CT Perfusion for Lesion-symptom Mapping in Large Vessel Occlusion Ischemic Stroke

James W Garrard[1,2*], Ain A Neuhaus[2,3*], Davide Carone[1,2], Olivier Joly[1], Armin Zarrintan[4], Alejandro A Rabinstein[4], Thien Huynh[4], George Harston[1,2], Waleed Brinjikji[4], David F Kallmes[4]

1 Brainomix Ltd., Oxford, UK
2 Department of Stroke, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
3 Acute Stroke Programme, University of Oxford, Oxford, UK
4 Mayo Clinic, Rochester, MN

*James W Garrard and Ain A Neuhaus contributed equally to this manuscript

Short title: CT perfusion lesion-symptom mapping in stroke

Corresponding author: Dr James W Garrard

Address: Brainomix Ltd, Level 1, Seacourt Tower, Oxford, OX2 0JJ

Email: jgarrard@brainomix.com

Abstract: 250 words

Word count: 3429 words

Tables: 1

Figures: 3

Abstract

Background

Identifying eloquent regions associated with poor outcomes based on CT perfusion (CTP) may help inform personalized decisions on selection for endovascular therapy (EVT) in large-vessel occlusion (LVO) ischemic stroke patients. This study aimed to characterize the relationship between CTP-defined hypoperfusion and National Institutes of Health Stroke Scale (NIHSS) subitem deficits.

Methods

Patients with anterior circulation LVO, baseline CTP, itemized NIHSS at presentation and 24-hours were included. CTP was analyzed using e-CTP (Brainomix, UK). Tmax prolongation was defined as >6 seconds, and penumbra as the difference between Tmax and ischemic core (relative cerebral blood flow <30%). Voxel-lesion-symptom mapping was performed using sparse canonical correlation analysis. For each NIHSS subitem, and total NIHSS, the associations were plotted between Tmax voxels with baseline NIHSS, and penumbra voxels with delta NIHSS (24-hour minus baseline).

Results

This study included 171 patients. Total NIHSS was predicted by hypoperfusion in left frontal cortex and subcortical white matter tracts. Voxels associated with neurological recovery were symmetrical and subcortical.

Limb deficits were associated with respective motor cortex regions and descending motor tracts, with negative correlation within the contralateral hemispheres. A similar but smaller cluster of voxels within the penumbra was associated with NIHSS improvement. Language impairment correlated to left frontal cortex and superior temporal gyrus voxels. With the exception of dysarthria, significant associations were observed and more diffusely distributed in all other NIHSS subitems.

Conclusions

These results demonstrate the feasibility of hypoperfusion-to-symptom mapping in LVO. Symptom-based mapping from presenting imaging could refine treatment decisions targeting specific neurological deficits.

What is already known on this topic

Previous studies have used lesion-symptom mapping software to identify eloquent areas of stroke location associated with worse outcomes. Identifying optimal candidates for EVT remains an ongoing priority to maximize treatment efficacy. A personalized approach, based on the location of the perfusion deficit, may offer one potential solution to this.

What this study adds

This study of patients with anterior circulation LVO demonstrates areas within the CTP defined ischemic core which are associated with neurological deficits, using the itemized NIHSS. In addition, areas from within the CTP defined penumbra associated with early improvement in the NIHSS subitems are demonstrated. Language areas are within the left frontal cortex and superior temporal gyrus voxels, and relevant motor areas within the motor cortex regions and descending motor tracts .

How this study might affect research, practice or policy

Using CTP defined ischemic core and penumbra at presentation might refine the prediction of potential treatment effects from reperfusion therapies for individual patients and better inform risk-benefit decisions for EVT.

Introduction

Whilst endovascular thrombectomy (EVT) has demonstrated superiority over medical management in large vessel occlusion (LVO) ischemic stroke, treatment outcomes remain variable, with only 46% of LVO patients achieving functional independence (1). Identifying optimal candidates for EVT remains an ongoing priority to maximize treatment efficacy and to understand the likelihood of neurological recovery in individual patients.

