Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Normative Measurement of Apparent Diffusion Coefficient on Brain Magnetic Resonance Imaging

Suraj Sah

nomadicsurajnp@gmail.com

National Academy of Medical Sciences, Bir Hospital

Avinesh Shrestha

National Academy of Medical Sciences, Bir Hospital

Bikesh Jaiswal

National Academy of Medical Sciences, Bir Hospital

Pradip Sharma

Civil Service Hospital

Elisha Sunar

National Academy of Medical Sciences, Bir Hospital

Dipak Kumar Oli

National Academy of Medical Sciences, Bir Hospital

Ranju Shrestha

Nepalese Army Institute of Health Sciences, Shree Birendra Hospital

Rakhi Mallik

B.P. Koirala Institute of Health Sciences

Abinash Jha

National Academy of Medical Sciences, Bir Hospital

Bikash Raj Thapa

National Trauma Center

Research Article

Keywords: Apparent Diffusion Coefficient, Diffusion-Weighted Imaging, Magnetic Resonance Imaging, Brain Aging

Posted Date: September 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10965611/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Normal brain aging is associated with microstructural alterations that influence tissue water diffusivity. Diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping provides quantitative assessment of brain tissue characteristics and is widely used in clinical neuroradiology. However, ADC values vary according to age, anatomical location, MRI acquisition parameters, and population characteristics. Establishing normative ADC values is essential for accurate interpretation of diffusion abnormalities and differentiation of physiological variation from pathological changes. This study aimed to evaluate regional ADC values across selected brain regions among individuals with normal brain MRI findings and assess variations according to age, sex, and hemispheric laterality.

Methods

A quantitative cross-sectional observational study was conducted among 87 individuals aged 12–86 years with clinically normal brain MRI examinations. MRI examinations were performed using a 1.5 Tesla scanner. ADC values were measured in selected bilateral brain regions, including the caudate nucleus, thalamus, centrum semiovale, cerebellum, pons, and vermis. Statistical analysis was performed using one-way analysis of variance (ANOVA), independent samples t-test, paired samples t-test, and Spearman correlation analysis.

Results

The study included 87 individuals with normal brain MRI findings, comprising 33 males and 54 females. Mean ADC values were relatively higher in the adolescent group and remained comparable across adult age groups. No statistically significant association was observed between age and global ADC values ($\rho = -0.145$, $p = 0.179$). No significant differences were identified in ADC values between males and females. Most evaluated brain regions demonstrated comparable bilateral ADC values; however, the centrum semiovale showed significantly higher ADC values in the left hemisphere compared with the right hemisphere ($p < 0.001$).

Conclusions

This study provides regional normative ADC reference values among individuals with normal brain MRI findings. The observed age-associated variations and hemispheric differences highlight the importance of considering physiological ADC variability during clinical interpretation of diffusion-weighted imaging. These findings may provide supportive reference data for evaluating abnormal ADC patterns within comparable MRI acquisition protocols.

Background

The normal adult brain undergoes significant morphological changes with advancing age, characterized on autopsy by decreased brain weight and increased cerebrospinal fluid (CSF)-filled spaces resulting from ventricular dilatation and sulcal enlargement.[1] Neuropathological investigations indicate that age-related cortical neuronal loss is less extensive than previously recognized, suggesting that white matter (WM) alterations and subcortical atrophy-predominantly affecting the striatum through reduced cell size and minimized gray matter loss-outweigh gray matter changes during normal human aging.[2,3]

Neuroimaging advances, particularly magnetic resonance imaging (MRI), have revolutionized the *in vivo* study of human brain dynamics. Diffusion-weighted imaging (DWI) provides a non-invasive assessment of tissue microarchitecture by quantifying the random Brownian motion of water molecules driven by thermal energy.[4,5] The apparent diffusion coefficient (ADC), derived using standard b-values, commonly including 1000 s/mm², serves as a quantitative marker of water diffusivity within brain tissue and may detect subtle microstructural alterations not evident on conventional MRI.[6,7]

Despite the extensive clinical utility of DWI in diagnosing acute cerebral infarction, characterizing neoplasms, and monitoring neurodegenerative pathologies, literature regarding normal lifespan trajectories of brain tissue water diffusivity remains inconsistent.[8,9] While some investigations report significant late life increases in ADC due to unavoidable tissue senescence and atrophy, others suggest that healthy brain microstructure remains remarkably stable throughout adulthood.[10,14] Furthermore, prior studies frequently suffer from small sample sizes or rely on heterogeneous clinical populations. [19]

Crucially, there is a notable absence of robust, population-specific normative baseline values within South Asian and Nepalese cohorts to distinguish normal physiological aging from early neurodegenerative or pathological alterations.[11,12] Because clinical radiologists heavily depend on diffusion-weighted metrics for diagnostic interpretation, establishing regional reference data is a critical clinical necessity.[11,13] Therefore, this study aimed to investigate regional apparent diffusion coefficient values across multiple brain regions in individuals with normal brain MRI findings spanning a broad age range and to assess variations according to age, sex, and hemispheric laterality.

