Published in final edited form as:

Brain Imaging Behav. 2018 August ; 12(4): 1121–1140. doi:10.1007/s11682-017-9775-y.

Stability of MRI metrics in the advanced research core of the NCAA-DoD concussion assessment, research and education (CARE) consortium

Andrew S. Nencka¹, Timothy B. Meier², Yang Wang¹, L. Tugan Muftuler², Yu-Chien Wu³, Andrew J. Saykin³, Jaroslaw Harezlak⁴, M. Alison Brooks⁵, Christopher C. Giza⁶, John Difiori⁷, Kevin M. Guskiewicz⁸, Jason P. Mihalik⁸, Stephen M. LaConte⁹, Stefan M. Duma¹⁰, Steven Broglio¹¹, Thomas McAllister¹², Michael A. McCrea², and Kevin M. Koch¹

¹Department of Radiology, Medical College of Wisconsin, Milwaukee, WI, USA

²Department of Neurosurgery, Medical College of Wisconsin, Milwaukee, WI, USA

³Department of Radiology and Imaging Science, Indiana University School of Medicine, Indianapolis, IN, USA

⁴Department of Epidemiology and Biostatistics, Indiana University, Bloomington, IN, USA

⁵Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

⁶Department of Pediatrics and Neurosurgery, UCLA Steve Tisch BrainSPORT Program, University of California Los Angeles, Los Angeles, CA, USA

⁷Department of Orthopedics, University of California Los Angeles, Los Angeles, CA, USA

⁸Department of Exercise and Sport Science, University of North Carolina, Chapel Hill, NC, USA

⁹Virginia Tech Carilion Research Institute, Virginia Tech, Blacksburg, VA, USA

¹⁰Institute for Critical Technology and Applied Science, Virginia Tech, Blacksburg, VA, USA

¹¹Department of Kinesiology, University of Michigan, Ann Arbor, MI, USA

¹²Department of Psychiatry, Indiana University School of Medicine, Bloomington, IN, USA

Abstract

The NCAA-DoD Concussion Assessment, Research, and Education (CARE) consortium is performing a large-scale, comprehensive study of sport related concussions in college student-athletes and military service academy cadets. The CARE “Advanced Research Core” (ARC), is focused on executing a cutting-edge investigative protocol on a subset of the overall CARE athlete population. Here, we present the details of the CARE ARC MRI acquisition and processing protocol along with preliminary analyses of within-subject, between-site, and between-subject stability across a variety of MRI biomarkers. Two experimental datasets were utilized for this

Correspondence to: Andrew S. Nencka.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11682-017-9775-y>) contains supplementary material, which is available to authorized users.

analysis. First, two “human phantom” subjects were imaged multiple times at each of the four CARE ARC imaging sites, which utilize equipment from two imaging vendors. Additionally, a control cohort of healthy athletes participating in non-contact sports were enrolled in the study at each CARE ARC site and imaged at four time points. Multiple morphological image contrasts were acquired in each MRI exam; along with quantitative diffusion, functional, perfusion, and relaxometry imaging metrics. As expected, the imaging markers were found to have varying levels of stability throughout the brain. Importantly, between-subject variance was generally found to be greater than within-subject and between-site variance. These results lend support to the expectation that cross-site and cross-vendor advanced quantitative MRI metrics can be utilized to improve analytic power in assessing sensitive neurological variations; such as those effects hypothesized to occur in sports-related-concussion. This stability analysis provides a crucial foundation for further work utilizing this expansive dataset, which will ultimately be freely available through the Federal Interagency Traumatic Brain Injury Research Informatics System.

Keywords

MRI; Stability; Reproducibility; Quantitative imaging; Concussion; mTBI

Introduction

Mild traumatic brain injury (mTBI) is a major public health issue in the United States (U.S.) and worldwide. From a broad perspective, sport-related concussion (SRC), a sub-category of mTBI, has been the focus of dramatically increased attention across the clinical, research, and lay communities (McCrory et al., 2013, 2009, 2005; DeKosky et al., 2010; Kelly 1999; Langlois et al., 2006; Centers for Disease Control and Prevention 2007).

