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DISSERTATION

Improvements of Magnetic Resonance Imaging Techniques for Clinical Diagnosis in Cerebrovascular Disease

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Doctor of Philosophy in Medical Neurosciences
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ABBREVIATIONS

ACA	Anterior Cerebral Artery
ASL	Arterial Spin Labeling
ATDA	Arterial Transit-Delay Artifact
ATT	Arterial Transit Time
AUC	Area-under-the-curve
CBF	Cerebral Blood Flow
CT	Computed Tomography
CVR	Cerebrovascular Reserve Capacity
DSA	Digital Subtraction Angiography
DSC	Dynamic susceptibility-weighted contrast-enhanced
DWI	Diffusion-weighted Imaging
ECST	European Carotid Surgery Trial
ERB	Ethical Review Board
FLAIR	Fluid-Attenuated Inversion Recovery
ICA	Internal Carotid Artery
MCA	Middle Cerebral Artery
MMD	Moya-Moya-Disease
MPRAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NIHSS	National Institute of Health Stroke Scale
PASL	pulsed ASL
PCA	Posterior Cerebral Artery
PET	Positron Emission Tomography
ROC	Receiver-operating Characteristic
rSI	Relative Signal Intensity
SNR	Signal-to-Noise-Ratio
SPECT	Single Photon Emission Computed Tomography
T	Tesla
TRAIT	Treatment-Relevant Acute Imaging Target

SUMMARY

Abstract in English

Introduction

Cerebrovascular disease is a terrible medical and economic burden. Current diagnostic methods for cerebrovascular disease provide limited diagnostic information leading to low numbers of treated patients. Thus, we targeted diagnostic improvements in three subprojects, where improvements are warranted. Subproject 1: to develop quantitative MRI-biomarkers for the allocation of patients with acute stroke to the thrombolysis time window, Subproject 2: to increase the diagnostic accuracy of new MRI-based contrast-agent free perfusion methods, i.e. Arterial Spin Labeling (ASL), in chronic steno-occlusive disease and subproject 3: to develop new angiography methods at 7 Tesla MRI to improve stenosis detection and to replace invasive digital subtraction angiography (DSA) of patients with steno-occlusive disease.

Methods

In subproject 1, a retrospective analysis of a bicentric database was performed. Quantitative imaging values were analyzed in regression models and the allocation of patients to the thrombolysis time window was evaluated by ROC-curve analysis. In subproject 2, a prospective imaging study including patients with steno-occlusive disease was established and performed. The performance of ASL vs. standard MRI perfusion methods was analyzed with qualitative and quantitative methods. In subproject 3, a new magnetic resonance angiography technique at 7.0 Tesla was validated against standard MRI methods and gold-standard DSA.

Results

In seven publications, we could provide significant diagnostic benefits for each predefined imaging target. In subproject 1, we established a quantitative image-driven model, which allocated patients to the thrombolysis time window with unprecedented accuracy (2 publications). In subproject 2, we validated a highly reliable contrast-agent free perfusion method for patients with steno-occlusive disease (3 publications). In subproject 3, our new 7.0 Tesla angiography method performed better than standard MRI angiography and was able to replace gold standard DSA angiography in the pre-surgical workup of Moya-Moya-patients (2 publications).

Conclusion

The results of the present thesis provide significant advancements for MRI-based diagnosis in cerebrovascular disease. A direct benefit for patients can be anticipated in the diagnosis of acute stroke and for the assessment of perfusion status and vessel status in patients with steno-occlusive disease, especially Moya-Moya-disease.

Abstract in German

Einleitung

Zerebrovaskuläre Erkrankungen sind eine große Belastung für Patienten und Gesundheitssysteme. Aktuelle Diagnosestrategien in zerebrovaskulären Erkrankungen gewähren nur limitierte diagnostische Information, was zu einer geringen Zahl von optimal behandelten Patienten führt. In der hier präsentierten Doktorarbeit wurden daher drei imaging-basierte Zielgrößen definiert, bei deren Diagnose methodische Verbesserungen notwendig sind. Unser Ziel war in Subprojekt 1: Neue quantitative MRT-Biomarker für die Zuordnung von Patienten mit akutem Hirninfarkt zum Thrombolysezeitfenster zu entwickeln; in Subprojekt 2: die diagnostische Wertigkeit von konstrastmittelfreien MRT-Perfusionsbildgebungstechniken (Arterial Spin Labeling [ASL]) für die Darstellung von Steno-okklusionen zu verbessern und in Subprojekt 3: eine neuartige Angiographie-Technik für die Darstellung von Steno-okklusionen bei einer Feldstärke von 7 Tesla im Vergleich zum Gold-Standard digitale Subtraktionsangiographie zu validieren.

Methoden

In Subprojekt 1 führten wir eine retrospektive Analyse einer bizentrischen Datenbank durch. Quantitative Werte wurden fortgeschrittenen Regressionsmodellen zugeführt und die Zuordnung zum Thrombolysezeitfenster mittels ROC-Kurven-Analyse ermittelt. In Subprojekt 2 wurden Patienten mit Steno-Okklusionen der Hirngefäße in eine prospektive Imaging-Studie eingeschlossen. Die Wertigkeit von neuartigen ASL-Techniken im Vergleich zur Standard-MRT-Perfusionsbildgebung wurde quantitativ und visuell ermittelt. In Subprojekt 3 wurde eine neuartige Angiographiemethode bei 7.0 Tesla mit dem klinischen MRT-Standard und dem Goldstandard DSA visuell verglichen.