Methods

Study design and Study setting

This cross-sectional observational study was conducted in the Department of Radiology and Imaging at Bir Hospital, National Academy of Medical Sciences (NAMS), Kathmandu, Nepal. Data acquisition took place from April 2025 to April 2026. Ethical approval was obtained from the Institutional Review Board of NAMS (Ref: 501/079/80-2079/8/29).

Study population and sample size

Using consecutive sampling, we included patients who underwent routine brain MRI examinations during the study period and whose examinations were reported as normal by the attending radiologist having 15 years of work experience. The sample size (n = 87) was determined using the formula for descriptive cross-sectional studies based on a standard normal distribution table value (Z = 1.96 for a 95% confidence level) described by Miller et al.[2] [$n = \frac{Z^2\sigma^2}{d^2}$] Standard Deviation (σ) = 0.14×10^{-3} mm²/s, based on the reported SD of the right cerebellar ADC in the reference study.[18] and d = 0.03×10^{-3} mm²/s was set as the allowable absolute error (precision).

Ethical Approval and Consent:

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Ethical approval was granted by the Institutional Review Board (IRB) of the National Academy of Medical Sciences (NAMS), Bir Hospital, Kathmandu, Nepal (Ref No. xxx/xxx/xx-xxxx/xx/xx). Written (or verbal) informed consent was obtained from all individual participants prior to inclusion in the study.

Inclusion Criteria

Routine brain MRI examinations reported as normal by the radiologist, including normal DWI and ADC findings.

Exclusion Criteria

Patients with a history of major neurological or psychiatric disorders, previous cerebrovascular disease or intracranial surgery, and examinations degraded by severe artifacts or distortion that interfered with ADC measurement.

MRI Acquisition Protocol

Imaging was performed on a 1.5-T MRI scanner (Achieva, Philips Medical Systems) using a standard clinical brain protocol that includes axial, sagittal spin echo T1-weighted images (T1WI); axial, coronal spin echo T2-weighted images (T2WI); axial spin echo fluid- Attenuated Inversion Recovery (FLAIR); fast field-echo T2* weighted images; and axial diffusion- weighted spin-echo single-shot echo-planar (DW SE-SS-EPI) sequences.

DWI MRI parameters: Repetition time (TR) / Echo time (TE) (ms): 3000/85; minimum TR: 2694 ms; acquisition matrix M×P: 128×126; section thickness: 4 mm; interslice gap: 2.8 mm; echo-planar imaging factor: 63; b-values: 0 and 1000 s/mm²; duration of each DWI protocol: 36 seconds; dB/dt: 62.8 T/s; max B1 + rms: 152 μT; fat suppression: SPIR; and acquisition mode: Cartesian. Isotropic ADC maps and trace images were generated automatically.

ADC Measurement: Data were transferred to an off-line workstation for quantitative analysis. Circular ROIs of 10–20 mm² were manually placed by a radiologist experienced in brain MRI interpretation on

ADC maps, avoiding CSF spaces, vascular structures, and partial volume effects. ROIs were placed in the bilateral heads of the caudate nuclei, thalami, centrum semiovale, and cerebellar hemispheres, as well as in the pons and cerebellar vermis as shown in Fig. 1. The cohort was divided into four age groups: For group-wise analysis, participants were categorized into four predefined age groups: 12–24, 25–44, 45–64, and 65–86 years.[1,2] These categories were used to facilitate comparison of ADC values across the age distribution of the study population. Age was additionally analyzed as a continuous variable using correlation analysis.

Statistical Analysis

Data were entered and cleaned in Microsoft Excel and analyzed using SPSS version 25. Spearman's rank correlation coefficient was used to assess the relationship between age and ADC values. One-way ANOVA was conducted to compare mean ADC values among age groups for each ROI, with Tukey post hoc tests performed only if the ANOVA was statistically significant. Independent-samples t-tests evaluated sex differences in ADC values, and paired-samples t-tests assessed right–left differences in bilateral ROIs. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Participant Demographics: A total of 87 participants (33 males [37.9%] and 54 females [62.1%]) with clinically normal brain MRI examinations were included in the study. The overall cohort had a mean age of 40.24 ± 17.68 years, spanning an age range from 12 to 86 years. For group-wise analysis, participants were categorized into four predefined age groups: 12–24 years (n = 18), 25–44 years (n = 35), 45–64 years (n = 25), and 65–86 years (n = 9). The complete baseline distribution of the study population across age brackets and gender is summarized below Table 1.