While previous studies have improved best practices in the evaluation and monitoring of SRC (McCrea et al., 2003; Guskiewicz et al., 2003), its management remains a significant challenge in the sports medicine community. These challenges stem from a variety of factors, including a lack of objective diagnostic tools, under-reporting of injuries and symptoms, and operational constraints of the competitive environment.

Large prospective studies have sought to improve patient management by clarifying the time course of clinical recovery after SRC (McCrea et al., 2003, 2005, 2009, 2010). Though these studies have shed light on the underlying nuances of SRC progression, no objective biomarker of physiological recovery yet exists. In particular, biomarkers that relate the acute physiological effects of SRC on brain structure and function remain elusive. It is thus difficult to identify the window of cerebral vulnerability that extends beyond the point of clinical recovery (McCrory et al., 2017). This period of vulnerability is of substantial importance, as it may point to a physiologically compromised brain state that potentially increases the risks of repetitive injury.

The NCAA-DoD Grand Alliance: Concussion Assessment, Research and Education (CARE) Consortium is a large-scale, multi-site study of the natural history of concussion in both sexes across multiple sports. The published mission of this study, which is studying collegiate athletes and military service academy cadets, is to “gain a better understanding of

the neurobiopsychosocial nature of concussive injury and recovery in order to ultimately enhance the safety and health of our student-athletes, service members, youth sports participants, and the broader public (CARE 2015).”

The CARE project includes a Clinical Science Core (CSC) and an Advanced Research Core (ARC). While the CSC is focused on expansive longitudinal clinical testing of subjects, the ARC is focused on advanced biomarker assessment in athletes participating in high impact collision sports with a higher incidence of concussion and head impact exposure. Magnetic resonance imaging (MRI), is one of the key components of the CARE ARC biomarker assessment project.

While the primary goal of the CARE MRI study is to develop and validate imaging biomarkers of recovery following SRC, the the present study focused on a more fundamental effort to determine the stability and reproducibility of key MRI metrics in non-injured individuals, against which to reliably measure the effects of concussion on brain structure and function. Following a detailed introduction to the CARE ARC MRI protocol, an analysis the stability of targeted quantitative MRI biometrics is presented. The results of this stability analysis are summarized so as to inform future retrospective analyzes that will utilize the data when it is publicly available in the Federal Interagency Traumatic Brain Injury Research (FIBIR) database.

The Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) project is another large TBI study that is leveraging MRI biomarkers (Yue et al., 2013). The CARE MRI protocol was modeled after the TRACK-TBI MRI protocol, with additional modalities and application in very different cohorts of injured and non-injured NCAA student-athletes. The imaging biometric stability work presented here is also an extension of recently published TRACK-TBI stability analyzes focused primarily on diffusion imaging (Palacios et al., 2016). The present CARE MRI stability analysis expands this approach to a number of other MRI parameters and also leverages longitudinal control imaging sessions acquired under the ARC study protocol to perform within-subject stability analyzes. The presented study therefore serves as a novel exploration of quantitative MRI biometric stability, which may be of value to the broader neuroimaging community.

Methods

Study design

Under the CARE MRI protocol, concussed athletes undergo advanced, multi-modal MRI studies at the following time points: within 48 hours post-injury, the point at which the concussed athlete is cleared to begin return to play progression (RTP), 7 days post-RTP, and 6 months post-injury. For each concussed athlete, two matched control athletes (contact sport control and non-contact sport control) undergo the same MRI protocol at the same time points. While this subject population allows for consideration of concussion and head impact exposure, only non-contact sport athletes (without concussion or head impact exposure) were included in this study of stability. Physiological changes will induce longitudinal biometric variation within these control subjects. This variance serves as a background above which any potential biomarker effect must rise.

Each MRI exam includes anatomical and quantitative acquisitions tailored for assessment of mTBI. The imaging protocol is similar to the TRACK-TBI protocol, including T_1 , T_2 FLAIR, and T_2^* weighted structural imaging contrasts, along with diffusion tensor imaging (DTI) and resting state functional MRI (rs-fMRI) quantitative acquisitions. To this protocol, CARE ARC adds arterial spin-labeling (ASL) for quantitative perfusion assessment, and T_2^* mapping for quantitative assessment of iron content and calcification. This protocol has been deployed to the four CARE ARC study sites (UCLA, UNC, VT, UW), spanning Siemens Trio and GE MR750 3T MRI systems.