Ergebnisse

In insgesamt sieben Veröffentlichungen konnten wir signifikante Verbesserungen für jede vordefinierte diagnostische Zielgröße erreichen. In Subprojekt 1 konnten wir ein Bilddaten-basierendes Modell validieren, welches Patienten mit bisher unerreichter Genauigkeit dem Thrombolysezeitfenster zuordnen kann (2 Publikationen). In Subprojekt 2 konnten eine neuartige ASL-Sequenz mit hoher diagnostischer Zuverlässigkeit für die Bildgebung bei zerebro-vaskulären Erkrankungen validieren (3 Publikationen). In Subprojekt 3 schließlich konnten wir in 2 Veröffentlichungen zeigen, dass die neue 7.0 Tesla Angiographie-Methode Gefäßveränderungen

zuverlässiger zeigen kann als das jetzige klinische Standardverfahren und in Moya-Moya-Patienten Gefäßveränderungen gleichwertig zum Gold-Standard DSA darstellen konnte.

Schlussfolgerung

Die Ergebnisse dieser Doktorarbeit führten zu signifikanten Verbesserungen der Diagnostik bei zerebrovaskulären Erkrankungen gegenüber den aktuell verfügbaren diagnostischen Möglichkeiten. Es kann erwartet werden, dass ein direkter diagnostischer Vorteil für die Behandlung von Patienten mit akutem Schlaganfall und chronischen Gefäßprozessen entstehen wird.

Introduction

Cerebrovascular disease is a terrible medical and economic burden. Stroke, the most acute consequence of cerebrovascular disease, is a leading cause of death and disability in first world countries[1]. However, only about 10% of patients receive causal treatment, i.e. thrombolysis. On the other hand, developing chronic steno-occlusive disease, e.g. with atherosclerotic etiology or as an effect of Moya-Moya-Disease, is a diagnostic challenge, where only potentially harmful invasive diagnostic techniques are available to retrieve necessary diagnostic information. Consequently, diagnostic advances in cerebrovascular imaging are highly warranted. Neuroimaging plays a key role in this endeavor and magnetic resonance imaging (MRI) is a common neuroimaging method due to its inherent advantages: It is non-invasive, offers high spatial resolution and has no known long-lasting harmful effects on patients. Improved and new MRI neuroimaging methods have the potential a) to increase the validity of current diagnostic tools, b) to lead to new diagnostic tools and c) to replace current invasive and potentially risky diagnostic measures. The key question is, however, which diagnostic targets should be the aim of methodological advances. The international research community has developed a terminology to define diagnosis relevant imaging targets in acute stroke, so called "Treatment-Relevant Acute Imaging Targets" (TRAITS)[2]. These TRAITS serve as markers for inclusion or exclusion of patients into certain treatment protocols. This definition is beneficial, as it focuses imaging research on goals which are directly beneficial for patients. While TRAITS were predominantly developed for the use in acute stroke, a use in chronic forms of cerebrovascular disease such a steno-occlusive disease or Moya-Moya-disease is justified, as the imaging targets are similar. For the current thesis we defined three different TRAITS in three subprojects, where diagnostic improvements are warranted, and analyzed them in 7 publications:

1) Subproject 1: Identification of patients with acute stroke eligible for thrombolysis in the <4.5-hour window by neuroimaging (2 publications)
2) Subproject 2: Perfusion status, i.e. measurement of CBF in steno-occlusive disease (3 publications) and
3) Subproject 3: Vessel imaging in steno-occlusive disease and Moya-Moya-disease (2 publications)

1. Identification of patients with acute stroke in the <4.5-hour window by neuroimaging

Patients with acute ischemic stroke are not eligible for thrombolytic treatment, if the time-from-stroke-onset is not known[3]. This applies to up to 25% of ischemic stroke patients. Thus, there is a need for clinically applicable methods to predict the current thrombolysis time window of <4.5 h after stroke. Qualitative visual MR-imaging biomarkers, such as the DWI-FLAIR mismatch (DWI: diffusion weighted imaging; FLAIR: fluid attenuated inversion recovery) have been introduced for this purpose[4]. A promising alternative are quantitative methods, where relative signal intensity (rSI) values are applied. These quantitative approaches are advantageous, as they are less user-biased and offer the possibility of an automated analysis. However, results for rSI biomarkers are inconsistent to date[5,6]. Thus, in the present work we aimed to clarify the relationship of DWI and FLAIR based quantitative biomarkers to the time-from-stroke-onset (Publication III) and to establish these biomarkers as valid alternatives to visual techniques in determining stroke age in patients with acute stroke (Publication I).

2. Perfusion status in steno-occlusive disease

The measurement of brain perfusion, i.e. cerebral blood flow (CBF) in MRI, is an important diagnostic method in patients with cerebrovascular disease[7]. Dynamic susceptibility weighted contrast-enhanced (DSC) MR-imaging is a clinical standard of CBF-measurement. It is fast and offers a reliable estimate of CBF. However, the main drawback of DSC-MR imaging is the application of a gadolinium-based contrast agent. This requires invasive measures, can cause anaphylactic reactions and patients with renal insufficiency cannot be measured owing to the possibility of nephrogenic systemic sclerosis. Also, repeated measurements are difficult to perform owing to limited clearance of gadolinium contrast agents from the blood. Arterial spin labeling (ASL) is a noninvasive alternative MRI technique to assess brain perfusion[8]. In contrast to DSC-MRI, ASL offers unique advantages: It is a noninvasive technique, can be used for repetitive measurements, and is suitable for all patients, also with contraindications to gadolinium-based contrast agents. ASL, however, needs to be available in the clinical setting, e.g., as a product sequence from a vendor, and must offer a diagnostic value similar to DSC-MRI in various neurologic diseases. Among those, steno-occlusive disease is especially challenging for ASL owing to increased arterial transit times (ATTs). Increased ATTs require long delays between ASL-labeling and ASL-image acquisition to ensure the imaging of labeled blood in all voxels. However, as the labeled blood relaxes with the T1 of blood and tissue, the perfusion-weighted

signal and with it the signal-to-noise ratio (SNR) decrease comparably fast. The necessary long imaging delays may decrease the SNR below a critical level. Thus, ASL sequences must be validated for the use in cerebrovascular disease. This has the biggest clinical impact, if product-sequences are tested, as new findings can immediately be translated to the clinical setting. In the present thesis we optimized and validated two ASL-product sequences in steno-occlusive disease in direct comparison with the clinical standard DSC-MRI (Publications IV, V and VI)

