Multiple MRI measures to predict disability in MS patients: which works best?

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INTRODUCTION

Motor deficit plays a major role in global clinical disability in multiple sclerosis (MS). Despite its high prevalence and detrimental effects on patients' daily life activities[1], its structural substrates have yet to be fully elucidated[2].

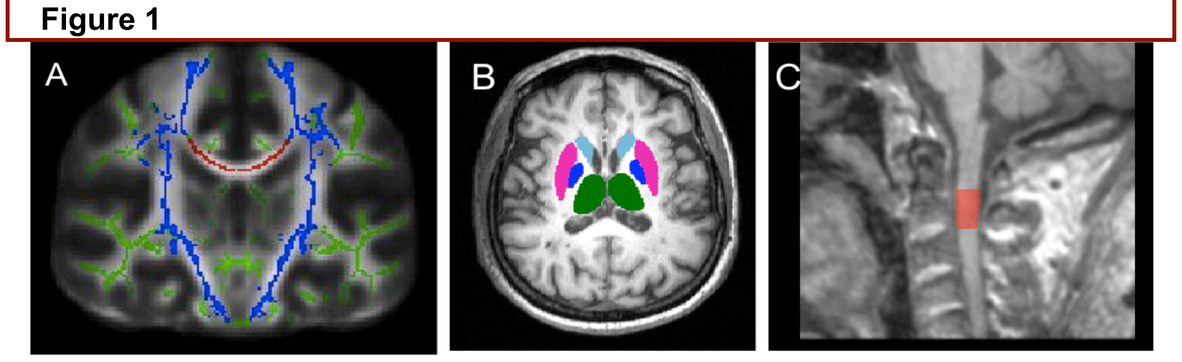
OBJECTIVE

- To assess the influence of structural damage in different sites of the motor system in a cross-sectional evaluation on a cohort of patients with MS.
- To longitudinally identify which magnetic resonance imaging (MRI) measure can predict the evolution of disability in the following years.

METHODS

We consecutively collected clinical and MRI data of 100 patients with MS. Follow-up (FU) clinical evaluation (median FU: 3, range 1-6 years) was performed on 92 MS patients from the baseline cohort. Clinical assessment at baseline and FU included 9-hole peg test (9HPT), 25-foot walking test (25FWT) and Expanded Disability Status Scale (EDSS).
MRI examination at baseline was performed with a 3T Siemens Verio Magnetom and included the following brain sequences: dual-echo fast spin-echo, 3D T1-weighted, Diffusion tensor imaging (DTI).
We then calculated the following MRI measures: corticospinal tract (CST) and corpus callosum (CC) fractional anisotropy (FA); deep grey matter (DGM) normalized volumes as thalamus (ThV), caudate (CaV), putamen (PuV), and pallidum (PaV); total and infratentorial lesion load (LL, LLit respectively); normalized spine volume at C2-C3 level (SV) (Figure 1).
Volumetric measures and maps of FA were obtained by using FIRST and TBSS, part of FSL(http://fsl.fmrib.ox.ac.uk/fsl/) respectively. LL and SV were determined using Jim 7.0 (Xinapse Systems, Northants, England).
We carried out a partial correlation of the aforementioned MRI measures with baseline scores and we applied a generalized linear model (GLM) weighted for length of FU and relapses, to identify MRI variables predictive of future disability.

Figure 1



A. Skeleton maps of CST (dark blu) and CC (red); **B**. DGM structures segemented using FIRST: thalamus (green), caudatus (light blu), putamen (pink), pallidum (dark blu); **C**. Representation of the outline of the cord segmented at C2 level.

RESULTS

Demographic, clinical and MRI data of study cohort are shown in **TABLE 1 (below)**.

