Neuroimaging and Delirium

5th Annual Delirium Boot Camp

November 2017

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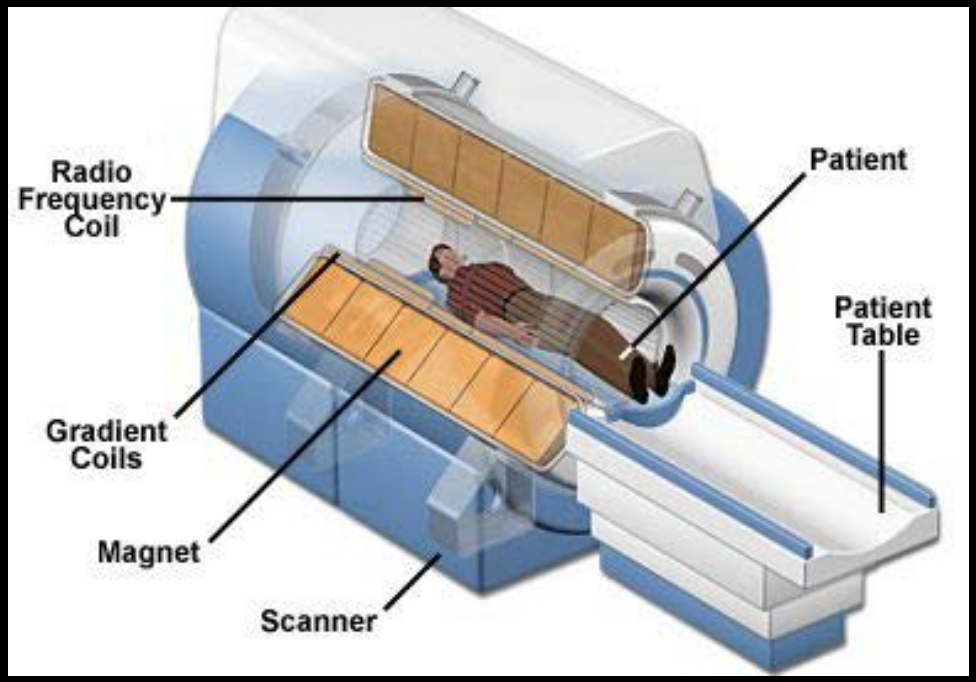
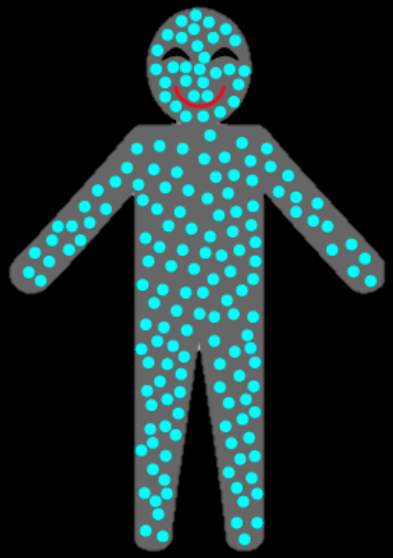
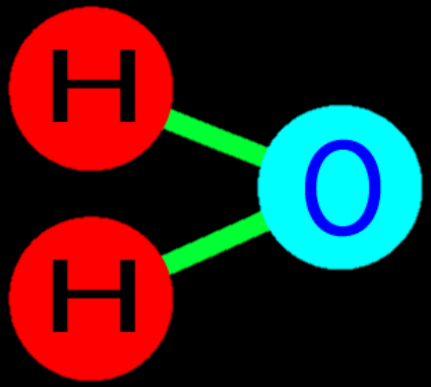
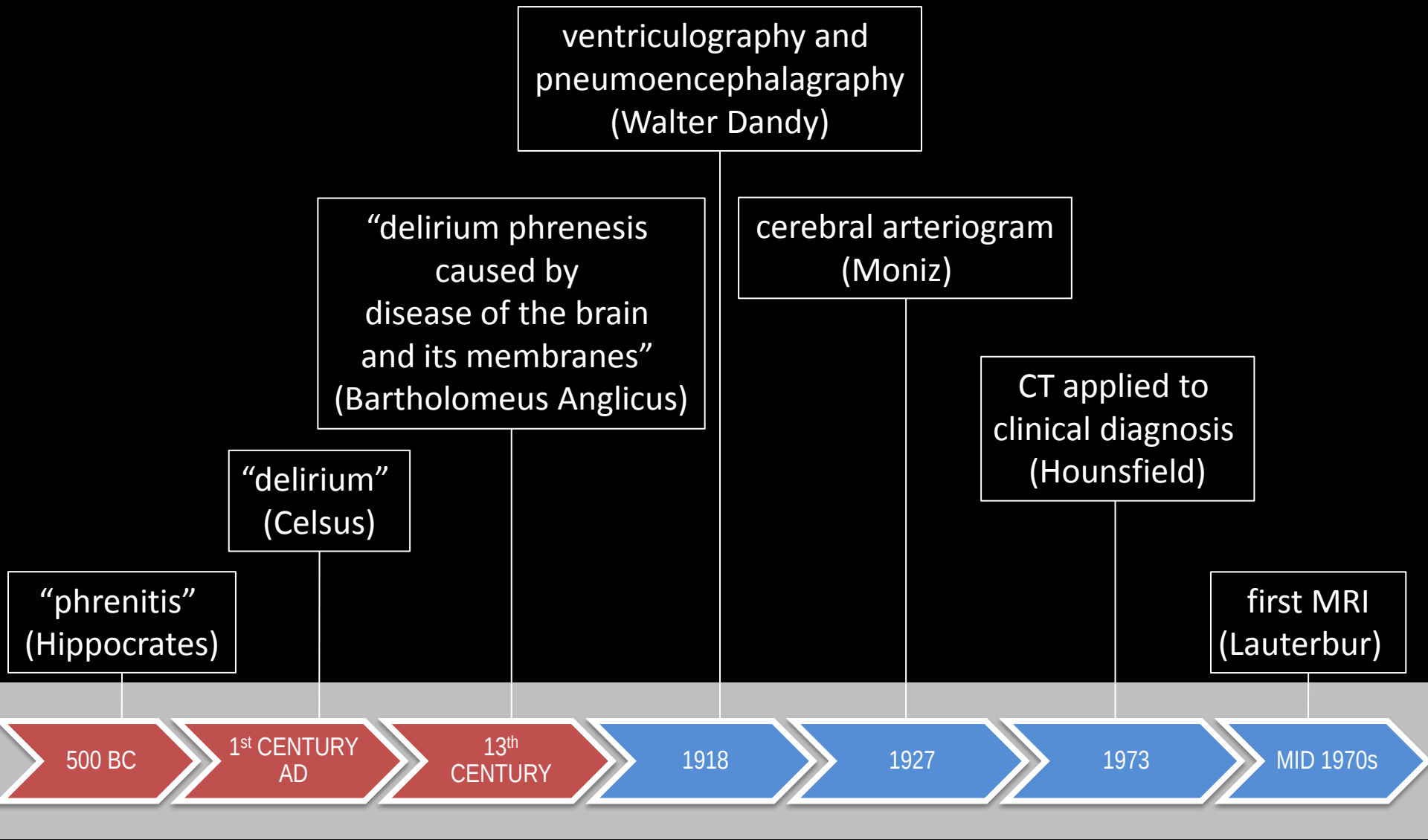
MRI : What Do We Measure?





