Degenerative diseases of the CNS: Quantitative Neuroimaging

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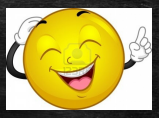
- Department of Neurosurgery, University of Athens - Greece

Quantitative Neuroimaging - Biomarkers: Do we need all this information ?

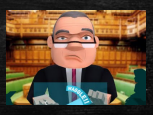
Why ? ? ?



Personalized

(Precision)

Medicine



DEMENTIA

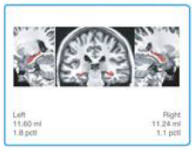
- Incidence
  - 44 Million Worldwide
  - 850 Thousand people in the UK
  - 38% of the population has a family member or close friend with dementia
- Cost
  - £360 billion worldwide
  - £23 billion UK

DIADEM Clinical Report

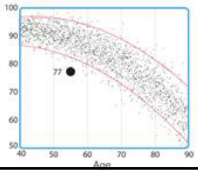
PATIENT INFORMATION & GLOBAL ANALYSIS

Name	Year of Birth	Gender	Scan Date
Joanna Miller	1932	Female	12/01/2008

HIPPOCAMPAL VOLUME
Volume (ml) and percentile (pctl)



BRAIN VOLUME
% of total intracranial volume

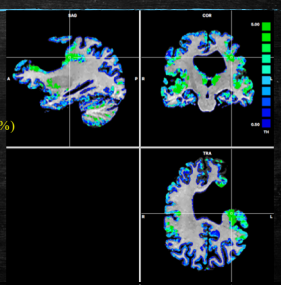


QUALITY CONTROL
assessment score

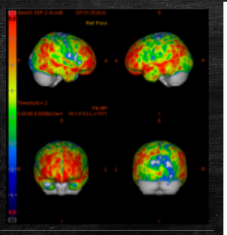
Metric	Type	Score	Status
SNR	GM	18.2	Pass
	WM	20.1	Pass
CNR	WM/GM	2.4	Pass
	GM/CSF	1.8	Caution
Aquisition	Movement	0.2	Pass
	Aliasing	0	Pass
	RF band	0.1	Pass
	Coverage	100%	Pass
Processing	Model Fit	2.2×10^{2}	Pass
	Abnormality	1.4 σ	Pass

Degenerative Diseases of CNS – Dementias Classification

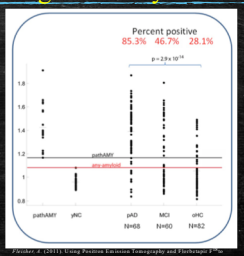
- Dementias
  - Alzheimer's disease (62%)
  - Vascular dementia (17%)
  - Mixed dementia (10%)
  - Lewy's body dementia (4%)
  - Other rare causes of dementia (3%)
  - Frontotemporal dementia (2%)
  - Corticobasal degeneration
  - Creutzfeld-Jakob's disease
  - Multiple Sclerosis
  - Parkinson's disease dementia



Alzheimer's Disease Diagnosis: amyloid-PET



Stereotactic Surface Projection (**SSP**)

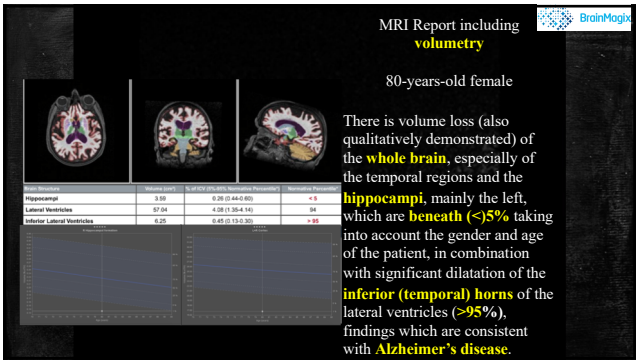


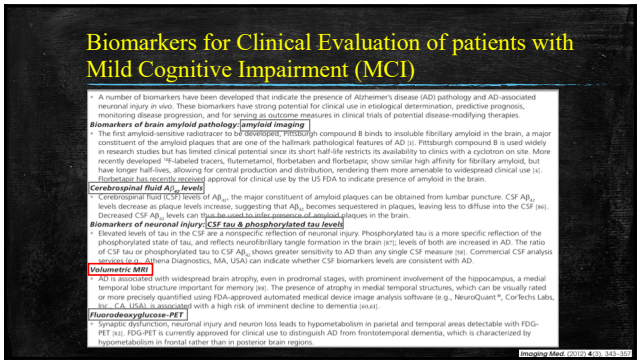
Role of Quantitative Neuroimaging in the Evaluation of Alzheimer's Disease

