Supplemental Methods

Enrollment Criteria for Parent Studies

UCSF Alzheimer's Disease Research Center (Autopsy Series Participants)

The UCSF ADRC is focused on heterogeneity of dementia and enrolls cognitively unimpaired older adults, as well as several neurodegenerative disease populations including those meeting criteria for mild cognitive impairment (Albert et al.), Alzheimer's disease dementia (McKhann et al.), behavioral variant frontotemporal dementia (Rascovsky et al.), primary progressive aphasia (Gorno-Tempini et al.), corticobasal degeneration (Armstrong et al.), and progressive supranuclear palsy (Movement Disorders Society). Beginning in 2011, the UCSF ADRC has also been enrolling a "TBI cohort" consisting of individuals with prior known TBI or RHI and present with cognitive, behavioral or motor changes. Research participants are eligible for the UCSF ADRC if they meet the following inclusion criteria: stable medical condition for 3 months prior to screening, reliant informant with frequent contact with participant who is available to provide observations of participant, fluent in English, Spanish, or Chinese, age > 18, able to complete baseline assessments, education or work history sufficient to exclude intellectual disability, physically capable to participate as confirmed by medical history, physical exam, neurological exam, and clinical tests. Exclusion criteria at the time of enrollment in the ADRC are: Korsakoff encephalopathy, active substance abuse, hepatitis C, diabetes mellitus, opportunistic brain infection, active neoplastic disease, multiple sclerosis, history of clinically significant stroke, history of epilepsy in the last 2 years, major psychiatric disorder (psychosis, major depression, bipolar disorder, etc.), significant sensory loss, residence in a skilled nursing facility.

Based on consensus conference, a multidisciplinary team determines study eligibility and makes recommendations to specific ADRC cores and subprojects that include specific biomarker collection (e.g., PET neuroimaging, structural MRI). Cognitive assessment, blood draw, lumbar puncture, and enrollment in the UCSF Neurodegenerative Disease Brain Bank autopsy program are offered to all ADRC participants.

UCSF Program Project Grant (Frontotemporal Dementia; Autopsy Series Participants)

The UCSF PPG enrolls participants > 18 years old with frontotemporal dementia spectrum conditions likely due to either Alzheimer's disease or frontotemporal lobar degeneration. Participants must have a reliable informant who has frequent contact with the participant and is available to provide information about the participant. The participant's diagnosis of dementia is based on history of progressive functional decline over at least 6 months with a Clinical Dementia Rating scale global score $\geq$ 0.5 at the time of evaluation. Diagnosis will be based upon a neurological history and examination, neuropsychological testing, and visual inspection of a CT scan or MRI. Participants with conditions due to several potential underlying causes will be considered, including FTLD-tau (e.g., progressive supranuclear palsy, corticobasal degeneration, Pick's disease), FTLD-TDP43, AD, tuberous sclerosis complex (TSC), as well as primary psychiatric conditions (e.g., major depressive disorder, bipolar disorder). Exclusion criteria at the time of enrollment are: Korsakoff encephalopathy, substance abuse, brain tumor, multiple sclerosis, epilepsy, communicating or non-communicating hydrocephalus, schizophrenia, intracerebral hemorrhage, B12 deficiency, hypothyroidism, HIV positive, renal failure, liver failure, respiratory failure, extra-axial brain tumor with visible compression of brain parenchyma, cerebral infarct, large confluent white matter lesions, significant systemic medical

illnesses such as deteriorating cardiovascular disease. Use of psychotropic medication is not outright exclusionary and is reviewed on a case-by-case basis.

Based on consensus conference, a multidisciplinary team determines study eligibility and makes recommendations for subprojects that include specific biomarker collection (e.g., PET neuroimaging). All participants are asked to complete neuropsychological testing, structural MRI, blood draw, and lumbar puncture. Enrollment in the UCSF Neurodegenerative Disease Brain Bank autopsy program is offered to all PPG participants.

UCSF Longitudinal Brain Aging Program (Healthy Control Reference Groups)

Community-dwelling, clinically normal adults provided reference data for standardization of neuropsychological test scores, neuroimaging outcomes, and plasma biomarker concentrations. These healthy controls are participants in the UCSF Longitudinal Brain Aging Program (Hillblom Aging Network; https://memory.ucsf.edu/research-trials/research/brain-aging-study). Inclusion criteria this study are medical stability for at least the 3 months prior to enrollment, a reliable informant, English or Spanish speaking fluency, age 30 or older, and good physical health confirmed by medical history, physical exam, and neurologic exam. Exclusion criteria at the time of enrollment are major memory concerns, substance abuse, neurologic and other medical conditions (Korsakoff encephalopathy, brain tumor, active neoplastic disease, Parkinson's disease, untreated multiple sclerosis, history of stroke, sleep apnea, psychiatric disorders), or significant sensory deficits preventing participation in study protocols. Onset of such conditions *after* enrollment does not preclude continued participation in research protocols.

Enrollment requires completion of neuropsychological testing, a blood draw, and clinical interview. Participation in neuroimaging protocols is offered to all study participants but is not required for enrollment.

Healthy Control Reference Group Participants for the Current Study

Neuropsychological Testing

For neuropsychological testing, individual test raw scores in our study were converted to z-scores based on the distribution of raw scores obtained from English-speaking participants in the Longitudinal Brain Aging Project (N per test = 231-763; 65±13 years old, range 30-99 years old; 60% female, 16.8±2.4 years of education, range 12-24 years). All participants in the reference sample met enrollment criteria for the parent Longitudinal Brain Aging Program study and underwent at least one neuropsychological evaluation in the course of study enrollment. The first available visit for each healthy control with neuropsychological test data was used to generate the score distributions for determining z-scores in our autopsy series participants.

Plasma Biomarkers

For plasma biomarker concentrations, participants from the Longitudinal Brain Aging Program were identified to serve as a control group for a separate study evaluating the effects of RHI on brain health in older adults. This project additionally required known Alzheimer's disease biomarker status based on beta-amyloid PET neuroimaging in order to rule out the effects of AD pathology on biomarker concentrations. All healthy control participants therefore met criteria for enrollment in the parent Longitudinal Brain Aging Program, had negative beta-amyloid PET

scan, and provided a blood sample. The final sample used to derive age-adjusted w-scores for plasma biomarker concentrations was: N = 108, age 73.2±7.3 years old, range 52-91 years old; 50% female. Sex was not associated with plasma biomarker concentrations in the healthy control sample and therefore was not included as a covariate in the w-score calculation.

Structural MRI (T1-weighted and DTI)

Neuroimaging is completed by participants in the Longitudinal Brain Aging Program on a volunteer basis. Standard MRI protocols include T1-weighted MRI and diffusion tensor imaging (among others). We identified available healthy controls for these sequences matched to study participants on scanner and acquisition protocols to derive the study participant-specific w-scores for grey matter volumes (T1-weighted MRI) and fractional anisotropy (DTI). The scanner-specific healthy control reference sample for grey matter w-score calculation was: Trio: N = 478, age 66.2±11.8 years old, range 30-99 years old; 44% male; 17.5±5.8 years of education; Prisma: N = 106, age 63.3±13.1 years old, range 30-99 years old; 41% male, 16.6±2.3 years of education). The 6 study participants who underwent DTI scans completed the scans on the same scanner. The healthy control reference sample for fractional anisotropy values was: N = 376, age 66.7±12.2 years old, range 30-99 years old; 44% male; 17.5±4.8 years of education.

FDG-PET

For FDG-PET, healthy controls from the Longitudinal Brain Aging Program who volunteered to undergo PET imaging (both FDG and beta-amyloid) were used to establish participant-specific w-scores representing brain glucose metabolism. All healthy controls for the FDG-PET analysis had a negative beta-amyloid PET scan. Most of this healthy control sample (30 of 34) was used similarly to generate glucose metabolism w-scores in a prior study of multimodal neuroimaging in research participants with known RHI (see Lesman-Segev et al., 2019; *Neuroimage: Clinical*). The healthy control reference sample in the present study was: N = 34, age 71.0±11.8 years old, range 49-90 years old; 100% male, 17.0±2.3 years of education.

Neuroimaging

Structural MRI

We report data from a total of 18 structural MRI scans obtained from the nine patients with TES (N = 5 with 2+ scans; first available scan: 4.1±1.4 years before death, range 2-6 years; last available scan: mean 2.7±2.6 years before death range 0-6 years). Structural T1-weighted MRI was acquired using magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence on a 3T Siemens Tim Trio scanner (N = 12) or 3T Siemens MAGNETOM Prisma (Siemens Medical Systems) (N = 6) at the UCSF Neuroimaging Center as previously described[1]. Both scanners had very similar acquisition parameters (sagittal slice orientation; slice thickness = 1.0 mm; slices per slab = 160; in-plane resolution = 1.0 × 1.0 mm; matrix = 240×256; repetition time = 2,300 ms; inversion time = 900 ms; flip angle = 9°), although echo time differed slightly (Trio: 2.98 ms; Prisma: 2.90 ms).

Before processing, all T1-weighted images were visually inspected for quality control and those with excessive motion or image artifact were excluded. Magnetic field bias was corrected using the N3 algorithm[2]. Tissue segmentation was performed using unified segmentation in SPM12[3]. Each subject's gray matter segmentation was warped to create a study-specific template using

Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL)[4]. Subject's native space gray and white matter segmentations were then normalized and modulated to study-specific template space using nonlinear and rigid-body transformation. Each subject's segmentation was carefully inspected to ensure robustness of the process. Quantification of volumes in specific brain regions was accomplished by transforming a standard parcellation atlas (Desikan[5]) into International Consortium for Brain Mapping (ICBM) space and summing all modulated gray matter within each parcellated region of interest (ROI)[5].

Brain volume w-scores were then calculated voxel-wise and by ROIs based on the distribution of volumes obtained from 584 brain scans of clinically normal older adults enrolled in a longitudinal healthy aging study (see prior Supplemental Methods – "Healthy Control Reference Participants for the Current Study"). W-scores represent the regression-based standardized brain volume adjusting for age, sex, years of education, and scanner and are interpreted similar to a z-score. W-score maps were created that demonstrated the number of patients (out of nine) with significantly low volume ($W \leq -2.0$) in a given voxel. Voxel clusters with a high frequency of patients with low volume were interpreted as shared regions of atrophy across the cohort.

We identified ROIs and extracted the mean W-score across all voxels within the ROI for each patient. ROIs were selected corresponding to general lobar volumes and specific subregions of interest based on visualization of the voxel-wise W-score frequency map: dorsal frontal (caudal anterior cingulate, caudal middle frontal, superior frontal), ventral frontal (medial and lateral orbitofrontal, rostral anterior cingulate, rostral middle frontal), temporal (hippocampus, entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, middle temporal, superior temporal, temporal pole, transverse temporal), parietal (inferior parietal, postcentral gyrus, posterior cingulate, precuneus, superior parietal, supramarginal gyrus), occipital (cuneus, lateral occipital, pericalcarine), thalamus, and the medial temporal subset of the overall temporal lobe (hippocampus, entorhinal, amygdala, parahippocampal).

Diffusion Tensor Imaging

DTI was obtained in 6 participants using a 3T Siemens MAGNETOM Prisma (mean 3.7±1.9 years before death, range 1-6 years). DTI processing began with denoising[6]. The b = 0 image was co-registered with the diffusion direction images, followed by gradient direction, eddy current and distortion correction using FSL[7, 8]. Diffusion tensors were calculated using a non-linear least-squares algorithm in Dipy[9]. Registration of diffusion data was accomplished through the DTI-TK software package (http://dti-tk.sourceforge.net) based on previously published methods[10]. DTI-TK implements a tensor-based registration paradigm, maximizing the alignment of white matter structures and minimizing interpolation of DTI images. An inter-subject template was created through iterative linear and non-linear registration of diffusion tensor images. Diffusion tensor images in the group space were diagonalized into eigenvectors from which fractional anisotropy (FA) maps were calculated.

Fractional anisotropy w-scores (age- and sex-adjusted) were then calculated voxel-wise and by ROIs based on the mean and standard deviation of FA values obtained from 376 clinically normal older adults enrolled in a longitudinal healthy aging study (see prior Supplemental Methods – "Healthy Control Reference Participants for the Current Study"). Voxel clusters with a high frequency of patients with low FA ($W \leq -2.0$) were interpreted as shared regions of decreased white matter integrity across the cohort. We additionally identified ROIs from the ICBM-DTI-81 white matter labels and tract atlas and extracted the mean FA across all voxels

within the ROI for each patient [11]. We selected ROIs based on visualization of the voxel-wise W-score frequency map and prior research on DTI in RHI populations (superior longitudinal fasciculus, superior fronto-occipital fasciculus, genu of the corpus callosum, uncinate fasciculus, fornix, cingulum-hippocampal bundle) as well as a presumably less affected ROI for comparison (posterior corona radiata)[12].

FDG-PET Acquisition and Processing

Five participants underwent (18)F-fluorodeoxyglucose-PET (FDG-PET) scans (mean 4.3±1.2 years before death, range 3-6 years). Acquisition protocols FDG-PET have previously been described[13]. PET scans were acquired at Lawrence Berkeley National Laboratory (LBNL) on a Siemens Biograph 6 Truepoint PET/CT scanner in 3D acquisition mode. Attenuation correction was performed using a low-dose CT/transmission scan acquired prior to PET. FDG-PET was acquired for 30 minutes (6x5min frames) after 30 minutes of eyes-open, quiet rest following intravenous injection of ~10 mCi ^{18}F-FDG. Scans were reconstructed using an ordered subset expectation maximum (OSEM) algorithm with weighted attenuation and were smoothed using a 4mm Gaussian kernel with scatter correction (calculated image resolution 6.5 x 6.5 x 7.25 mm using Hoffman phantom). Neuroimaging data was processed using Statistical Parametric Mapping version 12 (SPM12, https://www.fil.ion.ucl.ac.uk/spm/) software in MATLAB, 2015. MRI scans were segmented and spatially normalized to the Montreal Neurological Institute (MNI) space with SPM12. PET frames were realigned for motion correction, averaged, and co-registered onto the participant's MRI. Standardized Uptake Value Ratios (SUVR) maps were created at 30-60 minutes post injection using the pons as the reference region (defined based on FreeSurfer-derived v5.3 Desikan-Killiany atlas).

FDG-PET hypometabolism w-scores were then calculated based on the FDG-PET of cognitively unimpaired controls (see prior Supplemental Methods – "Healthy Control Reference Participants for the Current Study"). For this, PET images were warped to MNI space using the respective MRI-based transformation parameters. PET images were smoothed with a Gaussian kernel of 4 x 4 x 4. Voxel-wise regressions were then performed adjusting for age in the control group, and used to compute W-score maps for each patient. W-maps were then created that demonstrated the number of patients (out of 5) with significant hypometabolism ($W \leq -2.0$) in a given voxel.

References (Supplemental Methods)

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Components of TES Diagnosis	Method of Ascertainment	Operationalization
Primary Diagnostic Criteria		
(I) Substantial Exposure to Repetitive Head Impacts	Review of all available medical and research records, comprehensive neurological interviews and exams, and publicly available online records for participation in high exposure collision sports, military service, or other sources of repetitive head impacts. Qualifying collision sports included American football, ice hockey, soccer, rugby, wrestling, mixed martial arts, or other high risk activities. Military service must have documentation of repetitive head impacts through blast exposure or training activities (e.g., breachers, boxing).	$\geq$ 5 years of American football or equivalent level of exposure from individual or combined activities as determined by investigator consensus. Participants with documented exposure to American football without explicit mention of duration were included based on investigator determination of cumulative exposure (e.g., documentation of an additional high risk activity) but assigned a maximum "Suggestive of CTE" level of diagnostic certainty.
(II) Core Clinical Features		
(IIa) Cognitive Impairment	Neurological examination and formal comprehensive neuropsychological testing including the domains of memory and executive functioning. A composite memory score was calculated based on average standardized performance of 3 test scores: a) CVLT – Short Form total immediate recall, b) CVLT – Short Form delayed recall, c) Benson figure delayed recall. A composite executive functioning score was calculated based on average standardized performance of 5 test scores: a) modified trail making test, b) lexical fluency, c) digit span backwards, d) Stroop Inhibition, e) design fluency.	Investigator consensus based on review of records that 1) the participant and/or informant reported cognitive changes, which 2) represented significant decline from prior functioning, *and* 3) included deficits in at least memory and/or executive functioning. Objective neuropsychological testing revealed composite memory *or* executive functioning performance was $\geq$ 1.5 SD below the mean of a large, clinically normal (CDR=0) older adult sample at any time point, *or* a decline of $\geq$ 1.5 SD from an earlier objective evaluation in either domain.

(IIb) Neurobehavioral regulation	Neurological examination (including comprehensive history and clinical interview with participant and/or informant)	Investigator consensus based on review of records that 1) the participant and/or informant reported neurobehavioral changes, which 2) represented a significant change from prior functioning, *and* 3) included behaviors like poor emotional regulation (explosiveness, impulsivity, rage, violent outbursts, "short fuse," "mood swings") that do not appear to be transient responses to life events.
(IIc) Progressive Course	Neurological examination and/or formal comprehensive neuropsychological testing.	Investigator consensus based on review of records that 1) there was evidence of worsening of clinical features over a period of at least 1 year without continued head impact/TBI exposure supported by either a) serial neuropsychological testing *or* b) clear historical evidence per clinician, participant, or informant)
(III) Not Fully Accounted for by Other Disorders	Neurological examination and formal comprehensive neuropsychological testing.	Investigator consensus based on review of records that the pattern of cognitive and neurobehavioral deficits was not fully accounted for by other preexisting, established, or non-degenerative nervous system, medical, or psychiatric condition. This criterion was applied liberally given ongoing ambiguity regarding CTE-specific symptoms and inability to confidently determine that alternate neuropathologies might *fully* account for all observed symptoms in patients with substantial prior head trauma exposure.

(IV) Level of Functional Independence	Neurological examination and Clinical Dementia Rating (CDR) scale	"Independent": reported independence in all instrumental and basic activities of daily living *and* global CDR = 0. "Subtle/Mild Functional Limitation": reported slight challenges but with mostly maintained independence in completing some instrumental activities of daily living *and* maintained independence with basic activities of daily living *and* global CDR = 0.5. "Mild" to "Severe" Dementia: *minimum* of definite impairment with instrumental activities of daily living *and* requiring cues for basic activities of daily living *and* global CDR $\geq$ 1.
Supportive Features		
Delayed Onset	Neurological examination	Investigator consensus based on review of records establishing a period (years) of stable functioning after repetitive head impact exposure ends without evidence that symptoms represent ongoing effects of a prior traumatic brain injury or other preexisting condition
Motor Signs	Neurological examination	Investigator consensus based on review of records indicating positive findings of parkinsonism (bradykinesia, rigidity, rest tremor, parkinsonian gait disorder), other motor signs (dysarthria, ataxia, imbalance with frequent falls), and/or motor neuron disease (weakness, dysphagia, lower motor neuron signs, upper motor neuron

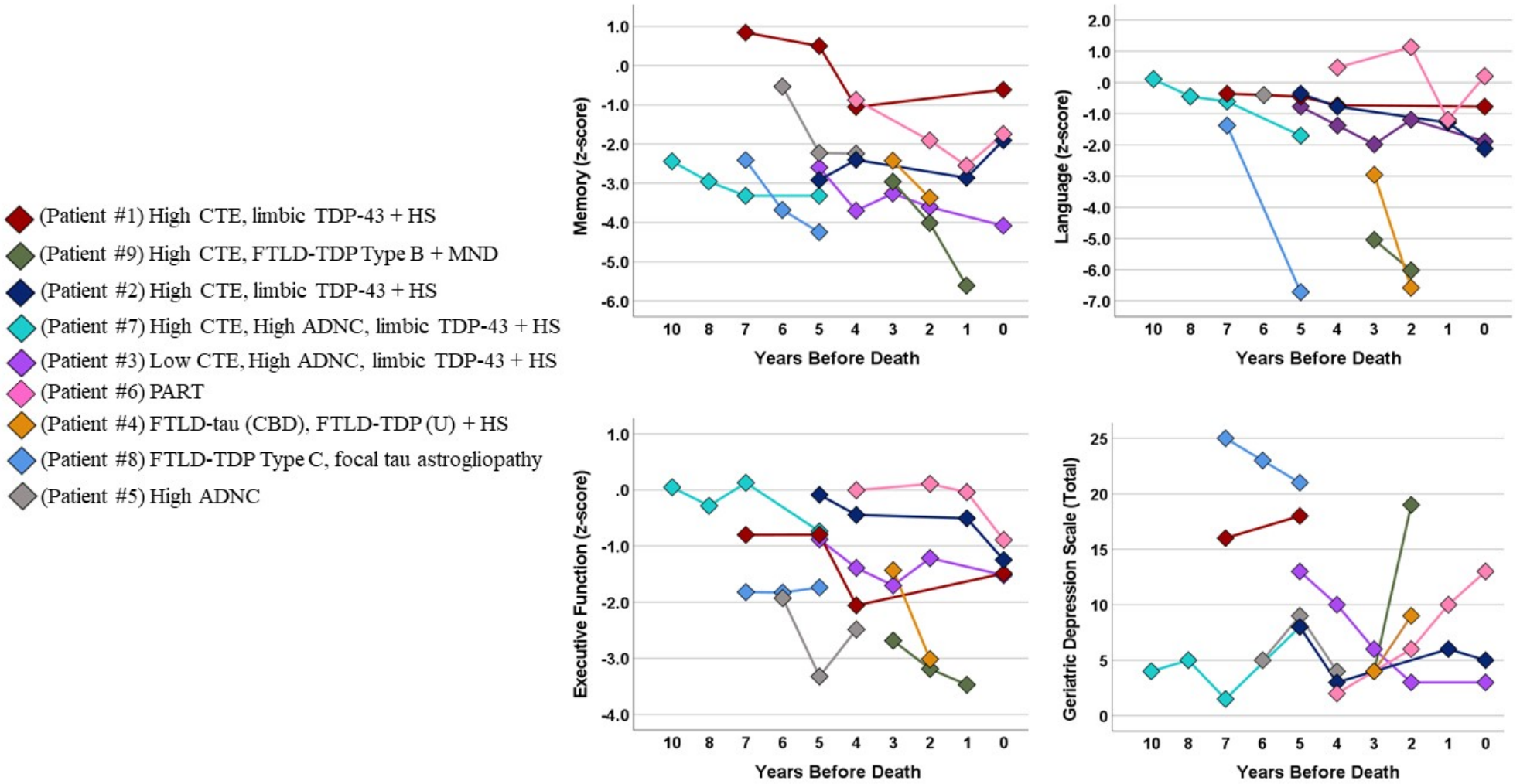
		signs, diagnosis of amyotrophic lateral sclerosis).
Psychiatric Features (distinct from Neurobehavioral Dysregulation features)	Neurological examination and/or standardized assessments (when available), including but not limited to the Geriatric Depression Scale, Beck Depression Inventory, Geriatric Anxiety Scale, Beck Anxiety Inventory, Apathy Evaluation Scale, or Neuropsychiatric Inventory	Investigator consensus based on review of records indicating evidence of persistent anxiety, apathy, depression, and/or paranoia based on participant or informant report, history of treatment/diagnosis, clinical observation, or self-report questionnaires exceeding established cutoffs for clinically significant symptoms

Supplemental Table 1: Methods of ascertainment and operationalization of specific criterion from the 2021 research framework for traumatic encephalopathy syndrome (TES; Katz et al.).

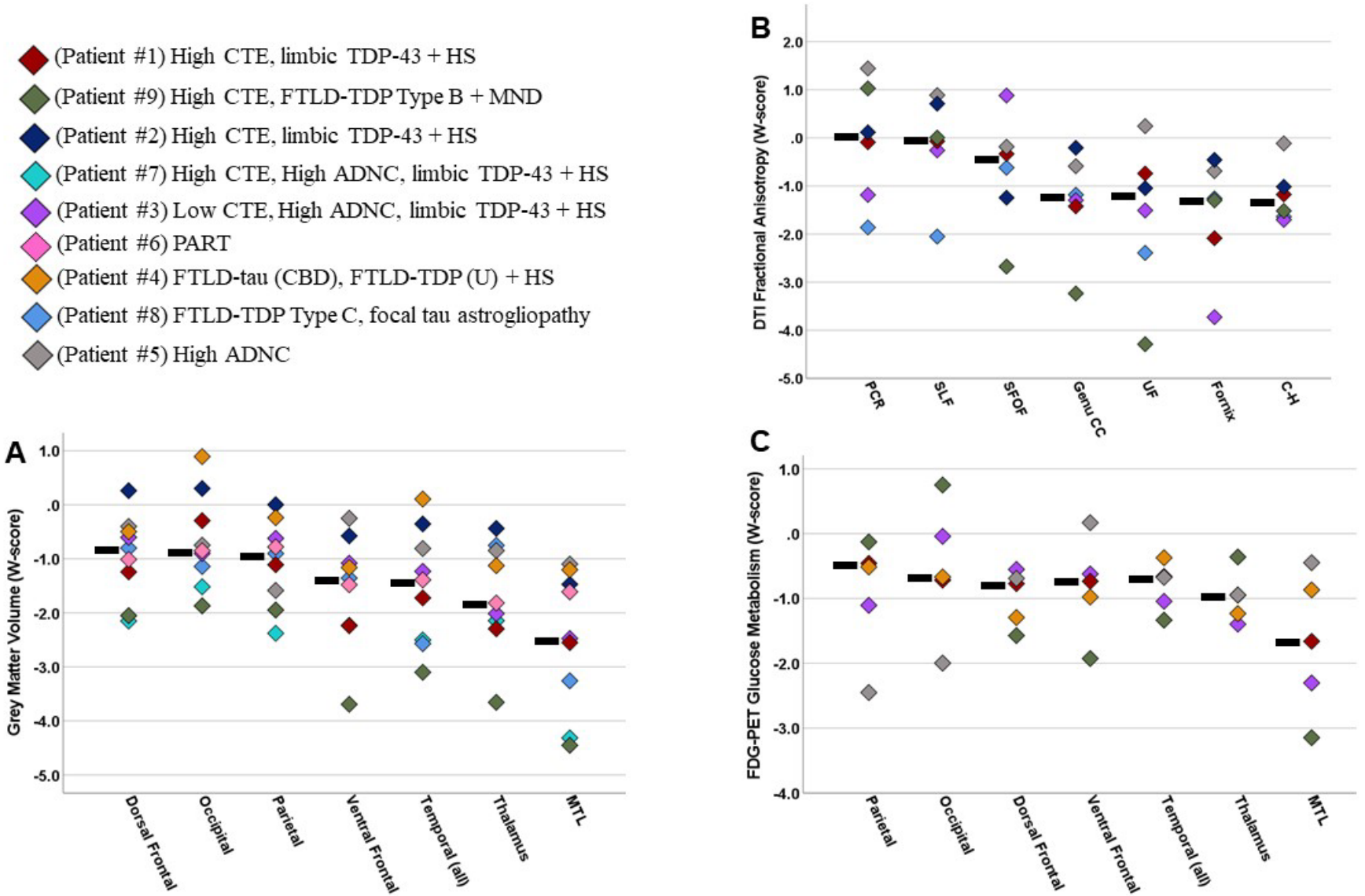
Patient #	DTI	FDG-PET	APOE Genotype	Age at First Scan (sMRI)	Age at Last Scan (All)	Age at Last Evaluation of Functional Status	Functional Status Closest to Death	Retrospective Functional Status (Postmortem)	Age at Death	Estimated Cause(s) of Death
1	Y	Y	E3/E3	68	sMRI: 72 DTI: 72 PET: 68	68	CDR Global: 0.5 CDR Box Score: 3.5 FTLD Box Score: 4.5	CDR Global: 0.5 CDR Box Score: 3.5	72	1) acute respiratory failure 2) Seizure 3) Diastolic congestive heart failure
2	Y	N	E3/E3	69	sMRI: 69 DTI: 69 PET: na	73	CDR Global: 0.5 CDR Box Score: 2.5 FTLD Box Score: 2.5	CDR Global: 2.0 CDR Box Score: 10.5	74	1) acute blood loss/anemia 2) uncontrolled seizures 3) glioblastoma
3	Y	Y	E3/E3	74	sMRI: 78 DTI: 77 PET: 74	78	CDR Global: 1.0 CDR Box Score: 4.5 FTLD Box Score: n/a	n/a	79	n/a
4	N	Y	E3/E3	46	sMRI: 47 DTI: na PET: 47	47	CDR Global: 1.0 CDR Box Score: 6.5 FTLD Box Score: 9.5	n/a	49	n/a
5	Y	Y	E3/E4	51	sMRI: 51 DTI: 51 PET: 51	55	CDR Global: 1.0 CDR Box Score: 4.5 FTLD Box Score: n/a	CDR Global: 1.0 CDR Box Score: 9.5	58	1) complications of dementia 2) difficulty swallowing 3) terminal fever
6	N	N	n/a	78	sMRI: 81 DTI: na PET: 81	81	CDR Global: 0.5 CDR Box Score: 2.0 FTLD Box Score: 2.0	n/a	81	n/a
7	N	N	E4/E4	78	sMRI: 78 DTI: na PET: na	83	CDR Global: 2.0 CDR Box Score: 15.0 FTLD Box Score: n/a	CDR Global: 2.0 CDR Box Score: 12.0	84	1) cardiac arrest 2) respiratory failure 3) atherosclerotic heart disease 4) difficulty swallowing/breathing
8	Y	N	E2/E3	65	sMRI: 65 DTI: 65 PET: na	65	CDR Global: 2.0 CDR Box Score: 13.0 FTLD Box Score: 17.0	CDR Global: 3.0 CDR Box Score: 18.0	70	1) cerebral anoxia 2) cardiac arrest 3) arteriosclerosis 4) Pneumonia/difficulty swallowing
9*	Y	Y	E2/E3	55	sMRI: 57 DTI: 56 PET: 55	58	CDR Global: 2.0 CDR Box Score: 12.0 FTLD Box Score: n/a	n/a	59	n/a

Supplemental Table 2: Available neuroimaging data for each of the nine patients with RHI and TES along with Apolipoprotein E genotype, ages of first (structural MRI) and most recently acquired scans (all modalities), age of most recent clinical evaluation that included an assessment of functional status, functional status closest to death (Clinical Dementia Rating [CDR] scale global score, CDR sum of boxes, and CDR sum of boxes plus behavior and language [FTLD module] box score), retroactive assessment of functional status during the final three months of life, and estimated causes/contributors to the patient's death. All participants underwent at least one structural MRI.

