Functional Perfusion Imaging Using Continuous Arterial Spin Labeling With Separate Labeling and Imaging Coils at 3 T

Toralf Mildner,* Robert Trampel, Harald E. Möller, Andreas Schäfer, Christopher J. Wiggins, and David G. Norris

Functional perfusion imaging with a separate labeling coil located above the common carotid artery was demonstrated in human volunteers at 3 T. A helmet resonator and a spin-echo echo-planar imaging (EPI) sequence were used for imaging, and a circular surface coil of 6 cm i.d. was employed for labeling. The subjects performed a finger-tapping task. Signal differences between the condition of finger tapping and the resting state were between –0.5% and –1.1 % among the subjects. The imaging protocol included a long post-label delay (PLD) to reduce transit time effects. Labeling was applied for all repetitions of the functional run to reduce the sampling interval. Magn Reson Med 49:791–795, 2003. © 2003 Wiley-Liss, Inc.

Key words: perfusion; fMRI; arterial spin labeling; arterial transit time; motor cortex

Functional perfusion imaging using magnetically labeled water as an endogenous tracer has proven to be a valuable tool for investigating task-related brain activity (1,2). The advantages of perfusion-based functional imaging in comparison to the widely used blood oxygenation level-dependent (BOLD) technique include a potentially better localized area of activation (3) and the feasibility of quantification (4–6). This study shows that functional perfusion imaging with continuous arterial spin labeling (CASL) can be performed with a separate labeling coil located above the common carotid artery in humans. For functional imaging, the temporal resolution of CASL is poor because it requires labeling periods of several seconds prior to image acquisition. A quantification of the cerebral blood flow (CBF) during task activation requires the acquisition of images with and without CASL, and would further increase the effective sampling interval. Therefore, in this study, labeling was applied for all repetitions of the functional run, and as a result the temporal resolution and the sensitivity of the functional study were increased by factors of 2 and $\sqrt{2}$ (7), respectively, while the ability to quantify blood flow changes was maintained.

Max Planck Institute of Cognitive Neuroscience, Leipzig, Germany.

Christopher J. Wiggins is now at the Department of Radiology, Massachusetts General Hospital NMR Center, Boston, Massachusetts.

David G. Norris is now at the FC Donders Center for Cognitive Neuroimaging, Nijmegen, The Netherlands.

*Correspondence to: T. Mildner, Ph.D., Max Planck Institute of Cognitive Neuroscience, Stephanstr. 1a, 04103 Leipzig, Germany. E-mail: mildner@cns.mpg.de

Received 2 October 2002; revised 10 December 2002; accepted 17 December 2002.

DOI 10.1002/mrm.10438

Published online in Wiley InterScience (www.interscience.wiley.com).

CASL approaches (8,9) for measuring the CBF are in principle more sensitive than methods based on pulsed labeling, but their use in humans is confronted with two major problems (10). First, the application of long off-resonance radiofrequency (RF) pulses causes magnetization-transfer (MT) effects. Second, the transit time from the labeling plane to the imaging slice results in a loss of sensitivity due to the relaxation of spins in the arterial blood. Finally, at 3 T RF power deposition may also be an issue of concern. The first problem can be addressed by keeping the MT influence constant for the labeling and control experiments (11,12). Complete elimination of MT effects is achieved by using separate labeling and imaging coils, which additionally removes the need for RF pulsing during the control acquisition (13,14), and in general reduces the total RF-power requirement. Multislice perfusion imaging can easily be implemented by this method. However, influences from transit-time differences in the brain are increased if labeling is performed at the neck, and quantitative maps of CBF cannot easily be obtained. Alsop and Detre (15) showed that the introduction of a post-label delay (PLD) markedly reduces transit-time effects, provided that the longitudinal relaxation times of arterial blood and brain tissue are nearly equal, a condition that holds for 1.5 T and 3 T. Gonzalez-At et al. (16) reported arterial transit-time changes during task activation. They concluded that this effect significantly contributes to the signal change measured with arterial spin labeling (ASL) during task activation. The use of short PLDs may be preferable for functional perfusion imaging if quantification of the perfusion change is not required. However, a PLD of the order of the maximum transit time to the brain, as used in the present study, facilitates quantification of the CBF change. In that case, according to theory (15), the absolute value of the transit time and also the task-related decrease of the transit time during motor activation do not influence the obtained CBF change.

