SwiftSight Brain Normative Database White Paper

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1. Introduction

Brain volumetry - the quantitative measurement of regional and global brain structures from structural magnetic resonance imaging (MRI) - has become an indispensable biomarker in modern neurology [1]. It plays a critical role in the diagnostic workup and longitudinal monitoring of a wide spectrum of neurological conditions, including Alzheimer's disease (AD), mild cognitive impairment (MCI), multiple sclerosis (MS), temporal-lobe epilepsy, and traumatic brain injury (TBI).

While qualitative visual assessment remains a cornerstone of radiology, raw volumetric measurements are inherently difficult to interpret in isolation. A patient's hippocampal volume, for instance, must be contextualized against their age, sex, and total intracranial volume (TIV) before a clinician can distinguish between healthy aging and pathological atrophy [2]. Without standardized quantitative metrics, subtle structural changes may be overlooked, particularly in the early stages of neurodegenerative disease.

Volumetric measurements are accompanied by a normative database, which addresses the challenge of interpretability by mapping a raw measurement to a percentile rank or a z-score relative to a healthy reference population. This comparison provides clinicians with a single, actionable number that indicates how a patient's brain volume compares to that of healthy individuals of the same age and sex.

Historically, several commercial and research databases have been developed for brain volumetric analysis. While these frameworks have contributed substantially to the adoption of quantitative neuroimaging in clinical and research settings, differences remain in cohort composition, statistical modeling strategies, and approaches to percentile estimation. In particular, some methods rely on highly flexible statistical fitting procedures that may be less directly linked to biologically interpretable patterns of age-related brain change [3]. As quantitative MRI continues to gain clinical relevance, there is increasing interest in normative frameworks that provide stable age- and sex-adjusted volumetric assessment while maintaining intuitive and clinically interpretable modeling behavior. To provide a new standard for age- and sex-specific brain analysis, AIRS Medical has developed a novel "shifted-softplus normative model" for SwiftSight-Brain volumetric analysis. This method captures the biologically realistic pattern of the brain - while simultaneously modeling the age-dependent growth in inter-individual variance (heteroscedasticity).

The following sections detail the composition of the SwiftSight-Brain reference population, the statistical methodologies underlying the shifted-softplus model, and representative clinical cases that demonstrate how this framework translates into clinically meaningful, biologically grounded volumetric assessments.

2. Reference Population

Our normative database comprises 3D T1-weighted MRI data from 32,615 subjects, collected from consent-governed proprietary sources, publicly available research databases, and from collaboration with our business and research partners. The database spans ages 18 to 97, with broad regional and ethnic representation including the United States and worldwide populations.

To improve the robustness and generalizability across real-world clinical environments, the cohort database includes MRI data acquired from major scanner vendors (Siemens Healthineers, GE Healthcare, and Philips Healthcare), spanning both 1.5T and 3T systems and commonly used clinical 3D T1-weighted protocols including MP-RAGE, BRAVO, and TFE sequences.

The reference population was designed to represent structurally normal brain anatomy across the adult lifespan. Subjects were derived from cognitively or neurologically healthy research cohorts as well as clinical imaging datasets interpreted as radiologically normal during routine clinical review.

2.1 Demographic Composition

For normative percentile estimation, the critical metric is the sample size within each sex × age group cell. The following table demonstrates sufficiency across all 10-year age bins:

Age Group	Male	Female	Total
18-19	1,029	1,355	2,384
20-29	5,064	5,409	10,473
30-39	1,340	1,153	2,493
40-49	1,145	1,202	2,347
50-59	1,053	1,507	2,560
60-69	1,665	2,484	4,149
70-79	2,530	3,081	5,611
80+	1,366	1,232	2,598

3. Statistical Backbone:
Modeling the Biological Trajectory of Aging

3.1 The Shifted-Softplus Model

Traditional normative databases often rely on generalized additive models (GAM) or smooth splines to fit brain volume data. While these methods are effective for capturing complex nonlinear relationships in imaging data, highly flexible curve-fitting strategies can become sensitive to local sampling variability and outlier observations. This effect may become more pronounced in advanced age ranges, where healthy normative data are relatively limited and inter-subject variability naturally increases, potentially leading to unstable or biologically implausible trajectory estimation.