A common approach for selecting patients has been to estimate the volume of ischemic core, as patients with large areas of tissue already irreversibly damaged have been historically considered unable to benefit from EVT.(2,3) The latest recanalization trials have however shown that patients can still achieve a good outcome even in the presence of a large ischemic core,(4) suggesting that other factors such as lesion location and its relationship with ongoing neurological symptoms might be critical in identifying patients able to benefit from recanalization treatment.

Different cortical and subcortical anatomical regions are thought to contribute disproportionately to overall disability. In line with this, retrospective analyses of the MR-CLEAN trial showed that models incorporating infarct volume in high-relevance regions outperformed models relying on total infarct volume alone.(5) Incorporating lesion location might also offer the opportunity to identify patients with the capacity to recover from specific neurological symptoms, allowing to select patients following a more individualized approach (6) This might be particularly relevant where the benefit from EVT is less established, such as patients with more distal occlusions.

CT Perfusion (CTP) imaging was key in the earliest successful clinical trials of extended time-window EVT by allowing estimation of ischemic core and penumbra volumes.(2) However, there is little data on its use in the acute setting to characterize the relationship between hypoperfusion location and specific neurological deficits, or between areas of subsequent reperfusion and early neurological recovery.

The aim of this study was to assess the feasibility of using CTP in acute stroke patients to explore the relationship between regional perfusion status, symptom severity and recovery following recanalization. A voxel-wise lesion-symptom mapping was used to generate anatomical maps of voxels to demonstrate the relationship between areas of time to maximal

contrast (Tmax) prolongation and NIHSS subitems, and areas within the reperfused penumbra with improvement in the NIHSS at 24-hours.

Methods

Study subjects

*We included patients who presented to two comprehensive stroke centers from January 2015 to February 2020, with LVO subsequently treated with EVT. Of the 531 total cases, we restricted our analyses to patients with 1) age ≥18, 2) anterior circulation stroke, 3) available CTP imaging at presentation and 4) itemized NIHSS at presentation and at 24-hours. Exclusion criteria included evidence of non-stroke intracranial pathology, significant imaging artefacts, undocumented NIHSS items and refusal of consent following research authorization checking. The study was given ethical approval by the institutional review board.*Click or tap here to enter text.*Image analysis*

CTP data were analyzed using an FDA-cleared postprocessing software, e-CTP (Brainomix, UK). Briefly, pseudonymized DICOM files were pre-processed and corrected for positional transformations, and deconvolution approach was used for generating the time-to-maximal peak (Tmax), and relative cerebral blood flow (rCBF) perfusion maps.

The ischemic core (IC) was defined as the region where rCBF < 30% (8). Tmax was thresholded at >6 seconds to derive a binary mask, in keeping with prior data suggesting this provides the best estimate of mixed gray and white matter perfusion threshold for infarction (9). Penumbra was defined as Tmax voxels subtracted by IC voxels. All regions of interest were registered to MNI-152 template space using non-linear registration (10).

Data analysis

For lesion-symptom mapping, we used sparse canonical correlation analysis (SCCAN), a modified form of principal component analysis with improved accuracy over conventional univariate models, implemented using the LESYMAP package (https://github.com/dorianps/LESYMAP) in the R-toolbox.(11) Lesion data were extracted from binarized Tmax and penumbra maps and restricted to voxels that were affected in at least 10% of scans. Symptom scores were defined as NIHSS, using either individual items or total NIHSS. Delta NIHSS was defined as the difference between 24-hour and baseline NIHSS, and binarized in instances of worsening of NIHSS to restrict the analysis to neurological improvement.

Binarized Tmax maps were used to localize areas associated with symptom severity. Penumbra maps of patients with excellent recanalization (TICI 2B-3) were used to localize areas associated with improvement in NIHSS.