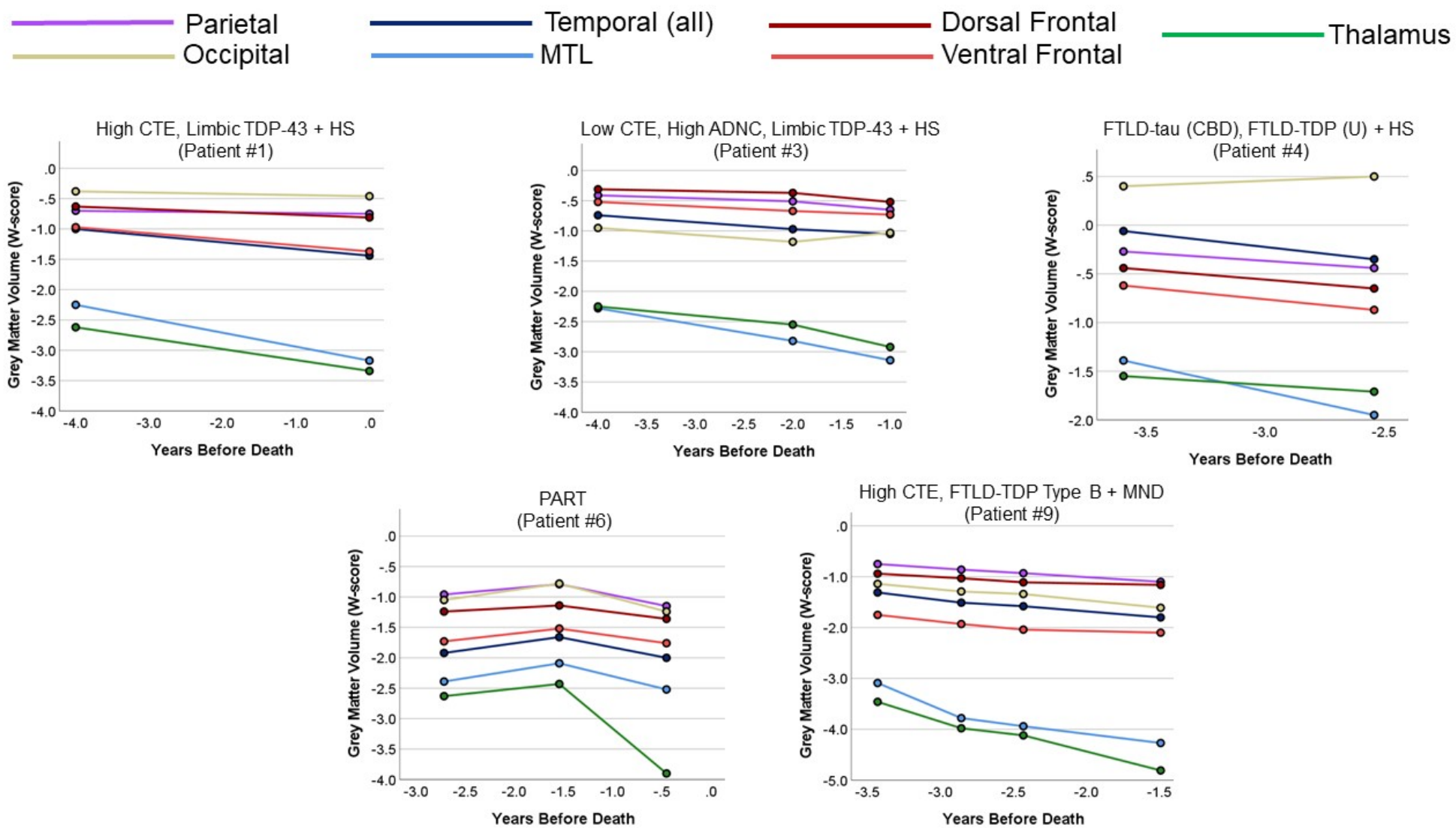
*Additional genetic testing for Patient #9 revealed a variant of the neuronal ceroid lipofuscinosis gene major facilitator superfamily domain-containing protein 8 (MFSD8; variant rs11098943). This gene encodes a lysosomal transmembrane protein of unknown structure and function but has a suggested role in small-solute transport across the lysosomal membrane (Siintola et al., 2007). Rare MFSD8 variant enrichment has been associated with greater risk for frontotemporal lobar degeneration (Geier et al., 2019).



Supplemental Figure 1: Longitudinal neuropsychological test data for each of the nine patients with RHI and TES. Data are shown as z-scores for 3 cognitive domains – memory, executive functioning, and language. Longitudinal self-reported depression symptoms are also shown (Geriatric Depression Scale). Neuropathological features for each patient are listed along with the specific "Patient #," which corresponds with additional clinical history provided in Table 1.



Supplemental Figure 2: Cross-sectional, region of interest-based W-scores for the nine autopsy series patients based on the **(A)** structural MRI obtained closest to death (N = 9; mean 2.7±2.6 years before death, range 0-6 years) as well as **(B)** diffusion tensor imaging (N = 6; mean 3.7±1.9 years before death, range 1-6 years) and **(C)** FDG-PET (N = 5; mean 4.3±1.2 years before death, range 3-6 years). Black bars represent the group median for the region of interest. Neuropathological features for each patient are shown along with the specific "Patient #," which corresponds with additional clinical history provided in Table 1. Abbrev: C-H = cingulum-hippocampus bundle, genu CC = genu of the corpus callosum, MTL = medial temporal lobe, PCR = posterior corona radiata, SFOF = superior fronto-occipital fasciculus, SLF = superior longitudinal fasciculus, UF = uncinate fasciculus



Supplemental Figure 3: Longitudinal grey matter volumes for 5 patients who underwent multiple antemortem brain scans. Data represent within-patient changes in the mean W-score for each of seven ROIs. Some patients underwent MRI acquisition on two different scanners in the course of their research participation. For visualization of longitudinal data, each patient's W-scores were derived based on a reference sample scanned on the same scanner as the patient's first evaluation to avoid artificial W-score fluctuations reflecting a change in scanner and reference group longitudinally. Neuropathological features for each patient are shown along with the "Patient #," which corresponds with clinical history provided in Table 1.

Supplemental Figures: Multi-Slice Brain Images for each Patient

Patient #1 (Age at Death: 72)
TES classification: Probable CTE
Neuropathology: High CTE (McKee Stage IV), limbic TDP-43 with hippocampal sclerosis, left subiculum infarcts, limbic AGD, ARTAG
Imaging: T1-weighted MRI (age 72), DTI fractional anisotropy W-map (age 72), FDG-PET (age 68)

Patient #2 (Age at Death: 74)
TES classification: Probable CTE
Neuropathology: High CTE (McKee Stage III), limbic TDP-43 with hippocampal sclerosis, mild arteriolosclerosis, ARTAG, infiltrating glioma, Low ADNC (A1 B1 C0)
Imaging: T1-weighted MRI (age 69), DTI fractional anisotropy W-map (age 69)

Patient #3 (Age at Death: 79)
TES classification: Probable CTE
Neuropathology: Low CTE (McKee Stage I), High ADNC (A3 B3 C3), limbic TDP-43 with hippocampal sclerosis, lymphocytic leukemia, mild arteriolosclerosis, limbic AGD
Imaging: T1-weighted MRI (age 78), DTI fractional anisotropy W-map (age 77), FDG-PET (age 74)

Patient #4 (Age at Death: 49)
TES classification: Probable CTE
Neuropathology: No CTE, FTLD-tau (CBD), FTLD-TDP43 (unclassifiable) with hippocampal sclerosis, limbic AGD
Imaging: T1-weighted MRI (age 47), DTI fractional anisotropy W-map (age 47), FDG-PET (age 47)

Patient #5 (Age at Death: 58)
TES classification: Probable CTE
Neuropathology: No CTE, High ADNC (A3 B3 C3), limbic AGD, mild arteriolosclerosis, mild CAA, Lewy body disease (amygdala-predominant), ARTAG
Imaging: T1-weighted MRI (age 51), DTI fractional anisotropy W-map (age 51), FDG-PET (age 51)

Patient #6 (Age at Death: 81)
TES classification: Possible CTE
Neuropathology: No CTE, PART, vascular brain injury, limbic AGD, ARTAG
Imaging: T1-weighted MRI (age 81)

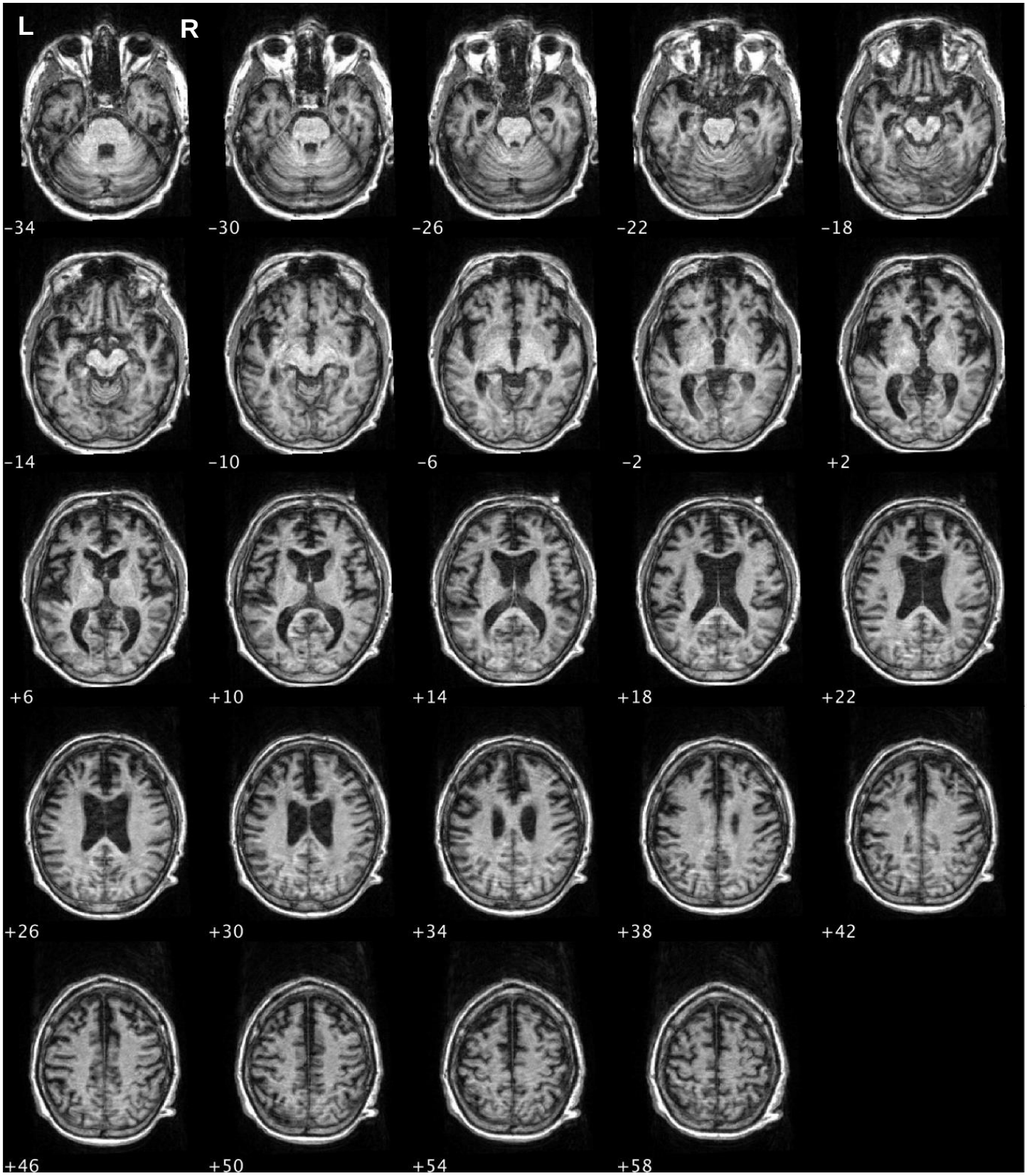
Patient #7 (Age at Death: 84)
TES classification: Uncertain TES (exposure duration unknown)
Neuropathology: High CTE (McKee Stage III), High ADNC (A3 B3 C3), limbic TDP-43 with hippocampal sclerosis, limbic AGD, mild arteriolosclerosis, Lewy body disease (Braak IV), subdural hematoma, white matter rarefaction
Imaging: T1-weighted MRI (age 78)

Patient #8 (Age at Death: 70)
TES classification: Uncertain TES (exposure duration unknown)
Neuropathology: No CTE, FTLD-TDP43 Type C, focal traumatic tau astrogliopathy, limbic AGD, thalamic infarcts, moderate arteriolosclerosis, Low ADNC (A1 B2 C1)
Imaging: T1-weighted MRI (age 65), DTI fractional anisotropy W-map (age 65)

Patient #9 (Age at Death: 59)
TES classification: Uncertain TES (exposure duration unknown)
Neuropathology: High CTE (McKee Stage IV), FTLD-TDP43 Type B with MND, limbic AGD, mild arteriolosclerosis, ARTAG, ATAC
Imaging: T1-weighted MRI (age 57), DTI fractional anisotropy W-map (age 56), FDG-PET (age 55)

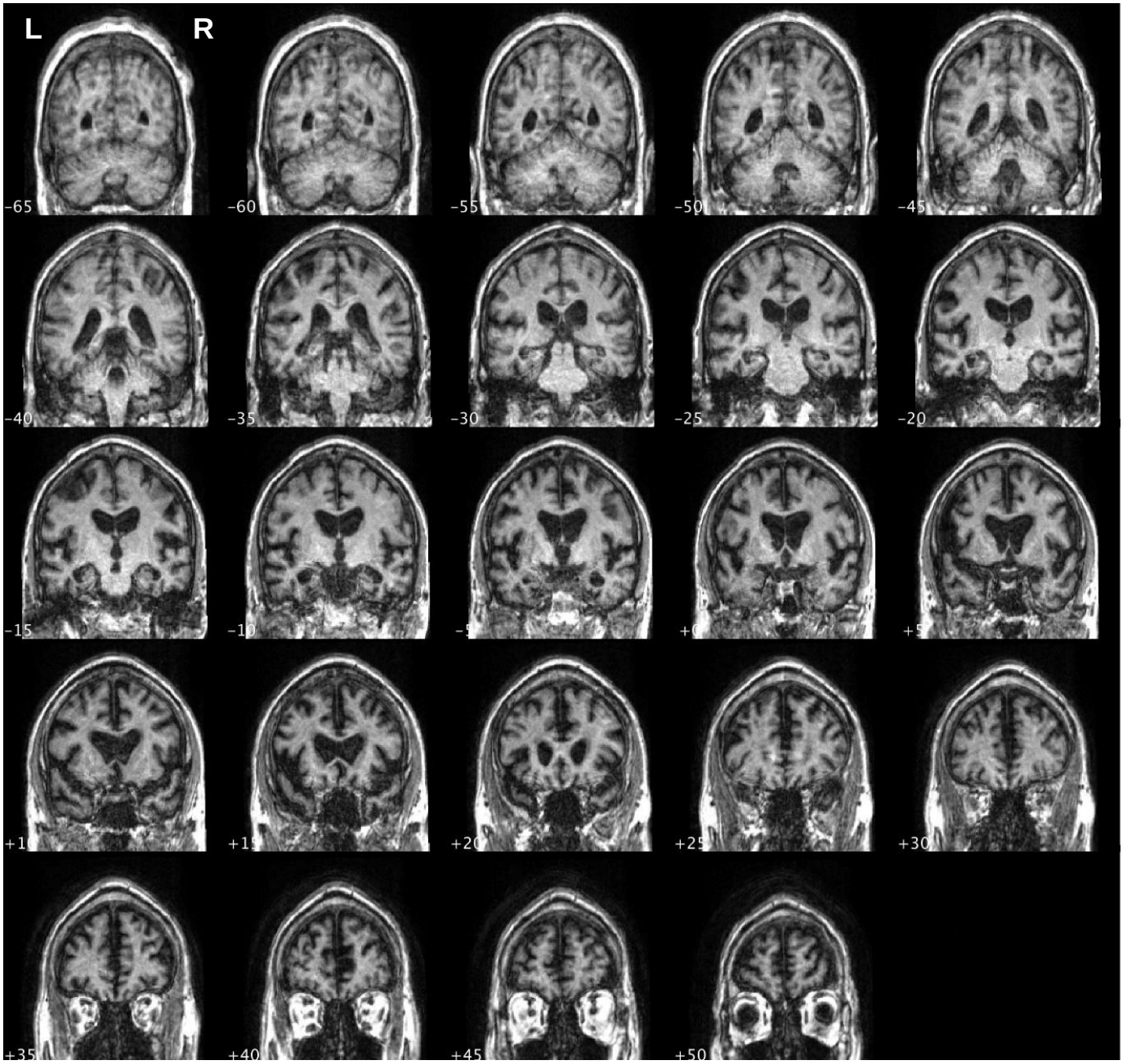
Patient #1
Neuropathology: High CTE (McKee Stage IV), limbic TDP-43 with hippocampal sclerosis, left subiculum infarcts, limbic AGD, ARTAG

Axial T1-weighted MRI (scan age: 72, age at death: 72)



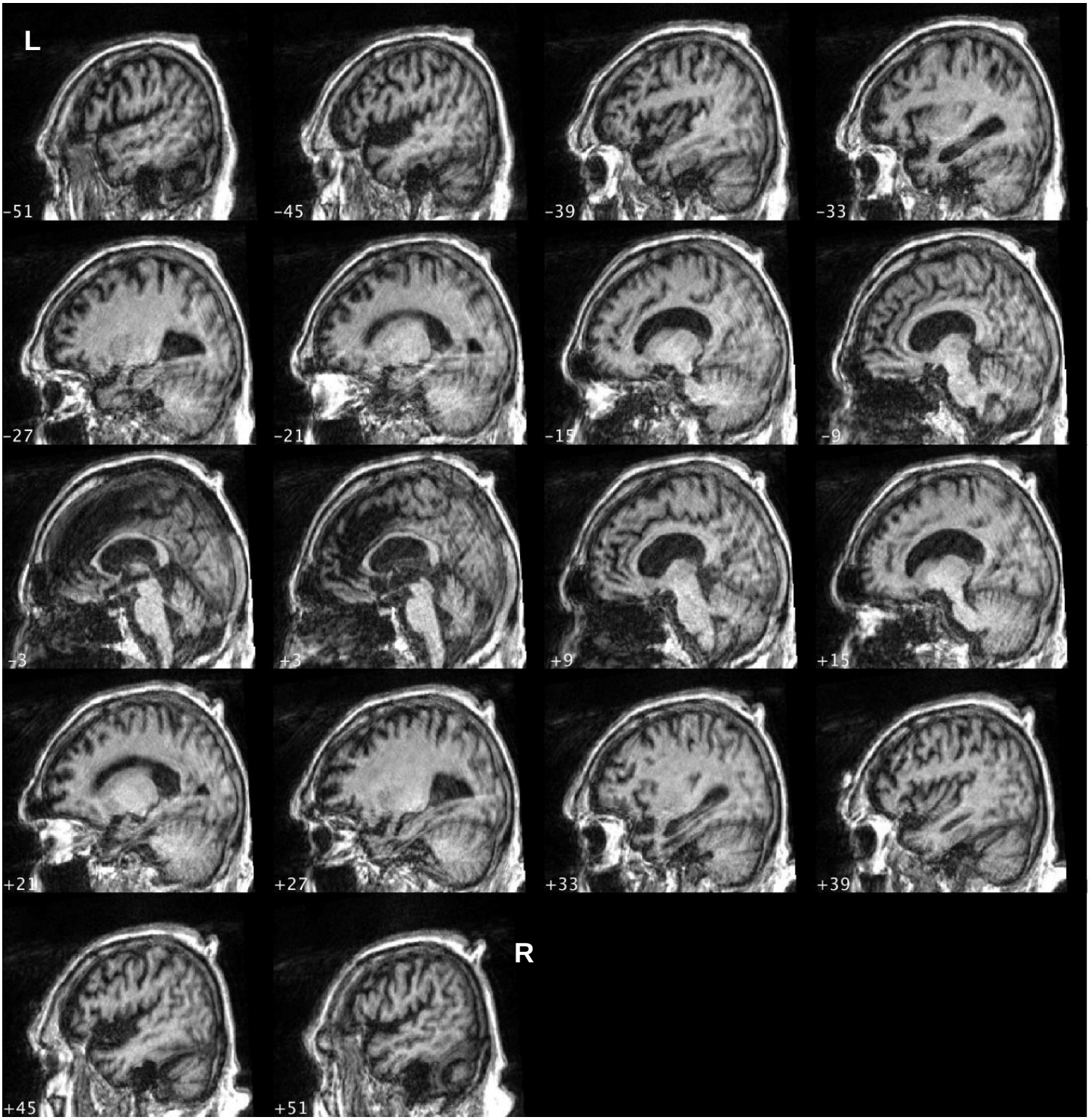
Patient #1
Neuropathology: High CTE (McKee Stage IV), limbic TDP-43 with hippocampal sclerosis, left subiculum infarcts, limbic AGD, ARTAG

Coronal T1-weighted MRI (scan age: 72, age at death: 72)



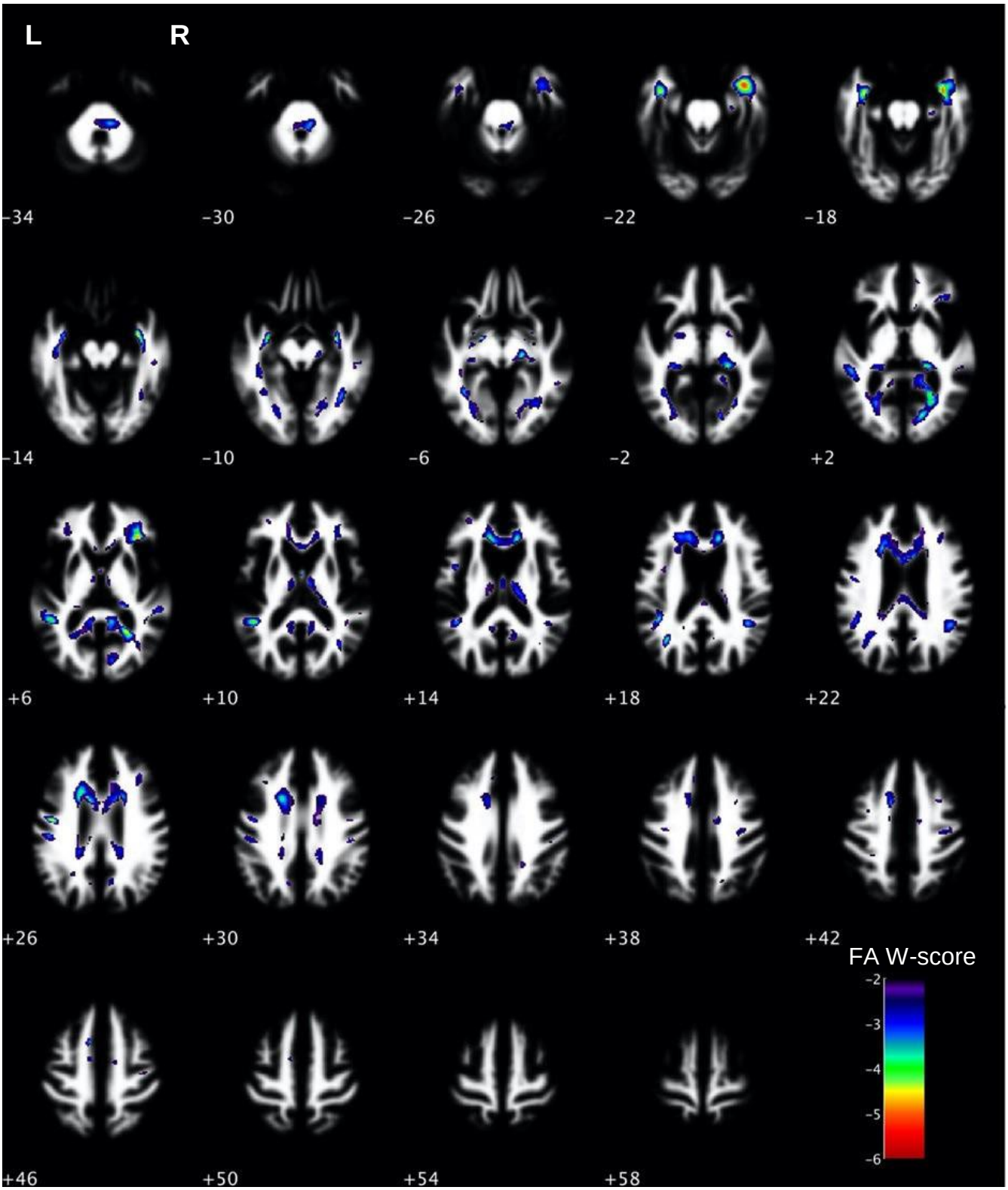
Patient #1
Neuropathology: High CTE (McKee Stage IV), limbic TDP-43 with hippocampal sclerosis, left subiculum infarcts, limbic AGD, ARTAG

Sagittal T1-weighted MRI (scan age: 72, age at death: 72)



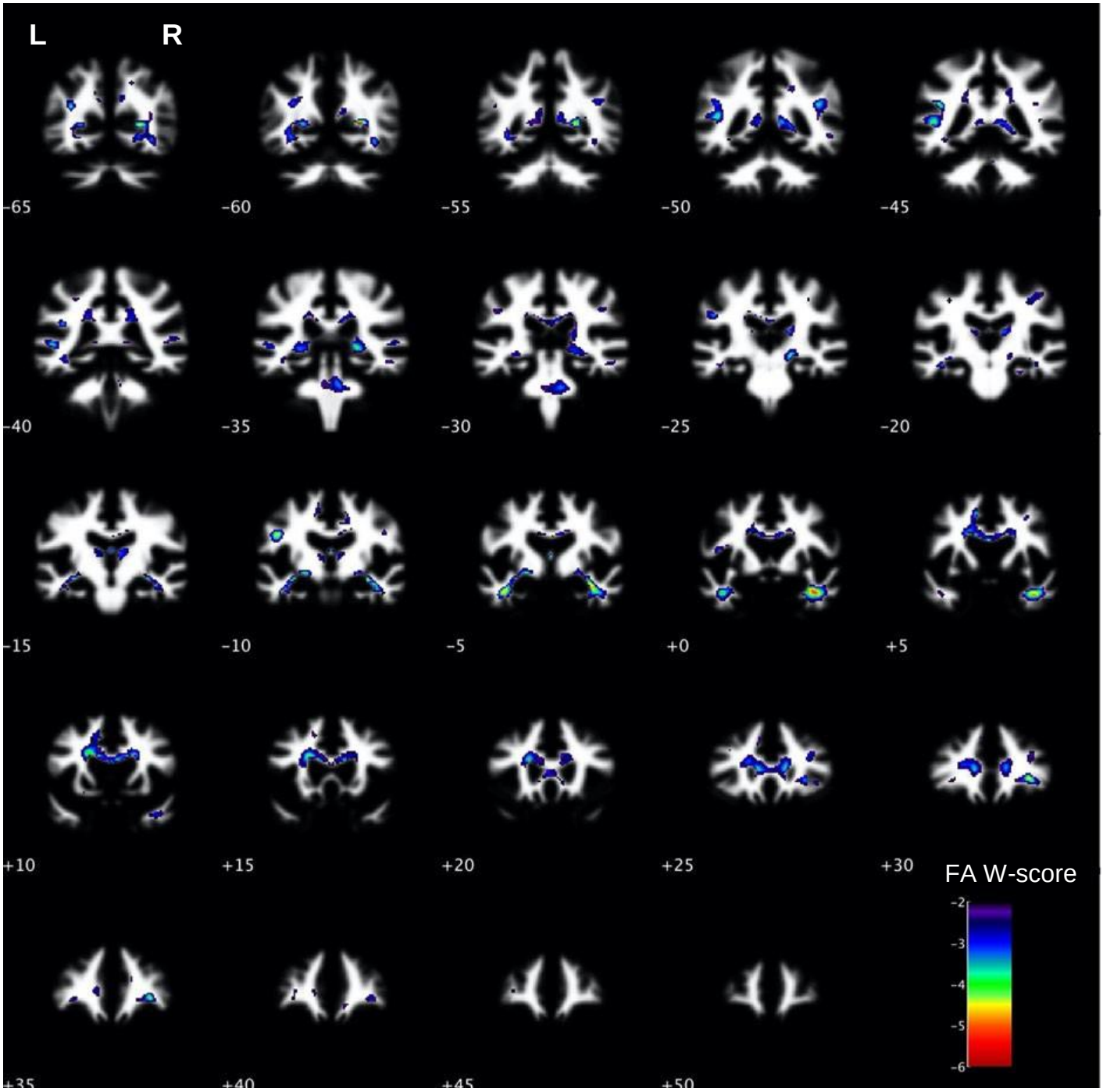
Patient #1
Neuropathology: High CTE (McKee Stage IV), limbic TDP-43 with hippocampal sclerosis, left subiculum infarcts, limbic AGD, ARTAG

