

Aus dem Centrum für Schlaganfallforschung  
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

**Evaluation of automated and manual perfusion MRI post-processing:  
the search for accurate tissue fate prediction in acute ischemic stroke**

zur Erlangung des akademischen Grades  
Medical Doctor – Doctor of Philosophy in Medical Neurosciences  
(MD/PhD in Medical Neurosciences)

vorgelegt der Medizinischen Fakultät  
Charité – Universitätsmedizin Berlin

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Datum der Promotion: 1. Februar 2013

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## **SUMMARY**

*Evaluation of automated and manual perfusion MRI post-processing:  
the search for accurate tissue fate prediction in acute ischemic stroke*

### **Abstract**

#### **Background**

In perfusion magnetic resonance imaging a manual approach to delineation of regions of interest is, due to rater bias and time intensive operator input, clinically less favorable than an automated approach would be. We have compared the performances of these approaches, testing the hypothesis that automated protocols suffer from numerous artifacts which result in a false estimation of hypoperfused tissue. An additional goal of our study was to find a minimally biased yet maximally useful perfusion post-processing protocol which could offer the treating physician an estimate of tissue fate.

#### **Methods**

One hundred and eighty-four patients were included in this study, of which 39 control patients with neither a fresh infarction visible nor a final diagnosis of stroke and 145 patients with a confirmed diagnosis of acute ischemic stroke. Using three different software packages (Perfscape/Neuroscape, PMA and Stroketool) maps of mean transit time (MTT), cerebral blood flow (CBF) and Tmax were created. Three different thresholds were applied on each parameter map and subsequent volumes of hypoperfused tissue were calculated using both a manual and an automated protocol.

#### **Results**

The median difference between the automatically and manually derived volumes was up to 210 ml in Perfscape/Neuroscape, 123 ml in PMA and 135 ml in Stroketool. Correlation coefficients between perfusion volumes and radiological and clinical outcome were much lower for the automatic volumes than for the manually derived ones. Using the manual approach in patients with a persistent vessel occlusion a CBF map with a restrictive threshold had shown volumes of tissue at definite risk of infarction in up to a 100% of patients. The additional use of a CBF map with a high threshold had enabled identification of patients without penumbra.

#### **Conclusions**

The agreement of the automated and manual method was very poor, with the automated use producing falsely exaggerated volumes of hypoperfused tissue. No one combination of software, map and threshold was able to give a reliable estimate of tissue fate. However in patients with a vessel occlusion, a combination of a CBF map with a low threshold and a high threshold can provide a calculation of the minimum volume of brain tissue inevitably to be lost if the occlusion persists.

## **Introduction**

In magnetic resonance imaging (MRI) it is presently assumed that the technique of diffusion-weighted imaging (DWI) shows the area of irreversibly injured tissue, whereas perfusion imaging (PI) shows the area of reduced cerebral perfusion<sup>1</sup> with the mismatch between the two areas representing the ischemic penumbra<sup>2</sup>. This mismatch hypothesis is frequently being used in studies of acute ischemic stroke (AIS) and even clinical practice<sup>3</sup>. Two different approaches are available to assess areas of reduced cerebral perfusion: visual mismatch assessment and volumetric measurements. As visual assessments have been demonstrated as insufficiently reliable for use in clinical practice<sup>4</sup>, more weight is being placed on various commercial and academic software packages developed for volumetric calculations. Most of these programs offer the possibility to delineate regions of interest manually but also, to a lesser or greater extent, automatically. Manual approaches to delineation of hypoperfused volumes are biased and require time intensive operator input. Therefore a mostly automated procedure, if accurate, would be preferred in clinical practice. Despite many studies which have dealt with the issue of comparing different calculation methods and parameters for deriving perfusion maps<sup>5-9</sup>, there is still no scientific consensus on which parameter, method of delineation or software tool should ideally be used and there is a continuing need for systematical evaluation and validation of currently existing software packages for PI<sup>10</sup>.

## **Goals**

Our hypothesis was that existing software solutions, when automated, exaggerate volumes of hypoperfused tissue on account of numerous artifacts. We therefore calculated volumes using a fully automated procedure applied to a cohort of patients with no infarct as well as examined what the difference between an automated and manual approach would be in patients with acute ischemic stroke. An additional goal of our study was to find a PI protocol which could, for patients presenting with a pathophysiologically relevant vessel occlusion, offer the treating physician a useful estimate of tissue fate.

