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

DISSERTATION

Imaging-Based Predictive Modeling in Acute Ischemic Stroke

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

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Michelle Livne

aus Haifa, Israel

Datum der Promotion: 01.03.2019

Table of Contents

Abbreviations ..... - 2 -
Summary ..... - 3 -
Abstract in English ..... - 3 -
Abstract in German ..... - 5 -
Introduction ..... - 7 -
Goals ..... - 9 -
Methods ..... - 10 -
Results ..... - 13 -
Discussion ..... - 17 -
Bibliography ..... - 19 -
Affidavit ..... - 21 -
Declaration of share in publications ..... - 22 -
Print copies of selected publications ..... - 25 -
Publication I ..... - 26 -
Publication II ..... - 27 -
Publication III ..... - 28 -
Curriculum Vitae ..... - 29 -
Complete List of Publications ..... - 31 -
Acknowledgments ..... - 32 -

ABBREVIATIONS

AIS	Acute Ischemic Stroke
AUC	Area Under the Curve
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CT	Computed Tomography
DSC	Dynamic Susceptibility-weighted Contrast-enhanced
DWI	Diffusion Weighted Imaging
ERB	Ethical Review Board
FLAIR	Fluid Attenuated Inversion Recovery
FU	Follow Up
GLM	Generalized Linear Model
LOO	Leave One Out
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
MTT	Mean Transit Time
NIHSS	National Institute of Health Stroke Scale
PET	Positron Emission Tomography
ROC	Receiver Operating Characteristic
SVD	Singular Value Decomposition
T	Tesla
Tmax	Time to Maximum
TTP	Time to Peak

SUMMARY

Abstract in English

Introduction

Stroke is a dire medical and economic burden. While the current treatment of acute ischemic stroke (AIS) is restricted to a limited time-window, stroke-imaging facilitates novel tissue-based personalized stratification approaches. In this thesis we targeted the standardization of stroke imaging and the development of predictive models for individual assessment of stroke progression. Subproject 1 aimed to improve diagnostic perfusion imaging in MRI by standardization of the imaging post-processing through comparison of the two most common deconvolution methods, i.e. standard- and block-circulant singular-value-decomposition (sSVD and bSVD). Subproject 2 aimed at improving the detection of tissue-at-risk by establishing a multi-parametric perfusion imaging model. Finally, in subproject 3 we aimed to develop a multi-modal MRI framework for prediction of final-infarct and identification of the important imaging-markers for patients with recanalization and persistent-occlusion.

Methods

In subproject 1, a retrospective analysis was performed on dynamic-susceptibility-contrast-enhanced (DSC)-MRI and positron-emission-tomography (PET) cerebral-blood-flow (CBF) scans of stroke patients. The two deconvolution methods were used to derive perfusion-maps and were systematically compared quantitatively against the PET gold-standard. In subproject 2, in a retrospective analysis a multi-parametric model integrating five different perfusion-parameters was established and compared against the single perfusion parameters. The models were validated for assessing penumbral-flow using PET-CBF maps. In subproject 3, a retrospective study of multi-centric data was performed. The XGBoost algorithm was used to establish an integrative multi-modal nonlinear model based on perfusion imaging as well as DWI and FLAIR imaging for final infarct prediction and was compared to the standard linear approach. The important imaging-markers for stroke-progression were systematically identified.

Results

In three publications, we improved image post-processing and imaging-based prediction of clinical targets in AIS. In subproject 1, we identified the bSVD deconvolution method as the standard to derive DSC-MRI perfusion-imaging maps in stroke. In subproject 2, we validated a novel DSC-

MRI based multi-parametric model for detection of individual tissue-at-risk for stroke patients with very high accuracy. In subproject 3, we established a multi-modal MRI model for final-infarct prediction using the XGBoost algorithm and demonstrated significant improvement over the standard linear model. Finally, we identified the imaging parameters MTT, TTP, Tmax and DWI as most valuable for infarct prediction.

Conclusion

The results of the present thesis provide an advanced framework of imaging-based predictive modeling in acute stroke applicable for the clinical setting. These advancements support personalized medicine in stroke-imaging and will benefit the diagnosis and stratification of acute stroke patients.

Abstract in German

Einleitung

Der akute ischämische Schlaganfall (AIS) ist eine medizinische Herausforderung. Eine Therapie im AIS ist zur Zeit lediglich in einem definierten Zeitfenster möglich. Die Bildgebung des zentralen Nervensystems („Neuroimaging“) jedoch hat das Potential eine personalisierte Therapiestrategie basierend auf rettbarem Gewebe (tissue-at-risk) zu etablieren. Die vorliegende Dissertation hatte zum Ziel in drei Teilschritten das Neuroimaging im akuten Schlaganfallsetting zu standardisieren und Modelle der Schlaganfallprogressionsvorhersage zu etablieren. Teilprojekt 1 zielte darauf ab, die Nachbearbeitung der Durchblutungsbildgebung in der Magnetresonanztomographie (MRT) zu standardisieren. Hierfür wurden die meistverbreiteten Dekonvolutionsmethoden validiert. Teilprojekt 2 hatte zum Ziel die Darstellung von tissue-at-risk mittels eines Vorhersagemodells darzustellen, das verschiedene Durchblutungsparameter kombiniert. In Teilschritt 3 entwickelten wir ein multimodales bildgebungsbasiertes MRT-Vorhersagemodell, welches den finalen Infarkt vorhersagen kann, sowie die wichtigsten Parameter für die Vorhersage in Patienten mit Rekanalisation und Patienten mit persistierender Okklusion identifizieren kann.

Methoden

In Teilprojekt 1 führten wir eine Bildgebungsanalyse von konsekutiven Dynamic-Susceptibility-Contrast-enhanced (DSC)-MRT und PET-cerebral blood flow (CBF) Bildgebungen durch. Die standard- und block-circulant singular-value-decomposition (sSVD und bSVD)Methoden wurden genutzt um DSC-Durchblutungsparameterkarten zu erstellen, welche mittels PET-CBF validiert wurden. In Teilprojekt 2 wurden fünf Durchblutungsparameter in einem multiparametrischen Modell integriert und deren Vorhersagekraft für die Darstellung von verminderter Durchblutung mit den Einzelparametern verglichen. Diese Modelle wurden mittels PET-CBF Bildgebung validiert. In Teilprojekt 3 wurde an multizentrischen Bildgebungsdaten der treeboosting-Algorithmus XGboost verwendet um ein multimodales Modell für die Infarktprädiktion zu entwickeln, welches Durchblutungsbildgebung, diffusionsgewichtete Bildgebung (DWI) und Fluid-Attenuated-Inversion-recovery-Bildgebung (FLAIR) enthielt und es erlaubte, die einzelnen Bildgebungsparamater nach ihrer Vorhersagekraft zu ordnen.

