DIPARTIMENTO DI MEDICINA CLINICA E SPERIMENTALE
AZIENDA OSPEDALIERO-UNIVERSITARIA PISANA
U.O. C. NEUROLOGIA-NEUROFISIOPATOLOGIA
SCUOLA DI SPECIALIZZAZIONE IN NEUROLOGIA

Biomarkers in Clinical Neurosciences

U. Bonuccelli,G.Siciliano, R.Ceravolo, M.Mancuso, L.Pasquali,

G.Tognoni, F.Giorgi, F.Baldacci, D.Frosini, L.Kiferle,E.Bonanni (m.d.)

A. Lo Gerfo, L. Chico , L.Petrozzi (biol.)

F.Sartucci

E.Santarcangelo

ALS: CAUSATIVE GENE

Genome Wide Association study

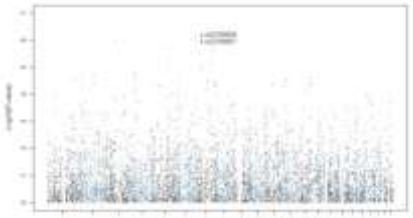
Hum Mol Genet. 2014 Jan 21. [Epub ahead of print]

A genome-wide association meta-analysis identifies a novel locus at 17q11.2 associated with sporadic amyotrophic lateral sclerosis.

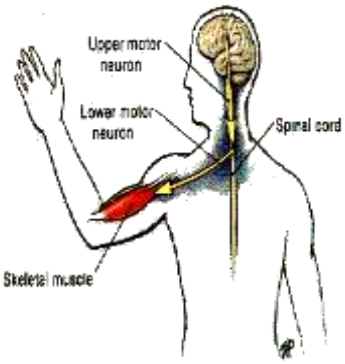
Fogh I, Ratti A, Gellera C, Lin K, Tiloca C, Moskvina V, Corrado L, Sorarù G, Cereda C, Corti S, Gentilini D, Calini D, Castellotti B, Mazzini L, Querin G, Gagliardi S, Del Bo R, Conforti FL, Siciliano G, Inghilleri M, Saccà F, Bongioanni P, Penco S, Corbo M, Sorbi S, Filosto M, Ferlini A, Di Blasio AM, Signorini S, Shatunov A, Jones A, Shaw PJ, Morrison KE, Farmer AE, Van Damme P, Robberecht W, Chiò A, Traynor BJ, Sendtner M, Melki J, Meininger V, Hardiman O, Andersen PM, Leigh NP, Glass JD, Overste D, Diekstra FP, Veldink JH, van Es MA, Shaw CE, Weale ME, Lewis CM, Williams J, Brown RH, Landers JE, Ticozzi N, Ceroni M, Pegoraro E, Comi GP, D'Alfonso S, van den Berg LH, Taroni F, Al-Chalabi A, Powell J, Silani V, the SLAGEN Consortium and Collaborators.

A two-stage genome-wide association study of sporadic amyotrophic lateral sclerosis

Human Molecular Genetics, 2008, Vol. 18, No. 8 1524–1532
doi:10.1093/hmg/ddp059
Advance Access published on February 4, 2009



Malattia neurodegenerativa cronica progressiva che coinvolge selettivamente, in modo variabile o combinato, il motoneurone superiore (corticale) ed il motoneurone inferiore (spinale)



Italy

Heterozygous SOD1 D90A mutation presenting as slowly progressive predominant upper motor neuron amyotrophic lateral sclerosis

Neurol Sci (2006) 32:317–320
DOI 10.1007/s10072-006-0525-6

Marco Luigetti · Amelia Conte · Francesco Madia · Giuseppe Marangi · Marcella Zollino · Irene Mancuso · Michele Dileone · Alessandro Del Grande · Vincenzo Di Lazzaro · Pietro Attilio Tonali · Mario Sabatelli

J Med Genet. 2010 Mar;47(3):166-9. doi: 10.1136/jmg.2009.071027. Epub 2009 Oct 26.

Mutations of FUS gene in sporadic amyotrophic lateral sclerosis.

Corrado L, Del Bo R, Castellotti B, Ratti A, Cereda C, Penco S, Sorarù G, Carlomagno Y, Ghezzi S, Pensato V, Colombrita C, Gagliardi S, Cozzi L, Orsetti V, Mancuso M, Siciliano G, Mazzini L, Comi GP, Gellera C, Cereda M, D'Alfonso S, Silani V.

Amyotroph Lateral Scler. 2010;11(1-2):210-5. doi: 10.3109/17482960802566592.

G41S SOD1 mutation: A common ancestor for six ALS Italian families with an aggressive phenotype.

Battistini S, Ricci C, Giannini F, Calzavara S, Greco G, Del Corona A, Mancuso M, Battistini N, Siciliano G, Carrera P.

