

MAGNETOM Flash

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„Preclinical imaging is an enabling technology which allows new information to be obtained.“

Dear MAGNETOM user,

Preclinical imaging research is beginning to take shape after a steady learning process. We are currently observing a significant demand for small animal imaging driven by molecular based medical research. This need has been responded to by academic sites, pharmaceutical companies and funding agencies (e.g. National Institutes of Health (NIH) or framework programs of the European Community) which are willing to invest in preclinical imaging technologies.

Perceived advantages of pre-clinical imaging are firstly that it decreases research time by avoiding invasive and time consuming tissue sampling, i.e. it is an enabling technology which allows new information to be obtained, and secondly that it looks at progression of disease in

vivo. Thus the researcher can make repetitive observations in the same animal, each animal serves as its own control and the total number of animals required to obtain a statistically solid data basis is reduced.

While new imaging modalities – such as near-infrared-fluorescence tomography and chemo-luminescence imaging – opened up a vast variety of new imaging application in life science in the past years, MRI remains a mainstay of preclinical imaging of disease models.

This special issue of MAGNETOM Flash aims to demonstrate that notwithstanding the complexity of MRI, there are possibilities to image small animals with just a minor adaptation of clinical MRI systems.

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Small Animal Imaging on 1.5T MR Systems

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Introduction

In recent years an increasing number of small animal studies have been performed since MR Imaging (MRI) offers an excellent soft tissue contrast, enables imaging in arbitrary slice orientations and does not use ionizing radiation. MRI is especially suited for longitudinal studies where, for example, the influence of a drug treatment is studied in the same animal over several weeks. Small animal MRI is usually performed using dedicated MRI systems with high field strengths ($B_0 > 4$ Tesla) and bore sizes that are chosen depending on the size of animals. Since small animal imaging facilities are not necessarily available in clinical research institutions, in these environments the existing clinical whole-body MR imaging systems have been utilized for small animal MRI [1].

Besides their availability, clinical MR imaging systems offer further advantages. Firstly, small animal studies at clinical field strengths ($B_0 = 1.5\text{--}3$ Tesla) yield image contrasts that are comparable to image contrasts in clinical studies since relaxation times are field-strength dependent. Secondly, susceptibility and chemical shift artifacts are smaller at lower field strength so that the delineation of tissue interfaces is facilitated. Finally, a clinical MR system with optimized user interface is easier to use, the same operating personnel can perform both animal and human studies and a large variety of imaging and post-processing protocols and applications exists.

Clinical whole-body MRI systems offer a cost-effective imaging alternative to dedicated small animal MR systems if only a limited number of small animal studies is performed and a sufficient amount of imaging time is available (e.g. during night times). Though feasible, small animal MRI at clinical systems is challenging due to

the lower signal-to-noise ratio (SNR), the limited spatial resolution and the shortage of appropriate animal handling and supervision hardware (e.g. ECG monitoring). In this article we describe several hardware and software modifications to enable small animal studies at 1.5T and 3T MRI systems. For a comparison of dedicated small animal MRI systems and clinical MRI units, refer to Box 1. For those researchers looking for a dedicated small animal MRI system with clinical user interface, the ClinScan 7T MR system has been developed (ClinScan, Bruker BioSpin, Ettlingen, Germany). ClinScan combines high-performance small animal gradient systems and radio-frequency hardware with the clinically known syngo control software and applications.

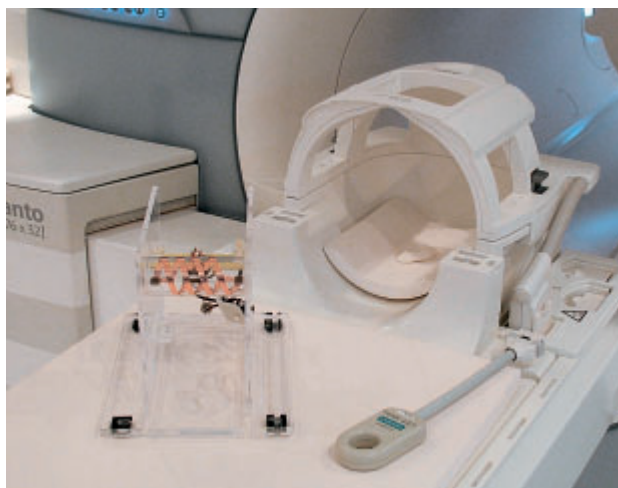
Small Animal RF Coils

A 4,000 times weaker MR signal is measured in a mouse (weight: 25 g) than in a 100 kg man if the same imaging RF coil is used, because the spatial resolution needs to be scaled relative to the anatomy

so that a typical clinical voxel size of 10 mm^3 scales down to 0.0025 mm^3 in a mouse [2]. To overcome this SNR limitation the field strength can be increased, although the SNR gain is approximately proportional to the ratio of the field strengths only. A much higher gain in SNR is achieved if smaller rf coils are used [3], [4]. As in human studies, the size of the coil is governed by the imaging application and different coils will be required for whole-body mouse MRI or mouse head imaging.

Initial animal experiments can be performed on clinical systems using existing loop coils. Loop coils are available in various diameters (4, 7, 11 cm) and for all clinical field strengths (1.5 and 3T), and allow imaging without modification to the MR system.

To further optimize mouse imaging at 1.5T we constructed a dedicated receive-only coil prototype which is connected to the existing flex interface of the MR system. The solenoid receive coil has a 36 mm diameter and is 90 mm long to conveniently accommodate a medium-



■ The photograph shows three different RF coils in an MR system: the receive-only coil prototype (left), a head coil (center) and a flex loop coil (right). In addition, a new series of loop coils are available with 3, 7 and 11 cm diameter to be used with a new 4-channel preamplifier module. These coils are available for 1.5 and 3T, whereas the shown coil is only available for 1 and 1.5T systems.

size mouse of 30 g body weight (Fig. 1). For comparison, gradient and spin echo images of an ex-vivo mouse were acquired with the mouse coil, a small loop coil and the head coil (Fig. 2). The head coil is much larger than the mouse and thus provides a good homogeneity over the whole sample. Unfortunately, due to the low filling factor, the SNR is compromised. The small loop coil offers the highest SNR at the center; however, SNR rapidly decreases with distance from the coil center. The dedicated mouse coil provides a slightly lower SNR, but is homogeneous over the whole sample so that whole-body mouse imaging becomes possible.

Quantitative SNR comparisons were measured in a phantom setup (cylindrical phantom, 35 ml physiologic saline solution, 0.5% Gd-DTPA) (Fig. 3). The results in Tab. 1 show that the mouse coil has the highest SNR when averaged over the dimensions of the mouse. A homogeneous and high SNR is important, for example, in tumor studies where the location of metastases is not known a priori [5] or in phenotyping experiments that aim to detect small morphologic changes [2].

A further advantage of clinical MR systems is the possibility of imaging several animals simultaneously [6]. Several small animal coils can be mounted side by side in the large bore of the clinical MR magnet [7]. In principle, the dedicated mouse coils described above can be utilized for simultaneous imaging, however, special care must be taken to avoid coupling between the coils.

Anaesthesia and Life Support

Small animals need to be anesthetized during MR imaging. The anaesthetic of choice is currently isoflurane, a gaseous anaesthetic which is applied through an MR-compatible ventilator. Though simple to use, isoflurane is known to affect physiological parameters – myocardial blood flow, for example, is highly sensitive to isoflurane concentration [8].

A cost-effective, although more complicated, alternative to gaseous anaesthesia is the injection of Xylazine/Ketamine. For this procedure it is important to supervise the depth of anaesthesia by monitoring, for example, breathing frequency. ECG and respiratory triggering are challenging

	Clinical MR systems at reasonable resolutions	Dedicated small animal MR systems
Field strength B_0	1.5 – 3.0 Tesla	7 – 11 Tesla
Gradient strength G	30 – 45 mT/m	50 – 1000 mT/m
Slew rate	100 – 200 T/m/s	400 – 1200 T/m/s
Coil diameter	4 – 15 cm	1 – 6 cm
TR / TE (for a gradient echo sequence)	10 – 25 ms / 5 – 12 ms	3 ms / 1.5 ms
T1 contrast	Excellent, moderate T_1 -relaxation, short repetitions	Longer TR required (T_1 increases with B_0)
T2 contrast	Acceptable. Suffers from low SNR.	Good
Single Shot EPI	Not applicable due to insufficient gradient strength / EPI only with high number of segments.	Possible
Consequences	Morphologic imaging is possible with competitive quality but with long measurement times.	Full range of applications possible. SN is not 1000 times better.

Box 1: Comparison of a clinical MR system and dedicated small animal MR units.

Coil	Diameter [mm]	Length [mm]	SNR _{max}	SNR _{ave}
Head coil	~290	~320	6	6
Flex loop small	~30	20 (casing)	144	70
Mouse coil	36	90	89	78

Tab. 1: SNR comparison for three different coils.