Ergebnisse

In drei Publikationen konnten Fortschritte in der Standardisierung der Bildgebung im AIS und in der bildbasierten Infarktprädiktion erzielt werden. In Teilprojekt 1 identifizierten wir die bSVD-Dekonvolution als Standard für die Erstellung von DSC-Durchblutungsparameterkarten im AIS. In Teilprojekt 2 validierten wir ein multiparametrisches Modell für die Vorhersage des tissue-at-risk, welches eine sehr hohe Präzision zeigte. In Teilprojekt 3 entwickelten wir mittels des neuartigen XGBoost Algorithmus ein integratives multimodales MRT-basiertes Modell der Infarktprädiktion. Dieses nicht-lineare Modell zeigte deutliche Verbesserungen gegenüber dem linearen Standardmodell der Infarktprädiktion. Wir konnten zudem zeigen, dass die Parameter MTT, TTP, Tmax und DWI sowohl in Patienten mit Rekanalisation als auch in Patienten mit persistierender Okklusion die stärkste Vorhersagekraft hatten.

Schlussfolgerung

Die Ergebnisse dieser Dissertation bilden ein erstes Rahmenwerk für bildgebungsbasierte prädiktive Modelle für AIS Patienten, die auch im klinischen Setting anwendbar sind. Damit unterstützen diese Resultate die Entwicklung personalisierter Ansätze in der AIS-Therapie, um die Diagnostik und Stratifizierung zukünftig deutlich zu verbessern.

Introduction

Acute ischemic stroke (AIS) is a leading cause of death and disability in first world countries.[1] Casual treatment of AIS patients (e.g. recanalization) in the clinical setting, however, is limited by a restricted time-window according to the medical guidelines.[2–4] This time-based stratification approach results in only about 10% of patients receiving treatment using pharmacological- or mechanical recanalization.[5] Consequently, improved diagnostic tools for AIS patients stratification into treatment are highly warranted.

Major efforts are invested in the field to establish a tissue-based approach to provide a more reliable and individualized stratification tools to replace the current time-clock paradigm. Neuroimaging plays a key role in providing a personalized and reliable diagnosis in the clinical settings. While the time-clock approach is over generalizing, an imaging-based tissue-clock is inherently tailored to the individual patient. Magnetic resonance imaging (MRI) provides a multi-modal imaging technique that allows the examination of numerous aspects of brain ischemia. Diffusion-weighted imaging (DWI) informs about cell death, fluid-attenuated-inversion-recovery (FLAIR) can help to estimate the age of lesions and perfusion-weighted imaging (PWI) reflects perfusion status. Brain imaging is thus the most promising method to achieve robust stratification of AIS patients into treatment beyond a purely time-based approach.

A heavily pursued non-time based framework using neuroimaging is the detection of penumbral flow, coined tissue-at-risk in MR-imaging. Here, dynamic-susceptibility-enhanced-contrast (DSC) -MRI is often used to identify the tissue-at-risk. In DSC-MRI, a time-series signal based on gadolinium compounds is used as a contrast agent. Together with a chosen arterial input function (AIF) the residual curve is derived by which most perfusion parameters are calculated. While DSC-MRI is broadly available and promising, its use is currently limited as it lacks standardization due to the complexity of imaging post-processing and due to the absence of an available gold-standard validation. In the present thesis we thus applied three proceeding steps for the standardization of DSC-based stroke imaging and development of imaging-based predictive models.

In the first step we focused on the basic post-processing of DSC perfusion maps. Here, a major pressing matter is the unanswered question which type of deconvolution method should be applied. The choice of deconvolution method is crucial in DSC-MRI processing due to the tremendous effect on the acquired perfusion maps. This is caused by the influence of signal characteristics such as long time-delays which are typical in acute stroke imaging. A reason for the lack of standardization of deconvolution is the sparsity of validations against gold standards. Thus, we compared the two most common deconvolution approaches using different software and validated

them with gold-standard positron emission tomography (PET) perfusion-imaging (see publication 1). Having established standardized perfusion images we aimed in the next step to integrate different perfusion parameters in one predictive model. Normally, only single perfusion parameters maps are used to identify the tissue-at-risk (i.e. penumbral-flow). An integration, however, of several perfusion maps holds the promise to improve the assessment of penumbral flow. To address this challenge we integrated the standard perfusion parameters using a generalized linear model (GLM) to predict penumbral flow in AIS and validated it against PET-imaging (see publication 2).

Naturally, the best results for stratification can be expected, if different MR-modalities – not only perfusion imaging - are combined in a multimodal imaging approach. Here, however, there is no consensus, which imaging parameter(s) allow for the best prediction of the tissue-at-risk. The technological advancement in the field of machine learning allow to apply new integrative models to answer this question. Thus, in the last step we developed a framework using the novel tree-boosting XGboost to integrate different MR-modalities for final-infarct prediction, where the final-infarct serves as a surrogate for the tissue-at-risk. Using two sub-models for the cases of successful-recanalization and persistent-occlusion, the model provides complementary information for final infarct prediction in AIS patients. This allowed us to identify the most important imaging-markers for both cases of successful-recanalization and persistent occlusion (see publication 3).

Goals

The following measures are necessary to improve the diagnostic possibilities in AIS the clinical setting: to standardize brain-imaging and to provide new diagnostic tools as replacement for the current time-window approach. Among the different MRI modalities, perfusion imaging particularly holds critical information about the stroke progression and the tissue at risk. Thus, in the present thesis we set out to standardize perfusion imaging post-processing using sound gold-standard validation and develop MRI-based predictive models as diagnostic measures in AIS. The imaging-based multi-parametric and multi-modal predictive models allow to better capture the individual stroke progression and therefore take a step forward towards personalized medicine in stroke. In a multidisciplinary approach and clinical imaging studies we aimed to

a) Subproject 1: Compare the two most common deconvolution methods in AIS and validate the results using PET gold-standard.
b) Subproject 2: Integrate the different DSC-MRI perfusion parameters to predict the tissue-at-risk and validate the results using PET gold-standard
c) Subproject 3: Integrate multi-modal MRI imaging to predict the final infarct for the cases of successful-recanalization and persistent-occlusion and identify the relevant imaging-markers for final-infarct prediction.