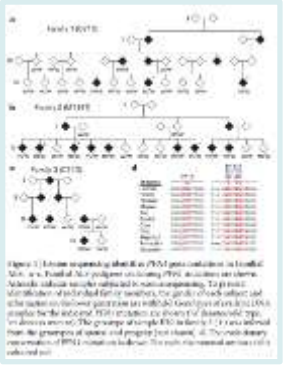
TARDBP (TDP-43) sequence analysis in patients with familial and sporadic ALS: identification of two novel mutations

European Journal of Neurology 2008, 15: 727–731

R. Del Bo[a], S. Ghezzi[a], S. Corti[a], M. Pandolfo[b], M. Ranieri[b], D. Sampaolo[b], I. Ghione[b], A. Prelle[b], V. Orsetti[c], M. Mancuso[c], G. Sorarù[d], C. Briani[e], C. Angelini[e], G. Siciliano[c], N. Bresolin[a] and G. P. Comi[a]

LETTER

Mutations in the profilin 1 gene cause familial amyotrophic lateral sclerosis



Pis

Lack of association between the *APEX1* Asp148Glu polymorphism and sporadic amyotrophic lateral sclerosis

Fabio Coppedè[a,*], Annalisa Lo Gerfo[b], Cecilia Carlesi[a], Selina Piazza[a], Michelangelo Mancuso[a], Livia Pasquali[a], Luigi Murri[a], Lucia Migliore[a], Gabriele Siciliano[a]

Neurosci Lett. 2007 Jun 13;420(2):163-8. Epub 2007 May 5.

Association of the hOGG1 Ser326Cys polymorphism with sporadic amyotrophic lateral sclerosis.

Coppedè F, Mancuso M, Lo Gerfo A, Carlesi C, Piazza S, Ricchi A, Petrozzi L, Nesti C, Micheli D, Bacci A, Migliore L, Murri L, Siciliano G.

Amyotroph Lateral Scler. 2010;11(1-2):122-4. doi: 10.3109/17482960903220297.

Association study between XRCC1 gene polymorphisms and sporadic amyotrophic lateral sclerosis.

Coppedè F, Migheli F, Lo Gerfo A, Fabbrini MR, Carlesi C, Mancuso M, Corti S, Mazzina N, del Bo R, Comi GP, Siciliano G, Migliore L.

Neurobiology of Aging

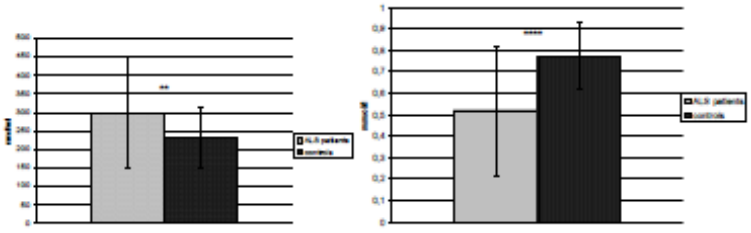
journal homepage: www.elsevier.com/locate/neuaging

Negative results

Screening of the *PFN1* gene in sporadic amyotrophic lateral sclerosis and in frontotemporal dementia

Cinzia Tiloca[a,b,*], Nicola Ticozzi[a], Viviana Pensato[a], Lucia Corrado[a], Roberto Del Bo[a,f], Cinzia Bertolin[g], Chiara Fenoglio[a,f], Stella Gagliardi[b], Daniela Calini[a], Giuseppe Lauria[h], Barbara Castellotti[i], Alessandra Bagaretti[g], Stefania Corti[a,f], Daniela Galimberti[a,f], Annachiara Cagnin[j], Carlo Gabelli[k], Michela Ranieri[a,l], Mauro Ceroni[b,l], Gabriele Siciliano[m], Letizia Mazzini[n], Cristina Cereda[b], Elio Scarpini[a,f], Gianni Sorarù[c], Giacomo P. Comi[a,f], Sandra D'Alfonso[g], Cinzia Gellera[a], Antonia Ratti[a,f], John E. Landers[o,1], Vincenzo Silani[a,b,1], The SLAGEN Consortium

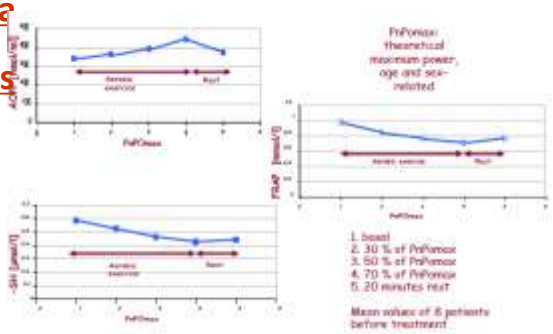
ALS: PATHOGENIC MECHANISMS



Increased plasmatic AOPP levels in ALS ($p<0,05$)

