Comparison of Corpus Callosum Area and whole Brain Volume as markers of brain atrophy in Multiple Sclerosis

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INTRODUCTION

Measures of brain volume (BV) loss are currently used as valid methods for evaluating atrophy in MS clinical trials alongside MRI measures of disease activity. However, the currently available methods for measuring brain atrophy based on BV show poor sensitivity and high variability both among and within individuals, a characteristic that limits their effectiveness when applied to clinical trials, and prevents their use for the evaluation of brain atrophy at individual level.

Measures of corpus callosum (CC) have been proposed as alternative markers of brain atrophy, but their effectiveness and relation with BV still need to be defined. The purpose of this study is to compare the intra-individual variations of normalized brain volume (NBV) with corpus callosum area (CCA) as markers of brain atrophy in MS, to assess their correlation with clinical parameters and to evaluate their relative effectiveness as outcome measures for clinical trials.

METHODS

Patients (n=40) were selected from those attending the local Multiple Sclerosis Regional Center of the Careggi University Hospital. Inclusion and exclusion criteria: a) diagnosis of MS (McDonald 2010); b) relapsing-remitting (RR) course; c) availability of an MR scan within the first year from the diagnosis (from 1 to 12 months after the diagnosis; baseline) and five years after the first scan (51-69 months after the first scan); d) no evidence of CNS comorbidity beside MS; f) age, 18-55. To take into account the fact that some patients progressed several points in the EDSS scale during the period of observation, and that a difference in the EDSS score of two steps can be considered a strong index of clinical change, the change in EDSS was categorized with the following score: 1, for patients who did not progress during the period of observation; 2, for patients who progressed up to two steps (1 whole point) in the EDSS scale between 0 and 5.0 (and one step above 5.5); 3, for each further whole point of progression in the scale.

All the MR scans were performed on a 1.5 Tesla MRI machine (Philips, Gyroscan). Corpus callosum area (CCA) was measured with a semiautomatic method using the software MIPAV on sagittal T2 SE weighted scans (TR/TE: 2500/100; slice thickness: 5 mm), and calculated as the mean of corpus callosum area in the midsagittal slice and the two adjacent slice. The operator was masked to patients data through a custom script. Brain volume was evaluated with SIENA and SIENAX software, tools provided by the FSL library, on axial T1 weighted magnetization transfer contrast (MTC) scans (TR/TE: 500/15; slice thickness: 4 mm). SIENA was used in order to estimate the percentage brain volume change longitudinally, while SIENAX was used to estimate brain tissue volume, normalized for subject head size, in the cross sectional analysis.

RESULTS

The demographic, clinical and MRI characteristics of the patients at baseline are summarized in Table 1. The results of the measurements of CCA and of NBV are summarized in table 2 and fig. 1A and 1B. Correlation between t_1 and t_5 was high for CCA and low for NBV (Table 3; fig. 1C and 1D). Absolute and percentage mean change of CCA and of NBV within 5 years is reported in Table 3; the percent change of CCA was greater than NBV change ($p < 0.05$). Association of CCA and of NBV with a number of clinical and MRI variables was tested with a multivariate analysis. Greater disability progression and an high lesion load were associated with increased odds (respectively 3.34; 95%CI 0.64 -19.39; 1.24; 95%CI 1.1; 1.48) of a greater percent variation of CC area, but not of BV (Table 4). Using these data, power comparison of the two biomarker as outcome measures in clinical trials was carried out, indicating that using CCA would yield approximately a 50% reduction of the sample size (Table 5).

CONCLUSIONS

A wider intra-individual variability of NBV compared with CCA is indicated by the smaller internal correlation coefficient between the values obtained in the t_1 and the t_5 MRIs. Among the factors that may account for the wider intra-individual variability of BV there are biological factors, technical factors and factors related to the software used for the postprocessing. The results in our sample suggest that the factors that affect brain volume may have less impact on CCA.