Thirty subjects were imaged at multiple time points for within-subject stability measurements in the first 18 months of the CARE project. Thirty-five subjects were imaged at least once at each site and were utilized for between-subject variance measurements. Table 1 reports the number of non-contact sport control subjects at each site whose images were used in this analysis. Numbers below 30 in the top section and 35 in the lower section in Table 1 indicate subjects which were excluded by quality control processes; primarily due to the presence of motion artifacts.

Beyond the non-contact control athletes, a set of two “traveling human phantom” subjects were scanned on two occasions at each site in the study. The resulting data were utilized to estimate the site-to-site variation of the acquisition protocol (Table 2).

Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Imaging protocol

T_1 weighted imaging— T_1 weighted images were acquired for gray/white matter segmentation, registration of images to standard space, and volumetrics. Some recent work has shown changes in brain volume within two weeks of injury (Jarrett et al., 2016). On the Siemens platform, a 3D Magnetization Prepared Rapid Gradient Echo (3D MP-RAGE) acquisition was used, while on the GE platform, a 3D BRAin Volume (BRAVO) acquisition was utilized. In both cases, a 3D fast gradient recalled echo acquisition is coupled with an initial inversion pulse to enhance gray/white matter contrast. Acquisition parameters are shown in Tables 3 and 4.

T_2 FLAIR weighted imaging— T_2 weighted images acquired using fluid-attenuated inversion recovery (FLAIR) improve the conspicuity of white matter lesions due to severe TBI (Ashikaga et al., 1997). To investigate the presence of subtle lesions with mTBI, the ARC MRI protocol includes a T_2 FLAIR acquisition utilizing variable flip angle schemes within extended echo train fast-spin-echo sequences. On the GE and Siemens platforms these sequences are respectively Cube and SPACE, with parameters included in Tables 3 and 4.

T_2^* weighted imaging and T_2^* mapping—The CARE-MRI 3D gradient recalled echo T_2^* weighted protocol acquires multiple echo times that can be used for quantitative T_2^* map computations. The longest echo time image of the acquisition set is additionally utilized as a conventional T_2^* weighted image. These acquisitions are very sensitive to micro-hemorrhages and have been shown useful in more severe cases of mTBI (Liu et al., 2016). The parameters for these sequences are presented in Tables 3 and 4.

Diffusion weighted imaging—Diffusion weighted imaging (DWI) is a well-studied MRI modality for quantitative assessments of mTBI. DWI is sensitive to variations in white matter integrity and is therefore a probe of axonal injuries that could be a source of post-injury symptoms (Shenton et al., 2012). A number of studies have shown that diffusion-tensor (DTI) processing of DWI data can detect differences in injured groups compared to control populations (Eierud et al., 2014; Dodd et al., 2014; Bigler 2013); primarily in mean diffusivity (MD) and fractional anisotropy (FA). However, the polarities of these observed effects are conflicting (Dodd et al., 2014), necessitating further investigations with larger cohorts and more sophisticated diffusion modeling.

The CARE DWI approach utilizes multiple elevated diffusion weightings that enable computation of diffusion kurtosis imaging (DKI) metrics (Lu et al., 2006), in addition to standard DTI metrics. DKI provides increased sensitivity microstructural changes and have shown preliminary advantages in analyses of concussed cohorts (Lancaster et al., 2016). Though DKI parameters can be computed using the CARE MRI data, this analysis focuses only on the two core DWI metrics that have seen the most attention in mTBI: FA and MD. The parameters for these diffusion sequences are presented in Tables 3 and 4.