Axial DTI – FA W-map (scan age: 72, age at death: 72)



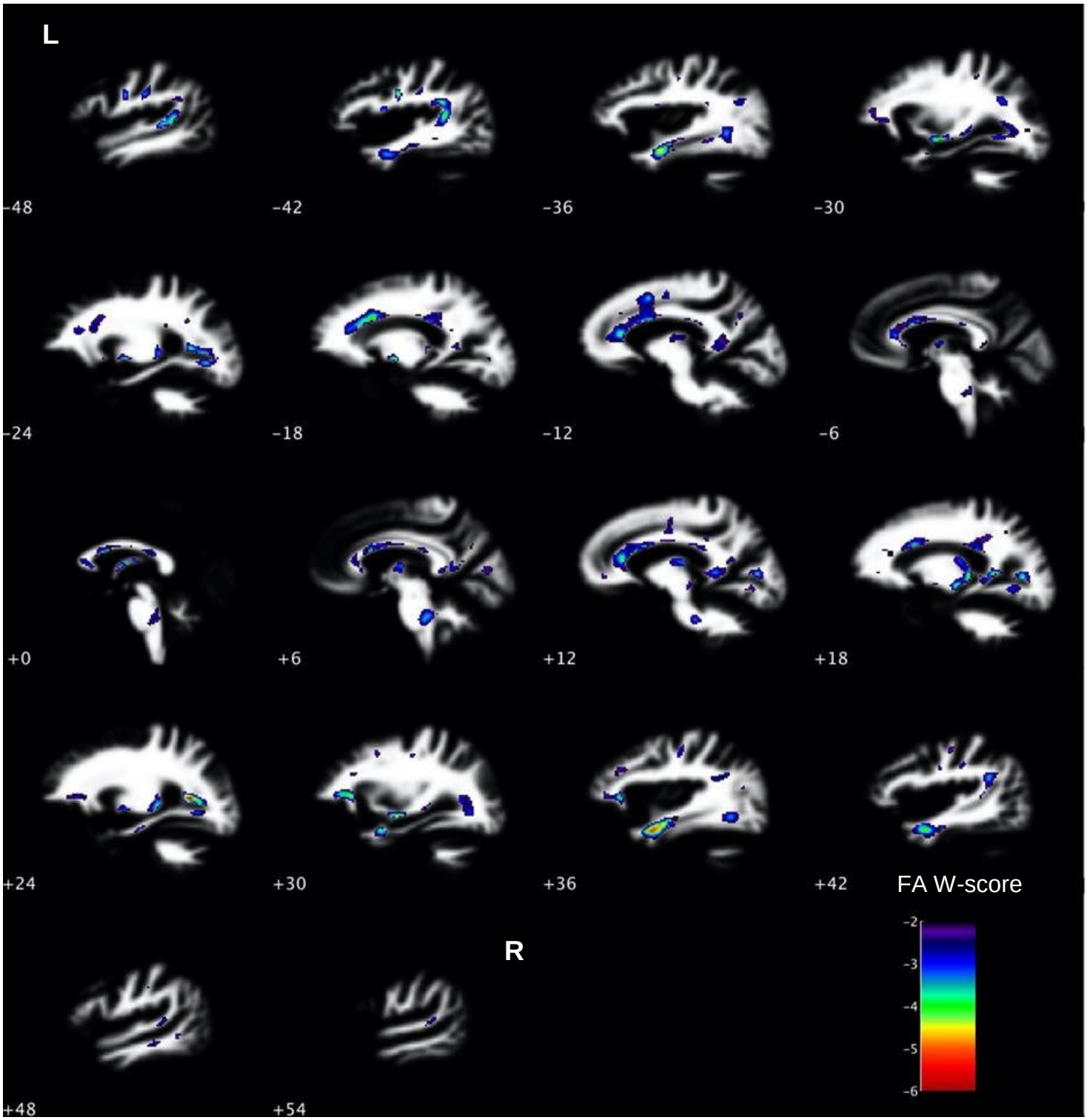
Patient #1
Neuropathology: High CTE (McKee Stage IV), limbic TDP-43 with hippocampal sclerosis, left subiculum infarcts, limbic AGD, ARTAG

Coronal DTI – FA W-map (scan age: 72, age at death: 72)



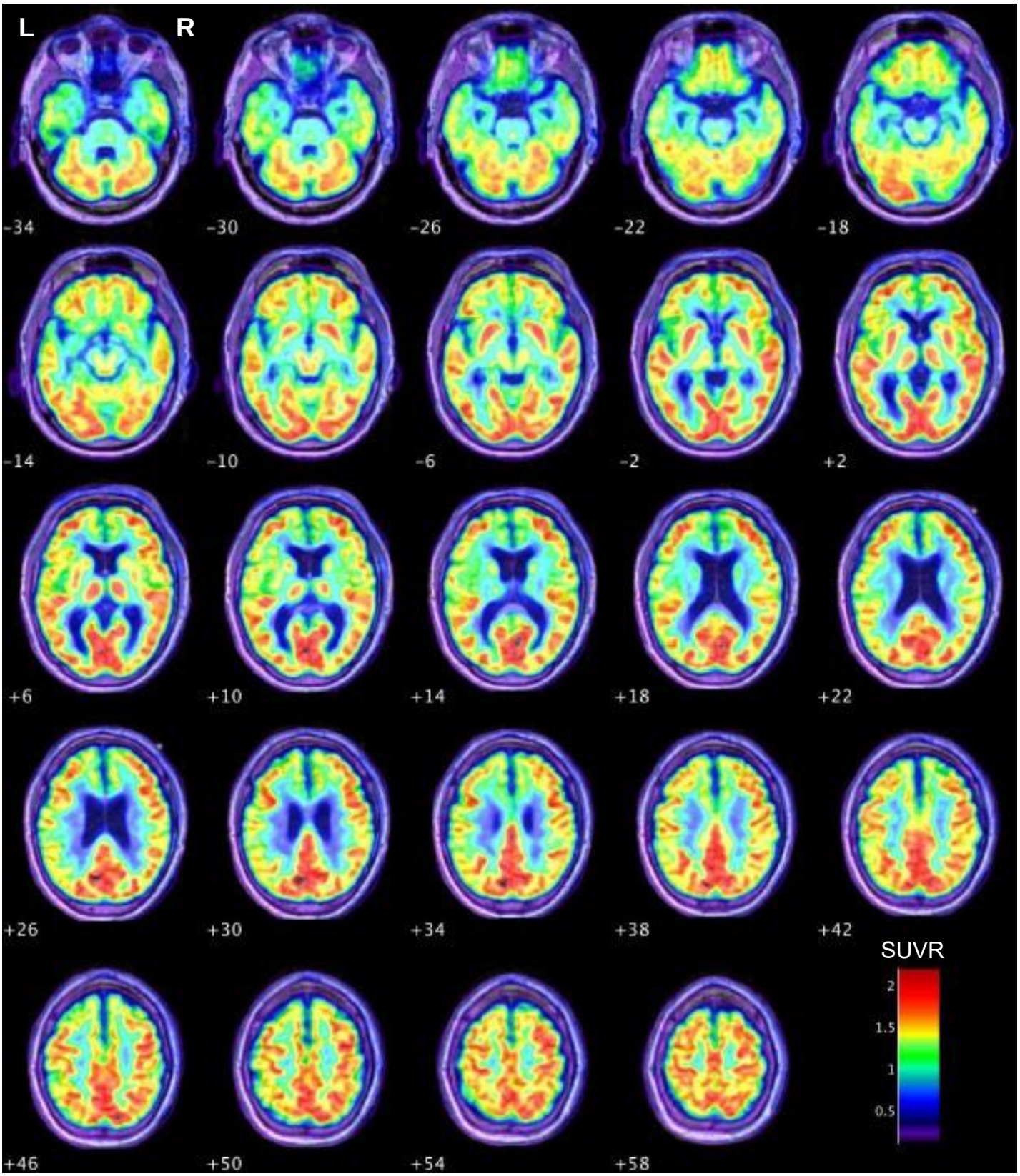
Patient #1
Neuropathology: High CTE (McKee Stage IV), limbic TDP-43 with hippocampal sclerosis, left subiculum infarcts, limbic AGD, ARTAG

Sagittal DTI – FA W-map (scan age: 72, age at death: 72)



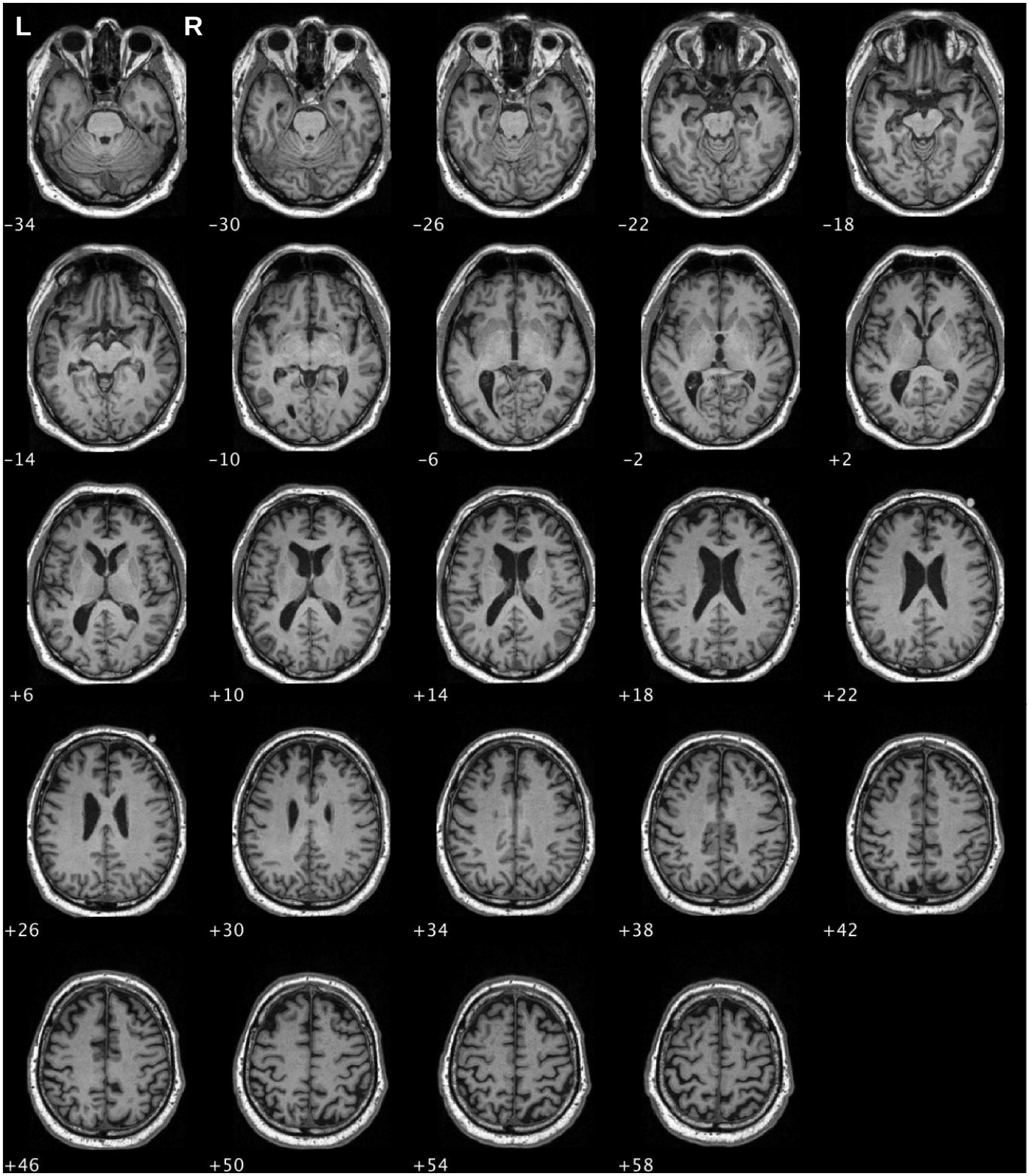
Patient #1
Neuropathology: High CTE (McKee Stage IV), limbic TDP-43 with hippocampal sclerosis, left subiculum infarcts, limbic AGD, ARTAG

FDG-PET (scan age: 68, age at death: 72)



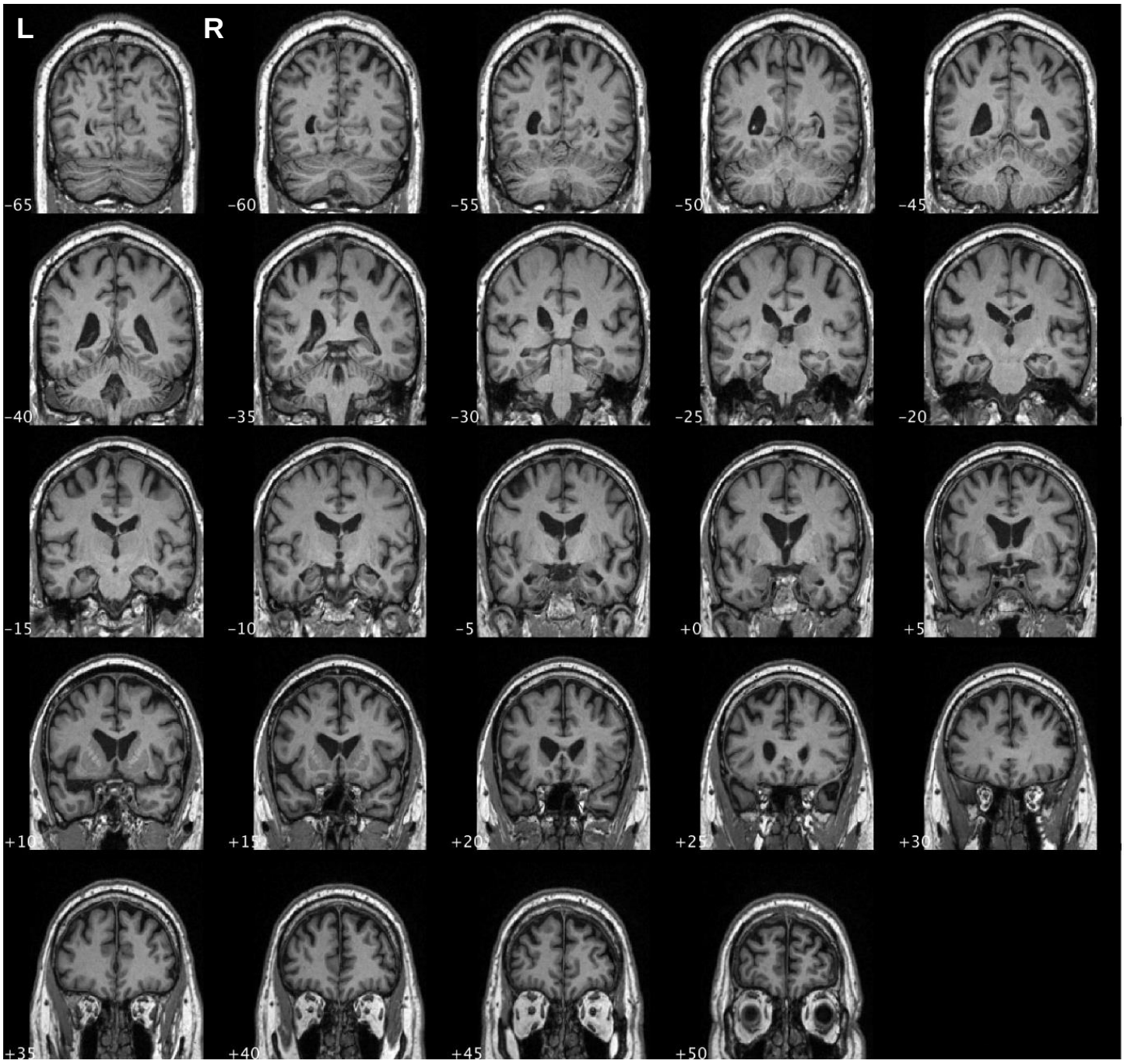
Patient #2
Neuropathology: High CTE (McKee Stage III), limbic TDP-43 with hippocampal sclerosis, mild arteriolosclerosis, ARTAG, infiltrating glioma, Low ADNC (A1B1C0)

Axial T1-weighted MRI (scan age: 69, age at death: 74)



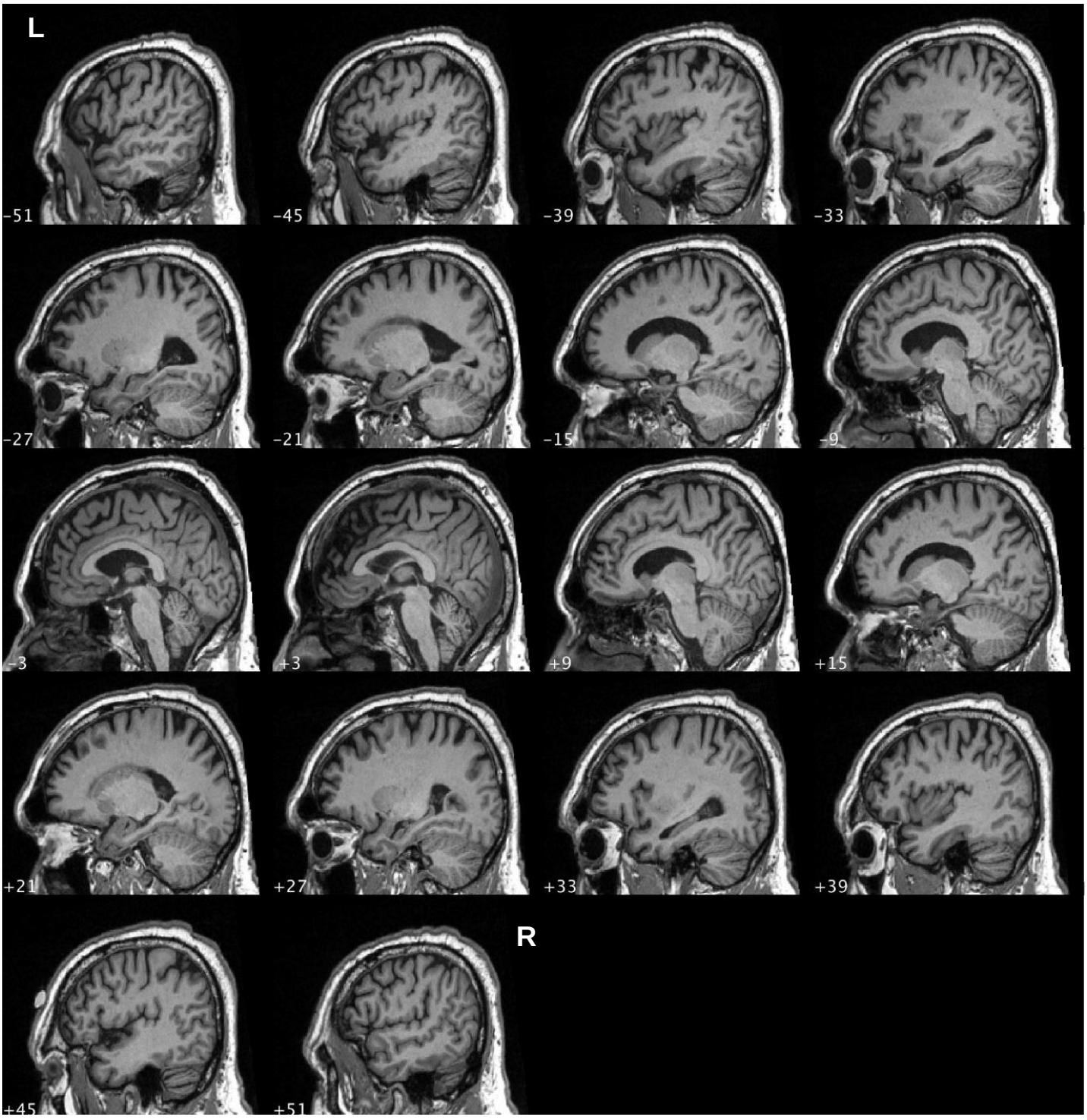
Patient #2
Neuropathology: High CTE (McKee Stage III), limbic TDP-43 with hippocampal sclerosis, mild arteriolosclerosis, ARTAG, infiltrating glioma, Low ADNC (A1B1C0)

Coronal T1-weighted MRI (scan age: 69, age at death: 74)



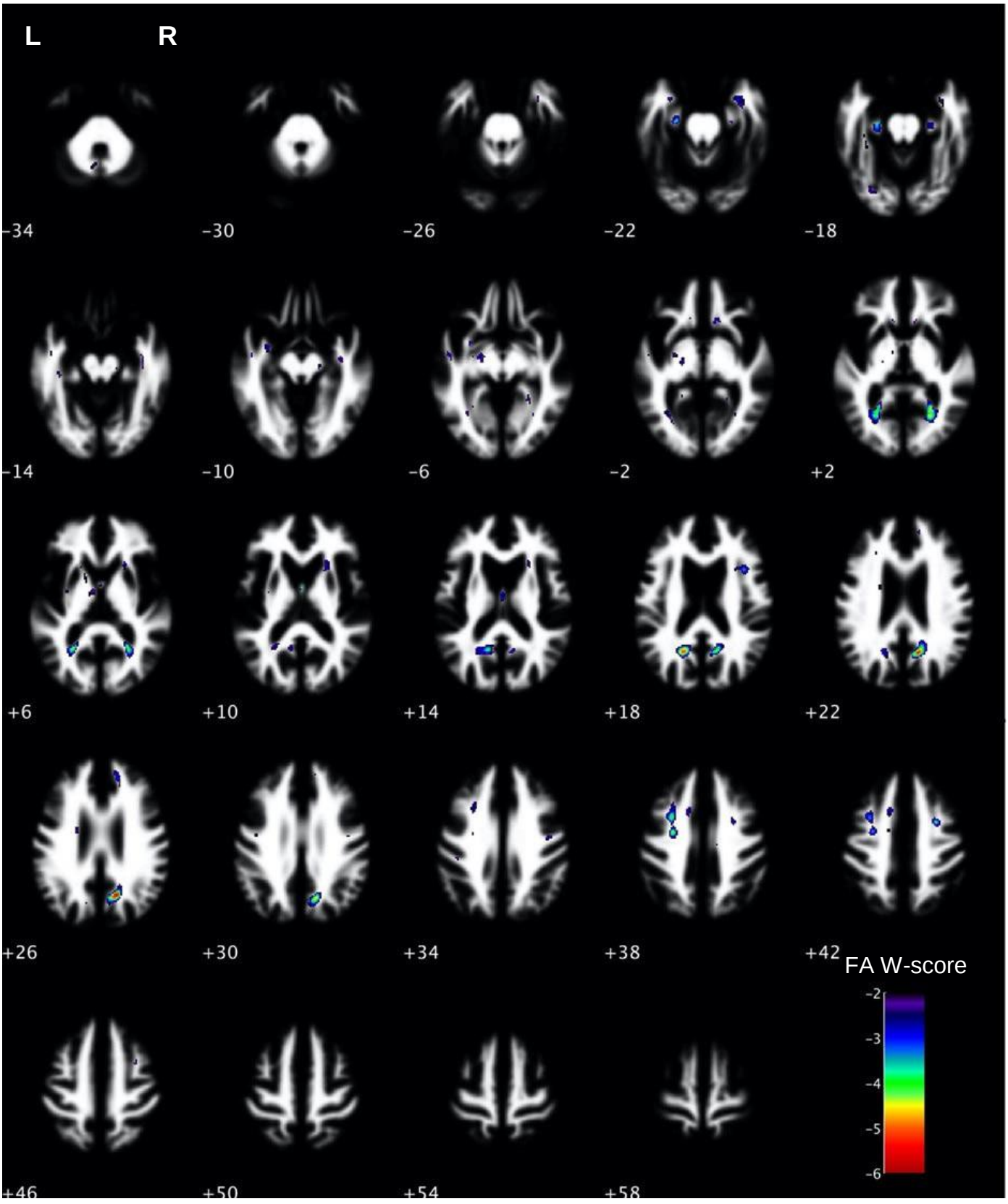
Patient #2
Neuropathology: High CTE (McKee Stage III), limbic TDP-43 with hippocampal sclerosis, mild arteriolosclerosis, ARTAG, infiltrating glioma, Low ADNC (A1B1C0)

Sagittal T1-weighted MRI (scan age: 69, age at death: 74)



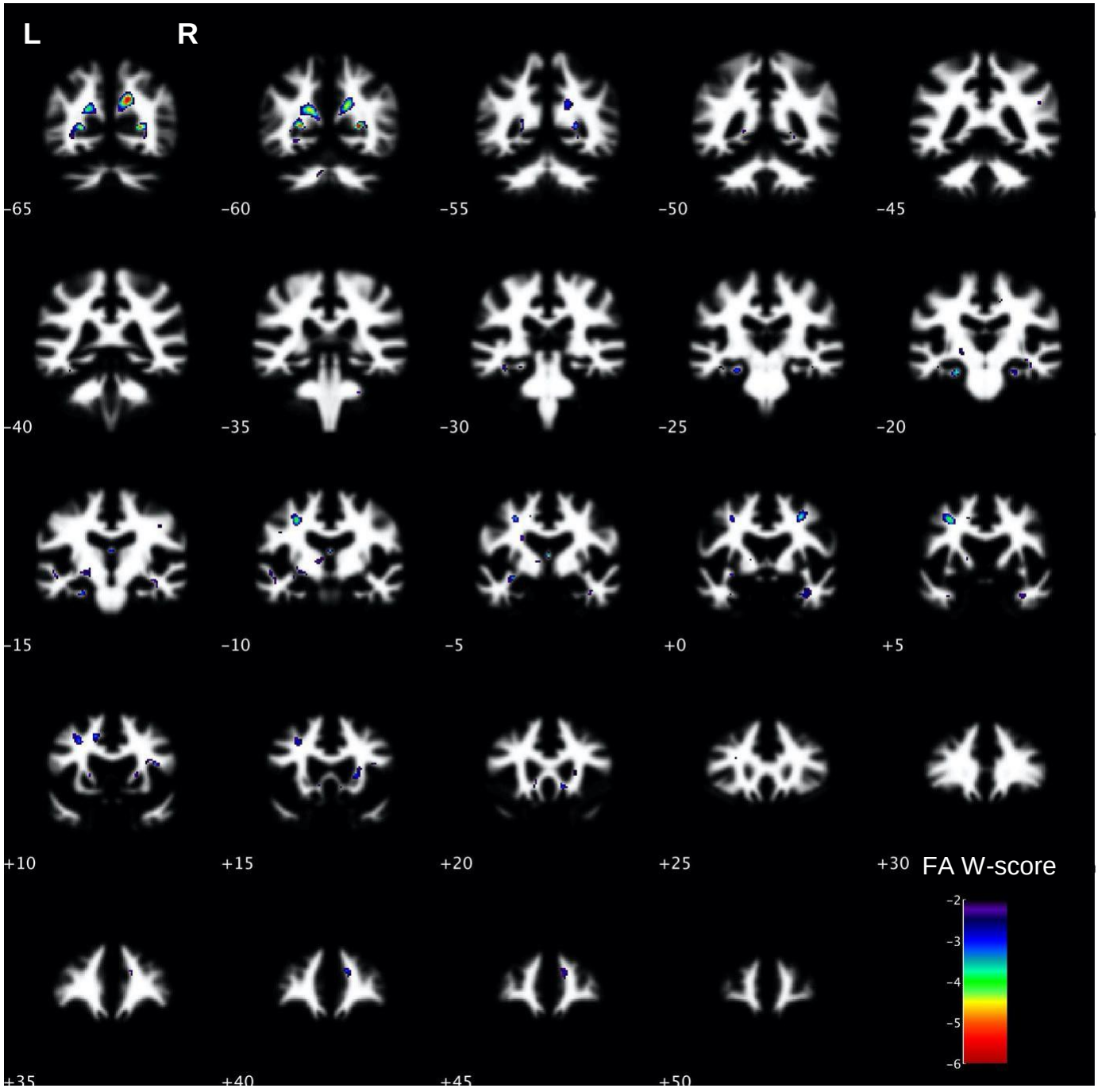
Patient #2
Neuropathology: High CTE (McKee Stage III), limbic TDP-43 with hippocampal sclerosis, mild arteriolosclerosis, ARTAG, infiltrating glioma, Low ADNC (A1B1C0)

Axial DTI – FA W-map (scan age: 69, age at death: 74)



