Published in final edited form as:

Magn Reson Med. 2018 September ; 80(3): 969–975. doi:10.1002/mrm.27090.

Cardiac-triggered pCASL: A cost-effective scheme to further enhance the reliability of ASL MRI

Yang Li^{1,2}, Deng Mao^{1,2}, Zhiqiang Li³, Michael Schär¹, Jay J. Pillai^{1,4}, James G. Pipe³, and Hanzhang Lu^{1,2,5}

¹The Russell H. Morgan Department of Radiology & Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD 21287

²Graduate School of Biomedical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas 75390

³Imaging Research, Barrow Neurological Institute, Phoenix, AZ 85013

⁴Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD 21287

⁵Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21287

Abstract

Purpose—Arterial-Spin-Labeling (ASL) MRI is intrinsically a low SNR technique. This study aims to enhance its sensitivity by quantifying physiological noise attributed to cardiac pulsation and devising an improved sequence, cardiac-triggered ASL, to minimize this noise.

Methods—A total of 16 healthy subjects were studied on a 3T MRI system. The influence of cardiac pulsation on pseudo-continuous ASL (pCASL) signal was first investigated by performing a regular pCASL sequence while the cardiac phase of the image acquisition was recorded by a pulse oximeter. We then designed a new sequence, cardiac-triggered pCASL, to align the cardiac phases of the control and labeled scans. The performance of the new sequence was evaluated in the context of single-shot 3D GraSE acquisition, multi-shot 3D spiral acquisition, and hypercapnia-induced CBF changes.

Results—In regular pCASL, the signal intensities of both control and labeled images were strongly modulated by the cardiac phase. In single-shot acquisitions, this results in signal instability in regions near large vessels. In segmented acquisitions, it results in ghosting artifacts in the image and, furthermore, the signal fluctuation is smeared along the segmentation direction to affect more brain regions. Cardiac-triggered pCASL enhanced the temporal SNR by 94% and 28% in single-shot and segmented 3D acquisition, respectively. When applied to detect CBF changes, the triggered sequence revealed a greater statistical power in terms of both the number of significant voxels and t-score histograms.

Conclusion—Cardiac-triggered pCASL represents a potential scheme to enhance the reliability of ASL signal.

Keywords

arterial spin labeling; cardiac-triggered; pulsation; cardiac phase

INTRODUCTION

Arterial Spin Labeling (ASL) MRI permits the measurement of perfusion without the use of contrast agents (1,2). However, ASL suffers from an intrinsically low signal-to-noise ratio (SNR), because the difference between control and labeled images is <1% of the original tissue signal. Over the past decade, several techniques have been developed to improve the sensitivity of ASL MRI (3–13). For example, background suppression (BS) is now routinely applied to reduce the signal intensity of static tissue (3,4,8). Pseudocontinuous labeling scheme was developed to increase the labeling efficiency of the continuous ASL method (7,9,11). However, further enhancing the signal or reducing the noise remains an essential mission of ASL technical development efforts.

Noise in ASL can be attributed to thermal or physiological factors, e.g. cardiac pulsation. With the recommended long post-labeling delay time (1.8 seconds) and background suppression (9), it is generally thought that the effect of cardiac pulsation should be minimal (14,15). However, it is often observed that there exist large fluctuations in the difference image (i.e. control-label) signal intensity from one image volume to another, especially in regions with large blood vessels. These fluctuations are spatially correlated (i.e. the entire image is bright or dark), thus suggesting a physiological origin rather than random noise. We hypothesize that, if one can identify the source of these fluctuations and account for them in acquisition, there may be a cost-effective opportunity for further enhancing the SNR of ASL.

In this work, we first demonstrated that global signal fluctuations in ASL images are largely attributed to cardiac phase differences from one image volume to another. Then we designed a new ASL sequence, referred to as cardiac-triggered pCASL, and showed that this sequence can substantially suppress such fluctuations and thereby increase the SNR, at a modest cost of scan time. We demonstrated the potential benefit of cardiac-triggered pCASL in the context of two acquisition schemes, specifically single-shot gradient-echo-and-spin-echo (GraSE) 3D (5,16) and multi-shot cylindrically-distributed-spiral 3D sequences (17,18). We further examined whether cardiac-triggered pCASL can improve the detection of CBF changes, using hypercapnia as a physiological challenge (19–22).

