Supplementary Materials

1 Single- and two-compartment model fitting for multi-delay ASL

The single-compartment model fitting for multi-delay pCASL can be described by Eq. S1,

\[
\Delta M(w) = \frac{2f_\alpha M_0}{\lambda R_{1a}} \left[ \exp((\min(\sigma - w, 0) - \sigma)R_{1a}) - \exp(-(\tau + w)R_{1a}) \right]
\]

[S1]

where \( w \) is PLD, \( \Delta M(w) \) is the single-compartment magnetization of labeled blood, \( f \) is CBF, \( \sigma \) is ATT, \( R_{1a} \) (0.63 s\(^{-1}\)) is the longitudinal relaxation rate of blood at 3T, \( M_0 (=1) \) is the equilibrium magnetization of brain tissue, \( \alpha (=0.8) \) is the labeling efficiency, \( \lambda (=0.9 \text{ g/ml}) \) is the brain blood partition coefficient, and \( \tau (=1.5 \text{ s}) \) is the labeling duration. Subsequently, the two-compartment model for the ASL signal can be defined as the combination of the signals arising from single-compartment and the macrovascular component:

\[
\Delta M_{2C}(w) = (1 - aCBV) \times \Delta M(w) + aCBV \times A(w)
\]

where \( \Delta M_{2c}(w) \) is the two-compartment magnetization of labeled blood, \( \Delta M(w) \) is the magnetization from tissue as given by Eq. S1, \( A(w) \) is the magnetization from macro-vasculature.

2 NRMSEs measured in in-vivo data with different KWIA configurations

In section 4.2 and 4.3, the KWIA configurations of 1.73-fold-SNR KWIA \((N = 3)\) and 2-fold-SNR KWIA \((N = 4)\) were chosen as the best parameters to be tested for dMRA and multidelay ASL, respectively, based on the simulation result in section 4.1. To support our selection of parameters,
we calculated the NRMSEs between the original and the six in-vivo datasets that were processed by KWIA with the same six configurations applied to the digital phantom in section 3.1. The in-vivo result shown in Fig. S1 demonstrates a good consistency between the in vivo and simulation results as displayed in Fig. 3. On average, NRMSE of less than 1% (0.4%±0.3% for GM and 0.9%±0.5% for WM) was achievable for multi-delay ASL by 2-fold-SNR KWIA (N = 4). The NRMSE could be increased to 0.7%±0.5% for GM and 1.7%±0.9% for WM if 2-fold-SNR KWIA (N = 3) was applied. However, more conservative KWIA configuration with a SNR ratio of 1.7 should be chosen for dMRA due to an increased temporal error caused by KWIA. To achieve 1.7-fold SNR ratio, the KWIA configuration of N = 3 outperformed that of N = 4 with a lower mean NRMSE across five subjects. Specifically, for KWIA with N = 3, the measured NRMSE were 1.5%±0.9% in MCA, 2.5%±0.9% in PCA, and 5.5%±0.9% in distal small vessels, while the corresponding NRMSE increased to 1.8%±0.9%, 2.7%±1.1%, and 5.8%±3.4% for KWIA with N = 4, respectively.

Figure S1: Bar plots showing NRMSEs between the original and 6 KWIA-processed datasets measured in in-vivo data. The measurement was conducted for MCA, PCA, and distal small vessels in the dMRA images of five subjects, and for GM and WM in the multi-delay ASL images of another five subjects. The result is in good accordance with the simulation result shown in Fig. 3.
3 NRMSEs of in-vivo data processed by weighted moving average with different sliding window widths

Table S1: NRMSEs (%) of in-vivo data processed by weighted moving average with different sliding window widths.