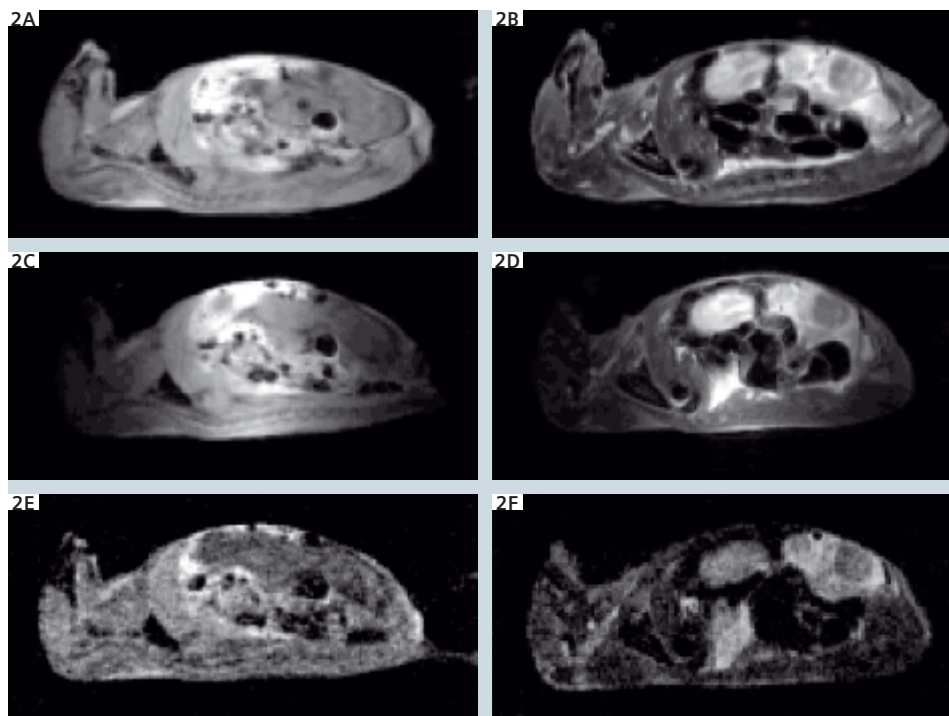
as the typical respiratory rate of mice is about 150 per minute and the heart rate is around 600 beats per minute, i.e. about 10 times faster than in humans. Nevertheless, breathing monitoring can be achieved by connecting a paediatric breathing sensor (VitalAire, Altmannstein, Germany) to the animal (Figs. 4/5). Triggered measurements are not possible since the respiratory triggering algorithm of the patient monitoring unit (PMU) detects only respiratory cycles greater than 1 s.

To circumvent problems with ECG and respiratory triggering, self-gating methods can also be used to directly measure the heart beat-correlated and breathing-correlated variations of the MR signal. This elegant concept requires modifications to the pulse sequence [9]. Under anaesthesia, animals frequently

lower their body temperature, and the additional cooling by the anaesthetic gas flow can lead to potentially lethal hypothermia. To maintain their body temperature, mice require warming, whereas with rats it may be sufficient to thermally isolate the animal. A cost-effective solution for warming is to blow warm air over the animal, which can be achieved with, for example, an external hairdryer connected to a coil housing by a long flexible tube. Another solution is a radiative heating system with halogen light bulbs that are placed at a sufficiently large distance from the coil to prevent artifacts (Fig. 6).

Pulse Sequence Optimization

Small animal imaging with clinical MRI systems is already feasible without major system modifications (refer to Box 2 for



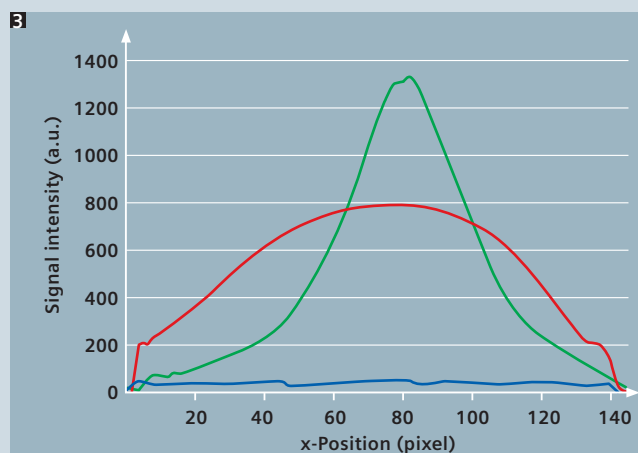
2 Visual signal-to-noise (SNR) comparison for three different imaging coils.

A, B: dedicated mouse coil

C, D: flex loop small

E, F: head coil

In the 3D gradient echo images (left) as well as in the 2D T2-weighted TSE images (right) the whole mouse is optimally visualized in the mouse coil, whereas a slightly higher SNR is seen in the shorter loop coil, although only a limited portion of the mouse is illuminated.

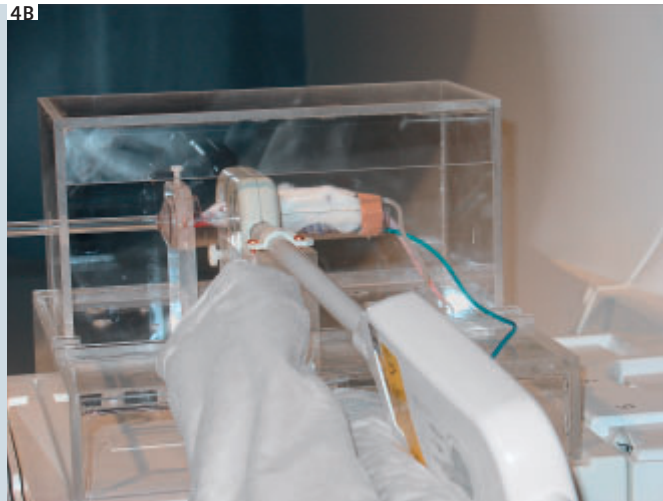
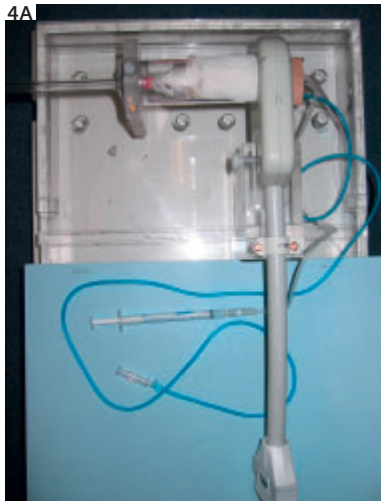


3 MR-signal intensities along a homogeneous 10 cm long phantom, acquired in the head-coil (blue), flex-loop-small (green) and the dedicated mouse coil (red).

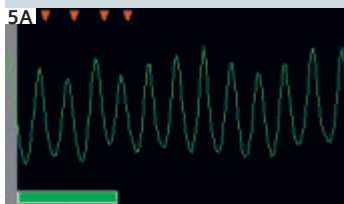
possible pitfalls). To further improve image quality, pulse sequences can be adapted to the small field of view. For mouse imaging, an approximately 10-fold greater absolute spatial resolution (0.1 mm) is required as for humans (1 mm). The spatial resolution Δx in an MR system is given by (see e.g. [10])

$$\Delta x = \frac{1}{G_x \gamma} \cdot BW \quad (1)$$

where G_x is the gradient strength in read-out direction, BW the receiver bandwidth per pixel and γ denotes the gyromagnetic ratio (42.577 MHz/T for ^1H). At constant BW the spatial resolution can be increased by increasing the readout gradient strength, although gradient amplitudes are limited to typical values between 30 and 40 mT/m. Therefore, at maximum gradient strength the only possibility of achieving smaller pixel sizes is to lower the receiver bandwidth. But smaller bandwidths result in stronger chemical



4 A, B: Acrylic glass box and a syringe filled with narcotic agents and connected to a butterfly located in the abdomen. The blue tube belongs to the paediatric respiratory sensor and can be connected with an adapter to the standard ECG/Respiratory-module.



Deep anaesthesia 4 cycles/s
Green bar = 1s

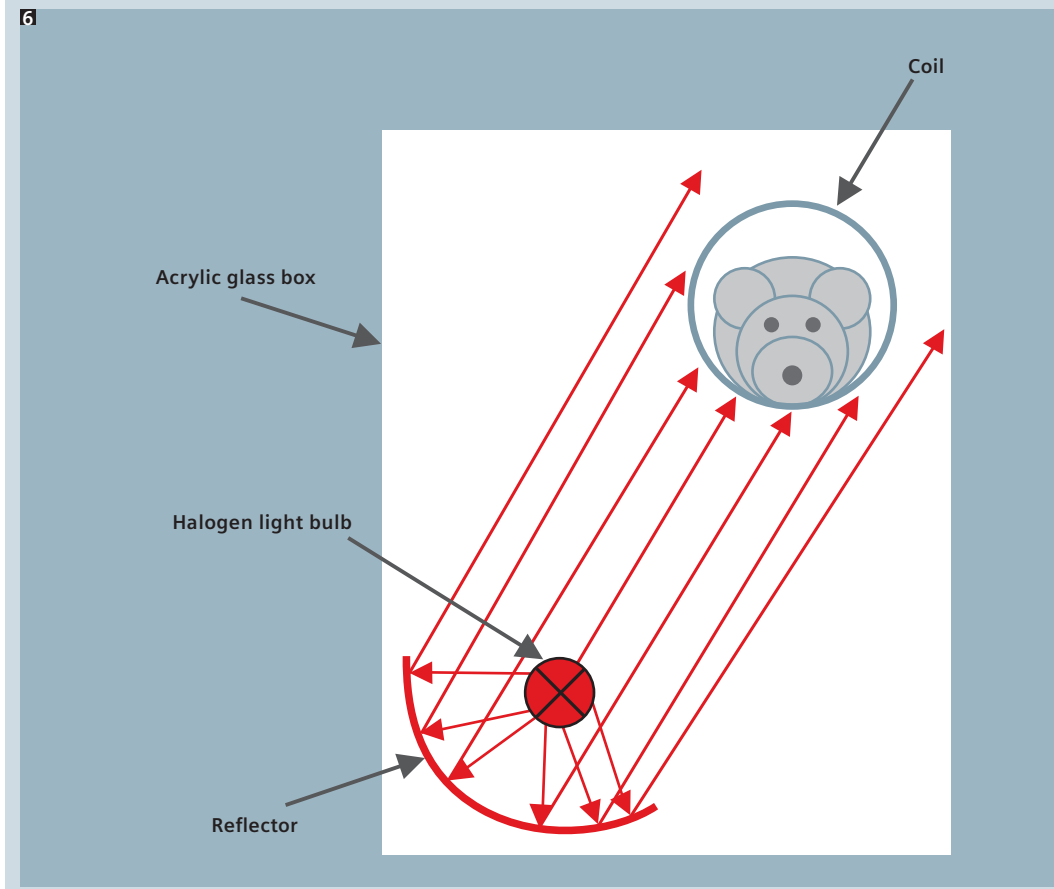


Anaesthesia becomes weak,
6 respiratory cycles/s,
a new injection is needed.