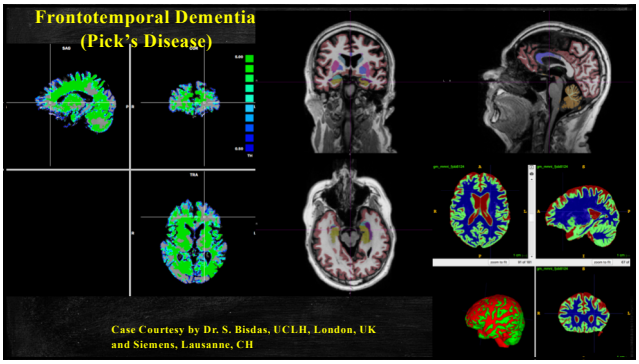
- MRI-based measurements of ***brain atrophy*** are regarded as **valid neuroimaging biomarkers** of the **state** and **progression** of Alzheimer's disease.
- Rates of **whole-brain atrophy** have been estimated at ***1.4–2.2% per year*** in **Alzheimer patients**, whereas the rates of atrophy during **normal aging** usually do not exceed ***0.7% per year***.
- This atrophy can be quantified, by **automated segmentation** of the brain parenchyma.

Role of Quantitative Neuroimaging in the Evaluation of Alzheimer's Disease

- **Atrophy of the hippocampus** is also a **valid biomarker** of mild cognitive impairment (**MCI**) and **Alzheimer's** disease progression.
- The rate of atrophy varies from ***3 to 6% per year*** **in Alzheimer's** disease, whereas it is limited to ***0.3–2.2% per year*** **in normal aging**.
- Although visual rating scales or the manual outlining of the hippocampus can be used, ***automated software programs*****, reduce the interaction time and increase the reliability of the measurement**.
- A **harmonized protocol for hippocampal volumetry** has been defined in order to reduce the variability between the studies.







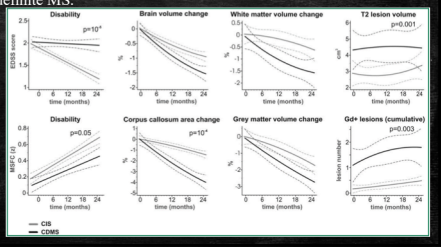
Role of Quantitative Neuroimaging in the Evaluation of Multiple Sclerosis

- Automated volumetric MR imaging offers an opportunity to extend brain atrophy measurements to the routine management of Multiple Sclerosis (MS) patients by showing regional and whole brain atrophy, which can be monitored over time.
- In MS patients, brain volume loss, specifically of the ***cerebral cortex and thalamus***, has been correlated with disability progression and cognitive impairment.
- According to several studies, ***brain volume loss*** is **an applicable measure** of widespread central nervous system damage leading to clinical disease progression, and serves as a ***useful outcome in evaluating MS therapies***.

Early identification of patients with clinically isolated syndrome (CIS) at high risk of converting to definite MS is essential in providing timely and appropriate treatment.

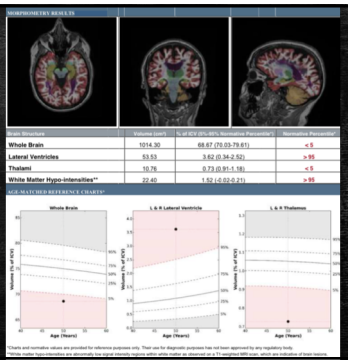
Volumetric MRI data provides measurements of the whole brain, gray and white matter volumes can potentially ***serve as biomarkers*** for this conversion and provide an assessment an individual's risk of developing clinically definite MS.

Figure* shows disability and volumetric MRI parameters in patients with CIS and in those converting to MS, with the dashed lines displaying confidence intervals



*Kalincik T, et al. 2012.*Volumetric MRI Markers and Predictors of disease Activity in early Multiple Sclerosis: A Longitudinal Cohort Study.*

Multiple Sclerosis



What else do we need in quantification of MS ?

- Measures/Volumes of lesion load
  - FLAIR hyperintensities
  - T1-W (before Gadolinium) "black holes"
  - Enhancing lesions
- New lesions
- Enlarging lesions
- Monitoring in order to
  - define the dissemination of the disease in space and time
  - treatment control

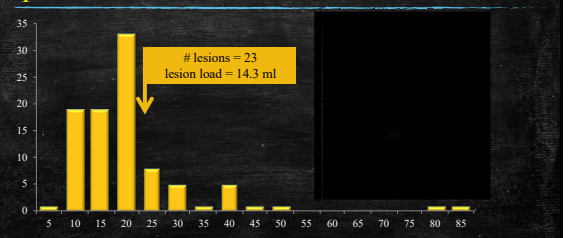
MRI in MS

Radiological report:

Supratentorial, there are many T2-hyperintense lesions from the subcortical to the deep periventricular white matter in both hemispheres. Multiple lesions run perpendicular to the lateral ventricles. Moderate global cortical atrophy. No Gd enhancing lesions were seen.

Courtesy by Wim van Hecke, Icometrix, Belgium

How many lesions do you count in this MS patient's brain?

