
L. Fleysher1, N. Oesingmann2, R. Brown1, H. Jaggi1, G. Wiggins1, D. Sodickson1, and M. Inglese1,3
1Radiology, NYU School of Medicine, New York, New York, United States, 2Siemens Medical Solutions USA, Malvern, PA, United States, 3Neurology, NYU School of Medicine, New York, New York

Introduction

Since increasing age is the greatest known risk factor for neurodegenerative disease, it is important to understand the pathophysiology of normal brain aging and the associated changes in brain volumes. MRI is a very useful tool for measuring age-related brain tissue changes (1-7). Despite the histological evidence that white matter (WM) undergoes age-related microstructural transformations (8,9), morphology-based MRI studies have provided conflicting results about age-related WM changes (1-6) while consistently reporting age-associated volume loss of the cerebral gray matter (GM) (1-3). Sodium MRI is used for the quantification of the bulk tissue sodium concentration (TSC) which represents a weighted average of the extracellular and intracellular sodium contents. Since the extracellular (ESC) and the intracellular (ISC) sodium concentrations remain relatively constant in healthy individuals at about 140 mmol/L and 10-15 mmol/L, respectively, TSC is sensitive to changes in the intracellular sodium volume fraction (ISVF) via cellular death, shrinkage and swelling. Due to the ability of healthy cells to maintain large cross-membrane sodium concentration gradients, it is expected that TSC will increase as a result of cellular loss or shrinkage associated with aging. Consequently, the aim of this cross-sectional study was to investigate the influence of aging on TSC and brain volume and to assess age-related rates of the cellular loss or shrinkage.

Theory. Assuming that the brain tissue can be described by the intracellular and extracellular compartments only, it is possible to relate age-related TSC (ρ_t) changes to the corresponding changes in ISVF (η_t):

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\begin{align*}
\rho_t &= \frac{M_e + M_w}{V_e + V_w} = \rho_{\text{cellar}} - (\rho_{\text{cellar}} - \rho_{\text{iso}}) \eta_t \\
\eta_t &= \frac{V_e}{V_e + V_w} = \eta_{\text{iso}} + B \frac{\beta}{\eta_{\text{iso}} - A}
\end{align*}
\]

where \(M_e\) and \(M_w\) are the intra- and extra-cellular sodium contents (in moles) occupying volume \(V_e\) and \(V_w\) respectively, \(\rho_{\text{iso}}/\rho_{\text{iso}}\) stand for ISC and ESC. Thus, the rate of fractional ISVF loss (\(\beta\)) can be obtained from sodium MRI, by computing the slope (\(B\)) and the intercept (\(A\)) of TSC dependence as a function of volunteer age (\(t\)) [1,2].

Methods. Ten healthy volunteers (ages 19-54) were enrolled in this IRB-approved study. Sodium experiments were performed on a 7T whole-body MAGNETOM scanner (Siemens Healthcare, Erlangen, Germany) with a custom-built dual-tuned TX/RX 1H/23Na head coil (10) while structural MRI images were acquired on a 3T MAGNETOM Trio, A Tim System by the same manufacturer. TSC was measured as described in (11,12) with GRE sequence using 5mm isotropic resolution; TR=150ms, TE=6.8ms, FA=90° with 3 averages. 3D MPRAGE images were acquired with 1mm isotropic resolution, TR=2400ms, TE=2.7ms, TI=900ms, FA=12°. Normalized brain, gray and white matter volumes (NBV, WMV, GMV) were measured on MPRAGE images using SIENAX (13). TSC and MPRAGE images where co-registered using FSL (14) and corresponding GM and WM masks were applied to TSC maps. TSC and volumetric data were analyzed using linear regression to assess the fractional rates.

Results and Conclusions. Decline of the GM and WM volumes observed in this study is in line with previously published data (1-6) TSC level increases in gray and white matter with age consistent with cellular loss or shrinkage. However, WM and GM ISVF loss measured by means of sodium-based technique was different (p<0.02) from WMV and GMV loss measured by means of morphology-based MRI (see Figure and Tables 1,2 ). Specifically, WM ISVF loss was higher than WMV loss and GM ISVF loss was lower than GMV loss. We speculate that since age-related WM degeneration is accompanied by expansion of the capillary network and swelling of the perivascular space (8,9), these two opposing effects can lead to very small change in the tissue volume but cannot mask the ISVF loss. Neuronal shrinkage may cause GM volume reduction without significant alteration in cellular packing leading to smaller fractional GM ISVF loss compared to GM volume loss. Our results are based on the assumptions that ESC=140 mmol/L and that there is no age-related change in ISC in the healthy brain tissue. If there were a systematic increase in ISC as a function of age, it would have lead to an under-estimation of the ISVF loss.

In summary, we have found that TSC increases in the GM and WM indicating cellular loss or shrinkage. Based on these data we have computed fractional ISVF loss which was found to be significantly different from fractional tissue volume loss measured by morphologic MRI. This study is ongoing and results from a larger sample size will be reported.

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