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Relevance of Brain Regions Eloquence Assessment in Patients With a Large Ischemic Core Treated With Mechanical Thrombectomy

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ABSTRACT

Objective

Individualized patient selection for mechanical thrombectomy (MT) in patients with acute ischemic stroke (AIS) and large ischemic core (LIC) at baseline is an unmet need.

We tested the hypothesis, that assessing the functional relevance of both the infarcted and hypo-perfused brain tissue, would improve the selection framework of patients with LIC for MT.

Methods

Multicenter, retrospective, study of adult with LIC (ischemic core volume > 70ml on MR-DWI), with MRI perfusion, treated with MT or best medical management (BMM).

Primary outcome was 3-month modified-Rankin-Scale (mRS), favourable if 0-3. Global and regional-eloquence-based core-perfusion mismatch ratios were derived. The predictive accuracy for clinical outcome of eloquent regions involvement was compared in multivariable and bootstrap-random-forest models.

Results

A total of 138 patients with baseline LIC were included (MT n=96 or BMM n=42; mean age±SD, 72.4±14.4years; 34.1% females; mRS=0-3: 45.1%). Mean core and critically-hypo-perfused volume were 100.4ml±36.3ml and 157.6±56.2ml respectively and did not differ between groups. Models considering the functional relevance of the infarct location showed a better accuracy for the prediction of mRS=0-3 with a c-Statistic of 0.76 and 0.83 for logistic regression model and bootstrap-random-forest testing sets respectively. In these models, the interaction between treatment effect of MT and the mismatch was significant (p=0.04). In comparison in the logistic regression model disregarding functional eloquence the c-Statistic was 0.67 and the interaction between MT and the mismatch was insignificant.

Conclusion

Considering functional eloquence of hypo-perfused tissue in patients with a large infarct core at baseline allows for a more precise estimation of treatment expected benefit.

GLOSSARY

AIC = acute ischemic stroke; **LVO** = large vessel occlusion; **ASPECTS** = Alberta-Stroke-Program-Early-CT-score; **MT** = Mechanical Thrombectomy; **BMM =** best medical management; **mRS =** modified Rankin Scale; **i.v.tPA** = intraveinous tissue plasminogen activator; **VLSM =** voxel-based lesion symptom mapping; **HE =** brain regions with high eloquence; **HE-I =** high-eloquence infarct; **HE-P =** high-eloquence critically hypo-perfused tissue; **E-MR =** eloquent mismatch ratios; **HE-MR =** high eloquence mismatch radio; **G-I =** global infarct volume; **G-P=** Global critically hypo-perfused tissue; **G-MR** = global mismatch ratio; **NNT =** number needed to treat; **SIT-uv =** severely ischemic tissue of uncertain viability**;**

INTRODUCTION

Patients with acute ischemic stroke (AIS) due to anterior large vessel occlusion (LVO) and an unfavourable imaging profile at baseline were excluded in 4 of the 7 randomized clinical trials that validated mechanical thrombectomy (MT),[1] precluding to draw strong conclusions regarding the benefits of MT in this subgroup.[2,3]

A unfavourable imaging profile, is commonly defined as a large ischemic core (LIC), assessed using MRI diffusion weighted imaging (by a volume of tissue with an Apparent Diffusion Coefficient (ADC) of 0.6×10^{-3} mm²/s or less volume > 70ml), or the CT-based-Alberta-Stroke-Program-Early-CT-score (ASPECTS < 6), and is amongst the most common reasons to decline MT in clinical practice due to potential futility.

Yet, evidence is growing that a subsample of patients with a LIC at baseline may benefit from revascularization, even if outside currently validated eligibility criteria for MT[4], leading AHA and European recommendations to reconsider this subgroup as potentially eligible on a case by case evaluation of anticipated benefit.[2,3]

Perfusion imaging can be used in the diagnostic work-up of AIS to identify hypo-perfused yet not infarcted (i.e. ‘at-risk’ or ‘salvageable’) brain tissue,[5] and recent data have demonstrated its added value[6] for the selection of patients with a deemed unfavourable imaging profile before MT, contributing to the accumulating evidence on the key role of tissue-based evaluation in patients with AIS-LVO.[7,8]

The involvement of specific “eloquent” brain regions within the infarcted core has been shown to be of high relevance for determining functional outcome,[9–12] suggesting a greater benefit of revascularization for patients with salvageable eloquent regions. Identifying persistent salvageable eloquent brain areas is especially relevant in patients with large baseline infarct volumes to reduce over-selection (that is, to decline MT to a patient that may have benefited from revascularization). In that sense, considering the functional relevance of both infarcted and hypo-perfused brain tissue in the framework of patients' selection may help improve individualized decision making.

In a large multicentric retrospective cohort of patients with an AIS due to large vessel occlusion and a large ischemic core at presentation, we tested the hypothesis that the integration of the regional functional relevance of both infarcted and salvageable tissue would enhance the accurate detection of patients likeliest to benefit from endovascular revascularization.

