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Three-Dimensional Amide Proton Transfer MR Imaging of Gliomas: Initial Experience and Comparison with Gadolinium Enhancement

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Abstract

Purpose—To investigate the feasibility of a three-dimensional amide-proton-transfer (APT) imaging sequence with gradient- and spin-echo readouts at 3T in patients with high- or low-grade gliomas.

Materials and Methods—Fourteen patients with newly diagnosed gliomas were recruited. After B₀ inhomogeneity correction on a voxel-by-voxel basis, APT-weighted images were reconstructed using a magnetization-transfer-ratio asymmetry at offsets of ± 3.5 ppm with respect to the water resonance. Analysis of variance post-hoc tests were used for statistical evaluations, and results were validated with pathology.

Results—In six patients with gadolinium-enhancing high-grade gliomas, enhancing tumors on the post-contrast T₁-weighted images were consistently hyperintense on the APT-weighted images. Increased APT-weighted signal intensity was also clearly visible in two pathologically proven, high-grade gliomas without gadolinium enhancement. The average APT-weighted signal was significantly higher in the lesions than in the contralateral normal-appearing brain tissue ($P < 0.001$). In six low-grade gliomas, including two with gadolinium enhancement, APT-weighted imaging showed iso-intensity or mild punctate hyperintensity within all the lesions, which was significantly lower than that seen in the high-grade gliomas ($P < 0.001$).

Conclusion—The proposed three-dimensional APT imaging sequence can be incorporated into standard brain MRI protocols for patients with malignant gliomas.

Keywords

APT imaging; CEST imaging; glioma; tumor grade; gadolinium enhancement

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Currently, brain MRI is the key modality for assessing malignant gliomas in the clinic. It is used to determine the extent of involvement, guide treatments, and assess therapeutic response (1, 2). However, conventional MRI sequences [T_2 -weighted, fluid-attenuated inversion recovery (FLAIR), and gadolinium-enhanced T_1 -weighted] are not sufficiently tissue-specific, and suffer from some serious clinical limitations. For example, gadolinium enhancement is a marker of blood-brain-barrier disruption and does not demonstrate tumor activity directly. It has been reported that roughly 10% of glioblastomas and 30% of anaplastic astrocytomas demonstrate no gadolinium enhancement (3). In addition, gadolinium enhancement is not always specific for tumor grade, as low-grade gliomas occasionally enhance (4). Specifically, it is becoming increasingly apparent that conventional MRI is not adequate to assess treatment response due to a lack of specificity (5). In recent years, there have been numerous investigations into the ability of functional and molecular imaging techniques, such as diffusion, perfusion, and proton MR spectroscopy, to assess tumor tissue properties and treatment effects (6–9). Although promising, results have been mixed. Therefore, new imaging technologies are urgently needed to better define the various regions of tumor and distinguish areas of treatment-induced effects from recurrent tumor.

Amide proton transfer (APT) imaging is a new molecular MRI technique that can give contrast due to endogenous mobile proteins and peptides and tissue pH (10, 11). This technique is based on the chemical exchange saturation transfer (CEST) mechanism (12–15). Technically, the APT imaging signal is measured as a reduction in bulk water intensity due to chemical exchange with magnetically labeled backbone amide protons (at ~3.5 ppm downfield of the water resonance) of endogenous mobile proteins and peptides (16). Thus, information about the cellular protein content and tissue physico-chemical properties (pH and even temperature) that influence the exchange rate is obtained indirectly through the bulk water signal usually used in imaging. APT-MRI has expanded the range of molecular MRI techniques to the endogenous protein level, allowing the noninvasive assessment of brain tumors, in which many proteins are over-expressed (17).

