The effect of diabetes on cortical function in stroke: implications for post-stroke plasticity.

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Abstract

Diabetes may impair the capacity for neuroplasticity such that patients experience a slower and poorer recovery after stroke. The current study aimed to investigate changes in cortical function in stroke patients with diabetes to determine how this comorbidity may impact post-stroke cortical plasticity and thereby functional recovery. From a cohort of 57 participants, threshold-tracking transcranial magnetic stimulation was utilised to assess cortical function over the ipsi- and contralesional hemispheres in 7 diabetic patients following an acute stroke, and compared to 12 stroke patients without diabetes. Cortical function was also assessed in 8 diabetic patients without stroke and 30 normal controls. Following acute stroke, short-interval intracortical inhibition (SICI) was reduced over both motor cortices in non-diabetic stroke patients compared to normal controls, while in diabetic stroke patients SICI was only reduced over the contralesional but not the ipsilesional cortex when compared to diabetic controls. Additionally, SICI was significantly reduced in the diabetic controls compared to normal controls. These results have demonstrated absence of ipsilesional cortical excitability change following diabetic strokes, suggesting impaired capacity for neuroplasticity over this hemisphere as a consequence of a “double-hit” phenomenon because of pre-existing alterations in cortical function in non-stroke diabetic patients. The reliance on reorganization over the contralesional cortex following stroke will likely exert influence on post-stroke recovery in diabetic patients.
Introduction

Diabetes is associated with an increased risk of ischemic stroke. Post-stroke, diabetic patients were predisposed to a slower and poorer recovery of function, even after adjusting for factors such as stroke severity and age (1-4). Furthermore, it remains plausible that diabetes may impair the plasticity of neural circuitry following stroke. Successful recovery from stroke requires the brain to remap sensorimotor functions to surviving and functionally homologous regions within the brain network (5, 6).

Separately, diabetes may directly impair the central nervous system with impairments in cognitive function, synaptic plasticity, synaptogenesis and neurogenesis (3), as well as direct damage to neurons (7). Structural and functional imaging has consistently revealed varying degrees of brain atrophy with disturbed white matter connectivity in diabetics relative to controls (8-12).

Neuroplasticity is defined as the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function and connections. More specifically, it is important to recognize that neuroplasticity is defined by change in neuronal structure or function, not the observation of change in behaviour. For this reason, it can be viewed as adaptive when associated with a gain in function or as maladaptive when associated with negative consequences such as loss of function (13, 14).

Transcranial magnetic stimulation is a useful way to non-invasively index neuroplasticity through measures of cortical excitability. The assessment of inhibitory and facilitatory cortical circuits provides an important component of understanding how neuroplastic change
are mediated and how they underlie associated behavioural and functional changes, following disease or injury (15, 16).

Given this background, the current study hypothesized there may be cortical dysfunction present in diabetic patients and that diabetic patients may demonstrate an impaired capacity for cortical plasticity following an acute stroke. Consequently this may have implications for future developments of neuroprotection and clinical trials aimed at facilitating post-stroke recovery. In this regard, the current study utilised threshold-tracking transcranial magnetic stimulation to assess intracortical excitability and thereby function over both the lesioned and contralesional motor cortices of stroke patients with and without diabetes, and compared results to findings obtained from a cohort of non-stroke diabetic patients and normal controls.

**Methods**

**Subjects**

Patients diagnosed with acute unilateral ischemic stroke (with brain MRI demonstrating acute infarct on diffusion weighted imaging) after presenting to a tertiary teaching hospital stroke unit were recruited and studied within the acute period post-stroke. Exclusion criteria were (i) previous history of stroke; (ii) cognitive impairment or dysphasia sufficient to affect informed consent; (iii) drugs or neurological disorders beyond stroke that may affect cortical excitability; and (iv) any contraindications to TMS. All subjects provided written informed consent and study was approved by the local Health and Research Ethics Committee.