In conclusion, CC area seems more sensitive and reliable than BV as an atrophy marker. CC area changes over time also seem more closely associated to disability changes. CCA could therefore be used as a biomarker in clinical MS practice as well as in clinical trials investigating atrophy, providing greater reliability at the intra-individual level and lowering sample size required in longitudinal research when used as an outcome measured.

Table 1 – Clinical, radiologic and demographic characteristics of the patients

N	Males	12
	Females	28
	Total	40
Age (years)	Mean (SD)	33.7 (± 9.71)
EDSS	Median (interquartile range)	1.0 (0.0; 1.5)
Disease duration (months)	Mean (SD)	49 (± 59.2)
Number of relapses	Median (Interquartile range)	1 (1; 2)
Lesion load (cm^3)	Mean (SD)	5.33 (± 4.02)

Table 2 – Cross sectional analysis of CCA and of NBV

MR	Corpus callosum area (CCA) mm^2 Mean	Median	St. Dev.	CV
t_1 MR	551.5	558.7	110.66	0.21
t_5 MR	496.1	494.3	109.38	0.22

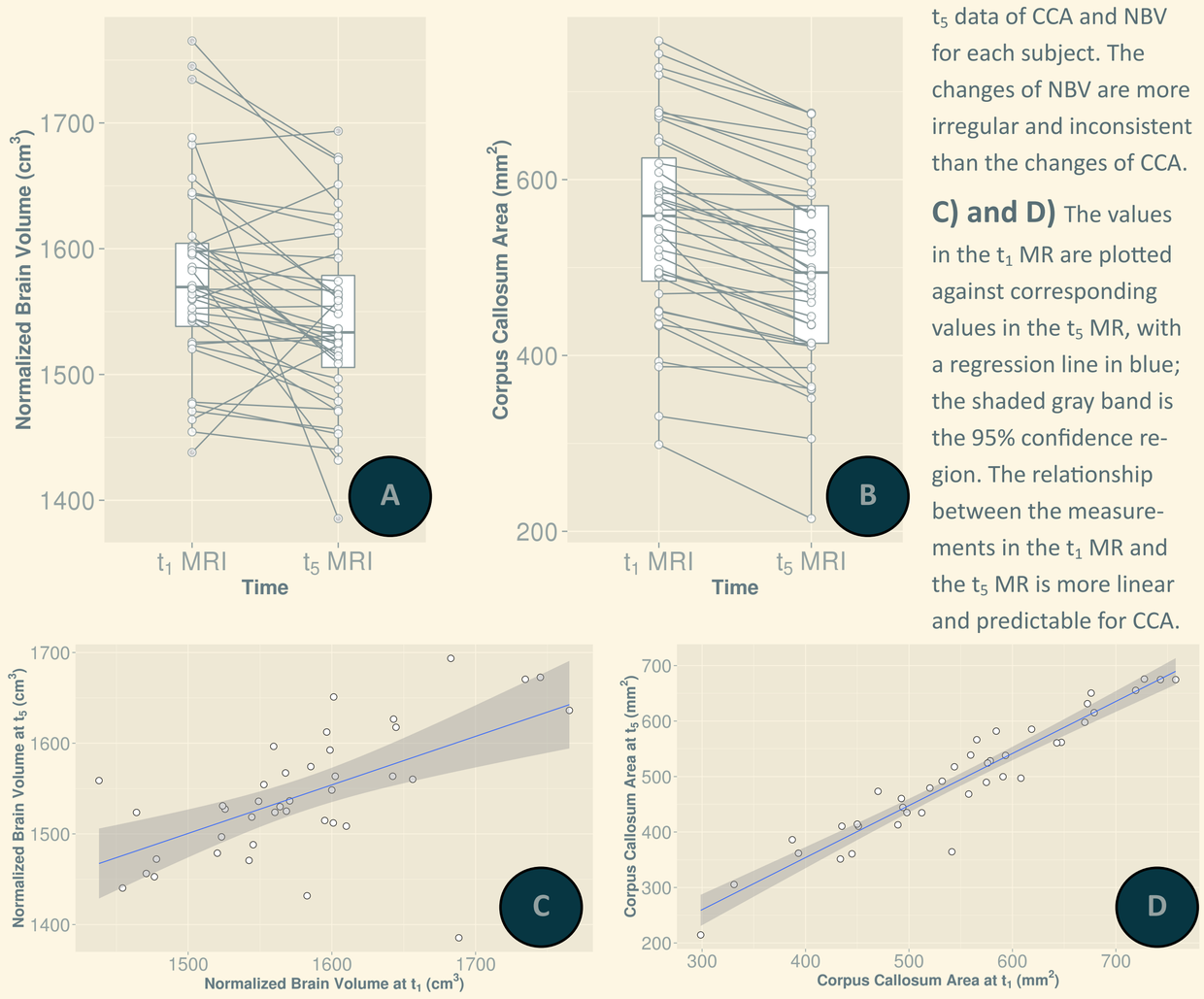
MR	Normalized Brain Volume (NBV) cm^3 Mean	Median	St. Dev.	CV
t_1 MR	1579.38	1579.38	77.04	0.05
t_5 MR	1543.00	1533.46	69.81	0.05