The APT technique was first applied to patients with brain tumors in 2006 (18). This and subsequent research has shown that APT imaging has the potential for the detection and characterization of malignant brain tumors (19, 20) and other cancers (21) at the protein level. These clinical applications for APT are promising, but have mostly been limited to single-slice acquisitions. A few technical limitations for this include a long scan time (used to acquire multiple saturation images and different frequencies) and specific absorption rate (SAR) requirements. Clinical exams will be most useful if whole-brain acquisition, multi-slice or three-dimensional (3D), can be performed. Recently, several volumetric APT (or generally CEST) imaging sequences with multi-slice readouts have been proposed for use on clinical MRI scanners (22–24). Although promising, the multi-slice readouts are complicated by corrections for APT signal losses due to T_1 relaxation with respect to the order in which the slices are acquired. In principle, APT MRI is most compatible with 3D acquisition. Notably, Zhu et al. (25) developed a relatively fast and sensitive, 3D gradient- and spin-echo (GRASE) approach for APT imaging at 3T, which can produce a uniform contrast across all slices on a homogenous protein phantom and in healthy human subjects in less than 11 min. In this work, we demonstrate the feasibility of applying this fast 3D APT sequence to patients with brain tumors.

MATERIALS AND METHODS

Patient Recruitment

The study was approved by the Johns Hopkins Institutional Review Board. Prior to involvement in this study, written, informed consent was obtained from all patients. Fourteen patients (ten males, four females; median age, 46.5 years; age range, 25–82 years; Table 1) with newly diagnosed, suspected gliomas of varying grades, who were referred for biopsy or resection for presumed glioma, were recruited prior to the surgery that confirmed their diagnosis.

APT Pulse Sequence

Experiments were performed on a Philips 3T human MRI scanner (Achieva; Philips Medical Systems, Best, The Netherlands) using a body coil excite and a 32-channel phased-array coil for reception (Invivo, Inc., Gainesville, FL). The GRASE 3D APT imaging sequence developed recently (25) was used in this study. Briefly, this GRASE sequence (Fig. 1) consists of three sections: radiofrequency saturation (four block radiofrequency pulses of 200 ms duration and 2 μ T amplitude, each followed by a crusher gradient of 10 ms duration and 10 mT/m strength); lipid suppression (chemical-shift-selective removal with an asymmetric frequency modulated pulse); and GRASE 3D image acquisition (a single slab-selective 90° excitation pulse, a turbo-spin-echo factor of 22 in the right-left direction and an echo-planar imaging factor of 7 in the superior-inferior direction, with readout in the anterior-posterior direction). It has been demonstrated previously that a saturation power of 2 μ T causes an optimal hyperintense APT-MRI signal in the tumor and an optimal hypointense signal in stroke (26), compared to approximately isointense normal brain tissue. Other imaging parameters were: field of view, 212×186 mm²; resolution, 2.2×2.2 mm²; 15 slices; thickness, 4.4 mm; sensitivity-encoding acceleration factor, 2, in the right-left direction; repetition time, 3 s; and SAR, 1.1 W/kg, which is within the U.S. Food and Drug Administration guidelines.

Acquisition Protocol

The APT signal is usually measured by a magnetization-transfer-ratio (MTR)-asymmetry analysis between signal intensities of ± 3.5 ppm with respect to the water frequency. As a consequence, the quality of APT imaging greatly depends on the B_0 homogeneity over the volume imaged, which affects the water resonance position. In this study, localized shimming using a field map (27) was first performed (Fig. 2a). The calculated optimal shim parameters and scanner's center frequency F_0 were applied to the subsequent APT and other scans. To correct for residual B_0 inhomogeneity effects, APT imaging was acquired with a six-offset protocol (S_0 , ± 3 , ± 3.5 , ± 4 ppm from water; 1, 1, 4, 1 averages, respectively), as proposed previously (19), which was acquired twice and averaged during data processing. More acquisitions at ± 3.5 ppm were obtained to increase the APT signal-to-noise ratio. The achieved signal-to-noise ratios were estimated to be about 53, 122, and 69 for images at ± 3 , ± 3.5 , and ± 4 ppm (25), respectively, which are high enough for detecting the APT signal of 2–3% of the bulk water intensity. The total scan time was 10 min 42 s. The water saturation shift referencing method (28) was used to determine B_0 maps (range, -1.5 to 1.5 ppm; interval, 0.125 ppm; saturation power, 0.5 μ T; saturation time, 200 ms; repetition time, 1.25 s; scan time, 2 min 15 s).

