Tracking Longitudinal Change in Brain Volumes through Conditional Quantiles

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BACKGROUND

Changes in brain structure in people living with multiple sclerosis (MS) can be attributed to natural aging processes or pathological atrophy due to the disease. Furthermore, differences in baseline brain volumes make it challenging to interpret changes over time in many cases due to regression to the mean.

The field of growth chart modeling has recognized that personalized charts that consider prior measurements yield markedly more informative representations and are less susceptible to issues. However, no such conditional brain charts are available for the study of brain volume changes.

OBJECTIVE

To develop and implement statistical models that incorporate heterogeneously and longitudinally acquired magnetic resonance imaging (MRI) measurements to establish personalized and informative brain charts.

METHODS

Experimental Methods: Data were acquired at 5 multiple sclerosis (MS) centers using 13 MRI scanner models from 2 scanner manufacturers employing a variety of protocols that included T1-weighted and T2-weighted FLAIR imaging. 273 people with MS were imaged between 2 and 4 times over a period of up to 6 years, and image processing was conducted using the FDA-cleared NeuroQuant software tool (NeuroQuant MS, v3.1, Cortechs.ai). Automated image quality assessment was employed using the MRIqc tool. Total ventricle volumes and intracranial volumes (ICV) were extracted from NeuroQuant output.

Statistical Methodology: Longitudinal analysis of growth curves is more complex than standard cross-sectional modeling. This is due to documented biases as well as the importance of the conditional interpretation. After observing a ventricular volume on a previous MRI, the interpretation of each subsequent measurement changes; to address this, there have been several methodologies proposed. However, in light of the World Health Organization's recommendation for child growth curve modeling using generalized additive modeling for location, scale, and shape (GAMLSS), this approach was employed. GAMLSS allow for the modeling of data whose distribution does not follow an exponential family as in standard generalized additive modeling. Furthermore, this approach allows for modeling the mean structure as well as the variance, skewness, and kurtosis in terms of flexible nonlinear associations with covariates of interest. All calculations were conducted in the R statistical environment, using code modified from the GAMLSS package.

Model Building: Based on exploratory data analysis, the Box-Cox transformation employed by Cole and Green was selected. Raw volumes were modeled, and results were compared with normalization and adjustment for ICV. Although GAMLSS are theoretically capable of modeling longitudinal data using random subject-level effects to address intrasubject correlations, mixed-effect GAMLSS did non converge in this dataset likely due to limited sample size. Instead, the first two observations from each subject were retained and cross-sectional GAMLSS were employed.

Visualizations of scatterplots motivated a model with mean ventricular volume at follow-up predicted by a patient age, previous ventricle volume measurement as well as its interaction with the time between MRIs, as well as the contrast-to-noise ratio from the T1-weighted scan (T1 CNR). For the ICV-adjusted case, ICV was also included in the mean model. The log variance was modeled using the same terms. An intercept term alone was employed for skewness, which allowed for shared skewness across the age span. Model fit was assessed via visual inspection of estimated quantiles and using worm plots.

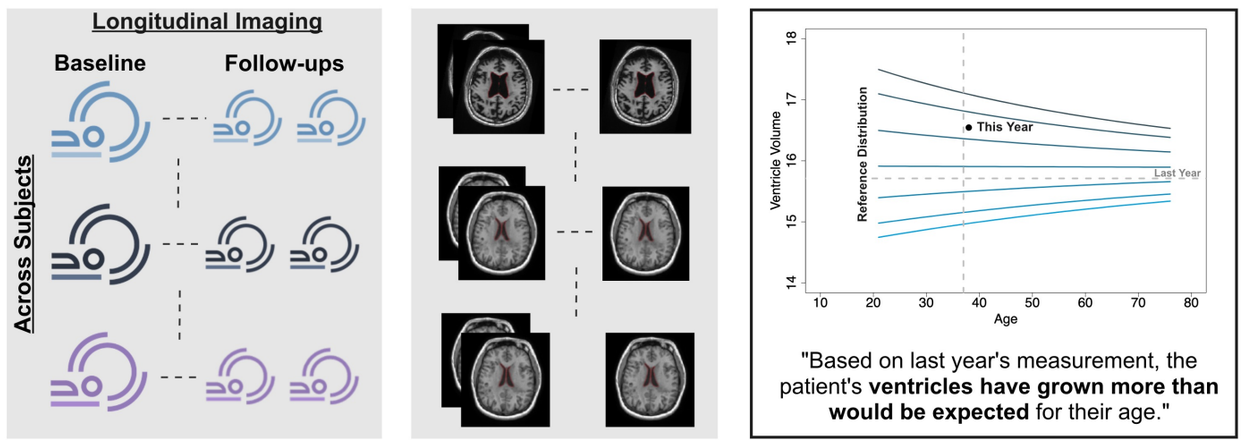

Figure 1. Longitudinal centile analysis generates expected change distributions for brain volumes based on previous measurements, patient demographics, and current brain volume and image characteristics.

RESULTS

- Predictors of ventricle volume distribution included patient age ($p<0.001$), prior ventricle volume ($p<0.001$), & the time interval of observation ($p<0.01$).
- Higher image quality was associated with less variance in volumes ($p<0.02$).
- ICV-adjusted and ICV-normalized modeling resulted in similar conclusions.
- Assessment of fitted conditional centiles indicated that they provide intuitive visualizations of longitudinal changes in ventricle volume.

