Scuola Superiore di Neurologia Sin
V CORSO
Neuroimmagini nella Malattia di Parkinson e Parkinsonismi
Genova, 21-22 febbraio 2017

Iron Imaging

Gennarina Arabia, MD, MSc
Università "Magna Graecia" di Catanzaro

Iron Imaging

- Role of Iron in brain
- Iron and ageing
- Iron and movement disorders:
  - Parkinson disease
  - Atypical Parkinsonisms
  - Essential Tremor
  - Neurodegeneration with Brain Iron Accumulation

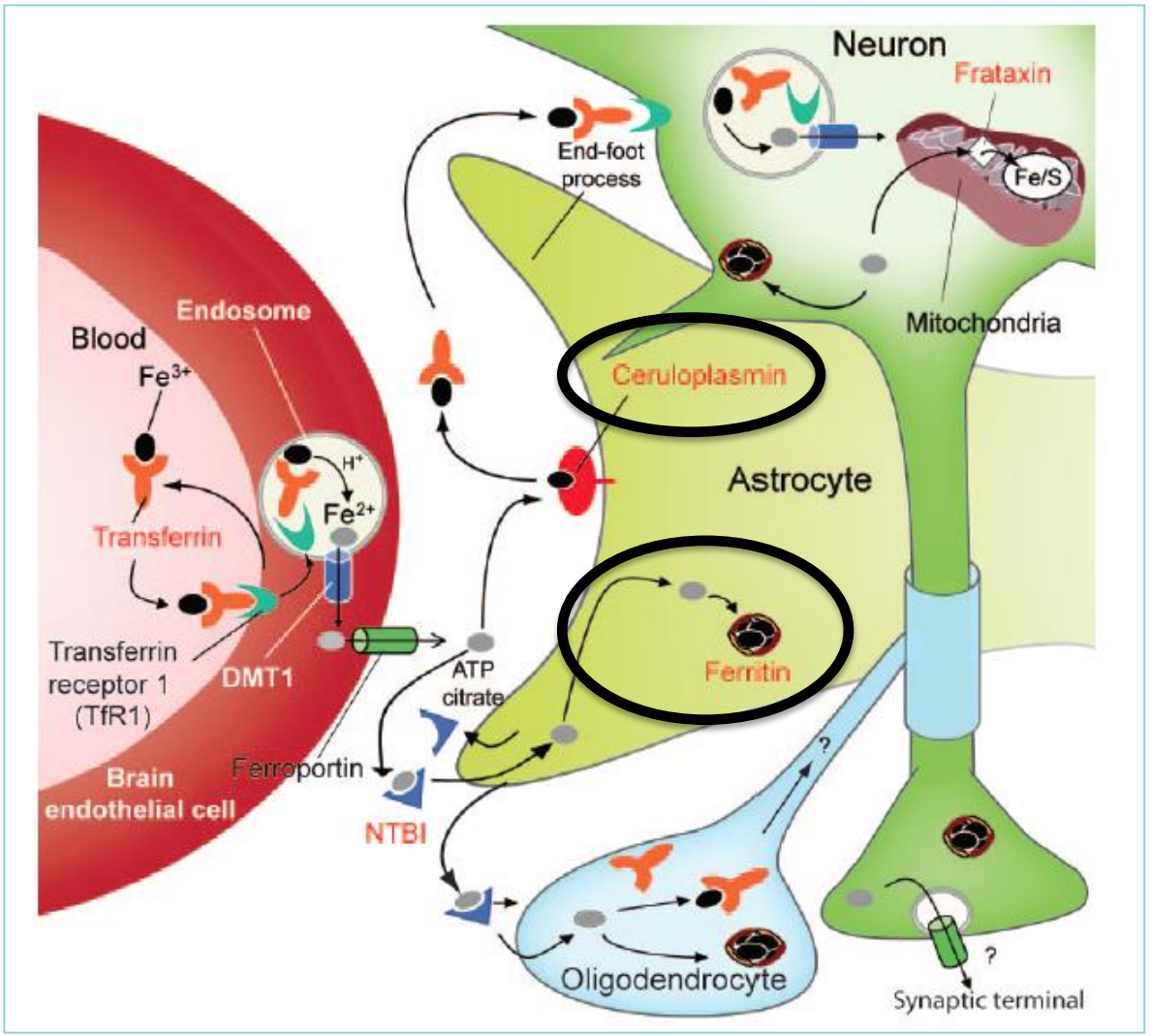
The role of Iron in brain

- Myelin synthesis
- Neurotransmitter synthesis and metabolism
- Developmental processes
- Iron homoeostasis against toxic free iron (ferritin and neuromelanin)

CLINICAL IMPLICATIONS OF NEUROSCIENCE RESEARCH

Section Editor
Eduardo E. Benarroch, MD

Brain iron homeostasis and neurodegenerative disease



Neurology 2009

Iron changes in brain ageing

Increased iron concentrations with ageing may be caused by:

- Increased blood–brain barrier permeability
- Neuroinflammation with increased release of pro-inflammatory cytokines
- Redistribution of iron within the brain
- Changes in iron homoeostasis leading to apoptosis in neurons

Total iron concentrations increase with age in the substantia nigra, putamen, globus pallidus, caudate nucleus, and cortex

Contents lists available at ScienceDirect

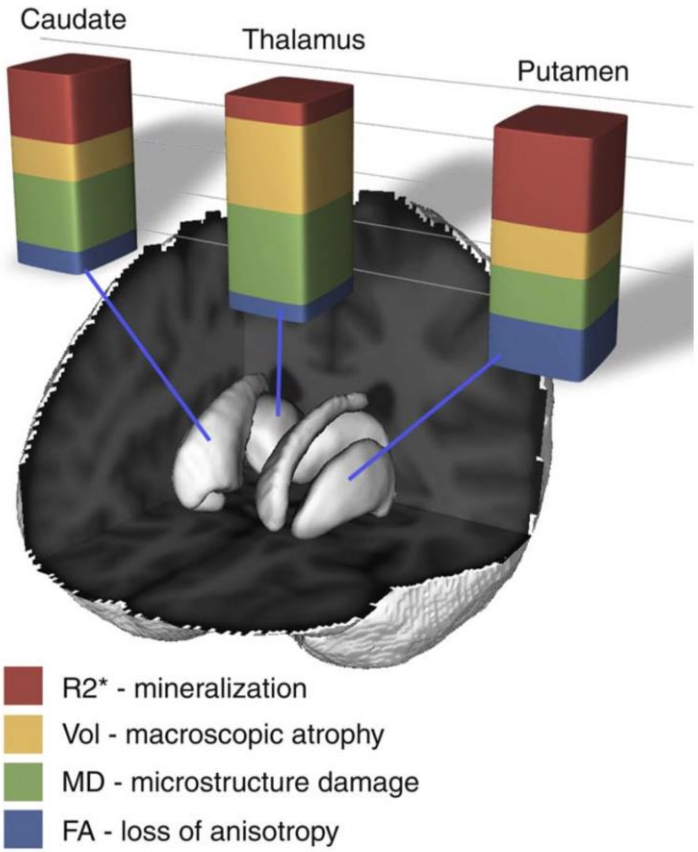
NeuroImage

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

NeuroImage 2009;48:29-36

Aging of subcortical nuclei: Microstructural, mineralization and atrophy modifications measured in vivo using MRI

Andrea Cherubini [a,*], Patrice Péran [a,b], Carlo Caltagirone [a,c], Umberto Sabatini [a], Gianfranco Spalletta [a]

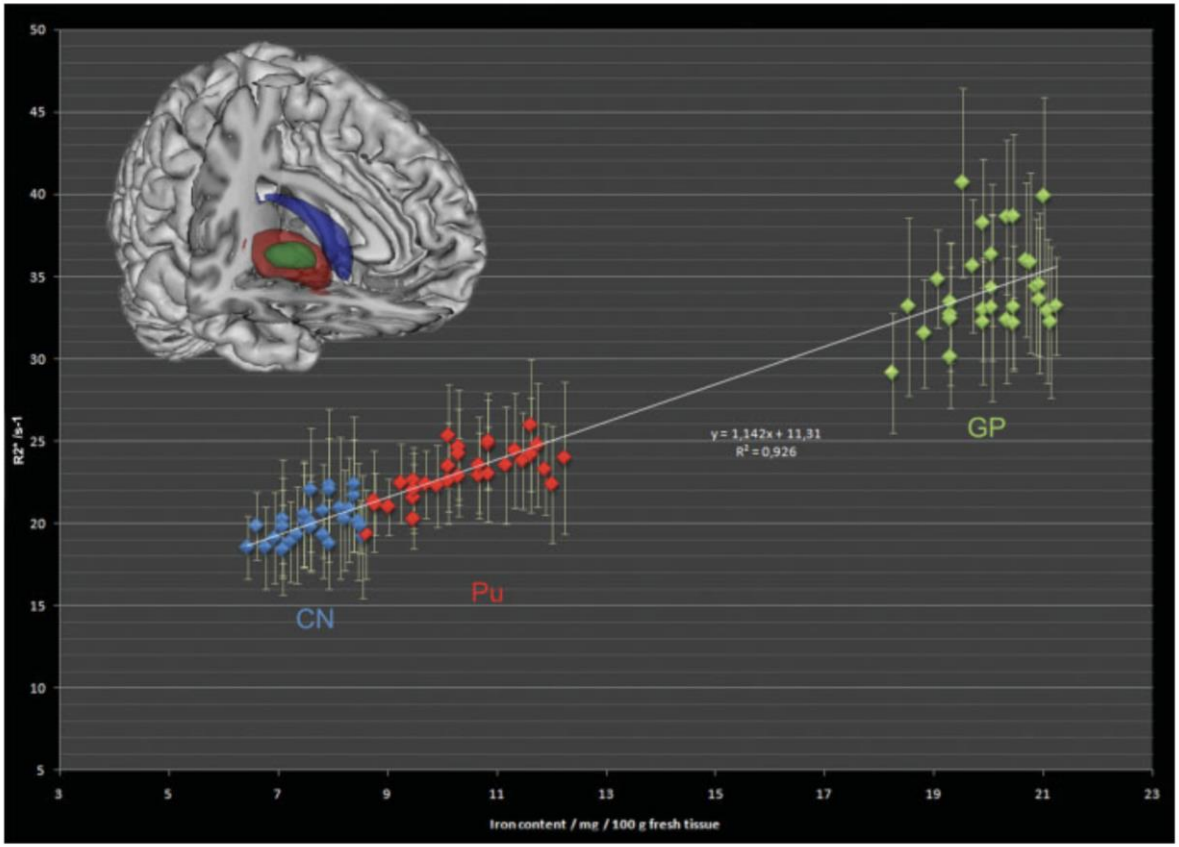


Physiological aging of deep grey matter nuclei by simultaneously measuring quantitative magnetic resonance parameters (volume atrophy, iron deposition, microstructural damage)

Multiple regression analyses revealed the best predictors of physiological aging were the progressive mineralization in the striatum (caudate and putamen), and volume atrophy and increasing diffusivity of thalamus