| Width | dMRA MCA | dMRA PCA | dMRA Distal | Multi-delay ASL GM | Multi-delay ASL WM |
|-------|----------|----------|-------------|---------------------|---------------------|
| 3     | 5.8±2.0  | 7.5±2.2  | 8.6±2.1     |                     |                     |
| 4     | 7.2±1.3  | 8.0±1.5  | 9.7±1.4     | 8.9±2.1             | 14.6±4.1            |
| 5     | 7.7±1.7  | 8.8±2.1  | 12.9±1.6    | 7.0±2.1             | 12.1±3.2            |
| Width 6 | 8.8±1.0  | 9.0±1.6  | 13.4±0.7    | 8.1±3.6             | 11.6±2.7            |
| 7     | 10±0.7   | 9.7±1.6  | 14.6±0.6    | 6.6±1.8             | 10.7±2.3            |
| 8     |          | 7.0±1.4  | 10.8±2.2    |                     |                     |
| 9     |          | 7.3±1.4  | 11.3±2.4    |                     |                     |

4 Visualization of dynamic flow

See the online animations demonstrating the visualization of dynamic flow for the MIP image of a ASL-based dMRA data and three representative slices of a 14-delay pCASL ASL data.

5 Quantitative parametric values of in-vivo dMRA

Table S2: aBF and ATT measured in PCA and distal small vessels for original and KWIA-processed in-vivo dMRA.

|          | aBF (ml/ml/min) | ATT (ms)  |
|----------|-----------------|-----------|
| Original | 350.6±110.4     | 399.9±116.4 |
| PCA      |                 |           |
| KWIA     | 356.7±143.3     | 429.8±95.0 |
| p-value  | 0.38            | 0.14      |
| Original | 135.8±32.4      | 389.4±34.7 |
| Distal   |                 |           |
| KWIA     | 146.5±44.3      | 424.0±47.2 |
| P-value  | 0.06            | 0.04      |
6 Temporal SNR map

The measurements of SNR provided in this study were based on the spatial information of images. However, the temporal stability of the signal is also important for dynamic MRI techniques. In this section, temporal SNR (TSNR) was analyzed for the original and KWIA-processed PWIs that were shown in section IV. C. The temporal SNR (TSNR) was estimated by dividing the mean by the SD of a perfusion signal, and the TSNR ratio was given as the ratio of TSNR measured in KWIA-processed to the original PWIs. Note that this method of measuring TSNR ignores the signal fluctuation caused by physiological signal change which could result in an overestimated TSNR and an underestimated TSNR ratio.

Fig. S2 shows the TSNR map and the map of TSNR ratio of multi-delay ASL for a representative subject at a single axial slice. It can be observed that TSNR measured for KWIA-processed PWIs is higher than that for the original PWIs, suggesting the noise reduction caused by KWIA can translate into reduced temporal fluctuation and increased TSNR. Despite that the TSNR ratio was underestimated by the physiological signal change, the TSNR ratio in WM was 1.69±0.04 across five subjects which demonstrates the effective SNR improvement of KWIA.

Figure S2: The temporal SNR map and the map of temporal SNR ratio of multi-delay ASL for a representative subject at a single axial slice.
7 Quantitative parametric values of in-vivo multi-delay ASL

Table S3: CBF, ATT, aCBV, aBAT, and residue measured for original and KWIA-processed in-vivo 14-delay ASL.

|          | GM CBF (ml/100g/min) | WM CBF (ml/100g/min) | GM ATT (ms)    | WM ATT (ms)    | aCBV (%) | aBAT (ms)  | Residue (x 10^-4) |
|----------|-----------------------|-----------------------|----------------|----------------|---------|------------|------------------|
| Original | 52.7±6.3              | 33.8±4.6              | 1402.9±103.8   | 1690.7±103.9   | 8.6±0.4 | 780.3±9.6  | 2.8±0.3          |
| KWIA     | 52.4±6.4              | 33.6±4.6              | 1372.1±103.6   | 1667.5±108.9   | 8.1±0.4 | 782.1±12.3 | 1.0±0.1          |
| P-value  | 0.02                  | 0.02                  | 0.003          | 0.002          | 0.01    | 0.4        | 0.0001           |

Table S4: The SNR values of CBF, ATT, aCBV, and aBAT measured for original and KWIA-processed in-vivo 14-delay ASL.

