

Scuola Superiore di Neurologia

CORSO RESIDENZIALE SIN

Update su diagnosi e monitoraggio delle epilessie

Genova, 24 - 25 febbraio 2015

Accademia Nazionale di Medicina - Via M. Piaggio 17/6 - Genova

An impressionist painting in warm, vibrant colors (reds, oranges, yellows, greens) depicting a family scene. A man in a blue and white checkered shirt is on the left, looking towards a woman on the right. The woman has dark hair and is looking down at a child. Another child is visible in the foreground on the right. The background is a soft, abstract mix of colors, suggesting an indoor setting with a window.

**Imaging
morfometrico
avanzata nelle
epilessie focali**

Angelo Labate

Professore Associato di Neurologia, Università di Catanzaro

HISTORY OF EPILEPSY 1909–2009: THE ILAE CENTURY

A history of neuroimaging in epilepsy 1909–2009

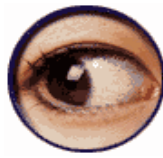
Simon D. Shorvon

UCL Institute of Neurology, University College London, London, United Kingdom

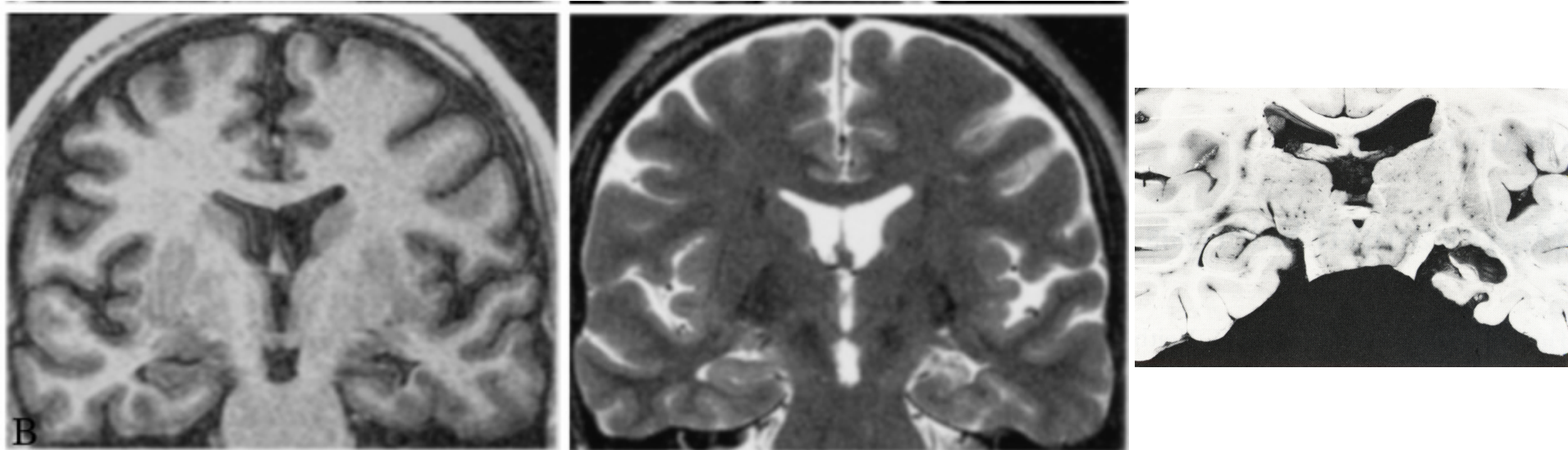
1 onda (1930): EEG

2 onda (1995): genetica

3 onda
(1980): RM



neuroradiologist's eye



Sclerosi Ippocampale (SI) l'anormalità più comune nei pazienti affetti da epilessia temporale (ELT)

SI = epilessia severa e farmacoresistente

Hippocampal Sclerosis in Epilepsy
Meencke HJ, Veith G

Epilepsy Surgery, edited by Hans Luders, Raven Press, New York 1991; 705-715

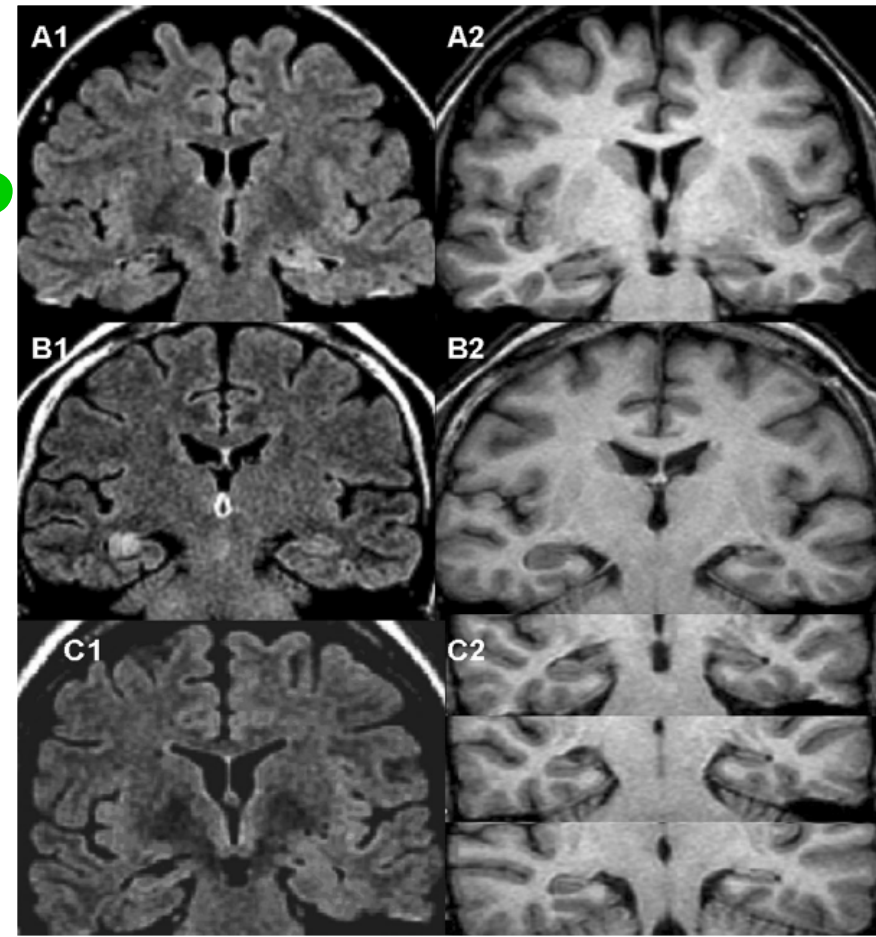
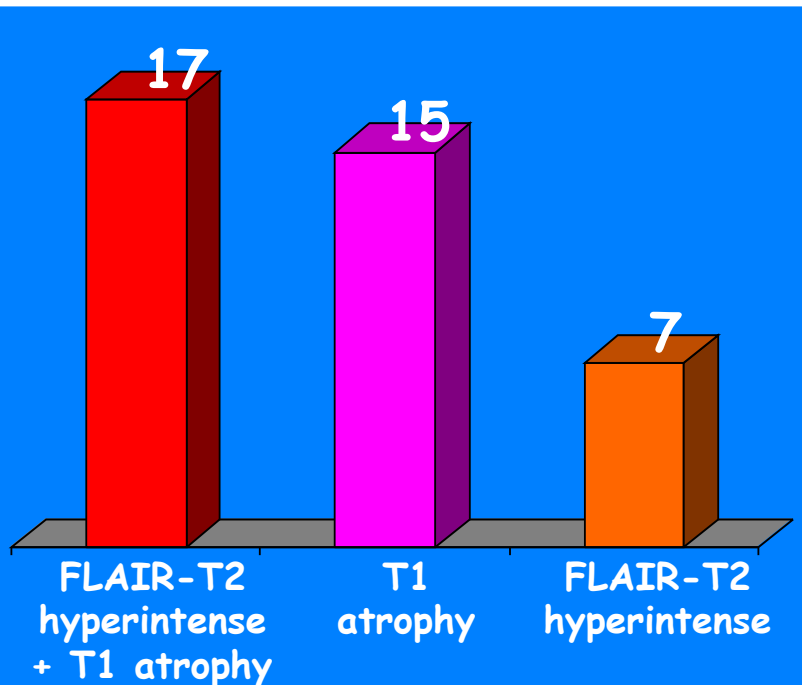
MRI evidence of mesial temporal sclerosis in sporadic “benign” temporal lobe epilepsy

A. Labate, MD; P. Ventura, MD; A. Gambardella, MD; E. Le Piane, MD; E. Colosimo, MD; U. Leggio, MD;
R. Ambrosio, MD; F. Condino, PhD; D. Messina, MD; P. Lanza, MD; U. Aguglia, MD;
and A. Quattrone, MD

Neurology. 2006 Feb 28;66:562-5

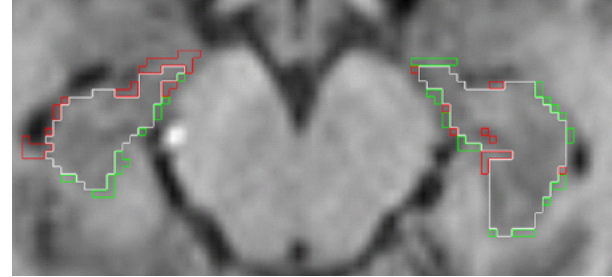
101 patients with mild TLE

~40%

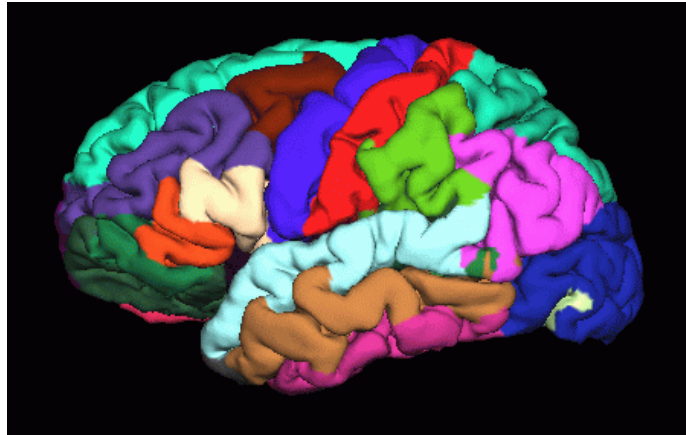


Voxel-Based Morphometry (VBM)

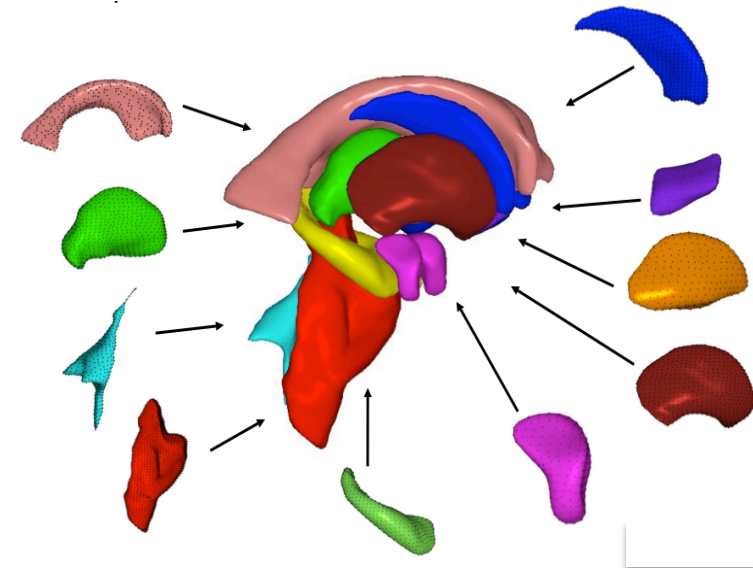
Automatic/Manual volume quantification
ROI analysis



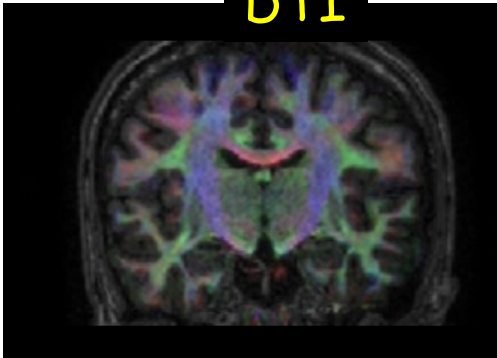
Cortical thickness



Shape analysis



DTI





Advanced Imaging Techniques in the Diagnosis of Nonlesional Epilepsy: MRI, MRS, PET, and SPECT

2013

Heath Pardoe, PhD and Ruben Kuzniecky, MD, FANA, FAAN

1 lesione potrebbe non esistere

2 la lesione esiste ma è talmente piccola che le indagini standard non sono sufficienti a discriminare tra la lesione ed il tessuto patologico

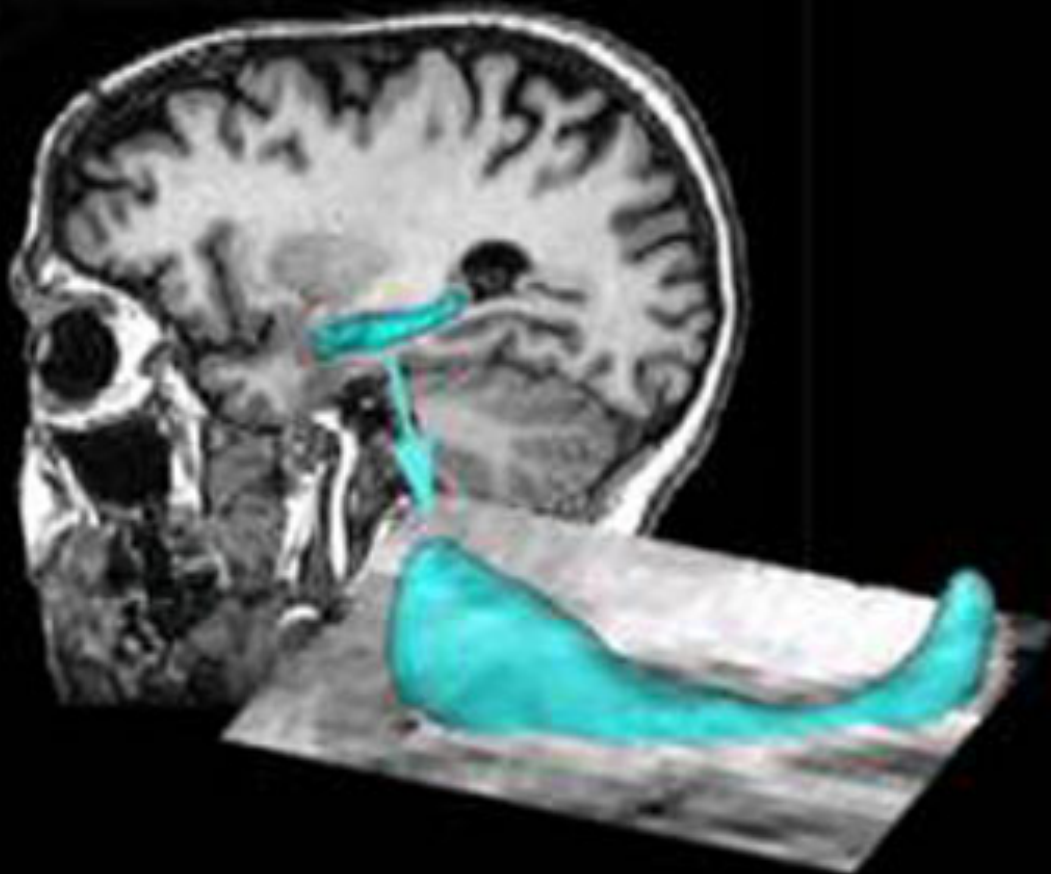
RM morfologica avanzata nello studio dell'epilessia focale

singolo caso (rare)  Planning prechirurgica

gruppi di pazienti  fisiopatologia

- Osservare in vivo la fisiopatologia di alcune sindromi
- Definire meglio le sindromi epilettiche
- Identificare aree cerebrali responsabili di specifiche funzioni
- Identificare lesioni occulte alla RM tradizionale

ROI analysis



Marked asymmetric **hippocampal atrophy** with a ratio of smaller to larger hippocampus of less than 70% is readily detected by experts, while lesser degrees of hippocampal atrophy generally require quantification.

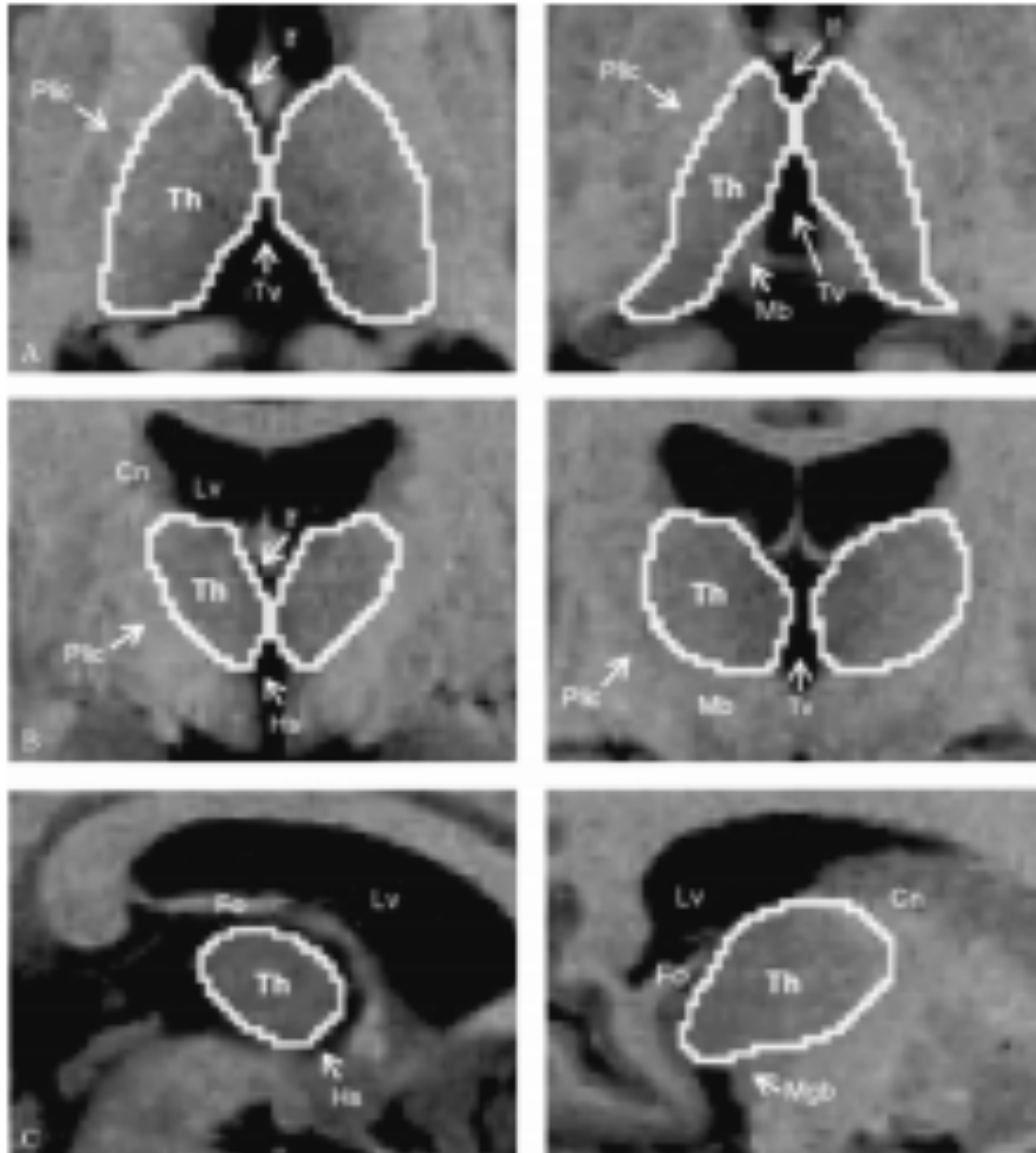


Fig. 1 Major anatomical boundaries of mesial temporal lobe on coronal MRI. **A** is the most rostral and **H** is the most caudal MRI section. Only MRIs displaying critical landmarks are shown. (**A**) The anterior border of the perirhinal cortex (PC) is located at the level of the limen insulae (LI). (**B**) The anterior border of the entorhinal cortex (EC) begins on average 2 mm behind the *limen insulae*. This coincides with the appearance of the temporal stem (TS). (**C**) Section through the hippocampal head (HH). (**D**) The posterior border of the EC is located at the posterior limit of the gyrus intralimbicus (GI) and coincides with the anterior border of the hippocampal body (HB). (**E**) The posterior border of the PC is situated 2 mm caudal to the posterior end of the EC. (**F**) The rostral border of the posterior parahippocampal cortex (PPC) is situated 1 mm caudal to the posterior end of the PC. (**G**) The anterior border of the hippocampal tail (HT) coincides with the crus fornix (CF) becoming fully visible. (**H**) The posterior border of the PPC is situated at the level of the posterior end of the hippocampal tail (HT). AM = amygdala; CS = collateral sulcus; FI = fimbria.