Several standard MR images were acquired for reference. The parameters used were: T₂-weighted (repetition time, 4 s; echo time, 80 ms; 60 slices; thickness, 2.2 mm); FLAIR (repetition time, 11 s; echo time, 120 ms; inversion recovery time, 2.8 s; 60 slices; thickness, 2.2 mm); and gadolinium-enhanced T₁-weighted (3D magnetization-prepared-rapid-gradient-echo sequence; repetition time, 3 s; echo time, 3.7 ms; inversion recovery time, 843

ms; flip angle, 8°; 150 slices; isotropic voxel, 1.1 mm³). This gadolinium-enhanced T₁-weighted imaging was the last sequence acquired.

Image Processing

The raw images were co-registered with the Oxford Centre for Functional MRI of the Brain linear image registration tool (University of Oxford, Oxford, UK) and then processed using an interactive data language (Version 7; Exelis Visual Information Solutions, Inc., Boulder, CO, USA). To determine the B₀ field inhomogeneity, the full z-spectrum with 25 offsets, acquired using the water saturation shift referencing method (28), was fitted through all offsets using a 12th-order polynomial on a voxel-by-voxel basis (19). After this, the fitted curve was calculated using an offset resolution of 1 Hz (namely, 385 points). The actual water resonance was assumed to be at the frequency with the lowest signal intensity. The deviation from the water frequency in Hz was used to form a map of water center frequency offsets.

The procedures to correct for the field inhomogeneity effects on APT images are as follows (Fig. 2b). The acquired APT data were organized according to the offsets, and the images with the same offsets were averaged. Then, the data for offsets (+4, +3.5, +3 ppm or +512, +448, +384 Hz at 3T) for each voxel were interpolated to 385 points over the range from +5 to +2 ppm (namely +640, +639, ..., +256 Hz) and shifted using the fitted z-spectrum central frequency offset at the same voxel. A similar procedure was applied to the negative-offset data (−3, −3.5, −4 ppm). Based on the shift-corrected data, the APT image (exactly, the APT-weighted image; see the DISCUSSION section below) was calculated using an MTR asymmetry at ±3.5 ppm (19). The calculated image was thresholded based on the signal intensity of the S₀ image to remove voxels outside the brain.

Targeted Tissue Sampling

For each patient, the imaging data were processed immediately after completion of the MRI. The neurosurgeons (ML and AQ) and the other investigators associated with the study reviewed the images together and decided the most feasible and meaningful regions of interest for biopsy, based on APT-weighted intensity and gadolinium enhancement. Only regions of interest that were clinically feasible and ethically appropriate, or within the clinically planned resection areas, were chosen. These pre-determined regions of interest were labeled on the co-registered, gadolinium-enhanced T₁-weighted or FLAIR images in the BrainLab neuro-navigation system that was used in the operating room. All targeted biopsies were obtained at the start of the procedure, before any resection or tumor debulking was initiated, to minimize the coregistration error from brain shift after craniotomy. The centers of the regions of interest were targeted to further limit the error in coregistration. For each sample, the exact site of sampling was marked on the neuro-navigation system by a screenshot image. Two to four samples were obtained from each patient. The tissue was evaluated by a neuropathologist (CGE) blinded to the MRI features. Tumor grade was determined based on the 2007 WHO criteria.

Image Analysis

The images were reviewed by two experienced neuro-radiologists (MGP and SAM, with 21 and 8 years of experience, respectively). Specifically, we evaluated APT-weighted imaging features within regions of abnormality on standard MRI sequences. For each patient, a single slice showing the maximum tumor area was chosen for quantitative analysis. Two regions of interest (tumor and contralateral normal-appearing brain tissue) were drawn manually on the FLAIR images and then transferred to identical sites on the APT-weighted images (Fig. 3). The tumor region was defined according to the signal abnormalities on the standard MR images. For gliomas with gadolinium enhancement, the tumor region consisted of areas

encircled by the gadolinium enhancement as well as some adjacent areas with the T₂ and FLAIR hyperintensities. For gliomas that did not enhance, the tumor region was assigned according to the T₂ and FLAIR signal abnormalities.

