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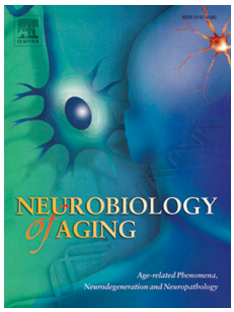

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Estimates of age-dependent cut-offs for pathological brain volume loss using SIENA/FSL – A longitudinal brain volumetry study in healthy adults

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Keywords: brain atrophy, aging, multiple sclerosis, brain volume loss, SIENA, cut-off

Abstract

Brain volume loss (BVL) has gained increasing interest for monitoring tissue damage in neurodegenerative diseases including multiple sclerosis (MS). In this longitudinal study 117 healthy participants (age range 37.3–82.6 years) received at least 2 magnetic resonance imaging examinations. BVL (in %) was determined with SIENA/FSL and annualized. Mean BVL per year was 0.15%, 0.30%, 0.46%, and 0.61% at ages 45, 55, 65, and 75, respectively. The corresponding BVL per year values of the age-dependent 95th percentiles were 0.52%, 0.77%, 1.05% and 1.45%. Pathological BVL can be assumed if an individual BVL per year exceeds these thresholds for a given age. The mean BVL per year determined in this longitudinal study was consistent with results from a cross-sectional study that was published recently. The cut-off for a pathological BVL per year at age 45 (0.52%) was consistent with the cut-off suggested previously to distinguish between physiological and pathological BVL in MS patients. Different cut-off values, however, need to be considered when interpreting BVL assessed in cohorts of higher ages.

Introduction

Brain atrophy determined by structural magnetic resonance imaging (MRI) is an increasingly recognized measure of degenerative pathology in neurodegenerative disorders including multiple sclerosis (MS). Brain volume loss per year (BVL per year) between 0.1% and 0.3% has been reported in young, healthy individuals (Takao, et al., 2012). In contrast, MS patients of comparable age show BVL per year that typically cluster between 0.50% and 1.35% (Chard and Miller, 2009). Such BVL per year clearly falls beyond what seems related to physiological aging and thus may serve as a potential early marker of disease progression (Fisniku, et al., 2008, Popescu, et al., 2013). Recently, a cut-off of 0.52% BVL per year (with an error rate of 5%) or 0.40% BVL per year (with an error rate of 20%) has been suggested to distinguish between physiological and pathological BVL in MS patients (De Stefano, et al., 2016).

Several cross-sectional (Fjell, et al., 2009, Fjell, et al., 2013, Marcus, et al., 2007, Schippling, et al., 2017, Ziegler, et al., 2012), as well as longitudinal studies (Driscoll, et al., 2009, Hedman, et al., 2012, Marcus, et al., 2010, Taki, et al., 2011), found that BVL critically depends on age, in both, MS patients and healthy individuals. A recent study reported age dependent mean BVL per year values in physiological aging (Schippling, et al., 2017). However, the data in that study were extrapolated from cross-sectional brain volumetry data using a non-parametric fitting approach. As discussed before (Schippling, et al., 2017), cross-sectional data allows the determination of mean BVL per year values of a given cohort, but lacks estimates of the biological variability (age-dependent standard deviations) of BVL per year values for a specific age range. To interpret BVL per year in disease models correctly, it is of utmost importance to do so against the background of measurements derived from longitudinal studies in healthy aging populations, to allow a correction for physiological aging. The aim of this study was to validate BVL per year in healthy individuals that some of the authors of this study previously investigated cross-sectionally (Schippling, et al., 2017) using a longitudinal cohort of healthy individuals. We assessed the mean and the variability of the BVL per year for each age range. Beyond confirming results of other longitudinal studies on physiological aging (Driscoll, et al., 2009,Hedman, et al., 2012,Marcus, et al., 2010,Taki, et al., 2011), in a large single-scanner cohort, the aim of this study was to provide cut-off values to discriminate physiological from pathological BVL in an age-dependent manner.