MRI volumetry of the thalamus in temporal, extratemporal, and idiopathic generalized epilepsy

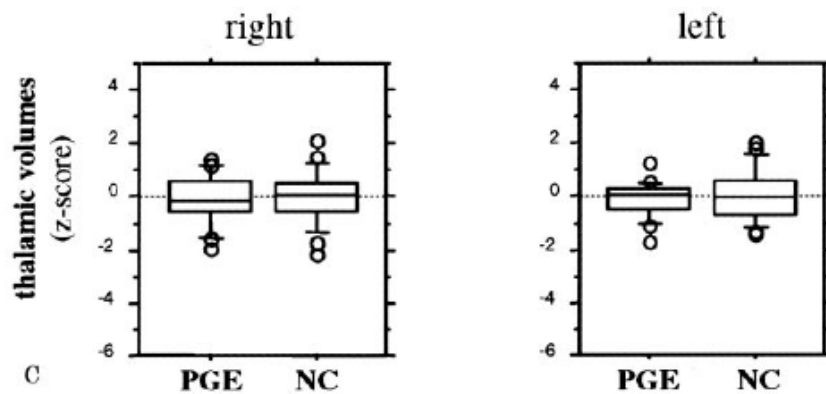
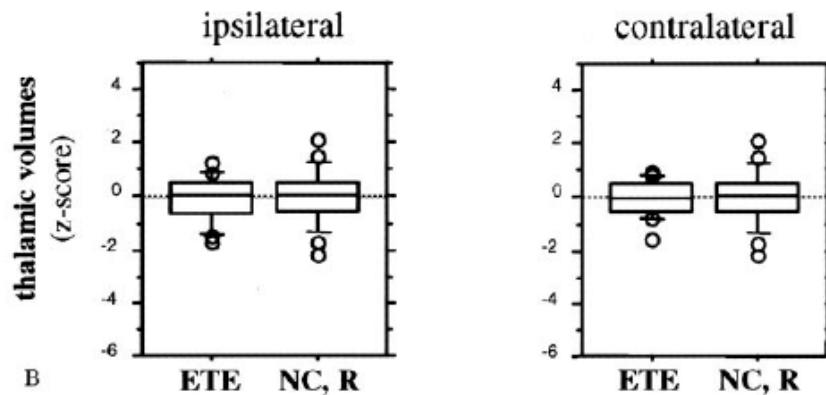
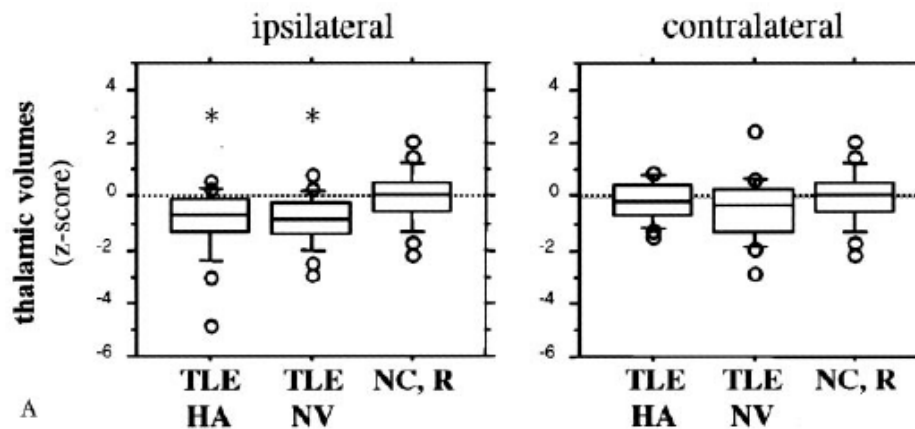
Jun Natsume, MD, PhD; Neda Bernasconi, MD; Frederick Andermann, MD; and Andrea Bernasconi, MD

40 rTLE
16 extraTLE
17 IGE



THALAMUS

40 rTLE
16 extraTLE
17 IGE



THALAMUS

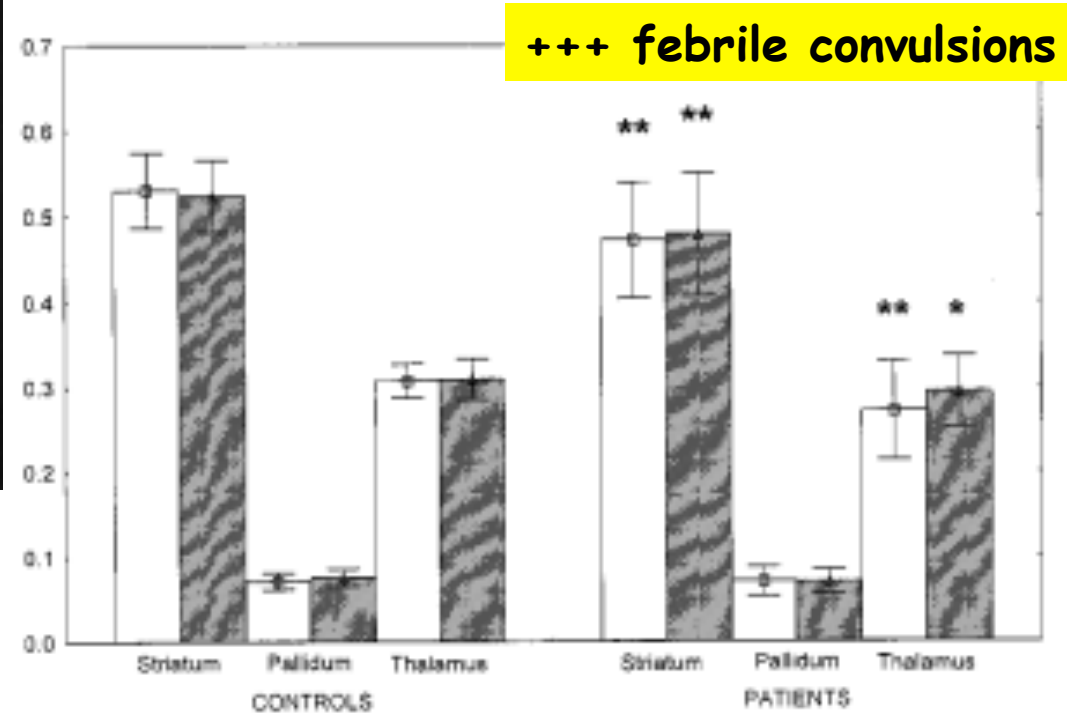
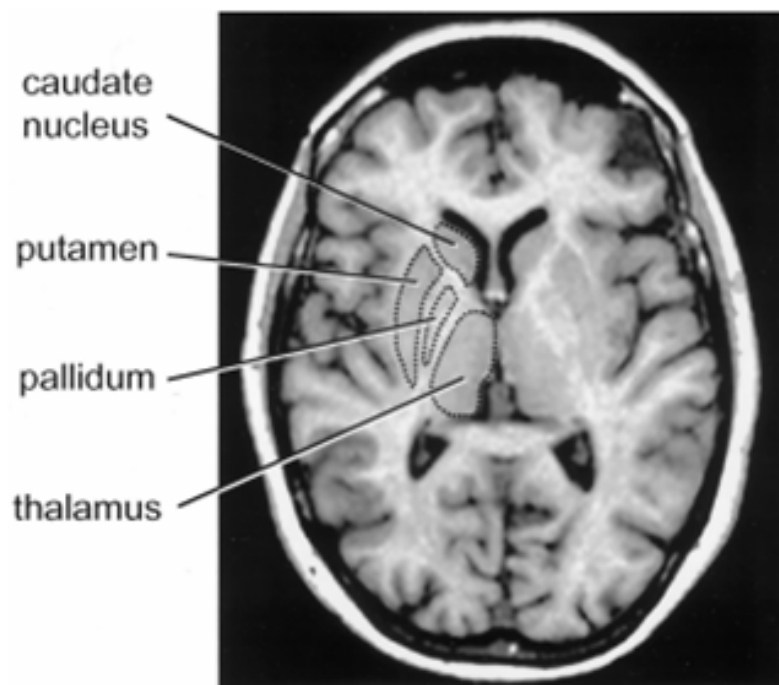
Volumetric measurements of subcortical nuclei in patients with temporal lobe epilepsy

S. Dreifuss, MD; F.J.G. Vingerhoets, MD; F. Lazeyras, PhD; S. Gonzales Andino, PhD; L. Spinelli, PhD; J. Delavelle, MD; and M. Seeck, MD



2001; 57; 1636-41

27 rTLE



MR Imaging Volumetry of Subcortical Structures and Cerebellar Hemispheres in Temporal Lobe Epilepsy



2006;27:2155-60

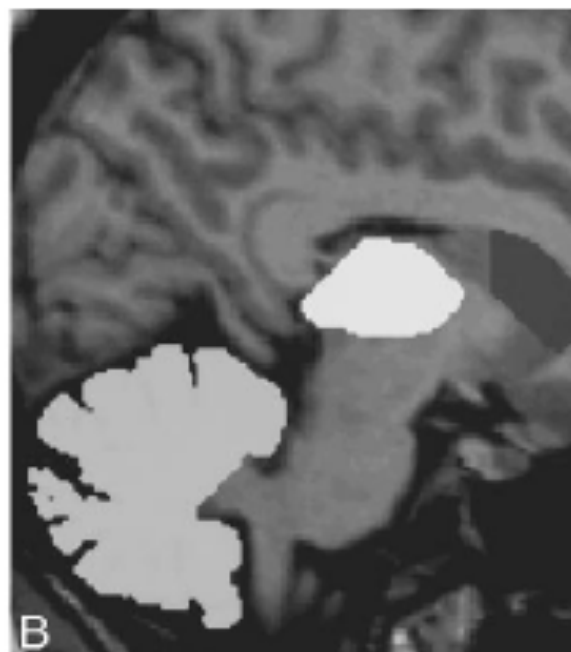


Table 2: Volumetric data of control participants and patients with temporal lobe epilepsy

Structures	Subjects		
	Control Participants	Right TLE	Left TLE
Hippocampus			
Mean R volume	3011 (408)	2101 (506)*	3078 (501)
Mean L volume	2857 (409)	2943 (510)	2238 (729)*
R/L volume ratio	1.06 (0.05)‡	0.73 (0.22)‡	1.47 (0.38)‡
Amygdala			
Mean R volume	1608 (167)	1533 (248)	1667 (237)
Mean L volume	1497 (186)	1610 (185)	1440 (400)
R/L volume ratio	1.08 (0.06)‡	0.95 (0.16)‡	1.24 (0.41)‡
Thalamus			
Mean R volume	6360 (445)	5217 (797)*	5811 (1056)‡
Mean L volume	6484 (575)	5716 (862)*	5361 (884)†
R/L volume ratio	0.98 (0.07)	0.91 (0.09)‡	1.09 (0.11)‡
Caudate head			
Mean R volume	3263 (445)	3236 (362)	3248 (440)
Mean L volume	3297 (394)	3382 (449)	3271 (514)
R/L volume ratio	0.99 (0.06)	0.96 (0.05)	0.99 (0.06)
Cerebellar hemispheres			
Mean R volume	71451 (8589)	66890 (9465)	66756 (8907)
Mean L volume	72210 (8347)	68093 (9164)	68134 (9258)
R/L volume ratio	0.99 (0.03)	0.98 (0.03)	0.99 (0.03)

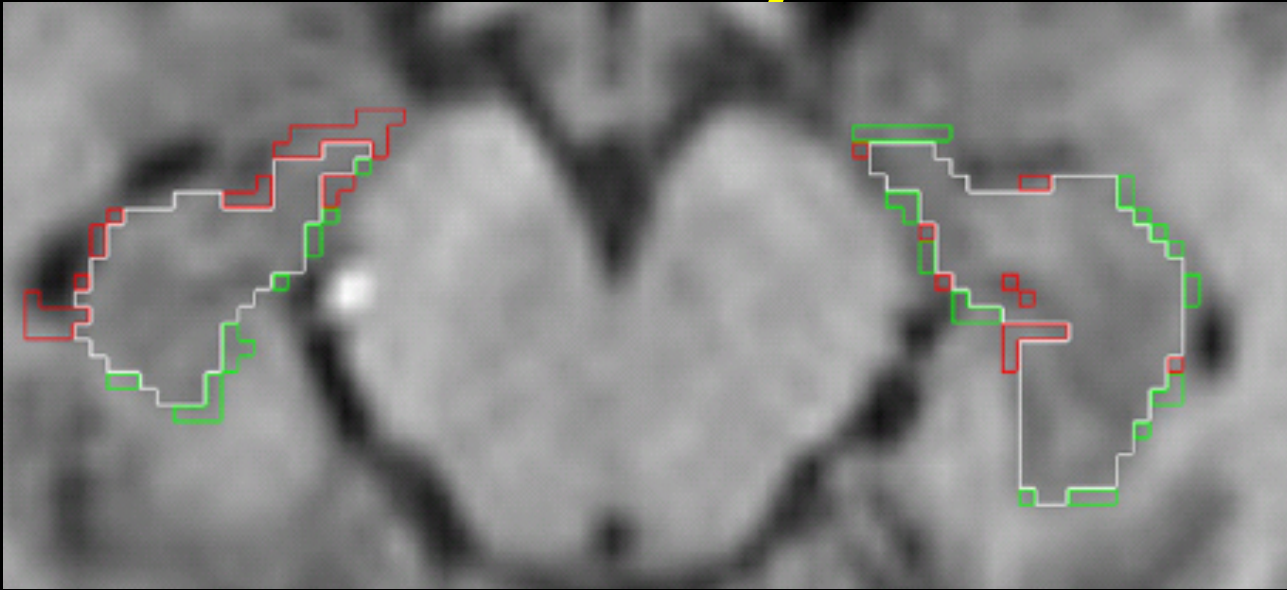
Note:—Volumes expressed as mm³, () indicate standard deviations, R indicates right; L, left; R/L, right divided by left; TLE, temporal lobe epilepsy/resection.

*Statistically significant difference between the patient groups and control subjects ($p < .0001$).

†Statistically significant difference between one patient group and control subjects ($p < .02$).

‡Statistically significant difference between 2 or 3 groups ($p < .05$).

ROI analysis



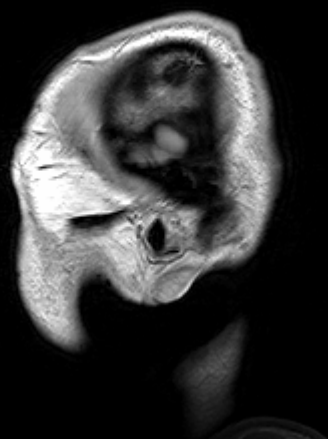
- **ADVANTAGES**

Sensitivity and specificity.

Consistent with the postmortem MRI literature.

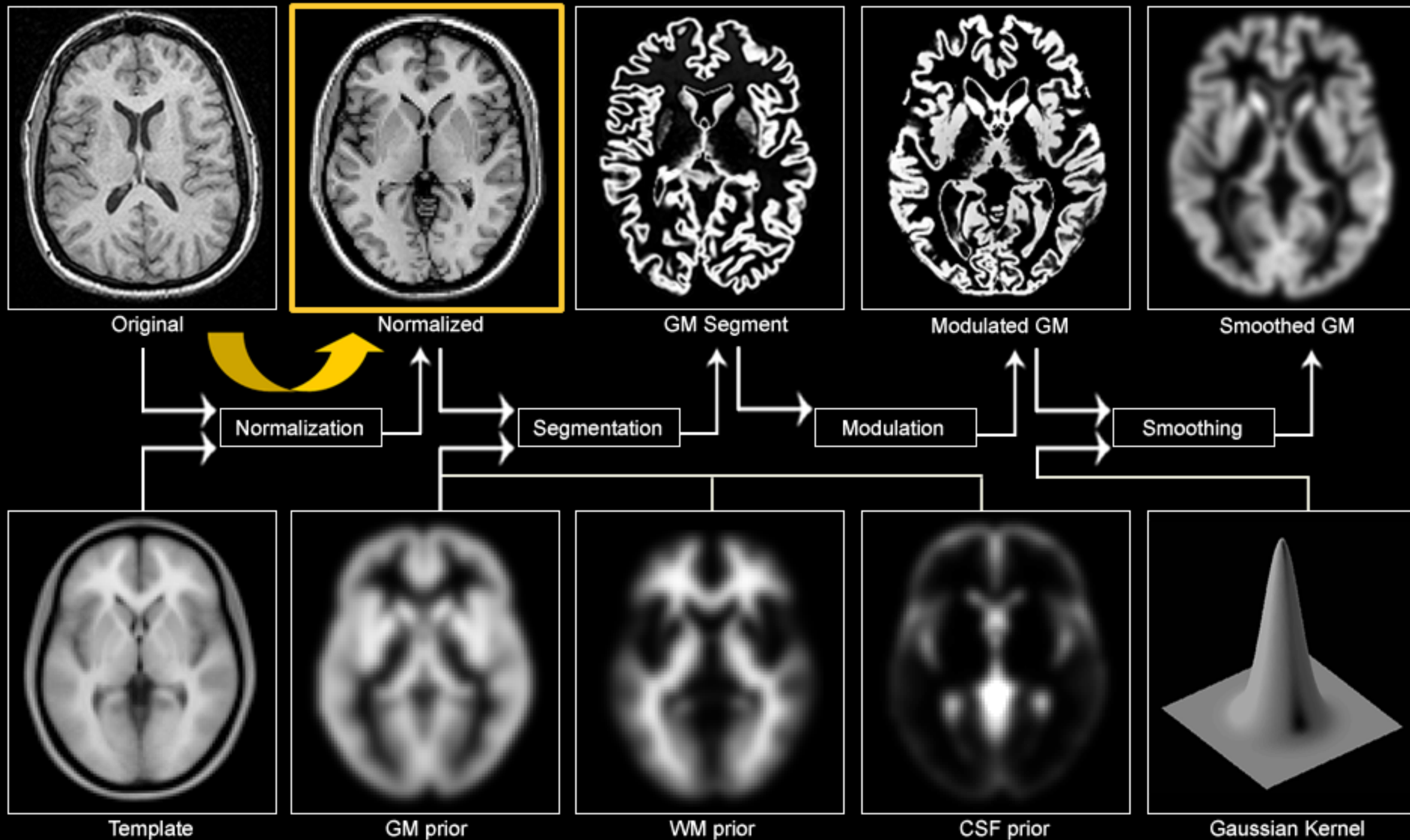
- **DISADVANTAGES**

Disadvantages include the need for trained operators, workstations and software, as well as substantial time commitments (60 min per dataset).