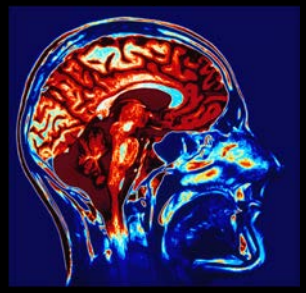


Historical Perspective

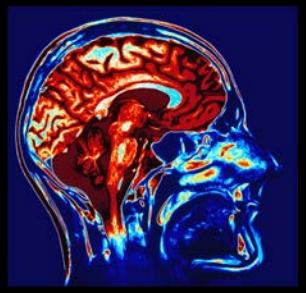


Role of Neuroimaging

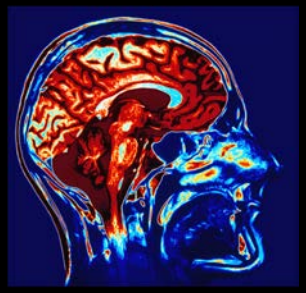
DELIRIUM (syndrome)



Predisposing Factors
Vulnerability



What Happens
During Delirium
(Methodologically Challenging)



Long-term Effect

1. QUANTIFY

1. LOCALIZE

Acquisition

Safety
PMK, metal, kidney function for contrast-MRI

Motion
≥30 min exam

$$$
Price/hour

Physicist
Non-conventional sequences

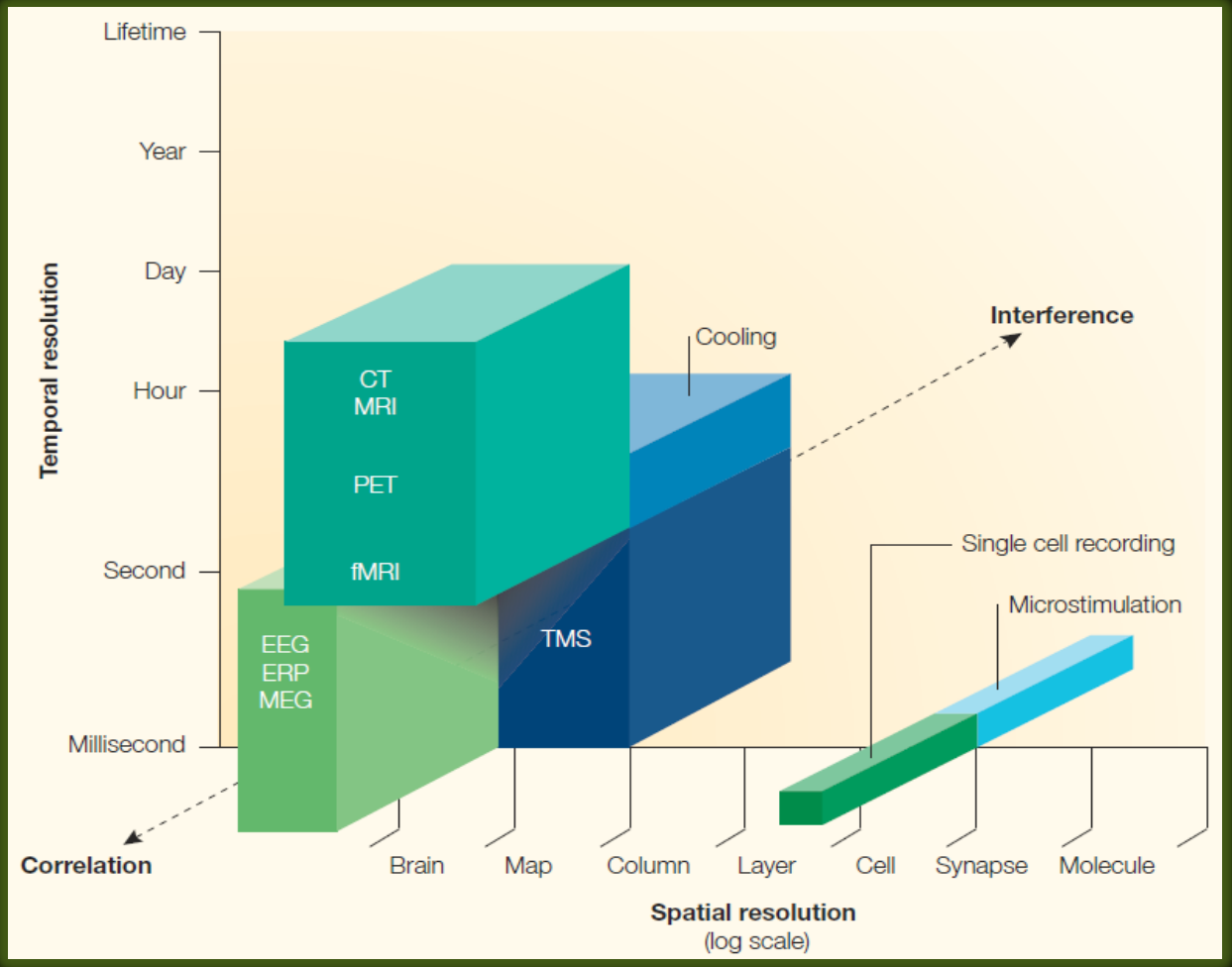
Analysis

Image Analysts
Supervised postdoc/RA

Computer Scientist
Non-conventional analyses, improve workflows

Time-consuming
Human-interactive tools, quality control

Is MRI the Right Tool to Answer Your Scientific Question?