3. Vessel imaging in steno-occlusive disease and Moya-Moya-disease at Ultrahigh-fields of 7.0 Tesla

Vessel pathology in patients with cerebrovascular disease is of high clinical relevance, as it influences disease stage, stroke risk and therapeutic options[9]. Time-of-Flight (TOF) MRI angiography (MRA) at 3.0 Tesla (T) is the clinical MRI standard for vessel evaluation. At 7.0 T, TOF-MRA benefits from the higher field strengths leading to increased spatial resolution and improved depiction of small blood vessels. However, there are also challenges for 7.0 T TOF-MRA imaging. Radio frequency power deposition constraints reduce brain coverage, cause long scanning durations and make 7.0 T MRA-TOF not suitable in the clinical practice[10]. Thus, there is a need for alternative vessel imaging techniques at 7.0 T. Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequences, which are usually used for structural parenchyma imaging, show high signal-intensity of arteries at 7.0 T similar to the TOF-technique[11]. Thus, MPRAGE-MRA at 7.0 T was introduced as a new technique for whole-brain vessel imaging and a good sensitivity to detect general vessel pathologies and cerebral aneurysms was suggested. A validation in cerebrovascular disease, however, is not available to date. Thus, we examined the diagnostic potential of MPRAGE-MRA at 7.0 T in patients with steno-occlusive disease in comparison to the current clinical standard, TOF-MRA at 3.0 T (Publication II). In a second step, we aimed to show that this new technique can replace invasive and potentially harmful digital subtraction angiography (DSA) in the pre-surgical routine examination of Moya-Moya-patients (Publication VII).

Goals

The following measures are necessary to improve the diagnostic possibilities in cerebrovascular disease in the clinical setting: to improve current diagnostic tools and to provide new diagnostic tools as replacement for current invasive and potentially risky methods. Thus, in the present thesis we set out to develop and improve MRI-based diagnostic measures in cerebrovascular disease. In a multidisciplinary approach and clinical imaging studies we aimed to

a) Subproject 1: develop quantitative MRI-biomarkers to allow allocation of patients with acute stroke to the thrombolysis time window
b) Subproject 2: increase the accuracy of current MRI-based contrast-agent free perfusion methods in chronic steno-occlusive disease, and
c) Subproject 3: develop new angiography methods at 7.0 Tesla MRI to improve stenosis grading and to replace risky digital subtraction angiography (DSA) in the imaging of patients with steno-occlusive disease.

Methods

As this thesis encompasses seven 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 detailed 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 III), the Charité-Universitätsmedizin Berlin (Publications I, III, IV V, VI) and by the authorized governmental Berlin state ERB and the German state authority (Federal Institute for Drugs and Medical Devices) (Publications II and VII).

Clinical study populations

For *Subproject 1* (Publications I and III), a dual center retrospective observational imaging study was performed. Imaging data was acquired from two stroke imaging databases: 1) University of Cologne, neurological imaging data base. Stroke patients available for the analysis were imaged consecutively between 2/2002 and 5/2004, 430 patients in total; 2) Charité-Universitätsmedizin Berlin, stroke imaging data base. Stroke patients available for the analysis were imaged consecutively between 3/2008 and 8/2010, 347 patients in total. Databases were screened and patients were included according to the following main criteria: 1) clinically proven stroke, 2) confirmed symptom onset <12 h, 3) confirmed unilateral stroke lesion in DW-imaging, 4) available FLAIR imaging. Main exclusion criteria were: 1) insufficient image quality, 2) incomplete clinical data. Due to slightly differing inclusion criteria, e.g. it was shown between the works in the literature that infratentorial stroke should be treated as a separate entity, 97 patients were included in Publication III and 82 patients in Publication I.

For *Subproject 2* (Publications IV, V and VI), an observational prospective imaging study (PEGASUS, WHO international Clinical trials registry No. DRKS00003198) was performed. Patients with steno-occlusive disease were recruited at the Clinic of Neurology or the Neurological outpatient clinic of the Charité between September 2013 and March 2015. Inclusion criteria were as follows: (1) stenosis > 70% of the internal carotid artery (ICA) or middle cerebral artery (MCA) according to the European Carotid Surgery Trial (ECST) criteria, (2) aged 18-80, and (3) clinically and hemodynamically stable status. Prior to the MR measurement, the grading of stenosis was confirmed via duplex sonography and/or computed tomography/MRI angiography. Exclusion

criteria were: (1) magnetic implants, (2) claustrophobia, (3) aphasia or reduced level of consciousness, (4) severe allergic reactions in the previous medical history, (5) allergic reactions against Gadolinium-based contrast agents in the past, (6) renal insufficiency (defined by a GFR under <30 mL/minute/173 m²), (7) pregnancy, (8) unstable clinical status, and (9) contralateral stenosis >50% (ECST criteria). For each patient, relevant clinical data were assessed prior to the MR measurement. In each study, different ASL-sequences were tested (PICORE-PASL-ASL; 3D-GRASE-PASL-ASL; 3D-GRASE-PASL-ASL with TOPUP-correction), so the following number of patients were included in the studies: Publication IV 13 patients, Publication V 43 patients, Publication VI 28 patients.

