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# Abnormal corpus callosum induced by diabetes impairs sensorimotor connectivity in patients after acute stroke

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## Abstract

**Objectives** To test the hypothesis that abnormal corpus callosum (CC) induced by diabetes may impair inter-hemispheric sensorimotor functional connectivity (FC) that is associated with poor clinical outcome after stroke.

**Methods** Forty-five patients with acute ischaemic stroke in the middle cerebral artery territory and 14 normal controls participated in the study. CC was divided into five subregions on three-dimensional T1-weighted image. The microstructural integrity of each subregion of CC was analysed by DTI and the inter-hemispheric FCs in primary motor cortex (M1-M1 FC) and primary sensory cortex (S1-S1 FC) were examined by resting-state functional magnetic resonance imaging.

**Results** Diabetic patients ($n = 26$) had significantly lower fractional anisotropy (FA) in the isthmus of CC ($CC_{isthmus}$) when compared with non-diabetic patients ($n = 19$) and normal controls ($p < 0.0001$). In addition, diabetic patients had the lowest M1-M1 FC ($p = 0.015$) and S1-S1 FC ($p = 0.001$). In diabetic patients, reduced FA of $CC_{isthmus}$ correlated with decreased M1-M1 FC ($r = 0.549$, $p = 0.004$) and S1-S1 FC ($r = 0.507$, $p = 0.008$). Decreased M1-M1 FC was independently associated with poor outcome after stroke in patients with diabetes (odds ratio = 0.448, $p = 0.017$).

**Conclusions** CC degeneration induced by diabetes impairs sensorimotor connectivity and dysfunction of motor connectivity can contribute to poor recovery after stroke in patients with diabetes.

**Key points**

- *Abnormal isthmus of corpus callosum in stroke patients with diabetes.*
- *Abnormal isthmus of corpus callosum correlated with decreased inter-hemispheric sensorimotor connectivity.*
- *Decreased motor connectivity correlated with poor stroke outcome in diabetic patients.*

**Keywords** Stroke · Diabetes mellitus · White matter · Cerebral cortex · Magnetic resonance imaging

**Abbreviations**

| | |
|---|---|
| CC | Corpus callosum |
| CST | Corticospinal tract |
| FA | Fractional anisotropy |
| FC | Functional connectivity |
| FPG | Fasting plasma glucose |
| M1 | Primary motor cortex |
| MD | Mean diffusivity |
| NC | Normal controls |
| NIHSS | National Institute of Health Stroke Score |

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S1 Primary sensory cortex
WMH White matter hyperintensities

## Introduction

Cerebral white matter plays an important role in functional improvement after ischaemic stroke, but it may be especially susceptible to hyperglycaemia. It has been reported that hyperglycaemia upregulates matrix metalloproteinases expression, resulting in an increased cell death of oligodendrocyte in white matter [1]. Some clinical studies have showed that diabetic patients have more severe white matter hyperintensities (WMHs), compared with controls [2, 3]. Furthermore, the extent of WMHs is associated with the elevated levels of haemoglobin A1c, which is a biomarker of long-term glycaemic control [4]. A growing number of studies using diffusion tensor imaging (DTI) have showed that diabetes causes decreased integrity in widespread white matter tracts, including corpus callosum (CC), corticospinal tract, superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, anterior and posterior thalamic radiations [5–9]. Therefore, it is important to pay attention to the effect of white matter injury induced by diabetes on post-stroke recovery. CC is the largest white matter fibre bundle and can be divided into different anatomical and functional subregions containing different fibres transferring motor, sensory, and cognitive information between two hemispheres [10]. For stroke patients, CC plays a crucial role in regaining the motor skills during stroke recovery. Previous studies focused on the microstructure of CC at the chronic stage of stroke and found that CC injury caused by stroke lesions through axonal degeneration correlated with poor motor recovery [11–15]. At the acute stage of stroke, it is plausible that pre-stroke abnormal microstructure of CC induced by diabetes may also influence post-stroke recovery.

CC injury induced by diabetes in some subregions may result in disruption of the inter-hemispheric sensorimotor connectivity which is important for stroke recovery. In addition, several studies using functional magnetic resonance imaging (fMRI) have revealed that acute stroke alone could cause a decrease in inter-hemispheric function connectivity (FC) within motor network, which is associated with change in clinical assessment of motor function [16–18]. Inter-hemispheric imbalance of somatosensory function has also been reported in patients with acute stroke and it influences both sensory and motor functions [19]. Therefore, the superimposition of abnormal CC caused by diabetes may lead to greater reduction of inter-hemispheric sensorimotor FC in the acute phase, which contributes to poor recovery after stroke. An improved understanding of the relationship between microstructure of CC and sensorimotor FC during acute phase of stroke in patients with diabetes is needed to help develop potential targets of rehabilitation interventions.