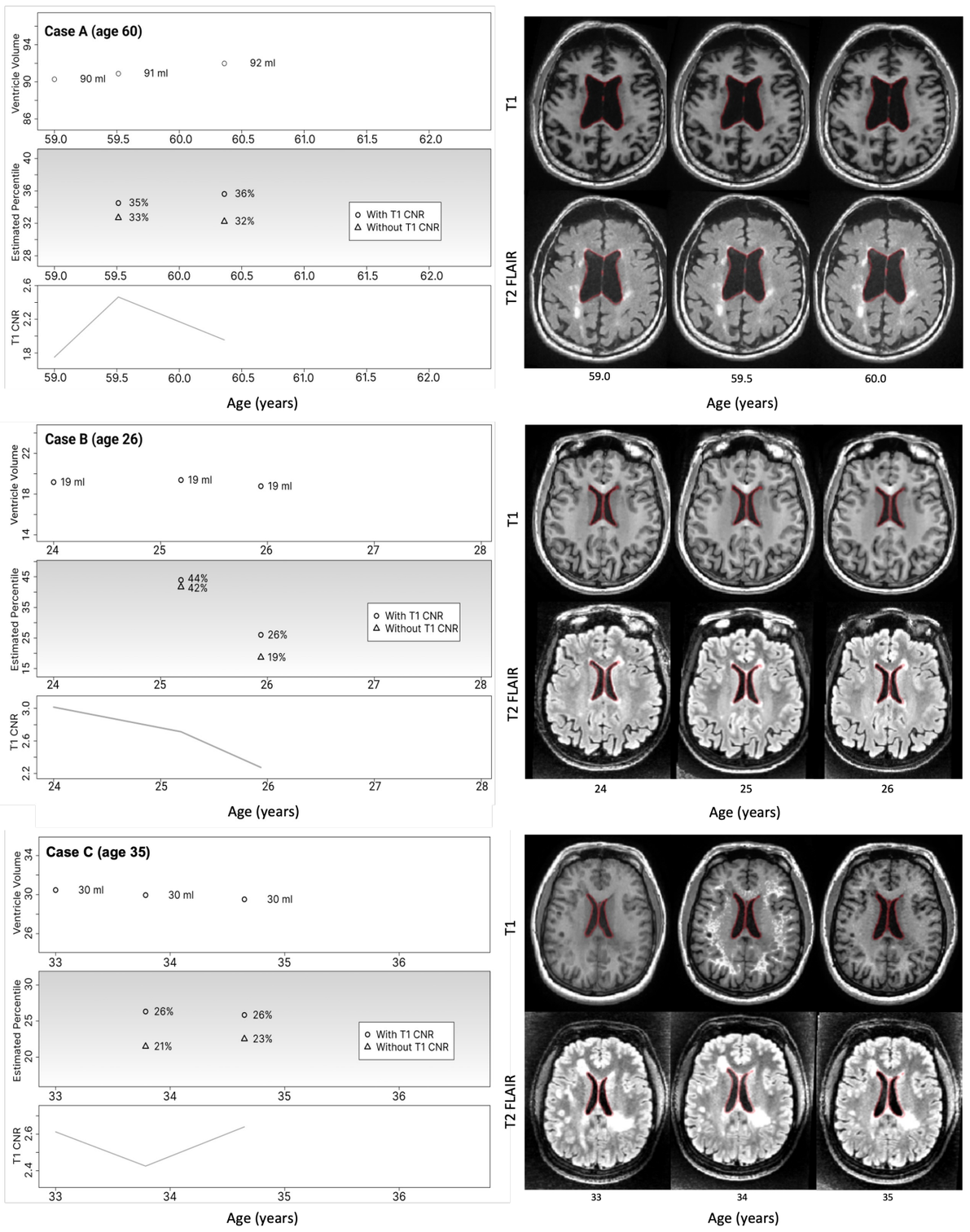

Figure 2. Three case studies of longitudinal centile estimation (A, B, C). Right column shows T1-weighted and T2-weighted FLAIR imaging at three time points each. Left column shows total ventricle volumes (top row), estimated centiles (middle), and T1 CNR measurements over acquisitions (bottom row). Note that longitudinal centiles accounting for image quality are much more easily interpreted than raw volumes.

CONCLUSIONS

- Brain growth changes in people with MS can be challenging to interpret due to statistical biases and age-related changes.
- Advanced growth chart modeling accounting for image quality metrics can improve interpretability of atrophy measures.
- Longitudinal, personalized brain charts can potentially reform physician decision support systems for the management of MS.

REFERENCES

[1] O. Esteban, D. Birman, M. Schaer, O. O. Koyejo, R. A. Poldrack, and K. J. Gorgolewski, "MRIQC: Advancing the automatic prediction of image quality in MRI from unseen sites," *PLOS ONE*, vol. 12, no. 9, p. e0184661, Sep. 2017, doi: 10.1371/journal.pone.0184661.
[2] D. M. Stasinopoulos and R. A. Rigby, "Generalized Additive Models for Location Scale and Shape (GAMLSS) in *R*," *J. Stat. Softw.*, vol. 23, no. 7, 2007, doi: 10.18637/jss.v023.i07.
[3] E. Borghi et al., "Construction of the World Health Organization child growth standards: selection of methods for attained growth curves," *Stat. Med.,* vol. 25, no. 2, pp. 247–265, Jan. 2006, doi: 10.1002/sim.2227.
[4] T. J. Cole and P. J. Green, "Smoothing reference centile curves: The lms method and penalized likelihood," *Stat. Med.*, vol. 11, no. 10, pp. 1305–1319, 1992, doi: 10.1002/sim.4780111005.

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