METHODS

General

Experiments were performed on a total of 16 healthy subjects (age 27 ± 5 years, 9 males, 7 females) using a 3 T MRI scanner with a 32-channel receive-only head coil (Philips Healthcare, Best, The Netherlands). Informed consent was obtained using a protocol approved by the institutional review board. We conducted three sub-studies in this work.

Study 1: Proof of principle of cardiac-triggered pCASL in single-shot 3D GraSE acquisition

Eight healthy subjects (3 males) were scanned in this sub-study. A total of ten ASL scans were performed on each participant. Five of them were a regular (non-triggered) pCASL and the other half were a cardiac-triggered pCASL. The repetitions allowed the assessment of coefficient-of-variation (CoV) across runs. For the non-triggered sequence, a pulse oximeter (Invivo, Gainesville, FL) was attached to the index finger of the subject and the timing of cardiac pulse was recorded with reference to the pulse sequence timing (specifically time of the excitation RF pulse). This allows the investigation of the relationship between pCASL signal intensity and cardiac phase. A single-shot 3D GraSE (5,23) acquisition was used in this proof-of-principle study, because cardiac pulsation primarily affects the signal intensity in a single-shot scan whereas its effects in a multi-shot acquisition are more complex.

For cardiac-triggered pCASL (see Figure 1 for diagram), the sequence is similar to the non-triggered one except that, after the acquisition module of the previous TR, the scanner will wait for the next cardiac pulse before starting the sequence components of the next TR. The time gap between the cardiac pulse and the beginning of the next TR was 6 ms, which was the shortest time allowed on our scanner. This time was necessary for the real-time algorithm to detect the pulse and for the hardware to respond to the trigger. The triggered sequence ensures that the cardiac phase of the beginning of each TR is matched. This scheme does increase the scan duration, ranging from 0 to one full cardiac cycle per TR. On average, the scan duration of the triggered scan was $20.9 \pm 4.3\%$ ($N=8$) longer than non-triggered pCASL. Ten pairs of control/label images were acquired in both regular and cardiac-triggered pCASL. The average scan duration of the non-triggered and triggered pCASL was 1 min 24 sec and 1 min 40 sec, respectively.

Other scan parameters followed recommendations of the ASL consensus paper (9). We used pCASL labeling with background suppression. Imaging parameters for the pCASL sequence were: labeling duration = 1800 ms, post labeling delay = 1800 ms, FOV = $180 \times 180 \times 104$ mm³, 13 slices, voxel size = $4.5 \times 4.5 \times 8$ mm³, SENSE factor on phase encoding direction = 2.2. The background suppression module contains a pre-saturation pulse placed 10 ms before the labeling module and two adiabatic inversion pulses placed 80 ms and 1300 ms after end of labeling, respectively.

To further confirm that the signal fluctuations observed in the pCASL data are attributed to cardiac pulsation, a cardiac-gated time-resolved phase contrast (PC) MRI was performed to measure the blood flow velocity in the middle-cerebral-artery (MCA) as a function of cardiac phase. The following parameters were used: FOV = 200×200 mm², matrix = 400×400 , FA = 15° , TE = 9.2 ms, VENC = 100 cm/s, 15 phases with an interval of 60 ms, a single coronal slice of 5-mm thickness at right MCA was imaged with a scan time of 6 min.

Data analysis was conducted using the software SPM (University College London, UK) and in-house MATLAB (MathWorks, Natick, MA) scripts. Image subtractions were performed between the control and labeled images. CBF values in ml/100g/min were calculated from the difference images using a general kinetic model (9). Cardiac phase at which the excitation RF pulse was played out was determined based on its location within the R-R interval, and was written in radians (ranging from 0 to 2π) (24). Relationship between ASL

signal and cardiac phase was assessed. CoV was calculated using standard deviation across the five scans divided by their mean. Both voxel-wise map and region-of-interest values were obtained for the CoV. Within each scan, temporal SNR (tSNR) was calculated as mean across dynamics divided by their standard deviation.