For *Subproject 3* (Publications II and VII), patients were included in a prospective imaging study (7.0 Tesla Ultra-High Field Project, "7UP-Study", WHO International Clinical Trials Registry No. DRKS00003193, http://apps.who.int/trialsearch/Trial.aspx?TrialID=DRKS00003193). Inclusion criteria were: (1) subacute/chronic ischemia or transitory ischemic attack (TIA), (2) age 18–80 years, (3) ability to give informed consent and (4) legal competence. Exclusion criteria were: (1) cardiac pacemakers or any other electronic implants, (2) any metallic implant, (3) pregnancy or breast feeding period, (4) claustrophobia, (5) chronic or episodic vertigo, (6) retinal diseases and (7) dental bridges and more than two metallic dental crowns in a row. Neurological status was assessed using the National Institute of Health Stroke Scale (NIHSS) at time of admission for index stroke and before MR imaging. Imaging was performed first at 3.0 T, immediately followed by 7.0 T. A neurologist specialized in stroke supervised the patients during MRI. In total, 18 patients were eligible for Publication II and 6 patients for Publication VII, which was performed on the subset of Moya-Moya-patients (n=6).

Imaging Hardware

For *Subproject 1* (Publications I and III), MR-imaging was performed at 1.5 T on a Philips Gyroscan Intera Master whole-body system (Philips Medical Systems, Best, The Netherlands). At 3.0 T, a Magnetom Tim Trio whole-body system (Siemens Healthcare, Erlangen, Germany) was used.

For *Subproject 2* (Publications IV, V and VI), MR-imaging was performed on a 3.0 T whole-body system (Magnetom Trio, Siemens Healthcare, Erlangen, Germany) using a 12-channel receive radio frequency (RF) coil (Siemens Healthcare, Erlangen, Germany) tailored for head imaging.

For *Subproject 3* (Publications II and VII), MR-imaging was performed on a 3.0 T whole-body system (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) using a 12 channel receive RF coil (Siemens Healthcare, Erlangen, Germany) tailored for head imaging. At 7.0 T, a whole body system (Magnetom 7.0 T, Siemens Healthcare, Erlangen, Germany) equipped with a 60 cm magnet bore (Magnex Scientific, Oxford-shire, UK) and an Avanto gradient system (Siemens Healthcare, Erlangen, Germany) was used together with a 1/24-channeltransmit/receive coil (Model NM 008-23.0-7.0S, Nova Medical, Wakefield, MA, USA) designed for head imaging.

Study methodology

As this thesis encompasses seven publications, where each publication deals with complex methods validation with unique methodology, 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 referenced in the publication overview on page 40. Detailed information about the applied methods for each publication can be found in the print copies of each publication following page 29.

Subproject 1, Publication I: Patients from two centers with proven stroke with onset <12 hours were retrospectively included. The DWI lesion was segmented and overlaid on ADC and FLAIR images. Mean and standard deviation (SD) of relative signal intensity (rSI) values were calculated as the following ratio: (mean ROI value/mean value of the unaffected hemisphere). The visual DWI-FLAIR mismatch was evaluated for comparison. Prediction of the thrombolysis time window was assessed by the area-under-the-curve (AUC) derived from receiver-operating-characteristic (ROC) curve analysis. Association of age, NIHSS, MRI field strength, lesion size, vessel occlusion and Wahlund-Score with rSI was investigated and the models were adjusted and stratified.

Subproject 1, Publication III: In a dual-center MR-imaging study we retrospectively included patients with acute stroke and time-from-stroke onset <12 hours. DWI- and FLAIR-maps were coregistered. The largest lesion extent in DWI was defined for further analysis. FLAIR-lesions were identified by 3 raters, marked as regions-of-interest (ROIs) and mirrored on the DW-images. Circular ROIs were placed within the DWI-lesion and labeled according to the FLAIR pattern (FLAIR+ or FLAIR2). ROI-values were normalized by a ROI of the unaffected hemisphere. Adjusted and non-adjusted receiver operating-characteristics (ROC) curve analysis on patient level was performed to analyze the ability of a DWI- and ADC-rSI threshold to predict the presence of

FLAIR-lesions. Spearman correlation and adjusted linear regression analysis were performed to analyze the relationship between DWI-intensity and time-from-stroke-onset.

Subproject 2, Publication IV: A pulsed ASL (PASL) sequence combined with a 3D-GRASE readout at multiple inflow times (multi-TI) was used to explore correction for susceptibility distortions using the FMRIB Software Library (FSL) implemented tool TOPUP. We performed qualitative (three expert raters) comparison of the diagnostic accuracy and quantitative (volume of interest [VOI]-based) correlation of ASL and DSC imaging in 13 patients with chronic steno-occlusive disease.

Subproject 2, Publication V: Patients with unilateral stenosis >70% of the internal carotid or middle cerebral artery (MCA) at 3 Tesla were included. We compared pulsed arterial spin labeling (PASL) at multiple inflow times (multi-TIs) with the clinical standard dynamic susceptibility-weighted contrast-enhanced imaging–magnetic resonance imaging (DSC-MRI). We performed qualitative (assessment by three expert raters) and quantitative (region of interest (ROI)/volume of interest (VOI) based) comparisons.

Subproject 2, Publication VI: Patients with unilateral stenosis >70% of the internal carotid or middle cerebral artery (MCA) at 3 Tesla were included. We compared a clinical pulsed ASL sequence (PICORE) with the clinical standard dynamic susceptibility-weighted contrast-enhanced imaging–magnetic resonance imaging (DSC-MRI). Images were acquired on a 3T MRI system and qualitatively analyzed by 3 raters. For a quantitative analysis, cortical ROIs were placed in co-registered ASL and DSC images. Pooled data for ASL-cerebral blood flow (CBF) and DSC-CBF were analyzed by Spearman's correlation and the Bland-Altman (BA)-plot.

