The role of corticofugal fibres involvement in motor deficit following subcortical stroke

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Complete List of Authors:	Phan, Thanh; Monash Medical Centre, Neurology de Voort, Sanne; Monash University, Medicine chen, jian; Monash University, Medicine Beare, Richard; Monash University, Medicine Ma, Henry; Monash University, Medicine Clissold, Benjamin; Monash University, Medicine Ly, John; Monash University, Medicine Foster, Emma; Monash Medical Centre, Stroke Thong, Eleanor; Monash Medical Centre, Stroke Srikanth, Velandai; Monash University, Medicine
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The role of corticofugal fibres involvement in motor deficit following subcortical stroke

Thanh G Phan, FRACP, PhD, Sanne van der Voort, Jian Chen, ME, Richard Beare, PhD, Henry Ma, FRACP, Benjamin Clissold, FRACP, John Ly, FRACP, Emma Foster, MBBS, Eleanor Thong, MBBS, Velandai Srikanth FRACP, PhD

Stroke Unit, Monash Medical Centre[1] and Stroke and Aging Research Group[2], Neurosciences, Southern Clinical School, Monash University[1]

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Corresponding Author:
Prof Thanh G Phan
Department of Neurology, Monash Health, 246 Clayton Road, Clayton
Stroke and Aging Research Group, Department of Medicine, Monash University
Victoria, Australia, 3168, Phone: +613 9594 2240, Fax: +613 9594 6241
Email: Thanh.Phan@monash.edu

Background: Motor outcome following subcortical stroke may depend on integrity of the descending motor corticofugal tracts (primary motor cortex (M1), premotor area (PMdv) and supplementary motor area (SMA)). We hypothesise that motor deficit from subcortical stroke is associated with involvement of corticofugal fibres.

Methods: Patients with subcortical infarcts on MR imaging admitted to our institution (2009-2011) were included. Outcome at 3 months days were classified according to the National Institute of Health Stroke Scale (NIHSS) sub-scores for arm and leg motor deficit at 90 days. The infarcts were manually segmented, registered into standard space. In normal subjects (n=16), the corticofugal fibres were delineated using diffusion tractography and registered to standard space. Results: The area under the ROC curve (AUC) for the volume of overlap with infarct (and M1/PMdv/SMA fibres) and motor outcome was calculated. There were 57 patients (57% male) with mean age 64.3± 14.4 year-old. The AUC for the association with arm motor deficit from M1 fibres involvement was 0.80 (95% CI 0.66-0.94), PMdv was 0.76 (95% CI 0.61-0.91) and SMA was 0.73 (95% CI 0.58-0.88). The AUC for leg motor deficit from M1 fibres involvement was 0.69 (95% CI 0.52-0.85), PMdv was 0.67 (95% CI 0.50-0.85), SMA was 0.66 (95% CI 0.48-0.84). The AUC for disability from M1 fibres involvement was 0.88 (95% CI 0.79-0.97), PMdv was 0.83 (95% CI 0.70-0.97), SMA was 0.82 (95% CI 0.67-0.97).

Conclusion: In this small series, the diagnostic accuracy of the corticofugal fibres for neurological deficit following subcortical stroke was variable. A poor motor outcome was not universal following subcortical stroke.

Article Summary

Focus

1. Motor outcome following subcortical stroke *may* depend on integrity of the descending motor corticofugal tracts.
2. We hypothesise that motor deficit from subcortical stroke is associated with involvement of corticofugal fibres
3. Diffusion tractography was used to segment the corticofugal fibres in normal subjects and the segmentation products were overlapped with subcortical infarcts from MR images of patients.

Key messages

1- Motor deficit from subcortical stroke is usually associated with involvement of corticofugal fibres.

2- The strength of this involvement was higher for arm than leg motor deficit.

3- A poor motor outcome was not universal following subcortical stroke.

Strength and limitations

1. Relatively small sample size
2. Retrospective analysis of clinical data

Introduction

Motor deficit has been found to be the most common impairment in stroke patients[1]. Inpatient hospitalization, rehabilitation and nursing home care contribute significantly to the economic burden of stroke care[2]. Stroke clinicians and rehabilitation specialists are often faced with making difficult decisions regarding long-term prognosis and potential rate of motor recovery for patients. It has been suggested that the volume of infarct is an important factor influencing clinical outcome, but infarct volume appears to be moderately correlated with clinical outcome measurements and mainly in anterior circulation stroke[3-4]. This may have been related to the motor structures located in the territory of the internal carotid artery. Investigators have recently evaluated the impact of the location of infarcted tissue on neurological deficit and pointing to the importance of the corticospinal tract involvement to motor outcome [5-10] and the role of the premotor cortex in gait outcome [11], motor deficit and post-stroke disability[5].

Damage to the primary motor cortex (M1) or its descending corticospinal fibre has previously been considered to result in persistent hemiparesis[10 12-15]. Investigators have related loss of integrity of fibre tracks from M1 to poor motor outcome in more than 100 patients with cortical and/or subcortical stroke [10 12-13 16]. This idea has been re-inforced by suggestion of poor motor outcome in patients with early Wallerian degeneration of the corticospinal fibres following stroke [6]. Investigators have described other descending corticofugal fibres which may play an important role in modifying the impact of lesions affecting the descending pathway (n = 49 cortical and/or subcortical stroke patients)[15 17-19]. These corticofugal fibres come from pre-motor or non-primary motor cortices such as the supplementary motor area (SMA),

cingulate motor areas and dorsal and ventral premotor cortices (PMdv). The corticofugal fibres descend in the subcortical white matter and hence patients with subcortical strokes were chosen in this study to explore the direct impact of such lesions on the motor pathway. Some of the studies described above included both cortical and subcortical stroke and thus introduced the additional complexity of cortical infarcts impacting on clinical outcome [16-17]. To resolve this issue we plan to study contribution of involvement of corticofugal fibres by subcortical stroke to motor outcome. We hypothesise that motor deficit from subcortical stroke is associated with involvement of corticofugal fibres.

Methods

Subjects

We examined data of all patients who had been admitted to the stroke unit between August 2009 until October 2011. Patients were included into this project if they had suffered a subcortical ischaemic infarct and have had MR imaging. Patients who have had a symptomatic previous infarct, and patients with a history of neurodegenerative disease, were excluded to prevent misattribution of symptoms. In this study different investigators were involved in segmenting infarct, performing tractography and extracting clinical outcome data at 3 months. This study was approved by the Research Directorate of Southern Health.

Clinical outcome.

Neurological deficit from stroke on admission and at 90 days were determined retrospectively from the medical records using the National Institute of Health Stroke Scale (NIHSS) [6]. In this study, we used NIHSS sub-scores to summarise deficit in individual domains. For motor deficit, we used the NIHSS sub-scores for left arm motor deficit (Items 5a), left leg motor deficit (Item 6a), right arm motor deficit (Items 5b), right leg motor deficit (Items 6b). Clinical outcomes were dichotomised as good (modified Rankin scale score ≤2) or poor (modified Rankin scale score >2).

MR image processing

MRI scans were performed on a 1.5 Tesla superconducting imaging system (General Electric Medical Systems, Milwaukee, WI and Siemens Medical Solutions, Malvern, Pennsylvania) with echo-planar imaging capabilities. Fluid attenuated inversion recovery T_2 images (FLAIR) were acquired using thickness 5mm, matrix 256 x 220,

and TR/TE/TI 8802/130/2200. The 3-D time of flight MRA was performed using TR/TE 38/6.9, 25^0 flip angle, thickness 1.4 mm, slab thickness 60 mm, matrix 256 X 224, field of view 180 mm. All images were manually aligned to a standard stereotaxic coordinate space. The manual registration step was performed by choosing individual landmarks for each patient using an interactive display package (Register, available at http://www.bic.mni.mcgill.ca/software/) that allowed the user to ensure that landmark selection progressively improved image registration as evidenced by visual inspection of the alignment of corresponding anatomical structures. These steps led to creation of a 12-parameter linear transformation matrix which allowed for rotation, translation and independent scaling of the patient image along each of the three principal axes [20]. Infarcts were manually segmented on inversion recovery T_2-weighted images using interactive mouse driven software at standardised intensity windows to optimise infarct visualization (Display, available at **http://www.bic.mni.mcgill.ca/software/**).

MR image processing of normal subjects

Non-stroke subjects were obtained from another study on a 3T MR scanner (Siemens Medical System). These diffusion tensor images (DTI) were acquired with the following parameters: TE/TR 87/8000 ms, 60 diffusion weighted directions, 2 diffusion weighting values 0 and 2000 s/mm^2. MRTrix software was used to pre-processing the DTI image and performing the streamline tracks (http://www.brain.org.au/software). This software was used to generate diffusion tensor map, Fraction Anisotropic (FA) map and Eigenvector (EV) map. Streamline tractography then used to delineates fibre tract according to the principal long axis to preserve voxel-voxel directional information.

Definition of corticospinal tracts

The major cortical areas (primary motor cortex (M1), supplementary motor cortex (SMA) and premotor cortices (PMdv)) known to contribute to the descending motor tracks were defined using 16 healthy subjects. The volunteer's T1 weighted image were co-registered to into standard space as defined by the Montreal Neurological Institute (MNI) template. The co-registration process was done using FSL linear registration tool (http://www.fmrib.ox.ac.uk/fsl). The motor cortex (M1) and supplementary motor area (SMA) for both left side and right side were defined using the BrainMap database in MNI space. We used Freesurfer 5.1 (http://surfer.nmr.mgh.harvard.edu/fswiki) to perform parcellation to determine the location of the premotor areas and the primary motor area. Dorsal promotor area (PMd) was identified as superior part of precentral sulcus and ventral premotor area (PMv) was identified as inferior part of precentral sulcus. In this study, PMd and PMv were combined together as premotor area (PMdv). Streamline tracking algorithm was used to trace the tracts connection from these motor areas to pontine nuclei. Once the tracks were obtained we then converted the tracks files into image maps of the fraction of tracks to enter each voxel. These probabilistic maps of descending motor corticofugal tracks from these subjects were finally transformed to standard space (Figure 1). Masks of the corticofugal fibres were created from these maps. Involvement of the corticofugal fibres by stroke was determined by multiplying the corticofugal fibre masks and the infarct. The volumes of overlap between the infarct and the fibre masks were determined by voxel counting method.

Statistical analysis

Different studies reported different metrics of association between motor deficit and corticofugal fibre involvement. To provide comparison data, we provided several metrics of the associations between the volume of infarct overlapping with corticofugal fibres and clinical outcome. Clinical outcome was measured by National Institute of Health Stroke Scale (NIHSS) sub-score for arm/leg motor (dichotomised at zero) and modified Rankin score (dichotomised at two or less to signify mild disability).

