White Matter Degeneration after Ischemic Stroke: A Longitudinal Diffusion Tensor Imaging Study

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Keywords: Ischemic stroke, diffusion tensor imaging, National Institutes of Health Stroke Scale, white matter degeneration.

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jon.12556.

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Acknowledgments and disclosures: no conflicts of interest

Abstract

Background and purpose: Degeneration of gray matter and subcortical structures after ischemic stroke has been well described. However, little is known about white matter degeneration after stroke. It is unclear whether white matter degeneration occurs throughout the whole brain, or whether patterns of degeneration occur more in specific brain areas.

Methods: We prospectively collected National Institutes of Health Stroke Scale (NIHSS) scores and diffusion tensor imaging (DTI) in patients with acute ischemic stroke within the first week after onset (baseline), and at 1 and 3 months. DTI was processed to produce maps of fractional anisotropy, apparent diffusion coefficients, and axial and radial diffusivity. DTI parameters in specified regions-of-interest corresponding to items on the NIHSS were calculated and changes over time were assessed using linear mixed-effect modeling.

Results: Seventeen patients were included in the study. Mean age (SD) was 71 (11.7) years, and median (IQR) baseline NIHSS 9 (5-13.3). Changes over time were observed in both visual cortices, contralesional primary motor cortex, premotor cortex, and superior temporal gyrus ($P < .05$). Changes in the ipsilesional motor cortex and inferior parietal lobule were only seen in patients with scores on the respective NIHSS-items ($P < .05$). No significant changes in global white matter diffusivity parameters were identified ($P > .05$).

Conclusion: White matter changes after stroke may be localized rather than a global phenomenon.

Introduction

Ischemic stroke leads to structural and functional disruption of neural tissue in the region of infarction, which can result in significant disability.$^{1,2}$ In addition to the localized damage from...
ischemic infarction, secondary processes such as selective neuronal loss and white matter degeneration can occur remote to infarction. Remote degeneration after stroke has been attributed to the inflammatory process elicited in response to ischemia through the upregulation of cytokines, and increased activity of macrophages and glial cells. Neurodegeneration can manifest itself as a loss of gray matter, which has been well characterized. However, studies on white matter changes are limited and have mostly focused on specific tracts within the brain. Data on further remote changes are lacking, and it is therefore not clear whether white matter integrity changes are related to stroke-related deficits or a phenomenon occurring in multiple brain regions, such as global white matter degeneration.

Diffusion tensor imaging (DTI) can be used to measure the integrity of white matter using the parameters of axial diffusivity (AD; diffusion along axon), radial diffusivity (RD; diffusion perpendicular to AD), apparent diffusion coefficient (ADC; mean of AD and RD), and fractional anisotropy (FA; scalar between 0 and 1 representing degree of anisotropy). With DTI, it has been shown that reduced FA of the corticospinal tract is associated with poorer motor performance as well as poorer rehabilitation treatment outcomes after ischemic stroke. These findings indicate that there is a loss of white matter integrity in areas associated with neurological deficits; however, it is currently unclear whether white matter changes are restricted to affected tracts, or whether degeneration of white matter occurs remotely from the lesion as well.

In the current study, we aimed to investigate whether white matter degeneration occurred outside of the primary DWI lesion after ischemic stroke. We quantified white matter DTI parameters in (1) global white matter to assess whether a process of generalized degeneration occurred after stroke, and, to assess whether localized changes in white matter integrity occur after stroke. We also quantified DTI parameters in (2) brain areas with
functions associated with individual items of the National Institutes of Health Stroke Scale (NIHSS), in order to adjust for the presence of neurological deficits.

Methods

Patients

Acute ischemic stroke patients with an anterior circulation vessel occlusion presenting to the Royal Melbourne Hospital (Victoria, Australia) were enrolled in this study and underwent multimodal MRI imaging within 1 week of stroke onset (baseline), and at 1 and 3 months after stroke. Intravenous thrombolysis or endovascular clot retrieval was performed on eligible patients according to the local treatment guidelines. Inclusion criteria for this study were age >18 years, ability to give informed consent (including by a next of kin), no contraindications for MRI scanning, and confirmed ischemic lesion on CT or MRI. A stroke neurologist (NY) assessed clinical stroke severity using the NIHSS at the time of each MRI scan. Additionally, baseline demographics and stroke risk factors were recorded. Written informed consent was obtained from all participants and the study was approved by the Melbourne Health Research Ethics Committee.