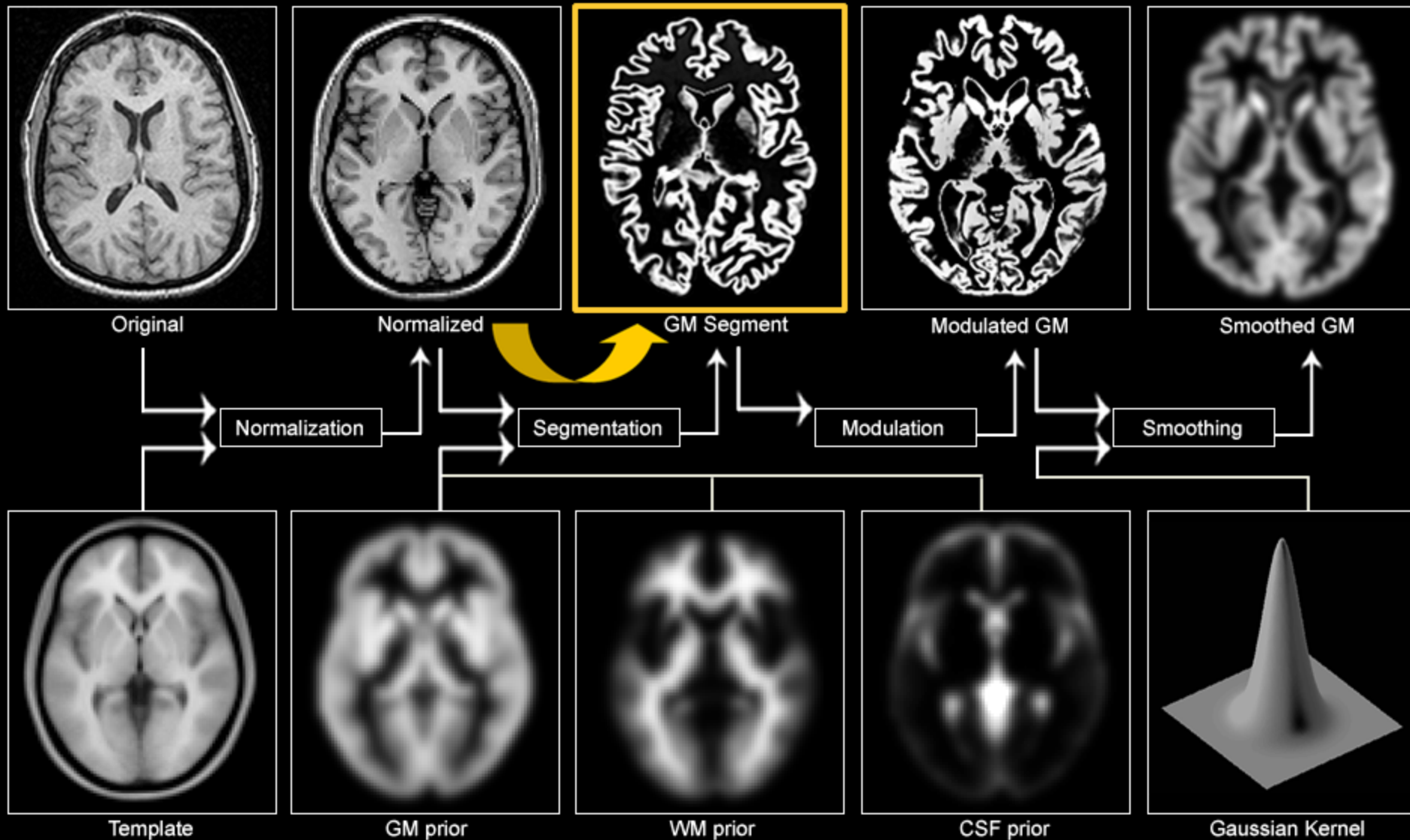
Voxel-Based Morphometry

Pre-processing Overview



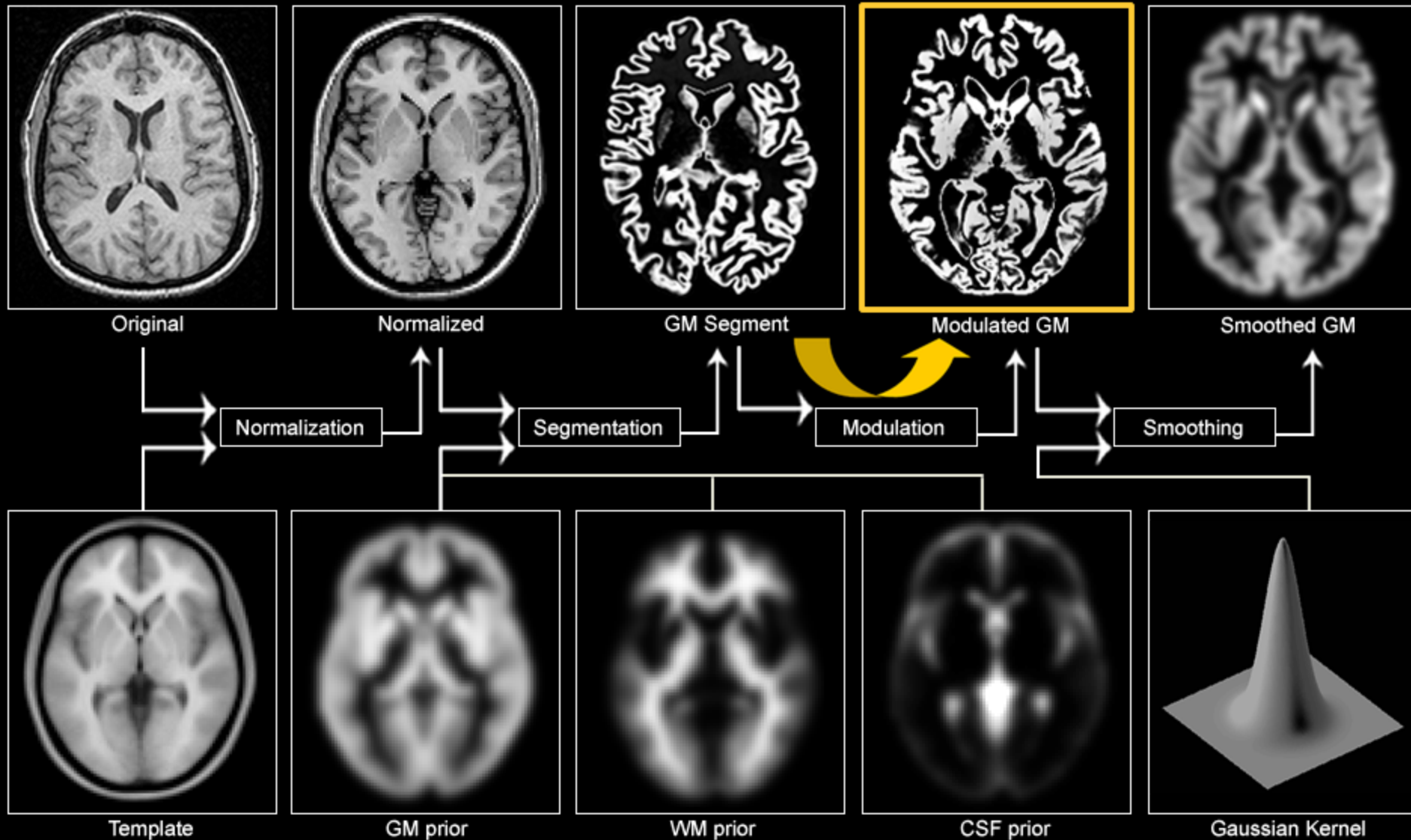
Voxel-Based Morphometry

Pre-processing Overview



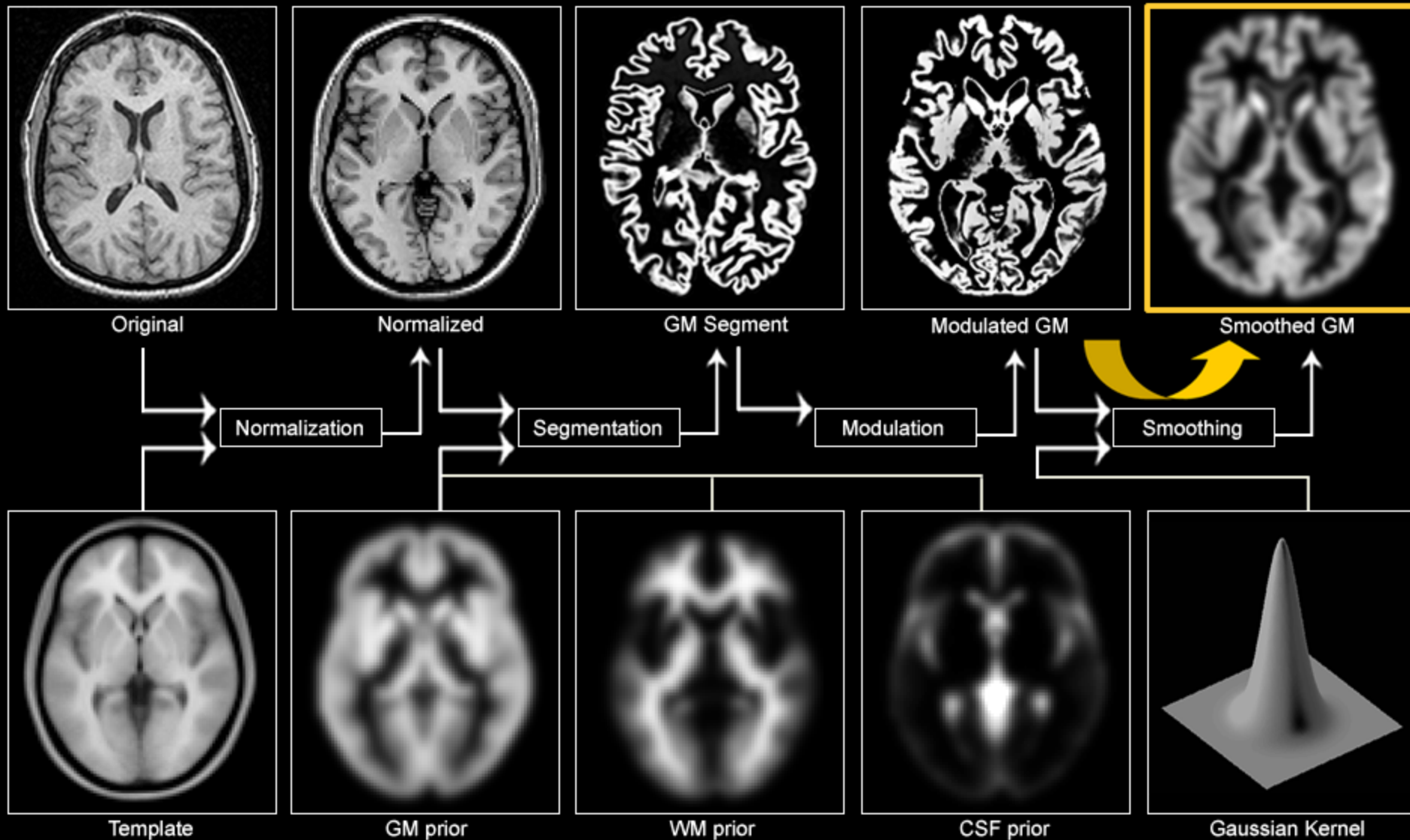
Voxel-Based Morphometry

Pre-processing Overview

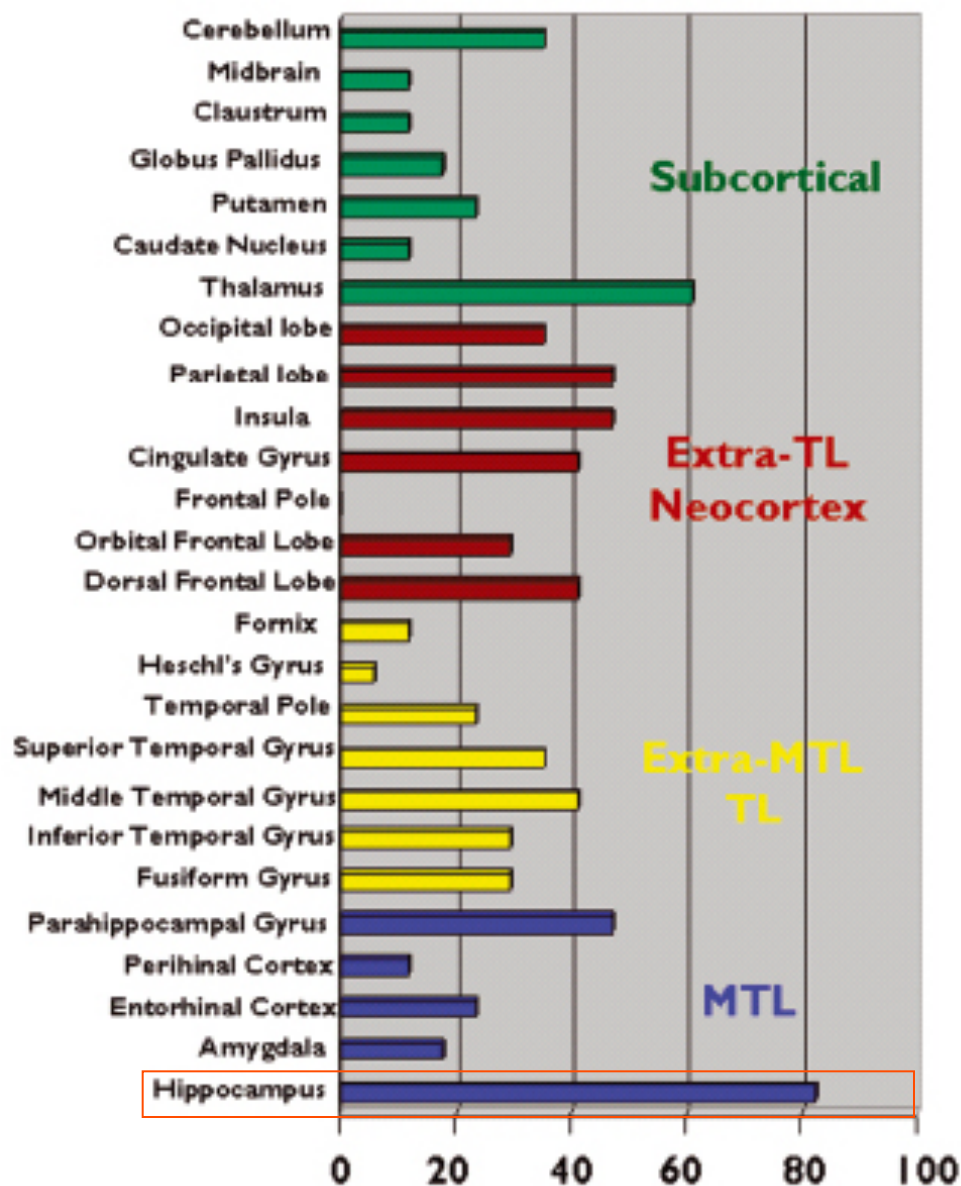


Voxel-Based Morphometry

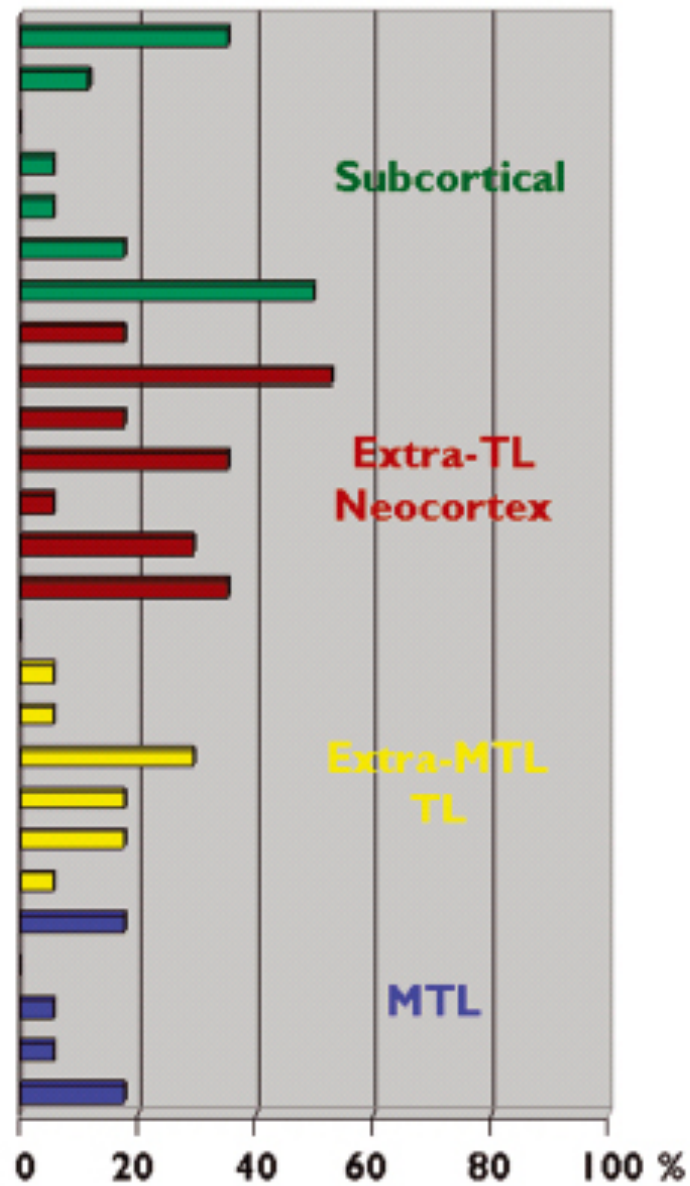
Pre-processing Overview



Ipsilateral



Contralateral

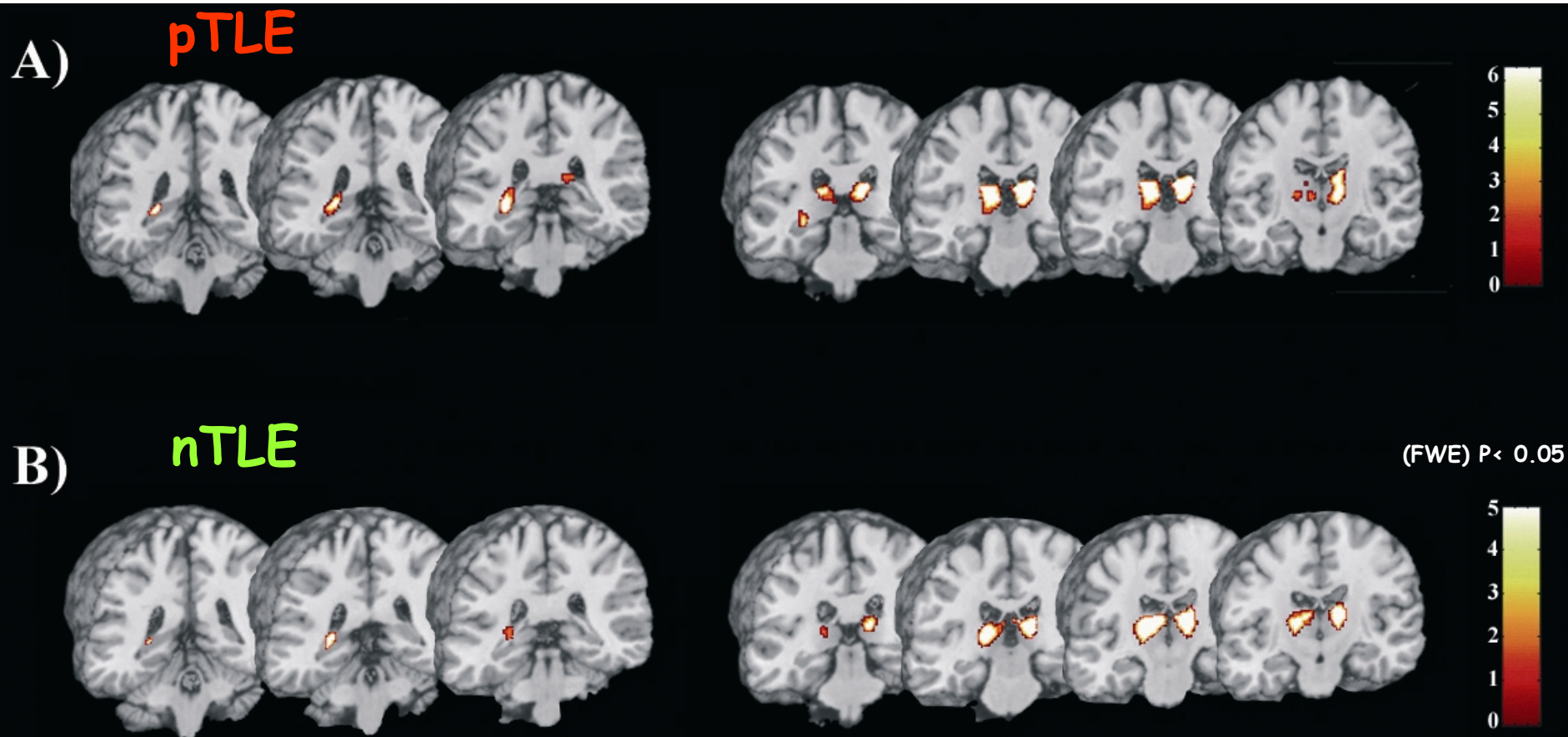


A. Labate, MD
A. Cerasa, PhD
A. Gambardella, MD
U. Aguglia, MD
A. Quattrone, MD

Hippocampal and thalamic atrophy in mild temporal lobe epilepsy

A VBM study

Neurology® 2008;71:1094-1101



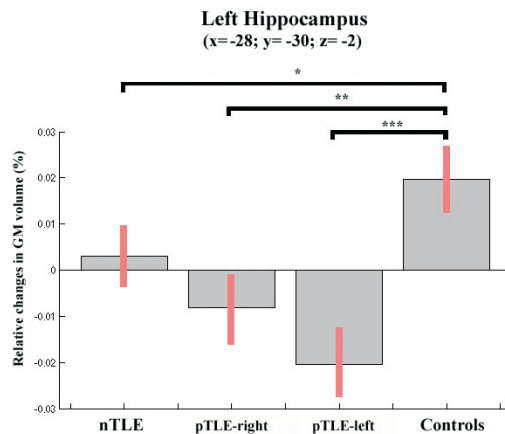
A. Labate, MD
A. Cerasa, PhD
A. Gambardella, MD
U. Aguglia, MD
A. Quattrone, MD