Resting state functional—Functional MRI (fMRI) is a time-series acquisition that measures blood oxygenation level dependent (BOLD) contrast. BOLD is sensitive to neurovascular coupling and neuronal activity, specifically arising from changes in cerebral blood flow (CBF) and cerebral blood volume (CBV). In the context of mTBI, neurotrauma can cause changes in synchronous neuronal activation, degrade the structural integrity of cerebral microvasculature, and alter cerebrovascular reactivity. In combination with the effects of mTBI on CBF, fMRI can probe of physiological changes after SRC. Numerous studies have identified fMRI signal alterations potentially caused by mTBI, predominantly focused on longer term changes in activation patterns (Mayer et al., 2015).

Like TRACK-TBI, the CARE protocol utilizes resting state fMRI (rs-fMRI), thus enabling a broad survey of functional activation metrics and network analyses. The details of the rs-fMRI acquisitions are included in Tables 3 and 4. Though a wide variety of metrics could be explored using this functional data, we focus on the stability of two voxel-wise rs-fMRI metrics: REgional HOmogeneity (REHO) of BOLD signal fluctuations (Zang et al., 2004) and Fractional Amplification of Low-Frequency Fluctuations (FALFF) (Zou et al., 2008).

Arterial spin labeling—Modulation of the cerebrovascular complex is a substantial factor in physiological reactions to mTBI (Tan et al., 2014). Arterial spin labeling (ASL) is an MRI modality that can estimate cerebral blood flow (CBF) by tagging inflowing blood using

radiofrequency pulses (Detre et al., 1992). Recent longitudinal ASL experiments on concussed athletes have shown trends in decreased CBF which agree with results from animal models (Meier et al., 2015; Wang et al., 2016; Ginsberg et al., 1997; Muir et al., 1992; Yamakami & McIntosh 1989).

Within the CARE MRI protocol, vendor and software variations between sites necessitated deployment of two different ASL approaches. Further, one site (VT) did not have license to utilize an ASL sequence. On the GE MRI platform (UW), a three dimensional (3D) pseudo-continuous ASL (3D-pCASL) was utilized. On the Siemens MRI Trio platform (UNC, UCLA), the only commercially available ASL acquisition was a two-dimensional (2D) pulsed ASL (2D-pASL). Compared to 2D-pASL, 3D-pCASL provides improved signal-to-noise ratio (SNR) and acquisition efficiency (Chen et al., 2011; Vidorreta et al., 2013; Wu et al., 2007). Despite these differences, both techniques are capable of providing estimates of relative CBF (rCBF). The details of the deployed ASL sequences are provided in Tables 3 and 4.

Processing pipelines

For reproducibility and transparency, detailed processing commands employed in each pipeline are offered in Supplemental Material to this manuscript. A summary of the implemented processing pipelines is presented in the following sections.

T₁ weighted—In native space, SPM 12 (Penny et al., 2011) was used to segment gray matter, white matter, and cerebrospinal fluid. Skull stripping was performed by multiplication with the union of these masks. The skull stripped brain was then registered to the MNI-152 template's skull stripped T₁ weighted image (Mazziotta et al., 2001) using the FMRIB's Linear and Nonlinear Image Registration Tools (FLIRT and FNIRT in FSL) (Jenkinson et al., 2012). Transformation parameters for this registration were saved for ensuing registration operations. To account for system gain differences that can vary on a per-exam basis, the final T₁ weighted MNI-space skull-stripped image data was scaled and self-normalized to have an average intensity of unity.

T₂ FLAIR—To align T₂ FLAIR datasets to MNI space, a 6 degree of freedom registration, FLIRT, was performed in native-space to map the T₂ FLAIR and the T₁ weighted datasets. The transformation arising from this registration was then applied sequentially with the aforementioned nonlinear transformation computed for registration of the T₁ weighted image to MNI-space. Like the T₁ weighted images, MNI-space skull-stripped brain volume intensity was scaled and self-normalized.

T₂^{*}—To compute T₂^{*}, a weighted linear least squares fit was performed using the natural logarithm of the image intensity for each echo time for each voxel. The slope of this regression was utilized to estimate the T₂^{*} relaxation rate. This regression was implemented using customized C++ software.

The last echo time collected for each dataset was also utilized as single T₂^{*} weighted image.