Methods

As this thesis encompasses three publications, the summary methods overview will be concise due to the official page restrictions. Detailed information about the applied methods can be found in the methods section of each publication.

Ethics statement

All patients gave informed written consent prior to the study. All studies were conducted according to the principles expressed in the Declaration of Helsinki and were approved by the authorized ethical review boards (ERB) of the University of Cologne (Publications I and II) and with the Aarhus, Hamburg, Lyon, and Girona hospitals and their respective regional ethics committees (Publication III).

Clinical study populations

For *Subproject 1 and 2* (Publications I and II), a retrospective analysis of database of (sub)-acute ischemic hemispheric stroke patients with comparative MR- and PET imaging (University of Cologne) was conducted. Stroke patients available for the analysis were imaged consecutively between 2003 and 2006. The database was screened and patients were included according to the following main criteria: 1) clinically proven stroke, 2) confirmed unilateral stroke lesion in DW-imaging, 4) available consequent DSC-MRI and PET imaging. Main exclusion criteria were: 1) patients with thrombolysis 2) patients with a change of the National Institute of Health Stroke Scale (NIHSS) score >2 points during the imaging procedure 3) insufficient image quality. Due to slightly differing inclusion criteria, e.g. standardization of the TR scan-parameter in publication II and different requirements for the quality of concentration-curves, there is a slight difference in the number of datasets in both studies (18 and 17).

For *Subproject 3* (Publications III), in a retrospective analysis, patients with acute ischemic hemispheric stroke from the I-Know European multicenter study and the Ischemic Per-conditioning trial were included.[6,7] Databases were screened and patients were included according to the following main criteria: 1) clinically proven stroke, 2) confirmed unilateral stroke lesion in DW-imaging, 3) available acute DWI, FLAIR and DSC-MRI imaging 4) available follow-up (FU) FLAIR imaging. Main exclusion criteria were: 1) insufficient image quality, 2) final-infarct volume<0.12mL. 195 patients were included in Publication III.

Imaging Hardware

For *Subproject 1 and 2* (Publications I and II), MR-imaging was performed at 1.5 T on a Philips Intera Master whole-body system (Philips Medical Systems, Best, The Netherlands). PET was performed on a ECAT EXACT HR scanner (Siemens/CTI, Knoxville, TN).

For *Subproject 3* (Publication III), MR-imaging was performed at the admitting hospital :GE Signa-Excite 1.5T, GE Signa-Excite 3T, GE Signa-HDx 1.5T, GE Signa-Genesis 1.5T, Milwaukee, WI; Siemens-TrioTim 3T, Siemens-Avanto 1.5T, Siemens-Sonata 1.5T, Erlangen, Germany; Philips-Gyroscan NT 1.5T, Phillips-Achieva 3T, and Philips-Intera 1.5T, Best, Netherlands.

Study methodology

As this thesis encompasses three different publications with distinct and complex methodologies, the methods cannot be explained in detail due to the official page number limitation. Thus, only an abstract-style methods overview will be given in the following. These overviews are slightly modified from the original abstract texts of the publications listed in the publication overview on page 31. Detailed information about the applied methods for each publication can be found in the print copies of each publication following page 24.

Subproject 1, Publication I: In a retrospective study of (sub)acute stroke patients with consecutive MRI and H2O15 PET imaging, DSC-MRI maps were calculated applying two deconvolution methods: standard- and block-circulant single value decomposition, i.e. SSVD and BSVD respectively. Two standardized analysis methods were used for this comparison: a region of interest–based and a voxel-based analysis, where PET cerebral blood flow masks of <20 mL/100 g per minute (penumbral flow) and gray matter masks were overlaid on DSC perfusion-parameter maps. For both methods, receiver-operating-characteristic (ROC) curve analysis was performed to identify the accuracy of each DSC-MR map for the detection of PET penumbral-flow.

Subproject 2, Publication II: In a retrospective analysis of 17 subacute stroke patients with consecutive MRI and H2O15 PET scans, standard perfusion maps of cerebral-blood-flow (CBF), cerebral-blood-volume (CBV), mean-transit-time (MTT), time-to-maximum (Tmax) and time-to-peak (TTP) were constructed and combined using a generalized linear model (GLM). Both the GLM maps and the single perfusion maps alone were cross-validated with PET-CBF scans to predict penumbral flow on a voxel-wise basis. Performance was tested using receiver-operating-characteristics (ROC) curve analysis as indicated by the area-under-the-curve (AUC) and the

models were statistically compared using the likelihood-ratio test. A standard significance level of $p<0.05$ was applied

Subproject 3, Publication III In a multi-center retrospective analysis of 195 AIS patients, fluid-attenuated-inversion-recovery (FLAIR), diffusion-weighted-imaging (DWI) and 10 perfusion parameters were derived from acute MRI scans. They were integrated to predict final infarct as seen on follow-up T2-FLAIR using the tree-boosting algorithm XGBoost and compared to a standard generalized-linear-model (GLM) approach using two cross-validation (CV) approaches: leave-one-out (LOO) and 5-folds. Sub-models for recanalization- and persistent-occlusion were calculated and were used to identify the important imaging markers. The contribution of each imaging-modality, also termed as gain, was calculated according to the cumulative average of the modality-gain over all the constituent decision-trees in the ensemble-model. Performance in infarct-prediction was analyzed with receiver-operating-characteristics (ROC). Resulting areas-under-the-curve (AUC) and accuracy-rates were compared using Wilcoxon signed rank test. A standard significance level of $p<0.05$ was applied.

Results

Subproject 1

The goal of subproject 1 was to improve the standardization of perfusion imaging post-processing by comparing the two most commonly applied deconvolution methods, sSVD and bSVD.

In 18 data-sets (median time after stroke onset: 18 hours; median time PET to MRI: 101 minutes), the ROC analysis showed that the bSVD deconvolution-method performed significantly better in PET penumbral-flow detection only for MTT maps (see figure 1). Over both deconvolution methods, the deconvolved perfusion-parameter Tmax had the highest performance in penumbral-flow detection independent of the deconvolution method.