Mouse is awakening
Hurry up!

5 A–C: The respiratory sensor counts the number of breaths per second thus monitoring the physiological status of the animal.



6 Schematic of a radiative heating system with a halogen light bulb in the coil setup.

Possible Pitfalls of Small Animal Imaging at Clinical MR Systems

- Compared to human applications, the trade-off between temporal and spatial resolution is even more pronounced since, for example, the heart rate is significantly higher. In particular, first pass contrast agent studies are thus difficult to perform.
- Chemical shift: In very small structures a shift between the fat and the water signal of a few pixels aggravates interpretation of images. The chemical shift artifacts increase at low bandwidths.
- Fat saturation: Higher order shimming is not possible due to the shim coil design – effectively, only linear shims can be adjusted since they are realized by gradients.
- Steady state free precession (TrueFISP) sequences: Longer TRs create significant banding artifacts. Unfortunately, shorter TRs are only possible with stronger gradients (gradient inserts).
- ECG-Triggering: Sampling rates and filters for ECG systems are currently optimized for human applications. At high heart rates, blood signal suppression cannot be achieved with inversion recovery preparation (black blood). Other options (dephasing, saturation) are still possible.

Box 2: Possible pitfalls

shift artifacts (i.e. position shifts of fat vs. water), which can only be reduced by increasing the bandwidth.

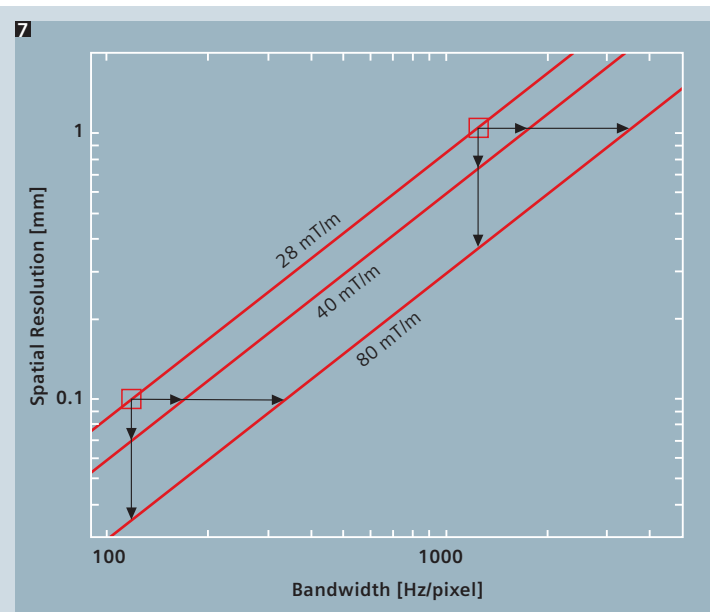
Gradient amplitudes of clinical MR scanners are often confined to about 70% of the maximum gradient strength to allow angulating the image slices at all times [11], [12]. When a slice is angulated against the physical axes x, y and z, slice selection, phase encoding and readout gradients are realized as a combination of the x-, y- and z-gradients. If, for example, the maximum gradient strength is applied in phase encoding direction, a higher gradient amplitude than physically achievable might be necessary. Limiting the gradient amplitudes avoids this gradient overflow condition and pulse sequences can always be realized. In small animal imaging slice angulation is often of minor importance. To fully exploit the available gradient strength for small animal imaging we have designed pulse sequences where the possibility to angulate slices is switched off. In Fig. 7 these sequences are compared with conventional pulse sequences with restricted gradient amplitudes. At constant BW the optimized sequences can achieve approximately a

40% higher spatial resolution, or, if chemical shift artifacts are a limiting factor, the increased gradient amplitudes can be used to increase the readout bandwidth. Equation 1 is also valid for the slice selection direction: here, the slice thickness depends on the slice selection gradient and on the bandwidth of the rf pulse. Thus, in addition to increasing the slice selection gradient, dedicated rf pulses with low bandwidth were implemented to achieve sub-millimeter slice thicknesses. In general, these rf pulses are longer than their conventional counterparts which results in prolonged minimal echo times. The optimizations for high resolution imaging are shown in the example of a Turbo Spin Echo (TSE) pulse sequence. At a 1.5T system (MAGNETOM Symphony) with $G_{\max} = 30$ mT/m the minimal slice thickness could be reduced to 0.24 mm compared to the conventional TSE pulse sequence with 0.7 mm. In Fig. 8 image examples of a new-born mouse are shown which were obtained with the optimized TSE sequence (T2-weighted: TR 3000 ms / TE 98 ms / FoV 40×28 mm²/ matrix 136×192 / 15 slices / slice thickness 0.24 mm / number of averages 350 /

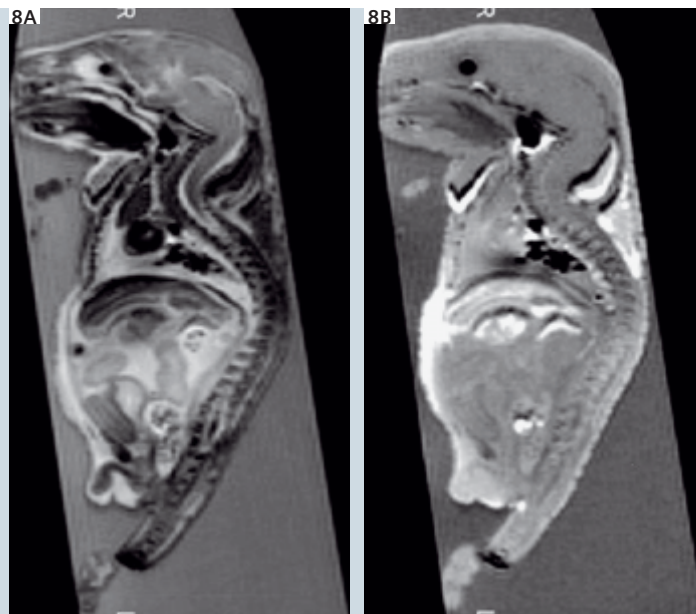
echo train length: 7; T1-weighted: TR 756 ms / TE 27 ms / FoV 40×27 mm²/ matrix 128×192 / 15 slices / slice thickness 0.24 mm / number of averages 200). Another possibility of increasing the resolution in slice selection direction is the use of 3D imaging techniques. Here, slice resolution is defined by a second phase encoding which can achieve a similar resolution as the in-plane phase encoding. However, 3D techniques are difficult to combine with spin echo acquisitions because the long TRs necessary to establish the SE contrast lead to excessive imaging times. Gradient echo techniques such as FLASH, however, naturally lend themselves to 3D encoding, and spatial resolutions of 100 µm can be achieved in reasonable imaging times of about 1 hour (Fig. 9). The imaging parameters were: TR 20.3 ms / TE 7.2 ms / FoV 100×50 mm²/ matrix 1024×512×218/ partition thickness 100 µm.

Gradient Inserts

Higher spatial resolution can be achieved with shorter TEs and TRs if the gradient amplitude is increased. For small animal



7 Plot of the minimum spatial resolution as a function of readout bandwidth. The absolute gradient amplitude of the clinical MR system (40 mT/m, in this example) is significantly higher than the maximum gradient strength for tilted slices (here: 28 mT/m). If slice angulation is switched off, the higher gradient amplitude can be used which allows either reducing the pixel size or increasing the readout bandwidth. Alternatively, a gradient insert can deliver a gradient amplitude of 80 mT/m or even more.



8 A T2-weighted (A) and a T1-weighted (B) TSE *ex vivo* image of a new-born mouse. A spatial resolution of $240 \times 210 \times 210 \mu\text{m}^3$ was achieved and a signal-to-noise ratio of about 50 was observed in the animal's brain.

