Brain Parenchymal Fraction in Healthy Adults—A Systematic Review of the Literature

Mattias Vågberg¹ *, Gabriel Granåsen², Anders Svenningsson¹,3

¹ Department of Pharmacology and Clinical Neuroscience, Umeå University, Umeå, Sweden,
² Epidemiology and Global Health Unit, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden,
³ Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden

* mattias.vagberg@umu.se

Abstract

Brain atrophy is an important feature of many neurodegenerative disorders. It can be described in terms of change in the brain parenchymal fraction (BPF). In order to interpret the BPF in disease, knowledge on the BPF in healthy individuals is required. The aim of this study was to establish a normal range of values for the BPF of healthy individuals via a systematic review of the literature. The databases PubMed and Scopus were searched and 95 articles, including a total of 9269 individuals, were identified including the required data. We present values of BPF from healthy individuals stratified by age and post-processing method. The mean BPF correlated with mean age and there were significant differences in age-adjusted mean BPF between methods. This study contributes to increased knowledge about BPF in healthy individuals, which may assist in the interpretation of BPF in the setting of disease. We highlight the differences between post-processing methods and the need for a consensus gold standard.

Introduction

Pathological loss of brain parenchyma due to neurodegeneration, i.e. brain atrophy, is an important aspect of many diseases affecting the central nervous system (CNS), such as multiple sclerosis,[1] dementia [2] and Huntington’s disease [3]. It is of interest both in the clinical setting [4, 5] and in research and is frequently measured as an endpoint in studies of neurodegenerative diseases.

In order to lessen the impact of inter-individual variation in the amount of brain parenchyma, the volume of parenchyma can be normalized to the size of the intracranial cavity. The intracranial volume (ICV) remains stable during the adult life [6, 7] and can thus be used as a normalization factor independent of age. This normalization can be performed by calculating the ratio of brain parenchymal volume (BPV) to ICV. This ratio was, to the best of our knowledge, initially termed percentage of brain parenchyma [8]. The ratio is now often referred to as brain parenchymal fraction (BPF) after work done by Rudick et al. [1]. Although the definition presented above is the most widely used, small variations in the definition of the term can be seen.
In order to be able to properly interpret levels of BPF in the setting of disease, thorough knowledge of the values in a non-diseased state is necessary.

The goal of this study was to present cross-sectional data on BPF in neurologically healthy individuals via a systematic review of the literature and to relate these values to the ages of the participants and to the method used for the brain segmentations. The primary endpoint for the study was a meta-regression of mean BPF in relation to age. Secondary endpoints were differences in age-adjusted mean BPF between different post-processing methods and method-specific regressions of mean BPF in relation to age.

Materials and Methods

Ethics

Since the study only encompasses a review of the literature, it was not subjected to review by an ethical review board.

Systematic review

The literature search was performed in the two databases PubMed and Scopus on the 7th of January 2016, with the following search string:

("brain parenchymal fraction" OR BPF) AND ("MRI" OR "magnetic resonance imaging" OR "MRT" OR "magnetic resonance tomography" OR "MR" OR "CT" OR "computed tomography")

To increase sensitivity for studies presenting the required data but having used a different terminology than BPF, we redid the search adding a second, separate search string. Keeping the second part of the search string identical ("MRI" OR "magnetic resonance …” etc.) we replaced the first part with “brain volume”. Due to the high number of search results (>20,000) we narrowed it down to (“brain volume” AND (“fraction” or “fractional”)). This still generated a high number of search results (>2,000). Therefore, we further narrowed the search done with this string by restricting it from “all fields” to “article title, abstract, keywords”.

The search was then redone on the 5th of June 2016 with the two search strings:

1. All fields: ("brain parenchymal fraction" OR BPF) AND ("MRI" OR "magnetic resonance imaging" OR "MRT" OR "magnetic resonance tomography" OR "MR" OR "CT" OR "computed tomography")

2. Article title, abstract, keywords: ("brain volume" AND ("fraction" OR "fractional")) AND ("MRI" OR "magnetic resonance imaging" OR "MRT" OR "magnetic resonance tomography" OR "MR" OR "CT" OR "computed tomography")

The literature search is outlined in Fig 1. The numbers described here and in Fig 1 represent the combined results of the two search dates, with duplicates removed. A total of 1434 articles were found in the initial search and two additional articles were added due to personal knowledge, resulting in 1436 articles. Two reviewers (M.V. and A.S.) examined the titles and abstracts of these and 273 articles were found to likely present required data. The reference tables of these 273 articles were examined by both reviewers, and all articles with titles indicating measurement of brain atrophy or brain size in healthy individuals were selected. This yielded 116 new articles, resulting in a total of 389 articles for final examination. The full article texts of these were examined by one reviewer (M.V.) for inclusion according to the criteria below.

The study should be written in English and present:
• data for an adult population (age > 18 years old) free from neurological disease
• age of the study population
• data on BPF or data that enables the calculation of BPF
• BPF measured across the whole intracranial cavity using either MRI or CT

Any uncertainties regarding inclusion were brought up to consensus discussion between the two reviewers. In cases where it was confirmed or highly likely that two or more articles...
presented data from the same subjects only one of the studies was included. Data on BPF, age, imaging modality and method to determine BPF were extracted from each article.

In cases when the study population was presented as two or more individual subgroups and BPF and age were available for each, the data from each subgroup was extracted instead of the combined data of the whole study population. This allowed for a higher number of age-specific data points and thus a better stratification of BPF by age.

In cases where further specification regarding the methodology would have been of value, an attempt was made to contact the corresponding author to clarify [9–15]. We were able to get in touch with two of the corresponding authors [9, 10] and assessed the methodology of the rest of the mentioned articles according to our best effort.

In cases where an article had determined the BPF in the same population two or more times using different segmentation methods, only one set of BPF data was entered into this review [2, 16, 17]. If the same method had been applied using different MRI scanners, values presented here represents the mean from those measurements [18].

**Definition of BPF**

The term BPF was originally presented as the ratio between the BPV and the total volume contained within the brain surface contour (BSC) [1]. The term has later been used both according to the original definition and also to represent the ratio between the BPV and the ICV, the latter now having become predominant.

**Statistics**

The statistical calculations were performed in SPSS23 (2015, IBM Corp. Armonk, NY, US), Microsoft Excel 2013 (2012, Microsoft Corporation, Redmond, WA, US) and R 3.2.5 (2016, R Core Team, Vienna, Austria). Visual inspection of histograms in conjunction with Shapiro-Wilks test was used to assess normality of distribution.

In cases when an article included for review did not present the value for BPF, but presented data from which BPF could be calculated, the BPF was calculated together with an estimation of the standard error (SE) in accordance with standard calculation of error propagation [19]. It is noted in Table 1 for which of the studies such calculations were made.

Only studies presenting data on mean BPF and mean age were included in the aggregated statistical calculations. When median age and/or BPF was presented instead of the mean, the median was noted in the study summary in Table 1 but the study was excluded from the aggregated statistical calculations [12, 17, 20–25].

A meta-regression using weighted mixed effects linear regression was used to explore the relationship between mean BPF and age. The age dependency was explained by a linear and a quadratic term. By weighting the observations by the inverse of the standard deviations from the BPF-estimates the analysis handled differences in sample sizes and precision between the studies. A random effect was used for controlling for study specific bias in cases when two or more individual populations originated from the same study.

Spearman’s Rho was used for correlation testing. Estimated marginal means were calculated from the regression models in order to compare age-adjusted mean BPF-levels between methods. Corresponding p-values were adjusted using the Bonferroni-Holm method.

