IL **CERVELLO CHE CAMBIA 8**

Sabato 10 novembre 2018

Genova, Aula Magna Clinica Neurologica

IL DISEASE MANAGEMENT TEAM CDCD - CENTRO DISTURBI COGNITIVI E DEMENZE AL POLICLINICO SAN MARTINO

La Medicina Nucleare

Silvia Morbelli

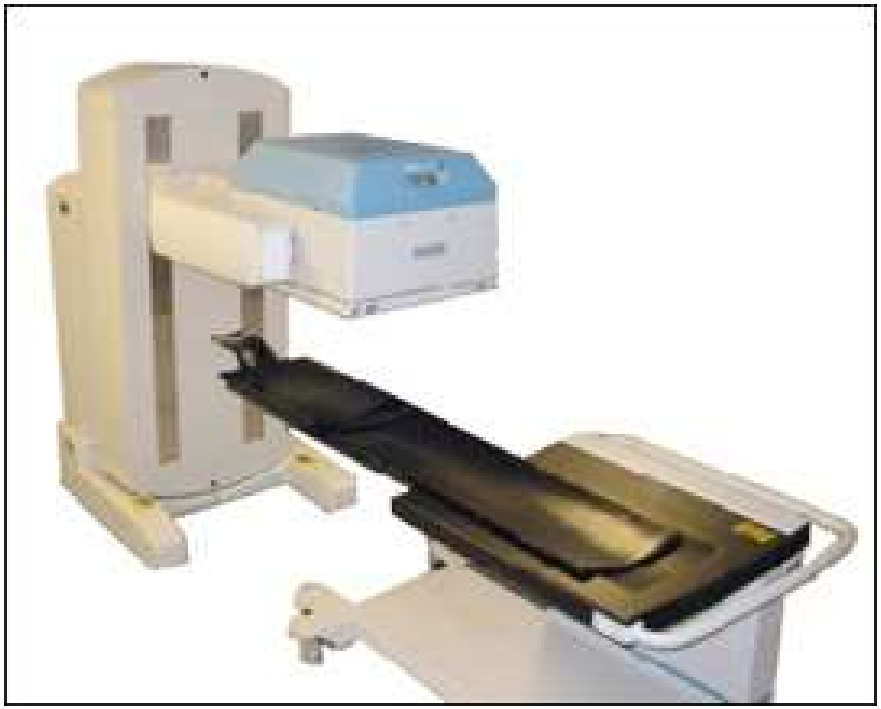
S.C. Medicina Nucleare

IRCCS Policlinico San Martino,

Dipartimento di Scienze della Salute

Universita' di Genova

Da dove veniamo? Dove siamo e Dove vogliamo andare?