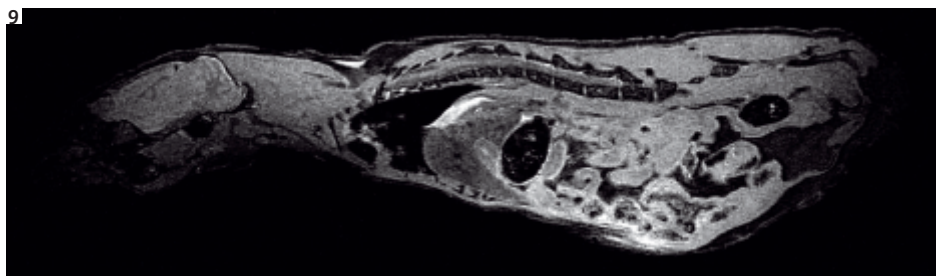
MRI at clinical systems this may be realized by so-called gradient inserts, i.e. small additional gradient coils, which provide gradient amplitudes of 80 mT/m and more over a limited FoV. This requires additional gradient hardware which is a cost-factor, and the set-up of the small animal imaging system will become more time-consuming.

Parametric Imaging

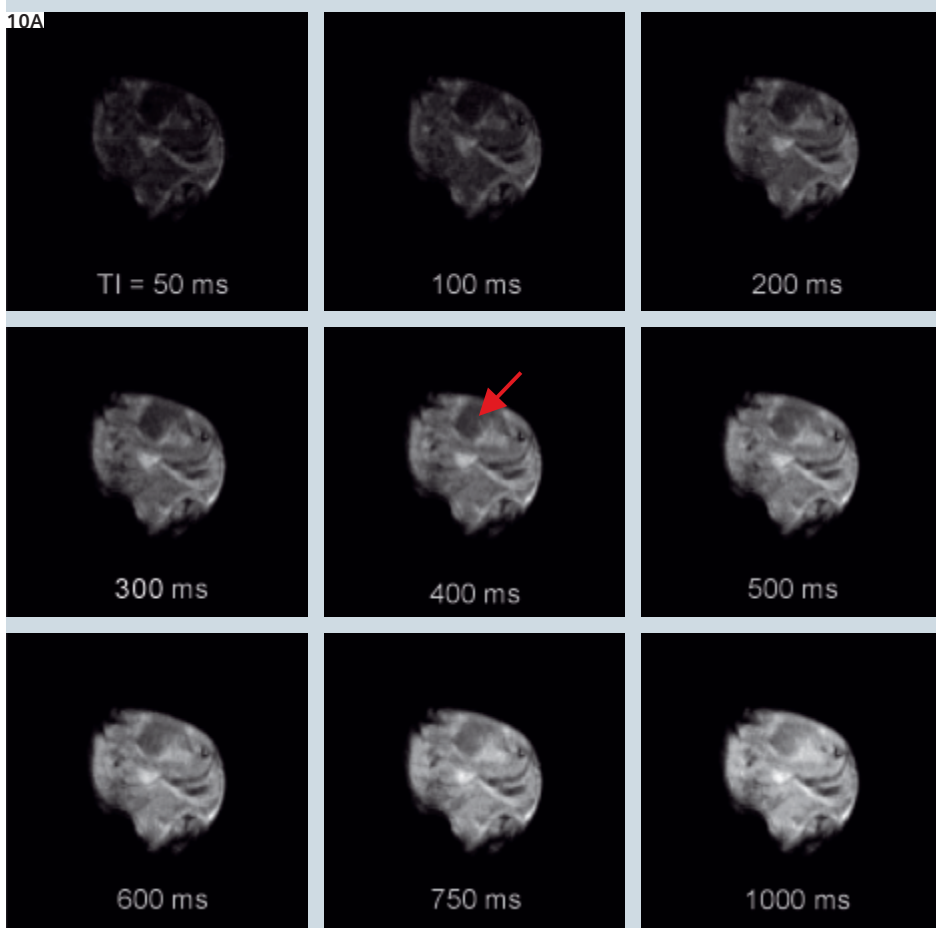
In addition to the morphologic information, MRI offers several functional imaging techniques such as diffusion imaging, flow measurements, temperature mapping, and relaxometry. The latter is of special importance in small animal studies where often magnetically labelled substances are investigated. To assess the concentration of these substances after administration, preferably the local change of the relaxation times T1, T2 and T2* is measured. The concentration information is then used, for example, to quantify organ perfusion, an important

parameter in tissue viability studies. In addition, relaxation studies can be used to measure local vessel sizes (vessel size imaging [13]) which might help to differentiate normal from tumour tissue. Finally, relaxation time measurements can be used to optimize the image contrast: Thus the T1 information can be utilised to suppress signals from tissue using an inversion recovery preparation with an appropriately selected TI [14]. The very fast contrast agent transit in the animals' vascular system makes relaxometry studies difficult to perform during first pass. Additionally, echo planar imaging (EPI) cannot be used for data acquisition, since the low acquisition bandwidths associated with the limited gradient amplitudes lead to very long EPI echo trains. Despite these restrictions, conventional relaxometry pulse sequences for the measurement of T1, T2, and T2* and existing post-processing tools can be applied. A standard method to determine the longitudinal relaxation time T1 is the saturation

recovery (SR) or inversion recovery (IR) technique, where the longitudinal magnetisation is prepared with a 90° (SR) or a 180° (IR) pulse. After a recovery delay TI an image is acquired with a single-shot acquisition module (e.g. HASTE). This procedure is repeated for different TIs, and T1 is calculated from the signal recovery on a pixel-by-pixel basis. In particular, the combination of SR signal preparation with a turboFLASH readout module is advantageous, and the established T1 contrast is maximised when data are acquired with centric k-space reordering [15]. For small animal applications we have additionally implemented a segmented SR turboFLASH acquisition technique, which further reduces image blurring due to variable T1 contrast during data acquisition (Fig. 10). To measure T1 in larger volumes (e.g. in a solid tumour and the surrounding tissue), variable flip-angle methods can also be applied. Here, a series of 3D FLASH data sets is acquired and T1 is calculated using the known signal equation. This

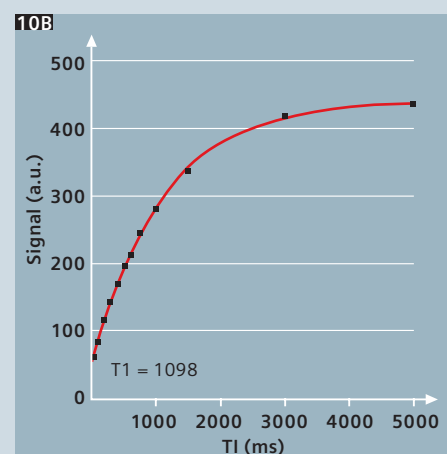


9 A 3D FLASH *ex vivo* image of a mouse with an isotropic resolution of 100 μm . The mouse was prepared by MR staining [2] using Gd-DTPA. Thus, a good T1-contrast could be achieved with a short-TR FLASH sequence resulting in a measurement time of only 48 min.



10 A: Transverse saturation recovery TurboFLASH images of a mouse tumor model (arrow). The saturation recovery delay time TI between preparation and data read-out varied between 50 ms and 1000 ms.

B: The signal intensity in a region of interest in the mouse tumor against the saturation recovery delay time TI. The exponential fit gives a spin-lattice relaxation time $T_1 = 1089$ ms.



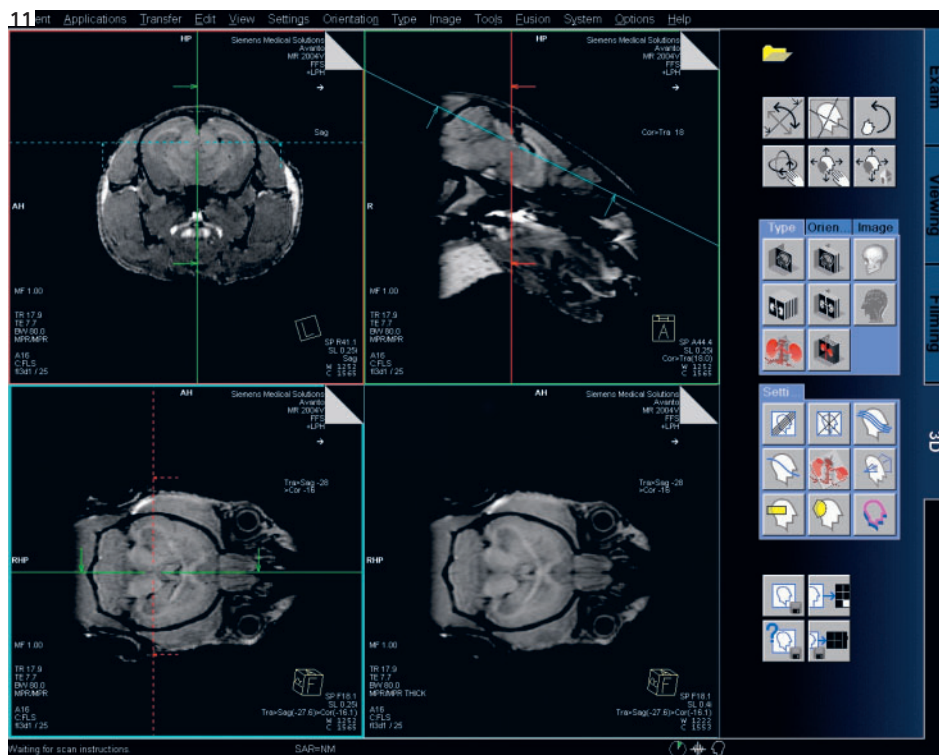
technique has the additional advantage that the computation of the relaxation times can be simplified using a linearised form of the FLASH equation [16]. The quantification of the transverse relaxation times T_2 and T_2^* is performed with multi-echo pulse sequences, where signal is multiply refocused using either spin echoes (T_2) or gradient echoes (T_2^*). A multi spin echo pulse sequence with up to 32 echoes is implemented for T_2 measurements, and T_2 post-processing (i.e. the calculation of T_2 maps) is

available within the standard *syngo* environment. Multi-echo T_2^* measurement sequences are currently developed, and due to the similarity in the signal equation, the same post-processing tools can be utilised. In the application of either technique care must be taken that noise does not adversely affect the T_2/T_2^* mapping results. Image noise at long echo times can lead to an overestimation of T_2/T_2^* - in the post-processing software this is considered by a manually selectable amplitude threshold, which