In this study, we examined the microstructural integrity of CC subregion and inter-hemispheric sensorimotor FC in a subset of patients with acute stroke and aimed to test the following hypotheses: (1) diabetic patients had microstructural abnormality in the subregion of CC, compared with non-diabetic patients; (2) abnormality in the subregion of CC correlated with decreased inter-hemispheric connectivity in primary sensorimotor cortex; (3) decreased inter-hemispheric sensorimotor connectivity was a contributor to poor outcome after stroke in diabetic patients.

## Materials and methods

### Patients

The study was approved by the Medical Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine and written informed consent was obtained from all subjects.

Patients with first-ever ischaemic stroke in the vascular territory of unilateral middle cerebral artery were prospectively recruited. Inclusion criteria were: (1) 3-7 days after onset; (2) ≥18 years; (3) no evidence of haemorrhagic infarction; (4) no thrombolytic or recanalisation therapies. Exclusion criteria were: (1) history of neurological or psychiatric disorders; (2) pre-stroke modified Rankin scale (mRS) > 1; (3) duration of diabetes <1 year; (4) periventricular or deep WMHs with a Fazekas score >1 on T2 FLAIR (fluid-attenuated inversion recovery) images [20]. We further excluded patients with any involvement of primary motor cortex (M1), primary sensory cortex (S1) or CC by stroke lesions. Finally, a total of 45 patients with acute stroke were recruited. Diabetic patients were diagnosed according to American Diabetes Association criteria [21]. The duration of diabetes, levels of fasting plasma glucose (FPG) and $HbA_{1c}$ on admission were recorded.

### Clinical assessment

The neurological deficits at the acute stage was assessed using the scores of National Institute of Health Stroke Score (NIHSS) and Barthel index. The degree of sensorimotor deficits was evaluated using the motor and sensory components of NIHSS (ms-NIHSS). Clinical outcome at 3 months was assessed using mRS: (good outcome = mRS < 3) [22]. An experienced stroke neurologist who was blinded to the imaging findings assessed clinical scores.

## Normal controls

A group of 14 normal controls (NC), matched to the stroke population for age and gender were also recruited (mean age, 57.6 ± 8.8 years; range, 45-71 years; 42.9% male). Exclusion criteria included any history of neurological or psychiatric disease, diabetes, hypertension or hyperlipidaemia. No focal abnormalities were found on their conventional brain MR images.

## MRI protocol

All subjects were imaged during 3-7 days after stroke onset using a 3.0-T whole body scanner (MR750; GE Healthcare, Chicago, IL, USA) with an eight-channel phased array head coil. The MRI sequences were as follows: (1) high-resolution 3D sagittal T1-weighted imaging was acquired using a fast spoiled gradient-recalled echo sequence (TR/TE = 7.3/3 ms, TI = 450 ms, flip angle = 8°, slice thickness = 1 mm, matrix = 250 × 250, FOV = 25 cm) ; (2) DTI with four *b* values (three *b* = 0 s/mm$^2$ and one *b* = 1,000 s/mm$^2$ in 30 gradient directions) was acquired using an EPI acquisition (TR/TE = 5,000/95 ms, flip angle = 90°, slice thickness = 4 mm, matrix = 256 × 256, FOV = 24 cm); (3) resting-state fMRI data with a total of 180 brain volumes were obtained using a gradient-echo single-shot EPI acquisition (TR/TE = 2,000/30 ms, flip angle = 77°, slice thickness = 4 mm, matrix = 64 × 64, FOV = 24 cm); (4) DWI was acquired using an EPI acquisition (TR/TE = 4,000/79 ms, flip angle = 90°, slice thickness = 4 mm, matrix = 256 × 256, FOV = 24 cm, *b* = 1,000 s/mm$^2$ along three orthogonal directions); (5) T2 FLAIR was acquired using a fast spin-echo acquisition (TR/TE = 7,500/152 ms, TI = 2,100 ms, flip angle = 90°, slice thickness = 4 mm, matrix size = 320 × 256, FOV = 24 cm).

## CC segmentation and classification

The steps of CC segmentation were as follows: (1) 3D T1-weighted images were rotated to a true sagittal plane ensuring the maximum length of CC using the software package Mango (http://rii.uthscsa.edu/mango/); (2) the outline of the CC was defined using a semi-automatic snake model based on image intensity using the ITK-SNAP software package (http://www.itksnap.org/); (3) CC segmentation was manually refined by an experienced neuroradiologist based on the following anatomical boundaries. The superior, anterior and posterior boundaries of CC were bounded by the callosal sulcus and the cingulate gyrus, the inferior boundary of CC by the ventricular surface, and the lateral boundary as a straight line joining the callosal sulcus and the lateral-superior corner of the caudate nucleus or lateral ventricle. Finally, the segmented CC was further divided into five subregions corresponding to the anterior third, anterior and posterior midbody, isthmus and splenium (Fig. 1) according to the method proposed by Witelson [23].