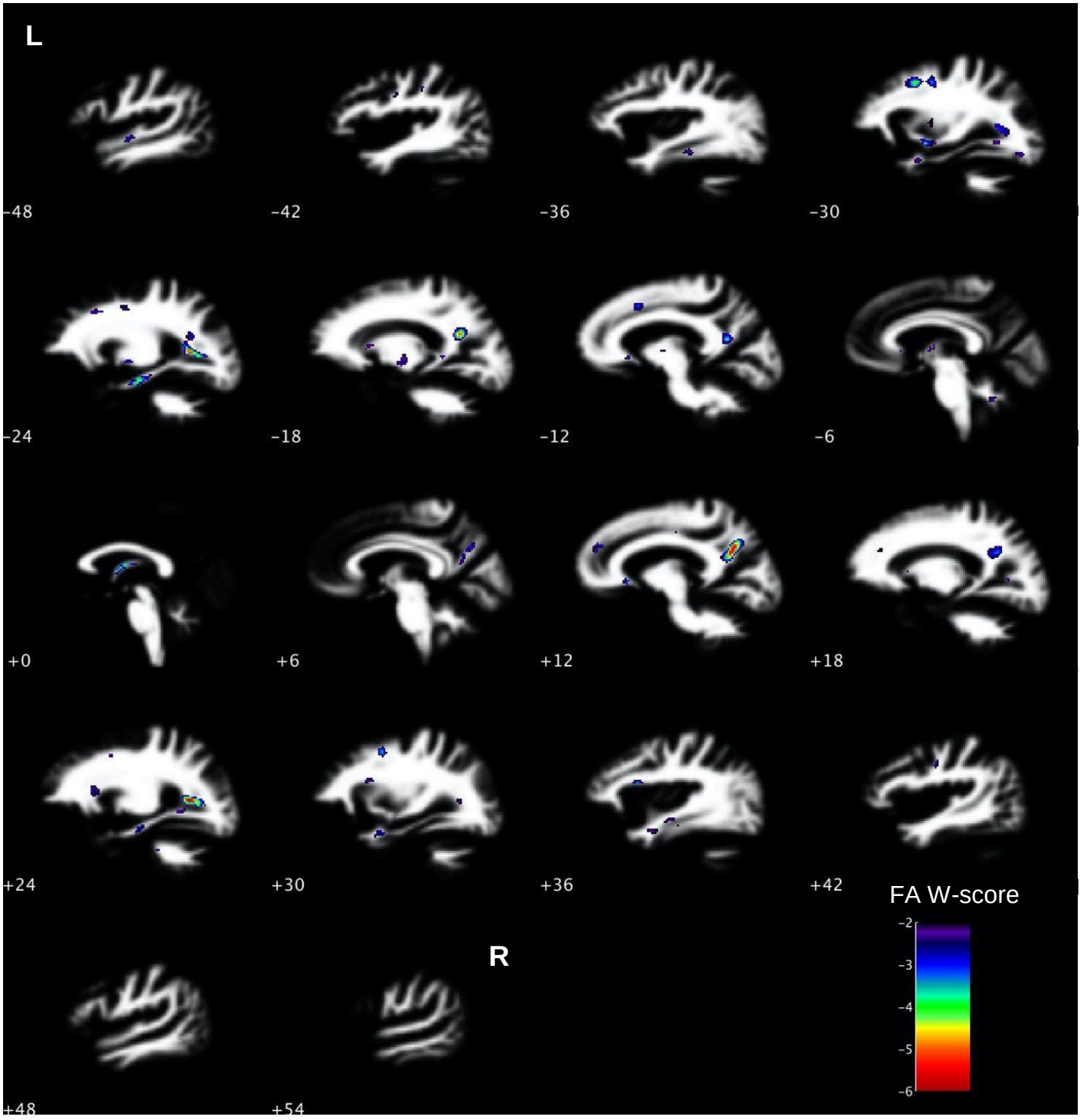
Patient #2
Neuropathology: High CTE (McKee Stage III), limbic TDP-43 with hippocampal sclerosis, mild arteriolosclerosis, ARTAG, infiltrating glioma, Low ADNC (A1B1C0)

Coronal DTI – FA W-map (scan age: 69, age at death: 74)



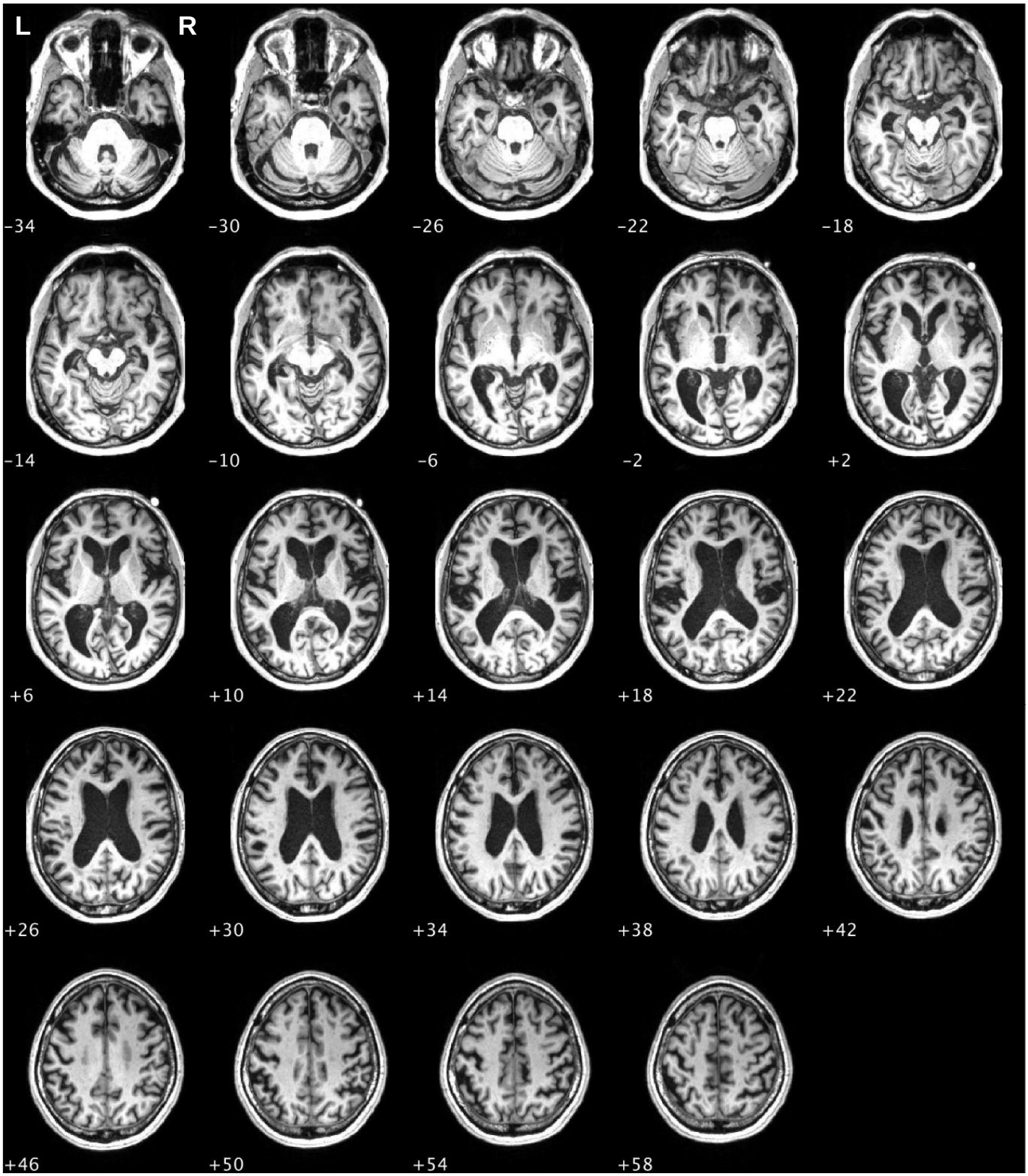
Patient #2
Neuropathology: High CTE (McKee Stage III), limbic TDP-43 with hippocampal sclerosis, mild arteriolosclerosis, ARTAG, infiltrating glioma, Low ADNC (A1B1C0)

Sagittal DTI – FA W-map (scan age: 69, age at death: 74)



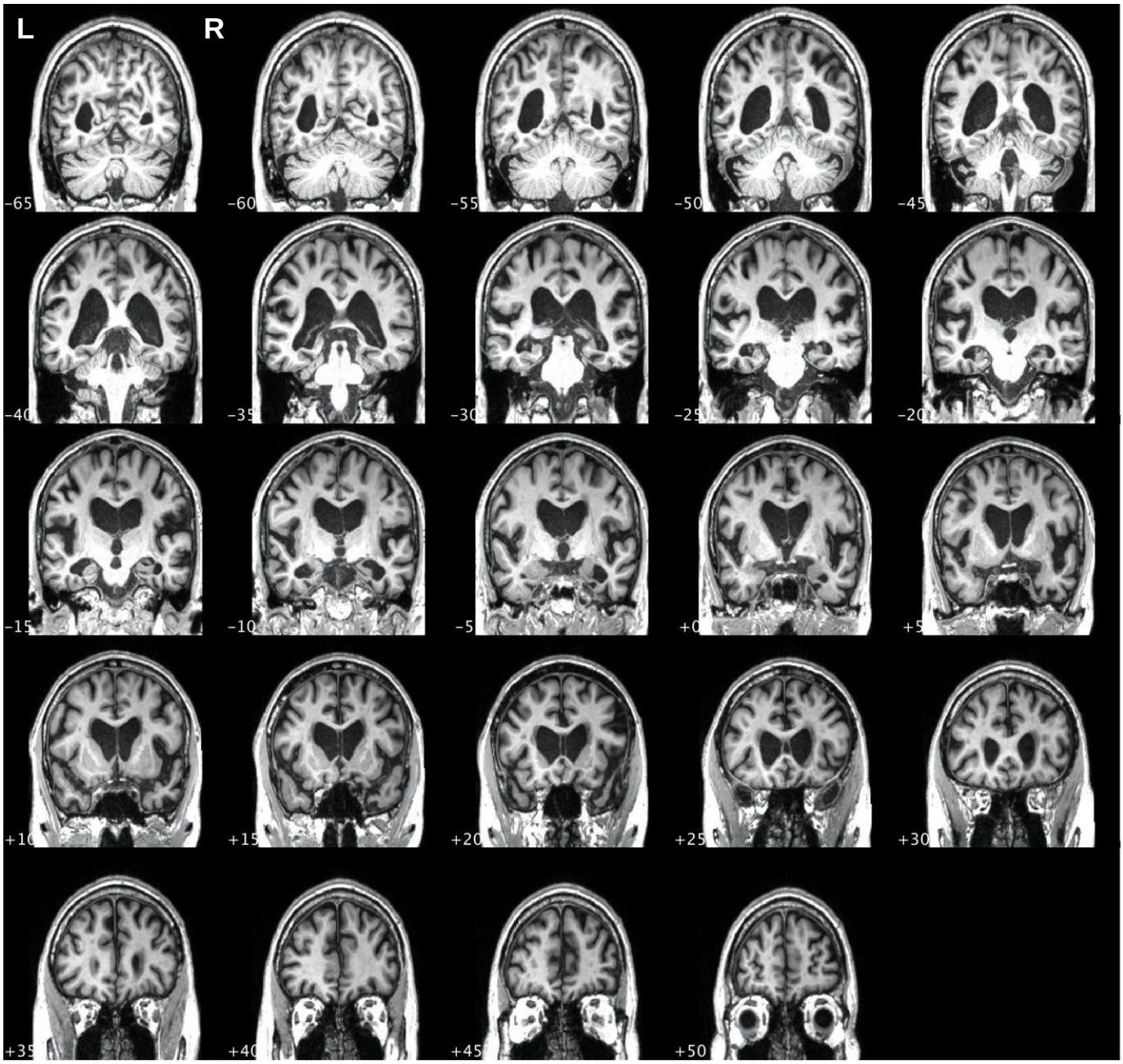
Patient #3
Neuropathology: Low CTE (McKee Stage I), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, lymphocytic leukemia, mild arteriolosclerosis, limbic AGD

Axial T1-weighted MRI (scan age: 78, age at death: 79)



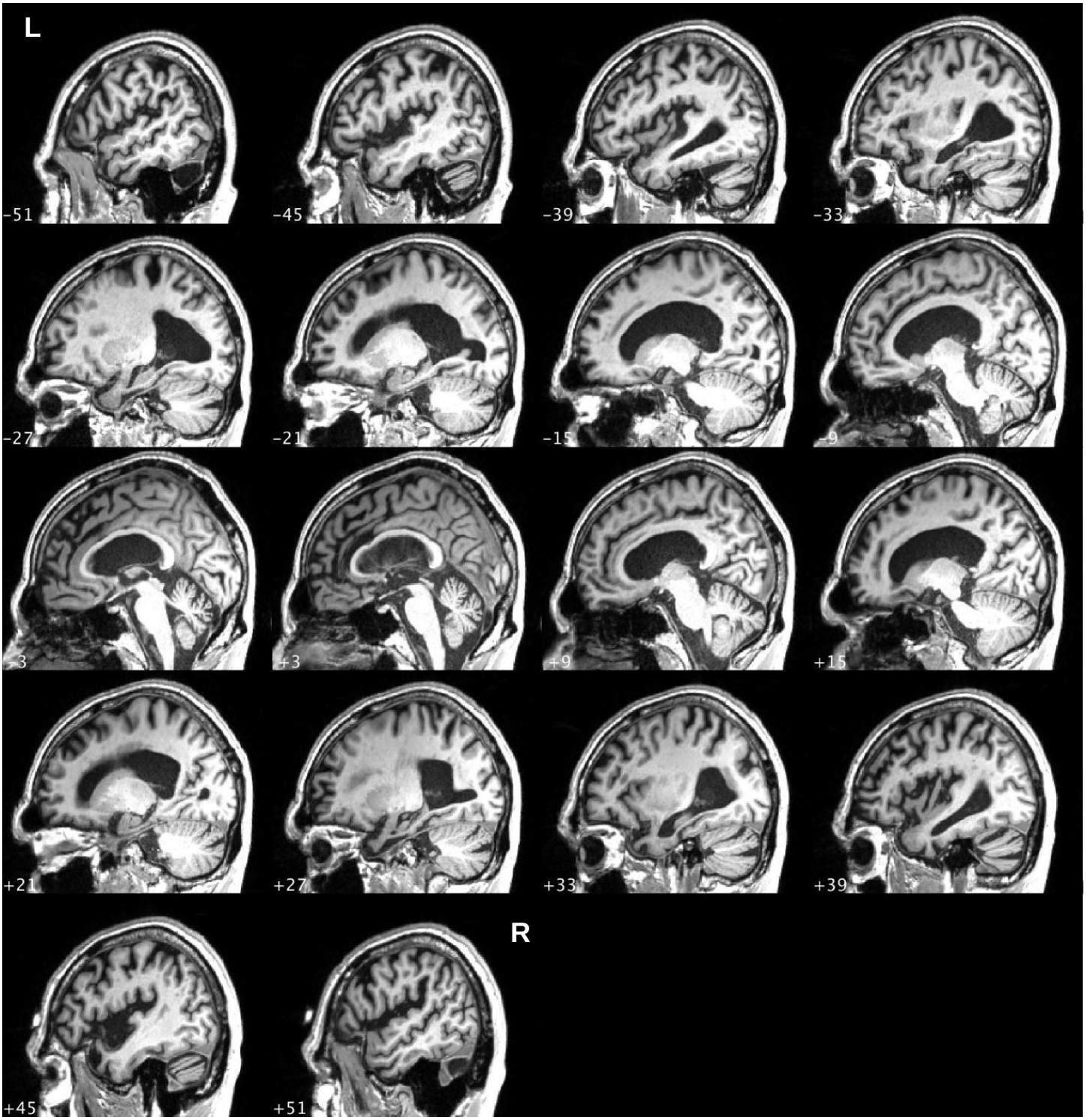
Patient #3
Neuropathology: Low CTE (McKee Stage I), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, lymphocytic leukemia, mild arteriolosclerosis, limbic AGD

Coronal T1-weighted MRI (scan age: 78, age at death: 79)



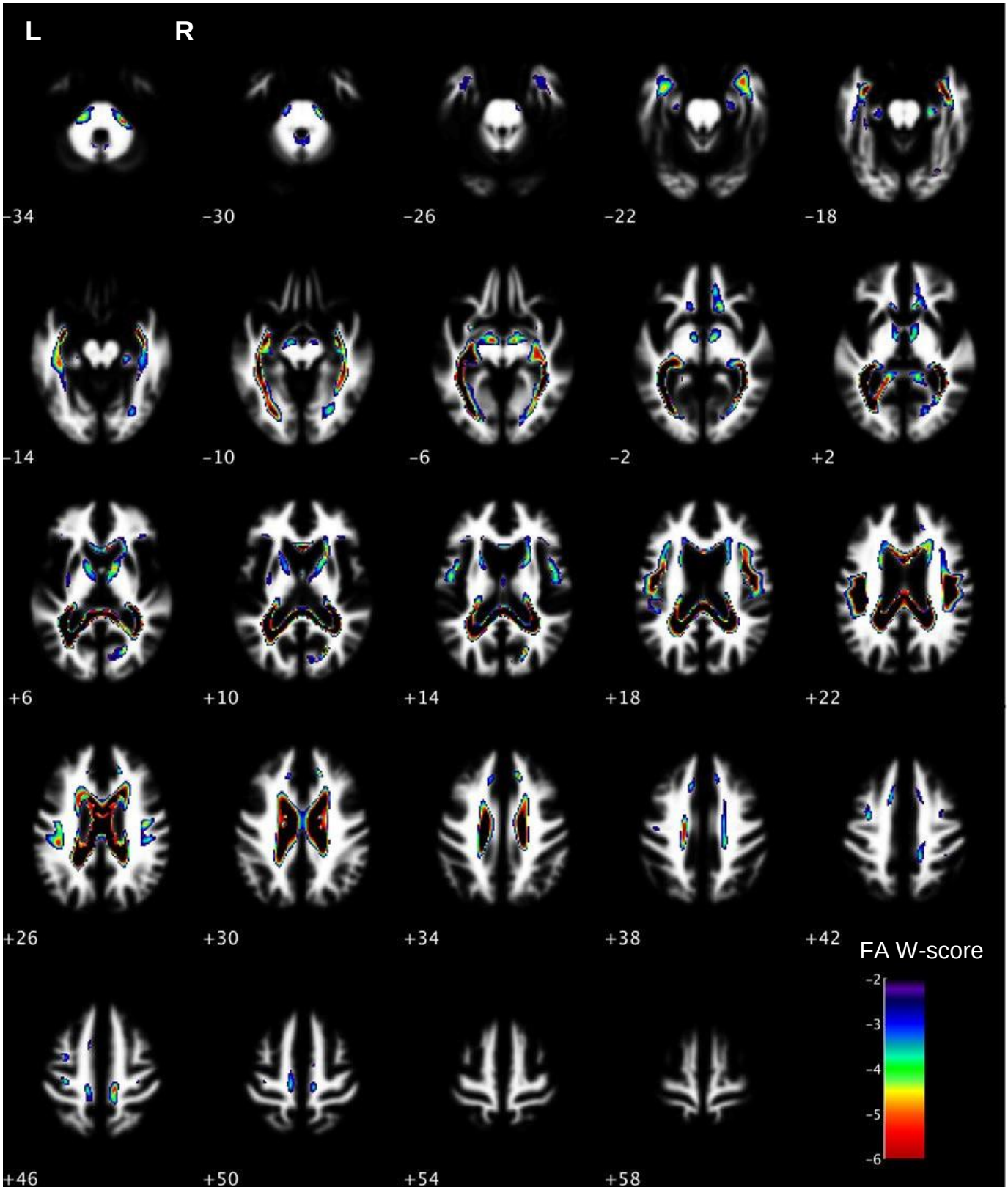
Patient #3
Neuropathology: Low CTE (McKee Stage I), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, lymphocytic leukemia, mild arteriolosclerosis, limbic AGD

Sagittal T1-weighted MRI (scan age: 78, age at death: 79)



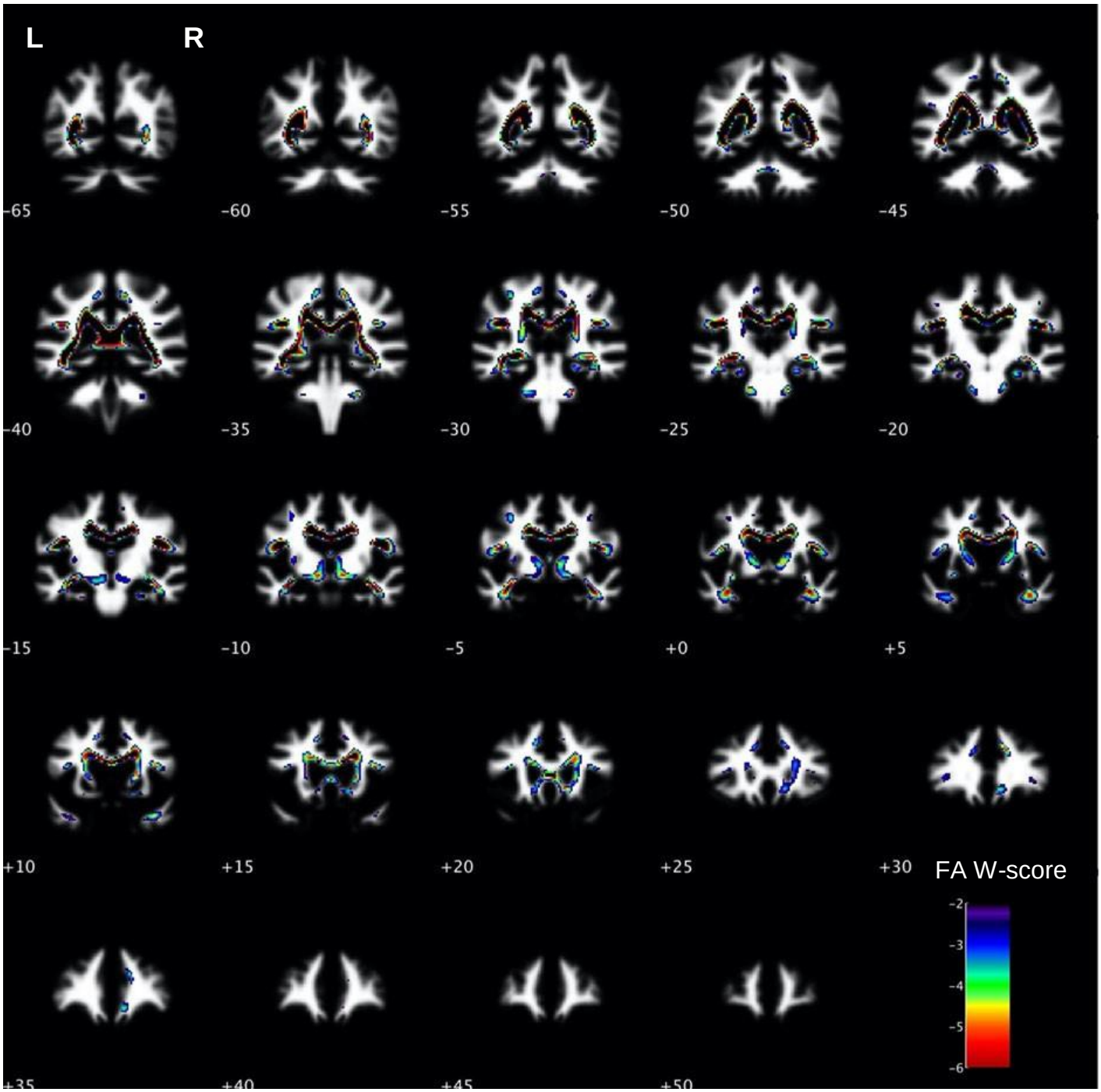
Patient #3
Neuropathology: Low CTE (McKee Stage I), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, lymphocytic leukemia, mild arteriolosclerosis, limbic AGD

Axial DTI – FA W-map (scan age: 77, age at death: 79)



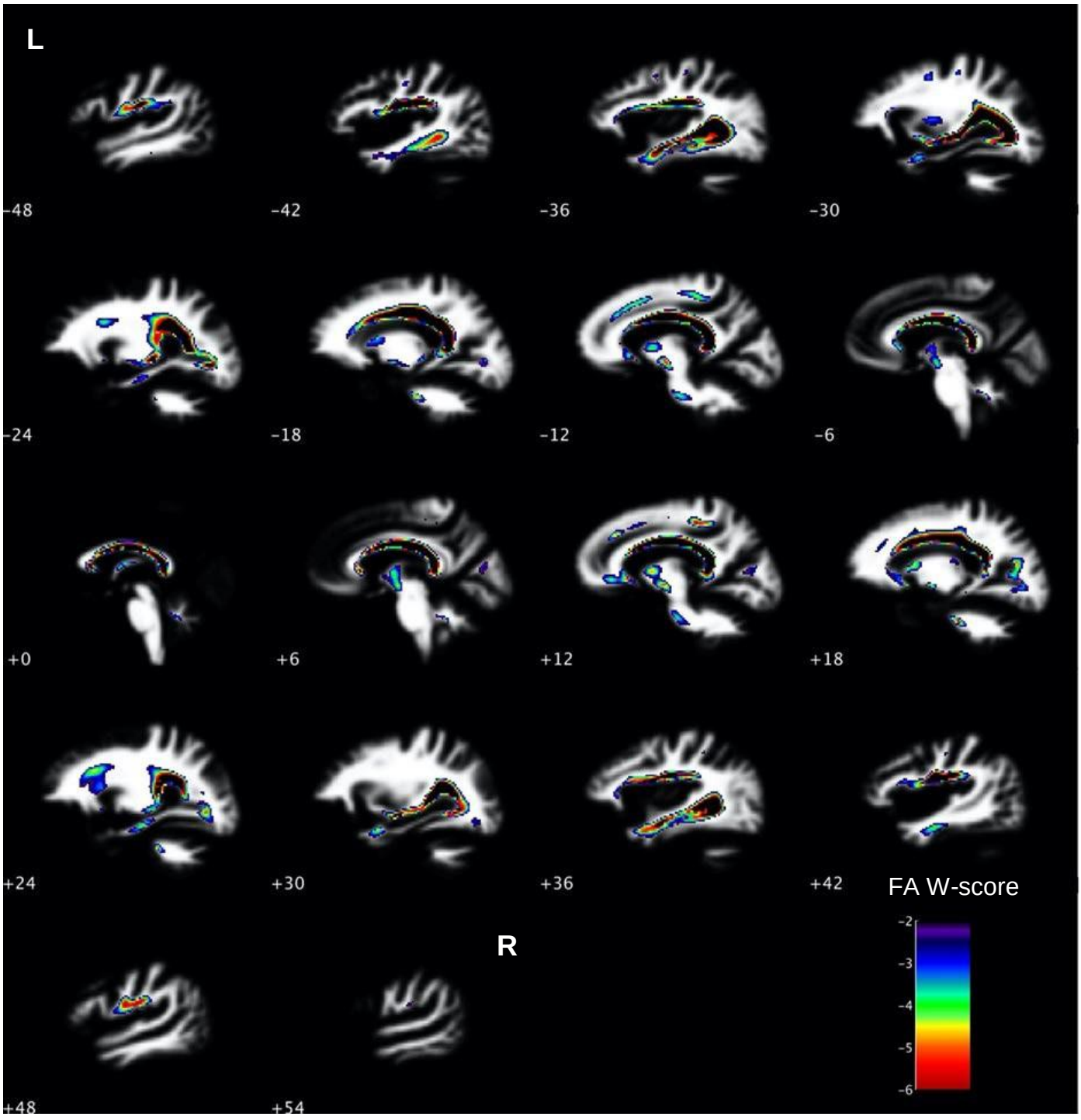
Patient #3
Neuropathology: Low CTE (McKee Stage I), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, lymphocytic leukemia, mild arteriolosclerosis, limbic AGD

Coronal DTI – FA W-map (scan age: 77, age at death: 79)



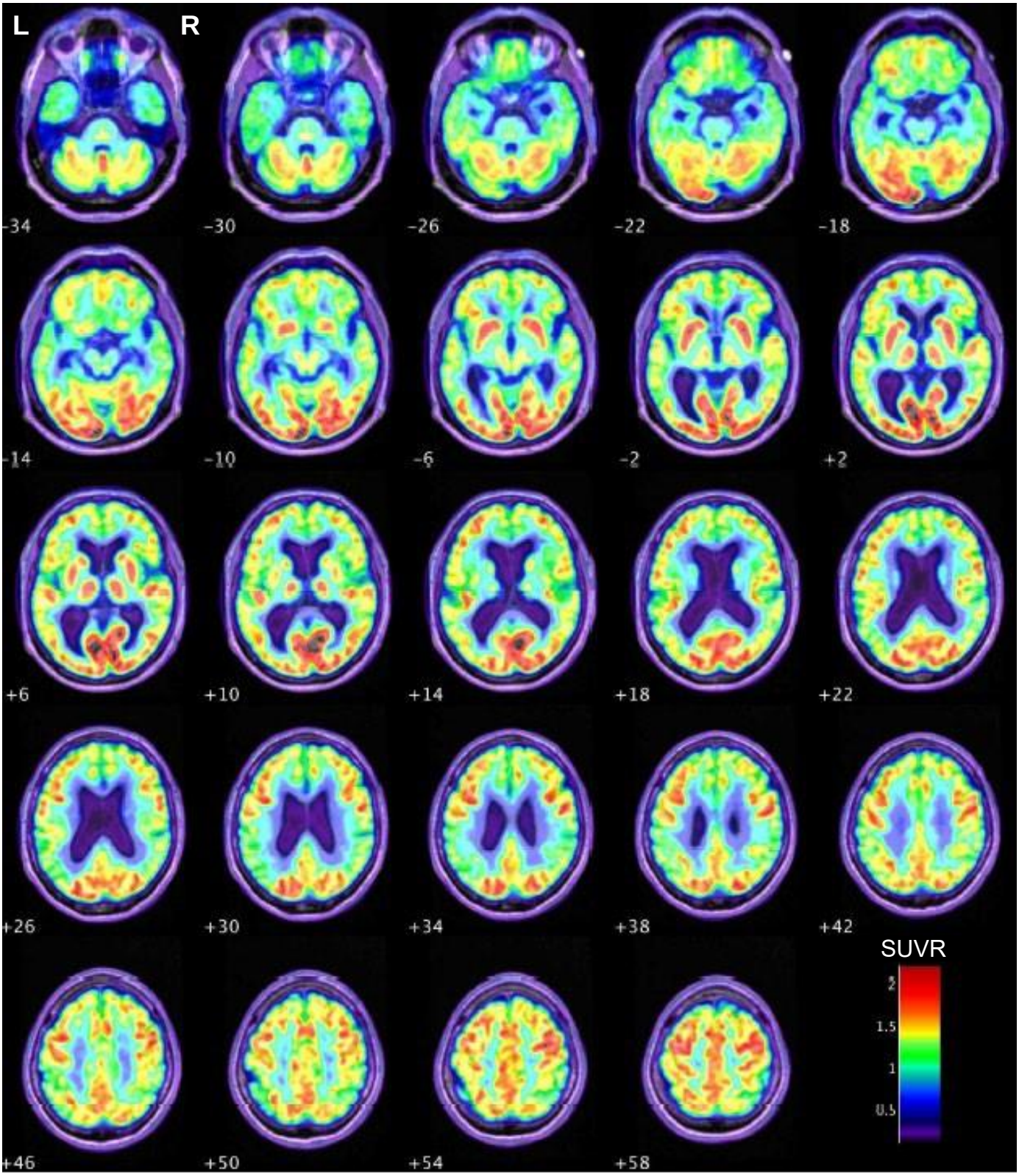
Patient #3
Neuropathology: Low CTE (McKee Stage I), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, lymphocytic leukemia, mild arteriolosclerosis, limbic AGD

