Risonanza magnetica funzionale, metodiche di studio avanzate e nuove frontiere nello studio delle disautonomie

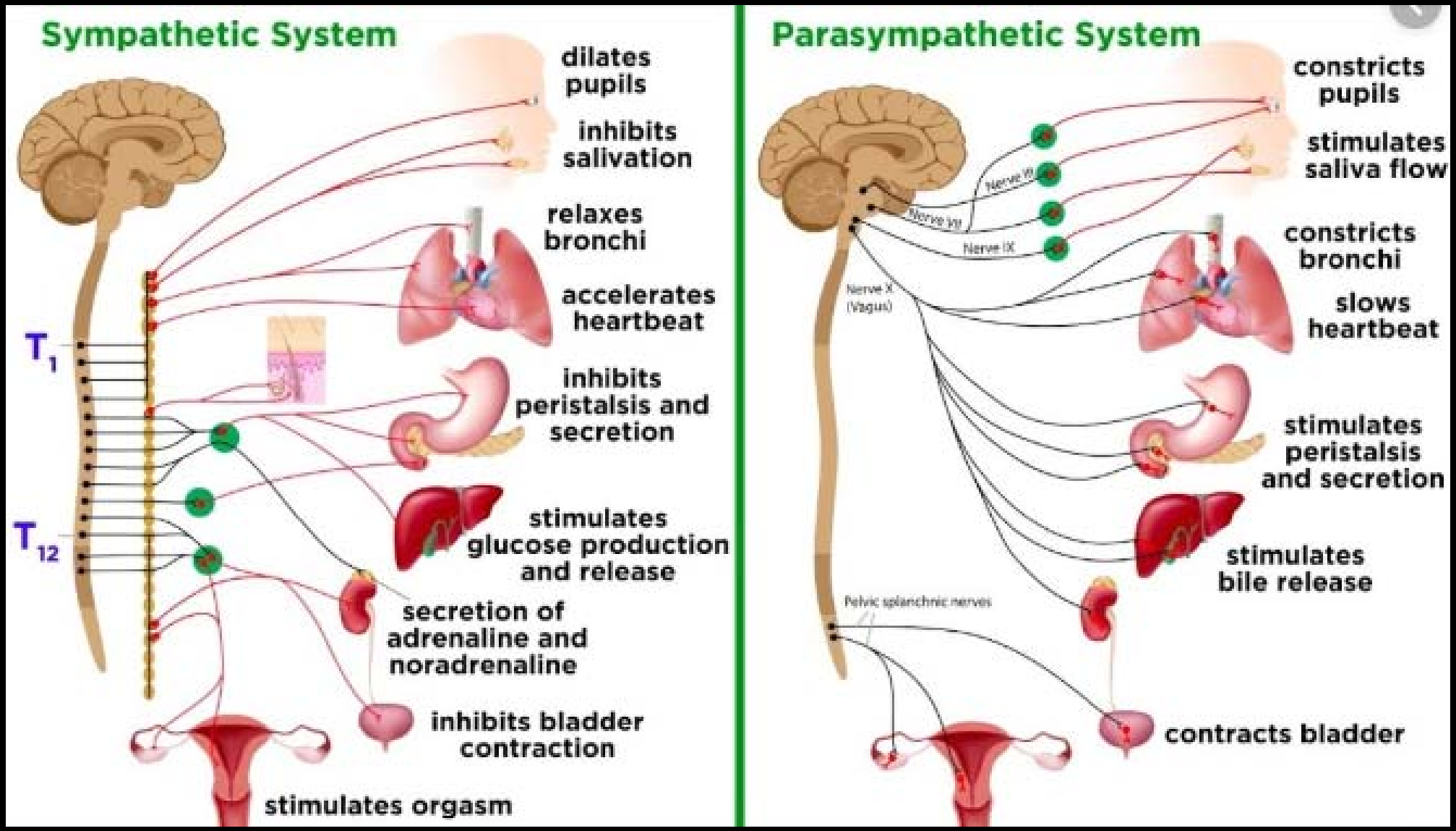
Marco Bozzali

'Rita Levi Montalcini' Department of Neuroscience,
University of Torino, Turin, Italy

Outline

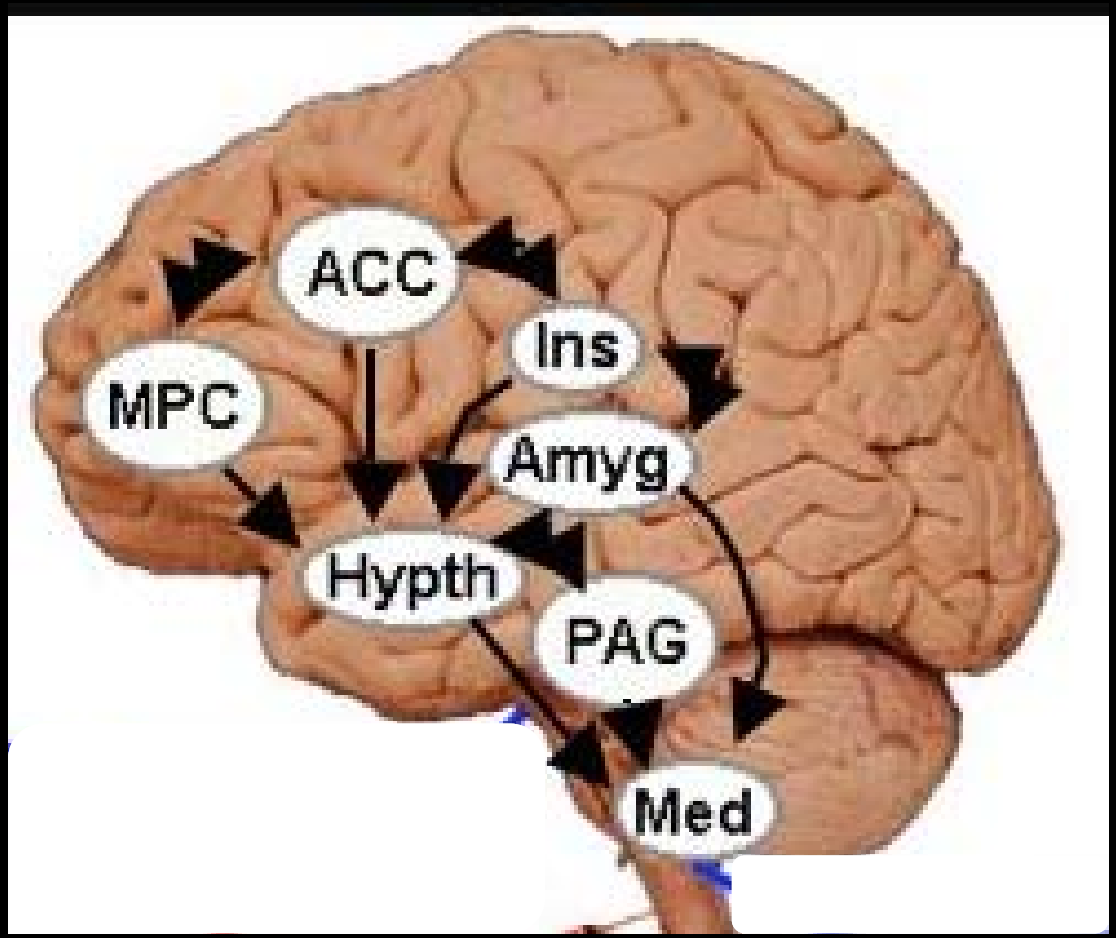
- Introduction
- Quantitative MRI (task driven fMRI; resting state fMRI)
- fMRI experiments in healthy subjects
- Alpha-synucleinopaties (DLB; PD)

Introduction



Introduction

The central autonomic network (CAN) is a complex network of brainstem and forebrain regions that are implicated in baseline autonomic nervous system (ANS) function, as well as in the modulation of ANS in response to changing environments.



Introduction

PHILOSOPHICAL TRANSACTIONS A

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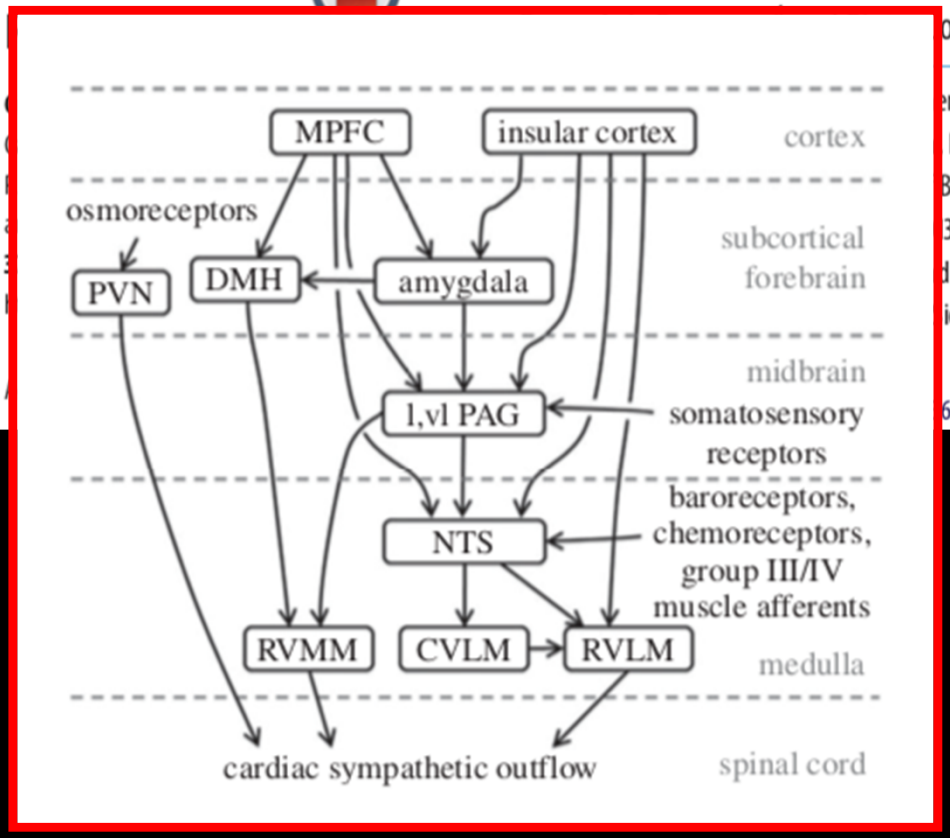
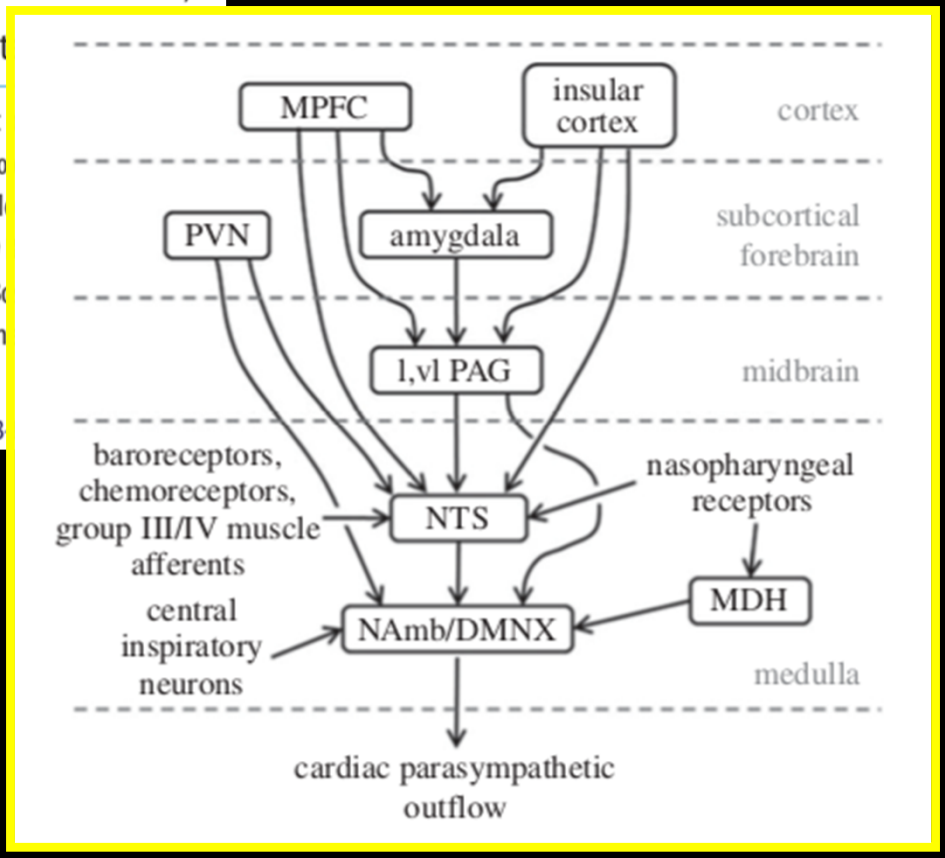
Brain–heart interactions: physiology and clinical implications

