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Evaluation of diffusion kurtosis imaging stroke lesion with hemodynamic and metabolic MRI in a rodent model of acute stroke

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Abstract

Objective: Diffusion kurtosis imaging (DKI) has emerged as a new acute stroke imaging approach, augmenting the routine diffusion weighted imaging (DWI). Whereas it has been shown that diffusion lesion without kurtosis abnormality is more likely to recover upon reperfusion while the kurtosis lesion shows poor response, little is known about the underlying pathophysiology between the kurtosis lesion and kurtosis/diffusion lesion mismatch.

Materials and methods: We performed multiparametric MRI, including arterial spin labeling (ASL), pH-sensitive amide proton transfer (APT) and DKI in an embolic middle cerebral artery occlusion (MCAO) rodent model of acute stroke. Diffusion and kurtosis lesions were semiautomatically segmented, and multiparametric MRI indices were compared between kurtosis lesion, diffusion lesion, kurtosis/diffusion lesion mismatch and the contralateral normal area.

Results: We confirmed a significant difference between diffusion and kurtosis lesion volumes (151 ± 65 vs. 125 ± 47 mm³, $P < 0.05$). Although the ischemic lesions have significantly reduced cerebral blood flow (CBF) from the contralateral normal tissue, we did not find significant CBF difference between kurtosis lesion and the kurtosis/diffusion lesion mismatch (0.53 ± 0.10 vs. 0.47 ± 0.14 ml/g-min, $P > 0.05$). Importantly, pH in the kurtosis lesion was significantly lower from that of the lesion mismatch (6.81 ± 0.08 vs. 6.89 ± 0.09 , $P < 0.01$).

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Conclusions: Our work confirmed that DKI provides an expedient approach for refining the heterogeneous DWI lesion that is associated with graded metabolic derangement, which is promising to improve infarction core definition and ultimately help guide stroke treatment.

Keywords

Acute stroke; Amide proton transfer (APT); Diffusion kurtosis imaging (DKI); Diffusion weighted imaging (DWI); pH

Introduction

Diffusion weighted imaging (DWI) has often been used to define the most severely damaged infarction core that is unlikely to recover.[1, 2] Perfusion weighted imaging (PWI), on the other hand, characterizes tissue hemodynamic state so that critically hypoperfused ischemic tissue can be identified.[3] The combined use of DWI and PWI provides a mismatch paradigm (i.e., DWI/PWI mismatch) that has been postulated as a practical imaging approximation of the salvageable ischemic tissue at risk of infarction (penumbra).[4, 5] The development of a reliable penumbra imaging approach is key to guide thrombolytic therapy, particularly in patients beyond the standard thrombolytic window[6]. Despite the initial enthusiasm, it has been recognized that the DWI/PWI mismatch paradigm is very crude. The perfusion lesion includes not only critically hypoperfused penumbral tissue but also benign oligemic area that is not at immediate risk of infarction.[7] More importantly, multiple reports have documented that the DWI lesion may partially reverse with early and effective recanalization, particularly in patients following endovascular recanalization.[8–12] Hence, the approximation of infarction core using the routine DWI may underestimate the penumbral tissue and restrict thrombectomy therapy to a subpopulation of stroke patients who could have benefited from late recanalization. As such, it is urgent to develop new imaging approaches to delineate the mildly injured and potentially reversible DWI lesion from the irreversibly damaged infarction core.

Although apparent diffusion coefficient (ADC) has been widely used, the severity of ADC drop is unable to predict DWI reversibility.[13] It has been shown that metabolic disruption within the DWI lesion is graded, yet the relatively low spatiotemporal resolution of lactate/phosphorus MR spectroscopy (MRS) and no readily access of positron emission tomography (PET) in the emergency setting limit their routine use. [14, 15] It is worth mentioning that amide proton transfer (APT) imaging is an emerging endogenous chemical exchange saturation transfer (CEST) MRI approach that probes pH-dependent exchange between amide protons from mobile proteins/peptides and bulk tissue water, which has been applied to map ischemic tissue acidification during acute stroke.[16–19] Indeed, pH MRI has revealed promising results in delineating the metabolic penumbra from benign oligemia.[20–22] Unfortunately, the spatiotemporal resolution of endogenous pH-sensitive APT MRI is not sufficient to directly resolve the tissue heterogeneity within the DWI stroke lesion, and new imaging means is urgently needed.