Sagittal DTI – FA W-map (scan age: 77, age at death: 79)



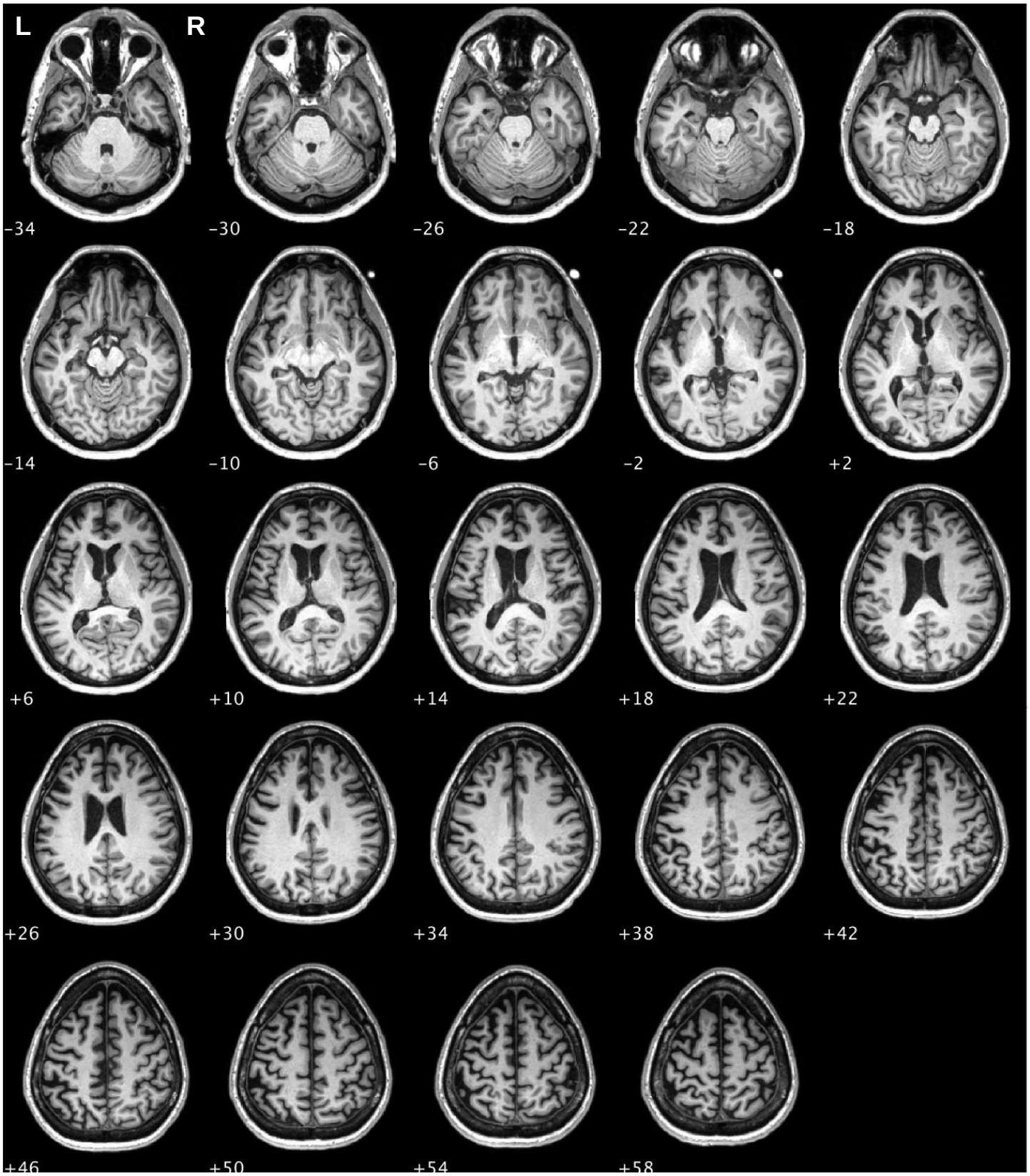
Patient #3
Neuropathology: Low CTE (McKee Stage I), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, lymphocytic leukemia, mild arteriolosclerosis, limbic AGD

FDG-PET (scan age: 74, age at death: 79)



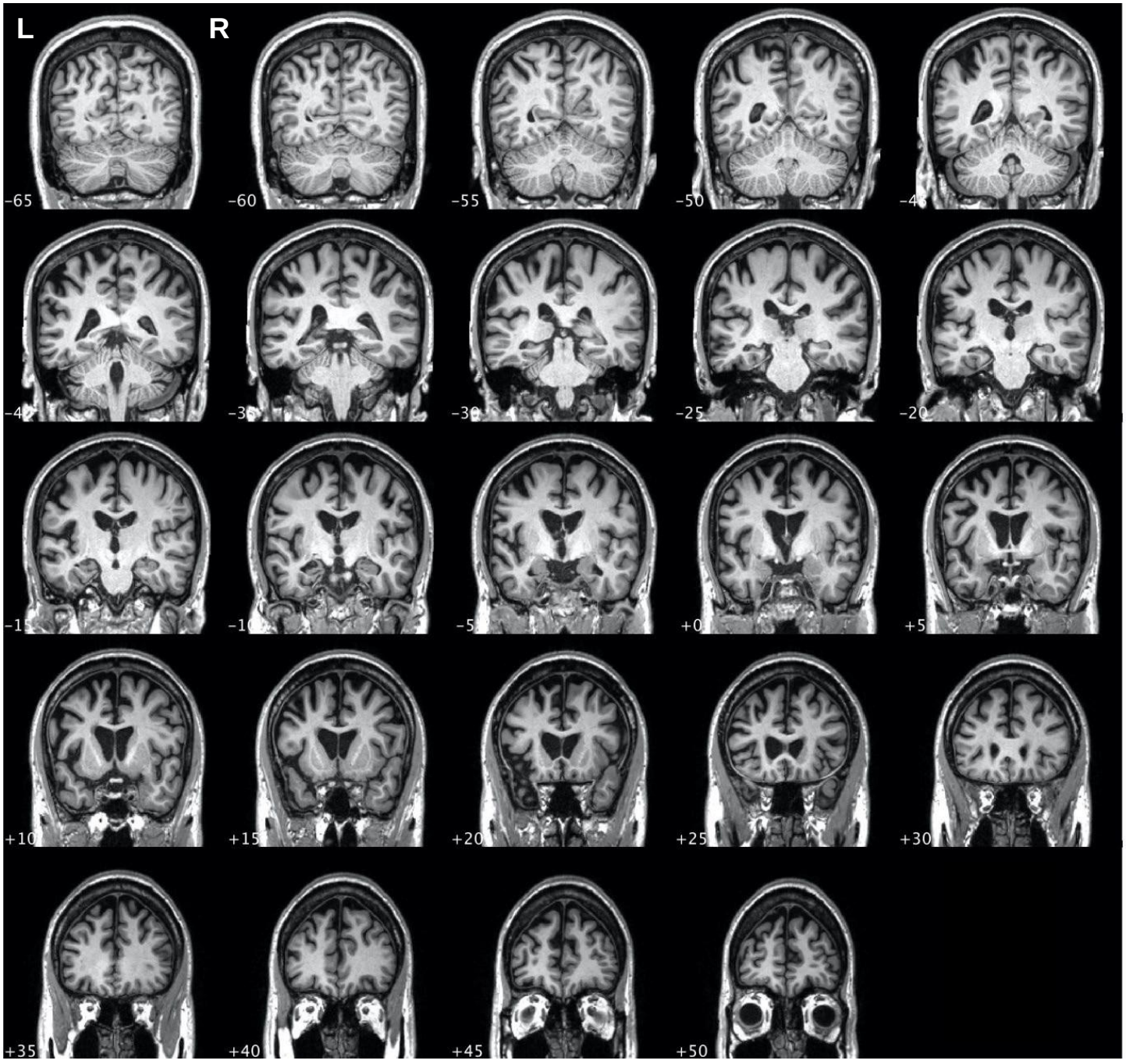
Patient #4
Neuropathology: No CTE, FTLD tau (corticobasal degeneration), hippocampal sclerosis, FTLD TDP-43 (unclassifiable), limbic AGD

Axial T1-weighted MRI (scan age: 47, age at death: 49)



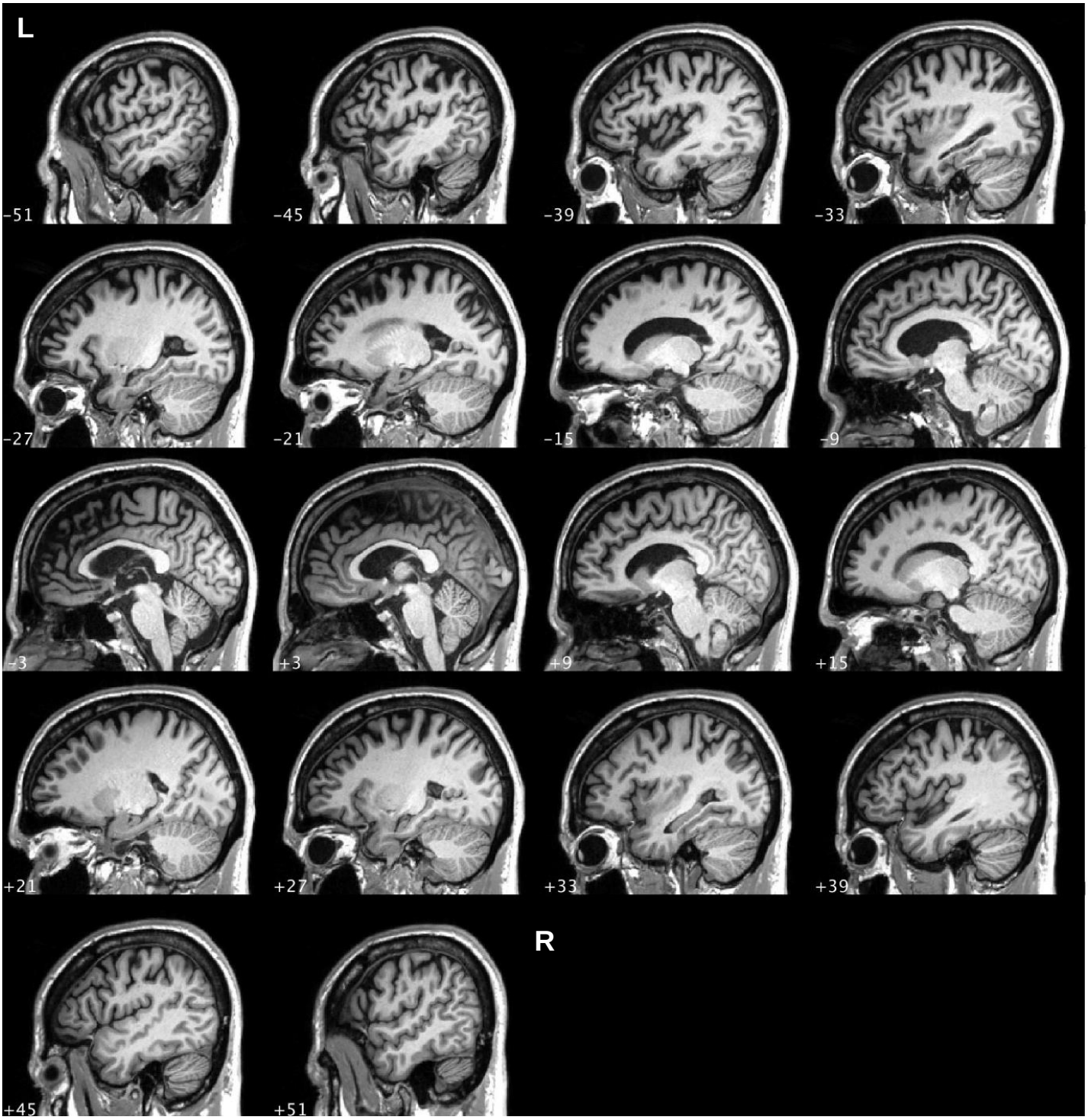
Patient #4
Neuropathology: No CTE, FTLD tau (corticobasal degeneration), hippocampal sclerosis, FTLD TDP-43 (unclassifiable), limbic AGD

Coronal T1-weighted MRI (scan age: 47, age at death: 49)



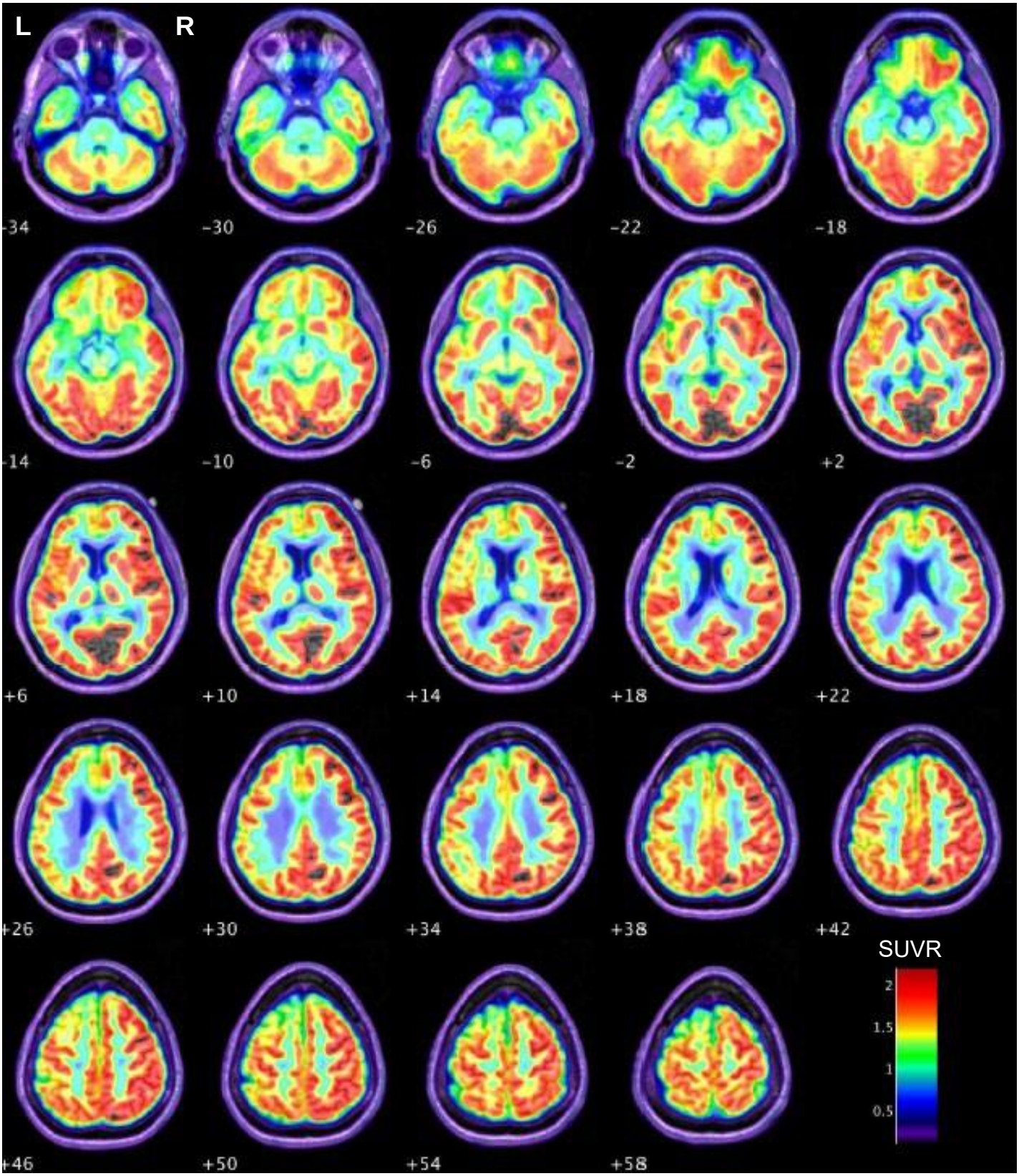
Patient #4
Neuropathology: No CTE, FTLD tau (corticobasal degeneration), hippocampal sclerosis, FTLD TDP-43 (unclassifiable), limbic AGD

Sagittal T1-weighted MRI (scan age: 47, age at death: 49)



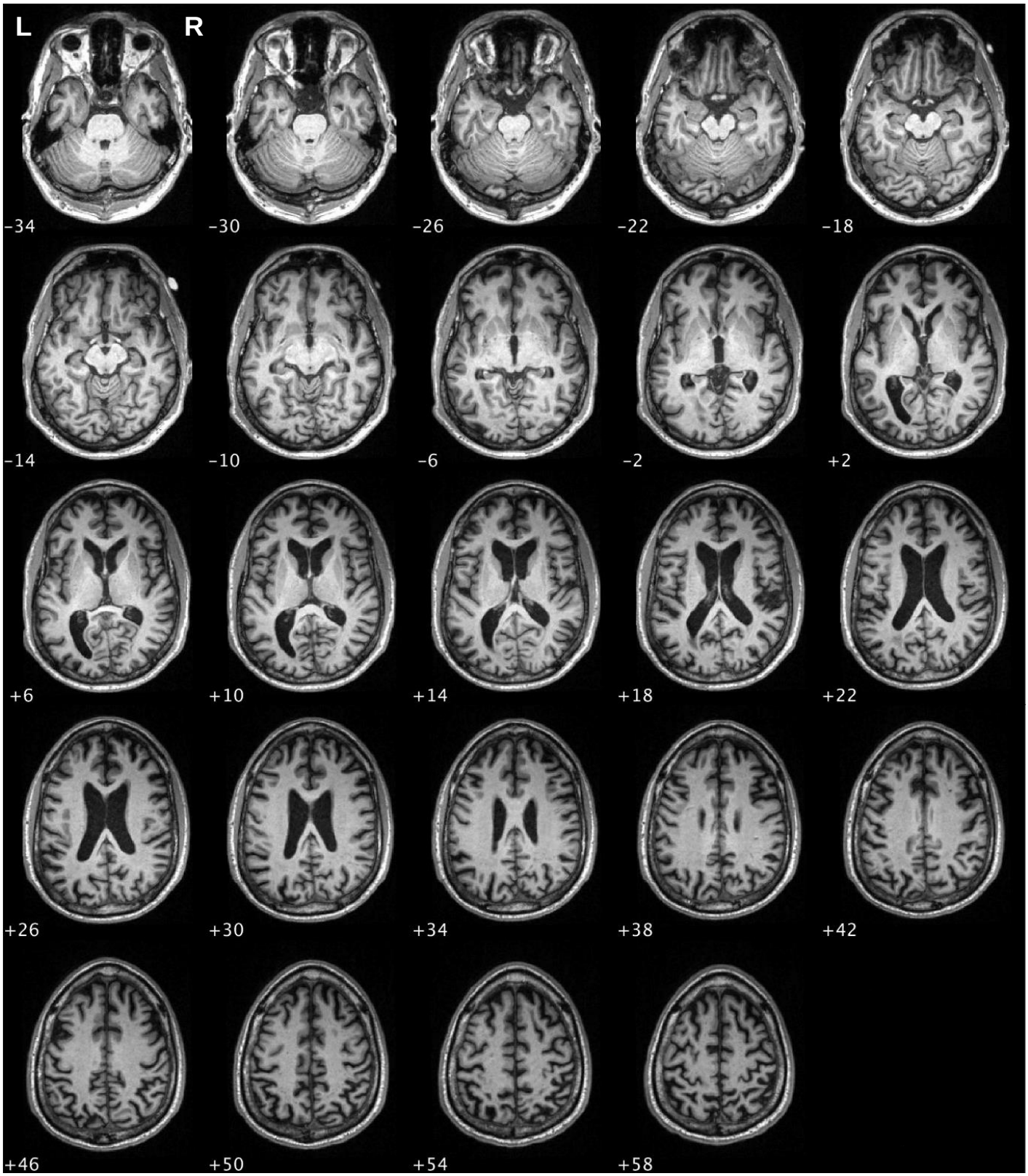
Patient #4
Neuropathology: No CTE, FTLD tau (corticobasal degeneration), hippocampal sclerosis, FTLD TDP-43 (unclassifiable), limbic AGD

FDG-PET (scan age: 47, age at death: 49)



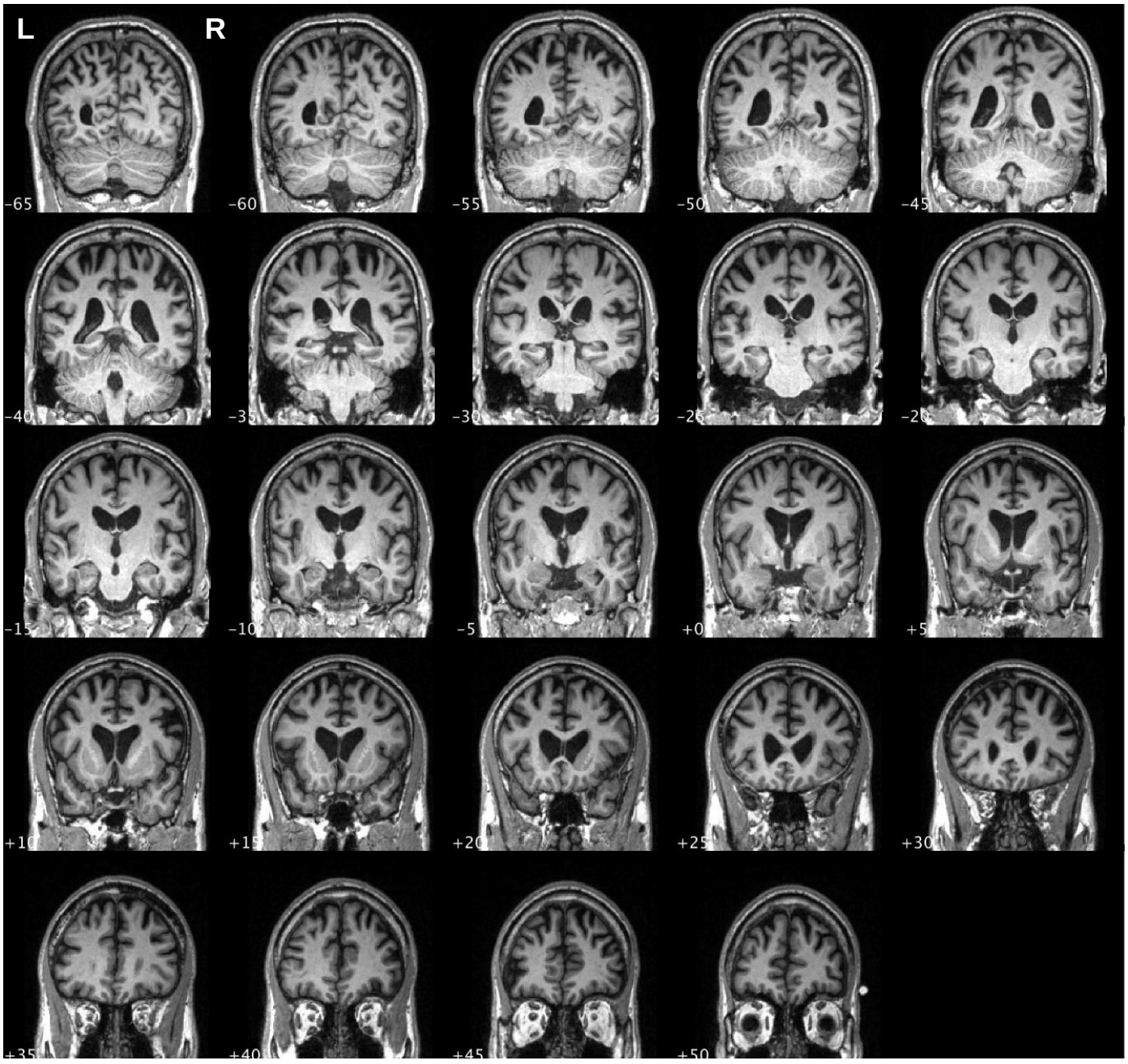
Patient #5
Neuropathology: No CTE, High ADNC (A3B3C3), limbic AGD, mild arteriolosclerosis, mild CAA, Lewy body disease (amygdala-predominant), ARTAG

Axial T1-weighted MRI (scan age: 51, age at death: 58)



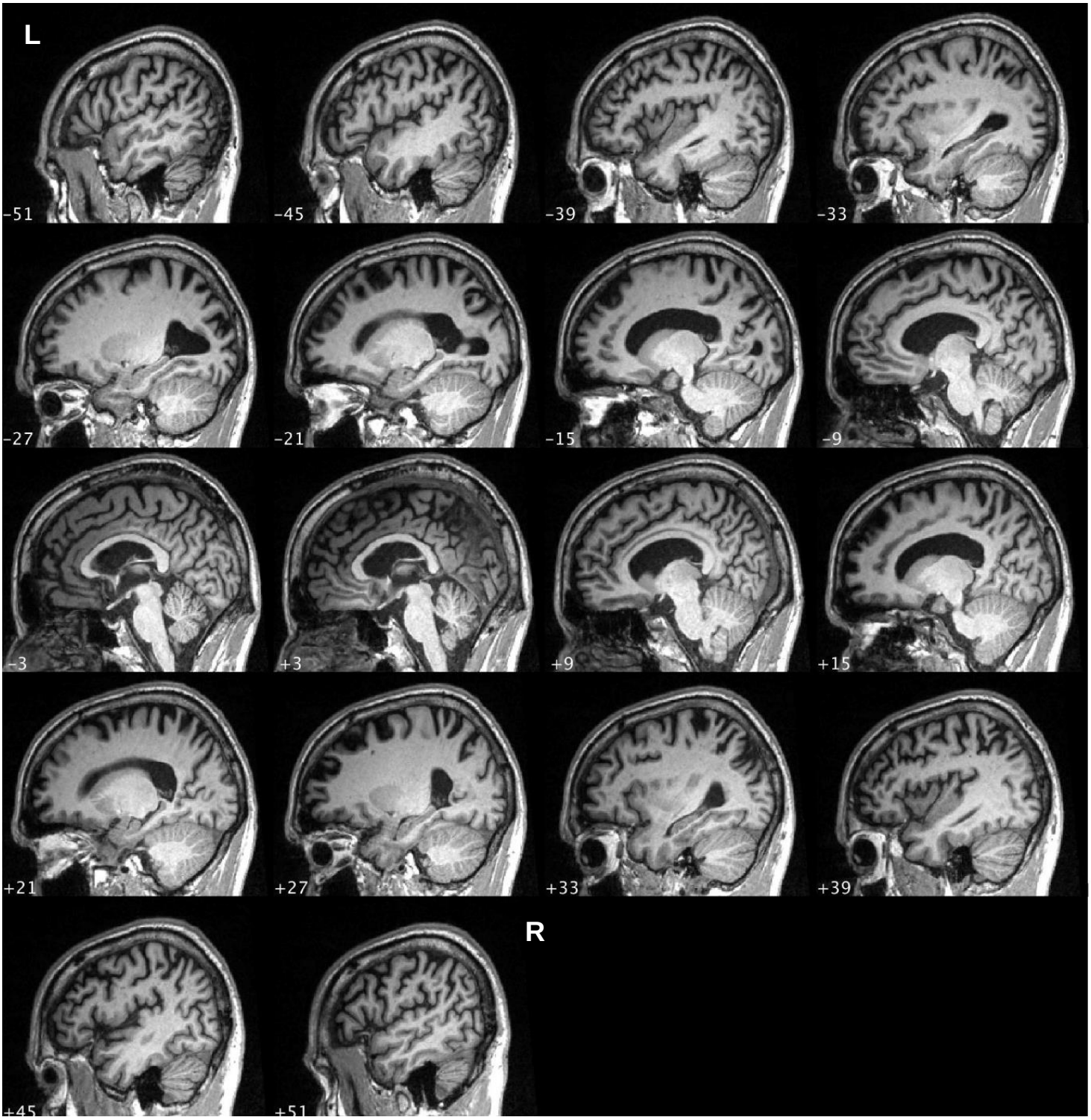
Patient #5
Neuropathology: No CTE, High ADNC (A3B3C3), limbic AGD, mild arteriolosclerosis, mild CAA, Lewy body disease (amygdala-predominant), ARTAG

Coronal T1-weighted MRI (scan age: 51, age at death: 58)