The same processing pipeline as described for T₂ FLAIR registration to MNI-space was applied to the T₂* maps and T₂* weighted images. Only T₂* weighted images were scaled and self-normalized.

Diffusion—The diffusion weighted imaging protocol included an extra acquisition with no diffusion gradients ($b = 0$) and reversed phase encoding polarity. This dataset, coupled with the $b = 0$ image from the diffusion weighted acquisition, was input into the “topup” function of FSL (Andersson et al., 2003). The resulting distortion correction map was applied to the entire DTI dataset. The brain was then extracted using the FSL brain extraction tool and the dataset corrected for eddy currents using the FSL “eddy” algorithm (Andersson & Sotiropoulos 2016).

A weighted fitting procedure in FSL calculated FA and MD maps (Jenkinson et al., 2012). Resulting FA maps were registered to MNI-space using FLIRT (affine registration) and FNIRT (non-linear registration) paired with the MNI-space FA template (Mazziotta et al., 2001). The resulting transformation was also applied to the MD map.

Functional—Resting state fMRI data was processed using standard functions available with AFNI (Cox 1996) and FSL (Jenkinson et al., 2012). Temporal outliers were removed with AFNI’s “3dDespike”. The time series first image was registered to the T₁ weighted anatomical image through boundary-based registration in FSL’s “epi_reg” for use later in the pipeline. Slice timing correction was applied using quintic interpolation through AFNI’s “3dTshift”. Motion correction was achieved through the use of AFNI’s “3dvolreg” with cubic interpolation. The registration calculated for the first image to the T₁ weighted image was concatenated to the transformation from the T₁ weighted image to MNI-space with FSL’s “convert_xfm” function, and applied to the motion corrected time series with FSL’s “applywarp” function.

Nuisance regression utilized a number of standard regressors. A time series of motion parameters and their first temporal derivatives were generated with AFNI’s “1d_tool.py”; white matter and CSF time series were generated using AFNI’s “3dmaskave” with MNI-space masks. Regression was performed in two steps. First AFNI’s “3dDeconvolve” function was run with the following inputs: the six motion parameters and their derivatives, up to third order polynomials, white matter and CSF signals, and the option of “x1D_stop” to create outputs for the use of “3dTproject” for nuisance regression, which was run as the second step.

Images were smoothed to an effective 10 mm full width at half maximum Gaussian point-spread using AFNI’s “3dBlurToFWHM.” This normalizes smoothness across datasets from different equipment and is standard in multi-site functional imaging studies (Friedman et al., 2006).

The fALFF functional metric was calculated on the smoothed data set utilizing AFNI’s “3dRSFC” function with a bandpass filter of 0.01 to 0.10 Hz. REHO was calculated on the smoothed data using the AFNI function of “3dREHO.”

Arterial spin labeling—Blood flow was estimated using the relative CBF (rCBF) parameter, computed using the commercial software algorithms on the respective MRI platforms. The resulting maps were transformed to MNI-space through linear registration (FSL FLIRT) of baseline (untagged) dataset to the T_1 weighted dataset followed by an application of the transformation connecting the T_1 weighted image to MNI space. This sequence of transformations was then applied to the rCBF maps as well.

Coefficient of variation calculation—Coefficients of variation (CVs) were computed across individual subject exam sessions, across the imaging sites in traveling human phantoms, and across subjects. CVs represent the proportion of variation relative to the mean value of the metric. These CVs illustrate the relative stability of the computed metrics for repeated measurements on individual subjects, repeated measurements across each of the imaging sites, and different subject measurements within an imaging site. Given the diversity of contrasts considered in this work, this relatively simplistic method allows for the comparison of stability between computed metrics.

The algorithm for computing CVs utilized standard AFNI functions. Repeated measurements were concatenated using AFNI's "3dTcat." The mean and standard deviation were calculated on the concatenated data set using "3dTstat." The ratio of the standard deviation to the mean, the final CV, was calculated using AFNI's "3dCalc." Averaging CVs across subjects or sites included concatenating the computed CVs with "3dTcat" and averaging with "3dTstat."