Statistical Analysis

The analysis was performed using the statistical package SPSS for Windows (Version 18, Chicago, IL). For each patient, the APT-weighted imaging intensities from two observers were averaged. The average APT-weighted imaging intensities and corresponding 95% confidence intervals were calculated for each tissue type. The analysis of variance post-hoc tests were used to determine whether the differences in these APT-weighted intensities were significant. The level of significance was set at $P < 0.05$.

RESULTS

Image Features

Eight of the fourteen patients were confirmed with histopathology to have high-grade gliomas (six with glioblastoma; two with anaplastic astrocytoma; Table 1). Of these, six tumors showed gadolinium enhancement, and two did not. All of these high-grade gliomas, including the two without gadolinium enhancement, consistently had markedly increased APT-weighted signal intensities. Figure 3 shows APT-weighted and conventional MR images for a patient with a confirmed glioblastoma (patient 1). It can be seen that the gadolinium-enhancing areas on the post-contrast T₁-weighted images were hyperintense on the APT-weighted images, compared to the contralateral normal-appearing white matter. The abnormal areas on the APT-weighted images were a little bit smaller than those on the T₂-weighted and FLAIR images, but comparable to or a little bit larger than those on the post-contrast T₁-weighted images. It is interesting to note that the cystic areas within the tumor also demonstrated the high signal on APT-weighted imaging. Figure 4 shows APT-weighted and conventional MR images for another patient with a confirmed glioblastoma (patient 4). Similar to Fig. 3, the gadolinium-enhancing tumor rim on the post-contrast T₁-weighted image was hyperintense on the APT-weighted image, compared to the edematous tumor periphery and surrounding normal-appearing white matter. Notably, the non-enhancing necrotic center had a low APT-weighted signal. This result means that APT-weighted imaging can distinguish between the enhancing rim and the non-enhancing necrotic center on the post-contrast T₁-weighted image. The hyperintense areas on the APT-weighted image were much smaller than the abnormal areas on T₂-weighted and FLAIR and appeared associated with the most solid aspects of the lesion (gadolinium-enhancing portion) and some areas nearby. Therefore, APT-weighted imaging could provide a tumor appearance unique from conventional MRI.

Figure 5 shows APT-weighted and conventional MR images for a patient with a confirmed grade-3 anaplastic astrocytoma (patient 8). This brain lesion showed no gadolinium enhancement and was initially presumed to be low-grade. However, APT-weighted hyperintensity was clearly visible in the lesion, which predicted the high-grade pathology. This patient was found to have a high-grade glioma on histopathology when tissue from the region of increased APT-weighted intensity was sampled. Our early data suggest that the APT-weighted hyperintensity (compared to the contralateral normal-appearing white matter) is a typical feature of high-grade gliomas.

Six patients were histopathologically diagnosed with low-grade glioma (two with low-grade oligodendroglioma; three with low-grade astrocytoma; one with low-grade oligoastrocytoma). Of these, four tumors demonstrated no gadolinium enhancement, but two did show small areas of gadolinium enhancement. All six low-grade gliomas consistently

showed low APT-weighted signals. Figure 6 shows one example (patient 9) of typical APT-weighted and conventional MRI images in patients with histologically confirmed low-grade gliomas, namely, no gadolinium enhancement and APT-weighted iso-intensity (compared to the contralateral normal-appearing white matter). Therefore, no obvious lesion can be found using either the APT-weighted or post-contrast T₁-weighted images. Figure 7 gives APT-weighted and conventional MR images for a case with a confirmed grade-2 astrocytoma (patient 14) that showed gadolinium enhancement and was presumed high-grade. However, the APT-weighted signal intensity was low (iso-intensity to mild punctate hyperintensity) within the lesion, consistent with the APT-weighted features of a low-grade glioma. These results suggest that APT has the potential to distinguish high-grade from low-grade tumors and more specifically delineate heterogeneous regions of complex gliomas.