METHODS

Study design, inclusion and exclusion criteria

Analyses used data from a multicenter, retrospective, core lab adjudicated, cohort study of patients with proximal vessel occlusion, a large ischemic core (initially set as a DWI-ASPECTS of 0-6 in order to simplify recruitment, but finally redefined after quantitative core measures as DWI ischemic core volume ≥70cc), with pre-treatment MRI perfusion, treated with MT (2015-2018) or best medical management alone (BMM; before 2015). This cohort results from the collaborative work of a trainee-led research network (Jeunes en Neuroradiologie Interventionnelle, JENI).[13] We included consecutive adult patients with AIS, an occlusion of the intracranial internal carotid artery or of the M1 segment of the middle cerebral artery, a large pretreatment ischemic core volume defined as 70ml or more on MR-DWI as assessed centrally, no preexisting handicap (modified Ranking scale, mRs >1), and if pre-treatment DSC (dynamic susceptibility contrast) perfusion sequence had been performed. Patients were collected by retrospectively querying the prospective MT stroke data bases at eight university hospitals (MT group) and the prospective i.v. tPA stroke data base at a single university hospital (BMM group, not treated with MT). The control group included patients treated before MT-related guidelines in 2015 and was obtained from a single center at which perfusion imaging was routinely performed at the acute phase of stroke, and at which a prospective registry was maintained. Data from other centers were more scarce, oftentimes nonconsecutive, explaining our pragmatic decision so as to limit biases linked to patients in which perfusion was performed.

The primary endpoint was a favourable functional outcome, defined as a modified Rankin scale (mRS) of 0-3, taking into account the inherent severity of AIS with baseline LIC, and in line with recent literature in this subgroup.[14] Sensitivity analyses analyzed the functional independence defined as mRS of 0-2.[15]

All the patients included in the current analysis have been previously reported in a distinct manuscript with a larger study sample.[6] The prior report was focused on the overall core/perfusion mismatch influence on MT for AIS-LIC patients independent of brain eloquence, whereas in this manuscript, the analyses are aimed to determine the relevance of eloquent core/perfusion mismatch in determining anticipated treatment benefit. Hence, due to the motion-sensitive nature of the post-processing method used in this work, slight to moderate diffusion/perfusion artifacts led to exclusion for the current work whereas only patients with marked artefact were excluded in the previous reported manuscript. In turn, 34 additional patients were deemed ineligible for the current analysis because of insufficient imaging quality compared to the previously reported analyses (See Flowchart in eFigure 1, http://links.lww.com/WNL/B570).

This report was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[16]

Imaging analysis

Acute ischemic stroke protocol was standardized in all centers by the Consensus Guidelines of the French Society of Neuroradiology (SFNR).[17] The vast majority of MRIs were acquired on a 1.5-Tesla unit. Echo-planar DWI sequences were generally acquired with 128x128 matrix, 24 cm field-of-view, 6-mm thick slices, with b0 s/mm2 and b1000 s/mm2 with gradients applied in 3 orthogonal directions. ADC maps were computed based on DWI acquisition. DSC (dynamic susceptibility contrast) perfusion sequence was acquired after injection of a contrast bolus of gadolinium-based contrast agent using an echo-planar T2* sequence with a 96x64 matrix, 24 cm field-of-view, 6-mm thick slices, 25 temporal phases. However, because of the retrospective design of the study, we acknowledge possibility of minor technical variations between centers.

Post-processing and images' interpretation were performed centrally after complete de-identification, by an internal core-lab (B.K., J.B. and G.B.) blinded to clinical data. See Figure 1 for a detailed visual representation of imaging post-processing.

Ischemic lesion segmentation

Perfusion maps were generated using the Olea-Sphere® 3.0 software (olea-medical.com). Having verified all automated outputs and manually corrected artifacts, we performed the segmentation of both ischemic core lesions (Apparent Diffusion Coefficient (ADC) of 0.6×10^{-3} mm²/s or less) and critically hypo-perfused lesions

(Tmax > 6 seconds)[18] using a semi-automatic method with the Mango® software (MANGO, v3.1.1, Research imaging Institute, UTHSCSA), as described before.[6]

Atlas registration and labelling of the main brain regions

Diffusion-weighted and perfusion lesion masks were co-registered to the standard MNI-152 template using the FSL Software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki).[19] We mapped the "JHU DTI based white-matter atlases" and "the Automated Anatomical Labelling (AAL)" atlases of brain white and grey matter regions respectively in the MNI-152 space referential, and computed the overlap of the segmented ischemic core and critically hypo-perfused lesions with each individual brain region, allowing to derive within each region the volume of infarcted and critically hypo-perfused brain tissue.

Definition of eloquent regions

Based on previous knowledge of brain regional relevance with regards to 3-month mRs derived from Voxel-based Lesion Symptom Mapping (VLSM) studies [10–12,20,21], we highlighted in the anatomic atlases, the brain regions with High Eloquence (HE). See Figure 2.

Definition of imaging variables

Ischemic core and critically hypo-perfused volumes were labelled according to their overlap with HE brain regions. Ischemic core volume of HE regions was defined as "high-eloquence infarct" (HE-I), and the critically hypo-perfused volume of HE regions was defined as "high-eloquence critically hypo-perfused tissue (i.e.penumbra)" (HE-P). Using these intermediate variables, we explored eloquent mismatch ratios (E-MR) at two different levels:

- First, at the regional level, where the mismatch ratio (Region-E-MR) was defined as the ratio of critically hypo-perfused volume to the ischemic core volume within each individual region.

- Second, at the “eloquent group level” where regions in the same eloquence group were considered a whole. In this second analysis, we defined the High Eloquence Mismatch Ratio (HE-MR) as the sum of the Region-E-MR in the HE group divided by the number of regions in this group.