It is worth mentioning that displacement profile of water molecules in the cerebral tissue is not exactly Gaussian due to the restricted diffusion and complex microstructures. As such,

the routine ADC measurement is overly simplistic and may not capture the rich information embedded within the DWI dataset. The emerging diffusion kurtosis imaging (DKI) quantifies the degree of deviation from the standard Gaussian displacement profile, providing a new index that complements routine DWI and ADC analyses. [23–25] DKI thus provides more detailed information for an ischemic insult, in comparison to standard DWI MRI. [26–31] Indeed, experimental stroke studies have shown that kurtosis/diffusion lesion mismatch often renormalizes following prompt recanalization while kurtosis lesion shows poor recovery.[32] The recently developed fast DKI approach provides an expedient measurement of mean diffusion and kurtosis, facilitating in vivo evaluation.[33–36] Previously, we performed multiparametric MRI in a filament middle cerebral artery occlusion (MCAO) rodent model of acute stroke to investigate the underlying pathophysiological difference between kurtosis lesion and kurtosis/diffusion lesion mismatch. [37] Compared to filament model, embolic model more closely mimics the pathophysiology of human MCAO with heterogeneous tissue damage, the possibility to apply thrombolytic therapy and a prolonged therapeutic window [38, 39]. In this study, we further investigated the tissue perfusion and pH states of kurtosis/diffusion lesion mismatch in an embolic MCAO model, which more closely mimics acute stroke than filament model with graded hemodynamic and metabolic change. We applied the inherent correlation-based normalization (ICON) analysis to suppress intrinsic kurtosis heterogeneity not related to ischemia, and enabled semiautomatic lesion segmentation.[40] The tissue perfusion, pH, diffusion and relaxation indices were measured from the contralateral normal area, kurtosis lesion and the kurtosis/diffusion lesion mismatch. Although perfusion and relaxation were not significantly different between the kurtosis lesion and the kurtosis/diffusion mismatch, we documented significantly lower pH within the kurtosis lesion from that of the kurtosis/diffusion lesion mismatch, substantiating the postulation that DKI demarcates the heterogeneous DWI lesion of graded metabolic derangement.

Material and Methods

Rodents

In vivo studies have been approved by the local institutional animal care and use committee. Briefly, adult male Wistar rats (Charles River Laboratory, Wilmington, MA) were anesthetized with 1.5–2.0% isoflurane/air mixture throughout the study, with physiological parameters (e.g., respiratory and rectal temperature) monitored and maintained within their normal ranges. Fifteen acute stroke rats (n = 15) were imaged 1 hr after acute embolic MCAO. One animal showed a very small ischemic lesion likely due to clot autolysis, and was excluded from the study. Briefly, homologous blood clots were prepared the day before the occlusion and stored overnight at 4°C [41]. Two blood clots (2 cm/each) were injected through the right internal carotid artery (ICA) to block the middle cerebral artery (MCA) under the guidance of laser doppler flowmetry (LDF).

MRI

We performed multiparametric echo planar imaging (EPI) of 5 consecutive slices (slice thickness = 2 mm, field of view = 20×20 mm², matrix = 48×48) at a 4.7 T Biospec MRI scanner (Bruker Biospin, Billerica, MA). Briefly, DWI was performed using single-shot

isotropic diffusion-weighted MRI with two b-values of 250 and 1,000 s/mm² (repetition time (TR)/echo time (TE) = 3250/54 ms, 16 averages, scan time=2 min) [42]. In addition, fast DKI protocol was obtained (gradient duration/diffusion time (δ/Δ) = 6/20 ms, repetition time (TR)/echo time (TE) = 2500/36.6 ms, 4 averages, scan time = 3 min).[33] The fast DKI protocol consisted of one b = 0 s/mm² reference image, followed by three images of b = 1,000 s/mm² along three gradient directions of (1,0,0), (0,1,0) and (0,0,1), and nine images of b = 2,500 s/mm² along nine diffusion directions. We also collected amplitude-modulated ASL MRI (TR/TE = 6500/15 ms, B₁ = 4.7 μ T, time of saturation = 3250 ms, labeling distance of 15 mm, modulation frequency of 250 Hz, 32 averages and scan time = 7 min). [43, 44] In addition, we performed fast pH-weighted APT MRI with unevenly segmented RF irradiation (Recovery time = 3000 ms, primary RF saturation time = 3000 ms, secondary RF saturation time = 500 ms, and B₁ = 0.75 μ T).[45] The unsaturated control scan was signal-averaged 8 times, while the saturated images were averaged 32 times (scan time = 4 min). Moreover, T₁-weighted images were acquired using inversion recovery EPI, with seven inversion delays from 250 to 3000 ms (recovery time = 6500 ms, TE = 15 ms, 4 averages, scan time = 4 min); T₂-weighted images were obtained with two TEs of 30 and 100 ms (TR = 3250 ms, 4 averages, scan time = 0.5 min).