Image Acquisition and Analysis

All scans were performed on a clinical 3T MRI scanner (MAGNETOM Trio, Siemens, Erlangen, Germany). For each subject, a high-resolution T1-weighted anatomical image (TR = 1,900 milliseconds, TE = 2.82 milliseconds, inversion time = 900 milliseconds, flip angle = 8°, FOV = 512 × 512 × 192, and voxel size = .5 × .5 × 1 mm) was obtained. Diffusion weighted images were acquired (TR = 9,200 milliseconds, TE = 95, flip angle = 90°, FOV voxel size = 2.03 × 2.03 × 2 mm) using a multidirectional (64) diffusion-weighted sequence and consisted of 1 b0 image and 64 b1000 images. All images of participants with a left hemispheric stroke were reoriented to standardize the lesioned hemisphere.
Imaging analysis was performed using the Functional Magnetic Resonance Imaging of the Brain software library (FSL; version 5.2, Oxford, UK), mrtrix3 (version 3.0, Melbourne, Australia), Statistical Parametric Mapping (SPM; version 12, London, UK), and Advanced Normalization Tools. DWI images were de-noised, corrected for motion, eddy-current, and B0 inhomogeneities using mrtrix3’s dwidenoise, dwipreproc, and dwibiascorrect, respectively. To delineate changes in white matter and gray matter, MPRAGE images were segmented using SPM12’s segment. Resulting white and gray matter maps were registered to the DWI images using FSL’s FMRIB’s Linear Registration Tool, and subsequently binarized at a .5 threshold to create respective matter masks. We visually checked segmentation and registration results to ensure their quality. Lesions were manually drawn on the DWI b1000 images at baseline and were registered to the DWI volumes obtained at 1 and 3 months post-stroke.

Subsequently, a diffusion tensor model was obtained. Diffusion tensor modeling of DWI imaging produces three eigenvalues and three orthogonal eigenvectors that describe the direction of diffusion in 3D-space for each voxel, where eigenvalues represent the amount of diffusion and the eigenvectors the direction of diffusion. The eigenvector with the largest magnitude represents AD, whereas the smaller eigenvalues represent the radial diffusivities. The ADC is defined as the average of the three eigenvalues. RD is the average value of the two eigenvalues perpendicular to the eigenvalue that represents AD. FA is a scalar that can range from 0 to 1 and represents a combination of three diffusion coefficients. Lesioned areas were masked in further analysis, so that mean DTI parameter-values represent the diffusivity of nonlesioned brain tissue (Fig 1).

*Study Analysis: NIHSS-Items and Regions-of-Interest*

Patients were categorized into two groups according to their NIHSS-score for each item. Participants with a score of 0 on an NIHSS item were placed in the NIHSS-negative group.
and participants scoring ≥1 in the NIHSS-positive group. Due to poor reliability or redundancy of the measurements, the items level of consciousness (1), ataxia (7), facial palsy (4), and dysarthria (10) were not included in the analysis. Motor leg (6) was included over motor arm (5), as the proportion of NIHSS-negative patients for the latter item did not allow for a valid statistical analysis.

We prespecified specific ROIs of interest based on the neuro-anatomical function of brain areas that are associated with NIHSS-items. Included ROIs were the visual cortex (item 3; visual), the motor cortex and premotor cortex (PMC) (items 6; motor leg), the somatosensory cortex (item 8: sensory), Brodmann’s areas 44/45 and the superior temporal gyrus (item 9; best language), and the inferior parietal lobule (IPL) (item 11; inattention and extinction).

ROI location was defined using the probability maps of Oxford Anatomical Atlases and the Juelich Anatomical Atlas as integrated in FSLeyes. ROI-probability maps were thresholded at 30% to create binary masks for each ROI. To transform the ROI-masks to DWI-space, we used rotation matrices and warp coefficients from the registration of the MNI-template to the DWI b0-volume obtained using AntsRegistration. To facilitate this registration, DWI lesion masks were included.