**Cortical Function**
Measures of cortical excitability were assessed by applying a 90mm circular-coil and assessing motor cortices ipsilateral and contralateral to the infarct separately, with recordings measured over the contralateral abductor pollicis brevis muscle (APB) (Figure 1). In non-stroke subjects, the left motor cortex was studied. The side of stimulation was dependent on the side of the coil (A or B) facing upwards. The induced current flow was from the posterior to anterior direction in both hemispheres, such that when stimulating the left motor cortex, side A of the coil was facing up ensuring a posterior-to-anterior current flow within the left motor cortex, while side B was facing up when stimulating the right motor cortex. The coil was adjusted tangentially over the patient’s scalp until optimal position for a motor evoked potential (MEP) was obtained from the APB. To determine the optimal cortical location of each subject’s APB, TMS was first delivered initially over the vertex of the scalp, and then moved in the antero-posterior and medial-lateral directions, until a position produced the largest MEP amplitude at the lowest TMS output was located. This “hot spot” on the scalp was subsequently marked with an “X” using ink.

Currents were generated by two magnetic stimulators connected via a BiStim200 (Magstim Co., UK), such that both conditioning and test stimuli were independently set and delivered through the one coil. Recordings of MEPs were amplified and filtered [3 Hz–3 kHz] using a Grass ICP511 AC amplifier [Grass-Telefactor, Astro-Med, Inc., West Warwick, RI] and sampled at 10 kHz using a 12-bit data acquisition card [National Instruments PCI-MIO-16E-4]. Data acquisition and stimulus delivery were controlled by QTRACS software [© Professor Hugh Bostock, Institute of Neurology, Queen Square, London, UK].

Paired-pulse threshold-tracking transcranial magnetic stimulation (TMS) techniques were utilized to assess intracortical neuronal excitability according to a previously reported and
validated method using threshold-tracking (17-20). The technique was developed to overcome the variability in MEP amplitudes with consecutive stimuli that resulted in limitations using the constant-stimulus method (21). This method was first developed by Fisher and colleagues in 2002 (17), later validated by Vucic and colleagues in 2006 (18), and is currently used and published widely in numerous pathological studies (22-27). Importantly, as suggested by Fisher et al, measurement of intracortical excitability at a constant MEP response using threshold-tracking methods limits the contribution of spinal and peripheral elements to the output measurement.

The threshold-tracking strategy used a target response of 0.2mV (±20%) located in the middle of the established linear relationship between the logarithm of the MEP amplitude and the stimulus intensity (18). By selecting a target that is located in the steepest portion of the stimulus response (SR) curve, relatively large variations in the MEP amplitude translate to relatively small variations in stimulus intensity or threshold.

Resting motor threshold (RMT) was determined in the initial part of the protocol, and was defined as the stimulus intensity required to consistently (average 10 trials) produce and maintain the target MEP response of 0.2mV peak-to-peak, with the patient seated comfortably and testing limb relaxed. Stimulus-response for cortical stimulation was determined by increasing the intensity of the magnetic stimulus to the following levels: 60, 80, 90, 100, 110, 120, 130, 140, and 150% RMT. Three stimuli were delivered at each intensity level and the maximum MEP amplitudes determined.

The cortical silent period (CSP) is mediated by both spinal mechanisms, in its early part, and cortical inhibitory neurons acting via GABA-B receptors in the latter part. Since the duration
is determined by the latter part, the CSP is a measure of cortical inhibition (28). CSP was evoked by single-pulsed TMS with intensities that varied as per the SR curve, and recordings made with participants performing a weak voluntary contraction (10-30% maximum voluntary contraction). This was achieved through the use of a force transducer to measure APB contraction with output processed and displayed using Spike2 data acquisition software (CED, UK) that plots the maximum force generated by a given patient and sets a “window” between 10-30% of this maximum whereby patients are encouraged to keep their subsequent generated force within this window during the CSP protocol. Maximum CSP duration was measured as per convention (29), from the beginning of MEP to the return of EMG activity at 150% RMT stimulus intensity. The selection for this weak tonic voluntary contraction was based on initial studies on CSP with subsequent studies demonstrating no effect of differing levels of contraction on the CSP duration (29-32).