Alessandro Silvani[1], Giovanna Calandra-Buonaura[2,3],

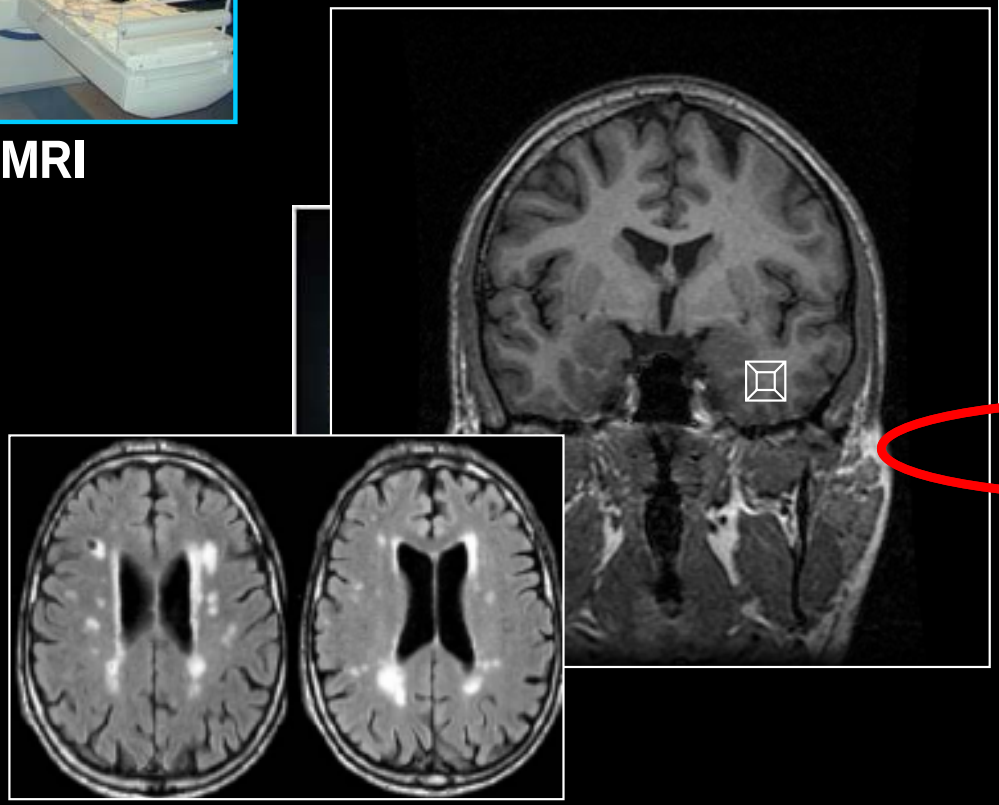




MRI – a powerful, non invasive tool for brain investigation *in vivo*

MRI

"quantitative" MRI



What can we measure?

T1

T2

Diffusion tensor: mean diffusivity, anisotropy, fiber directionality,…

Volumetrics

fMRI

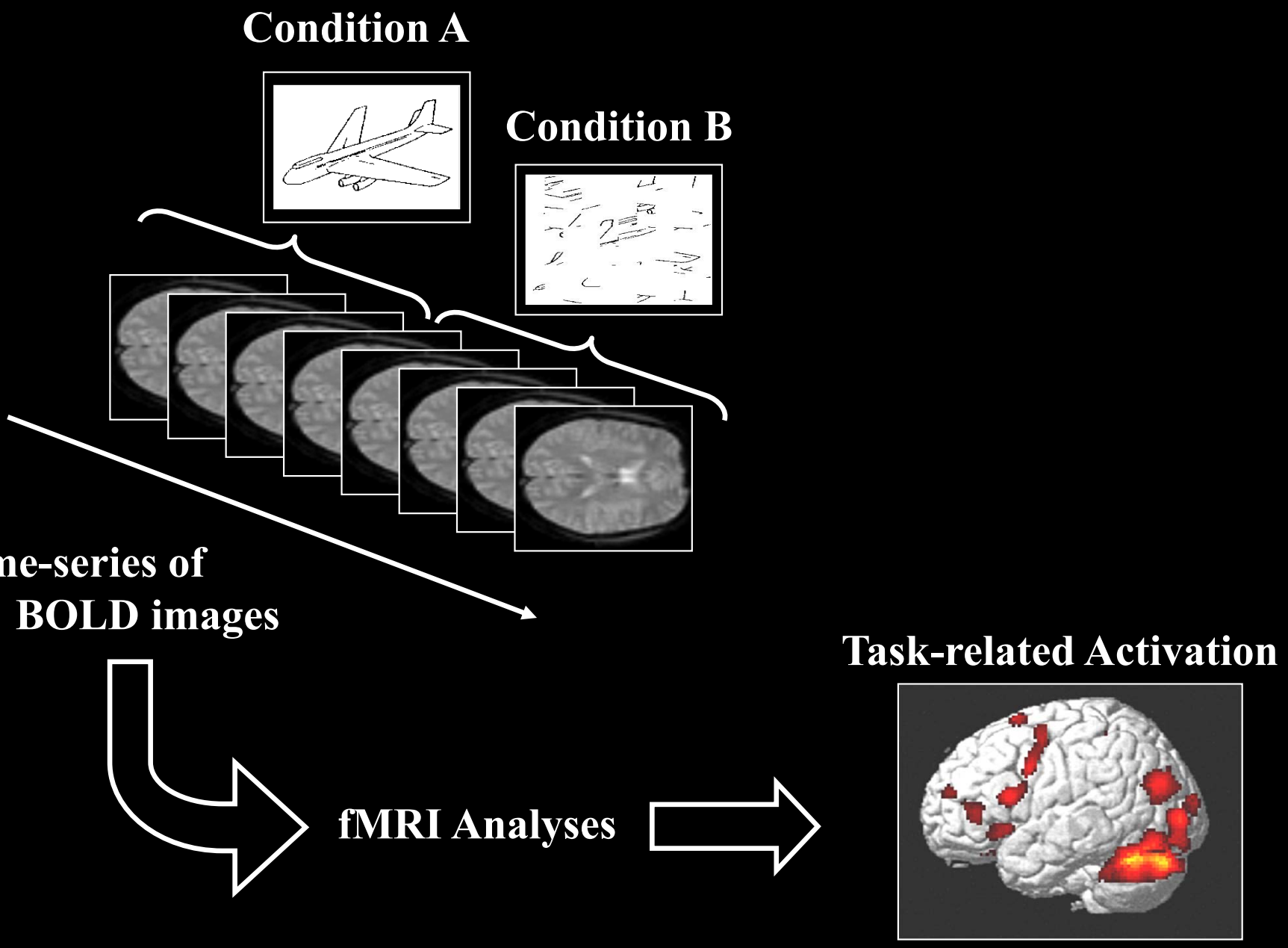
Perfusion: CBF, CBV,MTT,…

MT: MTR, qMT,…. ^{1}HMRS

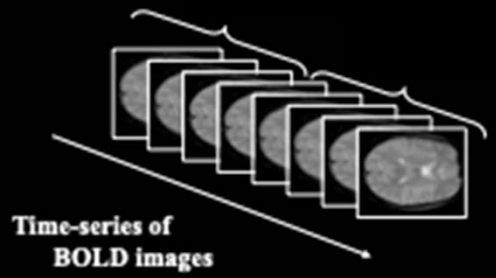
•Etc…

These are all INDIRECT measures of physical quantities which allow the macro-microscopic tissue structure and damage to be assessed

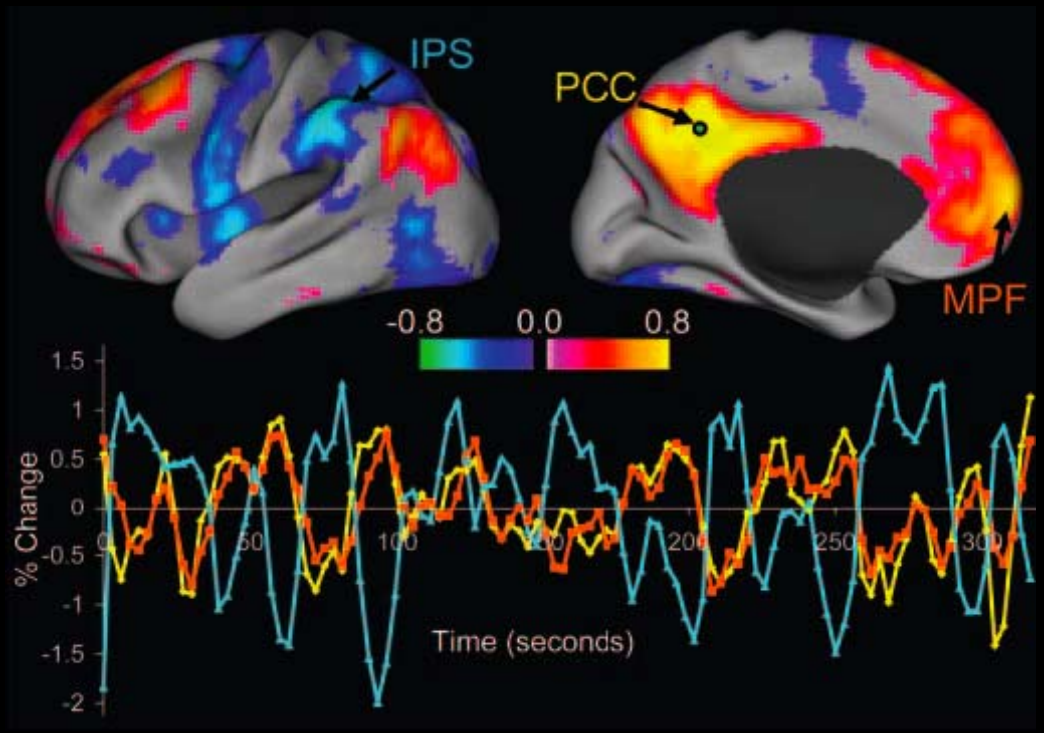
functional MRI – task driven



functional MRI – at rest

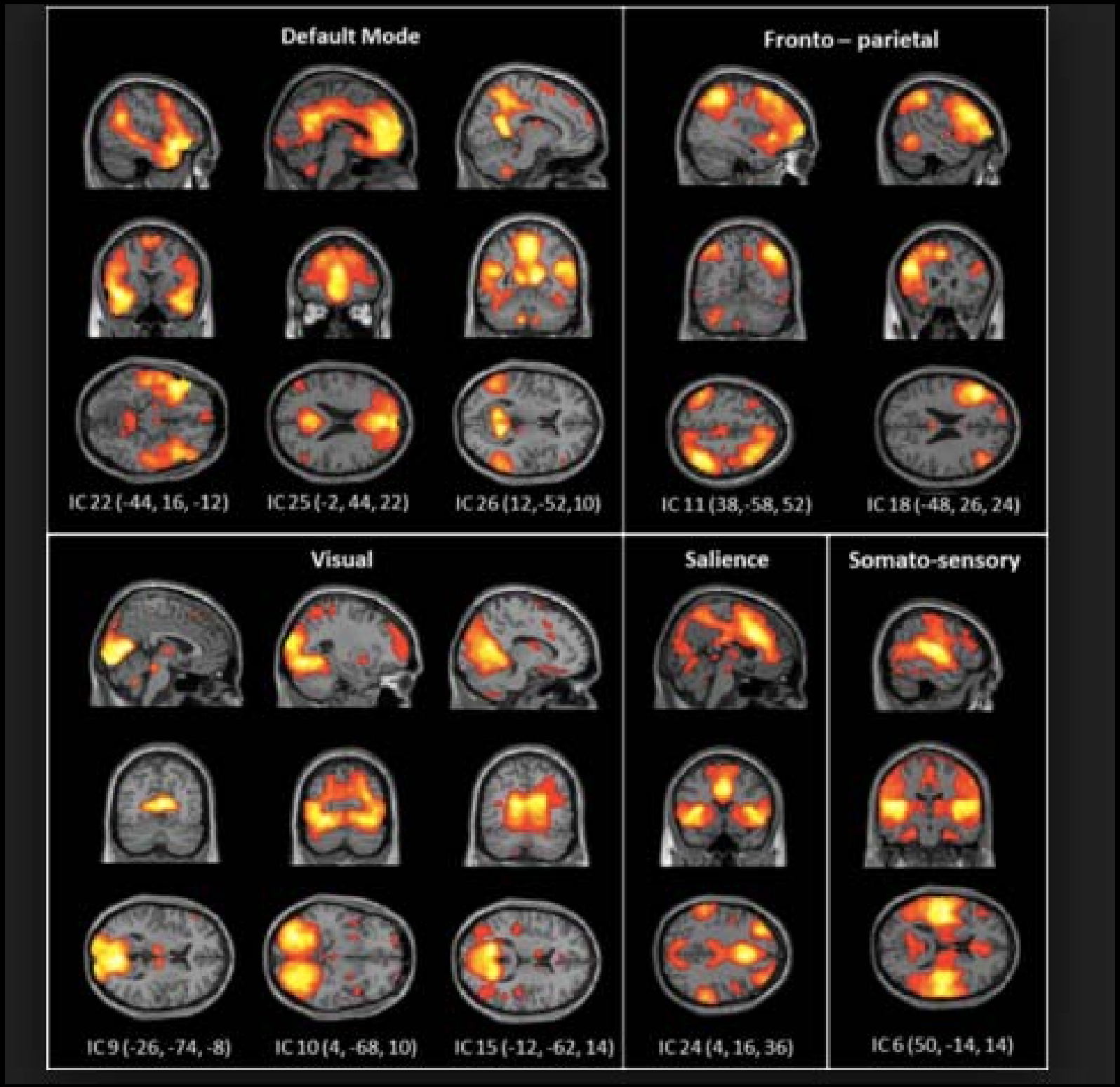


Low Frequency Intrinsic Correlations between PCC and all other Voxels in the Brain during Resting Fixation



0.01 Hz < f < 0.08 Hz

Fox MD et al, *PNAS* 2005; 102, 9673-9678


Default Mode
Fronto – parietal
IC 22 (-44, 16, -12)
IC 25 (-2, 44, 22)
IC 26 (12,-52,10)
IC 11 (38,-58, 52)
IC 18 (-48, 26, 24)
Visual
Salience
Somato-sensory
IC 9 (-26, -74, -8)
IC 10 (4, -68, 10)
IC 15 (-12, -62, 14)
IC 24 (4, 16, 36)
IC 6 (50, -14, 14)

functional MRI and ANS -Metanalysis

The Journal of Neuroscience, June 19, 2013 • 33(25):10503–10511 • 10503

Systems/Circuits

The Auto
Meta-An

Florian Beissner,[1]
[1]Pain and Autonomics
Medical Psychology, Lu
Radiology, Massachuse