Table 1
Demographic characteristics of the study population (N = 87).

Age Group	Age Range (Years)	Total (n)	Male (n, %)	Female (n, %)
Adolescence	12–24	18	7	11
Mid-Adulthood	25–44	35	15	20
Older/Middle Age	45–64	25	5	20
Senior	65–86	9	6	3
Total	12–86	87	33 (37.9%)	54 (62.1%)

Age-Related Changes in Global Brain Diffusivity

Lifespan analysis revealed a non-linear pattern of global brain diffusivity, characterized by an early developmental growth phase followed by structural stabilization. As illustrated in the global line chart Fig. 2, mean Apparent Diffusion Coefficient (ADC) values peaked during adolescence (12–24 years) at

approximately 0.75×10^{-3} mm^2/s, reflecting higher water mobility and extracellular space fraction during active structural organization and axonal packing.

As white matter matured into mid-adulthood, mean global ADC values decreased and plateaued at approximately 0.73×10^{-3} mm^2/s, maintaining structural stability across the adult lifespan. A One-way ANOVA demonstrated no statistically significant differences in global ADC across the four age groups ($p > 0.05$), with data distributions overlapping closely in group-wise evaluations. Similarly, Spearman's rank correlation indicated a weak, non-significant overall correlation between age and global brain diffusivity ($\rho = -0.145$, $p = 0.179$), reflecting that global normative brain tissue integrity is largely preserved across healthy adult aging.

Regional-Specific Analysis and Fitting Curves

Detailed regional-specific trajectory and curve-fitting analyses Fig. 3 demonstrated heterogeneous age-related changes across individual Brain Regions of Interest (ROIs). White matter regions and periventricular areas, including the frontal, occipital, and parietal lobes, as well as the centrum semiovale, exhibited mild positive linear trends ($r \approx 0.3–0.6$), showing a gradual progressive increase in ADC values ADC ($\approx 0.1–0.3 \times 10^{-3}$ mm^2/s) across advancing decades. Conversely, deep gray matter structures such as the thalamus exhibited a nearly flat slope, indicating negligible age-related alterations in water diffusion parameters. Regional scatter plots (≈ 20–40 observations per region) further revealed tighter data clustering among younger cohorts compared to slightly greater variability among senior participants, underscoring region-specific structural stabilization profiles over nearly nine decades of normal human brain aging.

ADC ($\times10^{-3}$ mm^2/s)

Age (Years)

Comparison of ADC Values by Gender

Apparent Diffusion Coefficient (ADC) values were compared between male (n = 33) and female (n = 54) participants using Student’s independent samples t-tests. Gender exerted no statistically significant effect on brain diffusivity across any of the measured Regions of Interest ($p > 0.05$). Mean ADC values demonstrated high concordance between genders, with minimal variation observed in structures such as the left thalamus ($p = 0.99$) and the left centrum semiovale ($p = 0.88$). These findings indicate that brain tissue water diffusivity is sex-independent in normative cohorts, supporting the combination of male and female data for broader lifespan analyses.

Hemispheric Laterality Comparison

Apparent Diffusion Coefficient (ADC) values showed high bilateral symmetry across most subcortical and cerebellar structures, including the head of the caudate nucleus (0.74×10^{-3} mm^2/s bilaterally; p =

0.33), thalamus (0.74 vs. 0.75 10^{-3} mm^2/s; p = 0.12), and cerebellum (0.68 vs. 0.69 10^{-3} mm^2/s; p = 0.35). Conversely, a statistically significant lateralization was observed in the centrum semiovale, where ADC values were significantly higher in the left hemisphere ($0.76 \pm 0.04 \times 10^{-3}$ mm^2/s) compared to the right ($0.71 \pm 0.05 \times 10^{-3}$ mm^2/s); paired t-test, $p < 0.001$ as shown in the bar chart Fig. 4.

Discussion

The adult brain undergoes progressive microstructural alterations with age, particularly within white matter. Diffusion-weighted imaging (DWI) provides a noninvasive method to evaluate these microscopic changes, as apparent diffusion coefficient (ADC) values detect subtle variations invisible on standard MRI.[16,18] This study establishes normative baseline ADC values for normal-appearing brain tissue across different ages, genders, and hemispheric laterality to enhance our understanding of physiological aging and improve diagnostic precision.