SAGES
Successful AGing after Elective Surgery

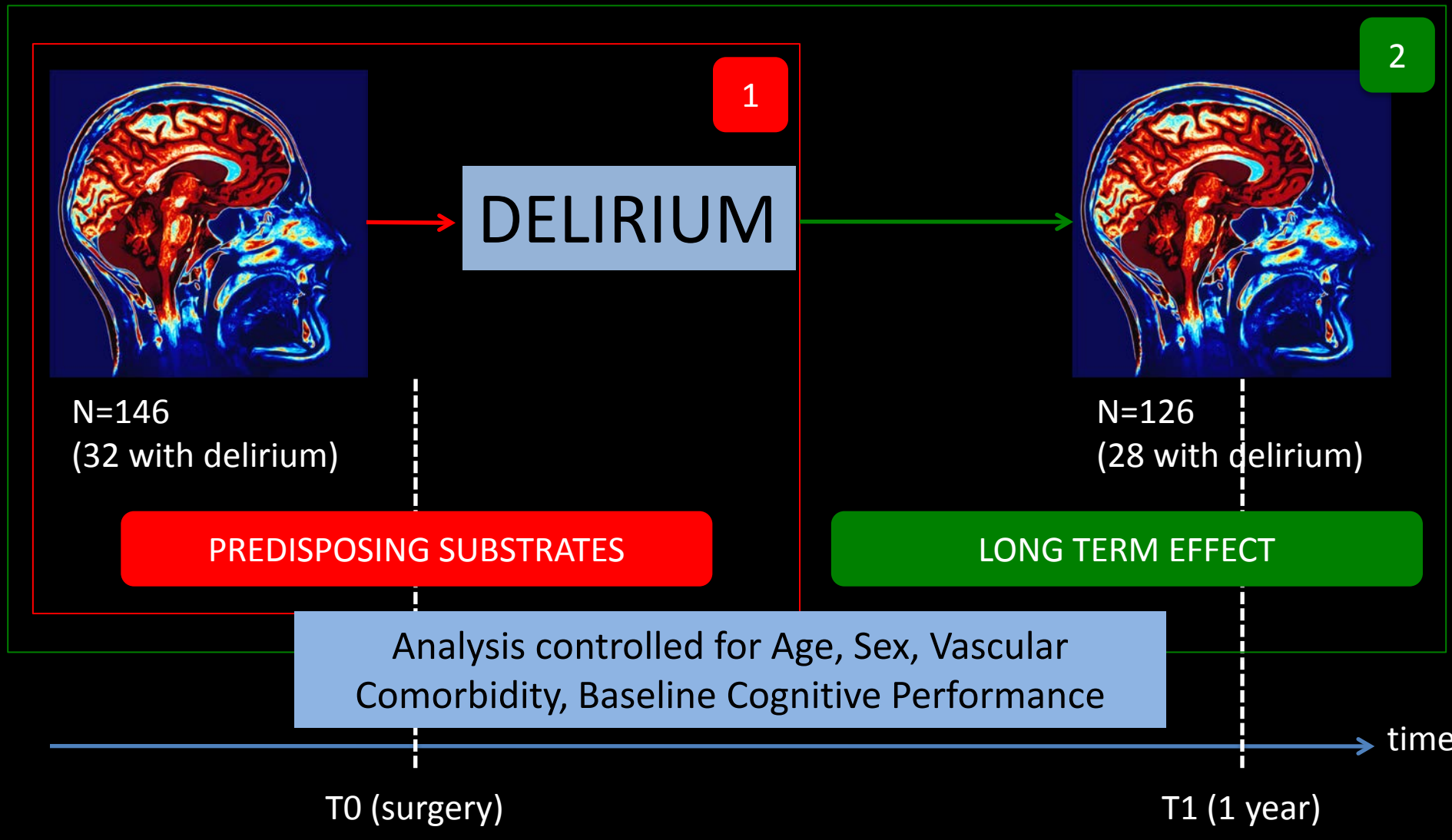
Successful AGing after Elective Surgery

Study Participants

- Older Individuals ≥70 years
- Dementia-free
- Non-cardiac Elective Surgery

Successful AGing after Elective Surgery

Study Design and Aims



Successful AGing after Elective Surgery
MRI Measures

- STRUCTURAL (T1, T2, FLAIR)
  - Global Brain Atrophy
  - Hippocampal Volume
  - Cortical Thickness
  - White Matter Hyperintensity Volume
- PERFUSION (Arterial Spin Labeling)
  - Cerebral Blood Flow
- DIFFUSION TENSOR IMAGING (DTI)
  - Microstructural Brain Abnormalities

SAGES Study / MRI Measures

- STRUCTURAL (T1, T2, FLAIR)
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Contents lists available at ScienceDirect

Neurobiology of Aging

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

Brain atrophy and white-matter hyperintensities are not significantly associated with incidence and severity of postoperative delirium in older persons without dementia

Michele Cavallari [a], Tammy T. Hshieh [b,c], Charles R.G. Guttmann [a], Long H. Ngo [d], Dominik S. Meier [a], Eva M. Schmitt [c], Edward R. Marcantonio [d], Richard N. Jones [e,f], Cyrus M. Kosar [c], Tamara G. Fong [c,g], Daniel Press [g], Sharon K. Inouye [c,d], David C. Alsop [h,*], on behalf of the SAGES Study Group

Table 2
Quantitative presurgical MRI measures of brain parenchymal damage

	All subjects ($n = 146$)	No delirium ($n = 114$)	Delirium ($n = 32$)	p Value
WMH volume (cc)	11.27 ± 9.46	11.55 ± 9.94	10.24 ± 7.59	0.710[a]
BPV (cc)	1013.91 ± 113.11	1018.71 ± 114.32	996.79 ± 108.68	0.334[b]
Hippocampal volume (cc)	3.24 ± 0.43	3.23 ± 0.43	3.25 ± 0.47	0.862[b]
ICV (cc)	1416.71 ± 158.51	1417.88 ± 163.73	1410.05 ± 138.23	0.805[b]

Data are expressed as mean ± SD. p-values refer to group comparison no delirium versus delirium by the statistical tests as indicated.
Key: BPV, brain parenchymal volume; ICV, intracranial cavity volume; MRI, magnetic resonance imaging; WMH, white-matter hyperintensity.
[a] Kruskal-Wallis test.
[b] Student t test.

