Combining SIENA and SIENAx for improved quantification of grey and white matter atrophy

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Introduction: The quantification of brain atrophy with MRI is vital for understanding the normal aging brain as well as understanding and treating people affected by neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis. Although several cross-sectional and longitudinal methods exist for the quantification of atrophy [1], SIENA and its cross-sectional counterpart SIENAx [2-3] are currently the most widely used in research and in clinical trials. SIENA has been shown to be robust and accurate (0.15% error) [3], but provides a measure only of whole brain atrophy. SIENAx, on the other hand, provides tissue-specific volumes, but computing change from serial cross-sectional measurements is much less precise (0.5-1% error) [3]. We propose a method to combine the sensitivity of SIENA with the tissue classification feature of SIENAx for a more accurate and precise measurement of tissue-specific atrophy.

Methods: Brain tissue volumes normalized for subject head size were estimated using SIENAx. In addition to a whole brain volume (**WB**), separate estimates of grey matter (**GM**), white matter (**WM**), and cortical grey matter (**cGM**) were obtained. SIENAx was run at each timepoint, and the serial change between the two timepoints was calculated as a simple percent difference of the cross-sectional measures. Where applicable, SIENAx was run with the lesion masking option to account for erroneous WM lesion misclassifications.

Our proposed longitudinal method for detecting change relies on the tissue volume output from SIENAx but also on the percent brain volume change (**PBVC**) output from SIENA. To calculate the longitudinal change in GM, for example, we calculate the percent difference between the normalized GM volume at each timepoint. At the first timepoint, the volume is simply the normalized GM volume as output from SIENAx. At the subsequent timepoint, however, the GM volume is obtained by first estimating the normalized brain volume of the second timepoint, by multiplying the normalized brain volume of the first timepoint by (1+ PBVC/100), and then multiplying by the GM fraction obtained at the second timepoint (i.e., GM volume/WB volume). The algorithm is illustrated in Figure 1.

For this study, two different T1-weighted images (**T1w**) were acquired for each dataset; one with 1.5mm thick slices (**HIGHRES**) and the other with the more clinically common 3mm slice thickness (**LOWRES**). Both had in plane resolutions of 0.97 mm^2.

A scan-rescan dataset was used to assess reproducibility. For each scan-rescan pair, the subject was scanned, removed from the scanner, repositioned, and then immediately rescanned. (N=12 @ HIGHRES, N=10 @ LOWRES). To evaluate the accuracy of each technique, a known amount of atrophy was simulated by creating an "atrophied" version of the baseline image from the above scan-rescan dataset by replacing the brain with a scaled version of itself. Only the brain was scaled as skull size is used as a normalization factor within the method. A global scaling of ~86% was achieved using a linear transform with a 0.95 scaling factor in each of the x, y, and z dimensions. (N=12 @ HIGHRES, N=10 @ LOWRES). Lastly, we used a clinically relevant dataset from a multi-centre clinical trial in which a certain degree of atrophy was expected but unknown. This dataset comprises subjects with relapsing remitting multiple sclerosis (**RRMS**) being treated with glatiramer acetate (with or without steroids) and scanned 3 years apart. (N=59 for both the LOWRES and HIGHRES sequences).

Results: Reproducibility as assessed with the scan-rescan dataset revealed that, for the LOWRES dataset, the absolute error for our proposed longitudinal method was significantly lower than repeated cross-sectional measurements in the WM and WB tissue compartments (p=.019, p=.007, respectively), and trended towards significance for GM and cGM (p=.09). Interestingly, no such improvement was detected with the HIGHRES dataset. By contrast, each method performed qualitatively slightly worse when applied to the HIGHRES dataset compared to its LOWRES counterpart in terms of reproducibility.

Detection of atrophy in each tissue compartment (cGM, GM, WM, WB) was significantly better (p<.01) in the simulated LOWRES dataset using our longitudinal method rather than repeated cross-sectional measurements (Figure 2).