We chose to use ROI templates in this study as it was shown that a template of the corticospinal tract yielded similar correlations with motor impairment after stroke in comparison with a tractography approach. This suggests that using a standardized and automated approach with ROI templates can detect associations with clinical outcomes.

Statistical Analysis

Statistical analysis was performed using R (version 3.4.3). Descriptive statistics were used to characterize the patient cohort and are presented with the mean and standard deviation.
unless stated otherwise. To assess changes over time in DTI parameters, we used mixed effect models with time, group (NIHSS-negative and NIHSS-positive) and the time*group interaction as fixed effects and subject as a random effect. DTI parameters have shown to be dependent on factors such as age and physical fitness, and therefore we modeled individual intercepts as a random effect. We examined the residuals of the fitted model to assess the assumptions for linear modeling (heteroscedasticity and normal distribution of the residuals). Two outliers were removed from the data, as due to their presence assumptions of the models were violated. This did not, however, affect our main results. We performed post-hoc analyses to identify significant differences after a main effect was identified. P-value for ROI diffusivity changes was adjusted for multiple comparisons (indicated as $P_{corr}$) using the Tukey method.

Results

During the study period, 20 participants were recruited. One participant was excluded due to a malignant MCA infarction requiring decompressive craniectomy (affecting coregistration) and one due to missing DWI scans at two time points. Three participants completed the 3-month clinical assessment but withdrew from MRI scanning, but were included as they completed one follow-up scan.

The 18 included stroke patients had a mean age of $71.0 \pm 11.65$, 6 (66.7%) were female, and 9 participants (50%) had a stroke originating in the left hemisphere. Thirteen patients received tissue plasminogen activator (tPA), two received a carotid endarterectomy in addition to tPA, and one received endovascular treatment after tPA. Baseline scans were performed at $68.6 \pm 38.5$ hours after stroke onset and were performed after patients received their respective treatments (median time between treatment and MRI: 61 hours; IQR = 19.8-74). Median baseline DWI lesion volume was 10.3 (IQR = 4.65-27.75).
Participants had a median baseline NIHSS of 9 (IQR = 5-13.3), and a median 24-hour NIHSS of 3 (IQR = 1.25-3). At admission, 7 (38.9%) of the participants had visual field deficits, 11 (61.1%) had motor deficits of the arm, 9 (50%) had motor deficits of the leg, 11 (61.1%) had sensory deficits, 8 (44.4%) had language deficits, and 9 (50%) had inattention and extinction. At 1 month after stroke, six participants had residual NIHSS-scores of three (N = 1), two (N = 8), and one (N = 2). At 3 months, one participant had a residual NIHSS-score of three, two participants had a residual score of two, and three participants had a score of one.

**Global White Matter Changes**

Total white matter FA, ADC, AD, and RD did not change significantly over time (FA: F = .140, P = .870; ADC: F = .229, P = .780, AD: F = 1.320, P = .282; and RD: F = .211, P = .811; Table 1).

**Ipsilesional ROI Changes**

Mixed-effect modeling showed a main effect of time in the ADC-values of the ipsilesional primary visual cortex (F = 4.423, P = .021). ADC-values were significantly lower at 3 months after stroke onset compared to baseline (t = 2.66, P<sub>corr</sub> = .033; Fig 2).

Within the primary motor cortex (M1), ipsilesional ADC-values significantly decreased from baseline to 1 month after stroke in the NIHSS-positive group for motor leg (t = 3.22, P<sub>corr</sub> = .034). No significant changes were observed in the NIHSS-negative group and there was no main effect of group or time (Fig 3).

In the IPL, there was a significant interaction effect for the ADC-values between group and time (F = 3.695, P = .038). Post-hoc analysis showed that there was a significant increase in ADC-values from baseline to 3 months after stroke in the NIHSS-positive group (t
The main effect of time \((F = 4.346, P = .023)\) was not reproduced in post-hoc analysis \((P_{\text{corr}} > .05)\). RD-values of the IPL significantly changed over time \((F = 5.002, P = .014)\), with post-hoc analysis showing a significantly higher RD at 3 months after stroke compared to baseline \((t = 2.78, P_{\text{corr}} = .025)\) and compared to 1 month after stroke \((t = 2.78, P_{\text{corr}} = .025; \text{Fig 4})\). No further differences were observed in any of the other DTI parameters in the ipsilesional hemisphere \((P > .05; \text{Table 2})\).