Our findings demonstrate a physiological plateau in mean ADC values, which remain relatively stable from early adulthood through late middle age. This stable trajectory indicates that brain microstructural integrity does not necessarily diminish uniformly with age in a healthy cohort. This observation reflects healthy adult homeostasis, contrasting sharply with the rapid diffusivity decreases seen during pediatric maturation, where Sotardi et al.[12] noted stabilization by 2.4 years due to active myelination, and the age-related elevations in older seniors caused by myelin loss, neuronal degeneration, or extracellular space expansion.[13,16,17]

Comparing our results with existing literature reveals general consensus regarding adult brain stability alongside regional specificities. While Chun et al.[13] and Klimas et al.[5] reported minimal overall age-related global diffusion changes, Gideon et al.[19] observed progressive cerebral white matter increases. Our regional data supports these subtleties, showing stable deep gray matter (such as the thalamus) paired with subtle periventricular white matter increases. Furthermore, our analysis confirms that brain tissue microstructure is sex-independent, aligning with previous findings by Helenius et al.[14] and Klimas et al.[5]. Regarding hemispheric laterality, while most subcortical and cerebellar structures demonstrated high bilateral symmetry matching prior studies, a notable and statistically significant lateralization was observed in the centrum semiovale, highlighting inherent microstructural white-matter asymmetry.[12,14]

Establishing these site-specific, normative ADC baselines holds substantial clinical utility. They serve as critical diagnostic benchmarks that empower radiologists to accurately differentiate normal physiological aging variations and inherent hemispheric asymmetries from early neurodegenerative or neurovascular pathologies.

Several limitations should be acknowledged. The single-center, single-scanner design and uneven senior sample distribution restrict broader generalizability. Manual region-of-interest (ROI) selection introduces potential investigator bias and partial-volume effects, while the cross-sectional framework precludes

longitudinal tracking. Finally, the absence of formal cognitive or neuropsychological correlations limits direct clinical translation.

Conclusions

This study establishes robust normative ADC benchmarks demonstrating that brain tissue diffusivity exhibits a physiological plateau throughout healthy adulthood, shows no gender-dependence, and displays selective white matter asymmetry confined to the centrum semiovale. From a clinical implication standpoint, these reference values provide vital diagnostic tools for neuroradiologists to reliably differentiate normal structural variants from early neuropathological alterations. Future research implementing multi-center automated frameworks and longitudinal tracking will be essential to enhance the precision and predictive power of neuroimaging biomarkers in clinical practice.

Abbreviations

ADC Apparent Diffusion Coefficient

CSF Cerebrospinal Fluid

FOV Field of View

IRB Institutional Review Board

DKI Diffusion Kurtosis Imaging

DTI Diffusion Tensor Imaging

DWI Diffusion Weighted Imaging

FA Fractional Anisotropy

FLAIR Fluid Attenuated Inversion Recovery

GM Gray Matter

ICH Intracranial Hemorrhage

MRI Magnetic Resonance Imaging

NAMS National Academy of Medical Sciences

NSA Number of Signal Average

ROI Region of Interest

SD Standard Deviation

SI Signal Intensity

SPSS Statistical Package for Social Sciences

T Tesla

TE Time of Echo

TR Time of Repetition

WM White Matter

Declarations

Ethics approval and consent to participate: This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Ethical approval was granted by the Institutional Review Board (IRB) of the National Academy of Medical Sciences (NAMS), Bir Hospital, Kathmandu, Nepal (Ref No. xxx/xxx/xx-xxxx/xx/xx). Written informed consent was obtained from all participants prior to inclusion. All patient data were anonymized to ensure confidentiality, with no identifying information retained.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Authors' contributions: (CRediT)

SS: Conceptualization, Methodology, Investigation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Project Administration.

AS: Formal Analysis, Writing – Review & Editing.

BJ: Investigation.

PS: Validation, Resources.

ES: Visualization, Investigation.

DKO: Writing – Review & Editing, Resources.

RS: Writing – Review & Editing.

RM: Writing – Review & Editing.

AJ: Supervision, Validation, Writing – Review & Editing.

BRT: Supervision, Validation, Writing – Review & Editing.

Acknowledgements: The authors acknowledge the use of generative AI and AI-assisted technologies in the preparation of this manuscript. Grammarly and Quillbot were utilized for grammatical corrections and paraphrasing. ChatGPT and Gemini were used to assist with initial brainstorming, outline organization, drafting, and statistical guidance. The authors reviewed, verified, and edited all AI-generated content and take full responsibility for the final manuscript, data interpretations, and revisions. No patient-identifiable or sensitive data were inputted into any AI tools.

Authors' information: Not applicable.