White-Matter Hyperintensities Predict Delirium After Cardiac Surgery

Yutaka Hatano, M.D., Jin Narumoto, M.D., Ph.D., Keisuke Shibata, M.D., Ph.D., Teruyuki Matsuoka, M.D., Shogo Taniguchi, M.D., Yuzuru Hata, M.D., Kei Yamada, M.D., Ph.D., Hitoshi Yaku, M.D., Ph.D., Kenji Fukui, M.D., Ph.D.

RETROSPETIVE Design
CONFOUNDERS

Association of pre-operative brain pathology with post-operative delirium in a cohort of non-small cell lung cancer patients undergoing surgical resection

James C. Root[1,2]*, Kane O. Pryor[2], Robert Downey[1,2], Yesne Alici[1,2], Marcus L. Davis[3], Andrei Holodny[1,2], Beatriz Korc-Grodzicki[1,2] and Tim Ahles[1,2]

The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: The VISIONS cohort magnetic resonance imaging study*

Max L. Gunther, PhD; Alessandro Morandi, MD, MPH; Erin Krauskopf, BS; Pratik Pandharipande, MD, MSCI; Timothy D. Girard, MD, MSCI; James C. Jackson, PsyD; Jennifer Thompson, MPH; Ayumi K. Shintani, PhD; Sunil Geevarghese, MD, MSCI; Russell R. Miller III, MD, MPH; Angelo Canonico, MD; Kristen Merkle, BA; Christopher J. Cannistraci, MS; Baxter P. Rogers, PhD; J. Chris Gatenby, PhD; Stephan Heckers, MD, MSC; John C. Gore, PhD; Ramona O. Hopkins, PhD; E. Wesley Ely, MD, MPH; for the VISIONS Investigation (VISualizing Icu SurvivOrs Neuroradiological Sequelae)

NO CONTROL Group
NO Pre-Delirium MRI

Pre-existing cerebral infarcts as a risk factor for delirium after coronary artery bypass graft surgery

Sumi Otomo*, Kengo Maekawa, Tomoko Goto, Tomoko Baba and Atsushi Yoshitake

NO Association with Global WMH score

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Alzheimer's-related cortical atrophy is associated with postoperative delirium severity in persons without dementia

Annie M. Racine [a,b,c,*], Tamara G. Fong [a,b,d], Thomas G. Travison [a,b], Richard N. Jones [e], Yun Gou [a], Sarinnapha M. Vasunilashorn [b,f], Edward R. Marcantonio [b,f], David C. Alsop [b,g], Sharon K. Inouye [a,b,f,1], Bradford C. Dickerson [b,c,h,1]