The sensitivity of spin-labeling techniques for perfusion measurement increases significantly with increasing field strength because of both the improved sensitivity and the reduced longitudinal relaxation during the transit period. There is thus great interest in using CASL methods at 3 T; however, the effort involved in implementing a second RF transmitter coil proves prohibitive for many users. In this article we present the first activation studies to use this technique at 3 T, in this instance combined with a PLD that ensures that the contrast obtained is due solely to perfusion changes, and without time-consuming control measurements.

EXPERIMENTS

All MRI experiments were performed using a 3 T whole-body scanner (Bruker Medical, Ettlingen, Germany). The maximum gradient strength was 45 mT/m, switchable within 320 μs. For image acquisition a helmet resonator of 24-cm diameter (17) was used. T_1-weighted anatomical images were obtained with a modified driven equilibrium Fourier transform (MDEFT) sequence (18).

CASL can be achieved by RF irradiation in the presence of a magnetic field gradient along the carotid artery, which results in an adiabatic inversion of the flowing spins (19). A circular surface coil of 6-cm diameter and the MR scanner gradients were used under pulse program control in order to produce the required RF and the magnetic field gradient. At an RF power level of 0.4 W the gradient strength required to fulfill the adiabatic condition was determined experimentally by measurements with a tube flow phantom. The mean flow in the tube was adjusted to a velocity of 40 cm s^{-1} to match typical conditions in the human common carotid artery. The labeling coil was placed 3 cm above the tube. After a labeling pulse, which was sufficiently long to ensure that the length of the tube to be imaged was filled with labeled water, a set of 13 axial slices (slice gap = 15 mm, slice thickness = 5 mm) was acquired with a spin-echo EPI sequence using a birdcage resonator. The distance between the center slice and the labeling coil was 25 cm. Subsequently, an identical set of slices was acquired using the same technique but without labeling. The inversion efficiency can be calculated from the magnetization ratio with and without labeling $M_z/M_{z,0}$ at the location of the labeling coil as $\alpha = (1 - M_z/M_{z,0})/2$. The quantity $M_z/M_{z,0}$ was determined by extrapolating a T_1 fit over the magnetization ratios (depending on the position of the 13 slices) to the location of the labeling coil. Gradient strengths of 1.5–4 mT m^{-1} repeatedly yielded an inversion efficiency above 90% at the RF power level of 0.4 W. A value of 2.5 mT m^{-1} was used for the experiments.

The surface coil was placed at the neck at a distance of 14 cm from the center of the magnet. This results in a distance of about 20 cm between the helmet resonator and the labeling coil. This distance was sufficient to obviate the need for additional detuning of the labeling coil during the acquisition of the images. The frequency of irradiation was determined by the gradient strength necessary to fulfill the adiabatic condition, and the offset between the labeling coil and the center of the magnet. This frequency was corrected for any deviation caused by the actual room-temperature shim.

In this study, six healthy male volunteers (25–35 years old) were examined while they were in the resting state (two subjects) or while they performed a finger-tapping paradigm (four subjects). In the functional study, subjects alternated between 30-s periods of rest and finger tapping. They were instructed to tap slowly and to press the fingers at every tap.

For the resting-state perfusion maps, spin-echo EPI images of four axial slices (field of view = 19.2 cm, voxel size = 3 × 3 × 5 mm, slice gap = 2 mm) were acquired with an acquisition matrix of 64 × 64, an acquisition bandwidth of 100 kHz, and an echo time (TE) of 45 ms, and with the echo position at 50% of the echo train length. A total of 120 repetitions were recorded, with a repetition time (TR) of 8 s. Each repetition included a labeling period of 4 s and a PLD of 2 s (15). For control measurements, RF irradiation in the surface coil was omitted during even repetitions; that is, images with ASL and control scans without labeling were recorded in an interleaved fashion.