## Calculation of DTI parameters in CC subregions

DTI images were pre-processed by skull-striping and correction for head motion and eddy current distortion using the FMRIB Software Library (FSL, version 5.0; FMRIB, Oxford, UK). Then, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity ($\lambda_1$) and radial diffusivity ($\lambda_{23}$) were generated. For each patient and NC, DTI parameters were coregistered into their individual 3D T1-weighted images so that the mean values of FA, MD, $\lambda_1$ and $\lambda_{23}$ could be extracted from the region of interest (ROI) of each CC subregion.

## Interhemispheric sensorimotor functional connectivity

ROI-based FC analysis was performed using Statistical Parametric Mapping Version 12 (SPM12; Wellcome Department of Cognitive Neurology, UCL, London, UK) and the resting-state fMRI data analysis toolkit [24]. The pre-processing steps include: discarding first ten volumes, correcting head motion, normalising into the Montreal Neurological Institute (MNI; Montreal, Canada) template, re-sampling to 3 × 3 × 3 mm$^3$, smoothing with a Gaussian filter 6 mm full width at half maximum, filtering band-pass between 0.01 and 0.08 Hz and regressing out the nuisance variables including white matter, cerebrospinal fluid, global signal and

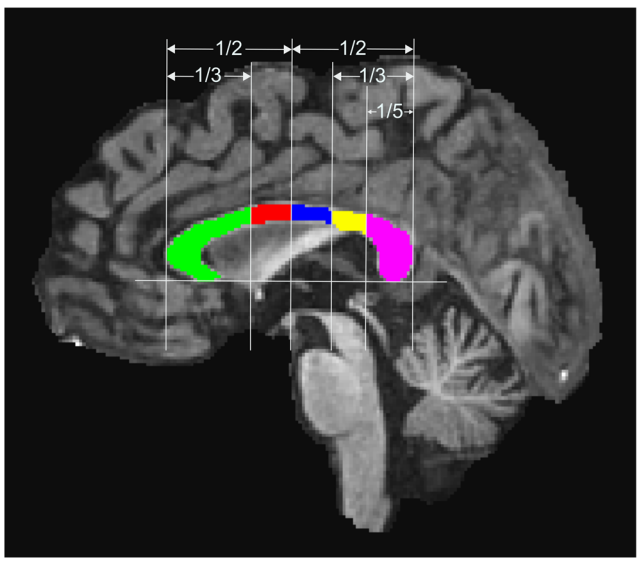


**Fig. 1** Segmentation of corpus callosum (CC) on 3D T1-weighted image. Six *perpendicular lines*, perpendicular to the anterior-posterior axis, divide the CC into five subregions: anterior one-third (CC1, *green*), anterior midbody (CC2, *red*), posterior midbody (CC3, *blue*), isthmus (CC4, *yellow*) and splenium (CC5, *purple*)

head motion. ROIs of M1 and S1 were drawn on individual 3D T1-weighted images by another experienced neuroradiologist and then were normalised into MNI space, limiting to the precentral and postcentral gyrus above the highest section of the stroke lesion (Fig. 2). Lastly, FCs of interhemispheric M1 (M1-M1 FC) and S1 (S1-S1 FC) were calculated using Pearson's correlation coefficient between the mean time series of bilateral M1 and S1. A Fisher's r-to-z transformation was applied to improve the normality of these correlation coefficients.

### Lesion volume and CST damage

The volume of stroke lesion was determined on diffusion-weighted imaging (DWI) images and the extent of corticospinal tract (CST) damage was calculated according to the overlap between stroke lesion and CST, which were described in our previous study [9].

### Statistics

Statistical analysis was performed using SPSS software version 20.0 for Windows (IBM, Armonk, New York). A two-tailed value of $p < 0.05$ was considered significant. The differences in basic information between two groups were compared using two sample independent *t*-test or Mann-Whitney *U* test for continuous variables and Pearson $\chi^2$ test or Fisher exact test for categorical variables. The differences in DTI parameters of CC, M1-M1 FC and S1-S1 FC among three groups were compared using a general linear model, adjusting for age and gender. Multiple comparisons corrected *p* values of 0.0025 and 0.025 were respectively used for DTI parameters (0.05/20, five subregions and four parameters) and FC (0.05/2, two regions). The effect sizes were estimated using partial eta-squared ($\eta_p^2$). Least significant difference was used for post-hoc test. The correlations between the duration of diabetes, FPG and $HbA_{1c}$ with abnormal DTI parameters of CC were analysed using partial correlation, adjusting for age and gender. The relationships between abnormal DTI parameters of CC with M1-M1 FC and S1-S1 FC were analysed using Pearson's correlation and further corrected by partial correlation, adjusting for age, gender and CST damage. In diabetic patients, multivariate logistic regression was used to identify the independent factor associated with clinical outcome, and the odds ratio (OR) and its 95% confidence intervals (CI) were estimated. Receiver operating characteristic (ROC) curve was further performed to determine the independent factor in predicting stroke outcome.