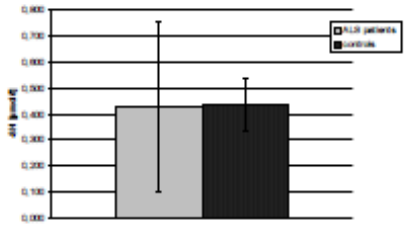
Reduced plasmatic FRAP in ALS ($p<0.0001$)

Exercise, mitocondria and…oxidative stress



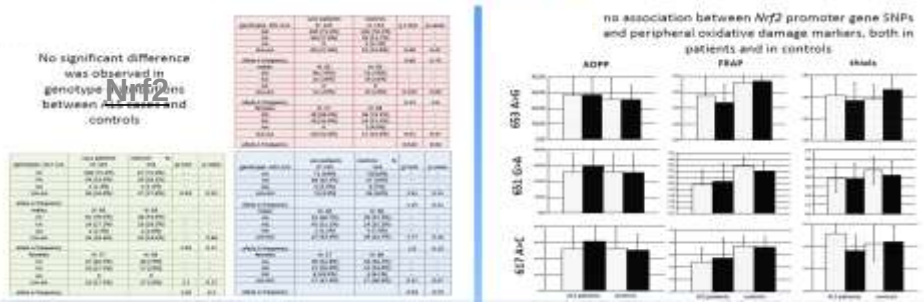
Oxidative stress

At onset disease

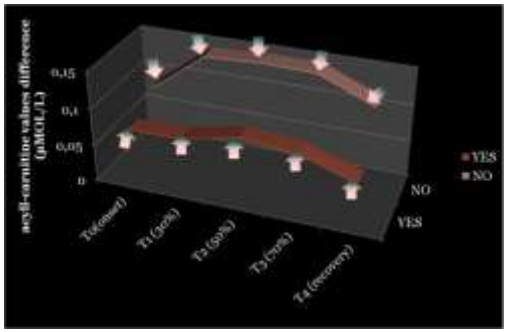


No difference in plasmatic total thiols levels

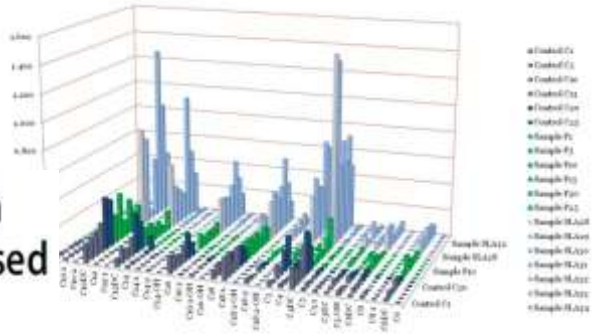
Genetic suscetibility

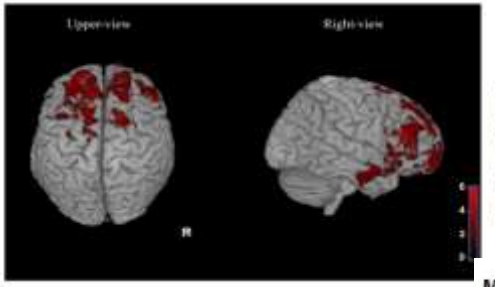


Plasma carnitines



Mass spectroscopy and plasma





PLOS ONE | July 2013 | Volume 8 | Issue 7 | e68279

Mapping Cortical Degeneration in ALS with Magnetization Transfer Ratio and Voxel-Based Morphometry