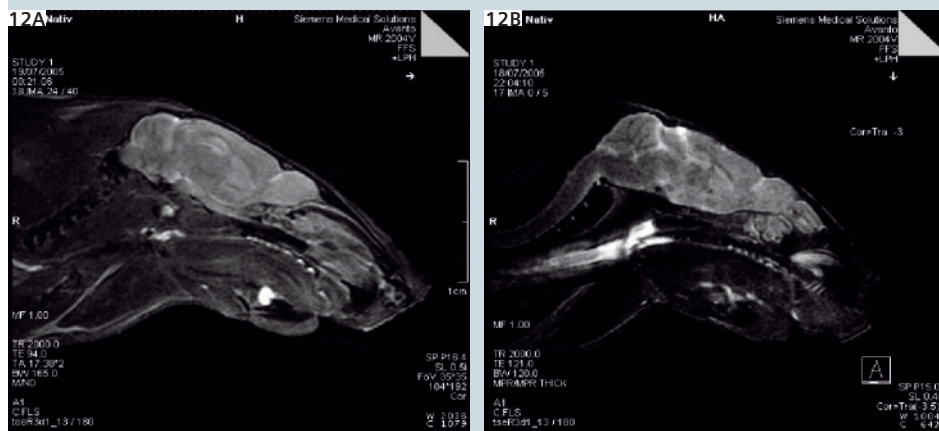
should be set to about 3–5 times the mean of the noise amplitude.

Conclusion

Small animal MRI with clinical 1.5T MRI systems gives sufficient image quality. Existing RF coils and standard pulse sequences can be utilized although, for some applications, even better results can be achieved with optimized rf coils and dedicated pulse sequences.



11 High resolution T1-weighted images showing the fine sub-structures of the cerebellum were acquired with a standard VIBE sequence (45 minutes *in vivo* scan, resolution $125 \times 125 \times 250 \mu\text{m}^3$). To achieve a high SNR, a 3D-measurement with large volume coverage, a high number of partitions, and a moderate number of averages was performed. For contrast effects, the SNR can be increased by reconstructing thicker slices (see lower right quadrant). Each necessary orientation can be calculated via 3D-MPR (3D multi-planar reformatting), i.e. only one data set has to be acquired and all orientations can be derived from these data.



12 A, B: T2-weighted standard TSE images are shown (6 slabs, 8 partitions/slab, 2 concatenations, compensation of T2-decay). The left measurement took 35 minutes for a $180 \times 180 \times 500 \mu\text{m}^3$ resolution. The image on the right shows $125 \times 125 \times 400 \mu\text{m}^3$ resolution. The measurement time was 2 h.

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Please note: Figures 4B, 5, 11, and 12 have been created in collaboration with PD Dr. Andreas Hess, University hospital Erlangen, Germany.

High-Resolution Small Animal Imaging on 3T Clinical MR Scanners

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Introduction

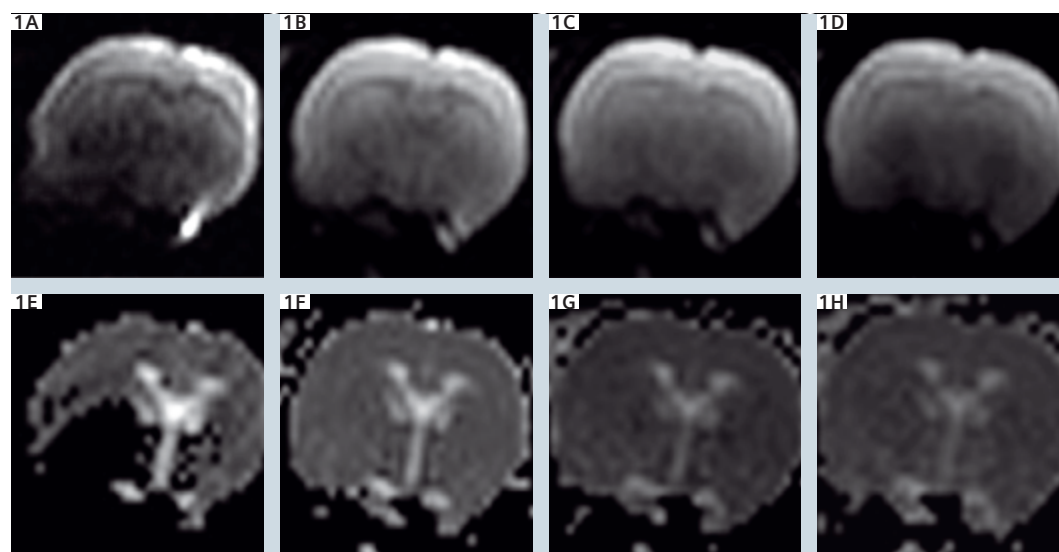
Whenever the subject of small animal imaging comes up, people imply the use of dedicated small animal high field MR scanners with field strengths in the range of 7T to 17.6T. Currently, only few research facilities rely on conventional clinical MR scanners with field strengths of 1.5T to 3.0T for small animal studies. It is quite interesting to note that these "low field" systems also offer some advantages for small animal studies and a closer look at the options available can be of some importance.

In comparison to clinical MR scanners, dedicated small animal systems offer higher field strengths as well as stronger and faster gradients. This available high field strength directly translates into a

higher signal-to-noise ratio (SNR) even though it comes at a price. There are four primary field-strength related effects which can diminish image quality.

Susceptibility effects: Living organisms are made up of various soft tissue types, air cavities and bones, all with different magnetic susceptibility values. Large susceptibility jumps, resulting from sudden transitions between tissues with significant susceptibility differences, can cause local field inhomogeneities in conjunction with the high main field in MRI. These inhomogeneities, which scale with the magnetic field strength, act as additional local gradients and are responsible for local deformations of the object geometry in the resulting MRI image.

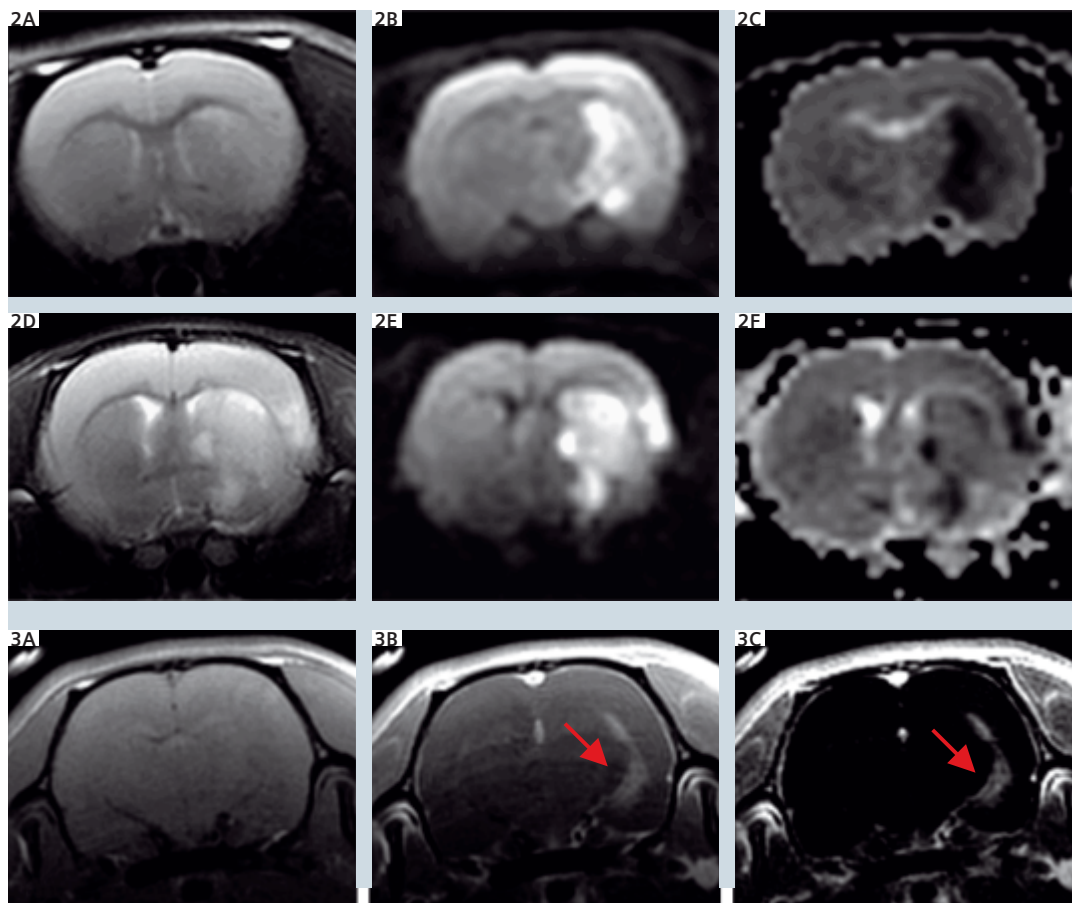
T2* relaxation: The MR signal in general decays with a time constant T2*, which is otherwise known as the apparent T2. In addition to the tissue-dependent transversal- or T2 relaxation of the underlying tissue, other effects are also included in this phenomenon. For instance, unavoidable inhomogeneities of the main magnetic field, the afore mentioned susceptibility jumps and effects such as flow and diffusion lead to a shortening in the relaxation time constant T2*. Whenever the readout train of an imaging sequence is not small compared to T2*, the T2* relaxation will affect the MR signal. Ultra-fast imaging techniques like Echo Planar Imaging (EPI), Turbo Spin Echo (TSE) or HASTE are particularly plagued by a



1 Single-shot diffusion-weighted (DW) EPI of the rat brain on a clinical MR scanner (MAGNETOM Allegra) at 3T using a 4-channel phased array head coil for the rat.

