Sex-Specific Brain Charts for Multiple Sclerosis

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BACKGROUND

Many algorithms provide quantitative assessments of brain volume in people living with multiple sclerosis (MS) based on magnetic resonance imaging (MRI). Average brain volumes differ across the sexes, and men living with MS tend to have accelerated brain volume loss compared to women. Clinical interpretation of brain volumetrics can be challenging due to confounding with age-expected changes and other demographic factors in addition to image quality variation.

OBJECTIVE

To establish brain charts for ventricle volume based on MRI for people living with MS that account for patient biological sex, age, 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. 379 people (290 female and 89 male) living with MS aged 20 to 76 were imaged. Total ventricle volumes were extracted using the FDA-cleared NeuroQuant software tool (NeuroQuant MS, v3.1, Cortechs.ai), and automated image quality assessment was employed using the MRIqc tool [1].

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 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. 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 [4].

Brain charts were fit to address sex-specific differences using two approaches: 1) sex was considered as a covariate for mean and variance models. Other variables included in the modeling were contrast-to-noise ratio (CNR) from MRIqc from the T1-weighted imaging (mean and variance models) and manufacturer (mean only). 2) separate models were employed for each of the sexes. 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.

FIGURES

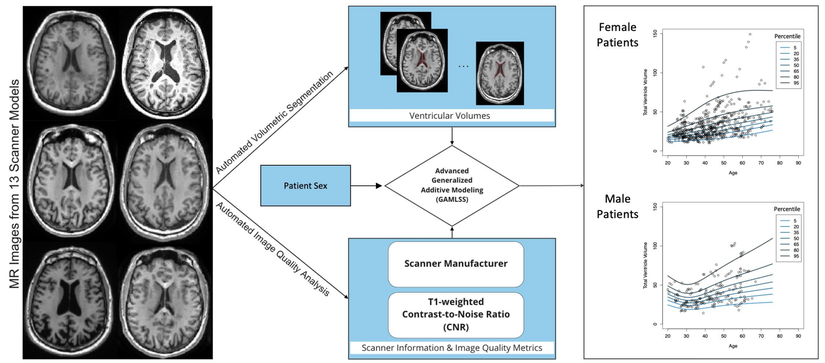

Figure 1. Brain chart modeling strategy integrating structural image analysis auxiliary information (left) for accurate brain chart estimation (right).

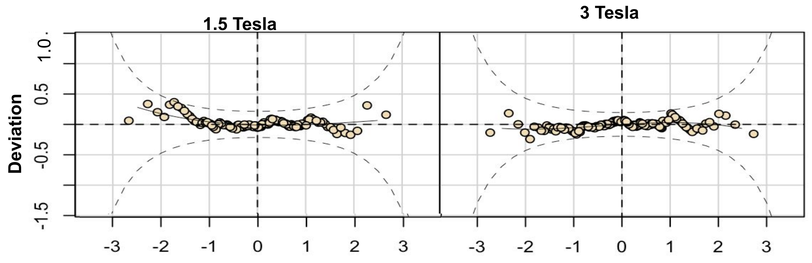

Figure 2. Model diagnostic chart examples demonstrating good model fit in females. Similar findings were observed in male participants.

RESULTS

- Average ventricle volume evolved through the age span in MS ($p<0.001$) and differed across the sexes ($p<0.001$).
- Variance in ventricular volume was also associated with CNR on T1-weighted imaging ($p<0.01$) but not sex ($p=0.09$).
- Visual review of case studies indicates interpretable results from brain charts. Further examination demonstrates the value of sex-specific modeling compared with covariate adjustment.

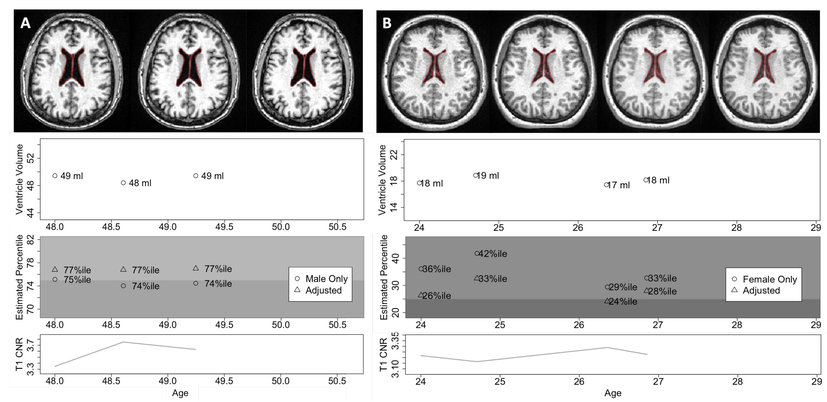

Figure 3. Two example brain chart assessments (A & B). Top row shows axial views of T1-weighted images acquired approximately 6 months (A) to 1 year (B) apart, with ventricles outlined in red. Middle row shows estimated total ventricle volumes, and bottom row shows T1 CNR for each visit. Bottom row shows estimated percentiles based on brain charts, comparing sex-specific with sex-adjusted models. Note more stable measurements for the sex-specific model for case B, consistent with visual inspection.

CONCLUSIONS

- **Brain charts for people living with MS are a promising method turning quantitative volumetrics into knowledge about an individual patient's disease.**
- **By providing demographic-specific information, these tools can further aid with precise clinical interpretations.**

REFERENCES

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