Global Mismatch Ratio (G-MR) was defined according to previous large studies, and as previously described,[6] as the total critically hypo-perfused volume divided by the ischemic core volume.

Substantial reperfusion after MT was defined as a modified TICI score of 2b, 2b or 3.[22]

Standard Protocol Approvals, Registrations, and Patient Consents

As for all non-interventional retrospective studies of de-identified data, written informed consent was waived and a commitment to compliance (Reference Methodology CPMR-4) was filed to the French data protection authority (CNIL) prior to data centralization, in respect to the General Data Protection Regulation. Patients and proxies were informed they could oppose the use of their data for research purposes.

Statistical Analysis

Statistical analysis was performed using JMP Pro 14 (SAS Institute Inc. 2015. JMP® Pro 14. Cary, NC: SAS Institute Inc) software. Continuous variables were summarized using means (± standard deviation, SD) or median [interquartile ranges, IQR] where appropriate, and discrete variables were summarized using counts (percentages).

We compared baseline characteristics of patients in the MT and control groups. Chi-square test, Fisher's exact test, t test, Mann-Whitney U test were used as appropriate for the univariable analysis, with a p-value < 0.05 (two-tailed) as the threshold for statistical significance. Multivariable analyses were adjusted for five prespecified baseline prognostic variables (age, diabetes mellitus, internal carotid artery (ICA) occlusion, intravenous fibrinolysis (i.v.tPA), delay between symptom-onset (or symptoms discovery if unwitnessed stroke) to imaging) as per previous knowledge on clinical imaging predictors of outcome after AIS-LVO.[23]

We tested two distinct approaches to study the effect of incorporating the functional relevance of both infarcted and hypo-perfused brain tissue in determining functional outcome:

- First we compared the predictive accuracy for favourable functional outcome (mRS 0-3) of the "standard model" (that included only the global infarct volume [G-I] and the global mismatch ratio [G-MR] as imaging variables) with two other statistical models where only the involvement of the brain tissue with High Eloquence were considered. In the standard model (model 1), the G-I and the G-MR were entered into a binary logistic regression model amongst the other clinical outcome predictors. Model 2 was built similarly with HE-I and HE-MR instead of G-I and G-MR, hence exploring the functional relevance at the "eloquent group level". Model 3 relied on a bootstrap random forest approach, where the mismatch within each HE region was seen as an independent variable, alongside the HE-I and the clinical outcome predictors. In the two binary logistic regression models (model 1 and model 2), the interaction between mismatch ratio (G-MR in model 1 and HE-MR in model 2, respectively) and MT was tested by including the multiplicative mismatch-ratio-by-treatment term in regression models. This approach was repeated with analogous models (models 1bis, 2bis and 3bis) using functional independence (mRS 0-2) as the dependent variable. Additional sensitivity analyses were performed for logistic regression models 1 and 2 on two subgroups of patients: 1) only on the MT group; 2) On a sub-population resulting from propensity scores (Nearest neighbor matching 1:1; Caliber 0,1; pairing on variables that differed significantly between the two groups.

To compare the predictive accuracy of the different models, we built contingency matrix and ROC curves (c-Statistic) and computed Precision, Accuracy and Balance Accuracy for randomly selected training sets (75% of the data) and testing sets (25% of the data).

- The second approach aimed to test whether a patients' selection based on the HE-MR could increase the treatment effect of MT as well as the subset of patients which might be identified as benefiting from this treatment, in comparison to a selection based on the G-MR. Hence, the number needed to treat (NNT, i.e. 1/absolute risk reduction) to achieve mRS 0-3 with MT versus BMM was calculated for a range of G-MR and HE-MR thresholds.

Data Availability:

Data will be made available upon reasonable request to the corresponding author.

RESULTS

Baseline characteristics of MT group versus BMM group

Between January 2015 and July 2018, 96 patients were included and analyzed in the MT group. Before 2015, a total of 154 patients with DWI-ASPECTs 0-6 were screened for inclusion in the BMM group, and 42 met study criteria. A total of 138 patients were hence analyzed (n=96 in the MT group and n=42 in the BMM group). A flowchart of patients' selection is presented in eFigure 1, http://links.lww.com/WNL/B570. Baseline characteristics are detailed in Table 1. Compared with the BMM group, patients in the MT group were younger (67.3±15y vs 77.6±13.5y; p<0.001), more frequently females (40.6% vs 19%; p<0.014), more frequently transferred patients (i.e. "drip&ship patients", 21.9% vs 0%; p<0.001) and received less frequently i.v.tPA (45.8% vs 100%; p<0.001). Demographics, past medical history, and baseline clinical assessment were similar between patients treated with MT or BMM.

Mean G-I and G-P volumes were 100.4ml±36.3ml and 157.6±56.2ml respectively and did not differ between groups. Mean HE-I and HE-P were 70.7±30.6 ml and 85.5±37.8 ml respectively and did not differ between groups. At three months, 60/133 (45.1%) patients had a favourable functional outcome (mRS 0-3), with no difference amongst groups (49.5% in the MT group vs 35.7%; p=0.14). Altogether, 34/133 (25.6%) were functionally independent, with no difference amongst groups (26.4% in the MT group vs 23.8%; p=0.138). Symptomatic intracranial hemorrhage occurred in 29/129 (22.5%) patients and 41/133 (30.8%) patients were deceased at 3 months with no difference between groups (both p>0,05).

