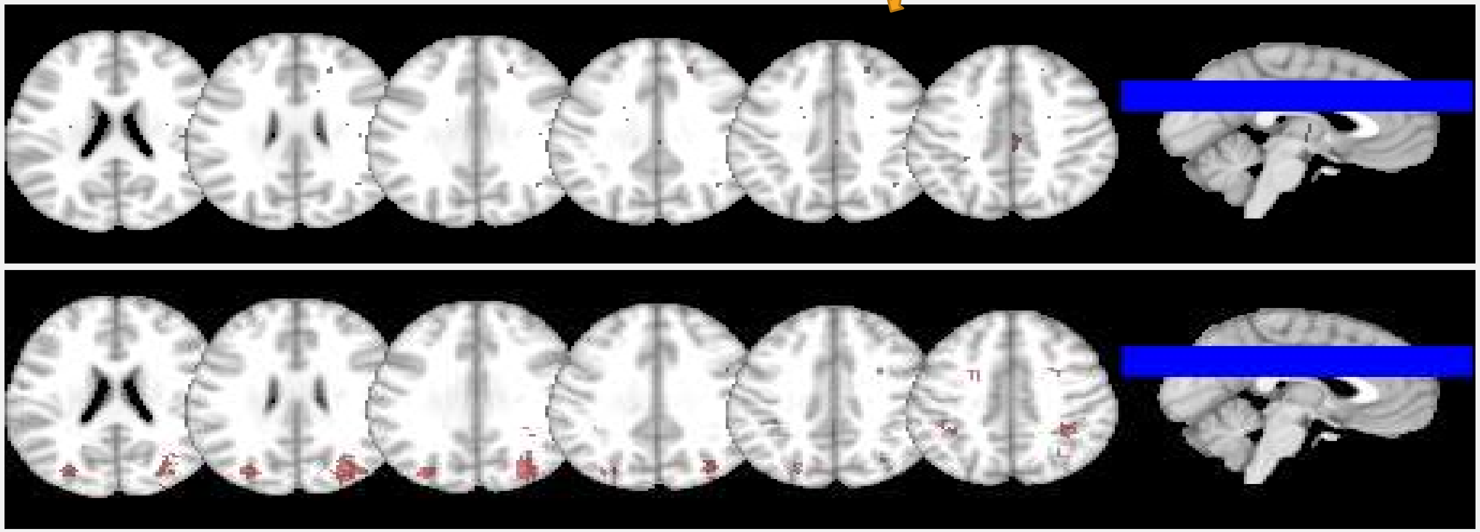
- Striatal ID volume and BMBs did not increase 1 year after the ischaemic stroke
- ID volume correlated with age at both time points (ρ = 0.248 and 0.271 respectively, $p<0.001$)

Valdés Hernandez et al. Int J Mol Sci 20(6):1293 (2019)

BRAIN IRON DEPOSITS AND MICROBLEEDS IN PATIENTS WITH MILD STROKE

Baseline (N = 264) and 1-year post-stroke (N=190)

Probability distribution of BMBs in our sample



Reverse Inference Map of the brain regions that were preferentially related to the term visuospatial in 224 studies (Generated using http://www.neurosynth.org/)

- Baseline ID volume was not associated with cognition 1 year after the stroke
- Baseline BMB volume was associated with the visuospatial abilities 1 year after the stroke

Valdés Hernandez et al. Int J Mol Sci 20(6):1293 (2019)

CURRENT WORK

- Systematic review update 2010-present on advances and findings related to brain iron deposition in ageing and neurodegenerative diseases
- Re-evaluation and update of the segmentation protocol in the currently acquired sequences (MSS3 imaging protocol), not only to detect brain iron deposition in the basal ganglia, but also to separate venules from vessel calcifications
- Study longitudinal change in iron accumulation and calcification
- Study wider implications and correlates of iron accumulation in small vessel disease

FUNDING - THANKS

laci-2 LACunar Intervention TRIAL 2

R4VaD Rates Risks and Routes to Reduce Vascular Dementia

SVDS @target

Perivascular spaces in small vessel disease
Fondation Leducq Transatlantic Network of Excellence

THE UNIVERSITY of EDINBURGH
Row Fogo Centre for Research into Ageing and the Brain
Small Vessel Diseases Research

UK Dementia Research Institute

Dementias Platform UK
Medical Research Council

Fondation Leducq

BRAIN RESEARCH IMAGING CENTRE Edinburgh

SINAPSE
Scottish Imaging Network - A Platform for Scientific Excellence

British Heart Foundation

wellcome

MRC
Medical Research Council

ARUK

age UK
Love later life

EPSRC

CHIEF SCIENTIST OFFICE

CHEST, HEART & STROKE SCOTLAND

JPND research
EU Joint Programme – Neurodegenerative Disease Research

Stroke association

Alzheimer's Society
United Against Dementia

FUNDING - THANKS

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Small Vessel Diseases Research

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Edinburgh

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