Magnetization Transfer Imaging Shows Tissue Abnormalities in the Reversible Penumbra

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Background and Purpose—In the concept of ischemic penumbra, the volume of salvaged penumbra is considered as the volume of FLAIR normalization on follow-up MRI compared with early diffusion and perfusion abnormalities. Using magnetization transfer imaging, very sensitive to macromolecular disruption, we investigated whether FLAIR normalization was a good marker for tissue full recovery.

Methods—We prospectively included 30 patients with acute middle cerebral artery stroke. Diffusion-weighted imaging (DWI) and perfusion-weighted imaging were performed within 12 hours after onset (MRI.1), and the final infarct was documented by MRI with FLAIR and magnetization transfer at 1-month follow-up (MRI.2). We compared magnetic transfer ratio of a normal region with values measured at 1 month (MRI.2) in 4 regions of interest: (1) the initial DWI hypersignal (CORE=DWI_MRI.1); (2) the infarct growth area (infarct growth=FLAIR_MRI.2−DWI_MRI.1); (3) the hypoperfused area that normalized (reversible perfusion abnormalities=perfusion-weighted imaging_MRI.1−FLAIR_MRI.2); and (4) the early DWI abnormalities that normalized (reversible diffusion abnormalities=DWI_MRI.1−FLAIR_MRI.2).

Results—In comparison with values obtained in normal tissue (magnetic transfer ratio =49.8%, SD = 1.9), magnetic transfer ratio at 1 month was significantly decreased in reversible perfusion abnormalities (45.2%, SD = 2.5; P<0.0001) and reversible diffusion abnormalities (43.2%, SD = 2.8; P = 0.0156). It was also markedly reduced, as expected, in the CORE (40.9%, SD = 5.2) and infarct growth regions (43.1%, SD = 2.0).

Conclusions—Magnetic transfer ratio assessed presence of microstructural damages in the MRI-defined salvaged penumbra. This may imply cellular loss and partial infarction. Evaluation of the efficacy of therapies that promote reperfusion or neuroprotection may benefit from this additional information. (Stroke. 2007;38:3165-3171.)

Key Words: acute cerebral infarction ■ incomplete infarct ■ ischemic penumbra ■ magnetization transfer imaging

Ischemic penumbra has been defined as tissue hypoperfused that is at risk for infarction but still salvageable. It is distinguished from the ischemic core, the tissue that is already irreversibly injured even if blood flow is re-established. It is a region of intense interest2,3 because it is the target of recanalization or neuroprotective therapies and the volume of salvaged penumbra calculated on MRI has become one criteria to evaluate the efficacy of thrombolitics and neuroprotective drugs.

MRI can identify the ischemic penumbra with the concept of perfusion/diffusion mismatch.1,4 The region with diffusion abnormalities and normal diffusion imaging (“mismatch”) identifies tissue that is hypoperfused but has not yet experienced advanced bioenergetic failure and represents the penumbra. This simple model is nevertheless only a rough approximation of the ischemic penumbra. Notably, recent publications suggest that diffusion abnormalities overestimate irreversible damage,5,6 with many reports of final infarct volume smaller than the initial diffusion hyperintensity.7–9 On the basis of these findings, penumbra includes not only diffusion/perfusion mismatch but also portions of the initial diffusion abnormality itself.1 Therefore, the volume of salvaged penumbra is considered as the volume of perfusion or even diffusion abnormalities seen on early MRI studies, and normalized on T2 or FLAIR-weighted images obtained at follow-up MRI.

However, such follow-up images only identify gross anatomical changes of cerebral tissue after an acute ischemic event but are not sensitive enough to investigate the microstructural changes present in the “normal” brain tissue located around the final infarct core, ie, in the previous ischemic penumbra. Such abnormalities could be investigated using...
magnetization transfer (MT) imaging. From this MRI sequence, numeric data called MT ratio (MTR) are calculated pixel by pixel and represented as a color-coded map.\(^\text{10}\) MTR gives an indication of the quantity of bound protons present in the tissue, and these are mostly located in the cholesterol-containing membrane lipid bilayer of cells.\(^\text{11}\) Therefore, MTR provides information proportional to the macromolecular content that are different from conventional parameters such as T2. Furthermore, MTR depicts microstructural damage whereas the same region could appear normal using T2.\(^\text{12}\) It is a very robust sequence widely validated, with histological correlations in human and animal studies in multiple sclerosis and several other conditions.\(^\text{13}\)

We hypothesized that ischemic damages could be present in an at-risk region that appears “normal” on follow-up FLAIR imaging and we used MTR as a marker to investigate damage in this “reperfused penumbra”.