In the functional study, the duration of the labeling period and the TR were set to 3 s and 6 s, respectively, whereas the PLD of 2 s was maintained. One scan lasted 70 repetitions. The labeling RF was switched on for all repetitions of the scan. A spin-echo EPI partial Fourier sequence with an acquisition matrix of 64 × 36 was used (TE = 13 ms, echo position at 11.1% of the echo train length). The reconstruction to an image matrix of 64 × 64 was performed by the half-Fourier technique described in Ref. 20. Other imaging parameters were the same as in the resting-state experiments.

Crusher gradients (separated by the 180° pulse of the spin-echo sequence) were used for the reduction of intravascular signal contributions (21). Their strength corresponded to a b-value of 2 s mm^{-2} for the experiments in the resting state, and, due to the shorter TE, to only b = 0.2 s mm^{-2} in the functional experiments. This was sufficient to suppress signal contributions from very large vessels.

In the data analysis, the image time series was corrected for bulk motion using a routine incorporated in the LIPSIA software package developed at the Max Planck Institute of Cognitive Neuroscience (22). Then, a spatial Gaussian filter with a standard deviation of 0.8 with respect to a voxel size of 3 mm was applied, and drifts of the baseline signal were corrected to first order. For the resting-state experiments, the images measured during the labeling and control conditions were averaged and a difference map was created, whereas for the functional study z-scores were calculated on the basis of a t-test. The resting periods and the periods of finger tapping were compared, except for the first time point of each period, which was neglected in the statistical analysis. This accounts for a possible delay in the reaction of the subjects as they changed back and forth from periods of rest to finger tapping. The percentage signal change between these conditions was averaged over the seven cycles of stimulation and rest for voxels above a statistical threshold of $z = 3.09$ ($P = 0.001$). The evaluation was performed with respect to the slices as acquired perpendicular to the physical z-axis of the magnet (axial slices). Therefore, slice angulation is slightly different for the subjects.

RESULTS

A perfusion map obtained from the signal difference between the conditions of ASL and no labeling by use of Eq. [1] is depicted in Fig. 1. The labeling coil was placed over the right common carotid artery of the subject. The percentage signal change $\Delta M_z/M_{z,0}$ (where ΔM_z is the difference of the magnetizations with and without labeling, and $M_{z,0}$ is the magnetization of the control image) obtained for gray matter was −0.4 and −1.3%. This corresponds to CBF values of 50–170 ml/min/100 g. The average value found for CBF in gray matter was about 80 ml/min/100 g.

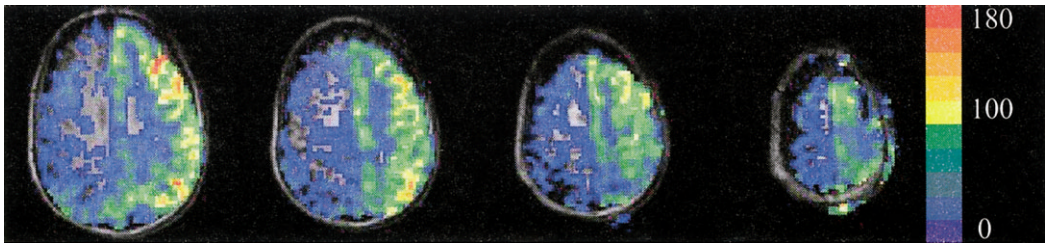

FIG. 1. Perfusion maps overlaid onto T_1-weighted anatomical images, which were obtained in the resting state by ASL at the position of the right carotid artery. The colors correspond to perfusion values in ml/100 g/min.