Table 3 – Analysis of CCA and NBV longitudinal changes over t_1-t_5

		Change t_1-t_5 Mean	Median	1st Qu.	3rd Qu.	St. Dev.	CV	r	R^2
CCA	Absolute (mm^2)	-55.43	-51.7	-82.24	-32.04	34.96	0.631	0.95	0.91
	Percent (%)	-10.25	-8.99	-13.62	-6-44	6.91	0.674		
NBV	Absolute* (cm^3)	-36.38 *	-26.83 *	-66.01 *	-4.48 *	66.74 *	1.83 *	0.59	0.35
	Percent (%)	-1.98	-1.71	-2.86	-1.17	1.94	0.981		

* Absolute change was calculated with approximation using SIENAX data.

Fig 1 – Comparison of changes in CCA and of NBV over t_1-t_5



A) and B) Matched t_1-t_5 data of CCA and NBV for each subject. The changes of NBV are more irregular and inconsistent than the changes of CCA.

C) and D) The values in the t_1 MR are plotted against corresponding values in the t_5 MR, with a regression line in blue; the shaded gray band is the 95% confidence region. The relationship between the measurements in the t_1 MR and the t_5 MR is more linear and predictable for CCA.

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A

Variable	OR	95% CI	p
Disability progression (1-2)	3.75	0.69; 22.55	0.131
Disability progression (2-3)	**14.95**	**2.6; 105.73**	**0.004**
New lesion volume	1.25	0.71 ; 2.33	0.444
New lesion number	1.10	0.79; 1.55	0.563
Baseline total lesion volume	**1.25**	**1.1; 1.48**	**0.004**
Disease duration	1.01	1; 1.02	0.187
Clinical relapses	1	0.78; 1.26	0.99
Age	0.94	0.86; 1.03	0.192
Gender	1.04	0.23; 4.72	0.956

B

Variable	OR	95% CI	p
Disability progression (1-2)	1.92	0.38; 10.27	0.432
Disability progression (2-3)	0.69	0.13; 3.61	0.663
New lesion volume	1.03	0.57 ; 2.1	0.928
New lesion number	1.06	0.74; 1.49	0.732
Baseline total lesion volume	**1.08**	**1; 1.18**	**0.060**
Disease duration	1.00	0.98; 1.01	0.666
Clinical relapses	1.04	0.82; 1.33	0.72
Age	1.00	0.92; 1.08	0.91
Gender	1.17	0.29; 4.81	0.83

Table 4 - Association with CCA (a) or NBV (b) of the following variables (multivariate analysis)

Sample Size (n) required...	CCA	BV
...to detect a 30% difference in atrophy rate	79	163
...to detect a 40% difference in atrophy rate	44	92
...to detect a 50% difference in atrophy rate	28	59

Table 5 — Sample size estimate for a clinical trial aiming to prevent brain atrophy measured as percent reduction of CCA or BV (α= 0.05; β= 0.80).