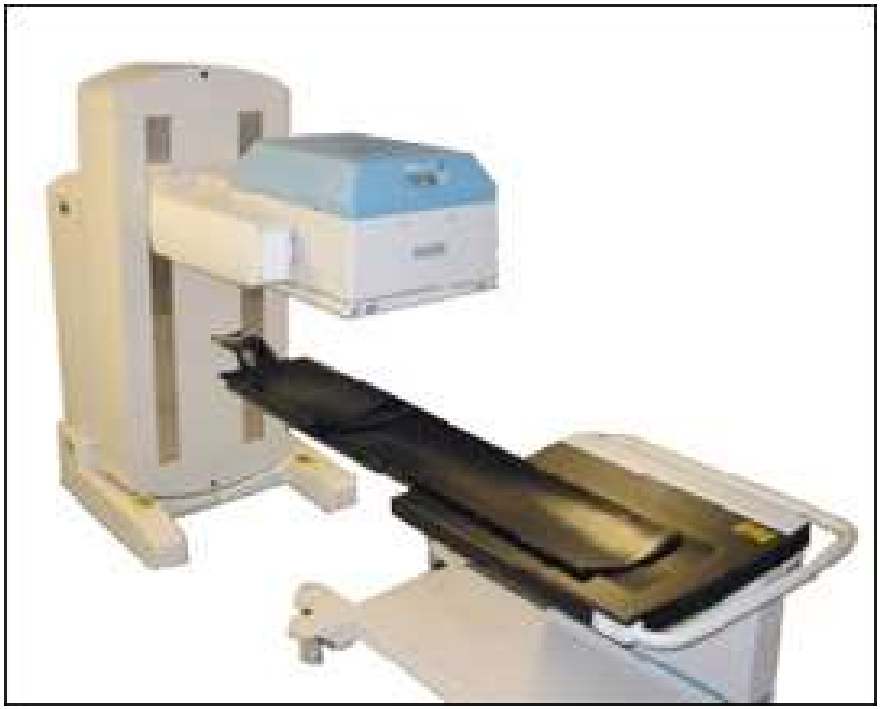


Genova, Ospedale San Martino

2003

Ceraspect

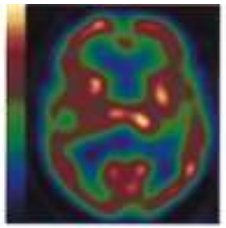
Da dove veniamo? Dove siamo e Dove vogliamo andare?

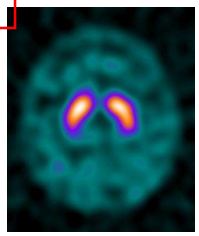


Genova, Ospedale San Martino

2003

SPECT
di Flusso

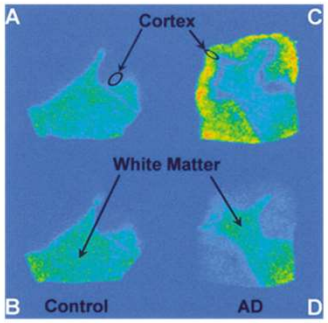




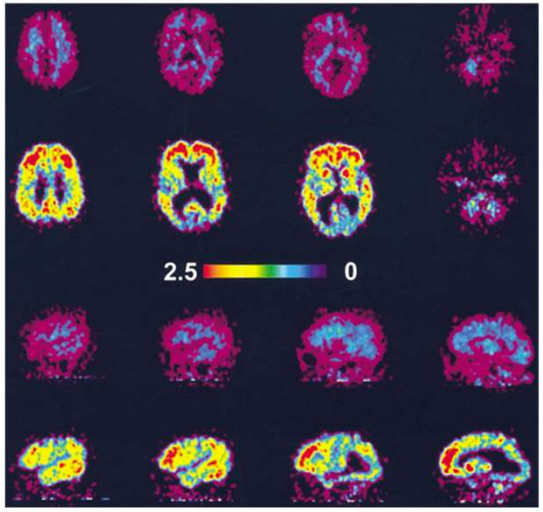
DAT
SPECT

Amyloid Imaging with 11C-PIB

Ann Neurol 2004;55:306–319



post-mortem



Controllo

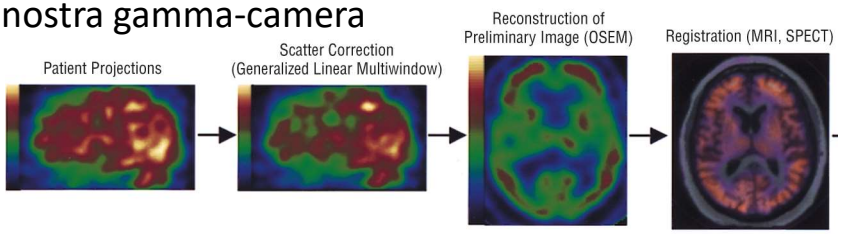
AD

Controllo

AD

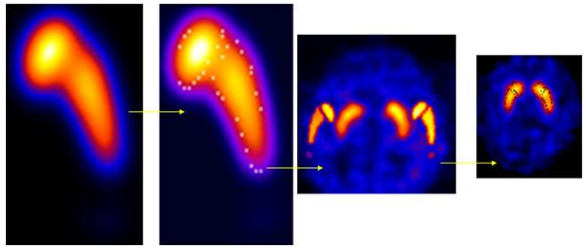
There are no problems, only opportunities!

Ricostruzione OSEM customizzata sulla nostra gamma-camera

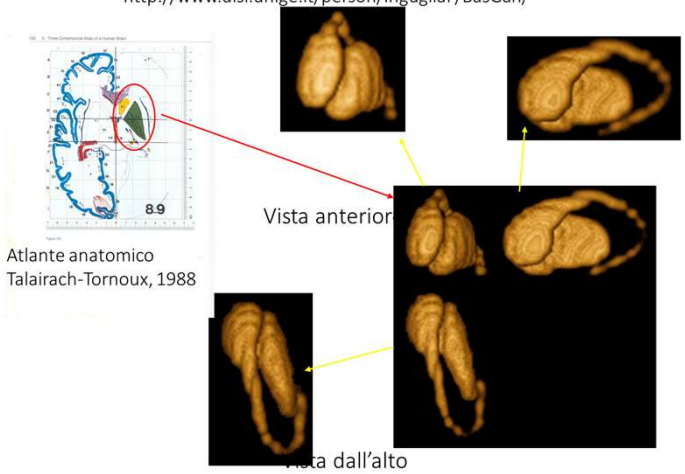


Analisi Semiquantitativa

"blurring" della maschera 3D per il successivo posizionamento automatico sulle immagini SPECT