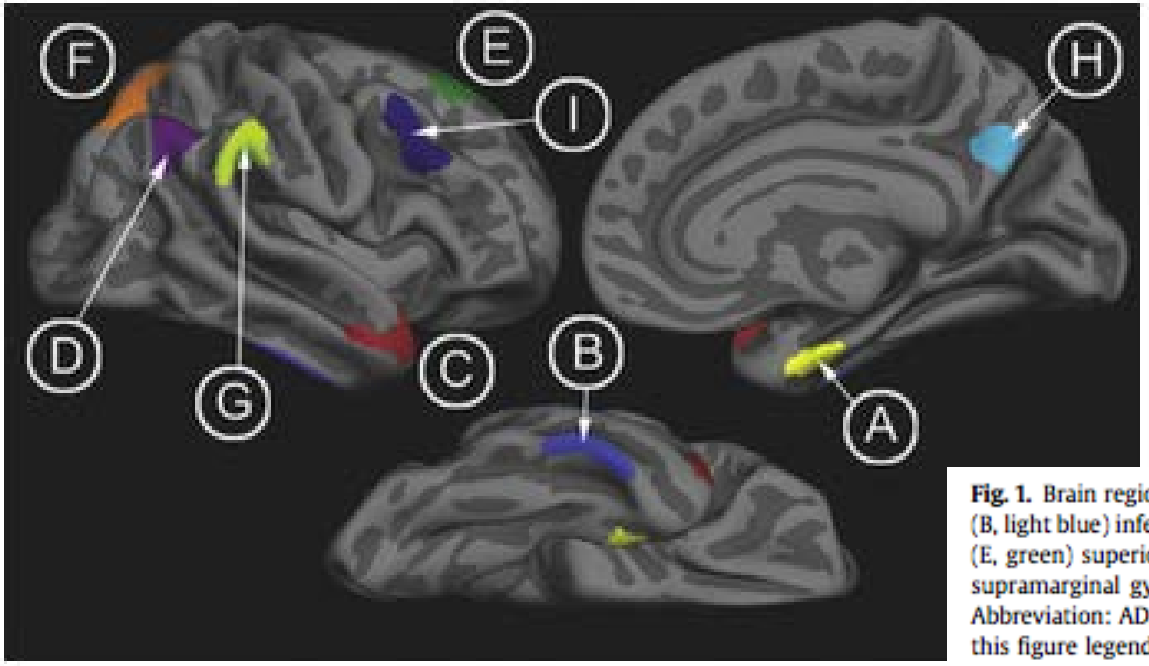


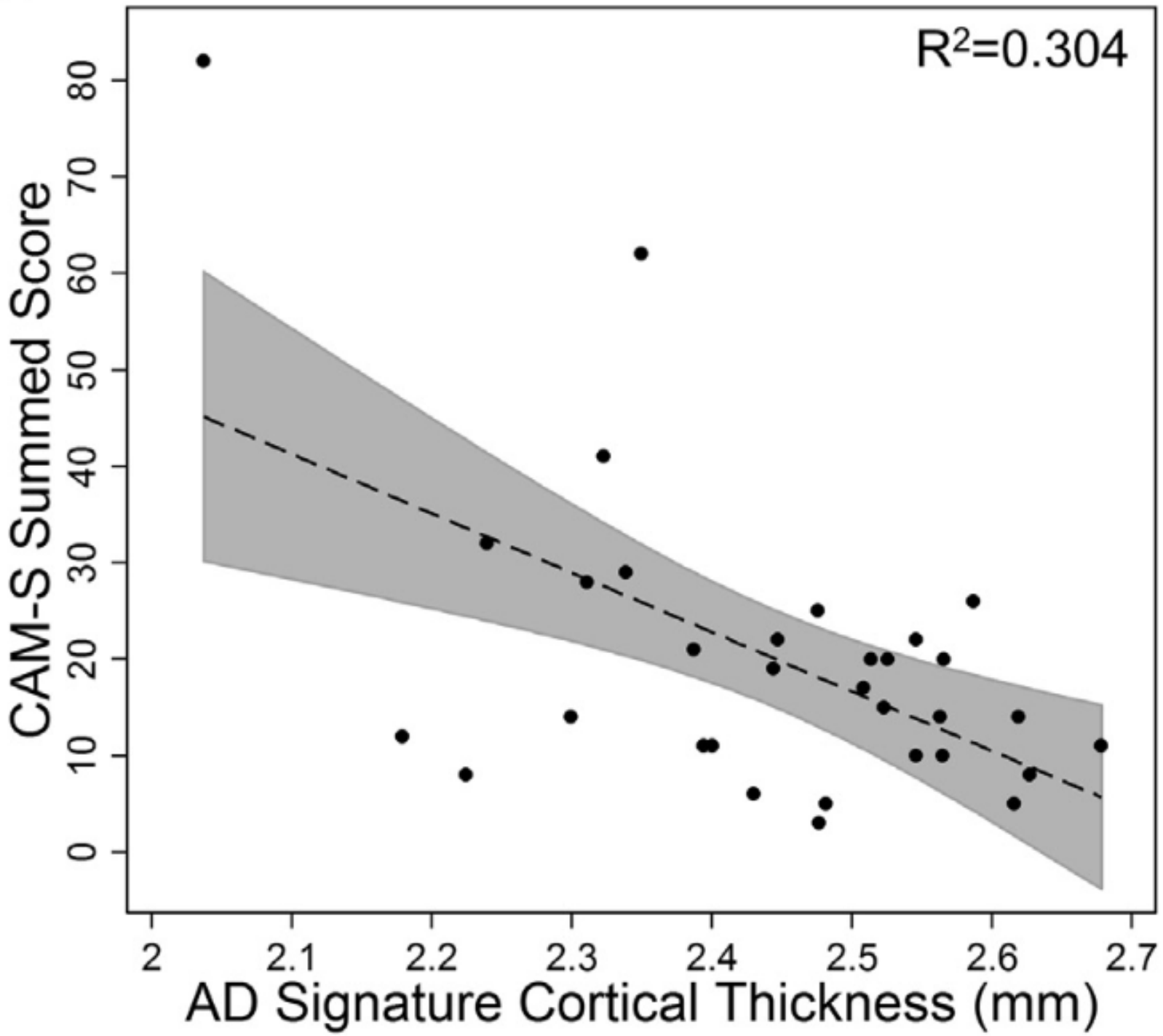
Fig. 1. Brain regions comprising the AD signature: (A, yellow) medial temporal cortex, (B, light blue) inferior temporal gyrus, (C, red) temporal pole, (D, purple) angular gyrus, (E, green) superior frontal gyrus, (F, orange) superior parietal lobule, (G, chartreuse) supramarginal gyrus, (H, aqua) precuneus, and (I, dark blue) inferior frontal sulcus. Abbreviation: AD, Alzheimer's disease. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Association between the AD signature and delirium incidence (CAM)

Model covariates	Odds ratio (SE)	95% CI	*p*-value
Age (y)	1.03 (0.05)	0.95, 1.13	0.40
Female sex	1.55 (0.67)	0.66, 3.62	0.32
AD signature (mm)	1.15 (0.18)	0.84, 1.57	0.38

Table 3
Association between the AD signature and delirium severity (CAM-S peak or CAM-S sum) in the delirium group only (N = 32)

Model covariates	Regression coefficient (SE)	95% CI	*p*-value	R^2	R^2 change[a]
(A) CAM-S Peak					
Age (y)	−0.03 (0.2)	−0.36, 0.29	0.84		
Female sex	0.43 (1.4)	−2.41, 3.27	0.76		
AD signature	−1.2 (0.5)	−2.20, −0.27	0.014	0.21	0.20
(B) CAM-S Sum					
Age (y)	0.01 (0.6)	−1.31, 1.32	0.99		
Female sex	−2.3 (5.6)	−13.83, 9.30	0.69		
AD signature	−6.0 (1.9)	−9.83, −2.13	0.004	0.31	0.25


R²=0.304
CAM-S Summed Score
0
10
20
30
40
50
60
70
80
2
2.1
2.2
2.3
2.4
2.5
2.6
2.7
AD Signature Cortical Thickness (mm)

Preliminary Longitudinal Structural MRI Analysis

- **Accrual of Global Brain Atrophy and WMH Volume** over time across the entire cohort
- **No association** of Global Brain Atrophy and WMH accrual with **delirium** occurrence and severity
- WMH volume increase was mainly a result **expansion of existing lesions**. No evidence of new embolic type infarcts potentially resulting from surgery

SAGES Study / MRI Measures

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- DIFFUSION TENSOR IMAGING (DTI)
  - Microstructural Brain Abnormalities

Original Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
0(00) 1–12

DOI: 10.1177/0271678X16656014
jcbfm.sagepub.com
SAGE

Cerebral blood flow MRI in the nondemented elderly is not predictive of post-operative delirium but is correlated with cognitive performance

Tammy T Hshieh[1,2], Weiying Dai[3,4], Michele Cavallari[5], Charles RG Guttmann[5], Dominik S Meier[5], Eva M Schmitt[2], Bradford C Dickerson[6], Daniel Z Press[7], Edward R Marcantonio[8], Richard N Jones[2,9], Yun Ray Gou[2], Thomas G Travison[2,8], Tamara G Fong[2,7], Long Ngo[8], Sharon K Inouye[2,8,*], David C Alsop[3,*] and on behalf of the SAGES Study Group