Figure 2 shows combined anatomical and functional images from four subjects who performed the finger-tapping task with the left hand. The labeling coil was placed over the right common carotid artery. Voxels with *z*-scores below a threshold of –3.09 ($P = 0.001$) are shown colored. The brain area with the most significant activation was the omega-shaped area of the primary motor cortex (Broca's knee) in all four subjects. The maximum percentage signal change for this area during motor activation varied from about −0.5% to –1.1% between subjects. No significant activation of the supplementary motor area was found. The extent of activation in the postcentral sulcus and the intraparietal sulcus was different among the subjects. Activation of these areas is typical for the specific task, i.e., slow finger tapping and light pressure. Some scattered activation located superior in the margin of the brain was probably caused by subject motion.

Functional experiments were performed for control in the same manner, except that the RF irradiation for labeling was omitted. In this case, the finger-tapping task produced no significant signal changes in the primary motor cortex.

DISCUSSION

This study shows that contrast created by ASL at the carotid artery in human subjects can be used to map functional changes of perfusion during finger tapping. The application of separate labeling and imaging coils to functional perfusion imaging is useful for several reasons. Multislice perfusion imaging is facilitated by removing the need to subtract out MT-induced signal losses at each slice position (13,14). We found significant differences between the conditions of ASL and no labeling only for the hemisphere where the labeling coil was placed (Fig. 1). The vanishing signal differences in the contralateral hemisphere confirm the absence of MT effects (14). The RF power deposition from the perfusion experiment can

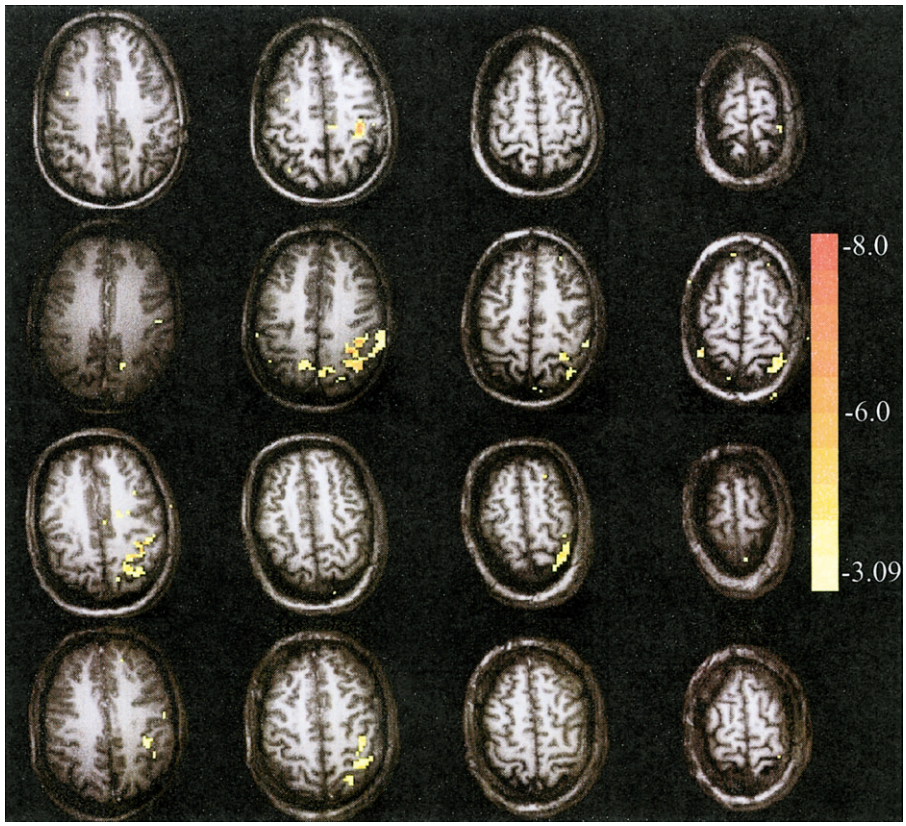

FIG. 2. T_1-weighted anatomical images obtained from four subjects (rows). The overlaid colored maps of the *z*-scores (threshold = –3.09) were obtained by evaluating seven 30-s cycles of finger tapping with the left hand and rest. ASL was performed at the right carotid artery.

therefore be reduced by a factor of 2. Another advantage, as outlined in Ref. 14, is that labeling at the carotid artery removes venous artifacts, i.e., veins flowing from inferior to superior will not be labeled. A drawback of our current setup is the limited coverage provided by the helmet coil. Further improvement of the technique can be achieved by an active detuning of the labeling coil (14) in combination with a birdcage resonator for imaging.