Semi-quantificazione automatica con il software BasGan
http://www.disi.unige.it/person/IngugliaF/BasGan/



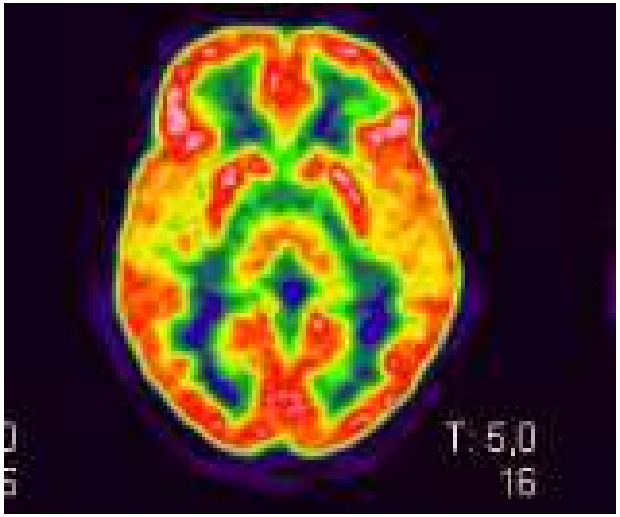
Calvini et al EJNMM 2007

Cosa stiamo facendo:
- Core-lab in studi multicentri europei (consorzio E-DLB; RBD)
- Verifica appropriatezza prescrittiva con il supporto del neurologo

Criticita': solo 3 esami a settimana (problemi di liste di attesa)

- **Analisi**: Semiquantificazione effettuata in tutti i pazienti (consegnata con il referto)

2007: Primo Tomografo PET/CT a San Martino



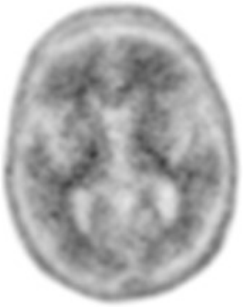
Cosa stiamo facendo:
5-6 esami 18F-FDG PET a settimana.

Indicazioni:
-sospetta demenza neurodegenerativa in paziente **MCI**
-supporto alla clinica per la DD in pazienti con **demenza e presentazione atipica**
-supporto alla diagnosi differenziale nei pazienti con **parkinsonismo** di sospetta natura neurodegenerativa…

IL CERVELLO CHE CAMBIA

Sabato 10 novembre 2018

Genova, Aula Magna Clinica I



IWG-1

Lancet Neurol 2007; 6: 734–46

Panel 2: **Diagnostic criteria for AD**

Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria

A. Presence of an early and significant episodic memory impairment that includes the following features:

1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features

B. Presence of medial temporal lobe atrophy
- Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

C. Abnormal cerebrospinal fluid biomarker
- Low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
- Other well validated markers to be discovered in the future

D. Specific pattern on functional neuroimaging with PET
- Reduced glucose metabolism in bilateral temporal parietal regions
- Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

Cosa stiamo facendo: dal 2013 nell'ambito di Trial clinici (8 Trial effettuati; 3 attualmente attivi)

Dal 2014: 2 pazienti al mese

Criticita': appropriatezza prescrittiva (pazienti "giovani", disturbo cognitivo peristente non spiegato, presentazioni atipiche)

IWG-2

Lancet Neurol 2014; 13: 614–29

Panel 5: **Definition of AD biomarkers**

Diagnostic marker — **amiloidosi**
- Pathophysiological marker
- Reflects in-vivo pathology
- Is present at all stages of the disease
- Observable even in the asymptomatic state
- Might not be correlated with clinical severity
- Indicated for inclusion in protocols of clinical trials

Progression marker — **MRI, FDG-PET**
- Topographical or downstream marker
- Poor disease specificity
- Indicates clinical severity (staging marker)
- Might not be present in early stages
- Quantifies time to disease milestones
- Indicated for disease progression

