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Clinical Applications of Synthetic MRI of the Brain

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Cover: R1 map of glioblastoma

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“Invisibility – there are things we can’t see now, that are embedded, that it really takes time in order to be able to see”.....“that takes the technology of another generation or so in order to uncover”

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ABSTRACT

Magnetic Resonance Imaging (MRI) has a high soft-tissue contrast with a high sensitivity for detecting pathological changes in the brain. Conventional MRI is a time-consuming method with multiple scans that relies on the visual assessment of the neuroradiologist. Synthetic MRI uses one scan to produce conventional images, but also quantitative maps based on relaxometry, that can be used to quantitatively analyse tissue properties and pathological changes. The studies presented here apply the use of synthetic MRI of the brain in different clinical settings.

In the first study, synthetic MR images were compared to conventional MR images in 22 patients. The contrast, the contrast-to-noise ratio, and the diagnostic quality were assessed. Image quality was perceived to be inferior in the synthetic images, but synthetic images agreed with the clinical diagnoses to the same extent as the conventional images.

Patients with early multiple sclerosis were analysed in the second study. In patients with multiple sclerosis, contrast-enhancing white matter lesions are a sign of active disease and can indicate a need for a change in therapy. Gadolinium-based contrast agents are used to detect active lesions, but concern has been raised regarding the long-term effects of repeated use of gadolinium. In this study, relaxometry was used to evaluate whether pre-contrast injection tissue-relaxation rates and proton density can identify active lesions without gadolinium. The findings suggest that active lesions often have relaxation times and proton density that differ from non-enhancing lesions, but with some overlap. This makes it difficult to replace gadolinium-based contrast agent injection with synthetic MRI in the monitoring of MS patients.

Malignant gliomas are primary brain tumours with contrast enhancement due to a defective blood-brain barrier. However, they also grow in an infiltrative, diffuse manner, making it difficult to clearly delineate them from surrounding normal brain tissue in the diagnostic work-up, at surgery, and during follow-up. The contrast-enhancing part of the tumour is easily visualised, but not the diffuse infiltration. In studies three and four, synthetic MRI was used to analyse the peritumoral area of

malignant gliomas, and revealed quantitative findings regarding peritumoral relaxation changes and non-visible contrast enhancement suggestive of non-visible infiltrative tumour growth.

In conclusion, synthetic MRI provides quantitative information about the brain tissue and this could improve the diagnosis and treatment for patients.

SVENSK SAMMANFATTNING

Bilder tagna med magnetresonanskamera (MR) har en hög mjukdelskontrast vilket ger en hög känslighet för att hitta sjukliga förändringar i hjärnan. Vanlig MR är en tidskrävande metod med flera undersökningsmoment som ger bilder vilka bedöms visuellt av en röntgenläkare. Vanliga MR bilder har varierande gråskala, vilket gör det svårt att mäta i gråskalan och jämföra förändringar i hjärnan mellan olika MR-undersökningar. Syntetisk MR har endast ett undersökningsmoment, vilket producerar vanliga MR-bilder, men också kvantitativa kartor baserat på relaxometri (hur vävnaden reagerar vid MR-undersökningen). De kvantitativa kartorna kan användas för att analysera vävnadsegenskaper och patologiska förändringar på ett upprepbart och mätbart sätt, vilket ger möjlighet till jämförelse mellan undersökningar över tid. De studier som presenteras här implementerar och analyserar syntetisk MR av hjärnan vid olika kliniska tillämpningar.

I den första studien jämfördes bilder från syntetisk MR med konventionella MR-bilder hos 22 patienter med olika diagnoser. Kontrast, kontrast-brus förhållande och diagnostisk kvalitet bedömdes. Bildkvaliteten uppfattades som sämre i de syntetiska bilderna, men de syntetiska bilderna stämde med den kliniska diagnosen i samma utsträckning som de konventionella bilderna.

Patienter med multipel scleros (MS) följs regelbundet med MR, där gadoliniumbaserat kontrastmedel används för att upptäcka kontrastuppladdande vitvävnadslesioner, MS-lesioner. Kontrastuppladdande MS-lesioner i hjärnan är ett tecken på aktiv sjukdom, vilket kan indikera att man behöver byta behandling. Under senare år har studier visat att gadolinium till viss del lagras in i hjärnan vid upprepade kontrastmedelsinjektioner. Den kliniska relevansen av denna inlagring är inte helt klarlagd, men om det fanns möjlighet att upptäcka aktiva MS-lesioner utan kontrastmedelstillförsel skulle det kunna vara en fördel. I den andra studien användes syntetisk MR för att utvärdera om vävnadens relaxationstider och protontätheten innan kontrastmedelsinjektion kan användas för att identifiera aktiva MS-lesioner. Fyndet tyder på att aktiva lesioner ofta har avvikande relaxationstider och protontäthet jämfört med icke-

kontrastladdande lesioner, men att det finns en viss överlappning vilket gör att det är svårt att helt ersätta gadoliniumbaserat kontrastmedel med syntetisk MR i utvärderingen av MS patienter.

Maligna gliom är elakartade, primära hjärntumörer med kontrastuppladdning på grund av en defekt blod-hjärn-barriär. Dessutom växer dessa tumörer infiltrativt och diffust vilket gör det svårt att urskilja var gränsen går mot omgivande frisk hjärnvävnad, både vid såväl diagnostik och kirurgi, som vid uppföljning. Den kontrastladdande delen av tumören är lätt att urskilja visuellt, men inte den diffusa infiltrationen. I studie tre och fyra användes syntetisk MR för att analysera det peritumorala området hos maligna gliom, med fynd av relaxationsförändringar och osynlig kontrastuppladdning kring tumören, vilket kan indikera osynlig infiltrativ tumörväxt.

Syntetisk MR ger kvantitativ information om hjärnvävnaden vilket kan komma att förbättra såväl diagnostik som behandling av patienter.

LIST OF PAPERS

- I. **Ida Blystad**, Marcel Warntjes, Örjan Smedby, Anne-Marie Landt-blom, Peter Lundberg, Elna-Marie Larsson:
Synthetic MRI of the brain in a clinical setting
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- II. **Ida Blystad**, Irene Håkansson, Anders Tisell, Jan Ernerudh, Örjan Smedby, Peter Lundberg, Elna-Marie Larsson:
Quantitative MRI for analysis of active multiple sclerosis
Am J Neurorad 2016 Jan; 37(1): 94-100. © 2016 American Society of Neuroradiology. Reprinted with permission.
- III. **Ida Blystad**, Marcel Warntjes, Örjan Smedby, Peter Lundberg, Elna-Marie Larsson, Anders Tisell:
Quantitative MRI for analysis of peritumoral edema in malignant gliomas
PLOSone 2017 ; doi.org/10.1371/journal.pone.0177135
- IV. **Ida Blystad**, Marcel Warntjes, Örjan Smedby, Peter Lundberg, Elna-Marie Larsson, Anders Tisell
Quantitative MRI using relaxometry in malignant gliomas detects non-visible peritumoral contrast enhancement
(Manuscript prepared for European Radiology)

AUTHOR CONTRIBUTIONS

- **Paper I:** Participated in the development of idea and study design as well as in planning and carrying out the study. Participation in analysis and interpretation of the results. First author of manuscript's first and final draft and responsible for the correspondence with the journal publishing the manuscript.
- **Paper II:** Participation in the development of idea and study design, and in data acquisition. Participation in analysis and interpretation of results. First author of manuscript's first and final draft and responsible for the correspondence with the journal publishing the manuscript.
- **Paper III:** Development of idea and study design. Authored the application to the Ethical Board and application for research grant (Medical Research Council of Southeast Sweden). Responsible for recruitment of patients and data collection. Participation in data analysis and interpretation of results. First author of manuscript's first and final draft and responsible for the correspondence with the journal publishing the manuscript.
- **Paper IV:** Development of idea and study design. Authored the application to the Ethical Board and application for research grant (Medical Research Council of Southeast Sweden). Responsible for recruitment of patients, data collection. Participation in data analysis and interpretation of results. First author of manuscript's first and final draft and responsible for the correspondence the journal publishing the manuscript.

ABBREVIATIONS

BBB	Blood-brain barrier
BPF	Brain parenchymal fraction
CNR	Contrast-to-noise ratio
CNS	Central nervous system
CSF	Cerebrospinal fluid
DSC	Dynamic susceptibility contrast
DTI	Diffusion tensor imaging
DWI	Diffusion weighted image
EPI	Echo planar imaging
FLAIR	Fluid attenuated inversion recovery
FSE	Fast spin echo
FSPGR	Fast spoiled gradient echo
Gd	Gadolinium
GM	Grey matter
GRE	Gradient echo
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
NAWM	Normal appearing white matter
PD	Proton density
PP	Primary progressive
PWI	Perfusion weighted image
qMRI	Quantitative magnetic resonance imaging
R ₁	Longitudinal relaxation rate [s ⁻¹]
R ₂	Transverse relaxation rate [s ⁻¹]
rCBV	Relative cerebral blood volume
RF	Radiofrequency
ROI	Region of interest
RR	Relapsing-remitting
SE	Spin echo
SP	Secondary progressive
SyMRI	Synthetic magnetic resonance imaging

T1	Longitudinal relaxation time [s]
T2	Transverse relaxation time [s]
T1WI	T1 weighted image
T2WI	T2 weighted image
TE	Echo time
TR	Repetition time
TSE	Turbo spin echo
WM	White matter

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INTRODUCTION

This thesis is dedicated to applying a new quantitative MR sequence, synthetic MRI, in different groups of patients with varying neurological conditions. The brain is therefore in focus, and the main diagnoses examined are multiple sclerosis (MS) and malignant glioma.