Quantitative Analysis

The APT-weighted intensity is a continuum and is quantified as a percentage of the bulk water signal. For all high-grade gliomas ($n = 8$), the average APT-weighted image intensities were significantly higher in the tumor than in the contralateral normal-appearing brain region (2.50% vs. 0.30%; $P < 0.001$; Table 1). The observed APT-MRI contrast between the tumor and the contralateral brain tissue was 2.21%. For all low-grade gliomas ($n = 6$), the average APT-weighted image intensities were marginally significantly higher in the region of FLAIR hyperintensity than in the contralateral brain tissue (1.09% vs. 0.51%; $P = 0.046$), and the contrast was small (0.51%), consistent with the fact that no marked APT-weighted hyperintensity was clearly seen on the images. When all high- and low-grade gliomas were compared, the average APT-weighted image intensities were significantly higher in high-grade gliomas than in low-grade gliomas ($P < 0.001$). The initial study indicates that APT-weighted hyperintensity is a characteristic feature of high-grade gliomas and more tissue-specific than gadolinium enhancement.

DISCUSSION

We have evaluated a relatively fast and sensitive GRASE 3D APT imaging sequence and a reliable data acquisition protocol for their use in human gliomas on a 3T human MRI scanner with a 32-channel phased-array coil for reception. The imaging sequence relies on a pulse-train saturation scheme (total duration, 800 ms; power, 2 μ T). With this method, we were able to perform APT imaging of brain tumors, with 15 slices of 4.4 mm thickness, within a clinically relevant time frame (10 min 40 s for APT data acquisition and a short time for B₀ mapping). Several different methods, such as the water saturation shift referencing method (28) and the multiple-gradient-echo method (29), can be used to determine B₀ maps. The corrected APT-weighted images show reliable image quality: hyperintensity in high-grade tumors and homogenous signal intensity in most normal-appearing brain areas, although some artifacts could be seen in the skull, near air-tissue interfaces (sinus, ear), and ventricles. These results show that the GRASE 3D APT imaging technique with a reasonable scan time and a low SAR is feasible to be translated into clinical use.

Several other 3D APT-MRI sequences have been designed in the past years (30–33). However, it seems that all of these pulse sequences have a disadvantage. For example, the pulse-train pre-saturation (used to satisfy amplifier requirements regarding unblank time and duty cycle on clinical MRI scanners) followed by fast low-angle shot image readouts has been used by different researchers (30, 31). The pulsed steady-state CEST sequence is another important type of 3D APT-MRI sequences (32). This sequence consists of numerous brief saturation pulses, each followed by a segmented imaging acquisition. However, these promising 3D techniques suffer from a small flip-angle image acquisition, thus leading to large APT signal losses. The GRASE 3D APT imaging sequence utilized a 90° excitation

pulse and should have a higher detection sensitivity. Finally, compared to the GRASE 3D APT imaging sequence evaluated in this study, the newly developed 3D turbo spin echo-based APT sequence has a relatively high SAR (2.7 W/kg) and a relatively small volume coverage (up to 8 slices) (33). For APT imaging on animal systems (10, 11), the radiofrequency saturation is typically applied using a block pulse of several seconds to maximize effects. Based on a time-interleaved, dual transmission saturation scheme for minimizing power amplifier limitations, the long block saturation pulse of several seconds has become feasible on human MRI scanners (34). This novel parallel transmission-based CEST technology can be incorporated with the GRASE 3D APT imaging sequence, but not with the turbo spin echo-based 3D APT sequence due to the strict SAR limitation.