Volume and Iron Content in Basal Ganglia and Thalamus

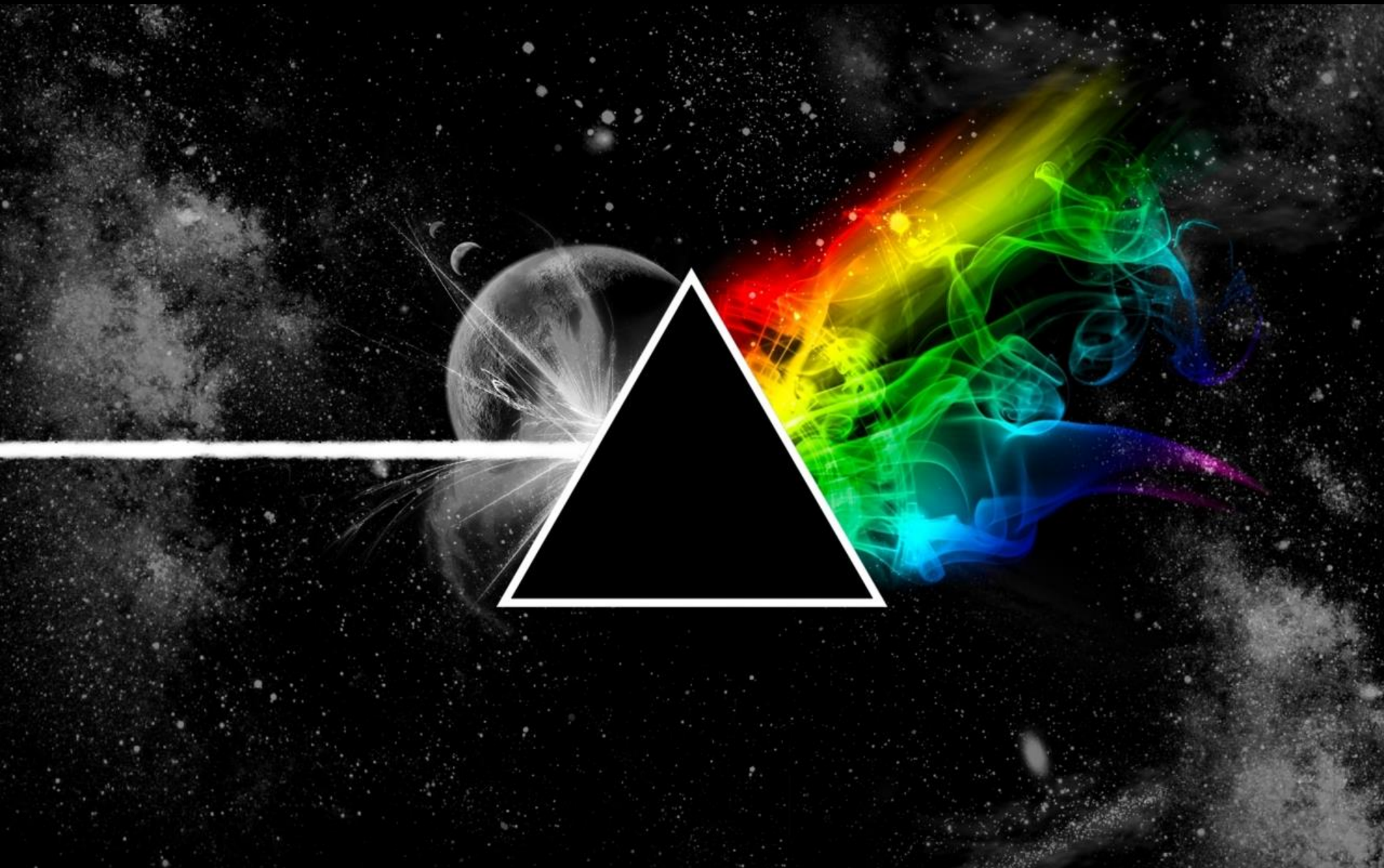
Patrice Péran,[1,2*] Andrea Cherubini,[1,3] Giacomo Luccichenti,[1]
Gisela Hagberg,[4] Jean-François Démonet,[2] Olivier Rascol,[2,5] Pierre Celsis,[2]
Carlo Caltagirone,[3,6] Gianfranco Spalletta,[3,6] and Umberto Sabatini[1]



Correlation between iron concentration derived from published post-mortem data in function of age and R2* mean values of each entire subcortical structure

Human Brain Mapping 2009;30:2667-75

THE DARK SIDE OF THE IRON



BRAIN
A JOURNAL OF NEUROLOGY

UPDATE

Iron and dopamine: a toxic couple

Dominic J. Hare[1,2] and Kay L. Double[3]

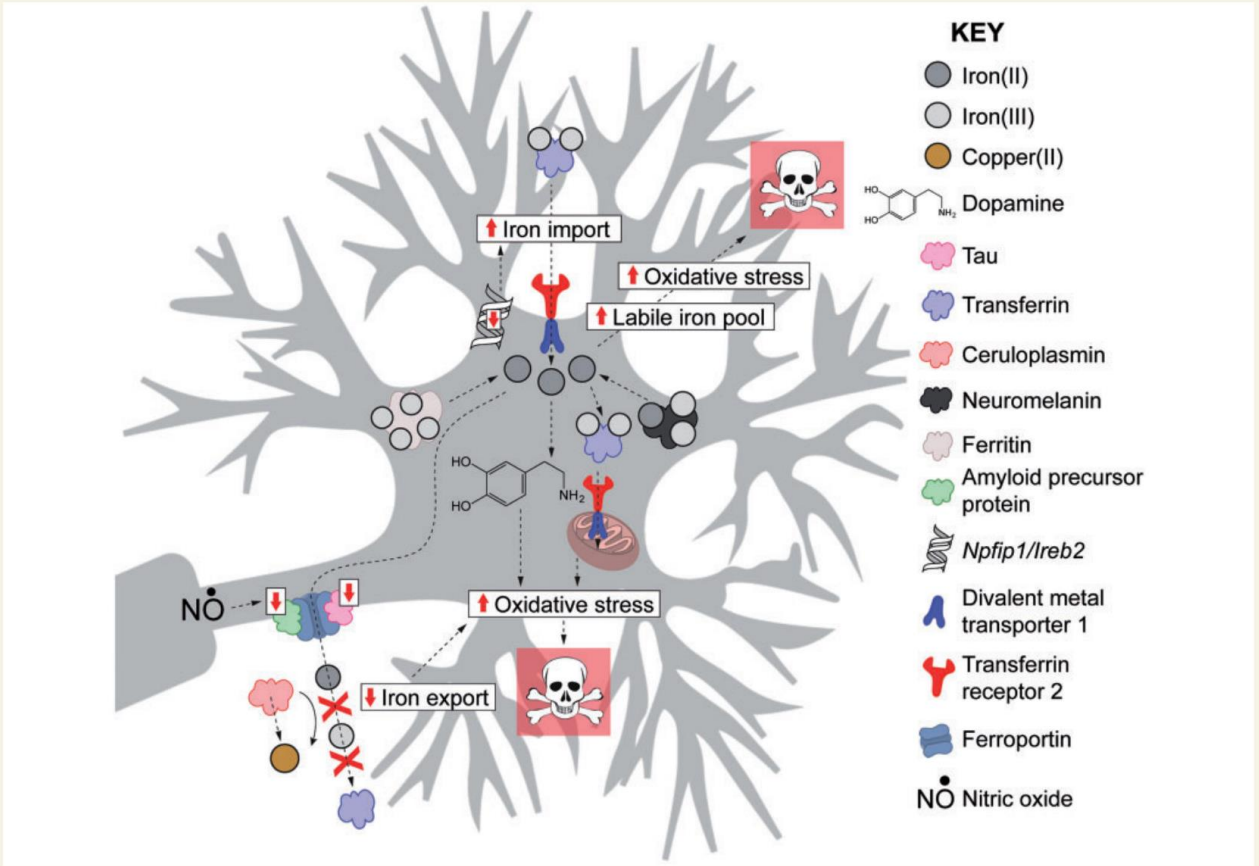


Figure 1 Breakdown of iron metabolism in Parkinson's disease. Proposed mechanisms of iron accumulation in dopaminergic neurons and sources of oxidative stress.

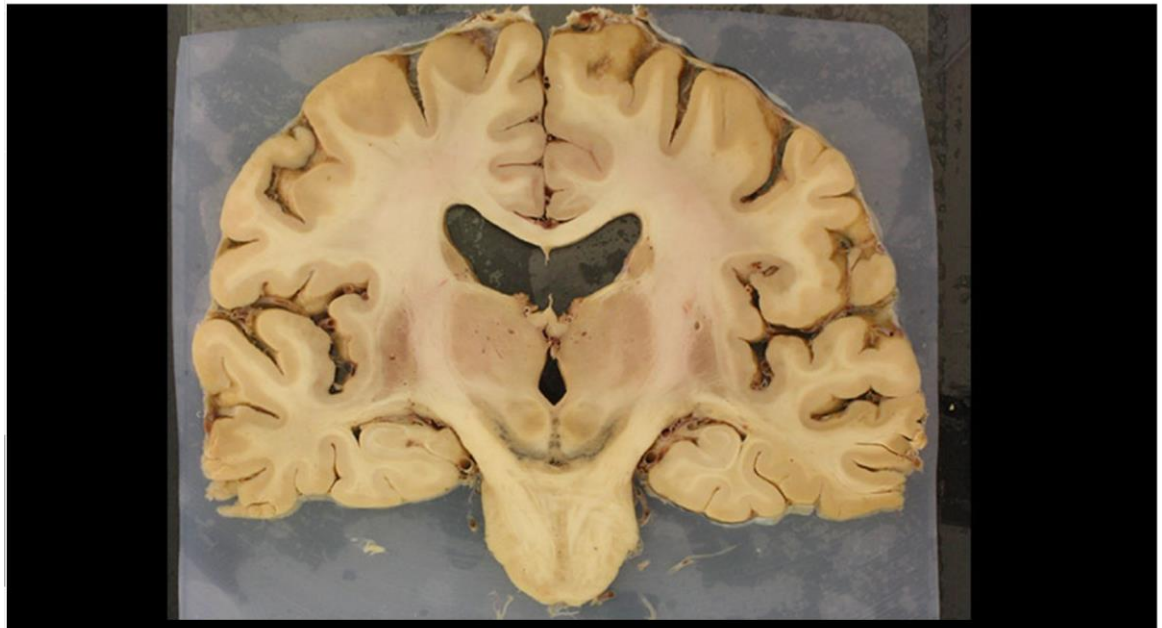
ScienceNews
MAGAZINE OF THE SOCIETY FOR SCIENCE & THE PUBLIC

NEWS NEUROSCIENCE, BIOMEDICINE, HEALTH

Evidence conflicts on iron's role in Parkinson's disease

Researchers debate whether too much or too little of heavy metal in the brain raises risk