## Results

### Patient characteristics

Among 45 patients, there were 26 patients with diabetes and 19 without diabetes. In patients with diabetes, the duration of diabetes was 7.3 ± 4.2 years (range, 2-20 years). Diabetic patients had a significantly higher FPG ($p < 0.001$), HbA1c

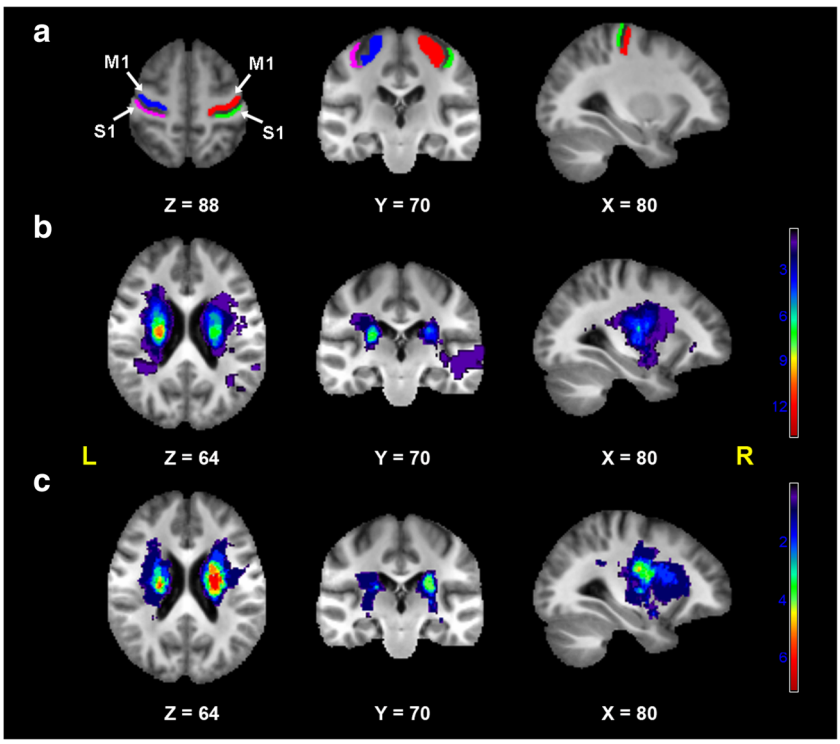


**Fig. 2** Regions of interest of primary motor cortex (*M1*) and primary sensory cortex (*S1*) (**a**) and lesion overlap maps of diabetic patients (**b**) and non-diabetic patients (**c**). M1, S1 and lesion maps were visualised by overlaying onto the group-averaged normalised 3D-T1 weighted image. The *colour bars* in **b** and **c** indicate the number of patients with a lesion in that voxel. *L* left and *R* right

($p < 0.001$) and a relatively higher ms-NIHSS ($p = 0.086$), compared with non-diabetic diabetes (Table 1).

## Abnormal CC among groups

Figure 3 shows the comparisons of DTI parameters measured in different subregions of CC among three groups. Diabetic patients had significantly decreased FA only in the isthmus of the CC ($CC_{isthmus}$) when compared to non-diabetic patients and NC ($p < 0.0001$, $\eta_p^2 = 0.400$). Post-hoc analysis further revealed that the FA of $CC_{isthmus}$ was significantly lower in diabetic patients than that in non-diabetic patients ($p < 0.0001$) and in NC ($p < 0.0001$). There was a trend towards an increasing of $\lambda_{23}$ of $CC_{isthmus}$ in diabetic patients ($p = 0.030$, $\eta_p^2 = 0.176$), but not of MD ($p = 0.241$, $\eta_p^2 = 0.095$) and $\lambda_1$ ($p = 0.718$, $\eta_p^2 = 0.037$). No significant differences were found in MD, $\lambda_1$ and $\lambda_{23}$ in other CC subregions among three groups. FA of $CC_{isthmus}$ was significantly correlated with HbA1c ($r = -0.347$, $p = 0.023$) but not with the duration of diabetes ($r = -0.095$, $p = 0.658$) and FPG ($r = -0.217$, $p = 0.161$).

