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DISSERTATION

Standardized T1w/T2w Ratio as a Marker of Microstructural Tissue Damage in Neurological Disorders /

Standardisierter T1w/T2w-Quotient als Marker für mikrostrukturelle Gewebeschäden bei neurologischen Erkrankungen

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Synopsis

List of Abbreviations

MRI	magnetic resonance imaging
T1w/T2w ratio	ratio of T1-weighted to T2-weighted images
MS	multiple sclerosis
NEDA-3	No Evidence of Disease Activity
DTI	diffusion tensor imaging
CIS	Clinically Isolated Syndrome
NAWM	normal-appearing white matter
MSA	multiple system atrophy
NAGM	normal-appearing gray matter
CSF	cerebrospinal fluid
BCAN	Berlin Center for Advanced Neuroimaging
FLAIR	Fluid-attenuated Inversion Recovery
VIMS	Visual Imaging in Multiple Sclerosis
ANTs	Advanced Normalization Tools
FSL	FMRIB Software Library
FLIRT	FMRIB's Linear Registration Tool
EDSS	Expanded Disability Status Scale
FAST	FMRIB's Automatic Segmentation Tool
ICARS	International Cooperative Ataxia Ranking Scale
AUC	area under the curve

Abstract (English)

Introduction

Microstructural tissue damage in neurological disorders is typically measured using advanced magnetic resonance imaging (MRI) techniques, such as diffusion-based or quantitative imaging, that require additional scan time and expertise in post-processing, limiting their feasibility in the clinical routine. The ratio of T1-weighted to T2-weighted images (T1w/T2w ratio) was proposed as an alternative to measure tissue microstructure, as it uses scans typically acquired in clinical routine and has simple post-processing. This dissertation investigates the feasibility of a standardized T1w/T2w ratio method and its sensitivity to microstructural tissue damage in multiple sclerosis (MS) and multiple system atrophy (MSA).

Methods

In Study I, the standardized and conventional T1w/T2w ratios in the gray and white matter were compared between 47 MS patients and healthy controls (matched for age and sex) and clinical correlates (e.g. lesion load, disease severity) were investigated. Study II investigated longitudinal changes in standardized T1w/T2w ratio in the white matter from the first clinical presentation of 102 MS patients and evaluated its association with cortical thickness and disease activity, defined using the No Evidence of Disease Activity (NEDA-3) criteria. Study III investigated whether standardized T1w/T2w ratio values in the middle cerebellar peduncle differed between 28 MSA patients and healthy controls matched for age and sex.

Results

The standardized T1w/T2w ratio was shown to reduce variability of white matter values and enhance sensitivity to normal-appearing white matter (NAWM) damage in MS patients (Study I). We showed that NAWM standardized T1w/T2w ratio values did not significantly differ from controls in early MS at first clinical presentation but that these values were significantly associated with increasing lesion volume and decreasing cortical thickness over time, mediated by disease activity (Study II). In MSA we showed that the middle cerebellar peduncle standardized T1w/T2w ratio had a high sensitivity and specificity to classify MSA patients compared to controls (Study III).

Conclusions

This dissertation demonstrates that the standardized T1w/T2w ratio is a valid and more sensitive marker of microstructural tissue damage compared to the conventional T1w/T2w ratio. Furthermore, the standardized T1w/T2w ratio can be used to investigate microstructural damage in neurological disorders such as MS and MSA, corroborating and expanding on findings from more established measures of microstructural damage, such as diffusion tensor imaging. The standardized T1w/T2w ratio represents an important and promising measure of microstructural damage in settings where additional scan time is limited or for retrospective studies where quantitative or diffusion-based MRI data are not available.

Abstract (Deutsch)

Einführung

Mikrostrukturelle Gewebeschäden bei neurologischen Erkrankungen werden typischerweise mit fortschrittlichen Magnetresonanztomographie-Techniken (MRT) wie diffusionsbasierte oder quantitative Verfahren gemessen, die zusätzliche Scan-Zeit und Expertise in der Nachbearbeitung erfordern, was ihre Durchführbarkeit in der klinischen Routine einschränkt. Das Verhältnis von T1-gewichteten zu T2-gewichteten Bildern (T1w/T2w-Verhältnis) wurde als Alternative zur Messung der Gewebemikrostruktur vorgeschlagen, da es Scans verwendet, die im klinischen Alltag aufgenommen werden und eine einfache Nachbearbeitung ermöglichen. Diese Dissertation untersucht die Durchführbarkeit einer standardisierten T1w/T2w-Ratio-Methode und ihre Sensitivität für mikrostrukturelle Schäden bei Multipler Sklerose (MS) und Multipler Systematrophie (MSA).

Methoden

In Studie I wurden die standardisierten und konventionellen T1w/T2w-Verhältniswerte in der grauen und weißen Substanz zwischen 47 MS Patienten und gematchten gesunden Kontrollen (gematcht für Alter und Geschlecht) verglichen sowie klinische Korrelate (wie z.B. Läsionslast, Krankheitsschwere) untersucht. Studie II untersuchte longitudinale Veränderungen des standardisierten T1w/T2w-Verhältnisses in der weißen Substanz ab der ersten klinischen Präsentation von 102 MS Patienten und bewertete ihre Assoziation mit der kortikalen Dicke und der Krankheitsaktivität, definiert anhand der “No Evidence of Disease Activity” (keine Hinweise auf Krankheitsaktivität; NEDA-3) Kriterien. In Studie III wurde untersucht, ob sich die standardisierten T1w/T2w-Verhältniswerte im mittleren Kleinhirnstiel zwischen 28 MSA Patienten und für Alter und Geschlecht gematchten gesunden Kontrollen unterscheiden.

Ergebnisse

Es wurde gezeigt, dass das standardisierte T1w/T2w-Verhältnis die Variabilität der Werte der weißen Substanz reduziert und die Sensitivität für normal erscheinende Schäden der weißen Substanz bei MS Patienten erhöht (Studie I). Wir konnten zeigen, dass sich die Werte des standardisierten T1w/T2w-Verhältnisses der normal erscheinenden weißen Substanz bei der ersten klinischen Präsentation der MS nicht signifikant von denen der Kontrollgruppe unterscheiden, dass diese Werte jedoch signifikant mit dem zunehmenden Läsionsvolumen und der abnehmenden kortikalen Dicke im Laufe der Zeit verbunden sind, was durch die

Krankheitsaktivität vermittelt wird (Studie II). Bei MSA zeigten wir, dass das standardisierte T1w/T2w-Verhältnis des mittleren Kleinhirnstiels eine hohe Sensitivität und Spezifität zur Klassifizierung von MSA Patienten im Vergleich zu Kontrollen aufweist (Studie III).

Schlussfolgerungen

Diese Dissertation zeigt, dass das standardisierte T1w/T2w-Verhältnis ein valider und sensitiverer Marker für mikrostrukturelle Schäden im Vergleich zum konventionellen T1w/T2w-Verhältnis ist. Darüber hinaus kann das standardisierte T1w/T2w-Verhältnis zur Untersuchung mikrostruktureller Schäden bei neurologischen Erkrankungen (MS und MSA) verwendet werden und bestätigt und erweitert die Ergebnisse etablierter Maße für mikrostrukturelle Schäden wie diffusionsbasierte MRT Verfahren. Das standardisierte T1w/T2w-Verhältnis stellt ein wichtiges und vielversprechendes Maß für mikrostrukturelle Gewebeschäden in Situationen dar, in denen zusätzliche Scan-Zeit begrenzt ist oder für retrospektive Studien, in denen quantitative oder diffusionsbasierte MRT-Daten nicht verfügbar sind.

Introduction

Magnetic resonance imaging (MRI) revolutionised modern neurology by enabling the acquisition of three-dimensional images of the human brain. Today, various different MRI sequences are used in the clinical routine to enable the detection of structural irregularities, such as brain lesions, and assess atrophy in the whole brain or specific areas. MRI is therefore a critical tool in the diagnostic workup and monitoring of diseases such as multiple sclerosis (MS) [1] and multiple system atrophy (MSA) [2,3]. However, routine MRI scans have limited sensitivity to microstructural damage, which has high clinical relevance, and current techniques to investigate this require additional scantime and extensive post-processing. This limits our ability to investigate microstructural damage in neurological disorders as well as restricts the measurement of microstructural damage in the clinical routine, where time and resources are lacking. Recently, the ratio of T1-weighted to T2-weighted scans (T1w/T2w ratio) has been proposed as a measure of microstructural damage in neurological disorders. This measure has the benefit of making use of routine clinical scans, enabling retrospective analysis of microstructural damage in already available data as well as enabling an analysis of microstructural damage as part of the clinical routine.

