Assessing the Clinical Effect of Residual Cortical Disconnection After Ischemic Strokes

Leonardo Bonilha, MD, PhD; Chris Rorden, PhD; Julius Fridriksson, PhD

Background and Purpose—Studies assessing the relationship between chronic poststroke language impairment (aphasia) and ischemic brain damage usually rely on measuring the extent of brain necrosis observed on MRI. Nonetheless, clinical observation suggests that patients can exhibit deficits that are more severe than what would be expected based on lesion location and size. This phenomenon is commonly explained as being the result of cortical disconnection. To understand whether disconnection contributes to clinical symptoms, we assessed the relationship between language impairments and structural brain connectivity (the connectome) in patients with chronic aphasia after a stroke.

Methods—Thirty-nine patients with chronic aphasia underwent language assessment and MRI scanning. Relying on MRI data, we reconstructed the individual connectome from T1-weighted and diffusion tensor imaging. Deterministic fiber tractography was used to assess connectivity between each possible pair of cortical Brodmann areas. Multiple linear regression analyses were performed to evaluate the relationship between language performance and cortical necrosis and cortical disconnection.

Results—We observed that structural disconnection of Brodmann area 45 (spared by the necrotic tissue) was independently associated with naming performance, controlling for the extent of Brodmann area 45 necrosis ($F=4.62; P<0.01$; necrosis: $\beta=0.43; P=0.03$; disconnection $\beta=1.21; P<0.001$).

Conclusions—We suggest that cortical disconnection, as measured by the structural connectome, is an independent predictor of naming impairment in patients with chronic aphasia. The full extent of clinically relevant brain damage after an ischemic stroke may be underappreciated by visual inspection of cortical necrosis alone. *(Stroke. 2014;45:00-00.)*

Key Words: aphasia ■ connectome ■ diffusion tensor imaging ■ stroke

The location of chronic poststroke brain damage is typically based on T1-weighted, T2-weighted, or fluid-attenuated inversion recovery MRI sequences.1–3 These are principles techniques providing information about the extent of the cortical and subcortical lesions. However, it is important to note that these methods may fail to detect the full extent of white matter injury. It is well known from animal and human studies that cortical and subcortical strokes are associated with white matter injury and anterograde and retrograde Wallerian degeneration.4–6 Therefore, cortical disconnections as a result of white matter injury may occur in areas not included in the frank lesion but still account for behavioral impairment.

Aphasia is an impairment of language processing, commonly observed after a dominant hemisphere stroke.7 The emergence of aphasia after a stroke is traditionally associated with structural damage affecting cortical regions related to language functions. Classically, deficits in speech production are expected to occur after lesions affecting pars opercularis and pars triangularis in the left inferior frontal gyrus (now referred to as Broca area, involving the cytoarchitectonic Brodmann areas [BAs] 44 and 45). Conversely, deficits in speech comprehension are typically associated with damage affecting portions of the temporal lobe, especially BA 22—Wernicke area.

It is a caveat that much of what we know about brain—language relationships has been derived from lesion studies that may have underappreciated the extent of cortical disconnection. In fact, circuit disconnections could account for ≤26% of exceptions to the classical radiological–clinical correlations in aphasia.9

Newer imaging methodologies now enable the comprehensive mapping of all neural connections in the brain at medium and large scale (the brain connectome).10–15 The purpose of this study was to examine 2 independent but complementary forms of cortical damage—necrosis and disconnection—in relation to global aphasia measures and naming impairments in patients with aphasia. For this purpose, we performed a comprehensive assessment of aphasia severity and naming impairments in a series of subjects with chronic aphasia caused by a left hemisphere stroke. We also assessed necrotic...
tissue damage and impaired neural connectivity from these subjects using high-resolution MRI. Furthermore, we introduce new connectome-mapping techniques to accurately assess the anatomy of cortical and subcortical lesions in subjects with stroke.

Methods

Subjects
We studied 39 individuals (mean age, 62.7±12.8 years; 22 men; 16 women) who had a left hemisphere ischemic stroke ≥6 months before enrolling in this study (Table I in the online-only Data Supplement). All subjects enrolled in this study were right-handed before the stroke. All subjects enrolled in this study were right-handed before the stroke. All subjects were recruited from the local community. They did not have a history or imaging evidence of other previous strokes and had no history of other neurological illnesses. None of the subjects had a history of intellectual or learning disabilities. All subjects were able to ambulate either with no assistance or with the use of a cane. Patients with a history of learning disability, with a history of uncontrolled seizures, or with more severe forms of motor impairment (ie, not able to ambulate) were excluded from this study.