## Abnormal sensorimotor connectivity among groups

Figure 4 showed the differences in M1-M1 FC and S1-S1 FC among three groups. Within the three groups, diabetic patients had the lowest M1-M1 FC ($p = 0.013$, $\eta_p^2 = 0.206$) and S1-S1 FC ($p = 0.001$, $\eta_p^2 = 0.292$). Significant difference in M1-M1 FC was found between diabetic patients and NC ($p = 0.005$). Diabetic patients had a lower M1-M1 FC than non-diabetic patients, but it did not reach significance ($p = 0.076$). Post-hoc analysis demonstrated significant difference in S1-S1 FC between diabetic and non-diabetic patients ($p = 0.009$), and between diabetic patients and NC ($p < 0.001$). No significant difference was found in both M1-M1 FC ($p = 0.216$) and S1-S1 FC ($p = 0.205$) between non-diabetic patients and NC.

## CC integrity correlated with sensorimotor connectivity

FA of $CC_{isthmus}$ was positively correlated with M1-M1 FC ($r = 0.511$, $p < 0.001$, Fig. 5a) and S1-S1 FC ($r = 0.553$, $p < 0.001$, Fig. 5b). After adjusting for age, gender and CST damage, the correlation between FA of $CC_{isthmus}$ and M1-M1 FC remained to be significant ($r = 0.471$, $p = 0.002$). After age and gender adjustment, FA of $CC_{isthmus}$ remained to be correlated with S1-S1 FC ($r = 0.509$, $p < 0.001$). In diabetic patients, FA of $CC_{isthmus}$ also showed positive correlations with M1-M1 FC ($r = 0.549$, $p = 0.004$, Fig. 5c) and S1-S1 FC ($r = 0.507$, $p = 0.008$, Fig. 5d). FA of $CC_{isthmus}$ remained to be correlated with M1-M1 FC ($r = 0.545$, $p = 0.007$) after adjusting for age, gender and CST damage, and S1-S1 FC ($r = 0.500$, $p = 0.015$) after adjusting for age and gender.

**Table 1** Clinical and imaging characteristics between stroke patients with and without diabetes

| Variables | With diabetes $n = 26$ | Without diabetes $n = 19$ | $p$ value |
|---|---|---|---|
| Age, mean ± SD, years | 62.3 ± 11.6 | 58.0 ± 13.3 | 0.253 |
| Men, no. (%) | 15 (57.7) | 8 (42.1) | 0.302 |
| Time to MRI examination, mean ± SD, days | 5.2 ± 1.2 | 5.7 ± 1.2 | 0.220 |
| FPG on admission, mean ± SD, mmol/L | 9.2 ± 3.8 | 5.3 ± 0.8 | < 0.001* |
| $HbA_{1c}$, mean ± SD, % | 8.4 ± 1.7 | 5.9 ± 0.7 | < 0.001* |
| Duration of diabetes, mean ± SD, years | 7.3 ± 4.2 | - | - |
| Hypertension, no. (%) | 17 (65.4) | 13 (68.4) | 0.831 |
| Hyperlipidaemia, no. (%) | 8 (30.8) | 2 (10.5) | 0.154 |
| Smoking, no. (%) | 11 (42.3) | 5 (26.3) | 0.351 |
| Drinking, no. (%) | 8 (30.8) | 4 (21.1) | 0.467 |
| Lesion left location, no. (%) | 11 (42.3) | 9 (47.4) | 0.736 |
| Lesion size, median, IQR, $cm^3$ | 3.8 (2.2–9.8) | 3.3 (2.0–9.8) | 0.765 |
| CST damage, mean ± SD, $cm^3$ | 1.0 ± 0.4 | 0.9 ± 0.6 | 0.666 |
| NIHSS score, mean ± SD | 8.2 ± 2.8 | 6.9 ± 2.6 | 0.118 |
| ms-NIHSS score, mean ± SD | 5.5 ± 2.1 | 4.3 ± 2.6 | 0.086 |
| Barthel index, mean ± SD | 41.7 ± 20.0 | 48.2 ± 25.1 | 0.345 |
| Poor outcome, No. (%) | 11 (44.0) | 6 (33.3) | 0.480 |

* $p < 0.05$

*SD* standard deviation, *MRI* magnetic resonance imaging, *FPG* fasting plasma glucose, *IQR* interquartile range, *CST* corticospinal tract, *NIHSS* National Institute of Health Stroke Score, *ms-NIHSS* motor and sensory components of NIHSS