## Materials and Methods

One hundred and eighty-four patients, admitted to our university hospital with a suspected diagnosis of an ischemic event and imaged between September 2008 and November 2009 were included in this study, of which 39 patients with neither a fresh infarction visible nor a final diagnosis of stroke (control patients) and 145 patients with a confirmed diagnosis of acute ischemic stroke, a visible area of hypoperfusion detectable on the initial PI examination and availability of two follow-up MRI scans. All dynamic susceptibility contrast-enhanced T2\*-weighted images were collected using a single-shot gradient-echo EPI sequence (TE= 29 ms, TR= 1390 ms, pixel size= 1,796 x 1,796 mm<sup>2</sup>, slice thickness= 5mm, interslice gap= 0.5 mm) on a clinical 3-Tesla MR scanner (Tim Trio, Siemens AG, Erlangen, Germany).

All commercially available software packages for post-processing of raw perfusion data known to us were considered for inclusion in the study. Three software packages were selected: Stroketool (Digital Image Solutions, Germany), PMA (v3.2.0.4 ASIST, Japan) and Perfscope/Neuroscope (Olea Medical SAS, France) were used to calculate perfusion maps of mean transit time (MTT), cerebral blood flow (CBF) and Tmax for each patient. The deconvolution method used in both Perfscope and PMA was block-circulant singular value decomposition and in Stroketool singular value decomposition.

For each parameter map, three different thresholds were applied. For all patients and in all three programs, the Tmax thresholds were 4, 6 and 8 seconds of delay. The MTT thresholds were 5, 6 and 8 seconds with the exception of Perfscope/Neuroscope being used on control patients where the thresholds were 3%, 6% and 10% of the MTT scale for each patient. Additionally, CBF thresholds were (from lowest to highest) 0.02, 0.03 and 0.04 in arbitrary units in Perfscope/Neuroscope, 20, 30 and 40 ml/100g/min in PMA and 15%, 20% and 25% of the highest value on the CBF scale for each patient in Stroketool.

In the automated protocol, once the thresholds have been applied and the resulting regions of interest (ROIs) saved, no further post-processing was done by a human rater save for a secondary step (only for maps produced in PMA and Stroketool) to cut away scalp and spaces filled with cerebrospinal fluid (CSF) using further automated post-processing in SPM8 (Wellcome Trust Centre for Neuroimaging, UK). This step was not necessary for maps created with Perfscope/Neuroscope, as this program has successfully implemented filtering. In the manual protocol the already thresholded maps were additionally manually corrected to exclude areas which the human rater judged as highly unlikely to be part of a credible perfusion deficit.

Radiological outcome was defined as the final lesion size, manually delineated by an expert neuroradiologist (JBF) on follow-up FLAIR images. Clinical outcome was defined as the National Institute of Health Stroke Scale (NIHSS) score at the time of discharge from the hospital.

Additionally, for patients with a persistent vessel occlusion (n= 41) all maps and thresholds were investigated for presence of mismatch and its usefulness, thus dividing patients into two groups: mismatch patients (MP) and non-mismatch patients (NMP) and four subgroups: significant mismatch patients (SMP), overestimated mismatch patients (OMP), true non-mismatch patients (TNMP) and false non-mismatch patients (FNMP). MP were those in whom the perfusion deficit was larger than the initial lesion (as measured on DWI) and NMP those presenting with a perfusion volume smaller than the initial lesion size. SMP were those in whom the perfusion volume, being bigger than the initial DWI lesion, still underestimated the final lesion volume or overestimated it by less than 5 ml or 20%. An overestimate of the final infarct size larger than 20% caused the patient to be classified as an OMP. TNMP were considered as those NMP in whom lesion growth between 1<sup>st</sup> day and final follow up was less than 5 ml or 20% and FNMP were those NMP in whom lesion growth was substantial and exceeded 5 ml and 20%.