All subjects signed an informed consent to participate in this study. Subjects were enrolled at the Medical University of South Carolina or at the University of South Carolina. The Institutional Review Boards at University of South Carolina and at Medical University of South Carolina approved this study.

Language Testing
All subjects underwent comprehensive behavioral testing at the time of enrollment in the study. Testing was performed by a speech pathologist and included the Western Aphasia Battery16 (WAB) and the Philadelphia Naming Test17 (PNT).

The main purpose of language testing was to provide an assessment of (1) aphasia severity and (2) naming performance. Aphasia severity was determined using the WAB aphasia quotient, a measure of aphasia severity ranging from 0 to 100 (>93.8 indicates language ability within normal limits). Conversely, naming performance was determined based on PNT performance. The PNT is a computer-based assessment of naming in patients with aphasia17 and includes 175 pictures representing mid- and high-frequency nouns from a word frequency list compiled by Francis et al.8

All subjects underwent a formal evaluation of speech apraxia based on the Subtest Six on the Apraxia Battery for Adults—Second Edition,19 to ensure that apraxia of speech was not a significant confounder accounting for naming difficulties.

MRI Acquisition
All subjects underwent MRI scanning at University of South Carolina or at Medical University of South Carolina. At both sites, MRI scanning was performed using the same type of MRI scanner (ie, a 3T Siemens Trio equipped with a 12-channel head coil). The MRI scanning protocol is described in detail in the online-only Data Supplement.

Preprocessing of MRI Data
To ensure adequate quantification of necrotic lesion burden and cortical connectivity, we optimized connectome-mapping methodology to evaluate structural brain properties while preserving anatomic authenticity in spite of the spatial distortions caused by the stroke lesion. MRI data preprocessing for connectome mapping involves multiple sequential steps,10 namely (1) segmentation of the cerebral cortex into multiple anatomically defined regions of interest (ROIs) and spatial registration of T1-weighted images; (2) transformation of white matter maps and cortical ROIs onto diffusion tensor imaging space; (3) fiber tracking and connectome reconstruction; and (4) cortical connectivity assessment. These steps can be challenging when applied to brains with large anatomic distortions (because of mass effects or pathological atrophy) caused by structural lesions (ie, necrotic tissue from the stroke).

Connectome methodology and necrotic lesion assessment are explained in the Methods section in the online-only Data Supplement and in Figures 1 and 2.

It should be noted that this method does not take into consideration physiological asymmetries between hemispheres. Our group previously assessed the degree of physiological asymmetries in the connectome in healthy older adults.20 None of the ROIs tested in this study are associated with a significant asymmetry in healthy subjects, except for a part of BA 45 (ie, the opercularis component of the inferior frontal

Figure 1. Image preprocessing steps used during the construction of the connectome. The top row demonstrates T1-weighted images from a representative subject. Necrotic tissue can be observed in the left hemisphere, affecting the insula and precentral dorsolateral regions. The middle row demonstrates the probabilistic maps of gray (cyan) and white matter (white) and their relationship with the necrotic lesion mask (in red, manually drawn on T2 images). The bottom row demonstrates the probabilistic map of gray matter segmented in accordance with the Brodmann area Atlas. Note the exclusion of the necrotic tissue from the segmented cortical map, as demonstrated by the 3-dimensional reconstructions on the third column.
gyrus), which demonstrates a leftward asymmetry. These findings are in accordance with previous literature.21 Thus, left-sided fiber reductions are not likely to represent a physiological pattern.

Statistical Analyses
We performed multiple linear regression analyses with the performance on naming measures defined as the dependent variable, with the following independent variables: (1) percentage of damage to each BA area, (2) percentage number of fibers of each BA area. Each BA area was analyzed separately. The explanatory power of the resulting regression model was determined as $R^2$ (proportional reduction in error) with the explanatory factors of interest entered into the regression analysis using a stepwise approach. The level of statistical significance was set at $P<0.05$, adjusted through Bonferroni correction based on the number of regressions investigated.