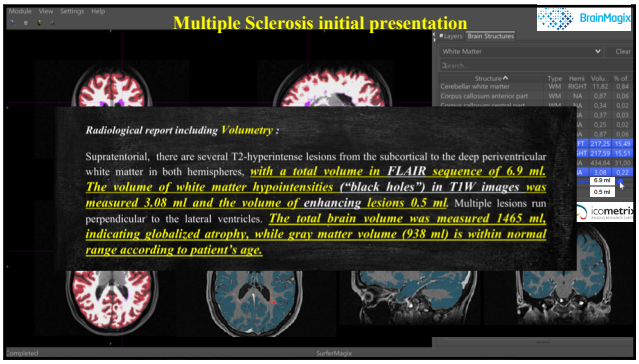


84 Participants
median = 16

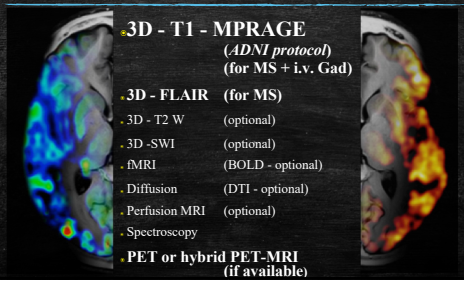
Courtesy by Wim van Hecke, Icometrix, Belgium

Count the spots!

Multiple Sclerosis initial presentation



Quantitative - Volumetric Methods



- **3D - T1 - MPRAGE** (*ADNI protocol*) (for MS + i.v. Gad)
- **3D - FLAIR** (for MS)
- 3D - T2 W (optional)
- 3D -SWI (optional)
- fMRI (BOLD - optional)
- Diffusion (DTI - optional)
- Perfusion MRI (optional)
- Spectroscopy
- **PET or hybrid PET-MRI** (if available)

Segmentation Methods may be grouped as:

- intensity-based methods (including thresholding, region growing, classification, and clustering)
- atlas-based methods — For Biomedical Engineers, PhD etc
- surface-based methods (including active contours and surfaces, and multiphase active contours)
- manual segmentation
- hybrid segmentation methods

Computational and Mathematical Methods in Medicine 2015

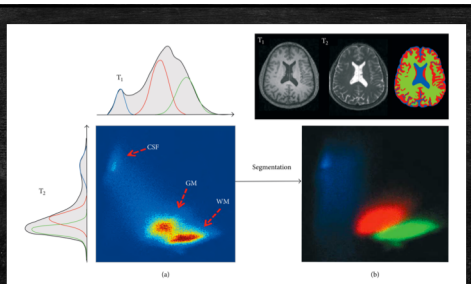


Figure 13: (a) Joint 2D intensity histogram of T_1-W and T_2-W MRI of the adult brain. The associated 1D histograms of each MRI modality are plotted on the left and top. Both individual histograms consist of three overlapped Gaussian distributions that approximate the expected tissue distribution of GM, WM, and CSF. (b) The scatter plot of the tissue intensities after applying tissue segmentation. The horizontal axis represents T_1-W intensities and the vertical axis represents T_2-W intensities. The red cloud corresponds to GM, the green to WM, and the blue to CSF.

Computational and Mathematical Methods in Medicine 2015

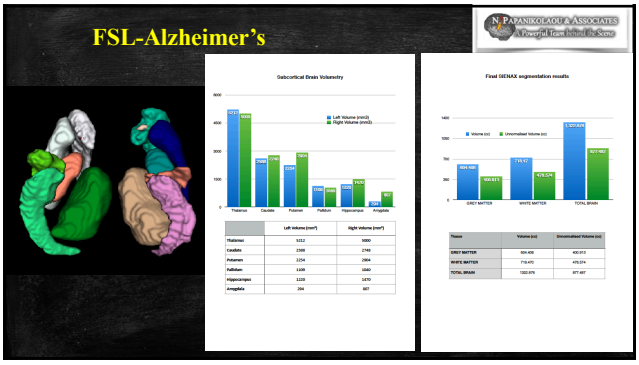
Segmentation Methods

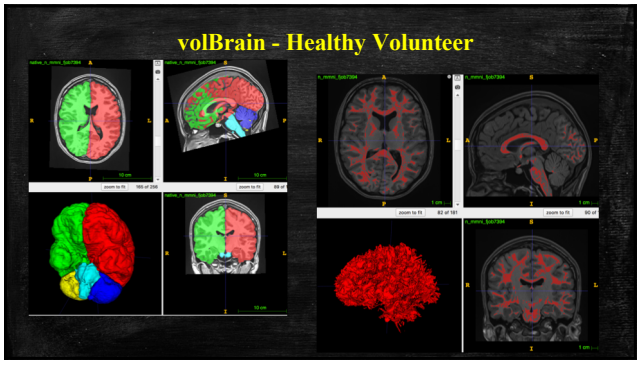
For Medical Doctors

- Fully Automated Segmentation
- Semi-Automatic Segmentation
- Manual Segmentation