### **Results**

From the 145 acute stroke patients 58 were female (40%) and the median age was 72 (interquartile range [IQR] 65 to 79.5 years) while from the 39 patients without stroke, 16 were female (41%) and the median age was 67 years (IQR 44 to 74 years). All initial MRI scans were, for patients with stroke, performed prior to the administration of tPA. For acute stroke patients the median difference between the automatically and manually derived volumes was up to 210 ml in Perfscape/Neuroscape, 123 ml in PMA and 135 ml in Stroketool (Table 1). The additional removal of CSF and scalp filtered out on average between 6.11 ml and 52.53 ml of proposed non-cerebral tissue in PMA and between 26.05 ml and 75.59 ml in Stroketool, bringing the median difference between the manual and the automated perfusion volumes down to between 0.77 ml and 64.91 ml for PMA and 1.67 ml and 67.28 ml for Stroketool (Table 1).

*Table 1. Difference of ROI volumes between the automated and the manual protocol*

Program	Perfscape /Neuroscape	PMA	PMA with filtering *	Stroketool	Stroketool with filtering *
Parameter	Median IQR	Median IQR	Median IQR	Median IQR	Median IQR
Tmax 4s	25.80 12.8 - 66.1	123.68 75.2 - 206.8	64.91 27.3 - 138.1	122.89 75.6 - 176.5	37.50 14.9 - 75.3
Tmax 6s	12.74 4.1 - 34.4	29.48 16.4 - 67.8	4.83 1.0 - 22.4	53.18 34.0 - 82.6	7.75 1.8 - 18.3
Tmax 8s	8.05 2.6 - 28.1	23.16 13.5 - 55.4	2.68 0.4 - 15.8	31.78 16.1 - 50.1	1.67 0.2 - 6.5
MTT 5s	186.78 151.4 - 248.5	35.12 17.8 - 87.8	11.59 3.4 - 44.1	129.35 82.5 - 225.7	58.74 21.8 - 130.5
MTT 6s	154.40 114.8 - 207.0	16.76 8.4 - 49.0	4.34 0.9 - 18.4	80.18 49.1 - 143.6	26.51 8.0 - 63.7
MTT 8s	94.24 55.0 - 143.3	7.36 3.8 - 17.4	0.77 0.3 - 3.9	33.82 20.9 - 57.6	6.07 1.6 - 18.8
CBF highest threshold	209.92 160.0 - 262.8	54.35 27.5 - 107.9	23.05 7.6 - 64.4	134.50 89.9 - 193.0	67.28 39.0 - 110.2
CBF medium threshold	151.93 97.6 - 212.2	36.14 18.6 - 65.9	10.51 3.7 - 36.5	87.28 59.4 - 134.0	35.27 18.1 - 61.7
CBF lowest threshold	63.66 39.6 - 119.4	23.40 13.3 - 39.3	4.33 1.4 - 15.3	53.95 37.2 - 83.0	12.73 6.6 - 28.4

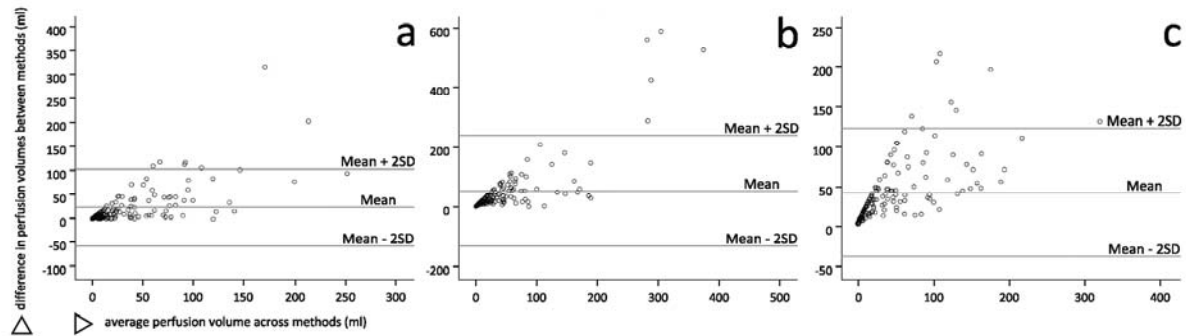
CBF indicates cerebral blood flow; MTT mean transit time; IQR interquartile range. All values are in ml.

\* Values indicate volumes after additional CSF filtering in SPM8.