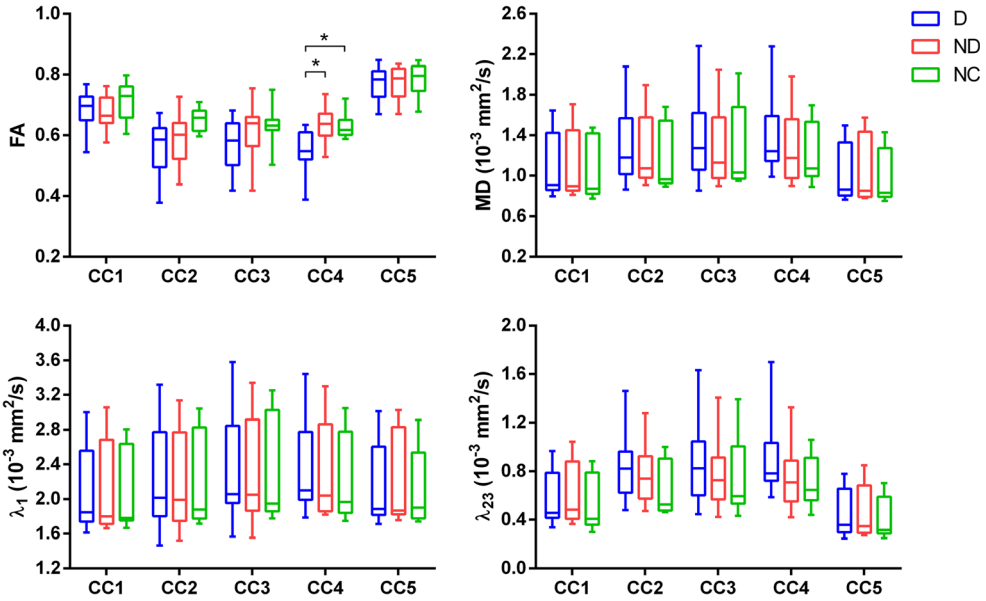


**Fig. 3** Comparisons of fractional anisotropy (*FA*), mean diffusivity (*MD*), axial diffusivity ($\lambda_1$) and radial diffusivity ($\lambda_{23}$) in each subregion of corpus callosum (from CC1 to CC5) among groups of diabetes (*D*), non-diabetes (*ND*) and normal controls (*NC*); * $p < 0.0025$

## Factor associated with prognosis in diabetic patients

In patients with diabetes, FA of $CC_{isthmus}$ ($p = 0.024$), M1-M1 ($p < 0.001$) and S1-S1 ($p = 0.002$) were significantly lower in poorly recovered patients. The differences in other variables were shown in Table 2. Multiparametric model, including age, gender, lesion size, CST damage, FA of $CC_{isthmus}$, M1-M1 FC, S1-S1 FC, NIHSS and ms-NIHSS, identified M1-M1 FC as the only independently variable correlating with poor outcome (OR = 0.448; 95% CI, 0.231-0.866; $p = 0.017$). ROC showed that M1-M1 FC with a threshold of 0.56 had a high sensitivity (83.3%) and specificity (100%) in predicting stroke outcome (Fig. 6).

## Discussion

In the current study, we found the following results: firstly, compared with non-diabetic patients and normal controls, diabetic patients had decreased white matter integrity in the isthmus of CC and reduced inter-hemispheric sensorimotor connectivity. Secondly, the decreased FA in the isthmus of CC correlated with inter-hemispheric sensorimotor connectivity. Thirdly, the interhemispheric motor connectivity was an independent contributor to poor outcome after stroke in diabetic patients.

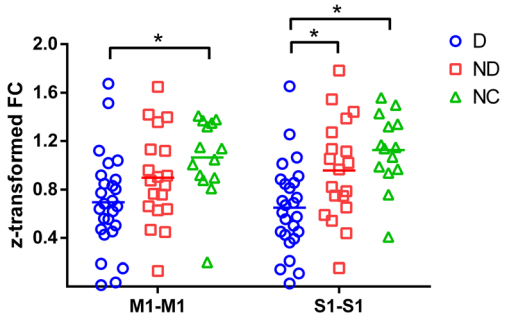


**Fig. 4** Scatter dot plots showed z-transformed inter-hemispheric functional connectivity (*FC*) of primary motor cortex (*M1-M1*) and primary sensory cortex (*S1-S1*) among groups of diabetes (*D*), non-diabetes (*ND*) and normal controls (*NC*); * $p < 0.025$

In diabetic patients with acute stroke, the evidence of microstructural changes, expressed as a reduction in FA is seen predominantly in the isthmus of CC. Furthermore, the decreased FA in the isthmus of CC negatively correlated with an increased HbA1c supporting the hypothesis that CC damage is mediated, either directly or indirectly by chronic hyperglycaemia. In addition to FA, other DTI metrics including MD, $\lambda_1$ and $\lambda_{23}$ are equally essential to characterise the pathological process affecting the white matter. We found that diabetic patients had an increased $\lambda_{23}$, but not $\lambda_1$ in the isthmus of CC, suggesting that demyelination is the main pathological change underlying the decreased integrity of $CC_{isthmus}$. Glycation of myelin may be the potential mechanism for white matter demyelination in diabetes. Metabolic pathways involving formation of advanced glycation end (AGE) products is implicated in hyperglycaemic nerve damage [25]. AGE-modified nerve myelin is susceptible to phagocytosis by macrophages, contributing to demyelination [25].

