Brain Charts for People Living with Multiple Sclerosis

A. Keshavan[1], K.M. Leyden[1], D. Peterson[1], R. Markello[1]
[1]Octave, Menlo Park, CA, USA

BACKGROUND

Multiple sclerosis (MS) is associated with brain volume loss through the disease course. Ventricular volume has been advocated for as a robust measurement of brain volume based on clinically acquired magnetic resonance imaging (MRI) and can be measured using FDA-cleared automated segmentation methods. However, ventricle volume changes naturally with age and may be susceptible to biases associated with acquisition hardware, imaging protocol, & image quality.

OBJECTIVE

To establish brain charts for ventricle volume based on MRI for people living with MS that account for demographics and differences in acquisition and image quality.

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. 374 people living with MS aged 23 to 76 were imaged, 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 [1]. As only 10 subjects were below the age of 22 years, these subjects were excluded from analysis. Total ventricle volumes were extracted from NeuroQuant output as were intracranial volume (ICV) measurements. 3 subjects with ventricle volume greater than 120mL were considered outliers and excluded. Three methods were employed for ICV-correction: 1) no ICV correction, with raw volumes being modeled; 2) ICV normalization, with ventricular volume divided by ICV for each subject; and 3) ICV adjustment, via linear model modeling. All subsequent modeling was conducted for each of these three methodologies and results were compared.

Brain Chart Development: To assess the distribution of ventricular volume through the age span, generalized additive modeling for location, scale, and shape (GAMLSS) [2] were employed. GAMLSS allows 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. This approach was advocated for by the World Health Organization for child growth curve modeling due to its principled statistical flexibility [3]. Briefly, the GAMLSS approach employs the specification of a 3- or 4-parameter model to link the mean, variance, skewness, and kurtosis to the predictor variables. This modeling approach was recently employed in a large international effort to develop brain charts in healthy participants.

Visualizations of scatterplots motivated a model with mean ventricular volume predicted by a non-linear age effect, the contrast-to-noise ratio from the T1-weighted scan (T1 CNR), and a factor variable for the scanner manufacturer. For the ICV-adjusted case, ICV was also included in the mean model. The log-variance of the ventricular volume was modeled nonlinearly in terms of age and linearly in terms of T1 CNR. 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.

