Trends in Brain Volume Change with Normal Ageing

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Abstract. In order to measure cerebral atrophy due to neurodegenerative diseases, the major confounding factor of normal age-related atrophy must be taken into account. We describe a normalisation for this effect, based on measuring CSF volumes in MR images of 70 normal volunteers. We also investigate the regional distribution of the atrophy, and conclude that age-related cerebral atrophy occurs uniformly across the brain at coarse scales and obeys a Weibull cumulative distribution function.

1 Introduction

Distinctive patterns of accelerated cerebral atrophy are a feature of a large number of neurodegenerative and dementing disorders such as Alzheimer's disease, frontotemporal dementia, Parkinson's disease and others. In previous work [7] we demonstrated the feasibility of using relatively coarse regional measurements of brain volume to diagnose the above diseases. However, atrophy also occurs in normal ageing, and this confounding effect must be removed in order to identify abnormal effects due to disease. The purpose of the work described here was to determine correction factors for age-related atrophy for arbitrary coarse ($\approx 10 - 100 cm^3$) regions of the brain.

Previous work on the effects of normal ageing on brain volume [2, 3, 9] has focused on measurements of grey and/or white matter volumes. We instead measured only cerebro-spinal fluid (CSF) volumes. Since the interior volume of the cranium is approximately fixed throughout adulthood [3], increases in CSF volume provide an accurate marker for decreases in grey and white matter volume. However, since the grey-level separation between CSF and the other tissues present is higher than the separation between grey/white matter and bone, fat and air, for the MR imaging sequence used here, the signal-to-noise ratio for the segmentation process is higher and thus the segmentation is more accurate. In addition, since the CSF volume is much lower than the combined grey and white matter volume ($\approx 7 - 9\%$ of the total intra-cranial volume between early childhood and adolescence [3]), any trends in the volume change are much more apparent. This allows such trends to be identified more accurately, and therefore allows some conclusions on the underlying biological processes that lead to age-related atrophy to be drawn. The drawback of measuring CSF is that volume changes cannot be ascribed to specific tissue locations. However, this issue did not affect the work described here since, as demonstrated below, no regional variation in age-related atrophy was detected between arbitrary ($\approx 10 - 100 cm^3$) volumes.

2 Method

Heavily T1-weighted inversion recovery MR image volumes were obtained from 70 normal volunteers (36 male and 34 female) ranging in age from 19 to 85 years with a mean age of 65.5, and real image reconstruction was performed. All MR volumes were then coregistered to the volume that represented the median of the patient group in terms of its atrophy pattern, using rigid Mutual Information based coregistration [1], allowing subsequent analysis of the results in a standard coordinate system. Segmentation of the CSF was achieved using a technique based on fitting a partial volume model of the tissues present in the head using the Expectation-Maximisation algorithm, as described in [6]. The segmented images were then multiplied with a set of binary masks produced in the standard coordinate system. The masking had two purposes: to delete non-CSF fluid spaces (e.g. eyes, sinuses) and to enforce a consistent inferior boundary to the measurement space, defined by drawing a line in the mid-sagittal section parallel to the horizontal axis that passed through the junction of the calvarium and the tentorium cerebelli. The anterior, posterior, lateral, and superior boundaries of the CSF space were automatically identified by locating the extremes of the CSF.

In order to avoid errors in the CSF volume measurements due to interpolation, all CSF measurements were performed in the original coordinate system of the data, and the coregistration was used only to align the masks. Therefore, normalisation for head size differences was also required. Division of brain volume measurements by total intra-cranial volume (TIV) has been shown [9] to be an effective normalisation for both inter-individual variations in head size and variation in voxel sizes in longitudinal studies, but assumes an accurate segmentation of the