The LOWRES multi-centre clinical trial dataset of subjects with RRMS showed that over the three years there was a mean whole brain atrophy of -1.45% (SD=1.13), driven by GM atrophy (mean=-2.14%, SD=2.42%), particularly in the cGM compartment (mean=-2.50%, SD=2.57%) more so than in the WM (mean=-0.81%, SD=1.87%). Similar findings were obtained with the HIGHRES dataset.

Discussion and Conclusions: While our method still uses SIENAx for tissue segmentation, and is thus subject to the error of that technique, we reduce our dependence on accurate and complete tissue segmentation by using only the ratio of the tissue of interest to the WB volume. The advantage becomes evident if the brain extraction at one timepoint were to include slightly less cortex than at the other timepoint. With a repeated cross-sectional measurement, the entirety of this error would appear as a smaller cGM volume at the second timepoint. With our longitudinal method, the cGM volume at the second timepoint would be reduced by only a fraction of this error. Also, the impact of geometric distortion is likely reduced by using a tissue fraction, since distortion-related fluctuations in the volume of each tissue should largely cancel out. In addition, we further reduce the error inherent in SIENAx by using only a single normalization factor. As previously reported, SIENAx normalizes the tissues at each timepoint independently via registration to a template, and each normalization contributes its own error [3]. While one could use the un-normalized volumes to avoid this problem, scanner changes and patient z-shift positioning causing gradient distortions would not be accounted for [4].

In terms of both reproducibility and sensitivity, our results indicate that using a higher resolution acquisition provides no observable advantage for this purpose over the more clinically practical sequence with a 3mm slice thickness. Our longitudinal method was more reproducible than simply using repeated cross-sectional measures, and our method more accurately captured the simulated atrophy. From the application to the RRMS dataset, it appears that the atrophy in that group was driven more by atrophy in the GM compartment than in the WM.

In summary, we present a longitudinal method to measure tissue-specific atrophy that is more precise and sensitive than serial cross-sectional measurements, and is applicable to the conventional-resolution T1w image typically obtained in clinical studies.

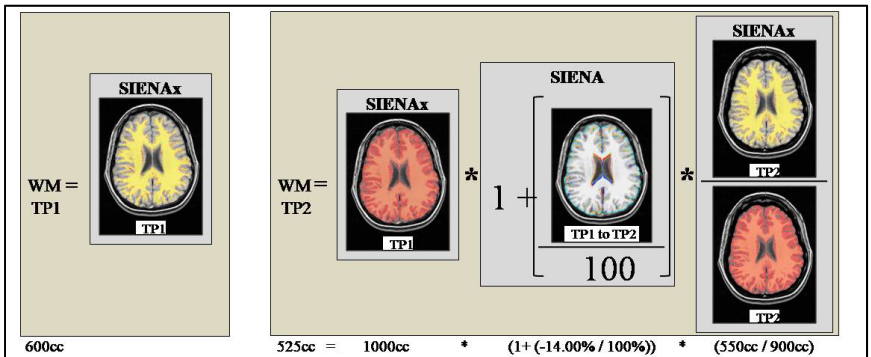

Figure 1 – Graphic illustration of how WM volume is calculated at the first timepoint (left) and the second timepoint (right). The numbers from a worked example are presented at the bottom of each panel

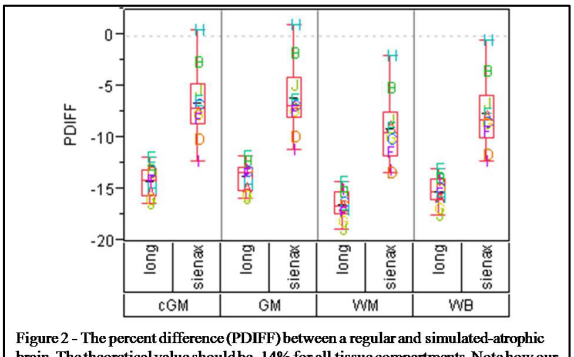

Figure 2 - The percent difference (PDIFF) between a regular and simulated-atrophic brain. The theoretical value should be -14% for all tissue compartments. Note how our proposed longitudinal method (long) outperforms repeated cross-sectional measures (sienax).

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