**Contralesional ROI Changes**

In the primary visual cortex, there was a significant main effect of time for FA \((F = 4.927, P = .014)\), ADC \((F = 4.172, P = .026)\), and RD-values \((F = 4.986, P = .014)\). At 3 months after stroke, FA was significantly higher \((t = 3.36, P_{\text{corr}} = .006)\), and ADC and RD were significantly lower \((t = 3.28, P_{\text{corr}} = .002\) and \(t = 3.12, P_{\text{corr}} = .011\), respectively) compared to baseline (Fig 2).

In primary motor cortex (M1) and PMC, temporal changes in ADC were observed \((M1: F = 3.717, P = .037; \text{PMC: } F = 4.329, P = .023)\). ADC-values were significantly lower at 3 months after stroke compared to baseline in both ROIs \(M1: t = 2.49, P_{\text{corr}} = .048; \text{PMC: } t = 2.73, P_{\text{corr}} = .028)\). Additionally, in the PMC, RD was significantly decreased at 3 months compared to baseline \((t = 2.90, P_{\text{corr}} = .019)\). In M1, there was an interaction effect between group and time in regard to AD \((F = 5.510, P = .010)\), as in the NIHSS-positive group, AD was decreased at 1 month \((t = 4.40, P_{\text{corr}} = .002)\) and 3 months \((t = 3.35, P_{\text{corr}} = .026)\) after stroke compared to baseline (Fig 5).

In the STG, mixed-effect modeling showed a main effect of time in ADC and AD-values \((\text{ADC: } F = 4.499, P = .020; \text{AD: } F = 3.262, P = .040)\), which corresponded to a significant increase in these metrics from baseline to 1 month \(\text{ADC: } t = 3.00, P_{\text{corr}} = .015; \text{AD: } t = 2.55, P_{\text{corr}} = .043)\). Modeling of RD in the STG showed the presence of a significant

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interaction effect, where in the NIHSS-positive group, RD significantly increased from baseline to 1 month after stroke ($t = 3.38, P_{corr} = .025$; Fig 5). Additionally, there was a significant group effect, as FA values were significantly higher in the NIHSS-negative group ($F = 6.479, P_{corr} = .022$).

No significant changes were observed in the contralesional primary sensory cortex, Brodmann's area 44/45, and IPL ($P > .05$; Table 3).

Discussion

We did not demonstrate a change in global white matter integrity at 1 and 3 months after stroke. However, we did identify white matter changes in both ipsilesional and contralesional regions-of-interest in the brain.

Temporal changes in ipsilesional cortical white matter were seen in the primary visual cortex (V1), primary motor cortex (M1), and IPL. M1 and IPL changes were only in the NIHSS-positive groups, which suggests that the observed white matter changes may arise in regions most closely related to the original infarct lesion. In M1 and V1, we observed a decrease in ADC, which is associated with an increase of structural integrity and plasticity. IPL ADC and RD increased with time, which is conversely associated with degradation of white matter; however, good recovery was observed so it is unclear how our findings relate to clinical symptoms, and that region-specific patterns can be observed after stroke. Absence of changes in other ipsilesional brain areas is indicative of stable ipsilesional white matter integrity after in patient with good-to-excellent recovery after stroke.

We did observe contralesional changes in diffusivity in V1, M1, the PMC, and the superior temporal gyrus. Contralesional DTI changes in the motor cortex after stroke have been observed in human and animal studies$^{23,24}$ and correlate with functional motor outcome.$^{25}$ All patients in this study with a deficit on the motor leg item at baseline recovered
by 1 month after stroke, and therefore these changes may reflect neurological recovery. The underlying mechanism may relate to brain activity, which can be assessed using functional MRI. Increased blood oxygen level-dependent (BOLD) signals in the contralesional motor areas are associated with motor recovery.\textsuperscript{26} Additionally, in chronic stroke patients, activation of secondary motor areas was positively correlated with performance in demanding hand tasks as well as damage to the corticospinal tract,\textsuperscript{27} which indicates that the brain recruits contralesional brain areas to compensate for damage to the ipsilesional corticospinal tract. Several studies have shown that BOLD activation is related to structural white matter integrity.\textsuperscript{28} Thus, the contralateral changes observed in this study may reflect a compensatory strategy of the brain.