Demyelination in strategic location of the CC causes decreased interhemispheric connections in corresponding cortical areas. In our study, we demonstrated reduction in inter-hemispheric M1-M1 and S1-S1 connectivity at a group level and further found that decreased FC in both M1-M1 and S1-S1 were paralleled with decreased FA of $CC_{isthmus}$. DTI tractography maps demonstrate connectivity of $CC_{isthmus}$ with both sensory and motor cortical areas [26]. Therefore, our

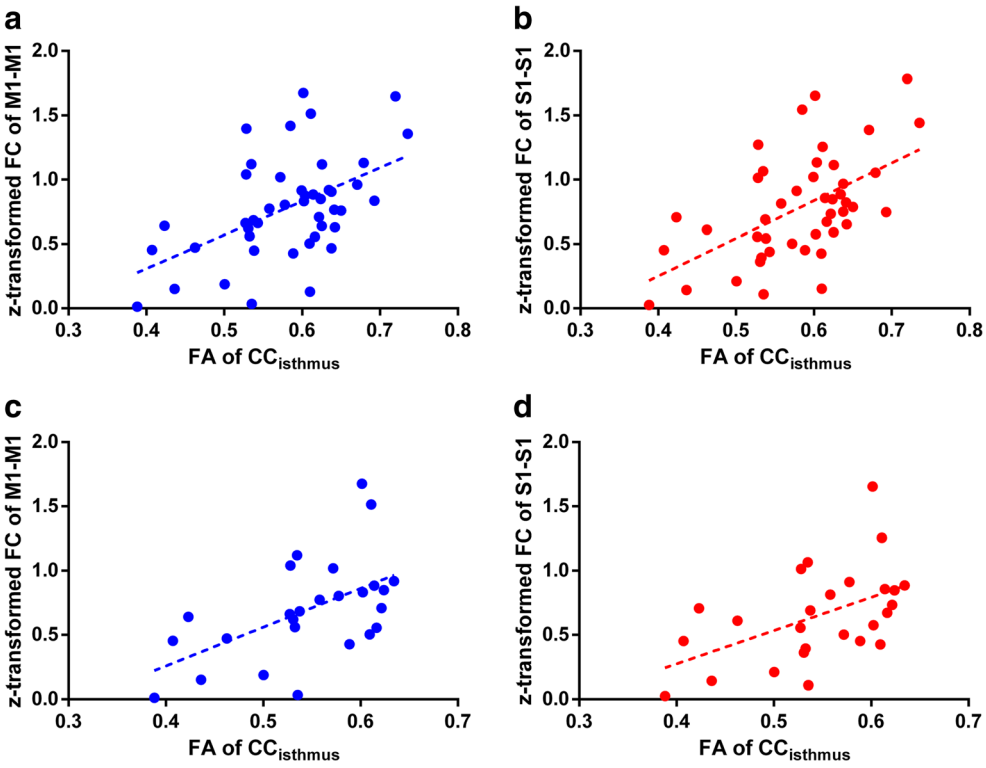


**Fig. 5** Scatter dot plots showed significant correlations between fractional anisotropy (*FA*) in the isthmus of corpus callosum ($CC_{isthmus}$) with functional connectivity (*FC*) of primary motor cortex (*M1-M1*) and primary sensory cortex (*S1-S1*) in the group of stroke patients (**a, b**) and subgroup of stroke patients with diabetes (**c, d**)

**Table 2** Clinical and imaging characteristics between diabetic patients with poor/good outcome after stroke

| Variables | Poor outcome $n = 12$ | Good outcome $n = 14$ | $p$ value |
|---|---|---|---|
| Age, mean ± SD, years | 64.9 ± 10.9 | 60.0 ± 12.1 | 0.290 |
| Men, no. (%) | 7 (58.3) | 8 (57.1) | 0.951 |
| Time to MRI examination, mean ± SD, days | 5.2 ± 1.2 | 5.3 ± 1.3 | 0.808 |
| FPG on admission, mean ± SD, mmol/L | 8.3 ± 2.7 | 9.9 ± 4.6 | 0.300 |
| HbA1c, mean ± SD, % | 8.2 ± 2.0 | 8.4 ± 1.7 | 0.804 |
| Duration of diabetes, mean ± SD, years | 7.7 ± 3.9 | 6.9 ± 4.7 | 0.668 |
| Hypertension, no. (%) | 8 (66.7) | 9 (64.3) | 1.000 |
| Hyperlipidaemia, no. (%) | 5 (41.7) | 3 (21.4) | 0.401 |
| Smoking, no. (%) | 5 (41.7) | 6 (42.9) | 0.951 |
| Drinking, no. (%) | 5 (41.7) | 3 (21.4) | 0.401 |
| Lesion left location, no. (%) | 5 (41.7) | 6 (42.9) | 0.951 |
| Lesion size, median, IQR, $cm^3$ | 9.2 (3.4–15.6) | 2.1 (1.6–3.8) | 0.001* |
| CST damage, mean ± SD, $cm^3$ | 1.1 ± 0.3 | 0.8 ± 0.4 | 0.032* |
| FA of $CC_{isthmus}$, mean ± SD | 0.51 ± 0.08 | 0.57 ± 0.05 | 0.024* |
| M1-M1, mean ± SD | 0.43 ± 0.31 | 0.93 ± 0.31 | <0.001* |
| S1-S1, mean ± SD | 0.43 ± 0.29 | 0.84 ± 0.32 | 0.002* |
| NIHSS score, mean ± SD | 9.7 ± 2.6 | 6.9 ± 2.3 | 0.009* |
| ms-NIHSS score, mean ± SD | 6.6 ± 2.2 | 4.6 ± 1.6 | 0.016* |
| Barthel index, mean ± SD | 37.1 ± 18.1 | 46.1 ± 21.2 | 0.241 |