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were measured according to a previously described and published protocol (18). Subthreshold conditioning stimuli at 70% RMT were delivered sequentially at interstimulus intervals of 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 10, 15, 20, and 30ms.

SICI was measured as the increase in test stimulus intensity required to evoke the target MEP, and calculated as follows (17, 18):

\[
SICI = \left[ (\text{Conditioned test stimulus intensity} - \text{RMT})/\text{RMT} \right] \times 100
\]

Facilitation was measured as the decrease in the conditioned test stimulus intensity required to evoke the target MEP. Averaged SICI was determined over the interstimulus intervals of 1 to 7ms, while averaged ICF was determined over the intervals of 10 to 30ms, as described previously (18).
Statistical analysis

Statistical analysis was performed using SPSS v22 (IBM Corp, USA). To address the cortical functional changes that may be present in diabetic patients, electrophysiological data were compared between the diabetic (without stroke) and normal control cohorts, using either Student t-test or Mann-Whitney U-test was used depending on normality of data distribution. To address the changes in cortical function that stroke may induce in those with and without diabetes, all electrophysiological data between the 4 groups were compared using a one-way ANOVA with between-group factor being diabetics (DM), stroke patients with diabetes (DM-stroke), stroke patients without diabetes (stroke) and normal controls. Post-hoc multiple pairwise comparisons were used for subgroup analyses and corrected for by the Tukey HSD test with the familywise significance level set at 0.05. Correlations were assessed by Spearman rank test. $P$-value of $<0.05$ was regarded as statistically significant. Results are expressed as mean ± standard error of the mean (SEM).

Results

Patients

Nineteen patients diagnosed with acute unilateral ischemic stroke were recruited and studied within the acute period (mean 5.8 days, range 1-18, Table 1). Of these stroke patients, 7 were diabetic (3 males; aged 63-86, mean 70.7 years; 6 type II and 1 type I) and 12 non-diabetic (7 males; aged 29-76, mean 63.3 years). The patients in both diabetic and non-diabetic groups were reasonably well matched for age ($P=0.22$), duration from stroke-onset to assessment (diabetic 4.7±0.92 days, non-diabetic 6.6±1.33 days, $P=0.35$) and size of stroke (diabetic 29.01±6.4mm, non-diabetic 24.1±5.1mm, $P=0.56$). The stroke locations were 3 cortical and 4 subcortical in the diabetic group, and 6 cortical and 6 subcortical in the non-diabetic group.
Subcortical infarcts were defined as lesions within the basal ganglia, internal capsule, or corona radiata and sparing the motor cortex, while cortical strokes were defined as wedge-shaped, superficial lesions in the territory of the large major cerebral arteries or lesions in a border zone that involved the motor cortex and potentially underlying white matter. Two patients in the non-diabetic and 2 in the diabetic stroke groups received acute reperfusion therapy.

The functional severity of strokes were similar between the diabetic (Barthel index: 83.6±6.9; Fugl-Meyer: 58.4±0.61; modified Rankin Score: 2.4±0.7) and non-diabetic groups (Barthel index: 73.8±8.3, P=0.38; Fugl-Meyer: 51.5±4.8, P=0.18; modified Rankin Score: 2.5±0.4, P=0.93). The fasting blood glucose levels (BGL) were higher in the diabetic stroke patients (mean 9.09 ±1.2 umol/L) compared with those stroke patients without diabetes mellitus (mean 6.38 ± 0.8 umol/L, P=0.036). In addition, eight patients with diabetes mellitus (4 males; aged 43-76, mean 65.6 years, 1 type I and 7 type II) and 30 control subjects (aged 37-73, mean 55.8 years) without prior history of stroke were recruited for the study. HbA1C were reasonably matched between the diabetic stroke (7.8±0.47%) and diabetic control groups (7.3±0.22%, P=0.46) as was the duration of diabetes (18.1±3.3 years and 19.5±3.6 years, P= 0.79). Six patients from the diabetic stroke group were taking metformin (one was also on gliclazide) and one was on insulin, whilst five patients from the diabetic controls were taking metformin (one also on gliclazide and one also on sitagliptin) and three were on insulin.