**Results**

**Final article inclusion**

The final article count for inclusion was 95. The included articles are presented in Table 1. The studies presented data on a total of 131 independent populations amounting to a total of 9269
### Table 1. All the studies included in the review. The individual studies included in the review, subgrouped when applicable. The age and BPF are mean values of the study population.

| First author | Subgroup | N(Female) | Age (SD) | BPF (1.96 SE) | Method | BPF-definition |
|--------------|----------|-----------|----------|---------------|--------|----------------|
| Abe[51]      |          | 42(20)    | 48.0(13.2)| 0.832(0.034)  | SPM    | BPV/ICV        |
| Bagnato[7]    |          | 12(6)     | 41.5(11.2)| 0.850(0.0057) | Other  | BPV/ICV        |
| Baltrusch[10]|          | 15(7)     | 30.5(5.9) | 0.860(0.0081) | SPM    | BPV/ICV        |
| Benedict[52] |          | 16(11)    | 38.3(9.6) | 0.884(0.017)  | Other  | BPV/ICV        |
| Berme[53]     |          | 17(13)    | 36.6(9.9) | 0.877(0.0095) | Other  | BPV/ICV        |
| Blatter*[54]  |          | 20(20)    | 21.3(2.5) | 0.936(0.037)  | Other  | BPV/ICV        |
|              |          | 24(24)    | 30.7(3.1) | 0.928(0.044)  | Other  | BPV/ICV        |
|              |          | 22(22)    | 40.7(3.0) | 0.918(0.045)  | Other  | BPV/ICV        |
|              |          | 24(24)    | 50.4(2.7) | 0.913(0.057)  | Other  | BPV/ICV        |
|              |          | 15(15)    | 59.8(2.2) | 0.890(0.046)  | Other  | BPV/ICV        |
|              |          | 24(0)     | 30.7(3.1) | 0.913(0.057)  | Other  | BPV/ICV        |
|              |          | 19(0)     | 30.7(3.1) | 0.913(0.057)  | Other  | BPV/ICV        |
|              |          | 15(0)     | 51.1(2.7) | 0.911(0.044)  | Other  | BPV/ICV        |
|              |          | 15(0)     | 60.6(3.0) | 0.877(0.045)  | Other  | BPV/ICV        |
| Calabrese[15]|          | 40(25)    | 36.2(10.2)| 0.854(0.0059) | Other  | BPV/ICV        |
| Carone[55]   |          | 39(26)    | 39.4(11.5)| 0.826(0.0072) | SPM    | BPV/ICV        |
| Chard‡[20]    |          | 29(16)    | 36.7(N/S) | *0.850(0.78–0.87)| SPM    | BPV/ICV        |
| Chen[56]     |          | 1(1)      | 33.0(0)   | 0.871(0.0055) | Other  | BPV/ICV        |
|              |          | 1(0)      | 33.0(0)   | 0.889(0.014)  | Other  | BPV/ICV        |
| Ciarmiello* [57]|         | 54(16)    | 36.8(13.9)| 0.900(0.0064) | Other  | BPV/ICV        |
| Cohen[58]    |          | 19(8)     | 35.2(10.5)| 0.892(0.014)  | Other  | BPV/ICV        |
| Cruz-Gomez[59]|          | 19(8)     | 35.2(10.5)| 0.892(0.014)  | Other  | BPV/ICV        |
| Davies[60]   |          | 19(10)    | 34.0(N/S) | 0.849(0.0072) | SPM    | BPV/ICV        |
| Davies[61]   |          | 17(10)    | 35.6(N/S) | 0.835(0.013)  | SPM    | BPV/ICV        |
| De Masi‡[11] |          | 12(5)     | 41.8(10.6)| 0.840(0.028)  | Other  | BPV/BSC        |
| De Andrade[62]|          | 10(9)     | 40.8(3.9) | 0.840(0.012)  | Other  | BPV/ICV        |
| DeCarli‡[32] |          | 948(0)    | 62.2(10.1)| 0.772(0.0023) | Other  | BPV/ICV        |
| Delano-Wood* [63]|         | 20(12)    | 78.3(6.3) | 0.802(0.040)  | Other  | BPV/ICV        |
| Del'Oglio[64]|          | 30(21)    | 43.9(6.3) | 0.846(0.0060) | SPM    | BPV/ICV        |
| Duning‡[21]  |          | 65(31)    | 46.0–77.0 | 0.787(0.0063) | SIENAX | BPV/ICV        |
| Enström[65]  |          | 19(14)    | 48.8(12.2)| 0.899(0.011)  | SyMap  | BPV/ICV        |
| Enzinger[66] |          | 201(96)   | 59.8(5.9) | 0.800(0.028)  | SIENAX | BPV/ICV        |
| Fisher[31]   |          | 17(10)    | 41.6(8.1) | 0.862(0.057)  | Other  | BPV/BSC        |
| Fisniku* [67]|          | 25(14)    | 41.7(7.7) | 0.800(0.055)  | SPM    | BPV/ICV        |
| Garcia-Lazaro* [68]| | 21(16) | 25.7(3.0) | 0.740(0.033) | SPM    | BPV/ICV        |
|              |          | 10(7)     | 70.2(4.0) | 0.678(0.050)  | SPM    | BPV/ICV        |
| Ge* [69]     |          | 32(N/S)   | 33.0(8.9) | 0.891(0.020)  | Other  | BPV/ICV        |
|              |          | 22(N/S)   | 67.0(10.4)| 0.816(0.022)  | Other  | BPV/ICV        |
| Ge[70]       |          | 10(4)     | **40.3(23.0–56.0)| 0.883(0.021) | Other  | BPV/ICV        |
| Glodzik[71]  |          | 102(38)   | 72.4(8.3) | 0.746(0.0085) | Other  | BPV/ICV        |
| Good* [72]   |          | 10(5)     | 60.0(6.0) | 0.788(0.021)  | VBM    | BPV/ICV        |
| Good* [72]   |          | 1(0)      | 30.9(11.1)| 0.764(0.0077) | VBM    | BPV/ICV        |
| Gordon-Lipkin [73]|        | 15(9)    | 33.0(7.3) | 0.782(0.015)  | SIENAX | BPV/ICV        |
| Granberg[27] |          | 23(18)    | 57.0(7.2) | 0.700(0.0090) | Freesurfer | BPV/ICV     |
| Granberg[26] |          | 5(2)      | 51.0(9.9) | 0.735(0.011)  | Freesurfer | BPV/ICV     |
| Gutmann* [39]|          | 10(4)     | 23.3(7.6) | 0.929(0.019)  | Other  | BPV/ICV        |
|              |          | 9(7)      | 45.6(2.7) | 0.901(0.013)  | Other  | BPV/ICV        |
|              |          | 8(4)      | 55.0(2.3) | 0.894(0.014)  | Other  | BPV/ICV        |
|              |          | 23(16)    | 66.0(2.9) | 0.877(0.012)  | Other  | BPV/ICV        |
|              |          | 22(19)    | 73.5(3)  | 0.866(0.0088) | Other  | BPV/ICV        |
| Harris[74]   |          | 57(15)    | 31.5(7.9) | 0.935(0.0068) | Other  | BPV/ICV        |