Microstructural Damage in Multiple Sclerosis

MS is a central nervous system disorder with a degenerative and inflammatory component. It is characterised by focal lesions with demyelination, axonal loss and reactive gliosis in the white and gray matter. MRI plays an important role in the diagnosis of MS, enabling the detection of lesions that are disseminated in time and/or space [1,4]. Patients typically first present with a clinically isolated syndrome (CIS; a mono- or multifocal attack, such as optic neuritis, myelopathy, fatigue and cognitive impairment) [5–8]. Some patients recover and retain their CIS diagnosis, but the majority of patients follow on to develop a demyelinating disease and receive a diagnosis of MS [6,9]. In both CIS and MS, a clinico-radiological paradox has been described, whereby the typical MRI findings (e.g. number and volume of lesions, amount of brain atrophy) from routine clinical MRI do not correlate with the severity of clinical disability [10,11]. One explanation for this paradox is that routine MRI is not sensitive to detect all pathology in the brain, such as microstructural damage in the so-called “normal-appearing” white matter (NAWM). NAWM refers to extra-lesional white matter damage that is frequently found in neuropathological examinations in MS but cannot be visually detected in MRI [12–14]. NAWM

is characterized by gliosis, axonal loss, mitochondrial injury, ionic dysregulation and demyelination [12,14,15], particularly in the relapsing-remitting phase. A key advancement in MS was the detection of pathology in the NAWM using advanced MRI techniques such as diffusion tensor imaging (DTI) [12,16,17] or quantitative MRI techniques [18]. Using such methods, it has been shown that NAWM is an early event in MS, even being detected in patients with CIS [19]. It has also been demonstrated to correlate with cognitive impairment [8,20,21].

In patients in the relapsing-remitting phase, NAWM damage was previously shown to be associated with cortical thinning, i.e. gray matter atrophy [22,23], suggesting that neurodegenerative cortical atrophy may be a retrograde process resulting at least partly from NAWM damage. This is particularly relevant as positive treatment effects on atrophy have only been reported after the first year of disease [24], although cortical atrophy is increasingly recognised as a critical marker of neurodegeneration in the first year of MS [23–25]. After one year of disease, irreversible neurodegenerative damage is likely to have already occurred and therefore methods that are sensitive to detect damage prior to atrophy are needed in the clinic [24]. Given the association between cortical thinning and NAWM integrity and the fact that NAWM damage can be detected early in the disease course, the measurement of NAWM damage may be one such marker in early MS.

Microstructural Damage in Multiple System Atrophy

MSA is an adult-onset progressive neurodegenerative order characterized by cerebellar ataxia, parkinsonism, autonomic failure, and pyramidal signs. It is classified into two clinical phenotypes, MSA with predominant cerebellar ataxia and MSA with predominant parkinsonism, dependent on the predominant motor symptom. The primary neuropathological sign of MSA is oligodendroglial cytoplasmic inclusions composed of α-synuclein [25]. Three categories of MSA diagnosis are described: possible, probable and definite, the latter of which can only be confirmed post-mortem. The diagnostic criteria [2] have been shown to have high predictive accuracy but the sensitivity, particularly in early stages of the disease, is not optimal [26,27].

The accepted MRI features of MSA only include pons and middle-cerebellar peduncle atrophy [2], however the presence of T2 hyperintensities in the middle-cerebellar peduncle have also been regularly described as supporting features for the MSA diagnosis in the cerebellar phenotype [3,28–33]. Such hyperintensities have been demonstrated to reflect myelin loss [28].

The presence of hyperintensities is not easily measured and therefore the quantification of microstructural damage in the middle-cerebellar peduncle, which is more objective, is of high clinical relevance, particularly in the early stages of the disease.

T1w/T2w Ratio

The measurement of microstructural changes in neurological disorders as described above is typically achieved using advanced MRI methods, such as quantitative MRI and DTI. However, the application of such techniques is limited in the clinical context, given the restriction of time at the scanner, clinician time and expertise in image processing, recently described as the biggest limiting factor to including quantitative techniques in the clinic [34]. However, microstructural changes have a high clinical relevance. One way to overcome this is to quantify images typically acquired in the clinical routine, such as the T1w/T2w ratio. This technique was originally introduced by Glasser and colleagues as a myelin contrast, given the rationale that T1w image intensity values are proportional to myelin and T2w image intensity values are inversely proportional to myelin [35]. The T1w/T2w ratio was therefore considered to enhance the myelin signal and it was shown that a cortical T1w/T2w ratio map is remarkably similar to known histologically-derived myelocortical maps in humans and macaques [35–37].

The specificity of the T1w/T2w ratio to myelin has been challenged. Studies comparing the T1w/T2w ratio in the cortex post-mortem have found that cortical tissue with higher myelination had higher T1w/T2w ratio values [38,39]. However, T1w/T2w ratio values in the cortex were not found to significantly correlate with cortical myelin [39] but rather with neurite [39] or dendrite [40] density. Furthermore, the T1w/T2w ratio has been found to positively correlate with DTI and the myelin water fraction, quantitative measures of myelin and microstructural damage, although with very small effect sizes [41–43]. As such, the T1w/T2w ratio has been posited to be a general marker of microstructural integrity that is influenced by, but not specific to, myelin [41,43] and has been shown to reflect pathological changes in a range of neurological disorders, including MS [38,40,44], Alzheimer's disease [45,46], Parkinson's disease [47] and Huntington's disease [48] and neuromyelitis optica spectrum disorders [49].

Despite its demonstrated clinical relevance, the conventional T1w/T2w ratio has technical limitations. Because it is based on weighted intensity values and not quantitative values, the T1w/T2w ratio intensity values are influenced by methodological factors such as field strength,

scanner manufacturer and bias field inhomogeneities, which limits a reliable and valid comparison of T1w/T2w ratio intensity values between subjects [50–52]. A recent standardization method of the T1w/T2w ratio overcomes many of these limitations [53] by reducing the influence of methodological factors by generating scaled intensity values and correcting for bias field inhomogeneities. The standardization also reduces the between-subject variability of intensity values, thereby reducing the amount of inherent noise in T1w/T2w.

Objectives

This dissertation aimed to evaluate the feasibility and sensitivity of the standardized T1w/T2w ratio to pathological microstructural integrity damage in neurological disorders. This involved validating the standardized T1w/T2w ratio compared to the conventional T1w/T2w ratio and then implementing these results to answer clinically relevant questions in MS and MSA. The eventual aim is to establish the standardized T1w/T2w ratio as a feasible and sensitive marker of tissue microstructure that can be used to answer clinically-relevant questions in research centers and hospitals where additional scan time is limited or only retrospective clinical and imaging data is available.

The specific objectives of this dissertation were as follows:

1. Study I (Publication 1): *Validate the standardized T1w/T2w ratio compared to the conventional T1w/T2w ratio in MS.*
2. Study II (Publication 2): *Investigate longitudinal changes in, and the association between, NAWM microstructural integrity measured by standardized T1w/T2w and cortical thickness in early MS. Additionally, determine whether longitudinal changes in NAWM integrity are modulated by disease activity.*
3. Study III (Publication 3): *Evaluate microstructural integrity in the middle cerebellar peduncle of MSA patients with cerebellar phenotype compared to healthy controls, and determine whether changes, if detected, are associated with clinical disability*.

Materials and Methods

This section provides a theoretical overview of the standardized T1w/T2w ratio and the implementation thereof in MS and MSA. A detailed description of study design, patient demographics and inclusion criteria, outcome measures, MRI protocols, and statistical analysis is available in the original publications [54–56].

Standardized T1w/T2w Ratio

The standardized T1w/T2w ratio method was originally developed by Misaki and colleagues [53] to enhance the homogeneity within tissues (gray and white matter and cerebrospinal fluid) and thereby increase the contrast between the three tissue classes to improve tissue segmentation. The procedure is based on the following information about T1w and T2w image contrasts: The T2w image has high intensity values in the cerebrospinal fluid and low intensity values in the white matter. The T1w image shows the opposite pattern, with low intensity values in the cerebrospinal fluid and high intensity values in the white matter. Both T1w and T2w images have an intermediate gray matter signal (Figure 1). Subtracting the T2w image from the T1w image therefore would enhance tissue contrast due to the complementary signal properties of cerebrospinal fluid and white matter in the context of similar signal intensities in the gray matter. Prior to this, the T2w image is scaled so that the median value of the gray matter voxels in T1w is equal to the median value of the gray matter voxels in T2w. This is done by first calculating a scaling factor (median gray matter intensity in T1w divided by the median gray matter intensity in T2w) and multiplying the T2w image by this scaling factor. This scaling reduces the inherent variability of the T1w and T2w intensity values relative to each other. This scaled T2w image is then subtracted from the T1w image (T1w - sT2). Finally, the T1w-sT2 image is normalised by dividing it by T1w+sT2. This cancels out the inhomogeneity of image intensities and normalises the values in each voxel regardless of absolute intensity to a value between -1.0 and 1.0, where negative values are in the cerebrospinal fluid, values around 0 are in the gray matter, and positive values are in the white matter. Each voxel intensity therefore reflects a relative difference between the T1w and sT2 images in that voxel.