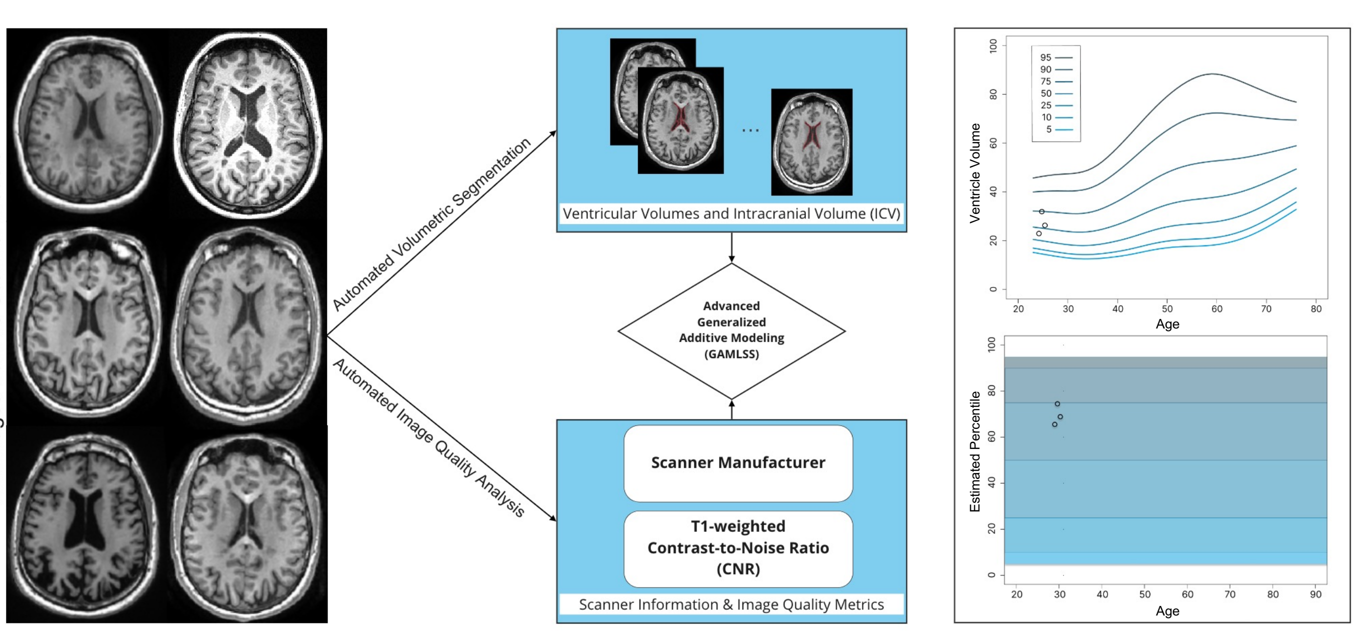

Figure 1. Brain charts for people with MS. Brain chart modeling strategy integrating structural image analysis auxiliary information (left) for accurate brain chart estimation (right).

CONCLUSIONS

- Brain charts for people living with MS are a promising method for translating quantitative volumetrics into interpretable knowledge about a patient's disease.
- Modeling differential image quality improved model fit and ease of interpretation of patient brain volumes
- Growing databases of heterogeneously acquired MRI in MS will facilitate increasingly precise assessments of brain structure in clinical practice settings.

RESULTS

- Average ventricle volume evolved through the age span in MS ($p<0.001$) and differed across scanner manufacturers ($p<0.01$).
- Variance in ventricular volume was also associated with contrast-to-noise ratio (CNR) on T1-weighted imaging ($p<0.03$).
- Results for ICV-adjusted and ICV-normalized modeling were similar.

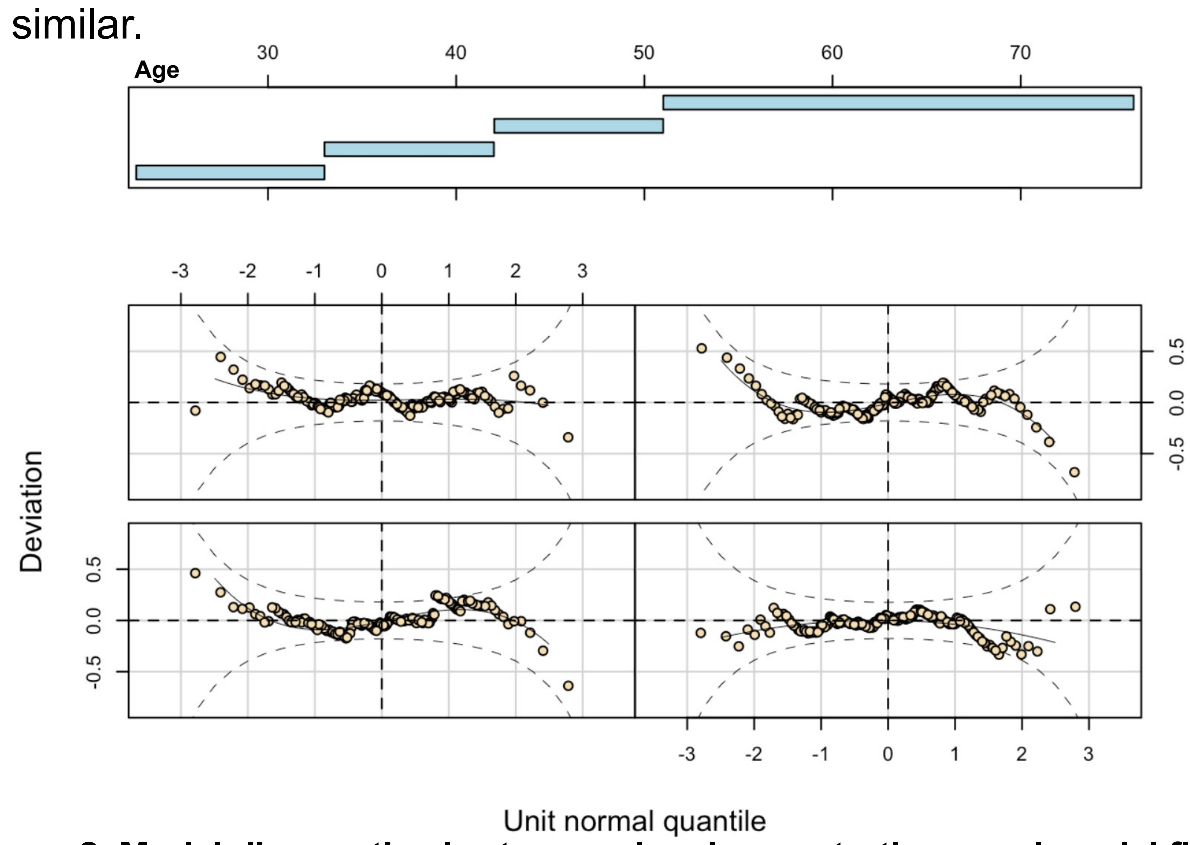

Figure 2. Model diagnostic chart examples demonstrating good model fit.