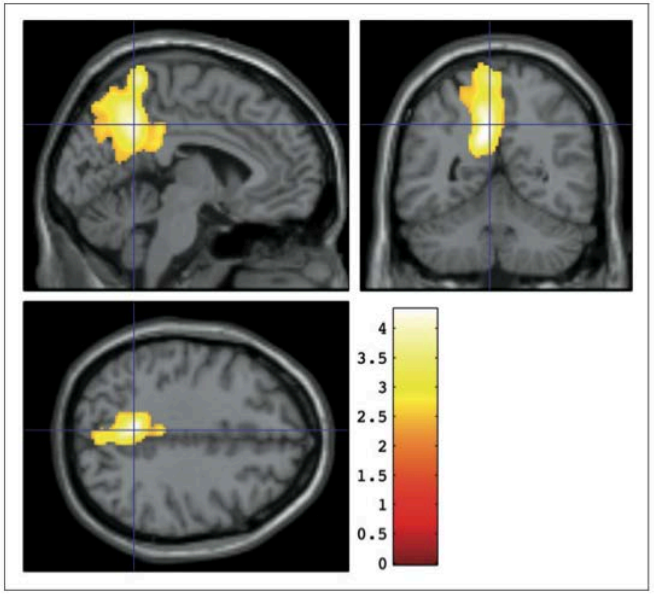

Figure 3. Brain regions with CBF significantly associated with the General Cognitive Performance composite measure. A voxel threshold of $p < 0.01$ and a corrected cluster threshold of $p < 0.05$ were applied. Colors indicate the t statistic for the suprathreshold cluster overlaid on the SPM canonical T1 image.

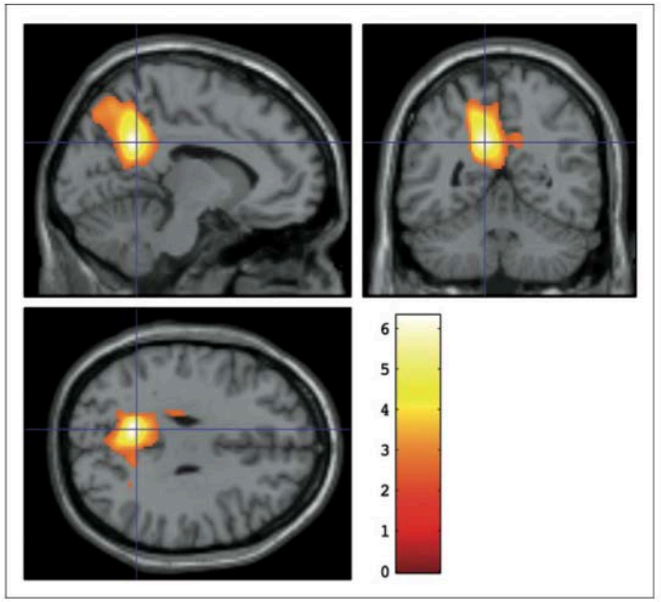

Figure 2. Brain regions with CBF significantly associated with the Hopkins Verbal Learning Test – Revised (HVLT-R) total scores. A voxel threshold of $p < 0.01$ and a corrected cluster threshold of $p < 0.05$ were applied. Colors indicate the t statistic for the suprathreshold cluster overlaid on the SPM canonical T1 image.

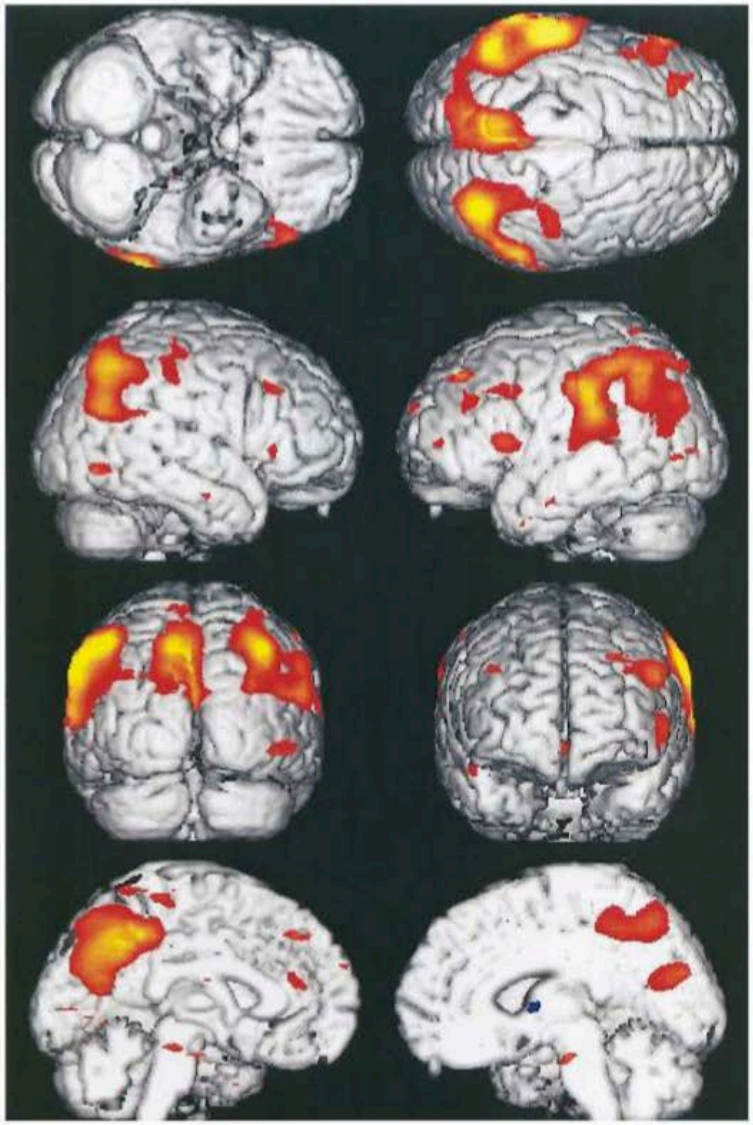

Fig 4. Significant correlations between decreased regional blood flow and severity of disease as measured by the decrease in Mini-Mental State Examination score. Significant results are overlaid in color on top of a surface rendering of the brain. Yellow colors are the most significant and dark red are the least significant.

(Alsop et al., Ann Neurol 2000)

- Reduced flow and metabolism in the posterior cingulate is the earliest functional predictor of cognitive impairment and Alzheimer's disease

- The absence of an association between blood flow in this region and delirium argues against a role for incipient AD in the risk of delirium in elderly subjects without dementia.