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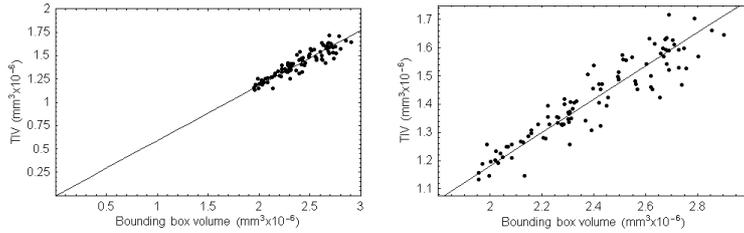* E-mail: paul.bromiley@man.ac.uk

Figure 1. The relationship between the TIV and the CSF bounding box size for head-size normalisation

intra-cranial space. In other work [7] we have used a simpler alternative, finding the product of the maximal CSF extents in the anterior-posterior, lateral, and superior-inferior directions, multiplying these to produce the volume of a bounding box on the CSF space, and dividing all volume measurements by this volume in order to normalise for head size. In order to compare the two, a simple TIV measurement was obtained through an independent segmentation technique, using a simple grey-level threshold. Figure 1 shows TIV plotted against CSF bounding box volume. The two measurements are directly proportional and the standard deviation of the fit residuals is approximately the same (R.M.S. error of 3.8% in both cases), showing that CSF bounding box and TIV normalisations are statistically equivalent. TIV normalisation was used for the remainder of the work, since the results are more easily related to tissue volumes. The main effect of this normalisation was to correct for sex-linked differences in head size, which was found (as in previous studies e.g. [3]) to be on average 12% lower in females than in males. The mean TIV across the patient group was $1.42 \pm 0.145l$, consistent with previous results [2, 3, 9].

3   Results

Figure 2 shows the distribution of normalised total CSF volumes with age. A markedly non-linear trend can be seen in the data. Previous studies [3] have produced some evidence for such a trend, but not at statistically significant levels. Its presence here allows speculation on the underlying biological causes of age-related atrophy. Several candidate functions were fitted to the data in order to explore its age dependence, and are shown in Fig. 2. The non-polynomial functions were fitted using the Levenberg-Marquadt technique. Since the data represent the result of a counting process they were subject to Poisson errors, and so were weighted by their square-root during the fitting process in order to normalise their variances [5]. No independent estimate of the errors was available and so χ^2 goodness-of-fit probabilities could not be calculated in the usual way. Instead a noise estimate was obtained from the Weibull CDF fit, which had the lowest residuals, assuming a χ^2 per degree of freedom of one, and used to calculate relative goodness-of-fit probabilities for the other functions. These are given in Table 1.