The Human Brain

The central nervous system (CNS) consists of the brain and the spinal cord, and it controls the human body. The two major components of the brain are grey matter (GM) and white matter (WM), with a maximum age-dependant GM/WM volume ratio of 1.5, with a peak of white matter volume in mid-life. [1]

The grey matter consists of neurons, nerve cell bodies with their dendrites, mainly located at the surface of the brain, the cortex. There is also grey matter located in the depth of the brain, where clusters of neurons form functional units in the basal ganglia and the midbrain.

The white matter consists of myelinated axons that conduct signals to and from the neurons, and interspersed in the white matter are glia cells (astrocytes, oligodendrocytes and microglia). The myelin envelopes the axons and increases the conduction of the nerve impulses. Myelin is rich in fat, which gives the white matter its characteristic whitish colour.

Figure 1: The grey and white matter of the brain in a supratentorial axial slice

The blood-brain barrier

Compared to the rest of the body, the walls of the vascular system in the CNS have a unique contexture: the blood-brain barrier (BBB) of the endothelium of the capillaries in the CNS. The BBB regulates the micro-environment of the CNS and protects it from injury and disease. The BBB has several components, one of which is the specialised, highly polarised endothelial cell in the vessel wall. These endothelial cells are held together by tight junctions, preventing paracellular movement of ions and molecules. They also lack fenestra, have low rates of transcytosis, express efflux transporters and specific transporters for essential nutrients and ions across the BBB. In this way, there is a controlled access of molecules, cells and drugs to the CNS. [2,3]

During disease, the BBB can become disrupted, e.g. due to inflammatory or malignant processes. This can be used diagnostically in radiology through the administration of intravenous contrast agents. Normally, intravenous contrast agents stay within the vascular tree, but with BBB damage, there is an abnormal passage (leakage) of contrast agent into the CNS as a sign of disruption, e.g. with contrast agent accumulation within brain tumours. [4]

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the CNS, manifested by demyelinating lesions predominantly in the white matter of the brain and spinal cord. The demyelination and inflammation give rise to different neurological symptoms and signs of varying degree, e.g. weakness, sensory disturbances, bowel and bladder dysfunction, ataxia, cognitive dysfunction. [5]

The disease has a predominance for females, with a 2:1 ratio, often with an onset in the 30s and an incidence of approximately 5-10/100 000. [6,7] The estimated worldwide number of people with MS is 2.3 million, and the prevalence shows a variation in different parts of the world. MS is more common in northern Europe and North America, with prevalence rates of approximately 100-180/100 000, compared to regions closer to the equator with rates of approximately 5-20/100 000. [8]

The diagnosis of MS is based on typical neurological symptoms and CNS lesions disseminated in space and time. Characteristic, demyelinating CNS lesions are located in the periventricular white matter, in the jux-

tacortical region, in the optic nerves, in the infratentorial region, and in the periphery of the spinal medulla. If the clinical syndrome is distinctive of MS, MRI can confirm the diagnosis if the image findings are typical. Analysis of the cerebrospinal fluid (CSF) can give additional information to support the diagnosis based on presence of IgG oligoclonal bands. [5]

The clinical course of MS can differ, and depending on the pattern of symptoms and clinical status development, the disease can be divided into different subgroups/phenotypes. The most common form of MS is the relapsing-remitting type (RR), affecting approximately 85% of patients. This type of MS is characterised by relapses (episodes of neurological dysfunction) followed by periods of remission. Approximately 15% of patients have a primary progressive MS (PP), with an insidious, slow progress of neurological disability over time. RR MS can convert into secondary progressive MS (SP) at a later stage, with a gradually worsening disability, exhibiting motor impairment, ataxia, and visual and cognitive dysfunction. [5,9,10] A first episode of neurological dysfunction suspicious for MS is called clinically isolated syndrome (CIS). Two-thirds of CIS patients will convert to MS, and abnormalities on the first baseline scan can predict the subsequent development of MS. [11]

There are at present several pharmacological treatment options for RR MS, but these drugs are only disease modifying and do not offer a cure. The MS drugs can have severe side effects, and the treatment needs to be individually tailored and evaluated with respect to desired clinical effect and possible side effects. [12] If the desired clinical response is not achieved, a therapy switch can be necessary. [13] The treatment effect is evaluated by the presence of disease activity manifested by clinical relapses and/or typical MRI findings in combination. [12] For PP and SP MS, there have been trials to try to find effective therapies to prevent worsening, but so far without much success. [9]

The MS lesion and neurodegeneration

Demyelinating white matter lesions are the hallmark of MS. The process of forming a demyelinating lesion is closely related to the activation and entrance of cells of the immune system into the CNS. [14] The acute MS plaque is hypercellular, characterised by inflammatory changes, an increase of lymphocytes (mainly T cells) and macrophages, with an ill-defined margin. The chronic plaque exhibits hypocellularity, loss of myelin and scarring, with a sharp border. [15,16]

The focal MS plaques are not only a site of demyelination, but they are also associated with axonal damage. [17] Axonal transection in the lesions can lead to Wallerian degeneration in other parts of the brain, and MS is also associated with a neurodegenerative process affecting the white matter and with the development of atrophy. [18] These general neurodegenerative processes are probably present from an early stage of the disease, but become more evident during the progressive phase of the disease. [19]

Malignant gliomas

Glioma is the most common primary malignant brain tumour, and depending on malignancy grade (WHO I-IV) gliomas have a varied prognosis. Highly malignant gliomas have a worse outcome, with a median survival of approximately 14 months for the most aggressive grade IV glioma subtype, the glioblastoma. [20–22]

In 2016, a new WHO classification for brain tumours was published. Previous classifications have been based on the histological properties of brain tumours, but the 2016 classification also takes molecular and genetic markers into consideration in the description of brain tumours. [23] The molecular markers now introduced as a routine part of the glioma classification are mutations in the isocitrate dehydrogenase gene (IDH) and the 1p/19q status. [24] With the introduction of these molecular markers, it is now recognised that malignant gliomas may have an appearance on MRI that not necessarily agrees with the expected malignancy grade. [25]

Damage to the BBB with subsequent contrast leakage is a hallmark of malignant gliomas. These tumours induce a pathological neoangiogenesis with an increase of local blood volume which can be detected with MR perfusion techniques [26], and a defective BBB [27] which can be detected by contrast enhancement on conventional MRI.

The contrast enhancing border of the tumour is usually defined as the tumour limit, e.g. at surgery, when resection is considered radical if all contrast enhancing parts of the tumour are removed. However, gliomas have a diffuse, infiltrative way of growing in the brain [28], and they exhibit peritumoral oedema, i.e. an increase in water content surrounding the tumour. This makes it difficult to truly delineate the tumour from the surrounding healthy brain tissue by visual assessment, both in imaging studies and also during surgery. [29] The infiltrative growth pattern is also a basis for metastatic spread, which makes these tumours very difficult

to treat [30], even though standard treatment is aggressive, including maximal safe surgical resection, with subsequent radio- and chemotherapy. The oncological treatment regimen typically includes temozolamide with concomitant radiotherapy followed by adjuvant chemotherapy with temozolamide. [22]

Magnetic Resonance Imaging

MRI is a non-invasive, non-ionizing radiation imaging technique which mainly uses the magnetisation of water protons of the body to depict the tissues. With a high soft tissue contrast, MRI has a high sensitivity for detecting pathological changes in the CNS and is a standard technique in neuroradiology.

The biological and physical bases for this technique is that the protons of the body possess magnetic properties, with a magnetic dipole moment similar to a small bar magnet. The protons also exhibit spin, i.e. an intrinsic angular momentum where they precess around the magnetic field axis.

Figure 2: A spinning proton exhibiting a magnetic dipole moment.

The MR scanner contains an extremely strong stationary magnetic field, B_0 , with the most common clinical field strengths of these super-

conducting electromagnetic coils being 1.5 or 3 Tesla. The MR also contains gradient coils in three different directions, which are used to produce in space linearly distributed and in time transient magnetic fields in the three orthogonal planes (x, y, and z). The application of linear gradients allows for spatial encoding, using the frequency and phase properties to establish the orientation of the tissue examined. Furthermore, the scanner depends on the application of radiofrequency pulses (RF), and detection of those, by transmitter and receiver functions. Typically, the transmitter coil is stationary, built into the bore of the magnet, whereas the receiving coils are more flexible to fit the anatomy under investigation.