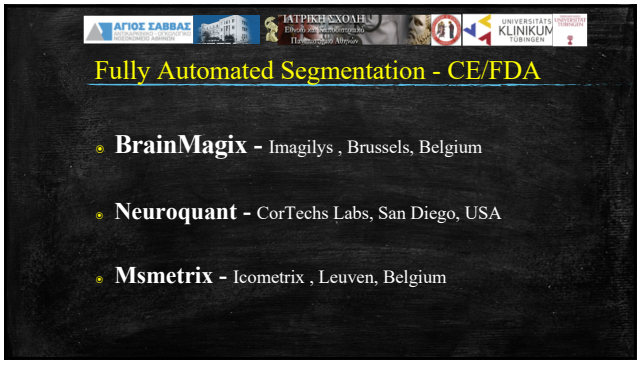
Fully Automated Segmentation - Open Source

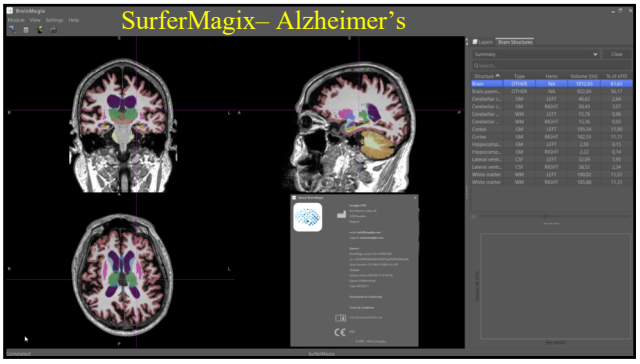
- **FreeSurfer** - Athinoula Martinos Center for Biomedical Imaging by the Laboratory for Computational Neuroimaging, Boston, USA
- **FSL** - Analysis Group, FMRIB, Oxford, UK
- **volBrain** - IBIME, UPV, Spain and LaBRI UMR 5800, Université de Bordeaux, CNRS, France

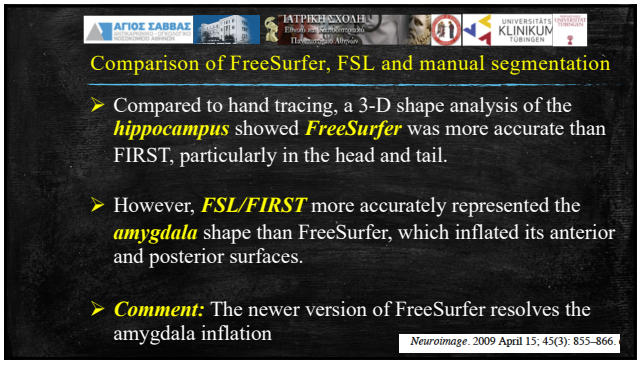

FSL-Alzheimer's
N. Papanikolaou & Associates
A Powerful Team behind the Scene
Subcortical Brain Volumetry
Final GENAX segmentation results

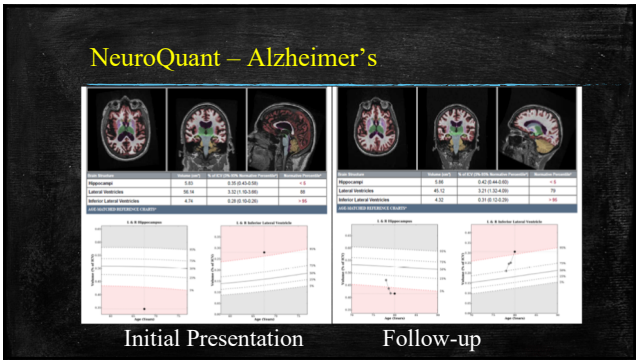

volBrain - Healthy Volunteer

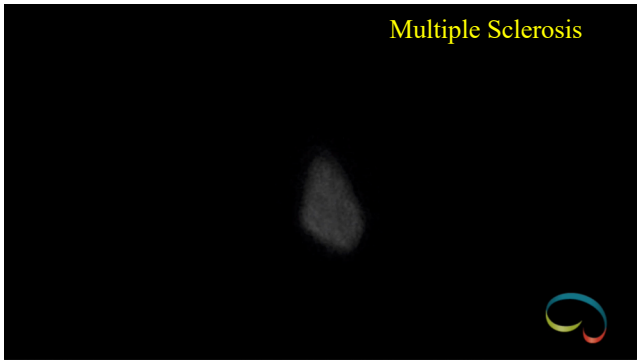

volBrain Volumetry Report
Healthy Volunteer

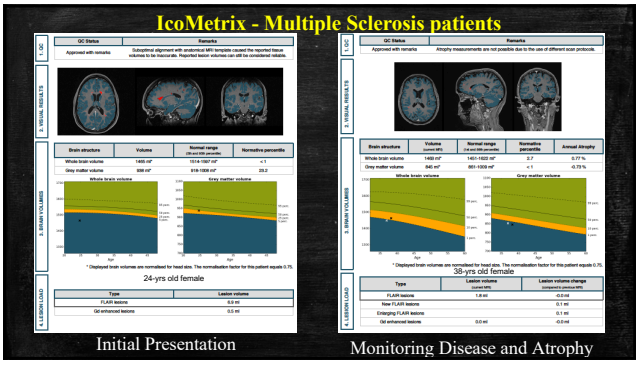

ΑΓΙΟΣ ΣΑΒΒΑΣ
ΙΑΤΡΕΙΚΗ ΣΧΟΛΗ
KLINIKUM TÜBINGEN
Fully Automated Segmentation - CE/FDA
BrainMagix - Imagilys , Brussels, Belgium
Neuroquant - CorTechs Labs, San Diego, USA
Msmetrix - Icometrix , Leuven, Belgium