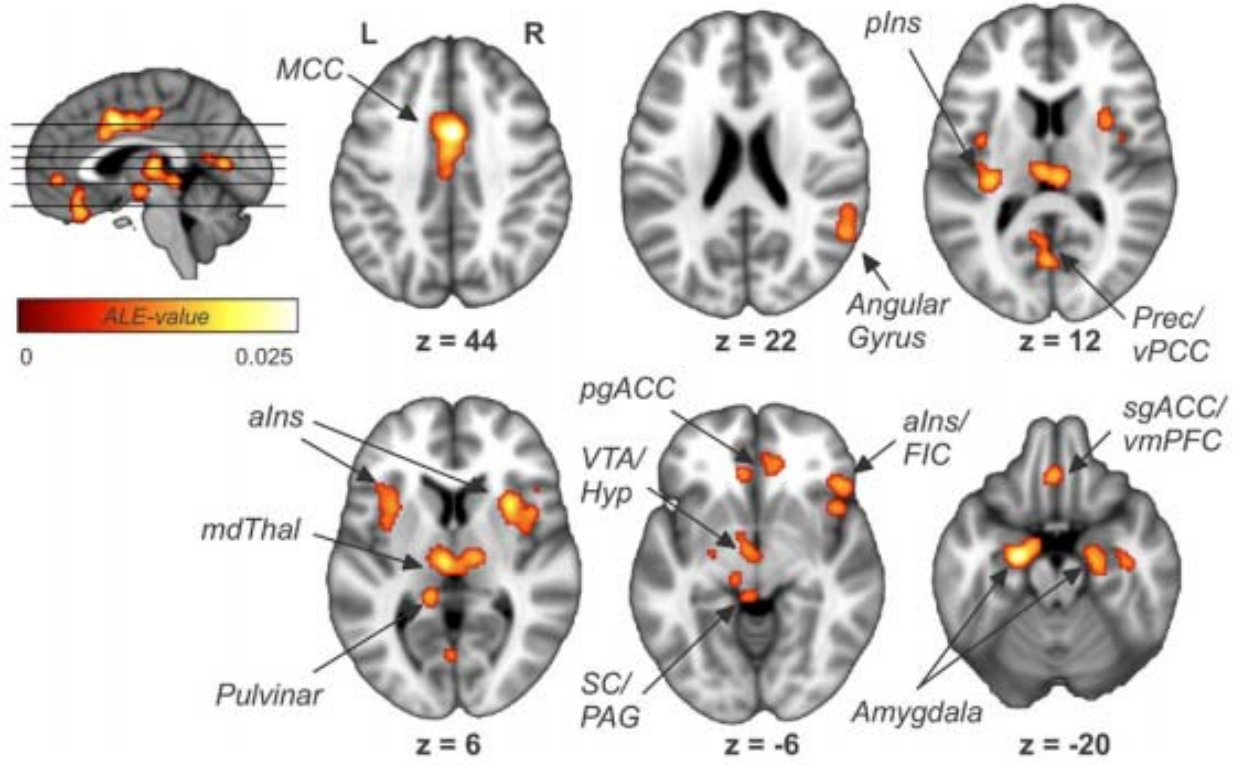
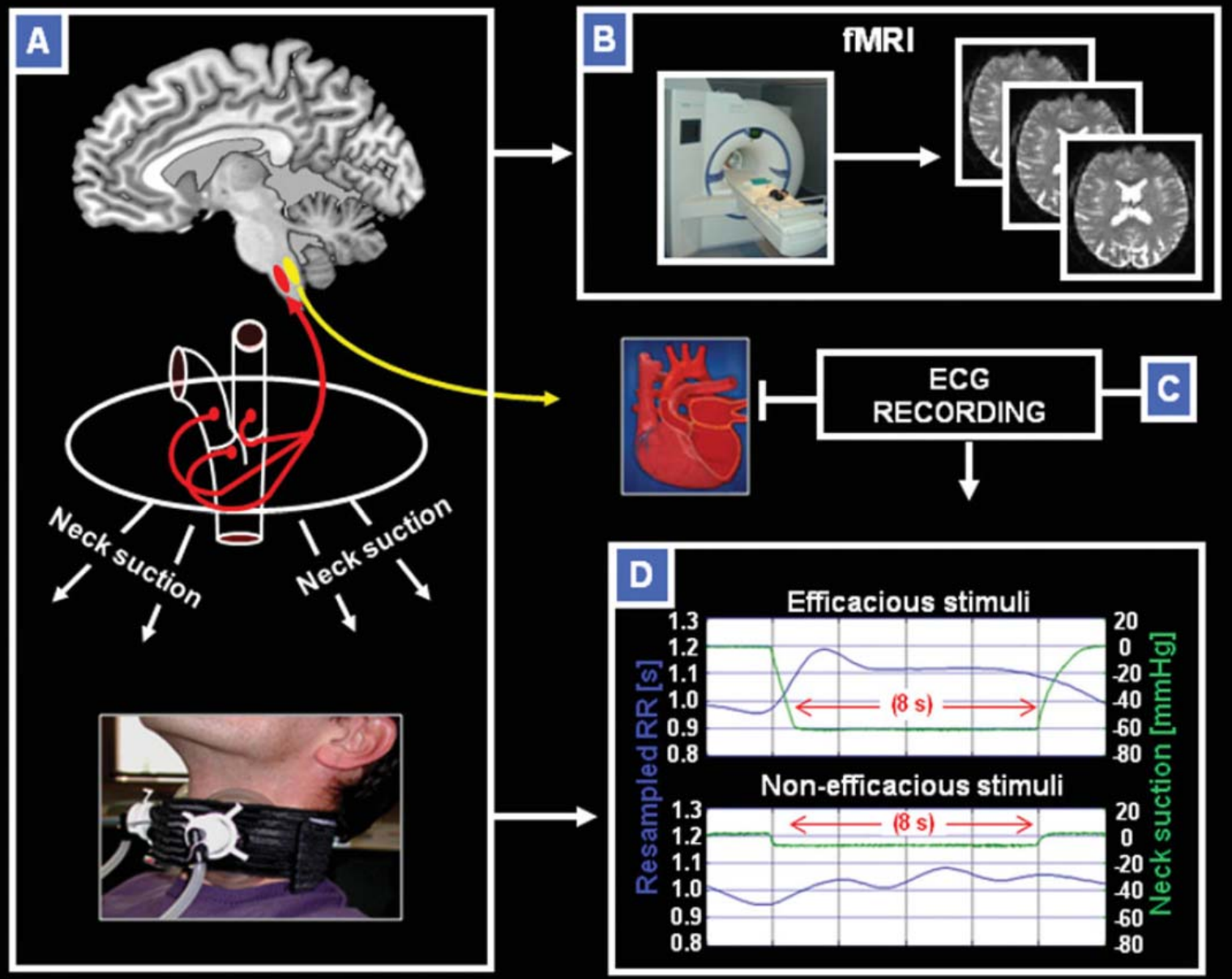


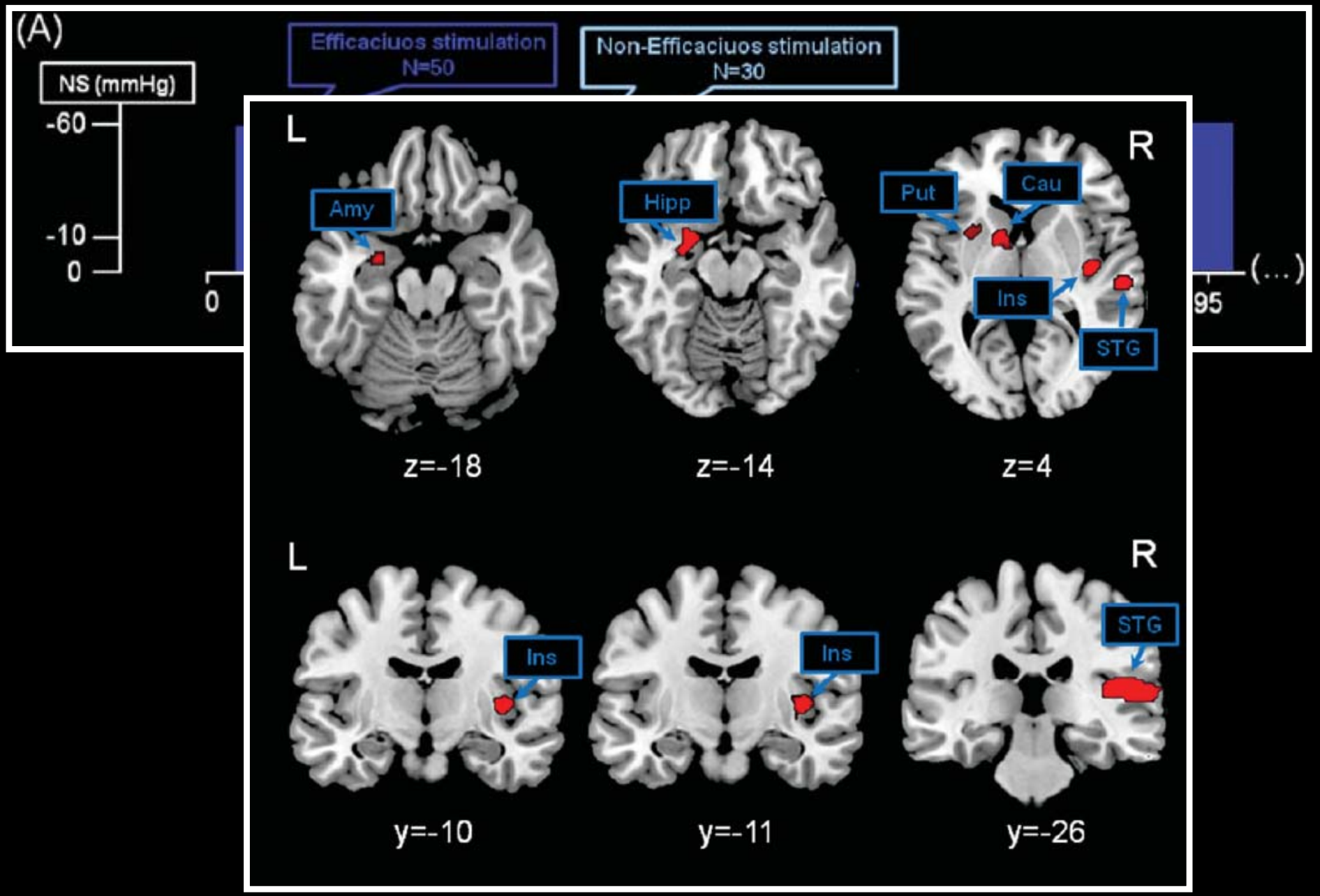
Figure 1. Results of the pooled analyses of all studies showing general brain regions involved in autonomic processing. Prec, Precuneus; vPCC, ventral posterior cingulate cortex; mdThal, mediodorsal thalamus; pgACC, pregenual ACC; VTA, ventral tegmental area; Hyp, hypothalamus; SC, superior colliculus; PAG, periaqueductal gray; FIC, frontoinsular cortex; L, left; R, right.

The Autonomic Nervous System



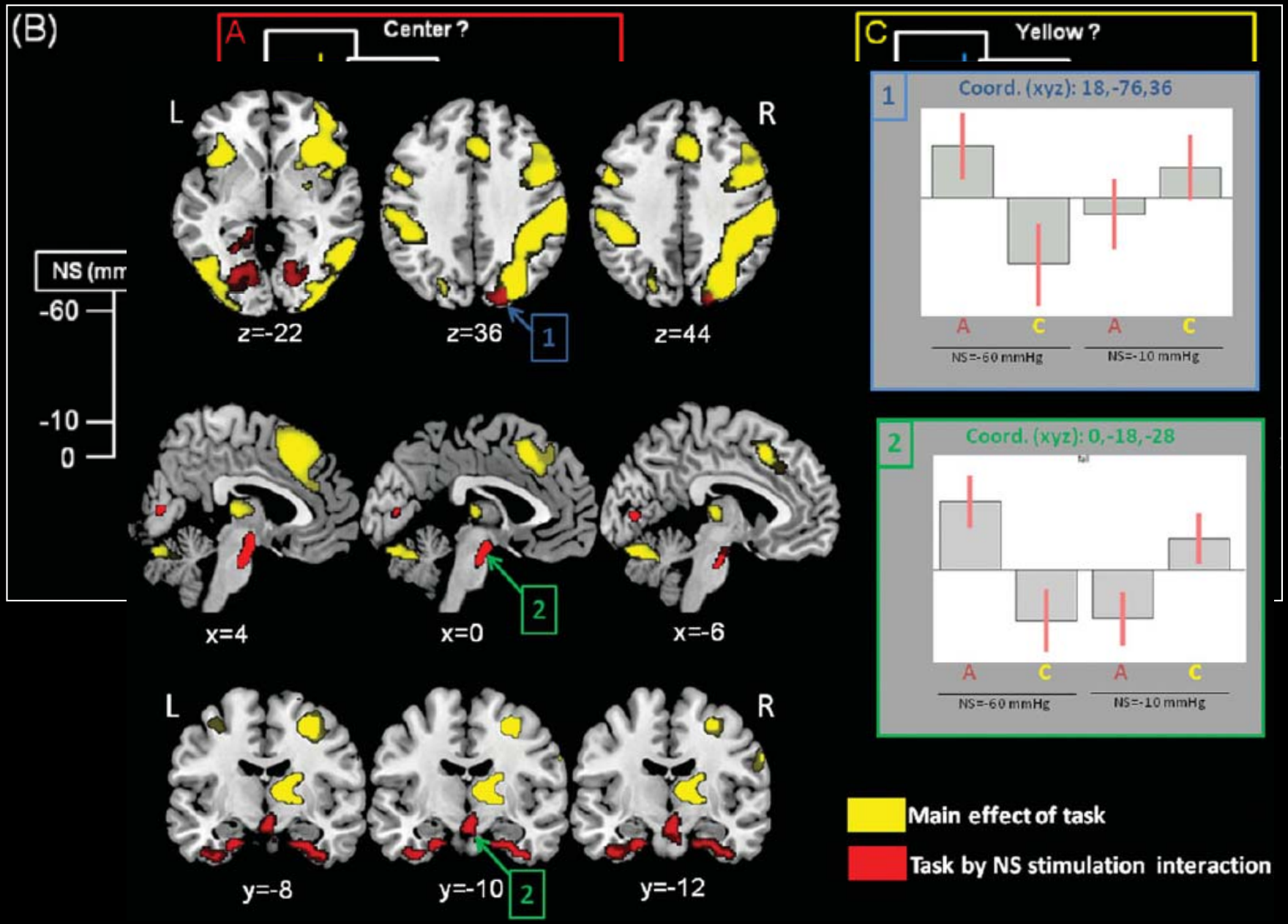
Basile et al., Hum Brain Mapp 2013;34:1605-1614.