To compare the cardiac-triggered results with other ASL physiological-correction methods, in two additional analyses, we used the regular pCASL data but performed CompCor (Component based noise correction method) (25) and RETROICOR (Image-based method for retrospective correction) (6,26) approach, respectively, to factor out physiological fluctuations in the ASL data. In the CompCor analysis, signals in voxels with the highest standard deviations were used to extract physiological fluctuations and then employed as regressors to correct the ASL data (25). The residual signal after regression was used for control/label subtraction and averaging. In the RETROICOR analysis, the measured signal was fitted to 4 Fourier functions of cardiac phase obtained from the pulse oximeter and the residual signal was used for further subtraction and averaging. CoV was compared among these methods.

Study 2: Cardiac-triggered pCASL in segmented 3D pCASL

Since segmented 3D pCASL is a more widely used acquisition scheme due to its higher spatial resolution and larger spatial coverage, we next applied a segmented 3D cylindrically-distributed-spiral TSE acquisition (17) and compared cardiac-triggered pCASL with conventional pCASL. Five subjects were studied. The parameters used in this study were identical to those in Study 1 except for the following: FOV = $200 \times 200 \times 120$ mm³, voxel size = $3 \times 3 \times 4$ mm³, 22 segments, echo train length (ETL) = 9, no parallel imaging acceleration, one pair of control and labeled images. For the acquisition of one segment, a centric view ordering was used in the slice encoding direction, which placed the first echo of the echo train at the center of k_z -space and later echoes alternatively toward the two edges. A total number of 198 spiral interleaves was acquired to cover the whole k-space. The 198 spiral interleaves were evenly spaced along the k_z encoding direction, and any adjacent interleaves were rotated by the golden angle in the k_x - k_y plane (17). Scan duration was around 3 min 45 sec for triggered and 3 min 8 sec for non-triggered sequence. Both sequences were repeated 4 times and a voxel-by-voxel CoV map was calculated. The raw MRI k-space data of 3D spiral pCASL was reconstructed offline using the Graphical Programming Interface software (<http://gpilab.com>) (27).

Study 3: Sensitivity to perfusion changes

To further examine whether cardiac-triggered pCASL can enhance the sensitivity of ASL in detecting perfusion changes, in three subjects we studied CBF differences between normocapnia (NC) and hypercapnia (HC). The subject inhaled room air for 3 min, followed by HC challenge (5% CO₂, 21% O₂, and 74% N₂) for 5 min (19,20,28). Data in the first 2 min of the HC period was discarded to allow the subject to reach a new steady state of end-tidal CO₂ (EtCO₂) level. ASL signals of the room air period and the last 3 min of the HC period were used to evaluate hypercapnia-induced CBF change. For comparison, regular pCASL was also performed using the same paradigm. The acquisition parameters are the same as those of Study 1 except that the number of averages was 20 for regular pCASL and

17 for triggered pCASL, so that both can be completed within 3 min. Voxel-wise paired t-test was performed between HC and NC ASL images to determine whether there were any voxel-level statistically significant differences ($P < 0.05$). Voxel-wise t-score on CBF difference images between NC and HC conditions was also calculated using mean value across averages divided by their standard error.

RESULTS

Study 1: Proof of principle of cardiac-triggered pCASL in single-shot 3D GraSE acquisition

Figure 2a top row shows 10 volumes of CBF maps using the regular pCASL. Their whole-slice-averaged values are displayed as blue lines. It is apparent that the measured CBF images exhibit pronounced fluctuations across image volumes.

The source of such fluctuations is illustrated in Figure 2b, which plots the control (blue circles) and labeled (blue triangles) signals as a function of the cardiac phase at the time of excitation. For completeness, data points from all five repeated scans are displayed (for a total of 50 image volumes). It is apparent that both control and labeled signals are modulated by the cardiac phase. Interestingly, the control and labeled curves have a similar (instead of upside-down) shape (see Discussion section for more explanations). The vascular origin of the fluctuations is further confirmed by the temporal pattern of the blood flow in the middle-cerebral-artery (MCA) (Figure 2c).

Volume-by-volume CBF images of the cardiac-triggered pCASL sequence are shown in Figure 2a bottom row. It can be seen that the image intensity and averaged CBF value (red line, Figure 2a) are less variable compared to the regular sequence. Figure 2b shows the cardiac-triggered pCASL signal (red symbols) as a function of cardiac phase. It can be seen that all image volumes (including both control and labeled images) are of a similar cardiac phase. When calculating the absolute phase differences between the control and labeled images, the cardiac-triggered sequence yielded $0.10\pi \pm 0.04\pi$ radians, which was significantly ($P < 0.003$) lower than that of the regular pCASL ($0.34\pi \pm 0.13\pi$ radians). The remaining phase differences in the triggered scan are likely due to slight variations in duration of cardiac cycle (i.e. heart rate) from one heartbeat to next. Whole-brain CBF obtained from the regular and cardiac-triggered ASL was 33.16 ± 6.34 ml/100g/min and 34.67 ± 5.83 ml/100g/min, respectively, showing no differences ($P = 0.13$) between the techniques.