To address this, SwiftSight-Brain departs from pure mathematical interpolation by introducing a biologically motivated parametric model known as the shifted-softplus model. This model is designed to reflect established patterns of age-related brain atrophy while maintaining stable age-dependent trajectory estimation.

Extensive neurological research has demonstrated that age-related brain atrophy does not progress at a constant rate across the adult lifespan [4]. Instead, many brain structures show relatively slower volumetric decline earlier in adulthood, followed by accelerated atrophy in later life, particularly after approximately 60 years of age [5].

The SwiftSight-Brain model is specifically engineered to capture this trajectory. By using a softplus function - a smooth approximation of a transition point - the model enables gradual transition between phases of age-related volumetric change while maintaining smooth and stable trajectory behavior across the adult lifespan. In fitted regional models, the estimated inflection age typically falls between 58 and 62 years, consistent with prior neuroimaging observations of accelerated atrophy in later life.

Each parameter of the SwiftSight-Brain model corresponds to an interpretable aspect of age-related volumetric change:

- **Curvature:** Controls the degree of accelerated atrophy observed in later life
- **Linear Slope:** Represents the baseline rate of volume change during early and middle adulthood
- **Inflection Age:** Defines the age at which accelerated decline emerges
- **Vertical Offset:** Sets the baseline volume at the inflection point

This compact parametric representation enables intuitive interpretation of regional aging trajectories while preserving stable percentile estimation across the lifespan.

3.2 Addressing the Age-Dependent Variance

A key challenge in normative brain volumetry is heteroscedasticity - the observation that individual differences in brain volume tend to grow as a population ages. Younger adult populations generally exhibit relatively narrow volumetric distributions, whereas older populations show progressively broader variability due to cumulative effects of genetics, lifestyle, vascular burden, and other health-related factors [4].

SwiftSight-Brain addresses this by jointly fitting percentile curves across multiple variance levels, allowing the normative distribution to widen naturally with advancing age. As a result, the percentile framework remains adaptive to age-dependent changes in population variability, particularly in older age ranges where inter-subject variance becomes substantially larger.

3.3 Sex-Invariant Trajectory Modeling

Sex differences are a well-established source of variation in regional brain volume, with male and female cohorts typically showing systematic differences in both baseline regional volume and variance characteristics. However, the overall shapes of age-related atrophy trajectories, including early-adult decline rates, later-life acceleration, and trajectory curvature, are generally comparable between sexes for most regional structures [6].

SwiftSight-Brain incorporates this observation by modeling sex differences as sex-specific baseline distributions on a shared age-related trajectory. Each sex retains independent baseline median and variance characteristics, while trajectory parameters such as curvature, slope, and inflection age are jointly estimated from the combined cohort. By leveraging information from both male and female cohorts during trajectory estimation, the framework improves parameter stability and reduces sensitivity to limited sample density. This design provides consistent normative trajectories across the regional atlas while preserving clinically interpretable sex-specific reference distributions.

4. Model Fitting and Quality Control

SwiftSight-Brain employs a structured fitting and quality-control framework to ensure stable and biologically plausible percentile estimation across the adult lifespan.

Initial age-dependent baseline distributions are estimated independently for male and female cohorts. Shared trajectory parameters are then jointly optimized using the combined population to improve robustness and reduce sensitivity to local sampling variability.

During model optimization, smoothness constraints are applied to prevent unstable trajectory behavior and to maintain biologically consistent aging patterns across percentile levels.

All fitted percentile curves undergo both quantitative and visual quality-control review prior to deployment. Scatter distributions and percentile trajectories are systematically inspected to confirm stable age-related behavior and appropriate alignment with the underlying population data.