The efficiency of adiabatic spin inversion in the human carotid artery, as reported in Ref. 14 and theoretically derived in Ref. 23, was confirmed in the present work. An RF power of 0.4 W, which produced a magnetic field of about 2.4 μT at the location of the carotid artery, was sufficient for labeling, in agreement with Refs. 14 and 23. However, the variation of the velocity of blood in the carotid artery, and the varying depth of the carotid artery among subjects influence the inversion efficiency (23), and the value of 90% measured in the flow phantom at 40 cm s^{-1} could be considered as an upper limit. According to theory (23), a doubling of the flow velocity to 80 cm s^{-1} under our experimental conditions would lead to a reduction of about 10% in the inversion efficiency.

The theory developed by Alsop and Detre (15) predicts a similar sensitivity for perfusion imaging in areas of the brain with different transit times if the PLD is longer than the maximum transit time. Maintaining this condition improves the ability to quantify perfusion changes, because transit-time maps are no longer needed. Maximum values of the transit time from the neck to the circle of Willis of 500 ms, and from the circle of Willis to any area of the brain of 1500 ms may be assumed (14). A PLD of 2 s was used in all our experiments, which is of the order of the maximum transit time. Therefore, transit-time effects could be neglected for quantification of the resting-state perfusion and the perfusion change upon stimulation.

The resting-state perfusion map shows the highest sensitivity to ASL in gray matter. The lower sensitivity of white matter can be explained by the shorter T_1 and the lower values of the cerebral blood flow compared to gray matter. Therefore, CBF values of white matter could not be extracted from our data. The average value of CBF in gray matter of about 80 ml/min/100 g agrees well with values obtained by other groups (10). However, small areas located in the two inferior slices shown in Fig. 1 yielded significantly higher values (up to 170 ml/min/100 g). Currently, we cannot exclude that this is due to remaining insufficiently suppressed intravascular signal.

The approximation for Eq. [A2], which is given in the Appendix, was used for the estimation of absolute blood-flow changes during finger tapping. This yielded increased blood flow upon finger tapping in the range of 60–130 ml/min/100 g for the subjects studied. Taking into account mean CBF values reported in literature (10), and the average CBF value obtained for the resting state in this study, the change of perfusion was about 100% during motor activation. Similar changes of perfusion have been reported by other groups (4,6). Some studies, however, found substantially smaller values (21,24). It is worth noting that the value for the CBF change obtained in this study was estimated by comparing experiments performed in separate sessions. The interleaved measurement of images with and without ASL, which is required for complete quantification during one session, can easily be implemented. However, the effective sampling interval will then be doubled, which makes it unfavorable for activation studies.

The control experiments without ASL indicate an insignificant influence of BOLD signal changes at TE = 13 ms for the spin-echo partial Fourier EPI sequence used here. Stroman et al. (25) found a non-BOLD mechanism for functional signal changes, which is supposed to produce signal changes even at zero TE and could be of importance for perfusion imaging. In the control experiments performed in this study, there was no evidence that this mechanism influenced our results. The negative signal change during motor activation is caused by the lower net magnetization as the result of an increased blood flow, which delivers more labeled water to the capillaries and surrounding brain tissue. Assuming that the effect of signal changes at zero TE is caused by changes of the proton density, it should be closely related to the mechanism exploited for the perfusion measurement. A contribution from such a mechanism (below the statistical threshold) could lead to slightly overestimated values for the CBF change.