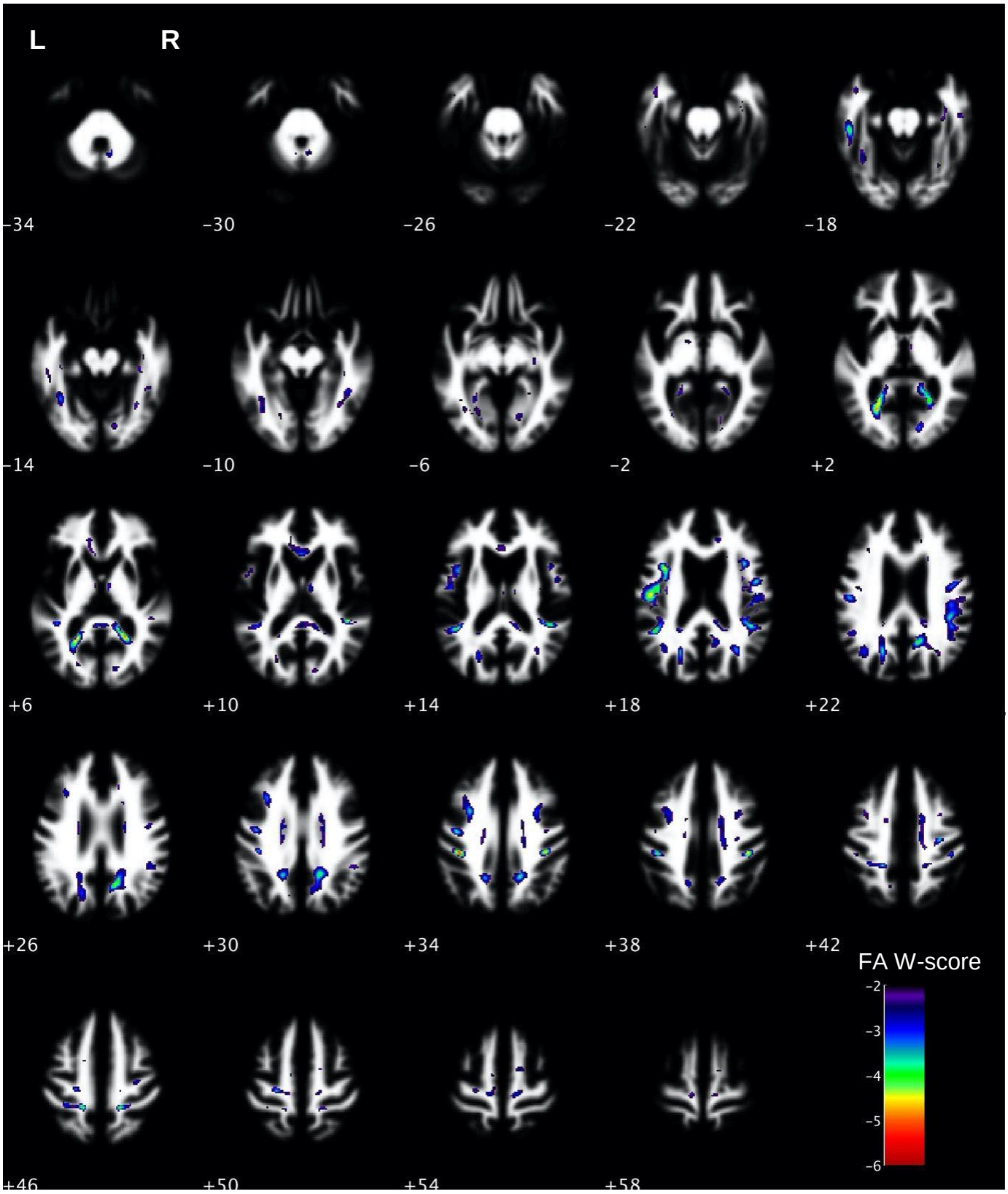
Patient #5
Neuropathology: No CTE, High ADNC (A3B3C3), limbic AGD, mild arteriolosclerosis, mild CAA, Lewy body disease (amygdala-predominant), ARTAG

Sagittal T1-weighted MRI (scan age: 51, age at death: 58)



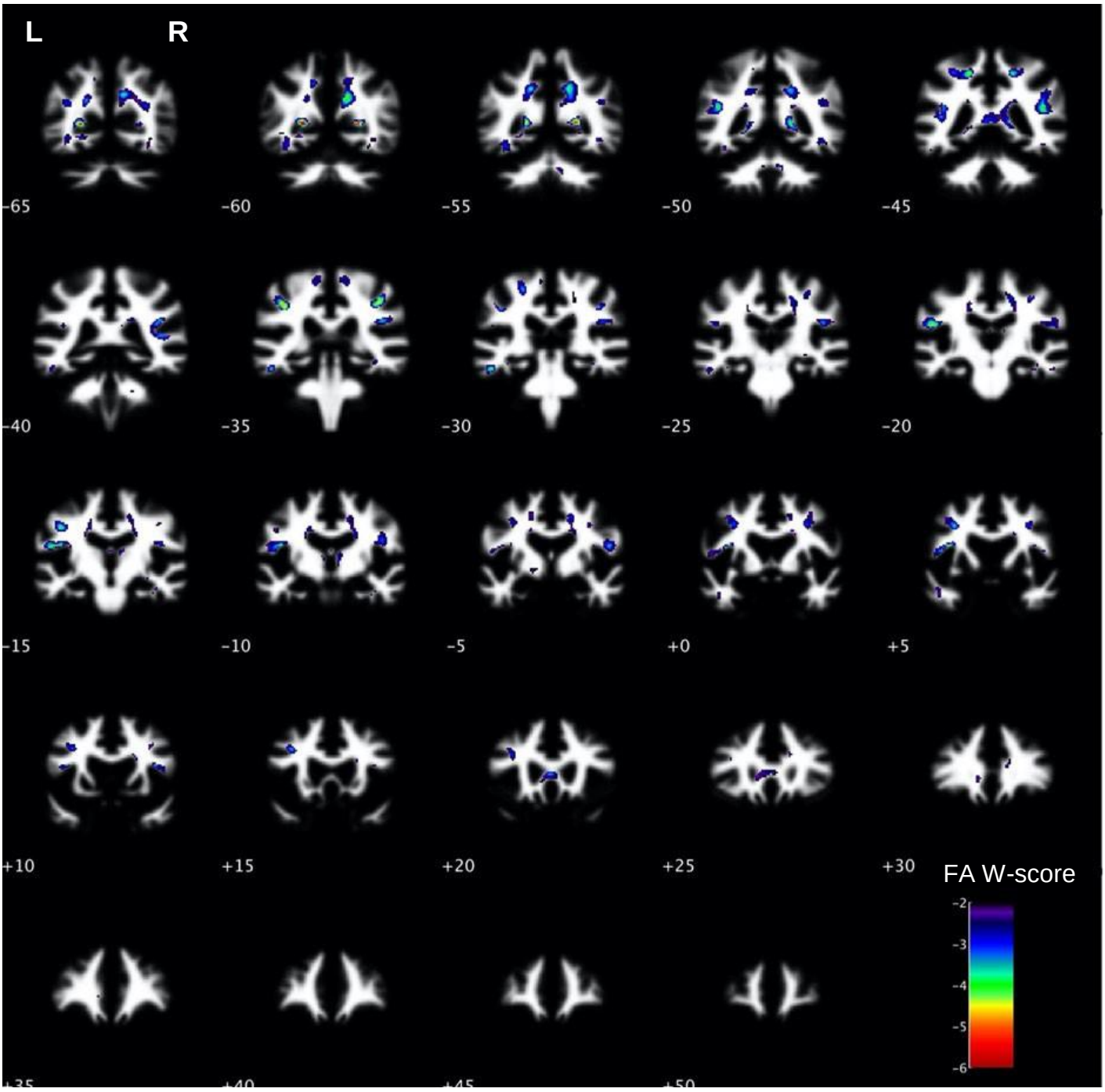
Patient #5
Neuropathology: No CTE, High ADNC (A3B3C3), limbic AGD, mild arteriolosclerosis, mild CAA, Lewy body disease (amygdala-predominant), ARTAG

Axial DTI – FA W-map (scan age: 51, age at death: 58)



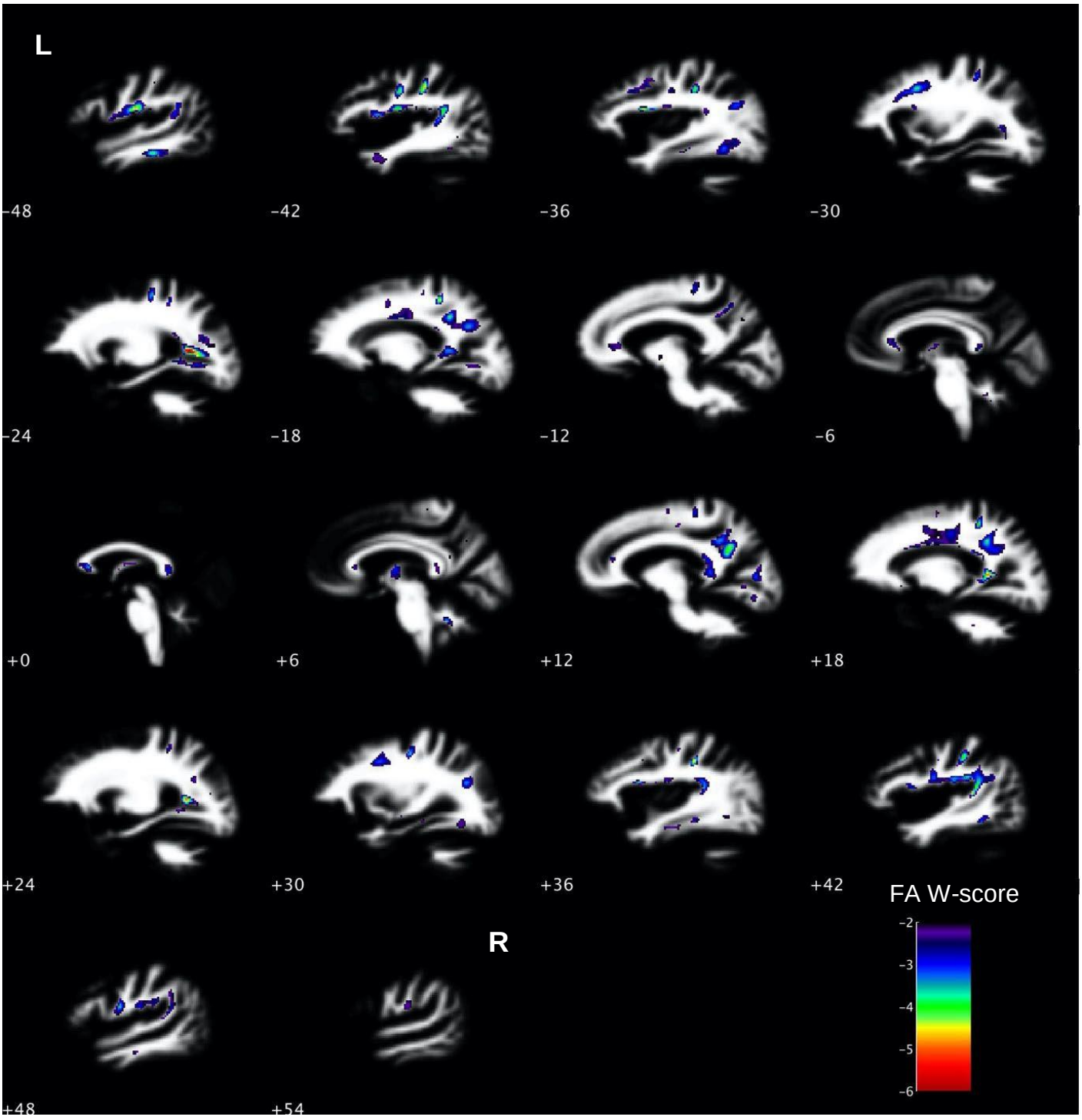
Patient #5
Neuropathology: No CTE, High ADNC (A3B3C3), limbic AGD, mild arteriolosclerosis, mild CAA, Lewy body disease (amygdala-predominant), ARTAG

Coronal DTI – FA W-map (scan age: 51, age at death: 58)



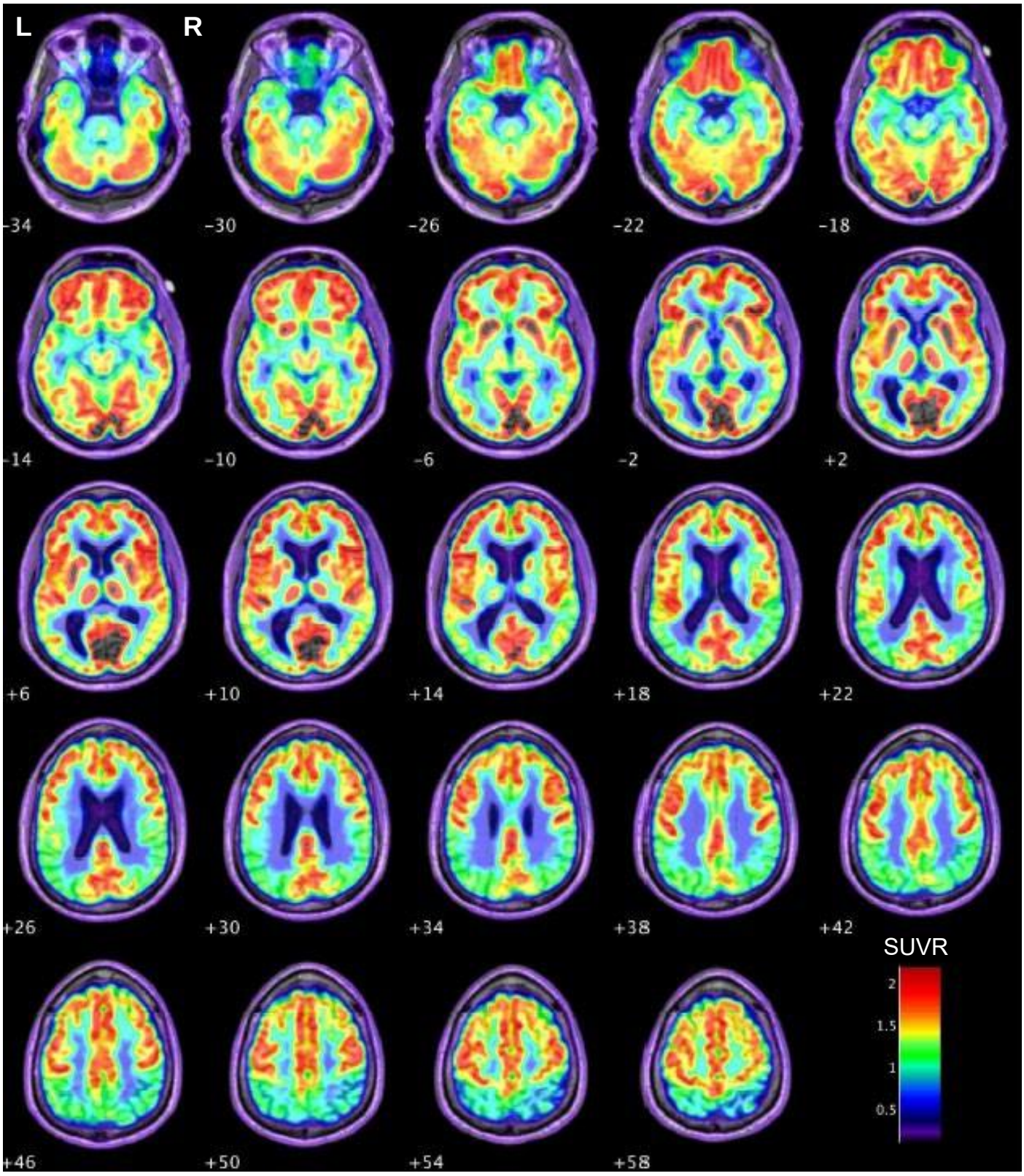
Patient #5
Neuropathology: No CTE, High ADNC (A3B3C3), limbic AGD, mild arteriolosclerosis, mild CAA, Lewy body disease (amygdala-predominant), ARTAG

Sagittal DTI – FA W-map (scan age: 51, age at death: 58)



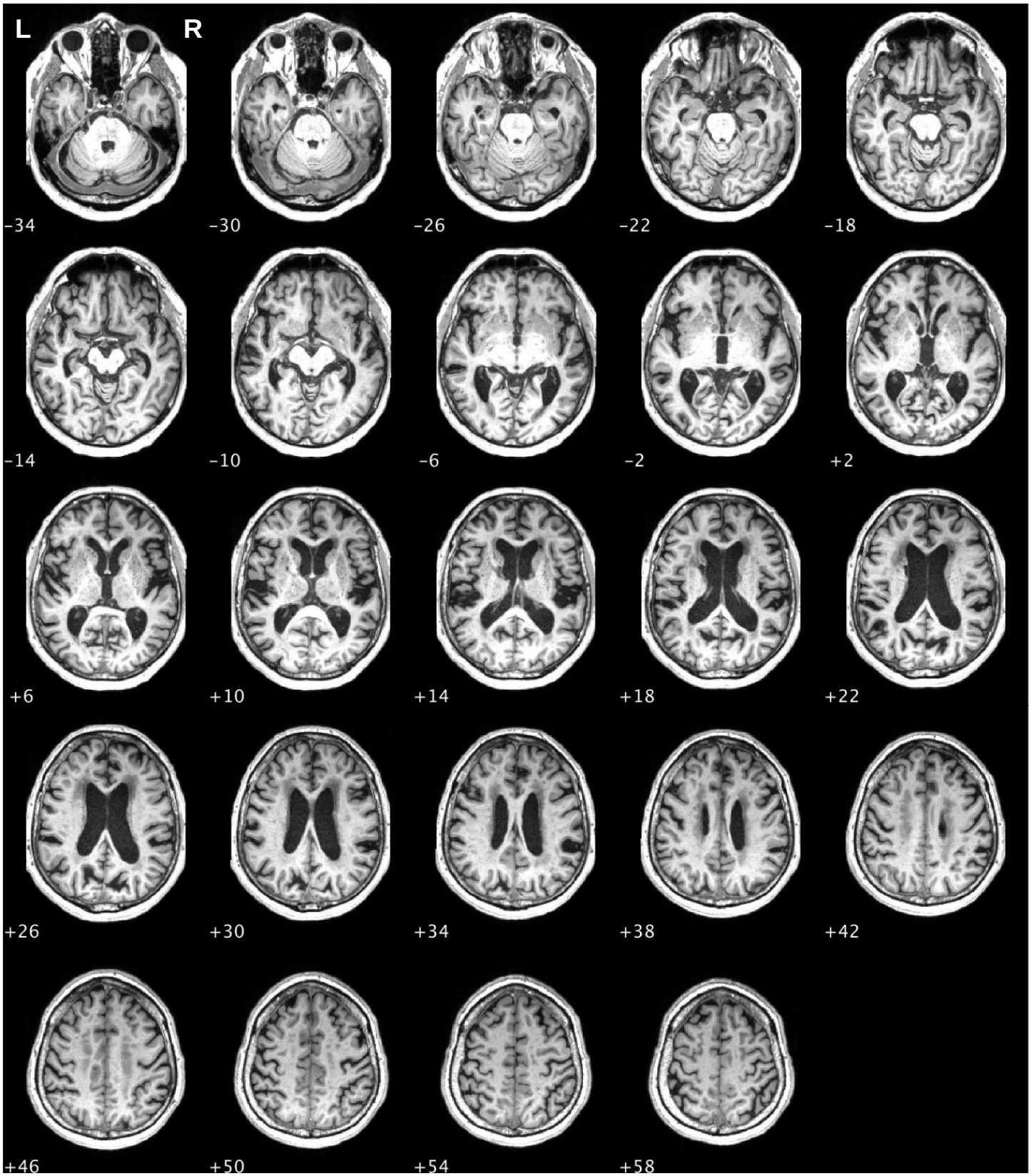
Patient #5
Neuropathology: No CTE, High ADNC (A3B3C3), limbic AGD, mild arteriolosclerosis, mild CAA, Lewy body disease (amygdala-predominant), ARTAG

FDG-PET (scan age: 51, age at death: 58)



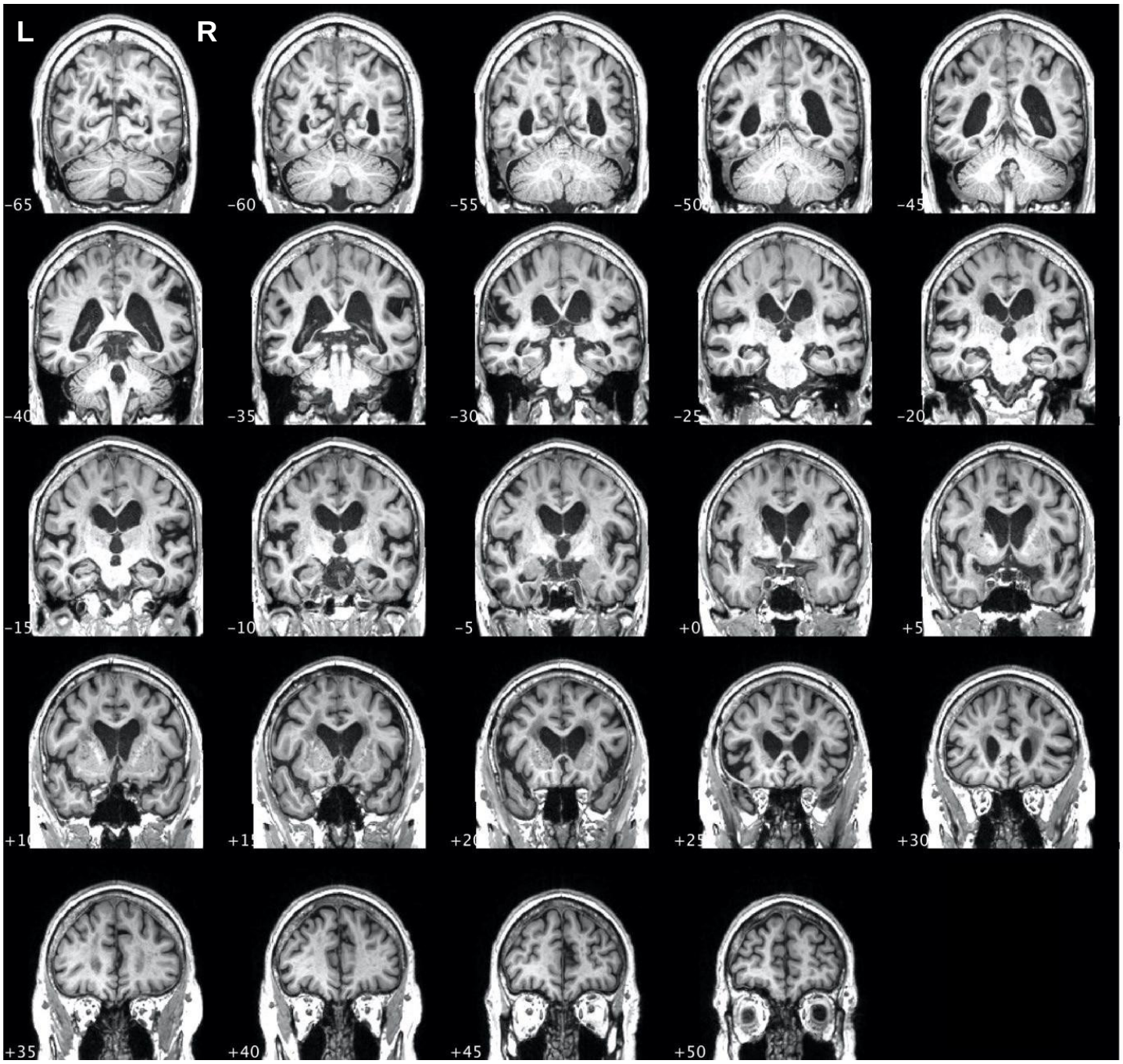
Patient #6
Neuropathology: No CTE, PART, vascular brain injury, limbic AGD, ARTAG

Axial T1-weighted MRI (scan age: 81, age at death: 81)



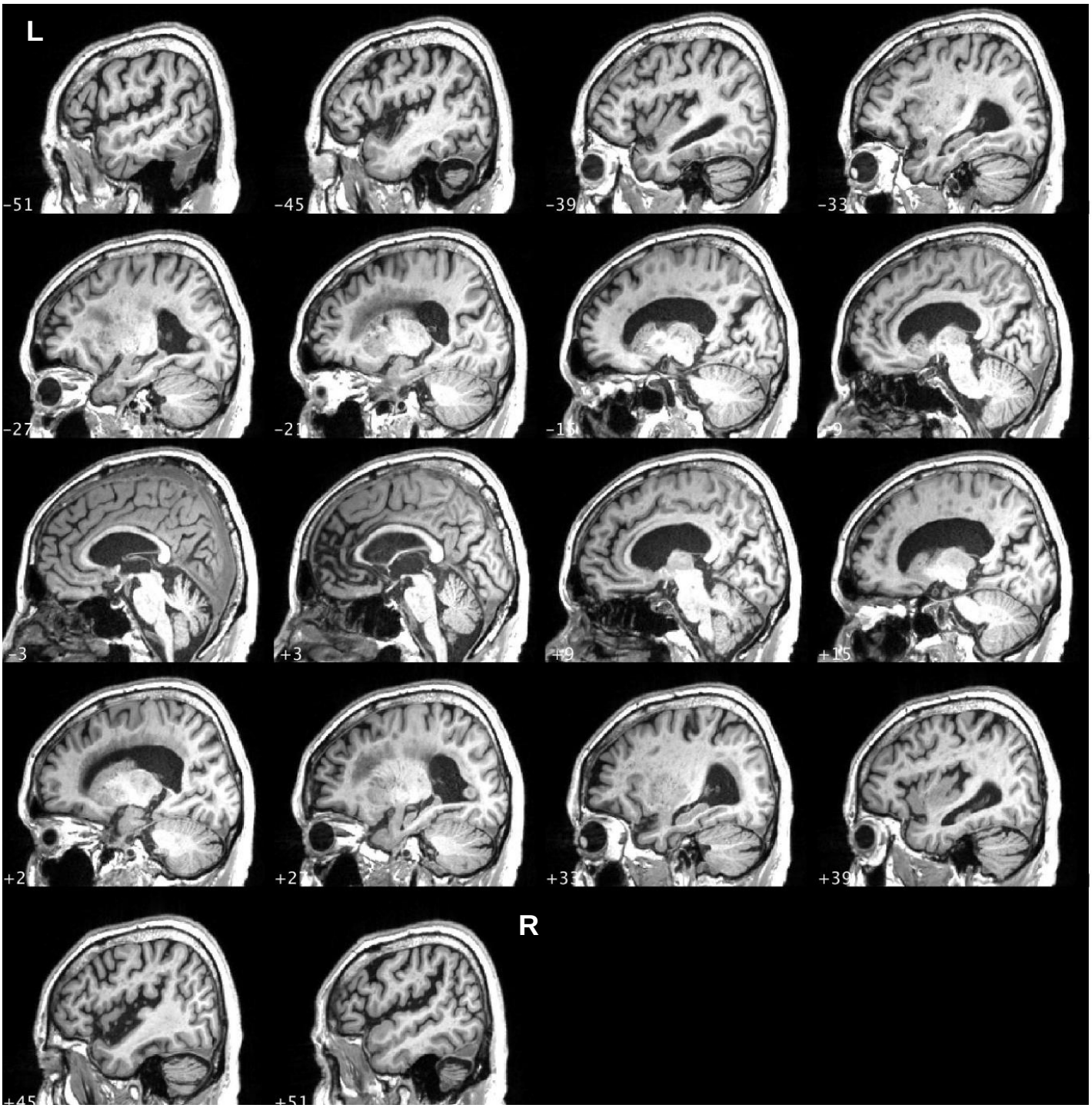
Patient #6
Neuropathology: No CTE, PART, vascular brain injury, limbic AGD, ARTAG

Coronal T1-weighted MRI (scan age: 81, age at death: 81)



Patient #6
Neuropathology: No CTE, PART, vascular brain injury, limbic AGD, ARTAG