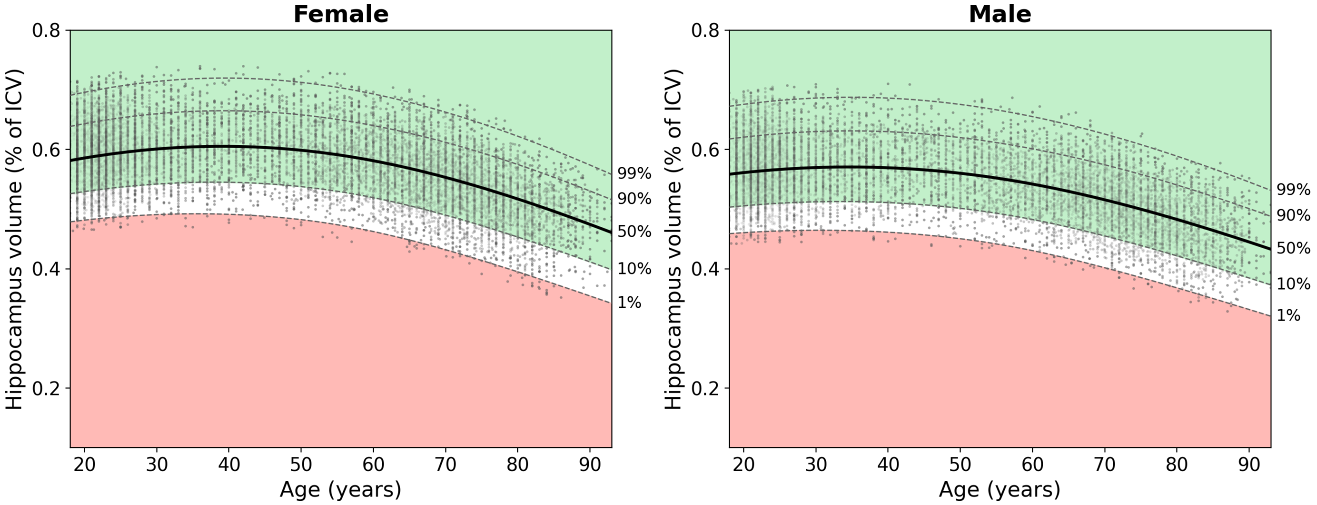

Figure 1. Volume scatter distribution map for the hippocampus. The plot visualizes actual recorded data points (dots) from SwiftSight-Brain normative database along with fitted percentile curves (dotted: 99th, 90th, 10th and 1th percentiles, solid: 50th percentile) for male and female populations.

5. Clinical Inference and Abnormality Classification

During clinical inference, each patient's regional brain volumes are normalized to total intracranial volume (TIV) and compared against the age- and sex-adjusted normative distribution derived from the SwiftSight-Brain reference population. Percentile estimates provide quantitative context for interpreting regional brain anatomy relative to structurally normal individuals of similar demographic background.

Because the normative database was constructed from cognitively and structurally normal subjects, the abnormality framework is designed to identify volumetric measurements that fall substantially outside the expected range of normal anatomical variation. Conservative percentile cutoffs are used to support robust interpretation and to reduce overinterpretation of physiological anatomical variation in routine clinical practice. Regional parenchymal structures are classified as abnormal when the estimated percentile falls below the 1st percentile of the normative population. Conversely, ventricular structures are classified as abnormal when the percentile exceeds the 99th percentile, reflecting ventricular enlargement commonly observed in cerebral atrophy and neurodegenerative conditions.

Percentile-based assessments are intended to support radiologic interpretation and should be considered alongside the patient's clinical presentation and other imaging findings.

6. Representative Clinical Cases

The clinical value of a normative database is ultimately determined by how meaningfully its percentile outputs align with the patterns radiologists encounter in everyday practice. A statistical model that fits well across a population is necessary but not sufficient; it must also produce percentile signals that are interpretable, stable, and consistent with the structural changes clinicians recognize at the bedside and at the reading room. The following section presents four representative clinical cases drawn from real-world neuroimaging to illustrate how the SwiftSight-Brain framework behaves in such scenarios.