Statistical analysis

All statistical analysis was performed in R, R Core Team (2024) Vienna, Austria. The relationship between the clinical data and imaging results was performed using the LESYMAP software previously mentioned. The differences in baseline clinical variables were compared between patients who demonstrated early neurological improvement, defined using an inclusive definition for an improvement of the NIHSS at 24-hours of 4 or more, or 24-hour NIHSS of zero, and those who did not. (7) Kruskal-Willis test for non-parametric data, and chi-squared for categorical variables.

Results

Demographics

Baseline characteristics for the 171 study participants is given in Table 1. The mean age was 70.2± 14.4 years, and 88 patients (51%) were female. The median presenting NIHSS 16 (IQR 11.5-22), and median 24-hour NIHSS was 12 (IQR 6-19). Of the 170 patients with procedural outcome data, 138 (80.7%) achieved TICI-2B or better reperfusion, with 66 patients (39%) achieving TICI-3.

Overall neurological function

The overall distribution of Tmax >6s voxels is displayed in Figure 1A, centered on the middle cerebral artery territories.

For total NIHSS, VLSM identified two clusters of statistically significant voxels from within areas of prolonged Tmax. The larger and more strongly associated cluster was in the left hemisphere, centered around left frontal cortex, left parietal lobe, and left subcortical white matter (Figure 1B), likely reflecting language function, and right arm and leg motor function contralateral to the left hemisphere. The second, small cluster was observed within the right insular and parietal lobe, with fewer significant voxels and weaker weighted association. Areas of early neurological recovery from within the penumbra were observed within broadly symmetrical clusters within the inferior frontal cortex and subcortical voxels.

An example of two cases, both with successful recanalization, are given in Supplementary Figure 1. Both cases demonstrate proximal occlusions affecting the left hemisphere, with speech disturbance at presentation. In Case A, there is a greater overlap between the ischemic core and eloquent areas of speech disturbance (NIHSS subitem 9), associated with no early recovery in speech, compared with Case B in which there is early improvement in speech subitem from three to one.

Early neurological deterioration was seen in 50.3% (86/171) of patients. As demonstrated in the Supplementary Table, there was no difference in any baseline demographic or clinical characteristics, or acute stroke treatment. Patients with early neurological improvement demonstrated lower 24-hour NIHSS ($p<0.0001$).

NIHSS subitems

NIHSS subitems relating to left arm and leg motor function (NIHSS 5A and 6A; Figure 2A,B) localized to the right hemisphere, whereas the subitems corresponding to the right arm and leg (NIHSS 5B and 6B; Figure 2C,2D) localized to the left hemisphere. In both cases, the voxels were predominantly in the frontal lobes with mixed cortical and adjacent white matter tract involvement. Negative associations were seen in the contralateral hemispheres of each of the four subitems. Areas associated with improvement in NIHSS were seen within the penumbral voxels from the corresponding hemispheres for all motor function NIHSS subitems, albeit in a smaller cluster of voxels.

Language function (NIHSS 9) at baseline localized voxels of prolonged Tmax primarily to left frontal, parietal, and insular cortex and subcortical white matter (Figure 3), with a negative association seen in the right, contralateral hemisphere. Improvement in language was predominantly associated with two, smaller clusters of penumbra voxels within the left frontal and parietal lobes.

Voxel distribution in the remaining items displayed less clear-cut correlation to expected anatomical substrates. Level of consciousness (NIHSS 1A; Supplementary Figure 2A) was associated primarily with left frontal and posterior parietal voxels, without significant voxels associated with neurological recovery. Orientation to time and age (NIHSS 1B; Supplementary Figure 2B) exhibited a cluster of left cortical and subcortical voxels, with negative correlation within right cortical voxels. Obeying commands (NIHSS 1C; Supplementary Figure 2C) was associated with a single large cluster of voxels encompassing much of the left hemisphere. A negative association was seen in the right hemisphere. Voxels associated with neurological recovery from within the penumbra were seen in a similar, but smaller distribution of left hemisphere voxels.