Two types of process could be envisaged: a mechanism resulting in continuous volume loss, such as might be seen in dehydration or demyelination that occurs in diseases such as alcoholism and multiple sclerosis, or a volume loss associated with the loss of discrete units (e.g. neurons). A continuous process with a constant rate of volume loss would result in a linear dependence: the bi-linear function represented this possibility, allowing for a non-zero age of onset for the atrophy (set to 55 years, identified in [3] as the age of onset of accelerated volume loss). This function can be rejected at the p=95% confidence level on the basis of the χ^2 tests. The quadratic function represented a continuous process with a linearly increasing rate of volume loss. Its relative goodness-of-fit probability was 41%: statistically a significantly worse fit than the Weibull CDF, although not sufficient for a categorical rejection. If the atrophy were due to the loss of discrete units with a constant probability, i.e. a Poisson process, then an exponential decrease in brain volume would be observed. However, this would produce a decrease in the rate of atrophy with age: the data show an increase. The goodness-of-fit probability for a function representing exponential growth of the CSF is statistically equivalent to that for the Weibull CDF, but it is difficult to envisage a biologically plausible mechanism that would lead to this dependence, since it takes no account of the grey and white matter volume, and extrapolates to a brain volume of zero at the unacceptably low age of 115 years. Finally, systems that exhibit loss of discrete units with a time-dependent probability usually exhibit a Weibull distribution. This function was originally used to describe failure rates in light bulbs [8], and is commonly observed in systems where the decay of a given unit increases the probability of decay in those remaining. Given the high level of interconnectivity in the brain, this is a more plausible mechanism for cerebral atrophy than exponential CSF growth. Therefore, although the goodness-of-fit probability for the Weibull CDF is statistically indistinguishable from that for the exponential function, we tentatively conclude that the data show a Weibull functional dependence. This function gives an average atrophy rate of 0.33% of the TIV per year between the ages of 60 and 80, consistent within errors to the 0.41% measured from a much smaller sample in [4].
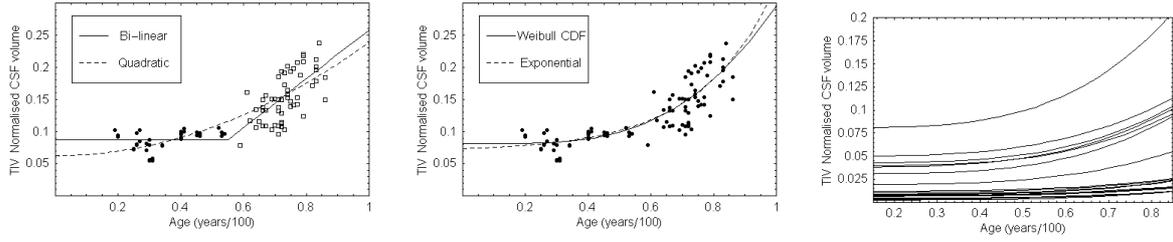
Figure 2. Bi-linear, quadratic, exponential and Weibull CDF fits to the normalised CSF volumes, and Weibull fits to all volumes and sub-volumes (right).
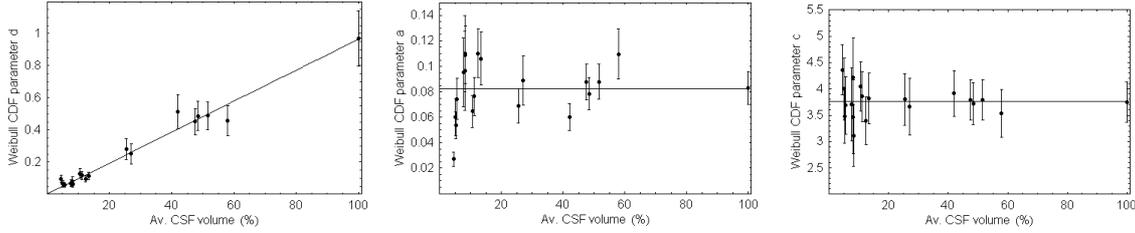

Figure 3. The Weibull fit parameters d, a, and c for all volumes and sub-volumes. Errors were estimated from the confidence interval on the fits themselves, and so are correlated across the parameters.

In order to investigate the regional distribution of the volume loss, the CSF space was divided into twelve equi-sized volumes as described in [7] and fitted using Weibull CDFs. Parameter "b" of the function sets the scales the abscissa: we instead required an overall multiplicative scale parameter (i.e. a scaling parameter on the ordinate), to account for sub-volumes containing less than 100% of the total TIV. Therefore, parameter "b" was fixed to the value determined from the fit to the whole CSF volume, and a multiplicative scale parameter "d" was applied to the function. Figure 2c shows Weibull CDF fits to all volumes and combinations of contiguous sub-volumes (the sums of the front, middle and back four volumes, and the sums of the left, right, top and bottom six volumes). The curves suggest that age-related atrophy shows no regional dependence i.e. that the fit parameters for a given region depend only on the proportion of the CSF that is located in that region. Ideally this proportion would be determined from an independent normal brain atlas: since the subject group used in this study was large, it was deemed acceptable to use an average of all subjects instead. Therefore, the parameters of the fits were plotted against the the percentage x of the total CSF volume in each region[1], and are shown in Fig.3. The fits are dependent only on the scale parameter d, which is directly proportional to x (where d/x is the ratio of total CSF volume to TIV, averaged over all subjects). Parameter "a" is the intercept of the fit to the total volume. The shape parameter "c" is constant to within errors, proving that for volumes of this size there is no regional dependence of age-related atrophy. Therefore, normalisation factors for age-related atrophy in arbitrary volumes can be interpolated using the parameters $d = 9.655 \times 10^{-3}x$, $a = 8.239 \times 10^{-2}$, and $c = 3.850$ obtained from the linear fits shown in Fig.3, $b = 1.409$, and the equation