The Autonomic Nervous System



Basile et al., Hum Brain Mapp 2013;34:1605-1614.

The Autonomic Nervous System



Basile et al., Hum Brain Mapp 2013;34:1605-1614.

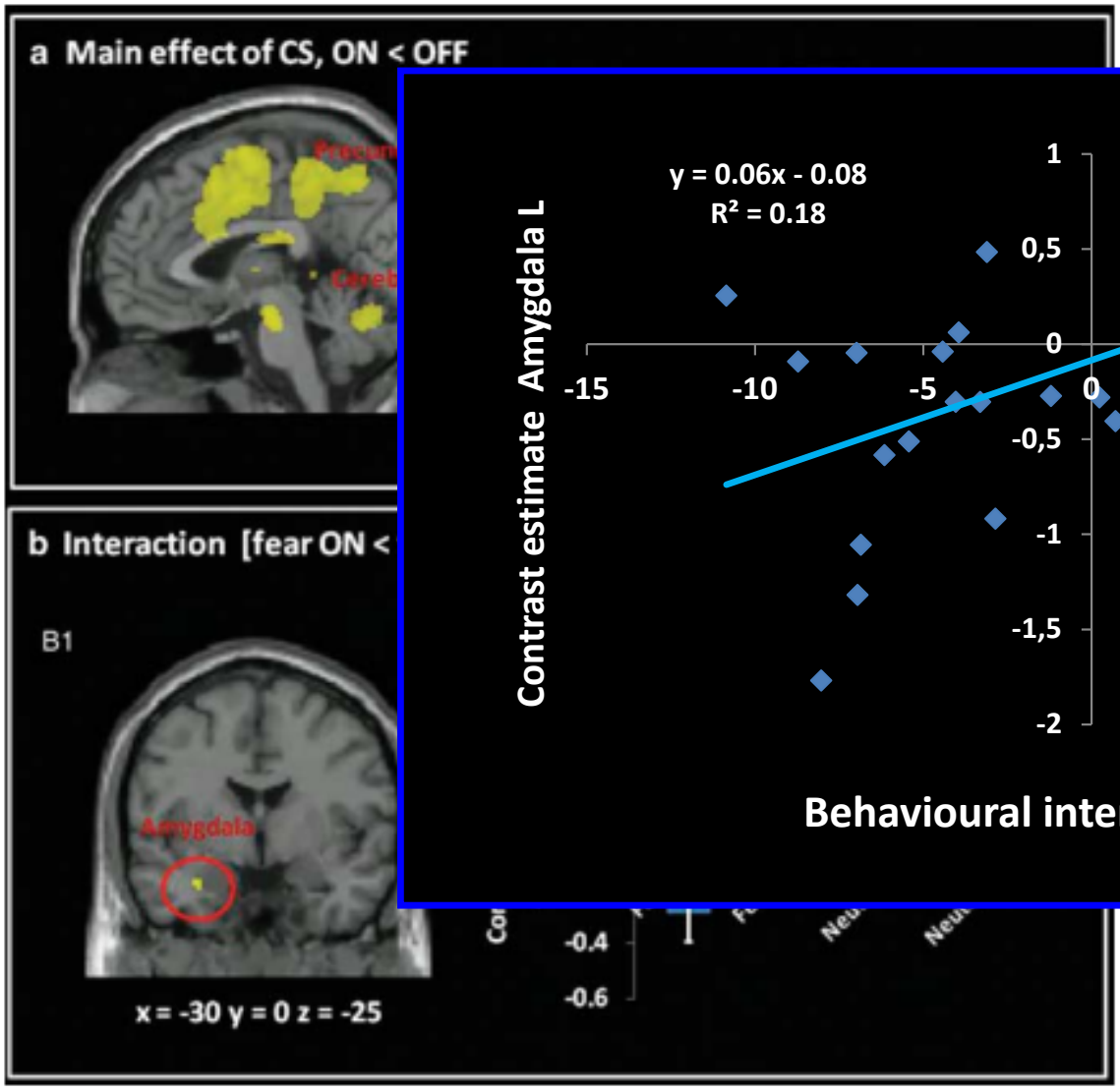
Neuropsychopharmacology (2015) 40, 1649–1658

www.neuropsychopharmacology.org

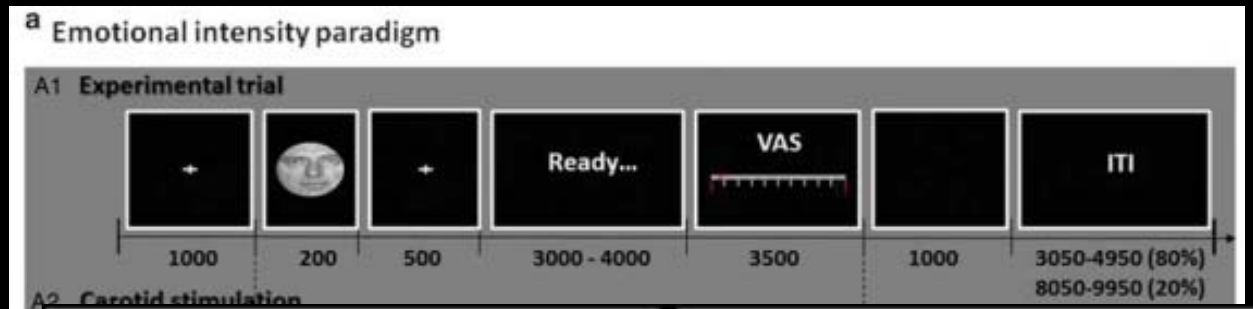
Effect of Parasympathetic St… Appraisal of Fearful Express…

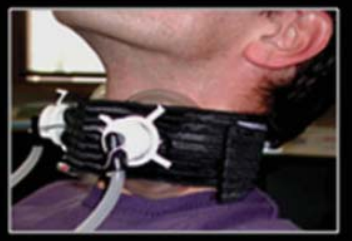
Elena Makovac*,[1], Sarah N Garfinkel[2,3], Andrea Mara Cercignani[1,5], Giovanni Calcagnini[6], Euge… Carlo Caltagirone[4,9], Marco Bozzali[1] and Hugo…

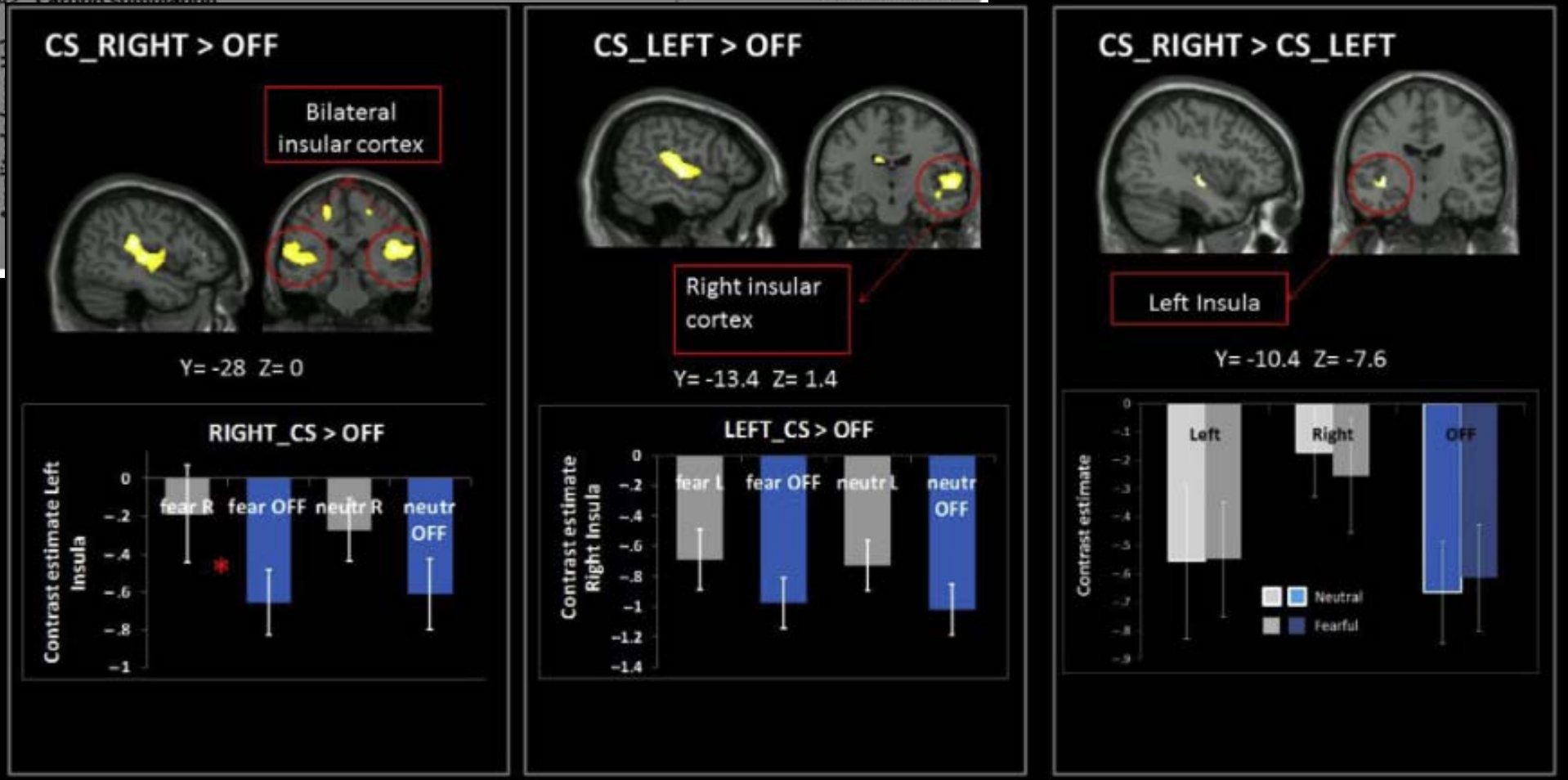
[1]Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Ro… Falmer, Brighton, UK; [3]Sackler Centre for Consciousness Scienc… Behavioural Neurology, IRCCS Santa Lucia Foundation, Rome, … University of Sussex, Brighton, UK; [6]Department of Technology a… Alma Mater Studiorum-University of Bologna, Bologna, Italy; [8]IR… Neuroscience, University of Rome 'Tor Vergata', Rome, Italy