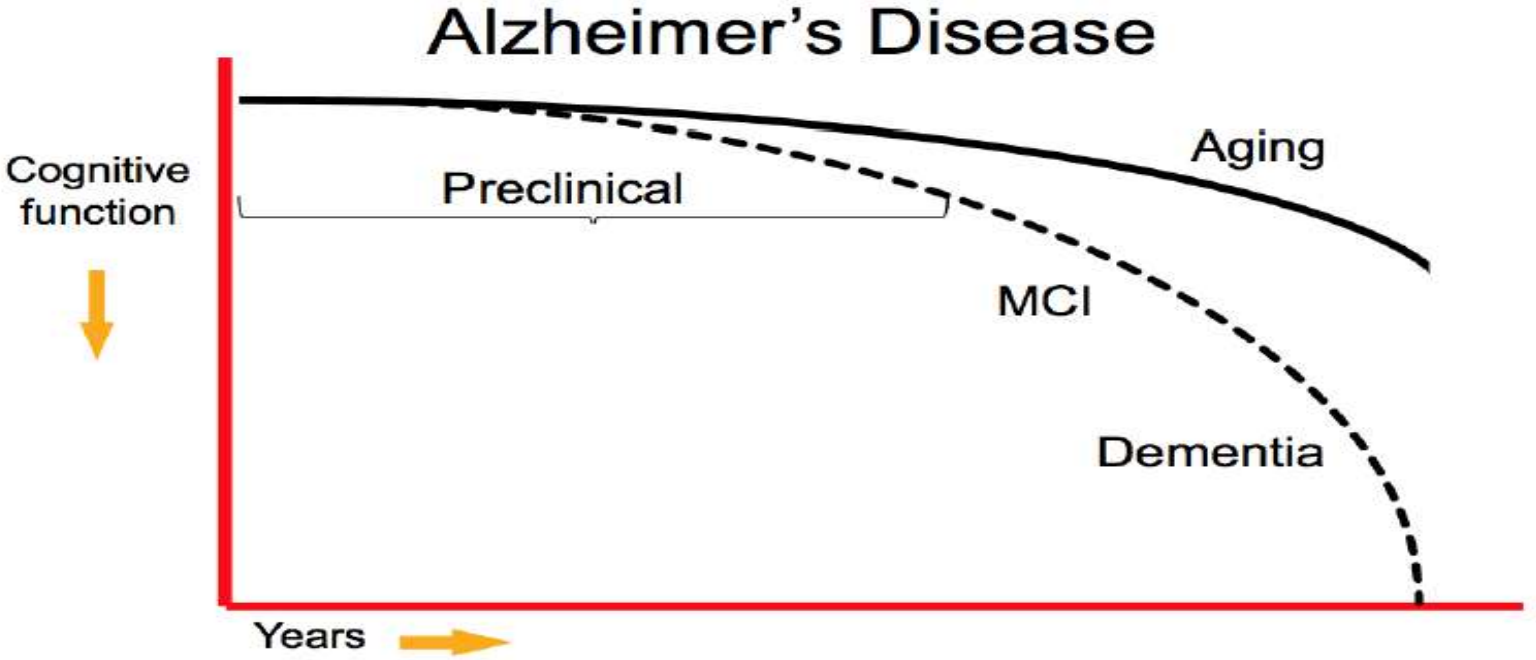
Mirco Cosottini[1,2]*, Paolo Cecchi[1,2], Selina Piazza[1], Ilaria Pesaresi[2], Serena Fabbri[1], Stefano Diciotti[3], Mario Mascalchi[3], Gabriele Siciliano[1], Ubaldo Bonuccelli[1]