To visualize the spatial distribution of the fluctuations, CoV maps of both regular and triggered pCASL averaged over eight subjects, as well as their subtractions, are displayed in Figure 3a. In the regular pCASL data, large signal fluctuations are apparent in regions with large arterial vessels such as the circle of Willis as well as distally involving the anterior, middle, and posterior cerebral arteries. The cardiac-triggered scheme effectively lowered these fluctuations. The difference of CoV maps revealed that cardiac-triggered pCASL can reduce ASL signal variation in large vessel areas as well as in parenchyma. Comparison of CoV in regions-of-interest (ROI) is shown in Figure 3b. In ROIs corresponding to large vessel, parenchyma, and whole-brain, the per-scan SNR ($1/\text{CoV}$) of the cardiac-triggered

pCASL data increased by $145\pm 29\%$, $84\pm 22\%$, and $94\pm 18\%$, respectively. Within-scan tSNR is displayed in Supporting Figure S1, revealing a similar benefit of cardiac triggering.

Additional analyses using the post-hoc correction methods revealed that CompCor and RETROICOR increased SNR of the regular pCASL data by $4.5\pm 9.5\%$ and $19.0\pm 16.4\%$, respectively, in the whole-brain. But the extent of benefit was lower than that of the cardiac-triggered method. CoV of these post-hoc methods are displayed in Supporting Figure S2.

Study 2: Cardiac-triggered pCASL in segmented 3D pCASL

Figure 4a shows a comparison between regular and triggered 3D segmented pCASL images. With regular pCASL, the CBF images are contaminated by ring-shaped artifacts (e.g. yellow arrows). In the triggered data, this artifact was not present. Figure 4b shows CoV maps using the two methods. It can be seen that, in the regular, segmented pCASL data, high CoV voxels are observed in a considerable portion of the brain including both vessels and parenchyma. This is different from the single-shot pCASL (c.f. Figure 3a) where high CoV is only seen in large-vessel regions. This is because segmented acquisition causes the signal fluctuation to spill over along the segmentation direction, resulting in more voxels affected by the artifact. Averaged across the whole brain, CoV of the triggered ASL image decreased significantly ($P<0.01$) by $22\pm 3\%$ when compared to regular pCASL (Figure 4c), which corresponds to a $28\pm 4\%$ increase in SNR.

Study 3: Sensitivity to perfusion changes

Figure 5 summarizes the CBF images under NC and HC conditions, as well as their difference, for both regular and triggered schemes. The average CBF increase measured by triggered pCASL was $36.7\pm 6.6\%$, which is similar to the one measured by regular pCASL of $35.8\pm 7.1\%$. The CBF difference image using the triggered sequence is more stable than the regular sequence with fewer bright or dark vascular artifacts. CoV of the difference images was $63\pm 12\%$ smaller in the triggered data. The higher sensitivity of triggered pCASL in detecting perfusion change can be further appreciated by examining the voxel-by-voxel paired t-test results, where triggered pCASL uncovered more activated voxels (right column, Figure 5a) ($P<0.05$) than regular pCASL and revealed overall higher t-scores in histograms (Figure 5b).

DISCUSSION

In this study, we characterized the effect of cardiac pulsation on ASL signal when using a pCASL protocol recommended by the consensus paper (9). We showed that, in single-shot acquisitions, this results in signal instability in regions near large vessels and, in segmented acquisitions, it results in ghosting artifacts and the signal fluctuation is smeared along the segmentation direction to affect more brain regions. To overcome this effect, we developed a cardiac-triggered pCASL scheme that was shown to enhance the temporal SNR by 94% and 28% in single-shot and segmented 3D acquisition, respectively. We further evaluated the sensitivity of cardiac-triggered pCASL in detecting CBF change by using hypercapnia challenge as a model. The results revealed less signal variance and greater statistical power compared with regular pCASL.