Unilateral carotid stimulation and emotion processing



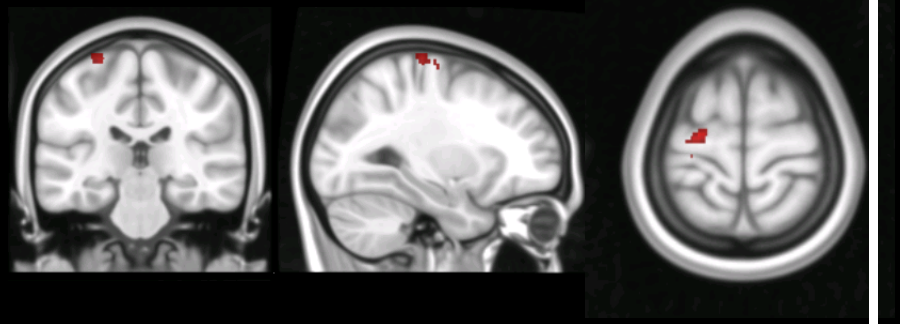


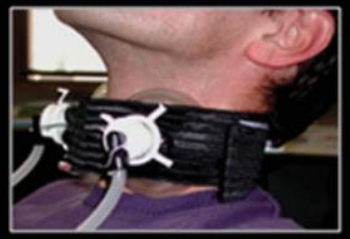


Macovak et al., Cortex 99 (2018) 200e212

Resting State fMRI

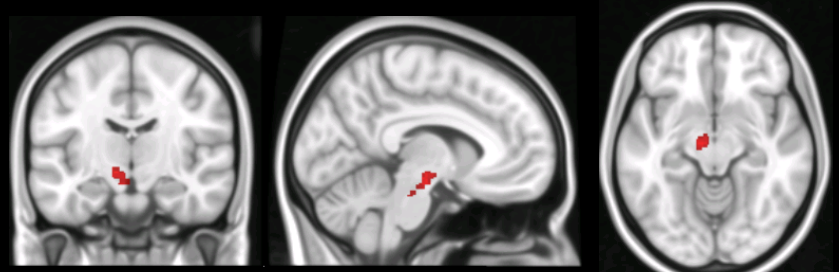
SENSORY-MOTOR



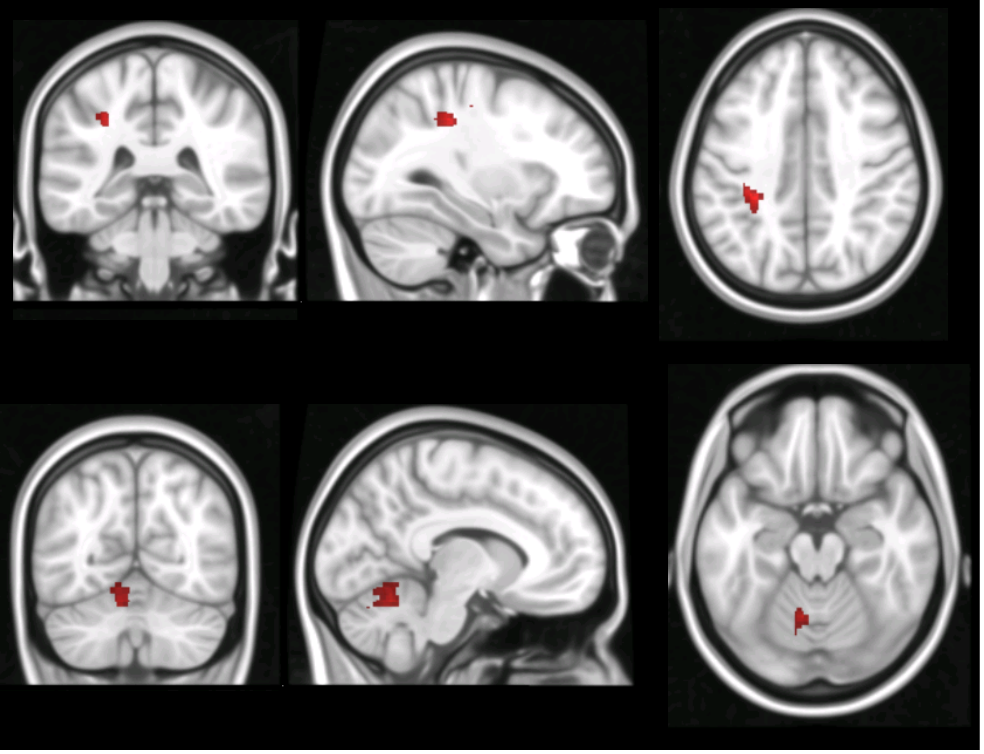


P-FWE cluster level corr < 0.05

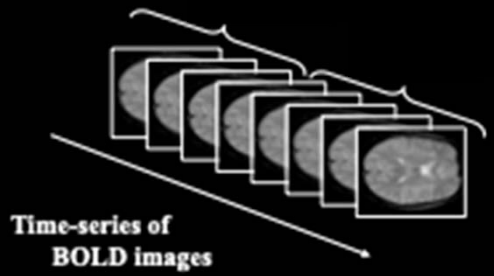
VISUAL

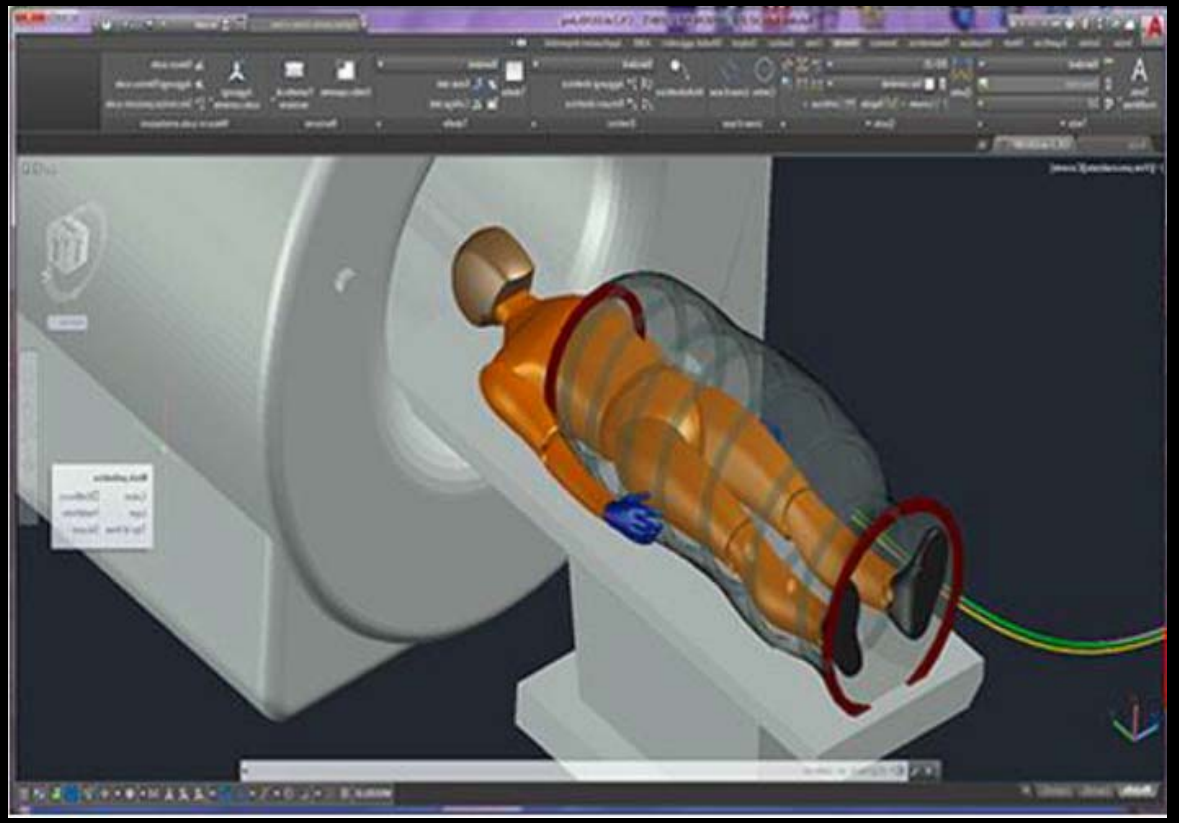


DORSAL ATTENTION



fMRI with lower body negative pressure application





J Physiol 569.1 (2005) pp 331–345

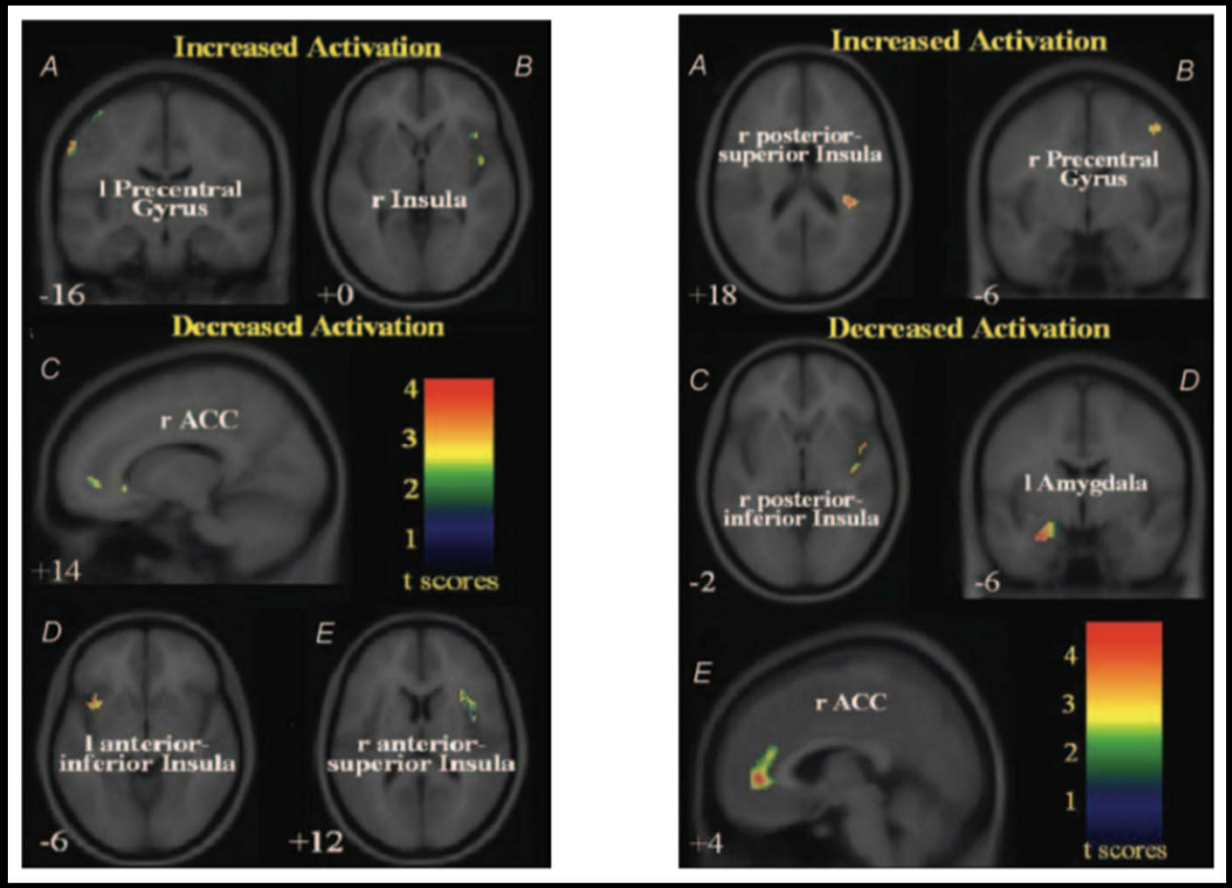
Cortical regions associated with autonomic cardiovascular regulation during lower body negative pressure in humans

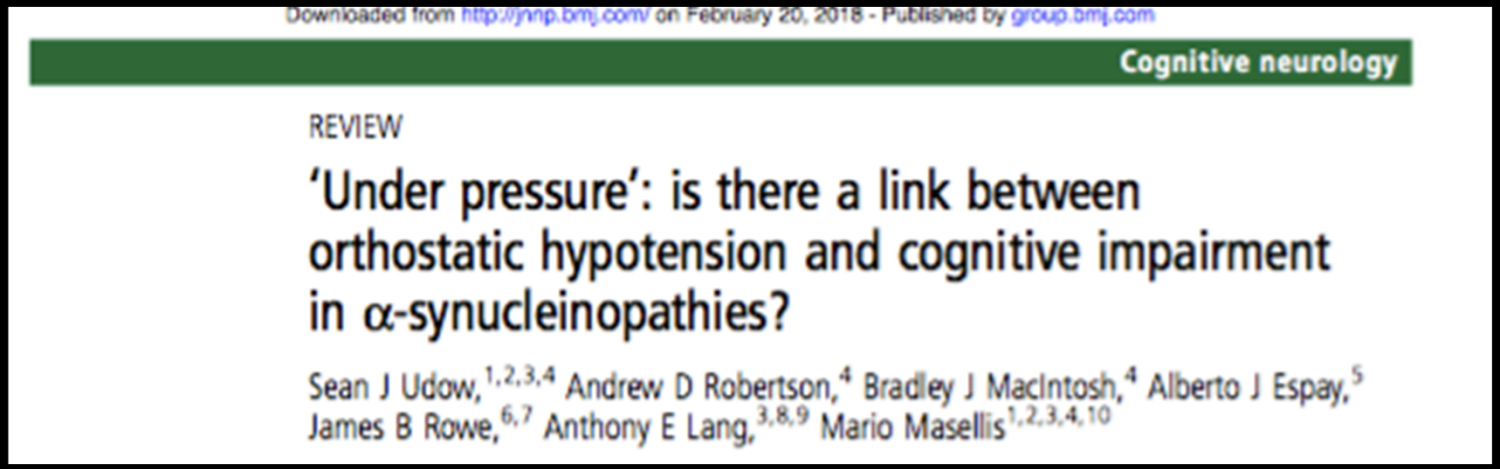
Derek S. Kimmerly[1], Deborah D. O'Leary[1], Ravi S. Menon[2], Joseph S. Gati[2] and J. Kevin Shoemaker[1,3]

[1]*Neurovascular Research Laboratory, Faculty of Health Sciences and School of Kinesiology, The University of Western Ontario, London, Ontario, Canada N6A 3K7*

[2]*Advanced Imaging Laboratories, Robarts Research Institute, London, Ontario, Canada N6A 5K8*

[3]*Department of Physiology and Pharmacology, The University of Western Ontario, London, Ontario, Canada N6A 3K7*





REVIEW

'Under pressure': is there a link between orthostatic hypotension and cognitive impairment in α-synucleinopathies?

Sean J Udow,[1,2,3,4] Andrew D Robertson,[4] Bradley J MacIntosh,[4] Alberto J Espay,[5] James B Rowe,[6,7] Anthony E Lang,[3,8,9] Mario Masellis[1,2,3,4,10]

Ten 'direct-evidence papers' were identified, seven of which reported a positive association between OH and cognitive impairment, while seven of 12 'indirect-evidence papers' similarly did as well.

The papers that reported no association between OH and cognitive impairment used less sensitive measures of cognition.

A relationship between OH and cognitive impairment in patients with α-synucleinopathies exists, but the underlying mechanisms remain unclear.