Contralesional changes may have implications on how DTI parameters should be presented in future studies. DTI parameters can vary between individuals, as it is modulated in response to motor training,\textsuperscript{29} age,\textsuperscript{20} and cardiovascular fitness.\textsuperscript{21} In many stroke studies, DTI parameters are normalized with regard to the contralesional hemisphere. This is done under the assumption that the DTI parameters of the contralesional hemisphere represent the normative values for a given individual. However, if contralesional white matter changes occur as a result of a compensatory strategy or due to degeneration, contralesional values may not be an appropriate representation of normative diffusivity.

DTI changes in V1 indicate that a generalized phenomenon is occurring after ischemic stroke. The increase of FA from baseline to 3 months after stroke suggests an improvement of white matter integrity; however, this finding was not reproduced in other brain areas. The ipsilesional V1 receives arterial supply from the posterior cerebral artery and would therefore be a remote area to middle cerebral artery lesions. It is possible that our observed changes relate to lesions of the optic radiation. There are limited studies comparing longitudinal DTI parameters of stroke patients with and without deficits. It is
therefore difficult to deduce possible mechanisms or implications of this finding. This further highlights the complicated interpretation of DTI data considering the multitude of factors that could contribute to changes in white matter integrity, such as degeneration and compensation. Future studies are needed to dissect processes influencing white matter structure and should address whether DTI can be used to differentiate between processes that influence white matter integrity in the recovering brain after ischemic stroke.

The main limitation of this study is its limited sample size, which may account for the reason that we did not observe differences between NIHSS-groups but did see changes within groups over time. Additionally, we only assessed cortical areas in the current study as they are related to measurable functions. We did not assess changes in subcortical areas, and therefore our findings cannot be extrapolated to subcortical structures, or other white matter structures, such as the corticospinal tract. Understanding the temporal progression DTI parameters in these structures may help to further elucidate white matter changes after ischemic stroke. Included patients showed a good recovery as reflected by the low NIHSS-scores at 1 and 3 months after stroke, and it is therefore likely that reperfusion of the tissue occurred. Future studies are needed to further explore white matter structural changes in patients with different recovery profiles as well as in other brain areas.

In conclusion, we did not find changes in DTI parameters of global white matter in the brain. However, we did observe significant time-dependent changes in ipsilesional and contralesional brain areas. This indicates that cortical white matter changes occur; however, they are limited to the certain brain areas and are not part of global changes in white matter diffusivity. Contralesional hemisphere changes indicate that normalization using the contralesional values may not be optimal.
References


Table 1. Global White Matter DTI Parameters

<table>
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<tr>
<th></th>
<th>FA (adj. mean + SE)</th>
<th>ADC (adj. mean + SE)</th>
<th>AD (adj. mean + SE)</th>
<th>RD (adj. mean + SE)</th>
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<td>3 months after stroke</td>
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<td>1.154 ± .006</td>
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Results from mixed-effect modeling with time as a fixed effect and subject as random effect. No significant changes were observed ($P > .05$). FA = fractional anisotropy; ADC = apparent diffusion coefficient; AD = axial diffusivity; RD = radial diffusivity; adj. mean = adjusted mean; SE = standard error.

Table 2. Ipsilesional DTI Parameters in Regions of Interest
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Results from mixed-effect modeling with time, National Institutes of Health Stroke Scale-item and their interaction (*) as fixed effects and subject as random effect. FA = fractional anisotropy; ADC = apparent diffusion coefficient; AD = axial diffusivity; RD = radial diffusivity; V1 = primary visual cortex; M1 = primary motor cortex; PMC = premotor cortex; S1 = primary somatosensory cortex; BA 44/45 = Brodmann’s area; STG = superior temporal gyrus; IPL = inferior parietal lobule.