References

1. Hsu JL, Leemans A, Bai CH, Lee CH, Tsai YF, Chiu HC, et al. Gender differences and age-related white matter changes of the human brain: a diffusion tensor imaging study. NeuroImage. 2008;39(2):566–77. 10.1016/j.neuroimage.2007.09.017. [PubMed].
2. Miller AK, Alston RL, Corsellis JA. Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser. Neuropathol Appl Neurobiol. 1980;6(2):119–32. 10.1111/j.1365-2990.1980.tb00283.x. [PubMed].
3. Salat DH, Greve DN, Pacheco JL, Quinn BT, Helmer KG, Buckner RL, et al. Regional white matter volume differences in nondemented aging and Alzheimer's disease. NeuroImage. 2009;44(4):1247–58. 10.1016/j.neuroimage.2008.10.030. [PubMed].
4. Watanabe M, Sakai O, Ozonoff A, Kussman S, Jara H. Age-related apparent diffusion coefficient changes in the normal brain. Radiology. 2013;266(2):575–82. 10.1148/radiol.12112420. [PubMed].
5. Klimas A, Drzazga Z, Kluczewska E, Hartel M. Regional ADC measurements during normal brain aging in the clinical range of b values: a DWI study. Clin Imaging. 2013;37(4):637–44. 10.1016/j.clinimag.2013.01.013. [PubMed].
6. Xing D, Papadakis NG, Huang CL, Lee VM, Carpenter TA, Hall LD. Optimised diffusion-weighting for measurement of apparent diffusion coefficient (ADC) in human brain. Magn Reson Imaging. 1997;15(7):771–84. 10.1016/s0730-725x(97)00037-4. [PubMed].
7. Stejskal EO, Tanner JE. Spin Diffusion Measurements: Spin Echoes in the Presence of a Time-Dependent Field Gradient. J Chem Phys. 1965;42(1):288–92. 10.1063/1.1695690. [DOI].
8. Venkataraman A, Zhong J. Basics of diffusion measurements by MRI. Diffusion-Weighted MR Imaging of the Brain, Head and Neck, and Spine. Springer; 2021. pp. 3–10. [DOI].
9. Mascalchi M, Filippi M, Floris R, Fonda C, Gasparotti R, Villari N. Diffusion-weighted MR of the brain: methodology and clinical application. Radiol Med. 2005;109(3):155–97. [PubMed].

10. Chen ZG, Li TQ, Hindmarsh T. Diffusion tensor trace mapping in normal adult brain using single-shot EPI technique. A methodological study of the aging brain. Acta Radiol. 2001;42(5):447–58. 10.1080/028418501127347160. [PubMed].
11. Dubois J, Dehaene-Lambertz G, Kulikova S, Poupon C, Hüppi PS, Hertz-Pannier L. The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. Neuroscience. 2014;276:48–71. 10.1016/j.neuroscience.2013.12.044. [PubMed].
12. Sotardi S, Gollub RL, Bates SV, Weiss R, Murphy SN, Grant PE, et al. Voxelwise and Regional Brain Apparent Diffusion Coefficient Changes on MRI from Birth to 6 Years of Age. Radiology. 2021;298(2):415–24. 10.1148/radiol.2020202279. [PubMed].
13. Chun T, Filippi CG, Zimmerman RD, Uluğ AM. Diffusion changes in the aging human brain. AJNR Am J Neuroradiol. 2000;21(6):1078–83. PubMed PMID: 10871018; [PubMed].
14. Helenius J, Soinne L, Perkiö J, Salonen O, Kangasmäki A, Kaste M, et al. Diffusion-weighted MR imaging in normal human brains in various age groups. Am J Neuroradiol. 2002;23(2):194–9. [PubMed].
15. Nomura Y, Sakuma H, Takeda K, Tagami T, Okuda Y, Nakagawa T. Diffusional anisotropy of the human brain assessed with diffusion-weighted MR: relation with normal brain development and aging. AJNR Am J Neuroradiol. 1994;15(2):231–8. [PubMed].
16. Mohammed NA, Abdullah DHS. Apparent diffusion coefficient value of normal brain in relation to age and gender in adults. Ann Med Health Sci Res. 2020;10:799–803. [GoogleScholar].
17. Naganawa S, Sato K, Katagiri T, Mimura T, Ishigaki T. Regional ADC values of the normal brain: differences due to age, gender, and laterality. Eur Radiol. 2003;13(1):6–11. 10.1007/s00330-002-1549-1. [PubMed].
18. Engelter ST, Provenzale JM, Petrella JR, DeLong DM, MacFall JR. The effect of aging on the apparent diffusion coefficient of normal-appearing white matter. AJR Am J Roentgenol. 2000;175(2):425–30. 10.2214/ajr.175.2.1750425. [PubMed].
19. Gideon P, Thomsen C, Henriksen O. Increased self-diffusion of brain water in normal aging. J Magn Reson Imaging. 1994;4(2):185–8. 10.1002/jmri.1880040216. [PubMed].