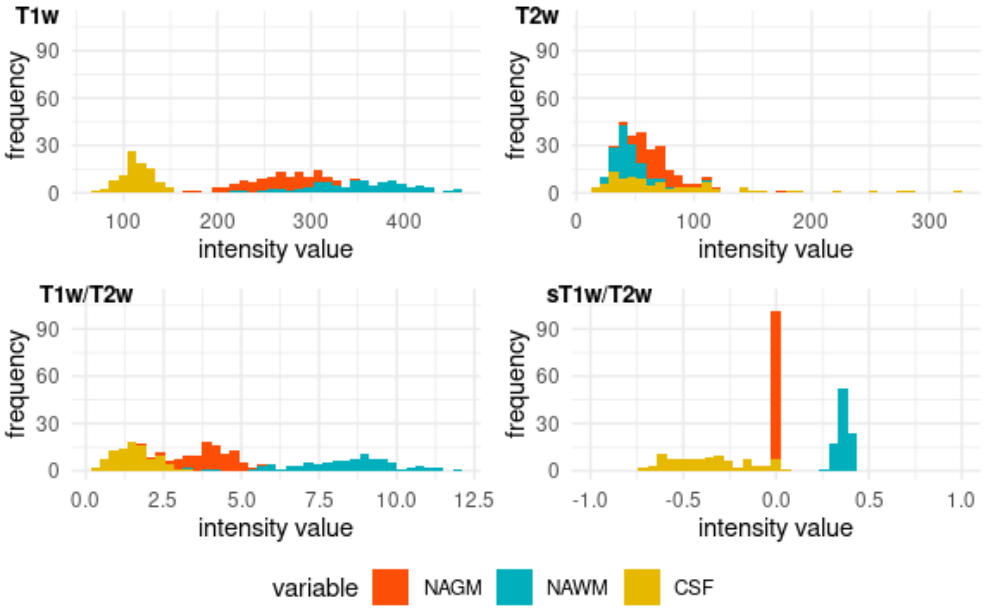

Figure 1. Frequency plot of intensity values in the normal-appearing gray matter (NAGM), normal appearing white matter (NAWM) and cerebrospinal fluid (CSF) in T1w, T2w, conventional T1w/T2w, and standardized T1w/T2w images from a MS cohort (Study I). Adapted from Cooper and colleagues, Figure 1 [54].

Multiple Sclerosis (Studies I & II)

All MS and associated healthy control data are derived from studies conducted at NeuroCure Clinical Research Center and Experimental and Clinical Research Center, Charité-Universitätsmedizin Berlin, Germany. These patients received identical 3D T1w and T2w MRI protocols at a 3T MRI scanner (Tim Trio, Siemens Medical Systems, Erlangen, Germany) at the Berlin Center for Advanced Neuroimaging (BCAN). A Fluid-attenuated Inversion Recovery sequence (FLAIR) was also acquired for MS lesion segmentation. MS and healthy control data for the validation study (Study I) were taken from a cross-sectional observational study on functional connectivity alterations in MS and the Visual Imaging in Multiple Sclerosis (VIMS) study, a longitudinal observational study. In the longitudinal MS study (Study II), data were taken from two longitudinal, observational studies: early MS data was derived from the Clinically Isolated Syndrome Study (CIS) and healthy controls data was derived from VIMS. An additional validation cohort of MS patients with a disease duration of greater than 10 years was included in Study II, also taken from the VIMS study. All three studies were approved by the

local ethics committee (Ethikkommission der Charité-Universitätsmedizin Berlin; EA1/182/10, EA1/163/12, EA1/189/13) and conducted in
accordance with the current applicable version of the Declaration of Helsinki and
German law. All patients provided written informed consent prior to participation in the study.

MRI Pre-Processing

The same MRI processing steps were conducted for all subjects in Studies I and II: T1w, T2w and FLAIR images were corrected for bias field inhomogeneities using a non-parametric, non-uniform intensity normalisation implemented in the Advanced Normalization Tools (ANTs) [57]. Images were then converted to a robust field of view and oriented to MNI space using the robustfov and fslreorient2std commands from the FMRIB Software Library (FSL) version 5.0.4 [58]. Baseline T2w and FLAIR images were linearly co-registered to the baseline T1w image and then all images were linearly co-registered to MNI space with a spline interpolation using FMRIB's Linear Registration Tool (FLIRT) from FSL [58–60]. Follow-up images (Study II) were linearly co-registered to MNI space and then to the baseline FLAIR image for each patient. Following co-registration, the Computational Anatomy Toolbox version 11.09 (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) implemented in SPM12 version 7219 was used to generate a gray matter, white matter and cerebrospinal fluid masks. All masks were binarized using the *fslmaths* command.

One of the characteristic features of MS is the presence of lesions in the white and gray matter [4]. These lesions appear hyperintense on T1w images and hypointense on T2w images, and therefore can induce a bias in the sT1w/T2w ratio. This is a well-described problem in image processing of MS images [61]. To control for this, lesions were removed from the images using the following procedure: At baseline, an automatic lesion mask was generated using the lesion prediction algorithm [62] as implemented in the Lesion Segmentation Toolbox version 2.0.15 (www.statistical-modelling.de/lst.html) in SPM12 version 7219. Lesion masks were then manually corrected by trained raters under the supervision of a board-certified Radiologist using ITK-SNAP [63] (www.itksnap.org). These masks were then overlaid on follow-up FLAIR images (Study II) and manually corrected using ITK-SNAP to determine whether lesions had grown or shrunk, or if new lesions had developed. Lesions were then subtracted from the gray and white matter masks using *fslmaths* to create a "normal-appearing" gray matter (NAGM) and NAWM mask, respectively.

Standardized T1w/T2w Ratio Calculation

All mathematical transformations for the standardized T1w/T2w ratio calculation were conducted using the *fslmaths* and *fslstats* commands. The median intensity value of the NAGM in T1w and T2w was calculated. A scaling factor was then calculated by dividing the median NAGM intensity value in the T1w image by the median NAGM intensity value in the T2w image. The T2w image was then multiplied by this scaling factor to create a scaled T2 image (sT2). The standardized T1w/T2w ratio was then calculated as described by Misaki and colleagues [53]:

$$s\frac{T1w}{T2w}ratio = \frac{T1w - sT2}{T1w + sT2}$$

Clinical Assessment

All MS patients in Studies I and II underwent a neurological examination from trained physicians under the supervision of a board-certified neurologist, which included the Expanded Disability Status Scale (EDSS) score [64] as a measure of disease severity. The EDSS is the standard measure of disease severity in MS, assessing impairment in eight functional systems including pyramidal, brainstem and sensory systems. The EDSS ranges from 0 (no disability) to 10 (death due to MS) in increments of 0.5. Each functional system is scored individually and a composite score is then calculated. The composite EDSS score is used in Studies I and II. In Study II, the No Evidence of Disease Activity (NEDA-3) criteria [65] was also calculated as a measure of disease progression. The NEDA-3 criteria are a binary categorisation based on the EDSS, lesion volume and presence of relapses. If a patient has a) one of more new enlarging T2w or T1w gadolinium enhancing lesions, b) relapsed, or c) has an increased EDSS since last assessment, the NEDA-3 criteria are failed, indicating disease progression. As EDSS is not a scalar measure, an increase by 1 indicated increased disease severity if previous EDSS was between 1 and 5.5. If previous EDSS was < 1 an increase of 1.5 indicated increased severity and if previous EDSS was > 5.5 an increase of 0.5 was required to indicate increased disease severity. Gadolinium-enhanced T1w scans were not acquired at follow-up visits due to safety concerns so only the absence of new T2w lesions was used for the lesion criteria. Failing any of the three criteria (relapse, new lesion, or increased EDSS) resulted in a failure to meet NEDA-3.

Multiple System Atrophy (Study III)

All MSA and healthy control data (Study III) were derived from clinical routine MRI data of patients seen at the Department of Neurology in Chiba Hospital, Japan. This retrospective study was approved by the local ethics committee and the need for informed consent was waived. All MRI data (3D T1w and 2D axial T2w scans) were acquired from the same 3T MRI scanner (GE DISCOVERY MR750, GE Healthcare, Milwaukee, Wisconsin, USA).