|          | GM CBF SNR | WM CBF SNR | GM ATT SNR | WM ATT SNR | aCBV SNR | aBAT SNR |
|----------|------------|------------|------------|------------|----------|----------|
| Original | 2.0±0.2    | 1.2±0.1    | 2.7±0.3    | 2.7±0.3    | 1.1±0.1  | 12.8±0.5 |
| KWIA     | 2.0±0.2    | 1.2±0.1    | 2.7±0.3    | 2.7±0.3    | 1.2±0.1  | 15.3±1.3 |
| P-value  | 0.4        | 0.4        | 0.1        | 0.1        | 0.06     | 0.01     |

8 Simulation of image-based KWIA and ksp-based KWIA

In this paper, we focus on image-based KWIA which works on the k-space data converted from the magnitude MR images. KWIA is also applicable for the raw k-space data obtained from scanner, which is referred as ksp-based KWIA. In this section, ksp-based KWIA was evaluated using the digital phantom simulation. The raw k-space can be simulated by adding the simulated complex zero-mean Gaussian noise with SD = 32 to the k-space of the digital phantom. Then, ksp-based KWIA was applied to denoise the k-space data with added Gaussian noise, and the results were compared to that using image-based KWIA.

The simulation results of both image-based KWIA and ksp-based KWIA with 1.41, 1.73, and 2-fold SNR improvement, the phantom images with and without simulated noise, and the phantom images with reduced noise are shown in Fig. S3(a). It can be observed that the two KWIA methods achieved very similar performance in noise reduction, and both retained the image features of the original image. However, there is a bias (approximately 1.26× original noise SD) in the background region of the images processed by image-based KWIA. This is because the noise distribution in background region of the original magnitude MR images follows Raleigh distribution that the mean is 1.26 times noise SD. Applying KWIA on magnitude image only reduces noise SD but does not
remove such mean value. The SSIM and PSNR values (shown under images) were measured using the image without noise as the reference, and with the removal of such bias for image-based KWIA. The PSNR and SSIM increase were similar across reduced SD, image-based KWIA, and ksp-based KWIA at 1.41-fold, 1.73-fold, and 2-fold SNR improvement, while a slight deficiency of PSNR was observed with image-based KWIA compared to ksp-based KWIA and reduced SD. In the SNR improvement profiles shown in Fig. S3(b), for all KWIA configurations, both ksp-based KWIA and image-based KWIA showed high consistency between the theoretical predictions and measured data points.

Figure S3: (a) Simulated phantom images with and without simulated noise, processed by image-based KWIA and ksp-based KWIA with SNR improvement of 1.41, 1.73, and 2, respectively, and with lower noise SD at 1.41, 1.73, and 2-fold SNR improvements. (b) Theoretical and measured SNR improvement profiles of KWIA with 2, 3, and 4 rings.
9 Comparison of image-based KWIA and ksp-based KWIA under SENSE

In this section, ksp-based KWIA was evaluated with SENSE reconstruction of multi-coils data, and compared to image-based KWIA. The multi-channel data was simulated by multiplying the original phantom image at each time frame with 32 simulated coil sensitivity maps, adding simulated noise, and undersampling along PE direction by an acceleration factor of 2 for SENSE. ksp-based KWIA was applied to the k-space data before SENSE reconstruction, while image-based KWIA was applied to the images after SENSE reconstruction. Fig. S4 shows that both ksp-based KWIA and image-based KWIA can achieve the same level of SNR improvement that is comparable to the original images with reduced SD. However, a bias in the background region can be observed in images processed by image-based KWIA. With the removal of such bias, ksp-based and image-based KWIA achieved similar SSIM and PSNR values.

Figure S4: Simulated phantom images reconstructed from simulated 32-channel data using SENSE with simulated 32 channel sensitivity maps. From left to right are the phantom images with simulated noise, lower noise SD at 2-fold SNR ratio, and processed by ksp-based KWIA and image-based KWIA with SNR ratio of 2 (N = 4). A similar performance was demonstrated between ksp-based KWIA and image-based KWIA.