Subproject 3, Publication II: In a World Health Organization-registered and prospective imaging trial, patients with stroke and/or Moya-Moya disease were included. TOF-magnetic resonance angiography (MRA) was performed at 3.0 T and magnetization-prepared rapid-acquisition gradient echo (MPRAGE)-MRA at 7.0 T. Two radiologists rated the MRAs independently for overall quality and local arterial segment visualization. The identification of steno-occlusive pathology was reported for each protocol.

Subproject 3, Publication VII: In a World Health Organization-registered and prospective imaging trial, patients with Moya-Moya-Disease were investigated at 7.0 T magnetization-prepared rapid-acquisition gradient echo (MPRAGE)-MRA and time-of-flight (TOF)-MRA, 3.0 T TOF-MRA, in

comparison with digital subtraction angiography (DSA). The identification of steno-occlusive pathology was reported for each protocol and compared visually.

Results

Subproject 1

The goal of Project 1 was to develop quantitative MRI-biomarkers to allow allocation of patients with acute stroke to the thrombolysis time window.

A prerequisite of a biomarker for the thrombolysis time window is an association with time-from-stroke-onset. In a first step (*Publication III*), we indeed showed that relative signal intensities (rSIs) based on DW-imaging were correlated with time-from-stroke-onset using both 1.5 Tesla and 3 Tesla MRI (figure 1). Additionally, we showed that DWI-rSI was able to predict the presence of FLAIR lesions. These findings argue that DWI-rSI contains information about time-from-stroke-onset and stroke progression.

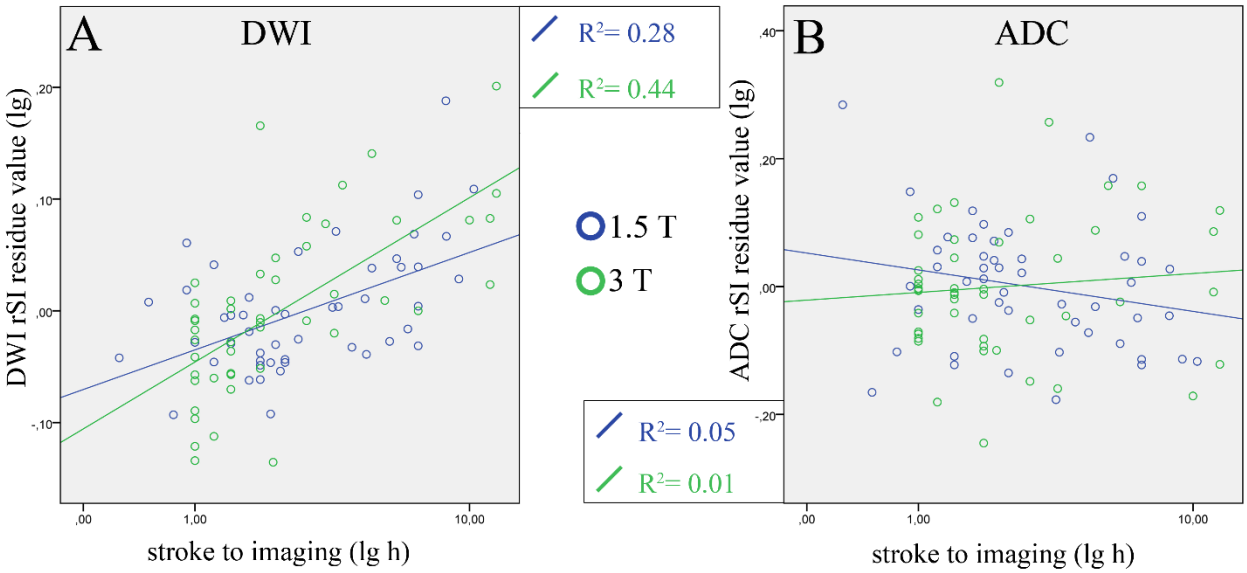

Figure 1: Adjusted linear regression analysis to evaluate the association of relative DWI-intensity and time-from-stroke-onset. At both 1.5 T (blue circles) and 3 T (green circle) a significant association was found for DWI (A) with moderate adjusted Rsquare values (1.5 T: 0.28; 3 T: 0.44). Adjusted correlation (Spearman's rank correlation) was: 1.5 T = 0.45 (p,0.001), 3 T = 0.69 (p,0.001). For ADC (B), no association between ADC-rSI and time-from-stroke-onset was found. Source of the image: Madai, Vince I., et al. "DWI intensity values predict FLAIR lesions in acute ischemic stroke." PloS one 9.3 (2014): e92295.

In the following step (*Publication I*), we evaluated whether rSIs based on DWI and FLAIR-imaging can predict the thrombolysis time window. We included easy to obtain clinical-radiological parameters in the prediction models.

The unadjusted rSI measures DWI-mean and DWI-standard deviation (SD) showed the highest AUCs (AUC 0.86; 0.87).

After adjustment for clinical–radiological covariates the results significantly improved for FLAIR-mean (0.87) and DWI-SD (0.91).

The best prediction results for single rSIs were found for the final stratified and adjusted models of DWI-SD (0.94) and FLAIR-mean (0.96). A multivariable DWI-FLAIR model performed equally well (0.95). The adjusted visual DWI-FLAIR mismatch performed equally without a significant difference (0.89). ADC-rSIs showed only fair performance in all models.

In conclusion, quantitative DWI and FLAIR MRI biomarkers and the visual DWI-FLAIR mismatch provide very good prediction of the thrombolysis time window in acute stroke, when clinical–radiological parameters are included in the prediction models.

Subproject 2

The goal of this subproject was to evaluate the performance of clinically available arterial-spin-labeling-techniques in patients with steno-occlusive disease in comparison with the clinical standard DSC-MR-imaging (*Publications IV, V and VI*).