Extraocular movements (NIHSS subitem 2; Supplementary Figure 3A) demonstrated one small cluster in the left cortical region, with multiple areas of poorly localized voxels associated with neurological recovery. Visual fields item (NIHSS item 3; Supplementary Figure 3B) was associated with clustered voxels in right frontal, right parietal and left insula, without any significant areas associated with neurological recovery.

Facial motor function (NIHSS 4; Supplementary Figure 4A) was associated with a small cluster of right inferior frontal gyri voxels, without any significant areas associated with neurological recovery. Limb ataxia (NIHSS item 7; Supplementary Figure4B) demonstrated a small cluster of voxels within the right parietal lobe associated with neurological recovery.

Sensory impairment (NIHSS item 8; Supplementary Figure 5A) was associated with right inferior frontal and subcortical voxels. Inattention (NIHSS 11; Supplementary Figure 5B) was centered on left pre- and postcentral gyri, right temporal lobe and scattered bilateral cortical foci, without any significant areas associated with neurological recovery. Of the 16 analyzed VLSM relations, only NIHSS item 10 (dysarthria) failed to demonstrate any significantly associated voxels.

Discussion

We have demonstrated the feasibility of using VLSM to map specific neurological deficits onto areas of acute CTP hypoperfusion in patients with LVO stroke, whilst identifying areas of early neurological recovery from within areas of penumbra. To our knowledge, this is the first study to examine the relationship between specific regional hypoperfusion on presenting CTP with neurological function at presentation in patients undergoing EVT.

Prior studies have demonstrated the application of VSLM methods based on follow-up imaging, to identify predictors of neurological outcome. This includes one large study which incorporated structural and functional dysconnectome maps to construct comprehensive maps of localization maps predictive of functional outcomes.(12,13) A previous CT Perfusion-based study demonstrated that infarcts in the insula, perisylvian cortex, motor strip, and ASPECTS M2 and M5, and hypoperfusion without infarction in sylvian fissure and M2 were associated with worse mRS at 90 days.(14) Our results provide similar localization for many of the NIHSS subitems but based on automated regions of interest from presentation CTP imaging, with localization of early neurological recovery from within areas of penumbra in patients with successful recanalization with EVT. Two example cases illustrate the potential clinical utility of such an approach with differing neurological outcomes despite both cases being successfully recanalized using EVT.

The use of eloquence in EVT populations has been explored, with two MR perfusion studies demonstrating that eloquence-based mismatch resulted in a better prediction of outcome following EVT, compared with more established methods including clinical variables and CTP mismatch.(15,16) The best regional mismatch predictors of outcome in their dataset were thalami, left superior longitudinal fasciculus, left post-central and supra-marginal gyri and the left retrolenticular internal capsule. This is consistent with the results of this study, where left-sided hypoperfusion regions were the predominant contributors to total NIHSS, reflecting lateralization of language and dominant limb motor function, and the weighting of NIHSS for speech function.(17) By contrast, the distribution of voxels associated with neurological recovery were more symmetric, indicating the benefit of recanalization regardless of hemisphere, and with no underlying differences in clinical characteristics to patients without neurological improvement. These results demonstrated an expected distribution of voxels

associated with limb weakness and NIHSS improvement, as well as corresponding areas within Broca's area and Wernicke's area associated with speech, which were expected and consistent findings to previous literature.(12) The presence of negative correlations in the opposite hemisphere are likely a reflection that stroke patients rarely present with bilateral lesions or symptoms (especially in the anterior circulation)-. As a consequence, a patient with an acute stroke affecting the right MCA territory will have high chances to present with left motor weakness, but a low probability of having right motor weakness as it will be unlikely for that same patient to be suffering from a bilateral stroke.