**Subjects and Methods**

**Patients**

The 30 patients prospectively included in this study were initially admitted to the emergency neurological ward of the University Hospital Pellegrin, Bordeaux, for a suspected cerebral infarct.

Primary inclusion criteria were as follows: men and women, older than 18 years, with a clinical diagnosis of moderate to severe cerebral infarct (NIHSS between 4 and 20) in the left or right middle cerebral artery territory evolving for 4–12 hours. Noninclusion criteria were: coma, transient ischemic attacks or lacunar syndrome, pregnant or breast-feeding women, or women without a negative pregnancy test, and contraindications to MRI. Written informed consent was obtained from all participants. The study was part of an approved national Research and Clinical Hospital Project called VIRAGE (VIRAGE for “Valeur predictive des paramètres IRM à l’aiguë de l’accident vasculaire cérébral: application à la gestion des essais thérapeutiques”). It was approved by the local research ethics committee.

**MRI Protocol**

Using VIRAGE data, 2 MRI studies were analyzed. The first was performed within 12 hours after the occurrence of stroke symptoms (MRI.1) and the second was performed between days 30 and 45 after the first (MRI.2). The NIHSS was assessed before MRI.1 and Barthel Index and Rankin modified scale before MRI.2. All data were reported on a standardized case report form.

MRI studies were performed on a 1.5-T magnet (Philips Gyroscan; Philips Medical System). MRI.1 protocol included diffusion-weighted images (DWI) and bolus tracking perfusion-weighted images (PWI). MRI.2 included a FLAIR and MT sequences. A 3-dimensional T1 was performed in both MRI studies to allow coregistration. All images were acquired in the anterior commissure–posterior commissure plane.

DWI were performed with a single-shot spin echo planar imaging sequence using the following parameters: 24 slices; slice thickness, 5 mm; TR/TE/TI, 6000 ms/114 ms/matrix, 128 × 128; and field of view, 240 mm. Gradients with 2 different b values (0 and 1000 s/mm\(^2\)) in the x, y, and z axes were used.

PWI were acquired by using the dynamic first-pass bolus tracking method and a single-shot echo planar imaging sequence: 24 slices 40 times every 2 seconds; slice thickness, 5 mm; TR/TE/\(\alpha\), 2000 ms/30 ms/45\(^\circ\); matrix, 128 × 128; and field of view, 240 mm. At the time of the fourth cycle of 24 slices, a dose of 0.1 mmol/kg Gd-DOTA was injected at a rate of 10 mL/s into a peripheral vein through an 18-gauge catheter by using a magnetic resonance-compatible power injector followed by a 10-mL saline flush at 5 mL/s.

For FLAIR sequences we used: 24 slices; thickness, 5 mm; TR/TE/TI, 10 000 ms/110 ms/2380 ms; matrix, 256 × 256; and field of view, 240 mm.

MT studies were obtained with a gradient echo imaging sequence with (\(M_s\)) and without (\(M_0\)) a saturating pulse (bandwidth of 250 Hz): 24 slices; thickness, 5 mm; TR/TE/\(\alpha\), 35 ms/2.3 ms 8\(^\circ\); matrix, 256 × 256; and field of view, 240 mm. Single-shaped radio frequency pulse of 15 ms duration with a flip angle of 520\(^\circ\) and an off-resonance frequency of 1500 Hz were used to get the MT effect.

The 3-dimensional T1 parameters were as follows: 80 slices; thickness, 3.4 mm with a slice gap of –1.7 mm; TR/TE/\(\alpha\), 20 ms/3 ms/30\(^\circ\); matrix, 256 × 256; and field of view, 240 mm.

**Data Processing**

**Maps**

By averaging the images obtained with the 3 diffusion weighting directions (b value of 1000 s/mm\(^2\)), trace diffusion-weighted images were generated for each section.

