CORTECHS Labs

The NeuroQuant Normative Database

Comparing Individual Brain Structures

White Paper

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Abstract

A key component of NeuroQuant is the normative database, which provides NeuroQuant the capability to compare an individual's brain structure volume measurements to a healthy population. This allows NeuroQuant to deliver a precise indication of where that individual's brain structure volume lies within an age- and gender- based reference chart, which aids physicians in their assessment of neurodegenerative conditions. This paper provides information on how CorTechs Labs' normative database was created for NeuroQuant.

NeuroQuant's normative database is built on a population-based sample data set, which was compiled as a normative reference with percentile charts (norms) using brain volume structures over a normal human age span from healthy children to seniors. Collected data from several thousand subjects from 3 to 100 years of age with an equivalence of gender are the building blocks of NeuroQuant's normative database. The measurements are comprised of brain segmentation ROIs created by NeuroQuant (57 independent measurements and 9 combined or interpolated measurements) and include such structures as the hippocampus and whole brain and the volume calculations of each. A Generalized Additive Model (GAM)-based data-fitting algorithm was developed to create data fitting curves, used for percentile curve calculation. Pearson's Chi-square goodness-of-fit test was used to evaluate the data distribution and its fit to the expected uniform distribution along the percentile. In addition, test data sets were used for visual inspection and/or evaluation of goodness-of-fit to the normative database.
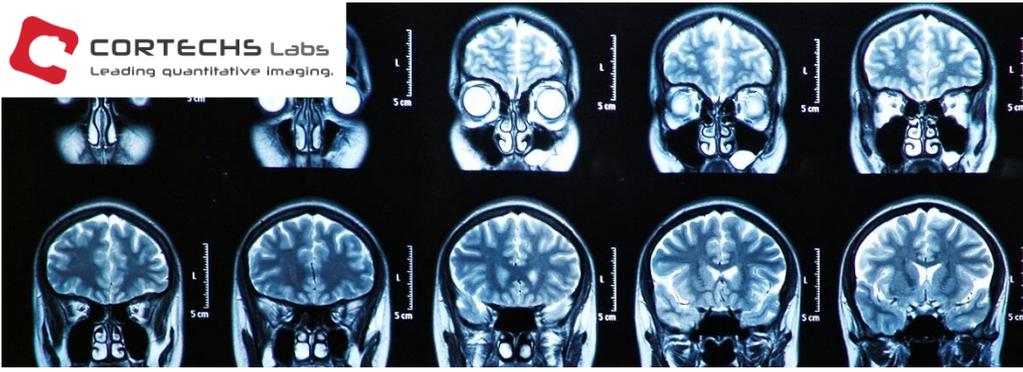
When evaluating quantitative volumetric information of brain structures, subject specific parameters such as age, gender, and overall head size are taken into consideration. Comparing the values of two subjects adjusted for these parameters significantly increases the quantitative and clinical value of volumetric information. The outcome becomes more meaningful when a subject's data is not only compared to another subject but is also compared to thousands of age- and gender-matched normal subjects within a database. Statistical models were used to provide medians and standard deviations, so subjects can be compared to normative reference percentile charts (norms), or more specifically, to norms of healthy normal population. The comparison of a single data point or subsets of data against healthy norms and its graphical representation has been used in clinical practice for many years [1].

NeuroQuant uses comparisons to a normative database to provide clinically relevant information to the user. NeuroQuant is an FDA cleared and CE marked automated volumetric MRI analysis tool that provides fast, accurate, and dependable brain segmentation. The resulting information from NeuroQuant is normalized for brain intracranial volume (ICV), gender and age and then compared to healthy norms.