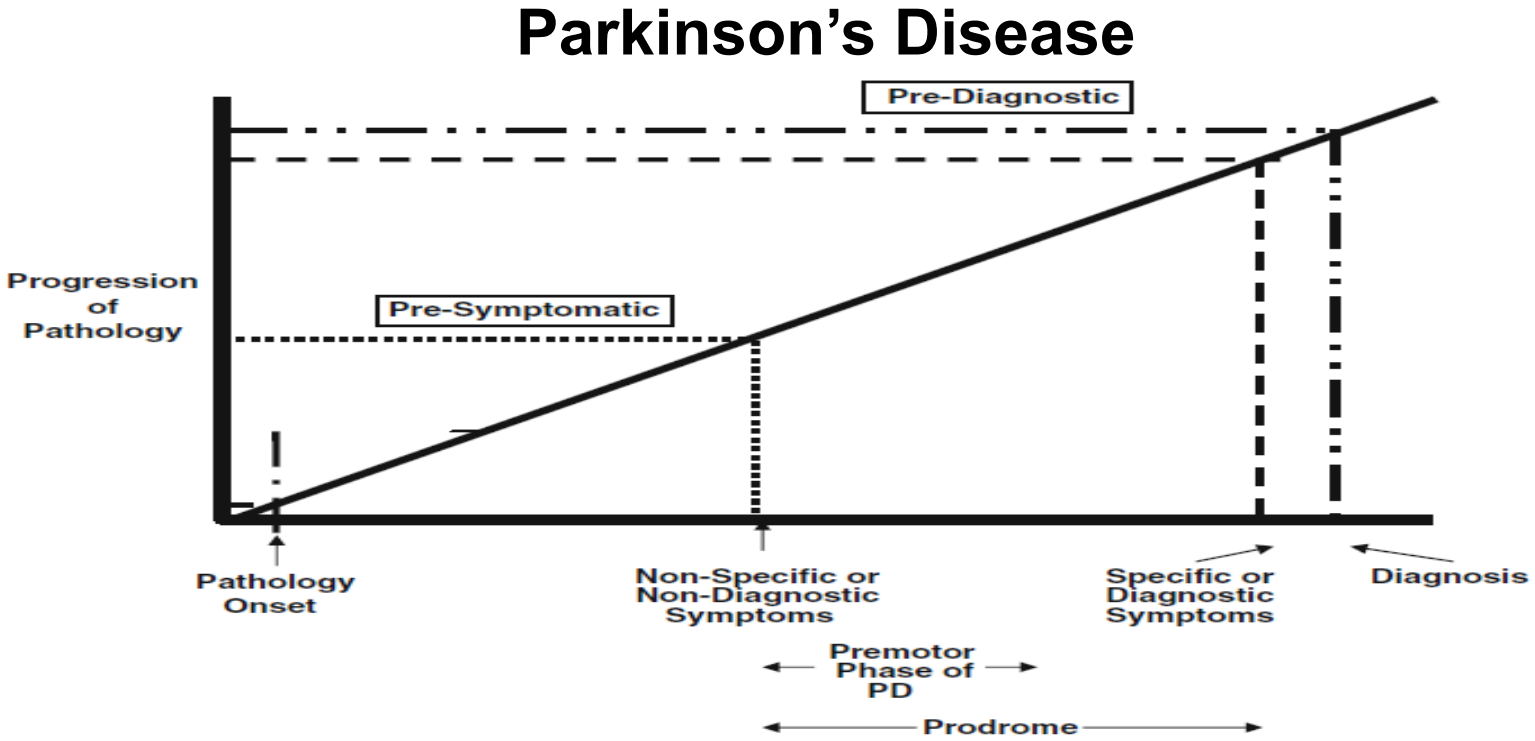
E. Contare alla rovescia

medico: " Mi conti all'indietro da cinque ad uno".
Paziente: "5... 3... 4...,
mi scusi, non riesco a farlo"

medico: "Mi sillabi all'inverso la parola 'mondi'".
Paziente: "M... N... O... D... I"

fase più avanzata
paziente vestita in modo sciatto, lenta, apatica, confusa, disorientata, con postura fissa


Alzheimer's Disease
Cognitive function
Aging
Preclinical
MCI
Dementia
Years


Parkinson's Disease
Pre-Diagnostic
Progression of Pathology
Pre-Symptomatic
Pathology Onset
Non-Specific or Non-Diagnostic Symptoms
Specific or Diagnostic Symptoms
Diagnosis
Premotor Phase of PD
Prodrome

LINES OF RESEARCH IN NEURODEGENERATIVE DISEASES

- Associated Genes of susceptibility to disease
- Molecular signatures of disease
- High field MRI (3 and 7 Tesla) Imaging
- Molecular Imaging with new tracers

Ongoing research on genetics & epigenetics of AD

In collaboration with the Alzheimer's Disease Genetic Consortium (ADGC):

PLoS One. 2014 Jun 12;9(6) 2014. Gene-wide analysis detects two new susceptibility genes for Alzheimer's **disease.**Escott-Price V, Bellenguez C, Wang LS et al.

Nat Genet. 2013 Dec;45(12):1452-8.Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's **disease.**Lambert JC, Ibrahim-Verbaas CA, Harold D, et al.

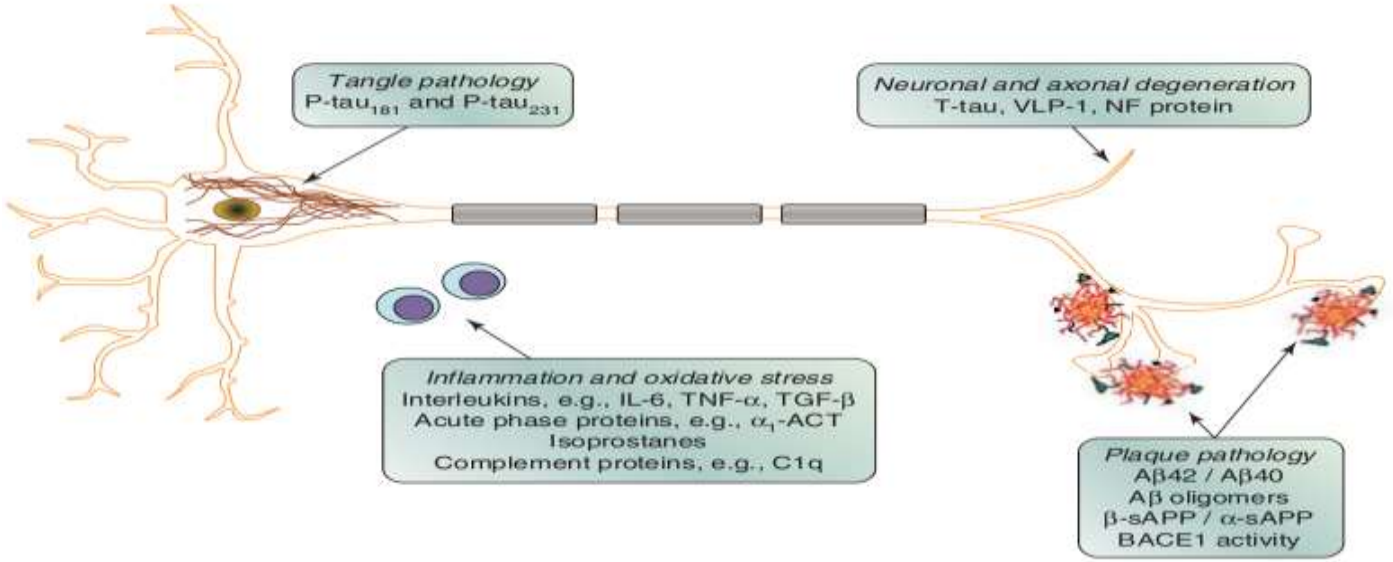
In collaboration with Prof. Migliore and Dr.Coppedè:

Identification of biomarkers of folate metabolism and their relation with

-Genetic biomarkers (gene polimorphisms: *MTHFR, RFC-1, MTR, TYMS, DNMT3A, DNMT3B*))

-Epigenetic biomarkers (methylation of genes associated to AD: presenilin1 *PSEN1* and beta-secretase *BACE1*)

Core biomarkers in AD measurable in CSF



Core biomarkers in PD measurable in CSF

Alfa synuclein :

CSF
Plasma
Skin
Salivary Glands

Alfa syn.oligomers :

CSF
Plasma

DIAGNOSTIC MARKERS
MONITORING PROGRESSION

Leonid Molochnikov[1†], Jose M Rabey[1†], Evgenya Dobronevsky[2], Ubaldo Bonuccelli[3], Roberto Ceravolo[3], Daniela Frosini[3], Edna Grünblatt[4,5], Peter Riederer[5], Christian Jacob[5], Judith Aharon-Peretz[6], Yulia Bashenko[7], Moussa BH Youdim[7,8] and Silvia A Mandel[7*]

2012

MOLECULAR NEURODEGENERATION

A molecular signature in blood identifies early Parkinson's disease

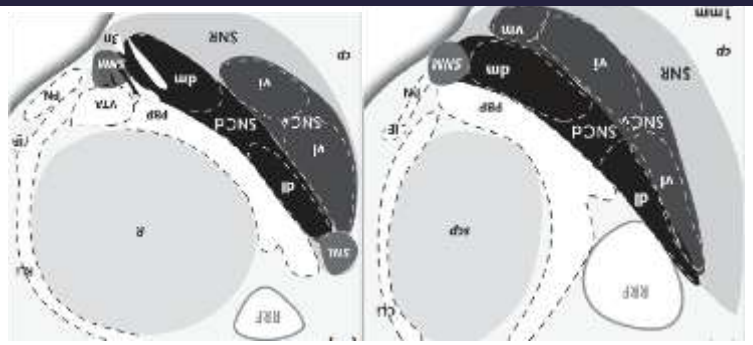
Stepwise multivariate logistic regression analysis identified five genes as optimal predictors of PD:

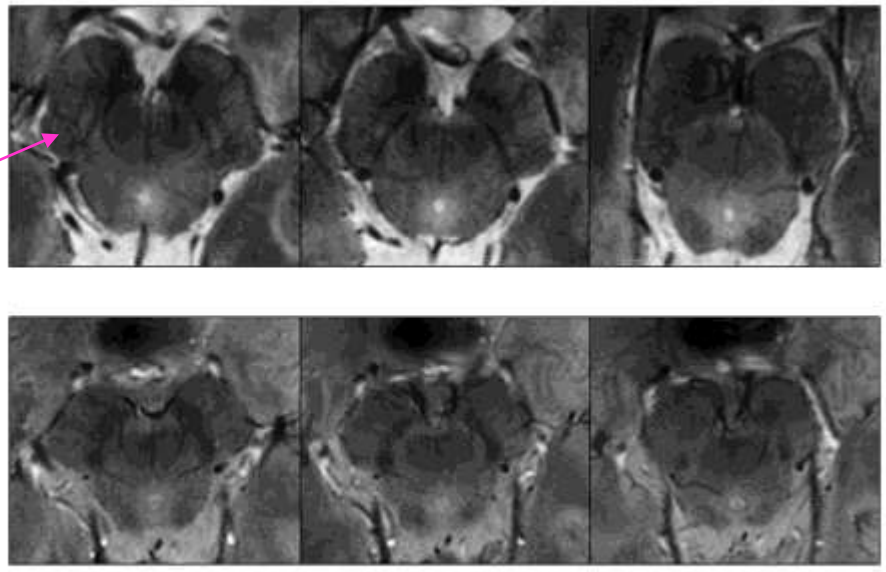
- **p19 S-phase kinase-associated protein 1°**
- **huntingtin interacting protein-2**
- **aldehyde dehydrogenase family 1 subfamily A1**
- **19 S proteasomal protein PSMC4**
- **heat shock 70-kDa protein 8**