Table 3. Contralesional DTI Parameters in Regions-of-Interest

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Results from mixed-effect modeling with time, National Institutes of Health Stroke Scale-item and their interaction (*) as fixed effects and subject as random effect. FA = fractional anisotropy; ADC = apparent diffusion coefficient; AD = axial diffusivity; RD = radial diffusivity; V1 = primary visual cortex; M1 = primary motor cortex; PMC = premotor cortex; S1 = primary somatosensory cortex; BA 44/45 = Brodmann’s area; STG = superior temporal gyrus; IPL = inferior parietal lobule.

Fig 1. Image processing.
(A). Diffusion weighted imaging (DWI)-B0 image, with DWI hyperintensity in parietal cortex; (B): DWI lesion with white matter regions in yellow (obtained from registration of white matter segmentation results of the T1 weighted image), lesion outlined in red, and lesion mirror region in blue; (C): T1 weighted image with segmentation results of white matter; (D): T1 weighted image; (E): fractional anisotropy map; (F): apparent diffusion coefficient map; (G): axial diffusivity; (H): radial diffusivity; (I): overlay of stroke lesions of all included participants in Montreal Neurological Institute space, colors indicate the number of patients with a lesion in each respective voxel.

Fig 2. DTI parameters of the visual cortex.

In the ipsilesional primary visual cortex, a decrease of the apparent diffusion coefficient (ADC) was observed ($t = 2.66$, $P = .033$) at 3 months after stroke onset compared to baseline. Contralesional fractional anisotropy (FA) was significantly increased at 3 months compared to baseline ($t = 3.36$, $P = .006$), and ADC and (radial diffusivity) RDs were significantly decreased at 3 months ($t = 3.28$, $P = .002$ and $t = 3.12$, $P = .011$, respectively).

No interaction effect of group (National Institutes of Health Stroke Scale-negative [NIHSS-negative] and NIHSS-positive) in regard to NIHSS-item 4 (visual) was present ($P > .05$). AD = axial diffusivity.
Ipsilesional apparent diffusion coefficient (ADC)-values of the primary motor cortex (M1) were significantly decreased in the National Institutes of Health Stroke Scale (NIHSS)-positive group (score ≥ 1 on item motor leg) at 1 month after stroke onset compared to baseline ($t = 3.22$, $P = .034$). There was a significant decrease of ADC-values in the contralesional M1, where ADC was lower at 3 months after stroke compared to baseline, when all participants were considered ($t = 2.49$, $P = .048$). Axial diffusivity (AD) was decreased at 1 month after stroke ($t = 4.40$, $P = .002$), and 3 months after stroke ($t = 3.35$, $P = .026$) in the NIHSS-positive group only. FA = fractional anisotropy; RD = radial diffusivity.
In the overall group, contralesional apparent diffusion coefficient (ADC) and axial diffusivity (AD) were significantly increased at 1 month after stroke compared to baseline ($t = 3.00$, $P = .015$ and $t = 2.55$, $P = .040$, respectively). In the National Institutes of Health Stroke Scale (NIHSS)-positive group (score $\geq 1$ on item best language), radial diffusivity (RD) was significantly increased at 1 month compared to baseline ($t = 3.38$, $P = .025$). † indicates a group difference between the NIHSS-positive group and the NIHSS-negative group (score $= 0$ on item best language). Fractional anisotropy (FA) was significantly higher in the NIHSS-negative group (main effect of group: $F = 6.479$, $P = .022$).

Fig 5. DTI parameters of the inferior parietal lobule.

In the National Institutes of Health Stroke Scale (NIHSS)-positive group (score $\geq 1$ on item 11: inattention and extinction), ipsilesional apparent diffusion coefficient (ADC) was significantly higher at 3 months after stroke compared to baseline ($t = 3.15$, $P = .043$). In the overall group, radial diffusivity (RD) was significantly higher at 3 months after stroke than at baseline ($t = 2.78$, $P = .025$) and 1 month after stroke ($t = 2.78$, $P = .025$). FA = fractional anisotropy; AD = axial diffusivity.
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Title:
White Matter Degeneration after Ischemic Stroke: A Longitudinal Diffusion Tensor Imaging Study

Date:
2019-01-01

Citation:

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