Figures

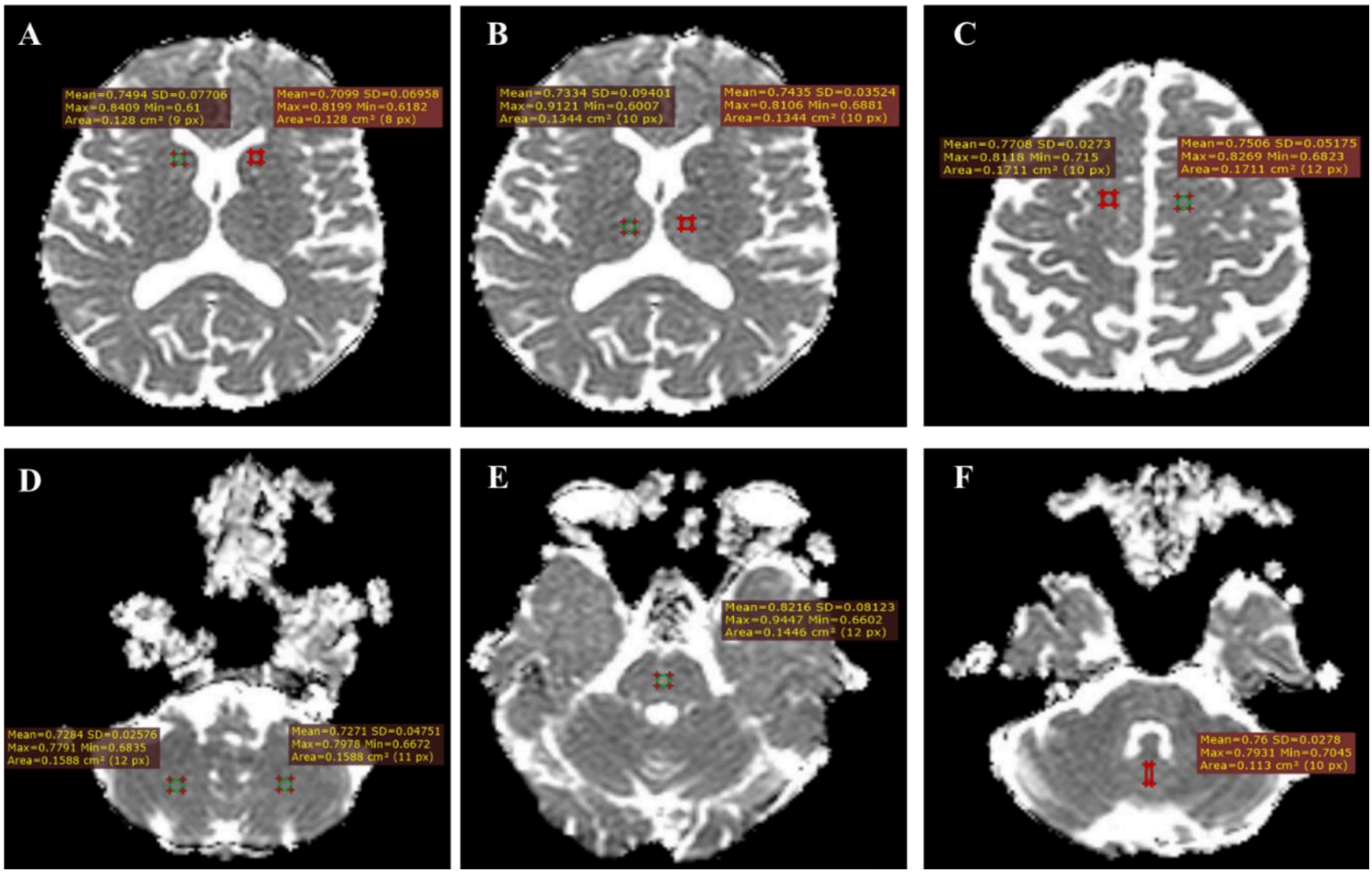


Figure 1

ROIs of gray and white matter of Brain