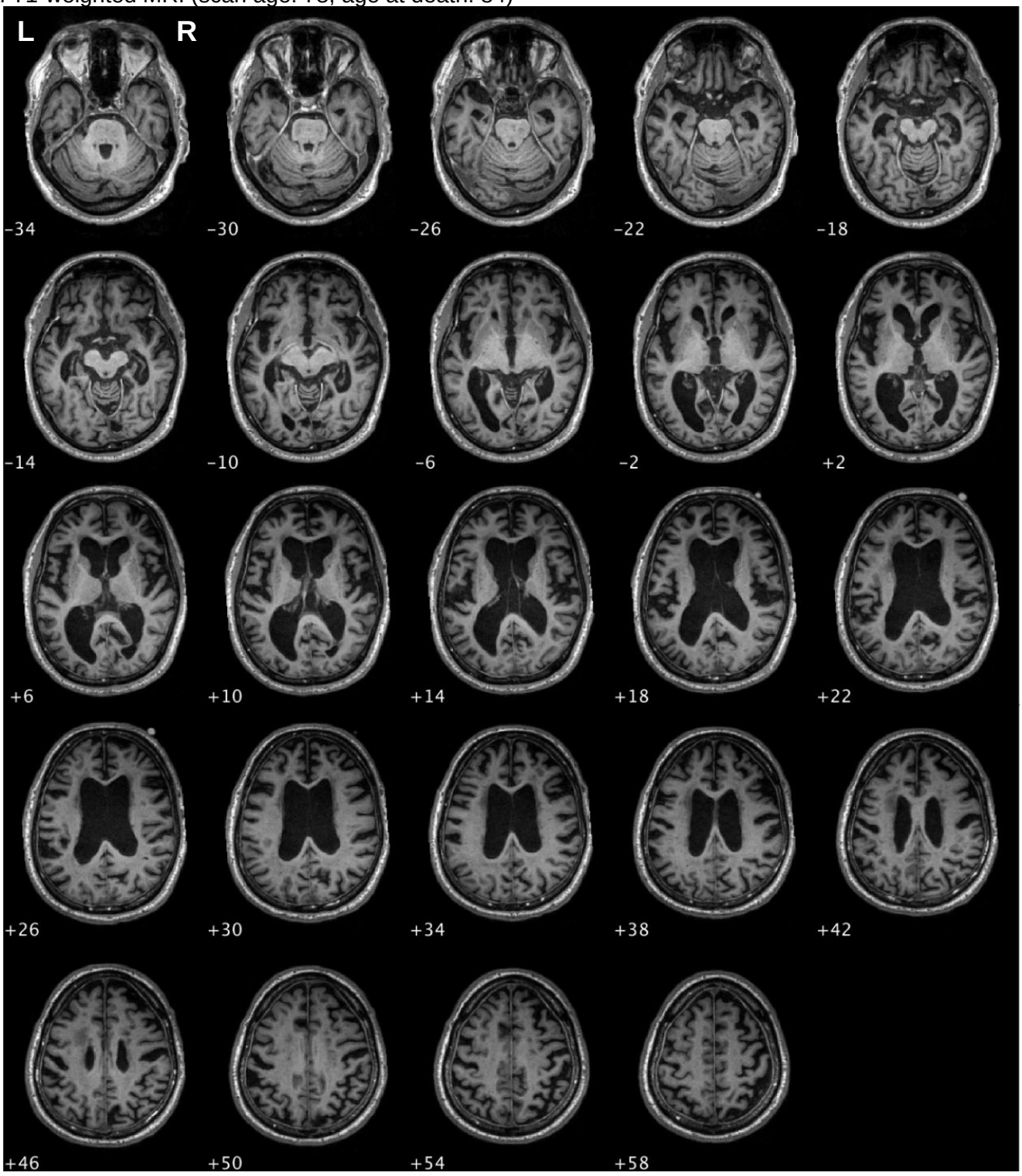
Sagittal T1-weighted MRI (scan age: 81, age at death: 81)



Patient #7

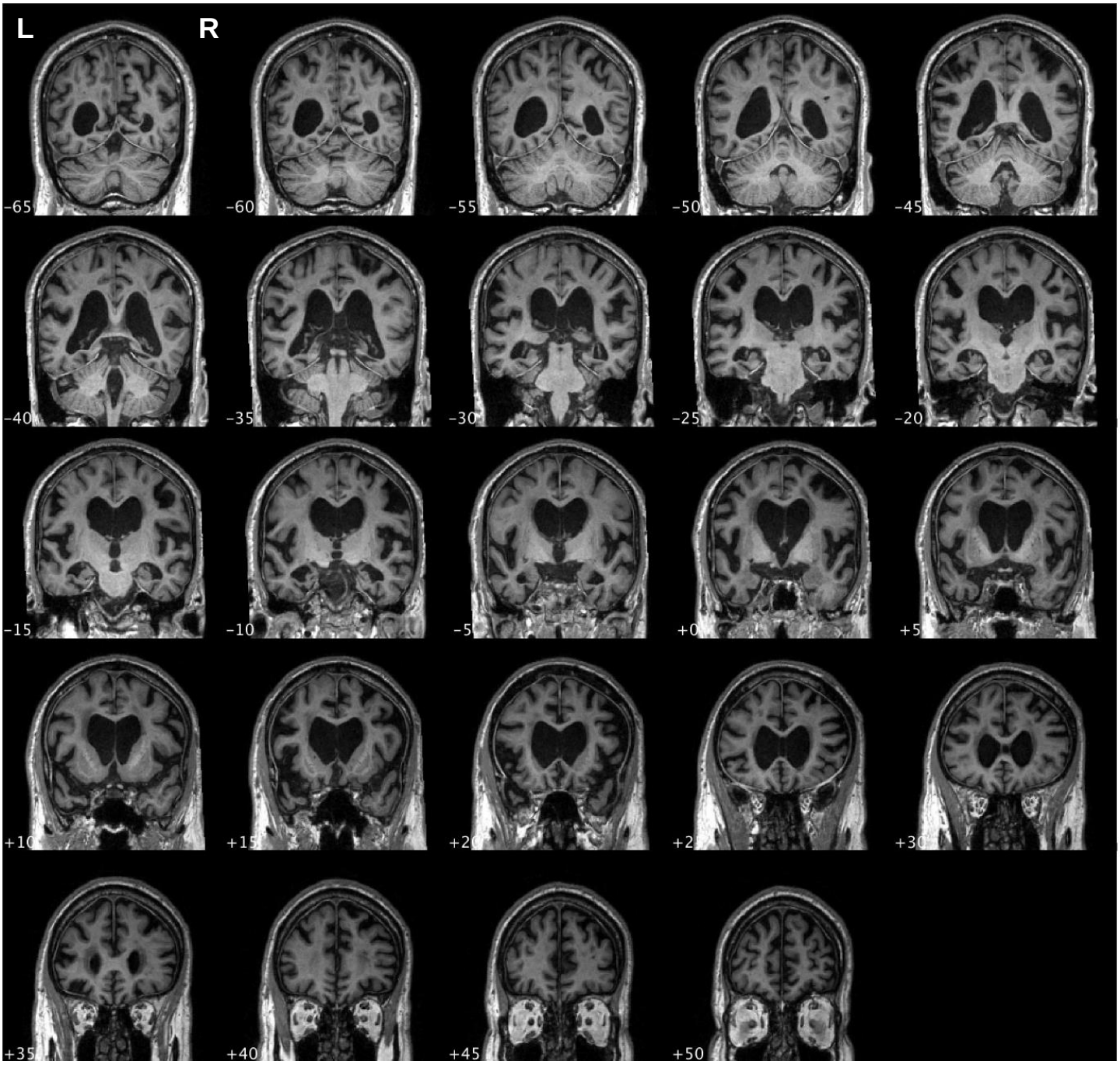
Neuropathology: High CTE (McKee Stage III), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, limbic AGD, mild arteriolosclerosis, Lewy body disease (Braak IV), subdural hematoma, white matter rarefaction

Axial T1-weighted MRI (scan age: 78, age at death: 84)



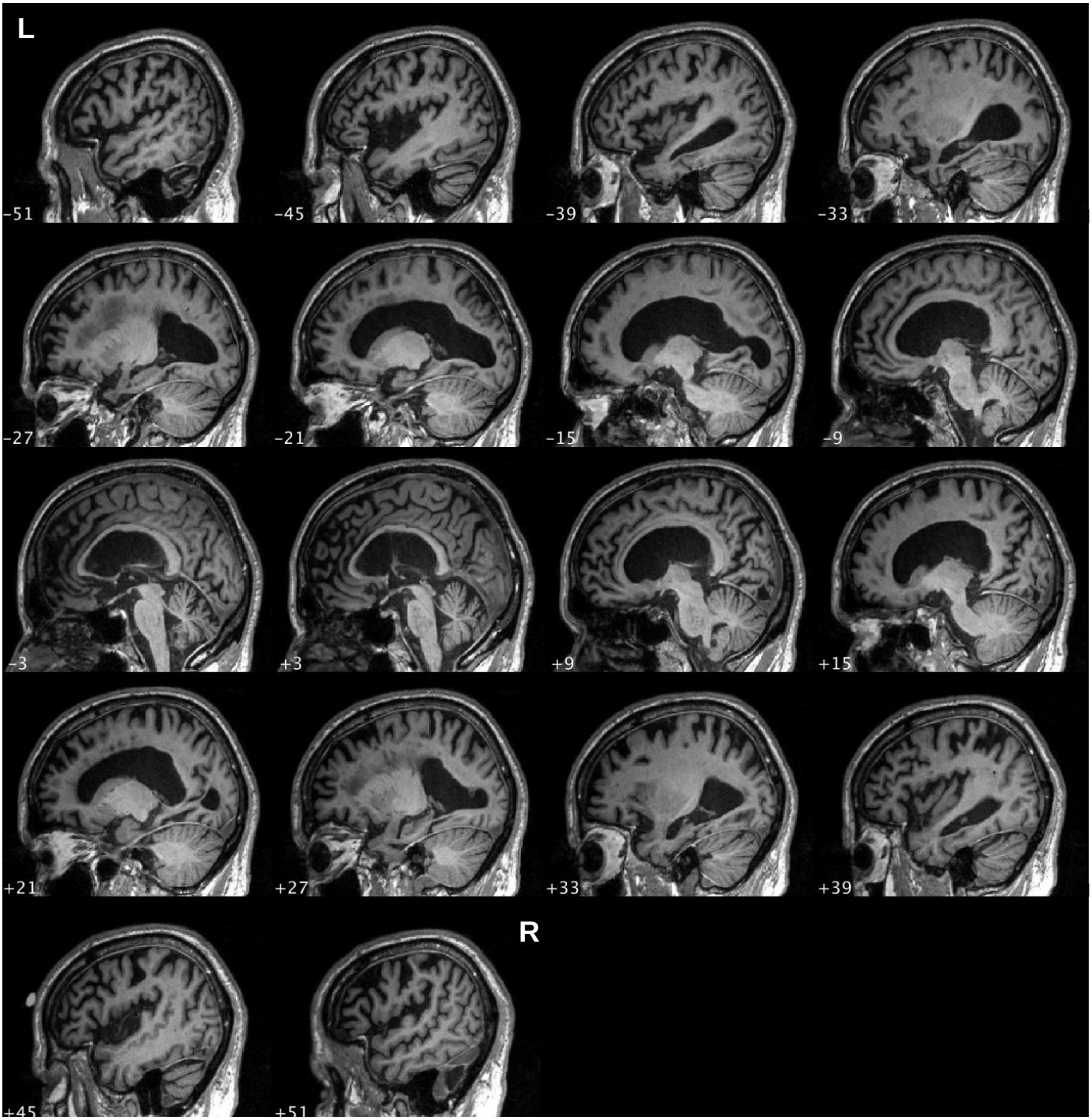
Patient #7
Neuropathology: High CTE (McKee Stage III), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, limbic AGD, mild arteriolosclerosis, Lewy body disease (Braak IV), subdural hematoma, white matter rarefaction

Coronal T1-weighted MRI (scan age: 78, age at death: 84)



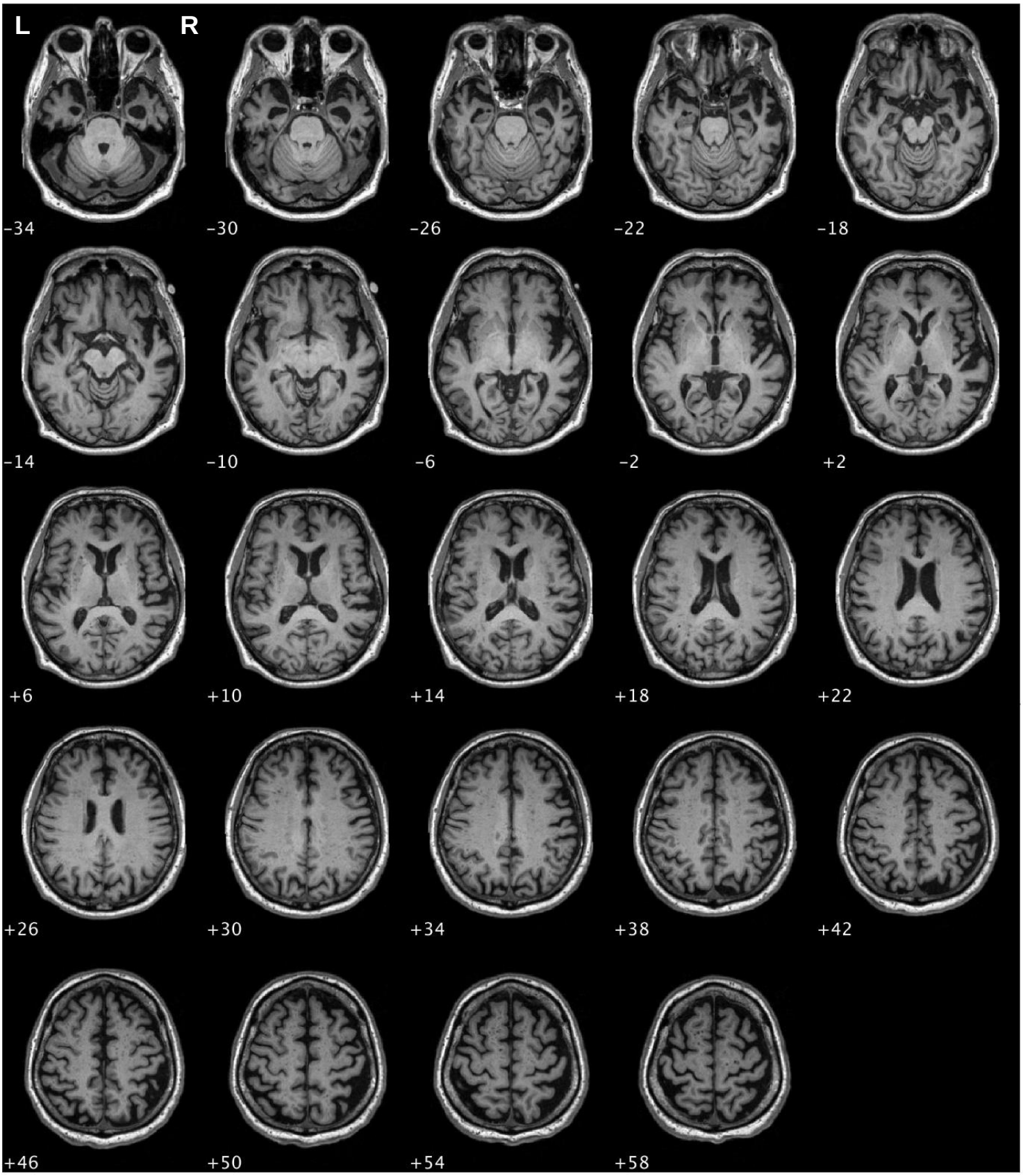
Patient #7
Neuropathology: High CTE (McKee Stage III), High ADNC (A3B3C3), limbic TDP-43 with hippocampal sclerosis, limbic AGD, mild arteriolosclerosis, Lewy body disease (Braak IV), subdural hematoma, white matter rarefaction

Sagittal T1-weighted MRI (scan age: 78, age at death: 84)



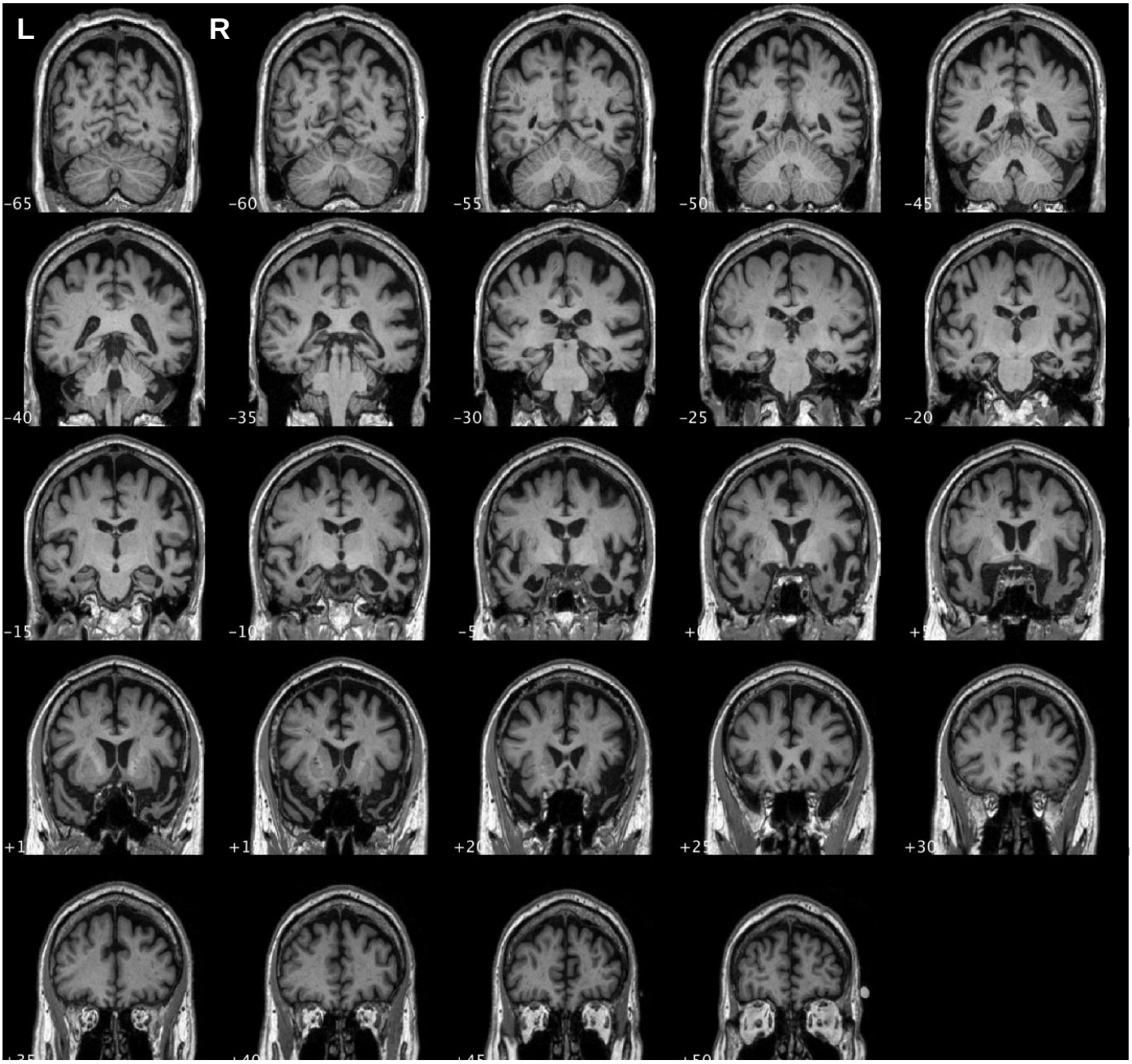
Patient #8
Neuropathology: No CTE, FTLD TDP-43 Type C, focal traumatic tau astrogliopathy, limbic AGD, thalamic infarcts, moderate arteriolosclerosis, Low ADNC (A1B2C1)

Axial T1-weighted MRI (scan age: 65, age at death: 70)



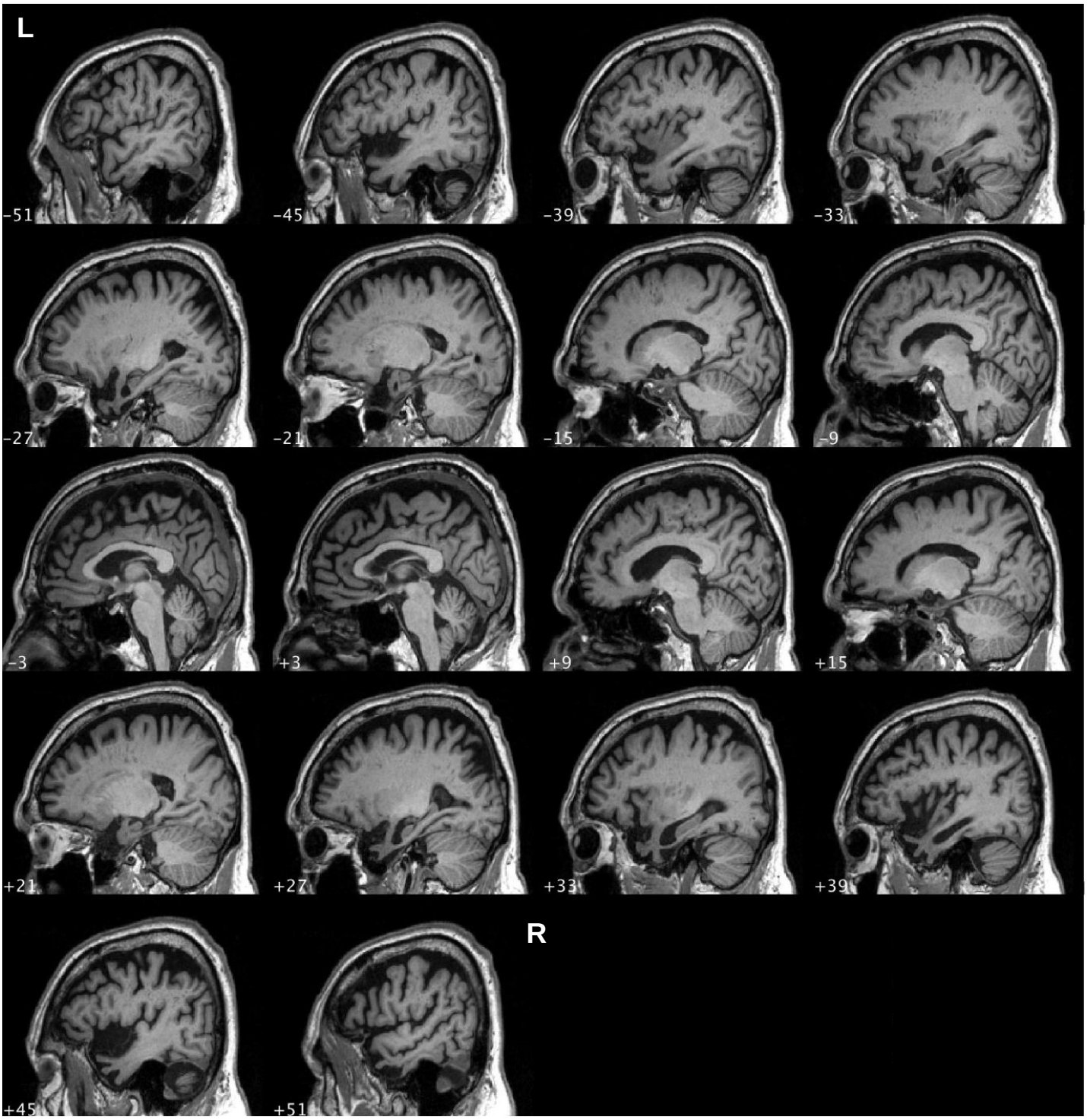
Patient #8
Neuropathology: No CTE, FTLD TDP-43 Type C, focal traumatic tau astrogliopathy, limbic AGD, thalamic infarcts, moderate arteriolosclerosis, Low ADNC (A1B2C1)

Coronal T1-weighted MRI (scan age: 65, age at death: 70)



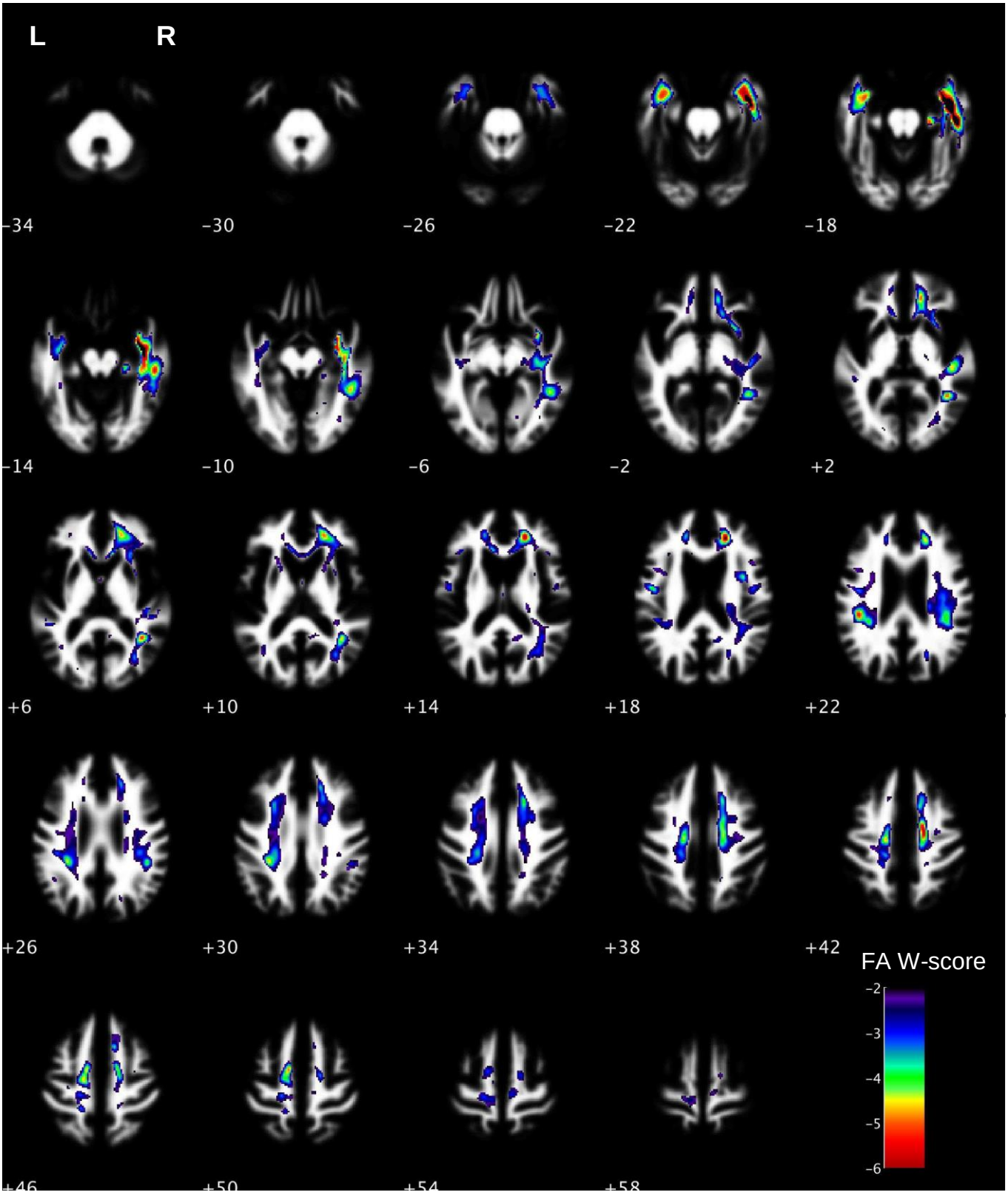
Patient #8
Neuropathology: No CTE, FTLD TDP-43 Type C, focal traumatic tau astrogliopathy, limbic AGD, thalamic infarcts, moderate arteriolosclerosis, Low ADNC (A1B2C1)

Sagittal T1-weighted MRI (scan age: 65, age at death: 70)



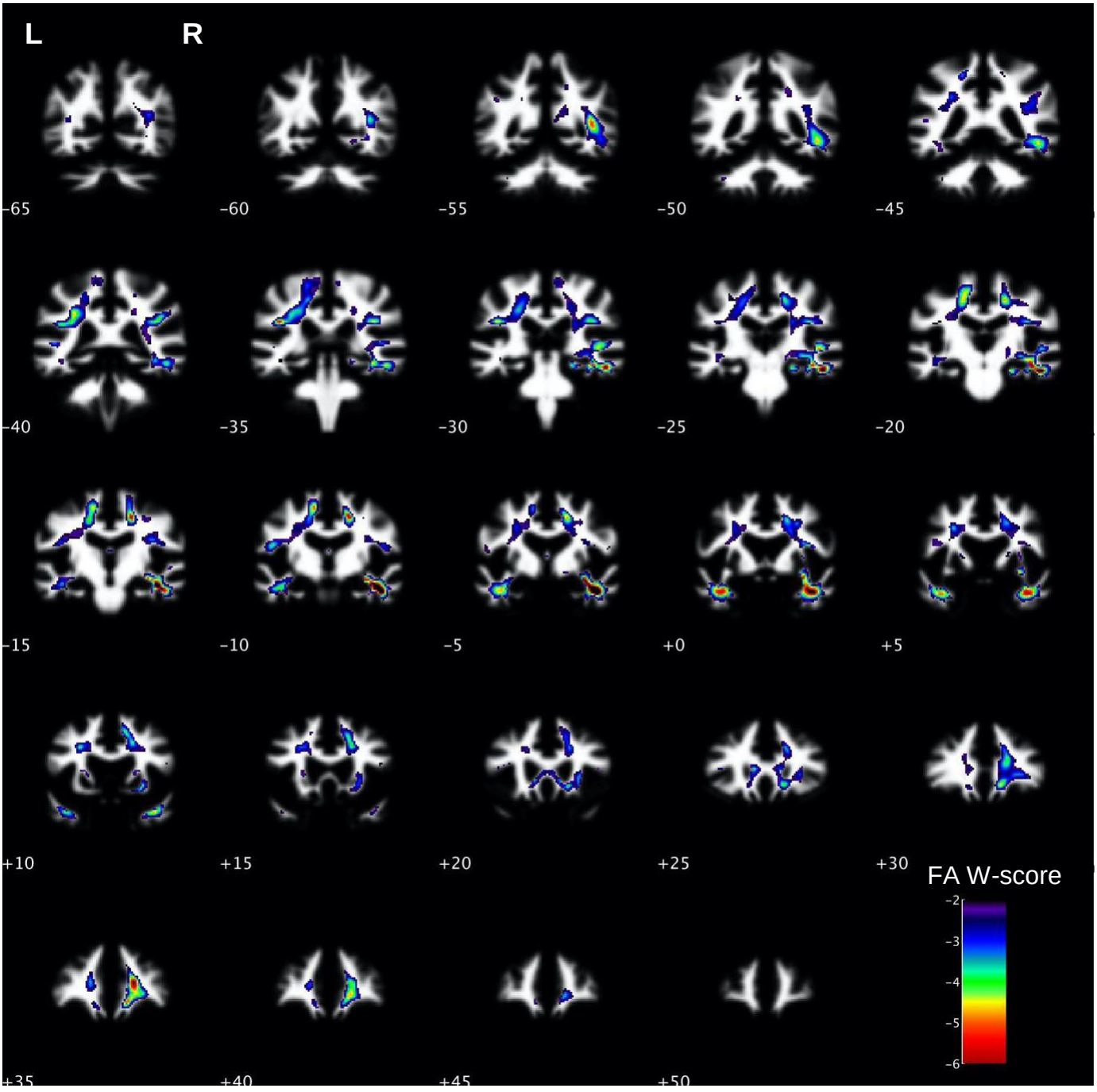
Patient #8
Neuropathology: No CTE, FTLD TDP-43 Type C, focal traumatic tau astrogliopathy, limbic AGD, thalamic infarcts, moderate arteriolosclerosis, Low ADNC (A1B2C1)