Methods

Study participants

The cohort was selected from a group of asymptomatic, healthy individuals undergoing a brain MRI scan as part of an extensive medical prevention program at the Medical Prevention Center (MPCH) in Hamburg, Germany. All participants gave written informed consent. The study was approved by the Ethics Committee of the Board of Physicians in Hamburg, Germany. Individuals participating in the prevention program were included into the final cohort if they had no history of or currently ongoing neurological or psychiatric condition, and if there were no structural abnormalities on the brain MRIs according to visual inspection by an experienced radiologist (C.G.). Eligible participants received at least two MRI examinations on the same 1.5 Tesla Magnetom Avanto® scanner (Siemens Medical Solutions, Erlangen, Germany, software version B15) using the identical 8-channel head coil and identical sequence settings

throughout the study. Originally, 119 participants were included in this study. Two of these participants were excluded; one participant (age 23.7 years) was more than 10 years younger than the second-youngest participant of the cohort. Similarly, the second excluded participant (age 88.9 years) was more than 5 years older than the second-oldest participant of the cohort. We excluded these patients to avoid non-linear effects in the fitting of the results for the whole cohort. From the remaining 117 participants, 93 were males and 24 were females and the mean age was 61.9 years (range 37.3–82.6 years). The cohort comprised 89 participants with exactly one follow-up scan, 20 participants with 2 follow-up scans, and 8 participants with more than 2 follow-up scans. Age distribution of the cohort is shown in Figure 1. The mean interval time between baseline and the latest follow-up scan was 3.2 years (standard deviation (SD) 1.54 years, range 2-7 years).

MRI protocol

The MRI protocol consisted of a 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence with a repetition time (TR) of 980 ms, echo time (TE) of 2.95 ms, inversion time (TI) of 600 ms, a flip angle of 15°, and an isotropic voxel grid of 1 mm. The MPRAGE sequence lasted for approximately 3:10 minutes. The MPRAGE sequence was applied as a diagnostic sequence as part of a larger protocol that included a whole body MRI examination with an angiogram. For the angiogram, a contrast agent (Gadovist®) was applied. The MPRAGE sequence analyzed for this study was obtained before contrast agent administration. As the scanner is a dedicated examination tool for the prevention program, protocol settings, head coil, and software version were kept unchanged throughout the study period. In less than 1% of the scans the MPRAGE sequence was repeated due to motion artifacts. Regular consistency measurements were performed on the scanner as an important part of the regular 3-4 months service intervals to ensure no deviation from former measurements. The images analyzed in this study are therefore comparable over the whole study period.

Brain volume loss (BVL) with SIENA

BVL of the whole brain between two time points was quantified using the SIENA method (Smith, et al., 2002) which is part of the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl). The performance of SIENA can differ greatly depending on parameter settings and pre-processing steps (Cover, et al., 2014, Popescu, et al., 2012). We used SIENA (Version 5.06) with optimized preprocessing parameters. As a first preprocessing step we applied the FSL script “fslreorient2std” to match the orientation of all images to that of the standard template image (MNI). In addition, we performed a neck removal as recommended (Popescu, et al., 2012). Skull-stripping with the brain extraction tool BET (FSL; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET/) was deployed and the SIENA settings were "-B -f 0.2 -m", which differ from the default settings. With the configuration described we calculated the BVL (in %) for all study participants. For several participants, more than two scans were available. In these cases the BVL was calculated for each pair of two consecutive MRI scans. Annualized BVL (BVL per year) was calculated for each participant from the slope of the regression line fitted to all BVL measurements for that participant. More precisely, if bvl_i denotes the percentage BVL measurement between two time points age_i and age_{i+1}, then the participant’s brain volume (denoted by vol) will change according to the

formula $vol_{i+1} = vol_i \cdot (1 - bvl_i/100)$. For each participant we then computed a linear regression function f fitting the data (age_i , vol_i). The final annualized percentage BVL for each study participant was then defined as $\frac{bvl}{year} := 100 \cdot \frac{f(age_0)-f(age_n)}{f(age_0)(age_n-age_0)}$ where age_0 is the age at baseline and age_n is the age at the last follow-up scan. Note, that $bvl/year$ computed with the formula above is independent from the brain volume vol_0 at baseline, which was set to 100. In the case of only two available MRI scans (and thus only one BVL measurement) the formula reduces to $100 \cdot \frac{f(age_0)-f(age_1)}{f(age_0)(age_1-age_0)} = \frac{bvl_1}{\text{age}_1-\text{age}_0}$. The latter expression is the known formula to annualize BVL measurements (BVL per year).