To induce a signal from the tissue, the transmitter emits a RF pulse, also called B₁, applied at the precession frequency of protons: 42.6MHz/T (the Larmor frequency). The transmitted RF pulse induces a rotation of the net magnetic moment to the transverse plane, perpendicular to the main magnetic field, with a loss of net magnetisation. As soon as the RF pulse ends the net magnetisation will start to recover to thermal equilibrium along the z-axis. This recovery is sampled using the receiver hardware which picks up very faint RF-signals from the tissue, via the detection coils close to the anatomy under investigation. The signal that has been obtained in this manner is then mathematically transformed into an image (Fourier transformation).

The images formed from the RF signal are converted into a grey scale image, but the scale is unique for each scan, depending on, e.g., scanner settings, magnetic field inhomogeneity, and coil imperfections. [31] This means that the values of the pixels in the images cannot be compared between different exams, i.e. there is an arbitrary intensity scaling of the conventional MR images. This is a disadvantage compared to another common modality, computed tomography, which has a somewhat more rigid correlation between tissue properties and image intensity.

Relaxation

When the patient is positioned in the B₀ magnetic field of the MR scanner, a net magnetisation (M₀) is formed in the z-direction (head-feet direction of the patient). The pulse sequence of choice is applied to the tissue by the transmission RF pulse and the gradients, and the tissue will

then recover under the influence of longitudinal and transverse relaxation.

The longitudinal relaxation, T_1 , affects the net magnetisation in the z-direction (along the magnetic field) and is the process by which the net magnetisation regains thermal equilibrium after the RF pulse. T_1 is also referred to as the spin-lattice relaxation, dependent on the interaction of the excited protons and the electromagnetic fields in the surrounding structures. This is also the basis for the effect of gadolinium (Gd)-based contrast agents, which have a T_1 shortening effect due to their paramagnetic properties. T_1 is by definition the time required to regain 63% of the longitudinal magnetisation.

Figure 3: T_1 relaxation curve

The transverse relaxation, T_2 , has an effect on the decay of the net magnetisation in the transverse plane, causing the MR signal to diminish due to dephasing of the precessing protons. T_2 is also referred to as spin-spin relaxation, as it depends on local magnetic field inhomogeneities. T_2 is defined as the time required for the transverse magnetisation to fall to 37% of its maximum level after excitation.

Figure 4: T2 relaxation curve

T1 is always longer than T2, although relaxation times will also vary with field strength and differ for various tissues. They both change to a different degree as a function of field strength; T1 increases with field strength, whereas T2 stays relatively constant at moderate changes of magnetic field.

At 1.5T, WM T1 values are reported to be approximately 500-600 ms and T2 values approximately 60-80ms. For GM, T1 is approximately 900-1100 ms and T2 80-100 ms. CSF is typically characterised by T1 values around 4000 ms and T2 values of 2000 ms. [32,33]

At 3T, WM T1 values are reported to be 800-900 ms and T2 values to be 70-80 ms. For GM at 3T, T1 has been reported to be 1200-1400 ms and T2 100-110 ms. [34] The relaxation rates, R1 and R2, are defined as the inverse of the respective time constant:

- R1 (longitudinal relaxation rate) = $1/T1$
- R2 (transverse relaxation rate) = $1/T2$.

Pulse sequences

Pulse sequences can for the most part be divided into two major groups, spin echo (SE) or gradient echo (GRE) sequences. The SE typically uses a 180° RF pulse to refocus the spins, whereas the GRE uses mag-

netic field gradients for the same purpose. The signal from the tissue is collected in a repeated manner (a number of "scans" are acquired and accumulated), and the time between each application of the complete pulse sequence is called the repetition time (TR). The echo time (TE) describes the time between the RF pulse train and the acquired echo. Depending on a range of scanner settings and parameters, different pulse sequences give rise to a wide range of different types of MR images, e.g. T1W, T2W, and T2FLAIR (figure 5).

Figure 5: Sample images of the brain; T1WI to the left, T2WI in the middle and T2FLAIR to the right.

On T1W images, tissues with a high concentration of slowly relaxing protons (like CSF) will appear dark. Tissue with more fat content and shorter T₁, like WM with myelin, will appear brighter than GM. In contrast, on T2W images CSF appears very bright with a high signal, whereas WM is darker than the GM. On T2 FLAIR images, freely moving (and slowly relaxing) water will appear dark due to application of an inversion pulse, whereas more restricted water in the tissue, i.e. oedema, will appear bright.

A typical MR examination can yield a large number of different images with characteristics depending on the specific pulse sequence that has been applied. Scan time of each image sequence vary, from approximately 2 to 10 minutes to acquire, and the total scan time of MR examinations is therefore longer than most other medical imaging modalities. A clinical MR examination normally takes 30-60 minutes, depending on which spe-

cific acquisition protocol that is used. In comparison, computed tomography, typically takes only a few minutes to acquire.

Quantification of relaxation

Since the images retrieved from conventional MR sequences depend on a multitude of scanner settings, the inhomogeneity of the radiofrequency field (B_1), and the coil sensitivity profile, the signal intensity will unavoidably vary between MRI examinations obtained on different occasions and between different patients and scanners. This makes it impossible to compare absolute signal intensities in the images obtained at different MR-examinations.

A solution to this difficulty is to quantify the physical properties of the tissue by measuring the relaxation characteristics, i.e. relaxometry. Quantitative data can improve characterisation of observed signal changes and allow for longitudinal comparisons in a repeatable and consistent manner. Since T_1 recovery and T_2 decay curves are exponential curves, it is possible to calculate the expected signal related to T_1 and T_2 from the acquired data by nonlinear curve-fitting algorithms.

Relaxometry is not a new concept, it was pointed out in the original work by Lauterbur, [35] and several relaxometry methods have since been published. However, they have not previously been widely implemented into the clinical workflow, due to very long acquisition times [36,37] or cumbersome post-processing requirements. [38] Many of these relaxometry methods have only been able to quantify one single parameter at a time, thus not having the ability for simultaneous T_1 and T_2 quantification. Recently, a new method with clinically acceptable scan-time for quantification of T_1 and T_2 has emerged: magnetic resonance fingerprinting (MRF). MRF uses a pseudo randomized acquisition with varying acquisition parameters (flip angle, TR etc). This causes the signal from different tissues to have a unique signal evolution in each voxel, known as “fingerprint”. After acquisition a pattern recognition algorithm is used to match the MRF data to a predefined “fingerprinting dictionary” of signal evolution. [34,39,40]

The work in this thesis is based on the quantitative sequence synthetic MRI; a 2D-FSE multi-dynamic, multiecho sequence for quantification of T_1 , T_2 , and PD.

Synthetic MR

Synthetic MR is based on a quantitative MR sequence measuring the longitudinal relaxation rate (R_1), the transverse relaxation rate (R_2), and the proton density (PD), with a scan time of 6-7 minutes. [33,41] It is a saturation recovery FSE sequence with several different saturation delays, and each acquisition consists of a multi-echo read-out. The slice-selective saturation pulse, with a flip angle of 120° , acts on slice n . The slice-selective excitation pulse acts on slice m , followed by acquisition of multiple echoes with refocusing pulses with an echo train length of 10. (Figure 6)

Figure 6: The synthetic pulse sequence, with the echoes numbered to identify the modulus images in figure 7.

By acquiring multiple echoes, several time-points on the T_2 relaxation curve are acquired within the same sequence, which makes it possible to calculate T_2 . The sequence is repeated several times with different saturation delays by changing the difference between n and m . The shortest delay time is used when $m = n + 1$, i.e. the acquisition is performed directly after the saturation pulse. The longest delay time is used when $m = n + \text{numSlices} - 1$, i.e., the acquisition is performed directly before the subsequent saturation and hence the delay time is nearly 1 TR . Thus several time-points on the T_1 relaxation curve are acquired within the same sequence, and T_1 can also be calculated. From this T_1 curve, it is then possible to determine the effective saturation flip angle and the effect of local

B1 field inhomogeneity. The eight readouts give eight modulus images (figure 7).

Figure 7: Modulus images from the quantitative scan, the numbers correspond to the echos in figure 6.

The modulus images are transformed into quantitative R1, R2, and PD maps (figure 8) that form the basis to create synthetic MR images with different parameters with a free range of TR and TE, e.g. T1W (short TE, long TR), T2W (long TE, long TR), and T2FLAIR (long TE, long TR, and with an inversion pulse to suppress CSF), (figure 9). The quantitative maps can be used for analysis of tissue relaxation time values, tissue segmentation, and volumetrics, and the synthetic images can be used to visually assess the tissue.

Figure 8: R1, R2, and PD maps of the brain.

Figure 9: Synthetic MR images in top row; T1 on the left, T2 in the middle, and T2FLAIR on the right, matching the conventional images underneath.

The most commonly used entities when working with relaxometry are the relaxation times T1 and T2. However, in this sequence, the relaxation rates, R1 and R2 are measured. The rationale for this is that R1 and R2

have a linear relationship with paramagnetism which makes them a more robust measure when calculating relaxation of the tissue and effects of Gd-based contrast agents.