The APT signal intensity, calculated using an MTR asymmetry at offsets of ± 3.5 ppm with respect to the water resonance, depends on the experimental parameters used, such as the radiofrequency irradiation power and duration (26). In this study, the APT-weighted images were generated using the optimal saturation power of 2 μ T, which achieved approximately zero APT-weighted intensity (green) in normal brain tissue, allowing easy identification of hyperintensities in high-grade tumors (yellow to red). It is also expected that at 2 μ T, the stroke lesions should show hypointensity (blue to purple), compared to the contralateral normal-appearing brain tissue. It is interesting that the APT-weighted signal intensities of high-grade tumors measured using the duration 800 ms and power 2 μ T in this study (2.5%) are lower than those measured previously using the duration 500 ms and power 3 μ T with a single-slice data acquisition protocol (3.8%), whereas the measured APT-weighted contrasts between the tumor and the contralateral brain tissue are very similar (2.2% vs. 2.1%).

Malignant gliomas in the brain typically consist of a solid tumor mass and individual tumor cells infiltrating into adjacent edematous brain tissue. Our data show that there are high APT-weighted signals in areas of solid tumors, particularly in areas with gadolinium enhancement, compared to surrounding edematous brain tissue and contralateral normal-appearing brain tissue. These results suggest that APT imaging has the potential to enhance the specificity of MRI for malignant gliomas in patients. For example, APT imaging has the potential to differentiate between solid tumors and peritumoral edema, to separate high- from low-grade gliomas, and to detect high-grade tumor masses that do not show gadolinium enhancement. Notably, this can be accomplished without exposure to contrast agents. In a recent pre-clinical study (35), the data showed that active glioma has a hyperintense signal on APT-weighted images, whereas a hypointense or isointense APT-weighted signal is seen in a brain with radiation necrosis. Therefore, the APT-MRI signal of amide protons, associated with endogenous mobile proteins and peptides, has the potential to be an important imaging biomarker for the accurate characterization of the recurrence of active brain tumor following treatment.

The APT signal measured through the MTR-asymmetry analysis at ± 3.5 ppm may include the possible inherent asymmetry of the solid-like macromolecular magnetization transfer effect, the possible nuclear Overhauser effect of aliphatic protons of mobile macromolecules, and the possible magnetization transfer effect of metabolites (36), which would contribute a negative background signal to the APT measurements. In addition, other CEST signals from other exchangeable protons of mobile proteins, peptides, amino acids, and metabolites resonating around the amide proton frequency may mix with the APT measurement (37, 38). However, these contributions should be negligible because these exchangeable protons do generally not obey the requirement of the slow or intermediate exchange at 3T. Finally, the APT imaging signal in tissue is primarily related to two factors: the mobile amide proton content, and the amide proton exchange rate, a parameter that depends on tissue pH. In addition, other tissue physico-chemical factors (such as water content and temperature) and technical factors (such as water spin-lattice relaxation times

and direct water saturation) may also affect the signal (18). Because often only a small intracellular pH increase (up to about 0.1 pH unit) is detected in the tumor (39) with respect to the normal brain tissue, this increasing APT effect in the tumor can be attributed primarily to increasing protein content. To reflect the fact that the APT effect is not clean and has multiple contributions, APT images defined by the MTR-asymmetry analysis at 3.5 ppm should in principle be APT-weighted images, although, for simplicity, they are sometimes called APT images in this and some other studies. The APT-weighted images seem valid for separating tumors from normal brain, as demonstrated in this study.

Our results have some limitations in the clinic applications. First, APT imaging detects endogenous mobile proteins and peptides in tissue (10, 11), such as those in the cytoplasm. The liquid-like cystic portion of the tumor shows the high APT signal (Fig. 3), as expected (40), because proteinaceous cysts contain many mobile proteins. The high APT signal in the cysts could potentially lead to false-positives in the clinic. To avoid misinterpretation, combining the APT images with standard T₂-weighted and FLAIR MRI (in which the cysts can readily be identified) is recommended. Second, the APT-MRI signal is relatively weak (roughly 2–3% bulk water intensity), and the dynamic range between high- and low-grade tumors is also relatively small (roughly 2% vs. 1% bulk water intensity). Using the current imaging sequence and data acquisition protocol, some artifacts could still be seen in the skull, near air-tissue interfaces (sinus, ear), and ventricles. Therefore, care should be taken when the 3D APT imaging technique is used as a quantitative MR imaging tool.