The selected cases were chosen to illustrate the principal quantitative dimensions of SwiftSight-Brain across distinct clinical settings: longitudinal stability in cognitively normal aging, longitudinal percentile trajectory through cognitive decline, region-specific atrophy patterning in established neurodegeneration, and lateralizing asymmetry in a focal pathology. Each case demonstrates how percentile-based analysis can surface information that complements - and at times sharpens - the visual interpretation of the radiologist. Together, the cases illustrate the multi-axis structure of normative volumetric information that SwiftSight-Brain makes available within the radiologic reading workflow.

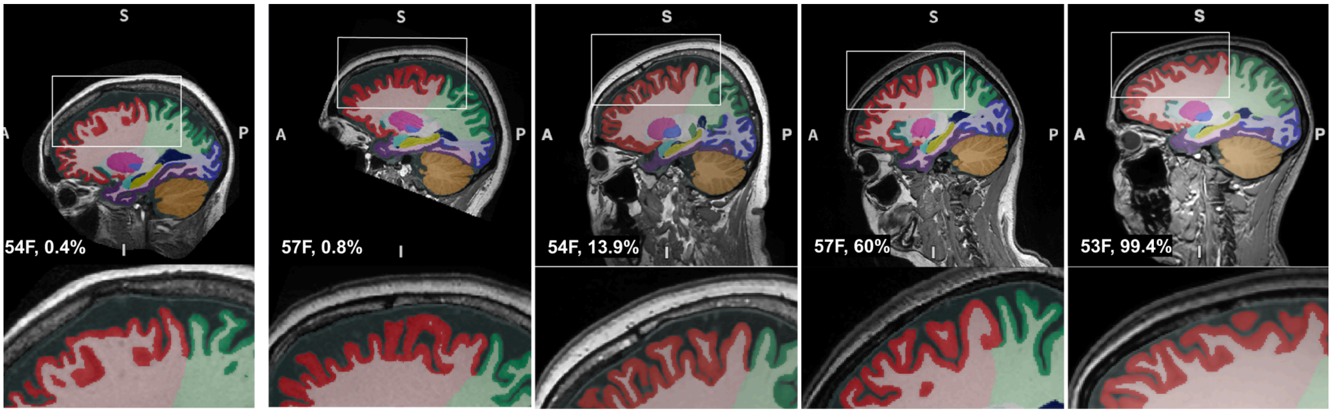

Figure 2. An example of percentile match & visual alignment within peer group. A single input MR exam (left) alongside four representative subjects (right) selected from the SwiftSight-Brain's reference population, all from the same demographic peer group (women aged 54-57). The input case and the four reference subjects span a wide range of whole-brain percentile estimates - from the lower extremity of the normative distribution through the central range to the upper extremity - and the regional volumetric patterns visible on the corresponding MR slices align consistently with their assigned percentile rank. The agreement between the quantitative percentile output and the visual impression of regional brain volume across this peer group illustrates that, within a demographically matched subset of the normative population, SwiftSight-Brain percentile estimates correspond to anatomic patterns recognizable upon visual interpretation of the images.