An example of how NeuroQuant demonstrates morphometry analysis results and how norms are used for comparing a patient against a normal population is shown below in Figure 1 and 2. The examples show report plots generated by NeuroQuant illustrating patients' brain structure measurements as a percentage of ICV against normative percentile curves for normal gender matched population.
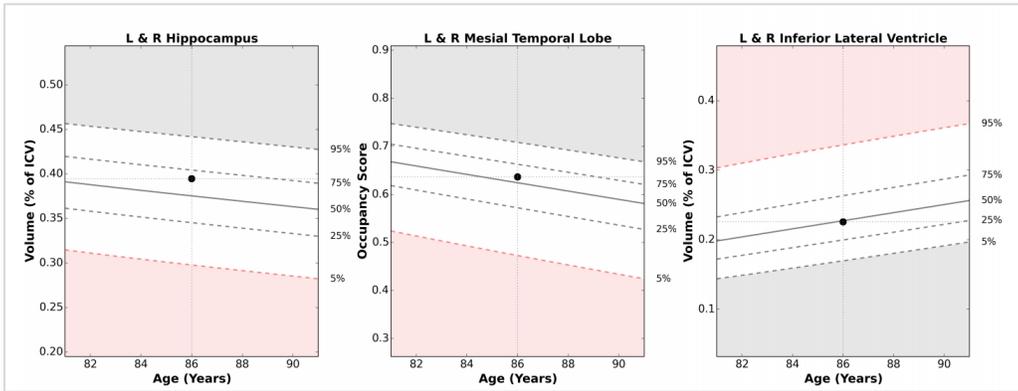

Figure 1. The three plots above show a male patient's total hippocampi volume, hippocampal occupancy score (mesial temporal lobe) and total inferior lateral ventricle as a percentage of ICV against percentile curves for normal male population.
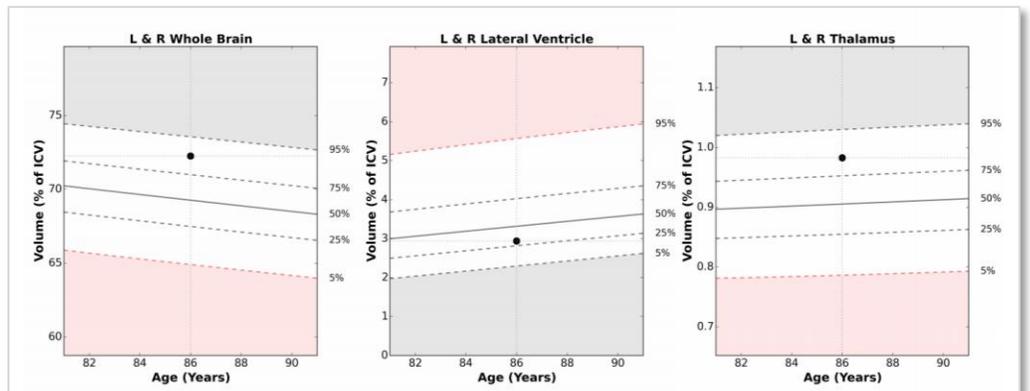
Figure 2. Three plots below show the female patient's whole brain, total lateral ventricle and total thalamus volumes as a percentage of ICV against percentile curves for normal female population.

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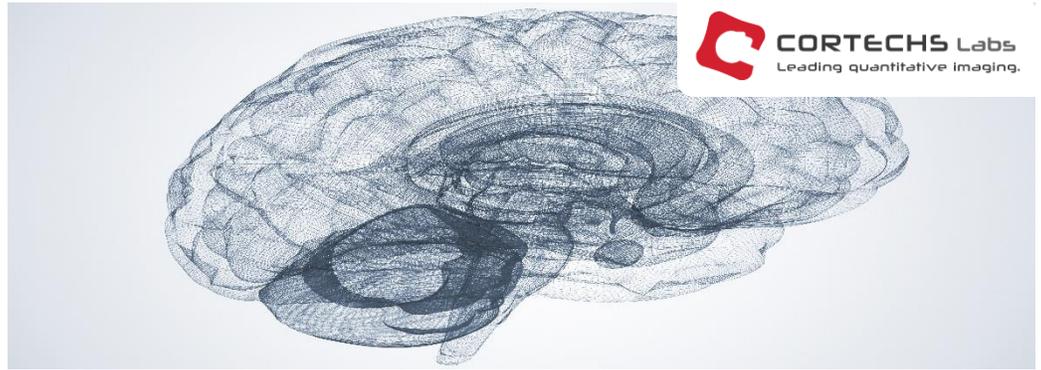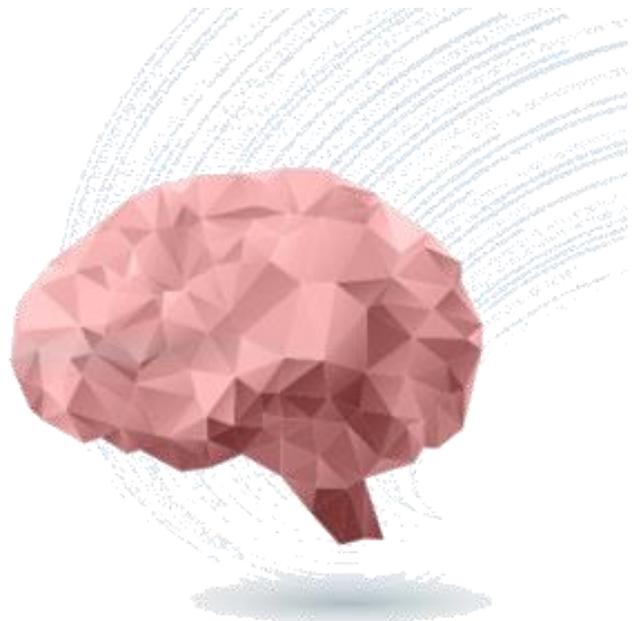
Establishing a Database