The receiver operating characteristics (ROC) curve method measures the trade off between sensitivity and false positive rate. This method was chosen as it may provide a metric of discrimination for motor deficit that can be interpreted clinically. The ROC curve was used to determine the accuracy of infarct overlap with corticofugal fibres and clinical outcome (dichotomised NIHSS sub-scores and modified Rankin score). We followed the suggestion by standard method [21] in the interpretation of the area under ROC (AUC). An AUC of 0.5 is classified as offering discrimination that is no better than by chance; 0.6–0.69 provides poor discrimination; 0.7–0.79 provides acceptable (fair) discrimination; 0.8–0.89 provides good (excellent) discrimination, and 0.9–1.0 provides outstanding discrimination.

Using data from the ROC curve analysis, we calculate the Youden index to determine the optimal threshold of volume of overlap between infarct and corticofugal fibres for discrimination of neurological deficit[22].

Logistic regression was used to analyse the relationships between the motor outcome (NIHSS motor sub-items or modified Rankin scale) against infarct volume overlapped with individual fibre (M1 or PMdv or SMA).

Results

Stroke Patient characteristics

There are 57 patients with mean age 64.3± 14.4 year-old. Fifty seven percent of the subjects were males. The frequencies of risk factors were hypertension 71.9%, diabetes 31.6%, hyperlipidaemia 63.2%, ever-smoker 28.1%, atrial fibrillation 15.7% and ischaemic heart disease 19.3%. The stroke mechanisms were: cardioembolic 11 (19.3%), undetermined 29 (50.9%), large artery 17 (29.8%). Patients were scanned 20.8 ± 25.5 days after stroke onset.

Non-stroke subjects

There were 16 subjects (44.6% male) who volunteered for DTI with mean age 60.1±5.6 year-old. The frequencies of risk factors were hypertension 50.9%, diabetes 50.0%, hyperlipidemia 51.8%, ever-smoker 44.4%, ischaemic heart disease 35.7%. No subjects had a clinical history of stroke nor MR imaging evidence of stroke.

Motor deficit:

The mean and standard deviation for the NIHSS on admission was 5.7±4.1. Motor deficit were initially present in 45/57 (78.9%) patients. The frequency of motor arm deficit was 26/57 (45.6%) and motor leg deficit was 20/57 (35.1%). The NIHSS at 3 months was 2.5±4.7. At this stage, the frequency of motor deficit had decreased to 42.1%; the frequency of motor arm deficit was 32.7%, motor leg deficit was 27.3%, and moderate to severe disability 17.6%.

Infarct volume

The mean infarct volume was 3.8 ± 8.9ml. The mean involvement of the M1 fibre tract by infarct was 1.17± 1.40 ml; PMdv fibre was 0.86± 1.09ml and SMA was 1.11± 1.44ml. There was no infarct which involved only the M1 fibre, or only the PMdv fibre or only SMA fibre. Infarcts locating only at the level of the posterior limb of the internal capsule occurred in 27/57 (47.4%) and corona radiata in 24/57 (42.1%).

Involvement of corticofugal fibres and outcome

The area under the receiver operating charcteristics curve (AUC) for arm motor deficit from M1 fibres involvement was 0.80 (95% CI 0.66-0.94), PMdv was 0.76 (95% CI 0.61-0.91) and SMA was 0.73 (95% CI 0.58-0.88). The AUC for leg motor deficit from M1 fibres involvement was 0.69 (95% CI 0.52-0.85), PMdv was 0.67 (95% CI 0.50-0.85), SMA was 0.66 (95% CI 0.48-0.84). The AUC for disability from M1 fibres involvement was 0.88 (95% CI 0.79-0.97), PMdv was 0.83 (95% CI 0.70-0.97), SMA was 0.82 (95% CI 0.67-0.97). The thresholded infarct volume which maximised the discrimination for any neurological deficit ranged between 0.86-1.06 ml (see Table 1 for display of the threshold infarct volumes and their associated sensitivity and specificity and Figure 2 for cases where infarction of the posterior limb of the internal capsule did not result in permanent motor deficit).

When each of the corticofugal fibre was entered separately in the equation, the regression model showed arm motor deficit was associated with involvement of fibres from M1 (OR = 2.90 per ml, 95% CI 1.41-5.99), PMdv fibres (OR=3.57 per ml, 95% CI 1.38-9.24) and SMA fibres (OR=2.00 per ml, 95% CI 1.09-3.68). Disability was associated with involvement of fibres from M1 (OR = 3.22 per ml, 95% CI 1.48-

6.97), PMdv fibres (OR=2.42 per ml, 95% CI 1.09-5.40) and SMA fibres (OR=2.66 per ml, 95% CI 1.29-5.50). Leg motor deficit was associated with M1 fibres (OR 1.99 per ml, 95% CI 1.15-3.46) and age (OR 1.06 per year increase, 95% CI 1.01-1.12); PMdv fibres (OR 2.98 per ml, 95% CI 1.32-6.73) and age OR 1.07 per year increase, 95% CI 1.01-1.14) and SMA fibres (OR 2.05 per year increase, 95% CI 1.17-3.60) and age (OR per 1.06 per year increase, 95% CI 1.01-1.12). The R^2 for these regression analyses are displayed in Table 1 and range from 0.18-0.31.

Discussion

We had expected to find that involvement of the descending motor corticofugal fibres, in particular the M1 fibres, would always be associated with severe motor deficit. There is a suggestion that the M1 fibres are more closely associated with arm than leg motor deficit. However, the associations between involvement of corticofugal motor fibres to stroke motor deficit and disability were variable. Importantly, prognosis for motor recovery after subcortical infarction was not readily determined by the finding of involvement of corticofugal fibres in our small series. This result may have implications for interpretation of clinical images and extrapolation of infarct location for prognostication on stroke recovery.

Corticofugal fibres

We observed an association between involvement of descending motor corticofugal fibres and motor deficit in stroke patients but cautiously did not draw conclusion regarding importance of one fibre tract over another. Using logistic regression methods, we were not able to assess the independent contribution of each fibre tract to motor outcome due to presence of collinearity (correlated data). This occurred because of overlap between these fibres in healthy volunteer, making it a rare occurrence to have infarct affecting only one fibre tract [17].

In this study, we used the area under the ROC curve and logistic regression to illustrate the effect of involvement of corticofugal fibres on motor coutcome. The expression of odds ratio is familiar to readers of this journal but this metric is not easily intrepreted clinically. For example, the association between arm motor deficit and M1 fibre was OR = 2.90 per ml or an increased odds of arm motor deficit of 2.90

for every 1 ml increased in volume of M1 fibre involvement. By contrast, the use of the AUC permit a clinical interpretation the following interpretations. In this study, the AUC results for M1 ranged from 0.69 (poor discrimination for motor leg deficit), 0.80 (good discrimination for motor arm deficit) to 0.88 (good discrimination for disability) suggesting that when randomly choosing from a group, the clinician may be incorrect 31% (for motor leg deficit), 20% (for motor arm deficit) and 12% (for disability) of the cases [23]. Further, we had determined the optimal threshold to provide another method for understanding the minimal infarct overlap (approximately 1ml) to impact on motor outcome.

With regards to M1 fibres involvement, our findings initially appeared at odd with other studies but this might be resolved when the results of other studies are examined in details[6 10]. Investigator described that there was a statistical association ($p<0.001$) between the weighted M1-lesion load and upper limb Fugl Meyer (FM) score (n=18) but with a partial R^2 of 0.22 the strength of this association was not very strong[10] (compare this result to those in this studies where the R^2 ranged from 0.18-0.31). There are exceptions with some studies reported a stronger association between M1 and FM score/grip strength obtaining R^2 of 0.67 (n=21) [16], R^2 of 0.73 (n=50)[10] and R^2 of 0.74 (n=13)[15]. Other investigators reported that involvement of the corticospinal tract led to arm motor deficit in 19 of 23 patients but closer inspection revealed that 16 of these 19 patients had very mild arm motor deficit[12]. Similarly leg motor deficit was present in 17 of 23 patients in that study with 13 of these 17 patients had mild leg motor deficit[12]. One explanation for the difference is that the NIHSS sub-score for arm motor deficit does not measure hand motor deficit well and hence we may have underestimated the strength of association between corticofugal fibres and hand motor

deficit from subcortical stroke. Inspite of this limitation, the higher odds ratio for arm than leg motor deficit with M1 fibre involvement possibly suggests a greater importance of this fibre tract for upper limb motor movement.

The importance of the M1 fibre to motor deficit is also argued from the point of early Wallerian degeneration of this fibre and possible correlation with poor motor outcome (n=20)[6]. However, the relationship between Wallerian degeneration of the corticospinal tract and motor outcome is inconclusive[24]. Investigators showed that in the setting of subcortical stroke, this MR finding may slow functional recovery but not the final rehabilitation outcome (n=77)[24]. From a practical point, these findings imply that that involvement of corticofugal fibres by stroke increased the odds of motor deficit but it does not mean that permanent motor deficit will always occur. Based on this data, one cannot use this knowledge of subcortical infarct location to prognosticate on stroke recovery or to determine eligibility for rehabilitation.

The findings of this study provide hypothesis generation that the corticofugal fibres may have large residual capacity and may not be associated with poor motor outcome unless all of the fibres are disrupted. Even though the MR scans were performed approximately 3 weeks after onset, another possibility is that the T_2 signal abnormality might have included oedema rather than just necrotic and gliotic tissue. As such the 'infarcted lesion' might not have resulted in significant disruption of the corticofugal fibres and hence our findings.

Study limitations

The limitations of this study include the retrospective nature. Although the sample size in this study is larger than some of the other studies on this subject, the sample size remains relatively small[17-18]. The severity of stroke deficit can be described as mild to moderate; this is not unexpected since we had chosen to evaluate subcortical stroke. In this study, the NIHSS was used to measure arm motor deficit but this tool did not measure hand motor deficit or finger dexterity, a deficit which may evolved from interruption of M1 fibre[25]. As such, we urge caution with our findings with regards to the less than perfect correlation between arm motor deficit and corticofugal fibres. Finally, the effects of corticofugal fibre involvement on clinical outcome are inferred from the likely overlap between the sites of the fibres and the patients' infarcts. We had not directly assessed for disruption of the corticofugal fibres in these patients. The reason was that the MR studies were performed as clinical scans and did not incorporate a dedicated diffusion tensor sequence. Further, there are technical issues associated with performing tractography in stroke patients [12 17-18].