MRI in MS

MRI plays a central role in the work-up of suspected MS, with specific criteria for the diagnosis of MS. [5,42,43] The demyelinating lesions of MS have a typical distribution (figure 10), in the periventricular white matter, in the juxtacortical region, in the optic nerves, in the infratentorial region, and in the periphery of the spinal cord.

Figure 10: Typical MS lesions, a juxtacortical lesion on the left, a subcortical lesion in the middle, and periventricular lesions in the middle and on the right.

However, the imaging findings have to be carefully correlated with the clinical neurological status since the MRI by itself is not pathognomonic. [44] Baseline MRI at the first onset of neurological symptoms is a predictive tool, where the number of brain T2 hyperintense lesions is the most robust predictor for conversion to MS over time and also for disability accumulation. [45] Other MRI measures associated with an increased risk of MS over time are spinal cord lesions and GM lesions. [46,47]

During follow-up, new T2 lesions or contrast-enhancing lesions are signs of active disease, which can indicate the need for a change in therapy. The image findings have to be correlated with the neurological status, since isolated progression on MRI is controversial as a criterion for new therapy. [12,13] Disease activity on MRI is, however, sometimes associat-

ed with apparent clinical stability [48], which can depend on lesions localised in a non-eloquent area of the brain.

Disease activity in the form of new and/or contrast-enhancing lesions is important to detect with MRI. Another imaging feature to evaluate with MRI in MS is the general neurodegenerative processes that occur in parallel, including diffuse WM changes and atrophy development, which are predictors of disability and short-term disease evolution in MS. [49–51] These changes can be more subtle and are not always easy to detect visually on conventional images, and therefore quantitative MR sequences can improve the assessment of these features. [52,53] Quantitative MR sequences for volumetric measurements have only recently emerged as part of standard MS imaging, and have not been implemented at all centres. With synthetic MR, it is possible to calculate the brain parenchymal fraction (BPF) for longitudinal follow-up of, e.g., atrophy development in MS patients. [53,54]

MRI of malignant gliomas

MRI is routinely used in the diagnostics of brain tumours as well as during follow-up for treatment evaluation. Standard MRI protocols for brain tumours include conventional images before and after Gd-based contrast agent injection for visual assessment, but also diffusion- and often perfusion scans [55,56] for more quantitative aspects.

The diagnostic MRI is performed for characterisation of the tumour, assessment of possible differential diagnoses, and for anatomical mapping of tumour location in relation to eloquent areas of the brain. After surgery, MRI is performed preferably within 48 hours to assess the extent of resection. Follow-up MRI is then performed every 3 months during the oncological treatment, or sooner if clinical deterioration occurs.

With the introduction of new molecular analyses for tumour classification and rapid technical developments in radiology, there is extensive research into finding imaging correlates of glioma genotypes and possible image markers for prediction of outcome. [57–61] Thus far it has not been possible to single out clearly distinguishing imaging features for 1p19q or IDH status, with the exception of 2-HG (hydroxyglutarate) ^1H MR spectroscopy. This method has great potential for the detection of IDH-mutated tumour activity, but since the implementation is a challenge, the clinical applicability is limited. [25,62]

The typical appearance of a highly malignant glioma on MRI is an irregular tumour with intense contrast enhancement in the periphery, a necrotic centre, and peritumoral oedema (figure 11).

Figure 11: T1WGD image of glioblastoma on the left and T2FLAIR on the right. The tumour exhibits contrast enhancement in the periphery, central necrosis, and peritumoral oedema.

The infiltrative, non-enhancing parts of the tumour are very difficult, or most often impossible, to distinguish from the peritumoral oedema on conventional images. Eidel et al., however, showed that the non-enhancing part of the tumour had a higher relative content of viable tumour cells compared to the contrast-enhancing part of the tumour, and Barajas et al. also found tumour cells in the non-enhancing part of the tumour. [63,64] Findings like these indicate the need for seeking methods for analysis and visualisation of this part of the tumour.

It is recognised that the extent of tumour resection and residual tumour volumes are associated with survival and recurrence. [65–68] There is also evidence that the resection of FLAIR or DTI abnormalities beyond the contrast-enhancing part of the tumour can have an impact on outcome in glioblastoma patients [69,70] and that tumours reoccur predominantly at the resection margin. [71] The peritumoral oedema is therefore an area which is being thoroughly investigated with different techniques for a better assessment of tumour infiltration, including, e.g., diffusion [64,72,73], perfusion [74], and relaxometry. [75]

MR perfusion of the peritumoral area of malignant gliomas shows an increase in relative cerebral blood volume (rCBV) compared to metastases [76] due to the pathological neoangiogenesis induced by the glioma. The perfusion properties of the non-enhancing part of the tumour have also been shown to provide prognostic information, with a high rCBV predicting a worse outcome. [77]

MR diffusion of the peritumoral area exhibits a gradient in ADC values, indicating increased cell density closer to the tumour, and diffusion tensor imaging identifies invasive peritumoral regions with white matter disruption. [78–80]

Relaxometry of the peritumoral area of gliomas displays shorter T2-values compared to nonglial tumours [75], and with quantitative T1-mapping it is possible to detect subtle contrast enhancement, that is invisible in standard MRI. [81]

All of these techniques indicate the diffuse tumour infiltration surrounding the contrast-enhancing part of malignant gliomas, the area of interest for the analyses of paper III and IV.

AIMS

The general aim of this thesis was to apply synthetic MRI in different clinical settings and to evaluate its quality and potential use in different patient populations. The specific aim for each study was as follows:

- I. To evaluate synthetic MRI of the brain in a clinical setting by assessing the contrast, the contrast-to-noise ratio (CNR), and the diagnostic quality compared to conventional MRI.
- II. To compare the relaxation rates and proton density (PD) of active MS lesions before contrast agent injection with quantitative values from non-enhancing lesions to determine whether active MS lesions can be identified by synthetic MRI without the administration of a Gd-based contrast agent.
- III. To analyse the relaxation properties of the peritumoral oedema in patients with malignant gliomas before surgery, using synthetic MRI to assess whether relaxometry can detect changes of the peritumoral oedema not visible on conventional images.
- IV. To investigate the contrast-enhancing properties of malignant gliomas and their peritumoral area with relaxometry using synthetic MRI, and to analyse the peritumoral area with quantification of contrast enhancement.

MATERIAL AND METHODS

Ethical aspects

All studies were performed at the Department of Radiology and CMIV, Linköping University Hospital, Linköping, Sweden. Permission was granted from the regional ethical review board and informed written consent was obtained from all participants.

- **Paper I:** ethical permit Dnr M88-07
- **Paper II:** ethical permit Dnr M2-09
- **Papers III and IV:** ethical permit Dnr 2011/406-31

Subjects

Paper I

In this study, 22 patients referred to the MR unit from the department of neurology were asked by their neurologist to participate, and the quantitative synthetic MR sequence was added to their clinical MRI scan of the brain. Mean age was 53 years; range 21-85. Eight patients had known MS, seven patients had experienced an ischaemic event, and seven patients had an unclear diagnosis.

Paper II

Forty-six patients with a clinical suspicion of MS were consecutively enrolled in a prospective longitudinal cohort study of early MS at the Department of Neurology and the University Hospital Linköping. Two patients were excluded, 1 due to withdrawal of consent and one due to the finding of another diagnosis.

Patients were classified as having possible MS (23) or MS (21) according to the revised McDonald criteria. Median age was 31; range 21-62, with eight males and 36 females.

MR imaging according to a standard clinical MS protocol with the addition of synthetic MRI before and after administration of Gd-based con-

trast agent was performed at inclusion (baseline) and after 1 year. In addition, 4 patients had an extra MR examination during the first year in relation to clinical relapse. In total, 92 MR examinations were performed and analysed.

Paper III

Twenty-four patients with typical radiological findings suggestive of a high-grade malignant glioma were prospectively included in the study. Diagnosis was confirmed by histopathological analysis according to WHO brain tumour classification 2007. Three patients were excluded due to other diagnoses and two patients were not analysed due to difficulties in delineating the contrast-enhancing part of the tumour from the peritumoral oedema.

In total, 19 datasets were analysed, mean age was 62; range 34-79, with 5 females and 14 men.

Paper IV

The same cohort of patients was used as in paper III, with the addition of one subject, leading to a total number of 20 patients for analysis. Mean age 60; range 34-79, 5 females and 15 men.

MR acquisition

Paper I

Patients were examined on a 1.5T scanner (Philips Achieva, Best, the Netherlands). Conventional T1W SE images, T2W TSE images and T2W FLAIR images were acquired in 3:39, 2:01, and 4:30 min (total scan time 10:10 min, slice thickness 5 mm for the standard brain protocol) and 5:11, 3:42, and 6:01 min (total scan time 14:54 min, slice thickness 3 mm for the MS protocol), respectively.