To establish the normative database CorTechs Labs combined data from several thousand scans including publicly available studies, studies by collaboration partners, and other proprietary data sources. All collected data sets were then processed using NeuroQuant 2.0. Only data that passed within the quality measures for image quality were included in the study.

Inclusion and Exclusion Criteria

Only normal healthy subject scans with verified age, gender, and clinical diagnostic information were included in the creation of the database. Only scans that were successfully processed by NeuroQuant 2.0 without errors were included. Scans without consent information were excluded. Only scans from MRI scanner manufacturers Siemens, GE and Philips were included. Scans from other manufacturers were excluded.

Resulting Values

The resulting data sets contained data acquired on Siemens, GE, and Philips; 1.5T and 3.0T scanners, which provided representative information for male and female subjects covering an age range of 3 to 100 years.

Data Fitting and Percentile Generation

Volumes of individually segmented structures (reported as the percentage of intracranial volume (ICV)), in addition to the patient's age and gender information, were entered into a MATLAB curve fitting and percentile generation program developed by CorTechs Labs.

Using one percent increments, the percentile reference curves [2] were fitted to the age-volume data using the MATLAB Generalized Additive Model (GAM) curve-fitting algorithm [3]. The GAM is a generalized linear model with a linear predictor involving the sum of smooth functions of covariates. The general model structure is shown here:

$$g(\mu_i) = X_i^* \theta + f_1(x_{1i}) + f_2(x_{2i}) + f_3(x_{3i,}x_{4i}) + \cdots \quad where \; \mu_i \equiv \mathrm{E}(Y_i)$$

Percentile Algorithm Summary

Data used in percentile generation included the patient's age and gender, the left, right and total segmentation volume, as well as additional customized structure volumes, such as the whole brain. All volume measurements were normalized to ICV.

The GAM function parameters include the ICV normalized measurement data, the smoothing penalty terms, as well as the patient's age and gender. Outliers were removed from the data and the percentile curves were calculated in one percent intervals based on the dispersion of the data along age.

Statistical Analysis for Good of Fit of Percentile Charts

Pearson's Chi-square test {4,5,6] is a statistical test applied to sets of categorical data to evaluate the conformity of the data distribution to an expected distribution. The Chi-square test is widely used when evaluating binned data such as histogram or frequency plots. Pearson's Chi-square tests a null hypothesis stating that the frequency distribution of the data observed is consistent with a particular theoretical distribution. Here, the observed frequency distribution is the histogram of the standard scores binned to a predefined percentile interval. The theoretical distribution is a uniform histogram (all percentile data shall have the same amount data based on the definition of the percentile). Pearson's Chi-square is used to test the goodness-of-fit. The basic mathematical formula of Chi-square test is as follows:

$$X^2 = \sum_{I=1}^{N} \frac{(O_i - E_i)^2}{E_i}$$

Here O_i is observed value and the E_i is expected value.

The square of the difference is used to compensate for the positive and negative values. The result is divided by the expected value for normalization purposes.

The null hypothesis in this study expected uniformity of the binned standard score data on percentile interval per the definition of the percentile histogram. The significance level was set to default (5%) and 25 bins were used. If the test result had a p -value lower than the significance level, the null hypothesis would be rejected.