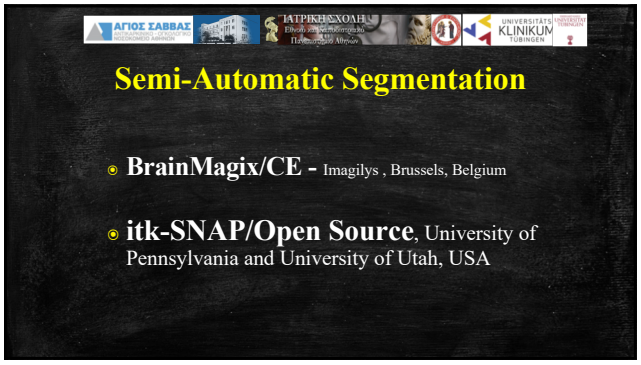

SurferMagix– Alzheimer's

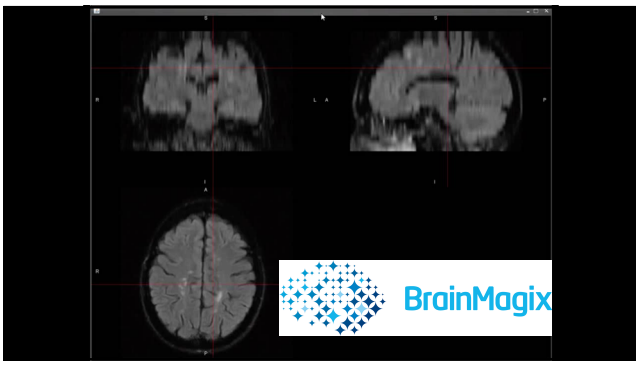

Comparison of FreeSurfer, FSL and manual segmentation
Compared to hand tracing, a 3-D shape analysis of the hippocampus showed FreeSurfer was more accurate than FIRST, particularly in the head and tail.
However, FSL/FIRST more accurately represented the amygdala shape than FreeSurfer, which inflated its anterior and posterior surfaces.
Comment: The newer version of FreeSurfer resolves the amygdala inflation
Neuroimage. 2009 April 15; 45(3): 855–866.

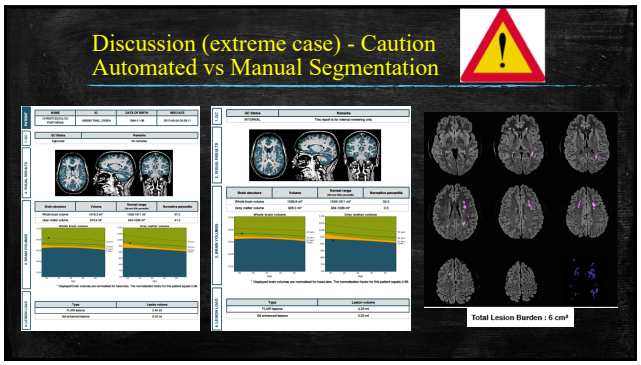

NeuroQuant – Alzheimer's
Initial Presentation
Follow-up


Multiple Sclerosis


IcoMetrix - Multiple Sclerosis patients
24-yrs old female
36-yrs old female
Initial Presentation
Monitoring Disease and Atrophy


Semi-Automatic Segmentation
BrainMagix/CE - Imagilys , Brussels, Belgium
itk-SNAP/Open Source, University of Pennsylvania and University of Utah, USA

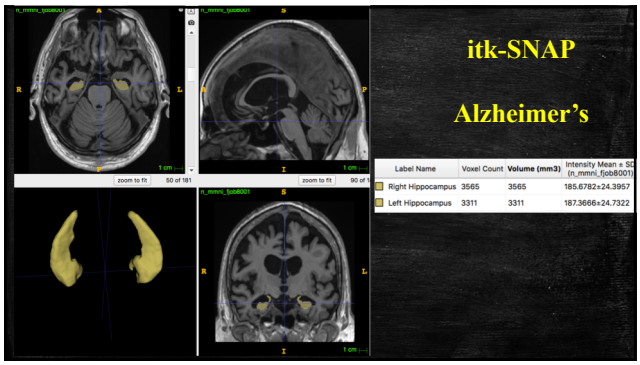

BrainMagix


Discussion (extreme case) - Caution
Automated vs Manual Segmentation
Total Lesion Burden : 6 cm³