Concerning PWI, time to peak (TTP) was the only parameter used in this study and refers to the time between the first imaging and the time at which the signal intensity reaches its minimum. A relative TTP delay superior to 4 seconds was chosen to define the area of perfusion abnormalities. This was chosen according to the literature indicating that this delay best identifies penumbral flow. Other parameter maps (relative cerebral blood volume and relative cerebral blood flow) were routinely calculated but not used in this study because the volume of the perfusion impairment was usually considerably more difficult to delineate on these maps than on the TTP one.\(^\text{3}\)

MTR maps were calculated on a pixel-by-pixel basis using the following equation:\(^\text{12}\)

\[
MTR = (M_0 - M_s)/M_0 
\]

Where \(M_0\) and \(M_s\) represent the signal intensity with the saturation prepulse off and on, respectively. MTR represented the percentage of signal loss after the saturation pulse and is proportional to the bound proton pools.\(^\text{10}\)

**Coregistration**

All MRI sequences have been spatially registered using a fully automated 3-dimensional registration algorithm (Theralys). It used mutual information as a similarity measure to assess the goodness of match between the reference volume and the source volume. A rigid 3-dimensional registration was used. According to mutual information and mutual information derivative values, a gradient descent technique was used to iteratively modify the transformation parameters (rotations and translations) to maximize the mutual information.

A multi-resolution, coarse-to-fine strategy was adopted. That is to say, registration started at low resolution and once the convergence is reached, a new iteration is initialized based on the result of the previous step. Such a strategy increases the robustness of the registration algorithm. Results have been quality controlled for each and every processed MRI sequence to detect potential misregistration that may occur for echo planar imaging-based sequences for which geometric distortion may disturb the registration process. In a few cases, the sequence was manually registered to ensure good spatial correspondence.

**Regions of Interest**

Images were sent to a workstation using customized software developed by Theralys in which one observer visualized for each patient on the same screen: DWI_MRI.1, PWI_MRI.1, FLAIR_MRI.1, and FLAIR_MRI.2. The 3-dimensional volumes were measured by manual contouring on each slice:

1. The abnormal bright area on the initial DWI at \(b = 1000\) s/mm\(^2\):
   - DWI_MRI.1
2. The area with a prolonged TTP >4 seconds on the initial TTP map:
   - PWI_MRI.1.
We defined 4 types of pathophysiological regions of interest (ROI) derived from these initial 3 sets of volumes:
1. The infarct CORE, defined as DWI_MRI.1.
2. The infarct growth (IG), defined as [FLAIR_MRI.2]−[DWI_MRI.1] (Figure 1A).
3. The reversible diffusion abnormalities (RDAs), defined when the final infarct on FLAIR was less important than the initial DWI volume as [DWI_MRI.1]−[FLAIR_MRI.2], which represented the initial DWI abnormality area that normalized (Figure 1C).
4. The reversible perfusion abnormalities (RPA), defined as [PWI_MRI.1]−[FLAIR_MRI.2], which represented the initial hypoperfused area that normalized (Figure 1B). In the cases in which RPA coexisted with RDA in a same patient, RPA was calculated as [PWI_MRI.1]−[DWI_MRI.1] so that RPA volume did not include RDA (Figure 1C).

The CORE, IG, RPA, and RDA volumes were calculated as the sum of the area of the ROIs on each slice multiplied by the slice thickness plus the interslice gap.

FLAIR_MRI.2 volume was mirrored to the unaffected hemisphere and adjusted to avoid focal contralateral hyperintensity. This normal contralateral mirror region was used as a control ROI for each patient.

### MTR Quantitative Measurements

CORE, IG, RDA, RPA, and mirror ROIs were automatically propagated on the final MT sequence obtained on MRI.2. This allowed generating MT histogram parameters in these different ROIs (mean, SD, median, and peak height) at 1-month follow-up. Mirror ROIs were assessed for each patient for normal value. This was performed because physiological age-related variations are known, and these are important to consider when evaluating MTR in pathological states. For each patient, this normal contralateral mirror region was used as a control ROI for every comparison (CORE, IG, RDA, RPA).

To minimize errors related to imprecise coregistration and contouring, MTR measurements were performed when CORE volume was >1 cm³ and when IG, RPA, and RDA volumes were >2 cm³. MTR values were thresholded at 15% to minimize partial volume averaging with cerebrospinal fluid that could lead to underestimate mean and median values.