Results

Language-Aphasia Severity and Naming Performance

Aphasia Severity
The mean aphasia quotient for the group of subjects was 57.94 (SD, 28.27). Performances on WAB subtests were as follows (mean±SD): comprehension=7.67±1.96; fluency=5.23±3.32; speech repetition=5.25±3.71; information content=5.69±3.20. Aphasia types were distributed as follows: 38% (15/39) anomic aphasia; 38% (15/39) Broca aphasia; 5% (2/39) Wernicke aphasia; 10% (4/39) with conduction aphasia; 8% (3/39) with global aphasia. Naming performance: subjects correctly named an average of 51±33% of the PNT items (Table I in the online-only Data Supplement).

Necrotic Lesion Location
All subjects exhibited a cortical/subcortical lesion in the left hemisphere, broadly distributed within the vascular territory of the left middle cerebral artery. A considerable variability in lesion location was observed within the middle cerebral artery territory. The insula and the subcortical aspect of the frontal operculum were the locations of maximal lesion overlap (Figure I in the online-only Data Supplement).

Connectome
The average connectome from all subjects is demonstrated in Figure 3. The relative reduction in connectivity for the BAs in the left hemisphere can be observed by the relative proportion of connectivity weight per BA in the left hemisphere when compared with the right hemisphere (Figure II in the online-only Data Supplement). This analysis excluded reciprocal connections to the region itself. Figure III in the online-only Data Supplement demonstrates the extent of necrosis of each BA. Interestingly, comparing the data from Figures II and III in the online-only Data Supplement, reduction in connectivity was observed in regions with a higher percentage of damage, but it was not a perfect match, indicating that connectivity damage and cortical necrosis are complementary factors. This relationship can be appreciated in Figure IV in the online-only Data Supplement, demonstrating the correlation between necrosis and connectivity, for each ROI.

Overall Necrosis Extent and Language Impairment
We did not observe a relationship between overall lesion size and aphasia quotient on the WAB ($r=-0.16$; $P=0.33$), the WAB naming subscore ($r=0.04$; $P=0.84$), and correctly named items on the PNT ($r=-0.07$; $P=0.67$).

Regional Necrosis and Connectivity and Language Impairment
We focused our analyses on general aphasia measures (assessed through the WAB): (1) comprehension of sequential commands and (2) speech fluency; and naming performance (measured by the PNT): (1) percentage of correctly named items. We assessed brain ROIs typically associated with speech and language, namely BA 22, 37, and 45.
We observed a significant relationship between number of correctly named items on the PNT and a model composed of BA 45 necrotic damage and BA 45 disconnection ($F=4.62$, $P<0.01$; necrosis: $\beta=0.43$, $P=0.03$; disconnection: $\beta=1.21$, $P<0.001$; Figure 4). We also observed a significant relationship between comprehension and a model composed by BA 22 necrosis and BA 22 disconnection ($F=3.05$, $P=0.047$; necrosis: $\beta=-0.35$, $P=0.43$; disconnection: $\beta=47$, $P=0.01$). However, in this model, necrosis was not independently associated with comprehension. Finally, we also observed significant relationship between fluency and a model composed by BA 45 necrosis and BA 45 disconnection ($F=4.62$, $P<0.01$; necrosis: $\beta=2.89$, $P=0.13$; disconnection: $\beta=7.52$, $P=0.025$). Similarly, in this model, necrosis alone was not an independent predictor of fluency (Figure 4).

Interestingly, aphasia severity (aphasia quotient) was not associated with a model composed by necrosis and disconnection in BA 45 ($P=0.34$), BA 22 ($P=0.8$), or BA 37 ($P=0.84$), suggesting that specific language impairments are distinctly associated with regional necrosis and disconnection.

**Discussion**

In this study, we evaluated the relationships between cortical necrosis and cortical disconnection with global aphasia measures and naming performance. We introduced new imaging methodology to assess connectome abnormalities in patients with chronic stroke, and we demonstrated that cortical disconnection and cortical necrosis are coexisting phenomena. We observed that correct naming is dependent upon the preservation of cortical integrity and the preservation of cortical connectivity of BA 45. It is important to note that this finding does not suggest that disconnection and necrosis in other cortical regions does not contribute to naming impairment. Rather, our study focused on a small set of cortical regions, including BA 45, to clearly demonstrate how disconnection contributes to behavioral impairment.