Future perspectives

- **The PDx assay ongoing study is intended to be an affordable blood test that can easily and specifically diagnose early PD with a potential to identify individuals at pre-symptomatic, prodromal stages of the disease**
- **The main objective of the study is to to validate the ability of the expression levels of EGLN, HIP2, HSPA8, ALDH1A1, PSMC4, SKP1A to differentiate between PD patients,HC and atypical parkinsonism patients.**

MR Imaging of the Substantia Nigra at 7 T Enables Diagnosis of Parkinson Disease





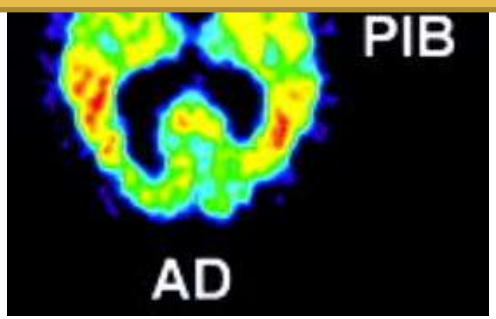
IMAGO7 *Cosottini et al.2014*

Alzheimer's Disease

- Cells loss

  atrophy

Ultra high field MRI



- Amyloid plaques
- Neurofibrillary tangle

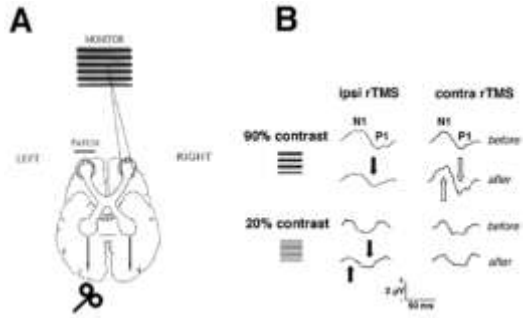
beyond the detection limit of any current MRI technology

NEUROMODULATION, ELECTROPHYSIOLOGY AND BRAIN DISORDERS

Department of Clinical and Experimental Medicine,
Cisanello Neurology Unit,
Pisa University Medical School
Chair: prof. Ferdinando Sartucci

Tommaso Bocci, M.D.; Andrea Di Rollo , M.D.; Elisa Giorli, M.D.;
Antonio Torzini, M.D.
Davide Barloscio, Michelangelo Bartolotta, Orietta Ricci, Laura Masoni, Michela Santin

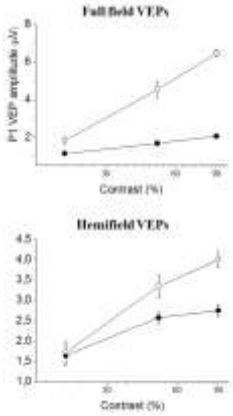
Corpus Callosum and Visual System: role in contrast gain control,



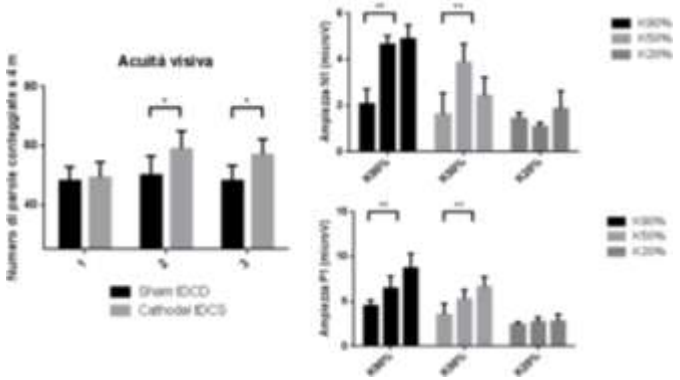
Evidence that a mechanism of transcallosal inhibition dampens neural responses at high contrasts in human visual cortex

Photosensitive Epilepsy

Photosensitivity could be due, at least in part, to a functional impairment of inter-hemispheric processing of gain contrast control

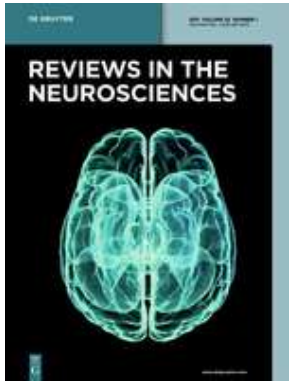


Corpus Callosum and Amblyopia



Evidence that neuromodulation techniques are able to dinamically interfere with visual cortex plasticity in amblyopic patients, by restoring a sub-normal visual acuity.