The quantitative synthetic MR sequence is a saturation recovery TSE with four different saturation delays at 130, 380, 1230, and 2580 ms. Each acquisition consisted of a multi-echo read-out with six echoes at multiples of 15 ms. The synthetic sequence was acquired in 5:48 min, with a slice thickness of 6 mm.

Synthetic images matching the conventional MR images were created using SyMRI Diagnostics (SyntheticMR AB, Linköping, Sweden).

Paper II

Images were acquired on a 1.5T Achieva scanner (Philips Healthcare, Best, the Netherlands). Conventional T2W FLAIR, T1W SE before and after Gd-based contrast agent injection, and T2W SE images were acquired as well as the quantitative synthetic MR sequence before and after Gd-based contrast agent injection.

The quantitative synthetic sequence had TE: 14, 28, 42, 56, and 70 ms. TR: 4244ms: TI: 0:0974, 0:5846, 1:8511, and 4:0919 s. Scan time was 6:09 min.

All images had a slice thickness of 3 mm without an intersection gap.

Paper III

Patients were examined on a 3T MR scanner (Discovery 750, GE Medical Systems Milwaukee, WI, USA), according to the clinical protocol for brain tumour investigation, with the addition of the quantitative MR sequence SyMRI MAGIC before and after Gd-based contrast agent injection.

The conventional images used in the study analysis included DSC perfusion GRE EPI, T1W SE images before and after Gd-based contrast agent injection, and T2W SE PROPELLER.

The quantitative synthetic MR sequence, qMRI MAGIC, measured 8 images per slice with TE 22 or 95 ms, TR 4000 ms, and TI 170, 670, 1 840 or 3 840 ms. The sequence was obtained before and after contrast agent injection. The scan time was 5:55 min.

Paper IV

Images were acquired as described for paper III, with the addition in this analysis of a 3D FSPGR Gd sequence.

Image analysis

Paper I

Image quality of synthetic images was compared to conventional images by measuring the contrast and CNR, and the diagnostic quality was assessed by visual grading assessment. Images were anonymised and transferred to a visual grading software package (ViewDEX, University of Gothenburg, Sweden) [82] and presented individually to the two neuro-radiologists in a random order at different times.

In all, 12 ROIs were drawn in different parts of the brain in each patient, including GM, WM, and CSF, to assess the contrast and the CNR. White matter lesions were present in 15 patients, and a ROI was drawn in one such lesion in each of these patients. The mean value and the standard deviation of the signal intensity within each ROI were recorded. The contrast between ROIs was calculated as the intensity difference divided by the sum of the intensities. The CNR was calculated as the intensity difference divided by the median standard deviation of all ROIs in each patient.

Image quality was evaluated by two neuroradiologists using a 4-point scale for eight different criteria. Four criteria were from applicable parts of the European guidelines for assessment on image quality [83], and four criteria were constructed along the same format for the purpose of the study. The neuroradiologists were also asked to make a probable diagnosis.

In the final evaluation, the corresponding conventional and synthetic images were placed adjacent to each other, and a visual evaluation was done to determine whether conventional or synthetic images were superior for the visualisation of white matter lesions.

Paper II

The relaxometric properties of contrast enhancing MS lesions were analysed by placement of ROIs in different types of MS lesions, before and after contrast agent injection. Synthetic images matching the corresponding conventional images were created using SyMRI Diagnostic software (SyntheticMR, Linköping Sweden) and anonymised using MeVisLab 2.4 (MeVis Medical Solutions, Bremen, Germany). For each patient the

matching images were displayed side by side to the neuroradiologists, and MS lesions were identified by visual assessment as enhancing or non-enhancing.

ROIs were placed in the synthetic images within MS lesions > 3 mm in diameter. ROIs in non-enhancing lesions were drawn in the sT2WI, and ROIs in enhancing lesions were placed in sT1WGd images (figure 12).

Figure 12: Synthetic T1WI to the right, synthetic T1WIGd to the left. Example of ROI placed in an active MS lesion close to the right lateral ventricle.

The sT1WGd was registered to the sT1W using rigid registration with the image registration toolkit in MeVisLab, and a transformation matrix was used to register the sT1WGd ROIs of enhancing lesions to the precontrast synthetic volume to obtain the ROI values before contrast agent injection.

ROIs were also placed in the synthetic T2WI in the NAWM in a corresponding location in the contralateral hemisphere (figure 13).

Figure 13: Synthetic T2WI. Example of ROI in the contralateral NAWM in the left hemisphere.

Paper III

In this paper the peritumoral oedema was analysed by measuring relaxation values and relative cerebral blood volume (rCBV) values in ROIs placed outside of the contrast-enhancing tumour border. Conventional T2W, T1W, and T1W-Gd images with corresponding synthetic images were transferred to software MeVisLab 2.7. The perfusion data were analysed with NordicICE (version 2.3.12, Nordic NeuroLab AS, Bergen, Norway). Motion-corrected realigned perfusion data were used to create whole brain CBV maps with auto-detected noise threshold and leakage correction. CBV values were normalised against the contralateral hemisphere to obtain rCBV.

ROIs were drawn by a neuroradiologist, and the contrast enhancing border of the tumour was manually delineated in the synthetic T1WGd image. A second free-hand ROI was drawn in the non-enhancing peritumoral oedema in the synthetic T2WI.

Figure 14: Synthetic T1WGd on the left, with ROI delineating the contrast-enhancing part of the tumour. Synthetic T2W image on the right with ROI in the peritumoral oedema

ROIs were also placed in the synthetic T2W images in NAWM adjacent to the tumour oedema and in the corresponding lobe in the contralateral hemisphere. The ROIs in the synthetic T2 image volume were directly applied to all images, and to qMRI maps that were calculated from the same qMRI volume. To apply the tumour ROI delineated in the qMRI volume post-Gd in the qMRI volume pre-Gd, a coordinate transformation matrix was calculated by rigid image registration in MeVisLab. The tumour ROI was subtracted from the oedema ROI to avoid overlap of contrast enhancement. The inverse transformation matrix was used to transform the ROIs in the oedema and the white matter to the qMRI-Gd volume.

The oedema ROI and the white matter ROIs were also transformed to the CBV map of the perfusion analysis to obtain the rCBV values of the peritumoral oedema. This transformation matrix was also calculated using rigid image registration in MeVisLab, with the synthetic T2W volume registered to the baseline EPI of the perfusion series.

Paper IV

The non-enhancing peritumoral area was analysed by subtracting native images from post-contrast images to detect possible subtle contrast enhancement. Conventional T2W, T1W, T1W-Gd, and 3D-FSPGR Gd images

and corresponding synthetic images were transferred to MeVisLab 2.7. ROIs were drawn by a neuroradiologist for the analysis.

The outer contrast enhancing borders of the tumours were delineated in the synthetic T1W-Gd images as well as in the conventional SE T1W-Gd and in the 3D-FSPGR-Gd images (tumour ROI). A second free-hand, extended tumour-ROI was placed approximately 1 cm outside of the tumour ROIs in the synthetic T1W-Gd and in the conventional T1W-Gd images (figure 15). Care was taken not to include contrast-enhancing structures, e.g. vessels or the choroid plexus.

Figure 15: One ROI delineates the contrast-enhancing part of the tumour (tumour ROI) and a second ROI encircles the non-enhancing peritumoral area (extended tumour ROI).

The peritumoral area was analysed by subtracting the tumour ROI from the extended tumour ROI, i.e. extended tumour ROI – tumour ROI = peritumoral ROI (fig 14). In tumours with a purely necrotic core, a ROI was placed in the necrosis.

ROIs were also placed in synthetic and conventional T1W-Gd images in the NAWM in the corresponding lobe at the same level in the contralateral hemisphere (NAWM ROI).

A transformation matrix was calculated for pre-Gd to post-Gd transformations by rigid registration of synthetic T2WI to synthetic T2W-Gd images using MeVisLab. The transformation matrix was used to trans-

form R1 maps from pre-Gd space to post-Gd space. The quantitative difference in R1 relaxation due to contrast enhancement was calculated as the difference between the R1 post-Gd maps and the transformed pre-Gd-R1 map (R1 difference map).

Similarly, contrast enhancement in conventional SE T1W images was calculated by registration of the pre-Gd T1WI to the post-Gd T1WI to obtain the difference map. The rigid registration was performed using MeVisLab. The difference in image contrast was calculated by subtracting the transformed T1W pre-Gd volume from the post-Gd T1W volume (T1 difference map).

All ROIs were directly applied to the corresponding R1 or T1 difference map. To correct for the effect of Gd in the blood, the normalised R1 and T1 differences in the peritumoral ROI were calculated for each subject by normalising the individual peritumoral ROI with the individual NAWM value. This was done by subtracting the NAWM-difference from the R1 difference of each subject.

Statistical analyses

Paper I

Correlations between the contrast and CNR measurements in synthetic and conventional images were analysed using linear regression. Scores for the image quality criteria were analysed with visual grading regression. [84] The agreement between observers concerning diagnosis was described with the unweighted kappa coefficient. The frequency of correct diagnosis was compared between conventional and synthetic acquisition with binary logistic regression.