Conclusion

The descending motor corticofugal fibres may have different effect on motor outcome at three months. Further research in this important area is needed to help with determining stroke outcome and understanding of the neural substrate of motor deficit.

Disclosure:

None

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Legends to Figures

Figure 1: The corticofugal fibres from M1 (blue), PMdv (green) and SMA (red).

Figure 2: Examples of patients with infarct involving the posterior limb of the internal capsule but no motor deficit at 90 days.

Table 1: Association between corticofugal fibres and clinical outcome

	M1	PMdv	SMA	
Arm > 0	2.90 (1.41-5.99) 0.22 0.80 (0.66-0.94) 0.96 (0.79, 0.82)	3.57 (1.38-9.24) 0.18 0.76 (0.61-0.91) 0.86 (0.74, 0.84)	2.00 (1.09-3.68) 0.13 0.73 (0.58-0.88) 0.99 (0.79, 0.79)	OR and 95% CI R^2 AUC and 95% CI Threshold volume (ml) sensitivity and specificity
Leg >0	1.75 (1.05-2.94) 0.18 0.69 (0.52-0.85) 1.06 (0.65, 0.75)	2.42 (1.09-5.40) 0.22 0.67 (0.50-0.85) 0.91 (0.59, 0.75)	1.86 (1.06-3.28) 0.19 0.66 (0.48-0.84) 0.99 (0.65, 0.70)	OR and 95% CI R^2 AUC and 95% CI Threshold volume (ml) Sensitivity and specificity
Modified Rankin >2	3.22 (1.48-6.97) 0.31 0.88 (0.79-0.97) 1.05 (1.00, 0.77)	4.42 (1.41-13.84) 0.29 0.83 (0.70-0.97) 1.01 (0.80, 0.77)	2.66 (1.29-5.50) 0.25 0.82 (0.67-0.97) 1.00 (0.80, 0.74)	OR and 95% CI R^2 AUC and 95% CI Threshold volume (ml) sensitivity and specificity

Different metrics of association between corticofugal fibres and outcome were presented to for ease of comparison with other studies. The threshold volume was determined by the Youden Index and presented along with the maximal sensitivity and specificity at that threshold.

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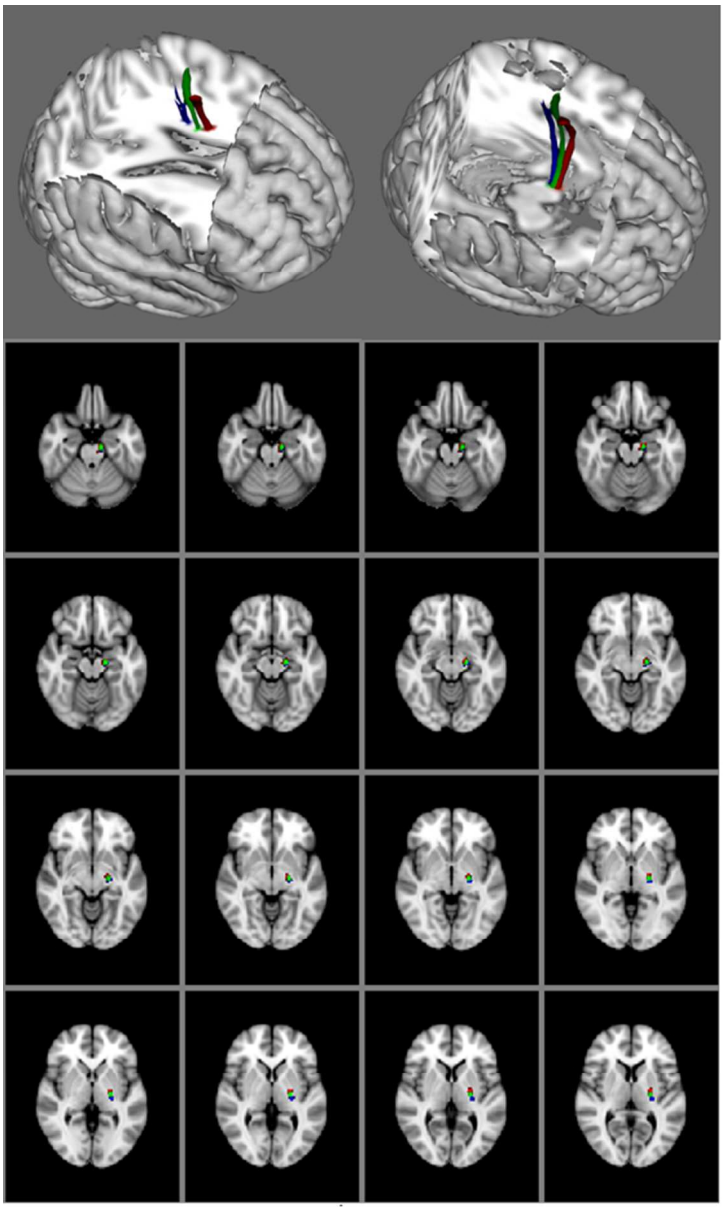

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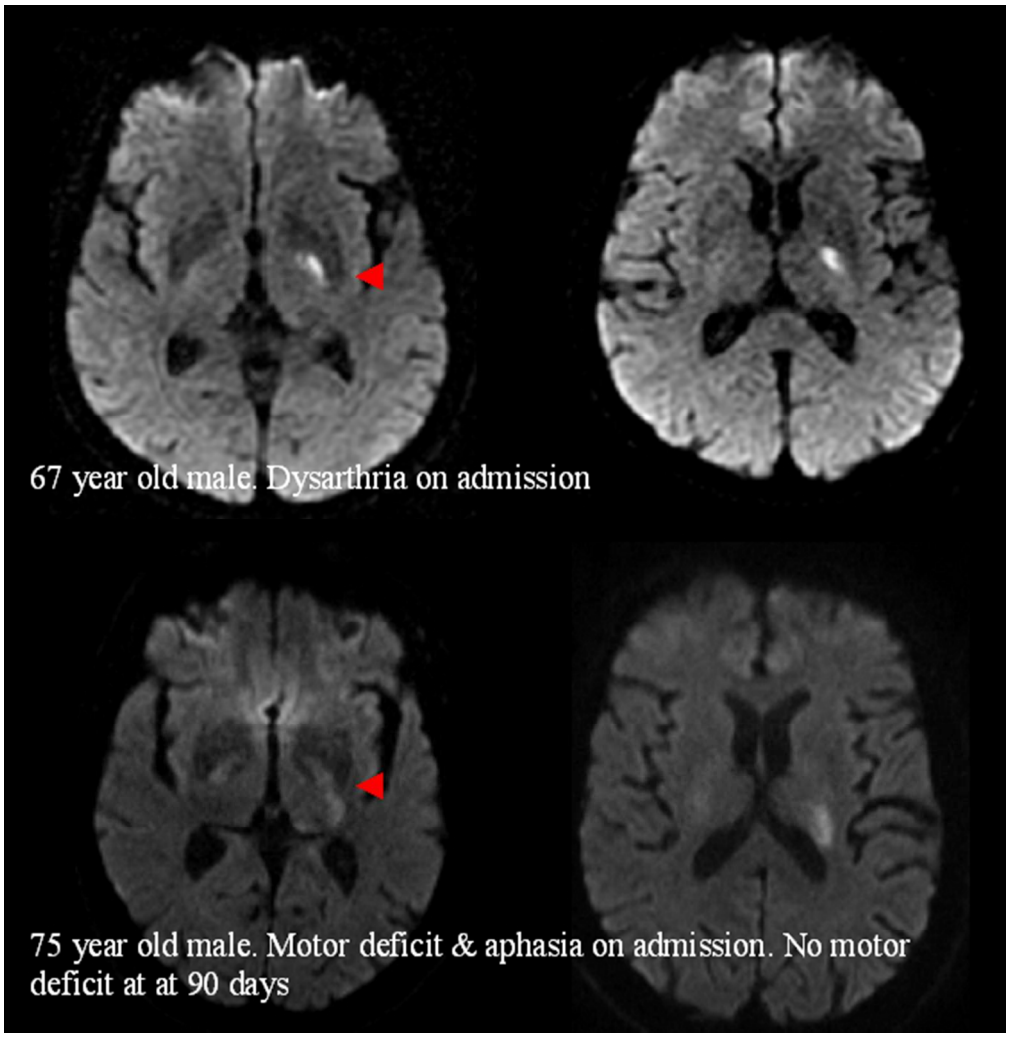

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Complete List of Authors:	Phan, Thanh; Monash Medical Centre, Neurology de Voort, Sanne; Monash University, Medicine chen, jian; Monash University, Medicine Beare, Richard; Monash University, Medicine Ma, Henry; Monash University, Medicine Clissold, Benjamin; Monash University, Medicine Ly, John; Monash University, Medicine Foster, Emma; Monash Medical Centre, Stroke Thong, Eleanor; Monash Medical Centre, Stroke Srikanth, Velandai; Monash University, Medicine
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Following subcortical strokes, corticofugal fibres involvement do not always result in permanent motor deficit

Thanh G Phan, FRACP, PhD, Sanne van der Voort, Jian Chen, ME, Richard Beare, PhD, Henry Ma, FRACP, Benjamin Clissold, FRACP, John Ly, FRACP, Emma Foster, MBBS, Eleanor Thong, MBBS, Velandai Srikanth FRACP, PhD

Stroke Unit, Monash Medical Centre[1] and Stroke and Aging Research Group[2], Neurosciences, Southern Clinical School, Monash University[1]

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Corresponding Author:
Prof Thanh G Phan
Department of Neurology, Monash Health, 246 Clayton Road, Clayton
Stroke and Aging Research Group, Department of Medicine, Monash University
Victoria, Australia, 3168, Phone: +613 9594 2240, Fax: +613 9594 6241
Email: Thanh.Phan@monash.edu

Background: Motor outcome following subcortical stroke may depend on integrity of the descending motor corticofugal tracts (primary motor cortex (M1), premotor area (PMdv) and supplementary motor area (SMA)). **The aim of this study is to correlate motor deficit with involvement of corticofugal fibres in patients with subcortical stroke**.