These findings are relevant to the understanding of the mechanisms underlying stroke-related impairments because they underscore 2 important factors: (1) cortical disconnection is an independent form of damage, which may not be readily appreciated by measurement of cortical necrosis and (2) cortical disconnection is a complementary factor that explains behavioral deficits, such as naming impairment.

**Cortical Disconnection as an Invisible Form of Damage**

The full extent of structural injury is usually appreciated only weeks or months after the ischemic event through structural MRI.22 Even though it is possible to define the extension of the necrotic lesions into subcortical regions, it is difficult to quantify, based on visual inspection alone, the magnitude of white matter reduction, particularly as it relates to fibers that connect cortical regions remote from the stroke site.

In this study, we demonstrated that cortical regions in the hemisphere affected by the stroke exhibit a reduction in connectivity when compared with their homologue counterparts in the nonaffected hemisphere. This observation suggests that cortical areas that are apparently intact during visual inspection of MRI images exhibit a reduction in structural connectivity. The degree of connectivity reduction cannot be inferred based on the location of the necrosis alone. This fact is perhaps best explained in Figure 5 where preservation of connectivity of the inferior frontal gyrus may occur for some subjects with anterior supra-Sylvian necrosis but is absent for other subjects with a relatively similar extent of damage.

To assess the extent of disconnection in different cortical regions, we relied on diffusion MRI tractography. Although MRI tractography has the advantage of providing in vivo information about structural brain integrity, it is not without technical limitations.23 In fact, structural connectome mapping is a novel methodological approach in neuroscience and neuroimaging, with growing popularity and applicability.11,12 In this study, we introduce new technical improvements to enable connectome mapping in subjects with stroke. Nevertheless, the results should be interpreted in the context of limitations of MRI tractography.

**Cortical Disconnection and Naming Performance**

We demonstrated that naming performance is associated with preservation of cortical integrity and cortical connectivity of BA 45. Importantly, cortical connectivity predicts naming performance when controlling for the volume of necrosis.

Our group has demonstrated that loss of white matter fibers supporting the dominant inferior frontal gyrus can lead to severe aphasia, even if the region seems to have been spared by the stroke.24 Our current study provides further evidence, suggesting that preserved cortical connectivity is an independent predictor of accurate naming performance in subjects with chronic aphasia. Furthermore, disconnection may play...
a role in aphasia recovery. Our group has demonstrated that naming recovery as a result of therapy is associated with functional modulation of the inferior frontal cortex, leading to an increase in the number of correctly named items. However, functional modulation of the frontal region does not occur in all subjects with a partially preserved frontal cortex. Subjects who do not achieve functional recruitment fail to improve, and a possible reason underlying suboptimal frontal recruitment is the lack of structural connectivity. This theory was not tested in the study, but it could be addressed by future research.

The results described in this article highlight the importance of subcortical lesions in patients with aphasia. Kreisler et al demonstrated that basal nuclei and subcortical lesions were frequently associated with almost all forms of language impairment. Cortical disconnection as a result of specific subcortical lesions may play a significant role in aphasia. In fact, unmeasured disconnection can account for discrepancies about the crucial anatomy supporting naming. Specifically, because lesion studies rely on the manual delineation of areas of frank necrosis, they may underappreciate damage as a result of remote cortical disconnection. Expressive deficits are commonly observed after strokes affecting the dominant inferior frontal gyrus (involving BA 44 and 45). However, naming involves a network of peri-Sylvian structures, and naming impairment may occur as a result of lesions affecting several aspects of the cortical language network. DeLeon et al demonstrated that several regions are essential for distinct processes underlying naming. Specifically, anomia may arise from combined dysfunction involving the left anterior, inferior and posterior middle/superior temporal cortex, posterior inferior frontal, and inferior parietal cortex. Baldo et al demonstrated that damage to the left midposterior middle temporal gyrus prevents the retrieval of names associated with objects (ie, lexical-semantic retrieval). These findings complement observations from Walker et al and Schwartz et al demonstrating that semantic errors during naming are associated with damage to the left anterior and mid middle temporal gyrus, whereas phonological errors are associated with lack of integrity of the left supramarginal gyrus and inferior frontal cortex. However, the results of Dronkers et al and Schwartz et al do not completely agree with the findings from Hillis et al. Importantly, disagreement among studies may be related to 2 issues. First, naming involves multiple cognitive domains, such as visual/auditory perception and processing, semantic decision, lexical retrieval, phonological encoding, and speech articulation. Second, it does not seem that factors, such as apraxia of speech, can account for our findings because it is typically associated with damage to BA 44 or premotor cortex and not BA 45. Finally, the location of damage or cortical dysfunction may be underestimated by current methods used to define the frank lesion. As such, more pervasive network damage can underlie a more salient lesion but be underappreciated by brain mapping techniques, and localization fails to define a crucial region or network.