Image Processing

The MRI pre-processing steps had to be altered slightly to accommodate for the different MRI scanner and the 2D axial T2w sequence. Images were pre-processed as follows: 3D T1w images were linearly co-registered to 2D axial T2w images using SPM12 version 7219. The Brain Extraction Toolbox from FSL version 5.0.11 [58] was used to skull-strip the co-registered T1w image, which was binarized using the *fslmaths* command. A gray and white matter mask was generated using the FMRIB Automatic Segmentation Tool (FAST) [66]. The standardized T1w/T2w ratio was then calculated as described above.

Clinical Assessment

All MSA patients in Study III received a neurological examination by a board-certified neurologist and included the International Cooperative Ataxia Rating Scale (ICARS) [67]. The ICARS is a measure of ataxia with four subscales: a) posture/gait disturbance, b) kinetic function, c) speech disorder, and d) oculomotor disorder. These four subscales are combined to form a composite ataxia score, which is the primary outcome measure of ataxia in Study III.

Results

Study I: Validation of Standardized T1w/T2w Ratio

The conventional and standardized T1w/T2w ratio methods in MS and healthy controls (matched for age [t = -0.75, p = 0.456] and sex [X^2 = 0.00, p = 1.000]) were compared in Study 1 [54]. Figure 2 shows the conventional and standardized T1w/T2w ratio map for an example patient and healthy control. We first showed that the standardized T1w/T2w ratio values in the NAWM had a significantly lower coefficient of variation, both in patients (9.82 vs 22.04, p < 0.001) and controls (7.06 vs 17.02, p < 0.001). We then investigated whether NAWM and NAGM T1w/T2w ratio values differed between patients and controls. NAWM standardized T1w/T2w ratio was the only contrast to significantly differ between MS patients and healthy controls (Figure 3). Lower NAWM standardized T1w/T2w ratio values in MS was confirmed in a linear regression analysis, showing that MS diagnosis and age were significantly associated with lower standardized T1w/T2w ratio values in the NAWM (adjusted R^2 = 0.21, p < 0.001). The conventional T1w/T2w, T2w and T2w image intensities did not have a significant association with diagnosis or age.

Given the detected group difference in the NAWM we used a linear regression analysis to investigate whether conventional and standardized T1w/T2w ratios in NAWM were associated with the following parameters in MS patients: age, sex (interacting with headsize [68]), T2 lesion volume and count, EDSS, disease duration (months), and the interaction between disease duration and age. We found that the standardized T1w/T2w ratio values were significantly associated with T2 lesion count (adjusted R^2 = 0.36, p < 0.001), while none of the clinical parameters were significantly associated with conventional T1w/T2w ratio values.

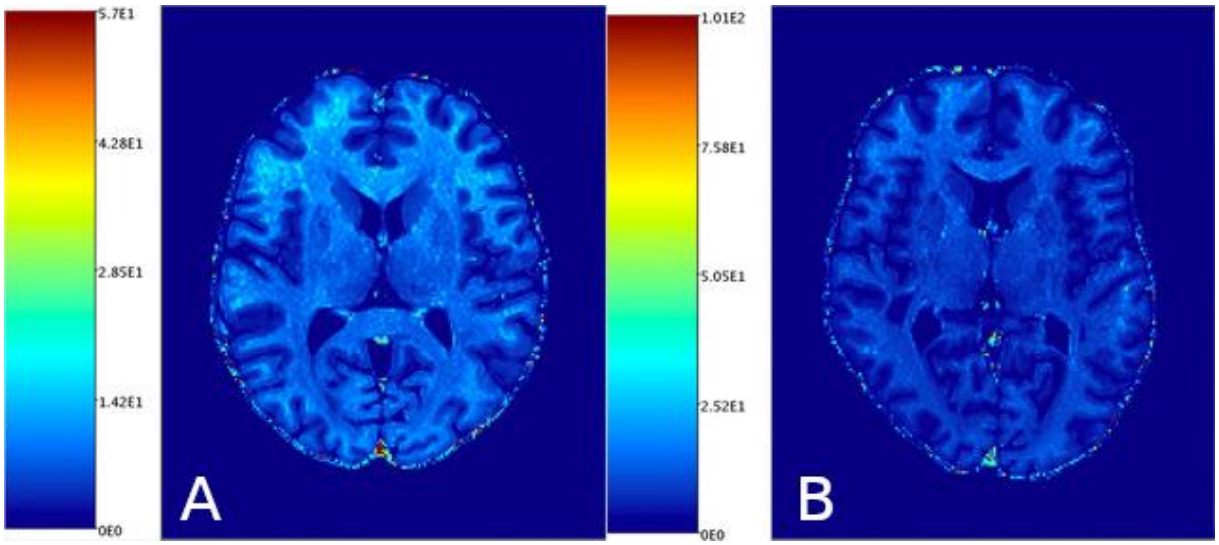

Figure 2a. Conventional T1w/T2w ratio maps compared between an exemplary healthy control (A) and MS patient (B). Adapted from Study I [54].

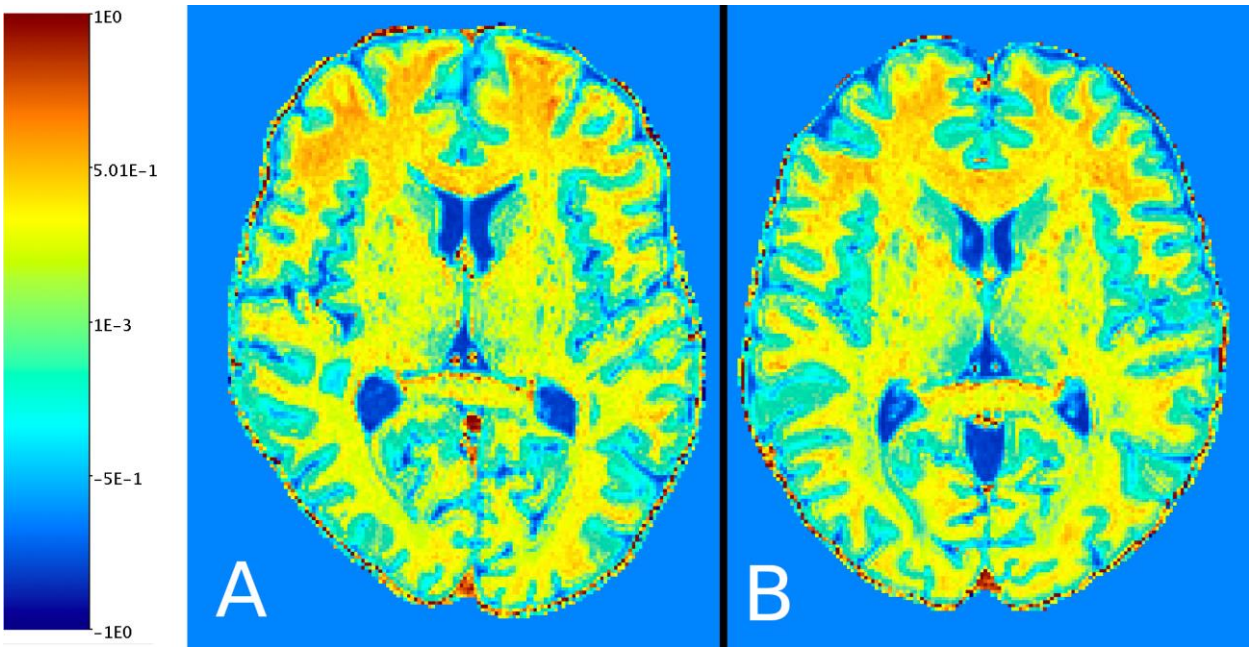

Figure 2b. Standardized T1w/T2w ratio maps compared between an exemplary healthy control (A) and MS patient (B). Adapted from Cooper and colleagues, Figure 3 [54].