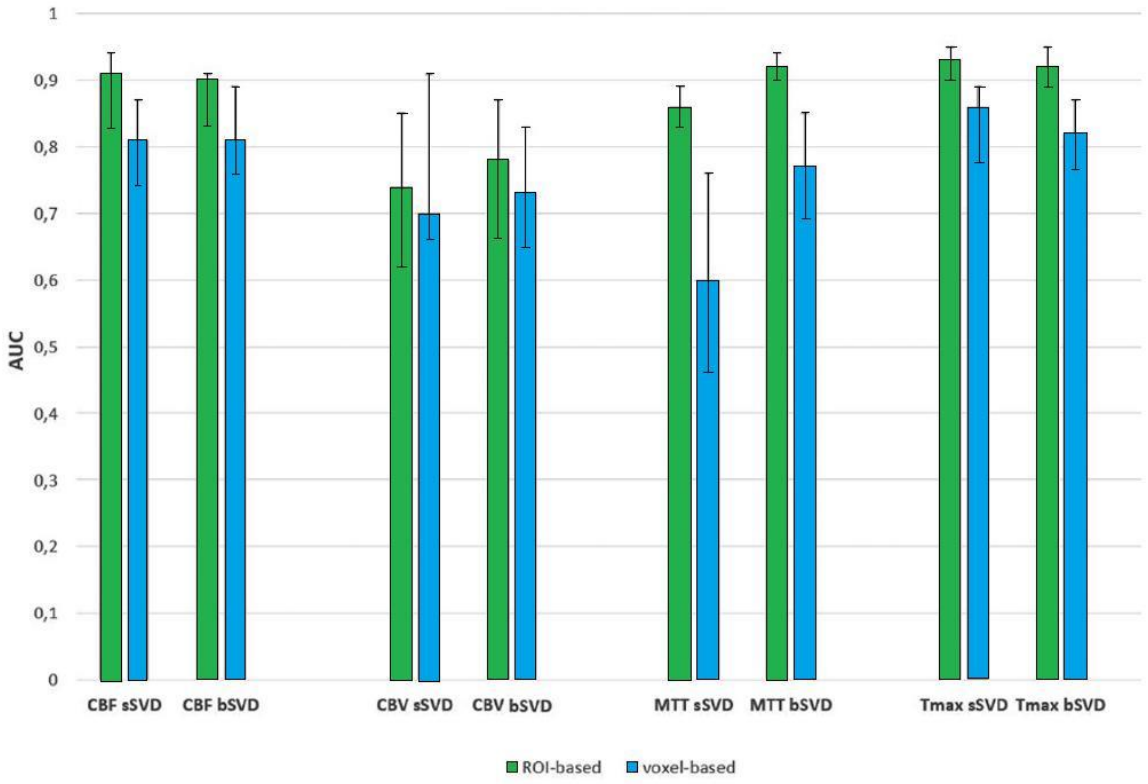

*Figure 1:*Graphic overview of the DSC-MRI parameter maps analyzed in our study arranged according to perfusion parameters and the deconvolution methods. The performance is measured by the area under the curve (AUC). Interquartile ranges are given as error bars. Abbreviations: bSVD, block-circulant single value decomposition; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; ROI, region of interest; sSVD, standard single value decomposition; and Tmax, time-to-maximum.

Subproject 2

The goal of this subproject was to integrate the standard perfusion parameters into one predictive model using GLM for identification of the tissue-at-risk as represented by penumbral-flow and validate the model using PET imaging.

The GLM model demonstrated significantly improved model fit compared with each of the single perfusion maps ($P<1\times e-5$) as indicated by the likelihood-ratio test. It also demonstrated higher performance with an AUC of 0.91 (see figure 2). Nonetheless, the absolute improvement in performance of GLM comparing with the best-performing perfusion parameter (Tmax) was relatively low (AUC difference of 0.04). An illustrative example is shown in figure 3.

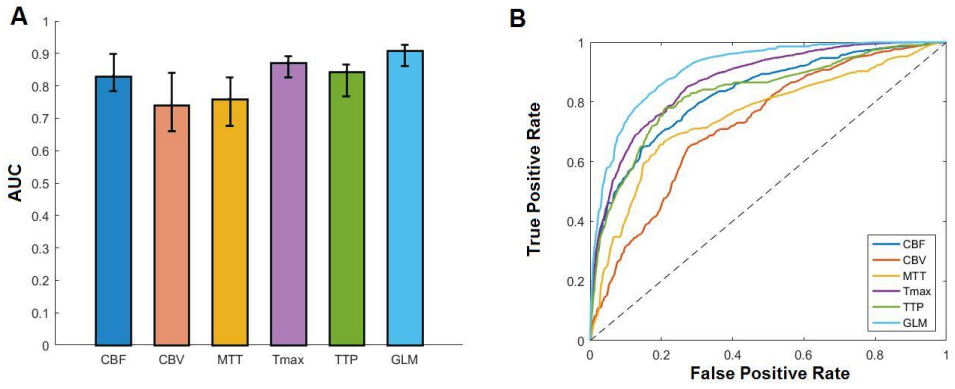

Figure 2: The figure shows the models performance in penumbral-flow prediction. The median area under the curve (AUC) for each of the models is displayed in A. Error bars represent the interquartile range (IQR). The performance curves for each of the models are shown in B. CBF indicates cerebral blood flow; CBV, cerebral blood volume; GLM, generalized linear model; MTT, mean transit time; Tmax, time-to-maximum; and TTP, time-to-peak.

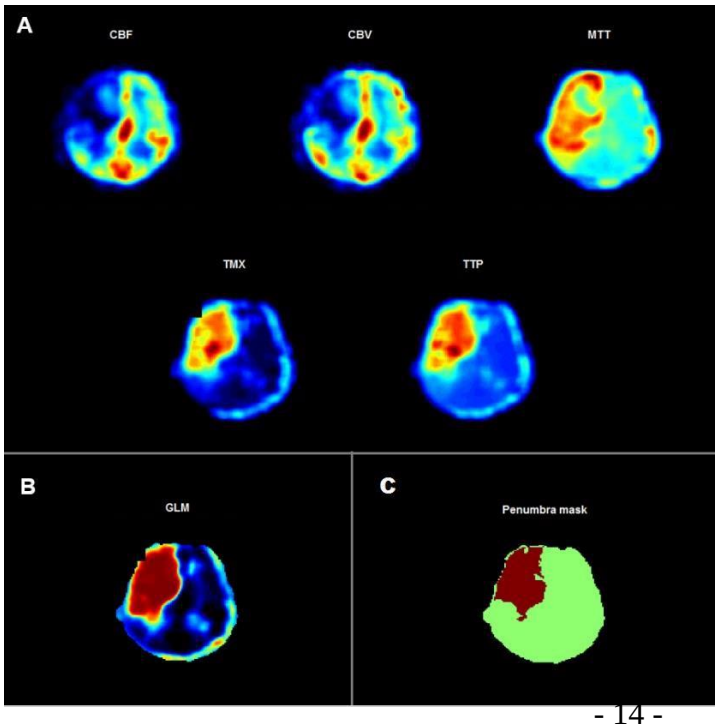

Figure 3: Illustration of the predictive maps for a representative patient.