First, we evaluated the performance of a clinical product sequence with single-time-point imaging (*Publication VI*). We found that about 1/3 of patient studies were uninterpretable due to motion artifacts (11 of 28 patients). Of the remaining 17 patients, 71% showed signs of a so called arterial transit delay artifact (ATDA) owing to delayed tracer arrival (figure 2). As ATDA plays no role in DSC-MR imaging, we found only a weak correlation of DSC-relCBF and ASL-relCBF ($r = 0.24$) and a large spread of values in the BA-plot.

In the next step (*Publication V*), we tested an ASL-sequence, which is also clinically available, but can correct for delayed arrival by measurements at multiple time points (multi-TI PASL-GRASE). In 43 patients, multi-TI PASL-GRASE showed perfusion alterations with moderate accuracy in the qualitative analysis. Additionally, moderate correlation coefficients were found for the MCA territory (ROI based: $r = 0.52$, VOI based: $r = 0.48$) in the quantitative analysis. Another main finding was that in the anterior cerebral artery (ACA) territory, a readout related right-sided susceptibility artifact impaired the correlation (ROI based: $r = 0.29$, VOI based: $r = 0.34$). In contrast to PICORE-PASL, ATDAs were found only in 12% of patients and thus the correlations highly improved. In conclusion, multi-TI PASL-GRASE can correct for arterial transit delay in

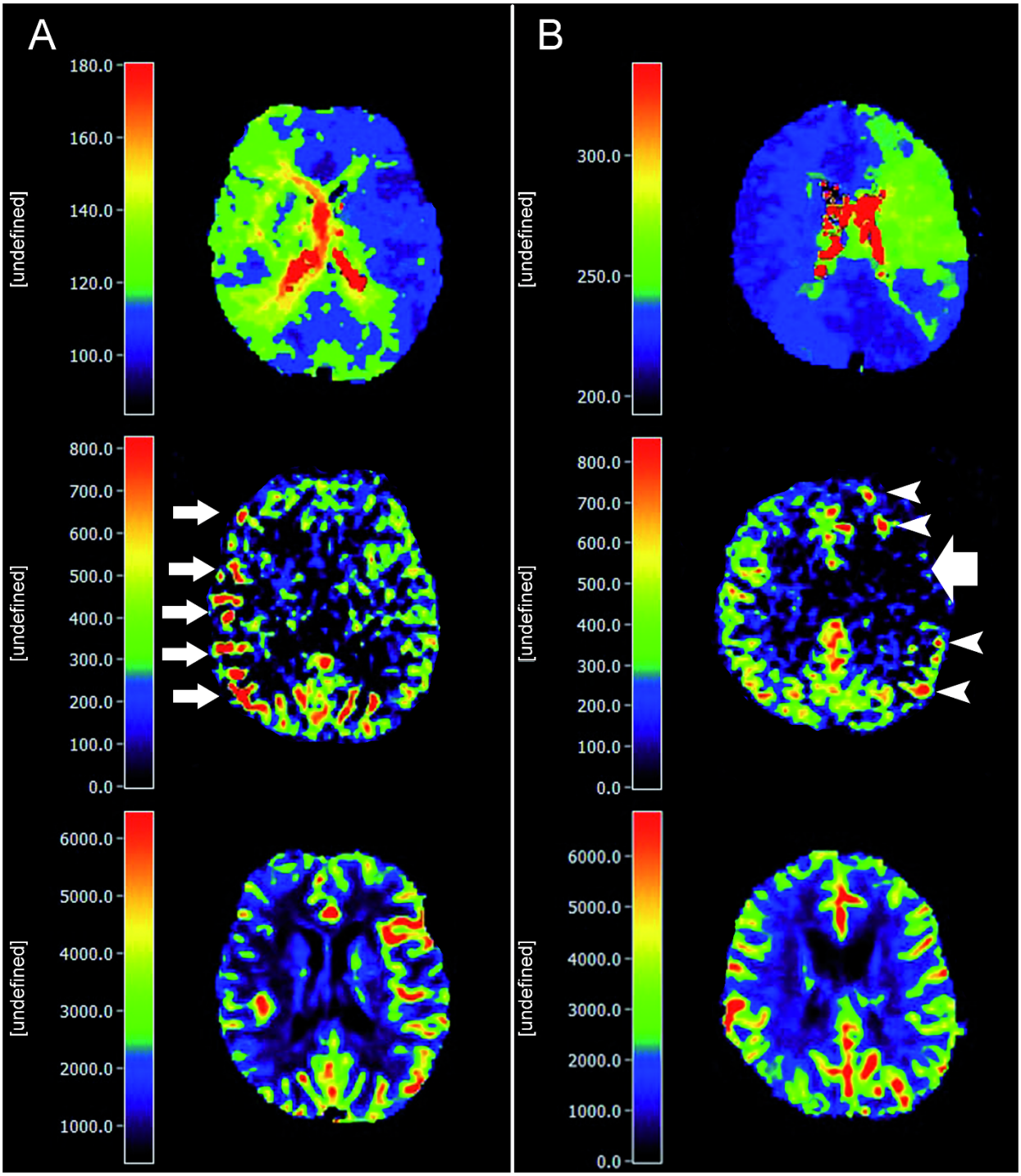

Figure 2: Exemplary patients showing blood arrival delay effects in ASL imaging.
A) 66-year-old female, occlusion of the right ICA. The TTP image shows a visible ipsilateral delay (relTTP = 0.8 sec). In the ASL image, hyperintense arterial transit delay artifacts are seen (small white arrows). On the reference DSC-CBF map, a hypoperfusion in the affected hemisphere is present. B) 45-year-old female, occlusion of the left middle cerebral artery. In the ASL image, a hypointensity is seen in the area affected by delay (large white arrow, relTTP = 1.5 sec). In contrast, no apparent changes are present in the DSC-CBF map. In patient A, a moderate blood transit delay leads to the presence of hyperintense ADTA. The more severe delay in patient B might explain the hypointense ADTA surrounded by hyperintense areas in its borderzone as a sign of collateral macrovessels. All slices are coregistered. The scales do not represent absolute values. Source of the image and the legend: Mutke, Matthias A., et al. "Clinical evaluation of an arterial-spin-labeling product sequence in steno-occlusive disease of the brain." PloS one 9.2 (2014): e87143.

patients with long ATTs and provides improved results compared to the previously investigated single-TI product sequence.