Models' accuracy for 3 months functional outcome

Primary endpoint: Favourable functional outcome (mRS 0-3)

In Model 1, independent predictors of 3-month favourable functional outcome included lower age (adjusted odd ratio, aOR 0.96 [0.93-0.98]; p=0.01), lower G-MR (0.15 [0.04-0.52]; p<0.01), lower G-I (aOR 0.98 [0.96-0.99]; p<0.01), and medical history of diabetes mellitus. See eTable 1, http://links.lww.com/WNL/B575. There was no significant interaction between MT effect and G-MR (p=0.17).

In Model 2, independent predictors of 3-month favourable functional outcome included: receiving MT (aOR 7.74 [1.24-48.24]; p=0.016), lower age (aOR 0.94 [0.90-0.97]; p<0.01), lower HE-MR (aOR 0.02 [0.01-0.26]; p<0,01), lower HE-I (aOR 0.96 [0.94-0.97]; p<0.01) and medical history of diabetes mellitus. See eTable 2, http://links.lww.com/WNL/B576. There was a significant interaction between MT effect and HE-MR p=0.045.

In the bootstrap random forest model 3, the first ten variables identified as the strongest 3-month favourable functional outcome predictors were: receiving MT (adjusted effect, aEF = 1), the absence of ICA occlusion (aEF = 1), lower HE-I (aEF = 0.401), decreasing age (aEF = 0.381) and the presence of eloquent mismatch within the following regions: the right thalamus (aEF = 0.243), the left thalamus (aEF = 0.188), the left superior longitudinal fasciculus (aEF = 0.179), the left post central gyrus (aEF = 0.145), the left retrolenticular part of internal capsule (aEF = 0.140) and the left supra marginal gyrus (aEF = 0.137). See eTable 3,, http://links.lww.com/WNL/B577 and eFigure 2, http://links.lww.com/WNL/B571. Predictive performance of the three models are summarized in Table 2 and eFigure 3, http://links.lww.com/WNL/B572. Models 2 and 3 considering the functional relevance of the infarct location showed a better predictive accuracy for favourable functional outcome with a c-Statistic of testing sets of 0.76 and 0.83 respectively compared to 0.67 for the logistic regression model 1 (p<0,001). Nonetheless, model

3 showed a slight weakest consistency between training set and testing set with a decreasing c-Statistic from 1 to 0.83 (versus 0.82 to 0.67 and 0.88 to 0.76 for model 1 and 2, respectively) likely indicating overfitting of the training set.

Sensitivity analyses

Using mRs 0-2 as the outcome measure, similarly to the primary outcome, bootstrap random forest (Model 3bis) was the most accurate to predict 3-month functional independence outcome compared to the two logistic regression models (model 1bis and model 2bis, please see the eTables 4 to 7, http://links.lww.com/WNL/B578, http://links.lww.com/WNL/B579, http://links.lww.com/WNL/B580, http://links.lww.com/WNL/B581, eAppendix,, http://links.lww.com/WNL/B587 and eFigure 4, http://links.lww.com/WNL/B573.

Finally, to validate the stability of our models we applied the logistic regression models 1 and 2 to two subgroups of patients: 1) Only on the MT group; 2) On a sub-population (27 MT and 27 BMM patients) resulting from propensity scores with paring on variables that differed significantly between the two groups (i.e., Age, Sex and Iv. tPA, see eFigure 5, http://links.lww.com/WNL/B574).

Model 2 appeared highly consistent across subsets. We note the fact that both imaging variables (i.e., Eloquent Ischemic Core Volume and Eloquent Mismatch Ratio) remained strong predictors across subsets further demonstrating the relevance of imaging parameters encompassing the functional eloquence. See eTables 8 to 11, http://links.lww.com/WNL/B582, http://links.lww.com/WNL/B583, http://links.lww.com/WNL/B584, http://links.lww.com/WNL/B585.

Global mismatch ratio and Eloquent mismatch ratio and the number needed to treat (NNT)

To explore the effect of incorporating functional relevance of penumbral and infarcted regions in the selection process for MT of patients with AIS-LVO and a LIC, we explored the variation of the NNT, based on G-MR (that is, not considering the eloquence) or HE-MR (that is, by factoring the extent of persistent mismatch in high eloquence regions).

Decreasing G-MR threshold was associated with a rapidly increasing NNT and the treatment effect of MT was no longer significant above a G-MR threshold of 1.6. In turn the largest subset of patient identified as benefitting from MT when patients' selection relied on G-MR was 68/138 (48.57% of the cohort). Conversely, using decreasing HE-MR threshold, the NNT increased more gradually and the treatment effect of MT remained significant above a HE-MR threshold of 0.2 (see figure 3 and eTable 12, http://links.lww.com/WNL/B586 for aOR and NNT associated with thresholds). In turn if patients' selection relied on HE-MR, the largest subset of patient identified as benefitting from MT was 107/138 (76.43% of the cohort).

DISCUSSION

In this multicenter cohort of patient with AIS-LVO and LIC at baseline, we demonstrated that: 1) In models considering the functional relevance of the ischemic tissue location, the predictive accuracy of both favourable functional outcome and functional independence models at 3-months was strengthened; 2) In such models, the interaction between treatment effect of MT and mismatch was reinforced; 3) Using a functional relevance based mismatch, we reduced the risk of over selection by showing a better outcome in a larger subset of patients after MT and by demonstrating a compelling reduction of the NNT for comparable subgroup size.