### Statistical Analysis

Statistical analyses were performed using SAS (version 9.1.3). Main characteristics of patients, MRI volumes, and MTR values were described using mean, SD, and range. MTR parameters for each patient (mean and SD) were calculated from pixels (MTR values) distribution within each ROI. Mean MTR values of each ROI (CORE, IG, RPA, and RDA) were compared with that of mirror ROI. Because of nonindependence of data and small samples sizes, comparisons were assessed by a nonparametric Wilcoxon test using intra-individual differences in MTR parameters between each ROI and the normal contralateral ROI defined in each patient. Intergroup comparisons of MTR value between ROIs used either a nonparametric Wilcoxon test when measurements were taken from 2 different samples that were independent or a linear mixed model when they were not. P<0.05 was considered as a statistically significant difference. Spatial heterogeneity was studied using MTR SD in each ROI as an indicator of MTR values dispersion.

In a last step we looked for a relationship between the severity of initial insult and the 1-month follow-up MTR. We performed a Spearman correlation of the mean relative TTP delay or mean apparent diffusion coefficient (ADC) at the early stage, and the mean MTR at the chronic stage.

### Results

Of the 30 subjects included, 11 were men and 19 women. They had a mean age of 61 years (SD,14; range, 23 to 79 years). For patients with delay data accurate to within the hour, MRI.1 was performed with a mean delay of 6.4 hours after the occurrence of stroke symptom (SD, 2.8; range, 2 to 11 hours; n=28). Two patients included within study had insufficiently accurate delay data but it was inferior to 12 hours. The mean NIHSS at admission was 8.4 (SD, 5.0; range, 4 to 20; n=29). Three patients underwent thrombolysis while the remaining received a anti-aggregation treatment. MRI.2 was obtained within a range of 30 to 44 days (mean, 36.0; SD, 4.4) and mean Barthel and Rankin scale were,
and MTR measured in RDA was significantly lower than MTR measured in RPA ($P=0.0154$). In each ROI, mean MTR is calculated from all pixels within the ROI that are normally distributed around this mean with an individual SD. Individual standard deviation in each ROI is an indicator of MTR value dispersion and thus of the spatial homogeneity or heterogeneity. The mean of individual SD was 0.77% ($n=30$) in normal region, 0.99% ($n=19$) in RPA, and 1.75% ($n=7$) in RDA.

Analysis of initial TTP delay and follow-up MTR value revealed a negative correlation ($r=-0.29$ in RDA and $-0.04$ in RPA), whereas there was a positive correlation between initial ADC and follow-up MTR ($r=0.4$ in the 4 regions). However, these correlations were weak.

### Discussion

The ischemic penumbra has become one of the main targets of the thrombolytics and neuroprotective drugs in recent years. The volume of this tissue at-risk that escaped from infarction according to the 1-month FLAIR sequence has become a criterion for the evaluation of the efficacy of these treatments. This study demonstrated the presence of microstructural brain damage inside this area as suggested by low MTR measured in the areas of “reversible perfusion and diffusion abnormalities” (RPA and RDA) 30 to 45 days after stroke onset.

MT is a very robust sequence much more specific and sensitive to macromolecular loss than conventional sequences. It consists of applying an off-resonance radio frequency pulse that saturates, immobilizes, or restricts macromolecular protons. This saturation is transferred to the protons of mobile free water. The percentage reduction in the signal when the saturation is applied (ie, MTR) is thus proportional to the bound protons and depends on the density and nature of the macromolecules in a given tissue. High degrees of correlation have been found between MTR values and histopathological findings of myelin loss or axon destruction. Furthermore, this technique can depict abnormalities that are not visible on conventional images, so-called normal-appearing white or gray matter and is thus very useful to depict subtle damage.

Low MTR values were previously reported in the CORE of cerebral infarct with a decrease starting 7 days after stroke onset. It is related to the progressive loss of protein and fluid with clearing of necrotic debris that begins 5 to 7 days after the onset, after the initial cellular infiltration (lymphocyte, monocyte). Our results confirmed very low MTR values at one month in the CORE volumes indicating that MTR is a good marker of microstructural damage related to stroke insult. To our knowledge this has not been studied in the ischemic penumbra.