Clinical phenotypes

Typical
- Amnestic syndrome of the hippocampal type

Atypical
- Posterior cortical atrophy
- Logopenic variant
- Frontal variant

Preclinical states

Asymptomatic at risk
- No AD phenotype (typical or atypical)

Presymptomatic (autosomal dominant mutation)
- No AD phenotype (typical or atypical)

Required pathophysiological marker
- CSF (low amyloid β^{1-42} and high T-tau or P-tau)

or
- Amyloid PET (high retention of amyloid tracer)

Cosa stiamo facendo: semiquantificazioni dell'amy-PET

Analisi Semiquantitativa

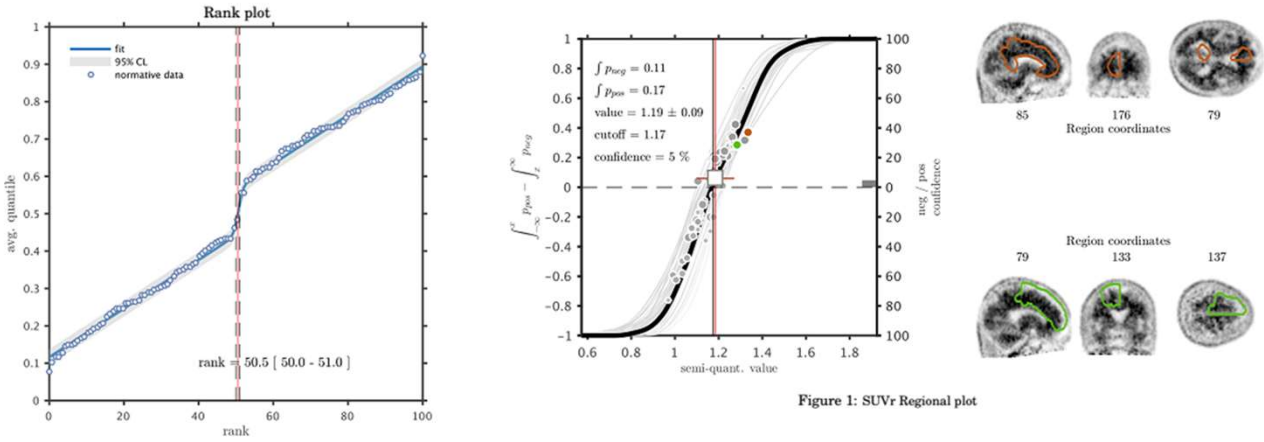


Figure 1: SUVr Regional plot

SUV ratio

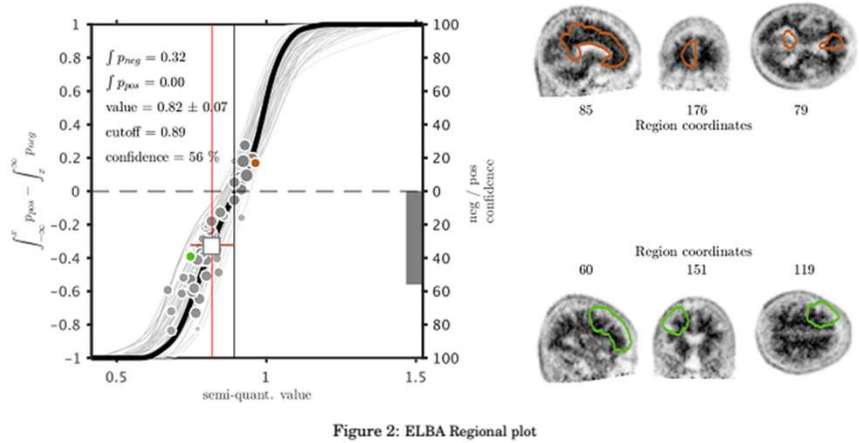


Figure 2: ELBA Regional plot

Sviluppo di metodi indipendenti dal SUV

Courtesy of Andrea Chincarini

Cosa vogliamo fare

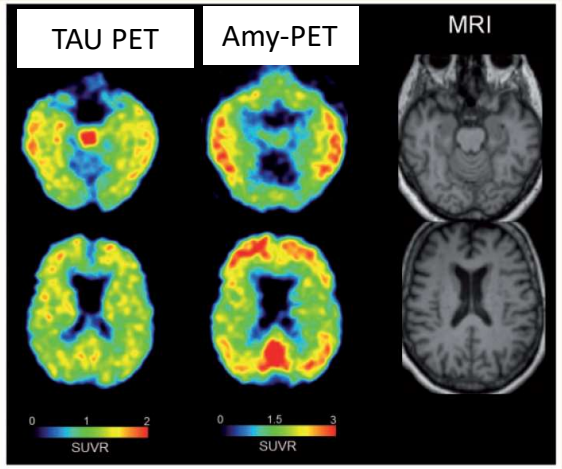
2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Alzheimer's & Dementia 14 (2018) 535-562