All correlation coefficients between perfusion volumes and radiological and clinical outcome were considerably lower for the automatic volumes than for the manually derived ones. In the automated protocol, the top performing map (based on the correlation to radiological outcome) was Tmax in all three programs, with correlation coefficients of 0.490 in Perfscape/Neuroscape, 0.498 in PMA and 0.473 in Stroketool (0.690, 0.698 and 0.668 respectively, when using manually delineated volumes). For each program, Bland-Altman plots of agreement between methods were made for the top performing automatic map and threshold (Figure 1).



Figure 1. Bland-Altman plots for the top performing automatic map and threshold, without additional CSF filtering for PMA and Stroketool



a - Perfescape/Neuroscape; b - PMA and c - Stroketool.

For each plot the mean and the limits of agreement (mean  $\pm$  2 standard deviations) are shown as solid lines. The difference in perfusion volumes between methods was calculated with the manually derived perfusion volumes being deducted from the automated perfusion volumes.

The median volume of the perfusion deficit varied greatly based on the map and threshold. The distributions of perfusion volumes, for the same map and threshold, were significantly different between programs (all  $p$  values  $< 0.01$ ). Spearman's correlation coefficients between volumes calculated in different programs were low for control patients (between 0.02 and 0.76) and somewhat higher for acute stroke patients (between 0.17 and 0.83). For AIS patients the correlation coefficients between perfusion volumes and outcome were between 0,301 and 0.416 for clinical outcome and between 0,592 and 0,713 for radiological outcome, which is comparable to those in literature. A sub-analysis showed that, in the group of patients with an occlusion on the initial scan and no recanalization by the time of the follow-up MRI scan, the correlation coefficients were improved as compared to the correlation coefficients for all 145 patients together (between 0,462 and 0,744 for clinical outcome and between 0,537 and 0,823 for radiological outcome).

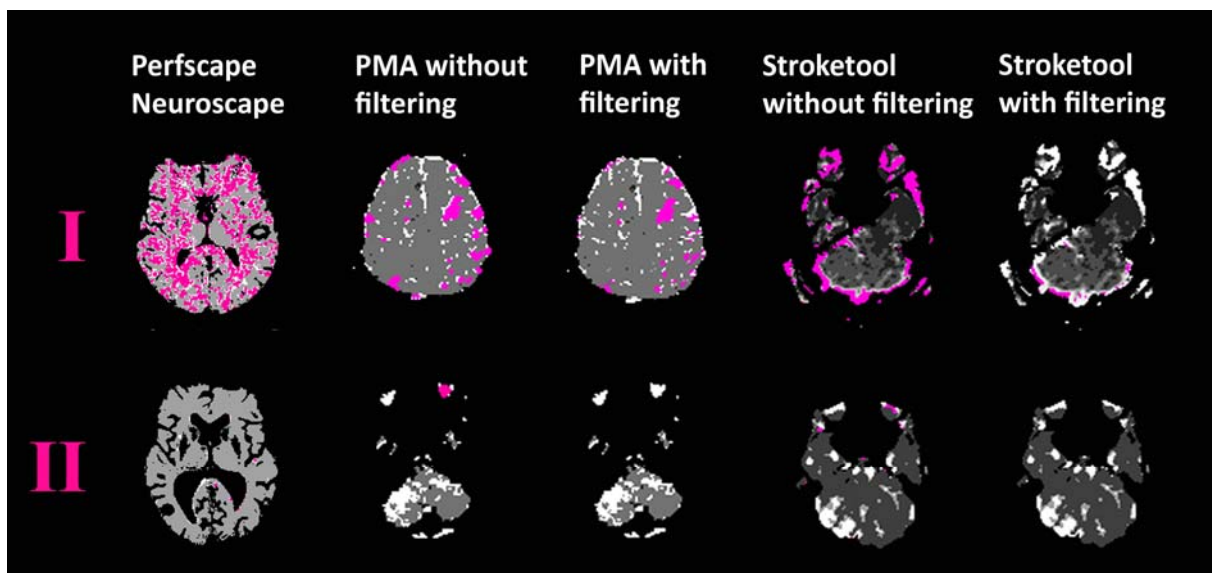
For this group of 41 patients with a persistent vessel occlusion, when further sub-grouped according to the presence and significance of mismatch (into SMP, OMP, TNMP and FNMP, as described in the Methods section) the best performing map was, in all three programs, CBF.