(Continued)
| First author | Subgroup | N(Female) | Age (SD) | BPF (1.96 SE) | Method | BPF-definition |
|-------------|----------|-----------|----------|---------------|--------|----------------|
| Henkel[75]  | -        | 15(3)     | 36.0(8.0) | 0.837(0.014)  | SPM    | BPV/ICV        |
| Horsefield[33] | 1       | 1(0)      | 21.0(0)  | 0.893(0.027)  | Other  | BPV/ICV        |
|              |          | 2(0)      | 41.0(0)  | 0.875(0.025)  | Other  | BPV/ICV        |
| Houtchens[76] | -        | 16(12)    | 46.5(9.3) | 0.883(0.012)  | Other  | BPV/ICV        |
| Hsu*[77]    | -        | 895(472)  | 65.8(9.7) | 0.809(0.0077) | VBM    | BPV/ICV        |
| Inglese[78] | -        | 1(0)      | 21.0(0)  | 0.893(0.027)  | Other  | BPV/ICV        |
| Janssen[36] | -        | 16(12)    | 46.5(9.3) | 0.883(0.012)  | Other  | BPV/ICV        |
| Jäncke*[28] | 1        | 275(275)  | 24.6(5.7) | 0.720(0.0091) | Freesurfer | BPV/ICV    |
|              | 2        | 258(0)    | 26.8(5.6) | 0.720(0.011)  | Freesurfer | BPV/ICV     |
|              | 3        | 177(177)  | 67.8(8.5) | 0.686(0.012)  | Freesurfer | BPV/ICV     |
|              | 4        | 146(0)    | 70.8(6.2) | 0.669(0.015)  | Freesurfer | BPV/ICV     |
| Kalkers‡[22] | -        | 12(7)     | 42.5(7.8) | 0.87(0.83–0.88)| Other | BPV/ICV        |
| Kassubek[79] | -        | 22(5)     | 59.0(11.0)| 0.803(0.015)  | SPM    | BPV/ICV        |
| Kassubek[8]  | -        | 70(27)    | 42.7(15.8)| 0.828(0.0086) | SPM    | BPV/ICV        |
| Keamey[80]  | -        | 28(19)    | 41.4(10.3)| 0.823(0.0056) | SPM    | BPV/ICV        |
| Kilsdonk‡[29] | -     | 11(6)    | 38.8(10.5)| 0.650(0.024)  | Freesurfer | BPV/ICV     |
| Klavitter[81] | -        | 21(16)    | 44.0(6.8) | 0.846(0.0064) | Other  | BPV/ICV        |
| Knutson*     | 1        | 38(0)     | 29.4(6.7) | 0.832(0.029)  | Other  | BPV/ICV        |
|              | 2        | 48(48)    | 31.4(7.5) | 0.825(0.030)  | Other  | BPV/ICV        |
|              | 3        | 177(177)  | 67.8(8.5) | 0.686(0.012)  | Freesurfer | BPV/ICV     |
|              | 4        | 146(0)    | 70.8(6.2) | 0.669(0.015)  | Freesurfer | BPV/ICV     |
| Leigh[34]   | -        | 5(2)      | 34.8(10.4)| 0.882(0.019)  | Other  | BPV/ICV        |
| Lermairè*[83] | 1       | 331(0)    | 69.5(3.1) | 0.734(0.0029) | VBM    | BPV/ICV        |
|              | 2        | 331(331)  | 69.6(2.95)| 0.747(0.0031) | VBM    | BPV/ICV        |
| Liptak[84]  | -        | 29(22)    | 46.2(12) | 0.870(0.015)  | Other  | BPV/ICV        |
| Liu[85]     | -        | 35(28)    | 32.2(10.13)| 0.860(0.0033) | SPM    | BPV/ICV        |
| Lukas[86]   | -        | 3(2)      | 32.0(4.6) | 0.863(0.019)  | Other  | BPV/ICV        |
| Marquis*[87] | -       | 60(34)   | 80.7(8.2) | 0.787(0.026)  | Other  | BPV/ICV        |
| Matsumae[88] | -       | 12(6)    | 35.0(6.0) | 0.930(0.0057) | Other  | BPV/ICV        |
|              | 2        | 15(5)     | 50.0(6.0) | 0.910(0.010)  | Other  | BPV/ICV        |
|               | 3        | 22(12)    | 72.0(5.0) | 0.850(0.012)  | Other  | BPV/ICV        |
| Metzler-Baddeley[89] | - | 39(22) | 67.6(8.6) | 0.692(0.013)  | SPM    | BPV/ICV        |
| Mezzapesa[90] | -       | 9(3)     | 51.8(12.7)| 0.849(0.012)  | SIENAX| BPV/ICV        |
| Minnerop[91] | -        | 13(5)    | 53.5(10.2)| 0.660(0.022)  | VBM    | BPV/ICV        |
| Mitchell[92] | -        | 290(0)   | 76.0(4.0) | 0.710(0.0046) | Other  | BPV/ICV        |
| Pardini[9]  | -        | 38(22)    | 67.6(8.6) | 0.692(0.013)  | SPM    | BPV/ICV        |
| Peinemann[96] | -       | 25(12)   | 42.9(9.8) | 0.824(0.018)  | VBM    | BPV/ICV        |
| Rudick[1]   | -        | 16(11)    | 32.3(7.1) | 0.871(0.0039) | Other  | BPV/SCG        |
| Santilippo[100] | -        | 18(12)   | 36.2(8.9) | 0.882(0.014)  | SPM    | BPV/ICV        |
| Sastre-Garriga[23] | - | 45(22) | 15(23)–67 | 0.830(N/S)  | SPM    | BPV/ICV        |
| Sharma*[16] | -        | 17(12)    | 35.9(8.9) | 0.880(0.014)  | SPM    | BPV/ICV        |
| Smith[101]  | -        | 67(40)    | 71.2(4.4) | 0.809(0.0093) | Other  | BPV/ICV        |
| Stosic[43]  | -        | 49(33)    | 44.0(10.9) | 0.829(0.0056) | SPM    | BPV/ICV        |
| Streitberger*[12] | - | 38(22) | 48.0(9.7) | ††0.980(0.96–0.99) | SIENAX| BPV/ICV        |
| Tavazzil[92] | -        | 38(21)    | 33.3(11.5)| 0.848(0.0032) | SIENAX| BPV/ICV        |

(Continued)
(4932 female) individuals reported to be neurologically healthy. For the studies reporting mean values, the mean BPF values (n = 119) ranged from 0.645 to 0.946 and the mean ages (n = 121) ranged from 21.0 to 82.0 years. Seventeen [1, 11, 12, 17, 20–32] of the 95 studies are presented in Table 1 but were excluded from part of, or all, of the aggregated statistical calculations on the basis of methodology or data presentation (see the section on statistics and the rest of the results section for further details). The final number of independent populations used for the complete aggregated statistical calculations were 103, presented in 78 studies and

| First author | Subgroup | N(Female) | Age (SD) | BPF (1.96 SE) | Method | BPF-definition |
|--------------|----------|-----------|----------|---------------|--------|----------------|
| Tiberio[103] | -        | 10(4)     | 37.1(N/S)| 0.836(0.017) | SPM    | BPV/ICV        |
| Tisell‡[24]  | -        | 20(15)    | 58.8(14.0)| 0.806(0.78–0.94) | SyMap  | BPV/ICV        |
| Torelli[94]  | -        | 14(5)     | 57.6(5.2)| 0.853(0.012) | Other  | BPV/ICV        |
| Tovar-Moll[13]| -       | 24(N/S)   | 41.9(8.3)| 0.840(0.0080) | SIENAX | BPV/ICV        |
| Traboulsee[104]| -     | 63(44)    | 39.6(9.4)| 0.850(0.0049) | SPM    | BPV/ICV        |
| Tseng*‡[30]  | 1        | 10(3)     | 72.4(5.6)| 0.663(0.040) | Freesurfer | BPV/ICV  |
|              | 2        | 10(2)     | 74.6(4.3)| 0.645(0.046) | Freesurfer | BPV/ICV  |
| Uçar[105]    | -        | 10(8)     | 31.5(5.0)| 0.856(0.0064) | Other  | BPV/ICV        |
| Vagberg‡[25] | -        | 35(19)    | 35.0(19.0–65.0)| 0.890(0.0080) | SyMap  | BPV/ICV        |
|              | 1        | 21(9)     | 22.8(4.5)| 0.887(0.037) | SyMap  | BPV/ICV        |
|              | 2        | 20(11)    | 33.9(3.1)| 0.870(0.032) | SyMap  | BPV/ICV        |
|              | 3        | 20(7)     | 44.1(4.6)| 0.866(0.029) | SyMap  | BPV/ICV        |
|              | 4        | 17(12)    | 52.6(6.9)| 0.837(0.033) | SyMap  | BPV/ICV        |
|              | 5        | 15(8)     | 67.3(5.8)| 0.811(0.041) | SyMap  | BPV/ICV        |
|              | 6        | 11(8)     | 75.3(4.8)| 0.778(0.071) | SyMap  | BPV/ICV        |
|              | 7        | 2(1)      | 82.7(4.5)| 10.697(0.060) | SyMap  | BPV/ICV        |
| West[18]     | -        | 10(6)     | 24.4(2.5)| 0.909(0.012) | SyMap  | BPV/ICV        |
| Wuerfel[14]  | -        | 30(16)    | 37.8(11.5)| 0.870(0.0072) | SIENAX | BPV/ICV        |
| Yaldizli[42] | -        | 27(17)    | 41.7(13.9)| 0.771(0.0098) | Other  | BPV/ICV        |
| Yamasue*[107]| -        | 76(38)    | 41.7(11.9)| 0.747(0.023) | VBM    | BPV/ICV        |
| Zimmerman[108]| -    | 20(12)    | 35.7(9.6)| 0.733(0.018) | VBM    | BPV/ICV        |
| Zito[109]    | -        | 15(11)    | 37.9(9.1)| 0.820(0.096) | VBM    | BPV/ICV        |
| Zivadinov[110]| -       | 19(10)    | 30.4(12)| 0.845(0.0027) | SIENAX | BPV/ICV        |

* denotes studies where the BPF was not presented directly but information was available to allow calculation.
** denotes a value that is presented as mean (range)
† denotes a value that is presented as median (interquartile range)
†† denotes a value that is presented as median (range)
‡ denotes a study that was excluded from the aggregated statistical calculations due to methodology or data presentation
BPF = Brain Parenchymal Fraction
BPV = Brain Parenchymal Volume
BSC = the volume within the Brain Surface Contour
ICV = Intracranial Volume
N/S = Not Specified
SD = Standard Deviation
SE = Standard Error of the Mean
SIENAX = Structural Image Evaluation Using Normalisation of Atrophy Cross-Sectional
SPM = Statistical Parametric Mapping
SyMap = Synthetic Tissue Mapping
VBM = Voxel Based Morphometry

doi:10.1371/journal.pone.0170018.t001
amounting to 5878 (3102 female) healthy individuals with mean BPF values ranging from 0.660 to 0.946 and mean ages ranging from 21.0 to 82.0 years.