BY LAURA SANDERS 9:00AM, MAY 2, 2016

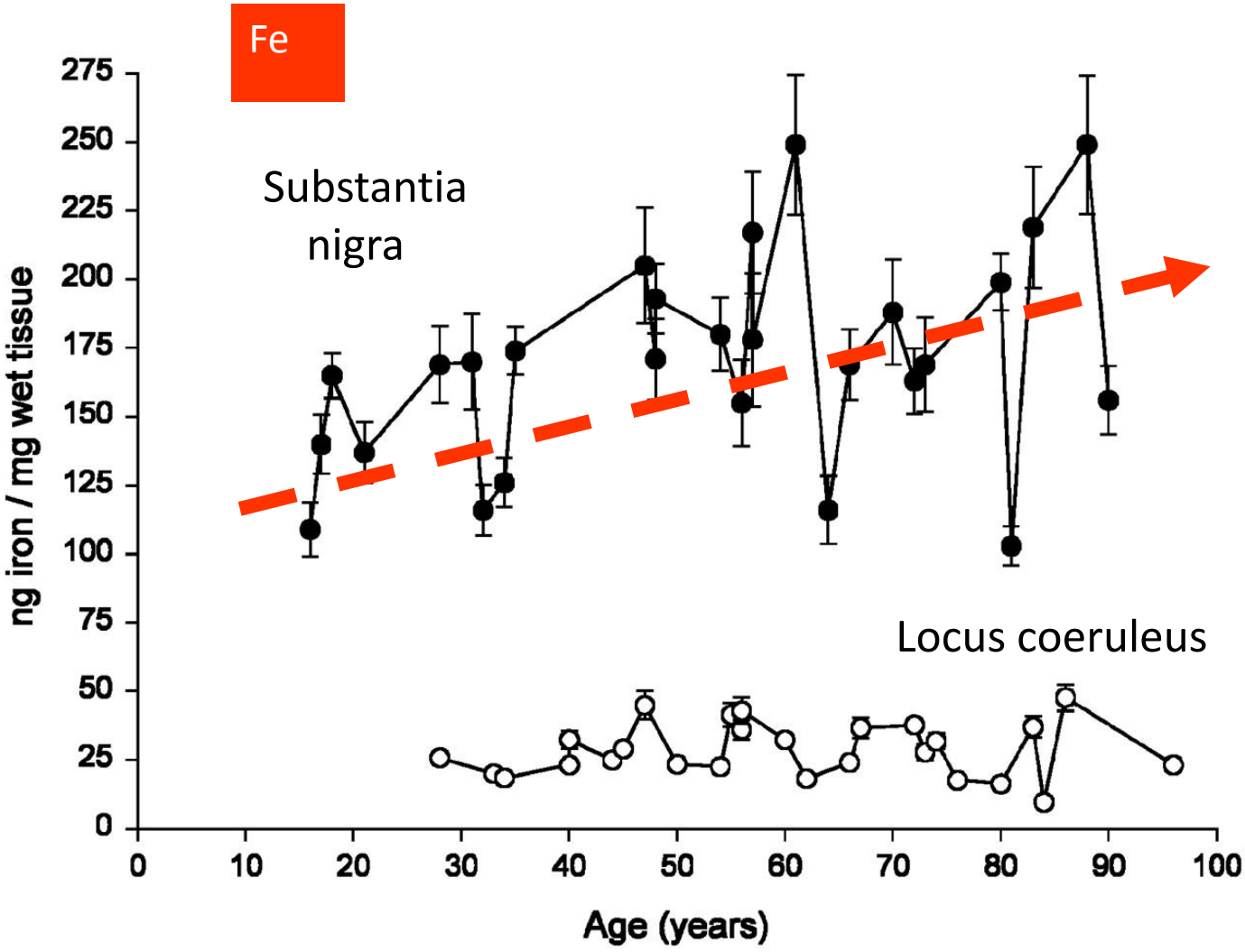


RISK FACTOR Pigmented nerve cells (black U-shape, center) in the human brain die in Parkinson's disease, destruction that may be affected by iron levels.

BRAINSCAPE/UNIVERSITY OF SYDNEY

Magazine issue: Vol. 189, No. 11, May 28, 2016, p. 14

Concentration of iron in LC and in SN of human normal subjects during aging

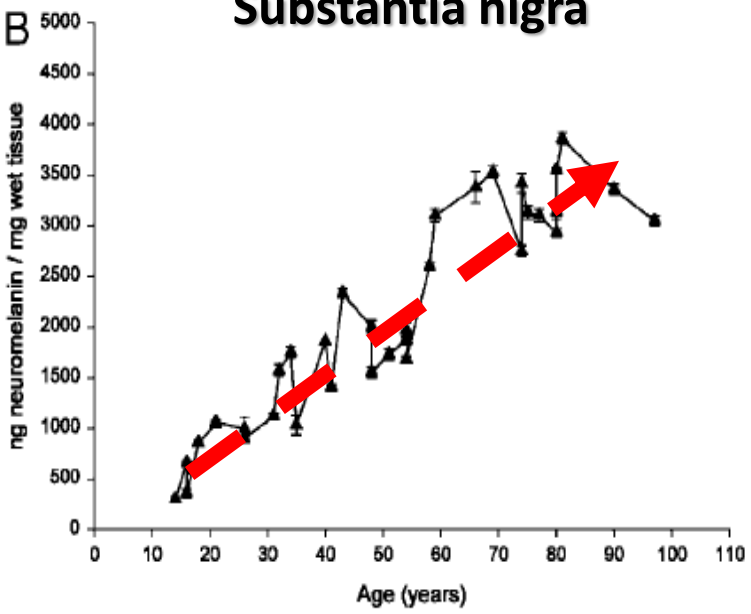


Zecca, Luigi et al. (2004) Proc. Natl. Acad. Sci. USA 101, 9843-9848

The role of iron and copper molecules in the neuronal vulnerability of locus coeruleus and substantia nigra during aging

Luigi Zecca*†, Antonella Stroppolo*, Alberto Gatti*, Davide Tampellini*, Marco Toscani*, Mario Gallorini‡, Giuseppe Giaveri‡, Paolo Arosio§, Paolo Santambrogio¶, Ruggero G. Fariello‖, Erdem Karatekin**, Mark H. Kleinman**, Nicholas Turro**, Oleh Hornykiewicz††, and Fabio A. Zucca*

Neuromelanin in Substantia nigra



SN and LC are both pigmented by Neuromelanin

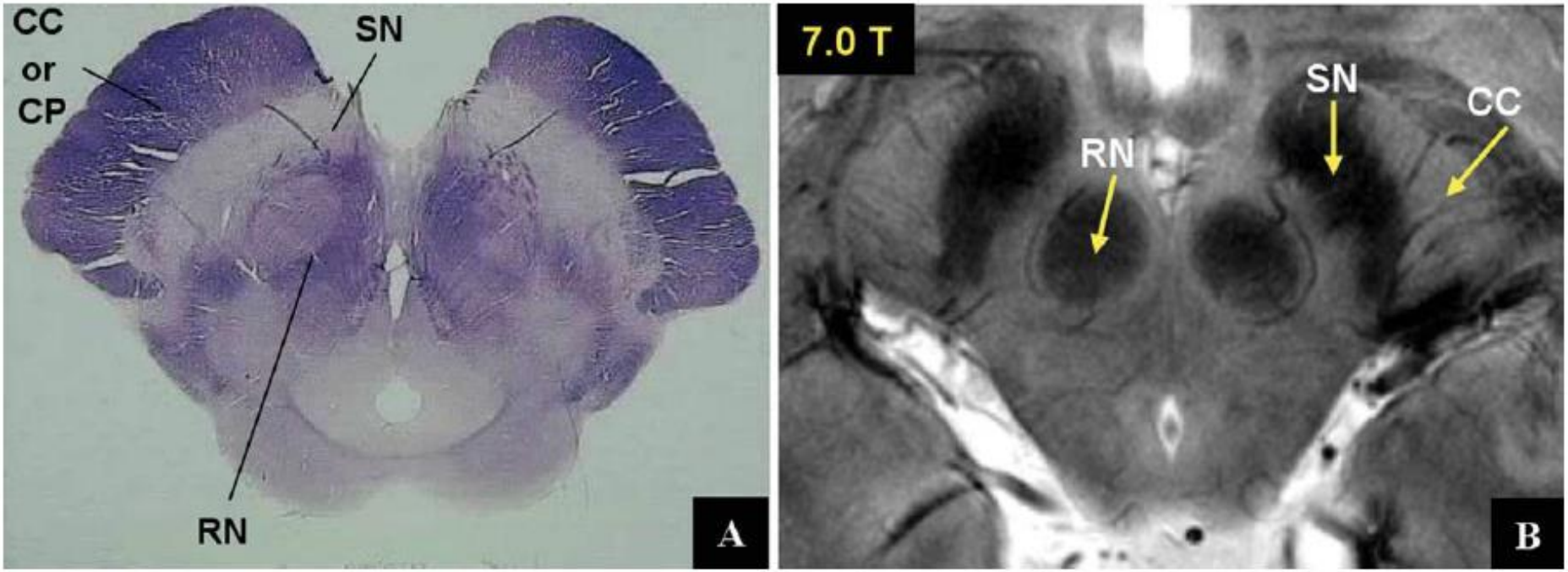
In PD, the bigger damage occurring in SN is probably the consequence of the higher presence of iron

Selective vulnerability of the SN to noxae involving iron-mediated oxidative stress damage

In-vitro and in-vivo studies show Neuromelanin able to activate microglia and to induce death of dopamine neurons

Proc. Natl. Acad. Sci. USA 2004

Iron Imaging



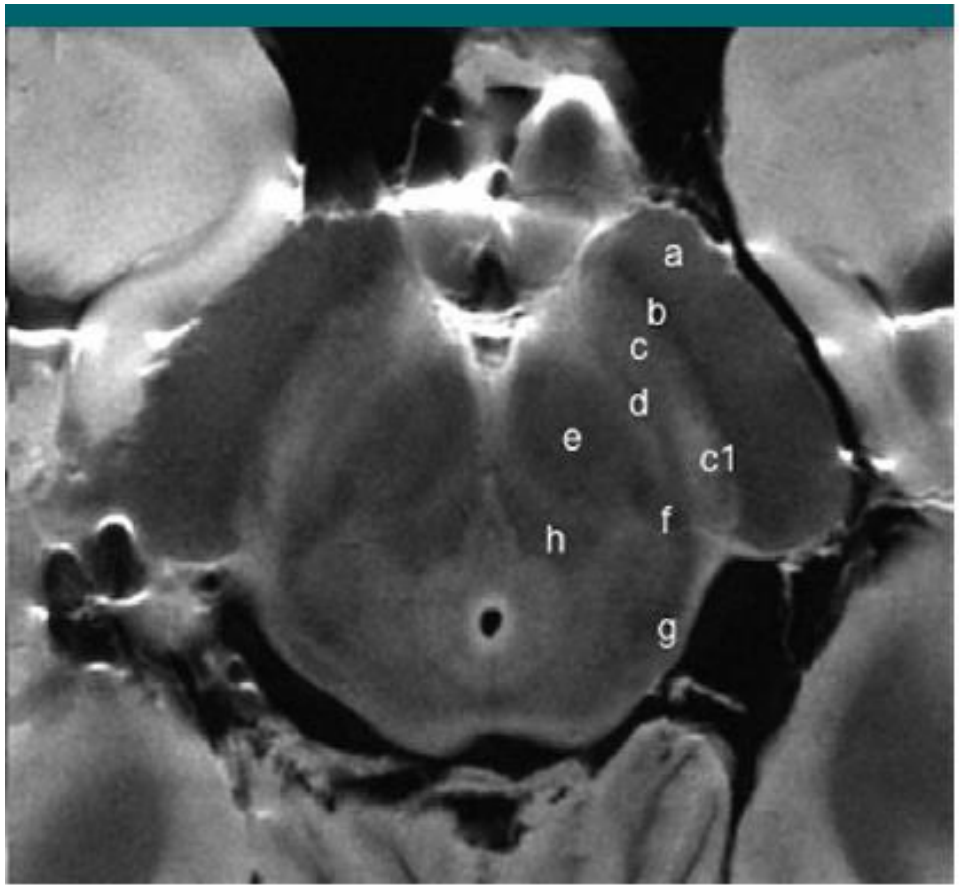
A. Cadaver image of a normal healthy subject showing the substantia nigra (SN), cerebral peduncle (CP) or crus cerebri (CC), red nucleus (RN)

B. MR images of the midbrain areas in a young normal healthy subject using 7.0T MRI

Cho ZH et al., Mov Disord, 2011

Radiology

MR Imaging of the Substantia Nigra at 7 T Enables Diagnosis of Parkinson Disease[1]



MR imaging at 7-T allows a precise characterization of the SN and visualization of its inner organization.