In control patients the median volume of hypoperfused tissue, for all the subjects, maps and thresholds put together, was 92.9 ml (IQR 13.3-323.4 ml) when calculated with Perfscope/Neuroscope, 30.42 ml (IQR 13.9-71.4 ml) when calculated with PMA and 78.71 ml (IQR 40.3-140.8 ml) when calculated with Stroketool. When the additional removal of CSF and scalp was applied, the median volume of hypoperfused tissue was 6.6 ml (IQR 1.8-35 ml) for PMA and 19.6 ml (IQR 6.3-60.9 ml) for Stroketool.

### Discussion

Our study has the advantage of being one with the largest sample of patients conducted at one centre and with a standardized imaging protocol. Firstly, it has confirmed our initial hypothesis that existing software solutions, when automated, produce exaggerated volumes of hypoperfused tissue on account of numerous artifacts, both those specific to a particular program as well as those common to all software packages. Typical examples of commonly encountered artifacts were the cortex proximal to the skull and cerebral and cerebellar tissue in direct proximity of the tentorium (Figure 2). In addition ROIs created with PMA and Stroketool suffered from such artifacts as the ventricles, eyeballs and scalp (Figure 2).

Figure 2. Typical software artefacts



All maps are Tmax with a threshold of 8 s. Calculated parameter maps are shown in greyscale and the regions of interest are depicted in pink. Row I shows the worst while row II shows the best map created in each program.

These artifacts largely explain the overshoot of the automated delineations as compared to the manual ones as well as the weak correlation coefficients between automated volumes and clinical and radiological outcome which were, for all maps and thresholds, notably inferior to the manual ones. On Bland-Altman plots of agreement between the manual delineation method and the automated approach most of the values fell within the limits of agreement (Figure 1). These limits are however much too broad when one takes into consideration the median final lesion volume for the cohort and also the fact that, based on location, even a lesion of a few ml can carry significant clinical impact.

Successful CSF filtering greatly reduced the differences between the automatic and the manual volumes, and with the choice of a high threshold the percentage of false perfusion deficits could be brought down to as low as 0% - 5%. However, an inherent flaw in simply using high thresholds to exclude noise lies in the risk of also excluding credible areas of perfusion deficit which merely present with lower values of hypoperfusion; thus resulting in false negative patients. Therefore, we believe that automated protocols would, in addition to successful filtering, also need to implement algorithms for judging asymmetry in perfusion values between hemispheres and allow human input in selecting vessel territory in order to produce a credible assessment of perfusion deficits.

In accordance to previous studies<sup>8,11</sup>, our manually derived volumes of hypoperfusion often overestimated the final lesion size and were very different between maps. A new although not entirely unexpected finding was that these volumes were also significantly different between programs for the same map and threshold. Even when measures were taken to make the maps and thresholds comparable the correlations between programs for the calculated volumes remained unexpectedly low. Also, in the control patients cohort, subjects sometimes suffered from a very different artifact load based on the program. A possible cause for all this could lie in the different choice of AIFs, the use of different deconvolution techniques, different implementations of the same calculation algorithm, differences in motion correction across different programs<sup>12,13</sup>, but potentially also rater bias during manual clean-up of ROIs. It was not possible for us to find a method which would offer a predictable estimate of final lesion size, either for all patients or for any subgroup of patients. Strong associations and negligible absolute volume differences between the perfusion volume estimate and the final infarct volume, averaged over a group of more than a hundred patients, are not the same as claiming that any of these maps and thresholds would offer a reliable estimate of tissue outcome on a patient-to-patient basis.

It is quite reasonable to conclude that ideal thresholds will vary from patient to patient<sup>14,15</sup>, due to individual differences in mean hemispheric flow, the presence and site of vessel occlusion, collateral blood flow and ratio of grey and white matter within the affected area. In our patients, CBF maps enabled the best prediction, especially for patients with a persistent vessel occlusion. At a low threshold, most of the MP in our cohort have been SMP, presenting with perfusion volumes corresponding to the minimum volume of tissue lost. The advantage of such a restrictive threshold was in giving very few to no patients in whom the perfusion volume overestimated the final infarct size. However, at such low thresholds approximately half of the patients presented as NMP. A subsequent switch to a high threshold in these NMP was able to identify whether this was an indication for the non-existence of penumbra (if the perfusion volume remained smaller than the initial DWI lesion), or whether the previous low threshold was simply too restrictive to demonstrate tissue at risk (in patients who, at this high threshold, presented with mismatch volumes). In a very small number of patients the persistent lack of mismatch (in both thresholds) was caused by a calculation error which produced FNMP.