$$CSF\ volume/TIV = d[a + (1-a)(1 - e^{-[\frac{age\ (years)}{100b}]^c})]$$

The RMS errors on both interpolated and fitted Weibull CDF functions for all volumes and sub-volumes are shown in Fig. 4. Since the fitting was performed in a variance-normalised domain, the fitting errors were expected to show a linear dependence on the averaged CSF volume: this can indeed be seen in the results, and linear fits to the data are shown. The averaged increase in the RMS error due to interpolation across all volumes was 2.17%: a statistically insignificant amount. The errors obey the dependence

$$RMS\ error = 1.155 \times 10^{-3} + 2.327 \times 10^{-2}x$$

Name	Function	Fit probability c.f.Weibull fit (%)
Bi-linear	$y = a$ $(x < 0.55)$ $\quad$ $y = bx + c$ $(x > 0.55)$	3.0
Quadratic	$y = ax^2 + b$	41.0
Exponential	$y = a + be^{cx}$	94.3
Weibull CDF	$y = a - (1-a)(1 - e^{-(x/b)^c})$	100

Table 1: Errors on functions fitted to the total normalised CSF volumes measurements shown in Figure 2.

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[1] This quantity was found to be independent of age: again showing that, at this scale, age-related atrophy occurs evenly throughout the brain.
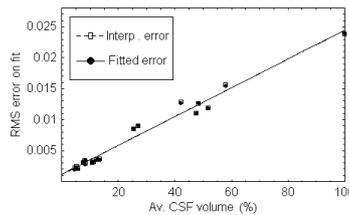
Figure 4. RMS error on fitted and interpolated Weibull CDFs for all sub-volumes.

4   Conclusion

In previous work [7] we have shown the feasibility of developing fully automatic diagnostic systems for neurodegenerative diseases using regional measurements of CSF volume as a surrogate for measuring cerebral atrophy. Normalisation for the major confounding effect of age-related atrophy is required in order to identify the influence of disease on such measurements. This paper has presented such a normalisation, and also the first statistically significant observation of a non-linear trend in age-related atrophy. It has shown that age-related atrophy can plausibly be described by a Weibull CDF, and that the atrophy occurs evenly throughout the brain at the scale of arbitrary ($\approx 10 - 100 cm^3$) volumes. Therefore, interpolated correction factors can be produced for any region based on the proportion of the CSF located in that region, determined from a normal brain atlas. However, this simple relationship may fail for small volumes containing specific structures, particularly in the brain stem. Cerebral volume measurements also frequently require normalisation for head size or variations in voxel dimensions, often achieved by normalising to TIV. This paper has shown that normalisations to the volume of the bounding box on the CSF space and to TIV are equivalent. Therefore, in studies that involve analysis of CSF distribution, this equivalence removes the need to measure TIV, avoiding a potential source of error and reducing the computational overhead.

Identification of the functional behaviour of age-related atrophy as a Weibull CDF allows speculation on the underlying biological processes. It indicates that the atrophy is due to the loss of discrete (presumably cellular) units within the brain, with a time-dependent (power law) probability of decay. Such behaviour is observed in systems where the decay of a given unit increases the probability of decay in those remaining: this is an entirely plausible mechanism in a highly interlinked system such as the brain.

Acknowledgements

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