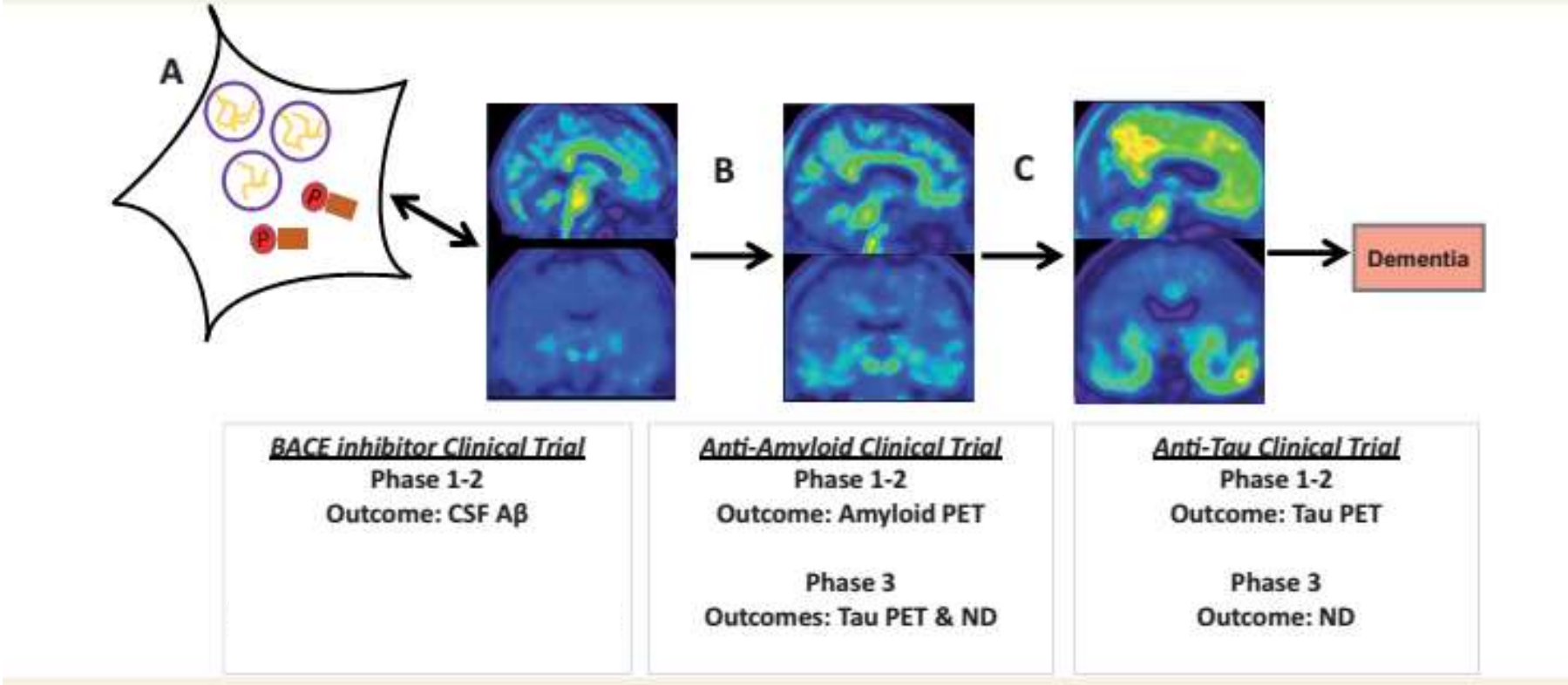
Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	