These results derive from rather complex analyses but might be summarized in a very clinically pertinent and routinely applicable way: in patients with large infarct core at baseline, those with persisting salvageable tissue in high eloquent regions have higher odds of favourable functional recovery if treated with MT, and the treatment effect of MT in determining favourable functional outcome is much more important in this subgroup than in that with no eloquent area in salvageable regions. In turn, when considering a patient with a large infarct for MT, the analysis of the involvement of eloquent brain regions in the infarct core may help for decision making.

The influence of ischemic lesion location on stroke recovery is long known, and has been already reported in several studies[11,24,25] However, in most studies such topographic parameters were usually considered only by assessing the infarct core (using MRI diffusion, CT-Perfusion or Noncontrast-CT), oftentimes after the hyperacute phase. Our results provide valuable additional arguments on the role of functional eloquence of lesion location, by allowing their analysis as a core/perfusion mismatch in the initial assessment of AIS patients. This approach was driven by the underlying hypothesis that the benefit of ischemic stroke treatment, aiming to reestablish flow to hypo perfused but still viable (i.e. ‘at-risk’ or ‘salvageable’) brain tissue would be maximum in patients with salvageable tissue located in high eloquent brain regions, and paltry in contrast for patients with salvageable tissue located in poor eloquent regions.

The eloquent region map was defined a priori according to dedicated VLSM studies, which is amongst the most informative imaging-based statistical method to determine lesion location significance for stroke outcomes,[10,11,24] and strongly correlates with anatomical-functional correlations. In our sample, the bootstrap random forest models highlighted several regions as having the most direct impact on stroke recovery. Both models, found a strong lateralization with more regions associated with poor outcome on the left hemisphere, in accordance with previous studies.[11,24] Both thalamus and two left white matter fiber tracts (the superior longitudinal fasciculus and the cortico-spinal tract) were identified as strongly reducing the probability of favourable functional outcome, when involved (model 3). The strong impact of the thalamic injuries was unexpected since being rare in anterior circulation ischemic stroke. By contrast, posterior limbs of the internal capsules have not been identified as key structures in the bootstrap model, despite the fact that they convey the cortico-spinal tracts, which are long known to be amongst key functional regions, due to the dramatic motor impairment associated with its injury. [26,27] Both results are very likely the consequences of a multifactorial lack of spatial resolution making difficult the distinction between small contiguous areas after co-registration. In turn considering the capsulo-thalamic region, rather than distinguishing thalamus and internal capsule, should be preferable in similarly built models. The superior longitudinal fasciculus is a thick white matter fiber tract linking the four lobes in each hemisphere. It plays a pivotal role in key processes such as attention, memory, emotions and language and his implication in poor mRS when injured is in line with both VLSM[10,24] and diffusion tensor imaging (DTI)[28,29] studies.

Through the different models compared in this study, two different ways of considering the eloquent mismatch parameter have been explored. In logical regression models 2 and 2bis, the eloquent mismatch was seen as a whole. By contrast, in the bootstrap random forest models 3 and 3bis, the mismatch within each eloquent region was an independent variable. The later supervised learning approach yielded more accurate results in our sample to predict both favourable functional outcome and functional independence at 3-month, despite being slightly more sensitive to overfitting. However, we do acknowledge that such complex imaging-based patient's selection, especially when relying on machine learning algorithm with multiple variables, would not be realistic in current practice unless integrated in a dedicated software. Nonetheless, our analysis strengthens the argument that analyzing the infarct core independently of eloquent regions involvement likely results in over selection, that is to deny MT to patients that may have strongly benefitted by limiting infarct progression in hypo-perfused, yet not infarcted eloquent regions. After further validation, the process of region identification, herein done with elaborated statistical tools, might be done visually at the time of patients' evaluation (i.e. "there's a large infarct in the anterior frontal area, but the central and capsulo-thalamic regions are not infarcted yes, despite being at-risk). In that sense, the individual region approach appears closer to bedside evaluation of per-region salvageability, than a global approach which doesn't seem reasonably doable in the clinical setting due to the multiple regions potentially involved or spared.

As previously discussed extensively in the literature,[6,30] the matter of the precise selection of AIS-LVO patients likeliest to benefit from revascularization is subjected to important limits. Indeed, as the complexity of clinical imaging selection increases, the number of patients being denied treatment is likely to decrease. It is unlikely that abrupt thresholds (ASPECTs < 6, ischemic core volume > 70 or 100ml) have any pathophysiological rationale, and are in turn responsible for an important over-selection (e.g. a patient with a 71ml right anterior frontal ischemic core, but a 150ml critically hypo-perfused lesion involving the central region is very likely to benefit from revascularization). The underlying question is whether MT is harmful for some patients (large infarct cores, older individuals, …), or if such an invasive and expensive treatment is appropriate when the odds of favourable functional outcome are very low. Altogether, our results only emphasize that LIC is not per se a good argument to deny MT, and that the consideration of eloquent regions may provide additional arguments in the face of genuine uncertainty.

Of note, there is ongoing debate on the concept of "ischemic core",[31] for which the term severely ischemic tissue of uncertain viability (SIT-uv) may more accurately define the uncertainty of the tissue viability. The notion of "core" is indeed challenged, amongst other, by the fact that it cannot individually account for functional outcome, as is demonstrated in this work. For clarity we preferred the term "core" in this work so as not to overburden the manuscript with an additional acronym. Nonetheless, our results come as a confirmation that "core" volume alone cannot be used to anticipate functional outcome, and also emphasizes that simple (and thresholded) imaging variables should not be used to deny MT based on anticipated futility.