TABLE 1

	Baseline N=100	Follow Up N=92	p
Gender Female/Male	74/26	67/25	--
Age, years	36,7 (8,3)	40,4 (8,2)	--
Clinical Phenotype CIS/RR/SP	5/85/10	0/79/13	--
Time since first symptoms, years	6,7 (6,8)	10,6 (6,8)	--
EDSS score- median [range]	2 [0-6]	3 [1-6.5]	<0,001
9HPT DH, sec	20,1 (6,1)	20,9 (10,2)	=0,23
9HPT NDH, sec	21,8 (7,8)	22,1 (7,0)	<0,05
25FWT, sec	7,1 (5,3)	15,1 (39,8)	<0,001
MRI measures			
Cortico-spinal tract FA	0,63 (0,02)	--	na
Corpus callosum FA	0,72 (0,05)	--	na
Thalamus Volume, cm^3	9,37 (0,93)	--	na
Caudate Volume, cm^3	4,51 (0,51)	--	na
Putamen Volume, cm^3	6,01 (0,66)	--	na
Pallidum Volume, cm^3	2,18 (0,23)	--	na
Total Lesion Load, mL	4,92 (5,26)	--	na
Infratentorial Lesion Load, mL	0,30 (0,35)	--	na
Normalized Spine Volume, cm^3	60,14 (9,46)	--	na

Cross-sectional analyses revealed significant association between clinical values and MRI measures at baseline, listed in **TABLE 2 (below)** as *r coefficient.*

TABLE 2

	Clinical Measures			
	EDSS	9HPT DH	9HPT NDH	25FWT
MRI Measures				
Corticospinal tract FA	0,082	0,085	0,013	-0,189
Corpus callosum FA	-0,156	**-0,348#**	**-0,394#**	**-0,410#**
Thalamus Volume	-0,138	**-0,327#**	**-0,374#**	**-0,227***
Caudate Volume	-0,004	-0,169	**-0,223***	-0,136
Putamen Volume	-0,065	**-0,286***	**-0,242***	-0,118
Pallidum Volume	-0,008	**-0,243***	0,212	-0,007
Total Lesion Load	0,110	**0,297***	**0,375#**	0,172
Infratentorial Lesion Load	**0,331#**	**0,340#**	**0,439#**	**0,393#**
Normalized Spine Volume	**-0,35#**	**-0,348#**	**-0,294***	-0,163

***** $p \leq 0,05$; **#** $p < 0,001$
Partial correlation corrected for age and gender
All DGM volumes are calculated as the mean of the right and left sides and normalized.
CST FA is calculated as the mean of the right and left side.

At FU evaluation 40% of patients showed worsening in at least one clinical measure (worsening greater than 20% at 9HPT and T25FWT, or greater than 1 point at EDSS). Small SV at baseline, low corticospinal tract CST and corpus callosum FA, as an higher amount of infratentorial lesion load were the best predictors of disability assessed at FU **(Table 3).**

TABLE 3

Outcome Clinical Measures (FU)	MRI Measures (Baseline)	Beta Coefficient	Confidence Interval, 95%		p
EDSS	LLit	1,35	0,51	2,17	0,001
	CST_FA	-0,009	-0,017	-0,001	0,03
9HPT_DH	SV	-0,16	-0,24	-0,13	0,03
	CC_FA	-0,104	-0,19	-0,10	0,03
9HPT_NDH	SV	-0,16	-0,31	-0,19	0,02
25FWT	SV	-0,12	-0,18	- 0,06	<0,001
	CST_FA	-0,03	-0,57	-0,007	0,01

Generalized Linear Model corrected for Annualized Relapse Rate (ARR) and length of FU in years
See text for abbreviation

CONCLUSIONS

•The effects of MS pathology on motor abilities likely depends on the interaction among structural damage and malfunctioning in the different components of the motor pathway. Our data confirm previous finding, where ultrastructural damage of the corpus callosum, spinal cord atrophy and infratentorial lesion burden seem to play a major role in disability of MS patients[3]. Moreover we demonstrated a link between thalamic atrophy and motor dysfunction in term of manual dexterity and walking performance.

•MRI measurers that predict worsening in future disability are those more linked with motor function as infratentorial lesion burden, spinal cord, corpus callosum and corticospinal tract. Among these, spinal cord seems to have a crucial role in counting for future motor disability. Thus this finding can potentially drive pharmacological and rehabilitative strategies in the next future.

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