Single parameter perfusion maps (CBF, CBV, MTT, Tmax, and TTP) (A) are shown here in comparison to a GLM-based probability map for penumbral flow detection (B). As can be observed, the GLM-based probability map yields an accurate prediction of penumbral flow as presented by the positron emission tomography (PET)-based penumbral-flow layout (C) in comparison with the single parameter perfusion maps. CBF indicates cerebral blood flow; CBV, cerebral blood volume; GLM, generalized linear model; MTT, mean transit time; Tmax, time-to-maximum; and TTP, time-to-peak.

Subproject 3

In this subproject, we aimed to integrate the different MRI modalities including DWI, FLAIR and DSC-MRI into one predictive model to identify the final-infarct for the case of successful recanalization and persistent occlusion. For this purpose, we used the ensemble-tree-boosting model XGboost which also allows rating of the different imaging-modalities according to their numerical contribution to the infarct-prediction.

The XGBoost model demonstrated significantly higher performance in infarct prediction compared to the standard GLM method in both CV approaches: 5-folds ($p<10e-16$) and leave-one-out (LOO) ($p<0.015$) as was indicated by the Wilcoxon signed rank test. The imaging parameters time-to-peak (TTP), mean-transit-time (MTT), time-to-maximum (Tmax) and DWI were indicated as most valuable for infarct-prediction by the systematic algorithm rating and accounted for 87% of the gain in both predictive-models. The rest of the parameters had less than 5% of contribution to the prediction of final-infarct. Notably, the performance improvement was higher with 5-folds CV approach than LOO. The full performance assessment is detailed in table 1.

Table 1: Performance of XGBoost and GLM models in final infarct prediction

Full cohort Model			
CV method	**XGB**	**GLM**	**p value**
LOO (AUC/Acc)	0.88/0.84	0.87/0.82	< 10e-6/<10e-10
5-folds (AUC/Acc)	0.92/0.84	0.86/0.78	< 10e-33/<10e-33
Model for Successful Recanalization			
CV method	**XGB**	**GLM**	**p value**
LOO (AUC/Acc)	0.89/0.83	0.88/0.80	<10e-3/<10e-5
5-folds (AUC/Acc)	0.93/0.84	0.87/0.79	< 10e-148/<10e-33
Model for Persistent Occlusion			
CV method	**XGB**	**GLM**	**p value**
LOO (AUC/Acc)	0.90/0.82	0.88/0.80	0.015/<10e-5
5-folds (AUC/Acc)	0.93/0.84	0.88/0.80	< 10e-63/<10e-33

Table 1: Comparison of the performance of the XGBoost (XGB) algorithm and the generalized-linear-model (GLM) in final infarct prediction using receiver operating characteristics (ROC) analysis as measured by the area under the curve (AUC) and the accuracy rate (Acc). The comparison was done using the non-parametric paired Wilcoxon signed rank test. The performance is listed for three models: 1) The general model, without integration of recanalization status 2) The model for successful recanalization and
3) The model for persistent-occlusion, for both cross validation (CV) approaches: Leave-one-out (LOO) and 5-folds. The higher p-values in the two sub-models are attributed to the smaller available datasets, comparing with the general model.

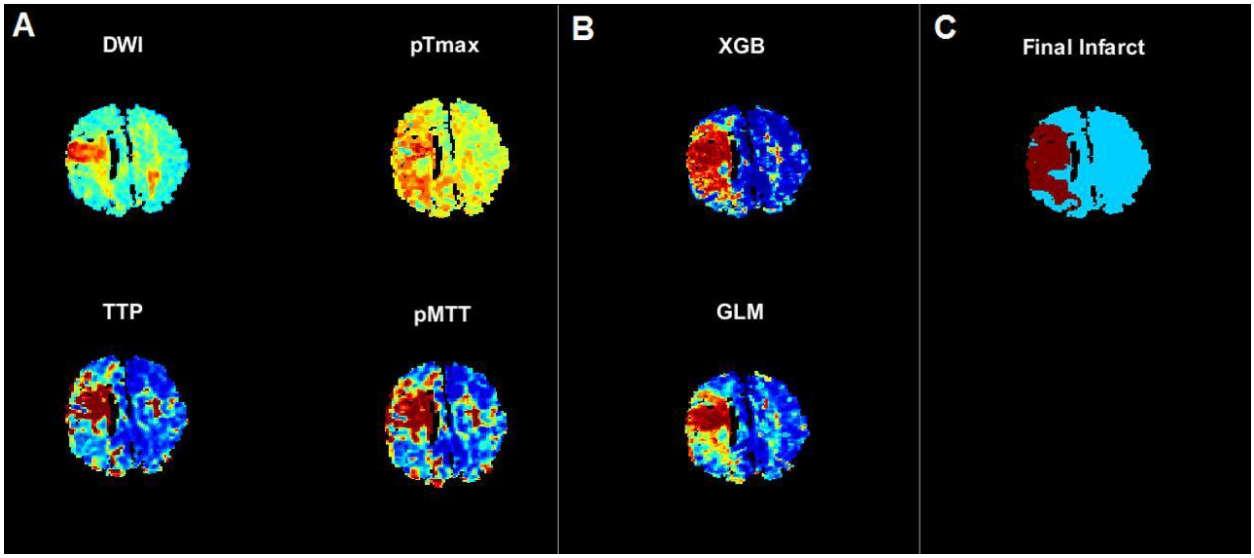

Figure 4: The figure illustrates the final infarct prediction for a representative patient. Here single parameter maps of diffusion-weighted-imaging (DWI), parametric time-to-maximum (pTmax), time-to-peak (TTP) and parametric mean-transit-time (MTT) (A) are shown in comparison to a generalized-linear-model (GLM)-based probability map (GLM) and XGBoost-based probability map (XGB) (B) for final infarct for a representative recanalized patient. As can be observed, the XGBoost-based probability map yields an accurate prediction of final infarct as presented by the T2-FLAIR- based final infarct layout (B) in comparison with the presented single imaging modalities and the GLM-based probability map (especially in the posterior areas). The illustration reflects the finding that the perfusion parameters pTmax, pMTT and TTP are valuable markers for acute infarction.