Technical considerations

Based on the comparison of CoV (e.g. Figure 3b) between the triggered and regular sequence, we estimate that at least 44% of the noise in the ASL data is attributed to cardiac pulsation. The actual fraction could be even bigger because the triggered data may still contain some residual cardiac effects (due to variations in heart rate during the scan). Spatially, the cardiac pulsation effects are most pronounced in regions near large arteries, such as in the base of the brain, around the brain stem, and adjacent to the Sylvian fissure. With multi-shot acquisition, however, the territory of artifacts could further expand along the segmentation direction to cover more brain areas (e.g. Figure 4b). Therefore, a scheme to minimize the cardiac pulsation effects in ASL would provide a sizable benefit in enhancing the quality of the ASL data.

The cardiac-triggered scheme proposed in this work requires a pulse device, which is a standard accessory available on most MRI scanners and is used routinely in cardiac and body MRI, although not usually in neuro scans. The scan time for the cardiac-triggered sequence is slightly longer than the regular pCASL sequence because the sequence needs to wait for the start of the next pulse to begin the next TR. This additional delay is between 0 and 1 cardiac cycle. In our data, the average scan duration of the cardiac-triggered sequence is about 20% longer than the regular pCASL. Considering an SNR increase of 28–94%, this is cost-effective and is considerably more efficient than increasing SNR by more averages. It should also be pointed out that, since the cardiac pulsation artifact is particularly severe in regions near vessels, this technique may be crucial in studies of brain perfusion or neural abnormality in selective brain regions such as hippocampus (29,30) or insula (31,32), which happen to be located next to major vessels.

The trigger point of our sequence was set to be immediately before the pre-saturation pulse. This is because the pre-saturation pulse can “reset” the magnetization of the spins so that the variations in actual TR from one repetition to next will not affect the measured signal intensity and the static signals in the control and labeled images can still cancel out. We had also considered placing the trigger point at the excitation RF pulse. However, in that case, the magnetization recovery time of static spins will be different across TRs, resulting in imperfect cancelation of static signals (33).

This study also compared the SNR benefit of cardiac-triggered pCASL to those based on post-hoc correction methods. The CompCor correction-based approach has the advantage that it does not require any additional physiological recording, and can provide a modest increase in SNR (Supporting Figure S2). The RETROICOR method requires a pulse oximeter to measure the cardiac phase of the data acquisition and has a greater SNR benefit than CompCor. On the other hand, the pulse sequence based approach proposed in this study appears to provide the largest augment in signal stability compared to the post-hoc correction methods. Moreover, it should be pointed out that the post-hoc methods noted above have primarily been used in single-shot ASL MRI. In contrast, the cardiac-triggered method can also be applied in multi-shot acquisitions, which represent a more widely used ASL acquisition scheme in recent literature (9).

Physiological considerations

Cardiac pulsation effect in ASL has been a topic of interest in a number of previous studies (6,14,24,34,35). Wu et al. and Fushimi et al. studied the effect of labeling timing in pulsed ASL (PASL) (34,35). A significantly higher CBF was observed when the bolus was labeled at systolic compared with diastolic phases. This CBF disparity was attributed to a difference in the transit delay of labeled spins. In CASL or pCASL sequences, however, this effect is expected to be smaller because of the long labeling duration used in CASL and pCASL and that the distribution of transit delays is likely similar across TRs. Verbree and van Osch varied the cardiac phase at the end of the labeling period and concluded that the ASL signal is not significantly affected by the end-of-labeling phase despite the expectation that more labeling effect should be observed when the labeling period ends at systolic phase (due to less labeling decay) (14). Indeed, our data support the notion that the labeled spins (or its variation across TR) are not the source of the fluctuation seen in our study. Had the number of labeled spins been the reason for the signal fluctuation, we would have seen that the phase-dependence of the control signal would be opposite from the labeled signal. As shown in Figure 2b, however, the labeled and control signals actually have the same pattern of cardiac phase dependence. We therefore propose that one possible contribution to the observed fluctuation is that, during the systolic phase, the arterial vessel is extended and more fresh, uninverted spins have arrived at the imaging voxel during the post-labeling delay. Another possible contribution is that faster flow during the systolic phase may also allow a larger number of fresh spins to reach the imaging voxel, independent of the blood volume effect. Regardless the volume or flow pulsation effects, these uninverted spins are present in both control and labeled scans, suggesting that they represent inflowing spins following the label/control bolus. These spins have a different level of magnetization from the static spins which are background suppressed, and thus can cause a signal fluctuation.