Statistics

For the analysis of each participant, age was defined as the mean of the age at baseline and the age at the last follow-up scan. Age and BVL per year were tested for differences between males and females with a two-sample t-test. We calculated a linear regression function reg between age (denoted by age_i) and $bvl/year$ for all study participants. Points on the regression line can be interpreted as mean BVL per year for a particular age. For each age we determined the variability of the measurements at that age by a sliding window technique. More precisely, for each age x all participants with ages within the interval x±15 years were used to compute the age dependent 80th and 95th percentile of the distances from the measured BVL per year to the regression line at the corresponding ages (more mathematically: for each age x we computed the percentiles(x) of the numbers $\{(reg(age_j) - bvl_j/year) : \text{all } j \text{ such that } x - 15 \leq age_j \leq x + 15\}$). For each age we can expect that 5% of the measurements exceed the 95th percentile and 20% of the measurements exceed the 80th percentile. Therefore, the 95th percentile can be used as a cut-off for pathological BVL per year with an error probability of 5% and the 80th percentile can be used as a cut-off with an error probability of 20%.

Results

Mean BVL per year was not significantly different between male (0.42% ± 0.37%) and female (0.36%± 0.35%) participants (p=0.51; Table 1). Mean BVL per year was 0.15%, 0.30%, 0.46%, and 0.61% at ages 45, 55, 65, and 75, respectively (Table 2 and regression line depicted in Figure 2). In Table 2, columns three and four show the 80th and 95th percentiles for BVL per year between ages 45 to 80 years. These values can serve as age-dependent cut-offs to distinguish physiological from pathological BVL with 80% and 95% specificity, respectively. The cut-offs for a pathological BVL per year (with an error probability of 5%) were 0.52%, 0.77%, 1.05%, and 1.45% at ages 45, 55, 65, and 75, respectively (Table 2 and Figure 2). Figure 2 shows the association of age with measured BVL per year and the resulting 95th percentiles. Figure 3 shows example slices of 3D T1-weighted images from a 46-year-old and a 72-year-old participant, illustrating the different BVL rates at different ages.

Discussion

BVL per year values reported here using SIENA/FSL in a longitudinal cohort of healthy individuals were consistent with BVL per year values extrapolated from cross-sectional data that some of the authors of this study reported before (Schippling, et al., 2017). Previously, 0.24% BVL per year at age 45 and 0.52% at age 70 was determined from cross-sectional data (Schippling, et al., 2017), whereas in this longitudinal study we found a BVL per year of 0.15% at age 45 and 0.53% at age 70. We therefore confirmed the previous observation that BVL increases concomitantly with age. The baseline MRIs of 29 participants of this longitudinal study were part of the data in the above mentioned cross-sectional study (Schippling, et al., 2017). Few other studies did not observe a similar relationship between BVL and aging (Jack, et al., 2008, Mueller, et al., 1998 , Scahill, et al., 2003). A possible limitation of these studies is the small sample size ($n \approx 40$). In addition, for longitudinal studies in particular, the methodology applied for the determination of BVL impacts greatly on the results (Durand-Dubief, et al., 2012). It is known that segmentation based methods usually feature a higher variability than registration based methods (Durand-Dubief, et al., 2012). Thus, it is important to measure BVL with a method featuring high accuracy and low variability. In this study, BVL was measured with SIENA/FSL which is a registration based method (Smith, et al., 2002). This software tool is well established in the assessment of longitudinal BVL and features a median error of 0.15% (Smith, et al., 2002). The interval between MRI examinations is critical and needs to be sufficiently long, to distinguish between changes due to physiological effects and those due to methodological and biological noise. For participants with only one follow-up, we annualized BVL values by dividing the value by the length of the interval between scans (which is the same as the slope of the regression line through the measurements divided by the scan interval) thereby improving the signal-to-noise ratio. The mean scan interval in this study was 3.2 years (range 2-7 years), hence the magnitude of the noise level of BVL per year in this study is approximately 0.15%/3.2 = 0.046%. Since the estimated noise level of 0.046% is approximately 10 times smaller than the measured effects (mean BVL per year is 0.42%) we can conclude that noise or measurement error has only a limited impact on our results.