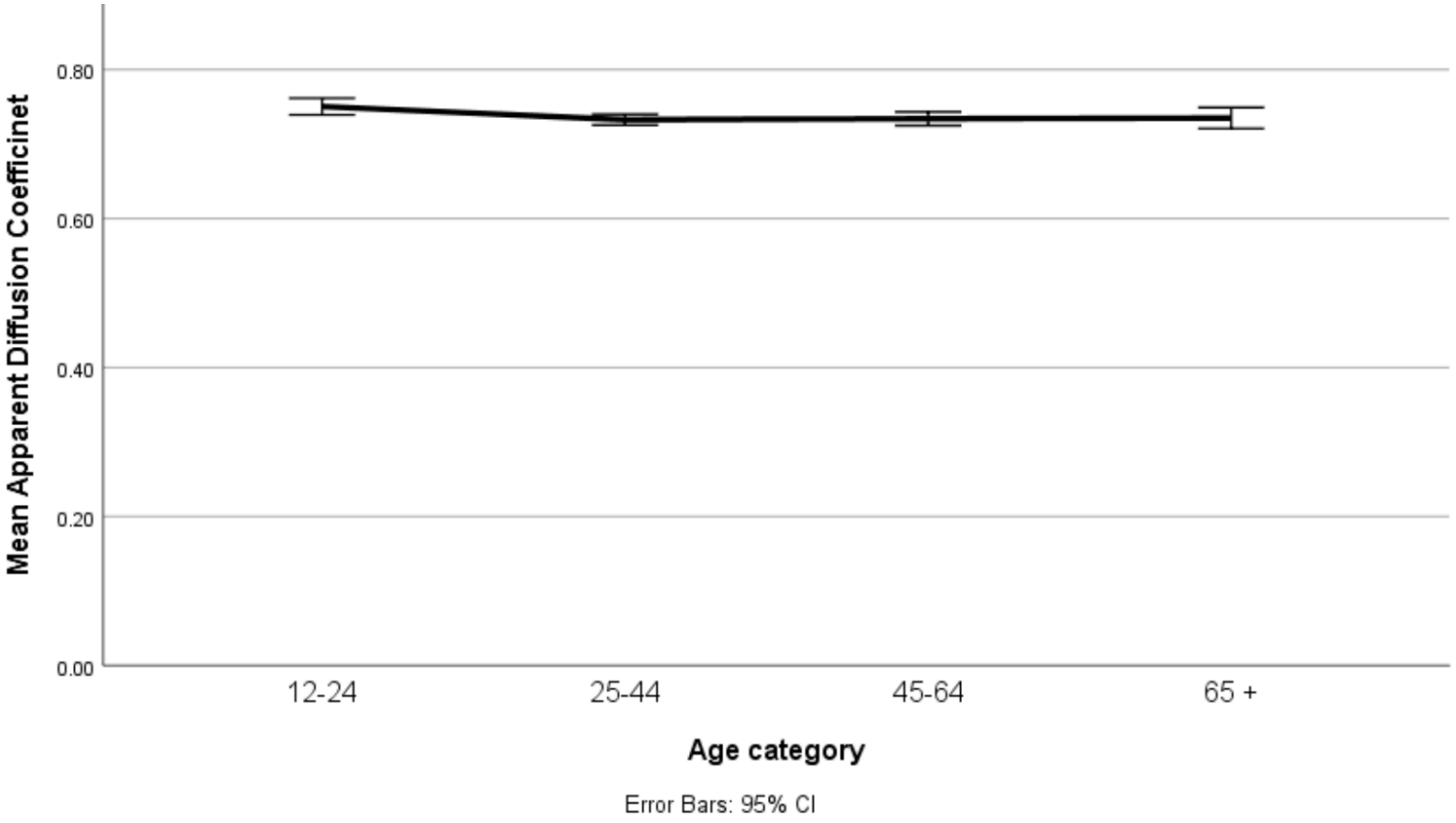


Figure 2

Line chart distribution of mean ADC and age category.