Okamura et al., Brain 2014

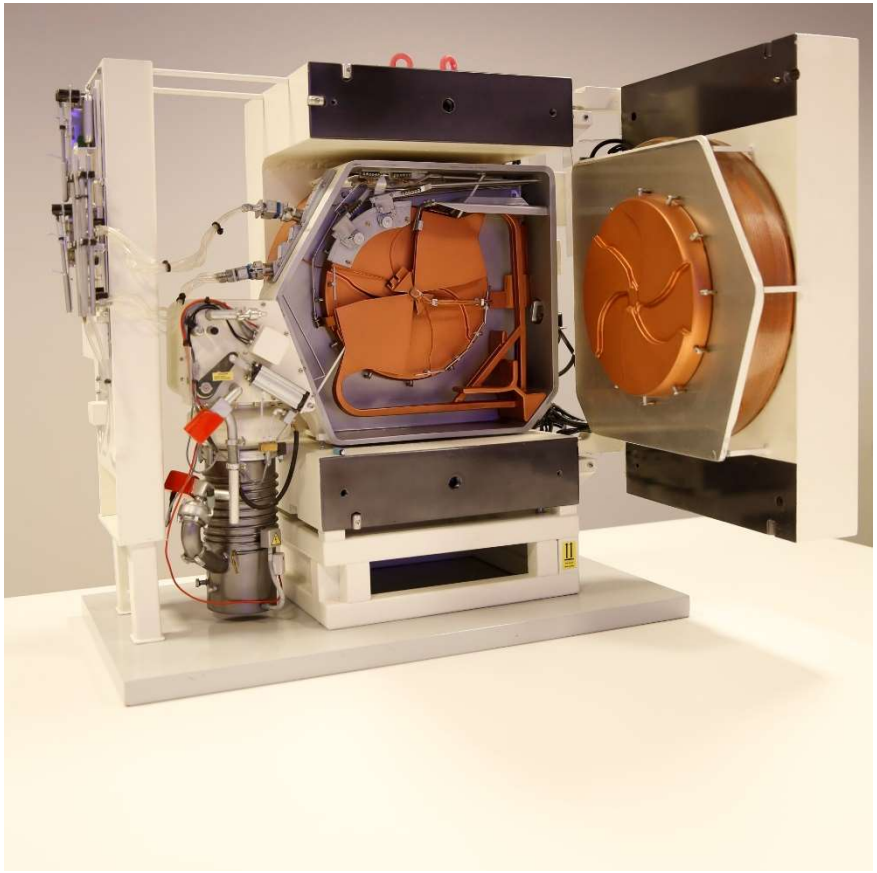
Brain PET in Clinical Trials with TAU tracers

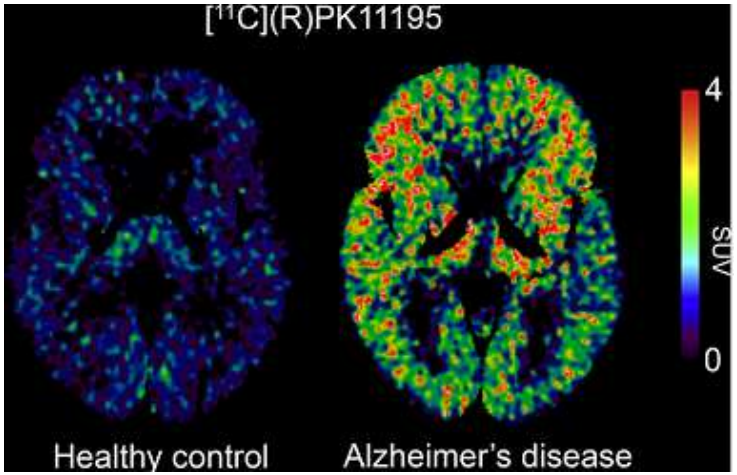


Hansson et al Brain 2018

Ad Ottobre 2018 e' stata completato l'accreditamento del nostro tomografo per il trial clinico GN39763 study che prevede 2 tipi di PET con tracciante per amiloidosi e per TAU