Methods: Patients with subcortical infarcts on MR imaging (2009-2011) were included. Outcome at 3 months days were classified according to the National Institute of Health Stroke Scale (NIHSS) sub-scores for arm and leg motor deficit at 90 days. The subcortical infarcts were manually segmented, registered into standard space. In normal subjects **obtained from another study** (n=16), the corticofugal fibres were delineated using diffusion tractography **using MRTrix software. The origins of the corticofugal fibres were determined using landmarks for premotor areas and the primary motor area. Masks of the corticofugal fibres were created from these maps. Involvement of the corticofugal fibres by stroke was determined by multiplying the corticofugal fibre masks and the infarct.**

Results: The area under the ROC curve (AUC) for the volume of overlap with infarct (and M1/PMdv/SMA fibres) and motor outcome was calculated. There were 57 patients (57% male) with mean age 64.3± 14.4 year-old. The AUC for the association with arm motor deficit from M1 fibres involvement was 0.80 (95% CI 0.66-0.94), PMdv was 0.76 (95% CI 0.61-0.91) and SMA was 0.73 (95% CI 0.58-0.88). The AUC for leg motor deficit from M1 fibres involvement was 0.69 (95% CI 0.52-0.85), PMdv was 0.67 (95% CI 0.50-0.85), SMA was 0.66 (95% CI 0.48-0.84).

Conclusion: **Following subcortical stroke, the correlations between involvement of the corticofugal fibres for upper and lower limbs motor deficit were variable.** A poor motor outcome was not universal following subcortical stroke.

Introduction

Motor deficit has been found to be the most common impairment in stroke patients [1]. Inpatient hospitalisation, rehabilitation and nursing home care contribute significantly to the economic burden of stroke care[2]. Stroke clinicians and rehabilitation specialists are often faced with making difficult decisions regarding long-term prognosis and potential rate of motor recovery for patients. It has been suggested that the volume of infarct is an important factor influencing clinical outcome, but infarct volume appears to be moderately correlated with clinical outcome measurements. **This correlation exists for anterior but not posterior circulation stroke[3 4]. This effect may be related** to the motor structures located in the territory of the internal carotid artery.

Damage to the primary motor cortex (M1) or its descending corticospinal fibre has previously been considered to result in persistent hemiparesis[5-9]. Investigators have related loss of integrity of fibre tracks from M1 to poor motor outcome in more than 100 patients with cortical and/or subcortical stroke [5-7 10]. This idea has been re-inforced by suggestion of poor motor outcome in patients with early Wallerian degeneration of the corticospinal fibres following stroke [11]. Investigators have described other descending corticofugal fibres which may modify the impact of lesions **interrupting** the descending pathway (n = 49 cortical and/or subcortical stroke patients)[9 12-14]. These corticofugal fibres come from pre-motor or non-primary motor cortices such as the supplementary motor area (SMA), cingulate motor areas and dorsal and ventral premotor cortices (PMdv). The corticofugal fibres descend in the subcortical white matter. **Hence** patients with subcortical strokes were chosen in this study to explore the direct impact of such lesions on the motor pathway. Some of the studies described above included both cortical and subcortical studies. **As such**

they introduced the additional complexity of cortical infarcts impacting on stroke outcome [10 12]. To resolve this issue we plan to study contribution of involvement of corticofugal fibres by subcortical stroke to motor outcome. **The aim of this study is to correlate motor deficit with involvement of corticofugal fibres in patients with subcortical stroke**.

Methods

Subjects

We examined data of all patients who had been admitted to the stroke unit between August 2009 until October 2011. Patients were included into this project if they had suffered a subcortical ischaemic infarct and have had MR imaging. **Subcortical infarct is defined in this study as infarct which involve either the white matter or deep grey matter but do not extend to involve the surface grey matter. P**atients who have had a symptomatic previous infarct, and patients with a history of neurodegenerative disease, were excluded to prevent misattribution of symptoms. In this study different investigators were involved in segmenting infarct, performing tractography and extracting clinical outcome data at 3 months. This study was approved by the Research Directorate of Southern Health.

Clinical outcome.

Neurological deficits from stroke on admission and at 90 days were determined retrospectively from the medical records using the National Institute of Health Stroke Scale (NIHSS) [15]. **Similar to previous study[16], we used NIHSS sub-scores to summarise deficits in individual domains and Rankin score to measure disability outcome.** For motor deficits, we used the NIHSS sub-scoresfor left arm motor deficit (Items 5a), left leg motor deficit (Item 6a), right arm motor deficit (Items 5b), right leg motor deficit (Items 6b). **Modified Rankin score (mRS) is an ordinal scale with 0 - 2 corresponding to no or mild disability, 3 and 4 to moderate disability, 5 to vegetative state and 6 to death.** Clinical outcomes were dichotomised as good (mRS ≤2) or poor (mRS >2).

MR image processing

MRI scans were performed on a 1.5 Tesla superconducting imaging system (General Electric Medical Systems, Milwaukee, WI and Siemens Medical Solutions, Malvern, Pennsylvania) with echo-planar imaging capabilities. Fluid attenuated inversion recovery T_2 images (FLAIR) were acquired using thickness 5mm, matrix 256 x 220, and TR/TE/TI 8802/130/2200. All images were manually aligned to a standard stereotaxic coordinate space. The manual registration step was performed by choosing individual landmarks for each patient using an interactive display package (Register, available at http://www.bic.mni.mcgill.ca/software/) that allowed the user to ensure that landmark selection progressively improved image registration as evidenced by visual inspection of the alignment of corresponding anatomical structures. These steps led to creation of a 12-parameter linear transformation matrix which allowed for rotation, translation and independent scaling of the patient image along each of the three principal axes [17]. Infarcts were manually segmented on inversion recovery T_2-weighted images using interactive mouse driven software at standardised intensity windows to optimise infarct visualization (Display, available at **http://www.bic.mni.mcgill.ca/software/**).

Rating of white matter hyperintensity

Rating of white matter hyperintensity (WMH) was performed using the Fazekas scale on the FLAIR images. The rating for the periventricular hyperintensity (scale 0-3) and deep white matter hyperintensity (scale 0-3) was combined to give a total score of 0 to 6 [18]. A score of 0 indicates no WMH and a score of 6

indicated confluent areas of WMH in the periventricular and deep white matter. This summed score was used for regression analysis.

MR image processing of normal subjects

Non-stroke subjects who had MR imaging for another research study (3T MR scanner,Siemens Medical System) were used to define the corticofugal fibres. These diffusion tensor images (DTI) were acquired with the following parameters: TE/TR 87/8000 ms, 60 diffusion weighted directions, 2 diffusion weighting values 0 and 2000 s/mm^2. MRTrix software was used to pre-processing the DTI image and performing the streamline tracks (http://www.brain.org.au/software). This software was used to generate diffusion tensor map, Fraction Anisotropic (FA) map and Eigenvector (EV) map. Streamline tractography then used to delineates fibre tract according to the principal long axis to preserve voxel-voxel directional information.

Definition of corticospinal tracts

The major cortical areas (primary motor cortex (M1), supplementary motor cortex (SMA) and premotor cortices (PMdv)) known to contribute to the descending motor tracks were defined using 16 healthy subjects. The volunteer's T_1 weighted image were co-registered to into standard space as defined by the Montreal Neurological Institute (MNI) template. The co-registration process was done using FSL linear registration tool (http://www.fmrib.ox.ac.uk/fsl). The motor cortex (M1) and supplementary motor area (SMA) for both left side and right side were defined using the BrainMap database in MNI space. We used Freesurfer 5.1 (http://surfer.nmr.mgh.harvard.edu/fswiki) to perform parcellation to determine the location of the premotor areas and the primary motor area. Dorsal promotor area

(PMd) was identified as superior part of precentral sulcus and ventral premotor area (PMv) was identified as inferior part of precentral sulcus in the In this study, PMd and PMv were combined combined together as premotor area (PMdv). Streamline track algorithm was used to trace the connection from these motor areas to pontine nuclei. The probabilistic maps of descending motor corticofugal tracks from these subjects were transformed to standard space (Figure 1). Masks of the corticofugal fibres were created from these maps. Involvement of the corticofugal fibres by stroke was determined by multiplying the corticofugal fibre masks and the infarct. The volumes of overlap between the infarct and the fibre masks were determined by voxel counting method.

Statistical analysis

To provide comparison data **with published studies**, we provided several metrics of the associations between the volume of infarct overlapping with corticofugal fibres and clinical outcome. Clinical outcome was measured by National Institute of Health Stroke Scale (NIHSS) subscore for arm/leg motor (dichotomized at zero) and modified Rankin score (dichotomized at two or less to signify mild disability).

The receiver operating characteristics (ROC) curve method, measures the trade off between sensitivity and false positive rate and may provide a metric that can be understood clinically. The ROC curve was used to determine the accuracy of infarct overlap with corticofugal fibres and clinical outcome (dichotomised NIHSS sub-scores and modified Rankin score). We followed the suggestion by Hosmer and Lemeshow [19] in the interpretation of the area under ROC (AUC). An AUC of 0.5 is classified as no better than by chance; 0.6–0.69 provides poor discrimination; 0.7–

0.79 provides acceptable (fair) discrimination; 0.8–0.89 provides good (excellent) discrimination, and 0.9–1.0 provides outstanding discrimination. Using data from the ROC curve analysis, we calculate the Youden index to deterimine the optimal threshold of volume of overlap between infarct and corticofugal fibres for discrimination of neurological deficit[20].

Logistic regression was used to analyse the relationships between the motor outcome (NIHSS motor sub-items or modified Rankin scale) against infarct volume overlapped with individual fibre tracts (M1 or PMdv or SMA). **We investigate the following covariates in the regression model: age, gender, smoking status, hypertension, diabetes status, treatment with recombinant tissue plasminogen activator (rt-PA), time to MRI scan. Only variables with p<0.20 on univariable analysis were entered into multivariable models.**

Results

Stroke Patient characteristics

There are 57 patients with mean age 64.3± 14.4 year-old. Fifty seven percent of the subjects were males. The distribution of risk factors were hypertension 71.9%, diabetes 31.6%, hyperlipidemia 63.2%, smoker 28.1%, atrial fibrillation 15.7% and ischaemic heart disease 19.3%. The stroke mechanisms were: cardioembolic 11 (19.3%), undetermined 29 (50.9%), large artery 17 (29.8%). **The frequency of patients receiving rt-PA was 29.8%.** Patients were scanned 20.8 ± 25.5 days after stroke onset.

Non-stroke subjects

There are 16 subjects (44.6% male) who volunteered for DTI with mean age 60.1±5.6 year-old. The distribution of risk factors were hypertension 50.9%, diabetes 50.0%, hyperlipidemia 51.8%, smoker 44.4%, ischaemic heart disease 35.7%. No subjects had a clinical hisory of stroke nor MR imaging evidence of stroke.

Motor deficit:

The mean and standard deviation for the NIHSS on admission was 5.7±4.1. Motor deficits were initially present in 45 (78.9%) patients. The frequency of motor arm deficits was 26 (45.6%) and motor leg deficits was 20 (35.1%). The NIHSS at 3 months was 2.5±4.7. At this stage, the frequency of motor deficits had decreased to 42.1%; the frequency of motor arm deficit was 32.7%, motor leg deficit was 27.3%, and moderate to severe disability 17.6%.