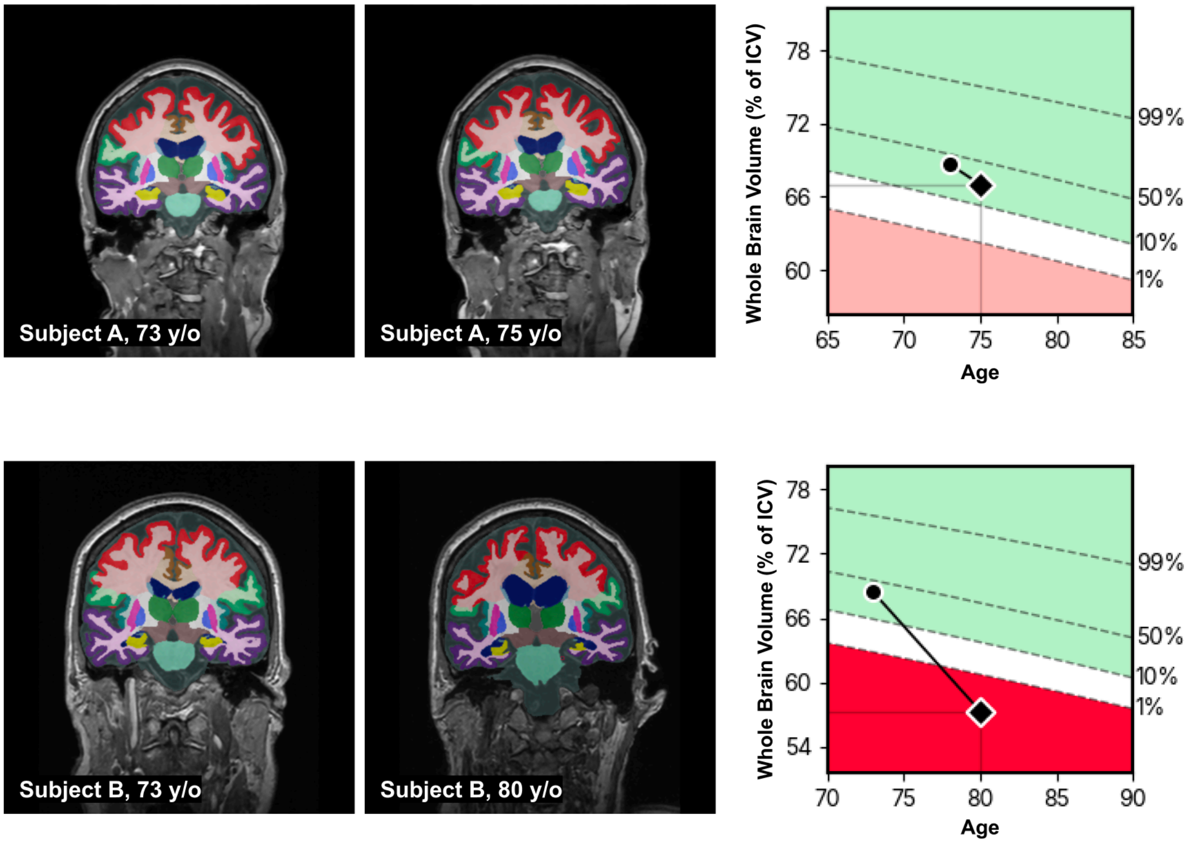

Figure 3. Tracking diverging visual atrophy patterns and longitudinal percentile declines. Longitudinal MR images for two female subjects (top and bottom rows, respectively) who began follow-up at the same baseline age (73 y) with closely matched initial whole brain volume percentiles (31.7 and 31.0). In their respective follow-up scans, visual assessment shows progressive volumetric changes in both patients with different magnitudes. Subject A (top) shows subtle changes to the general brain volume visible from both the MR images and the calculated percentiles. In contrast, subject B (bottom) has undergone relatively severe atrophic changes, which are depicted by marked loss of cortical (red, green, purple) and hippocampal (yellow) volumes seen in the follow-up MR image and decline in the volume percentiles. This example demonstrates that SwiftSight-Brain can track these two distinct patterns correspondingly, illustrating that percentile estimates reflect both the within-subject change visible across timepoints and the between-subject differences in volumetric pattern observable upon visual review.