Manual Segmentation - Open Source

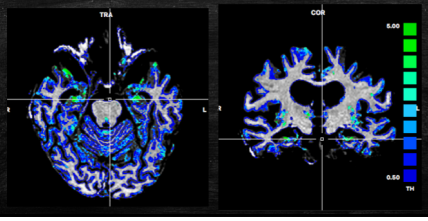
- **FreeSurfer** - Athinoula Martinos Center for Biomedical Imaging by the Laboratory for Computational Neuroimaging, Boston, USA
- **FSL** - Analysis Group, FMRIB, Oxford, UK
- **Osirix,** Pixmeo SARL, Bernex, Switzerland (*Osirix MD with FDA approval*)
- **itk-SNAP**, University of Pennsylvania and University of Utah, USA
- **ImageJ**, The Laboratory for Optical and Computational Instrumentation, University of Wisconsin-Madison, USA

II. Amygdala



Full Automated to Manual Segmentation – Research only

- **BrainVoyager,** Brain Innovation B.V.Maastricht The Netherlands



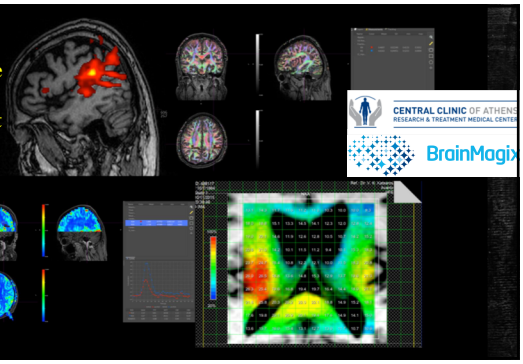
Case presentation

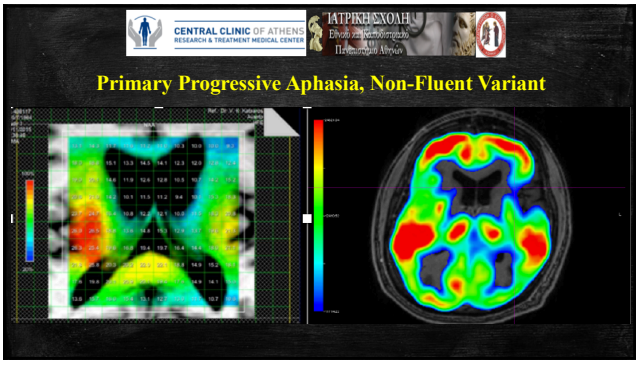
Normative Curves PDF

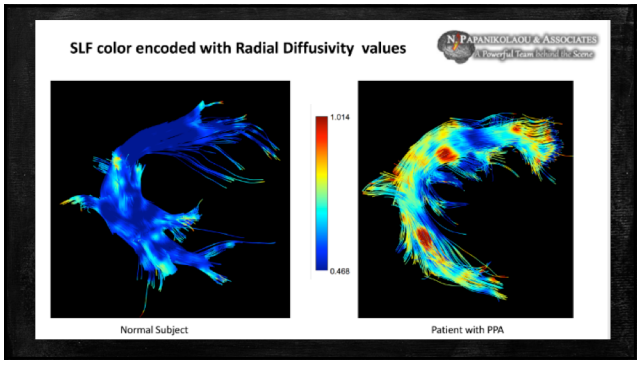
Based on a Database of 1770 subjects, normal and patients

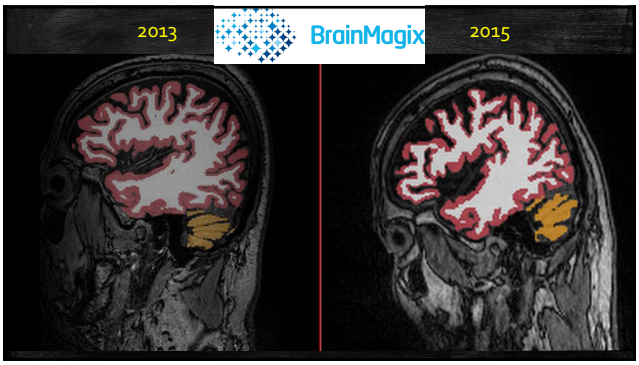
BrainMagix

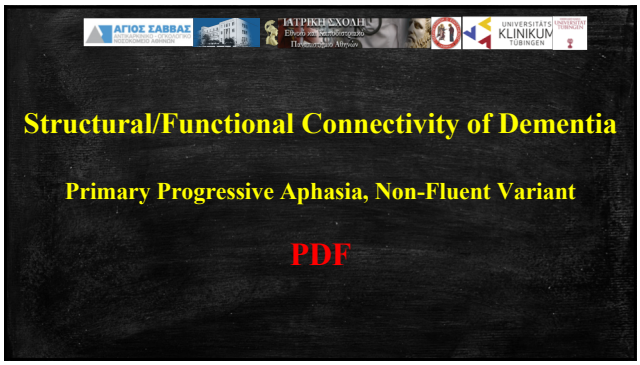
Primary Progressive Aphasia, Non-Fluent Variant