Hippocampal and thalamic atrophy in mild temporal lobe epilepsy

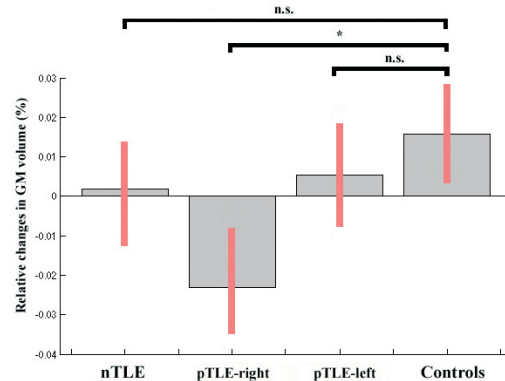
A VBM study

Neurology® 2008;71:1094-1101

Left MTS



Right Hippocampus
(x=23; y=-38; z=9)



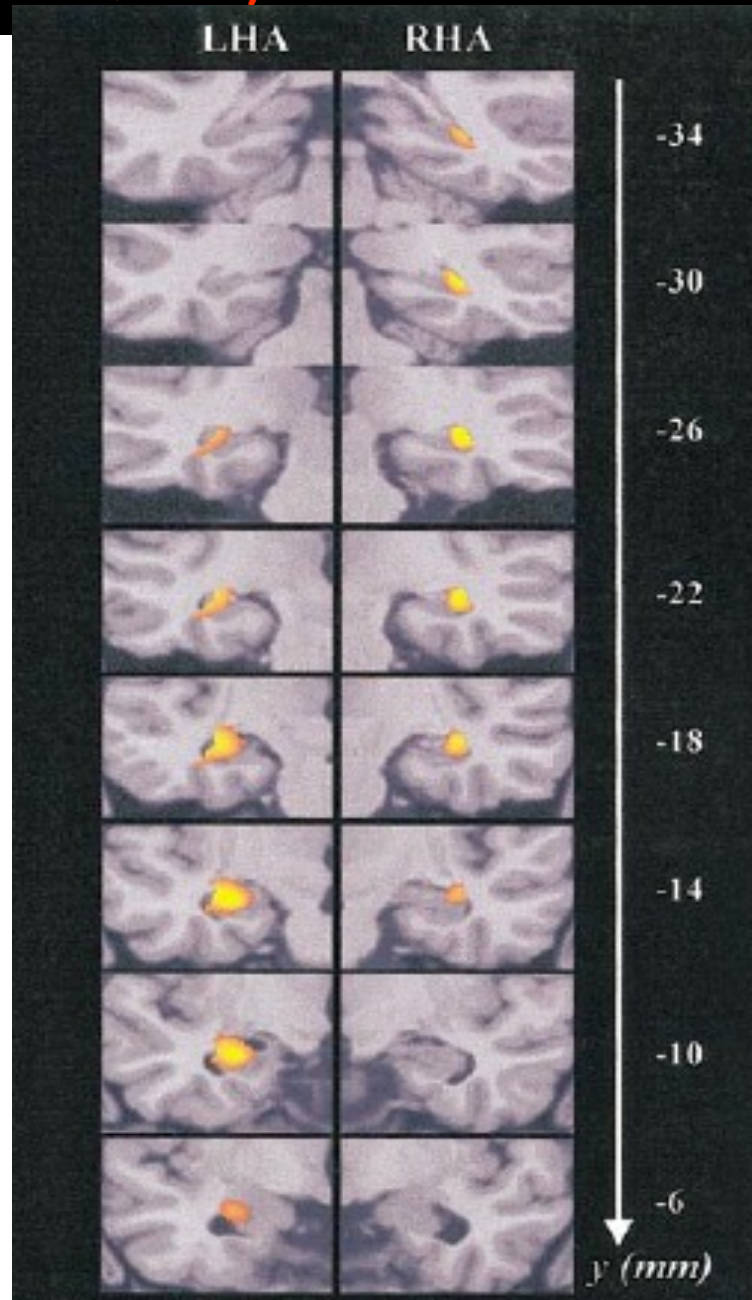
Right MTS



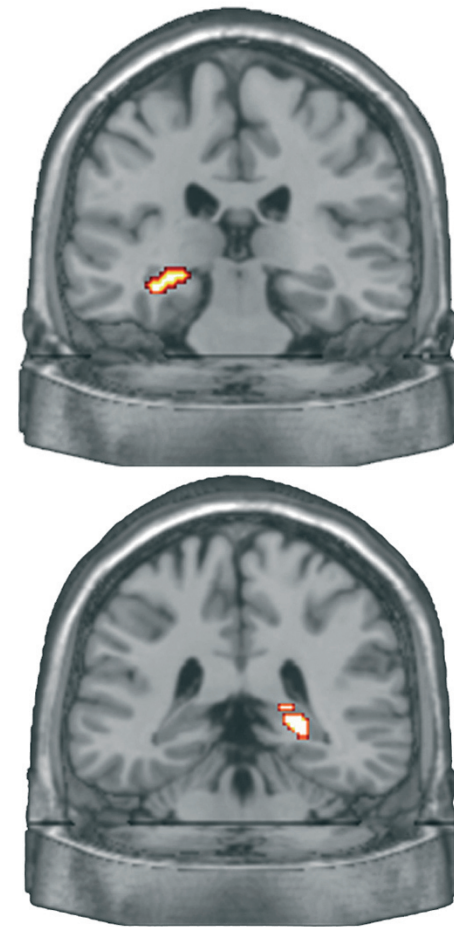
Voxel-Based Morphometry

Pre-processing Overview

Keller, 2002



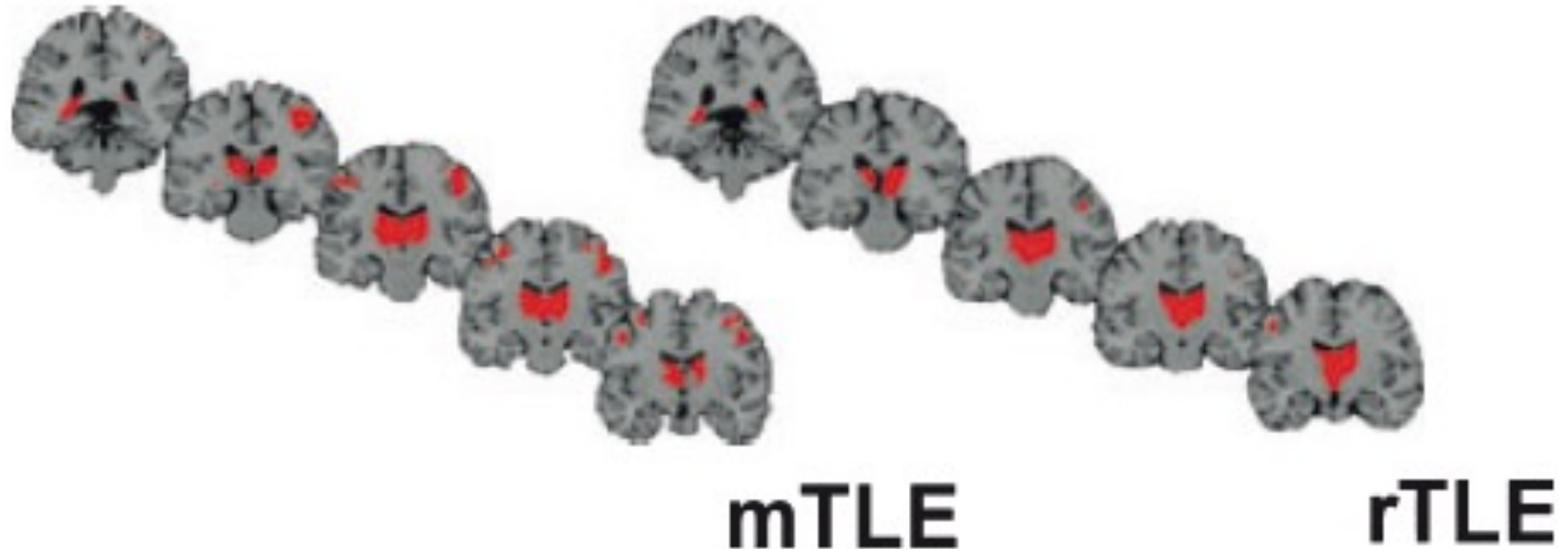
Labate, 2008



FULL-LENGTH ORIGINAL RESEARCH

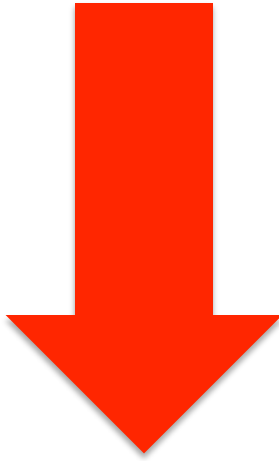
Voxel-based morphometry of sporadic epileptic patients with mesiotemporal sclerosis

*†Angelo Labate, †Antonio Cerasa, ‡Umberto Aguglia, *Laura Mumoli,
*†Aldo Quattrone, and *†Antonio Gambardella

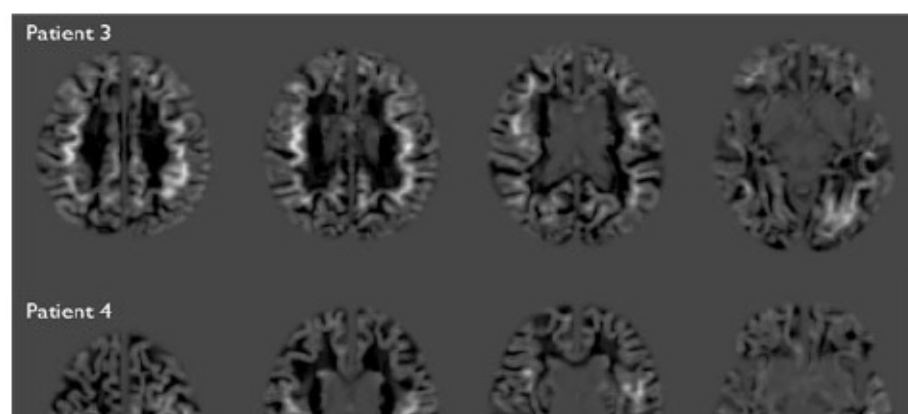
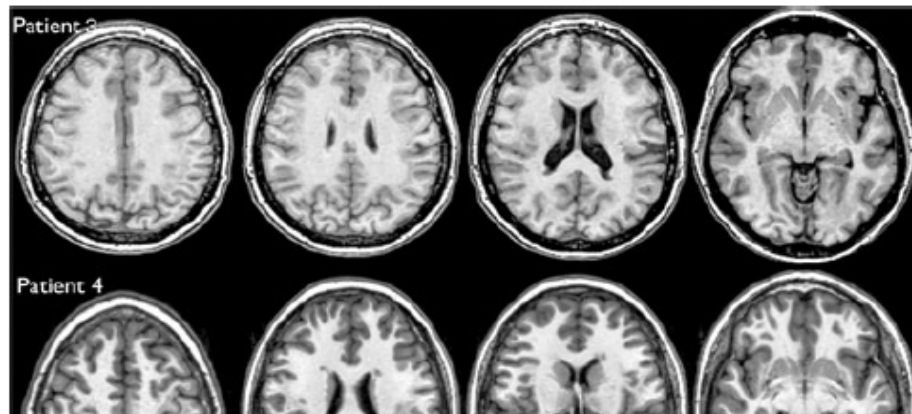


Voxel-Based Morphometry

Pre-processing Overview



Può essere utile anche nel singolo paziente epilettico?

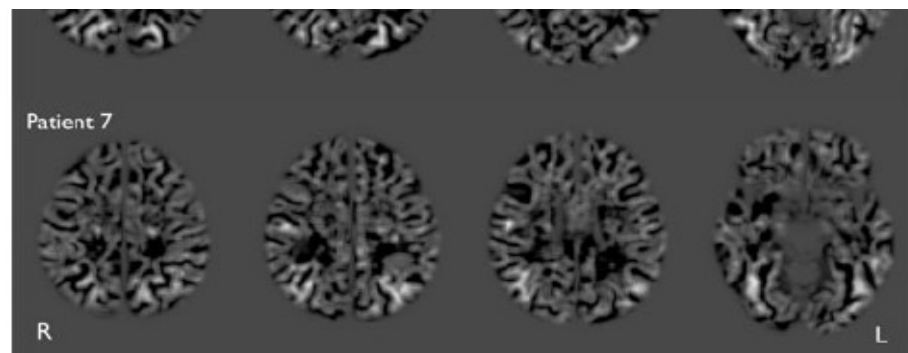
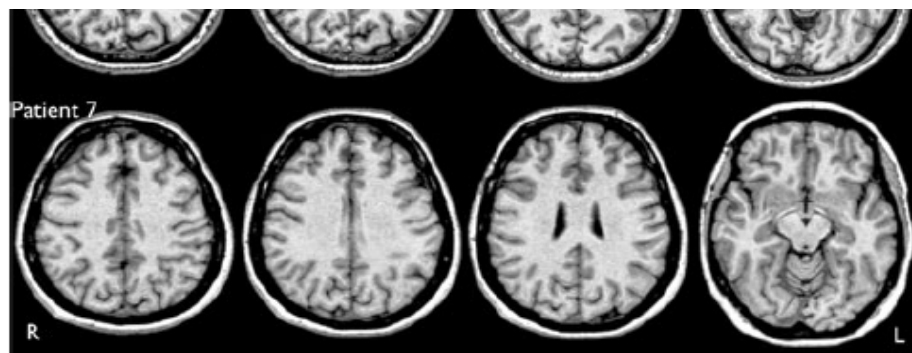


Epilepsia, 49(5):772–785, 2008
doi: 10.1111/j.1528-1167.2007.01436.x

FULL-LENGTH ORIGINAL RESEARCH

Voxel-based 3D MRI analysis helps to detect subtle forms of subcortical band heterotopia

*Hans-Jürgen Huppertz, †Jörg Wellmer, ‡Anke Maren Staack, §Dirk-Matthias Altenmüller, ¶Horst Urbach, and *Judith Kröll



Voxel based morphometry

• VANTAGGI

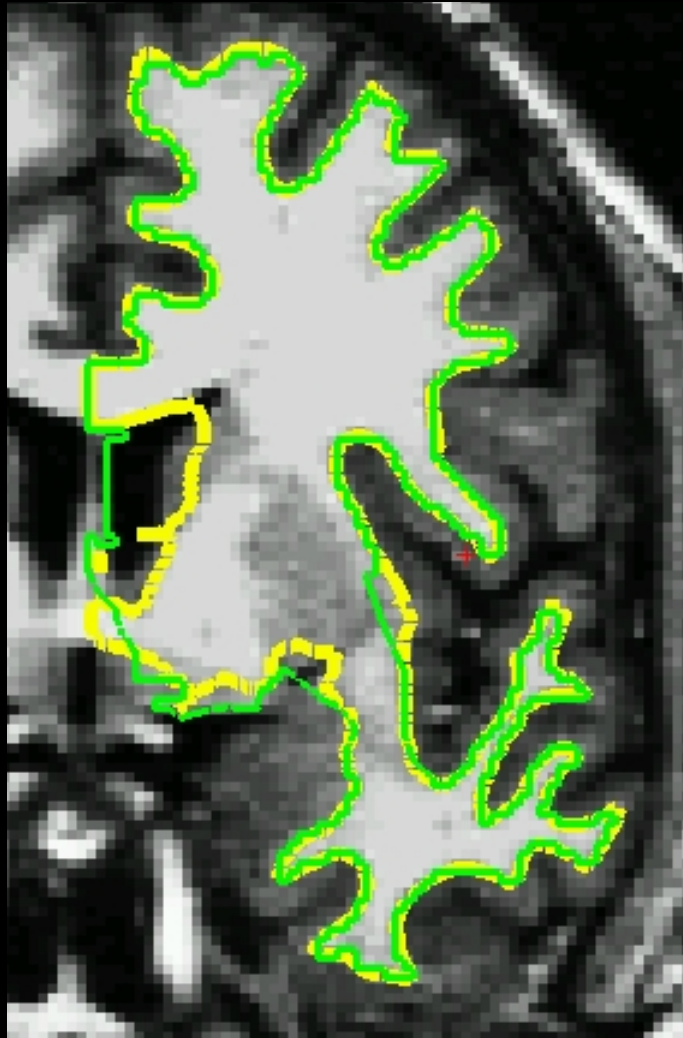
VBM rivela una distribuzione delle anomalie cerebrali paragonabili agli studi postmortem e alle regioni di interesse in RM della letteratura.

VBM non è influenzata dal magnete

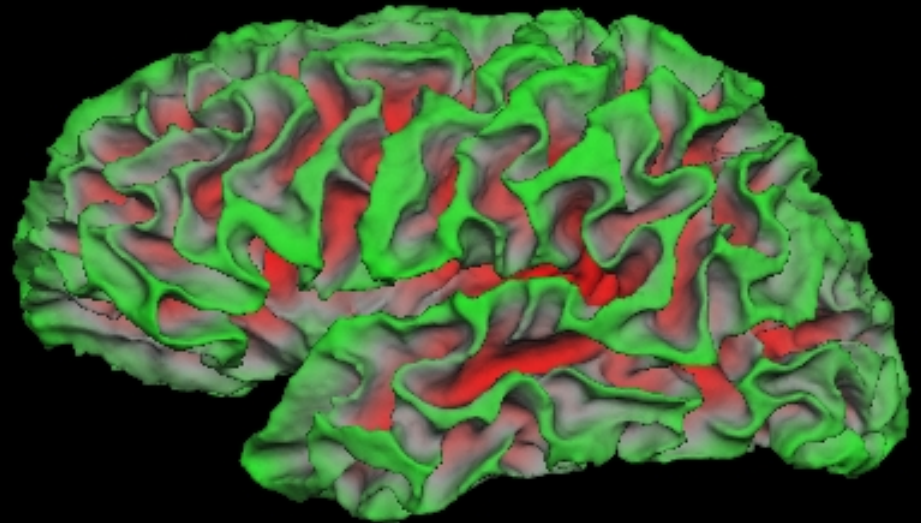
• SVANTAGGI

Ha poca utilità clinica in singoli soggetti soprattutto per la poca sensibilità e specificità in soggetti durante le valutazioni pre-chirurgiche.