* $p < 0.05$

*SD* standard deviation, *MRI* magnetic resonance imaging, *FPG* fasting plasma glucose, *IQR* interquartile range, *CST* corticospinal tract, *FA* fractional anisotropy, *CC* corpus callosum, *M1* primary motor cortex, *S1* primary sensory cortex, *NIHSS* National Institute of Health Stroke Score, *ms-NIHSS* motor and sensory components of NIHSS

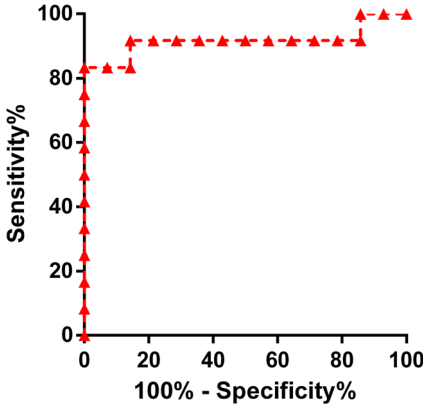


**Fig. 6** Receiver operating characteristic (ROC) curve showed that inter-hemispheric motor connectivity with a threshold of 0.56 predicts poor stroke outcome in diabetic patients with a sensitivity of 83.3% and specificity of 100%. The area under the ROC curve was 0.917

results suggest that selective demyelination in the isthmus part of CC results in slower conduction or complete failure of transferring sensory or motor information between the two hemispheres. Previous studies have focused almost exclusively on the M1-M1 [12, 16, 27], whereas studies of the S1-S1 are spare. Sensory connectivity contributes to the integration of sensor and motor signals necessary for skilled movement, which plays a crucial role in motor recovery after stroke [19]. Although decreased interhemispheric connectivity of M1-M1 and S1-S1 have been observed, it remains unclear whether the signal exchange is inhibitory or excitatory in nature.

In diabetic patients, we found that poor recovery after stroke is significantly more common in the presence of callosal degeneration and reduced sensorimotor connectivity. Following multi-parametric regression analysis, decreased motor connectivity was the only independent significant factor of outcome. These findings suggest that abnormal motor network is a more important biomarker of the likelihood of poor recovery after stroke than simple measures of structural degeneration. Early stroke recovery is associated with resolution of oedema and reperfusion of the ischaemic penumbra [28], while later recovery is related to brain plasticity [29]. Early decreased motor connectivity may influence the later reorganisation of the motor network after stroke. In addition, it should be noted that following demyelination, remyelination of CC may occur in some diabetic patients during stroke recovery, which explains callosal degeneration has no independent effect on stroke outcome. Animal studies have shown that endothelial progenitor cells, which are viewed as adult stem cells, are accumulated in the injured CC, contributing to CC remodelling [30, 31].

There are some limitations to this study. Firstly, it is a cross-sectional study and, therefore, the dynamic change in microstructure of CC and sensorimotor network during stroke recovery is unknown. Secondly, dichotomous analysis of clinical outcome based on mRS is probably too crude to reflect functional recovery and, thus, interpretation of our results should be cautious. Thirdly, the sample size of stroke patients with diabetes is small and, therefore, the prediction of inter-hemispheric motor connectivity in stroke outcome needs to be further validated in a large sample.

## Conclusions

This study demonstrates that in patients with acute stroke, CC degeneration induced by diabetes correlates with impairment of inter-hemispheric sensorimotor connectivity. The decreased inter-hemispheric motor connectivity is an independent factor contributing to poor recovery after stroke for diabetic patients.

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Minming Zhang.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**Statistics and biometry** No complex statistical methods were necessary for this paper.

**Informed consent** Written informed consent was obtained from all subjects in this study.

**Ethical approval** Institutional Review Board approval was obtained.

**Methodology**
- prospective
- cross-sectional study
- performed at one institution

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