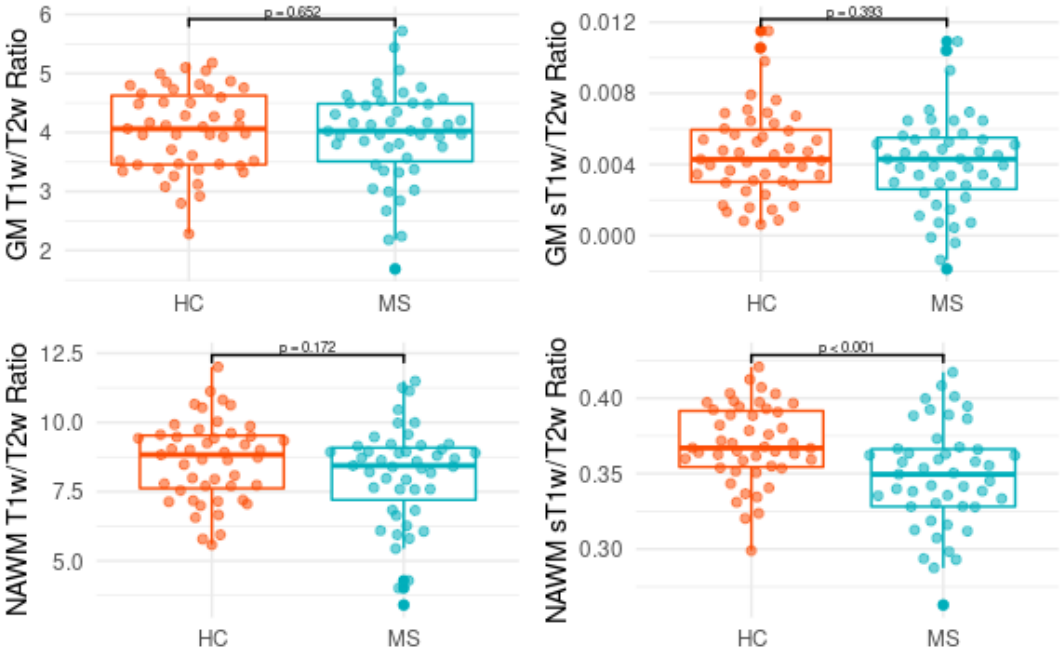

Figure 3. Comparison of the conventional T1w/T2w and standardized T1w/T2w ratio values in the gray matter and NAWM of patients with MS and healthy controls. Adapted from Study I [54].

Study II: Longitudinal Changes in Microstructural Integrity and Cortical Thickness in Multiple Sclerosis

In Study II [55], the standardized T1w/T2w ratio in the NAWM was investigated longitudinally in a cohort of early MS (disease duration < 13 months) and CIS patients from first clinical visit over an average of 2.8 ± 1.6 years. The association between NAWM integrity, cortical thickness and increase of clinical disability was assessed. No significant differences were found in the standardized T1w/T2w ratio in the NAWM of patients and controls at baseline (0.37 ± 0.03 vs 0.37 ± 0.03, $t = 1.44$, $p = 0.152$) and the standardized T1w/T2w ratio in the NAWM did not significantly change over time (Adjusted $R^2 = 0.002$, $p = 0.888$) (Figure 4). However, given the strong association between lesions found in Study I [54], as well as the observed distribution of lesions in the cohort (Figure 5), we performed a subgroup analysis based on total baseline lesion volume > 2 ml vs. < 2 ml, quantified as described above. All patients in the large lesion volume group were already diagnosed with relapsing-remitting MS at baseline, compared to 60% and 77.1% of the small lesion group at baseline and follow-up, respectively. No other differences in imaging parameters or clinical variables (age, sex, disease duration, EDSS and cortical thickness) were detected between the two subgroups. However, patients in the large lesion group

had significantly lower standardized T1w/T2w ratio values in the NAWM both compared to patients in the small lesion group ($p < 0.001$) and controls ($p < 0.001$).

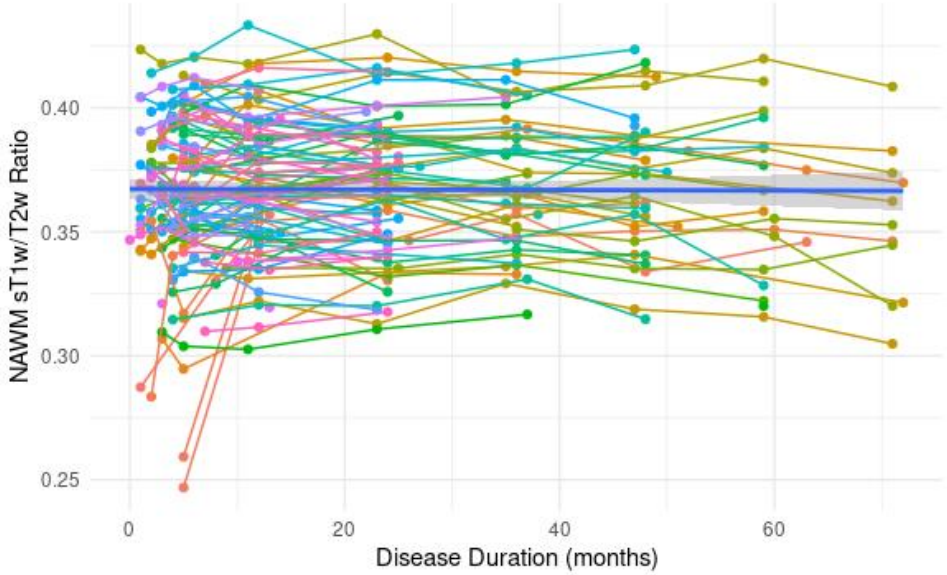

Figure 4. NAWM sT1w/T2w plotted against disease duration. Each patient is represented by a different coloured line to show individual within-patient change. The regression line for the mode fitting NAWM sT1w/T2w ratio against disease duration in the whole cohort is shown as a thick blue line with 95% confidence intervals (transparent blue). Adapted from Cooper and colleagues, Figure 1 [55].

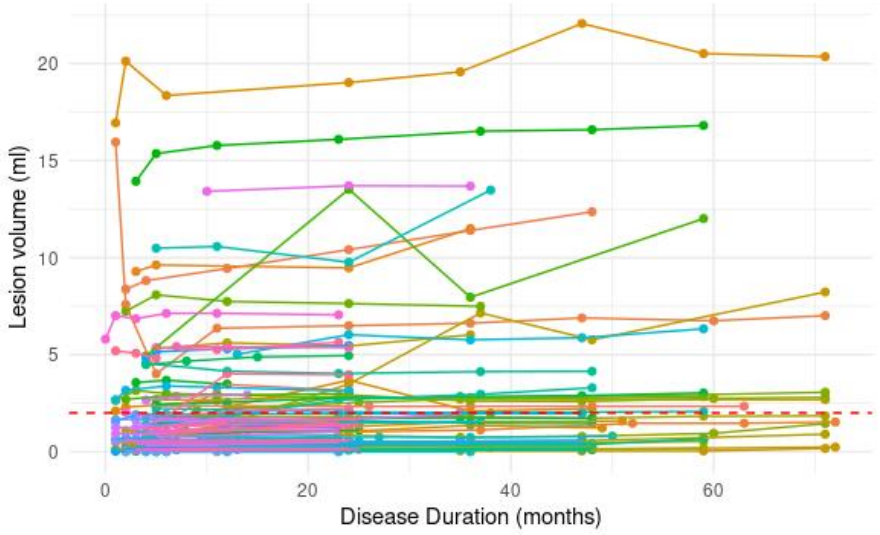

Figure 5. Lesion volume plotted against disease duration. Each patient is represented by a different coloured line to show individual within-patient change. The threshold of 2ml, used for subgrouping, is depicted with the red dashed line. Adapted from Cooper and colleagues, Figure 2 [55].

The best-fitting linear mixed model for NAWM standardized T1w/T2w ratio values included cortical thickness and the interaction between lesion volume and follow-up time (Marginal R^2 = 0.061, Conditional R^2 = 0.839). In the entire cohort, therefore, lower NAWM standardized T1w/T2w ratio values were associated with lower cortical thickness and increasing lesion volume. The impact of increasing clinical disability on the normal appearing standardized T1w/T2w ratio values over time was then investigated by including the effect of failing the NEDA-3 criteria into the model with cortical thickness and lesion volume. All NEDA-3 models increased the amount of variance explained by the model by ~40% and the best-fitting model was the one which included NEDA-3 as a random slope. Therefore, the steepness of the association between NAWM standardized T1w/T2w ratio values and cortical thickness and lesion volume was higher if patients failed NEDA-3 at each visit (Marginal R^2 = 0.097, Conditional R^2 = 0.913).
The final model with NEDA-3 and imaging parameters was also fitted to the two lesion subgroups. In the large lesion volume group, the amount of variance explained by the model was larger although the interaction between follow-up time and lesion volume was no longer significant (Marginal R^2 = 0.162, Conditional R^2 = 0.876). In the small lesion volume group, less variance was explained by the model and no imaging parameters were significant (Marginal R^2 = 0.023, Conditional R^2 = 0.921).

In order to confirm the longitudinal imaging findings in the early MS cohort, we additionally identified a group of 30 patients from the VIMS cohort with a long disease duration (> 10 years) and compared their NAWM standardized T1w/T2w ratio values with 30 patients from the early MS cohort (matched for age [t = -1.752, p = 0.086] and sex [X^2 = 0.68, p = 0.411]). The patients with a longer disease duration had significantly lower NAWM standardized T1w/T2w ratio values (t = 2.45, p = 0.018), lower cortical thickness (t = 2.85, p = 0.006) as well as higher lesion volume (W = 154, p < 0.001), confirming our results.