Infarct volume

The mean infarct volume was 3.8 ± 8.9ml. The mean involvement of the M1 fibre tract by infarct was 1.17± 1.40 ml; PMdv fibre was 0.86± 1.09ml and SMA was 1.11± 1.44ml. There was no single infarct which involved only the M1 fibre, or only the PMdv fibre or only SMA fibre. Isolated involvement at the level of the posterior limb of the internal capsule occurred in 27 (47.4%) and corona radiata in 24 (42.1%).

Involvement of corticofugal fibres and outcome

The area under the receiver operating charcteristics curve (AUC) for arm motor deficit from M1 fibres involvement was 0.80 (95% CI 0.66-0.94), PMdv was 0.76 (95% CI 0.61-0.91) and SMA was 0.73 (95% CI 0.58-0.88). The AUC for leg motor deficit from M1 fibres involvement was 0.69 (95% CI 0.52-0.85), PMdv was 0.67 (95% CI 0.50-0.85), SMA was 0.66 (95% CI 0.48-0.84). The AUC for disability from M1 fibres involvement was 0.88 (95% CI 0.79-0.97), PMdv was 0.83 (95% CI 0.70-0.97), SMA was 0.82 (95% CI 0.67-0.97). The thresholded infarct and their associated sensitivity and specificity are displayed in Table 1 and Figure 2.

Univariable analyses

The univariable analyses for motor deficit and disability are displayed in Table 1. **In this study, the following variables were not significant at the p =0.2 level: gender, hypertension, diabetes, smoking status, treatment with rt-PA, Fazekas score for WMH and time to MRI for arm motor deficit and disability. The variable time to MRI were significant for leg motor deficit and was entered into the multivariable model.**

Multivariable analyses for leg motor deficit and disability

Leg motor deficit was associated with M1 fibres (OR 1.99 per ml, 95% CI 1.15-3.46) and age (OR 1.06 per year increase, 95% CI 1.01-1.12); PMdv fibres (OR 2.98 per ml, 95% CI 1.32-6.73) and age OR 1.07 per year increase, 95% CI 1.01-1.14) and SMA fibres (OR 2.05 per year increase, 95% CI 1.17-3.60) and age (OR per 1.06 per year increase, 95% CI 1.01-1.12). The R^2 for these regression anlayses are displayed in Table 1 and range from 0.18-0.31.

Discussion

We had expected to find that involvement of the descending motor corticofugal fibres, in particular the M1 fibres, would ***always*** be associated with severe motor deficit. **However, the associations between involvement of corticofugal motor fibres and motor deficit or disability were variable. Importantly, prognosis for motor recovery (particularly leg motor deficit) after subcortical infarction was not easily predicted from infarct location. In our small series, the finding does not support the use of subcortical infarct location for prognostication on stroke recovery**.

Corticofugal fibres

We observed an association between involvement of descending motor corticofugal fibres and motor deficit in stroke patients but cautiously did not draw conclusion regarding importance of one fibre tract over another. Using logistic regression methods, we were not able to assess the independent contribution of each fibre tract to motor outcome due to presence of collinearity (correlated data). This occurred because of overlap between these fibres, making it a rare occurrence to have infarct affecting only one fibre tract [12].

In this study, we used the area under the ROC curve and logistic regression to illustrate the effect of involvement of corticofugal fibres on motor outcome. The expression of odds ratio is familiar to readers of this journal but this metric is not easily understood clinically. **By contrast, the** use of the AUC may permit a clinical interpretation. In this study, the AUC results for M1 ranged from 0.69 (poor discrimination for motor leg deficit), 0.80 (good discrimination for motor arm deficit)

to 0.88 (good discrimination for disability) suggesting that when randomly choosing from a group, the clinician may be incorrect 31% (for motor leg deficit), 20% (for motor arm deficit) and 12% (for disability) of the cases [21].

With regards to M1 fibres involvement, our findings initially appeared at odd with other studies. **With a partial R^2 of 0.22 for arm motor deficit in our study (Table 1) the strength of this association was not very strong. This discrepancy might be resolved when the results of those studies are examined in details.** Investigators reported that involvement of the corticospinal tract led to arm motor deficit in 19 of 23 patients. **However, 16 of those 19 patients** had very mild arm motor deficit[6]. Similarly leg motor deficit was present in 17 of 23 patients in this study with 13 of these 17 patients had mild leg motor deficit[6]. There are exceptions with some studies reported a stronger association between M1 and FM score/grip strength obtaining R^2 of 0.67 (n=21) [10], 0.73 (n=50)[5] and 0.74 (n=13)[9].

The importance of the M1 fibre to motor deficit is also argued from the point of early Wallerian degeneration of this fibre (n=18)[11]. However, the relationship between Wallerian degeneration of the corticospinal tract and motor outcome is inconclusive[22]. Investigators showed that in the setting of subcortical stroke, this MR finding may slow functional recovery but not the final rehabilitation outcome (n=77)[22]. From a practical point, these findings imply that that involvement of corticofugal fibres by stroke increased the odds of motor deficit but it does not mean that permanent motor deficit will always occur. Based on this data, one cannot use this knowledge of subcortical infarct location to prognosticate on stroke recovery or to determine eligibility for rehabilitation.

The findings of this study generate the hypothesis that the corticofugal fibres may have large residual capacity. Poor motor outcome may not occur unless all of the fibres are disrupted. Even though the MR scans were performed approximately 3 weeks after onset, another possibility is that the T_2 signal abnormality might have included oedema rather than just necrotic and gliotic tissue. As such the 'infarct lesion' might not have resulted in significant disruption of the corticofugal fibres and **hence our findings of imperfect correlation.**

Study limitations

The limitations of this study include the retrospective nature. Although the sample size in this study is larger than some of the other studies on this subject, the sample size remains relatively small[12 13]. The severity of stroke deficit can be described as mild to moderate; this is not unexpected since we had chosen to evaluate subcortical stroke. **In this study, the NIHSS was used to measure motor deficit as this tool had been deemed to be sensitive for prediction of 3 months outcome[23]. The NIHSS sub-item for arm motor deficit measures arm drift and hence it provides a measure of proximal arm strength. This tool does not explicitly measure hand motor deficit (item 12 on original NIHSS)[24]. However, the assessment of this scale by factor analysis showed that the hand motor item did not make any contribution towards the underlying nature of NIHSS[25]. The hand motor item (item 12) is no longer part of the NIHSS. Nevertheless**, we urge caution with our findings with regards to the less than perfect correlation between arm motor deficit and corticofugal fibres. Finally, the effect of corticofugal fibre involvement on clinical outcome are inferred from the likely overlap between the sites of the fibres

and the patients' infarcts. We had not directly assessed for disruption of the corticofugal fibres in these patients. The reason was that the MR studies were performed as clinical scans and did not incorporate a dedicated diffusion tensor sequence. Further, there are technical issues associated with performing tractography in stroke patients [6 12 13].

Conclusion

The motor outcome at three months following subcortical infarct was not **universal and varied between upper and lower limbs. The descending motor corticofugal fibres may have different effect on motor outcome between the upper and lower limbs.** Further research in this important area is needed to help with determining stroke outcome and understanding of the neural substrate of motor deficit.

Disclosure:

None

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Legends to Figures

Figure 1: The corticofugal fibres from M1 (blue), PMdv (green) and SMA (red).

Figure 2

Examples of patients with infarct involving the posterior limb of the internal capsule but no motor deficit at 90 days.

Table 1: Association between corticofugal fibres and clinical outcome

	M1	PMdv	SMA	
Arm > 0	2.90 (1.41-5.99) 0.22 0.80 (0.66-0.94) 0.96 (0.79, 0.82)	3.57 (1.38-9.24) 0.18 0.76 (0.61-0.91) 0.86 (0.74, 0.84)	2.00 (1.09-3.68) 0.13 0.73 (0.58-0.88) 0.99 (0.79, 0.79)	OR and 95% CI R^2 AUC and 95% CI Threshold volume (ml) sensitivity and specificity
Leg >0	1.75 (1.05-2.94) 0.18 0.69 (0.52-0.85) 1.06 (0.65, 0.75)	2.42 (1.09-5.40) 0.22 0.67 (0.50-0.85) 0.91 (0.59, 0.75)	1.86 (1.06-3.28) 0.19 0.66 (0.48-0.84) 0.99 (0.65, 0.70)	OR and 95% CI R^2 AUC and 95% CI Threshold volume (ml) Sensitivity and specificity
Modified Rankin >2	3.22 (1.48-6.97) 0.31 0.88 (0.79-0.97) 1.05 (1.00, 0.77)	4.42 (1.41-13.84) 0.29 0.83 (0.70-0.97) 1.01 (0.80, 0.77)	2.66 (1.29-5.50) 0.25 0.82 (0.67-0.97) 1.00 (0.80, 0.74)	OR and 95% CI R^2 AUC and 95% CI Threshold volume (ml) sensitivity and specificity

Different metrics of association between corticofugal fibres and outcome were presented to for ease of comparison with other studies.