In conclusion, we have demonstrated that GRASE 3D APT imaging at 3T is feasible in patients with brain tumors. The addition of APT imaging to the currently used MRI protocol (typically including FLAIR and gadolinium-enhanced T₁-weighted sequences) would enhance the specificity of MRI for malignant gliomas in patients. The early results in this study suggest that the APT-weighted signal may be a valuable biomarker by which to identify the spatial extent and pathological grade of primary brain tumors presurgically. This is particularly significant for patients with non-enhancing high-grade lesions, and for those with a contraindication to gadolinium administration. APT imaging could be used to guide a biopsy that could greatly increase the accuracy of pathology. Our ongoing further study shows that the APT-MRI signal, as a surrogate biomarker of active glioma, may have the potential to enhance the noninvasive diagnosis of active brain tumors vs. treatment effects. 3D APT may be a valuable addition to the MRI armamentarium that can potentially improve diagnosis and treatment planning by providing more accurate targets for biopsy, tumor resection, radiation therapy, and local chemotherapy.

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Figure 1.

a: Schematic GRASE 3D APT-MRI pulse sequence. The sequence consists of four block saturation pulses (200 ms each, total 800 ms; 2 μ T), a frequency-modulated lipid suppression pulse, and 3D GRASE image data acquisition. **b:** Example of the geometric prescription of 3D APT imaging in the brain. Fifteen slices were acquired.

Figure 2.

a: Six-offset APT data acquisition protocol. The first localized shimming preparation was used to calculate the optimal shim parameters and scanner's center frequency F_0 . Extra offsets ($\pm 3, \pm 4$ ppm) were acquired to correct for the residual B_0 inhomogeneity. The S_0 image without the radiofrequency saturation was acquired for the signal normalization. **b:** APT data processing flow chart. The procedures included the generation of a B_0 shift map and the correction of APT data using the B_0 map. The B_0 inhomogeneity correction was performed on a voxel-by-voxel basis, and APT images were reconstructed using an MTR asymmetry at offsets of ± 3.5 ppm.

Figure 3.

APT-weighted and conventional MR images for a patient with a glioblastoma (patient 1). **a:** T₂-weighted image and **b:** FLAIR image demonstrate a predominantly cystic mass in the right parietal lobe. **c:** Gadolinium-enhanced T₁-weighted image shows an enhancing rim with a non-enhancing central area. **d:** APT-weighted image shows hyperintensity in the gadolinium-enhancing area (red arrow) and in the centrally cystic area (black arrow), compared to the contralateral brain area (blue arrow). Five of 15 slices are shown. Examples of the regions of interest for quantitative image analysis are also shown on the FLAIR image: 1) tumor (encompassed by the red line); and 2) contralateral normal-appearing white matter (encompassed by the blue line).

Figure 4.

APT-weighted and conventional MR images for a patient with a glioblastoma (patient 4). **a:** T₂-weighted image and **b:** FLAIR image show a heterogeneously hyperintense lesion in the right frontal lobe. **c:** Gadolinium-enhanced T₁-weighted image demonstrates the typical imaging characteristics of a high-grade glioma: an enhancing rim with a non-enhancing necrotic center. **d:** APT-weighted image shows that the tumor rim (red arrow) is hyperintense, while the necrotic region (pink arrow) and peritumoral edematous area (yellow arrow) have low APT-weighted signals. Only one of 15 slices is shown.

Figure 5.