With the benefit of EVT being demonstrated in increasingly inclusive patient populations,(4) eloquence-based selection for EVT based on CTP might help optimizing the use healthcare resources by understanding the likelihood of neurological recovery in individual patients. Moreover, in areas of clinical equipoise, such as medium vessel occlusion (MeVO) or low NIHSS for example, eloquence may be able to aid in the risk stratification of EVT therapy, using a more personalized medicine, rather than a one-size-fits all based approach to EVT selection.(18)

There are limitations to our study. First, our cohort was limited to anterior circulation LVO, with mostly internal carotid artery (ICA) or proximal middle cerebral artery (MCA) (M1) occlusions, which would not capture contributions to NIHSS from brainstem and posterior cortical structures, and may underestimate the impact of anterior cerebral artery territories. We were also not able to explore how this CTP-based eloquence technique performs in medium or distal vessel occlusions based on this study population. A relative paucity of significant cortical voxels were observed, which may reflect underlying atrophy or technical limitations of CTP underestimating very superficial ischemia. Finally, although the identified regions were congruent with pre-existing knowledge for motor and language function, the voxel distributions for the remaining items were less clearly localized to expected anatomical substrates. This may reflect a relatively greater contribution from posterior structures to visual function and coordination but is also likely related to the relatively lower sample size for those items.

In conclusion, this study demonstrates the feasibility of mapping NIHSS items to CTP deficits at presentation in LVO stroke, and areas of penumbra associated with itemized early neurological recovery. Developing this approach might refine the prediction of potential

treatment effects from reperfusion therapies for individual patients and better inform risk-benefit decisions for EVT. Further work, including larger datasets and including low NIHSS or MeVO, are required.

Ethics Statement

MCR data collection was approved by the Mayo Clinic Institutional Review Board (IRB 17-005045). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JWG, AAN, DC contributed to the imaging analysis. JWG, AAN, DC, GH contributed to the preparation of the manuscript. AZ, AAR TH, WB and DWK have contributed in acquisition of the data. All authors contributed in conception and design of the study. As guarantor, JWG accepts responsibility for the work.

Funding Disclosure

There was no specific funding for this study.

Competing Interests

J.G., D.C., O.J. and G.H. are employees of Brainomix Ltd. D.F.K. discloses stockholder status in Superior Medical Experts, LLC, Nested Knowledge, LLC, Marblehead Medical, LLC, Conway Medical, LLC, and research support from Cerenovus, Insera Therapeutics, Medtronic, MicroVention. The remaining authors declare no conflicts of interest related to this work.

1. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. New England Journal of Medicine. 2015;372(11):1019–30.

2. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. New England Journal of Medicine. 2018 Feb 22;378(8):708–18.

3. Campbell BCV, Majoie CBLM, Albers GW, Menon BK, Yassi N, Sharma G, et al. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. Lancet Neurol. 2019;18(1):46–55.

4. Chen H, Colasurdo M. Endovascular thrombectomy for large ischemic strokes: Meta-analysis of six multicenter randomized controlled trials. Journal of NeuroInterventional Surgery. BMJ Publishing Group; 2024.

5. Ernst M, Boers AMM, Aigner A, Berkhemer OA, Yoo AJ, Roos YB, et al. Association of Computed Tomography Ischemic Lesion Location with Functional Outcome in Acute Large Vessel Occlusion Ischemic Stroke. Stroke. 2017 Sep 1;48(9):2426–33.

6. Menezes NM, Ay H, Zhu MW, Lopez CJ, Singhal AB, Karonen JO, et al. The real estate factor: Quantifying the impact of infarct location on stroke severity. Stroke. 2007 Jan;38(1):194–7.

7. Soize S, Fabre G, Gawlitza M, Serre I, Bakchine S, Manceau PF, et al. Can early neurological improvement after mechanical thrombectomy be used as a surrogate for final stroke outcome? J Neurointerv Surg. 2019 May 1;11(5):450–4.