This study has limitations inherent to its retrospective design, including non-exhaustively risks of selection, memorization and attrition biases yielding a decrease in external applicability. We acknowledge that the BMM group was biased by the fact that it included only patients who received i.v.tPA. This subselection may have yielded underestimated estimates of the benefit of MT over best medical management, in patients with persistent eloquent mismatch. Moreover, it is a selection bias that the MT data comes from eight different hospitals whereas the BMM group is from one center only. The use of MRI, first line imaging in almost all French Centers[32] make our results less generalizable to geographic regions using CT

The strengths include a large sample size for this subgroup of patients, the use of advanced robust imaging post-processing methods, and the multicentric nature of data acquisition.

CONCLUSION

Integrating functional eloquence assessment of infarcted and critically hypoperfused brain regions on the baseline MRI of patients with AIS-LVO and LIC might improve the global framework of patients' selection for MT and can be easily transposed to clinical practice, by evaluating the involvement of high eloquence regions in the infarct core to evaluate the likelihood of MT benefit.

TABLES AND FIGURES

Table 1: Baseline Characteristics of included patients

	MT (n=96)	BMM (=42)	Total (n=138)	p
Patients characteristics				
Age	67.3±15.3 N=96	77.6±13.5 N=42	72.4±14.4 N=138	<0.001
Female sex	40.6% (39/96)	19% (8/42)	34.1% (47/138)	0.014
Hypertension	52.1% (50/96)	57.1% (24/42)	53.6% (74/138)	0.583
Diabetes Mellitus	15.6% (15/96)	14.3% (6/42)	15.2% (21/138)	0.841
Dyslipidemia	33.3% (32/96)	47.6% (20/42)	37.7% (52/138)	0.111
Tobacco use (current or past)	29.2% (28/96)	38.1% (16/42)	31.9% (44/138)	0.301
Stroke Management				
Baseline NIHSS score	18.9±4.3 N=95	18.2±4.8 N=39	18.6±4.5 N=134	0.398
Unwitnessed onset	16.7% (16/96)	16.7% (7/42)	16.7% (23/138)	1
Drip & Ship	21.9% (21/96)	0% (0/42)	15.2% (21/138)	<0.001
Left-sided stroke	55.2% (53/96)	38.1% (16/42)	50% (69/138)	0.064
Iv. tPA	45.8% (44/96)	100% (42/42)	62.3% (86/138)	<0.001
ICA occlusion	18.8% (16/85)	23.8% (10/42)	20.5% (26/127)	0.613
M1 occlusion	70.6% (60/85)	61.9% (26/42)	67.7% (86/127)	
Symptom-onset* to imaging	152.3±103.5 N=86	157.7±107.6 N=42	155±105.5 N=128	0.788
Symptom-onset* to needle	159.5±44.4 N=38	189.5±90.3 N=38	174.5±67.4 N=76	0.071
Symptom-onset* to groin	303.9±104.4 N=71	/	/	/
Imaging parameters				
DWI ASPECTS	4 [2-5] N=85	4 [3-5] N=40	4 [2-5] N=125	0.199
Overall Core volume (in ml)	101.6±39.2 N=96	99.1±33.3 N=42	100.4±36.3 N=138	0.709
Overall Tmax<6s volume (in ml)	165.8±60.5 N=96	149.4±52 N=42	157.6±56.2 N=138	0.129
High Eloquence Core volume (in ml)	67.8±31.9 N=96	77.6±26.3 N=42	70.7±30.6 N=138	0.062
High Eloquence Tmax<6s (in ml)	87.8±40.4 N=96	80.1±30.6 N=42	85.5±37.8 N=138	0.216
Outcome measures				
Successful reperfusion (mTICI 2b-3)	83.7% (82/96)	/	/	/
90 day mRS 0-2	26.4% (24/91)	23.8% (10/42)	25.6% (34/133)	0.753
90 day mRS 0-3	49.5% (45/91)	35.7% (15/42)	45.1% (60/133)	0.138
90 day Mortality	29.7% (27/91)	33.3% (14/42)	30.8% (41/133)	0.671
sICH	25.8% (24/93)	13.9% (5/36)	22.5% (29/129)	0.146

Values are expressed as mean ± standard deviation (SD), or absolute value (percentage). Abbreviations: MT=Mechanical Thrombectomy; BMM= Best Medical Management; NIHSS=National Institutes of Health Stroke Scale; ASPECTs= Alberta Stroke Program Early CT Score; Iv. tPA= intraveinous tissue plasminogen activator; ICA=Internal Carotid Artery; M1 and M2: first and second segment of the middle cerebral artery; mTICI= Modified Treatment in Cerebral Infarction Scale; sICH= Symptomatic Intracranial Haemorrhage; *Or symptoms discovery if unwitnessed stroke

Table 2: Predictive performance of the tree models for favourable functional outcome