Data Analysis

MRI images were processed in Matlab (Mathworks, Framingham, MA). Specifically, for the fast DKI, mean diffusivity (MD) was calculated as the mean of MD_{x,y,z} derived from the formula published by Jensen et al.[24]:

$$\text{MD}_{x,y,z} = \frac{(b_1 + b_3)D_{x,y,z}^{(12)} - (b_1 + b_2)D_{x,y,z}^{(13)}}{b_3 - b_2} \quad (1)$$

where $D_{x,y,z}^{(ij)} = \frac{\ln S(b_i)/S(0) - \ln S(b_j)/S(0)}{b_j - b_i}$, $i = 1, j = 2, 3$, and $b_1 = 0$, $b_2 = 1,000$, and $b_3 = 2,500$ s/mm². The mean kurtosis (MK) was obtained following the fast DKI quantification algorithm described by Hansen et al. [33]:

$$\text{MK} = \frac{\frac{6}{15} \left(\sum_{i=1}^3 \ln \frac{S(b_3, \hat{n}^{(i)})}{S(0)} + 2 \sum_{i=1}^3 \ln \frac{S(b_3, \hat{n}^{(i+)})}{S(0)} + 2 \sum_{i=1}^3 \ln \frac{S(b_3, \hat{n}^{(i-)})}{S(0)} \right) + 6 \cdot b_3 \cdot \text{MD}}{b_3^2 \cdot \text{MD}^2} \quad (2)$$

Parametric T_1 map was obtained by least squares fitting of the signal as a function of the inversion time ($I(TI_i) = I_0 \left[1 - (1 - \eta)e^{-TI_i/T_{1w}} \right]$), where η is the inversion efficiency and TI_i is

the i th inversion time. ADC and T_{2w} maps were calculated as $ADC = \frac{\ln(I(b_1)/I(b_2))}{b_2 - b_1}$ and $T_{2w} = \frac{TE_2 - TE_1}{\ln(I(TE_1)/I(TE_2))}$, where $b_{1,2}$ and $TE_{1,2}$ are two diffusion b values and TE s, respectively.

In addition, cerebral blood flow (CBF) was calculated as $CBF = \frac{\lambda(I_{ref} - I_{tag})}{2\alpha \cdot I_{ref}} \cdot \frac{e^{w/T_{1a}}}{T_{1w}}$, where

I_{tag} is the label image, I_{ref} is the reference image, λ is the brain-blood partition coefficient for water, α is the degree of inversion with transient time correction, w is the post-labeling delay, and T_{1a} is the arterial blood longitudinal relaxation time. Moreover, pH-weighted APT MRI was calculated as the difference between the magnetization transfer ratio (MTR)

of the reference and label CEST scans (i.e. $MTR_{asym} = \frac{I_{ref} - I_{label}}{I_0}$, where I_{ref} and I_{label} are

reference and label CEST scans with saturation applied at -3.5 and 3.5 ppm, respectively, and I_0 is the control scan without pre-saturation). Tissue pH map was calibrated from APT MRI as published by Sun et al. [19]

$$pH = 6.4 + \log_{10} \left(\frac{R_{1w}}{f_s \left(\frac{\alpha \cdot (1 - \sigma)}{MTR_{asym} - \Delta MTR'_{asym}} - 1 \right)} / 5.57 \right) \quad (3)$$

where α is the labeling coefficient and σ is the spillover factor, calculated from relaxation images. In addition, f_s is the amide proton concentration with respect to bulk tissue water, derived to be 1:867, and MTR'_{asym} is the intrinsic asymmetry shift not due to pH-sensitive effect, being $-7.44\% \cdot 1.63/T_{1w}$. [19]