Study III: Middle Cerebellar Peduncle Microstructural Integrity in Multiple System Atrophy

Study III [56] was conducted using routine clinical MRI data of patients with MSA patients with cerebellar-onset phenotype. Here, the standardized T1w/T2w ratio was evaluated in a specific region of interest (the middle cerebellar peduncle), rather than the gray and white matter. The

middle cerebellar peduncle standardized T1w/T2w ratio values were found to be lower in MSA patients compared to controls (-0.05 ± 0.09 vs 0.18 ± 0.04, $p < 0.001$). Using a receiver operating characteristic analysis, MSA patients could be differentiated from controls with a high sensitivity (area under the curve [AUC] = 0.964) and specificity (AUC = 1.0) using the standardized T1w/T2w ratio values in the middle cerebellar peduncle. In the early-onset (disease duration < 2 years) MSA subgroup, the same results were found: lower standardized T1w/T2w ratio (-0.05 ± 0.10 vs 0.18 ± 0.04, $p < 0.001$) and a high sensitivity (AUC = 0.990) and specificity (AUC = 0.941) from the area-under-the-curve analysis. The middle cerebellar standardized T1w/T2w ratio value did not correlate with any clinical variable in the whole MSA cohort but did correlate with the ICARS score ($r = -0.530$, $p = 0.029$) in the early-onset subgroup, even when controlling for age at time of MRI ($r = -0.507$, $p = 0.045$).

Discussion

This dissertation evaluated the feasibility and sensitivity of the standardized T1w/T2w ratio to pathological microstructural tissue changes in patients with MS and MSA. The results show that the standardized T1w/T2w ratio outperforms the conventional T1w/T2w ratio and can detect relevant microstructural changes in both diseases using both MRI data acquired in clinical studies (Studies I & II) and MRI data acquired as part of the clinical routine (Study III).

Benefits of Standardized T1w/T2w Ratio

The aim of Study I was to *validate the standardized T1w/T2w ratio compared to the conventional T1w/T2w ratio in MS.* This was achieved and the standardized T1w/T2w ratio was shown to be superior to the conventional T1w/T2w ratio with reduced coefficient of variation and a higher sensitivity to detect NAWM damage in MS (Study I). Importantly, considering that the median gray matter T1w and T2w intensity values were used for scaling, we showed that there were no significant differences in the gray matter of T1w and T2w between patients and controls. As such, the presence of undetectable gray matter lesions or subtle changes in the gray matter in the MS context did not systematically affect the scaling method. As part of this dissertation, we demonstrate that the validated standardized T1w/T2w ratio is suitable to investigate microstructural changes in retrospective clinical data acquired systematically (Studies I & II) or as part of the clinical routine (Study III), expanding on previous conventional T1w/T2w ratio studies by also conducting studies longitudinally (Study II) and in specific regions of interest (Study III).

Standardized T1w/T2w Ratio in MS (Studies I & II)

Following validation in MS, the aim of Study II was to *investigate longitudinal changes in, and the association between, NAWM microstructural integrity measured by standardized T1w/T2w and cortical thickness in early MS.* Additionally, Study II aimed to *determine whether longitudinal changes in NAWM integrity are modulated by disease activity.* Both aims were achieved and Study II showed that NAWM damage was associated with decreasing cortical thickness and increasing lesion burden over time and that this was modulated by disease activity, as measured by NEDA-3. Both studies I and II consistently found that patients with MS had significantly lower sT1w/T2w ratio in the NAWM compared to controls, although in Study II only patients with a high baseline lesion burden differed from controls. The finding in Study I that only the sT1w/T2w was sensitive to NAWM integrity loss contrasts with previous work,

which showed significantly lower conventional T1w/T2w in the NAWM of patients with MS [44]. This difference in findings should be interpreted considering the known high variability of conventional T1w/T2w ratio values. Beer *et al.* [44] had a larger sample size compared to Study I (244 patients and 78 healthy subjects) with a higher power to find an effect in the conventional T1w/T2w ratio. This might be considered a further benefit of the sT1w/T2w ratio, as its lower variability requires a smaller sample size to find effects.

Study II confirms the findings of previous DTI studies, showing an association between NAWM damage and cortical thinning [22,23,69,70], supporting the hypothesis that microstructural NAWM damage and cortical atrophy are related processes in early MS. It also expands on this by using an earlier MS cohort (first clinical presentation compared to 2-7 years of disease duration) and a longitudinal study design, showing that NAWM damage can be detected on the group level prior to atrophy and that NAWM integrity loss is associated with cortical thinning over time. Further, Study II showed that disease activity, as measured by NEDA-3, modulates this association. Few studies have investigated the relationship between NEDA-3 and NAWM damage. One study showed that NAWM permeability predicts NEDA-3 status two years later [71]. The other study showed that NAWM diffusivity increased irrespective of NEDA-3 status [72]. Both of these studies were conducted in patients with a mean baseline disease duration ranging from 4 to 8 years, in contrast to the current study where the mean baseline disease duration was less than 13 months.

Standardized T1w/T2w Ratio in MSA (Study III)

Applying the standardized T1w/T2w ratio in MSA for the first time, Study III aimed to *evaluate microstructural integrity in the middle cerebellar peduncle of MSA patients with cerebellar phenotype compared to healthy controls, and determine whether changes, if detected, are associated with clinical disability*. This aim was also achieved, showing significantly reduced middle cerebellar peduncle sT1w/T2w ratio values in early and established MSA patients with cerebellar phenotype. This study represented an important development in the evaluation of middle cerebellar peduncle dysfunction in MSA. Previous work had shown that hyperintensities in this region had a high sensitivity for MSA cerebellar phenotype and correlated with cerebellar symptoms [28,31–33]. However, the presence of hyperintensities is a qualitative and subjective marker. Study III supports previous findings with a quantitative and objective measure of

damage in the middle cerebellar peduncle, suggesting that sT1w/T2w ratio is a useful clinical marker of middle cerebellar peduncle damage in MSA.

Limitations and Future Directions

As demonstrated in Study I, the main benefit of standardization is for white matter and not gray matter, potentially due to the use of gray matter intensity in the standardization. As such the sT1w/T2w ratio may be more suitable for white matter investigations, but not whole brain analyses. However, no cortical mapping of sT1w/T2w ratio has been conducted and future work comparing cortical maps may be of interest to elucidate the utility of sT1w/T2w in the gray matter. Even though the standardization of T1w/T2w significantly improves the coefficient of variation, the variability (Study I) and reported effect sizes in all studies (Studies I - III) are small to moderate, particularly when compared to equivalent quantitative MRI methods. This may limit the use of the sT1w/T2w as an individual biomarker. However, as demonstrated in this dissertation, the sT1w/T2w ratio is a useful MRI marker of microstructural tissue damage particularly for clinics that do not acquire research MRI data, enabling already acquired clinical MRI data to be used to answer new questions regarding microstructural damage in neurological diseases (Study III) as well as in longitudinal studies with a standardized protocol that did not previously include quantitative sequences (Studies I & II).

Although it is well-accepted that T1w/T2w ratio methods are sensitive to microstructural integrity in the whole brain, the underlying histopathological substrate of T1w/T2w ratio methods has yet to be determined. The combined MRI-histopathological studies conducted to date have only investigated the cortex, finding that although T1w/T2w ratio values are significantly lower in demyelinated cortex compared to myelinated cortex [38,39], the absolute values are not significantly associated with myelin. Instead, associations with neurite [39] and dendrite density [40] have been found. Whole brain combined MRI-histopathological studies are therefore sorely needed in order to assist in interpreting T1w/T2w ratio values in NAWM. This is particularly important for the standardized T1w/T2w, as the use of gray matter intensity as a scaling factor may introduce additional variability due to undetected gray matter pathology. In Study I we showed that the gray matter intensity values and scaling factors did not significantly differ between healthy controls and patients, which supports the validity of the method but cannot rule out the effects of gray matter pathology completely.

Particularly considering the small effect sizes reported in all studies, an investigation of the variability and scan-rescan repeatability of sT1w/T2w ratio in healthy subjects is required to help better interpret the findings presented here. This would be best conducted multi-center to test the comparability of the sT1w/T2w ratio between centres. Such work may enable cross-cultural investigations, for example in MS, where clinical differences have been found in German and Japanese patients but comparisons of imaging findings are limited.

Conclusion

In conclusion, this dissertation demonstrated that the standardized T1w/T2w ratio is a highly feasible marker of microstructural tissue damage in neurological disorders that outperforms the conventional T1w/T2w ratio. The standardized T1w/T2w ratio can be used to investigate important pathophysiological questions in neurological disorders in settings where alternative quantitative or diffusion-based techniques are not available.

