Measuring Brain Volume in Patients with Multiple Sclerosis: A Comparison of Three Common Approaches

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Synopsis

We compared three common approaches to calculating brain volume in MS: Collins' BICCR, Fisher's BPF and Losseff's ventricular/brain ratio and found that all three were highly intercorrelated - both in patients with RR and SP MS (*r*'s = 0.92 to 0.99). The addition of T_1 data to the T_2/PD data used in calculating these measures did not improve correlations with either EDSS or age. Surprisingly, the Losseff measure, which is much simpler to calculate than either the BICCR or the BPF, correlated as well - or better - with EDSS than these two more computationally-expensive measures of brain volume.

Introduction

Changes in brain volume have been shown to be associated with multiple sclerosis (**MS**) and have been measured using a number of different techniques. The present study is aimed at comparing three commonly-used such techniques in a sample of patients with either relapsing-remitting (**RR**) or secondary-progressive (**SP**) MS. These included: *(i)* Collins' **BICCR** (brain to intra-cranial capacity ratio), which is defined as the ratio of brain volume to that of the intra-cranial cavity **[1]**; *(ii)* Fisher's **BPF** (brain parenchymal fraction), which is defined using a similar ratio but excludes extra-cerebral CSF that lies outside of the sulci **[2]**; and *(iii)* Losseff's approach, which uses only four 5.5-mm-thick peri-ventricular slices in order to calculate a metric that is based on the ratio of brain volume to the sum of brain volume and ventricular volume (all within these four slices) **[3]**.

Methods (Data presented as mean (standard deviation)[range].)

Subjects: Measures of cerebral brain volume were studied in 44 RR-MS patients {age: 35.7 yrs (9.3)[14-56]; disease duration: 7.9 yrs (7.0)[0.3-30.8]; EDSS: 2.2 (1.2)[0-5]} and 14 SP-MS patients {age: 43.0 (10.7)[27-56]; disease duration: 15.7 (8.5)[3-36]; EDSS: 6.6 (1.9)[3.5-9.5]}. Using a z-transformation, these patient data were standardized relative to similar findings in 45 normal controls (NC) subjects {age: 34.1 (9.4)[20-59]}.

Image Acquisition: MRI was performed on a 1.5T, Philips Gyroscan ACS II using a body coil transmitter and a quadrature head-coil receiver. Fifty 3-mm thick, contiguous proton-density-weighted (**PD**) and T_2-weighted images were acquired parallel to the AC-PC line using a dual turbo spin-echo sequence (TR 2075 ms, TE 30/90 ms, 256×256 matrix, 250 mm field of view). T_1-weighted images were acquired with the same matrix using a 3D gradient-echo sequence (TR 35 ms, TE 10.2 ms, 40°excitation angle).

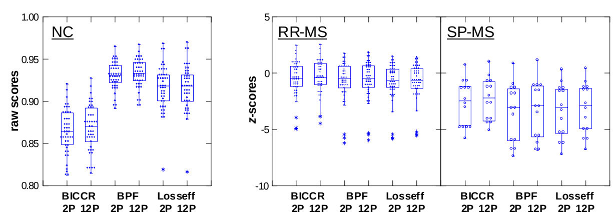
Image Processing: Each MRI volume was corrected for image intensity inhomogeneity **[4]**. The T_2/PD image pair was registered to the T_1 volume using mutual information **[5]**. The T_1 volume was registered into stereotaxic space to facilitate model-based structure segmentation. The resampled image volumes were input to a Bayesian tissue classification algorithm to identify grey matter (**GM**), white matter (**WM**), cerebrospinal fluid (**CSF**), and lesions (**L**) using either T_1,T_2, and PD volumes (yielding the measures subscripted by $_{12P}$ below) or only T2 and PD volumes (yielding the measures subscripted by $_{2P}$ below). Morphological operators were applied to the classified data to identify the intra-cranial space and create an intra-cranial mask (**ICM**).

Brain volumes: BICCR was defined as (GM+WM+L)/(GM+WM+L+CSF) within the ICM. BPF was defined with a similar ratio, but in this case masks defined in stereotaxic space were used to eliminate extra-cerebral CSF outside of the sulci. The Losseff metric was defined with brain and ventricles that were automatically segmented in stereotaxic space and it was calculated based on four 5.5-mm-thick peri-ventricular slices.

Results

Brain volume Values: The three approaches to quantifying brain volume in the NC subjects yielded very different absolute values, as can be seen below in the table and in the box and whisker plots (which show the individual data points, quartiles, and outliers). When expressed as z-scores, the three approaches yielded a similar distribution of scores in both the RR and SP patient subgroups.