Two articles had investigated BPF using several different pulse sequences and segmentation methods but only presented the mean values of all of these [33, 34]. One article had determined BPF two consecutive times six days apart and the values presented in this review are the means from those measurements. One article [35] had stated that the data spread was expressed as SE but the values presented were too large to be representing SE in relation to the reported range and were therefore assumed to be standard deviation (SD) instead. One article [12] did not specify if the presented value was median or mean. We decided to include this value in the statistical calculations as if it was the median. In one article the mean age of the population was stated for the whole population (n = 55) and not the subgroup that had undergone MRI (n = 40) [36]. We decided to approximate the mean age of the MRI group with that from the whole population. We decided to include one study that had examined individuals with ages ranging between 16 and 70 years old, but with a mean age and data spread that indicated that the population was predominantly adult [37].

Imaging modality and method of BPF determination

All articles in the final article count had determined BPF by MRI, using a variety of different post-processing methods. The method used by each study is noted in Table 1, categorized as Structural Image Evaluation Using Normalisation of Atrophy Cross-Sectional (SIENAX) [38], Voxel Based Morphometry (VBM) [39], Synthetic Tissue Mapping (SyMap) [25], Statistical Parametric Mapping (SPM) [40], Freesurfer [41] or “Other”. Freesurfer brain segmentation does not by default include the brainstem. For this reason, the Freesurfer studies [26–30] were excluded from the aggregated statistical analyses. However, since Freesurfer is a well-known segmentation method the studies were presented in Table 1 and included in the method specific calculations of the regression of BPF in relation to age and the estimated marginal means. The SyMap results are specified in Table 1 but were included in the category “Other” for the regression analyses, due to a low number of SyMap data points.

Definition of BPF

The definition of BPF used in each study included in this review could broadly be categorized as either BPF = BPV/ICV or BPF = BPV/BSC. This categorization is noted in Table 1. Studies using the definition BPF = BPV/BSC (n = 3) were excluded from the statistical analyses. In three cases the exact definition of BPF used was not clearly stated and attempts to contact the corresponding author were unsuccessful [13–15]. In these cases, the definition was assumed to be BPF = BPV/ICV.

There were slight differences among the included studies regarding the details of the calculation of ICV and BPV. As an example, the ICV could be defined as either the intracranial cavity measured directly [42] or as the sum of the volumes of GM, WM and CSF [43]. Only studies having included the complete intracranial space in the assessment of ICV were included in the aggregated statistical calculations. One study that had only reported the supratentorial ICV was entered into Table 1 [32]. Due to the large population size we considered the study important to report, but excluded it from the aggregated statistical calculations.

BPF in relation to age

There was a significant correlation between mean population BPF values and mean population ages (R = -0.41, p<0.001) (Fig 2). When examining the method specific residuals to the regression in Fig 2, all post-processing methods exhibited relatively uniform residuals in relation to
Fig 2. The mean BPF values of the study populations plotted in relation to age. Mean BPF value of each study population (vertical axis) is plotted against mean age (horizontal axis). The regression line is a mixed weighted regression model. The dashed lines represent 95% confidence interval. Seventeen studies were excluded from this figure (see the sections on statistics and results). BPF = Brain Parenchymal Fraction. SIENAX = Structural Image Evaluation Using Normalisation of Atrophy Cross-Sectional. SPM = Statistical Parametric Mapping. VBM = Voxel Based Morphometry.

doi:10.1371/journal.pone.0170018.g002
mean age with the exception of VBM, where the residuals indicated an age-dependent effect on the fit to the curve.

**BPF determined by different post-processing methods**

Fig 3 shows the BPF of the study populations in relation to population age, stratified by post-processing method. There were significant differences between the different post-processing methods ($p \leq 0.05$ for all comparisons) with the exception of the comparison of SIENAX to SPM ($p = 0.74$). The comparison of “Other” to SIENAX did not retain statistical significance after Bonferroni-Holm adjustment ($p = 0.088$). The estimated magnitude of difference in age-adjusted BPF between the methods (excluding non-significant differences) ranged between 0.038 and 0.17.

Three studies included in the aggregated statistical calculations had methodological uncertainties, which we did not succeed to clarify by an attempt to contact the corresponding author [13–15]. After exclusion of these studies, the comparison of SIENAX to VBM was still significant ($p = 0.044$) but did not retain significance after Bonferroni-Holm adjustment ($p = 0.11$). The three studies were not outliers and no other statistical significances changed if they were excluded.

**Discussion**

We here present a database of BPF in healthy individuals, stratified by age and method of segmentation, composed of data from a systematic review of the literature. The data may aid researchers and clinicians in the interpretation of BPF data in relation to method and age.

The regression indicates a progressive rate of atrophy with increasing age. This is supported by earlier findings in individual studies [6, 7, 17, 44, 45]. The biological background for this possibly progressive atrophy rate in healthy individuals is not clear. It could be hypothesized that increased prevalence of subclinical vascular/ischemic tissue damage with increasing age is a factor but more research is needed to elucidate this.

It is also noteworthy, although not surprising, that there seems to be a large degree of heterogeneity between different post-processing methods. Age-adjusted BPF values were significantly different between methods. This accentuates the need for caution when comparing BPF data between studies, especially if different post-processing methods have been used. This also highlights the problem that there is no generally accepted consensus regarding gold standard for BPF determination, or for quantifying brain atrophy at large. A consensus gold standard would simplify validation of new methods and provide a unified reference for discussions regarding brain atrophy.

It is of interest to mention that the BPF of all post-processing methods, with the exception of VBM, could be fitted relatively well to the quadratic mixed weighted regression model from the aggregated data from all populations (Fig 2). However, the VBM residuals indicated an age-dependent bias in the BPF determination if compared to the aggregated data from all methods. The issue of potential age bias in the VBM segmentation, perhaps in part explained by the atlas template used for the segmentation [46, 47], have been discussed previously [17] and is important to note.

A strength of the study is the systematic methodology used in order to maximize the possibility of covering most of the suitable studies in the databases searched. The choice of databases, PubMed and Scopus, encompass a large proportion of published clinical studies and are therefore likely to include most studies presenting BPF in healthy adults. It must be mentioned, however, that there could be studies that would have been suitable for inclusion but were not indexed in these databases.
Fig 3. The mean BPF values of the study populations plotted individually for each post-processing method. Mean BPF value of each study population (vertical axis) is plotted against mean age (horizontal axis). Individual mixed weighted regression lines are plotted for each post-processing method. Twelve studies were excluded from this figure (see the sections on statistics and results). BPF = Brain Parenchymal Fraction. SIENAX = Structural Image Evaluation Using Normalisation of Atrophy Cross-Sectional. SPM = Statistical Parametric Mapping. VBM = Voxel Based Morphometry.

doi:10.1371/journal.pone.0170018.g003
Another strength of the study is the presentation of method specific regressions of BPF over age. This could benefit researchers in providing literature values to use as a comparison for their own study data. More importantly, it emphasizes the difficulties in comparing data between studies if they are performed with different post processing techniques.

An obstacle to overcome was that other terms than BPF have been used to denote the same ratio. In an effort to identify as many relevant studies as possible, regardless of the terminology used, articles with titles and/or abstracts not specifically mentioning BPF but indicating that brain volume or brain atrophy measurements in healthy individuals had been investigated were also included in this review. Data for calculation of BPF was extracted whenever possible even if BPF was not reported directly in the article. Despite these efforts, however, it is likely that there are studies that have not been found due to usage of different terminology. It is also likely that the review has not identified the entirety of studies presenting suitable data for the calculation of BPF, in place of presenting BPF itself, as we for practical reasons chose to narrow the search from the more sensitive search term "brain volume".

A limitation of the study is the use of summary statistics from each study population in the form of mean age and BPF. More detailed statistical calculations could have been performed if data on individual values for each study participant had been available.

