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ORIGINAL ARTICLE

Brain parenchymal fraction in an age-stratified healthy population — determined by MRI using manual segmentation and three automated segmentation methods

Mattias Vågberg[a,*], Khalid Ambarki[b,c], Thomas Lindqvist[b], Richard Birgander[b], Anders Svenningsson[a]

[a] *Department of Pharmacology and Clinical Neuroscience, Section of Neuroscience, Umeå University, 90185 Umeå, Sweden*
[b] *Department of Radiation Sciences, Umeå University, Umeå, Sweden*
[c] *Centre for Biomedical Engineering and Physics, Umeå University, Umeå, Sweden*

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Summary
Background and purpose: Brain atrophy is a prominent feature in many neurodegenerative diseases, such as multiple sclerosis, but age-related decrease of brain volume occurs regardless of pathological neurodegeneration. Changes in brain volume can be described by use of the brain parenchymal fraction (BPF), most often defined as the ratio of total brain parenchyma to total intracranial space. The BPF is of interest both in research and in clinical practice. To be able to properly interpret this variable, the normal range of BPF must be known. The objective of this study is to present normal values for BPF, stratified by age, and compare manual BPF measurement to three automated methods.
Materials and methods: The BPFs of 106 healthy individuals aged 21 to 85 years were determined by the automated segmentation methods SyMap, VBM8 and SPM12. In a subgroup of 54 randomly selected individuals, the BPF was also determined by manual segmentation.
Results: The median (IQR) BPFs of the whole study population were 0.857 (0.064), 0.819 (0.028) and 0.784 (0.073) determined by SyMap, VBM8 and SPM12, respectively. The BPF decreased with increasing age. The correlation coefficients between manual segmentation and SyMap, VBM8 and SPM12 were 0.93 ($P < 0.001$), 0.77 ($P < 0.001$) and 0.56 ($P < 0.001$), respectively.

Abbreviations: BPF, brain parenchymal fraction; BPV, brain parenchymal volume; CSF, cerebrospinal fluid; ICV, intracranial volume; IQR, interquartile range; MNI, Montreal Neurological Institute; SPM, statistical parametric mapping; SyMap, synthetic tissue mapping; VBM, voxel-based morphometry.

* Corresponding author. Tel.: +46907850000.
E-mail address: mattias.vagberg@umu.se (M. Vågberg).

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Conclusions: There was a clear relationship between increasing age and decreasing BPF. Knowledge of the range of normal BPF in relation to age group will help in the interpretation of BPF data. The automated segmentation methods displayed varying degrees of similarity to the manual reference, with SyMap being the most similar.

Introduction

The occurrence of an increased rate of loss of brain parenchyma compared with healthy individuals, i.e. brain atrophy, is an important feature of many neurodegenerative disorders. Recognizing the importance of brain atrophy, there is an increasing interest to measure it not only in research but also in the clinical setting [1,2]. Several different methods to quantify brain atrophy exist. To directly measure the brain volume is suboptimal, however. A large inter-individual variability in brain size related to difference in overall skull size makes it difficult to determine if atrophy beyond the normal aging process has occurred. This can be circumvented by instead measuring the ratio of the total brain parenchymal volume (BPV) to the total intracranial volume (ICV), thus using the ICV to normalize the brain volume. The ICV only undergoes minimal change during adult life [3,4], allowing for age- or pathology-associated changes in BPV to be determined. Furthermore, since the normalization variable (ICV) is measured alongside the BPV for every new longitudinal measurement, the effects of subtle changes in magnetic resonance imaging (MRI) acquisition between time points are minimized. This ratio was first presented as percentage of brain parenchyma [5]. The now dominant term brain parenchymal fraction (BPF) was later introduced [6]. Slight differences in the definition of the term exist, but the definition presented above is the one most widely used.

The BPF has been used as a marker for brain atrophy in several different disease entities, including multiple sclerosis [6], dementia [7] and Huntington's disease [8]. In the example of multiple sclerosis, it has been shown that brain atrophy is a prognostic factor for future disability, correlating with the amount of inflammatory lesions [9] and, perhaps most importantly, can be attenuated by the use of disease modifying treatment [2].

In order to interpret the BPF in relation to pathology, knowledge of the BPF in healthy individuals is required. There is no widely accepted consensus regarding gold standard for BPF measurement but manual segmentation of MRI images is an attractive option as it allows for complete visual control over the segmentation. However, due to the time investment required for manual segmentation its usefulness is limited in the setting of large data sets or in the clinical workflow. For this reason, several automated ways to measure BPF exist.

In this article, we used the MRI-based methods synthetic tissue mapping (SyMap) [10], voxel-based morphometry (VBM) [11] and statistical parametric mapping (SPM) [12] to determine the BPF of 106 healthy individuals, stratified by age. As a reference, the BPF was also determined by manual brain segmentation for a subset of 54 randomly selected individuals. The study had two main goals. Firstly, to increase the knowledge on the normal range of BPF values, as determined by the three automated methods, in order to facilitate interpretation of BPF values in the setting of pathology. Secondly, to relate the BPF values from the automated segmentation methods to that of a manual reference method.

Material and methods

Study population

Healthy individuals were recruited through local advertising among hospital employees, medical students and spouses of patients at the neurology clinic of Umeå University Hospital and via newspaper advertising. All participants were interviewed by a research nurse to assess inclusion and exclusion criteria. In cases of uncertainty, the research nurse consulted one of the study physicians. The MRI of each individual was examined by a senior consultant in neuroradiology in conjunction with a senior consultant in neurology.

Inclusion criteria were:

- volunteering to participate and sign informed consent;
- age between 18 and 90 years old.

Exclusion criteria were:

- symptoms or history indicative of disease suspected to affect BPF measurement or first-degree relatives with such diseases:
  - 17 individuals (two cases of tumor/malignancy, three cases of cerebrovascular disease, two cases of previous inpatient care for neurological symptoms and nine cases of neurological disease in the family);
- contraindications for undergoing MRI:
  - 4 individuals (implantations that were not compatible with MRI);
- pathological MRI findings at study MRI:
  - 5 individuals (two cases of cerebral ischemic lesions, one case of possible intracerebral tumor, one case of meningioma combined with one ischemic lesion and one case of possible pineal gland tumor).

In addition, two individuals were excluded due to technical problems with the MRI acquisition. Individuals who had abnormal MRI findings not found to be of clinical significance and assumed to have minimal impact on BPF were included. These findings were unspecific white matter signal