Paper II

Mean values of R1, R2, and PD in each ROI were compared by using a mixed linear model. For comparison between types of ROIs, Tukey *t* test was used. In addition, receiver operating characteristic (ROC) analysis was performed after aggregating data to the ROI level (excluding NAWM). Lesions were classified as non-enhancing or enhancing by using each of the measured entities (R1, R2, and PD) and a linear combination of the 3, obtained with a logistic regression model; the corresponding area under curve was reported.

Paper III

Mean values for R1, R2, PD, and rCBV for each individual ROI were calculated. These values were used to obtain group mean and standard deviation of each ROI type.

In the oedema ROI, the relationship between the quantitative values and the distance of each individual voxel to the contrast enhancing part of the tumour was investigated using mixed linear models.

The difference in slope for R1 post-Gd compared to the slope in R1 pre-Gd was analysed using Student's *t* test.

Paper IV

Descriptive histograms were calculated and plotted in MatLab (Mathworks Inc, Natick, MA USA). The mean and standard deviation for each ROI were calculated in each subject. A one-sided *t* test was performed on the peritumoral ROI and the NAWM ROI.

RESULTS

Paper I

Visual evaluation

Scoring results from the visual grading assessment for five of the eight quality criteria is presented in figure 16. Criterion 1: differentiation of grey-white matter. Criterion 2: demarcation of caudate nucleus head. Criterion 3: demarcation of the lentiform nucleus. Criterion 4: demarcation of the sulci. Criterion 5: perceived level of signal to noise.

Figure 16: Visual scoring diagram for criteria 1-5 for T1W, T2W, and T2FLAIR images. For each column, the values for the conventional (c) images are given on the left, and for the synthetic images (s) on the right.

The differentiation between grey and white matter, and the demarcation of sulci were found to be better in the conventional images compared to the synthetic images ($p < 0.0001$ for T1WI and T2WI, $p = 0.046$ for

T2FLAIR). The demarcation of basal ganglia was better in the conventional T2WI ($p < 0.0001$) and FLAIR images ($p = 0.003$), whereas there was no significant difference in the T1WI. The perceived signal-to-noise level was lower in the synthetic images ($p = 0.009$).

There was no significant difference in pulsation artefacts between the sequences. Compared with corresponding conventional images, synthetic T1WI and FLAIR had more parallel imaging artefacts ($p < 0.0001$ and $p = 0.004$ respectively) and were more sensitive for other artefacts (e.g. motion) ($p < 0.0001$). The synthetic T2WI had fewer of other artefacts ($p = 0.009$).

Regarding the overall scoring for the eight quality criteria, 87% of the synthetic T1WI were assessed to be of sufficient diagnostic quality or better, compared to 90% for the conventional T1WI. For T2WI, the figures were 89% for the synthetic, compared to 95% for the conventional. Eighty-two percent of the synthetic FLAIR images were of diagnostic quality or better compared with 94% of the conventional FLAIR.

Lesion conspicuity was assessed to be better in all of the synthetic T1W images compared to the conventional images. For T2W and T2FLAIR, the conventional images had better lesion conspicuity (82% and 100% respectively).

With regard to diagnosis, synthetic T1W images had a higher frequency of correct diagnosis (73%) compared to conventional images (64%, $p = 0.02$). There was no significant difference regarding T2 and T2FLAIR. Inter-observer agreement regarding diagnosis was high. The greatest difference between the sequences was in the T1W images, with kappa values of 0.85 for synthetic and 0.48 for conventional. In the FLAIR sequences kappa values were 0.86 for conventional images and 0.65 for synthetic, and for T2W images, 0.80 for conventional and 0.86 for synthetic images.

Contrast and CNR measurements

The results of measurements of image contrast and CNR are presented in figure 17.

Figure 17: Correlation of contrast and CNR between conventional and synthetic images in % units. Markers indicate mean contrast and CNR value between each combination of the GM/WM (squares), CSF/GM (dots), CSF/WM (triangles), and lesion/WM. Error bars indicate one standard deviation.

Synthetic T1W images had 21% better contrast but 7% lower CNR than conventional T1WI. Synthetic T2W images had 16% better contrast and 16% lower CNR. T2FLAIR had 19% lower contrast and 38% lower CNR compared to conventional images.

Paper II

Out of the 92 MR examinations, 14 contained both contrast-enhancing and non-enhancing MS lesions. Forty-four had non-enhancing MS lesions only. These 58 examinations were obtained from 29 individuals. Thirty examinations had no lesions, or MS lesions that were < 3mm.

Forty-three ROIs were drawn in enhancing MS lesions, and 622 ROIs were drawn in non-enhancing lesions. One hundred and two ROIs were drawn in the NAWM, approximately 2 ROIs per examination with typical MS lesions.

Enhancing MS lesions had significantly higher precontrast mean R1, higher mean R2, and lower PD (table 1). Precontrast relaxation times were thus shorter for the enhancing lesions than the non-enhancing lesions.

Table 1: Quantitative measurements of NAWM, enhancing, and non-enhancing MS lesions before Gd-based contrast agent injection^a

	R1 (1/s)	R2 (1/s)	PD (%)
NAWM (n =102)	1.71±0.09	13.1±0.67	62.4±1.9
Enhancing lesions (n = 43)	1.22±0.36	9.8±2.6	77.0±11.2
Non-enhancing lesions (n = 622)	0.89±0.24	7.4±1.9	89.8±8.4
Difference between enhancing and non-enhancing lesions	+0.33 ^b	+2.43 ^b	-12.8 ^b

^a Data are means. Differences are estimated as least square means and are tested with the Tukey *t* test. ^b $p < .001$.

Distributions of mean R1, mean R2, and mean PD for enhancing and non-enhancing lesions are shown in figures 18-20. Enhancement was rare in lesions with a mean R1 value below 0.8 s⁻¹ (sensitivity 0.884). On the other hand, above this threshold, enhancing lesions were still less frequent than non-enhancing ones, and the specificity was only 0.360 (figure 18).

Figure 18: Histograms of mean R1 for enhancing and non-enhancing lesions.

Very few enhancing lesions had a mean R2 value below 6 s⁻¹ (sensitivity 0.954), whereas higher mean R2 values were not specific for enhancing lesions (specificity 0.249) (figure 19).

Figure 19: Histograms of mean R2 for enhancing and non-enhancing lesions.

Mean PD values above 95% were very seldom found in enhancing lesions (sensitivity 0.977), but even below this threshold, the enhancing lesions made up a minority of the findings (specificity 0.317) (figure 20).

Figure 20: Histograms of mean PD for enhancing and non-enhancing lesions

When sensitivity and specificity for all possible thresholds were combined in a receiver-operating characteristic analysis, the area under the curve was 0.764 for mean R1, 0.760 for mean R2, and 0.811 for PD. For the optimal linear combination of the three measurements obtained by logistic regression, the AUC was only slightly higher (0.832). Table 2 shows the sensitivity and specificity for a few different cut-off values for predicting enhancing MS lesions.

Table 2: Sensitivity and specificity for different cut-off values for relaxation values to predict enhancing MS lesions

Relaxation Value	Sensitivity (%)	Specificity (%)	Youden Index ^a
R ₁ measurement			
1.28	47	95	42
1.17	58	90	48
1.10	60	82	42
R ₂ measurement			
10	51	93	44
9.34	63	87	50
8.70	65	78	43
PD measurement			
77.69	54	92	46
79.96	61	87	48
82.53	63	82	45

^a Youden index = sensitivity + specificity -100

Paper III

Measurements of relaxation values in the peritumoral oedema revealed a decrease in R1 and R2 with increasing distance to the contrast-enhancing border of the tumour, with a significant ($p<0.0001$) gradient from the contrast-enhancing border to the periphery of the oedema. There was a slight increase in PD with increasing distance from the contrast-enhancing part of the tumour.

After Gd-based contrast-agent injection, there was a significant increase in gradient in R1 ($p<0.0001$), with higher R1 closer to the tumour. rCBV values were higher closer to the tumour, with a gradient from the contrast enhancing border of the tumour to the periphery of the peritumoral oedema. The gradients are seen in figure 21, which also depicts a

heterogeneous pattern of relaxation values within the first 10 mm of the peritumoral oedema.

Figure 21: Colour histograms of R_1 , R_2 , PD, and rCBV in the peritumoral oedema in relation to distance from the contrast enhancing part of the tumour of all patients. The thick black lines represent the regression line given by the mixed linear models, and the thin black lines are the confidence intervals.

Paper IV

Tumour structures vary and give rise to different appearances of malignant gliomas on MRI. This is also reflected in the relaxation patterns of the tumours. Figure 22 shows a typical glioblastoma with contrast enhancement in the periphery and a necrotic centre. The R1-difference graph for this tumour shows a peak around zero, corresponding to the necrotic centre, whereas the contrast-enhancing part of the tumour contributes to the right-shifted higher values on the x-axis.

Figure 22: T1WGd image of glioblastoma on the left, with intense contrast enhancement in the periphery and a necrotic centre. The corresponding R1-difference graph has a peak around zero accounting for the necrosis, and the contrast enhancement is evident on the x-axis.