With increasing age, the BVL per year measurements seem to have more variability (see scatter plot in Figure 2). From a biological perspective, a lifetime of influencing (including toxic) factors has accumulated in older participants and may impact on the actual brain volume. Also, it cannot be ultimately ruled out that in some older participants, subclinical or very early pathological effects impact brain tissue integrity. Therefore, determining the physiological BVL and reliably distinguishing it from pathological atrophy becomes even more challenging with older age. One aim of our study was to capture this age dependent variability by applying a sliding window technique when computing the 80^{th} and 95^{th} percentiles. We used a window size of 30 years (± 15 years) which we found to be large enough to capture a sufficient number of measurements for each window, while at the same time, small enough to capture the increasing variability. At the boundary of the data (age 45 and 80) the sliding window interval contained 54 measurements while at the center of the data (age 60) the interval contained 96 measurements. An alternative approach is to compute constant 80^{th} and 95^{th} percentiles over the whole age range. By doing so, the resulting age dependent 95^{th} percentiles are 0.73% per year, 0.88% per year, 1.04% per year, and 1.19% per year at ages 45, 55, 65, and 75, respectively (the corresponding values with the sliding window

technique are shown in Table 2, column 4). The resulting cut-offs using a constant 95th percentile seem to overestimate true variability for younger participants and to underestimate it for older individuals.

As mentioned above, a cut-off of 0.52% per year (error rate 5%) or 0.40% per year (error rate 20%) has been suggested based on a cohort of 35 healthy controls (mean age 37 years) to distinguish physiological from pathological BVL in MS (De Stefano, et al., 2016). The mean follow-up time in that study was 6.3 years and the BVL was computed with the same method (SIENA/FSL) as in our study. From this longitudinal cohort, we obtain cut-offs of 0.52% per year (error rate of 5%) and 0.33% per year (error rate of 20%) for 45-year-old patients which is consistent with the cut-offs proposed in that previous study. Our results also clearly show that for older age groups different cut-off values for pathological BVL need to be considered (Table 2).

It is not trivial to establish a sensitive cut-off that is able to discriminate between physiological and pathological BVL in MS patients as previously mentioned (Barkhof, 2016, De Stefano, et al., 2016) since the overlap between BVL in patients and healthy controls is significant. In particular, not all MS patients exhibit pathological brain atrophy. A number of disease (e.g. inflammatory edema, seemingly increasing brain volumes) and treatment related factors (e.g. washout of inflammatory edema leading to so-called "pseudo-atrophy") complicate the interpretation of single measures, especially when applied on short-term repeated MRI scans. Therefore, the increased variability of physiological BVL per year with age adds to the complexity of brain volume measures on a single patient level, rendering it difficult to reliably distinguish between physiological and pathological BVL. With the cut-offs provided here, it is, however, possible to estimate whether or not a measured BVL falls beyond the borders of the physiological range with satisfying specificity.

In contrast to other longitudinal studies on physiological ageing (Driscoll, et al., 2009, Hedman, et al., 2012, Marcus, et al., 2010, Taki, et al., 2011), this study includes a large cohort of healthy participants with a broad age range and a sufficiently long follow-up time. Furthermore, we used highly standardized MRI acquisitions over several years in a single-scanner setting. To our knowledge, this is the first study reporting mean BVL per year values as well as the biological variability of BVL per year in physiological aging for a broad age range. However, a possible limitation of this study is the male preponderance of the cohort, since particularly in MS, women are more frequently affected. We did not find, however, a significant difference in age or BVL per year between gender, the latter being consistent with previous publications (Fjell, et al., 2009, Takao, et al., 2012, Tang, et al., 2001).