Bocci et al., 2011 *Neuroscience* 187: 43-51



Bocci et al., 2014 *Reviews in the Neuroscience* 25(1): 113-27

Further Research Lines …

1) **Neuromodulation techniques (rTMS, tDCS, tsDCS) and pain treatment** (Truini et al., 2009 Eur J Pain 14(2): 222-5)
2) **Assessment of Olfactory Function in Neurodegenerative Disorders**
3) **Discover Visual System Plasticity as revealed by neuromodulation techniques** (Bocci et al., 2014 J Neural Transm, 121, 221-231)
4) **Visual System and Neurodegenerative Disorders** (Sannita et al., 2009 Vision Res 49(7): 726-34; Sartucci et al., 2010 Brain Res Bull 82(3-4): 169-176)
5) **Monitoring Amyotrophic Lateral Sclerosis and other Motor Neuron Diseases progression with neurophysiological assessment (MUNE, Macro-EMG)** (Sartucci et al., 2010 Neural Reg Res 5(8), 597-601; Sartucci et al., 2011 Intern J Neurosci, 121 (5)257-66; Bocci et al., 2011 Int J Mol Sci, 12, 9203-9215; Bocci et al., 2012 JNS 316 81-29:67-71; Bocci & Sartucci, 2012, J Neurol Neurophysiol 3 (3): e109)
6) **Brain mechanisms of Spinal-induced plasticity** (Bocci et al, 2014 Neurosci Lett. 2014 S0304-3940(14)00518-7)
7) **EEG-fMRI recordings in Epilepsies** (Cosottini et al., 2010 Magn Reson Imaging, 28(3): 388-93; Pesaresi et al., 2011 MAGMA, 24(5): 285-296; Guida et al., 2014 Funct Neurol, 75-79; Bartolini et al., 2014 EPI, 1-10)
8) **Computer-brain interfaces** (Bocci et al., 2013 Behav Brain Funct, 9(1), 14)

Institutional Network

CNR Neuroscience Institute, Pisa

Prof. Lamberto Maffei
Matteo Caleo, M.D. Ph.D.
Laura Restani, M.D. Ph.D.
Marta Pietrasanta, M.D. Ph.D.
Chiara Cerri, M.D. Ph.D.
Prof. Luciano Domenici
Nicola Origlia, Ph.D.

University of Chieti
Andrea Mazzatenta, Ph.D.

Department of Neurological and Neurosensorial Sciences, Neurology and Clinical Neurophysiology Section, Siena
Prof. Alessandro Rossi
Prof. Fabio Giannini
Simone Rossi, M.D. Ph.D.

Department of Neurological Sciences, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Milan, Italy
Prof. Alberto Priori
Gianluca Ardolino, M.D.
Filippo Cogiamanian, M.D.
Maurizio Vergari
Roberta Ferrucci

Bascom Palmer Eye Institute, Miami, FL, USA

Prof. Vittorio Porciatti, PhD

Ophtalmology Unit, Department of Surgical, Medical and Molecular Pathology, and Critical Area, Pisa University Medical School,
Prof. Marco Nardi
Francesco Nasini, M.D.

For references and further information: f.sartucci@neuro.med.unipi.it

Hypnotizability is a **cognitive trait** enabling individuals to accept suggestions by modifying perception, memory and behavior. It is measured by scales.

(American Psychological Association, 2005)

Hypnotizability is a <u>physiological trait</u>
- characterized by peculiar
a) cortical dynamic
b) sensori-motor integration
c) cardiovascular control
d) cognitive strategies in the ordinary state of consciousness and also in the absence of suggestions.

(Santarcangelo, 2014)

Subjects with high and low hypnotizability scores have different:

- **cortical dynamics** (*Madeo et al., 2013)*
- **internal models for posture and locomotion**
- **responsiveness to the alteration of various sensory modalities**
- **excitability of the spinal cord motoneurons**
- **haptic abilities**
- **degree of embodiment of mental images in neural circuits**
  (*Santarcangelo, Front Behav Neurosci 2014)*
- **blink rate** *(under revision)*
- **efficiency of the endothelial function** (NO availability)
  (Jambrik et al., 2004, 2005,2005)
- **heart rate variability in resting conditions**
  (Santarcangelo et al., Int J Clin Exp Hypn 2012)
- **interaction of imagery with other cognitive emotional traits in pain control**
  (Santarcangelo et al., Plos One 2013, Neurosci Lett 2013)
- **written production** *(Marinelli et al Int J Clin Exp Hypn, 2012)*

Hypnotizability is not merely a cognitive trait: its assessment is useful in clinical contexts and its related physiological and cognitive characteristics can be useful tools in neuro-rehabilitation therapies and pain control