Three hypotheses are proposed: (1) OH and cognitive impairment occur concurrently due to diffuse brain and peripheral deposition of α-synuclein, (2) OH-mediated cerebral hypoperfusion impairs cognition and (3) the two act synergistically to accelerate cognitive decline.

DEMENTIAS

Epidemiology

Table 3 Relative frequency (%) of different forms of dementia in this study and in FBB series

Type of dementia	FBB	Present study
Alzheimer's disease	42–77	76
Lewy bodies dementia	8–26	4
Frontotemporal dementia	4–5	5
Vascular dementia	3–18	15

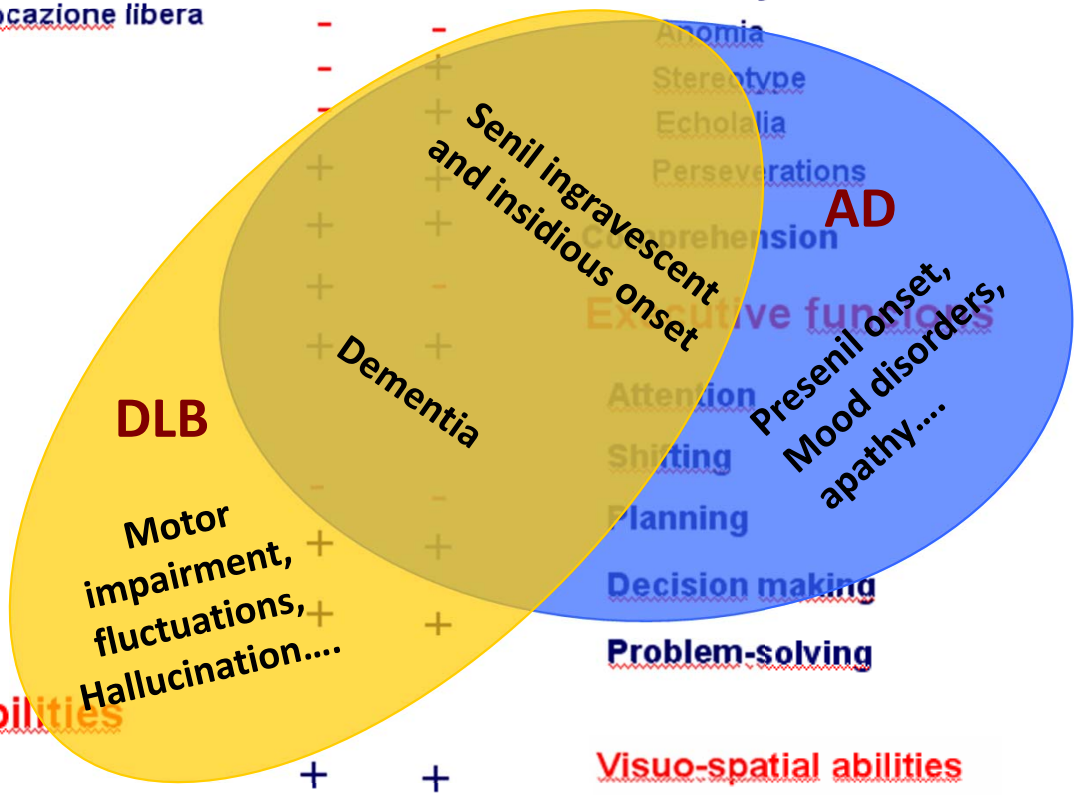
Musicco et al., Neurol Sci 2004;25:289-95.

AD compared to DLB

Neuropsychological features in the early stages

	AD	DLB
Memory		
Episodic MLT		
Learning	-	-
Free recallRievocazione libera	-	-
Cues recall	-	+
Recognition	-	+
Semantic MLT	+	+
MBT	+	+
Working memory	+	-
Implicit memory	+	+
Praxis		
Constructive	-	-
Ideomotor	+	+
Ideational	+	+
Recognition abilities		
Visual	+	+
Tactile	+	+
Acoustic	+	+

	AD	DLB
Language		
Production		
Fluency	+	+
Anomia	-	+
Stereotype	+	+
Echolalia	+	+
Perseverations	+	+
Comprehension	+	+
Executive functions		
Attention	-	-
Shifting	-	-
Planning	-	-
Decision making	-	-
Problem-solving	-	-
Visuo-spatial abilities		
Spatial orientation		
Visuo-spatial analysis		



Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

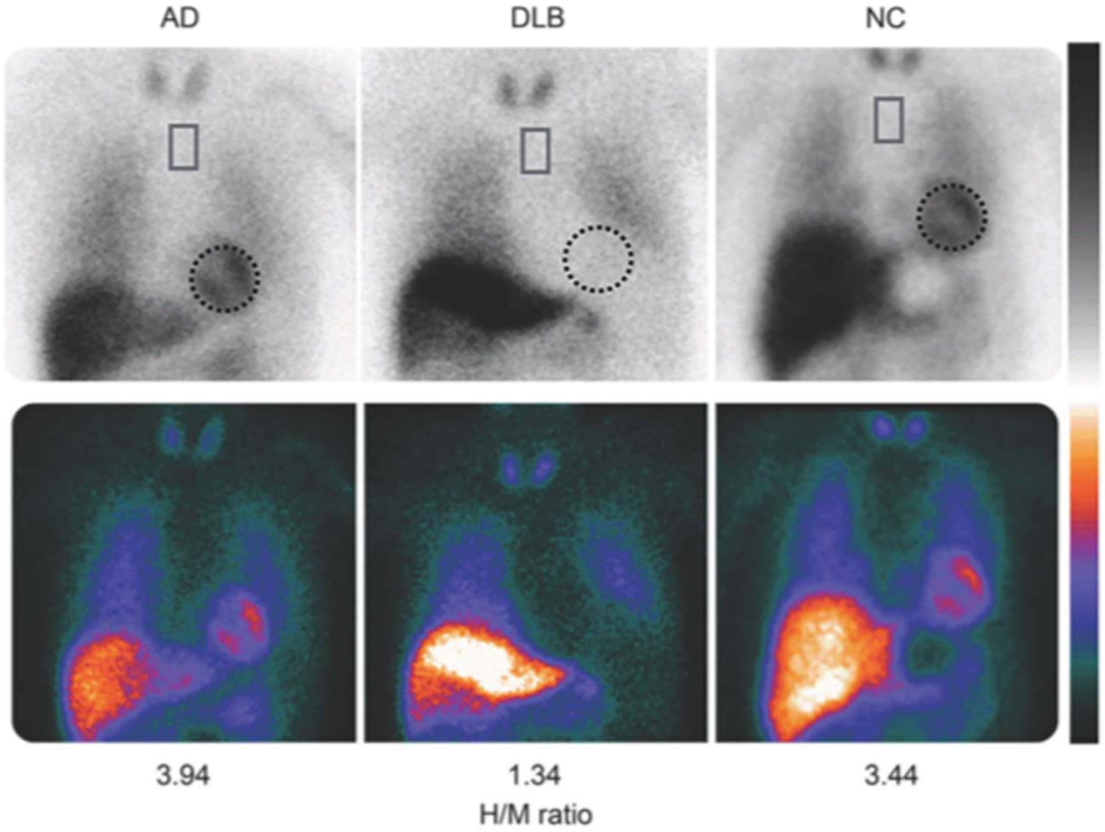
OPEN

Ian G. McKeith, MD, F Med Sci
Bradley F. Boeve, MD
Dennis W. Dickson, MD
Glenda Halliday, PhD
John-Paul Taylor, PhD, MRC Psych
Daniel Weintraub, MD
Dag Aarsland, MD
James Galvin, MD, MPH
Johannes Attems, MD
Clive G. Ballard, MRC Psych, MD
Ashley Bayston, BA, LLB
Thomas G. Beach, MD, PhD
Frédéric Blanc, MD, PhD
Nicolaas Bohnen, MD, PhD
Laura Bonanni, MD, PhD
Jose Bras, PhD
Patrik Brundin, MD, PhD
David Burn, MD, FRCP
Alice Chen-Plotkin, MD
John E. Duda, MD
Omar El-Agnaf, PhD
Howard Feldman, MD, FRCP
Tanis J. Ferman, PhD
Dominic ffytche, MD
Hiroshige Fujishiro, MD
Douglas Galasko, MD
Jennifer G. Goldman, MD, MS
Stephen N. Gomperts, MD, PhD
Neill R. Graff-Radford, MD
Lawrence S. Honig, MD, PhD
Alex Iranzo, MD, PhD

Table 1 Revised[1,2] criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Figure 2 ^{123}Iodine-metaiodobenzylguanidine myocardial imaging in patients with Alzheimer disease (AD), dementia with Lewy bodies (DLB), and age-matched normal controls (NC)



Images taken 3 hours after injection are shown in 2 color scales, and typical regions of interest are shown on the heart (dotted circle) and upper mediastinum (rectangle). Heart-to-mediastinum (H/M) ratios are standardized to the values comparable

st *throughout the course.*)

lertness.
tailed.

re bradykinesia (defined as
tremor, or rigidity.

falls; syncope or other
tion, e.g., constipation,
a; hallucinations in other

d by SPECT or PET.

l scan.
with reduced occipital

ations in the pre-alpha/

thout the presence of

dicative biomarkers.

one.

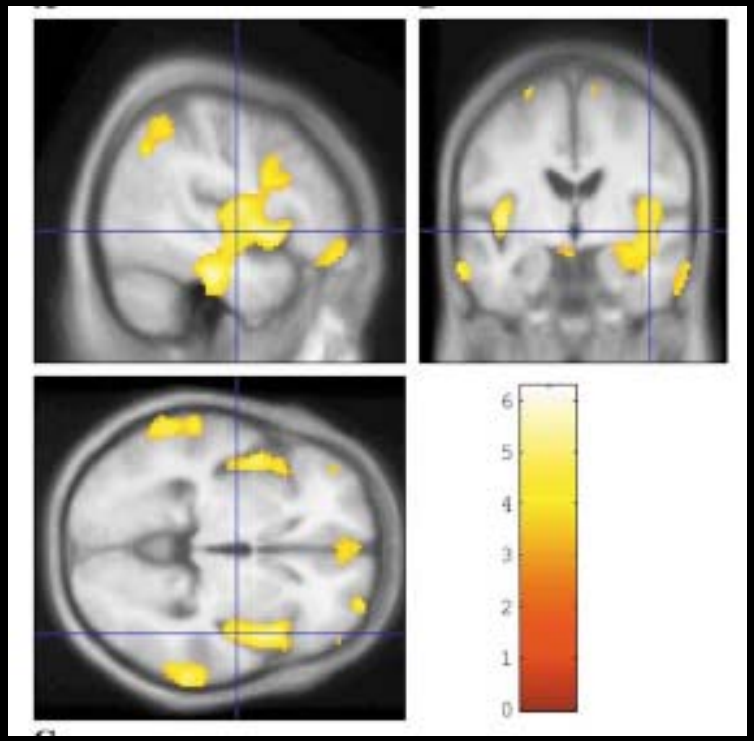
Possible DLB can be diagnosed if:

a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or

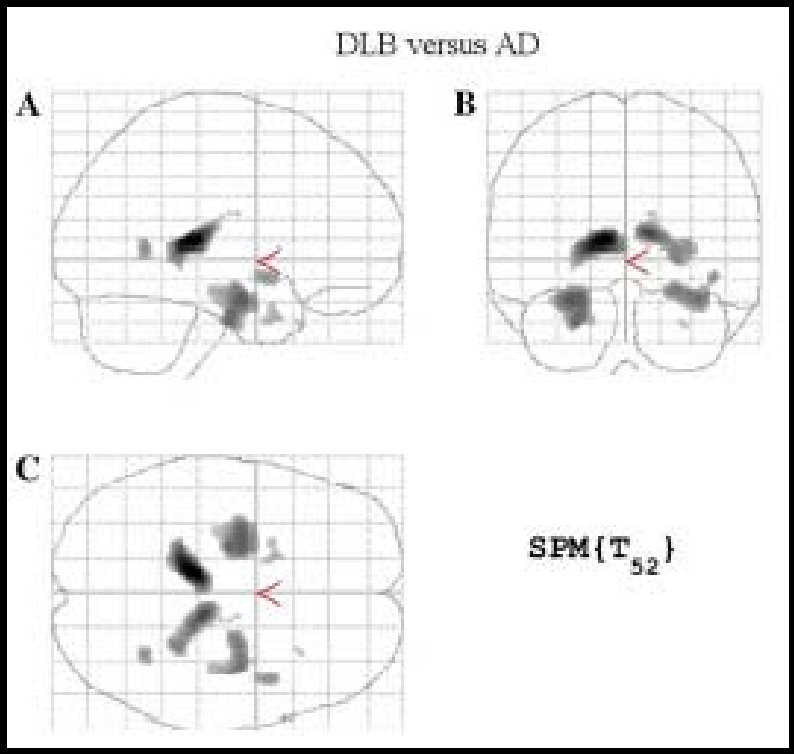
b. One or more indicative biomarkers is present but there are no core clinical features.