It is furthermore important to note that we specifically chose to limit this review to the BPF-ratio and that there are studies presenting brain volume or other morphological brain features biologically related to BPF while not presenting the data required for the calculation of BPF. The work by Taki and colleagues is a notable example [48]. We chose to limit this review solely on the BPF to facilitate a focused presentation of data. We also chose to be stringent regarding the measurements on which to base the BPF and chose not to include studies that only reported approximations on or parts of the volumes of interests. An example is the valuable work by Coffey and colleagues reporting brain volumetric data from 330 volunteers but, as the authors point out, having restricted the estimation of the ICV to a part of the true volume [49]. Therefore, we chose not to include it in this review. We made one notable exception to this rule in including the work by DeCarli and colleagues on the Framingham Heart Study, presenting brain volumetric data on ICV and BPV from 2081 individuals [32]. This is an important study to report due to the large population size. However, the measurements of ICV and BPV in the study, by which we calculated the BPF, were restricted to the supratentorial space. We chose to include the data in Table 1 but exclude it from the statistical analyses.

It is necessary to point out that this review only presents cross-sectional data on BPF and large inter-individual variations have been reported for such data [17]. This means that an individual BPF value would need to deviate far from the expected value for the age in order to be certain that the value is abnormal. Longitudinal data on brain atrophy, measured over several time points, provides a different perspective on the development of atrophy. However, the magnitude of physiological effects on brain volume that have been reported, for example in the setting of dehydration-rehydration [50], is not negligible in relation to the expected change in brain volume per year [45], complicating the quantification of annual changes in brain volume. We suggest that a combination of cross-sectional and longitudinal data would provide the most robust assessment of brain atrophy. More research is needed on this subject, especially regarding longitudinal rate of brain volume change in relation to age in the non-diseased state.

Conclusions
Knowledge of the normal range of brain atrophy assessments in relation to age is important when interpreting brain atrophy data. We believe that this article contributes to a base of such knowledge while we want to point out that further knowledge regarding longitudinal annual
atrophy rate in healthy individuals is needed. The data presented here may benefit researchers wanting to compare their own study data to literature values for their chosen method of segmentation. The heterogeneity existing between different methods for BPF determination emphasizes the need for a consensus gold standard.

Supporting Information

S1 File. PRISMA Checklist.

(DOC)

Acknowledgments

We would like to thank the staff at the neurology department at Umeå University Hospital for their help and assistance. We would like to thank Fredrik Toss for critical reading of the manuscript. We would furthermore like to thank the corresponding authors of included studies that we contacted, who graciously answered our questions regarding study data and/or methodology.

Author Contributions

Conceptualization: MV AS.
Data curation: MV GG AS.
Formal analysis: MV GG.
Funding acquisition: MV GG AS.
Investigation: MV AS.
Methodology: MV GG AS.
Project administration: MV AS.
Resources: MV GG AS.
Software: MV GG AS.
Supervision: AS.
Visualization: MV GG.
Writing – original draft: MV.
Writing – review & editing: MV GG AS.

References

1. Rudick RA, Fisher E, Lee JC, Simon J, Jacobs L. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Multiple Sclerosis Collaborative Research Group. Neurology. 1999; 53(8):1698–704. PMID: 10563615
2. Good CD, Scahill RI, Fox NC, Ashburner J, Friston KJ, Chan D, et al. Automatic differentiation of anatomical patterns in the human brain: validation with studies of degenerative dementias. Neuroimage. 2002; 17(1):29–46. Epub 2002/12/17. PMID: 12482066
3. Kassubek J, Landwehrmeyer GB, Ecker D, Juengling FD, Muche R, Schuller S, et al. Global cerebral atrophy in early stages of Huntington’s disease: Quantitative MRI study. NeuroReport. 2004; 15 (2):363–5. PMID: 15076769
4. Juengling FD, Kassubek J. Standardized calculation of brain parenchymal fraction: an approach to objective assessment of cerebral atrophy. AJNR Am J Neuroradiol. 2003; 24(7):1492–3; author reply 3. Epub 2003/08/15.
5. De Stefano N, Airas L, Grigoriadis N, Mattle HP, O’Riordan J, Oreja-Guevara C, et al. Clinical relevance of brain volume measures in multiple sclerosis. CNS Drugs. 2014; 28(2):147–56. Epub 2014/01/22. doi: 10.1007/s40263-014-0140-z PMID: 24446248
6. Courchesne E, Chisum HJ, Townsend J, Cowles A, Covington J, Egas B, et al. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. Radiology. 2000; 216(3):672–82. Epub 2000/08/31. doi: 10.1148/radiology.216.3.ro0au37672 PMID: 10966694
7. Bagnato F, Butman JA, Gupta S, Calabrese M, Pezawas L, Ohayon JM, et al. In vivo detection of cortical plaques by MR imaging in patients with multiple sclerosis. American Journal of Neuroradiology. 2006; 27(10):2161–7. PMID: 17110688
8. Phillips MD, Grossman RI, Miki Y, Wei L, Kolson DL, van Buchem MA, et al. Comparison of T2 lesion volume and magnetization transfer ratio histogram analysis and of atrophy and measures of lesion burden in patients with multiple sclerosis. AJNR Am J Neuroradiol. 1998; 19(6):1055–60. Epub 1998/07/22. PMID: 9672011
9. Pardini M, Yaldizli O, Sethi V, Muhlert N, Liu Z, Samson RS, et al. Motor network efficiency and disability in multiple sclerosis. Neurology. 2015; 85(13):1115–22. doi: 10.1212/wnl.0000000000001970 PMID: 26320199
10. Baltruschat SA, Ventura-Campos N, Cruz-Gómez TJ, Belenguer A, Forn C. Gray matter atrophy is associated with functional connectivity reorganization during the Paced Auditory Serial Addition Test (PASAT) execution in Multiple Sclerosis (MS). Journal of Neuroradiology. 2015; 42(3):141–9.
11. De Masi R, Vergara D, Pasca S, Aciero R, Greco M, Spagnolo L, et al. PBMCs protein expression profile in relapsing IFN-treated multiple sclerosis: A pilot study on relation to clinical findings and brain atrophy. Journal of Neuroimmunology. 2009; 210(1–2):80–6. doi: 10.1016/j.jneuroim.2009.03.002 PMID: 19329191
12. Streitberger KJ, Sack I, Krefting D, Pfüller C, Braun J, Paul F, et al. Brain viscoelasticity alteration in chronic-progressive multiple sclerosis. PLoS ONE. 2012; 7(1).
13. Tovar-Moll F, Evangelou IE, Chiu AW, Richert ND, Ostuni JL, Ohayon JM, et al. Thalamic involvement and its impact on clinical disability in patients with multiple sclerosis: A diffusion tensor imaging study at 3T. American Journal of Neuroradiology. 2009; 30(7):1380–6. doi: 10.3174/ajnr.A1564 PMID: 19369608
14. Wuerfel J, Haertle M, Waiczies H, Tysiak E, Bechmann I, Werneck KD, et al. Perivascular spaces—MRI marker of inflammatory activity in the brain? Brain. 2008; 131(P1):2322–40. doi: 10.1093/brain/awn171 PMID: 18676439
15. Calabrese M, Atzori M, Bernardi V, Morra A, Romualdi C, Rinaldi L, et al. Cortical atrophy is relevant in multiple sclerosis at clinical onset. Journal of Neurology. 2007; 254(9):1212–20. doi: 10.1007/s00415-006-0503-6 PMID: 17361339
16. Sharma J, Sanfilippo MP, Benedict RH, Weinstock-Guttman B, Munschauer Ii FE, Bakshi R. Whole-brain atrophy in multiple sclerosis measured by automated versus semiautomated MR imaging segmentation. American Journal of Neuroradiology. 2004; 25(6):985–96. PMID: 15205136
17. Vagberg M, Ambarki K, Lindqvist T, Birgander R, Svenningsson A. Brain parenchymal fraction in an age-stratified healthy population—determined by MRI using manual segmentation and three automated segmentation methods. J Neuroradiol. 2016; 43(6):384–91. doi: 10.1016/j.neurad.2016.08.002 PMID: 27720265
18. West J, Blystad I, Engström M, Warmtjes JBM, Lundberg P. Application of Quantitative MRI for Brain Tissue Segmentation at 1.5 T and 3.0 T Field Strengths. PLoS ONE. 2013; 8(9).
19. Ku HH. Notes on the use of propagation of error formulas. JOURNAL OF RESEARCH of the National Bureau of Standards—C Engineering and Instrumentation 1966; Vol. 70C(No.4, Oct–Dec 1966).
20. Chard DT, Brex PA, Ciccarelli O, Griffin CM, Parker GJ, Dalton C, et al. The longitudinal relation between brain lesion load and atrophy in multiple sclerosis: a 14 year follow up study. J Neurol Neurosurg Psychiatry. 2003; 74(11):1551–4. Epub 2003/11/18. doi: 10.1136/jnnp.74.11.1551 PMID: 14617714
21. Dunig T, Warnecke T, Mohammadi S, Lohmann H, Schifflbauer H, Kugel H, et al. Pattern and progression of white-matter changes in a case of posterior cortical atrophy using diffusion tensor imaging. Journal of Neuroradiology, Neurosurgery and Psychiatry. 2009; 80(4):432–6. doi: 10.1136/jnnp.2008.153148 PMID: 19289480
22. Kalkers NF, Bergers E, Castelijns JA, Van Walderveen MAA, Bot JCJ, Ander HJ, et al. Optimizing the association between disability and biological markers in MS. Neurology. 2001; 57(5):1253–8. PMID: 11591845
23. Sastre-Garriga J, Ingle GT, Chard DT, Ramio-Torrenta L, Miller DH, Thompson AJ. Grey and white matter atrophy in early clinical stages of primary progressive multiple sclerosis. NeuroImage. 2004; 22(1):353–9. doi: 10.1016/j.neuroimage.2004.02.008 PMID: 15110028
24. Tisell A, Leinhard OD, Warntjes JBM, Aalto A, Smedby Ø, Landtblom AM, et al. Increased Concentrations of Glutamate and Glutamine in Normal-Appearing White Matter of Patients with Multiple Sclerosis and Normal MR Imaging Brain Scans. PLoS ONE. 2013; 8(4).