Because kurtosis images, unlike diffusion MRI, display notable intrinsic heterogeneity in the intact brain tissue, suppression of such non-ischemia related variation is necessary for reliable lesion segmentation. To achieve this, we performed inherent correlation-based normalization (ICON) analysis of the MK map based on magnetization transfer and relaxation images.[40] Briefly, MK from the contralateral normal brain was correlated with

T_1 and mean MTR ($MMTR = \frac{I_{ref} + I_{label}}{2 \cdot I_0}$) using Pearson's correlation, excluding ventricular

cavities. The difference between the experimentally measured MK and that estimated from regression analysis assuming no ischemia was calculated as $MRMK = MK - MK_{est}$, where MK_{est} is the estimated MK map from the regression established from the contralateral normal brain tissue (i.e. $MK_{est} = C_0 + C_1 \cdot R_1 + C_2 \cdot MMTR + C_3 \cdot R_1 \cdot MMTR$), and C_s are coefficients determined from the contralateral normal brain.[37] The diffusion and kurtosis

lesions were determined using a K-means clustering-based algorithm.[22, 40] P values less than 0.05 were considered statistically significant.

Results

Fig. 1 shows multiparametric images from a representative acute stroke rat. T_1 (Fig. 1a), T_2 (Fig. 1b) and MMTR (Fig. 1c) images show relatively little change in the ipsilateral ischemic insult. In comparison, the CBF map (Fig. 1d) shows severe hypoperfusion in the right ipsilateral brain, evidencing successful MCAO. In addition, the pH-sensitive MTR_{asym} map (Fig. 1e) captures noticeable hypointensity, predominantly within the ipsilateral striatum, from the contralateral normal area. Notably, MTR_{asym} image shows non-negligible heterogeneity within the intact brain tissue, limiting its specificity to ischemia-induced pH change. To overcome this, tissue pH (Fig. 1e) was determined from pH-sensitive MTR_{asym} and relaxation images by correction of non-pH related signal shift (MTR'_{asym}), which confirmed severe pH drop within the striatum.[19]

Fig. 2 shows diffusion and kurtosis images in a representative acute stroke rat. The DWI image shows hyperintensity in the striatum and ventral lateral cortex regions from the intact tissue (Fig. 2a). The MD map (Fig. 2b) reveals ipsilateral ischemic insult, similar as that captured by the routine DWI. In comparison, MK image (Fig. 2c) shows hyperintensity predominantly within the striatum without involving the lateral cortex. Similar as pH-sensitive MTR_{asym} , the raw MK image is also susceptible to intrinsic tissue heterogeneity not related to ischemia. Fig. 2d shows magnetization transfer and relaxation normalized MK (MRMK) image that reasonably suppresses the intrinsic MK heterogeneity variation across the brain that has been dubbed ICON approach, enabling semi-automatic kurtosis lesion segmentation with MK and MD lesions shown in black and green, respectively (Fig. 2e). The MK and MD lesion volumes were determined to be 125 ± 47 and 151 ± 65 mm³, respectively, significantly different from each other ($P < 0.05$, paired t-test).

We analyzed perfusion, pH, diffusion, kurtosis and relaxation indices from the contralateral normal tissue, MD lesion, MK lesion and the MK/MD lesion mismatch (Table 1). Although CBF was reduced in the ischemic lesions (MD lesion, MK lesion and their mismatch), it did not show significant difference among intralesional regions (Fig. 3a). In addition to significant difference between normal tissue and ischemic lesions, pH decrease within the MK/MD lesion mismatch was significantly less than that of MD and MK lesions (Fig. 3b). Although MK lesion and MK/MD lesion mismatch have significantly different MD values from that of the MD lesion, MD did not differ between MK lesion and MK/MD lesion mismatch (Fig. 3c). Fig. 3d shows that MK in the MK lesion is significantly different from the contralateral normal, MD lesion and MK/MD lesion mismatch areas. It is important to point out that there was no significant MK difference between the contralateral normal and MK/MD lesion mismatch areas. This shows that MK/MD lesion mismatch has similar microstructural integrity as the normal tissue, indicating less injury than the MK lesion. Moreover, ischemic regions had significantly increased T_1 from that of the contralateral normal area, yet without significant intralesional difference. Interestingly, we found that the MK lesion, not MD lesion and the MK/MD lesion mismatch, had significant T_2 increase from that of the contralateral normal tissue, suggesting that the MK lesion has developed

more prominent edema from other regions, consistent with worsened changes in pH and kurtosis.