	NC Raw Scores (n=45)				RR-MS Z-Scores (n=44)				SP-MS Z-Scores (n=14)			
	Mean	StDev	Min	Max	Mean	StDev	Min	Max	Mean	StDev	Min	Max
$BICCR_{2P}$	0.868	0.028	0.815	0.927	-0.353	1.530	-4.473	2.538	-2.260	1.916	-5.054	1.026
$BICCR_{12P}$	0.865	0.026	0.812	0.920	-0.504	1.607	-4.971	2.483	-2.628	2.027	-5.791	0.740
BPF_{2P}	0.932	0.016	0.895	0.967	-0.656	1.777	-5.973	1.863	-3.205	2.545	-6.885	1.166
BPF_{12P}	0.930	0.016	0.891	0.965	-0.738	1.805	-6.203	1.770	-3.452	2.618	-7.372	0.871
$Losseff_{2P}$	0.917	0.027	0.816	0.970	-0.763	1.657	-5.515	1.439	-3.118	2.242	-6.752	0.460
$Losseff_{12P}$	0.917	0.026	0.819	0.968	-0.830	1.720	-5.805	1.501	-3.311	2.357	-7.183	0.343



Correlations: As shown in the Pearson correlation matrices below (which show *r*-values to the bottom-left, uncorrected *p*-values to the top-right), the six measures of brain volume yielded very high intercorrelations in both the RR- and SP-MS patient groups. As might be expected, the highest correlations were found amongst the two ways of calculating each of the three measures (i.e., T_2/PD vs. T_1,/T_2/PD calculations). Very high correlations were also found between the various BICCR and BPF approaches, with somewhat smaller (yet still very high) correlations found between these and the Losseff approach. Individuals' BICCR values seemed to be somewhat more related to their age and somewhat less related to their EDSS-measured clinical disability.

RR-MS	$BICCR_{2P}$	$BICCR_{12P}$	BPF_{2P}	BPF_{12P}	$Losseff_{2P}$	$Losseff_{12P}$	Age	EDSS
$BICCR_{2P}$	-	**<0.000001**	**<0.000001**	**<0.000001**	**<0.000001**	**<0.000001**	**0.042**	**0.009**
$BICCR_{12P}$	**0.995**	-	**<0.000001**	**<0.000001**	**<0.000001**	**<0.000001**	**0.034**	**0.010**
BPF_{2P}	**0.976**	**0.982**	-	**<0.000001**	**<0.000001**	**<0.000001**	0.076	**0.003**
BPF_{12P}	**0.968**	**0.978**	**0.998**	-	**<0.000001**	**<0.000001**	0.069	**0.003**
$Losseff_{2P}$	**0.927**	**0.936**	**0.970**	**0.972**	-	**<0.000001**	0.206	**0.003**
$Losseff_{12P}$	**0.919**	**0.930**	**0.966**	**0.970**	**0.999**	-	0.219	**0.003**
Age	**-0.308**	**-0.321**	-0.271	-0.276	-0.195	-0.189	-	0.185
EDSS	**-0.388**	**-0.386**	**-0.433**	**-0.433**	**-0.441**	**-0.438**	0.204	-

SP-MS	$BICCR_{2P}$	$BICCR_{12P}$	BPF_{2P}	BPF_{12P}	$Losseff_{2P}$	$Losseff_{12P}$	Age	EDSS
$BICCR_{2P}$	-	**<0.000001**	**<0.000001**	**<0.000001**	**0.000001**	**0.000001**	0.059	**0.013**
$BICCR_{12P}$	**0.998**	-	**<0.000001**	**<0.000001**	**0.000001**	**0.000001**	0.064	**0.012**
BPF_{2P}	**0.983**	**0.987**	-	**<0.000001**	**<0.000001**	**<0.000001**	0.071	**0.010**
BPF_{12P}	**0.982**	**0.986**	**0.999**	-	**<0.000001**	**<0.000001**	0.071	**0.011**
$Losseff_{2P}$	**0.936**	**0.933**	**0.945**	**0.946**	-	**<0.000001**	0.114	**0.009**
$Losseff_{12P}$	**0.935**	**0.934**	**0.946**	**0.948**	**0.999**	-	0.121	**0.010**
Age	-0.517	-0.507	-0.497	-0.496	-0.442	-0.434	-	0.799
EDSS	**-0.643**	**-0.649**	**-0.659**	**-0.655**	**-0.669**	**-0.665**	-0.075	-

Discussion

All of our brain volume metrics are highly intercorrelated, which is not surprising given that they are based on the same, similarly-segmented data. Nevertheless, slight differences in these measures are to be expected given that they vary in their *(i)* inclusion/exclusion of T_1 data in the segmentation process, *(ii)* definitions of the volume of interest (*i.e.*, whole brain vs 22-mm periventricular slab) and *(iii)* the inclusion/exclusion of extracerebral CSF. The high correlations between the two sets of calculations for each measure (*i.e.*, T_2/PD vs. T_1,/T_2/PD), as well as the fact that including T_1 data in the calculations does not increase the correlations with age or EDSS, suggest that the inclusion of T_1 data does not necessarily improve the calculation of brain volume. Surprisingly, the Losseff measure, which is relatively simple to calculate in comparison to either the BICCR or the BPF, correlates as well - or better - with EDSS than the two other, computationally more-expensive, measures of brain volume.

References

1. Collins *et al*. (2001) Annual Sympos on Inform Process in Med Imag. *2082*: 141-147. **2.** Fisher *et al*. (1999) Neurology. *52*: A352-3. **3.** Losseff *et al.* (1996) Brain. *119*(6): 2009-19. **4**. Sled *et al*. (1998) IEEE Trans Med Imaging. *17*: 87-97. **5**. Collins *et al*. (1994) J Comput Assist Tomogr. *18*(2):192-205.