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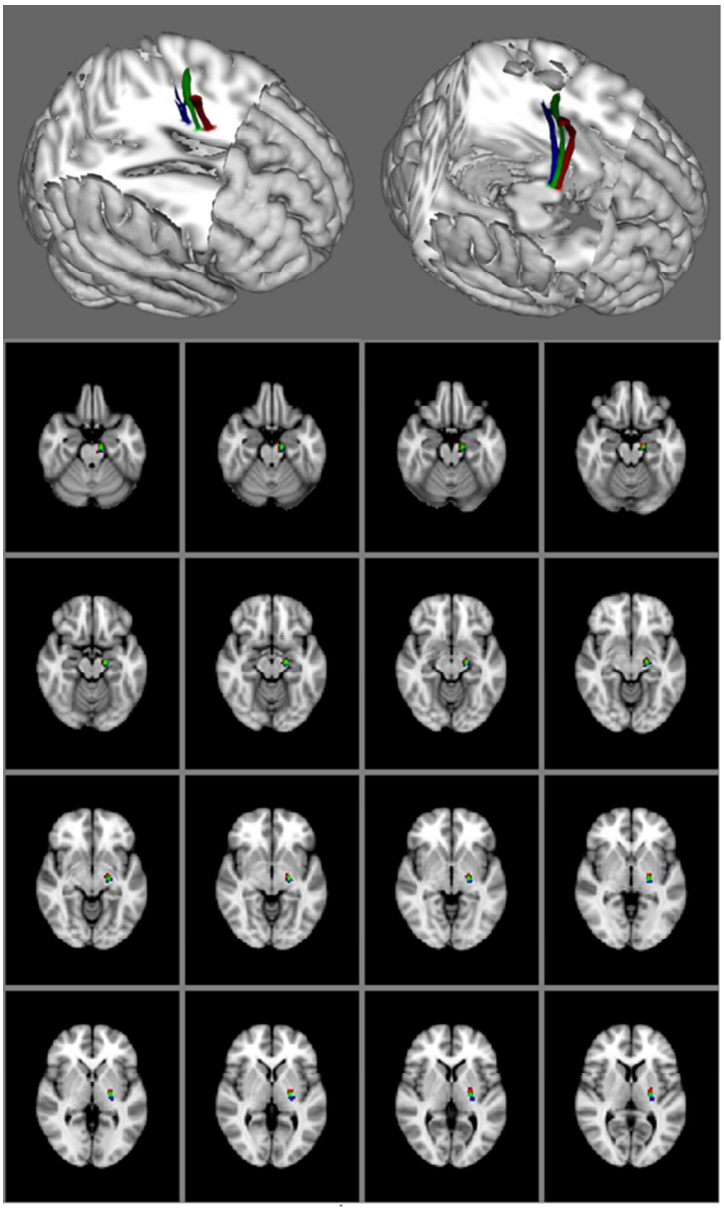

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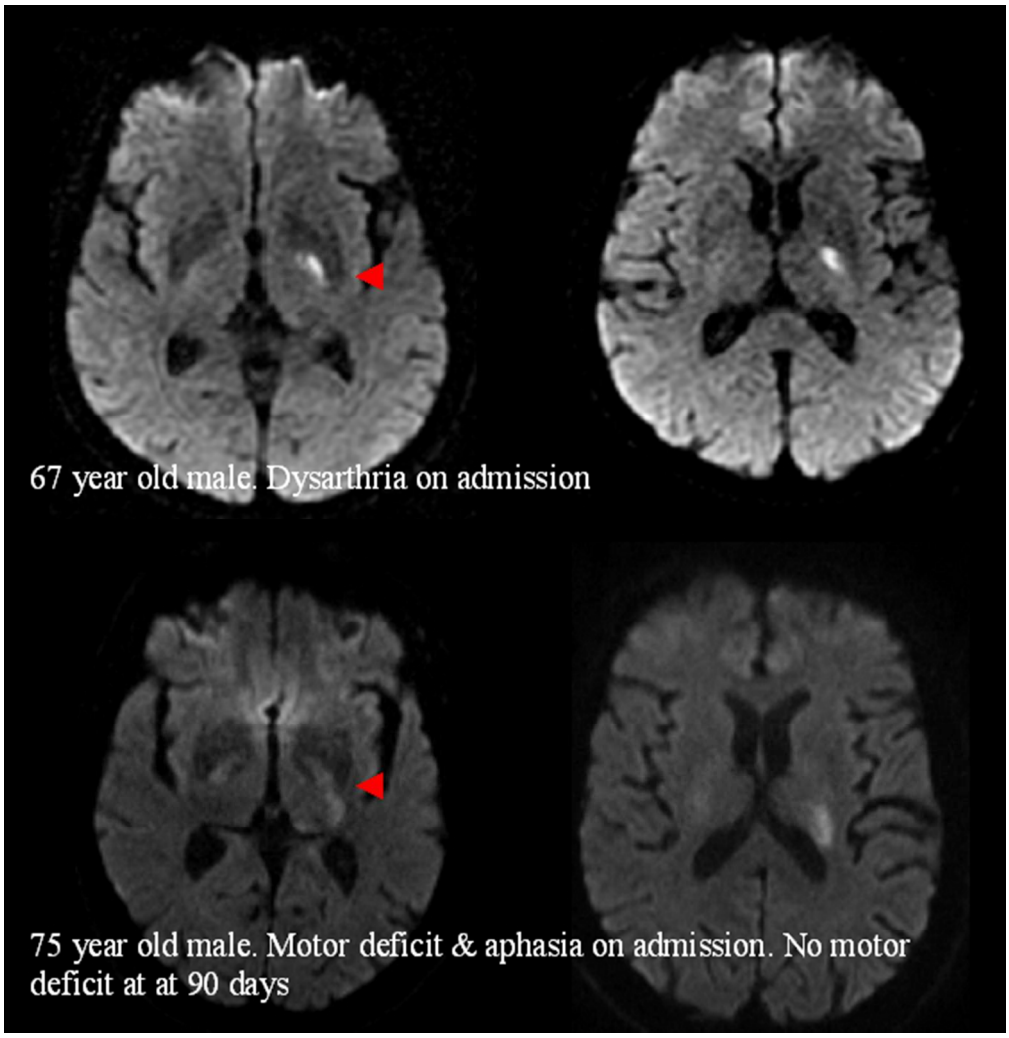

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Following subcortical strokes, corticofugal ~~fiber~~fibres involvement do not always result in permanent motor deficit

Thanh G Phan, FRACP, PhD, Sanne van der Voort, Jian Chen, ME, Richard Beare, PhD, Henry Ma, FRACP, Benjamin Clissold, FRACP, John Ly, FRACP, Emma Foster, MBBS, Eleanor Thong, MBBS, Velandai Srikanth FRACP, PhD

Stroke Unit, Monash Medical Centre[1] and Stroke and Aging Research Group[2], Neurosciences, Southern Clinical School, Monash University[1]

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Corresponding Author:
~~A/~~Prof Thanh G Phan
Department of Neurology, Monash Health, 246 Clayton Road, Clayton
Stroke and Aging Research Group, Department of Medicine, Monash University
Victoria, Australia, 3168, Phone: +613 9594 2240, Fax: +613 9594 6241
Email: Thanh.Phan@monash.edu

Background: Motor outcome following subcortical stroke may depend on integrity of the descending motor corticofugal tracts (primary motor cortex (M1), premotor area (PMdv) and supplementary motor area (SMA)). The aim of this study is to correlate motor deficit with ~~We hypothesise that motor deficit from subcortical stroke is associated with~~ involvement of corticofugal ~~fiber~~fibres in patients with subcortical stroke.

Methods: Patients with subcortical infarcts on MR imaging ~~admitted to our institution~~ (2009-2011) were included. Outcome at 3 months days were classified according to the National Institute of Health Stroke Scale (NIHSS) sub-scores for arm and leg motor deficit at 90 days. The subcortical infarcts were manually segmented, registered into standard space. In normal subjects obtained from another study (n=16), the corticofugal ~~fiber~~fibres were delineated using diffusion tractography using MRTrix software. The origins of the corticofugal fibres were determined using landmarks for premotor areas and the primary motor area. Masks of the corticofugal fibres were created from these maps. Involvement of the corticofugal fibres by stroke was determined by multiplying the corticofugal fibre masks and the infarct.~~and registered to standard space.~~

Results: The area under the ROC curve (AUC) for the volume of overlap with infarct (and M1/PMdv/SMA ~~fiber~~fibres) and motor outcome was calculated. There were 57 patients (57% male) with mean age 64.3± 14.4 year-old. The AUC for the association with arm motor deficit from M1 ~~fiber~~fibres involvement was 0.80 (95% CI 0.66-0.94), PMdv was 0.76 (95% CI 0.61-0.91) and SMA was 0.73 (95% CI 0.58-0.88). The AUC for leg motor deficit from M1 ~~fiber~~fibres involvement was 0.69 (95% CI 0.52-0.85), PMdv was 0.67 (95% CI 0.50-0.85), SMA was 0.66 (95% CI 0.48-0.84).

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~~The AUC for disability from M1 fibers involvement was 0.88 (95% CI 0.79-0.97), PMdv was 0.83 (95% CI 0.70-0.97), SMA was 0.82 (95% CI 0.67-0.97).~~

Conclusion: Following subcortical stroke~~In this small series~~, the ~~diagnostic accuracy~~ correlation between involvement of the corticofugal ~~fiber~~fibres for upper and lower limbs motor~~neurological~~ deficit ~~following subcortical stroke~~ was variable. A poor motor outcome was not universal following subcortical stroke.

Introduction

Motor deficit has been found to be the most common impairment in stroke patients [1]. Inpatient hospitalization, rehabilitation and nursing home care contribute significantly to the economic burden of stroke care[2]. Stroke clinicians and rehabilitation specialists are often faced with making difficult decisions regarding long-term prognosis and potential rate of motor recovery for patients. It has been suggested that the volume of infarct is an important factor influencing clinical outcome, but infarct volume appears to be moderately correlated with clinical outcome measurements. This correlation exists for ~~and mainly in~~ anterior ~~circulation stroke~~but not posterior circulation stroke[3] [4]. This effect ~~. This~~ may ~~have been~~be related to the motor structures located in the territory of the internal carotid artery. ~~Investigators have recently evaluated the impact of the location of infarcted tissue on neurological deficit and pointing to the importance of the corticospinal tract involvement to motor outcome [5-10] and the role of the premotor cortex in gait outcome [11], motor deficit and post-stroke disability[5].~~

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Damage to the primary motor cortex (M1) or its descending corticospinal ~~fiber~~fibre has previously been considered to result in persistent hemiparesis[5-9]. Investigators have related loss of integrity of ~~fiber~~fibre tracks from M1 to poor motor outcome in more than 100 patients with cortical and/or subcortical stroke [5-7 10]. This idea has been re-inforced by suggestion of poor motor outcome in patients with early Wallerian degeneration of the corticospinal ~~fiber~~fibres following stroke [11]. Investigators have described other descending corticofugal ~~fiber~~fibres which may ~~play an important role in~~ modify~~ing~~ the impact of lesions interrupting~~affecting~~ the descending pathway (n = 49 cortical and/or subcortical stroke patients)[9 12-14]. These corticofugal ~~fiber~~fibres come from pre-motor or non-primary motor cortices such as the supplementary motor

area (SMA), cingulate motor areas and dorsal and ventral premotor cortices (PMdv). The corticofugal ~~fiber~~fibres descend in the subcortical white matter. ~~and~~ H~~h~~ence patients with subcortical strokes were chosen in this study to explore the direct impact of such lesions on the motor pathway. Some of the studies described above included both cortical and subcortical studies. As such they ~~and thus~~ introduced the additional complexity of cortical infarcts impacting on stroke outcome [10 12]. To resolve this issue we plan to study contribution of involvement of corticofugal ~~fiber~~fibres by subcortical stroke to motor outcome. ~~We hypothesise that motor deficit from subcortical stroke is associated with involvement of corticofugal fibers.~~

The aim of this study is to correlate motor deficit with involvement of corticofugal fibres in patients with subcortical stroke.