**Cortical Function**

*Paired-pulse TMS studies*

*Ipsilesional hemispheric changes*
There was a significant difference present across subgroups when compared over the ipsilesional hemisphere of stroke patients (ANOVA, F=19.4, P<0.001). Short-interval intracortical inhibition (SICI) was significantly reduced over the ipsilesional cortex in the non-diabetic stroke patients (2.7±1.2%) when compared to normal controls (14.0±0.8%, P<0.001), but there was no significant change in SICI in diabetic stroke patients (6.6±2.3%) when compared to diabetic controls (8.9±1.4%, P=0.72) (Figure 2 and Figure 3). In other words, following a stroke, there is a change in cortical excitability (reduction in intracortical inhibition) observed over the stroke hemisphere in patients without diabetes, whilst no such change was demonstrated in diabetic patients following a stroke. Furthermore, there were no significant differences in SICI over the affected hemisphere in diabetic stroke patients when comparing between cortical and subcortical stroke locations (P=0.40).

**Contralesional changes**

When assessing changes over the contralesional cortex, there were also significant differences in SICI across subgroups (ANOVA, F=11.8, P<0.001). In particular, SICI was reduced over the contralesional motor cortex in non-diabetic stroke patients (2.8±2.7%) when compared to normal controls (14.0±0.8%, P=0.001). Of interest, there were also differences in SICI over the contralesional cortices of diabetic stroke patients (-4.0±6.1%) compared with diabetic controls (8.9±1.4%, P=0.013) (Figure 2 and Figure 3). In other words, following an acute stroke there was a significant change in cortical excitability (reduction in intracortical inhibition) observed over the unaffected hemisphere in both non-diabetics and diabetics when compared to their respective control groups. Furthermore, there were no significant differences in SICI over the unaffected hemisphere in diabetic stroke patients when comparing between cortical and subcortical stroke locations (P=0.20).
Control groups

Moreover, averaged SICI was significantly reduced in the diabetic controls (8.9±1.4%) compared with normal controls (14.0±0.8%, P=0.004) (Figure 4). That is, there is an abnormality in cortical excitability (reduction in intracortical inhibition) demonstrated in the control group with diabetes compared to the control group without diabetes that may suggest altered cortical function in diabetic patients which may potentially interfere with adaptive cortical reorganizational processes following an acute neurological insult such as stroke.

Following SICI a period of intracortical facilitation develops. In contrast to SICI findings, there were no significant differences in ICF between the subgroups when comparing the measures over the ipsilesional (ANOVA, F=1.3, P=0.28) and contralesional motor cortices (ANOVA, F=1.8, P=0.17).

When considered as an entire stroke cohort, there were no significant correlations between BGL and SICI over the lesioned (r=-0.14, P=0.6) and contralesional motor cortices (r=0.08, P=0.75). When analysed according to diabetic and non-diabetic stroke groups, there were similarly no significant correlations found (diabetic: lesional, r=-0.26, P=0.63, contralesional, r=0.66, P=0.16; non-diabetic: lesional, r=-0.26, P=0.45, contralesional, r=0.19, P=0.55).

Single-pulse TMS studies

The resting motor threshold (RMT) was comparable across all four subgroups over both ipsilesional (ANOVA, F=0.76, P=0.97) and contralesional (ANOVA, F=0.414, P=0.74) motor cortices. In addition, maximum MEP amplitude was also comparable across the 4 subgroups when measured over the ipsilesional (ANOVA, F=0.37, P=0.78) and contralesional (ANOVA, F=0.11, P=0.95) motor cortices. Of further relevance, maximum
CSP duration, was also similar across the groups (ipsilesional: F=0.37, P=0.77; contralesional: F=0.65, P=0.59).