Discussion

In the present PhD thesis, we targeted different aspects in imaging post-processing and imaging-based predictive modeling in AIS. In three publications, we established improved standardization of neuroimaging biomarkers and implemented new personalized predictive models for patient stratification. Our first work showed the advantage of the bSVD deconvolution method for acquisition of perfusion imaging in acute stroke and thus provides a gold-standard validation for the standardization of perfusion imaging processing. In a second step we established a perfusion-imaging-based multi-parametric model (GLM) for identification of the tissue at risk as a surrogate of penumbral flow and validated it using PET gold-standard. The multi-parametric model showed significant improvement in detection of penumbral-flow in AIS patients compared with single perfusion parameters. Lastly, we developed a multi-modal MRI model, integrating perfusion imaging with DWI and FLAIR in a non-linear approach (XGBoost) to detect the infarct progression in acute stroke patients and validated the superiority of the nonlinear model in final-infarct prediction compared with the standard linear model. Additionally, DWI, Tmax, TTP and MTT were identified as the important imaging-markers for infarct prediction.

While perfusion-imaging using DSC-MRI was shown to provide valuable information for stroke diagnostic, the complexity of the post-processing to yield the perfusion maps results in a large variety of respective methodologies and a lack of standardization.[8–14] The choice of deconvolution method is a central source of variation in perfusion-imaging acquisition. While the advantages of the bSVD deconvolution as a time-shift invariant method were previously discussed by Wu et al., our work provides first gold-standard based validation for the method.[9] Later reports confirmed corroborated our findings.[15]

Perfusion imaging using DSC-MRI was used extensively in the literature to depict the tissue-at-risk and therefore have significant implications for development of imaging-based stratification approach for AIS patients.[12,16–19] However, until now only single parameter perfusion maps were used separately as predictors. Here, we established for the first time an integrative model using GLM to provide a more accurate assessment of the tissue at risk.[20,21,17,22] Due to its simplicity, our model can be easily used in clinical settings, given the standard perfusion maps. In concert with the newly emerging therapeutic strategies, from normobaric oxygen therapy to thrombectomy, accurate identification of penumbral flow based on imaging is a key issue in stratification as well as monitoring and evaluation of the new techniques.

The most important advances in the field of stroke imaging in the last decade aspired to shift from the current time-window paradigm to a tissue-based paradigm for a more individual, reliable and

inclusive approach for stroke patients stratification into treatment. In accordance with technological advancement and available data, we believe that the future of stroke imaging lays in personalized medicine. While the tissue-based paradigm comprises the first steps towards personalized medicine in acute stroke, the technology of today allows integrating the different imaging modalities into one model and allow non-linear approaches to better fit the prediction for each patient individually. In our last study we thus used the XGBoost algorithm to establish an integrative multi-modal MRI model for prediction of final-infarct. Our results indicated clearly that the XGBoost model performs better than a standard linear model. Our findings also indicated the perfusion parameters MTT, TTP and Tmax as well as DWI as the most important bio-markers for final infarct prediction, and as a surrogate of that, the tissue at risk. These last findings emphasize the importance of perfusion parameters as reliable predictors of stroke severity and corroborate previous indications in the literature.[23]

In conclusion, the results of the present thesis provide important advancements for predictive modeling in stroke imaging. We present frameworks for clinically applicable models that can be used for future stratification approaches of AIS patients into treatment and provide a decision support system for clinicians. In our work we wish to inspire the necessary prospective studies to validate the presented models for clinical use. A direct benefit for patients can be anticipated in the diagnosis of acute stroke.

Bibliography

1. Towfighi, A. & Saver, J. L. Stroke Declines From Third to Fourth Leading Cause of Death in the United States: Historical Perspective and Challenges Ahead. *Stroke* **42,** 2351–2355 (2011).
2. Zoppo, G. J. del, Saver, J. L., Jauch, E. C. & Adams, H. P. Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous Tissue Plasminogen Activator: A Science Advisory From the American Heart Association/American Stroke Association. *Stroke* **40,** 2945–2948 (2009).
3. Goyal M, Yu AY, Menon BK, Dippel DW, Hacke W, Davis SM, Fisher M, Yavagal DR, Turjman F, Ross J, Yoshimura S, Miao Z, Bhatia R, Almekhlafi M, Murayama Y, Sohn SI, Saver JL, Demchuk AM & Hill MD. Endovascular Therapy in Acute Ischemic Stroke: Challenges and Transition From Trials to Bedside. *Stroke J. Cereb. Circ.* **47,** 548–553 (2016).
4. Evans, M. R. B., White, P., Cowley, P. & Werring, D. J. Revolution in acute ischaemic stroke care: a practical guide to mechanical thrombectomy. *Pract. Neurol.* practneurol-2017-001685 (2017). doi:10.1136/practneurol-2017-001685
5. Saver JL, Gornbein J, Grotta J, Liebeskind D, Lutsep H, Schwamm L, Scott P & Starkman S. Number needed to treat to benefit and to harm for intravenous tissue plasminogen activator therapy in the 3- to 4.5-hour window: joint outcome table analysis of the ECASS 3 trial. *Stroke J. Cereb. Circ.* **40,** 2433–2437 (2009).
6. Alawneh JA, Jones PS, Mikkelsen IK, Cho TH, Siemonsen S, Mouridsen K, Ribe L, Morris RS, Hjort N, Antoun N, Gillard JH, Fiehler J, Nighoghossian N, Warburton EA, Ostergaard L & Baron JC. Infarction of 'non-core–non-penumbral' tissue after stroke: multivariate modelling of clinical impact. *Brain* **134,** 1765–1776 (2011).
7. Hougaard KD, Hjort N, Zeidler D, Sørensen L, Nørgaard A, Thomsen RB, Jonsdottir K, Mouridsen K, Hansen TM, Cho TH, Nielsen TT, Bøtker HE, Østergaard L & Andersen G. Remote ischemic perconditioning in thrombolysed stroke patients: Randomized study of activating endogenous neuroprotection – design and MRI measurements. *Int. J. Stroke* **8,** 141–146 (2013).
8. Baron, J.-C. Perfusion Thresholds in Human Cerebral Ischemia: Historical Perspective and Therapeutic Implications. *Cerebrovasc. Dis.* **11,** 2–8 (2001).
9. Wu O, Østergaard L, Weisskoff RM, Benner T, Rosen BR & Sorensen AG. Tracer arrival timing-insensitive technique for estimating flow in MR perfusion-weighted imaging using singular value decomposition with a block-circulant deconvolution matrix. *Magn. Reson. Med.* **50,** 164–174 (2003).
10. Wintermark M, Sesay M, Barbier E, Borbély K, Dillon WP, Eastwood JD, Glenn TC, Grandin CB, Pedraza S, Soustiel JF, Nariai T, Zaharchuk G, Caillé JM, Dousset V, Yonas H. Comparative Overview of Brain Perfusion Imaging Techniques. *Stroke* **36,** e83–e99 (2005).
11. Butcher, K.S., Parsons, M., MacGregor, L., Barber, P.A., Chalk, J., Bladin, C., Levi, C., Kimber, T., Schultz, D., Fink, J. and Tress, B. Refining the perfusion-diffusion mismatch hypothesis. *Stroke J. Cereb. Circ.* **36,** 1153–1159 (2005).