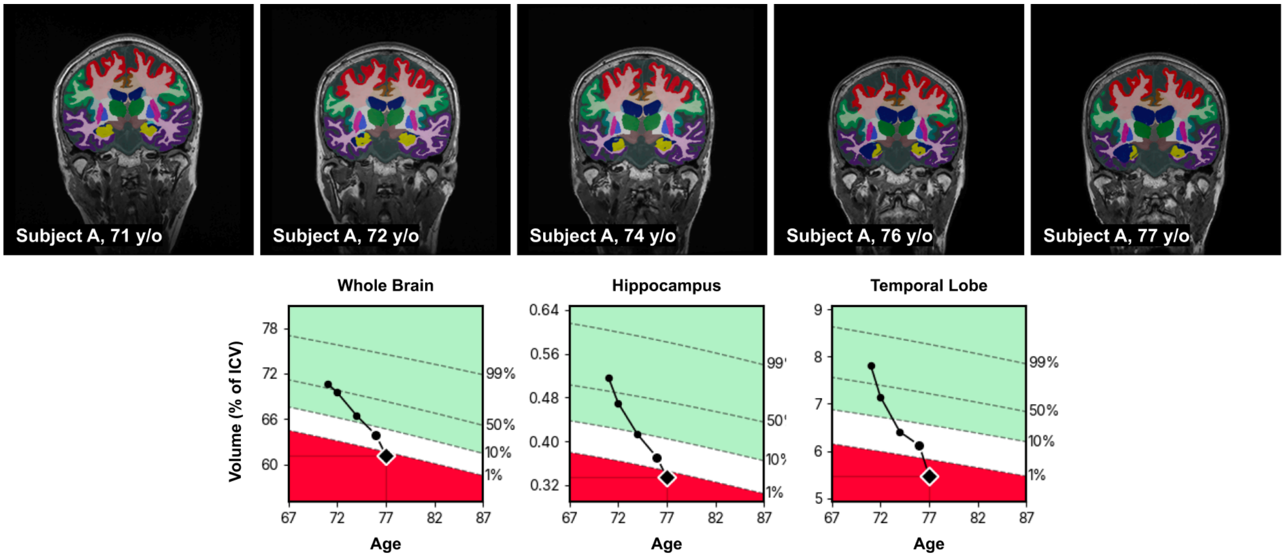

Figure 4. Tracking longitudinal course of atrophy. This example illustrates a longitudinal series for a female subject imaged from age 71 to 77. SwiftSight-Brain percentile estimates for whole brain, hippocampus, and temporal regions in this subject showed a sustained downward trajectory across the follow-up period, drifting from the central range to beyond the lower extreme of the normative distribution. This quantitative trajectory provides an objective complement to serial visual review, allowing progressive atrophy to be monitored over time and early departures from the normal range to be recognized before they become conspicuous on individual exams.