Discussion

The current study has provided insight into intracortical excitability, and thereby functional changes that occur following an ischemic stroke in diabetic patients and how they differ compared with their non-diabetic counterparts. In addition, the present study has also established changes in cortical function in non-stroke diabetic patients potentially contributing to the changes seen following acute stroke, with implications for post-stroke recovery.

The effect of diabetes on cortical function

The observed reduction in intracortical inhibition in diabetic control (non-stroke) patients reflect reductions in GABA-ergic pathways and may be explained by several mechanisms. Firstly, a loss of cortical GABA-ergic inhibitory neurons may in part underlie the findings in the present study. Structural changes have been demonstrated in human and animal subjects with diabetes that show reductions in grey matter volume (11, 33), with longer disease duration and increased fasting blood glucose appear to be inversely correlated with total grey matter volume (33), while cortical neuronal and axonal degeneration has been reported in animal models (9).

Of further relevance, hyperglycemia may result in neuronal damage through accentuated tissue acidosis and lactate generation (12). Altered glucose metabolism in diabetes has been suggested to result in alterations in neuronal glucose utilization and subsequent neuronal dysfunction. Impaired insulin within the central nervous system in diabetics may also lead to
changes in metabolic pathways necessary for synaptic maintenance (10). Impairment in brain neurotransmitter systems that include GABA (34), have been demonstrated in diabetic rats and can be a direct result from glucose dysregulation on GABA systems as well as through the impact on other neurotransmitters. Specifically, cholinergic and glutamic acid decarboxylase (GAD) activity, both of which modulate cortical GABA neurotransmission, are decreased in diabetic animal models that ultimately also result in reduction in GABA production (34).

Taken together, these mechanisms may underlie the observed reduction in SICI observed in the cohort of diabetic controls compared to normal controls, and consequently may impact the brain’s intrinsic ability to reorganize following a stroke.

**Implications for stroke**

The reductions in GABA-mediated intracortical inhibition observed in diabetics may influence the degree of damage following an acute ischemic stroke as well as negatively impact on the cortical reorganization required for subsequent functional recovery. In the acute phase immediately following stroke, extracellular levels of glutamate contribute to excitotoxic damage. Consequently, the reduced levels of GABA and resultant loss of inhibitory tone in diabetic patients may lead to increased neuronal damage (35). Following the immediate phase of stroke however, the role of GABA-mediated inhibition changes during the structural and functional reorganization process mediating recovery.

Assessing these inhibitory and facilitatory circuits (and thereby intracortical excitability) provide an important understanding of how neuroplastic changes may be mediated and how they underlie associated behavioural change and functional improvement after an insult such
as a stroke (16). Following the acute event, functional recovery will depend on the reorganization of neural networks in the brain that occur over both the ipsilesional and contralesional motor cortices. Previous studies have consistently demonstrated that immediately after an ischemic stroke, there is a reduction of GABA-mediated intracortical inhibition in both hemispheres and are associated with functional improvement over time (19, 20, 36, 37). Moreover, it has been shown that reducing GABA-mediated cortical inhibition promoted functional outcome after stroke (38). Further to this, other studies have also demonstrated that interfering with this intracortical excitability or reduction in SICI either via pharmacological or neuromodulatory interventions resulted in deterioration in stroke functional recovery (39, 40). Cortical hyperexcitability resulting from the reduced GABA-mediated inhibition is associated with greater long-term potentiation (41) and have been demonstrated to positively influence stroke recovery.