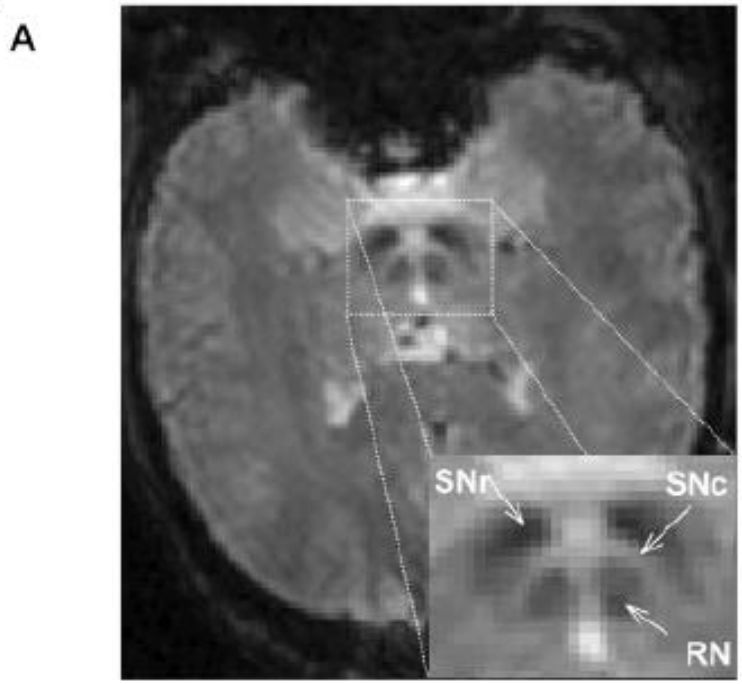
Three dimensional multiecho susceptibility-weighted images can be used to accurately differentiate healthy subjects from PD patients

Cosottini M, et al., Radiology, 2014

Midbrain iron content in early Parkinson disease

A potential biomarker of disease status

Figure 2 A typical image used for locating the substantia nigra and region of interest placement



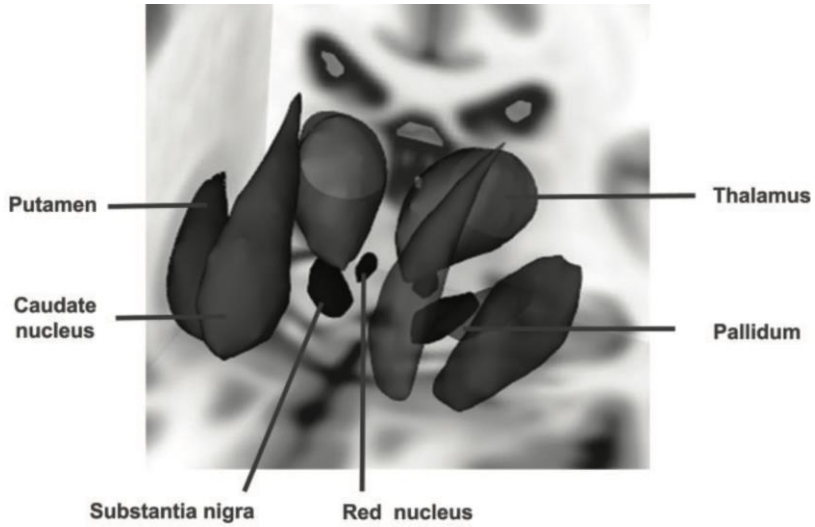
- A difference in measured R2* values between patients and controls was observed in lateral SNc (p 0.005).
- Linear regression indicated a correlation between the lateralized motor score from the clinically most affected side and R2* values from the opposite lateral SNc (p 0.01).

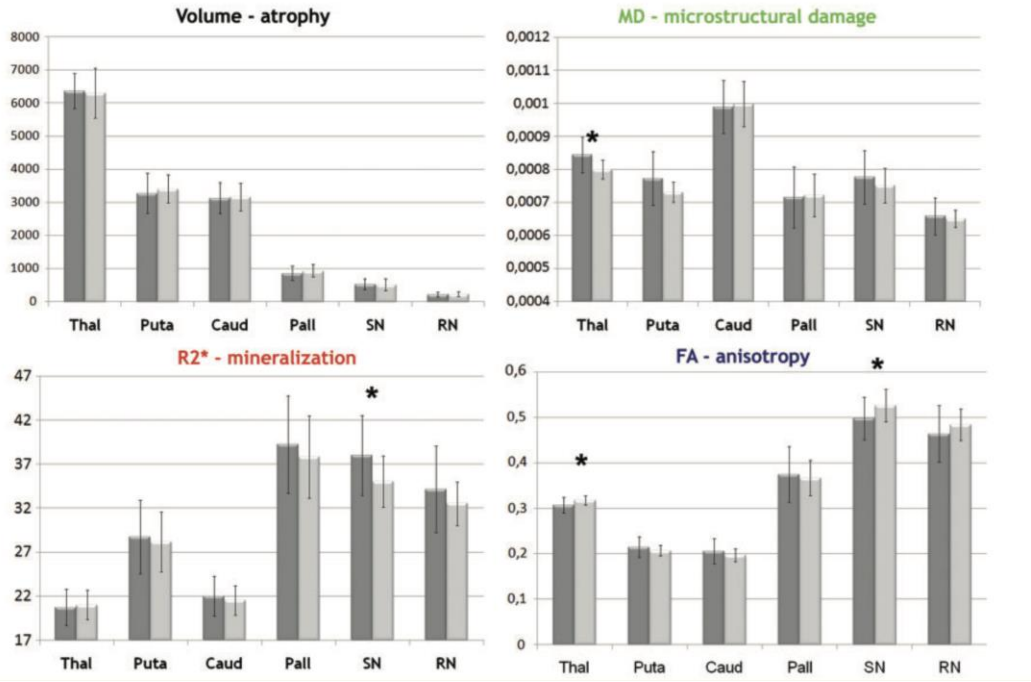
Martin WR, et al. Neurology® 2008;70:1411–1417

BRAIN
A JOURNAL OF NEUROLOGY

Magnetic resonance imaging markers of Parkinson's disease nigrostriatal signature

Patrice Péran,[1,2] Andrea Cherubini,[1] Francesca Assogna,[3] Fabrizio Piras,[3] Carlo Quattrocchi,[1] Antonella Peppe,[3] Pierre Celsis,[2] Olivier Rascol,[2,4] Jean-François Démonet,[2] Alessandro Stefani,[5] Mariangela Pierantozzi,[5] Francesco Ernesto Pontieri,[6] Carlo Caltagirone,[3] Gianfranco Spalletta[3] and Umberto Sabatini[1]





Brain 2010: 133; 3423–3433

BRAIN
A JOURNAL OF NEUROLOGY

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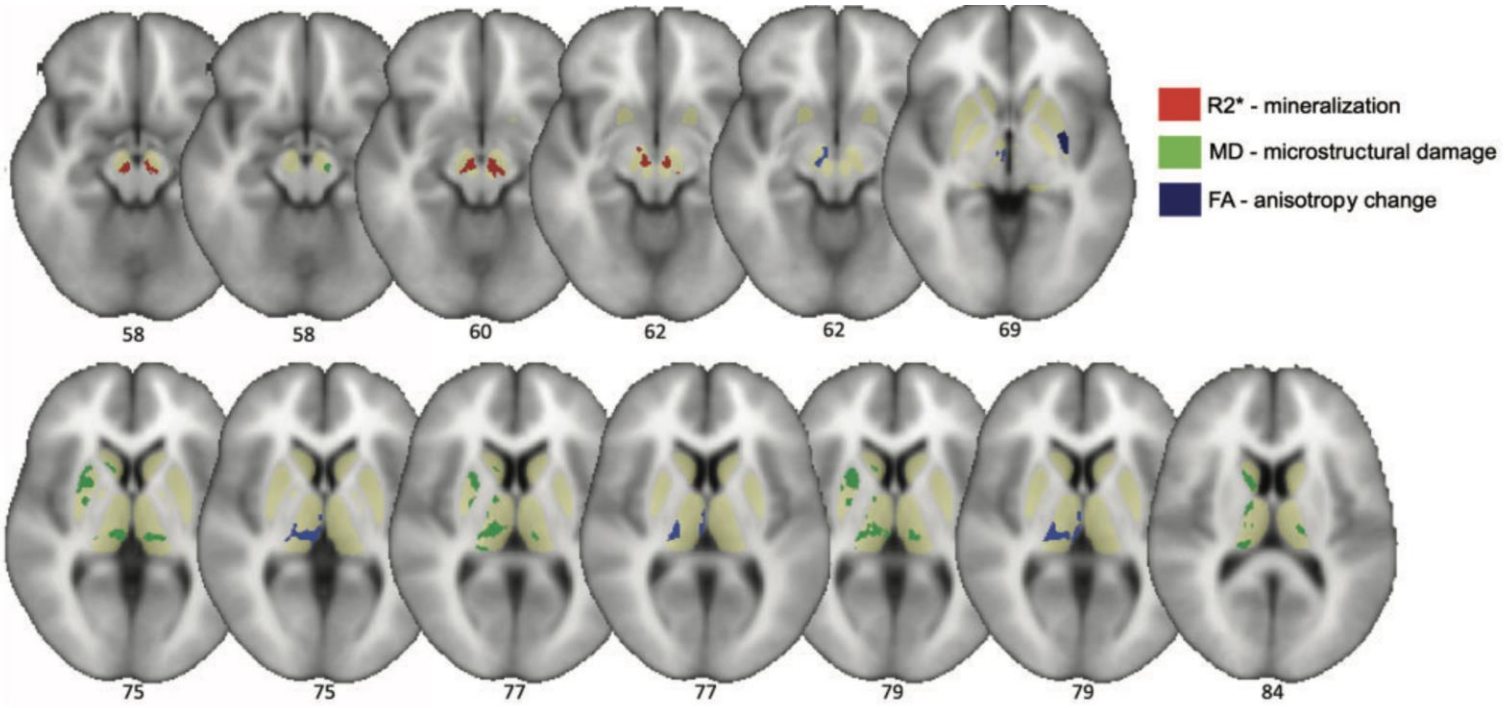
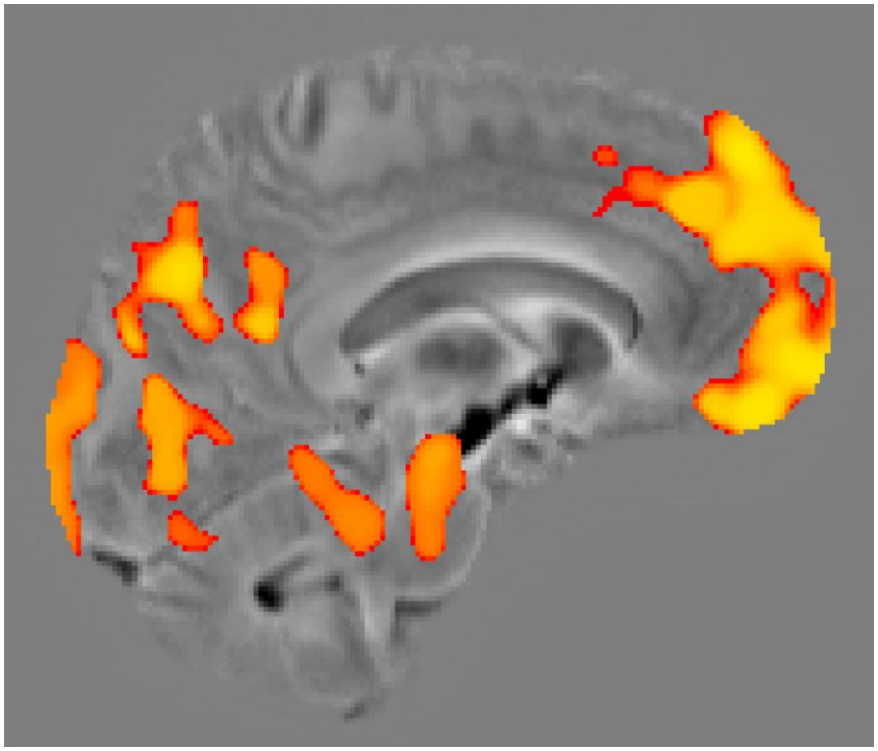


Brain 2010: 133; 3423–3433

The whole-brain pattern of magnetic susceptibility perturbations in Parkinson's disease



A newly validated iron-sensitive MRI measure maps whole-brain changes consistent with iron accumulation in Parkinson's disease. Susceptibility perturbations are seen in brainstem, midbrain, cerebellar and isocortical regions, concordant with patterns of Lewy pathology in late disease stages.