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Statutory Declaration

"I, Graham Cooper, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic Standardized T1w/T2w Ratio as a Marker of Microstructural Tissue Damage in Neurological Disorders/Standardisierter T1w/T2w-Quotient als Marker für mikrostrukturelle Gewebeschäden bei neurologischen Erkrankungen, independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date Signature

Declaration of Contribution to Publications

Graham Cooper contributed as follows to these publications:

1. Publication 1: **Cooper, G.**, Finke, C., Chien, C., Asseyer, S., Brandt, A.U., Ruprecht, K., Bellmann-Strobl, J., Paul, F., & Scheel, M. (2019). Standardization of T1w/T2w Ratio Improves Detection of Tissue Damage in Multiple Sclerosis. Frontiers in Neurology - Applied Neuroimaging. doi: 10.3389/fneur.2019.00334
    - Journal Impact Factor (2019): **2.889**
    - Contribution in detail: Graham Cooper conceived and designed this retrospective study, assisted with coordination and collection of clinical data, processed the sT1w/T2w ratio data and performed all statistical analysis and data visualisation. He also interpreted the results, wrote all drafts of the manuscript and coordinated the journal submission process.

2. Publication 2: **Cooper, G.**, Chien, C., Zimmermann, H., Bellmann-Strobl, J., Ruprecht, K., Kuchling, J., Asseyer, S., Brandt, A.U., Scheel, M., Paul, F.*, & Finke, C.* (2021) Longitudinal Analysis of T1w/T2w Ratio in Patients with Multiple Sclerosis from First Clinical Presentation. Multiple Sclerosis Journal *equal contribution
    - Journal Impact Factor (2021): **6.312**
    - Contribution in detail: Graham Cooper conceived and designed this retrospective study, assisted with coordination and collection of clinical data, processed the sT1w/T2w ratio data and performed all statistical analysis and data visualisation. He also interpreted the results, wrote all drafts of the manuscript and coordinated the journal submission process.

3. Publication 3: Sugiyama, A., Yokota, H., Hirano, S., **Cooper, G.**, Masuda, H., Mukai, H., Koide, K., Jiaqi, W., Ito, S., Finke, C., Brandt, A.U., Paul, F., & Kuwabara, S. (2020).

Middle cerebellar peduncle T1w/T2w ratio in multiple system atrophy. European Radiology. doi: 10.1007/s00330-020-07521-1

- Journal Impact Factor (2019): **4.101**
- Contribution in detail: Graham Cooper processed the sT1w/T2w ratio data. He also interpreted the results, reviewed the statistical analysis and final version of the manuscript for submission.

Signature, date and stamp of first supervisor

Signature of doctoral candidate

Excerpt from the Journal Summary List (ISI Web of Knowledge)

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI Selected Categories: **"NEUROSCIENCES"** Selected Category Scheme: WoS **Gesamtanzahl: 271 Journal**

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
132	STRESS-THE INTERNATIONAL JOURNAL ON THE BIOLOGY OF STRESS	2,915	3.102	0.004100
133	NEURAL PLASTICITY	4,271	3.093	0.011330
134	Purinergic Signalling	1,979	3.065	0.002350
135	NEUROSCIENCE	44,404	3.056	0.044770
136	Current Alzheimer Research	4,243	3.047	0.006240
137	DEVELOPMENTAL NEUROSCIENCE	2,190	3.041	0.002050
138	NEUROCHEMICAL RESEARCH	9,819	3.038	0.011300
139	ACTA NEUROPSYCHIATRICA	930	3.000	0.001790
139	Cognitive Neuroscience	628	3.000	0.001540
139	VISUAL NEUROSCIENCE	2,228	3.000	0.001320
142	NEUROTOXICITY RESEARCH	3,384	2.992	0.004030
143	BEHAVIOURAL BRAIN RESEARCH	26,293	2.977	0.030780
144	CLINICAL AUTONOMIC RESEARCH	1,674	2.968	0.001880
145	NEUROGASTROENTEROLOGY AND MOTILITY	7,567	2.946	0.011780
146	JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY	9,263	2.923	0.007160
147	NEUROLOGIC CLINICS	2,443	2.910	0.003310
148	Frontiers in Neurology	9,998	2.889	0.028270
149	JOURNAL OF NEUROENDOCRINOLOGY	5,853	2.886	0.005310
150	JOURNAL OF VESTIBULAR RESEARCH-EQUILIBRIUM & ORIENTATION	1,305	2.816	0.001640
151	BMC NEUROSCIENCE	4,722	2.811	0.004530
152	JOURNAL OF COMPARATIVE NEUROLOGY	29,259	2.801	0.014500
153	NEUROBIOLOGY OF LEARNING AND MEMORY	7,356	2.768	0.013440

Journal Data Filtered By: Selected JCR Year: 2019 Selected Editions: SCIE,SSCI Selected Categories: **"NEUROSCIENCES"** Selected Category Scheme: WoS **Gesamtanzahl: 271 Journale**

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
44	Multiple Sclerosis Journal	11,792	5.412	0.019460
45	BIPOLAR DISORDERS	4,838	5.410	0.006610
46	Dialogues in Clinical Neuroscience	3,842	5.397	0.005280
47	Biological Psychiatry-Cognitive Neuroscience and Neuroimaging	1,361	5.335	0.005880
48	NEUROBIOLOGY OF DISEASE	17,200	5.332	0.023770
49	Brain Connectivity	2,431	5.263	0.005180
50	Journal of Parkinsons Disease	2,244	5.178	0.005810
51	CEREBRAL CORTEX	30,815	5.043	0.056030
52	Developmental Cognitive Neuroscience	3,177	4.966	0.010180
53	CEPHALALGIA	11,053	4.868	0.011970
54	NEUROPSYCHOLOGY REVIEW	3,114	4.840	0.004050
55	SLEEP	22,296	4.805	0.024610
56	JOURNAL OF HEADACHE AND PAIN	3,898	4.797	0.007600
57	PSYCHONEUROENDOCRINOLOGY	19,287	4.732	0.027100
58	JOURNAL OF NEUROSCIENCE RESEARCH	13,098	4.699	0.010490
59	EXPERIMENTAL NEUROLOGY	20,154	4.691	0.020070
60	Molecular Brain	2,785	4.686	0.006510
61	Current Neuropharmacology	4,178	4.668	0.006280
62	JOURNAL OF PAIN	10,887	4.621	0.015040
63	JOURNAL OF PHYSIOLOGY-LONDON	50,045	4.547	0.037090
64	EUROPEAN JOURNAL OF NEUROLOGY	11,015	4.516	0.017330
65	MOLECULAR NEUROBIOLOGY	15,297	4.500	0.031350

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI Selected Categories: **"RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"**

Selected Category Scheme: WoS

Gesamtanzahl: 133 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	EUROPEAN RADIOLOGY	20,761	4.101	0.033260
22	SEMINARS IN RADIATION ONCOLOGY	2,531	4.076	0.003540
23	JOURNAL OF MAGNETIC RESONANCE IMAGING	17,046	3.954	0.024900
24	Biomedical Optics Express	11,090	3.921	0.025030
25	COMPUTERIZED MEDICAL IMAGING AND GRAPHICS	2,656	3.750	0.002940
26	JOURNAL OF DIGITAL IMAGING	2,494	3.697	0.003790
27	MAGNETIC RESONANCE IN MEDICINE	32,159	3.635	0.029700
28	Insights into Imaging	1,948	3.579	0.003260
29	INTERNATIONAL JOURNAL OF HYPERTHERMIA	4,397	3.574	0.004880
30	SEMINARS IN NUCLEAR MEDICINE	2,194	3.544	0.002420
31	AMERICAN JOURNAL OF NEURORADIOLOGY	23,135	3.381	0.027120
32	JOURNAL OF NUCLEAR CARDIOLOGY	3,600	3.366	0.004570
33	MEDICAL PHYSICS	26,445	3.317	0.027280
34	Quantitative Imaging in Medicine and Surgery	1,335	3.226	0.002800
35	NMR IN BIOMEDICINE	7,537	3.221	0.011610
36	Clinical Neuroradiology	935	3.183	0.002710
37	KOREAN JOURNAL OF RADIOLOGY	2,967	3.179	0.004490
38	Ultrasonography	618	3.075	0.001710
39	ULTRASONICS	7,808	3.065	0.008930
40	JOURNAL OF VASCULAR AND INTERVENTIONAL RADIOLOGY	9,045	3.037	0.009790
41	AMERICAN JOURNAL OF ROENTGENOLOGY	32,209	3.013	0.024770
42	Practical Radiation Oncology	1,879	2.948	0.005780