12. Sobesky J, Zaro Weber O, Lehnhardt FG, Hesselmann V, Neveling M, Jacobs A, Heiss WD. Does the Mismatch Match the Penumbra?: Magnetic Resonance Imaging and Positron Emission Tomography in Early Ischemic Stroke. *Stroke* **36,** 980–985 (2005).

13. Mouridsen, K., Christensen, S., Gyldensted, L. & Østergaard, L. Automatic selection of arterial input function using cluster analysis. *Magn. Reson. Med.* **55,** 524–531 (2006).

14. Meijs, M., Christensen, S., Lansberg, M. G., Albers, G. W. & Calamante, F. Analysis of perfusion MRI in stroke: To deconvolve, or not to deconvolve. *Magn. Reson. Med.* **76,** 1282–1290 (2016).

15. Schaafs, L.-A., Porter, D., Audebert, H. J., Fiebach, J. B. & Villringer, K. Optimising MR perfusion imaging: comparison of different software-based approaches in acute ischaemic stroke. *Eur. Radiol.* **26,** 4204–4212 (2016).

16. Albers GW1, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP; DEFUSE Investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: The diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann. Neurol.* **60,** 508–517 (2006).

17. Zaro-Weber, O., Moeller-Hartmann, W., Heiss, W.-D. & Sobesky, J. MRI Perfusion Maps in Acute Stroke Validated With 15O-Water Positron Emission Tomography. *Stroke* **41,** 443–449 (2010).

18. Straka, M., Albers, G. W. & Bammer, R. Real-time diffusion-perfusion mismatch analysis in acute stroke. *J. Magn. Reson. Imaging JMRI* **32,** 1024–1037 (2010).

19. Sobesky, J. Refining the mismatch concept in acute stroke: lessons learned from PET and MRI. *J. Cereb. Blood Flow Metab.* **32,** 1416–1425 (2012).

20. Christensen S, Mouridsen K, Wu O, Hjort N, Karstoft H, Thomalla G, Röther J, Fiehler J, Kucinski T & Østergaard L. Comparison of 10 Perfusion MRI Parameters in 97 Sub-6-Hour Stroke Patients Using Voxel-Based Receiver Operating Characteristics Analysis. *Stroke* **40,** 2055–2061 (2009).

21. Jonsdottir, K. Y., Østergaard, L. & Mouridsen, K. Predicting tissue outcome from acute stroke magnetic resonance imaging: improving model performance by optimal sampling of training data. *Stroke J. Cereb. Circ.* **40,** 3006–3011 (2009).

22. 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.* **32,** 186–193 (2011).

23. Jespersen, S. N. & Østergaard, L. The roles of cerebral blood flow, capillary transit time heterogeneity, and oxygen tension in brain oxygenation and metabolism. *J. Cereb. Blood Flow Metab.* **32,** 264–277 (2012).

AFFIDAVIT

I, Michelle Livne, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic “Imaging-Based Predictive Modeling in Acute Ischemic Stroke”. I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My contributions in the selected publications for this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author of correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

_____ _____

Date Signature

Declaration of share in publications

Michelle Livne had the following share in the following publications:

Co-authorships (including co-first-authorships marked by an *):

Publication I, co-first-authorship:

Olivier Zaro-Weber*, **Michelle Livne***, Steve Z. Martin, Federico C. von Samson-Himmelstjerna, Walter Moeller-Hartmann, Alexander Schuster, Peter Brunecker, Wolf-Dieter Heiss and Jan Sobesky. „*Comparison of the 2 Most Popular Deconvolution Techniques for the Detection of Penumbral Flow in Acute Stroke."*

Stroke. 2015;46:2795-2799.

Contribution in detail: The co-first author Michelle Livne applied the DSC-MRI image post-processing using the two software PMA and Stroketool including manual selection of arterial-input-function (AIF) from the contra-lateral M1 segment, additionally as part of the image post-processing she applied smoothing, coregistration and reslicing of both DSC-MRI- and PET data, she prepared the grey-matter, hemispheric- and penumbral flow masks, she conducted the receiver-operating-characteristics (ROC) curve analysis to numerically assess the performance of the different perfusion-maps in penumbral-flow prediction and wrote the first draft of the paper together with VIM and OZW.

First authorships:

Publication II, first authorship:

Michelle Livne, Tabea Kossen, Vince I. Madai, Olivier Zaro-Weber, Walter Moeller-Hartmann, Kim Mouridsen, Wolf-Dieter Heiss and Jan Sobesky. *"Multiparametric Model for Penumbral Flow Prediction in Acute Stroke."*

Stroke 2017;48:00-00.