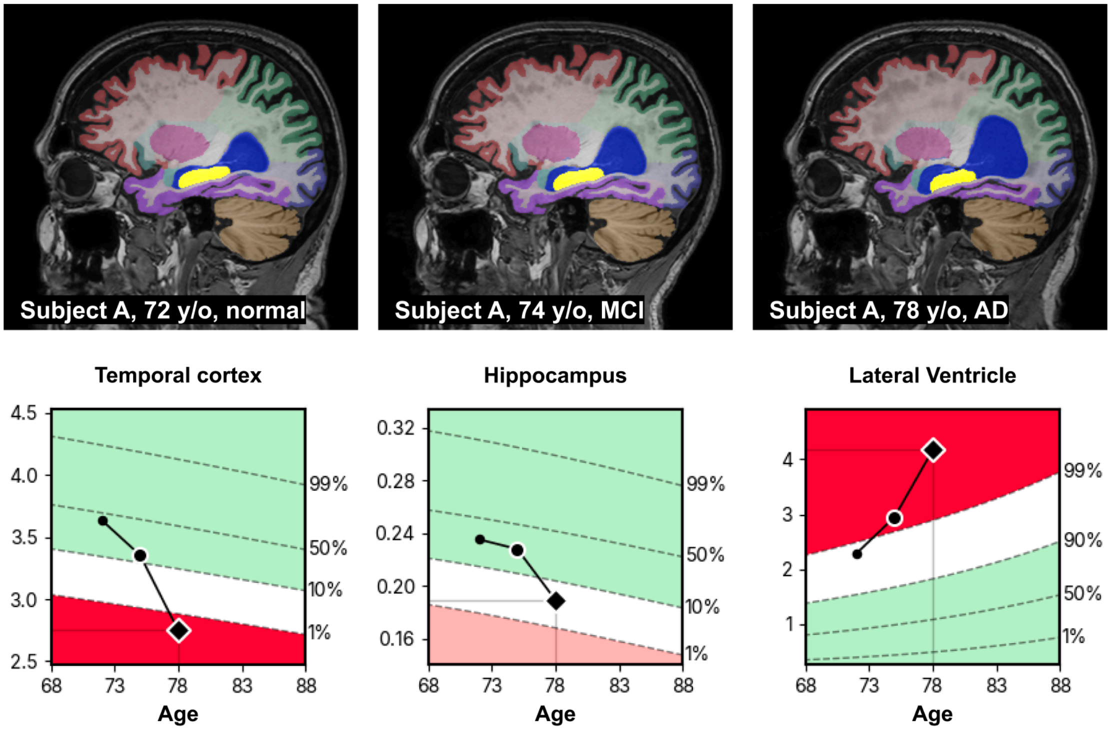

Figure 5. Recognizing region-specific atrophy patterns. This case is from a 72-year-old female with a 5-year clinical progression from cognitive normal (CN) to mild cognitive impairment (MCI) and subsequently to Alzheimer's disease (AD). Longitudinal MR volumetry shows progressive temporal cortical atrophy with marked ex-vacuo enlargement of the lateral ventricles. SwiftSight-Brain percentile estimates diverged markedly across regions: lateral ventricle volumes remained at the upper extremity of the normative distribution from the earliest timepoint and continued to rise, while temporal cortex percentile declined progressively from the central range into the lower extreme, and hippocampus percentile decline emerged later in the follow-up.