A–D: DW EPI with $b = 1000$ s/mm² using iPAT (syngo GRAPPA) with PAT factors of 1, 2, 3 and 4 (from A to D).

E–H: Corresponding ADC maps.



2 Small animal stroke imaging on a clinical MR scanner (MAGNETOM Allegra) at 3T using a 4-channel phased array head coil for the rat.

A–C: Rat A, 6 h after occlusion.

D–F: Rat B, 36 h after occlusion. (A and D) T2-weighted TSE, (B and E) DW EPI with PAT factor 3, (C and F) corresponding ADC maps.

3 Small animal post-contrast study on a clinical MR scanner (MAGNETOM Allegra) at 3T using a 4-channel phased array head coil for the rat: Rat A, 8 h after occlusion. The arrow indicates MR contrast agent leakage. A: Pre-contrast acquisition B: Post-contrast acquisition 30 min after injection of the contrast agent. C: Subtraction image demonstrates the region of the blood-brain-barrier (BBB) damage.

strong signal loss due to $T2^*$ relaxation. This signal attenuation is responsible for significant image blurring and produces a loss of small object contrast. The signal decay in high-field systems occurs much faster than at lower field strengths, as the $T2^*$ values at these higher fields are significantly shorter.

T1 relaxation: The magnetic field strength also affects the longitudinal or T1 relaxation. In general, there is no rule which describes the effect of the magnetic field on the T1 times of different tissues. These irregular and often unpredictable changes in T1 values lead to a different contrast behavior of MRI sequences at high field strength as compared to low field strength, which can be partially compensated by the use of a longer repetition time (TR), but this also implies a prolonged total acquisition time.

Specific absorption rate: Another high-field specific problem is the specific absorption rate (SAR), or the amount of energy (Watt x time) from high-frequency

pulses absorbed by the body per unit time and weight. As an example, the transition from 1.5T to 3.0T generally increases the SAR value by a factor of four. In general, imaging protocols which run at low field strength have to be adapted for higher field strength to stay below the SAR limit, e.g. by the use of a longer TR, which also prolongs the total acquisition time.

It is clear that clinical low field systems cannot compete in terms of SNR with dedicated small animal high field systems, but the field strength related problems described above are smaller at lower field strengths. This is of major importance for examinations based on fast imaging techniques, such as EPI or HASTE. Further, the use of parallel imaging (integrated Parallel Acquisition Technique, iPAT), which is routinely available on clinical MR scanners, improves the image quality of such studies. The animal handling for the experimental set up is easier, because clinical scanners offer more space than dedicated small animal systems.

In this study, we demonstrate that high image quality small animal imaging on clinical MR scanners can be obtained in acquisition times comparable to those used for human examinations. This enables a direct transfer of findings and protocols from the small animal model onto human studies, performed on the same MR system. Short acquisition times directly translate into a higher throughput, which is of major importance for large small animal studies. Additionally, a shorter scan time means less stress for the animal itself, which will reduce the mortality rate. The properties of small animal imaging on clinical MR systems described above can finally be used to reduce the total costs of large small animal studies.

Methods

Animal care and all experimental procedures were conducted in accordance with German laws governing animal care and with the European Communities Council

Protocol	Standard human	Animal model
T2-weighted TSE	0.6 x 0.4 x 5.0 mm 1 min 20 s	0.2 x 0.2 x 1.5 mm 2 min 18 s
T1-weighted SE	1.0 x 1.0 x 3.0 mm 5 min 19 s	0.2 x 0.2 x 1.0 mm 8 min 4 s
DW EPI	1.8 x 1.8 x 5.0 mm 1 min 14 s	0.5 x 0.5 x 1.6 mm 2 min 20 s

Tab 1: Comparison between the standard MR protocols used for clinical human examinations and adapted small imaging protocols. The resolution and the total acquisition time are listed for the three protocols used for stroke examination.

Directive (86/609/EEC). Protocols were approved by the Ethics Committee for animal research of the local authorities. All experiments were performed on 3T clinical MR scanners; either on a MAGNETOM Allegra (Siemens Medical Solutions, Erlangen, Germany) or on a MAGNETOM Trio, A Tim System (Siemens Medical Solutions, Erlangen, Germany). The Allegra was equipped with a 4-channel phased array head coil and a 4-channel phased array spine coil for the rat (RAPID Biomedical, Rimpar, Germany), while the Tim Trio was equipped with an 8-channel phased array whole body coil for the mouse (RAPID Biomedical, Rimpar, Germany).

Results

A conventional diffusion-weighted (DW) EPI examination of a healthy rat brain is shown in Fig. 1A. In comparison, Figs. 1B–1D show a series of DW EPI acquisitions with PAT factors from 2 to 4 using *syngo* GRAPPA [1]. The in-plane resolution being 500 μm and the slice thickness is 1.6 mm. Corresponding ADC maps can be found in the bottom row of Fig. 1. Images obtained from a rat model of cerebral ischemia (Rat A, 6 h after Middle Cerebral Artery Occlusion (MCAO)) are shown in Figs. 2A–2C. While the images in Figs. 2D–2F are from a different rat (Rat B) acquired 36 hrs after occlusion. T2-weighted TSE images are shown in Fig. 2A and Fig. 2D. The in-plane resolution is 200 μm with a 1.5 mm slice thickness. The total acquisition time of the TSE study was 2 min 18 s, with 11 slices. The corresponding DW EPI ($b = 1000 \text{ s/mm}^2$) images with a PAT factor of 3 are shown

in Figs. 2B and 2E. The in-plane resolution is 500 μm and the slice thickness is 1.6 mm. The total acquisition time of the DW EPI study with three directions and four b values was 2 min 20 s. Calculated ADC maps are shown in Figs. 2C and 2F. Results from a post contrast T1-weighted study to detect the blood-brain-barrier (BBB) permeability can be seen in Fig. 3. The acquisition time of each examination was 8 min 4 s, with the same in plane resolution as for the TSE study. Table 1 shows a direct comparison between the standard and the adapted small animal protocol parameters, in terms of resolution and total acquisition time.

Images obtained from a small animal model of hemorrhagic stroke acquired 2 hrs after blood injection are shown in Fig. 4. A single slice from a T2-weighted TSE acquisition is shown in Fig. 4A. The in plane resolution is 200 μm with a 1.0 mm slice thickness. The total acquisition time of the TSE study with 11 slices using 3 averages was 2 min 18 s. The corresponding susceptibility-weighted image is shown in Fig. 4B. Here, the in plane resolution is 400 μm with 1.6 mm slice thickness. The total acquisition time of the T2*-weighted gradient echo (GRE) sequence with 11 slices, using 2 averages was 1 min 76 s.

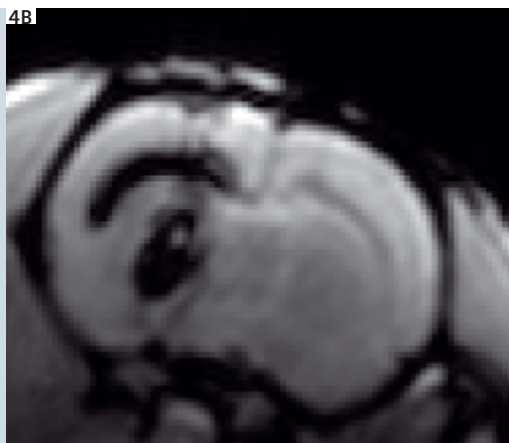
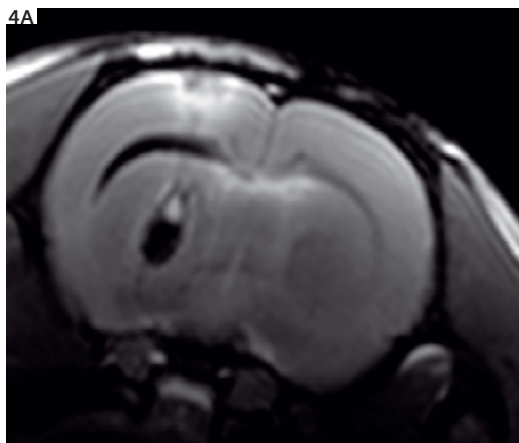
Single sagittal sections from two animals of a spinal contusion injury are shown in Fig. 5. The T2-weighted TSE acquisitions have an in-plane resolution of 200 μm with a slice thickness of 400 μm . The total acquisition time of the TSE study using 3 averages and 11 slices in 2 concatenations was 5 min 35 s. These images were acquired without respiratory or cardiac gating, which would improve the overall

image quality. A series of whole mouse images with PAT factors from 1 to 4 is shown in Fig. 6. Those images were obtained on a MAGNETOM Trio, A Tim System using an 8-channel phased array whole-body coil for the mouse. With the same set up, a contrast enhanced 3D FLASH acquisition was performed on a mouse with congested kidneys (Fig. 7). This study was obtained with a PAT factor of 2. The acquisition of this dataset with an isotropic resolution of 300 μm took about 4 min.