Other factors that might have an impact on accelerated atrophy in older age are related to lifestyle, like smoking or alcohol consumption, genetics, like apolipoprotein E expression as much as cardiovascular risk profiles, like diabetes or hypertension (Enzinger, et al., 2005). Even if biological factors are accounted for, methodological factors such as scanner, coil, and protocol changes greatly influence the results of BVL measurements. We tried to mitigate these effects by using scans that were acquired on the same MRI scanner with the same protocol and settings throughout the study. We used a widely applied software package (SIENA), which has been shown to have low test-retest variability (Cover, et al., 2011, Smith, et al., 2007). However, we have to emphasize that the provided cut-offs are only valid for results obtained using the same method. Finally, the method used here does not provide information on regional volume changes. Other methodologies such as Jacobian determinant (Ashburner and Ridgway, 2012) or Statistical

Parametric Mapping (Ashburner and Friston, 2000, Muhlau, et al., 2009) should be applied to obtain tissue specific cut-off values of BVL.

Disclosures

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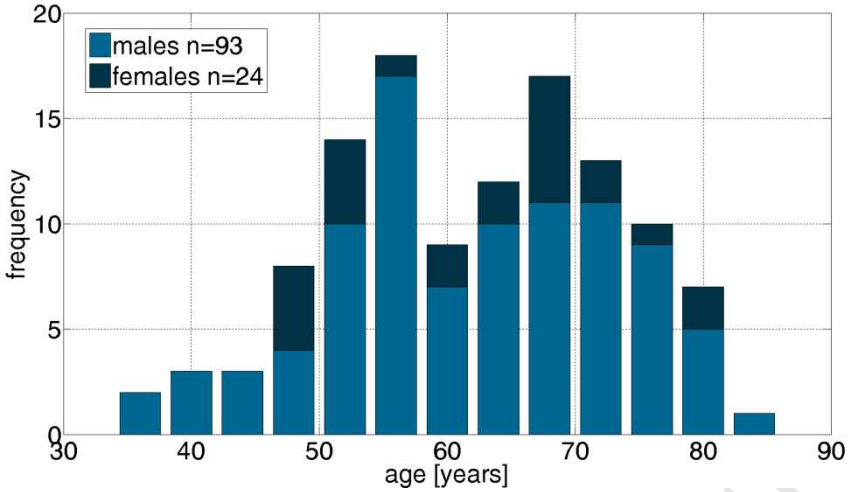

Figure 1. Age distribution (separated for males and females) of the cohort.

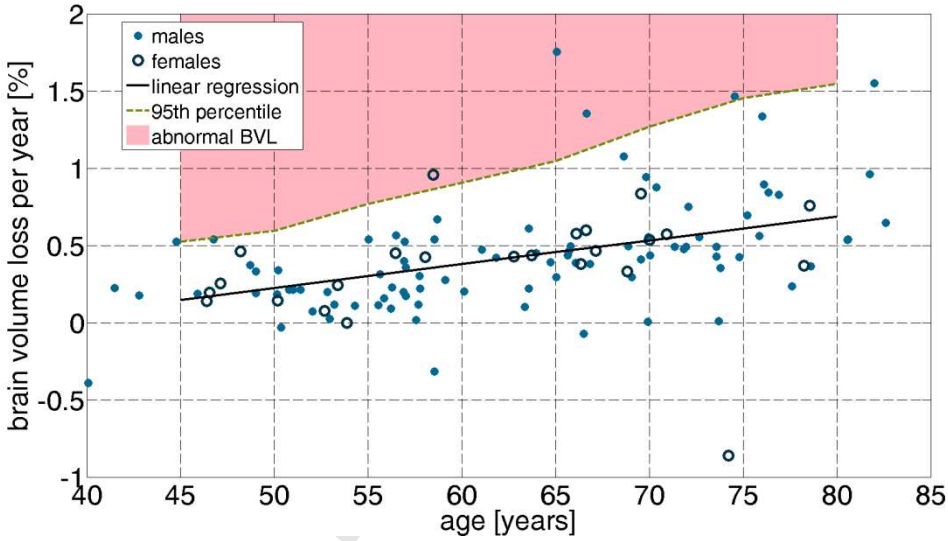

Figure 2. Association of age and measured brain volume loss (BVL) per year (in %). The dotted line represents the 95th percentile. The red area indicates values of abnormal BVL per year since 95% of all healthy study participants feature lower BVL per year.