8. Demeestere J, Wouters A, Christensen S, Lemmens R, Lansberg MG. Review of Perfusion Imaging in Acute Ischemic Stroke: From Time to Tissue. Vol. 51, Stroke. Wolters Kluwer Health; 2020. p. 1017–24.

9. Chen C, Bivard A, Lin L, Levi CR, Spratt NJ, Parsons MW. Thresholds for infarction vary between gray matter and white matter in acute ischemic stroke: A CT perfusion study. Journal of Cerebral Blood Flow and Metabolism. 2019 Mar 1;39(3):536–46.

10. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. Neuroimage [Internet]. 2012 Aug;62(2):782–90. Available from: http://www.pnas.org/content/103/10/3863.abstract%0Ahttp://www.sciencemag.org/cgi/content/full/science.1193125/DC1%0Ahttp://journal.frontiersin.org/article/10.3389/neuro.06.004.2008/abstract

11. Pustina D, Avants B, Faseyitan OK, Medaglia JD, Coslett HB. Improved accuracy of lesion to symptom mapping with multivariate sparse canonical correlations. Neuropsychologia. 2018 Jul 1;115:154–66.

12. Ding L, Liu H, Jing J, Jiang Y, Meng X, Chen Y, et al. Lesion Network Mapping for Neurological Deficit in Acute Ischemic Stroke. Ann Neurol. 2023 Sep 1;94(3):572–84.

13. Rajashekar D, Wilms M, MacDonald ME, Schimert S, Hill MD, Demchuk A, et al. Lesion-symptom mapping with NIHSS sub-scores in ischemic stroke patients. Stroke Vasc Neurol. 2022 Apr 1;7(2):124–31.

14. Haranhalli N, Mbabuike N, Grewal SS, Hasan TF, Heckman MG, Freeman WD, et al. Topographic correlation of infarct area on CT perfusion with functional outcome in acute ischemic stroke. J Neurosurg. 2020;132(1):33–41.

15. Fukutomi H, Yamamoto T, Sibon I, Christensen S, Raposo N, Marnat G, et al. Location-weighted versus Volume-weighted Mismatch at MRI for Response to Mechanical Thrombectomy in Acute Stroke. Radiology. 2023 Feb 1;306(2).

16. Kerleroux B, Benzakoun J, Janot K, Dargazanli C, Eraya DD, Ben Hassen W, et al. Relevance of Brain Regions' Eloquence Assessment in Patients With a Large Ischemic Core Treated With Mechanical Thrombectomy. Neurology [Internet]. 2021 Nov 16 [cited 2024 Feb 27];97(20). Available from: https://www.neurology.org/doi/10.1212/WNL.0000000000012863

17. Audebert HJ, Singer OC, Gotzler B, Vatankhah B, Boy S, Fiehler J, et al. Postthrombolysis hemorrhage risk is affected by stroke assessment bias between hemispheres [Internet]. 2011. Available from: www.neurology.org.

18. Al Saiegh F, Munoz A, Velagapudi L, Theofanis T, Suryadevara N, Patel P, et al. Patient and procedure selection for mechanical thrombectomy: Toward personalized medicine and the role of artificial intelligence. Vol. 32, Journal of Neuroimaging. John Wiley and Sons Inc; 2022. p. 798–807.

Table 1: Demographic information

Participants	**n**	**171**
Age	Mean (SD)	70.2 (14.4)
Female Sex	%(n)	51% (88/171)
Hypertension	%(n)	74% (126/171)
Diabetes	%(n)	27% (47/171)
Atrial Fibrillation	%(n)	39% (67/171)
Previous Stroke	%(n)	15% (25/171)
Smoking	%(n)	38% (65/171)
Baseline NIHSS	Median (IQR)	16 (11.5 to 22)
Thrombolysis	%(n)	40% (69/171)
24-hour NIHSS	Median (IQR)	12 (6 to 19)
Time from onset to CT	Median (IQR)	231.5 (84 to 423.5)
Right hemisphere LVO: **NIHSS**	N(%) Median (IQR)	78 (46)* 15.5 (6-18)
Left hemisphere LVO: N(%) **NIHSS: Median [IQR]**	N(%) Median (IQR)	92 (53)* 19 (9.75-24)
Occlusion location : N (%)	ICA	32 (19)
	M1	70 (41)
	M2/M3	24 (14)
	Tandem	45 (26)
Recanalization status, mTICI: N (%)	0 – 2A	32 (19)
	2B – 2C	72 (42)
	3	66 (39)
	No data	1 (0.6)