APT-weighted and conventional MR images for a patient with an anaplastic astrocytoma (patient 8). **a:** T₂-weighted image and **b:** FLAIR image show a hyperintense lesion in the left temporal lobe. **c:** Gadolinium-enhanced T₁-weighted image reveals no post-contrast enhancement. Thin white arrow: biopsied site. **d:** APT-weighted image shows hyperintensity in the lesion. Note the sinus-related image artifact (white arrow) and the image void on the right frontal lobe of the brain due to the large B₀ inhomogeneity effects in these areas. **e:** Hematoxylin and eosin-stained section (original magnification 400X) shows that this anaplastic astrocytoma (WHO grade-3) contains pleomorphic and hyperchromatic tumor cells (black arrow), as well as scattered mitotic figures (inset).

Figure 6. APT-weighted and conventional MR images for a patient with a low-grade glioma (patient 9). **a:** T₂-weighted image shows a rounded hyperintense mass in the right frontal lobe. **b:** FLAIR image shows a predominantly hyperintense lesion. **c:** Gadolinium-enhanced T₁-weighted image reveals no gadolinium enhancement, a typical MRI appearance for a low-grade glioma. **d:** APT-weighted image shows isointensity in the lesion, compared to the contralateral brain tissue.

Figure 7.

APT-weighted and conventional MR images for another patient with a low-grade glioma (patient 14). **a:** T₂-weighted image and **b:** FLAIR image demonstrate a hyperintense lesion in the left frontal lobe. **c:** Gadolinium-enhanced T₁-weighted image shows mild gadolinium enhancement. Thin white arrow: biopsied site. **d:** APT-weighted image shows a relatively low signal within the lesion, including in the region of the gadolinium enhancement. Note that the actual APT-weighted intensities in scattered punctate areas of minimal hyperintensity were less intense than those seen in high-grade gliomas. **e:** Hematoxylin and eosin-stained section (original magnification 400X) shows that this diffuse astrocytoma (WHO grade-2) lacks mitotic activity, but contains scattered gemistocytic tumor cells (black arrow).

Table 1

Patient characteristics and APT-weighted signal intensities

Patient no.	Age	Sex	Lesion location	Surgery	Pathology	Gadolinium enhancement	APT intensity (%)		
							Tumor core	Contralateral	Contrast
1	58	M	Right parietal	Resection	GBM	Yes	1.98	0.79	1.19
2	71	M	Left temporal	Resection	GBM	Yes	2.59	0.32	2.27
3	73	F	Right temporal	Resection	GBM	Yes	2.53	0.10	2.43
4	57	M	Right frontal	Resection	GBM	Yes	3.03	0.41	2.62
5	64	M	Right temporal	Resection	GBM	Yes	2.57	0.46	2.11
6	82	M	Left parietal	Biopsy	GBM	Yes	1.44	0.01	1.43
7	47	M	Right frontal	Resection	AA	No	2.81	0.36	2.45
8	46	M	Left temporal	Biopsy	AA	No	3.06	-0.09	3.14
Average 95% CI							2.50 (2.04, 2.96)	0.30 (0.06, 0.54)	2.21 (1.68, 2.74)
9	30	M	Right frontal	Resection	LGO	No	1.24	0.00	1.24
10	29	F	Left frontal	Biopsy	LGA	No	1.25	0.59	0.66
11	40	M	Right temporal	Resection	LGOA	No	1.08	0.69	0.39
12	25	M	Right temporal	Resection	LGA	No	1.47	1.06	0.41
13	25	F	Left frontal	Resection	LGA	Yes	0.28	0.49	-0.21
14	34	F	Left frontal	Resection	LGO	Yes	1.23	0.68	0.55
Average 95% CI							1.09 (0.65, 1.53)	0.58 (0.22, 0.94)	0.51 (0.02, 1.00)

The gadolinium enhancement was determined visually. The APT-MRI contrast was defined as the APT-weighted intensity of tumor core minus the APT-weighted intensity of the contralateral brain tissue. GBM = glioblastoma; AA = anaplastic astrocytoma; LGO = low-grade oligodendroglioma; LGA = low-grade astrocytoma; LGOA = low-grade oligoastrocytoma; 95% CI = 95% confidence interval.