Print Copies of Selected Publications

Cooper et al. (2019) Frontiers in Neurology

Cooper, G., Finke, C., Chien, C., Asseyer, S., Brandt, A.U., Ruprecht, K., Bellmann-Strobl, J., Paul, F., & Scheel, M. (2019). Standardization of T1w/T2w Ratio Improves Detection of Tissue Damage in Multiple Sclerosis. Frontiers in Neurology - Applied Neuroimaging. doi: 10.3389/fneur.2019.00334/full

https://doi.org/10.3389/fneur.2019.00334

Cooper et al. (2021) Multiple Sclerosis Journal

Cooper, G., Chien, C., Zimmermann, H., Bellmann-Strobl, J., Ruprecht, K., Kuchling, J., Asseyer, S., Brandt, A.U., Scheel, M., Paul, F.*, & Finke, C.* (2021) Longitudinal Analysis of T1w/T2w Ratio in Patients with Multiple Sclerosis from First Clinical Presentation. Multiple Sclerosis Journal *equal contribution. doi: 10.1177/13524585211003479 https://doi.org/10.1177/13524585211003479

Sugiyama et al. (2020). European Radiology

Sugiyama, A., Yokota, H., Hirano, S., **Cooper, G.**, Masuda, H., Mukai, H., Koide, K., Jiaqi, W., Ito, S., Finke, C., Brandt, A.U., Paul, F., & Kuwabara, S. (2020). Magnetic resonance T1w/T2w ratio in the middle cerebellar peduncle might be a sensitive biomarker for multiple system atrophy. European Radiology. doi: 10.1007/s00330-020-07521-1 https://doi.org/10.1007/s00330-020-07521-1

Curriculum Vitae

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

Complete List of Publications

An up-to-date list is available here: https://orcid.org/0000-0001-8383-6476

Peer-reviewed Original Research Articles

Sugiyama, A.***, Cooper, G.****, Hirano, S., Yokota, H., Mori, M., Shimizu, K., Yakiyama, M., Finke, C., Brandt, A.U., Paul, F., & Kuwabara, S. (2021). Cognitive impairment in multiple system atrophy is related to white matter damage detected by the T1w/T2w ratio. *European Neurology* *equal contribution
Journal Impact Factor (2014): **1.356**

Cooper, G., Chien, C., Zimmermann, H., Bellmann-Strobl, J., Ruprecht, K., Kuchling, J., Asseyer, S., Brandt, A.U., Scheel, M., Paul, F.*, & Finke, C.* (2021) Longitudinal Analysis of T1w/T2w Ratio in Patients with Multiple Sclerosis from First Clinical Presentation. Multiple Sclerosis Journal *equal contribution. doi: 10.1177/13524585211003479
Journal Impact Factor (2021): **6.312**

Otte, K., Ellermeyer, T., Suzuki, M., Röhling, H.M., Kuroiwa, R., Mansow, Model, S., **Cooper, G.**, Mori, M., Zimmermann, H., Brandt, A.U., Paul, F., Hirano, S., Kuwabara, S., & Schmitz-Hübsch, T. (2021) Cultural bias in motor function patterns: Potential relevance for predictive, preventive, and personalized medicine. *EMPA Journal*. doi: 10.1007/s13167-021-00236-3
Journal Impact Factor (2018): **4.80**

Asseyer, S., Masuda, H., Mori, M., Bellmann-Strobl, J., Ruprecht, K., Siebert, N., **Cooper, G.**, Liu, J., Sugimoto, K., Uzawa, A., Ohtani, R., Paul, F., Brandt, A.U., Zimmermann, H.G., & Kuwabara, S. (2021). AQP4-IgG autoimmunity in Japan and Germany: Differences in clinical onset, prognosis and treatment in neuromyelitis optica spectrum disorders. *Multiple Sclerosis Journal: Experimental, Translational and Clinical*
h5 index: 17

Sugiyama, A., Yokota, H., Hirano, S., **Cooper, G.**, Masuda, H., Mukai, H., Koide, K., Jiaqi, W., Ito, S., Finke, C., Brandt, A.U., Paul, F., & Kuwabara, S. (2020). Magnetic resonance T1w/T2w ratio in the middle cerebellar peduncle might be a sensitive biomarker for multiple system atrophy. *European Radiology.* doi: 10.1007/s00330-020-07521-1
Journal Impact Factor (2019): **4.101**

Cooper, G., Scheel, M., Brandt, A.U., Finke, C., Paul, F., Boehm-Sturm, P., & Hetzer, S. (2020). Quantitative Multi-Parameter Mapping Optimized for the Clinical Routine. *Frontiers in Neuroscience - Brain Imaging Methods.* doi: 10.3389/fnins.2020.611194
Journal Impact Factor (2019): **2.750**

Liu, J., Mori, M., Brandt, A.U., Havla, J., Tanaka, S., Sugimoto, K., Zimmermann, H.G., Oji, S., Uzawa, A., Schidt, F., Asseyer, S., **Cooper, G.**, Bellmann-Strobl, J., Ruprecht, K., Siebert, N., Masuda, H., Uchida, T., Ohtani, R., Nomura, K., Meinl, E., Kümpfel, T., Paul, F., & Kuwabara, S. (2020). MOG-IgG autoimmunity in Japan and Germany: different clinical profiles, treatment, and prognosis in MOG-IgG antibody-associated optic neuritis and encephalomyelitis. *Journal of Neurology, Neurosurgery and Psychiatry*. doi: 10.1136/jnnp-2020-324422
Journal Impact Factor (2019): **8.234**

Voskuhl, R.R., Patel, K., Paul, F., Gold, S.M., Scheel, M., Kuchling, J., **Cooper, G.**, Asseyer, S., Chien, C., Brandt, A.U., Meyer, C.E., Mackenzie-Graham, A. (2020). Sex differences in brain atrophy in multiple sclerosis. *Biology of Sex Differences*. doi: 10.1186/s13293-020-00326-3
Journal Impact Factor (2019): **3.130**

Juenger, V., **Cooper, G.**, Chien, C., Asseyer, S., Brandt, A.U., Ruprecht, K., Bellmann-Strobl, J., Paul, F., & Scheel, M. (2019). Evaluation of optic chiasm measures as markers of anterior optic pathway degeneration in neuromyelitis optica spectrum disorders. *European Radiology*. doi: 10.1007/s00330-020-06859-w
Journal Impact Factor (2019): **4.101**

Cooper. G., Finke, C., Chien, C., Asseyer, S., Brandt, A.U., Ruprecht, K., Bellmann-Strobl, J., Paul, F., & Scheel, M. (2019). Standardization of T1w/T2w Ratio Improves Detection of Tissue Damage in Multiple Sclerosis. *Frontiers in Neurology - Applied Neuroimaging.* doi: 10.3389/fneur.2019.00334
Journal Impact Factor (2019): **2.889**

Bartels, F., Nobis, K., **Cooper, G.**, Hennes, E., Anlar, B., Cleaveland, B., Kornek, B., Blaschek, A., Schimmel, M., Blankenburg, M., Baumann, M., Karenfort, M., Finke, C., & Rostásy, K. (2019). Childhood multiple sclerosis is associated with reduced brain volumes at first clinical presentation and brain growth failure. *Multiple Sclerosis Journal.* doi: 10.1177/1352458519829698
Journal Impact Factor (2021): **6.312**

Peer-reviewed Review Articles

Asseyer, S., **Cooper, G.**, & Paul, F. (2020). Pain in NMOSD and MOGAD: A Systematic Literature Review of Pathophysiology, Symptoms and Current Treatment Strategies. *Frontiers in Neurology - Neuroepidemiology.* doi: 10.3389/fneur.2020.00778
Journal Impact Factor (2019): **2.889**

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Oertel, F., Schließeit, J., **Cooper, G.**, Brandt, A.U., & Bellmann-Strobl, J. (2020). Primary and secondary mechanisms of fatigue in early multiple sclerosis. *Acta Neurologica Belgica*. doi: 10.1007/s13760-020-01545-6
Journal Impact Factor (2019): **1.722**

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Hoffmann, O., Zimmermann, H.G., Chien, C., **Cooper, G.**, Kuchling, J., Asseyer, S., Rust, R., Brandt, A.U., Ruprecht, K., Bellmann-Strobl, J., Paul, F. (2020). Utility of NEDA-3 status as a predictor of future disease activity. *MS Virtual 2020 (Joint ACTRIMS, ECTRIMS Meeting)*.

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Otte, K., Drebinger, D., Röhling, H., Kroneberg, D., Althoff, P., Schließeit, J., **Cooper, G.**, Arsenova, R., Belmann-Strobl, J., Brandt, A. U., Paul, F., & Schmitz-Hubsch, T. (2019). Investigating independent gait domains in patients with multiple sclerosis. *ECTRIMS 2019*

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