SAGES Study / MRI Measures

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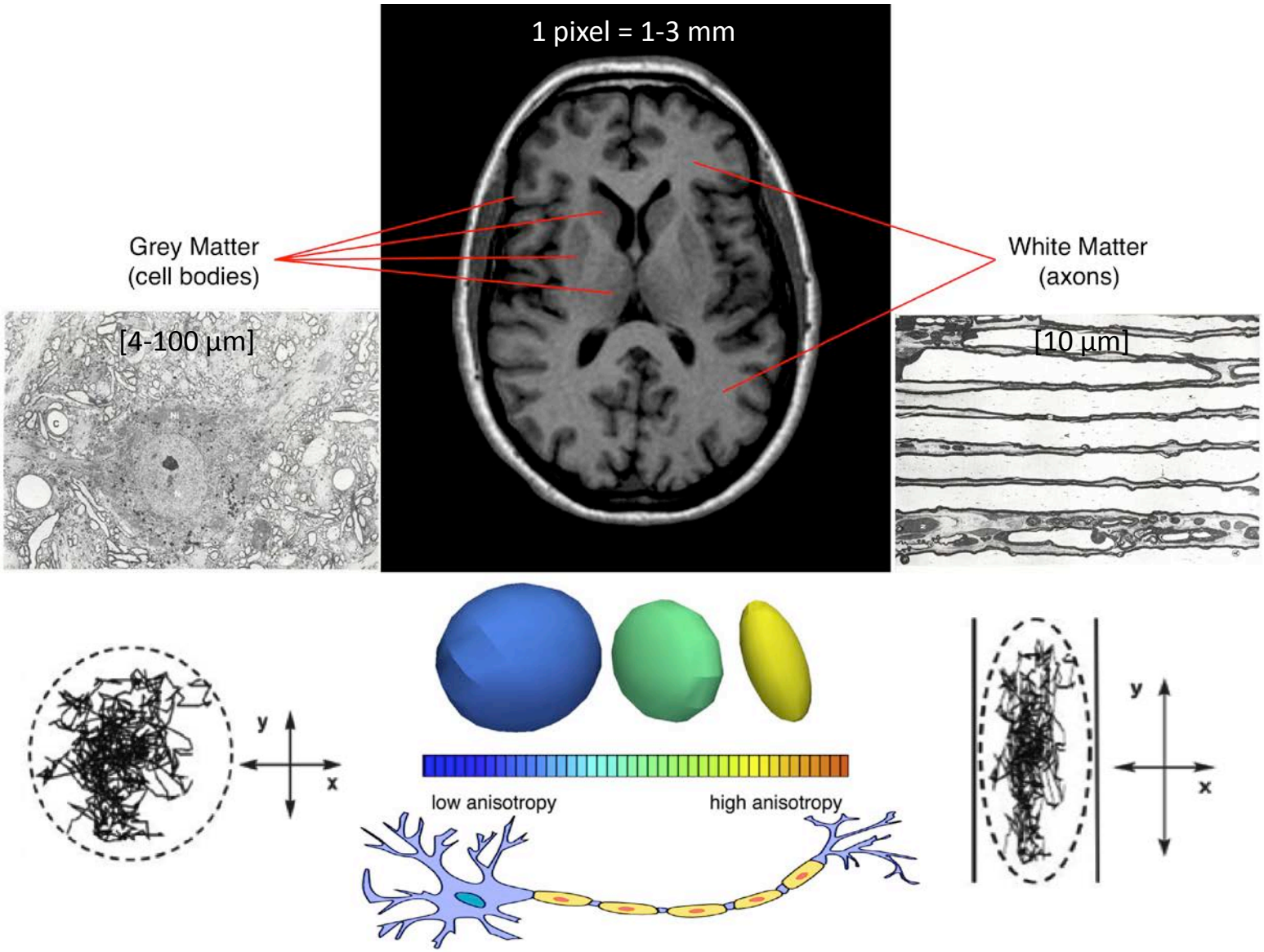
  - Microstructural Brain Abnormalities

DTI Abnormalities Indicate Brain Microstructural Damage



BRAIN
A JOURNAL OF NEUROLOGY

Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI

Michele Cavallari,[1] Weiying Dai,[2,3] Charles R. G. Guttmann,[1] Dominik S. Meier,[1] Long H. Ngo,[4] Tammy T. Hshieh,[5,6] Amy E. Callahan,[2] Tamara G. Fong,[6,7] Eva Schmitt,[6] Bradford C. Dickerson,[8,9,10] Daniel Z. Press,[7] Edward R. Marcantonio,[4] Richard N. Jones,[11] Sharon K. Inouye[4,6,*] and David C. Alsop[2,*] on behalf of the SAGES Study Group

	Delirium incidence				Delirium severity			
	AD	FA	MD	RD	AD	FA	MD	RD
Cerebellum	*ns*	$\downarrow\downarrow^{L}$	$\uparrow^{*,R}$	$\uparrow\uparrow^{*,R}$	$\uparrow^{**,B}$	*ns*	$\uparrow^{**,B}$	$\uparrow^{**,B}$
Cingulum	*ns*	$\downarrow\downarrow^{B}$	*ns*	*ns*	$\uparrow^{B}$	$\downarrow\downarrow^{B}$	$\uparrow^{B}$	$\uparrow\uparrow^{B}$
Corpus callosum	*ns*	$\downarrow\downarrow$	$\uparrow$	$\uparrow\uparrow$	*ns*	$\downarrow\downarrow$	$\uparrow$	$\uparrow\uparrow$
Hippocampus	*ns*	*ns*	*ns*	*ns*	$\uparrow\uparrow^{**,L}$	*ns*	$\uparrow\uparrow^{**,B}$	$\uparrow\uparrow^{**,B}$
Internal capsule	*ns*	$\downarrow\downarrow^{L}$	*ns*	*ns*	*ns*	$\downarrow\downarrow^{L}$	$\uparrow\uparrow^{**,B}$	$\uparrow\uparrow^{*,L}$
Occipital lobe	*ns*	*ns*	*ns*	*ns*	*ns*	$\downarrow\downarrow^{R}$	*ns*	$\uparrow\uparrow^{B}$
Parietal lobe	*ns*	*ns*	*ns*	*ns*	*ns*	$\downarrow\downarrow^{R}$	$\uparrow^{R}$	$\uparrow^{R}$
Temporal lobe	*ns*	*ns*	*ns*	*ns*	$\uparrow\uparrow^{**,L}$	*ns*	$\uparrow\uparrow^{**,B}$	$\uparrow\uparrow^{**,B}$
Thalamus	*ns*	$\downarrow\downarrow^{L}$	*ns*	*ns*	$\uparrow\uparrow^{*,L}$	$\downarrow\downarrow^{B}$	$\uparrow\uparrow^{**,B}$	$\uparrow\uparrow^{**,B}$