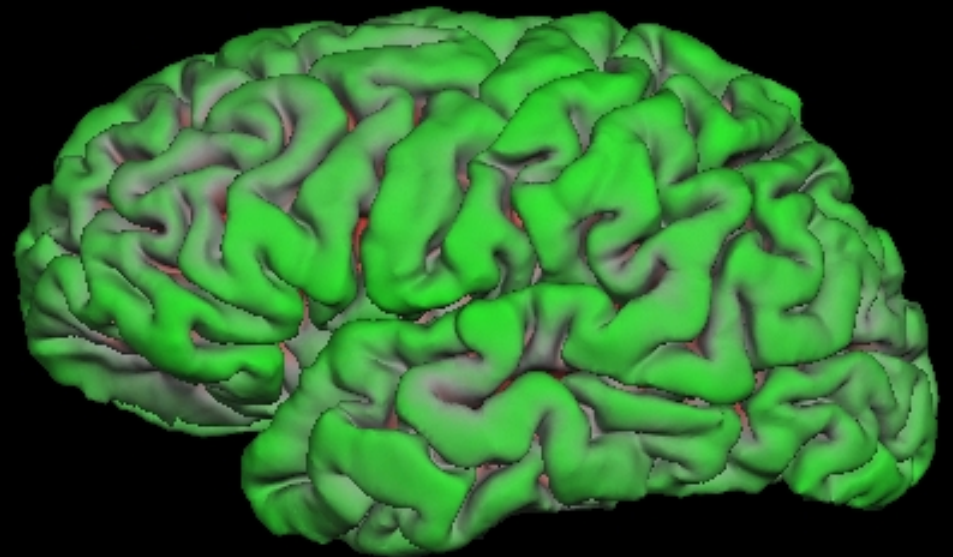
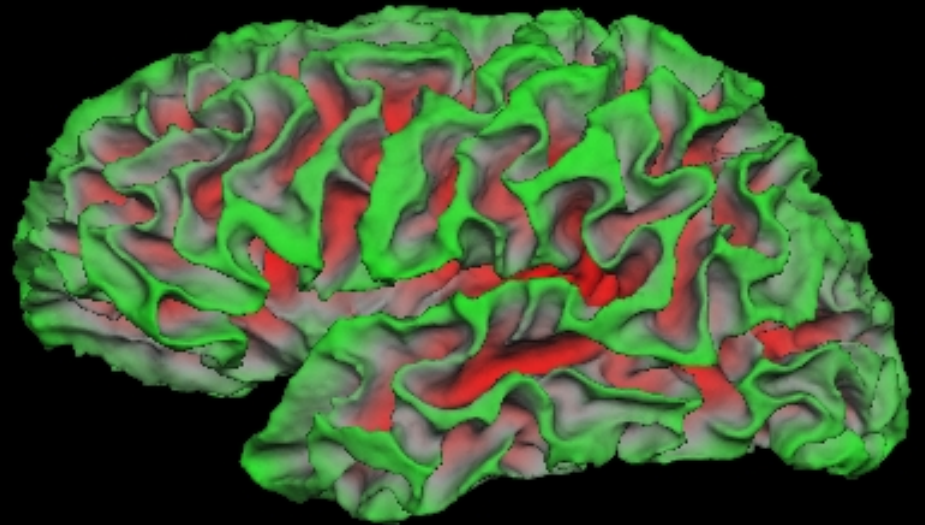
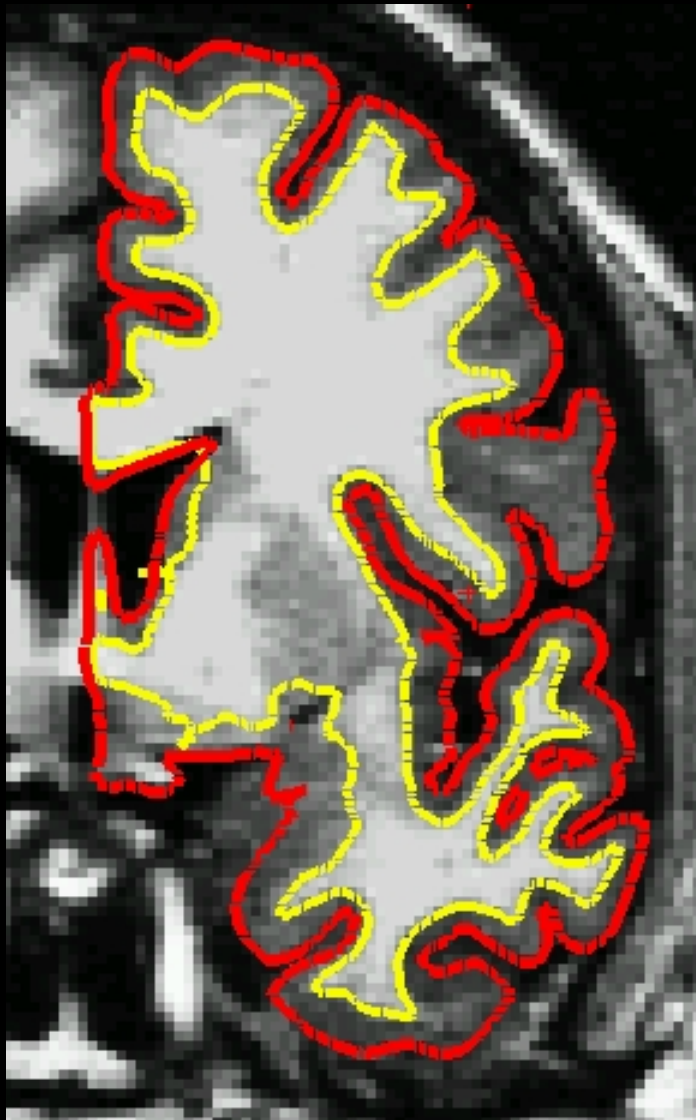
White Matter Surface



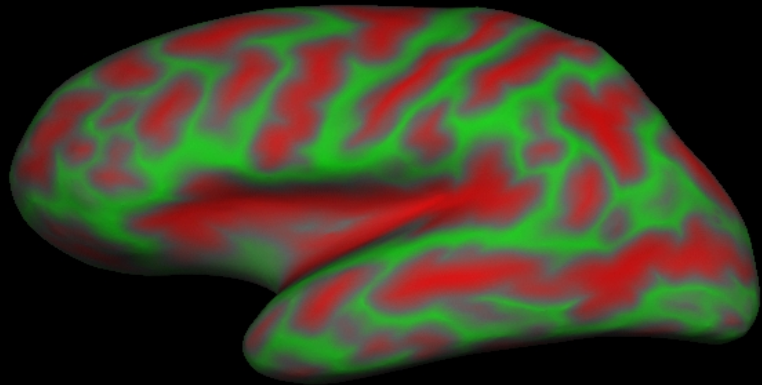
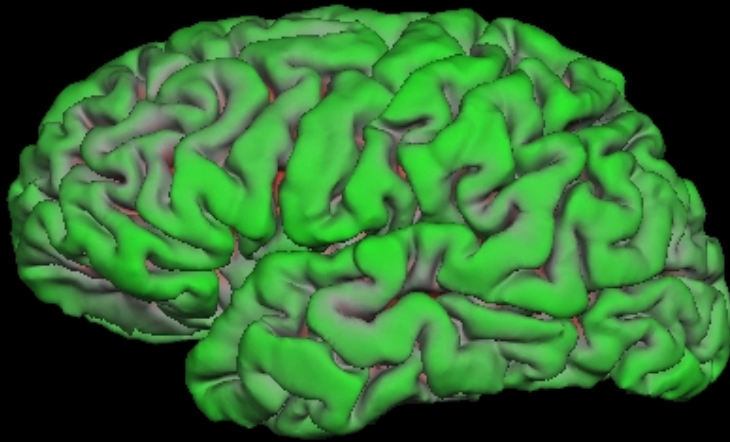
- Deform orig surface
- Follow T1 intensity gradients
- Smoothness constraint
- Vertex Identity (index) Preserved



Surfaces: White and Pial

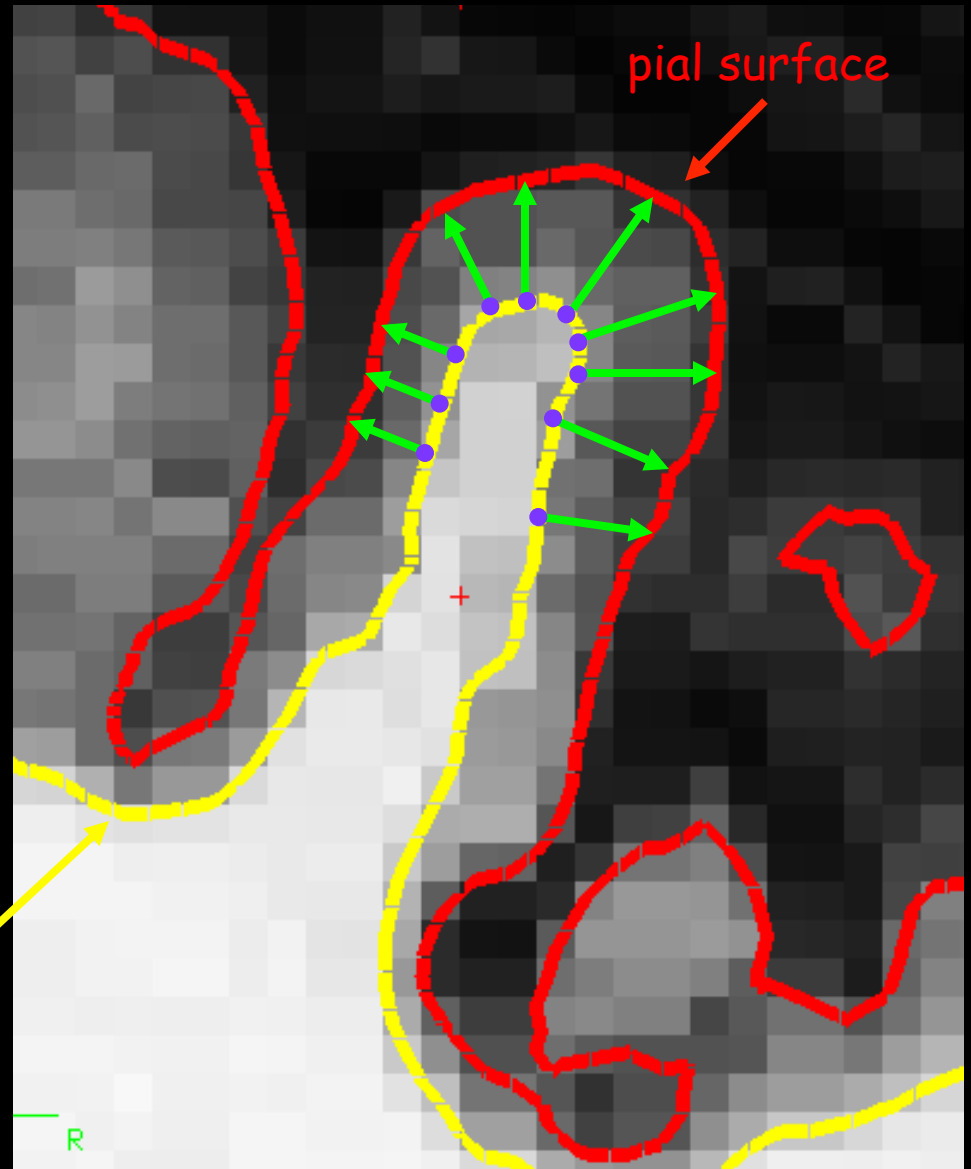


Cortical Thickness



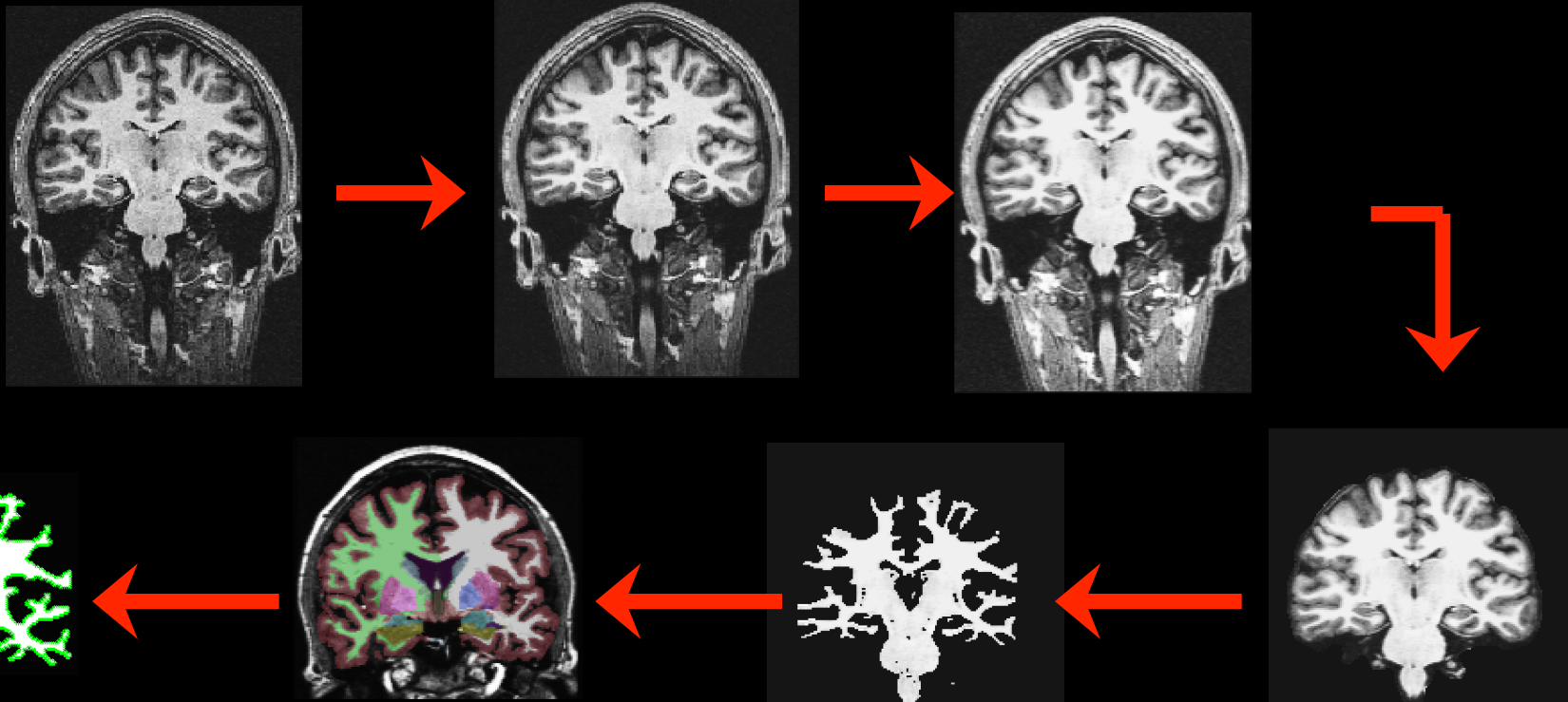
white/gray surface

lh.thickness, rh.thickness

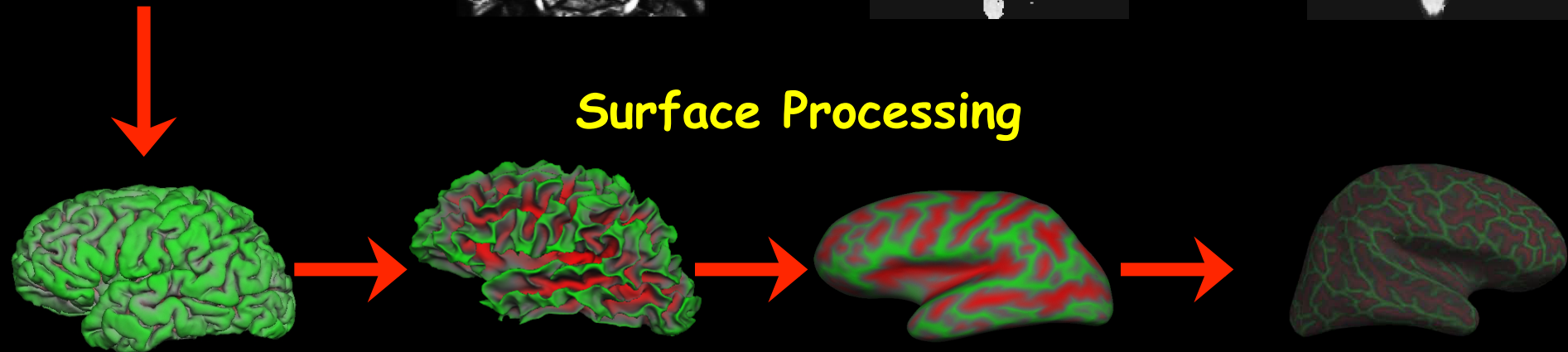


Cortical Reconstruction

Volume Processing



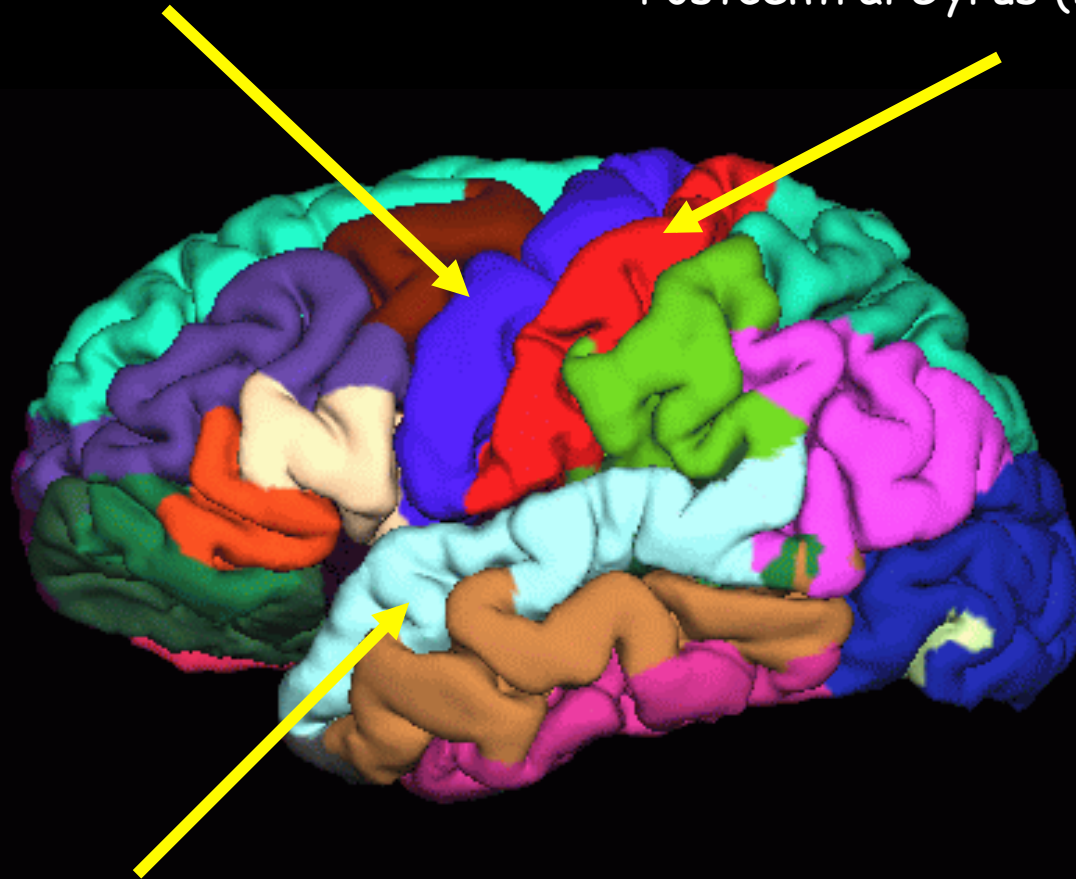
Surface Processing



Automatic Surface Segmentation

Precentral Gyrus (2.4 mm)