Limitations

One limitation of the proposed technique is that it may not be effective in participants whose R-R interval, i.e. heart rate, shows a large variation, because the cardiac triggering is applied at the beginning of the labeling period but not at the time of the excitation RF pulse. Thus the cardiac phase at the excitation may be out of synchronization in such patients. Another limitation is that the placement of the pulse device on the patient nonetheless represents an additional step in the workflow of the MRI technologist and could be viewed as a burden. Also, the patient will have to use the other hand to move or scratch since movement of the hand that is attached to the placed pulse oximeter may interfere with accurate assessment of cardiac rate/pulse. Similarly, if the pulse oximeter falls off or loses signal due to hand movement, the scan may stall. In order to continue the scan, the operator would need to enter scanner room and adjust the pulse oximeter.

CONCLUSION

We showed that regular pCASL sequence results in ASL signals that are sensitive to cardiac pulsation effects, reducing the fidelity of the data. Cardiac-triggered pCASL can enhance the SNR by 94% and 28% in single-shot and segmented acquisitions, respectively, at a modest cost of scan time. Thus, this technique may represent a cost-effective approach to improve

the reliability of ASL. We have demonstrated that the proposed sequence can improve ASL data quality in multiple settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Sponsors: NIH R01 MH084021, NIH R01 NS067015, NIH R01 AG042753, NIH R01 AG047972, NIH R21 NS095342, NIH R21 NS085634, and NIH P41 EB015909.

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Figure 1.

Schematic diagram of the cardiac-triggered pCASL pulse sequence. The scanner awaits the next cardiac pulse to begin a TR. The ASL sequence is a pCASL with two background-suppression pulses. The labeling duration and post-labeling delay followed recommendations of the consensus paper.

Figure 2.

Cardiac pulsation effects in a single-shot 3D pCASL. (a) Ten consecutive measurements of CBF images and their corresponding averages (colored box on the far right) from a representative subject. The top panel shows the regular pCASL; the bottom panel shows cardiac-triggered pCASL. The blue and red curves indicate whole-slice averaged signal intensities, illustrating a greater signal variation in the regular sequence. (b) ASL control and label signal intensities of 50 measurements as a function of cardiac phase. Data acquired with regular pCASL are shown in blue symbols; those acquired with triggered pCASL are shown in red. Control signals are shown in circles and labeled signals are shown in triangles. The gray curves represent the data fitting to 2nd-order Fourier series. (c) Flow velocity in a middle-cerebral-artery (MCA) as a function of cardiac phase, illustrating that the signal fluctuation patterns in ASL are the same as the flow pattern in major arteries.

Figure 3.

Comparison of coefficient of variation (CoV) between regular and cardiac-triggered pCASL.

(a) Group-averaged CoV maps (N=8) of CBF images in regular, triggered pCASL, and their difference, respectively. Six representative axial slices and one sagittal slice are shown. (b)

Region-of-interest CoV of CBF values in vessel, parenchyma, and whole brain. The error bars indicate standard error (N=8). (* $P < 0.05$, ** $P < 0.001$)

Figure 4.

Comparison between regular and cardiac-triggered pCASL when using multi-shot 3D spiral acquisition. (a) Representative slices of CBF maps from a subject. Yellow arrows point to ring-shaped artifacts in the regular pCASL. Green arrows point to the same regions in the cardiac-triggered data, illustrating an absence of artifacts. (b) Group-averaged CoV maps (N=5) of CBF images in regular and cardiac-triggered pCASL. Note that the cardiac fluctuations are smeared along the craniocaudal direction due to segmented acquisition. (c) Comparison of whole-brain averaged CoV values between the two methods. The error bars indicate standard error (N=5).

Figure 5.

Comparison between regular and cardiac-triggered pCASL in detecting perfusion change during hypercapnia challenge. (a) CBF maps of one subject with normocapnia (NC), hypercapnia (HC), and their corresponding difference map. Voxels showing statistically significant difference ($P<0.05$) between NC and HC, referred to as “activated voxels”, are also displayed (in color). (b) Histogram of voxel-wise t-score associated with CBF difference between NC and HC conditions.