In summary, we suggest that correct naming in subjects with chronic aphasia is dependent on the preservation of cortical integrity and the preservation of cortical connectivity of BA 45. We also suggest that structural evaluation of brain damage in relationship with language impairment after stroke can be improved by measuring the subcortical injury and its remote ramifications into distant cortical disconnection. This connectivity-based approach can improve the understanding of the mechanisms, leading to language and behavioral impairments after stroke. It may also provide evidence for degree of structural integrity supporting recovery.

Sources of Funding
This publication was supported by National Institute of Deafness and Communication Disorders (NIDCD), grant number DC009571. It was
also supported by the South Carolina Clinical & Translational Research (SCTR) Institute, with an academic home at the Medical University of South Carolina, through NIH Grant Number UL1 TR000062.

**Disclosures**

None.

**References**

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Stroke. published online March 11, 2014;

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SUPPLEMENTAL MATERIAL:

Methods:

1) **MRI acquisition parameters**

   A) T1-weighted images (3D MP-RAGE, TR = 2250ms, TE = 4.15ms, 256×256 matrix, 256×256mm FOV, parallel imaging GRAPPA=2, 80 reference lines, TA=377s);

   B) Diffusion EPI scan (30-directions with b=1000 s/mm² and b=2000 s/mm², TR = 6100ms, TE = 101ms, 82×82 matrix, 222x222mm FOV, parallel imaging GRAPPA=2, 80 45 contiguous 2.7mm axial slices, TA=390s).

2) Cortical segmentation and spatial registration of T1 weighted images.

   We employed an extension of the software Statistical Parametric Mapping (SPM) entitled “Clinical Toolbox” developed by our group. The Clinical Toolbox utilizes a cost-function approach to normalize the brain into the standard stereotaxic space (MNI space). This step employs a manually-defined map of the stroke lesion, drawn by one of the authors (Bonilha) to weigh tissue influence on normalization. Notably, the Clinical Toolbox exploits SPM's unified normalization-segmentation subroutines to yield probabilistic gray and white matter tissue maps. These were essential to guide subsequent connectivity assessment steps. Linear and non-linear normalization parameters obtained from the normalization of the brain to standard space were inverted and applied to a BA ROI Atlas in standard space (distributed with MRICro). The probabilistic map of gray matter in native T1 space was segmented into a map of cortical BA ROIs. Importantly, the areas originally involved in the hand-drawn lesion were excluded from this step in order to eliminate the erroneous segmentation of the necrotic tissue into viable cortical regions. These steps are demonstrated in Figure 1.

3) **Transforming white matter map and cortical ROIs onto DTI space.**

   To improve registration between T1 and DTI spaces, the native volumetric T2 weighted image was linearly co-registered onto the native T1 image using mutual information algorithms in SPM. This step generated a T2 weighted image matched to the native T1 image (the “registered T2 image”). The registered T2 image was linearly
co-registered onto the B0 image using FMRIB’s Linear Image Registration Tool (FLIRT). The transformation matrices were then applied to the map of segmented cortical ROIs and to the white matter probabilistic tissue map, yielding cortical ROIs and white matter maps in DTI space.

4) Fiber tracking and connectome reconstruction.

Whole brain tractography was reconstructed in DTI space using the software Diffusion Toolkit (DTK)\(^5\). Acquisition geometry and gradients were updated using the tool dcm2nii, as part of the software MRIcron. Tractography was reconstructed using a maximal angle threshold of 45 degrees, in accordance with the Fiber Assignment by Continuous Tracking (FACT) algorithm\(^6\). Two restriction maps were applied. The first one was a dynamic contrast range based on the diffusion-weighted image (DWI), as part of default DTK parameters. Importantly, the second restriction mask was the probabilistic white matter map transformed into DTI space. By applying a white matter restriction mask, we ensured that important quality benchmarks were met, namely: 1) tractography did not attempt to reconstruct fibers in the location of the necrotic lesion, where random diffusion can lead to erroneous fiber tracking and misrepresentation of connectivity; 2) the termination boundaries overlapped and extended into the cortical ROI map, thereby ensuring an accurate end point calculation for each white matter fiber. Once cortical ROIs and white matter maps were registered into DTI space, each and every white matter fiber was evaluated regarding its origin and termination. For each possible pair of BAs, the number of fibers connecting the pair was computed and recorded in a connectivity matrix. These steps were performed through in-house scripts written in MATLAB.