In the final step *(Publication IV*), we evaluated if the susceptibility correction algorithm TOPUP, which is implemented in the widely used FSL-imaging package, can correct for the susceptibility artifacts identified in publication V. Indeed, we found that distortion correction led to a strong increase in diagnostic precision of ASL compared to DSC in the anterior cerebral artery (ACA) perfusion territory, where the susceptibility artifact was most pronounced (specificity 8% vs. 75%). In the quantitative analysis, the correlation between ASL and DSC values increased, also here with the highest improvement for the ACA territory (for ACA, MCA and PCA territory: ACA: rho −0.22 vs. 0.71; MCA: rho 0.58 vs. 0.76; PCA: rho 0.58 vs. 0.63).

Subproject 3

In this subproject, it was our aim to validate a new magnetic resonance angiography (MRA) method to replace standard time-of-flight-MRA (TOF-MRA) for the imaging of cerebrovascular disease at 7.0 Tesla.

In the first step (*publication II*), we showed that an alternative MRA method based on magnetization prepared rapid gradient echo (MPRAGE) imaging provides better diagnostic accuracy for the imaging of steno-occlusion at 7.0 T than the clinical standard TOF-MRA at 3.0 T. In 18 patients (9 females; 6 patients with Moya-Moya-Disease), the image quality of 7.0 T MPRAGE-MRA was superior to 3.0 T TOF-MRA and we found better distinction of small structures compared to 3.0 T TOF-MRA. These findings were prominent in the proximal segments of the anterior cerebral artery (A1), middle cerebral artery (M1, M2), posterior cerebral artery (P1) and the posterior communicating artery. All steno-occlusive lesions could be visualized with the new technique. Most importantly, this could be achieved in a clinically feasible scanning time of 5 min and 40 seconds.

In a second step (*Publication VII*), we showed that 7.0 T MPRAGE-MRA can replace potentially harmful digital subtraction angiography (DSA) in the pre-surgical workup of Moya-Moya-patients prior to vessel surgery. In the subset of 6 patients with Moya-Moya-disease, all steno-occlusions visualized with the gold standard DSA could be visualized with 7.0 T MPRAGE MRA. Additionally, the visualization of the donor vessels for bypass surgery was successful with the new technique.

Discussion

For this PhD thesis, we identified three TRAITs, where improvements of clinically available methods are needed for better and safer diagnosis in cerebrovascular disease. In seven publications, we achieved significant improvements for all three TRAITs. 1) Advanced quantitative DWI and FLAIR models allow the allocation of patients to the thrombolysis time window with unprecedented accuracy. 2) New ASL-techniques, which entirely avoid exogenous contrast agents like Gadolinium, allowed the measurement of perfusion in patients with steno-occlusive disease with high clinical validity and unprecedented correlation to standard perfusion imaging. And lastly, 3) we could show that a new technique, MPRAGE-MRA at 7.0 Tesla, provides improved vessel imaging compared to the current clinical standard and may even replace the risky gold standard DSA, e.g. in the pre-surgical work-up of Moya-Moya-patients.

These results are very encouraging for the use of MRI for diagnosis in cerebrovascular disease. MRI is intrinsically one of the safest diagnostic methods as it is radiation free and no long-term side effects of short term magnetic field exposure are known.

In acute stroke, neuroimaging is a necessity to rule out bleeding. Due to lower costs of imaging and hardware, CT-imaging is the most widespread modality for diagnosis in acute stroke[7]. Our findings suggest, however, that with advanced MRI-methods more patients could receive causal treatment for stroke than to date, as a significant number of wake-up strokes could be included. Not only would this lead to a medical benefit for patients. It has also been shown in a model of wake-up stroke that the current visual DWI-FLAIR mismatch is already a cost-effective treatment option[12]. With the much higher accuracy of our quantitative models, this cost-effectiveness should even increase. Thus, next to medical benefits also economic benefits can be anticipated. It should be noted that the patient sample in our study was only moderate (n=82). However, our results have been confirmed in a recent retrospective study with a larger patient sample[13]. Nonetheless, our models should be confirmed in a prospective study in the near future.

In chronic steno-occlusive disease, the diagnostic options are limited to date. Ideally, repeated examinations of the cerebrovascular reserve capacity (CVR) would give the treating physicians the ideal knowledge-base to decide on further treatment[14]. CVR, however, can only be measured indirectly by ultrasound or by potentially harmful radiation employing methods such as SPECT or PET. Thus, the knowledge about CVR is either limited or full knowledge about CVR is restricted to high risk patients, where the advantages of the radiating methods outweigh the disadvantages. Here, our results are highly promising. We have validated an ASL perfusion imaging technique which leads to very reliable perfusion estimates in patients with prolonged blood transit arrival

times. As ASL employs no exogenous contrast agent, no harmful side effects can occur. Several publications have suggested that ASL can be used to measure CVR, e.g. in [15]. In these publications, however, the employed ASL-methods were not clinically approved sequences. In contrast, our analyzed sequence is the product sequence of one of the leading manufacturers of MR-scanners in the world. Thus, the development of a CVR-ASL techniques based on our results could be readily employed in the clinical setting and benefit patients in the clinical routine.