	Model 1 - Training	Model 1 - Testing	Model 2 - Training	Model 2 - Testing	Model 3 - Training	Model 3 - Testing
Sensitivity	75.00%	73.33%	75.61%	71.43%	100.00%	68.75%
Specificity	78.43%	80.00%	81.13%	76.47%	100.00%	76.47%
Precision	73.17%	78.57%	75.61%	71.43%	100.00%	73.33%
Negative predictive value	80.00%	75.00%	81.13%	76.47%	100.00%	72.22%
Accuracy	76.92%	76.67%	78.72%	74.19%	100.00%	72.73%
Balance Accuracy	76.72%	76.67%	78.37%	73.95%	100.00%	72.61%
AUC-ROC	0.82 [0.75-0.87]	0.67 [0.56-0.86]	0.88 [0.83-0.93]	0.76 [0.69-0.94]	1	0.83
RMSE	0.4157		0.3923		0.2393	
AISc	110.6		101.88		/	
BIC	133.02		124.66		/	

RMSE=Root Mean Squared Error; AISc=Corrected Akaike Information Criterion; BIC=Bayesian Information Criterion

FIGURE LEGENDS

Figure 1: Algorithm Development Outline

G-I=Global diffusion volume; G-P= Global critically hypo-perfused tissue; HE-I=Diffusion volume in High eloquent regions; HE-P= High eloquent critically hypo-perfused tissue

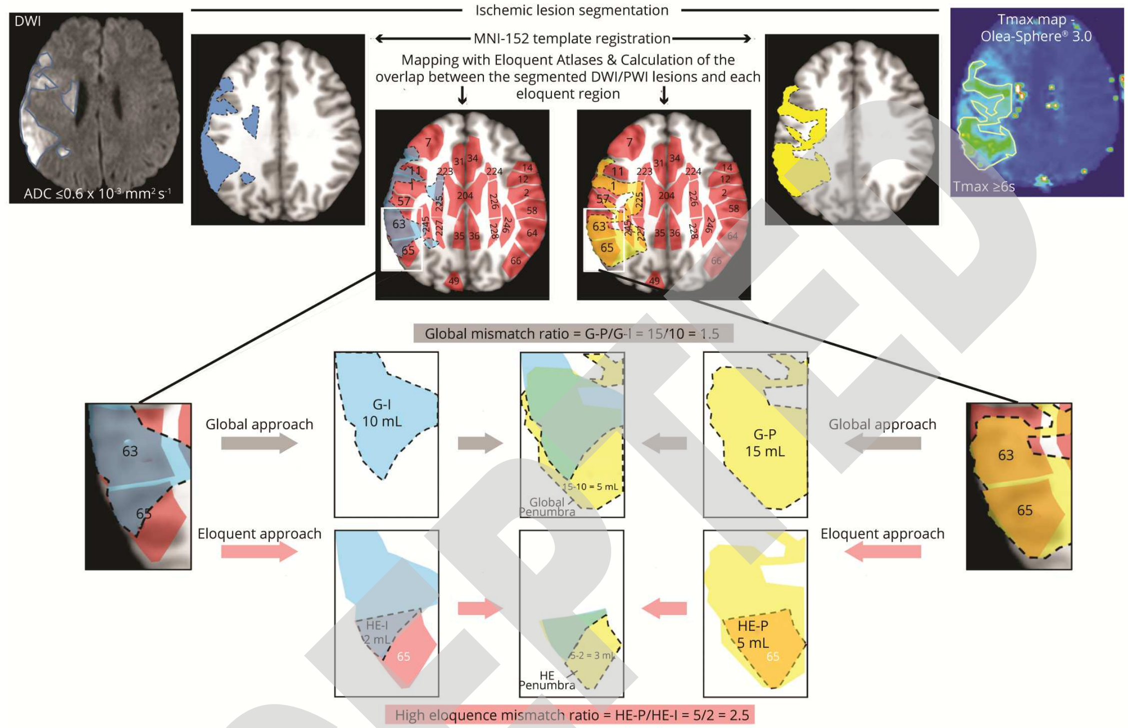


Figure 2: Brain regions with high functional eloquence

Axial T1 weighted MRI template sections showing the 61 high functional eloquent brain regions.