We therefore recommend the following protocol, graphically illustrated in Figure 3. A composite image showing the three typical patient outcomes when following our suggested two-step algorithm (SMP at a low CBF threshold, NMP at the low CBF threshold but SMP at the high threshold and TNMP confirmed at both thresholds) is given in Figure 4. These results suggest that a combination of two thresholds on a CBF map could differentiate between patients with penumbra and those without, as well as provide the minimum volume of tissue destined for infarction, therefore aiding the decision regarding the need for thrombolytic therapy.

*Figure 3.*

*A diagram illustrating the two-step algorithm for the clinical evaluation of penumbra.*

In the first step the initial lesion volume (based on DWI) is subtracted from the volume of hypoperfusion (calculated using a low threshold). If this produces mismatch, the patient is assumed to have tissue at risk equaling at least the mismatch volume. If the first step classifies a patient as not having mismatch, the second step of the evaluation would be to scroll to a high threshold and then recalculate the mismatch. If mismatch is present at this threshold, the physician assumes that this mismatch volume represents tissue at definite risk of infarction. If the volume of hypoperfusion is still equal to or smaller than the initial lesion volume then it can be assumed that there is no penumbra in this patient.

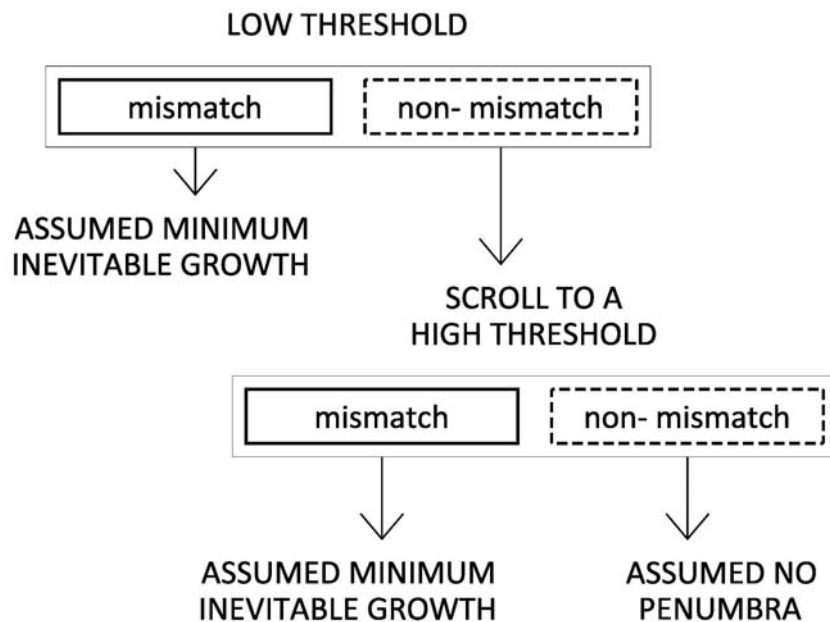
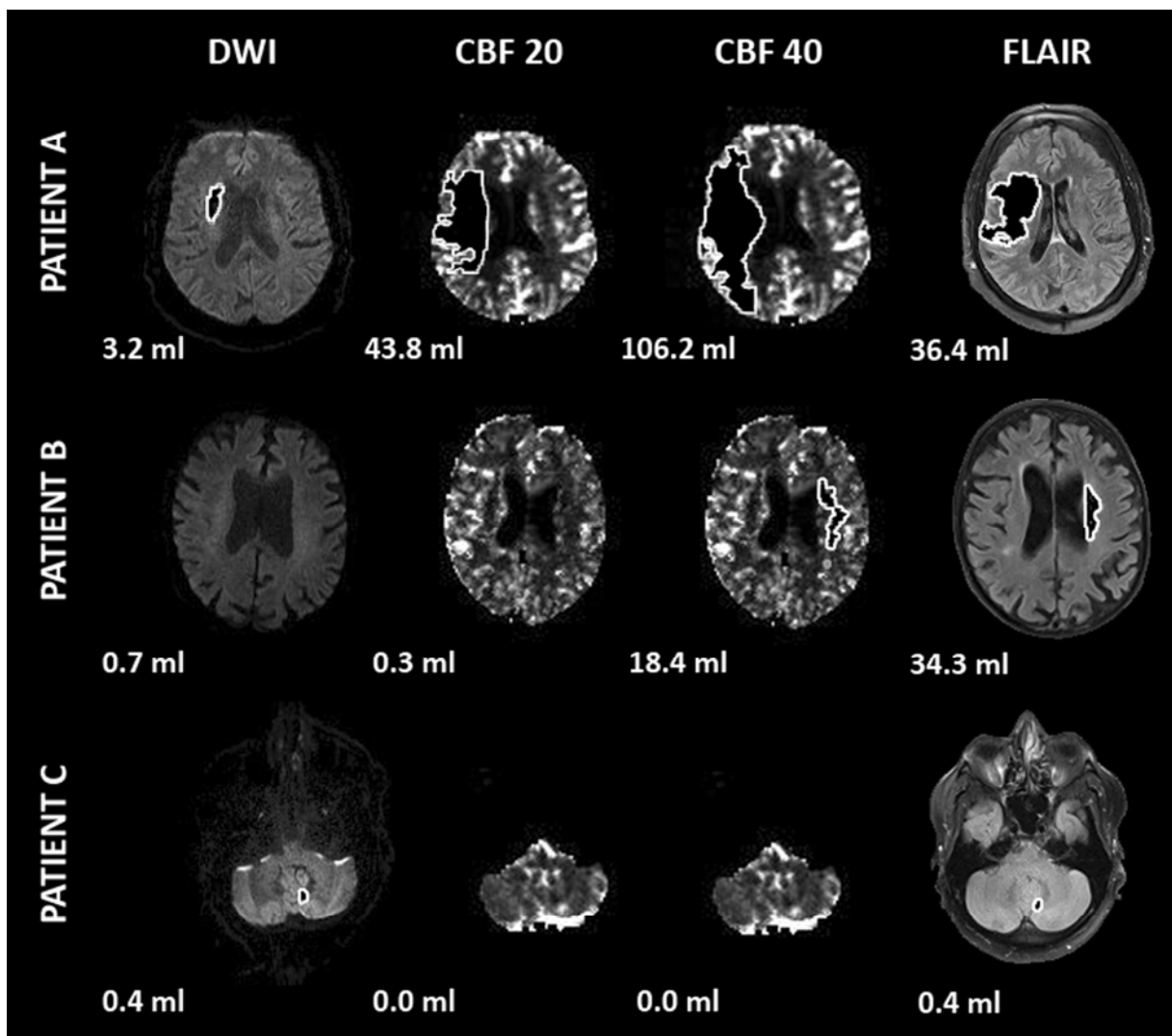