25. Vagberg M, Lindqvist T, Ambarki K, Warntjes JB, Sundstrom P, Birgander R, et al. Automated Determination of Brain Parenchymal Fraction in Multiple Sclerosis. AJNR Am J Neuroradiol. 2013; 34(3):498–504. doi: 10.3174/ajnr.A3262 PMID: 22976234

26. Granberg T, Hashim F, Andersen O, Sundal C, Karrenbauer VD. Hereditary diffuse leukoencephalopathy with spheroids—a volumetric and radiological comparison with multiple sclerosis patients and healthy controls. European Journal of Neurology. 2016; 23(4):817–22. doi: 10.1111/ene.12498 PMID: 26756564

27. Granberg T, Martola J, Bergendal G, Sundal C, Karrenbauer VD. Corpus callosum atrophy is strongly associated with cognitive impairment in multiple sclerosis: Results of a 17-year longitudinal study. Multiple sclerosis (Houndmills, Basingstoke, England). 2015; 21(9):1151–8. Epub 2014/12/07.

28. Jancke L, Merillat S, Liem F, Hanggi J. Brain size, sex, and the aging brain. Hum Brain Mapp. 2015; 36(1):150–69. doi: 10.1002/hbm.22619 PMID: 25161056

29. Kilsdonk ID, Steenwijk MD, Pouwels PJW, Zwanenburg JJM, Visser F, Luijten PR, et al. Perivascular spaces in MS patients at 7 Tesla MRI: A marker of neurodegeneration? Multiple Sclerosis Journal. 2015; 21(2):155–62. doi: 10.1177/1352458514540358 PMID: 25013150

30. Tseng BY, Gundapuneedi T, Khan MA, Diaz-Arastia R, Levine BD, Lu H, et al. White matter integrity in physically fit older adults. Neuroimage. 2013; 82:510–6. Epub 2013/06/19. doi: 10.1016/j.neuroimage.2013.06.011 PMID: 23769914

31. Fisher E, Lee JC, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: a longitudinal study. Ann Neurol. 2008; 64(3):255–65. Epub 2008/07/29. doi: 10.1002/ana.21436 PMID: 18661561

32. DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the Framingham Heart Study: establishing what is normal. Neurobiol Aging. 2005; 26(4):491–510. doi: 10.1016/j.neurobiolaging.2004.05.004 PMID: 15653178

33. Horsfield MA, Rovaris M, Rocca MA, Rossi P, Benedict RHB, Filippi M, et al. Whole-brain atrophy in multiple sclerosis measured by two segmentation processes from various MRI sequences. Journal of the Neurological Sciences. 2003; 216(1):169–77. PMID: 14607319

34. Leigh R, Ostuni J, Pham D, Goldsztal A, Lewis BK, Howard T, et al. Estimating cerebral atrophy in multiple sclerosis patients from various MR pulse sequences. Multiple Sclerosis. 2002; 8(5):420–9. PMID: 12356210

35. Guttmann CR, Jolesz FA, Kikinis R, Killiany RJ, Moss MB, Sandor T, et al. White matter changes with normal aging. Neurology. 1998; 50(4):972–8. Epub 1998/05/05. PMID: 9566381

36. Janssen MA, Meulenbroek O, Steens SC, Goraj B, Bosch M, Koopmans PP, et al. Cognitive functioning, wellbeing and brain correlates in HIV-1 infected patients on long-term combination antiretroviral therapy. AIDS (London, England). 2015; 29(16):2139–48. Epub 2015/11/07.

37. Kruggel F. MRI-based volumetry of head compartments: normative values of healthy adults. Neuroimage. 2006; 30(1):1–11. doi: 10.1016/j.neuroimage.2005.09.063 PMID: 16289929

38. Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. NeuroImage. 2002; 17(1):479–89. Epub 2002/12/17. PMID: 12482100

39. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. Neuroimage. 2000; 11(6 Pt 1):805–22. Epub 2000/06/22. doi: 10.1006/nimg.2000.0582 PMID: 10860804

40. Ashburner J, Friston KJ. Unified segmentation. NeuroImage. 2005; 26(3):839–51. doi: 10.1016/j.neuroimage.2005.02.018 PMID: 15955494

41. Reuter M, Schmansk y NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage. 2012; 61(4):1402–18. doi: 10.1016/j.neuroimage.2012.02.084 PMID: 22430496

42. Warntjes JBM, Tisell A, Landblom AM, Lundberg P. Effects of gadolinium contrast agent administration on automatic brain tissue classification of patients with multiple sclerosis. American Journal of Neuroradiology. 2014; 35(7):1330–6. doi: 10.3174/ajnr.A3890 PMID: 24699093

43. Stosic M, Ambrus J, Garg N, Weinstock-Guttman B, Ramanathan M, Kalman B, et al. MRI characteristics of patients with antiphospholipid syndrome and multiple sclerosis. J Neurol. 2010; 257(1):63–71. doi: 10.1007/s00415-009-5264-6 PMID: 1963967

44. Pfifferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch Neurol. 1994; 51(9):874–87. Epub 1994/09/01. PMID: 8080387
45. Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. Arch Neurol. 2003; 60(7):989–94. doi: 10.1001/archneur.60.7.989 PMID: 12873856

46. Fillmore PT, Phillips-Meek MC, Richards JE. Age-specific MRI brain and head templates for healthy adults from 20 through 89 years of age. Front Aging Neurosci. 2015; 7:44. doi: 10.3389/fnagi.2015.00044 PMID: 25904864

47. Huang CM, Lee SH, Hsiao IT, Kuan WC, Wai YY, Ko HJ, et al. Study-specific EPI template improves group analysis in functional MRI of young and older adults. J Neurosci Methods. 2010; 189(2):257–66. doi: 10.1016/j.jneumeth.2010.03.021 PMID: 20346979

48. Taki Y, Kinomura S, Sato K, Inoue K, Goto R, Okada K, et al. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity (Silver Spring). 2008; 16(1):119–24.

49. Coffey CE, Lucke JF, Saxton JA, Ratcliff G, Unitas LJ, Billig B, et al. Sex differences in brain aging: a quantitative magnetic resonance imaging study. Arch Neurol. 1998; 55(2):169–79. PMID: 9482358

50. Duning T, Kloska S, Steinstrater O, Kugel H, Heindel W, Knecht S. Dehydration confounds the assessment of brain atrophy. Neurology. 2005; 64(3):548–50. doi: 10.1212/01.WNL.0000150542.16969.CC PMID: 15699394

51. Abe O, Yamasue H, Kasai K, Yamada H, Aoki S, Inoue H, et al. Voxel-based analyses of gray/white matter volume and diffusion tensor data in major depression. Psychiatry Research—Neuroimaging. 2010; 181(1):64–70.