Discussion

In EPI the use of iPAT reduces blurring due to T2* relaxation and distortions due to off-resonance effects significantly [2]. It has been shown that this effect is especially important for stroke detection using DW EPI [3]. Further, the use of iPAT allows one to shorten the echo time (TE), in the example shown in Fig. 1, from 174 ms down to 77 ms. The reduction of TE increases the signal-to-noise ratio (SNR), which can balance out the inherent loss in SNR due to the use of iPAT in a certain range. The use of iPAT for DW EPI of small animals on a 3T clinical MR scanner is essential to obtain high image quality. In terms of off-resonance distortion reduction and achievable SNR, iPAT with an acceleration factor of 3 is found to perform best for this specific set up.

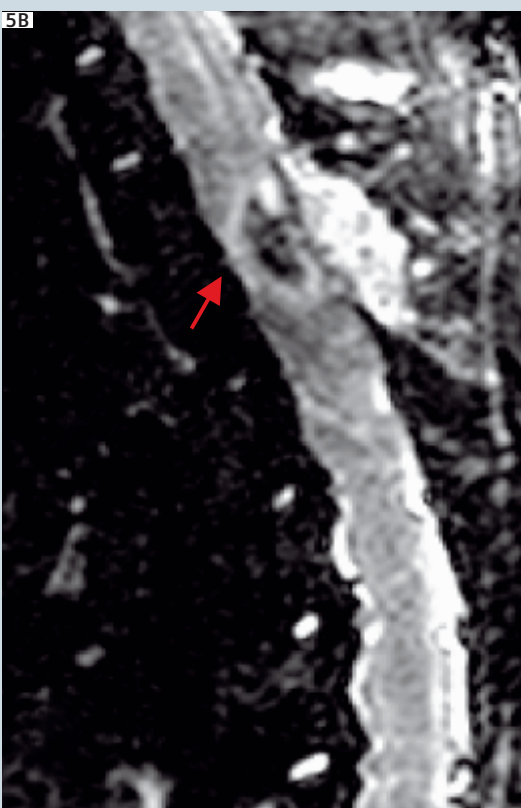
The feasibility of small animal imaging after experimental transient ischemia on a 3T clinical MR scanner is demonstrated in Figs. 2 and 3. High resolution, high quality images were obtained using standard Siemens product sequences with some protocol adaptations for the small



4 Small animal hemorrhagic stroke imaging on a clinical MR scanner (MAGNETOM Allegra) at 3T using a 4-channel phased array head coil for the rat:

A: T2-weighted TSE acquisition.

B: T2*-weighted GRE acquisition.



5 Imaging of spinal cord injury in rats on a clinical MR scanner (MAGNETOM Allegra) at 3T using a 4-channel phased array spine coil for the rat: T2-weighted TSE sequence with 200 μm in plane resolution and 400 μm slice thickness.

field of view and the high resolution. As shown in Table 1, the total acquisition time is comparable to standard imaging protocols used for human examinations. Besides a 4-channel phased array head coil for the rat and the animal handling system, no specific hardware had to be used. To achieve sufficient SNR in the high resolution small animal experiments, it was necessary to use more averages or to turn off the partial Fourier option, which explains the longer acquisition times com-

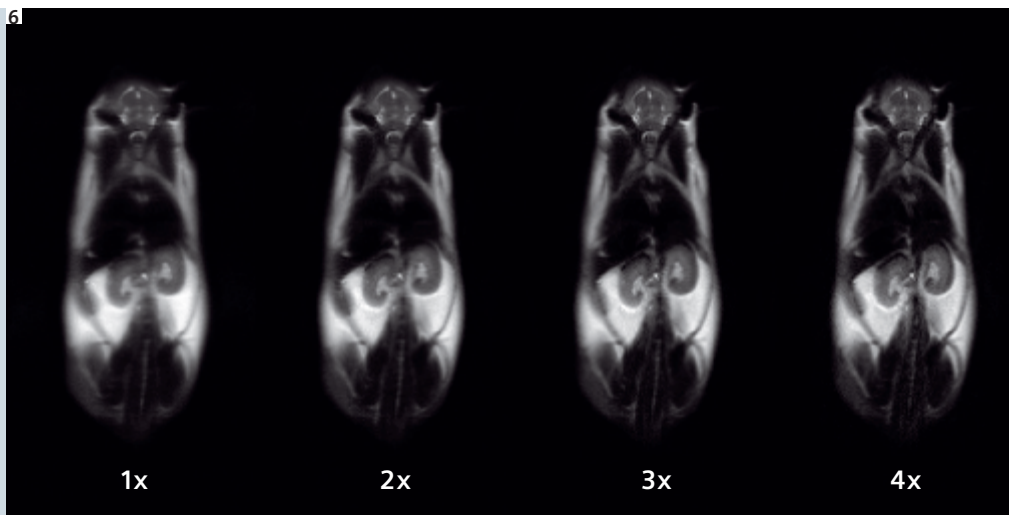
pared to the standard human protocols. As can be seen in Fig. 6, the use of iPAT in combination with the HASTE sequence [4] helps to increase the resolution of those acquisitions.

Conclusion

High resolution small animal imaging on 3T clinical MR scanners can be realized in scan times comparable to those used for human examinations. Since all imaging

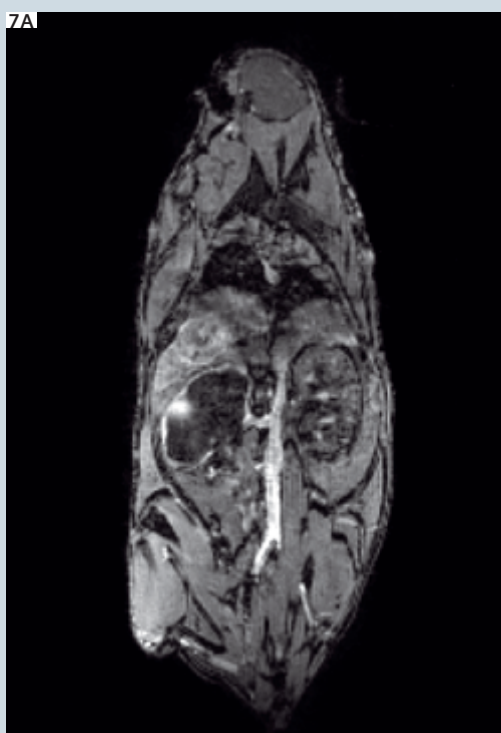
protocol parameters fall in a tolerable range for human applications, a direct transfer of the knowledge gained with those small animal models to human studies is possible.

The short acquisition times can be used to increase the animal throughput of the system and can reduce the mortality rate due to examination stress. Finally, this approach can reduce the overall cost of studies with a large number of small animals being examined.



6 Imaging of a whole mouse on a clinical MR scanner (MAGNETOM Trio, A Tim System) at 3T using an 8-channel phased array Body Matrix coil for the mouse: T2-weighted HASTE sequence with PAT acceleration factors from 1 to 4.

Images courtesy of Herbert Reinl, Grosshadern, Munic, Germany.



7 Imaging of a whole mouse with congested kidneys on a clinical MR scanner (MAGNETOM Trio, A Tim System) at 3T using an 8-channel phased array whole-body coil for the mouse: 3D FLASH with PAT factor 2.

Images courtesy of Herbert Reinl, Grosshadern, Munic, Germany.

Acknowledgement

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ClinScan – A New Preclinical Animal MRI Scanner Based on the syngo User Interface

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Bruker BioSpin MRI, Ettlingen, Germany

ClinScan is a user friendly animal MR imaging (MRI) system for preclinical imaging and translational research.

The ClinScan is a new 7T animal MRI and MR Spectroscopy (MRS) scanner designed to further facilitate translational research from 'mice to men' in the field of preclinical and molecular imaging. This allows to

be clinical from the very beginning. ClinScan is Bruker BioSpin's solution for an emerging market of research MRI systems that allows a direct and fast transfer of preclinical studies on animal models to clinical studies on humans. By virtue of the strategic alliance with Siemens Medical Solutions on human high-field MR systems, ClinScan uses the clinical user interface syngo MR. Its operation is iden-

tical to that of Siemens' MAGNETOM systems with Total imaging matrix (Tim). ClinScan is a high field MRI system for preclinical imaging with animal handling accessories for high throughput, animal welfare and monitoring that facilitates straightforward transfer of protocols from bench top to bedside and vice-versa.