Postcentral Gyrus (2.2 mm)

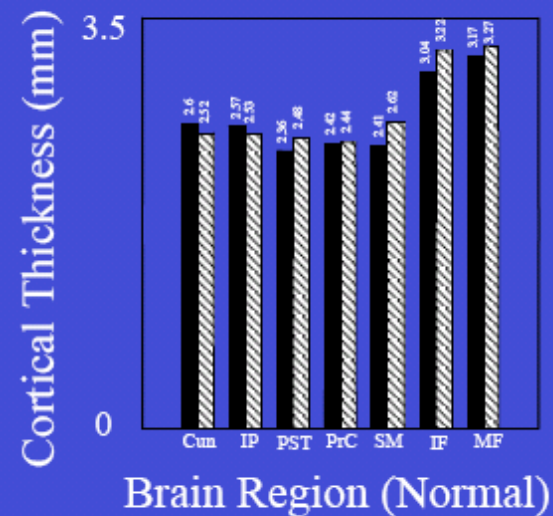
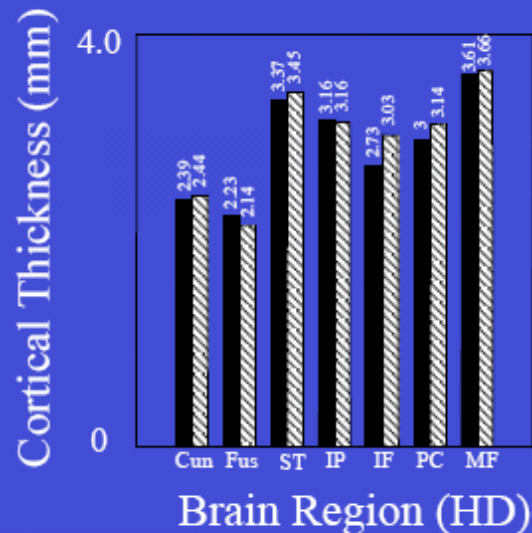
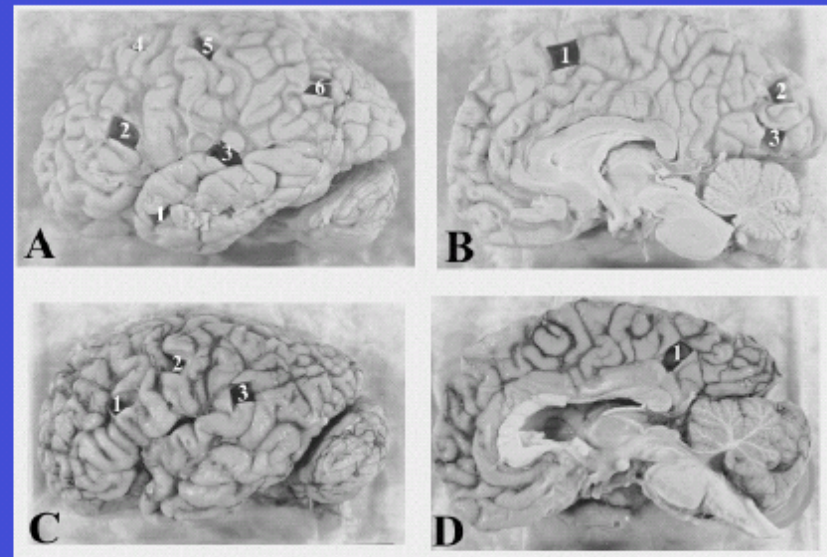
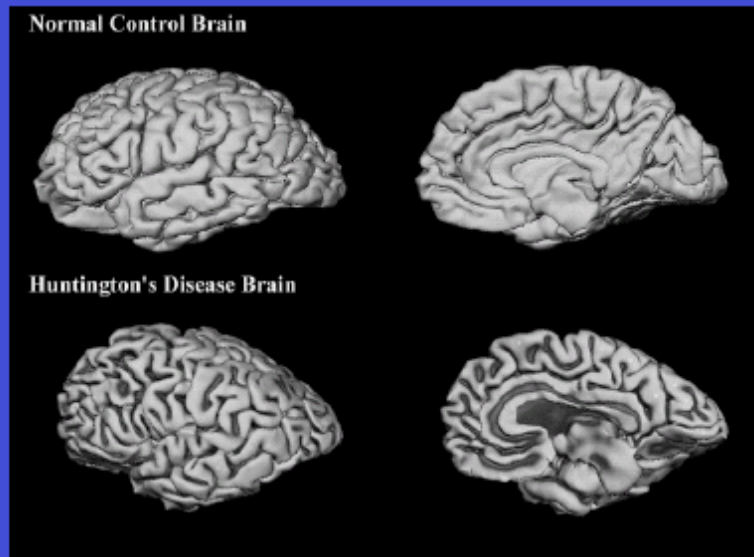


Superior Temporal Gyrus (2.9 mm)

Based on individual's folding pattern



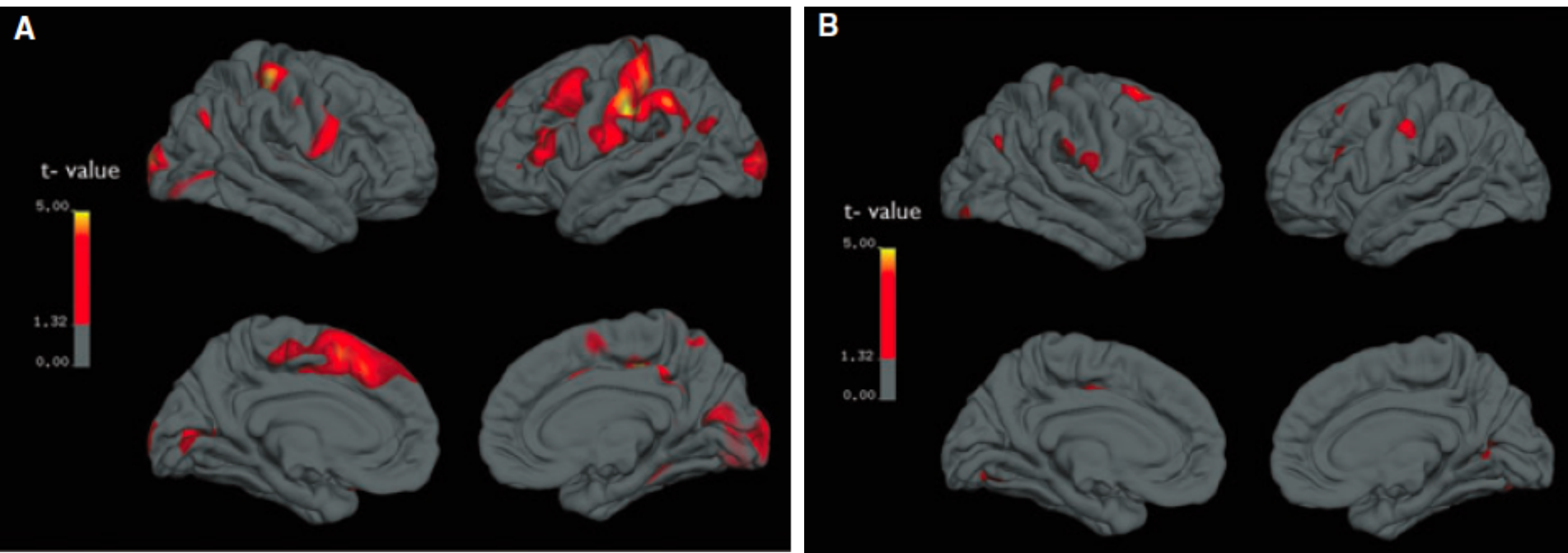
Histological Validation of Thickness Measures



FULL-LENGTH ORIGINAL RESEARCH

Neocortical thinning in “benign” mesial temporal lobe epilepsy

*†Angelo Labate, †Antonio Cerasa, *‡Umberto Aguglia, *Laura Mumoli, *†Aldo Quattrone, and
*§Antonio Gambardella



pTLE

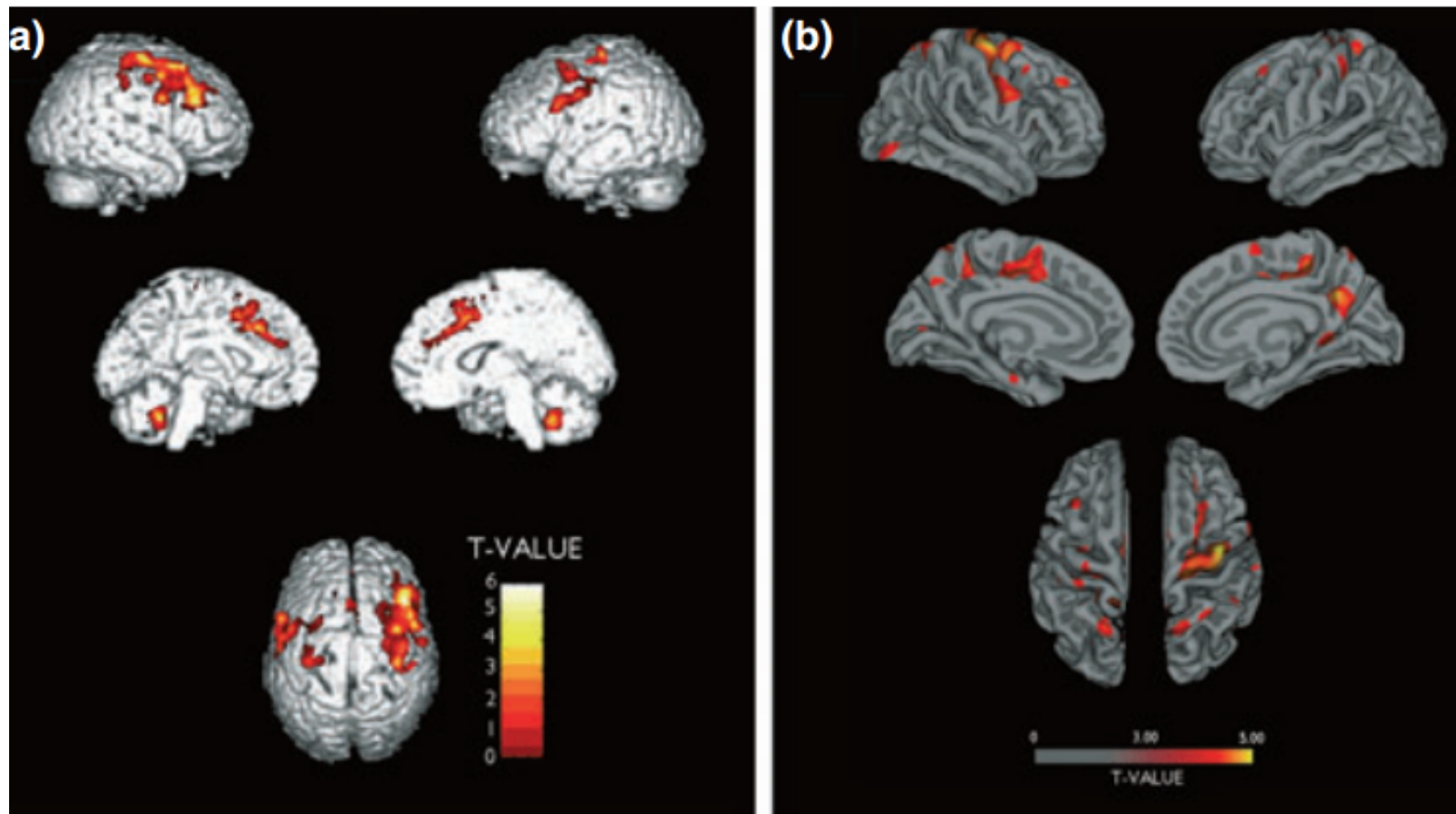
nTLE

Neuroanatomic correlates of psychogenic nonepileptic seizures: A cortical thickness and VBM study

*†Angelo Labate, †Antonio Cerasa, ‡Marco Mula, *Laura Mumoli, §¶Maria Cecilia Gioia,
*Umberto Aguglia, *†Aldo Quattrone, and *§Antonio Gambardella



53 (2) 377-385 2012



Cortical Thickness

• ADVANTAGES

Sensitivity to assess anatomical characteristics.

For an individual subject, you can ascertain what the individual thickness is of specific neuroanatomic areas. Clinically this information is of significant importance as you can then detail whether atrophy in specific regions is predictive of a clinical endpoint.

• DISADVANTAGES

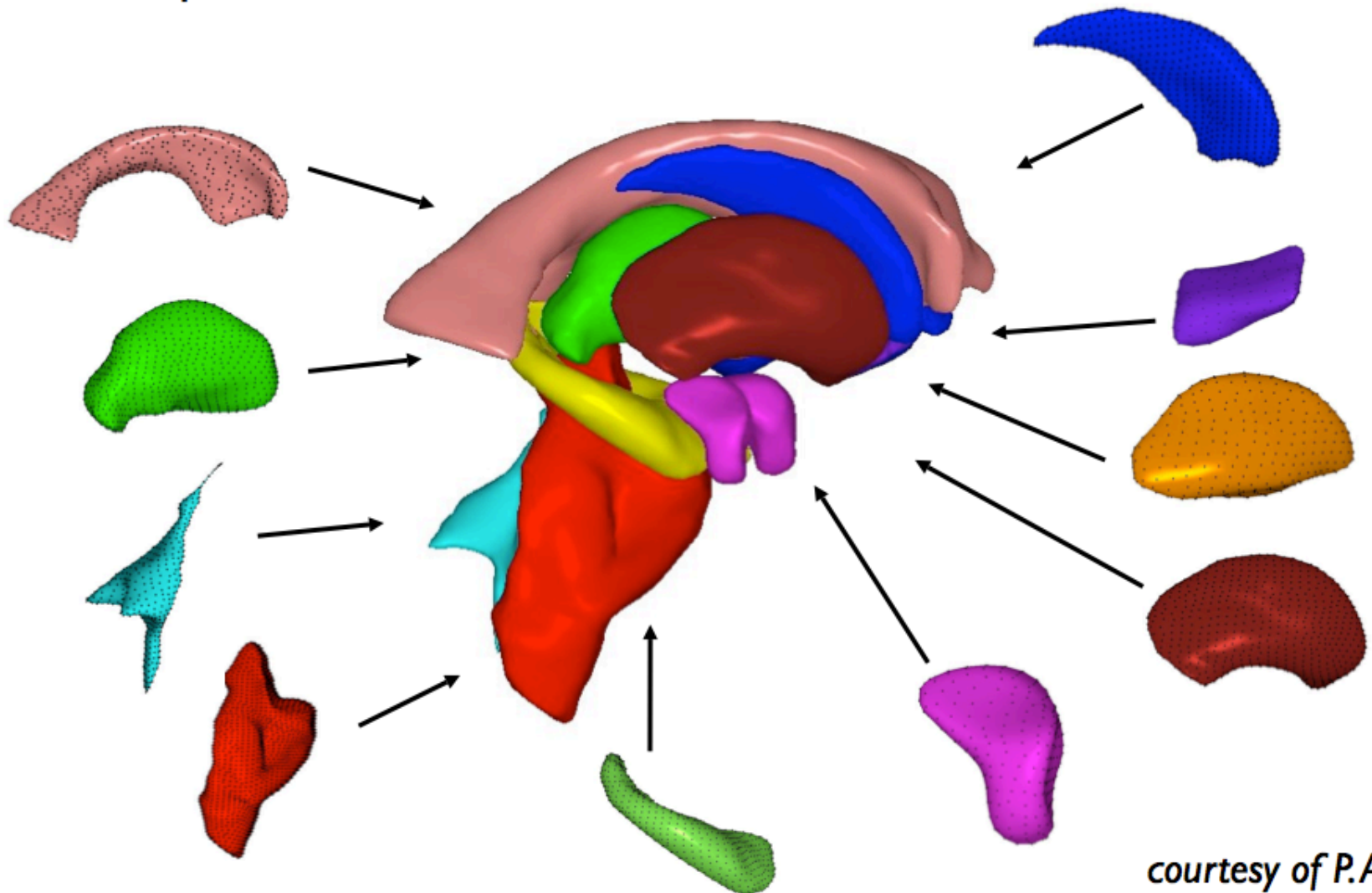
Very time-consuming: 24 h !!
For a single brain reconstruction

Requires high-quality T1 images (3Tesla)

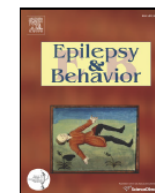


Shape analysis

Composite structure models built from concatenated ensemble



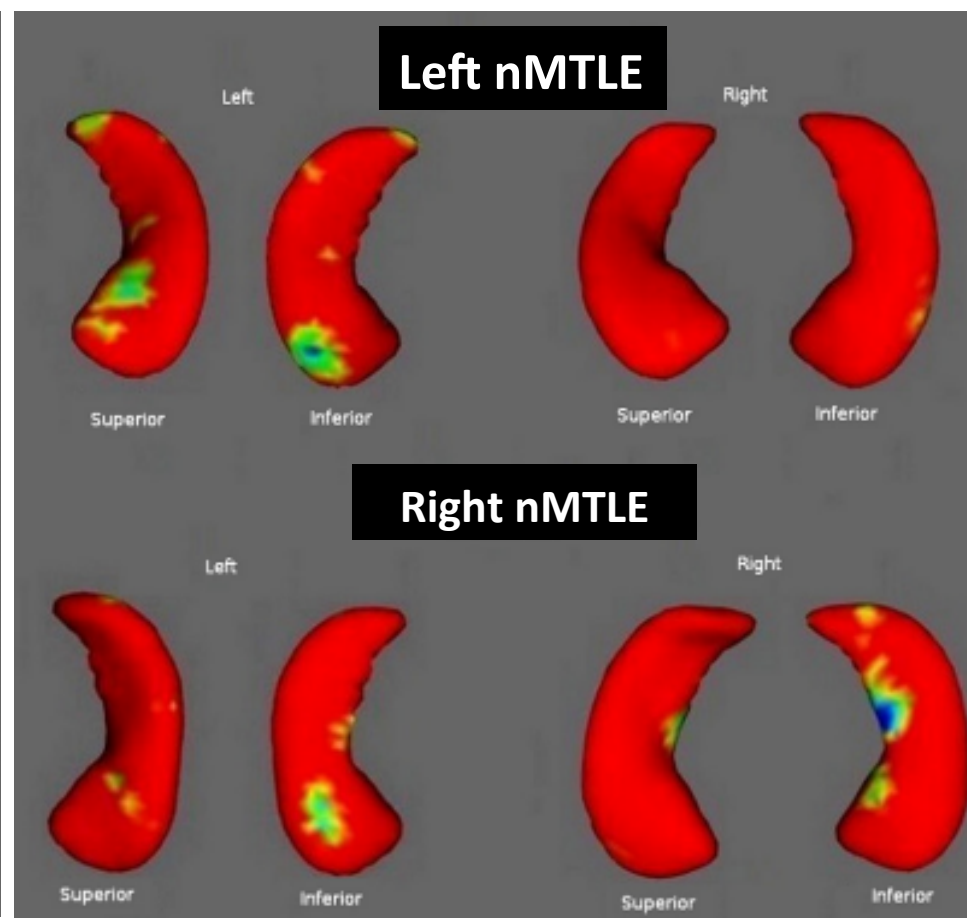
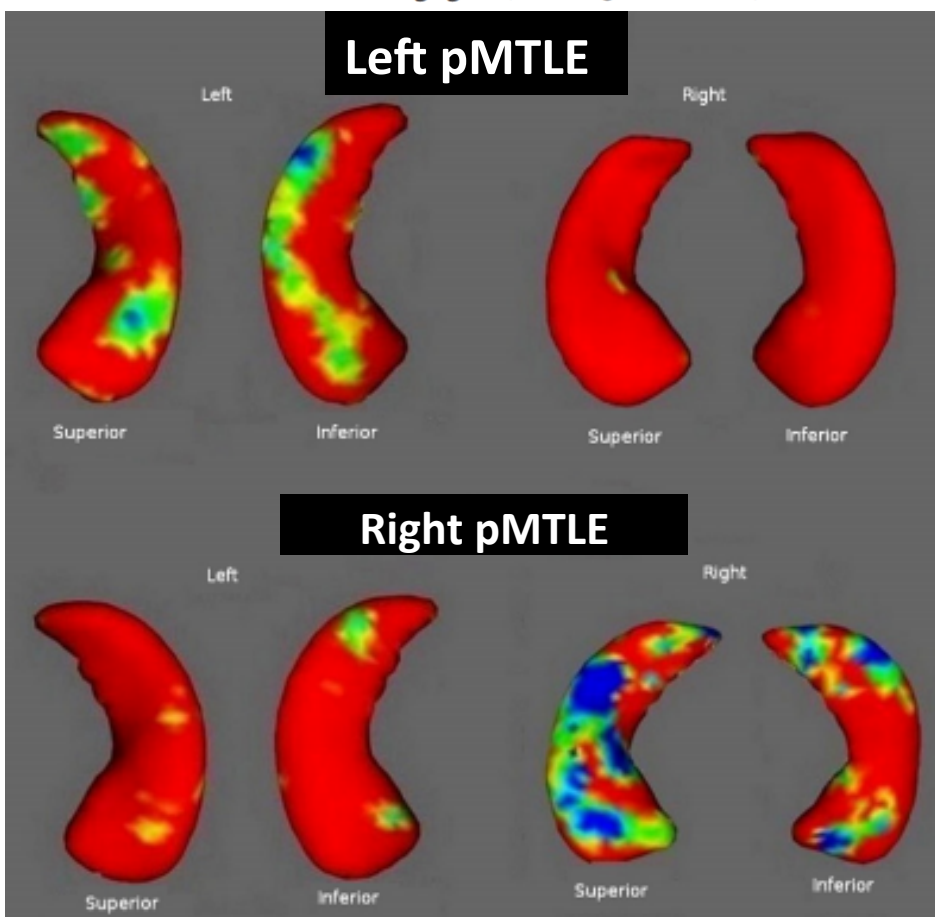
courtesy of P. Aljabar