5) Cortical connectivity.

In order to assess connectivity, we computed the weighted sum of all connections to four cortical areas that are typically implicated in language processing: BAs 22, 37, 44, and 45. Certainly, other regions play a role in language processing. **However, we chose** to focus on these four areas to highlight the potential importance of disconnection in functional impairment. Finally, to assess fiber reduction, the
percentage of fibers compared with the homologous BA in the right hemisphere is calculated (yielding the “percentage number of fibers”, as referred to in the sections below). These steps are performed through in-house scripts written in MATLAB. Importantly, this step aimed to eliminate the effect of bias caused by subjects having been scanned in different scanners or with different DTI sequences. Since each patient’s connectivity measures were adjusted based on the patient’s contralateral hemisphere, the final connectivity measure was normalized based on each subject’s imaging properties and therefore comparable across all subjects.

6) Necrotic lesion burden.

The percentage of damage to each cortical ROI is calculated by overlaying the hand drawn lesion map onto the parcellated cortical map in native T1 space, where the percentage of damage to each BA is calculated. These steps are performed through in-house scripts written in MATLAB.
Online Table I- Demographic and language information. Language performance was assessed through the Western Aphasia Battery (WAB) and Philadelphia Naming Test (PNT). Legends: RH=right handed; LH=left handed; M=male, F=female; W=white; AA= African-American; SD=standard deviation; AQ= aphasia quotient (WAB); Comp=comprehension (WAB); Flu=fluency (WAB); Repet=repetition (WAB); NamingSub=Naming Subscore (WAB); Naming=fraction of correctly named items (PNT).

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Online Figure I- The spatial distribution of necrotic lesion masks (transformed into standard MNI stereotaxic space) from all subjects included in this study is demonstrated by overlaying the lesion masks onto a T1-weighted atlas. Voxels are color-coded in accordance with the number of individuals with a lesion affecting each specific voxel.

Online Figure II- The relative number of fibers in representative BA ROIs in the left hemisphere, compared with the homologue BA in the right hemisphere (0= no remaining fibers, 1= left hemisphere fibers are at least equal in number to right hemisphere fibers). The box plots demonstrated the distributions across all subjects per each ROI.
**Online Figure III**- The degree of sparing from necrosis of representative BA ROIs (ranging from 1- the ROI was completely spared, to 0 – completely included by the necrosis). The box plots demonstrated the distributions across all subjects per each ROI.

**Online Figure IV**- The relationship between necrosis and disconnection for representative Bas. The scatter plots demonstrate percentage of necrosis (y-axis, 0= no necrosis; 1= complete necrosis) and percentage of remaining fibers compared with the right hemisphere (0= no remaining fibers, 1= left hemisphere fibers are at least equal in number to right hemisphere fibers). The correlation coefficient for each ROI is also demonstrated underlying each scatter plot. subjects per each ROI.
References

Assessing the Clinical Effect of Residual Cortical Disconnection After Ischemic Strokes

Leonardo Bonilha, MD, PhD; Chris Rorden, PhD; Julius Fridriksson, PhD

1 Department of Neurology, Medical University of South Carolina, Charleston; 2 Departments of Psychology; and 3 Communication Sciences and Disorders, University of South Carolina, Columbia

Abstract

Background and Objectives: After ischemic strokes, some functional and structural changes remain. The clinical effects of these residual disconnections have not yet been fully explored. We investigated whether residual cortical disconnection is associated with specific clinical outcomes.

Methods: We used structural MRI to identify cortical disconnection in a sample of 39 stroke patients, using deterministic tractography. We then compared the clinical outcomes of patients with and without cortical disconnection.

Results: Patients with cortical disconnection had worse clinical outcomes, particularly in the areas of motor function and language.

Conclusion: Our findings suggest that residual cortical disconnection may be a clinically relevant factor in stroke recovery.

Stroke 2014; 45: 988-993