*One patient had bilateral ICA occlusions.

Figure captions:

Figure 1. A) Distribution of Tmax >6 s voxels for the overall cohort. The frequency of included voxels is indicated by the color intensity on the heatmap. B) voxels correlated with total NIHSS in the overall cohort. Red indicates voxels with prolonged Tmax which are associated with NIHSS. Green indicates voxels associated with neurological recovery (using Delta NIHSS) from within the penumbra in patients with successful recanalization.

Figure 2. Voxels correlated with the motor components of the NIHSS. A) NIHSS 5A (Left arm), B) NIHSS 5B (Right arm), C) NIHSS 6A (Left leg), D) NIHSS 6B (Right leg) in the overall cohort. Red = Tmax voxels associated with NIHSS subitem. Blue = voxels negatively correlated with NIHSS subitem. Green = penumbra voxels associated with neurological recovery.

Figure 3. Voxels correlated with NIHSS 9 (language) in the overall cohort. Voxels of Tmax prolongation within the left hemisphere were positively associated with language disturbance on the NIHSS, whereas voxels of Tmax prolongation within the right hemisphere were negatively associated with speech disturbance. Penumbra voxels within the left hemisphere were positively associated with neurological recovery in language in patients with successful recanalization.

Supplementary Figure 1. Two examples of cases with successful recanalization. A) and D) demonstrate slices from the CT Angiogram scans with the occlusion identified. B) and E) demonstrate a slice of the prolonged ischemic core (blue) and penumbra area (green) for each case. In C) and F) the ischemic core (blue) and the eloquent area associated with speech disturbance (red-orange) are identified. There is more overlap between the ischemic core and eloquent areas in Case A compared with Case B.

Supplementary Figure 2. Voxels correlated with A) NIHSS 1A (level of consciousness), B) NIHSS 1B (orientation questions) and C) NIHSS 1C (response to commands) in the overall cohort. .

Voxels of Tmax prolongation within the left hemisphere were positively correlated with positive scores in NIHSS subitems 1B and 1C, whereas voxels of Tmax prolongation within the right hemisphere were negatively correlated with scores in these subitems. Voxels within the penumbra in the left hemisphere were significantly associated with neurological recovery in NIHSS subitem 1C.

Supplementary Figure 3. Voxels correlated with A) NIHSS 2 (gaze). Voxels of Tmax prolongation within both hemispheres were positively correlated with positive scores (Red). Voxels from within the penumbra were correlated with neurological recovery (green). B) Voxels of Tmax prolongation from both hemispheres were correlated with positive scores in NIHSS subitem 3 (extraocular movements) (red).

Supplementary Figure 4. A) Voxels of Tmax prolongation within the right posterior frontal cortex were correlated with positive scores on NIHSS subitem 4(facial movements).B) Voxels within the right hemisphere of the penumbra were correlated with improvement in NIHSS subitem 7 (limb ataxia) in the overall cohort.

Supplementary Figure 5. Voxels of Tmax prolongation correlated with positive scores for A) NIHSS 8 (sensory) and B) NIHSS 11 (extinction or inattention) in the overall cohort.

Supplementary Table. This demonstrates the baseline clinical and demographic data for patients with successful recanalization, and the comparison between patients with early neurological improvement (NIHSS improvement of >=8 at 24-hours, or NIHSS=0 at 24-hours) and those without.