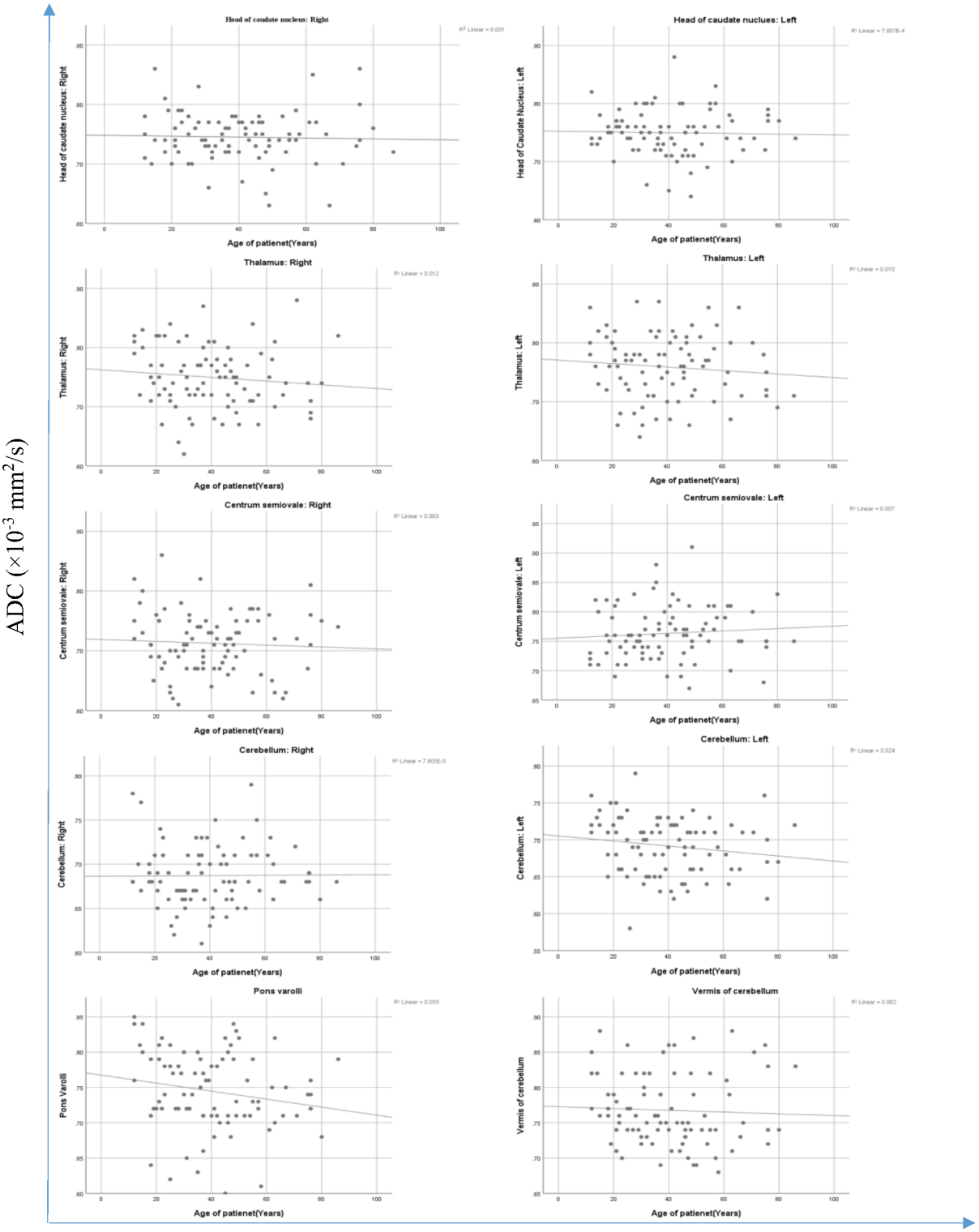


Figure 3 Scatter plots fitting curves of ADC as a function of age.

Figure 3

See image above for figure legend

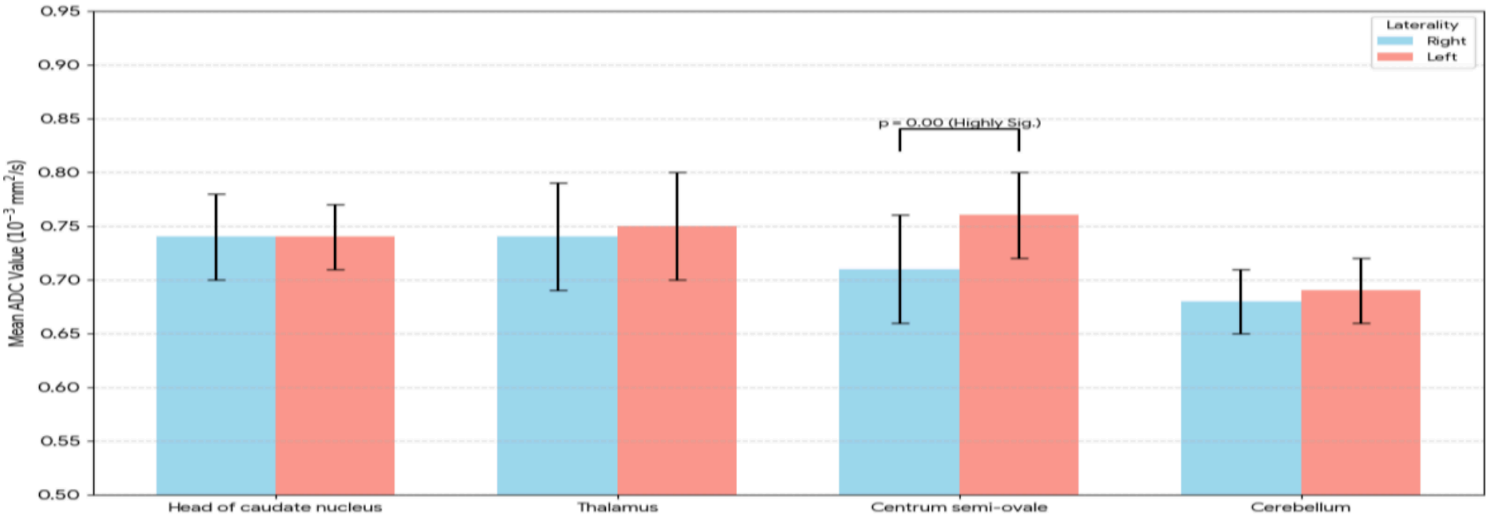


Figure 4 Bar Chart for Centrum Semiovale Laterality.

Figure 4

See image above for figure legend