Detection of hippocampal atrophy in patients with temporal lobe epilepsy: A 3-Tesla MRI shape



Laura Mumoli ^{a,1}, Angelo Labate ^{a,b,*,1}, Roberta Vasta ^b, Andrea Cherubini ^b, Edoardo Ferlazzo ^a, Umberto Aguglia ^a, Aldo Quattrone ^{a,b}, Antonio Gambardella ^{a,c}

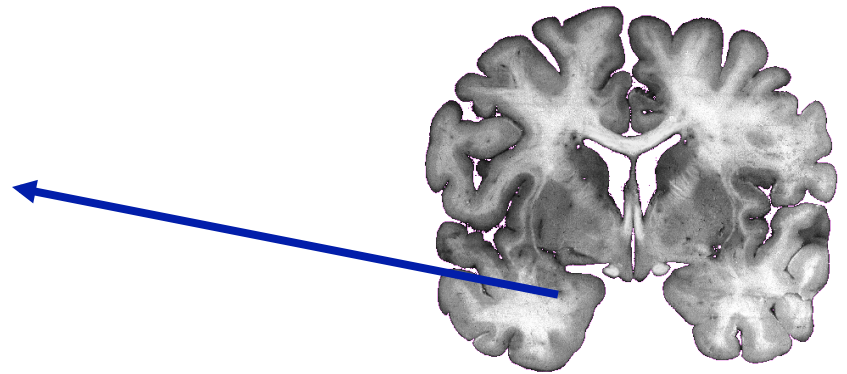


Diffusion Tensor Imaging



Fractional
anisotropy

Mean
Diffusivity



Ultra-structure damage

CONNECTIVITY

Diffusion tensor imaging in temporal lobe epilepsy

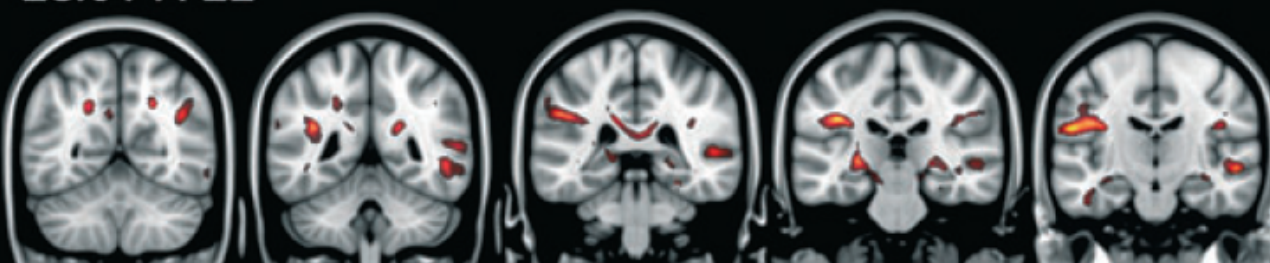
Donald W. Gross

Table 1. Summary of DTI findings in TLE

Reference	Age	TLE subtype	DTI abnormalities	Correlations
Arfanakis et al. (2002)	Adults	Not defined	EC, post CC	–ve
Concha et al. (2005)	Adults	Unilateral MTS	Bilateral F, C	na
Thivard et al. (2005)	Adults	Unilateral MTS	Ipsi TLWM	–ve
Gross et al. (2006)	Adults	Unilateral MTS	EC, genu CC	–ve
Focke et al. (2008)	Adults	Unilateral MTS	Ipsi TLWM + diffuse bilateral	–ve
Kim et al. (2008)	Adults	Mixed	Splenium CC	–ve
Lin et al. (2008)	Adults	Mixed	Ipsi UF, AF	+ve
Govindan et al. (2008)	Children	Nonlesional TLE	Ipsi UF, AF, ILF, CST	+ve
Nilsson et al. (2008)	Children	Mixed	TLWM, C (↑MD)	–ve
Concha et al. (2009)	Adults	Unilateral MTS + nonlesional TLE	MTS- F, C, EC, CC Nonlesional- EC, CC	–ve MTS +ve nonlesional

EC, external capsule; CC, corpus callosum; –ve, correlation not seen with disease duration; +ve, correlation demonstrated with disease duration; MTS, mesial temporal sclerosis; F, fornix; C, cingulum; na, not available; TLWM, temporal lobe white matter; UF, uncinate fasciculus; AF, arcuate fasciculus; ILF, inferior longitudinal fasciculus; CST, corticospinal tract; ↑MD, increased mean diffusivity.

Left MTLE



L

R

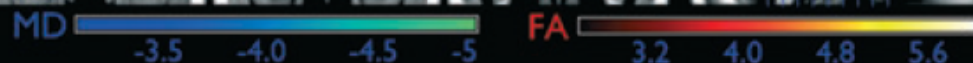


Right MTLE

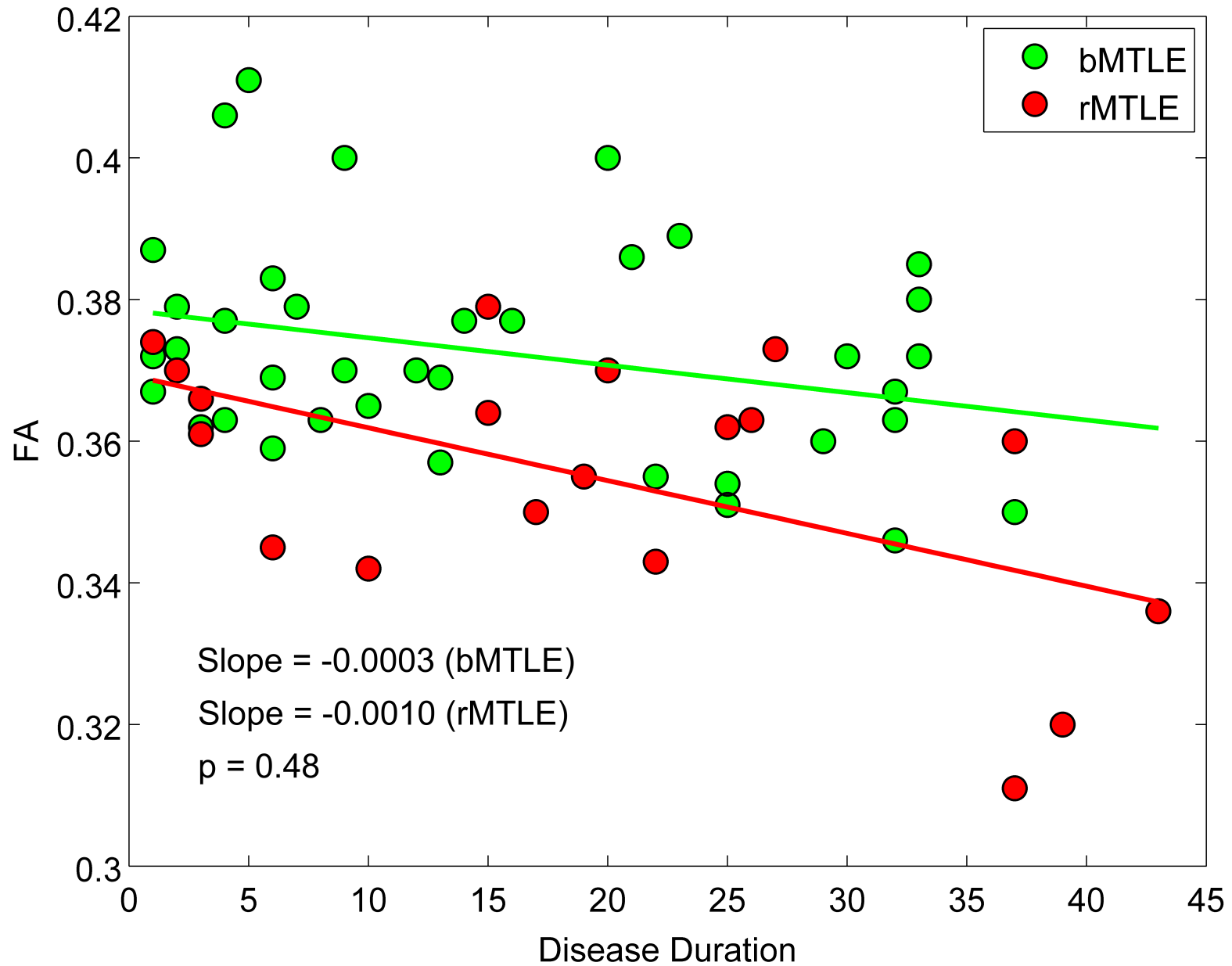


L

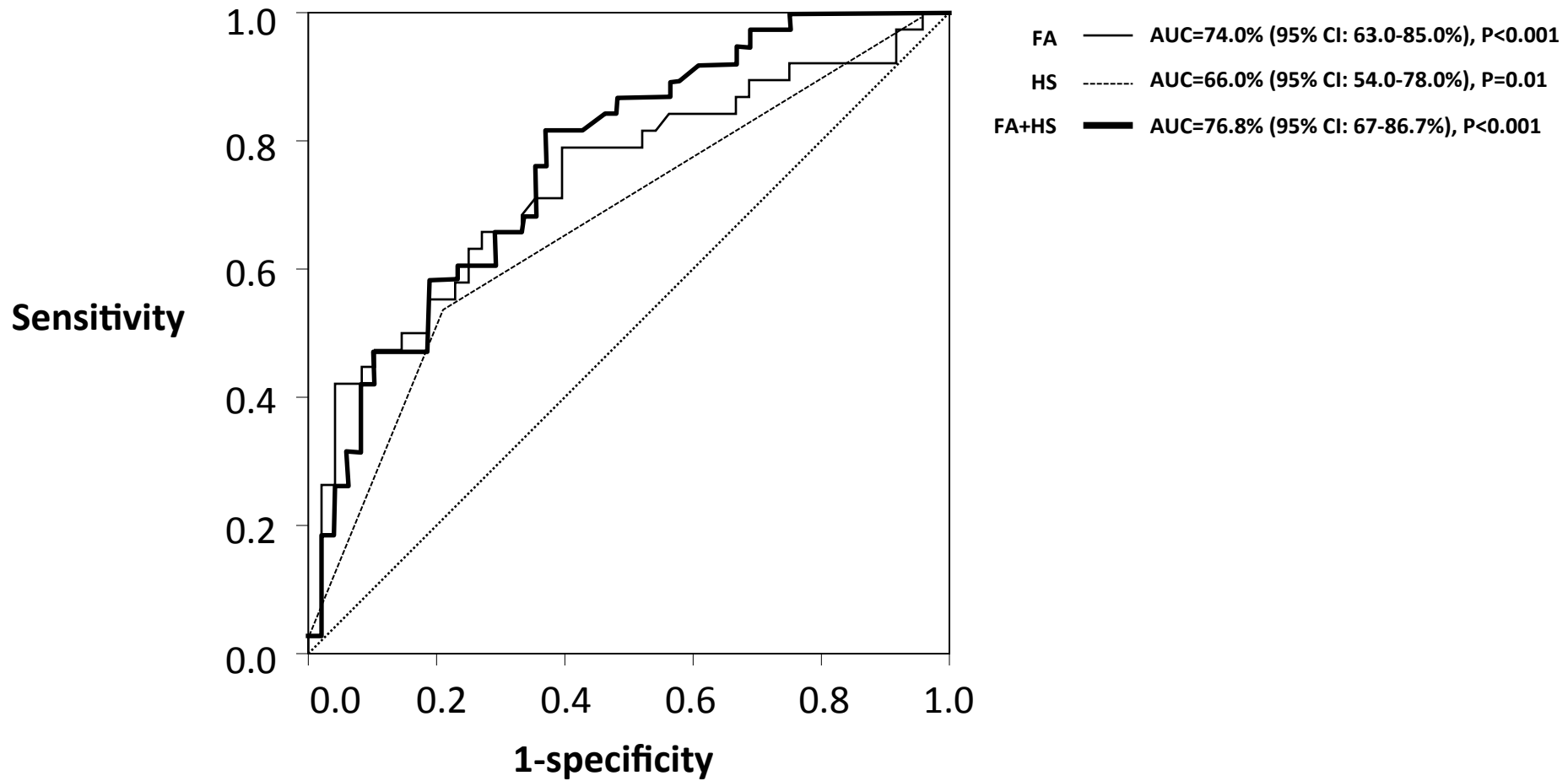
R



Temporal Lobe White Matter



**ROC curve analysis for discriminating patients
with bMTLE from those with rMTLE**



RM morfologica avanzata nello studio dell'epilessia focale

- Può rendere superfluo l'imaging tradizionale?

Caso clinico

Caso clinico

Donna di 45 anni

Familiarità negativa per malattie neurologiche

- ❖ Nata a termine di gravidanza fisiologica esitata in parto eutocico.
- ❖ Sviluppo psico-fisico regolare.
- ❖ Destrimane
- HA AVUTO DUE CONVULSIONI FEBBRILI ALL'ETA' DI 3 ANNI



Caso clinico

Dall'età di 40 anni, la paziente ha iniziato a presentare, fino a 20 volte al giorno, episodi caratterizzati da *strana sensazione epigastrica ascendente della durata di alcuni secondi seguita da perdita del contatto con l'ambiente, sguardo atterrito, versione del capo a sx ed estensione del braccio e della gamba sx*. Al termine la paziente, risponde prontamente ed in modo adeguato, riferendo di aver avvertito una sensazione "scossa".



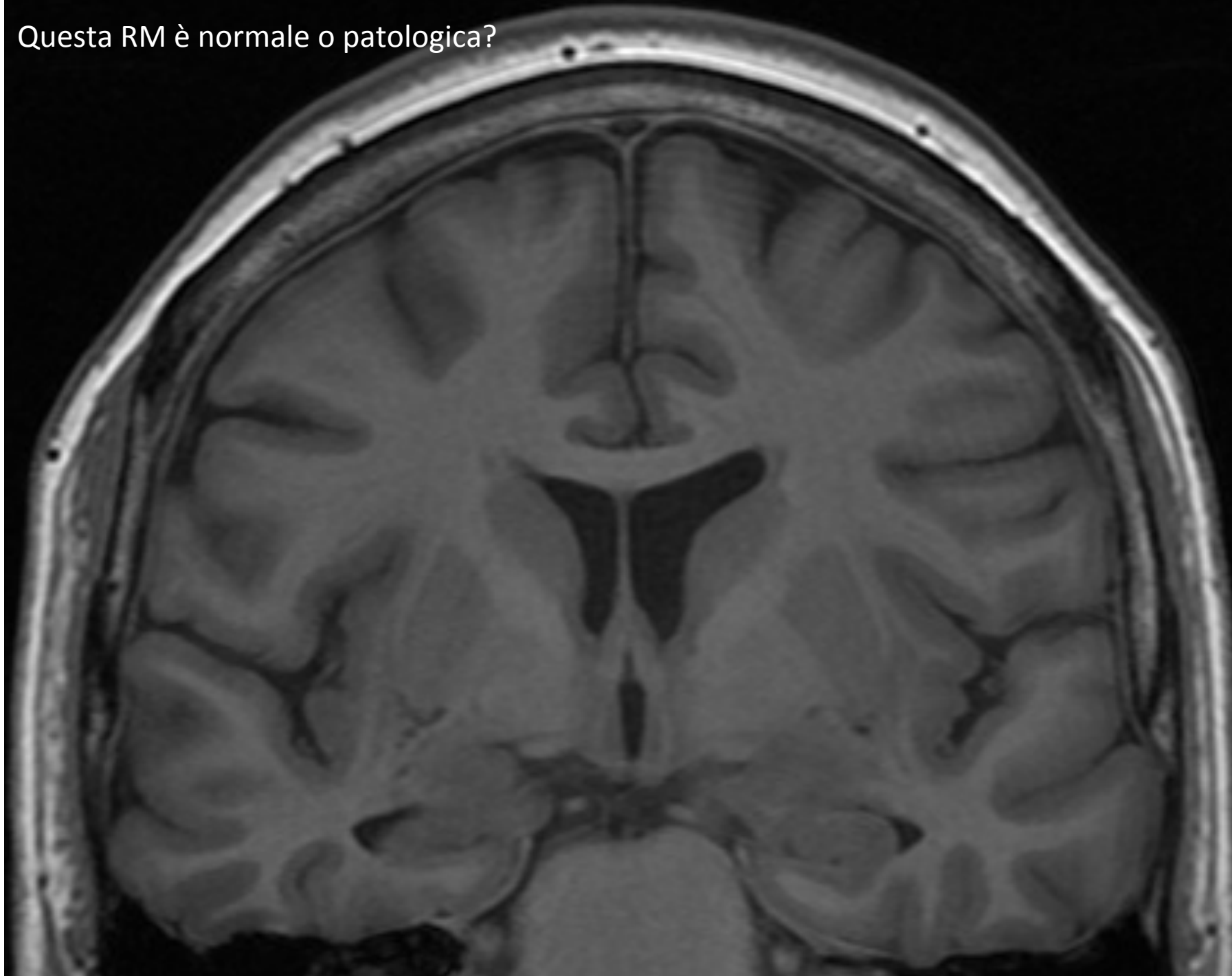
Caso clinico

L'obiettività neurologica risultava: nella norma

L' esame neuropsicologico evidenziava: un declino delle funzioni cognitive di grado lieve.

RM encefalo:

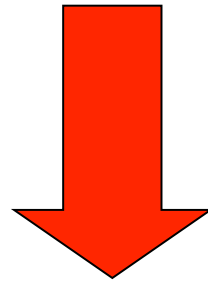
Questa RM è normale o patologica?