The results of the present study have demonstrated that following an acute stroke in diabetics, such cortical plasticity changes were observed only over the contralesional hemisphere and not the stroke side. This may facilitate pyramidal tract axonal sprouting originating from the contralesional motor cortex traversing the midline in order to reach neurons denervated by the stroke in the ipsilesional cortex that is less able to participate in the process of reorganization (42). In this regard, diabetes limits the brain’s capacity for repair and rewiring that is critical for stroke recovery, and there is reduced synaptic plasticity and dendritic density in the cerebral cortex (3). In particular, there is decreased axonal density in the ipsilesional motor cortex of diabetic stroke rat models compared with those stroke rats without diabetes, consequently resulting in impaired neuroplasticity after the ischemic lesion (43). Of further relevance, diabetes in rats prevented the re-emergence of forelimb sensory
representation onto peri-infarct regions in the stroke hemisphere and limited stroke-induced functional changes (3).

Studies in non-diabetic animals have shown that stroke upregulates production of growth-associated proteins, dendritic spines, axonal sprouting, microglial activity and angiogenesis all of which may need an unmasking effect by cortical disinhibition to occur (44, 45), which is not observed over the stroke hemisphere of our diabetic stroke patients. A potential explanation for why there is an inability for the ipsilesional cortex of diabetic subjects to undergo such functional change after stroke may be the “double-hit” phenomenon: an acute insult on a system that already had pre-existing impairments. Remodeling of ischemic brain tissue involves interactions between neurons, glial and microvascular cells that create a microenvironment in which neurological recovery may ensue. Specifically, it is related to the interaction of neuroblasts with the microvasculature in the vicinity of the ischemic lesion that creates an environment to nurture and foster brain remodeling (42). It is therefore possible that pre-existing microvascular damage from diabetes prevent the release of required neurotrophic factors critical in this coupling process needed for neuronal reorganization in the peri-infarct cortex. Compounding this, diabetic patients have network disorganization with inefficient connections between brain regions (7) and may not cope following further insults such as a stroke. This then poses limitations on the brain’s ability to reorganize and facilitate functional recovery with much of the post-stroke neuroplasticity dependent on the contralesional hemisphere. However, without a study examining the evolution of these cortical changes in the same diabetic population pre and post-stroke, this assumption remains speculative.
There is a large body of literature showing that stroke outcomes depend on changes in bihemispheric plasticity (46). Such changes can be adaptive or maladaptive that involve alterations in inter- and intrahemispheric connections. The pre-existing cortical excitability changes in the non-stroke diabetic patients may be considered as maladaptive that potentially limits the scope for optimal recovery by impairing the ability of the stroked hemisphere in diabetic patients to make the necessary alterations in cortical reorganization. Previous studies have shown significant relationship between lesioned and unlesioned hemispheres and how this interaction between hemispheres can be representative of post-stroke plasticity and its association with cortical engagement for motor recovery (46).

The current study has several limitations. Firstly the diabetic cohorts were relatively small in numbers and future studies utilising larger numbers will be needed to confirm the current findings. Being a cross-sectional study, only baseline electrophysiological changes and clinical scores were assessed without longitudinal data on changes in cortical function and clinical outcome measures. As such, longitudinal studies with clinical correlations will also need to be employed to assess whether the baseline changes in the diabetic stroke cohort represent an adaptive or maladaptive electrophysiological response after an ischemic stroke. Moreover, longitudinal studies will determine whether changes in cortical function between diabetic stroke groups with different lesion locations (cortical vs subcortical) evolve over the course of stroke recovery as they relate to outcome measures, and how these changes may be related to the baseline clinical and lesion characteristics and their stroke outcome (20). Of further interest, future studies may also specifically examine the effect of acute reperfusion therapies such as thrombolysis on cortical electrophysiological function. Unfortunately, the present study had only 2 patients who had undergone such therapy in either group and such small numbers would not permit a meaningful statistical analysis. In addition, selection of
patients with stroke into either the diabetic or non-diabetic groups were based on the patients’
background history and hence it may be possible that there may have been patients with
previously undiagnosed diabetes.