Imaging at 7.0 Tesla provides unprecedented spatial resolution. However, it is a new technology with inherent challenges, such as SAR-restrictions. Thus, new methods need to be tailored to specific clinical questions. In the present thesis, we validated a new magnetic resonance angiography technique, which provides better imaging quality than the current clinical MRI standard and was able to provide diagnostic information equal to gold standard DSA-imaging in pre-surgical Moya-Moya-patients. This is very encouraging for the use of 7.0 Tesla MRI in the clinical setting in patients with cerebrovascular disease, as it was announced recently that the first clinically approved 7.0 Tesla systems will be available soon. Currently, however, the availability of 7.0 Tesla MRI is mostly limited to research patients. Additionally, recruitment of patients for 7.0 Tesla MRI studies is very challenging due to very strict safety regulations. Also here, a broader use can be anticipated with clinically approved 7.0 Tesla MRI systems.

In conclusion, the results of the present thesis provide significant advancements for MRI-based diagnosis in cerebrovascular disease. A direct benefit for patients can be anticipated in the diagnosis of acute stroke and for the assessment of perfusion status and vessel status in patients with steno-occlusive disease.

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AFFIDAVIT

I, Vince Istvan Madai, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic “Improvements of Magnetic Resonance Imaging Techniques for Clinical Diagnosis in Cerebrovascular Disease”. 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.

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Date Signature

Declaration of share in publications

Vince Istvan Madai had the following share in the following publications:

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Cerebrovascular Diseases. 2016;42(1-2):57-65.

> **Contribution in detail:** The first author Vince I. Madai created the concept of the study together with JS, performed and/or supervised the image analysis of all patients, coordinated the statistical analysis by UG and SKP, wrote the first draft of the paper and coordinated the submission process.

Publication II, first authorship:

Madai, Vince I., von Samson-Himmelstjerna FC, Sandow N, Weiler F, Bauer M, Vajkoczy P, Günther M, Dusek P, Von Gottberg P, Niendorf T, Wuerfel J, Sobesky J. *Ultrahigh-field MPRAGE Magnetic Resonance Angiography at 7.0T in patients with cerebrovascular disease.*

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> **Contribution in detail:** The first author Vince I. Madai created the concept of the study together with JS, wrote the 7T study proposal according to German and EU medical product law, modified and tested the MPRAGE-MRA sequence with FCvH, recruited all patients, measured all patients at 3T and 7T, coordinated the visual analysis by JW and PvG, performed the statistical analysis, wrote the first draft of the paper and coordinated the submission process.

Publication III, first authorship:

Madai, Vince I., Ivana Galinovic, Ulrike Grittner, Olivier Zaro-Weber, Alice Schneider, Steve Z. Martin, Federico C. v. Samson-Himmelstjerna, et al. *"DWI Intensity Values Predict FLAIR Lesions in Acute Ischemic Stroke."*

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Journal of Neuroimaging. 2016 Jul;26(4):436-44.

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PLoS ONE. 2014 Feb 6;9(2):e87143.

Contribution in detail: The co-first author Vince I. Madai created the concept of the study together with JS and MAM, wrote the study proposal together with JS and MAM, supervised MAM in measuring the patients/analyzing the imaging data/performing the statistical analysis and wrote the first draft of the paper.

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Journal of Stroke and Cerebrovascular Diseases. 2016 Jun;25(6):1544-51.

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Signature of the doctoral candidate

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PRINT COPIES OF SELECTED PUBLICATIONS

Publication I

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Madai, Vince I., Carla N. Wood, Ivana Galinovic, Ulrike Grittner, Sophie K. Piper, G.S. Revankar, Steve Z. Martin, Olivier Zaro Weber, Walter Moeller-Hartmann, Federico C. von Samson-Himmelstjerna, Wolf-Dieter Heiss, M. Ebinger, Jochen B. Fiebach and Jan Sobesky. *"Clinical-Radiological Parameters Improve the Prediction of the Thrombolysis Time Window by both MRI Signal Intensities and DWI-FLAIR Mismatch."*
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Journal of Neuroimaging. 2016 Jul;26(4):436-44.

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Publication V

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Publication VII

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CURRICULUM VITAE

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

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COMPLETE LIST OF PUBLICATIONS

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1. **Madai, Vince I.,** Carla N. Wood, Ivana Galinovic, Ulrike Grittner, Sophie K. Piper, G.S. Revankar, Steve Z. Martin, Olivier Zaro Weber, Walter Moeller-Hartmann, Federico C. von Samson-Himmelstjerna, Wolf-Dieter Heiss, M. Ebinger, Jochen B. Fiebach and Jan Sobesky. *"Clinical-Radiological Parameters Improve the Prediction of the Thrombolysis Time Window by both MRI Signal Intensities and DWI-FLAIR Mismatch."* **Cerebrovascular Diseases.** 2016;42(1-2):57-65.

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Sobesky. *"3D GRASE Pulsed Arterial Spin Labeling at Multiple Inflow Times in Patients with Long Arterial Transit Times: Comparison with Dynamic Susceptibility-Weighted Contrast-Enhanced MRI at 3 Tesla."* **Journal of Cerebral Blood Flow & Metabolism**. 2015 Mar;35(3):392-401.

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Conference papers (selection)

1. 2015 German Neurological Society Conference, Düsseldorf, Germany, oral presentation
   "Prediction of the Thrombolysis Time Window by Quantitative DWI and FLAIR Improves with Adjustment for Clinical Confounders"

2. 2015 European Stroke Organization Conference, Glasgow, UK, oral presentation
3. "Clinical Confounders Modify Performance of Imaging Biomarkers of Lesion Age in Acute Stroke"

4. 2014 "Neuroweek" (Neurowoche), Munich, Germany, oral presentation
5. "DWI relative signal intensity at 1.5 and 3 Tesla allows the allocation of patients with acute stroke to the thrombolysis time window"

6. 2014 European Stroke Conference, Nice, France, e-poster with oral presentation
7. "Comparison of MPRAGE and time-of-flight (TOF)-angiography in patients with cerebrovascular disease: a 3 Tesla and 7 Tesla study"

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