Discussion

Our study confirmed significant kurtosis/diffusion lesion mismatch in an embolic MCAO model of acute stroke. We documented metabolic heterogeneity between kurtosis/diffusion lesion mismatch and kurtosis lesion, consistent with a prior report using a filament MCAO model.[37] Therefore, our study further supports the postulation that the kurtosis/diffusion lesion mismatch identifies portion of diffusion lesion of less severe ischemic injury.[32] By identifying the most severely injured ischemic lesion, DKI may augment routine DWI for improved definition of the infarction core, and ultimately aid imaging-guided stroke treatment (Fig. 4). It has also been shown that the outer boundary of ischemic penumbra can be refined with pH MRI. Specifically, hypoperfused tissue without measurable pH change likely represents ischemic tissue at no immediate risk of infarction (benign oligemia) while ischemic tissue with concomitant perfusion and pH decrease is at elevated risk of deterioration. Therefore, simultaneous acquisition of fast DKI and pH MRI provides a tangible means to demarcate the heterogeneous ischemic tissue into benign oligemia (hypoperfused tissue without pH change), metabolic penumbra (hypoperfused tissue without kurtosis abnormality) and infarction core (kurtosis lesion). Such a refined mismatch paradigm is consistent with that proposed by Kidwell et al., and it will be interesting to validate perfusion/pH/DKI-based tissue classification with acute histology and early reperfusion treatment.[46]

We applied magnetization transfer and relaxation normalization ICON algorithm to enhance the specificity of MK elevation to ischemia for lesion segmentation. This avoids manual lesion outline that may introduce inter/intra-rater variability. MRMK minimizes intrinsic heterogeneity for automatic lesion outline, yet it may overcorrect certain pixels, resulting in lesion highlighted by MRMK not MD. The number of such pixels are significantly less than the MK/MD mismatch. In addition, most of such pixels appear abnormal on DWI but not MD map (dorsal part of the striatum in Fig. 2a and 2b). Therefore, it might also arise from the slight errors in MD and MK quantification determined by the fast DKI approach, which assumes negligible high order diffusion and Rician noise terms [34]. Moreover, the MK map showed a stronger percentage change in lesions than that of MD, which may detect lesion even beyond the MD deficit with the automatic segmentation. Further investigation is needed to identify the origins underlying this reversed mismatch.

Our study used a dual coil setup that includes a volume transmitter and a small surface receiver to maximize the detection sensitivity without sacrificing radiofrequency (RF) field homogeneity. Although this configuration does not affect calculation of post-processed parametric maps such as CBF and pH images, it does introduce spatial variation in raw images, particularly DWI, as a function of the distance between the tissue and receiver coil. To map the profile of detection sensitivity, we modeled the signal drop using a polynomial function along the dorsal-ventral dimension on a plain EPI (TR/TE=3250/30 ms) image, correction of which yielded DWI images void of otherwise gross signal drop not related to ischemic insult (Fig. 2a). This allows comparison of routine diffusion images (DWI and

ADC) and those from fast DKI (MD and MK). We also would like to point out that our study chose a fast DKI protocol instead of tensor model-based DKI approach to minimize the scan time. Although fast DKI provides MK measurement at higher contrast to noise per unit time, it admittedly could not derive the axial and radial kurtosis, which may provide further information about the underlying tissue microstructural change.[35] More advanced DKI approach such as double diffusion encoding and symmetrized double pulsed field gradient MRI may provide novel insights of diffusion and kurtosis changes following stroke, which shall be investigated in the future.[47, 48]

Whereas DWI and MD images depicted similar lesion areas, MK map showed noticeably smaller lesion area than that defined from diffusion images (Fig. 2). Our results found that MK lesion and MK/MD lesion mismatch have similar MD values, suggesting that the MK elevation is likely attributable to diffusional heterogeneity within the voxel. In addition, the absolute percentage magnitude change in MK is significantly higher than that of MD lesion ($50 \pm 4\%$ vs. $24 \pm 3\%$, $P < 0.05$, paired t-test). This suggests that although the magnitude of diffusion change (i.e., ADC and MD) may be associated with graded ischemic insult within the DWI lesion, kurtosis provides a more sensitive and hence reliable index for demarcating the DWI lesion, consistent with the findings that the severity of ADC decrease does not reliably predict DWI reversibility.[13]