Figure 3a
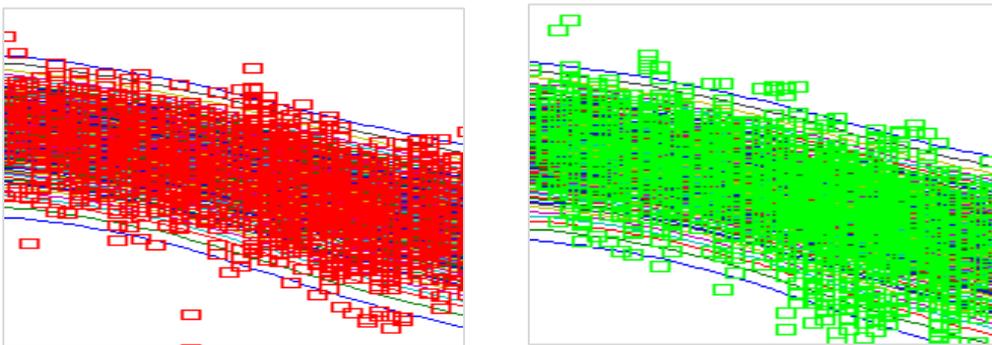
Figure 3b

Verification
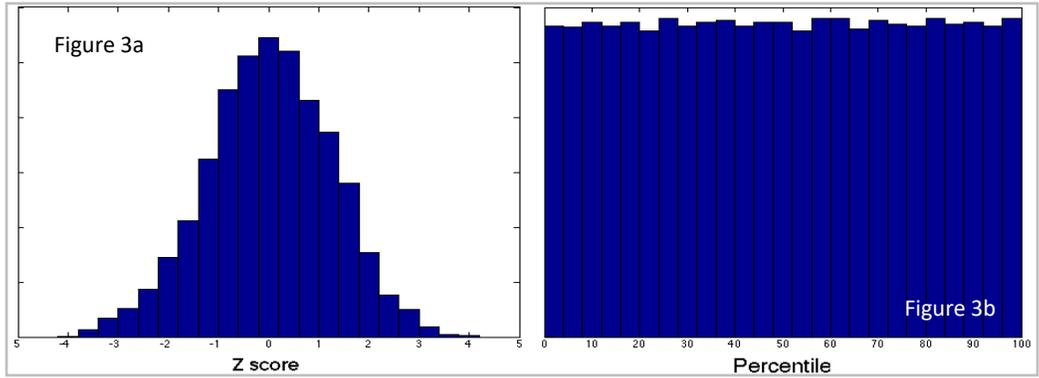
Test One

Using the Chi-square test, we applied all data used in percentile curve generation to evaluate the goodness-of-fit of the percentile curves (Figure 3). All structures had very high p-values (close or equal to 1) and all null hypotheses confirmed. This means the percentile chart has a good fit to the data. It was noted that the standard Z-score distribution would not necessarily be a normal bell shape distribution.

During Test One, we plotted the norm data used for creating the percentile chart on top of the percentile chart to provide a visual evaluation to determine whether the fitting algorithm worked correctly (Figure 4). All data showed good fit.

Figure 3a and 3b. Combined left and right hippocampal volume Z-score distribution and calculated percentile

Figure 4. Extract from the Hippocampus norm data plotted on the percentile chart.

Test Two

Two independent test data sets of several hundred healthy male and female subjects were used to evaluate performance of the percentile reference charts. Samples of the scatter plots of the individual subjects are shown below (Figure 5) along with an extract of the calculated percentile chart. Chi-square test showed the p-value for this data set much higher than the significance level (0.05) for the hippocampus and inferior lateral ventricle.
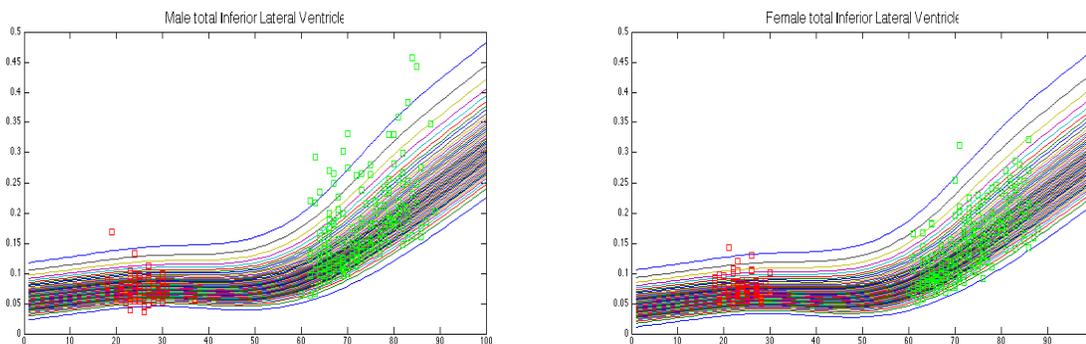