Visual review of case studies indicates interpretable results from brain charts. Further examination demonstrates how auxiliary information such as image quality metrics (T1 CNR) improve model performance.

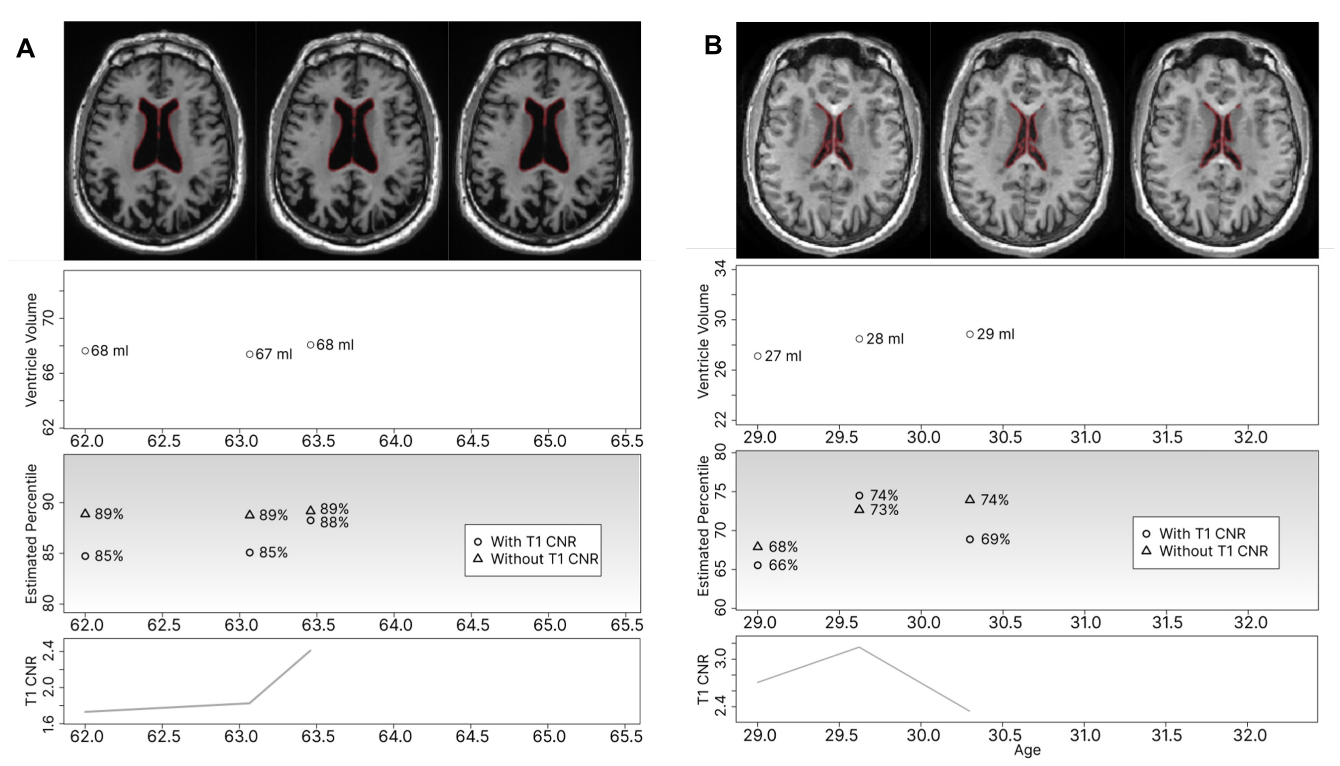

Figure 3. Two example brain chart assessments. Top row shows axial views of three T1-weighted images acquired approximately 6 months apart, with ventricles delineated in red, for two cases (A and B). Second row shows estimated total ventricle volumes, and the bottom row shows T1 CNR for each visit. The third row shows estimated percentiles based on brain charts. Note that when T1 CNR is accounted for, extreme measurements are mitigated when T1 CNR is relatively low.

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.

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