Acosta-Cabronero et al. Brain. 2016;140(1):118-131

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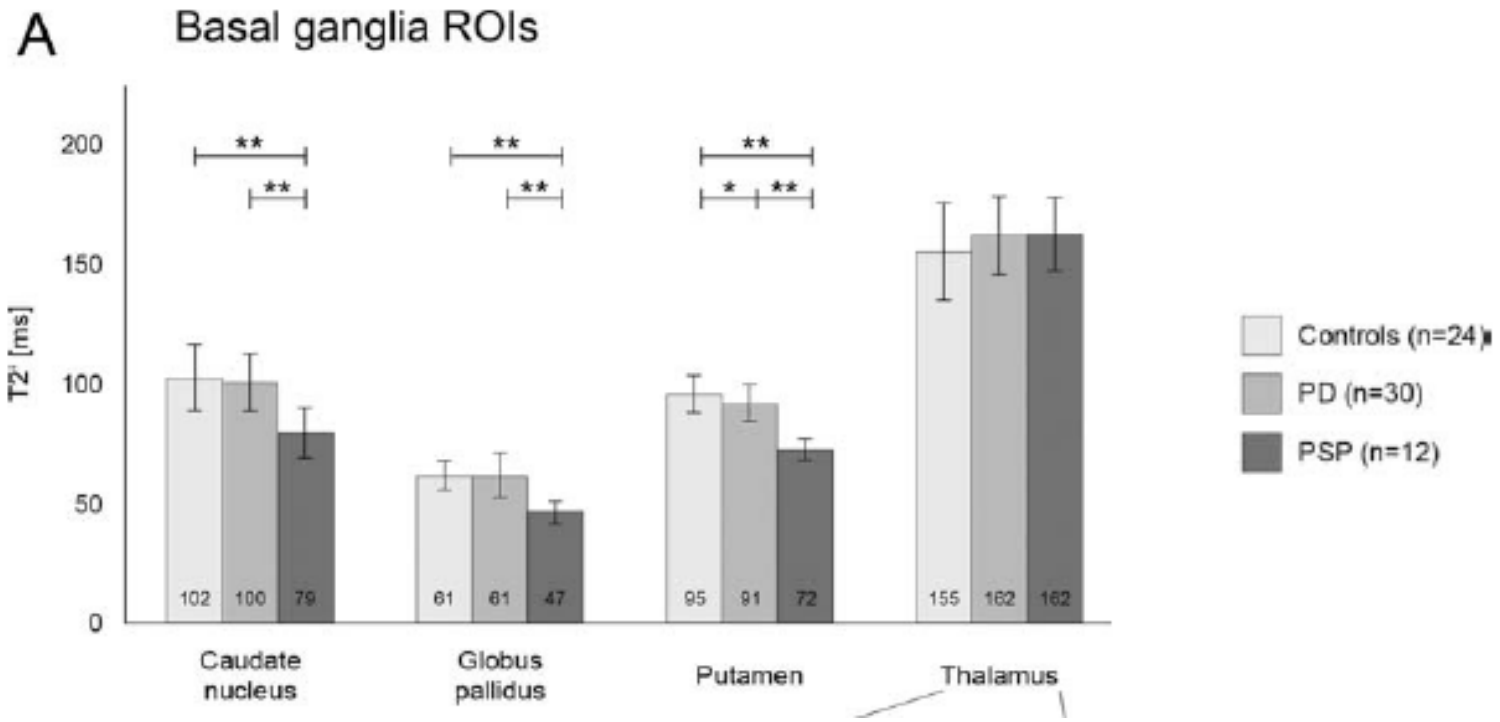
  - **Atypical Parkinsonisms**
  - Essential Tremor
  - Neurodegeneration with Brain Iron Accumulation

RESEARCH ARTICLE

Brain Iron Deposition Fingerprints in Parkinson's Disease and Progressive Supranuclear Palsy

Kai Boelmans, MD, PhD,[1*] Brigitte Holst, MD,[2] Marc Hackius,[1] Jürgen Finsterbusch, PhD,[3] Christian Gerloff, MD,[1] Jens Fiehler, MD,[2] and Alexander Münchau, MD[1]



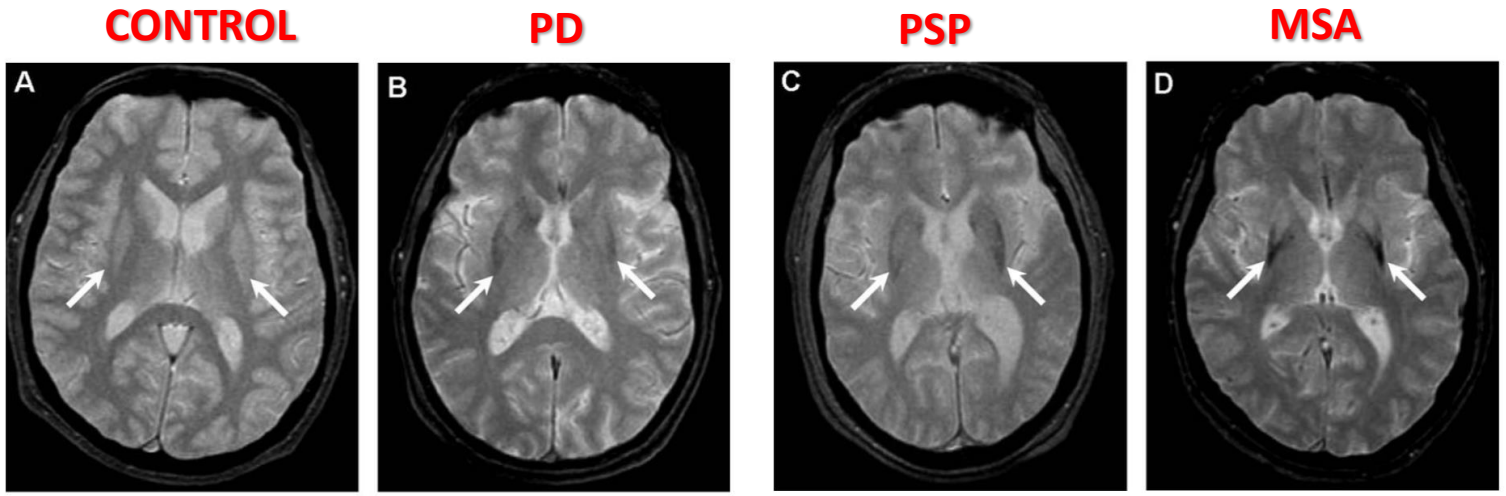
Shortened T2' values in the caudate nucleus, globus pallidus, and putamen in PSP compared to PD patients and controls

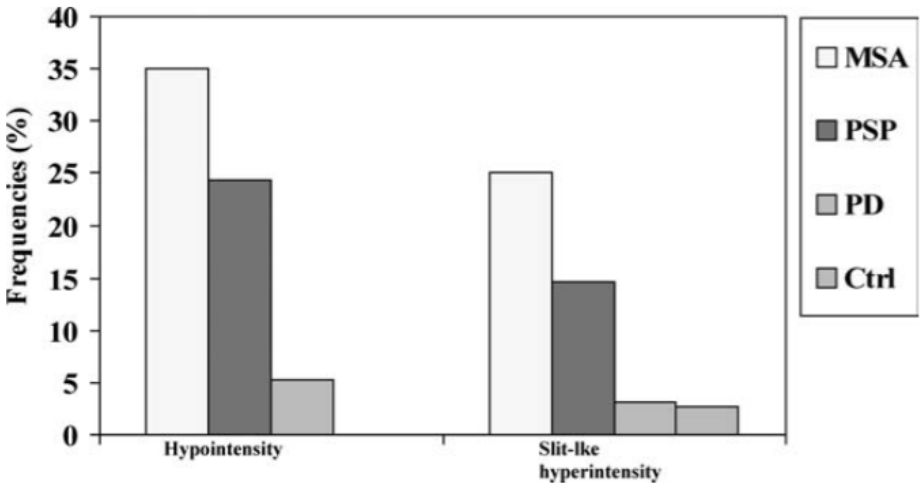
Mov Disord 2012

An Magnetic Resonance Imaging T2*-Weighted Sequence at Short Echo Time to Detect Putaminal Hypointensity in Parkinsonisms

Gennarina Arabia, MD, MSc,[1] Maurizio Morelli, MD,[1] Sandra Paglionico, MD,[1] Fabiana Novellino, MD,[1] Maria Salsone, MD,[1] Laura Giofrè, MD,[1] Giusi Torchia, STC,[2] Giuseppe Nicoletti, MD,[2] Demetrio Messina, MD,[2] Francesca Condino, PhD,[2] Pierluigi Lanza, MD,[2] Olivier Gallo, STC,[2] and Aldo Quattrone, MD[1,2]*

2010





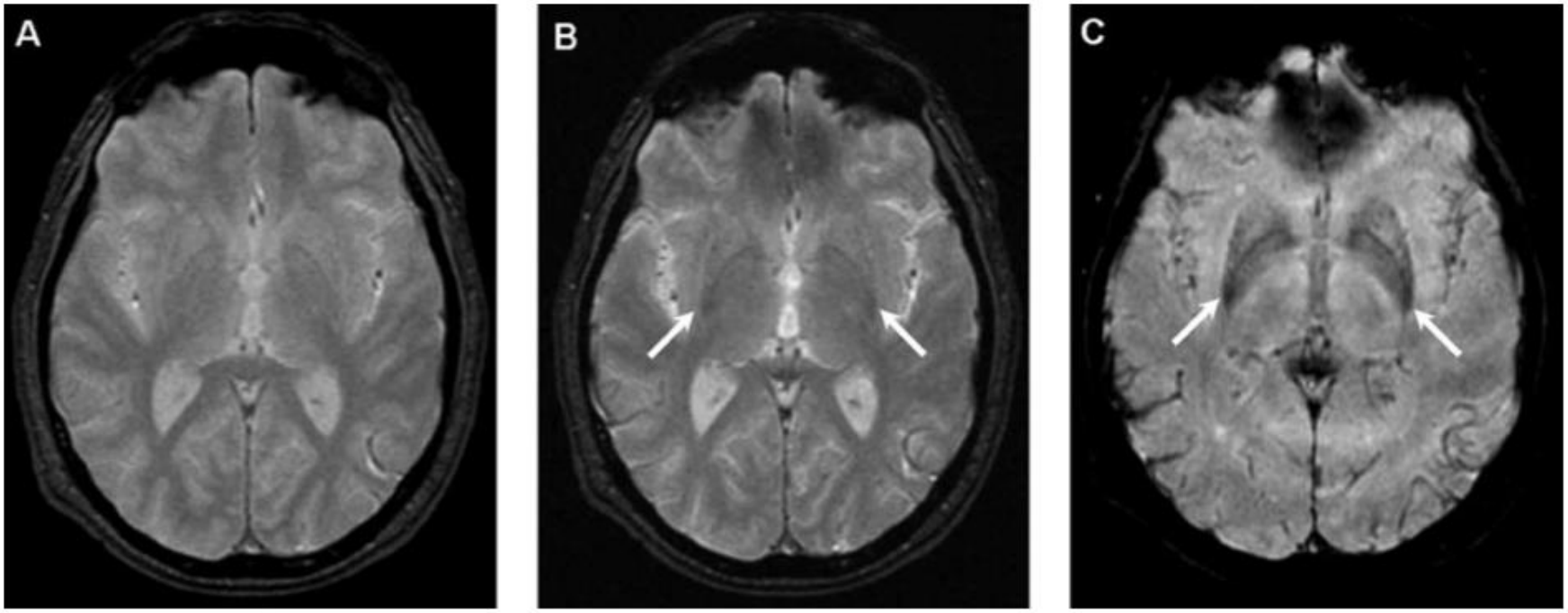
Putaminal hypointensities using T2*-weighted sequence TE=15 msec