A more solid appearing tumour is depicted in figure 23. Here, contrast enhancement is evident throughout the tumour, and the R1-difference graph has a different pattern, with a less dispersed, right shifted peak.

Figure 23: T1WGd image on the right of a glioblastoma with irregular contrast enhancement throughout the tumour, with the corresponding R1-difference graph on the right.

R1-difference graphs for the peritumoral area of all tumours and NAWM are seen in figures 24 and 25, respectively.

Figure 24: R1-difference graphs of the peritumoral area of all tumours.

Figure 25: R1-difference graphs of NAWM of all patients.

T1-difference graphs for the peritumoral area of all tumours and the NAWM are seen in figures 26 and 27, respectively.

Figure 26: The T1-difference graphs for the peritumoral area of all tumours.

Figure 27: The T1-difference graphs for NAWM in all patients.

Table 3 shows the mean and standard error of the peritumoral ROIs and the NAWM ROIs. There is significant peritumoral contrast enhancement in synthetic as well as conventional MRI, but also in the NAWM.

Table 3: Mean and standard deviation of R1- and T1-differences in ROIs of the peritumoral area and in the NAWM

Difference values for R1 and T1 in peritumoral area and in NAWM			
	Mean	SE	p-value
SyMRI R1-diff peritumoral area	0.057	0.007	<0.001
SyMRI R1-diff NAWM-ROI	0.024	0.008	0.002
Conventional MRI T1-diff peritumoral area	115	14	<0.001
Conventional MRI T1-diff NAWM-ROI	154	20	<0.001

When relaxation values in the peritumoral area were normalised to the NAWM (table 4), the R1-difference had a p-value of <0.001 for syn-

thetic MRI, but the T1-difference was not significant after normalisation since it was negative.

Table 4: Normalised difference values for R1 and T1 in peritumoral area

Normalised difference values for R1 and T1 in peritumoral area			
	Mean	SE	p-value
SyMRI R1-diff peritumoral area	0.033	0.009	<0.001
Conventional MRI T1-diff peritumoral area	-39	14	n.s.

DISCUSSION

Present work

This work has been carried out by applying synthetic MRI in different clinical settings. Synthetic MRI has two different fields of application: one is the synthetic images created for visual assessment and the other is the relaxometry which is the basis for quantitative assessment and analysis of tissue properties. Initial work was focused on the quality of the synthetic images and the possibility that they could replace conventional images. The subsequent studies were focused on the quantitative aspects of the sequence, with specific applications of relaxometry on MS and malignant gliomas.

Paper I

When it comes to radiology, the ongoing technical development has made it possible to continuously improve image quality and scan times, steadily providing images with higher resolution in less time, to facilitate the work of radiologists and to improve the basis for diagnosis. This applies to MRI as well as computed tomography, and therefore it is a challenge to introduce new methods that can be perceived to be of inferior image quality, but with other advantages, i.e. low-dose CT or synthetic MRI. New methods thus require validation and defined indications to be incorporated into clinical usage and to gain the trust of the radiologist.

With MRI, there is always a trade-off between scan time and image quality. With longer scan times, image quality generally improves - provided that the patient can refrain from movement. However, in the clinical workflow where there is a need for high throughput, MRI protocols are a compromise between adequate image requirements for diagnosis and a reasonable amount of time for the patient in the MR scanner. A sequence that potentially shortens scan time would therefore be desirable to implement, provided that the image quality is kept at a diagnostically acceptable level.

Visual assessment of image quality has by nature an element of subjectivity by the reader/radiologist. Even though image quality can be

scored and graded on a scale, the numbers are not absolute. This means that on a scale the differences in score do not always have the same meaning or value, i.e. on a scale of image quality criteria from 1 to 4 where 1 is the lowest value, the difference between 1 and 2 might not be the same as the difference between 3 and 4. This kind of data are ordinal-type data and need to be handled accordingly statistically. [84]

In this study synthetic images had lower scores on image quality compared to conventional images. However, they were comparable with conventional images when it came to a diagnostically acceptable level, with 82-89% of synthetic images having sufficient diagnostic quality compared with 90-95% of conventional images. A more recent study with a later version of the sequence for synthetic MR showed improved numbers, with 96% of synthetic images being rated as sufficient, compared to 98% for conventional images. [85] Tanenbaum et al. had a larger patient cohort with a wider range of diagnoses than our study, and they found that overall diagnostic image quality of synthetic images was statistically noninferior to conventional images.

Synthetic T1WI had higher lesion conspicuity than conventional T1WI, possibly due to the higher contrast, and this could explain the higher number of correct diagnoses in synthetic T1WI. This finding is in line with Granberg et al, who found the synthetic T1W images to have better image quality overall for diagnostic purposes in a group of MS patients. [54] Hagiwara et al performed a study on MS patients and were able to detect a higher number of MS lesions with synthetic double inversion recovery images compared to conventional double inversion recovery images, with a better contrast in synthetic images being a plausible explanation for the result. [86]

The synthetic FLAIR sequence had notably lower scores on image quality and more artefacts than conventional images. This is in line with other studies [54,85], reporting artefacts in FLAIR images especially in the interface between CSF and brain tissue, which makes it necessary to carefully assess the other sequences in order to classify these changes as artefacts and not pathological changes. These kinds of artefacts could be attributed to the difficulty of segmenting voxels containing two types of tissues, CSF and brain parenchyma, which is often the case in the interface of ventricle walls and at the sulci. [87]

In this study, the image sequences were assessed individually for probable diagnosis, which is a pseudo situation since assessment in a clin-

ical setting always comprises all sequences in an examination combined with clinical information. Nevertheless, it was possible to make the correct diagnosis to the same extent in the synthetic images as in conventional images, except for the T1W images, where synthetic images outperformed the conventional. The Tanenbaum 2017 study had similar results, with a larger patient cohort with varied diagnoses. [85]

Since synthetic MRI is dependent on only one scan, there could be concerns regarding motion artefacts corrupting the data, affecting all synthetic images. In this small cohort this was not an issue; Tanenbaum et al. reported motion artefacts in 7.5% of the synthetic images, which is lower compared to previous reports on motion artefacts in conventional studies, where up to 29% of images could be affected. [88]

This study had a small number of patients with a limited number of diseases, which is a limitation. Also, only two neuroradiologists scored the images, and the evaluation might have been strengthened from a higher number of raters. The conventional clinical MRI protocols differed in slice thickness and scan time, with the MS protocol having thinner slices and a longer scan, time resulting in better delineation of anatomical structures and lesions.

Paper II

The repeated use of Gd-based contrast agents has been associated with accumulation of Gd in deep structures of the brain, especially the dentate nucleus. The clinical significance of these findings has not yet been elucidated; however, a cautious approach has been suggested. [89–91]

For MS patients, repeated MR exams with Gd-based contrast agent are routine for follow-up and treatment monitoring. The contrast agent is necessary for detection of active lesions with damaged BBB and contrast leakage, which can impact the treatment regime. Since MS is a chronic disease, these patients will undergo several MR examinations during a life span, with the risk of accumulation of Gd in the brain. If it is possible to detect active lesions without the contrast agent injection, it would be beneficial for MS patients.

In this study, it was evident that active MS lesions had significantly higher R1 and R2 and lower PD than non-enhancing lesions. This could be attributed to the acute inflammatory reaction, with a higher cellular

content in the active lesion. Non-enhancing lesions are in a more chronic inflammatory state and contain more water and fewer cells. [16,92]

Previous reports of relaxation measurements in MS lesions have shown variable result. Some findings are in line with our study, with shorter T2 in enhancing lesions and longer T2 in non-enhancing lesions [93], and longer T2 in enhancing lesions compared to NAWM [94]. An early study reported a decrease in T1 and T2 over time in acute brain stem lesions. The classification of acute or chronic lesions was, however, based on the duration of symptoms, not on contrast enhancement in lesions. [95]

The definition and classification of the MS lesions and of contrast enhancement in different studies will affect the outcome. This could explain the findings of Jurcoan et al., which were not in line with our findings. They used a method for voxel-based automatic calculation of T1 shortening after contrast agent injection. [96] They found higher T1 values in enhancing lesions, and the reason for this is probably due to their definition of all FLAIR hyperintense areas, including dirty-appearing white matter, as lesions. This means that dirty-appearing white matter would constitute a great part of the non-enhancing lesions. Thus, the enhancing lesions apparently show a higher T1 than non-enhancing lesions, since dirty appearing white matter has lower values than lesions but higher than NAWM. [52] In our study, the comparison was made between enhancing and non-enhancing lesions, not including the dirty-appearing white matter.