Figure 5. Example validation dataset: male and female scatter-plots on normative percentile chart.
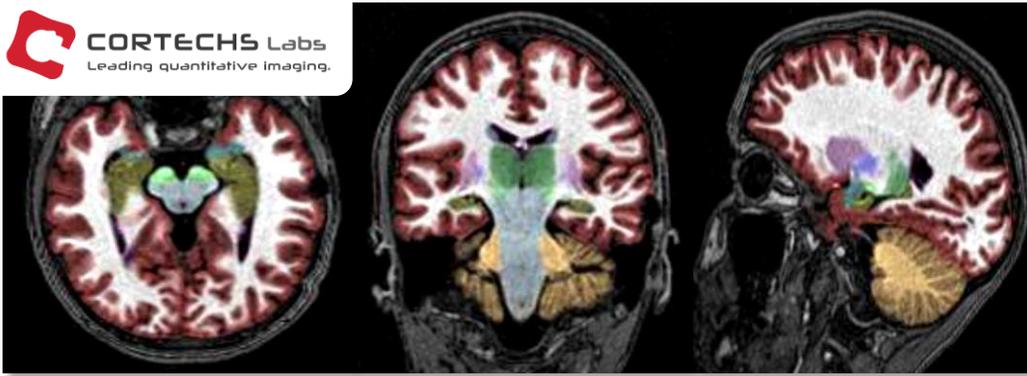
To validate the percentile reference charts, a large independent test data set of several hundred healthy male and female subjects was compared to a data set of neurodegenerative male and female subjects that had been diagnosed with Alzheimer's disease, early and late stage mild cognitive impairment (MCI) (figure 7), as well as those that had been diagnosed with temporal lobe epilepsy (hippocampal asymmetry) (figure 8). Samples of the scatter plots of the individual subjects are shown below.
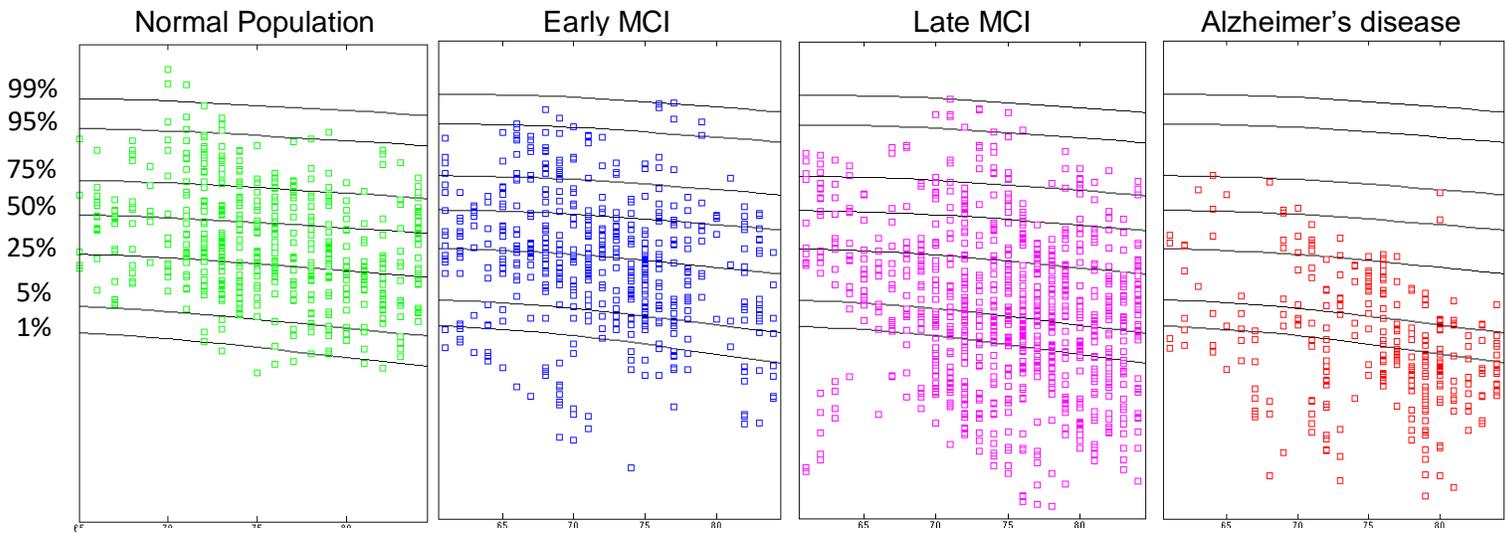
Figure 7. Normative reference percentile curves showed that the average of each of the data sets shift from close to 50% percentile curve (for normal population) to 5% percentile curve (for LMCI) and about 1% percentile curve (for AD). This is consistent with current understanding of hippocampus atrophy and Alzheimer's disease.
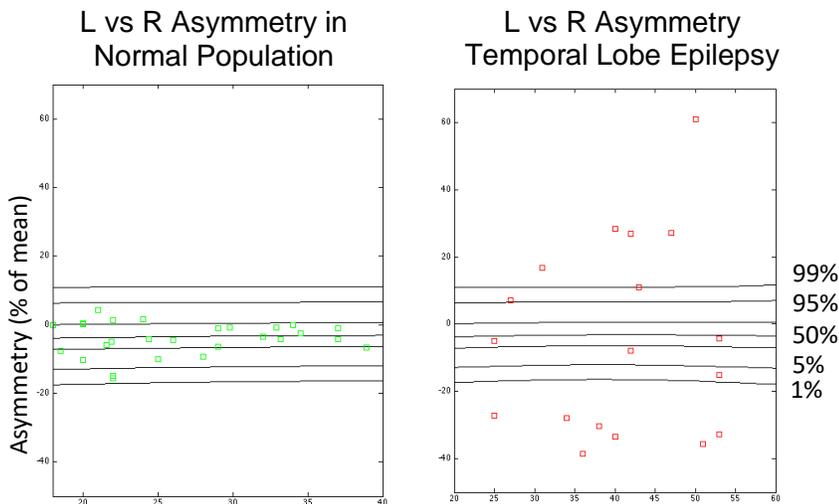
Figure 8. The temporal lobe epilepsy test data showed significantly higher asymmetry (data significantly dispersed toward 1% and 99% percentile curves) while normal data were within normative reference curves.