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Methods

Subjects

We examined data of all patients who had been admitted to the stroke unit between August 2009 until October 2011. Patients were included into this project if they had suffered a subcortical ischaemic infarct and have had MR imaging. Subcortical infarct is defined in this study as infarct which involve either the white matter or deep grey matter but do not extend to involve the surface grey matter. Patients who have had a symptomatic previous infarct, and patients with a history of neurodegenerative disease, were excluded to prevent misattribution of symptoms. In this study different investigators were involved in segmenting infarct, performing tractography and extracting clinical outcome data at 3 months. This study was approved by the Research Directorate of Southern Health.

Clinical outcome.

Neurological deficits from stroke on admission and at 90 days were determined retrospectively from the medical records using the National Institute of Health Stroke Scale (NIHSS) [15]. Similar to previous study[16]~~In this study~~, we used NIHSS sub-scores to summarise deficits in individual domains and Rankin score to measure disability outcome. For motor deficits, we used the NIHSS sub-scoresfor left arm motor deficit (Items 5a), left leg motor deficit (Item 6a), right arm motor deficit (Items 5b), right leg motor deficit (Items 6b). Modified Rankin score (mRS) is an ordinal scale with 0 - 2 corresponding to no or mild disability, 3 and 4 to moderate disability, 5 to vegetative state and 6 to death. Clinical outcomes were dichotomised as good (m~~odified Rankin scale score~~RS ≤2) or poor (mRS~~odified Rankin scale score~~ >2).

MR image processing

MRI scans were performed on a 1.5 Tesla superconducting imaging system (General Electric Medical Systems, Milwaukee, WI and Siemens Medical Solutions, Malvern, Pennsylvania) with echo-planar imaging capabilities. Fluid attenuated inversion recovery T_2 images (FLAIR) were acquired using thickness 5mm, matrix 256 x 220, and TR/TE/TI 8802/130/2200. The 3-D time of flight MRA was performed using TR/TE 38/6.9, 25^0 flip angle, thickness 1.4 mm, slab thickness 60 mm, matrix 256 X 224, field of view 180 mm. All images were manually aligned to a standard stereotaxic coordinate space. The manual registration step was performed by choosing individual landmarks for each patient using an interactive display package (Register, available at http://www.bic.mni.mcgill.ca/software/) that allowed the user to ensure that landmark selection progressively improved image registration as evidenced by visual inspection of the alignment of corresponding anatomical structures. These steps led to creation of a 12-parameter linear transformation matrix which allowed for rotation, translation and independent scaling of the patient image along each of the three principal axes [17]. Infarcts were manually segmented on inversion recovery T_2-weighted images using interactive mouse driven software at standardised intensity windows to optimise infarct visualization (Display, available at **http://www.bic.mni.mcgill.ca/software/**).

Rating of white matter hyperintensity

Rating of white matter hyperintensity (WMH) was performed using the Fazekas scale on the FLAIR images. The rating for the periventricular hyperintensity (scale 0-3) and

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deep white matter hyperintensity (scale 0-3) was combined to give a total score of 0 to 6 [18]. A score of 0 indicates no WMH and a score of 6 indicated confluent areas of WMH in the periventricular and deep white matter[22]. This summed score was used for regression analysis.

MR image processing of normal subjects

Non-stroke subjects who had MR imaging for another research study ~~were obtained from another study on a~~(3T MR scanner, (Siemens Medical System) were used to define the corticofugal fibres. These diffusion tensor images (DTI) were acquired with the following parameters: TE/TR 87/8000 ms, 60 diffusion weighted directions, 2 diffusion weighting values 0 and 2000 s/mm^2. MRTrix software was used to pre-processing the DTI image and performing the streamline tracks (http://www.brain.org.au/software). This software was used to generate diffusion tensor map, Fraction Anisotropic (FA) map and Eigenvector (EV) map. Streamline tractography then used to delineates ~~fiber~~fibre tract according to the principal long axis to preserve voxel-voxel directional information.

Definition of corticospinal tracts

The major cortical areas (primary motor cortex (M1), supplementary motor cortex (SMA) and premotor cortices (PMdv)) known to contribute to the descending motor tracks were defined using 16 healthy subjects. The volunteer's T_1 weighted image were co-registered to into standard space as defined by the Montreal Neurological Institute (MNI) template. The co-registration process was done using FSL linear registration tool (http://www.fmrib.ox.ac.uk/fsl). The motor cortex (M1) and supplementary motor area (SMA) for both left side and right side were defined using

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the BrainMap database in MNI space. We used Freesurfer 5.1 (http://surfer.nmr.mgh.harvard.edu/fswiki) to perform parcellation to determine the location of the premotor areas and the primary motor area. Dorsal promotor area (PMd) was identified as superior part of precentral sulcus and ventral premotor area (PMv) was identified as inferior part of precentral sulcus in the In this study, PMd and PMv were combined combined together as premotor area (PMdv). Streamline track algorithm~~ic~~ was used to trace the~~trace the tracts~~ connection from these motor areas to pontine nuclei. ~~Once the track were obtained we then converted the tracks files into image maps of the fraction of tracks to enter each voxel.~~ The~~se~~ probabilistic maps of descending motor corticofugal tracks from these subjects were ~~finally~~ transformed to standard space (Figure 1). Masks of the corticofugal ~~fiber~~fibres were created from these maps. Involvement of the corticofugal ~~fiber~~fibres by stroke was determined by multiplying the corticofugal ~~fiber~~fibre masks and the infarct. The volumes of overlap between the infarct and the ~~fiber~~fibre masks were determined by voxel counting method.

Statistical analysis

~~Different studies reported different metrics of association between motor deficit and corticofugal fiber involvement.~~ To provide comparison data with published studies, we provided several metrics of the associations between the volume of infarct overlapping with corticofugal ~~fiber~~fibres and clinical outcome. Clinical outcome was measured by National Institute of Health Stroke Scale (NIHSS) subscore for arm/leg motor (dichotomized at zero) and modified Rankin score (dichotomized at two or less to signify mild disability).

The receiver operating characteristics (ROC) curve method, measures the trade off between sensitivity and false positive rate and may provide a metric that can be understood clinically. The ROC curve was used to determine the accuracy of infarct overlap with corticofugal ~~fiber~~fibres and clinical outcome (dichotomis~~z~~ed NIHSS sub-scores and modified Rankin score). We followed the suggestion by Hosmer and Lemeshow [19] in the interpretation of the area under ROC (AUC). An AUC of 0.5 is classified as no better than by chance; 0.6–0.69 provides poor discrimination; 0.7–0.79 provides acceptable (fair) discrimination; 0.8–0.89 provides good (excellent) discrimination, and 0.9–1.0 provides outstanding discrimination.

Using data from the ROC curve analysis, we calculate the Youden index to deterimine the optimal threshold of volume of overlap between infarct and corticofugal ~~fiber~~fibres for discrimination of neurological deficit[20].

Logistic regression was used to analys~~z~~e the relationships between the motor outcome (NIHSS motor sub-items or modified Rankin scale) against infarct volume overlapped with individual ~~fiber~~fibre tracts (M1 or PMdv or SMA). We investigate the following covariates in the regression model: age, gender, smoking status, hypertension, diabetes status, treatment with recombinant tissue plasminogen activator (rt-PA), time to MRI scan. Only variables with $p<0.20$ on univariable analysis were entered into multivariable models.

Results

Stroke Patient characteristics

There are 57 patients with mean age 64.3± 14.4 year-old. Fifty seven percent of the subjects were males. The distribution of risk factors were hypertension 71.9%, diabetes 31.6%, hyperlipidemia 63.2%, smoker 28.1%, atrial fibrillation 15.7% and ischaemic heart disease 19.3%. The stroke mechanisms were: cardioembolic 11 (19.3%), undetermined 29 (50.9%), large artery 17 (29.8%). The frequency of patients receiving rt-PA was 29.8%. Patients were scanned 20.8 ± 25.5 days after stroke onset.

Non-stroke subjects

There are 16 subjects (44.6% male) who volunteered for DTI with mean age 60.1±5.6 year-old. The distribution of risk factors were hypertension 50.9%, diabetes 50.0%, hyperlipidemia 51.8%, smoker 44.4%, ischaemic heart disease 35.7%. No subjects had a clinical hisory of stroke nor MR imaging evidence of stroke.

Motor deficit:

The mean and standard deviation for the NIHSS on admission was 5.7±4.1. Motor deficits were initially present in 45 (78.9%) patients. The frequency of motor arm deficits was 26 (45.6%) and motor leg deficits was 20 (35.1%). The NIHSS at 3 months was 2.5±4.7. At this stage, the frequency of motor deficits had decreased to 42.1%; the frequency of motor arm deficit was 32.7%, motor leg deficit was 27.3%, and moderate to severe disability 17.6%.

Infarct volume

The mean infarct volume was 3.8 ± 8.9ml. The mean involvement of the M1 ~~fiber~~fibre tract by infarct was 1.17± 1.40 ml; PMdv ~~fiber~~fibre was 0.86± 1.09ml and SMA was 1.11± 1.44ml. There was no infarct which involved only the M1 ~~fiber~~fibre, or only the PMdv ~~fiber~~fibre or only SMA ~~fiber~~fibre. Isolated involvement at the level of the posterior limb of the internal capsule occurred in 27 (47.4%) and corona radiata in 24 (42.1%).

Involvement of corticofugal ~~fiber~~fibres and outcome

The area under the receiver operating charcteristics curve (AUC) for arm motor deficit from M1 ~~fiber~~fibres involvement was 0.80 (95% CI 0.66-0.94), PMdv was 0.76 (95% CI 0.61-0.91) and SMA was 0.73 (95% CI 0.58-0.88). The AUC for leg motor deficit from M1 ~~fiber~~fibres involvement was 0.69 (95% CI 0.52-0.85), PMdv was 0.67 (95% CI 0.50-0.85), SMA was 0.66 (95% CI 0.48-0.84). The AUC for disability from M1 ~~fiber~~fibres involvement was 0.88 (95% CI 0.79-0.97), PMdv was 0.83 (95% CI 0.70-0.97), SMA was 0.82 (95% CI 0.67-0.97). The thresholded infarct volume to maximise the discrimation for any neurological deficit ranged between 0.86-1.06 ml (see Table 1 for display of the threshold infarct volumes and their associated sensitivity and specificity and Figure 2 for cases where infarction of the posterior limb of the internal capsule did not result in permanent motor deficit).