CONCLUSIONS

Functional perfusion imaging at 3 T was demonstrated for the first time with a separate labeling coil at the carotid artery in several subjects performing a finger-tapping task. Activation of the primary motor cortex was detected with an imaging protocol that used a long PLD to reduce transit-time effects. It was shown that quantification of functional changes in the CBF is feasible with the use of this method.

ACKNOWLEDGMENTS

The authors thank Prof. D. Yves von Cramon for helpful discussions regarding the manuscript. Michael von Mengershausen, Thomas Riemer, and Karsten Müller helped perform the functional experiments. We also thank Wolfgang Driesel and Manfred Weder for technical assistance, and Anke Mempel, Mandy Naumann, and Claudia Buschendorf for support in the experiments.

APPENDIX

For quantification, the following equation can be derived (15) under the assumptions of equal longitudinal relaxation times of the arterial blood and brain tissue, a sufficiently long PLD, and the absence of both MT effects and intravascular signal contributions:

$$\frac{M_{label} - M_{control}}{M_{control}} = \phi(f) \cdot f \text{ with} \qquad [A1]$$

$$\phi(f) = -2\alpha \frac{T_{1e}}{\lambda} \exp\left(-\frac{w}{T_{1e}}\right)\left(1 - \exp\left(\frac{-\tau}{T_{1e}}\right)\right)$$

$$\text{and } \frac{1}{T_{1e}} = \frac{1}{T_{1b}} + \frac{f}{\lambda}.$$

The last factor of the function $\phi(f)$ (which was omitted in Ref. 15) accounts for the finite labeling period; f is the blood flow, w is the PLD, and τ denotes the length of the labeling period. The inversion efficiency at the carotid artery and the brain-blood partition coefficient are denoted as α and λ, respectively. T_{1b} is the longitudinal relaxation time of brain tissue, M_{label} is the longitudinal magnetization obtained with ASL during either the resting or the finger-tapping period, and $M_{control}$ is the magnetization without ASL. Equation [A1] can be used to calculate blood flow when the labeled and nonlabeled states are compared in the resting state, as well as to estimate CBF changes in a functional study, if two CBF levels are compared during the application of ASL. If two levels of blood flow f_1 (activated) and f_2 (rest) are compared, Eq. [A1] leads to the following expression:

$$\left.\frac{\Delta M}{M}\right|_{activated} = \frac{\phi(f_1)\cdot f_1 - \phi(f_2)\cdot f_2}{1 + \phi(f_2)\cdot f_2} \approx \phi(f_2)\cdot(f_1 - f_2). \quad [A2]$$

$\Delta M/M|_{activated}$ is the signal change between the two blood flow levels while labeling is applied during the entire experiment. The approximation in Eq. [A2] is valid under two conditions, namely $\phi(f_2)\ f_2 \ll 1$ and $\phi(f_1) \approx \phi(f_2)$, which are fulfilled for CBF values in the normal range. For quantification, a brain-blood partition coefficient λ of 0.9 ml g^{-1}, an inversion efficiency α of 0.92, and a T_{1b} of 1.33 s were assumed.