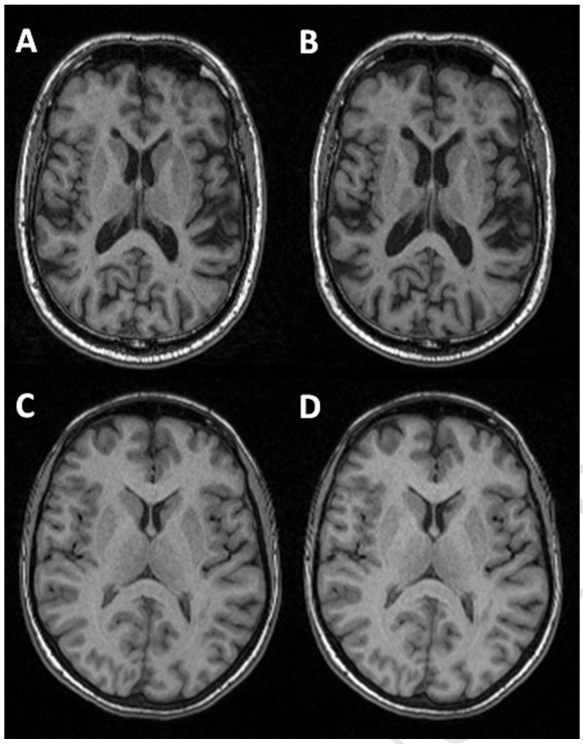

Figure 3. Example of axial slices of a 3D T1-weighted image for two participants illustrating different brain volume loss (BVL) values. The upper row shows 3D T1-weighted images of a 72-year-old male at baseline (A) and after 6.4 years (B) exhibiting a BVL of 3.6% (0.56% per year). The lower row shows 3D T1- weighted images of a 46-year-old female at baseline (C) and after 6.5 years (D) showing a BVL of 0.93% (0.14% per year).

Table 1. Age and brain volume loss (BVL) per year for male and female participants. For each participant the mean of the age at baseline and the age at the last follow-up scan is reported. Values are given as mean ± standard deviation.

	n	Age (years)	BVL (%) per year
males	93	62.1 ± 11.2	0.42 ± 0.37
females	24	61.04 ± 10.7	0.36 ± 0.35
p-value		0.77	0.51

Table 2. Brain volume loss (BVL) per year between 45 and 80 years. Data are given as mean (2nd column), 80th percentile (3rd column) and 95th percentile (4th column). The values in the last two columns can be used as age-dependent cut-offs for pathological BVL with an error probability of 20% and 5%, respectively.

age (years)	mean BVL (%) per year	Cut-off for pathological BVL (%) per year with an error probability of	
		20%	5%
45	0.15	0.33	0.52
50	0.22	0.38	0.59
55	0.30	0.43	0.77
60	0.38	0.50	0.91
65	0.46	0.60	1.05
70	0.53	0.72	1.27
75	0.61	0.80	1.45
80	0.69	0.93	1.55

Estimates of age-dependent cut-offs for pathological brain volume loss using SIENA/FSL – A longitudinal brain volumetry study in healthy adults

Highlights:

- Brain volume loss (BVL) assessed by MRI is a relevant marker of brain tissue damage.
- BVL rates were assessed in cohort of 119 healthy subjects longitudinally.
- BVL means and variability by age was computed using a sliding window technique.
- A list of age-dependent cut-offs for pathological BVL is provided.

Disclosures

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All subjects included in the study gave written informed consent. The study was approved by the Ethics Committee of the Board of Physicians in Hamburg, Germany.

We confirm that all authors had access to the full dataset and were involved in all stages of development and finalization of the manuscript.