MSA: 35%
PSP: 24.4%
PD: 5.3%
Controls: 0%

An Magnetic Resonance Imaging T2*-Weighted Sequence at Short Echo Time to Detect Putaminal Hypointensity in Parkinsonisms

2010

Gennarina Arabia, MD, MSc,[1] Maurizio Morelli, MD,[1] Sandra Paglionico, MD,[1] Fabiana Novellino, MD,[1] Maria Salsone, MD,[1] Laura Giofrè, MD,[1] Giusi Torchia, STC,[2] Giuseppe Nicoletti, MD,[2] Demetrio Messina, MD,[2] Francesca Condino, PhD,[2] Pierluigi Lanza, MD,[2] Olivier Gallo, STC,[2] and Aldo Quattrone, MD[1,2]*



Axial T2*-weighted GE images at echo time of 15 (A), 25 (B), and 40 millisecond (C) in a healthy subject

Iron Imaging

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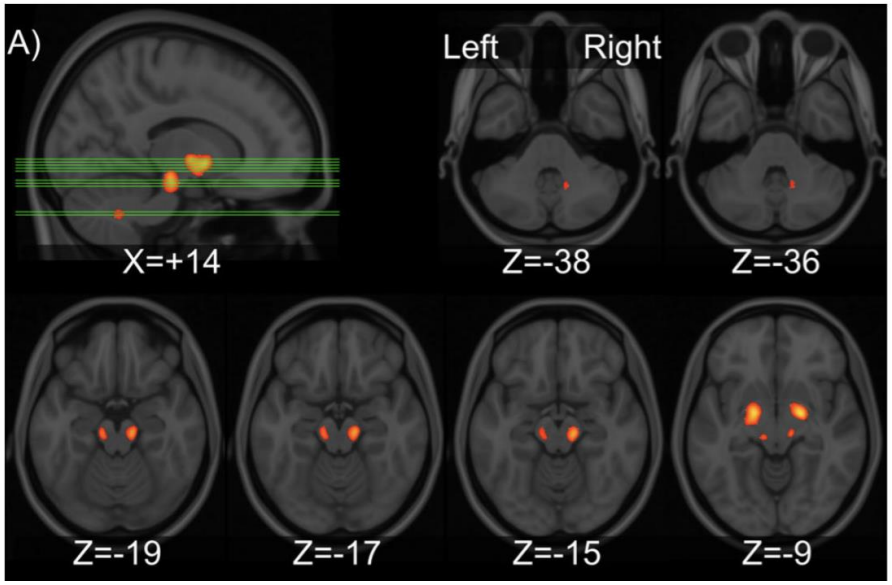
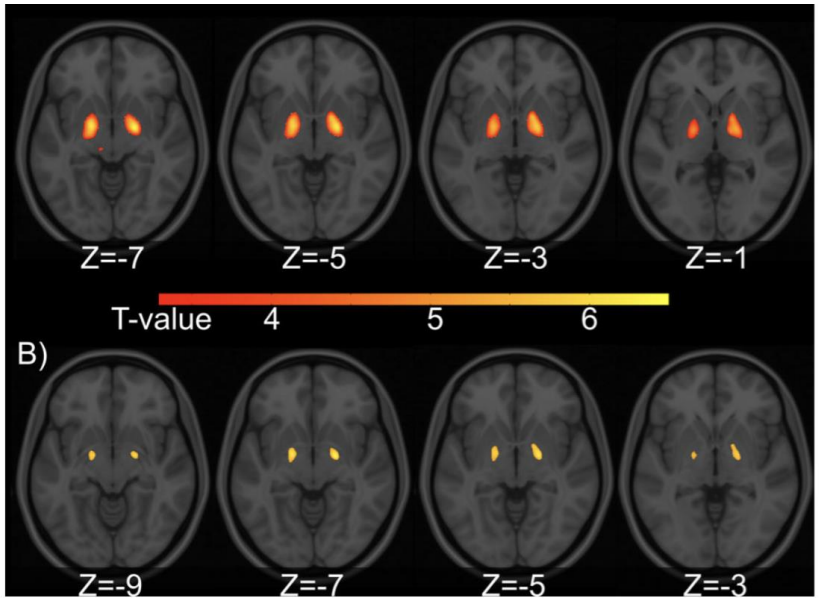
  - Atypical Parkinsonisms
  - **Essential Tremor**
  - Neurodegeneration with Brain Iron Accumulation

RESEARCH ARTICLE

Brain Iron Deposition in Essential Tremor: A Quantitative 3-Tesla Magnetic Resonance Imaging Study

Fabiana Novellino, MD,[1] Andrea Cherubini, PhD,[1] Carmelina Chiriaco, PhD,[1] Maurizio Morelli, MD,[2] Maria Salsone, MD,[2] Gennarina Arabia, MD, MSc,[2] and Aldo Quattrone, MD[1,2]*





Brain areas with iron content significantly higher in ET patients than HC ($P < .001$)
Whole brain voxel-based analyses revealed significant differences in iron content in bilateral globus pallidus, substantia nigra and right dentate nucleus.
Differences in bilateral globus pallidus survived to FWE correction for multiple comparisons

Iron Imaging

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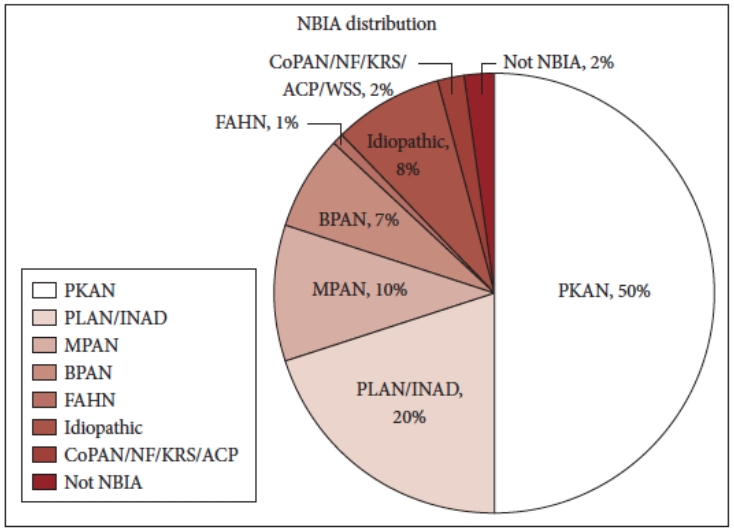
  - **Neurodegeneration with Brain Iron Accumulation**

Neurodegeneration with Brain Iron Accumulation



Heterogeneous group of inherited neurodegenerative disorders characterized by extrapyramidal movement disorders and abnormal iron accumulation in the deep basal ganglia nuclei of the brain

Table 1. The ten forms of NBIA described to date, with name, acronym, mutated gene, and mode of inheritance

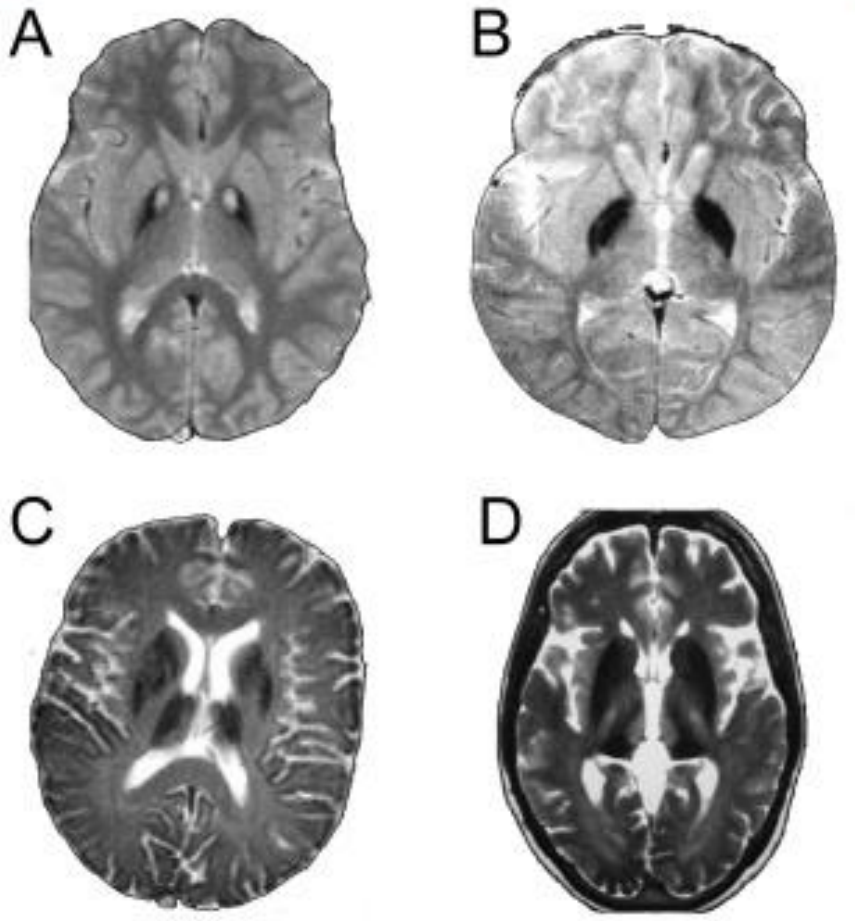
NBIA subtype	Gene	Mode of inheritance
Pantothenate kinase-associated neurodegeneration (PKAN)	*PANK2*	Autosomal recessive
Phospholipase A2-associated neurodegeneration (PLAN)	*PLA2G6*	Autosomal recessive
Mitochondrial membrane protein-associated neurodegeneration (MPAN)	*C19orf12*	Autosomal recessive
Beta-propeller protein-associated neurodegeneration (BPAN)	*WDR45*	X-linked dominant
Fatty acid hydroxylase-associated neurodegeneration (FAHN)	*FA2H*	Autosomal recessive
Coenzyme A synthase protein-associated neurodegeneration (CoPAN)	*COASY*	Autosomal recessive
Kufor-Rakeb syndrome	*ATP13A2*	Autosomal recessive
Woodhouse-Sakati syndrome	*DCAF17*	Autosomal recessive
Neuroferritinopathy	*FTL*	Autosomal dominant
Aceruloplasminemia	*CP*	Autosomal recessive

NBIA: neurodegeneration with brain iron accumulation.

Hogarth P. J Mov Disord 2015;8:1-13

T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation

Figure 1 T2 gradient echo images



PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION

INFANTILE NEUROAXONAL DYSTROPHY (INAD/PLAN)

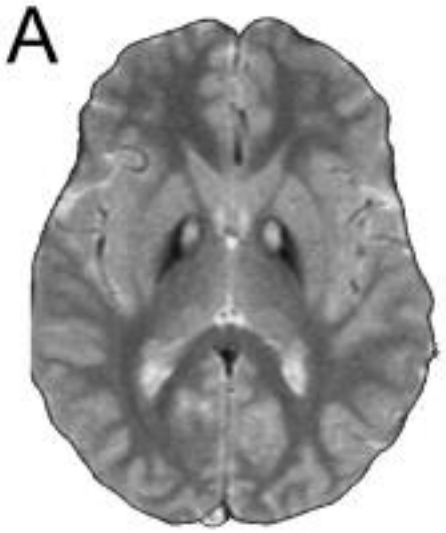
NEUROFERRITINOPATHY

ACERULOPLASMINEMIA

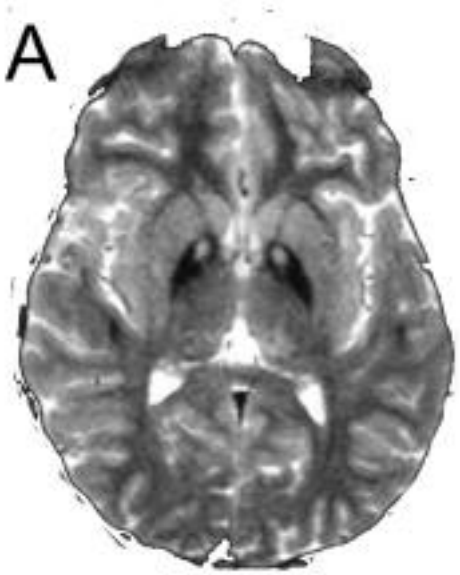
McNeill A. et al. 2008

Pantothenate kinase associated neurodegeneration (PKAN, NBIA type one, MIM 234200), formerly known as Hallervorden-Spatz syndrome

Early-onset form, rapidly progressive, development delay, dystonia, spasticity. Later-onset form, slowly progressive, dystonia, spasmodic dysphonia, dysarthria, parkinsonism, spasticity, neuropsychiatric symptoms.