Clinical Practice

NeuroQuant has been in clinical use since 2007. Since then, over 100,000 MRI scans have been successfully segmented. The resulting brain structure volumes were plotted against the NeuroQuant normative database as previously described.

Below are two clinical examples showing the use of NeuroQuant in the clinical routine. In both cases, the deviations from the norms for the observed structures confirm the clinical indication. Due to the extended use of NeuroQuant, clinical validation of the normative data is extensive.

Example 1: Alzheimer's Disease (AD)
In example 1, the AD patient had a much smaller hippocampus volume (normalized by ICV) and hippocampus occupancy score (Figure 9) confirming the expected result.
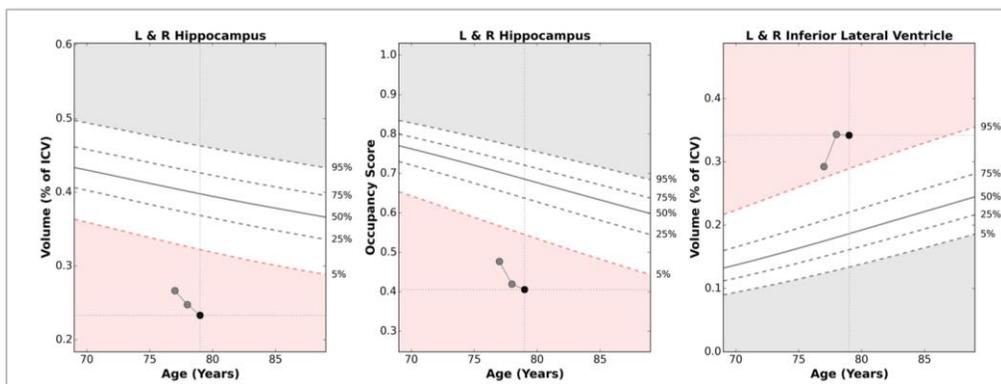