Figure 4.

An illustration of the three expected patient outcomes.

Each row depicts images from one example patient. In this figure, all perfusion maps were created using PMA; DWI represents the initial lesion on day 1, CBF 20 represents the low threshold and CBF 40 the high threshold of the CBF perfusion map while FLAIR represents the final day follow-up. ROIs are depicted as black and outlined in white. Volumetric values in the bottom left corner of each image represent the total volume of the given ROI.



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## ANTEILSERKLÄRUNG

***Ivana Galinovic contributed in the following percentage to the submitted publications:***

Publication 1: Galinovic I, Ostwaldt AC, Soemmer C, Bros H, Hotter B, Brunecker P, Fiebach JB: Automated vs manual delineations of regions of interest- a comparison in commercially available perfusion MRI software. BMC Med Imaging. 2012 Jul 18;12:16.

**\_75\_ percent (%)**

Beitrag im Einzelnen (bitte kurz ausführen):

The first author (Ivana Galinovic) identified and characterised the patient cohort, processed ca. 50% of the raw imaging data (creating perfusion imaging maps, delineating regions of interest and calculating their volumes), did 90% of the volumetric assessment of other sequences (diffusion weighted images and FLAIR images), performed statistical analysis (100%), drafted the manuscript and all its tables and figures and conducted the submission and revision process (90%).