CENTRAL CLINIC OF ATHENS
RESEARCH & TREATMENT MEDICAL CENTER
ΙΑΤΡΙΚΗ ΣΧΟΛΗ
Primary Progressive Aphasia, Non-Fluent Variant

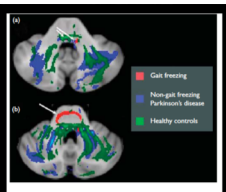

SLF color encoded with Radial Diffusivity values
N. PAPANIKOLAOU & ASSOCIATES
1.014
0.468
Normal Subject
Patient with PPA


2013
BrainMagix
2015


ΑΓΙΟΣ ΣΑΒΒΑΣ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ
UNIVERSITÄTS KLINIKUM TÜBINGEN
Structural/Functional Connectivity of Dementia
Primary Progressive Aphasia, Non-Fluent Variant
PDF

Parkinson's disease with Initial Presentation as Primary Freezing of Gait

BrainMagix



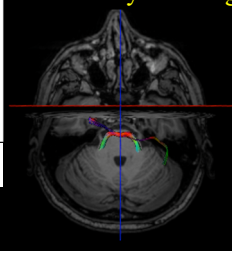
Probabilistic tractography displayed on the MNI152 standard brain. (a) Axial section through the upper pons and cerebellum. In FOG patients (red) connectivity with the cerebellum is absent, whereas non FOG PD patients show similar connectivity to control subjects. (b) Axial section through the mid- pons and cerebellum. FOG patients (red) showed anterior pontine connectivity (arrow) which was absent in non-FOG PD patients and controls.

Connectivity of the pedunculopontine nucleus in parkinsonian freezing of gait

Patrick M. Schweder[a], Peter C. Hansen[c], Alex L. Green[b], Gerardine Quaghebeur[a], John Stein[c] and Tipu Z. Aziz[b]

NeuroReport 2010, 21:914–916

Parkinson's disease with Initial Presentation as Primary Freezing of Gait



Magnetic Resonance Imaging–Based Volumetry Differentiates Idiopathic Parkinson's Syndrome from Multiple System Atrophy and Progressive Supranuclear Palsy

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By using three-dimensional magnetic resonance imaging–based volumetry, we studied atrophy of the caudate nucleus, putamen, brainstem, and cerebellum in patients with idiopathic Parkinson's syndrome (IPS, n = 11), progressive supranuclear palsy (PSP, n = 6), and multiple system atrophy with predominant parkinsonism (MSA-P, n = 12) or ataxia (MSA-C, n = 17). Patients were compared with a total of 46 controls, of whom 16 were age matched. Mean striatal, cerebellar, and brainstem volumes were normal in patients with IPS. We found significant reductions in mean striatal and brainstem volumes in patients with MSA-P, MSA-C, and PSP, whereas patients with MSA-C and MSA-P also showed a reduction in cerebellar volume. On an individual basis, volumes of structures in patients with MSA and PSP showed an extensive overlap with the normal range with the exception of brainstem volumes in patients with MSA-C. Therefore, groups could not be discriminated on the basis of individual structure volumetry. Application of stepwise discriminant analysis, however, allowed discrimination of all 12 patients with MSA-P, 15 of 17 patients with MSA-C, and 5 of 6 patients with PSP from the normal and IPS cohorts. However, patients with IPS could not be separated from controls and patients with MSA-P could not be separated from patients with PSP. In conclusion, total intracranial volume–normalized magnetic resonance imaging–based volumetric measurements provide a sensitive marker to discriminate typical and atypical parkinsonism.

Schulz JB, Skalej M, Wedekind D, Luft AR, Abele M, Voigt K, Dichgans J, Klockgether T. Magnetic resonance imaging–based volumetry differentiates idiopathic Parkinson's syndrome from multiple system atrophy and progressive supranuclear palsy. Ann Neurol 1999;45:65–74

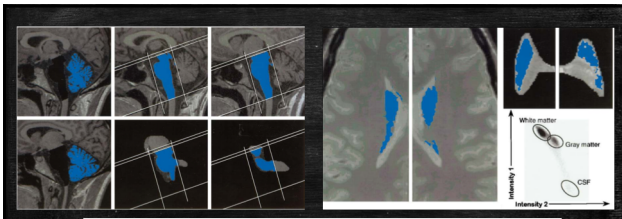
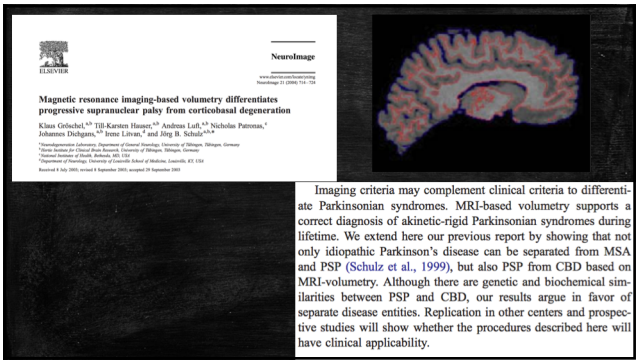