Univariable analyses

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When each of the corticofugal ~~fiber~~fibres was entered separately in the equation, the regression model showed arm motor deficit was associated with involvement of ~~fiber~~fibres from M1 (OR = 2.90 per ml, 95% CI 1.41-5.99), PMdv ~~fiber~~fibres

(OR=3.57 per ml, 95% CI 1.38-9.24) and SMA ~~fiber~~fibres (OR=2.00 per ml, 95% CI 1.09-3.68). Disability was associated with involvement of ~~fiber~~fibres from M1 (OR = 3.22 per ml, 95% CI 1.48-6.97), PMdv ~~fiber~~fibres (OR=2.42 per ml, 95% CI 1.09-5.40) and SMA ~~fiber~~fibres (OR=2.66 per ml, 95% CI 1.29-5.50). In this study, the following variables were not significant at the p =0.1 level: gender, hypertension, diabetes, smoking status, treatment with rt-PA, Fazekas score for WMH and time to MRI for arm motor deficit and disability. The variable time to MRI were significant for leg motor deficit and was entered into the multivariable model.

Multivariable analyses for leg motor deficit and disability

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Leg motor deficit was associated with M1 ~~fiber~~fibres (OR 1.99 per ml, 95% CI 1.15-3.46) and age (OR 1.06 per year increase, 95% CI 1.01-1.12); PMdv ~~fiber~~fibres (OR 2.98 per ml, 95% CI 1.32-6.73) and age OR 1.07 per year increase, 95% CI 1.01-1.14) and SMA ~~fiber~~fibres (OR 2.05 per year increase, 95% CI 1.17-3.60) and age (OR per 1.06 per year increase, 95% CI 1.01-1.12). The R^2 for these regression anlyses are displayed in Table 1 and range from 0.18-0.31.

Discussion

We had expected to find that involvement of the descending motor corticofugal ~~fiber~~fibres, in particular the M1 ~~fiber~~fibres, would ***always*** be associated with severe motor deficit. However, the associations between involvement of corticofugal motor ~~fiber~~fibres and~~to~~ stroke motor deficit or~~and~~ disability were variable.~~.~~ Importantly, prognosis for motor recovery (particularly leg motor deficit) after subcortical infarction was not easily predicted from infarct location~~readily determined by the finding of involvement of corticofugal fibers in our small series~~. ~~This result may have implications for interpretation of clinical images~~ In our small series, the finding does not support the use of ~~and extrapolation of~~ subcortical infarct location for prognostication on stroke recovery.

Corticofugal ~~fiber~~fibres

We observed an association between involvement of descending motor corticofugal ~~fiber~~fibres and motor deficit in stroke patients but cautiously did not draw conclusion regarding importance of one ~~fiber~~fibre tract over another. Using logistic regression methods, we were not able to assess the independent contribution of each ~~fiber~~fibre tract to motor outcome due to presence of collinearity (correlated data). This occurred because of overlap between these ~~fiber~~fibres~~ in healthy volunteer~~, making it a rare occurrence to have infarct affecting only one ~~fiber~~fibre tract [12].

In this study, we used the area under the ROC curve and logistic regression to illustrate the effect of involvement of corticofugal ~~fiber~~fibres on motor coutcome. The expression of odds ratio is familiar to readers of this journal but this metric is not easily understood clinically. By contrast, the use of the AUC may permit a clinical

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interpretation. ~~For example, the association between arm motor deficit and M1 fiber was OR = 2.90 per ml or an increased odds of arm motor deficit of 2.90 for every 1 ml increased in volume of M1 fiber involvement. Hence the use of the AUC may permit a clinical interpretation.~~ In this study, the AUC results for M1 ranged from 0.69 (poor discrimination for motor leg deficit), 0.80 (good discrimination for motor arm deficit) to 0.88 (good discrimination for disability) suggesting that when randomly choosing from a group, the clinician may be incorrect 31% (for motor leg deficit), 20% (for motor arm deficit) and 12% (for disability) of the cases [21]. Further, we had determined the optimal threshold to provide another method for understanding the minimal infarct overlap (approximately 1ml) to impact on motor outcome.

With regards to M1 ~~fiber~~fibres involvement, our findings initially appeared at odd with other studies. With a partial R^2 of 0.22 for arm motor deficit in our study (Table 1) the strength of this association was not very strong. T~~but~~ this discrepancy ~~-~~might be resolved when the results of those~~other~~ studies are examined in details~~-~~[5]. Investigators reported that involvement of the corticospinal tract led to arm motor deficit in 19 of 23 patients. However, ~~but~~ 16 of th~~o~~ese 19 patients had very mild arm motor deficit[6]. Similarly leg motor deficit was present in 17 of 23 patients in this study with 13 of these 17 patients had mild leg motor deficit[6].

~~Investigator described that there was a statistical association (p<0.001) between the weighted M1-lesion load and upper limb Fugl Meyer (FM) score (n=18)[11]. With a partial R^2 of 0.22 the strength of this association was not very strong[10] (compare this result to those in this studies where the R^2 ranged from 0.18-0.31).~~ There are exceptions with some studies reported a stronger association between M1 and FM score/grip strength obtaining R^2 of 0.67 (n=21) [10], ~~R^2 of~~ 0.73 (n=50)[5] and ~~R^2 of~~ 0.74

(n=13)[9]. ~~Other investigators reported that involvement of the corticospinal tract led to arm motor deficit in 19 of 23 patients but 16 of these 19 patients had very mild arm motor deficit[12]. Similarly leg motor deficit was present in 17 of 23 patients in this study with 13 of these 17 patients had mild leg motor deficit[12].~~

The importance of the M1 ~~fiber~~fibre to motor deficit is also argued from the point of early Wallerian degeneration of this ~~fiber~~fibre ~~and possible correlation with poor motor outcome~~ (n=~~20~~18)[11]. However, the relationship between Wallerian degeneration of the corticospinal tract and motor outcome is inconclusive[22]. Investigators showed that in the setting of subcortical stroke, this MR finding may slow functional recovery but not the final rehabilitation outcome (n=77)[22]. From a practical point, these findings imply that that involvement of corticofugal ~~fiber~~fibres by stroke increased the odds of motor deficit but it does not mean that permanent motor deficit will always occur. Based on this data, one cannot use this knowledge of subcortical infarct location to prognosticate on stroke recovery or to determine eligibility for rehabilitation.

The findings of this study ~~provide~~ generate the hypothesis ~~generation~~ that the corticofugal ~~fiber~~fibres may have large residual capacity. Poor outcome may not occur ~~and may not be associated with poor motor outcome~~ unless all of the ~~fiber~~fibres are disrupted. Even though the MR scans were performed approximately 3 weeks after onset, another possibility is that the T2 signal abnormality might have included edema rather than just necrotic and gliotic tissue. As such the 'infarct lesion' might not have resulted in significant disruption of the corticofugal ~~fiber~~fibres and hence our findings of imperfect correlation.

Study limitations

The limitations of this study include the retrospective nature. Although the sample size in this study is larger than some of the other studies on this subject, the sample size remains relatively small[12 13]. The severity of stroke deficit can be described as mild to moderate; this is not unexpected since we had chosen to evaluate subcortical stroke. In this study, the NIHSS was used to measure motor deficit as this tool had been deemed to be sensitive for prediction of 3 months outcome[23]. The NIHSS sub-item for arm motor deficit measures arm drift and hence it provides a measure of proximal arm strength. T~~arm motor deficit but t~~his tool ~~d~~does~~id~~ not explicitly measure hand motor deficit ~~or finger dexterity, a deficit which may evolved from interruption of M1 fiber~~[24]. The item 12 was used previously for measuring hand motor deficit in the NIHSS. However, the assessment of thisscale by factor analysis showed that the hand motor item did not make any contribution towards the underlying nature of NIHSS[25]. The hand motor item is no longer part of the NIHSS. As such, we urge caution with our findings with regards to the less than perfect correlation between arm motor deficit and corticofugal ~~fiber~~fibres. Finally, the effect of corticofugal ~~fiber~~fibre involvement on clinical outcome are inferred from the likely overlap between the sites of the ~~fiber~~fibres and the patients' infarcts. We had not directly assessed for disruption of the corticofugal ~~fiber~~fibres in these patients. The reason was that the MR studies were performed as clinical scans and did not incorporate a dedicated diffusion tensor sequence. Further, there are technical issues associated with performing tractography in stroke patients [6 12 13].

Conclusion

The motor outcome at three months following subcortical infarct was not universal and varied between upper and lower limbs. The descending motor corticofugal fibres may have different effect on motor outcome between the upper and lower limbs. ~~The descending motor corticofugal fibers may have different effect on motor outcome at three months.~~ Further research in this important area is needed to help with determining stroke outcome and understanding of the neural substrate of motor deficit.

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Disclosure:

None

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Acknowledgement

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Legends to Figures

Figure 1: The corticofugal ~~fiber~~fibres from M1 (blue), PMdv (green) and SMA (red).

Figure 2

Examples of patients with infarct involving the posterior limb of the internal capsule but no motor deficit at 90 days.

Table 1: Association between corticofugal ~~fiber~~fibres and clinical outcome

	M1	PMdv	SMA	
Arm > 0	2.90 (1.41-5.99) 0.22 0.80 (0.66-0.94) 0.96 (0.79, 0.82)	3.57 (1.38-9.24) 0.18 0.76 (0.61-0.91) 0.86 (0.74, 0.84)	2.00 (1.09-3.68) 0.13 0.73 (0.58-0.88) 0.99 (0.79, 0.79)	OR and 95% CI R^2 AUC and 95% CI Threshold volume (ml) sensitivity and specificity
Leg >0	1.75 (1.05-2.94) 0.18 0.69 (0.52-0.85) 1.06 (0.65, 0.75)	2.42 (1.09-5.40) 0.22 0.67 (0.50-0.85) 0.91 (0.59, 0.75)	1.86 (1.06-3.28) 0.19 0.66 (0.48-0.84) 0.99 (0.65, 0.70)	OR and 95% CI R^2 AUC and 95% CI Threshold volume (ml) Sensitivity and specificity
Modified Rankin >2	3.22 (1.48-6.97) 0.31 0.88 (0.79-0.97) 1.05 (1.00, 0.77)	4.42 (1.41-13.84) 0.29 0.83 (0.70-0.97) 1.01 (0.80, 0.77)	2.66 (1.29-5.50) 0.25 0.82 (0.67-0.97) 1.00 (0.80, 0.74)	OR and 95% CI R^2 AUC and 95% CI Threshold volume (ml) sensitivity and specificity

Different metrics of association between corticofugal ~~fiber~~fibres and outcome were presented to for ease of comparison with other studies.

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