When we combined sensitivity and specificity for all possible thresholds in a receiver-operating characteristic analysis, the area under the ROC curve was 0.832, which is a relatively high number. However, an overlap exists with the non-enhancing lesions which display a wider range of relaxation values and PD, which particularly affects the sensitivity of identifying the enhancing lesions. Cut-off values yield high specificity, over 90%, but the corresponding sensitivity is then only in the 50% range. One possible explanation for non-enhancing MS lesions having relaxation and PD values that overlap with enhancing lesions is remyelination, which occurs in some lesions. [97–99]

The number of enhancing MS lesions was rather small in this study, which is a limitation. Even though care was taken during manual ROI delineation of lesions not to include other structures to avoid partial volume, images were only available in the axial plane. Images with isotropic voxels

with possibility of reconstruction in three planes could have improved ROI placement accuracy. This study was performed on a 1.5T scanner, and since relaxation values differ between 1.5T and 3T, the relaxation values cannot be extrapolated to a 3T MR image setting.[100]

Papers III and IV

Malignant gliomas are not common in the general population, but constitute a regularly encountered diagnosis for neuroradiologists. These tumours pose a challenge with regard to both diagnosis and treatment, which is largely due to their inherent infiltrative nature. The infiltrative part of the tumour is interspersed in the peritumoral oedema, which makes it difficult to identify these areas of the tumour. DWI and PWI can give some guidance: DWI due to a decrease in the Brownian motion of water molecules if cell density in the tumour is high and PWI attributable to an increase in rCBV due to a pathological neoangiogenesis. [64,101] There is, however, no perfect imaging technique when it comes to identifying non-enhancing infiltrative tumour; histopathology is the gold standard.

Relaxometry adds information on malignant gliomas, both in their naïve state as well as during treatment follow-up. We have found a gradient in relaxation rates, from the contrast enhancing border of the tumour into the periphery of the peritumoral oedema. A challenge when working with these analyses is that the tumour infiltration is heterogeneous, and interspersed with peritumoral oedema. This means that subtle changes in relaxation variations can drown in the oedema. The complex pattern of the oedema, especially close to the contrast enhancing part of the tumour, could explain the relative low R^2 values of the regression line in paper III. With no histopathological proof of tumour cell presence, the connection between these findings and suspected tumour infiltration is circumstantial. However, using subtraction maps to quantify contrast enhancement in paper IV, we also found a subtle, non-visible contrast leakage in the peritumoral area, also indicative of tumour infiltration. This is a finding that is in line with other studies. [81,102]

In paper IV, we report what seems to be a significant contrast enhancement (difference) in the peritumoral area in conventional as well as synthetic images. However, when peritumoral difference values were normalised to the NAWM in the contralateral hemisphere, only the quantitative sequence showed a significant difference. The difference value of

the peritumoral area in the conventional images was negative compared to the NAWM, which showed a larger difference value, a finding that is not physiological. [103,104] This illustrates the difficulty in comparing signal intensities between different conventional scans, due to the variation in signal intensity of conventional images.

In addition to the peritumoral infiltration of malignant gliomas, there are also challenges regarding image assessment during the monitoring of oncological treatment after surgery. This is due to the potent effects of chemo- and radiotherapy, which can cause treatment-related changes in the brain, pseudoprogression. These treatment-related changes are very difficult to differentiate from tumour recurrence with imaging; and often constitute a diagnostic dilemma for neuroradiologists, neurosurgeons and oncologists. The difficulty lies in the different approaches of the two different diagnoses: tumour recurrence can indicate the need for new surgery, whereas pseudoprogression is a “wait-and-see” condition with a more favourable prognosis. [105] There are indications that measureable changes in relaxation occur in the tissue before changes become visually evident, and this could facilitate treatment monitoring. [106,107]

Anti-angiogenetic treatment can also cause changes that are difficult to interpret, with a decrease of contrast agent leakage due to an effect on the vascular permeability, even when there is a continued growth of tumour volume, a condition called pseudoresponse. [108] The assessment of these changes might benefit from relaxometry mapping. [109]

A limitation of this study is the lack of histopathological correlation of the relaxometry measurements in the peritumoral oedema, which makes the findings circumstantial, even though they seem to be in line with other studies showing tumour extension beyond radiological borders in gliomas. [110] The patient cohorts in papers III and IV were relatively small, 19 and 20 respectively, and a higher number of participants would have benefited the analysis. The histopathological classification in these studies did not include IDH or 1p19q status, which now is part of routine analysis and tumour classification.

Even though the tumour was manually segmented from the peritumoral oedema to avoid overlap, the accuracy of the ROI measurements might have been improved by a quantitative sequence with isotropic voxels and thinner slices. The R^2 values of the regression line are relatively low, which is interpreted as a reflection of the complexity of the peri-

tumoral oedema, especially in the area closest to the contrast-enhancing border of the tumour.

Future aspects

It is a challenge for radiologists to work with images that are perceived to be of inferior quality compared to those obtained using standard clinical imaging techniques, even if studies of synthetic MRI give evidence of “good-enough” diagnostic quality. [54,85,86] In this setting, it might be appropriate to consider the indications for different radiology examinations and modalities, and to speculate whether a short MRI protocol with synthetic MRI might be a sufficient substitute for some of the CT examinations performed, e.g., in the work-up of patients with non-specific headache and a low level of suspicion of pathological changes. This would be beneficial for the patients with regards to radiation aspects, and if it was possible to achieve a higher throughput in the MR suite with a short MR protocol it could be manageable for the radiology department. This would, however, probably require substantial investment in MR equipment as well as education of staff and radiologists to manage an increased number of MR examinations.

Recent technical development concerning the emergence of new quantitative MRI sequences that are within clinically acceptable scan times has made it possible to assess and evaluate tissue changes in the brain of patients with MS from new perspectives, adding information that is not obtainable in conventional MR images. This can contribute to the understanding of the pathological processes that take place, but research has yet to elucidate the clinical significance and indications for many of these techniques. For relaxometry, which enables tissue segmentation with the calculation of BPF, it is already implemented as part of the clinical MS MRI protocol at some centres with the expectation that it can contribute to the objective evaluation of atrophy development in MS patients.

Since relaxometry is a quantitative technique, it can provide additional information about malignant gliomas compared to conventional images. This work is indicative of tumour infiltration in the peritumoral oedema on a group level, and the next step is to work for individual visualisation of these changes, to facilitate individual treatment planning for the patient.

Some work has been done on relaxometry and malignant gliomas in the treatment phase. In the future, it would be of interest to analyse the follow-up of these patients during treatment to see whether it is possible to detect tissue changes in R_1 and R_2 before they become visible as tumour recurrence, and also to try and differentiate between tumour recurrence and pseudoprogression. It would also be of interest to look at outcome to see whether there is any correlation between degree of peritumoral R_1 changes and survival.

In conclusion, it seems that with the development and implementation of new techniques like relaxometry, MRI is moving from being a qualitative method for visual assessment towards a quantitative evaluation of tissue and pathology. At present there is no standardised method for relaxometry, and this is a challenge for the future; to meet the divergence of technical approaches. MR has a history (and present) of a very low grade of being standardised, with different manufacturers creating their own different pulse sequences and techniques, with different names and acronyms. From the medical point of view, there is work in progress in an effort to harmonise MR protocols to facilitate comparisons between different centres for different diagnoses, both on a national and an international level [111,112]. To aim for more standardised approaches regarding the technical aspects of MR would probably facilitate the work for radiologists and in the end be beneficial for the patients, but might not be as readily achieved.

CONCLUSIONS

This thesis has focused on the clinical use of synthetic MRI of the brain for various clinical applications. A general conclusion of the thesis is that synthetic MRI has the potential for clinical use in brain imaging of patients with MS and malignant glioma, with the possibility for quantitative tissue analyses. The following specific conclusions are made from the papers in this thesis:

Paper I

Synthetic MRI can potentially shorten the MRI examination time. Image quality differs between synthetic and conventional images. Synthetic T1WI have higher lesion conspicuity than conventional T1WI. Synthetic T2 FLAIR images underperform compared to conventional T2 FLAIR. Even though the image quality is perceived to be inferior, synthetic images agreed with the clinical diagnoses to the same extent as the conventional images and required half the scan time of the conventional images in this study.

Paper II

Contrast-enhancing MS lesions have PD and relaxation times that differ from those in non-enhancing lesions, with lower PD and shorter relaxation times in enhancing lesions compared with non-enhancing lesions. PD, which had the highest AUC value, still had only moderate ability to predict Gd enhancement. Even though synthetic MRI can provide additional information about the changes occurring in MS, it does not seem to be able to replace Gd-based contrast agent injection in the evaluation of MS lesions.

Paper III

Quantitative T1 and T2 mapping can detect tissue changes in the peritumoral region that are not visible on conventional MR images. Relaxation values in the peritumoral oedema have a heterogeneous pattern within the first 10 mm from the contrast enhancing portion of the tumour. There is a gradient in relaxation values from the contrast-enhancing part of the tumour into the peritumoral oedema. This may reflect non-visible tumour

infiltration into the surrounding tissue, and this information could be useful for the planning of surgery and radiation therapy.

Paper IV

The use of quantitative subtraction maps based on relaxometry makes it possible to detect non-visible contrast enhancement in the peritumoral area of malignant gliomas. This finding could represent tumour infiltration but needs to be validated in further studies.

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