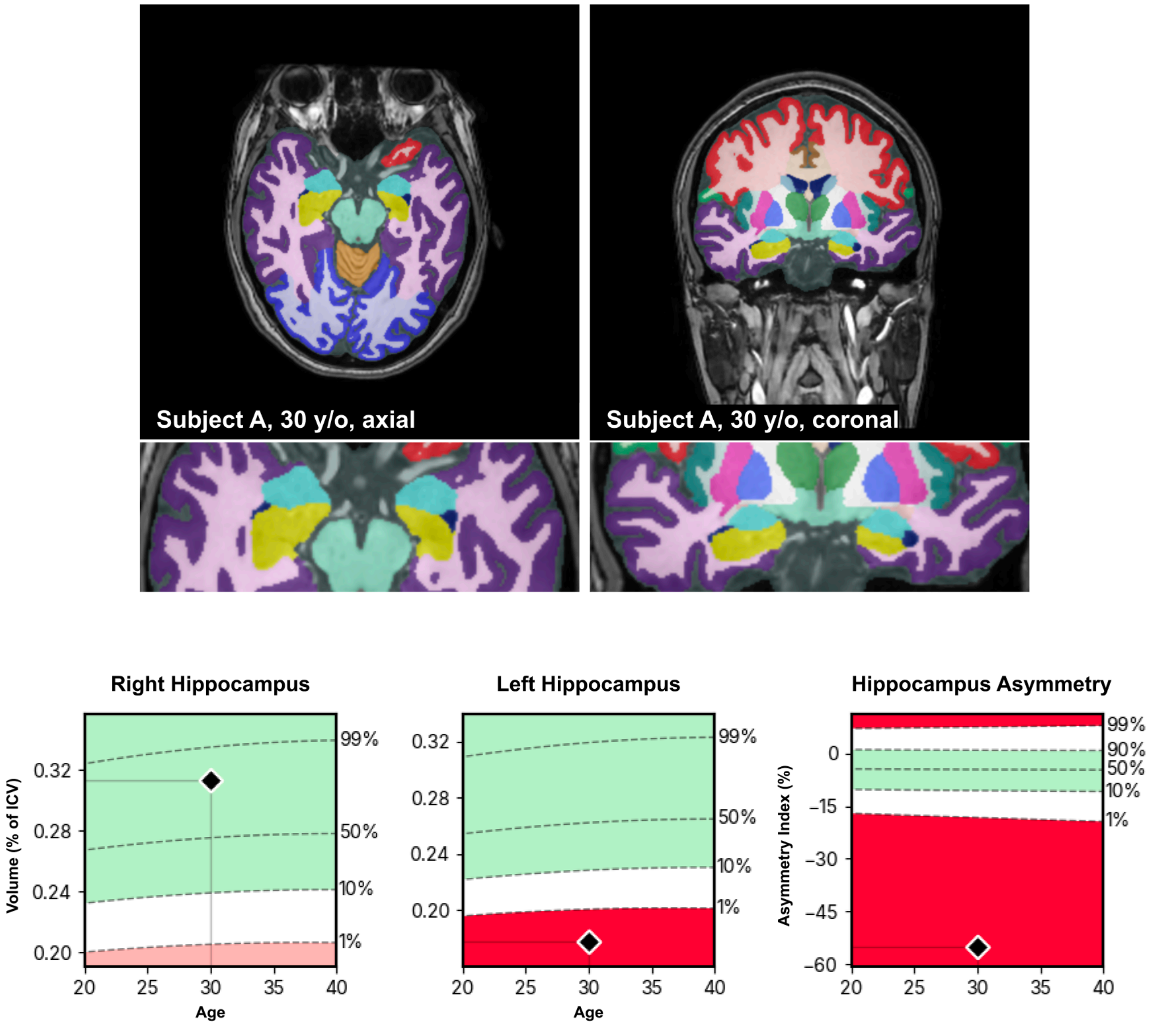

Figure 6. Hippocampal asymmetry in epilepsy. A single-timepoint volumetric assessment for a 30-year-old female undergoing pre-surgical evaluation for refractory temporal lobe epilepsy is presented. SwiftSight-Brain reports that the absolute hippocampal volumes are within the lower limit among peer group, yielding percentile values that would not, on their own, trigger conventional abnormality flags. The SwiftSight-Brain's asymmetry index for the hippocampus, however, fell well below the 1st percentile of the normative distribution, isolating a lateralization signal that absolute volumes alone did not capture. This case illustrates how percentile-based asymmetry analysis can play a crucial role in conjunction with unilateral volume measurements.

7. Conclusion

The normative database of SwiftSight-Brain is built on a deliberate methodological choice: rather than approximating age-related volumetric change through highly flexible curve-fitting strategies, the shifted-softplus model expresses the aging trajectory through a small set of biologically interpretable parameters - curvature, linear slope, inflection age, and vertical offset. This parametric design preserves established neurological observations of age-related atrophy, while jointly modeling age-dependent variance and sex-specific baseline distributions on a shared trajectory. The result is a normative framework that maintains stable percentile estimation across the adult lifespan while remaining mechanistically transparent and clinically interpretable.

In this whitepaper, the clinical relevance of this design is illustrated across the five representative cases. The framework’s ability to provide peer-based percentile values for the input image which also aligns with visual interpretation demonstrate the robustness of the normative database. Tracking longitudinal change in subjects with varying magnitude of atrophic progression has also been displayed, while region-specific percentile divergence in patients with neurological conditions reflect disease-specific atrophy patterns rather than a single global score. Also, the ability to capture asymmetry indices in hippocampal volumes provide additional insight for relevant clinical scenarios where absolute volumes alone may not be able to accurately depict the condition. Across longitudinal, regional, and lateralizing dimensions, SwiftSight-Brain extends the radiologic reading from an isolated absolute volume to a structured, multi-axis percentile representation of the patient's brain.

By providing clinically transparent, age- and sex-adjusted quantitative context alongside the patient's clinical presentation and other imaging findings, SwiftSight-Brain extends the radiologist's interpretive toolkit with a stable, biologically grounded reference frame. Together with AIRS Medical's existing SwiftMR™ platform, SwiftSight-Brain contributes to a broader vision of AI-driven, end-to-end quantitative neuroimaging - from acquisition through structural analysis - integrated into the real-world radiology workflow.

References

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