Axial DTI – FA W-map (scan age: 65, age at death: 70)



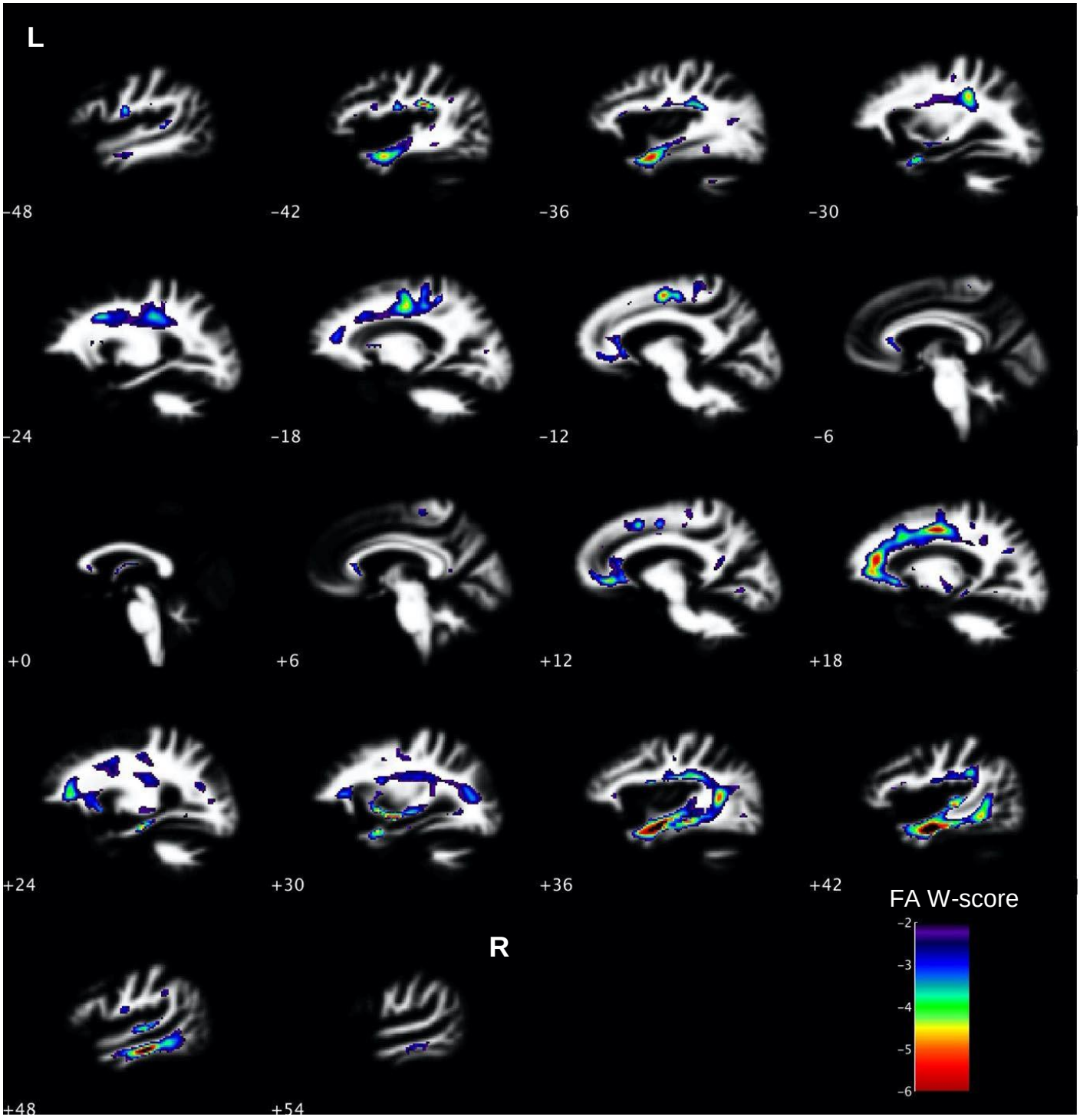
Patient #8
Neuropathology: No CTE, FTLD TDP-43 Type C, focal traumatic tau astrogliopathy, limbic AGD, thalamic infarcts, moderate arteriolosclerosis, Low ADNC (A1B2C1)

Coronal DTI – FA W-map (scan age: 65, age at death: 70)



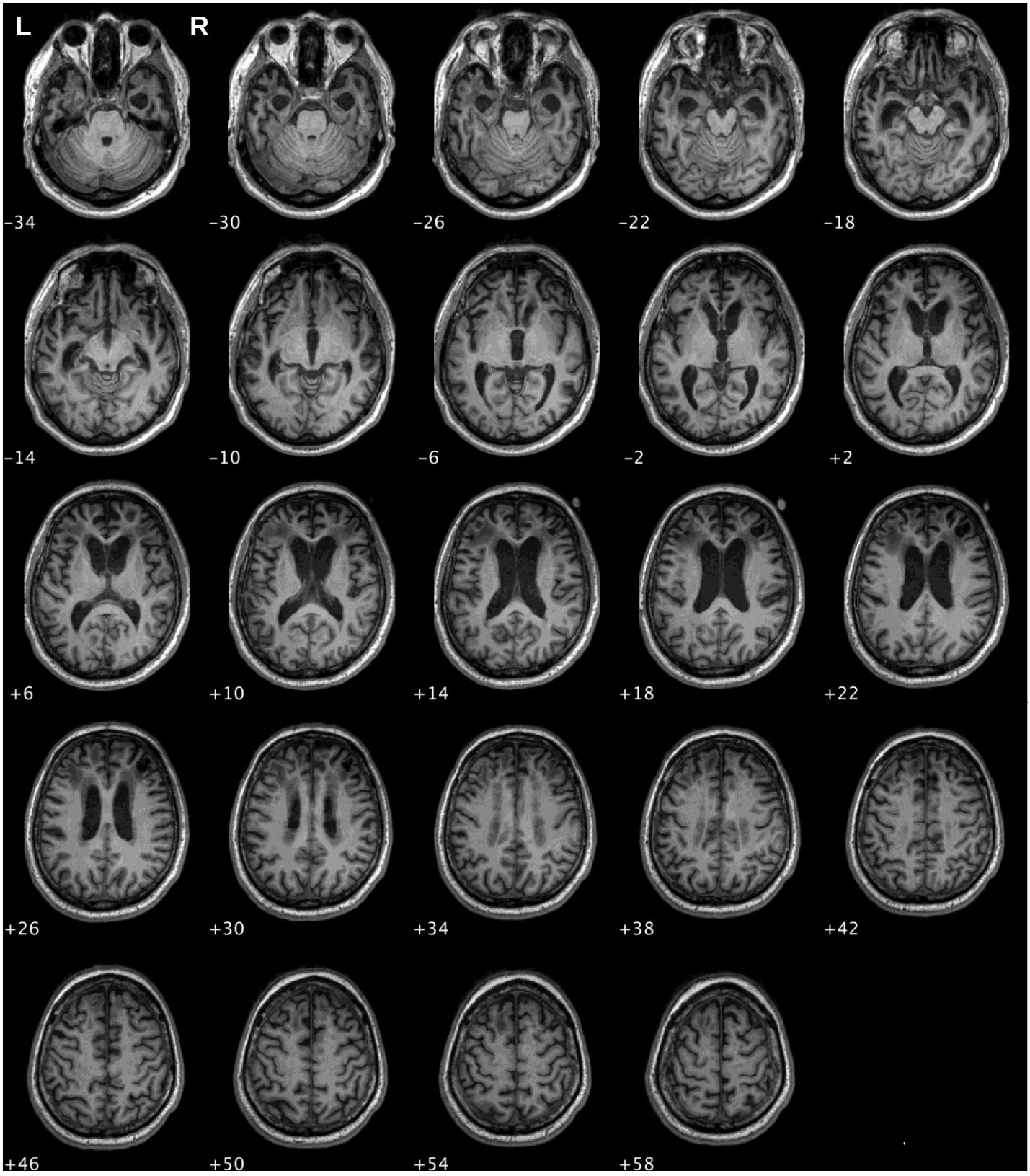
Patient #8
Neuropathology: No CTE, FTLD TDP-43 Type C, focal traumatic tau astrogliopathy, limbic AGD, thalamic infarcts, moderate arteriolosclerosis, Low ADNC (A1B2C1)

Sagittal DTI – FA W-map (scan age: 65, age at death: 70)



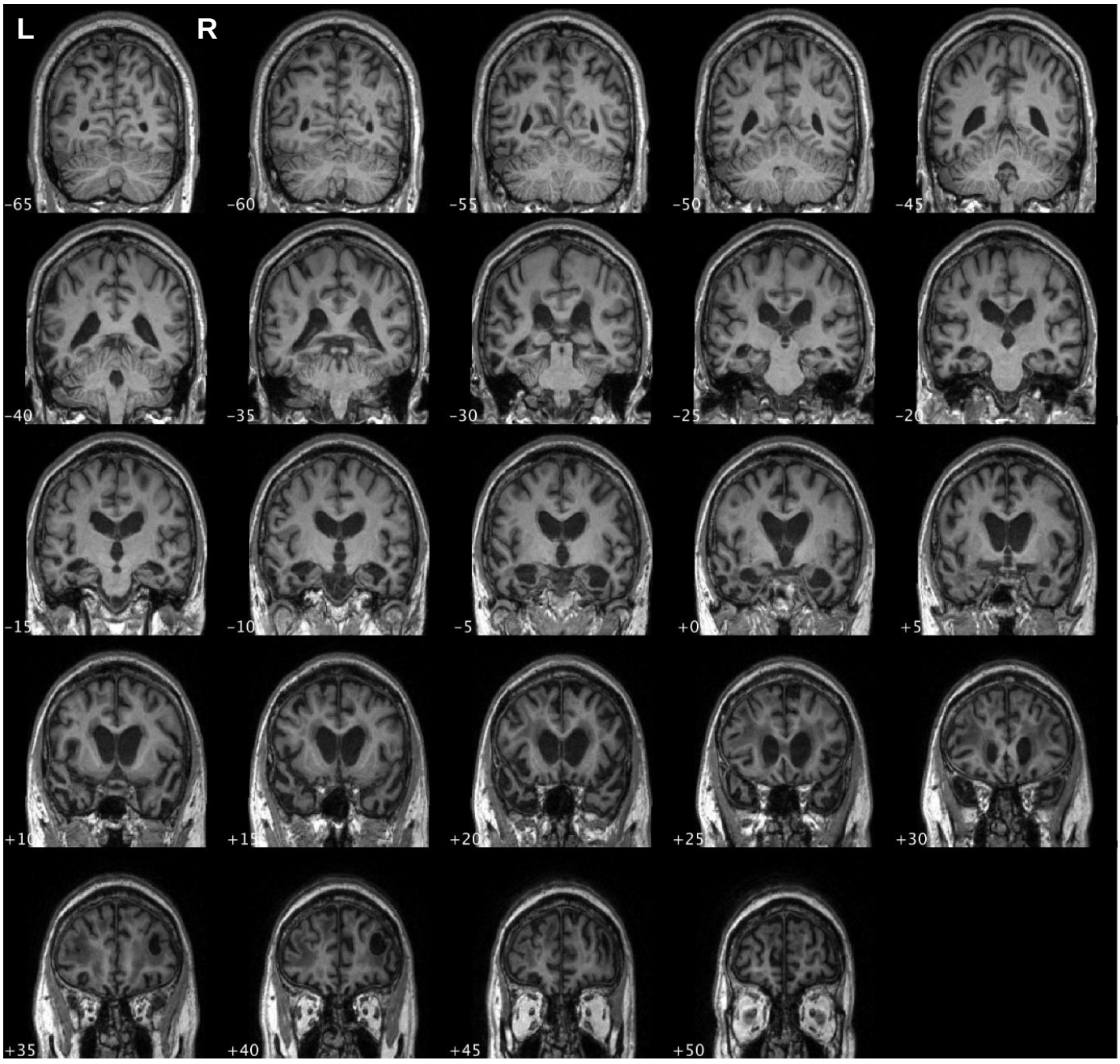
Patient #9
Neuropathology: High CTE (McKee Stage IV), FTLD TDP-43 Type B with MND, limbic AGD, mild arteriolosclerosis, ARTAG, ATAC

Axial T1-weighted MRI (scan age: 57, age at death: 59)



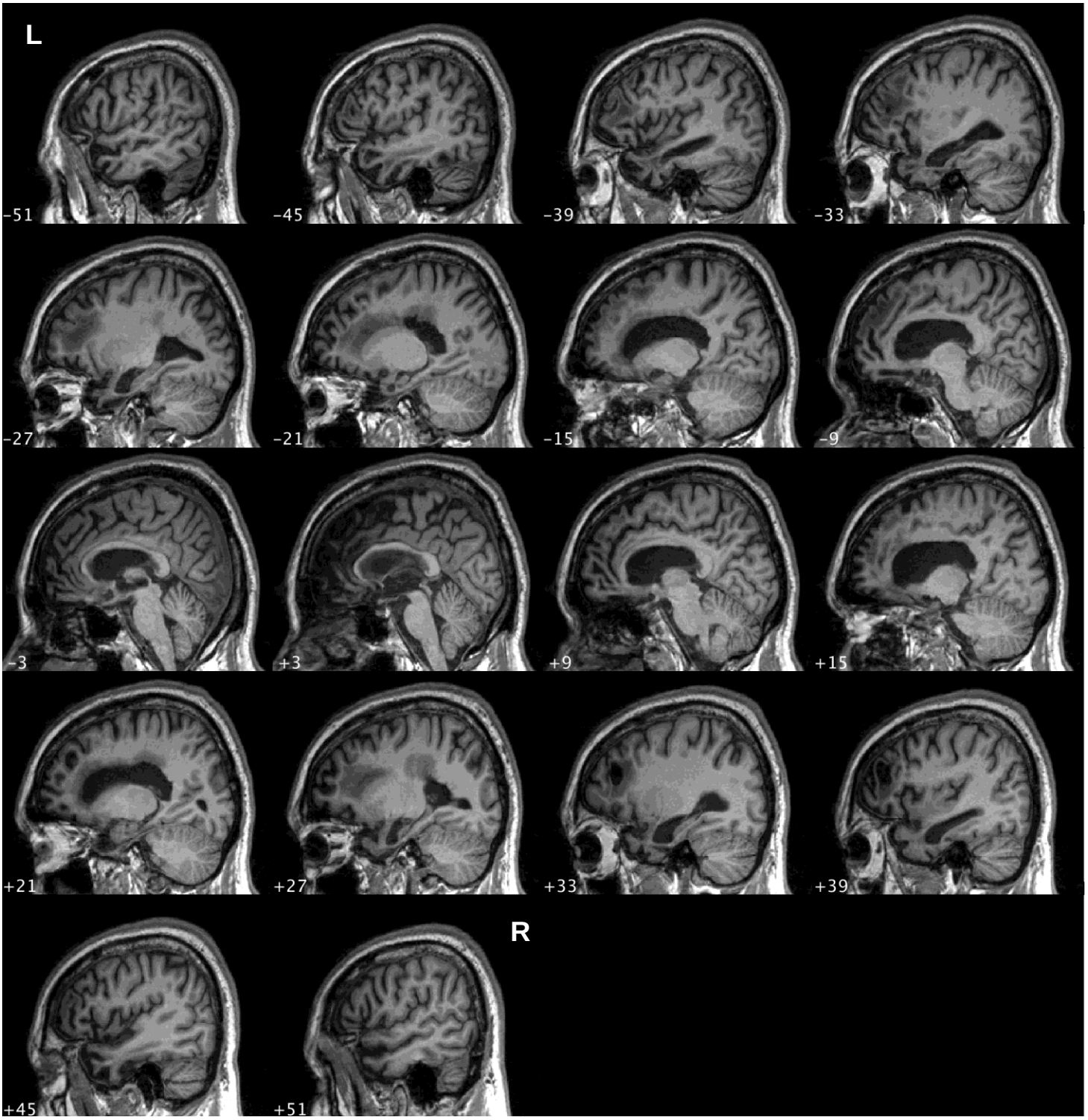
Patient #9
Neuropathology: High CTE (McKee Stage IV), FTLD TDP-43 Type B with MND, limbic AGD, mild arteriolosclerosis, ARTAG, ATAC

Coronal T1-weighted MRI (scan age: 57, age at death: 59)



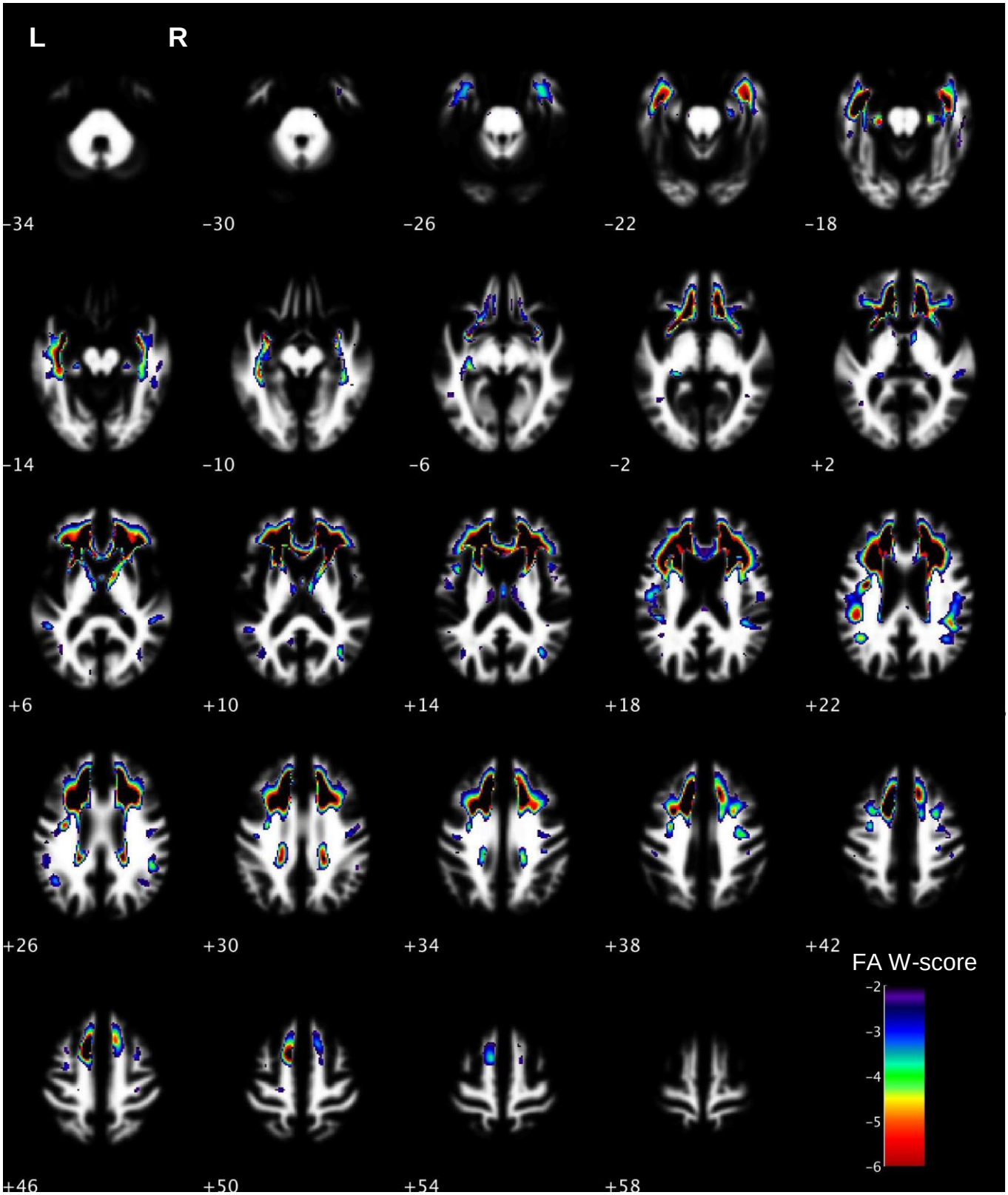
Patient #9
Neuropathology: High CTE (McKee Stage IV), FTLD TDP-43 Type B with MND, limbic AGD, mild arteriolosclerosis, ARTAG, ATAC

Sagittal T1-weighted MRI (scan age: 57, age at death: 59)



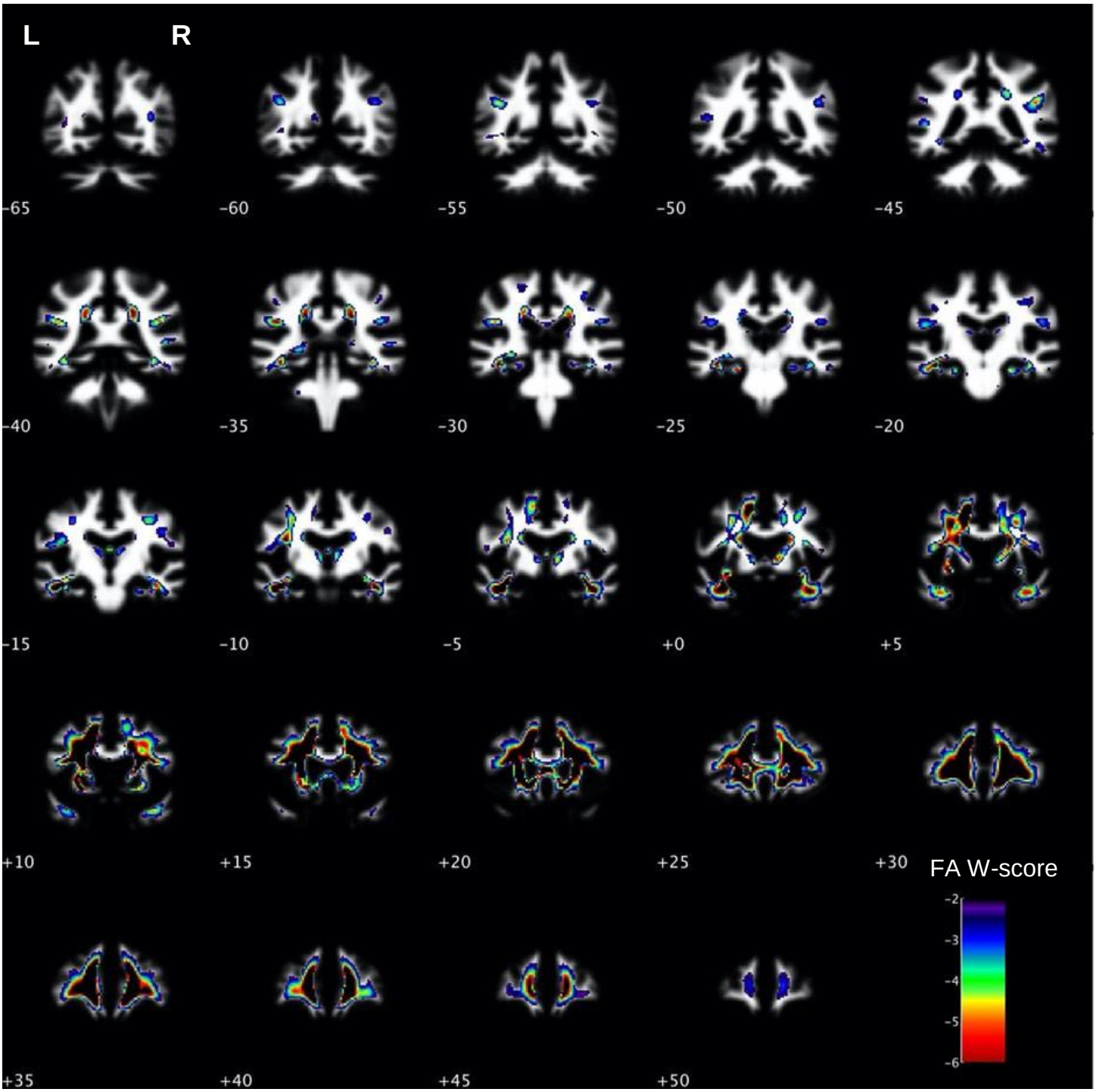
Patient #9
Neuropathology: High CTE (McKee Stage IV), FTLD TDP-43 Type B with MND, limbic AGD, mild arteriolosclerosis, ARTAG, ATAC

Axial DTI – FA W-map (scan age: 56, age at death: 59)



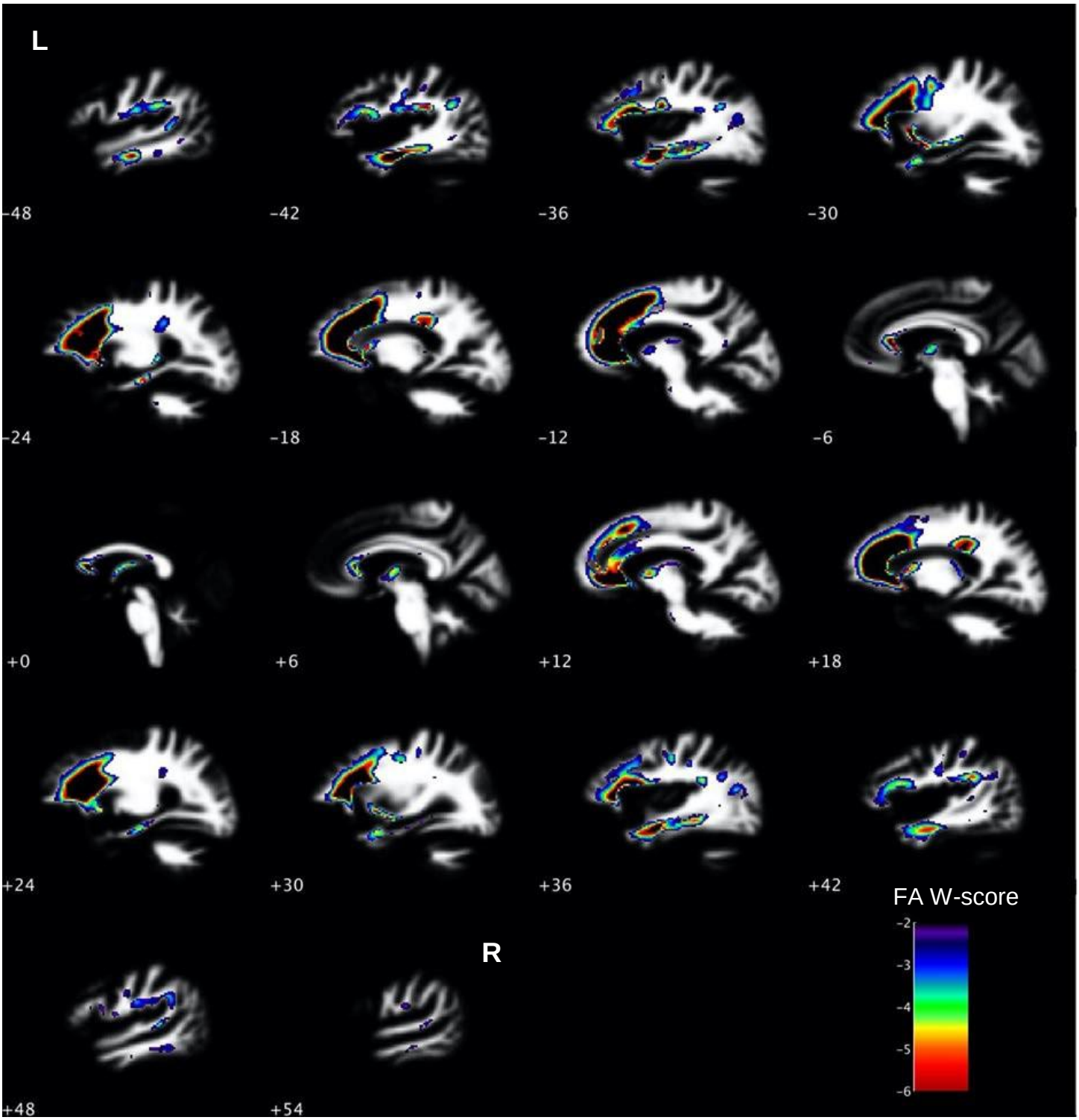
Patient #9
Neuropathology: High CTE (McKee Stage IV), FTLD TDP-43 Type B with MND, limbic AGD, mild arteriolosclerosis, ARTAG, ATAC

Coronal DTI – FA W-map (scan age: 56, age at death: 59)



Patient #9
Neuropathology: High CTE (McKee Stage IV), FTLD TDP-43 Type B with MND, limbic AGD, mild arteriolosclerosis, ARTAG, ATAC

Sagittal DTI – FA W-map (scan age: 56, age at death: 59)



Patient #9
Neuropathology: High CTE (McKee Stage IV), FTLD TDP-43 Type B with MND, limbic AGD, mild arteriolosclerosis, ARTAG, ATAC

FDG-PET (scan age: 55, age at death: 59)