Longitudinal diffusion changes following postoperative delirium in older people without dementia

Michele Cavallari, MD, PhD
Weiying Dai, PhD
Charles R.G. Guttmann, MD
Dominik S. Meier, PhD
Long H. Ngo, PhD
Tammy T. Hshieh, MD, MPH
Tamara G. Fong, MD, PhD
Eva Schmitt, PhD
Daniel Z. Press, MD
Thomas G. Travison, PhD
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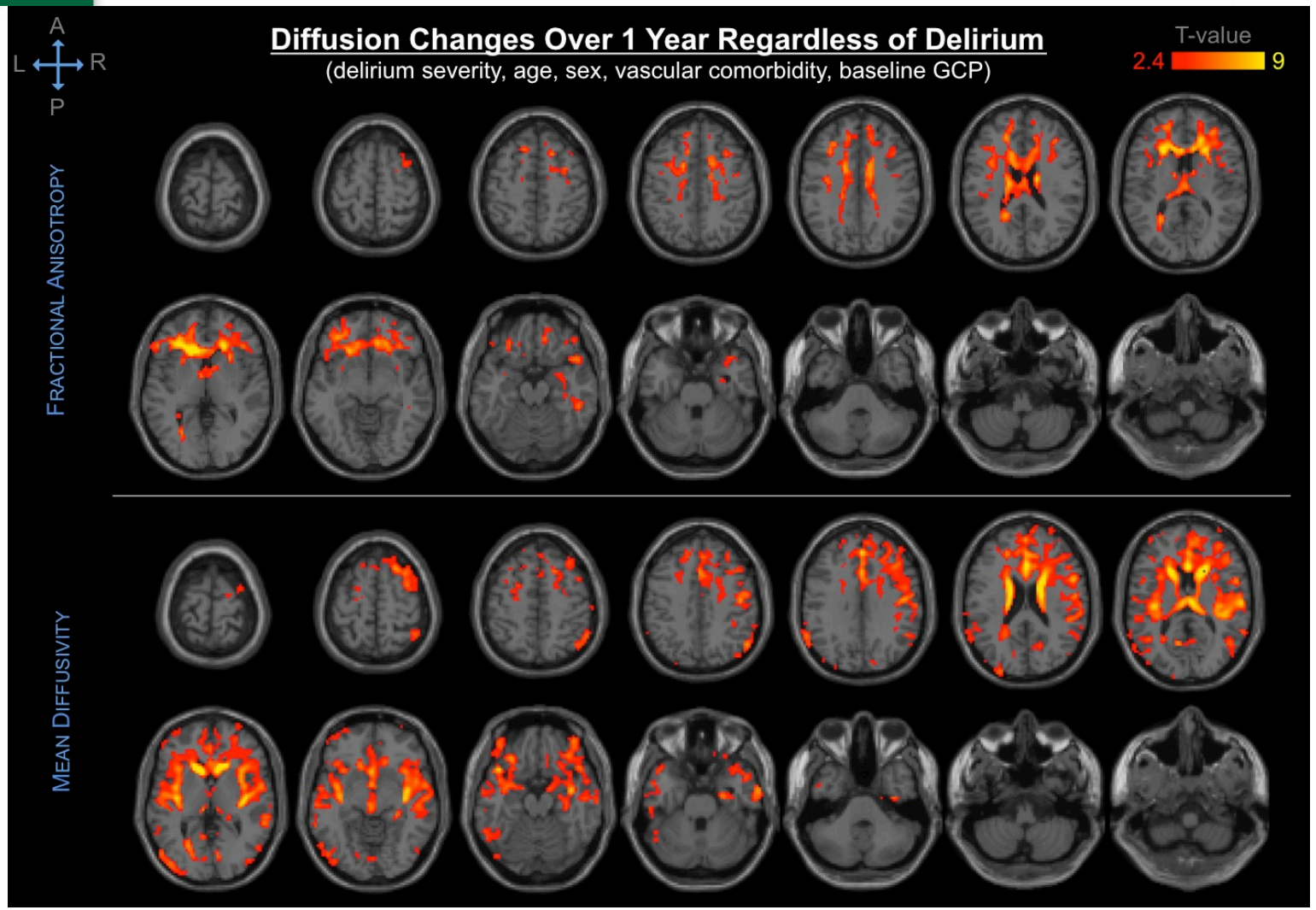
Richard N. Jones, ScD
Sharon K. Inouye, MD, MPH*
David C. Alsop, PhD*
On behalf of the SAGES Study Group



Neurology® 2017;89:1020-1027

WHAT WE LEARNED

- Microstructural tissue damage captured by **Diffusion MRI** underlies the occurrence of delirium.
- The spatial distribution and predominance of diffusion findings over dementia sensitive techniques like gray matter atrophy and perfusion suggest that **delirium is associated more with age related decline in white matter pathways** than neuronal loss and reduced perfusion or metabolism.
- Implications regarding the pathogenesis of delirium can come from the **regional specificity** of the abnormalities associated with delirium.
  - Baseline DTI abnormalities predisposing to delirium showed two separate phenomena (AD-like, and frontal/parietal)
  - Longitudinal DTI abnormalities seem more diffused, but the observed effect was too small to localize abnormalities with confidence

IMPORTANT FACTORS

Baseline scan

Control for confounders

Inclusion/exclusion criteria

- Generalizability
- Sensitivity/specificity

FUTURE WORK

- Relationship between **delirium and dementia**
  - long-term follow-up cognitive data
- Further explore the **regional specificity** of the relationship between brain damage and delirium
  - Regional WMH
  - Structural/Functional Connectivity (DTI Tractography, Resting-State fMRI)