Fig 1. Region growing–based segmentation of the cerebellum and brainstem. On the midsagittal (top panels) and the parasagittal (bottom panels) section on the left side, a successfully segmented cerebellum is shown. The four images on the right side display a segmented brainstem from medial (top middle) to lateral (bottom right) position. The brainstem is presegmented by using four planes (black) that are orthogonal to the sagittal plane. Each plane is adjusted for two landmarks (superior: mamillary body, posterior commissure, displaced downward for one-third of the height of the midbrain; inferior: posterior rim of the foramen magnum, parallel to the superior plane; posterior: posterior commissure, ebes, displaced backward as far as the inferior colliculus; the anterior plane was required by the software but is not needed to separate the brainstem from the cerebrospinal fluid. Therefore, anterior delineation was done by region growing). Subsequently, the region growing algorithm is able to define the exact outline of the brainstem in three dimensions. The segmented brainstem is then subtracted from the original images, resulting in a blackened area (images on the left). Subtraction avoided overlap between the volumes of brainstem and cerebellum. (Sequence type: three-dimensional, fast low-angle shot (FLASH); TE/TR = 5 msec/15 msec; slice thickness = 0.9 mm; resolution = 0.9 × 0.9 mm².)



NeuroImage

Magnetic resonance imaging-based volumetry differentiates progressive supranuclear palsy from corticobasal degeneration

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Imaging criteria may complement clinical criteria to differentiate Parkinsonian syndromes. MRI-based volumetry supports a correct diagnosis of akinetic-rigid Parkinsonian syndromes during lifetime. We extend here our previous report by showing that not only idiopathic Parkinson's disease can be separated from MSA and PSP (Schulz et al., 1999), but also PSP from CBD based on MRI-volumetry. Although there are genetic and biochemical similarities between PSP and CBD, our results argue in favor of separate disease entities. Replication in other centers and prospective studies will show whether the procedures described here will have clinical applicability.

Structural/Functional Connectivity

Multiple Sclerosis

PDF

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Comparing manual and automatic segmentation of hippocampal volumes: reliability and validity issues in younger and older brains.

Wenger E[1], Mårtensson J, Noack H, Bodammer NC, Kühn S, Schaefer S, Heinze HJ, Düzel E, Bäckman L, Lindenberger U, Lövdén M.

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Abstract

We compared hippocampal volume measures obtained by manual tracing to automatic segmentation with FreeSurfer in 44 younger (20-30 years) and 47 older (60-70 years) adults, each measured with magnetic resonance imaging (MRI) over three successive time points, separated by four months. Retest correlations over time were very high for both manual and FreeSurfer segmentations. With FreeSurfer, correlations over time were significantly lower in the older than in the younger age group, which was not the case with manual segmentation. Pearson correlations between manual and FreeSurfer estimates were sufficiently high, numerically even higher in the younger group, whereas intra-class correlation coefficient (ICC) estimates were lower in the younger than in the older group. FreeSurfer yielded higher volume estimates than manual segmentation, particularly in the younger age group. Importantly, FreeSurfer consistently overestimated hippocampal volumes independently of manually assessed volume in the younger age group, but overestimated larger volumes in the older age group to a less extent, introducing a systematic age bias in the data. Age differences in hippocampal volumes were significant with FreeSurfer, but not with manual tracing. Manual tracing resulted in a significant difference between left and right hippocampus (right > left), whereas this asymmetry effect was considerably smaller with FreeSurfer estimates. We conclude that FreeSurfer constitutes a feasible method to assess differences in hippocampal volume in young adults. FreeSurfer estimates in older age groups should, however, be interpreted with care until the automatic segmentation pipeline has been further optimized to increase validity and reliability in this age

Personalized (Precision) Medicine

Thank you

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References for QNI of Alzheimer's disease

- Frisoni et al. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 2010, 6:67–77.
- Frisoni & Jack. Harmonization of magnetic resonance-based manual hippocampal segmentation: a mandatory step for wide clinical use. Alzheimers Dement. 2011, 7:171-174.
- ***Hermoye, Katsaros*** et al. Quantitative Imaging Biomarker Software for Neurological Disorders. RSNA, Chicago 2014.

References for QNI of Multiple Sclerosis

- Radue, EW, et al. (2013). Brain Atrophy: An in-vivo Measure of Disease Activity in Multiple Sclerosis. Swiss Medical Weekly. 143: w13887.
- Sormani MP, Arnold DL, De Stefano N. (2014). Treatment Effect on Brain Atrophy Correlates with Treatment Effect on Disability in Multiple Sclerosis. Ann Neurol. 75:43-49.
- Kalincik T, et al. (2012). Volumetric MRI Markers and Predictors of disease Activity in early Multiple Sclerosis: A Longitudinal Cohort Study. PLoS ONE 7(11): e50101