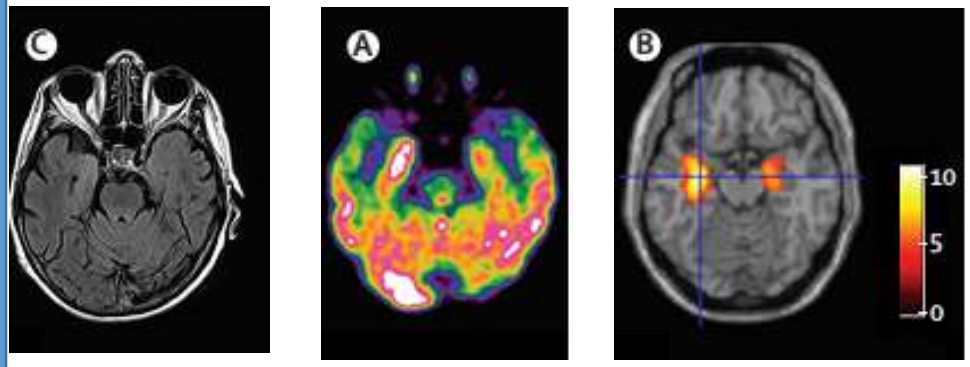
Nuovi traccianti



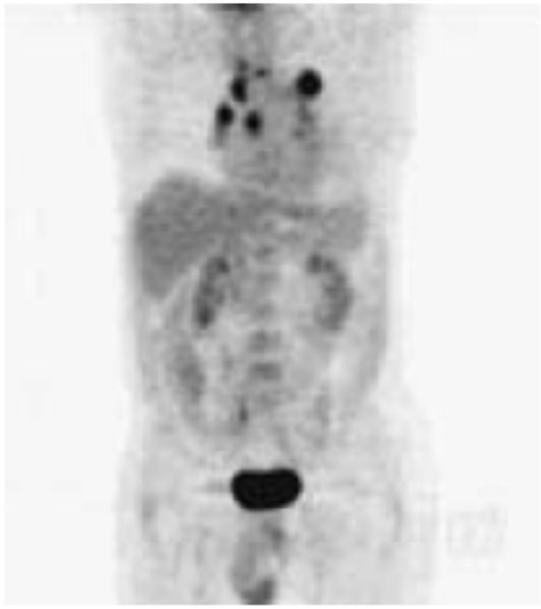


Zimmer et al
Journal of Neuroinflammation 2014

Indicazioni emergenti alla FDG PET: sospetta encefalite autoimmune



Morbelli et al Lancet Neurology 2016

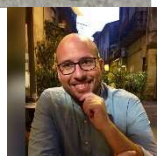


Collaborazione con Dott. Luana Benedetti, Luca Roccatagliata, Flavio Nobili

Grazie per l'attenzione ma soprattutto grazie a…

Medicina Nucleare

Neurologia



IRCCS Policlinico San Martino, Universita' di Genova

TRACCIANTI PET PER AMILOIDE - Form per il CLINICO INVIANTE:

Centro MN di _____Policlinico San Martino-IST_____

Medico inviante ____Nobili_____Telefono____77-7568____

e-mail:_flaviomariano.nobili@hsanmartino.it Centro UVA_Clinica Neurologica___

Sintomatologia soggettiva d'esordio:

x Memoria
☐Linguaggio
☐Visuospaziale
☐Esecutivo
☐Aprassie
☐ Attenzione
☐Comportamento (specificare cosa):

Sospetto diagnostico sindromico:

☐Decadimento Cognitivo Lieve o MCI
x Demenza di Alzheimer Possibile
☐ Demenza di Alzheimer Probabile (ma livello di certezza <85%)
☐ Demenza Fronto-temporale
☐ Demenza Vascolare
☐ Demenza a corpi di Lewy
☐ Demenza non altrimenti specificata

Deficit preminente (sulla base dei test neuropsicologici) di tipo:

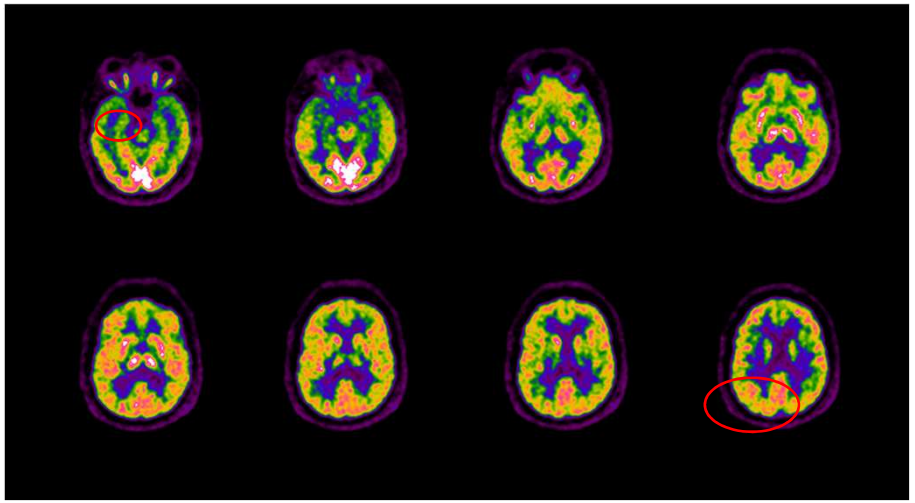
x Amnesico
☐Non-amnesico

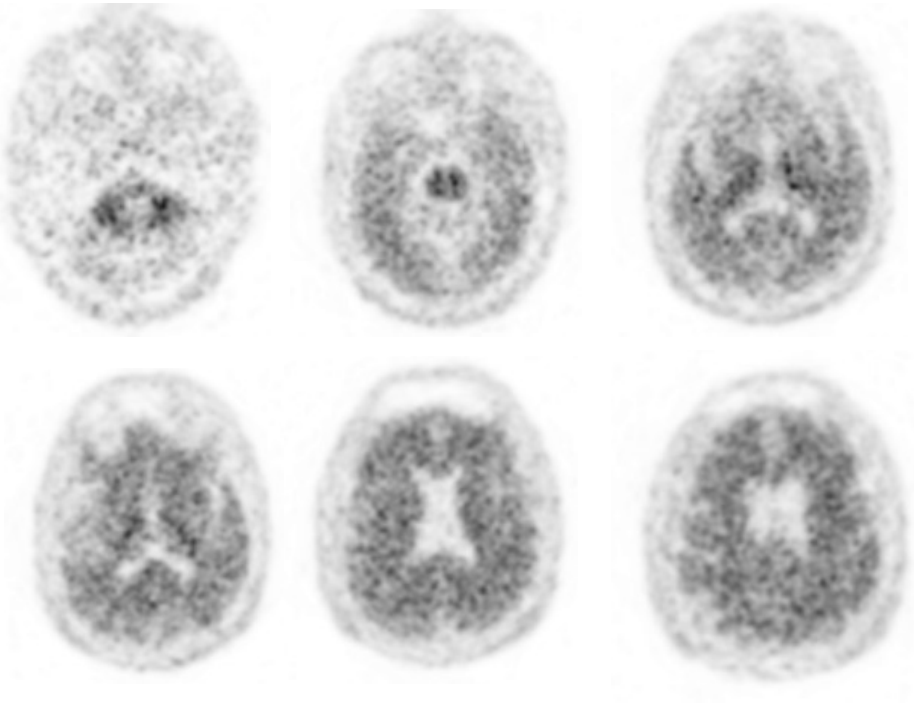
x Singolo dominio
☐Multi-dominio

La NPSY conferma deficit al Grober Buschke ad oggi con scarsa facilitazione ed raccontino bordeline.

Il deficit amnesico e' progredito e il racconto ecologico della famiglia è tale per cui il sospetto di AD è consistente nonostante la paucità del reperto FDG.

18F-FDG PET





2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

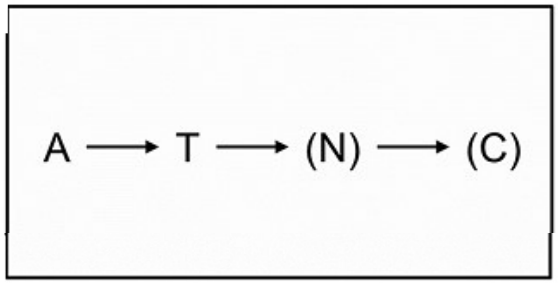
NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Alzheimer's & Dementia 14 (2018) 535-562

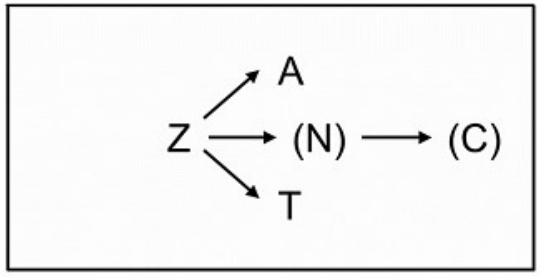
Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

15. Hypothesis testing using the research framework



Flexibility to incorporate new biomarkers



"Z could represent many different possible mechanisms, for example, immune function and over or under activation of inflammatory pathways"