ClinScan



- 7T Bruker USR magnet (Ultra Shielded Refrigerated, bore size 30 cm).
- Bruker gradient and shim coil (gradient strength of 290 mT/m, slew rate of 1160 T/m/s).
- Bruker RF array coil technology in combination with numerous animal handling accessories.
- Siemens MAGNETOM Avanto technology with up to 32 receiver channels.
- Clinical routine user interface syngo MR to enable efficient workflow and highly automated state-of-the-art MRI and MRS applications on small animals.

Clinical User Interface *syngo* MR

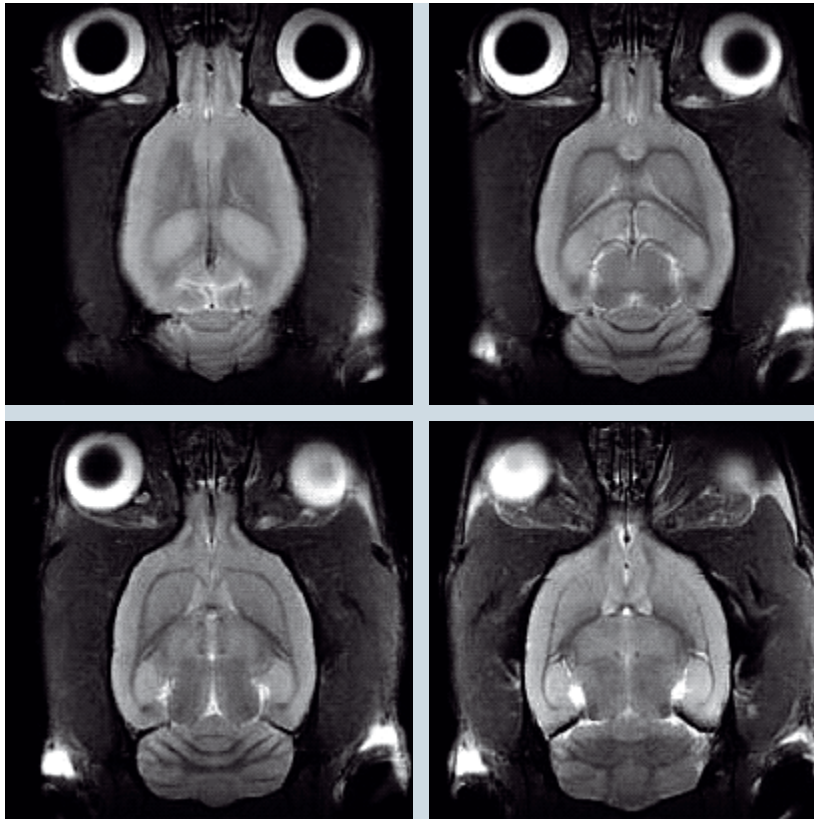
- *syngo* based graphical user interface offers optimized clinically oriented workflow.
- Parallel working and one-click exams are supported efficiently.
- Parallel scanning and reconstruction are standard. Images can be loaded and used for graphical slice planning during reconstruction.
- iPAT (integrated Parallel Acquisition Techniques) further increase the acquisition speed. iPAT is fully compatible with the optional phased array coils.
- Dynamic Analysis evaluation and Mean Curve software allows the calculation of functions and dynamic examinations.
- IDEA sequence development environment.

ClinScan *syngo*® is the link for translational molecular MRI. The *syngo* user interface facilitates straightforward transfer of protocols from bench top to bedside and vice-versa.



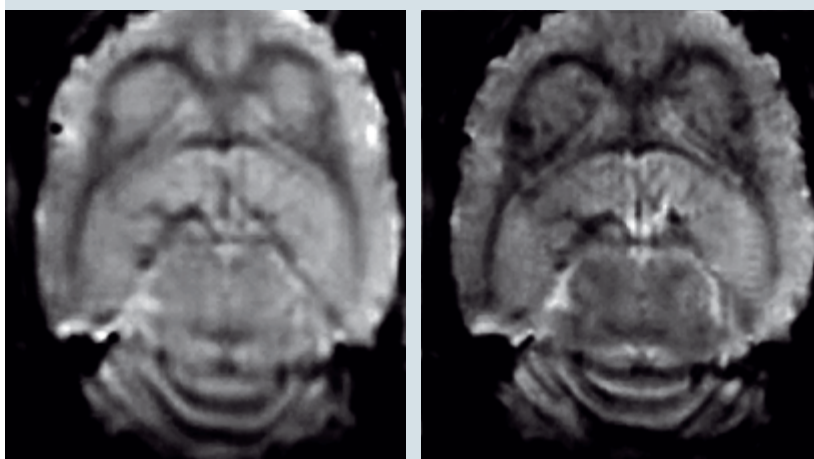
Application Packages

Application packages for animal MRI resemble the application packages already known from clinical MRI. Sequences and protocols are optimized for the specific needs in animal MRI.

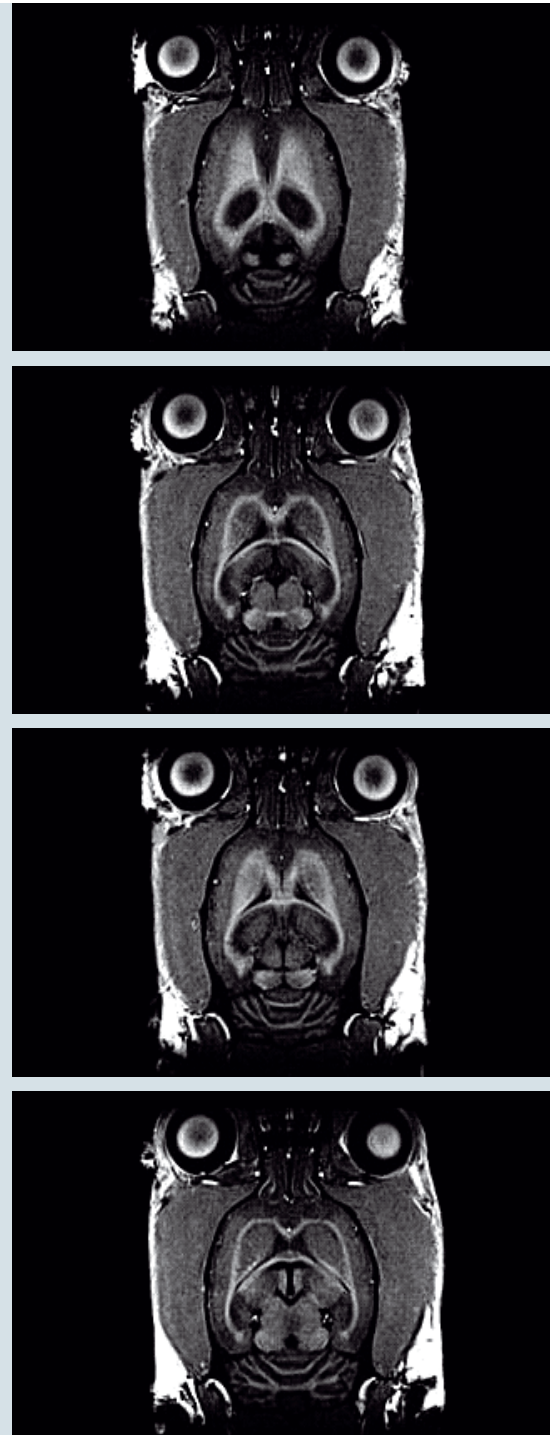


T2-weighted imaging (Turbo Spin Echo).

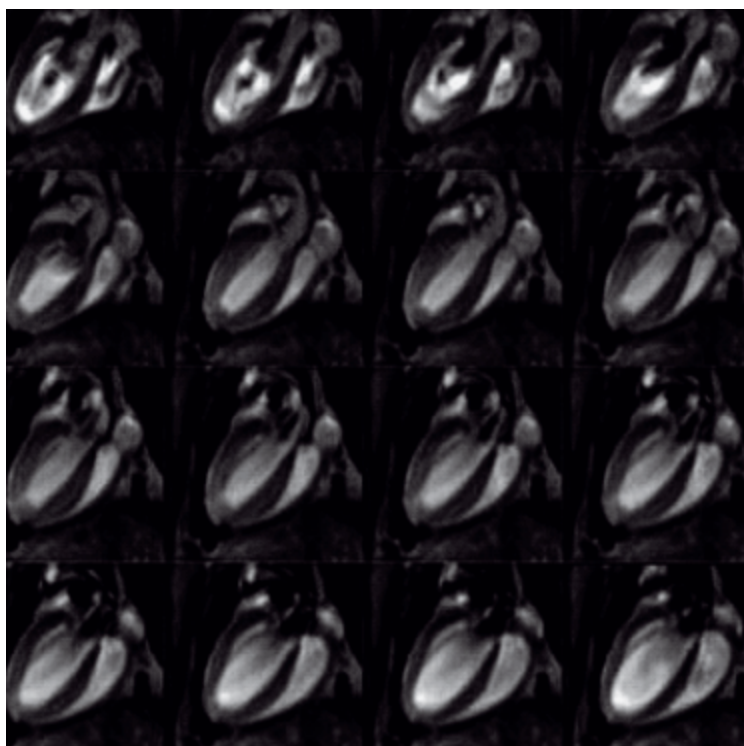
Courtesy: B. Pichler, Eberhard-Karls-University Tuebingen, Germany



Single shot EPI. Left: matrix size 96 x 128, PAT factor 1.
Right: matrix size 144 x 192, PAT factor 2.



High-resolution 3D T1-weighted imaging (MPRAGE) of rat brain in vivo.



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