T2 gradient echo



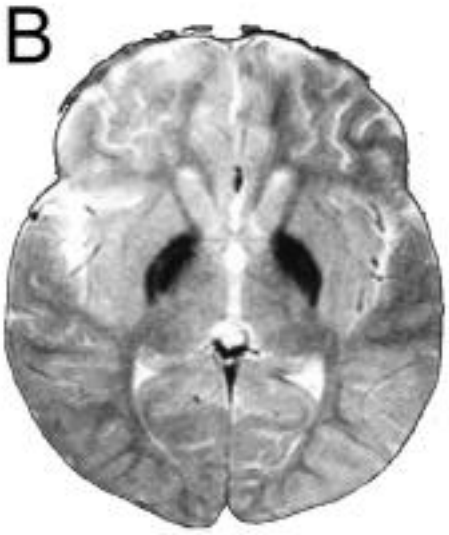
Fast spin echo

- Hypointensity of globus pallidus and substantia nigra
- “Eye of the tiger sign”
- A minority of PKAN cases with involvement of the dentate nuclei

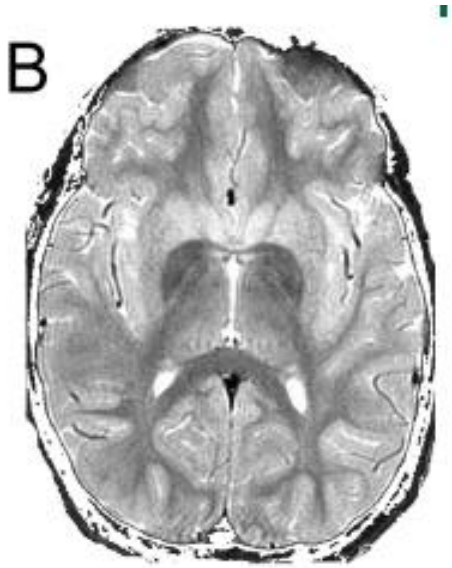
McNeill A. et al. Neurology 2008

Phospholipase A2-associated neurodegeneration (PLAN), caused by mutations in PLA2G6 gene.

Dystonia-parkinsonism, spasticity, cognitive and psychiatric features. Infantile neuroaxonal dystrophy (INAD), childhood onset of devastating neurodevelopmental regression.



T2 gradient echo



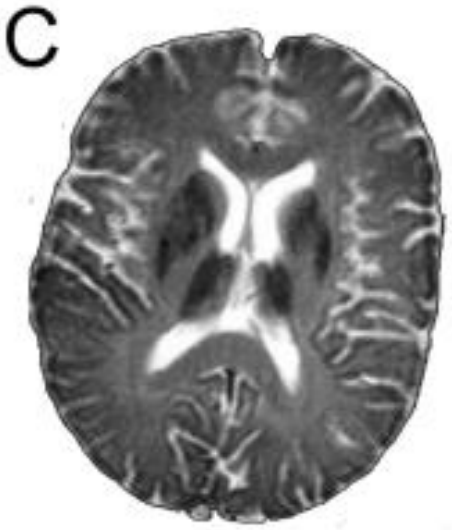
Fast spin echo

- Hypointensity of globus pallidus and substantia nigra
- Dentate hypointensity only on T2*

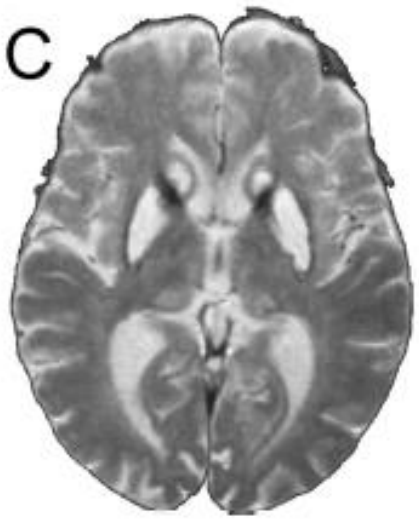
McNeill A. et al. Neurology 2008

Neuroferritinopathy (FTL, NBIA type two, hereditary ferritinopathy, MIM 606159)

Dominantly-inherited syndrome caused by mutations in the gene encoding ferritin light chain protein. Characterized by chorea, dystonia, parkinsonism, cognitive decline and low serum ferritin that typically presents in mid-life



T2 gradient echo



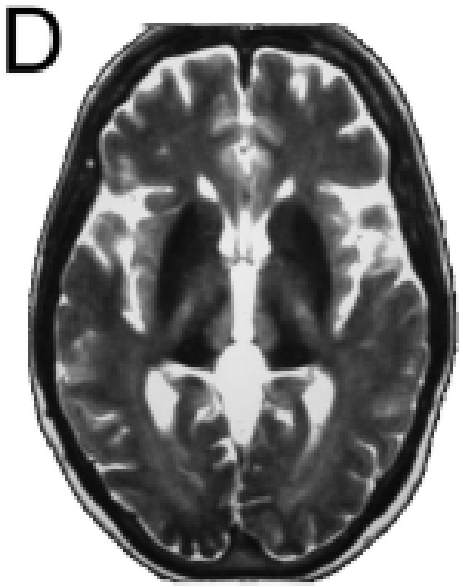
Fast spin echo

- In T2*, hypointensity of cerebral cortex, globus pallidus, putamen, caudate, SN, thalamus.
- In FSE, hyperintensity of caudates, globus pallidus and putamen, due to cavitation

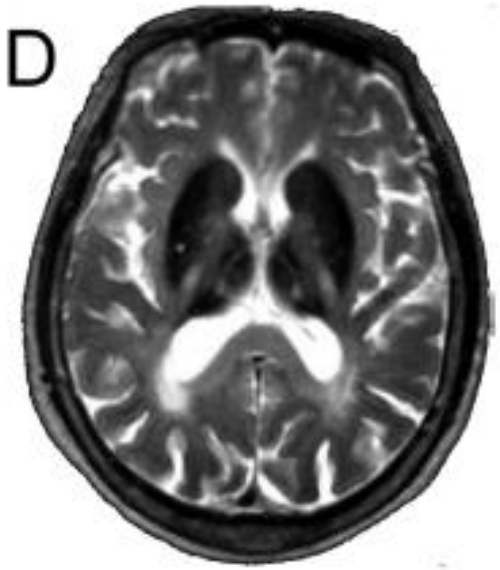
McNeill A. et al. Neurology 2008

Aceruloplasminemia (aCp, MIM 604290)

Autosomal recessive ceruloplasmin deficiency resulting in iron deposition in the reticuloendothelial system and brain, presenting with diabetes and extrapyramidal movement disorder in adult life



T2 gradient echo



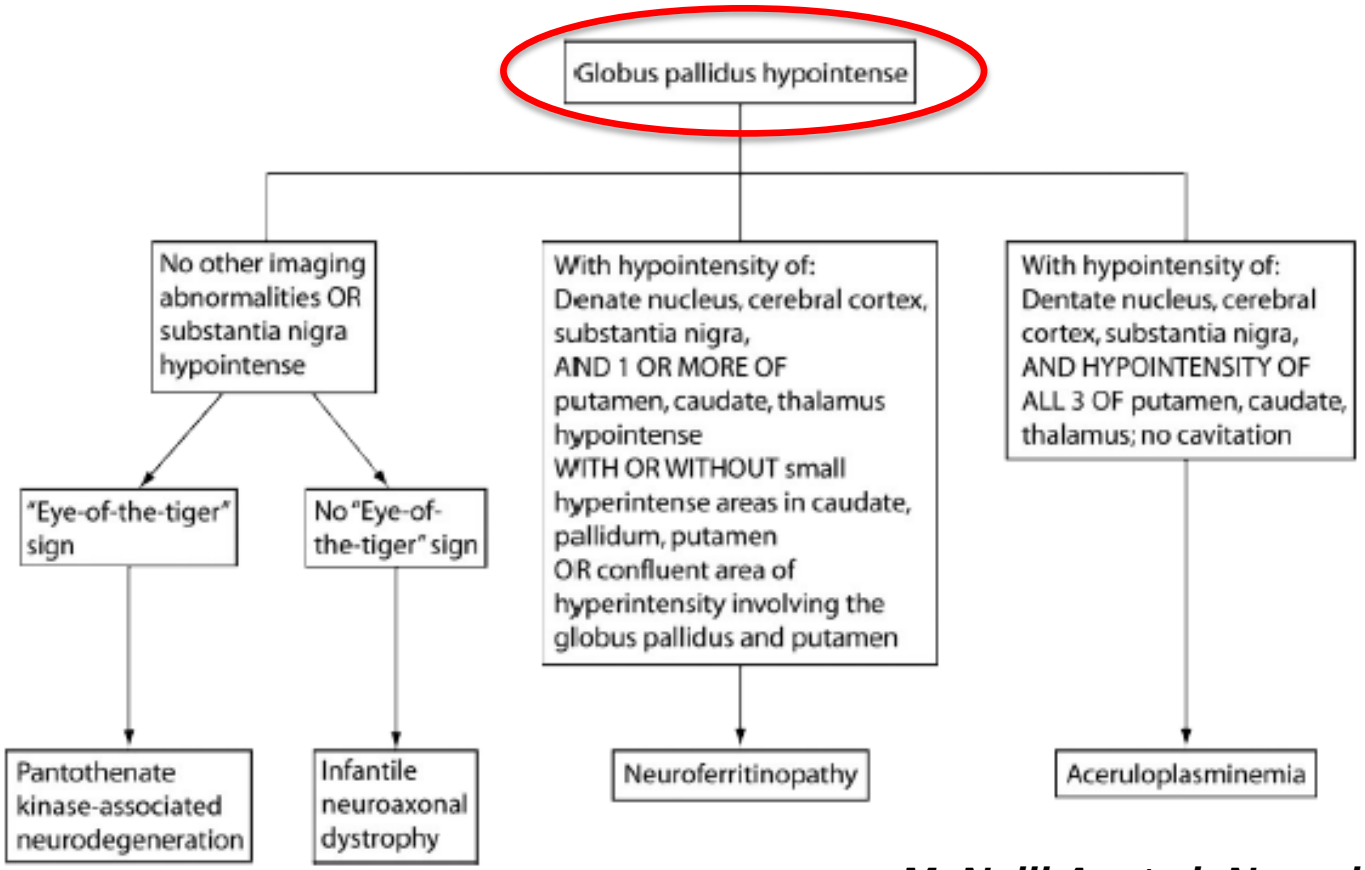
Fast spin echo

- Hypointensity of cerebral cortex, globus pallidus, putamen, caudate, SN, thalamus
- No cavitation

McNeill A. et al. Neurology 2008

T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation

Figure 4 Neuroimaging features distinguishing subtypes of neurodegeneration with brain iron accumulation