Conclusions

In conclusion, the current study has demonstrated that following an acute stroke, much of the
electrophysiological changes in diabetic patients occur over the contralesional and not the
ipsilesional motor cortex – unlike their non-diabetic counterpart where reductions in intracortical inhibition occur equally over both cortices. This potentially provides new insights into the neurophysiological mechanism underlying poor functional outcome after stroke in diabetic patients. The current study has also demonstrated alterations in cortical electrophysiology in patients with diabetes that may correlate with previously explored changes in cortical structure observed in neuroimaging, and may contribute to the impaired cortical plastic changes following stroke. The results of the current study may have implications towards the development of neuroprotective strategies for diabetic patients and particularly those suffering a stroke, and will guide the use of novel tools such as non-invasive brain stimulation at improving post-stroke recovery.

Author Contributions

W.H. researched data, wrote manuscript. N.K. researched data. A.R. reviewed/edited manuscript. A.K. contributed to discussion, reviewed/edited manuscript. C.L. reviewed/edited manuscript. S.V. reviewed/edited manuscript. M.K. reviewed/edited manuscript and contributed to discussion.

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References

**FIGURE LEGEND**

**Figure 1.** Transcranial magnetic stimulation excites a network of neurons in the underlying motor cortex with motor evoked potentials recorded over the contralateral abductor pollicis brevis muscle. The motor cortex is preferentially stimulated when the current flows in a posterior–anterior direction within the motor cortex. (Reproduced with permissions under the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license: Vucic et al. J Neurol Neurosurg Psychiatry 2013;84:1161-1170).

**Figure 2.** Averaged short-interval intracortical inhibition (SICI). (A) Non-Diabetic groups: significant reductions in SICI in both ipsilesional and contralesional motor cortices of stroke patients compared with controls; (B) Diabetic groups: SICI was reduced in the contralesional but not the ipsilesional motor cortex of diabetic stroke patients compared to diabetic controls. NS, non-significant; *P<0.05; ***P<0.001. Error bars represent the SEM (standard error of the mean).

**Figure 3.** Averaged short-interval intracortical inhibition (SICI) demonstrating changes observed following stroke over the ipsilesional and contralesional motor cortices in the non-diabetic (shaded) and diabetic patient groups (white). Error bars represent the SEM (standard error of the mean).
**Figure 4.** Averaged short-interval intracortical inhibition (SICI) was significantly reduced in the diabetic control group compared to the normal control group. **P<0.01.** Error bars represent the SEM (standard error of the mean).

### TABLES

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**Table 1.** Baseline patient characteristics. ¥ Handedness using the Edinburgh Handedness Inventory. € Time since onset of acute stroke to first study. HT, background of hypertension. Patient 7’s Fugl-Meyer score was difficult to assess given significant global aphasia.
Figure 1. Transcranial magnetic stimulation excites a network of neurons in the underlying motor cortex with motor evoked potentials recorded over the contralateral abductor pollicis brevis muscle. The motor cortex is preferentially stimulated when the current flows in a posterior–anterior direction within the motor cortex. (Reproduced with permissions under the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license: Vucic et al. J Neurol Neurosurg Psychiatry 2013;84:1161-1170).
Figure 2. Averaged short-interval intracortical inhibition (SICI). (A) Non-Diabetic groups: significant reductions in SICI in both ipsilesional and contralesional motor cortices of stroke patients compared with controls; (B) Diabetic groups: SICI was reduced in the contralesional but not the ipsilesional motor cortex of diabetic stroke patients compared to diabetic controls. NS, non-significant; *P<0.05; ***P<0.001. Error bars represent the SEM (standard error of the mean).
Figure 3. Averaged short-interval intracortical inhibition (SICI) demonstrating changes observed following stroke over the ipsilesional and contralesional motor cortices in the non-diabetic (shaded) and diabetic patient groups (white). Error bars represent the SEM (standard error of the mean).
Figure 4. Averaged short-interval intracortical inhibition (SICI) was significantly reduced in the diabetic control group compared to the normal control group. **P<0.01. Error bars represent the SEM (standard error of the mean).