NEURITE DAMAGE IN RELAPSING-REMITTING AND SECONDARY-PROGRESSIVE MULTIPLE SCLEROSIS

Barbara Spanò [1], G. Giulietti [1], V. Pisani [2], M. Cercignani [1,3], M. Morreale [4,5], E. Tuzzi [1], U. Nocentini [2,6], A. Francia [5], C. Caltagirone [6,7], Marco Bozzali [1].

[1] Neuroimaging Laboratory, Santa Lucia Foundation, IRCCS, Rome, Italy --- [2] Neurology and Neurorehabilitation Unit, Santa Lucia Foundation, IRCCS, Rome, Italy. --- [3] CISC, Brighton & Sussex Medical School, Brighton, United Kingdom. [4] Neurovascular Diagnosis Unit, Dep. of Medical and Surgical Sciences and Biotechnology – Section of Neurology, Sapienza, University of Rome, Rome, Italy. --- [5] MS Center, Dep. of Neurology and Psychiatry, Sapienza, University of Rome, Rome, Italy. [6] Dep. of Neuroscience, University of Rome "Tor Vergata", Rome, Italy. --- [7] Dep. of Clinical and Behavioural Neurology, Santa Lucia Foundation, IRCCS, Rome, Italy.

b.spano@hsantalucia.it

Introduction:

DTI provides markers of loss of WM integrity in MS. However, DTI is known to be less sensitive to GM damage. NODDI[1] is a new diffusion MRI technique that can be used to analyse the microstructure of dendrites and axons (neurites), providing more specific markers than standard indices from DTI. Aim was to apply NODDI to assess, for the first time, neurite damage both in NAWM and GM of RRMS and SPMS patients.

Methods:

Participant characteristics:

	HC	RRMS	SPMS
N	20	20	15
Age	44.5 (11.7)	42.9 (6.1)	50.7 (7.2)
Sex (F/M)	12/8	12/8	7/8
DD (years)	-	10.3 (8.3)	19.9 (9.5)
EDSS	-	2.0 (1.0-4.0)	5.0 (3.5 - 6.5)
PASAT	46.5 (10.3)	48.0 (9.3)	27.1 (11.8)
T2L volume (mL)	-	6.0 (6.5)	27.0 (10.3)

For Age, DD, PASAT and T2L volume, mean (SD) are shown.
For EDSS, median (range) are shown.

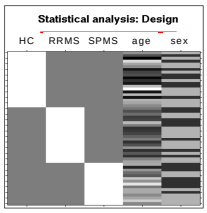
MR acquisition @ 3T (Philips Achieva):

- **FLAIR & Dual-echo scans** for T2L identification and outline
- **multi-shell DWI data** optimised for NODDI[1]

MRI DATA analysis:

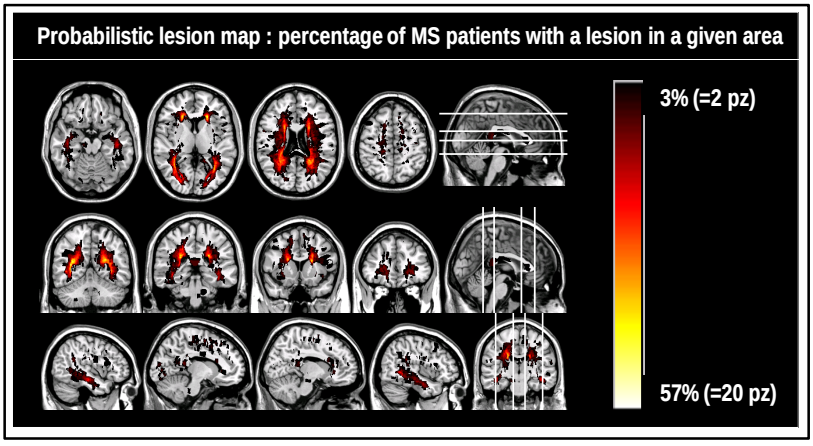
- Masks of T2L were computed for MS patients (using Jim 4.0)[2] and warped into standard space.
- A group probabilistic T2L mask was created by normalising every patient lesion mask to MNI space and averaging. The resulting map was binarized and used to confine the statistical analysis in the parenchyma excluding the areas where the patients had lesions.
- DWI data were analysed using the Accelerated Microstructure Imaging via Convex Optimization (AMICO)[4] toolbox, which is a linear implementation of the NODDI model[2]. Maps of NDI and ODI were generated and warped into standard space.