VBM in DLB – Regional GM loss

DLB < CTRLs

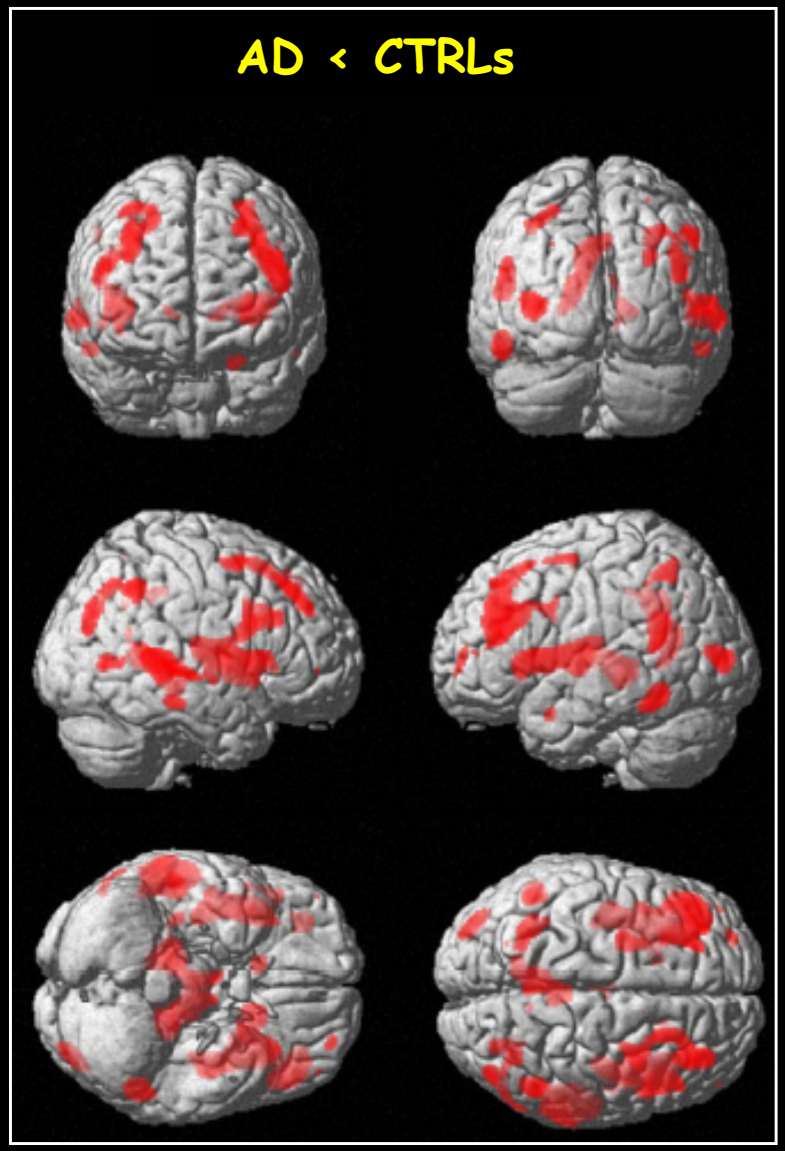


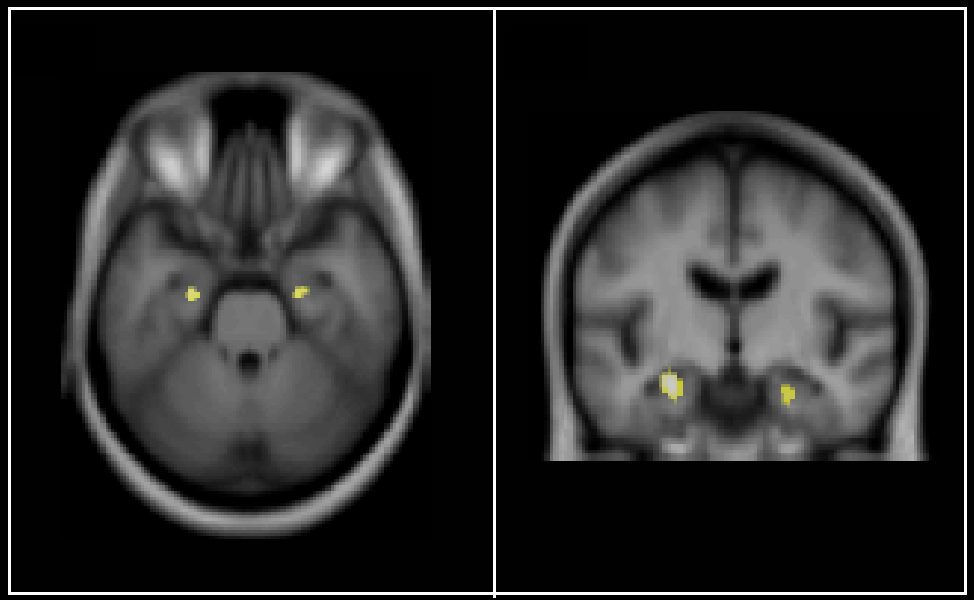
DLB>AD patients



Burton et al., Brain 2004; 127: 791-800.

VBM in AD- Regional GM loss





Correlation with
MMSE score

Bozzali et al., Neurology 2006; 67:453-460.

VBM in PD – Regional GM loss and apathy

Movement Disorders
Vol. 25, No. 14, 2010, pp. 2318–2325

Neuroanatom
Magneti

Disease: A
Based

Jennifer S.A
Pauline Aalten

PhD,[3]
D, PhD[1*]

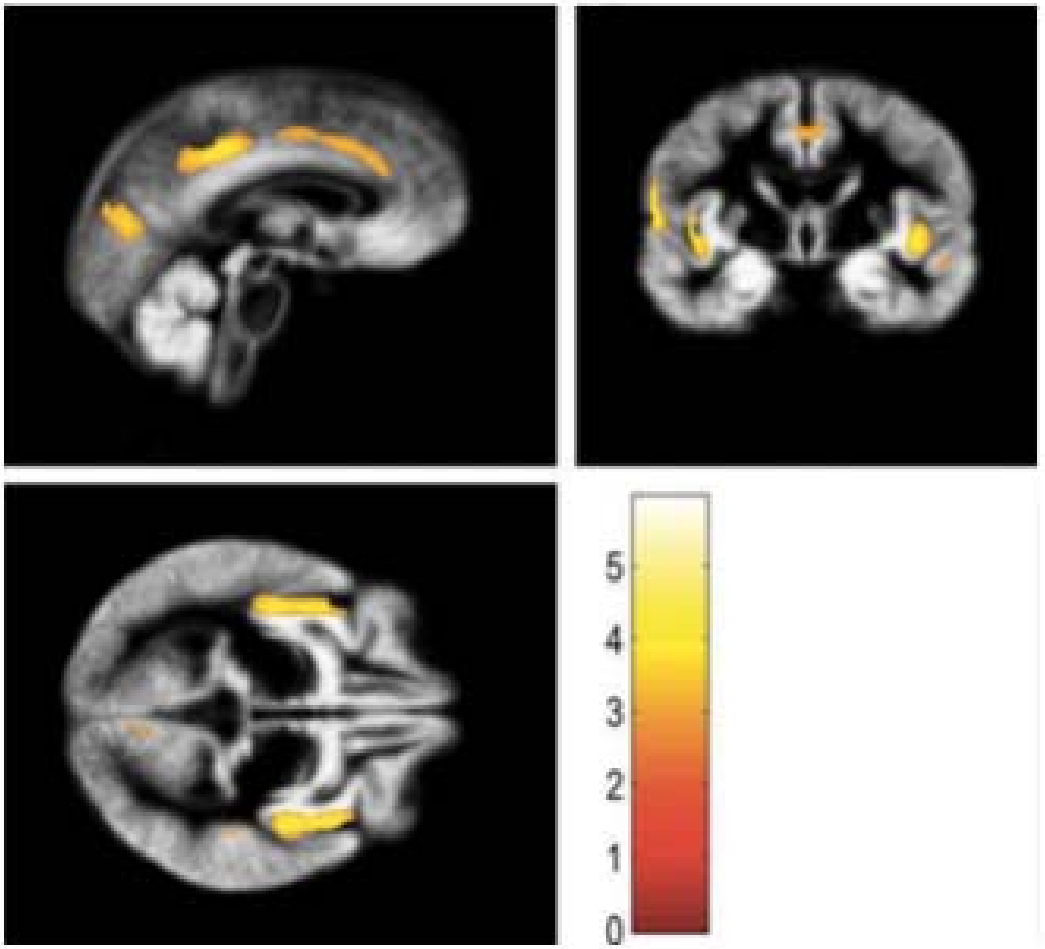
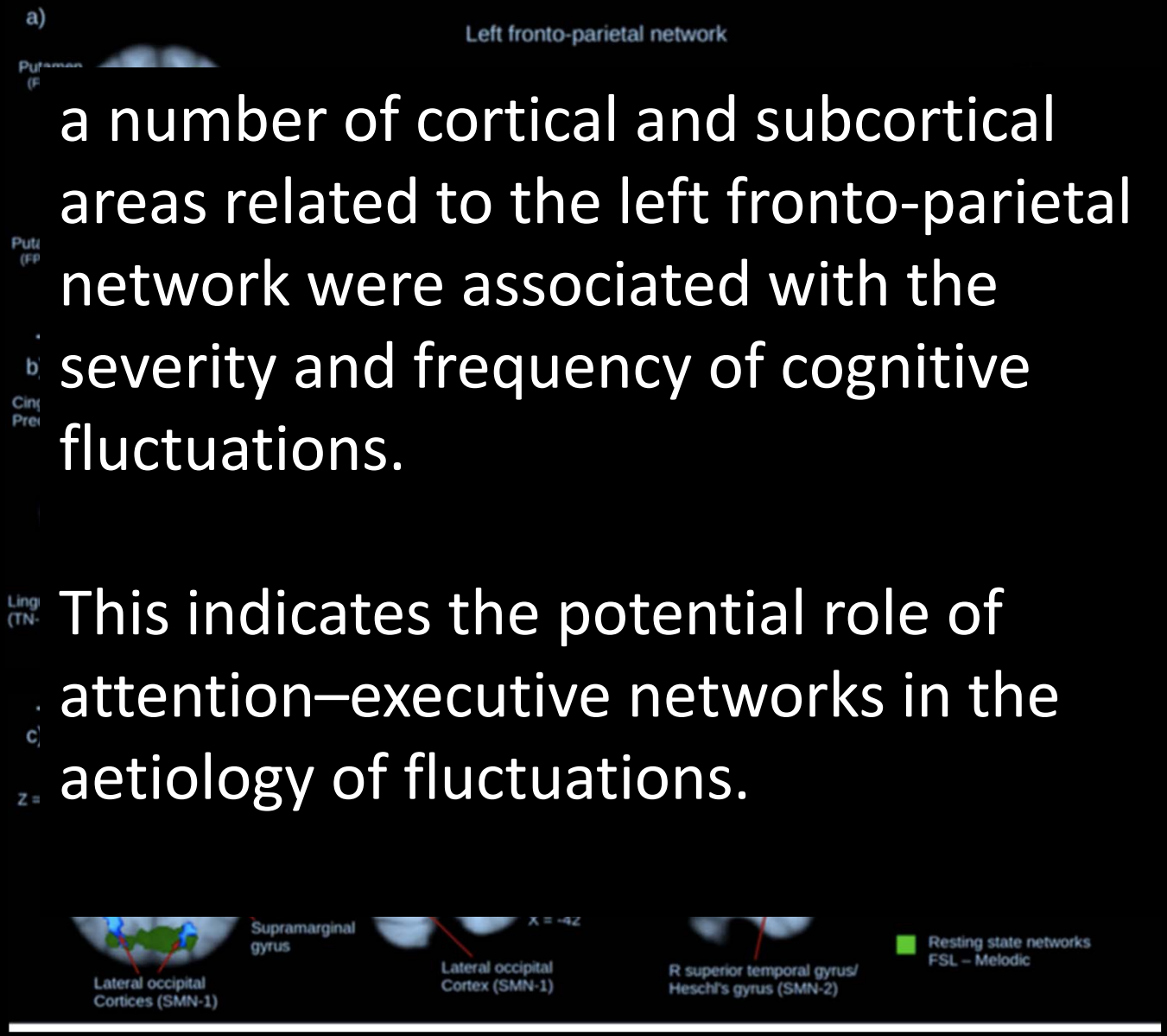


FIG. 1. Brain regions with significant negative correlation between gray matter density values and apathy scores measured with the Lille Apathy Rating Scale. Visible are the right (posterior) cingulate gyrus, the right precuneus, the bilateral insula, and the left inferior parietal gyrus (SPM coordinates: 1.5, 6.5, −3.5). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

DLB and Fluctuations



a number of cortical and subcortical areas related to the left fronto-parietal network were associated with the severity and frequency of cognitive fluctuations.

This indicates the potential role of attention–executive networks in the aetiology of fluctuations.

Peraza et al., NeuroImage Clinical 4 (2014) 558–565 .

◆ Human Brain Mapping

The Role of Dysfunctional Attentional C Networks in Visual Misperceptions in Par Disease

James M. Shine,[1] Glenda M. Halliday,[2,3] Moran Gilat,[1] Elie Mat J. Bolitho,[1] Maria Carlos,[1] Sharon L. Naismith,[1] and Simon J.