52. Benedict RHB, Zivadinov R, Carone DA, Weinstock-Guttman B, Gaines J, Maggiore C, et al. Regional lobar atrophy predicts memory impairment in multiple sclerosis. American Journal of Neuroradiology. 2005; 26(7):1824–31. PMID: 16091537

53. Bermel RA, Sharma J, Tjoa CW, Puli SR, Bakshi R. A semiautomated measure of whole brain atrophy in multiple sclerosis. Journal of the Neurological Sciences. 2003; 208(1–2):57–65. PMID: 12639726

54. Blatter DD, Bigler ED, Gale SD, Johnson SC, Anderson CV, Burnett BM, et al. Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life. AJNR Am J Neuroradiol. 1995; 16(2):241–51. PMID: 7726068

55. Capone DA, Benedict RHB, Dwyer MG, Cookfair DL, Srinivasaraghavan B, Tjoa CW, et al. Semi-automatic brain region extraction (SABRE) reveals superior cortical and deep gray matter atrophy in MS. NeuroImage. 2006; 29(2):505–14. doi: 10.1016/j.neuroimage.2005.07.053 PMID: 16169253

56. Chen D, Huang W, Christodoulou C, Li L, Qian H, Krupp L, et al., editors. A new method for quantitative analysis of multiple sclerosis using MR images2001.

57. Ciarmiello A, Cannella M, Lastoria S, Simonelli M, Frati L, Rubinsztein DC, et al. Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. J Nucl Med. 2006; 47(2):215–22. PMID: 16455626

58. Cohen BA, Inglese M, Rusinek H, Babb JS, Grossman I, Gonen O. Proton MR spectroscopy and MRI-volumetry in mild traumatic brain injury. American Journal of Neuroradiology. 2007; 28(5):907–13. PMID: 17494667

59. Cruz-Gomez AJ, Ventura-Campos N, Belenguer A, Avila C, Forn C. The link between resting-state functional connectivity and cognition in MS patients. Multiple sclerosis (Houndmills, Basingstoke, England). 2014; 20(3):338–48. Epub 2013/07/06.

60. Davies GR, Altmann DR, Hadjiprocopis A, Rashid W, Chard DT, Griffin CM, et al. Increasing normal-appearing grey and white matter magnetisation transfer ratio abnormality in early relapsing-remitting multiple sclerosis. J Neurol. 2005; 252(9):1037–44. doi: 10.1007/s00415-005-0808-x PMID: 15834645

61. Davies GR, Ramio-Torrenta L, Hadjiprocopis A, Chard DT, Griffin CM, Rashid W, et al. Evidence for grey matter MTR abnormality in minimally disabled patients with early relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry. 2004; 75(7):998–1002. doi: 10.1136/jnnp.2003.021915 PMID: 15201359

62. De Andrade DCO, Borda EF, Bonfá E, De Carvalho JF, Da Rocha AJ, Maia AC Jr. Quantifying subclinical central nervous lesions in primary antiphospholipid syndrome: The role of magnetization transfer imaging. Journal of Magnetic Resonance Imaging. 2008; 27(3):483–8. doi: 10.1002/jmri.21308 PMID: 18224670

63. Delano-Wood L, Stricker NH, Sorg SF, Nation DA, Jak AJ, Woods SP, et al. Posterior cingulum white matter disruption and its associations with verbal memory and stroke risk in mild cognitive impairment. Journal of Alzheimer's Disease. 2012; 29(3):589–603. doi: 10.3233/JAD-2012-102103 PMID: 22466061
64. Dell'Oglio E, Ceccarelli A, Gianz BI, Healy BC, Tauhid S, Arora A, et al. Quantification of Global Cerebral Atrophy in Multiple Sclerosis from 3T MRI Using SPM: The Role of Misclassification Errors. Journal of Neuroimaging. 2015; 25(2):191–9. doi: 10.1111/jon.12194 PMID: 25523616

65. Engström M, Wamptjes JBM, Tisel A, Landtblom AM, Lundberg P. Multi-parametric representation of voxel-based quantitative magnetic resonance imaging. PLoS ONE. 2014; 9(11).

66. Enzinger C, Fazekas F, Matthews PM, Ropele S, Schmidt H, Smith S, et al. Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. Neurology. 2005; 64(10):1704–11. doi: 10.1212/01.WNL.0000161871.83614.BB PMID: 15911795

67. Fisniku LK, Chard DT, Jackson JS, Anderson VM, Altmann DR, Miszkiel KA, et al. Gray matter atrophy is related to long-term disability in multiple sclerosis. Annals of Neurology. 2008; 64(3):247–54. doi: 10.1002/ana.21423 PMID: 18570297

68. Garcia-Lazaro HG, Becerra-Laparra I, Cortez-Conradis D, Roldan-Valadez E. Global fractional anisotropy and mean diffusivity together with segmented brain volumes assemble a predictive discriminant model for young and elderly healthy brains: A pilot study at 3T. Functional Neurology. 2016; 31(1):39–46. PMID: 27027893

69. Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, Kolson DL. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. AJNR Am J Neuroradiol. 2002; 23(8):1327–33. PMID: 12223373

70. Ge Y, Kolson DL, Babb JS, Mannon LJ, Grossman RI. Whole brain imaging of HIV-infected patients: Quantitative analysis of magnetization transfer ratio histogram and fractional brain volume. American Journal of Neuroradiology. 2003; 24(1):82–7. PMID: 12533331

71. Glodzik L, Sollberger M, Gass A, Gokhale A, Rusinek H, Babb JS, et al. Global N-acetylaspartate in normal subjects, mild cognitive impairment and Alzheimer’s disease patients. Journal of Alzheimer’s Disease. 2015; 43(3):939–47. doi: 10.3233/JAD-140609 PMID: 25125458

72. Good CD, Johnsrud I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult humans. Neuroimage. 2001; 14(3):685–700. doi: 10.1006/nimg.2001.0857 PMID: 11506541

73. Gordon-Lipkin E, Chodkowski B, Reich DS, Smith SA, Pulicken M, Balcer LJ, et al. Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis. Neurology. 2007; 69(18):1603–9. doi: 10.1212/01.wnl.0000295995.46586.ae PMID: 17938370

74. Harris GJ, Barta PE, Peng LW, Lee S, Brettschneider PD, Shah A, et al. MR volume segmentation of gray matter and white matter using manual thresholding: dependence on image brightness. AJNR Am J Neuroradiol. 1994; 15(2):225–30. PMID: 8192065

75. Henkel K, Danek A, Grafman J, Butman J, Kassubek J. Head of the caudate nucleus is most vulnerable in Chorea—Acanthocytosis: A voxel-based morphometry study. Movement Disorders. 2006; 21 (10):1728–31. doi: 10.1002/mds.21046 PMID: 16874760

76. Houtchens MK, Benedict RH, Killiany R, Sharma J, Jaisani Z, Singh B, et al. Thalamic atrophy and cognition in multiple sclerosis. Neurology. 2007; 69(12):1213–23. doi: 10.1212/01.wnl.0000276992.17011.b5 PMID: 17875909

77. Inglese M, Ge Y, Filippi M, Falini A, Grossman RI, Gonen O. Indirect evidence for early widespread gray matter involvement in relapsing-remitting multiple sclerosis. Neuroimage. 2004; 21(4):1825–9. doi: 10.1016/j.neuroimage.2003.12.008 PMID: 15050603

78. Kassubek J, Unrath A, Huppertz HJ, Lule D, Ethofer T, Sperfeld AD, et al. Global brain atrophy and corticospinal tract alterations in ALS, as investigated by voxel-based morphometry of 3-D MRI. Amyotrophy Lateral Scler Other Motor Neuron Disord. 2005; 6(4):213–20. doi: 10.1080/14660820510038536 PMID: 16319024

79. Kearney H, Altmann DR, Samson RS, Yiannakas MC, Wheeler-Kingshott CAM, Ciccarelli O, et al. Cervical cord lesion load is associated with disability independently from atrophy in MS. Neurology. 2015; 84(4):367–73. doi: 10.1212/WNL.0000000000001186 PMID: 25840312

80. Knutson B, Momenan R, Rawlings RR, Fong GW, Hommer D. Negative association of neuroticism with brain volume ratio in healthy humans. Biol Psychiatry. 2001; 50(9):685–90. PMID: 11704075
101. Smith EE, Egorova S, Blacker D, Killiany RJ, Muzikansky A, Dickerson BC, et al. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. Arch Neurol. 2008; 65(1):94–100. doi: 10.1001/archneurol.2007.23 PMID: 18195145