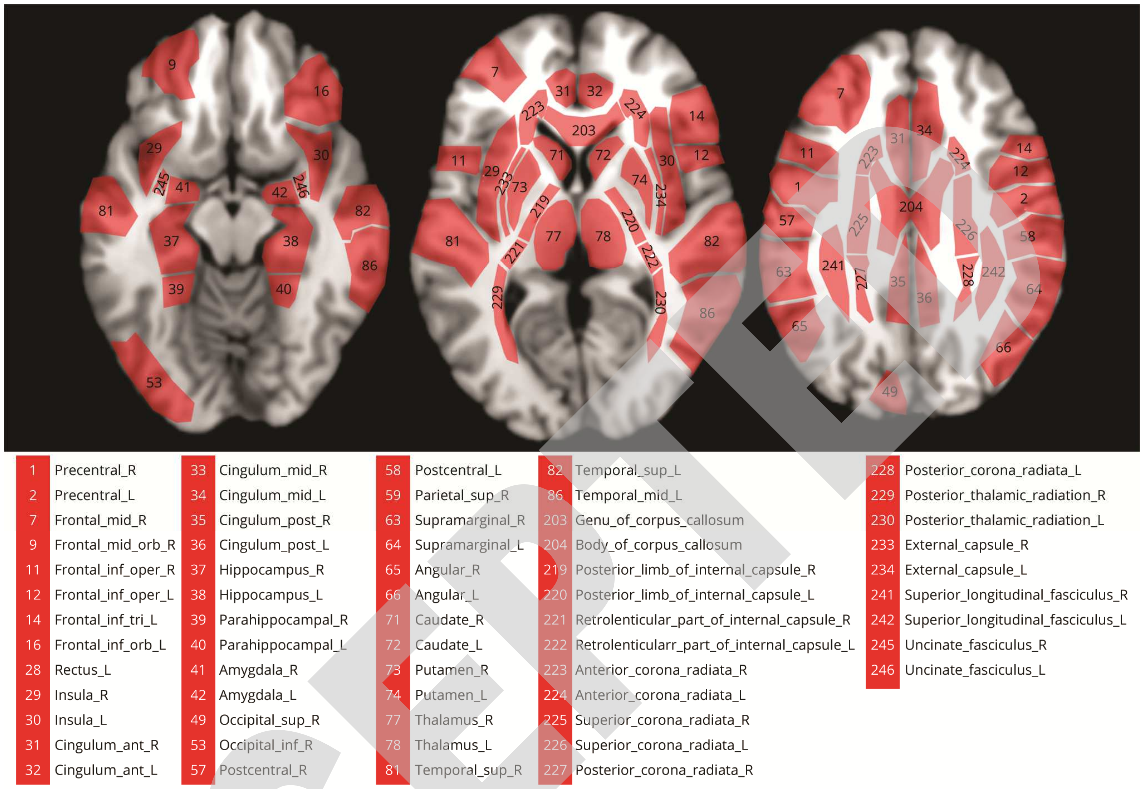
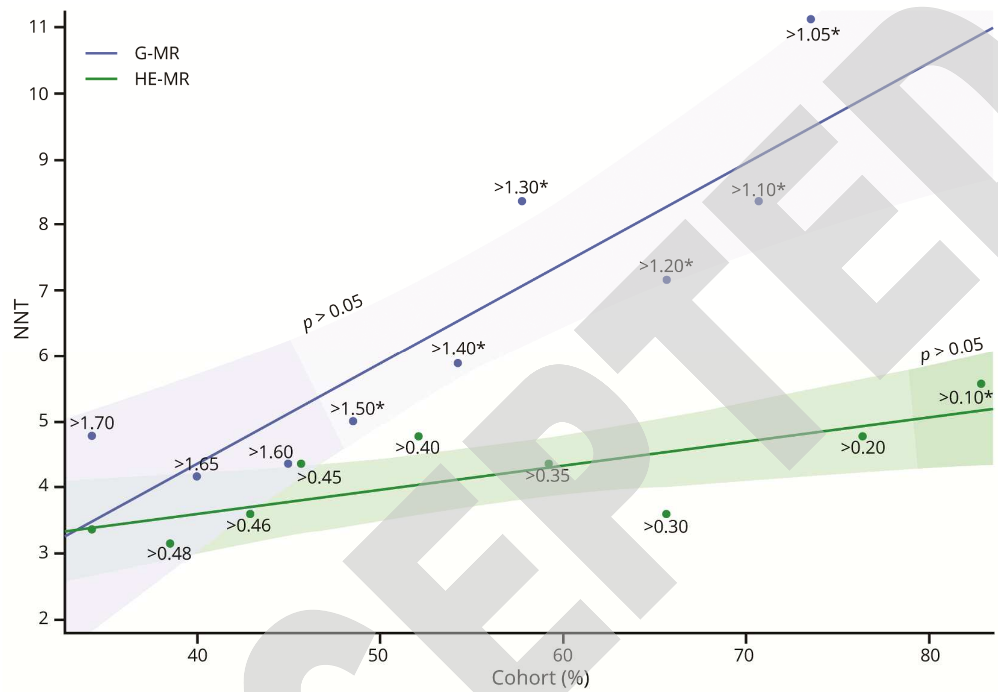


Figure 3: NNT associated with Global mismatch ratio and Eloquent mismatch ratio thresholds

NNT=Number Needed to Treat; G-MR=Global Mismatch Ratio; HE-MR= Mismatch Ratio in High Eloquent Regions



eFigure 1-http://links.lww.com/WNL/B570

eFigure 2-http://links.lww.com/WNL/B571

eFigure 3-http://links.lww.com/WNL/B572

eFigure 4-http://links.lww.com/WNL/B573

eFigure 5-http://links.lww.com/WNL/B574

eTable 1-http://links.lww.com/WNL/B575

eTable 2-http://links.lww.com/WNL/B576

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eTable 6-http://links.lww.com/WNL/B580

eTable 7-http://links.lww.com/WNL/B581

eTable 8-http://links.lww.com/WNL/B582

eTable 9-http://links.lww.com/WNL/B583

eTable 10-http://links.lww.com/WNL/B584

eTable 11-http://links.lww.com/WNL/B585

eTable 12-http://links.lww.com/WNL/B586

eAppendix-http://links.lww.com/WNL/B587

Appendix 2-http://links.lww.com/WNL/B588

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APPENDIX 1: AUTHORS

Name	Location	Contribution
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Kevin JANOT, MD	CHRU Tours, France	Major role in the acquisition of data; Revisions for critical intellectual content
Cyril DARGAZANLI, MD	Montpellier Hospital, France	Major role in the acquisition of data; revised the manuscript for intellectual content
Dimitri DALY ERAYA, MD	Montpellier Hospital, France	Major role in the acquisition of data
Wagih BEN HASSEN, MD	Sainte-Anne Hospital, Paris, France	Major role in the acquisition of data; revised the manuscript for intellectual content; Major Role in Propensity matched analysis
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