TABLE III. Brain regions displaying decreased BOLD response in both monostable bistable images (non-hallucinators versus hallucinators)

Neural region	x	y	z	Monostable cluster size	Bistable cluster size
Left frontal eye fields[a]	−27	0	64	129	64
Right frontal eye fields[a]	30	2	56	91	17
Midbrain	−2	−20	−6	91	139
pre-SMA[a]	0	20	46	77	56
L superior parietal lobule[a]	−22	−53	56	38	38
R superior parietal lobule[a]	22	−44	−18	11	32
Right visual area V2	11	−90	11	19	10

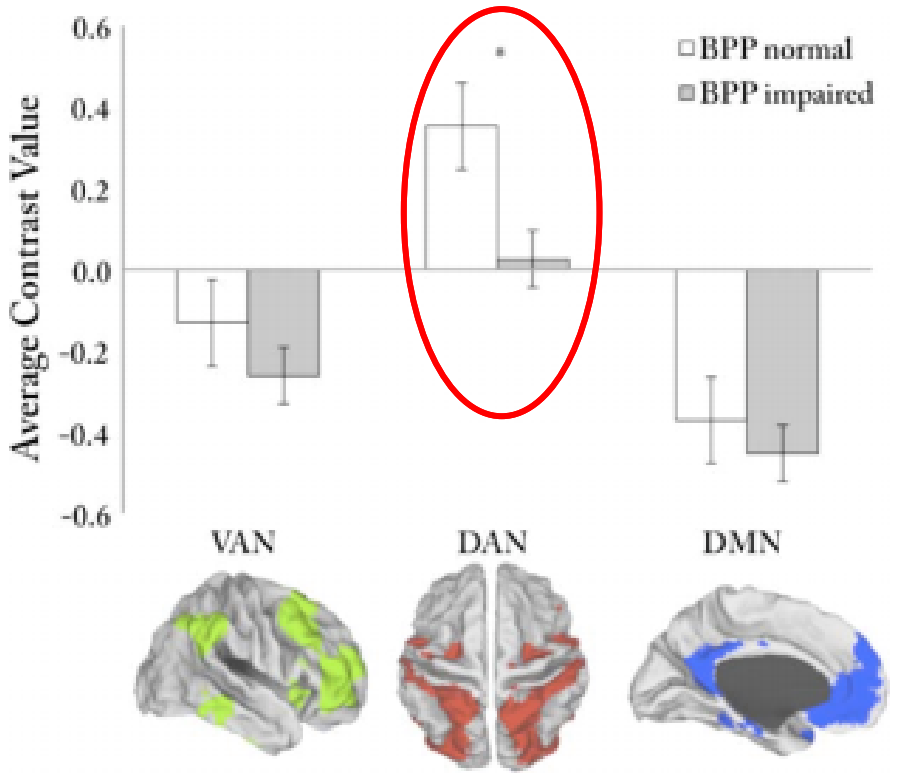
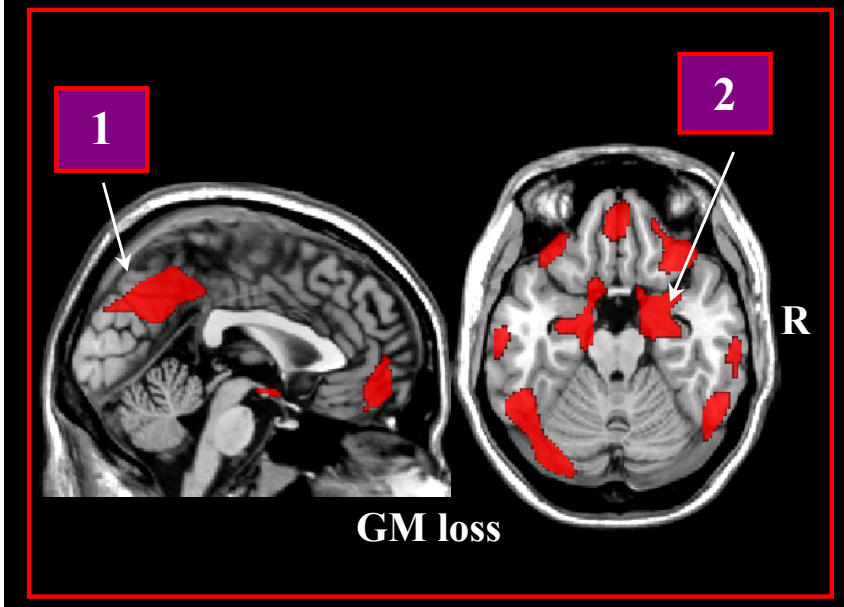


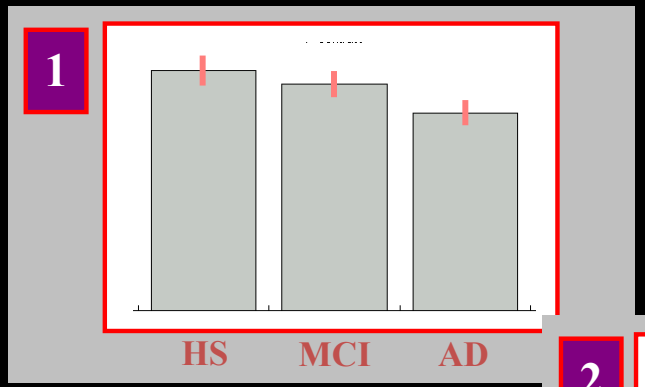
Figure 3.

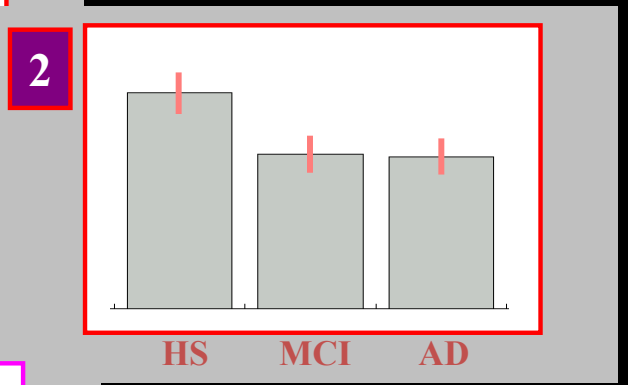
Results of the region-of-interest analysis. Results from the direct comparison of the average contrast values from the attentional networks when comparing non-hallucinators (white columns) with hallucinators (gray columns) during the viewing of a bistable image. The contrast value represents the average value seen in each network during both monostable and bistable images. While there were no significant differences between patients in the VAN or DMN, hallucinators were significantly more likely to have a negative average contrast value in the DAN. Key: L, left; R, right; VAN, ventral attention network; DAN, dorsal attention network; DMN, default mode network. Significance levels: $^*P < 0.05$. Though not explicitly shown here, the results were similar for the viewing of a monostable image. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Regional GM loss and Brain Disconnection within the DMN in AD

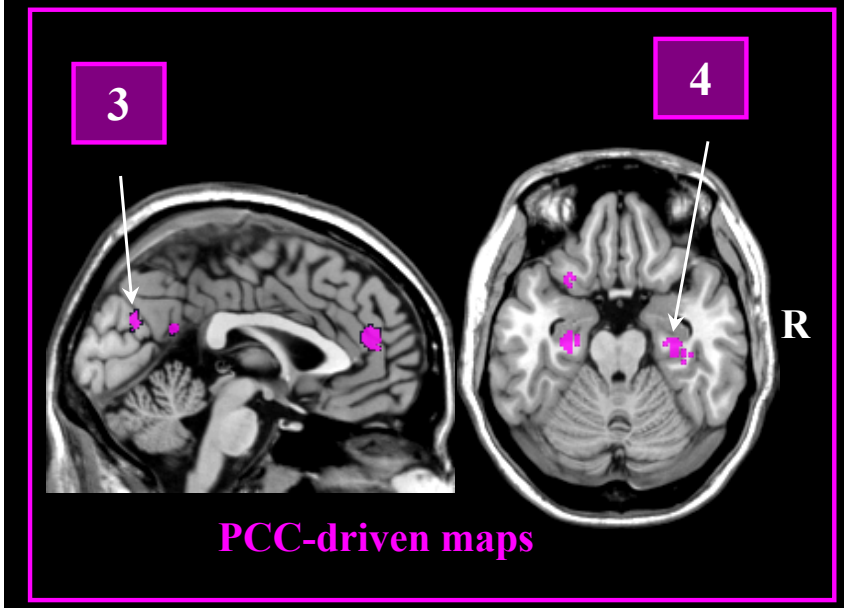
Volumetrics

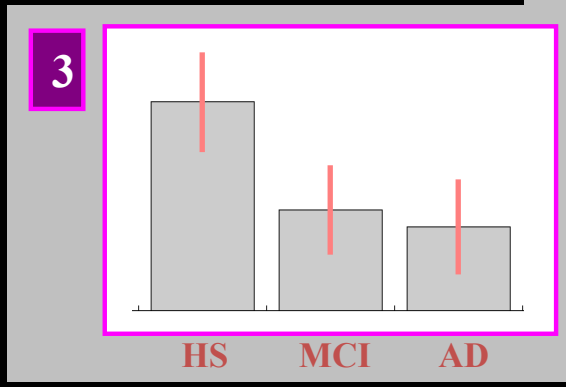


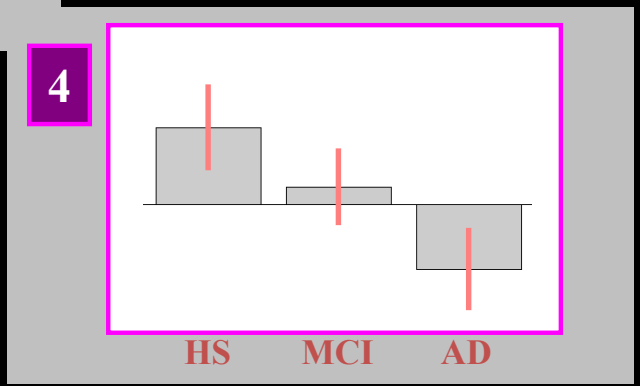




Functional connectivity







Gili et al., JNNP 2011; 82:58-66.

Just a few considerations to conclude

- From a clinical perspective, a relative preservation of the MTLs remains highy suggestive for a diagnosis of DLB (at least ints pure form).
- Quantitative MR technics are a unique tool for the pathophysiological investigation of the brain tissue in the absence of obvious abnormalities.
- Different aspects of damage can be identified, whose anatomical distribution account for brain dysfunction at a regional as well as a at a network level.
- This allows to understand the association between microscopic brain tissue changes and patients' clinical features, including cardinal features but also cognitive/behavioural symptoms.
- The ANS deserves to be further investigated for its potential role in determining higher level dysfunctions in DLB.

Hippocampal volumes predict risk of dementia with Lewy bodies in mild cognitive impairment

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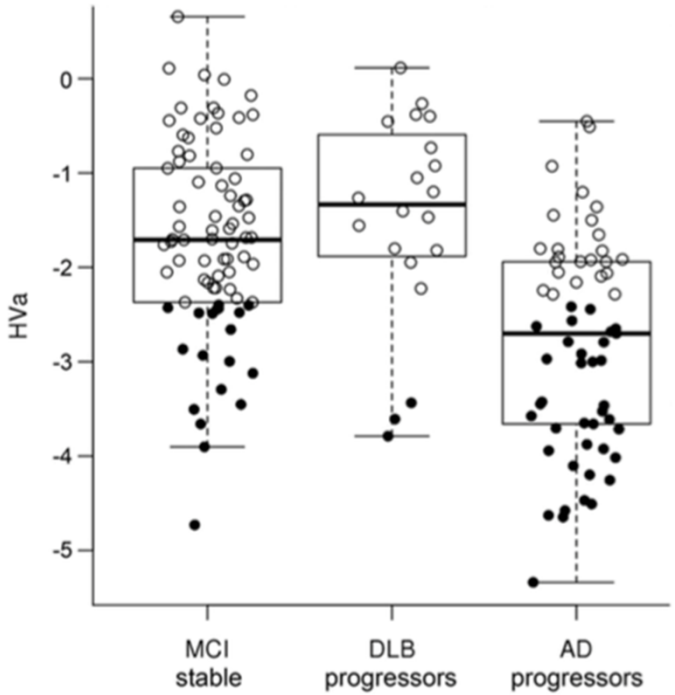
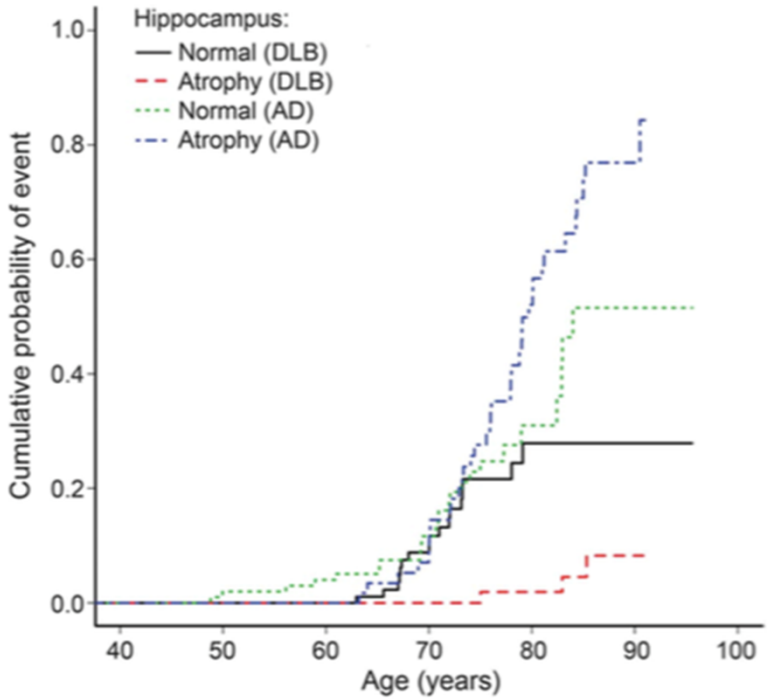
Figure 1 Hippocampal volumes adjusted for total intracranial volume (HVa) in patients with mild cognitive impairment (MCI)



HVa in patients with MCI who did not progress to Alzheimer disease (AD) or dementia with Lewy bodies (DLB), patients with MCI who progressed to DLB, and patients with MCI who progressed to AD during follow-up. Dark circles indicate those labeled as having abnormal HVa for the survival analysis.

Figure 2 Cumulative incidences of progression to dementia with Lewy bodies (DLB) and Alzheimer disease (AD)



Cumulative incidences of progression to DLB and AD in patients with mild cognitive impairment by normal (preserved) hippocampus vs hippocampal atrophy. Hippocampal volumes are adjusted for total intracranial volume. Age is used as the timescale.

Kantarci et al., Neurology 2016;87:2317–2323