100. Sanfilippo MP, Benedict RH, Zivadinov R, Bakshi R. Correction for intracranial volume in analysis of whole brain atrophy in multiple sclerosis: the proportion vs. residual method. Neuroimage. 2004; 22(4):1732–43. doi: 10.1016/j.neuroimage.2004.03.037 PMID: 15275929

99. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility—Reykjavik study. Brain. 2011; 134(11):3398–407. doi: 10.1093/brain/awr253 PMID: 22075523

98. Metzler-Baddeley C, O’Sullivan MJ, Bells S, Pasternak O, Jones DK. How and how not to correct for CSF-contamination in diffusion MRI. Neuroimage. 2012; 59(2):1394–403. doi: 10.1016/j.neuroimage.2011.08.043 PMID: 21924365

97. Rekimoto M, Kikinis R, Morocz IA, Lorenzo AV, Sandor T, Albert MS, et al. Age-related changes in white matter hyperintensities and brain volume in the prediction of mild cognitive impairment. Arch Neurol. 2008; 65(1):94–100. doi: 10.1001/archneurol.2007.23 PMID: 18195145

96. Oliveira de Andrade DC, Borba EF, Bonfa E, Freire de Carvalho J, Jose da Rocha A, Carlos Maia A Jr., Quantifying subclinical central nervous lesions in primary antiphospholipid syndrome: the role of magnetization transfer imaging. J Magn Reson Imaging. 2010; 116(2–3):255–9. PMID: 17296989

95. Mezzapesa DM, Caccarelli A, Dicuonzo F, Carella A, De Caro MF, Lopez M, et al. Whole-brain and regional brain atrophy in amyotrophic lateral sclerosis. American Journal of Neurology. 2007; 28(2):255–9. PMID: 17296989

94. Moriya J, Kakeda S, Abe O, Goto N, Yoshimura R, Hori H, et al. Gray and white matter loss along cerebral midline structures in myotonic dystrophy type 2. Journal of Neurology. 2008; 255(12):1904–9. doi: 10.1007/s00415-008-0997-1 PMID: 19224318

93. Mortyja J, Kakeda S, Abe O, Goto N, Yoshimura R, Hori H, et al. Gray and white matter volumetric and diffusion tensor imaging (DTI) analyses in the early stage of first-episode schizophrenia. Schizophrenia Research. 2010; 116(2–3):196–203. doi: 10.1016/j.schres.2009.10.002 PMID: 19854618

92. Torelli F, Moscufo N, Garreffa G, Placidi F, Romigi A, Zannino S, et al. Cognitive profile and brain morphological changes in obstructive sleep apnea. NeuroImage. 2011; 54(2):787–93. doi: 10.1016/j.neuroimage.2010.09.065 PMID: 20888921

91. Matsumae M, Kikinis R, Morocz IA, Lorenzo AV, Sandor T, Albert MS, et al. Age-related changes in white matter hyperintensities and brain volume in the prediction of mild cognitive impairment. Arch Neurol. 2008; 65(1):94–100. doi: 10.1001/archneurol.2007.23 PMID: 18195145

90. Liptak Z, Berger AM, Sampat MP, Charli A, Felssovalyi O, Healy BC, et al. Medulla oblongata volume: A biomarker of spinal cord damage and disability in multiple sclerosis. American Journal of Neuroradiology. 2008; 29(6):1465–70. doi: 10.3174/ajnr.A1162 PMID: 18556361

89. Peinemann A, Schuler S, Pohl C, Jahn T, Weindl A, Kassubek J. Executive dysfunction in early stages of Huntington’s disease is associated with striatal and insular atrophy: A neuropsychological and voxel-based morphometric study. Journal of the Neurologic al Sciences. 2005; 239(1):11–9. doi: 10.1016/j.jns.2005.07.007 PMID: 16185716

88. Divac J, Mandal AK, Stratford PE, Jordanova L, Urquhart M, Mészáros M, et al. Regional brain atrophy in multiple sclerosis: the proportion vs. residual method. Neuroimage. 2004; 22(4):1732–43. doi: 10.1016/j.neuroimage.2004.03.037 PMID: 15275929

87. Marquis S, Moore MM, Howieson DB, Sexton G, Payami H, Kaye JA, et al. Independent predictors of cognitive decline in healthy elderly persons. Arch Neurol. 2002; 59(4):601–6. PMID: 11939895

86. Liu Y, Wang J, Daams M, Weiler F, Hahn HK, Duan Y, et al. Differential patterns of spinal cord and brain atrophy in NMO and MS. Neurology. 2015; 84(14):1465–72. Epub 2015/03/13. doi: 10.1212/ WNL.0000000000001441 PMID: 25762714

85. Lukas C, Hahn HK, Bellenberg B, Rexilius J, Schmid G, Schirrmigk SK, et al. Sensitivity and reproducibility of a new fast 3D segmentation technique for clinical MR-based brain volumetry in multiple sclerosis. Neuroradiology. 2004; 46(11):906–15. Epub 2004/11/13. doi: 10.1007/s00234-004-1282-3 PMID: 15536555

84. Liptak Z, Berger AM, Sampat MP, Charli A, Felssovalyi O, Healy BC, et al. Medulla oblongata volume: A biomarker of spinal cord damage and disability in multiple sclerosis. American Journal of Neuroradiology. 2008; 29(6):1465–70. doi: 10.3174/ajnr.A1162 PMID: 18556361

83. Lemaître H, Crivello F, Grassiot B, Alperovitch A, Tzourio C, Mazoyer B. Age- and sex-related effects and dementia. Arch Neurol. 2008; 65(1):94–100. doi: 10.1001/archneurol.2007.23 PMID: 18195145
102. Tavazzi E, Dwyer MG, Weinstock-Guttman B, Lema J, Bastianello S, Bergamaschi R, et al. Quantitative diffusion weighted imaging measures in patients with multiple sclerosis. NeuroImage. 2007; 36(3):746–54. doi: 10.1016/j.neuroimage.2007.03.056 PMID: 17498974

103. Tiberio M, Chard DT, Altmann DR, Davies G, Griffin CM, Rashid W, et al. Gray and white matter volume changes in early RRMS: A 2-year longitudinal study. Neurology. 2005; 64(6):1001–7. doi: 10.1212/01.WNL.0000154526.22878.30 PMID: 15781816

104. Traboulsee A, Dehmeshki J, Peters KR, Griffin CM, Brex PA, Silver N, et al. Disability in multiple sclerosis is related to normal appearing brain tissue MTR histogram abnormalities. Multiple sclerosis (Houndmills, Basingstoke, England). 2003; 9(6):566–73.

105. Uçar CA, Yüceyar AN, Kitiş Ö, Köse T, Ekmekçi Ö, Sagduyu Kocaman A. Quantification of brain atrophy in early multiple sclerosis and its clinical relevance. Journal of Neurological Sciences. 2016; 33(2):233–43.

106. Yaldızlı Ö, Penner IK, Yonekawa T, Naegelin Y, Kuhle J, Pardini M, et al. The association between olfactory bulb volume, cognitive dysfunction, physical disability and depression in multiple sclerosis. European Journal of Neurology. 2016; 23(3):510–9. doi: 10.1111/ene.12891 PMID: 26699999

107. Yamasue H, Abe O, Kasai K, Suga M, Iwanami A, Yamada H, et al. Human brain structural change related to acute single exposure to sarin. Annals of Neurology. 2007; 61(1):37–46. doi: 10.1002/ana.21024 PMID: 17187377

108. Zimmermann H, Rolfsnes HO, Montag S, Wilting J, Droby A, Reuter E, et al. Putaminal alteration in multiple sclerosis patients with spinal cord lesions. Journal of Neural Transmission. 2015; 122(10):1465–73. doi: 10.1007/s00702-015-1406-4 PMID: 25971605

109. Zito G, Luders E, Tomasevic L, Lupi D, Toga AW, Thompson PM, et al. Inter-hemispheric functional connectivity changes with corpus callosum morphology in multiple sclerosis. Neuroscience. 2014; 266:47–55. doi: 10.1016/j.neuroscience.2014.01.039 PMID: 24486438

110. Zivadinov R, Banas AC, Yella V, Abdelrahman N, Weinstock-Guttman B, Dwyer MG. Comparison of three different methods for measurement of cervical cord atrophy in multiple sclerosis. American Journal of Neuroradiology. 2008; 29(2):319–25. doi: 10.3174/ajnr.A0813 PMID: 17974604