Figure 9. Displays a multiple time point analysis for an Alzheimer's disease patient with lower than normal hippocampus volume to ICV ratio, which continues to decrease as the patient ages.

Example 2: Multiple sclerosis (MS) case
In example 2, the MS patient had smaller whole brain volume than normal (Figure 10) as would be expected for a subject with MS.

Figure 10. Displays a multiple time point analysis for a MS patient with small whole brain volume to ICV ratio, which depicts change in the whole brain structure volume over the course of a year.
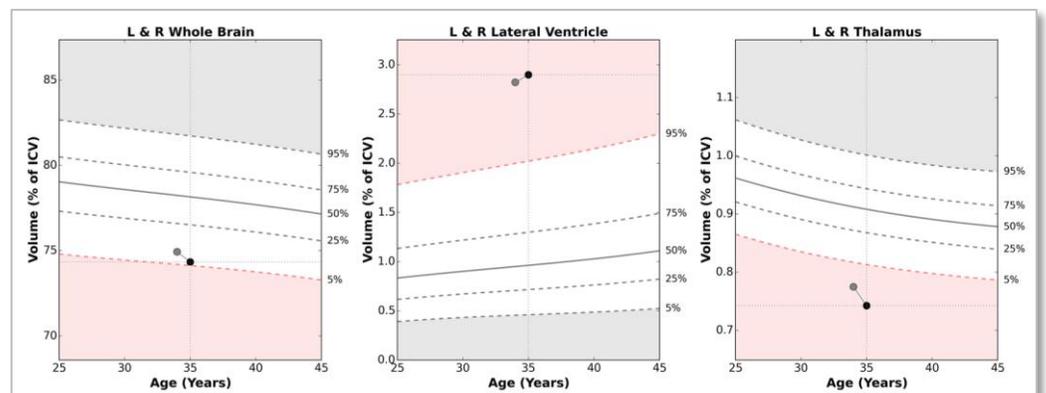
As demonstrated in these examples and in the evaluations in clinical use, the performance of the NeuroQuant normative database has been shown to accurately and robustly assign the data to appropriate percentile groups.

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Summary

NeuroQuant 2.0 utilizes a normative database that incorporates an age range from 3 to 100 years and provides fast, reliable volumetric assessments compared to normalized brain volumes. Several thousand data points from publicly available studies, clinical collaborators and proprietary subjects were used to build the database. Strict quality control ensured relevance and accuracy of all included data points. Thousands of clinical cases have been used to validate their accurate plotting with respect to the normative datasets.

Comparing patient brain volume results with healthy cohorts based on age and gender has been an integral part of FDA cleared and CE marked NeuroQuant since the commercial launch in 2007.

References

[1]   Department of Health and Human Services, CDC 2010 "2000 CDC Growth Charts for the United States: Methods and Development" http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf

[2]   Brain Development Cooperative Group, Total and Regional Brain Volumes in a Population-based Normative Sample from 4 to 18 Years: The NIH MRI Study of Normal Brain Development, Cereb Cortex. 2012 Jan:22(1):1-12

[3]   S Wood, Generalized Additive Models: An Introduction with R, CRC Press, Feb 27, 2006

[4]   Bennett, CA et al, Statistical Analysis in Chemistry and the Chemical Industry (Wiley, 1954).

[5]   Cao Y, Petzold L, Accuracy limitations and the measurement of errors in the stochastic simulation of chemically reacting systems. Journal of Computational Physics, Vol. 22, Issue 1, Pages 6-24, 2006

[6]   Bentler P., A Scaled Difference Chi-square Test Statistic for Moment Structure Analysis, Psychometrika, Vol. 66,   No. 4, 507-514.