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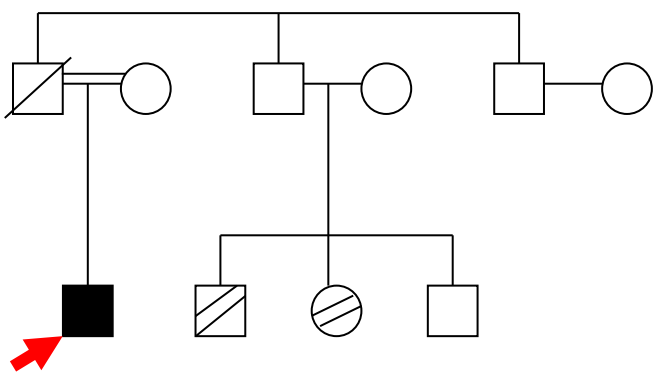
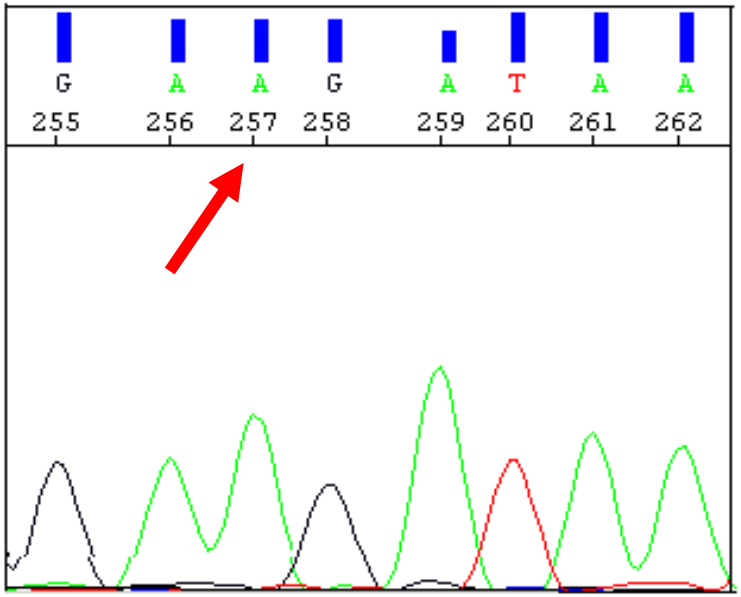
Aceruloplasminemia: variants



Aceruloplasminemia

Aceruloplasminemia with psychiatric disoders

Asyntomatic Aceruloplasminemia

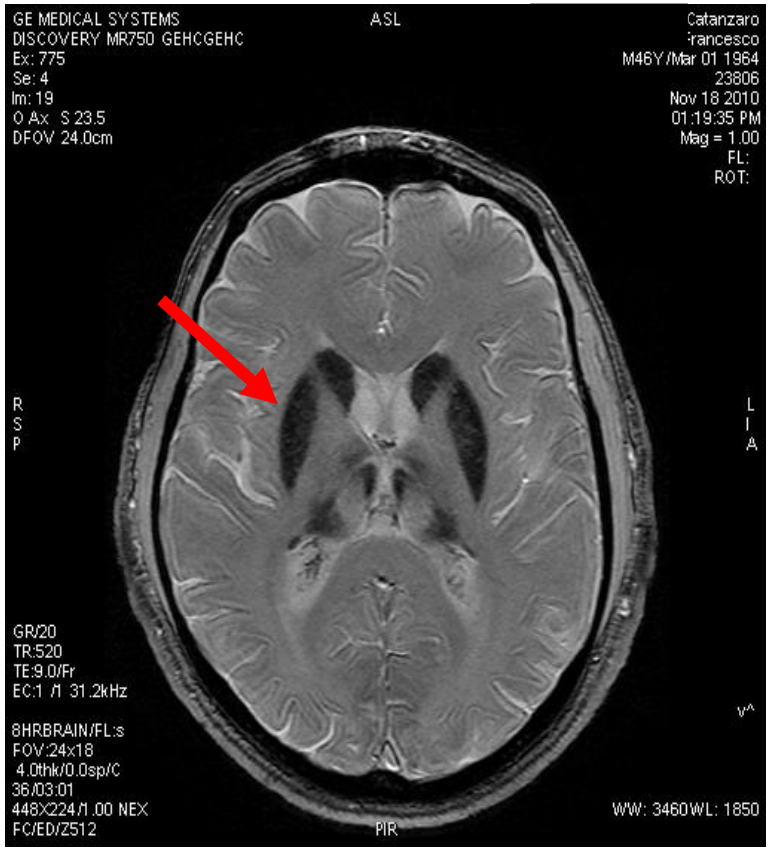


Proband

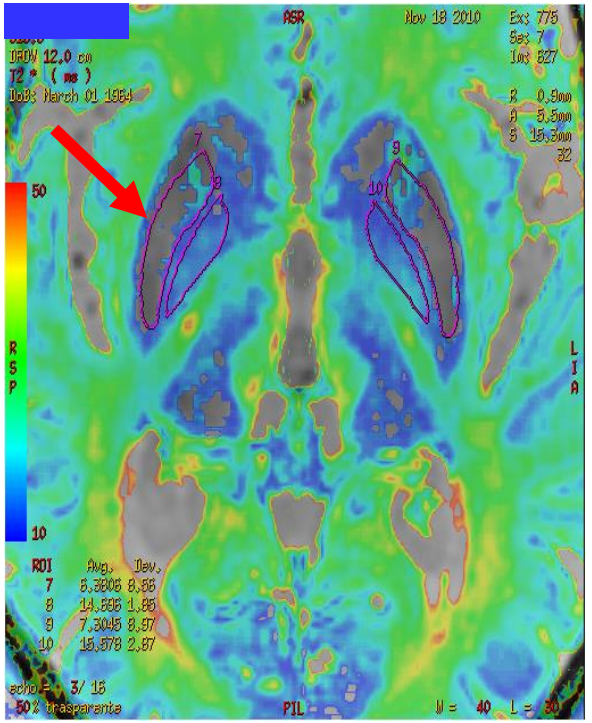
Homozygous mutation (IVS6+G ➔A) in CP gene

Aceruloplasminemia: variants

3T MRI



Gradient EchoT2 (T2*)



Iron Assessment

ASSENTE COINVOLGIMENTO NUCLEO PALLIDO

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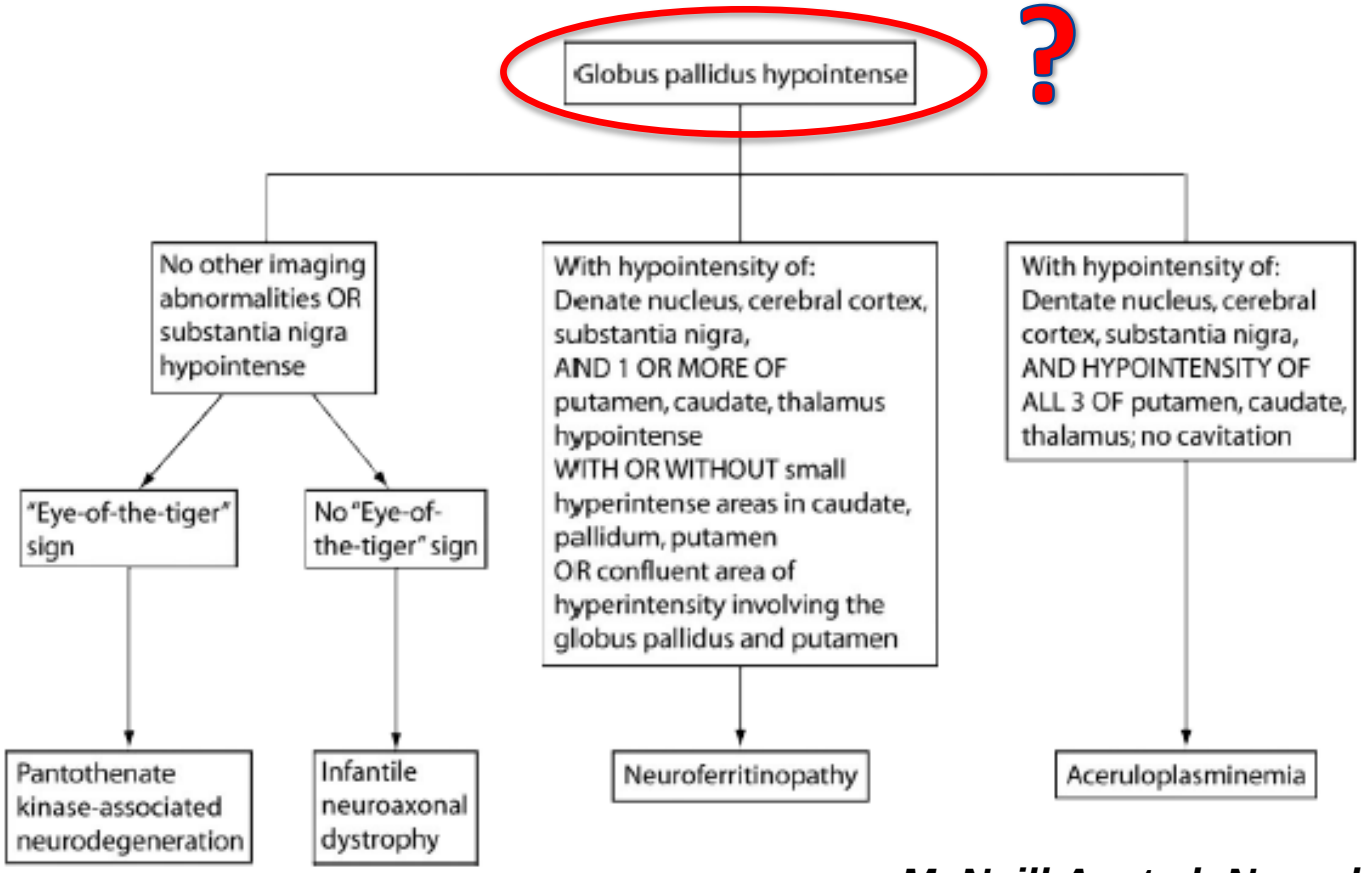
Figure 4 Neuroimaging features distinguishing subtypes of neurodegeneration with brain iron accumulation



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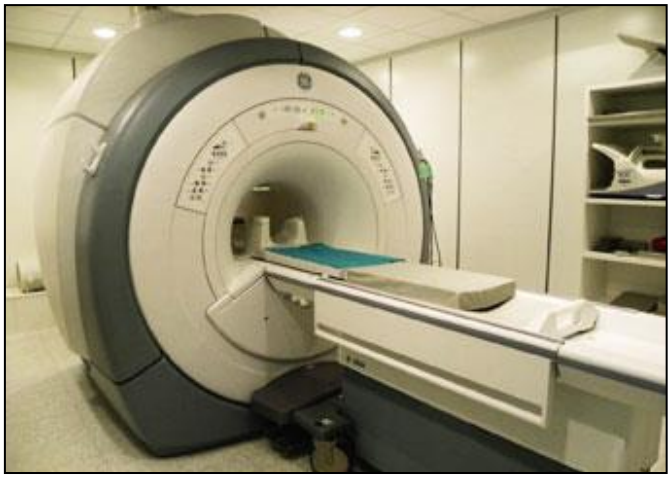
Conclusioni

- Il ferro è coinvolto in un numero molto elevato di cruciali processi cellulari
- Con l'invecchiamento, il ferro si accumula in alcune selettive aree cerebrali
- L'alterazione della normale omeostasi del ferro può indurre danno cellulare con meccanismi di stress ossidativo
- La Risonanza magnetica nucleare consente uno studio accurato degli accumuli di ferro sia in condizioni fisiologiche che in alcune patologie neurodegenerative

ACKNOWLEDGEMENTS



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IRON IMAGING

GRAZIE PER L'ATTENZIONE!