Therefore, regarding the main objective of this study that is to determine whether salvaged penumbra is fully reversible, the average MTR at 1 month is of particular interest in the 2 remaining volumes: RPA and RDA. In these regions that seem normalized according to the 1-month follow-up FLAIR, MTR values were significantly lower than in normal ROIs. Such abnormal MTR in normal-appearing white matter has already been reported in ischemic pathology, but in particular

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$A$ nonparametric test (Wilcoxon test) was used to compare MTR mean values in the different ROIs to the mirror ROIs. $P<0.05$ was considered as a statistically significant difference.

respectively, 94/100 (range, 20 to 100; $n=20$) and 1/5 (range, 0 to 5; $n=20$).

Among the 16 patients who were included within 6 hours of stroke onset, 3 of them had a lesion decrease (including 2 patients who received TPA), 9 patients had a stable lesion (1 of them received TPA and had no visible lesion), and 4 had an infarct growth. Among the 14 patients who were included between 6 and 12 hours after stroke onset, 4 of them had a lesion decrease, 3 had a stable lesion, and 7 had an infarct growth.

### Volumes

The mean CORE volume was 23.1 cm$^3$ (SD, 39.6; $n=30$). For 25 patients this volume was >1 cm$^3$ and for 5 it was <1 cm$^3$ impeding MTR measurement. One patient had no visible lesion on DWI_MRI.1 and on FLAIR_MRI.2 but was included in our study because that patient was seen 2 hours and 30 minutes after stroke onset of left hemiplegia and hemianesthesia, and presented a middle cerebral artery occlusion impeding MTR measurement. One patient had no visible lesion on DWI_MRI.1 on FLAIR_MRI.2 but was included in our study because that patient was seen 2 hours and 30 minutes after stroke onset of left hemiplegia and hemianesthesia, and presented a middle cerebral artery occlusion with a large hyperperfusion. The patient received thrombolytic treatment and fully recovered.

The mean final infarct volume on FLAIR_MRI.2 was 25.3 cm$^3$ (SD, 39.6; $n=30$). Comparing CORE and FLAIR_MRI.2 volumes showed: an infarct volume growth in 11 patients (mean, 11.8 cm$^3$ [SD, 11.0] ie, IG); an infarct volume decrease in 7 patients (mean, 9.3 cm$^3$ [SD, 6.0] ie, RDA); no significant volume change in the remaining 12 patients ($-2$ cm$^3$<volume<2 cm$^3$).

An area of prolonged TTP was observed in 25 patients with a mean volume of 56.2 cm$^3$ (SD, 44.0). For 19 patients this volume (mean, 60.0 cm$^3$; SD, 35.4) was significantly larger than the final infarct volume on FLAIR, allowing the calculation of RPA (mean, 35.7 cm$^3$; SD, 22.2).

### Repartition of MTR Parameters in the Different ROIs

The mean MTR in the contralateral, symmetric, normal-appearing parenchyma was 49.8% (SD, 1.9). We found a significant MTR decrease within all these ROIs compared with the symmetric contralateral hemisphere (Table). We found a continuum in mean MTR value repartition (Figure 2). Mean CORE value was the lowest, significantly different from IG and RDA ($P=0.039$ and $P=0.0289$, respectively). IG and RDA had similar degree of MTR decrease ($P=0.85$),
cases of patients with chronic hypoperfusion attributable to severe stenosis of the internal carotid artery, a clinical situation very different from acute stroke. Our results suggest a decrease of cellular content with potential neuronal loss despite normal appearance on FLAIR-weighted images. This can be put together with many histological observations performed on animal models. Garcia et al described lesions characterized by selective neuronal necrosis and various glial responses interpreted as incomplete infarction after arterial occlusions of short duration, entirely different from the pan necrosis/cavitation typical of an infarction. These rat models demonstrated that histological changes including neuronal necrosis were not completely detectable with conventional MRI sequence. As an example, after 10 minutes of transient focal ischemia, selective neuronal necrosis could reach 28% of the neurons with T2 remaining normal.

For humans, such partial damage has been observed using specific radiotracer. Nakagawara et al reported a mild but significant reduction of iomazenil binding (SPECT radioligand for the mapping of cortical neuronal integrity in vivo) in cortical areas exhibiting hypoperfusion on acute stage, but no evident infarct on structural imaging by MRI. Recently, Saur et al combined data of MRI and SPECT and also found a decrease of iomazenil cortical binding in ROIs equivalent to our RPA ROIs. We found that MTR is an attractive way to obtain the same type of information. Until now this additional information compared with conventional MRI needed a SPECT examination that implies a long duration of each scan, a spatial resolution less optimal than that of MRI, an exposure to ionizing radiation, and provided information concerning only cortical binding.