Publication 2: Galinovic I, Ostwaldt AC, Soemmer C, Bros H, Hotter B, Brunecker P, Schmidt WU, Jungehülsing J, Fiebach JB: Search for a map and threshold in perfusion MRI to accurately predict tissue fate: a protocol for assessing lesion growth in patients with persistent vessel occlusion. Cerebrovasc Dis. 2011

**\_75\_ percent (%)**

Beitrag im Einzelnen (bitte kurz ausführen):

The first author (Ivana Galinovic) identified and characterised the patient cohort, processed ca. 50% of the raw imaging data (creating perfusion imaging maps, delineating regions of interest and calculating their volumes), did 90% of the volumetric assessment of other sequences (diffusion weighted images and FLAIR images), performed statistical analysis (100%), drafted the manuscript and all its tables and figures and conducted the submission and revision process (90%).

Publication 3: Galinovic I, Brunecker P, Ostwaldt AC, Soemmer C, Hotter B, Fiebach JB: Fully automated postprocessing carries a risk of substantial overestimation of perfusion deficits in acute stroke magnetic resonance imaging. Cerebrovasc Dis. 2011

**\_75\_ percent (%)**

Beitrag im Einzelnen (bitte kurz ausführen):

The first author (Ivana Galinovic) identified and characterised the patient cohort, processed ca. 75% of the raw imaging data (creating perfusion imaging maps, delineating regions of interest and calculating their volumes), performed statistical analysis (100%), drafted the manuscript and all its tables and figures and conducted the submission and revision process (90%).

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Berlin, 04.09.2012

## LITERATURHINWEIS

Galinovic I, Ostwaldt AC, Soemmer C, Bros H, Hotter B, Brunecker P, Fiebach JB. Automated vs manual delineations of regions of interest- a comparison in commercially available perfusion MRI software. *BMC Med Imaging*. 2012 Jul 18;12:16. doi: 10.1186/1471-2342-12-16. PMID: 22809148.

Galinovic I, Ostwaldt AC, Soemmer C, Bros H, Hotter B, Brunecker P, Schmidt WU, Jungehülsing J, Fiebach JB. Search for a map and threshold in perfusion MRI to accurately predict tissue fate: a protocol for assessing lesion growth in patients with persistent vessel occlusion. *Cerebrovasc Dis*. 2011;32(2):186-93. doi: 10.1159/000328663. Epub 2011 Aug 15. PMID: 21849778.

Galinovic I, Brunecker P, Ostwaldt AC, Soemmer C, Hotter B, Fiebach JB. Fully automated postprocessing carries a risk of substantial overestimation of perfusion deficits in acute stroke magnetic resonance imaging. *Cerebrovasc Dis*. 2011;31(4):408-13. doi: 10.1159/000323212. Epub 2011 Feb 22. PMID: 21346342.

## CURRICULUM VITAE



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*Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.*

## PUBLICATIONS

### Original papers

1. Kufner A, **Galinić I**, Brunecker P, Cheng B, Thomalla G, Gerloff C, Campbell BC, Nolte CH, Endres M, Fiebach JB, Ebinger M: Early infarct FLAIR hyperintensity is associated with increased hemorrhagic transformation after thrombolysis. *Eur J Neurol.* 2012 Aug 20. doi: 10.1111/j.1468-1331.2012.03841.x. [Epub ahead of print]
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## **ERKLÄRUNG**

Ich, Ivana Galinovic, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: „Evaluation of automated and manual perfusion MRI post-processing: the search for accurate tissue fate prediction in acute ischemic stroke“ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.

Ivana Galinovic, MSc

Berlin, 04 September 2012



## ACKNOWLEDGEMENTS

*I would like to, first and foremost, thank my supervisor Jochen B. Fiebach for his guidance and mentorship; for always finding the time to discuss my questions and for unconditionally backing me up in my professional interests. I would also like to thank all of my colleagues at the Center for Stroke Research Berlin for their dedicated teamwork and the ever existing atmosphere of genuine warmth and friendship. Of my colleagues, I would especially like to single out Peter Brunecker for his invaluable IT support and my hardworking students: Ann-Christin Ostwaldt, Carina Soemmer and Helena Bros, for sharing the painstaking hours of data processing with me. Additionally, I thank my parents for making this future at all possible for me, and all my friends for their loving support. Last but never least; I need to thank Tihomir Viderman, for lending beauty and grace to everything in my life, including this PhD thesis.*