It is worth pointing out that embolic MCAO model, despite its variability, provides a closer representation of human stroke than the commonly used filament stroke models. As such, our study here highlighted the translational potential of DKI in the acute stroke setting. Although we found kurtosis lesion is of worsened pH drop from the mismatch, perfusion did not show significant intralesional difference. One plausible explanation is that the normal perfusion level varies within the intact brain tissue such as white and gray matter while the intact brain tissue has a relatively uniform intracellular tissue pH.[49, 50] Therefore, tissue pH change may be more specific to ischemia than perfusion. Also, our study used amplitude modulated ASL MRI sequence without a separate tagging coil. Although this configuration is easy to implement, it is of relatively low sensitivity to perfusion. It is likely that dynamic susceptibility contrast (DSC) MRI may provide more reliable and comprehensive perfusion measurement than ASL MRI, which may be investigated in the future. To summarize, our study showed that fast DKI is promising to demarcate the heterogeneous DWI lesion, and the refined DKI lesion classification is associated with graded metabolic disruption, warranting further investigation of DKI-guided late thrombectomy in the acute stroke setting.

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Fig. 1.

Multiparametric images of a representative acute embolic MCAO rat. a) T_1 map. b) T_2 map. c) MMTR image. d) CBF map. e) pH-sensitive MTR_{asym} image. f) Tissue pH map. Although relaxation and MT images show little signal change in the ipsilateral ischemic lesion, both perfusion and pH images reveal severe ischemia, evidencing acute MCAO.

Fig. 2. Multiparametric diffusion images following acute embolic MCAO. a) DWI image ($b=1000$ s/mm²). b) MD map ($\mu\text{m}^2/\text{ms}$). c) MK map. d) Magnetization transfer and relaxation-normalized MK image (MRMK). e) MK/MD lesion mismatch overlaid on the DWI image.

Fig. 3.

Regional analysis of multiparametric MRI indices of perfusion, pH, MD and MK values from the contralateral normal region, MD lesion, MK lesion and MK/MD lesion mismatch.

a) CBF (ml/g.min). b) pH. c) MD ($\mu\text{m}^2/\text{ms}$). d) MK.

Fig. 4.

Refined MRI mismatch paradigm of infarction core. a) Infarction core (black) defined using routine DWI. b) The proposed refined mismatch paradigm that includes infarction core (black) defined by MK lesion and potentially reversible DWI lesion (penumbra) identified by MK/MD lesion match (green).

Table 1:

Multiparametric MRI indexes for the normal, diffusion lesion, kurtosis lesion and their mismatch.

	Contralateral Normal	MD lesion	MK lesion	MD/MK mismatch
MD ($\mu\text{m}^2/\text{ms}$)	0.79 ± 0.02	$0.56 \pm 0.02^{*\$ \ddagger}$	$0.60 \pm 0.03^{*\$}$	$0.58 \pm 0.03^{*\ddagger}$
MK	0.65 ± 0.06	$0.85 \pm 0.06^{*\$ \ddagger}$	$0.97 \pm 0.03^{*\$ \ddagger}$	$0.62 \pm 0.06^{\ddagger \ddagger}$
CBF (ml/g.min)	1.12 ± 0.18	$0.43 \pm 0.08^*$	$0.53 \pm 0.10^*$	$0.46 \pm 0.13^*$
pH	7.04 ± 0.08	$6.81 \pm 0.09^{*\ddagger}$	$6.81 \pm 0.09^{*\ddagger}$	$6.88 \pm 0.09^{*\ddagger \ddagger}$
T ₁ (s)	1.54 ± 0.05	$1.67 \pm 0.06^*$	$1.65 \pm 0.08^*$	$1.67 \pm 0.06^*$
T ₂ (ms)	53.98 ± 0.86	54.83 ± 1.23	$55.15 \pm 1.64^*$	54.51 ± 1.04

Repeated measures of ANOVA with Bonferroni's multiple comparison analyses were performed with

*P<0.05 indicating significant difference between contralateral normal and lesion regions,

$\ddagger$ P<0.05 indicating significant difference between MD lesion and MK/MD lesion mismatch,

$\ddagger$ P<0.05 indicating significant difference between MK lesion and MK/MD lesion mismatch, and

$\$$ indicating significant difference between MD lesion and MK lesion, respectively.