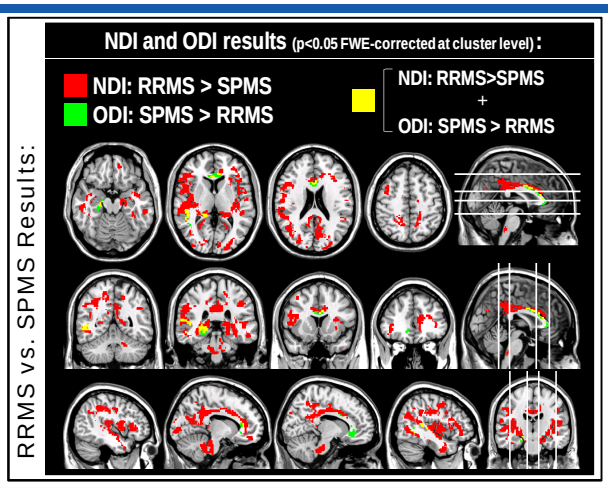
MRI Statistical Analysis:

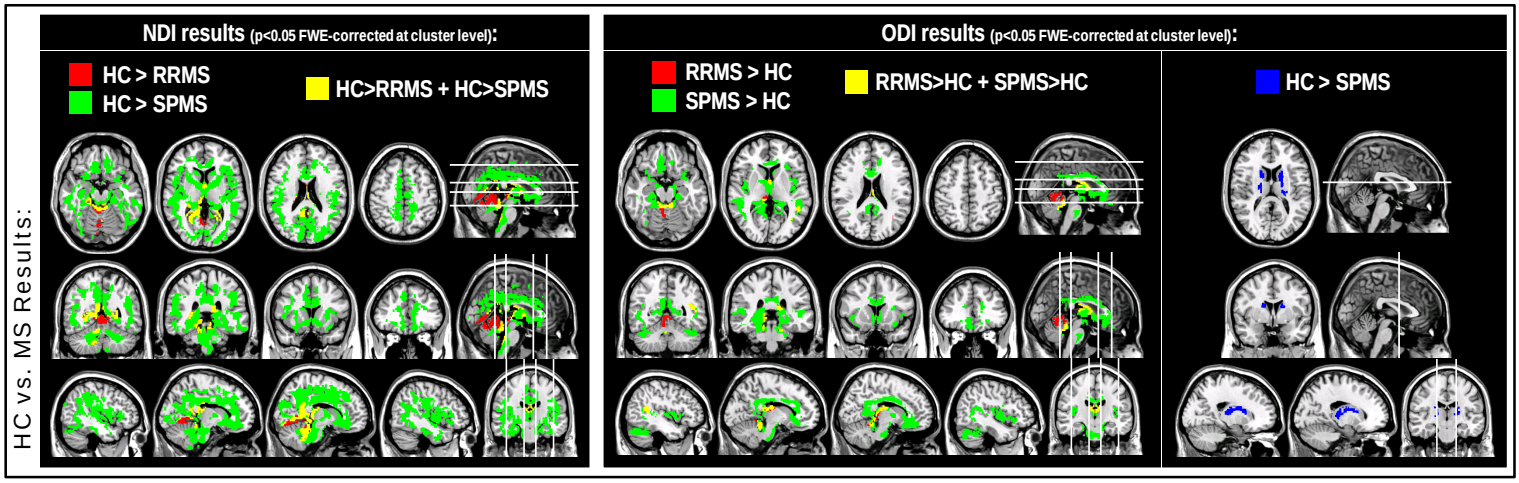


For both NDI and ODI, voxel-wise between-group comparison was carried out in SPM8[3], adjusting for age and sex.

Results:







Discussion and Conclusions:

We demonstrate, for the first time, the application of multi-shell NODDI in RRMS and SPMS.
Our findings suggest widespread loss of neurite integrity in both NAWM and GM in both RRMS and SPMS compared to HC. NODDI analysis further suggests a loss of fibre coherences (i.e. an increase of dispersion) in NAWM and GM, which cannot be directly detected with DTI metrics. The low ODI values found in SPMS compared to HC can be due to selective degeneration of a single fibre population, or to the severe loss of axonal tissue, which impairs the accurate estimation of dispersion.
Furthermore NODDI provided additional value by disentangling neurite density and dispersion in MS pathology, particularly in regions where intra-voxel fibre orientation coherence is naturally low.
NODDI opens a new perspective for clarifying in a more direct way the contribution of both WM and GM demyelination in MS.

Abbreviations:

DD= disease duration
DTI= diffusion tensor imaging
DWI= diffusion weighted imaging
EDSS= expanded disability status scale
F = female
GM= gray matter
HC= healthy controls
M= male
MS= multiple sclerosis
NDI= neurite density index
NODDI= neurite orientation and dispersion and density Imaging
NAWM= normal appearing WM
ODI= orientation dispersion index
PASAT= paced auditory serial addition test
RRMS= relapsing-remitting MS
SD= standard deviation
SPMS= secondary-progressive MS
T2L= T2-weighted visible lesions
WM= white matter

References:

[1] Zhang, et al. 2012 ,NeuroImage;61:1000-16. [2] www.xinapse.com
[3] Daducci, et al. 2015,Neuroimage;105:32-44. [4] www.fil.ion.ucl.ac.uk/spm