REFERENCES

1. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppell BE, Cohen MS, Turner R, Cheng HM, Brady TJ, Rosen BR. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 1992;89:5675–5679.
2. Edelman RR, Siewert B, Darby DG, Thangaraj V, Nobre AC, Mesulam MM, Warach S. Qualitative mapping of cerebral blood flow and functional localization with echo-planar MR imaging and signal targeting with alternating radio frequency. Radiology 1994;192:513–520.
3. Siewert B, Bly BM, Schlaug G, Darby DG, Thangaraj V, Warach S, Edelman RR. Comparison of the BOLD- and EPISTAR-technique for functional brain imaging by using signal detection theory. Magn Reson Med 1996;36:249–255.
4. Ye FQ, Smith AM, Yang Y, Duyn JH, Mattay VS, Ruttimann UE, Frank JA, Weinberger DR, McLaughlin AC. Quantitation of regional cerebral blood flow increases during motor activation: a steady-state arterial spin tagging study. NeuroImage 1997;6:104–112.
5. Yang Y, Frank JA, Hou L, Ye FQ, McLaughlin AC, Duyn JH. Multislice imaging of quantitative cerebral perfusion with pulsed arterial spin labeling. Magn Reson Med 1998;39:825–832.
6. Buxton RB, Frank LR, Wong EC, Siewert B, Warach S, Edelman RR. A general kinetic model for quantitative perfusion imaging with arterial spin labeling. Magn Reson Med 1998;40:383–396.
7. Callaghan PT. Principles of nuclear magnetic resonance microscopy. Oxford: Clarendon Press; 1991. p 178.
8. Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. Proc Natl Acad Sci USA 1992;89:212–216.
9. Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. Magn Reson Med 1992;23:37–45.
10. Calamante F, Thomas DL, Pell GS, Wiersma J, Turner R. Measuring cerebral blood flow using magnetic resonance imaging techniques. J Cereb Blood Flow Metab 1999;19:701–735.
11. Pekar J, Jezzard P, Roberts DA, Leigh JS, Frank JA, McLaughlin AC. Perfusion imaging with compensation for asymmetric magnetization transfer effects. Magn Reson Med 1996;35:70–79.
12. Alsop DC, Detre JA. Multisection cerebral blood flow MR imaging with continuous arterial spin labeling. Radiology 1998;208:410–416.
13. Zhang W, Silva AC, Williams DS, Koretsky AP. NMR measurement of perfusion using arterial spin labeling without saturation of macromolecular spins. Magn Reson Med 1995;33:370–376.
14. Zaharchuk G, Ledden PJ, Kwong KK, Reese TG, Rosen BR, Wald LL. Multislice perfusion and perfusion territory imaging in humans with separate label and image coils. Magn Reson Med 1999;41:1093–1098.
15. Alsop DC, Detre JA. Reduced transit time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow. J Cereb Blood Flow Metab 1996;16:1236–1249.
16. Gonzalez-At JB, Alsop DC, Detre JA. Cerebral perfusion and arterial transit time changes during task activation determined with continuous arterial spin labeling. Magn Reson Med 2000;43:739–746.
17. Merkle H, Driesel W, Andersen P, Adriany G, Ugurbil K, Garwood M. Circularly polarized RF helmet coil for brain studies at 7 Tesla. In: Proceedings of the 8th Annual Meeting of ISMRM, Denver, 2000. p 565.
18. Norris DG. Reduced power multislice MDEFT imaging. J Magn Reson Imaging 2000;11:445–451.
19. Dixon WT, Du LN, Faul DD, Gado M, Rossnick S. Projection angiograms of blood labeled by adiabatic fast passage. Magn Reson Med 1986;3:454–462.
20. Jesmanowicz A, Bandettini PA, Hyde JS. Single-shot half k-space high-resolution gradient-recalled EPI for fMRI at 3 Tesla. Magn Reson Med 1998;40:754–762.
21. Ye FQ, Mattay VS, Jezzard P, Frank JA, Weinberger DR, McLaughlin AC. Correction for vascular artifacts in cerebral blood flow values measured by using arterial spin tagging techniques. Magn Reson Med 1997;37:226–237.
22. Lohmann G, Mueller K, Bosch V, Mentzel H, Hessler S, Chen L, Zysset S, von Cramon DY. Lipsia—a new software system for the evaluation of functional magnetic resonance images of the human brain. Comput Med Imaging Graph 2001;25:449–457.
23. Maccotta L, Detre JA, Alsop DC. The efficiency of adiabatic inversion for perfusion imaging by arterial spin labeling. NMR Biomed 1997;10:216–221.
24. Francis ST, Gowland PA, Bowtell RW. Continuos saturation EPI with diffusion weighting at 3.0 T. NMR Biomed 1999;12:440–450.
25. Stroman PW, Krause V, Frankenstein UN, Malisza KL, Tomanek B. Spin-echo versus gradient echo fMRI with short echo times. Magn Reson Imaging 2001;19:827–831.