Contribution in detail: The first author Michelle Livne created the concept of the study together with JS, she applied the full imaging post-processing including perfusion maps derivation from the raw images, manual selection of arterial-input-functions (AIF), coregistration, reslicing as well as grey-matter, hemispheric- and penumbral flow masks preparation. She performed and/or supervised TK in the models construction including multicollinearity analysis, application of regularized and unregularized logistic-regression and application of performance analysis using different measures of accuracy rate, volumetric impact and receiver-operating-characteristics (ROC) curve analysis, she applied the statistical tests, wrote the first draft of the paper and coordinated the submission process.

Publication III, first authorship:

Michelle Livne, Jens K Boldsen, Irene K Mikkelsen, Jochen B Fiebach, Jan Sobesky and Kim Mouridsen. *"Boosted Tree Model Reforms Multi-Modal Magnetic Resonance Imaging Infarct Prediction in Acute Stroke."*

Stroke 2018; epub March 14, 2018 https://doi.org/10.1161/STROKEAHA.117.019440

Contribution in detail: The first author Michelle Livne created the concept of the study together with KM, she applied the data subsampling, conducted the full analysis of the predictive modeling including construction of the linear model as well as the nonlinear model using the extreme gradient boosting (XGBoost) package, she applied optimization of the models and assessed the models performance using two different cross-validation approaches, i.e. leave-one-out and 5-folds, using accuracy measure including volumetric implications and receiver-operating-characteristics (ROC) curve analysis, she applied the statistical tests, wrote the first draft of the paper and coordinated the submission process.

Signature, date and stamp of the supervising University teacher

_____

Signature of the doctoral candidate

_____

PRINT COPIES OF SELECTED PUBLICATIONS

Publication I

co-first-authorship

Olivier Zaro-Weber*, **Michelle Livne***, Steve Z. Martin, Federico C. von Samson-Himmelstjerna, Walter Moeller-Hartmann, Alexander Schuster, Peter Brunecker, Wolf-Dieter Heiss and Jan Sobesky. „*Comparison of the 2 Most Popular Deconvolution Techniques for the Detection of Penumbral Flow in Acute Stroke."*

Stroke. 2015;46:2795-2799.

DOI: http://doi.org/10.1161/STROKEAHA.115.010246

Publication II

first authorship

Michelle Livne, Tabea Kossen, Vince I. Madai, Olivier Zaro-Weber, Walter Moeller-Hartmann, Kim Mouridsen, Wolf-Dieter Heiss and Jan Sobesky. *"Multiparametric Model for Penumbral Flow Prediction in Acute Stroke."*

Stroke 2017;48(7):1849-54.

DOI: http://doi.org/10.1161/STROKEAHA.117.016631

Publication III

first authorship

Michelle Livne, Jens K Boldsen, Irene K Mikkelsen, Jochen B Fiebach, Jan Sobesky and Kim Mouridsen. *"Boosted Tree Model Reforms Multi-Modal Magnetic Resonance Imaging Infarct Prediction in Acute Stroke."*

Stroke 2017; 49(4):912-18.

DOI: http://doi.org/10.1161/STROKEAHA.117.019440

CURRICULUM VITAE

"MEIN LEBENSLAUF WIRD AUS DATENSCHUTZRECHTLICHEN GRÜNDEN IN DER ELEKTRONISCHEN VERSION MEINER ARBEIT NICHT VERÖFFENTLICHT."

CURRICULUM VITAE

"MEIN LEBENSLAUF WIRD AUS DATENSCHUTZRECHTLICHEN GRÜNDEN IN DER ELEKTRONISCHEN VERSION MEINER ARBEIT NICHT VERÖFFENTLICHT."

COMPLETE LIST OF PUBLICATIONS

(Shared*) first and last authorships

1. **Michelle Livne**, Jens K Boldsen, Irene K Mikkelsen, Jochen B Fiebach, Jan Sobesky and Kim Mouridsen. *"Boosted Tree Model Reforms Multi-Modal Magnetic Resonance Imaging Infarct Prediction in Acute Stroke."*
   Stroke 2017; 49(4):912-18.

2. **Michelle Livne**, Tabea Kossen, Vince I. Madai, Olivier Zaro-Weber, Walter Moeller-Hartmann, Kim Mouridsen, Wolf-Dieter Heiss and Jan Sobesky. *"Multiparametric Model for Penumbral Flow Prediction in Acute Stroke."*
   Stroke 2017;48:00-00.

3. **Michelle Livne**, Vince I. Madai, Peter Brunecker, Olivier Zaro-Weber, Walter Moeller-Hartmann, Wolf-Dieter Heiss, Kim Mouridsen and Jan Sobesky, . *"A PET Guided Framework Supports a Multiple Arterial Input Functions Approach in DSC-MRI in Acute Stroke".*
   Journal of Neuroimaging. 2017;27(5):486-492.

4. Olivier Zaro-Weber*, **Michelle Livne***, Steve Z. Martin, Federico C. von Samson-Himmelstjerna, Walter Moeller-Hartmann, Alexander Schuster, Peter Brunecker, Wolf-Dieter Heiss and Jan Sobesky. „*Comparison of the 2 Most Popular Deconvolution Techniques for the Detection of Penumbral Flow in Acute Stroke."*
   Stroke. 2015;46:2795-2799.

Conference papers (selection)

1. 2017 International Stroke Conference, Houston, Texas, poster presentation "A Multi-Parametric Perfusion Model Improves Assessment of Penumbral Flow in Stroke Imaging"

2. 2015 European Stroke Organization Conference, Glasgow, UK, poster presentation
   "Cluster-based arterial input functions improve penumbral flow detection in acute stroke"

ACKNOWLEDGMENTS

I would like to express my deepest gratitude to my mentors and supervisors Professor Dr. med. Jan Sobesky, Professor Dr. med Jochen Fiebach and Professor Kim Mouridsen as well as Prof. Ronen Talmon with which we pursued a long collaboration. I thank them for their unconditional support of my work and my research career.

I would also like to thank all of my colleagues at the Centre for Stroke Research Berlin for the productive and fortunately often humorous working atmosphere. A special thank goes to my mentee Tabea Kossen, who was the most diligent, friendly and cooperative student I could have ever wished for.

I would like to thank my colleagues in CFIN, Aarhus University, who made the ongoing collaboration a great pleasure.

My last thank is dedicated to Vince Madai, who supported me both professionally and personally throughout the PhD. Thank you for teaching me so much, thank you for your endless support, thank you for believing in me. תודה וינס שלי!