Delayed neuronal death could be caused by acute hypoperfusion but also reperfusion itself (so-called reperfusion injury), as well as inflammatory process, especially microglia activation. We found that MTR in RDA was lower than in RPA. This can be interpreted as an indirect link between the severity of initial insult and later damage given that ADC reduction had been shown to be closely related to reduced energy metabolism, whereas TTP can overestimated severe cerebral blood flow decrease. Unfortunately, we could not know when patients were recanalyzed, a point that can explain why correlation between early TTP and later MTR was weak and not statistically significant, as well as between early ADC and later MTR.

We observed a continuum in MTR decrease from the periphery to the center but without difference between MTR values measured in IG (hyperintense on FLAIR images) and RDA (normal-appearing on FLAIR images). Histopathologic substratum that could explain these radiological appearances in IG and RDA is only speculative. We can think that in RDA there is only a water shift from intracellular to extracellular compartments without total water content increase. That is to say that water shifts to intracellular at the acute phase is responsible for diffusion restriction. It could go back to extracellular compartments in relation with diffusion normal-

Figure 2. Repartition of mean MTR values in the different ROIs. The cross inside the box represents the mean. Middle bar is the median. Upper and lower extremities of the box are first and third quartiles, respectively. Maximum and minimum values are represented by extreme lines.
ization and coexists with partial neuronal death that would explain MTR decrease. In the case of IG, infarction evolution is probably more usual. FLAIR hypersignal could be caused by cystic changes in the damaged tissue but also to gliosis that can be important at the periphery and also results in prolongation of T1 and T2 relaxation times. This could lead to difficult and intricate modifications because we can speculate that neuronal death that would lead to MTR decrease could be underestimated because of astrocyte proliferation. Further experiments including histological correlations on animal models could help to go farther in the interpretation.

Any detrimental effect of these potential selective neuronal losses on neurological outcome/recovery remains poorly understood. Occasional persistence of dysphasia or hemineglect has been reported, despite apparently isolated striato
capsular infarct, which could be explained by a greater extension of selective neuronal loss.27,29 Two of the 30 capsular infarct, which could be underestimated because of astrocyte proliferation. Any clinical outcome remains the major criterion of treatment efficacy in trial design for acute ischemic stroke, radiographic measurements are also a major category of end point assessment. Because MTR is easy to perform, reproducible, and is a surrogate marker of macro
cellular content, it could be an attractive imaging marker in conjunction with other parameters such as infarct size or recanalization.

In such studies, several sources of potential bias should be avoided. First, in the study presented here, follow-up MRI was performed 30 to 45 days after stroke onset and atrophy seen in some cases could contribute to underestimate final infarct size. This was taken into account even if a little contribution of such shrinking phenomenon cannot be excluded. In the same way, edema at early stage could contribute to overestimate CORE volume especially after >6 hours from stroke onset. This was difficult to correct and could lead to increase RDA volume but would not drastically change the conclusion because if systematic correction could be applied, this potentially “false” RDA (with MTR decrease) would be part of RPA and would participate to RPA mean MTR decrease. Second, MTR decrease had more significance if it concerned a large part of the ROI and not only a small ring near to abnormalities already seen with FLAIR images, and it should be monitored by histogram dispersion. Third, other sequences could have been used instead of FLAIR to determine the size of the infarct at MRI.2 On the same group of patients we have compared the size of the infarct between DWI MRI and FLAIR MRI.2 The final infarct size on DWI was smaller than on FLAIR images. This resulted in larger RPA and RDA with even a lower MTR in the salvaged penumbra.

This study indicates that partial damage may occur in tissues that seem to escape infarction according to conventional MRI sequences and shows in vivo definitive structural abnormalities in the reperfused penumbra. This can be considered as a further graduation between complete infarction and complete tissue salvage. Applied in therapeutic trials, MTR may bring additional information to the current T2 or FLAIR protocols and help to evaluate drugs that have objective to reduce brain tissue damage.

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Disclosures
None.

References


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