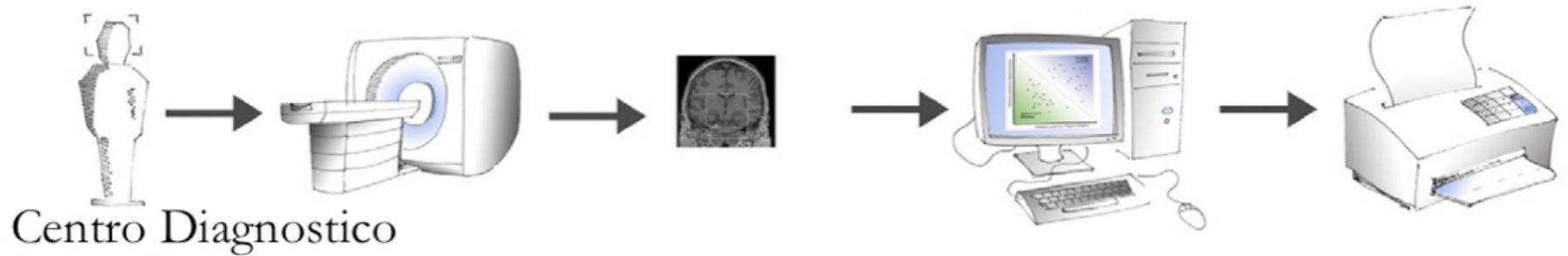
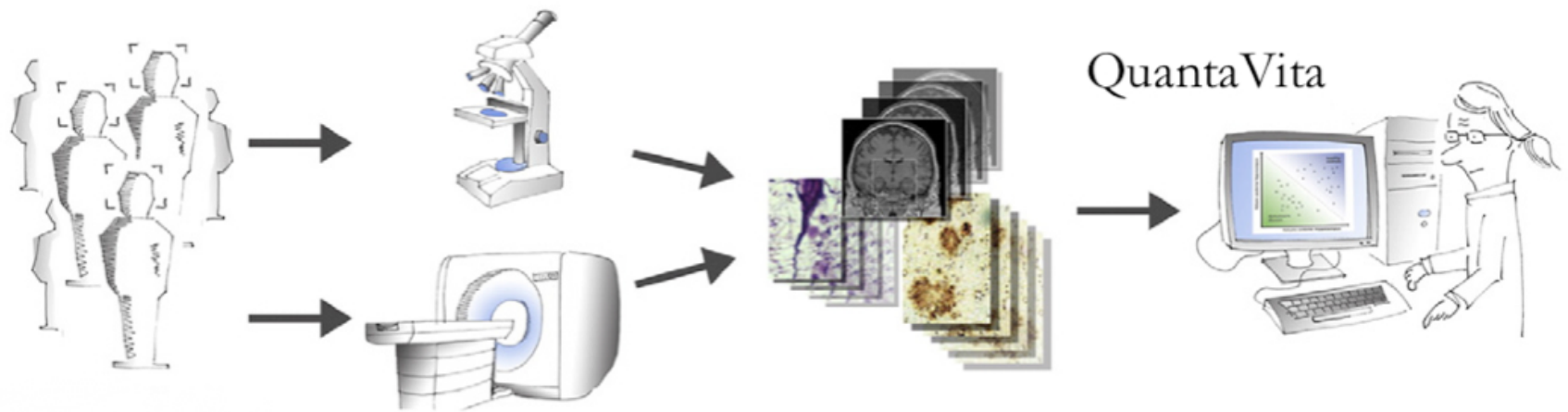
Follow-up (12 mesi)

✓ Carbamazepina posologia 1.0 gr/die: sospesa per evento avverso

LAMOTRIGINA: 150 mg/die + Gardenale 100 mg/die



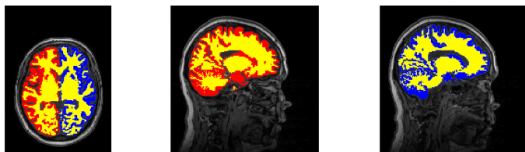
farmacoresistente



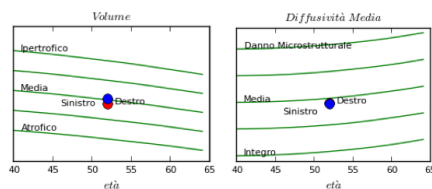
Automatized image analyses + Extraction of multiple **biomarkers** + Generation of **normative** ranges



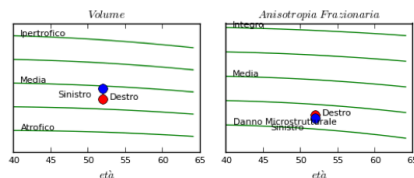
Parenchima cerebrale



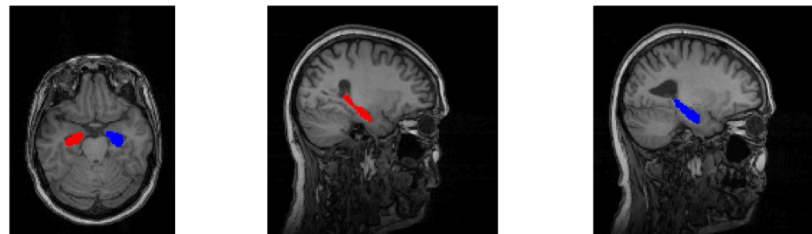
Sostanza grigia	Emisfero destro (rosso)	Emisfero sinistro (blu)	Dati Normativi
Volume [ml]	405.94	414.44	[341.44 - 486.34]
Diffusività [$10^{-4}mm^2s^{-1}$]	10.24	10.22	[8.80 - 12.00]



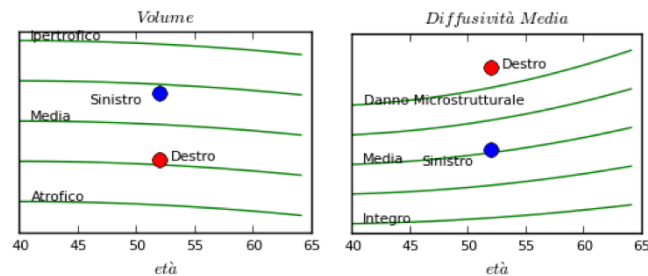
Sostanza bianca	Emisfero destro (rosso)	Emisfero sinistro (blu)	Dati Normativi
Volume [ml]	325.55	338.57	[285.13 - 399.87]
Anisotropia	0.37	0.37	[0.36 - 0.45]



Ippocampo



	Emisfero destro (rosso)	Emisfero sinistro (blu)	Dati Normativi
Volume [ml]	4.75	5.92	[3.99 - 6.79]
Diffusività [$10^{-4}mm^2s^{-1}$]	<u>11.82</u>	10.16	[8.82 - 11.43]



RM morfologica avanzata nello studio dell'epilessia focale

- Può rendere superfluo l'imaging tradizionale?

SI

CARDIOLOGIA

Test: quanto è sano il tuo cuore? Dizionario della salute/Cuore L'esperto risponde



» Corriere della Sera > Salute > Tanti episodi di «déjà vu»?

LO STUDIO

30 Maggio 2012

Tanti episodi di «déjà vu»? L'ippocampo è «ipereccitabile»

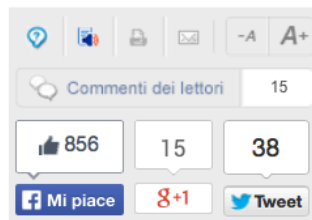
Il fenomeno inspiegabile per anni. Ora un gruppo di studiosi cechi e britannici ha elaborato una teoria neurologica



MILANO - Scoperto un legame tra déjà vu e strutture del cervello grazie a uno studio di ricercatori della Repubblica Ceca e del Regno Unito pubblicato sulla rivista Cortex. Gli studiosi dell'Istituto centrale europeo di tecnologia e dall'Università di

Masaryk (Ceitec Mu) nella Repubblica Ceca, ritengono che specifiche strutture del cervello abbiano un impatto diretto sul déjà vu, cioè la sensazione erronea di aver già visto un'immagine o di aver già vissuto precedentemente un avvenimento o una situazione che si sta verificando.

LO STUDIO - «Oltre cento soggetti sono stati sottoposti a risonanza magnetica cerebrale e ad altri metodi di analisi morfologica del cervello e le dimensioni di singole regioni del cervello sono state confrontate tra gli individui del gruppo che non avevano mai avuto déjà vu con quelli che ne avevano avuto», ha spiegato l'autore principale della ricerca, Milan



OGGI IN salute >

Antitrust, multa record a Roche e Novartis Dovranno pagare 180 milioni di euro

Cinquantenni attenti: carne e formaggi pericolosi come il fumo

Stamina, Baccarani presidente del comitato

Poche «Unità Ictus» in Italia E il Sud ne è quasi del tutto privo

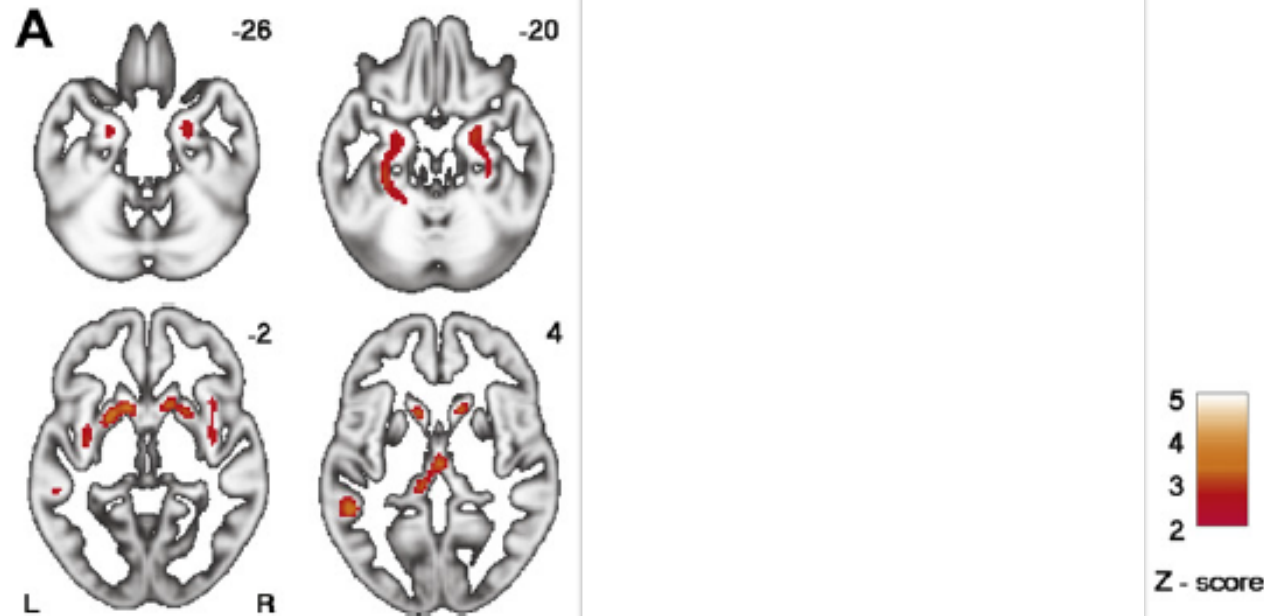
Chi ha il DV??

I soggetti sani
(60-80%)

I pazienti con
epilessia del lobo
temporale (TLE)

I pazienti
psichiatrici
(depressione e
schizofrenia)

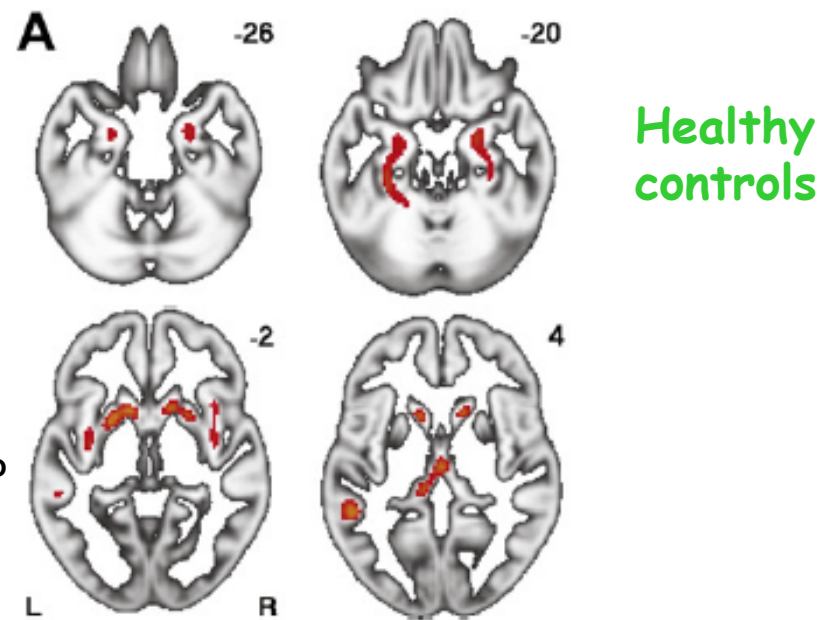
- COSA VEDETE IN QUESTA IMMAGINE DI VBM?



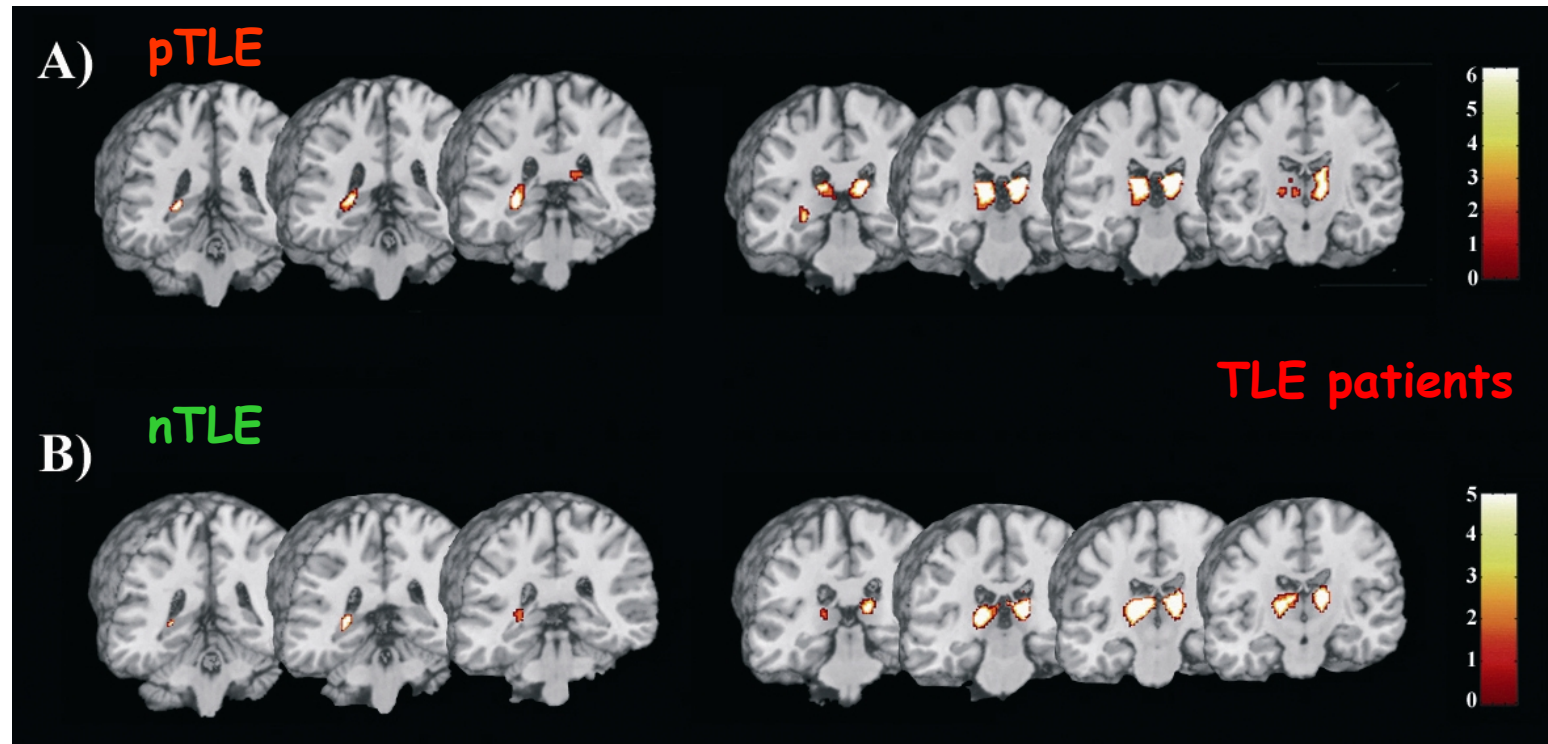


Brazdil M. 2012

CHE DIFFERENZE COGLIETE TRA QUESTE IMMAGINI?



Labate A. 2008



Benign mesial temporal lobe epilepsy

Angelo Labate, Antonio Gambardella, Eva Andermann, Umberto Aguglia, Fernando Cendes, Samuel F. Berkovic and Frederick Andermann

Box 1 | Clinical features of bMTLE

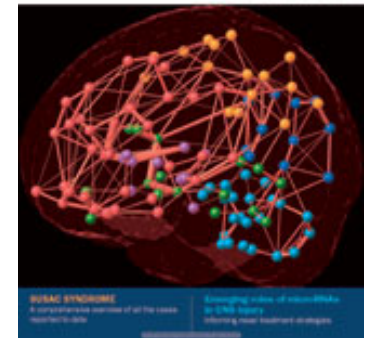
- Onset in late adolescence or adulthood
- Normal neurological examination
- Normal cognitive examination
- Unremarkable past medical history
- **≈30% have positive family history of febrile seizures or epilepsy**
- ≈15% have personal antecedents of simple febrile seizures
- Viscerosensory auras are the predominant symptoms
- Easily controlled with a single antiepileptic drug
- Misdiagnosis of panic attacks or gastrointestinal disturbances is very common

Abbreviation: bMTLE, benign mesial temporal lobe epilepsy.

Box 2 | EEG, MRI and genetics of bMTLE

- ≥60% have normal interictal EEG
- **Almost 40% have MRI evidence of hippocampal sclerosis**
- Genetic predisposition is known to exist
- Remarkable intrafamilial and interfamilial phenotypic heterogeneity
- Autosomal dominant inheritance is rare

Abbreviation: bMTLE, benign mesial temporal lobe epilepsy.



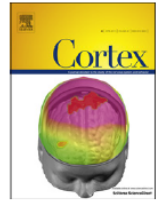
Nat. Rev. Neurol. 7, 237–240 (2011)

**Déjà vu often represents
the only type of seizure for
many years.....**

Commentary

**Comment on Brázdil (2012) “Unveiling the mystery of déjà-vù:
The structural anatomy of déjà-vù”**

Angelo Labate^{a,b,} and Antonio Gambardella^{a,c}*



CORTEX 49 (2013) 1162

- The healthy population recruited was fully investigated to exclude the diagnosis of TLE ?
- If the 13 subjects underwent MRI with a protocol routinely used for patients with epilepsy ?
- Were the controls fully investigated (EEG, MRI, ect)?

Commentary

The boundaries of epilepsy: Where is the limit? A reply to Labate and Gambardella

Milan Brázdil^{a,b,c,*} and Adam Zeman^d



- None of the healthy population recruited was fully investigated to exclude the diagnosis of TLE
- None of subjects underwent MRI protocol
- None of subjects underwent routine electroencephalography

So they did not exclude the possibility that some of the subjects recruited had a mild form of temporal lobe epilepsy

RM morfologica avanzata nello studio dell'epilessia focale

- Può rendere superfluo l'imaging tradizionale?

NO

Take home message

1 la lesione esiste ma è talmente piccola che le indagini standard non sono sufficienti a discriminare tra la lesione ed il tessuto patologico

2 rigore negli studi scientifici

3 GIUDICARE L'IMAGING MORFOMETRICO AVANZATO NEL CONTESTO CLINICO DEL PAZIENTE