To compute CVs across individual subject exam sessions, processed datasets for each metric in MNI-space were used to compute the average and standard deviation across all imaging time points for each subject. Individual CVs were computed for each subject and then averaged across all subjects.

Computation of CVs across imaging sites was performed by using processed datasets for each metric in MNI-space to compute the average and standard deviation across all sites for both of the traveling human phantoms. Between-site CVs were then generated averaging the CVs across both human phantoms.

To compute CVs across all subjects, processed data-sets for each modality in MNI-space for the first imaging time point were used to compute the average and standard deviation across all subjects at each imaging site. Between-subject CVs were then generated for each site. The final between-subject CV was then computed as the average of the between-subject CVs from each site.

Region of interest processing—The brain was subdivided into 143 regions of interest for quantitative analysis of CVs across distinct brain regions. These regions of interest were drawn from the Harvard-Oxford atlas of cortical and subcortical gray matter (Desikan et al., 2006), along with the Johns Hopkins atlas of white matter tracks (Mori et al., 2005). A joint atlas was generated as the union of the intersection of the MNI-space gray matter mask and the Harvard-Oxford gray matter atlas with the intersection of the MNI-space white matter mask and the Johns Hopkins white matter atlas. This union of intersections ensured that each

voxel was assigned to at most one region of interest. Mean CVs were extracted from each region of interest in this atlas in the within-subject, between-subject, and between-site data sets. This data is provided in tabular form in the Online Supplement to this study.

Results

Figures 1, 2, 3, 4, 5, 6, 7, 8, and 9 show the mean images and within-subject, between-site, and between-subject CV maps for normalized T_1 weighted, normalized T_2 FLAIR, normalized T_2^* weighted, quantitative T_2^* , MD, FA, REHO, fALFF, and rCBF, respectively.

Table 5 shows the average CVs for each contrast and comparison within gray/white matter and CSF regions of interest.

T_1 weighted

Mean images in Fig. 1 show clear distinction of gray matter, white matter, and CSF tissue compartments. As expected, the within-subject CV is very low, with observed tissue compartment differences resulting from the signal to noise ratio variations of these compartments. The between-site variations are larger, which is anticipated due to the differences between T_1 weighted pulse-sequence implementations on the different vendor platforms.

Between-subject measurements show the largest variation. This is consistent across many of the measured metrics. In this case, the variation is due to changes in detailed tissue composition from one subject to another. The natural variance of T_1 and T_2 values in normal brain tissue has been measured to be roughly 10% across most tissues for both relaxation rates (Just & Thelen 1988; Stevenson et al., 2000). Though the CV seen here is due to contrast changes, rather than absolute T_1 values, the variance in T_1 values is a likely explanation for this observed between-subject variance.

T_2 FLAIR

Again, in Fig. 2, the mean T_2 FLAIR images show clear distinction of gray matter, white matter, and CSF tissue compartments. Also following the results of the T_1 weighted analysis, the within-subject CV is very low, with the between-site and between-subject measurements showing substantially larger variations. Again, the between-site variances are likely the result of pulse-sequence differences between vendors, while the between-subject variance is due to the aforementioned known 10% variance in T_2 values across healthy subjects.

T_2^*

Mean T_2^* images show some distinction of gray matter, white matter, and CSF tissue compartments in Fig 3. Following the trend of the previous results, the within-subject CV is very low. However, in this case the between-site variations show increased CV values, particularly within the center of the brain (black arrow). This is due to reception coil and post-processing differences between the sites, whereby some of the coils had improved signal reception from deeper areas of the brain. The between-subject CV does not show as

substantial of an effect from the coil variations, due to the fact that between subject CVs were calculated on a site-by-site basis, then averaged across sites. Instead, a stronger CV is seen in the frontal lobe (white arrow). This region of increased between-subject CV is due to variations of sinus cavity geometry and composition (e.g. mucus) from subject to subject. Such variations change local magnetic field perturbations and consequently alter local signal integrity in T_2^* weighted images.

Mean T_2^* maps show some distinction of gray matter, white matter, and CSF tissue compartments in Fig. 4. The within-subject CV is again very low for this quantitative metric. In this case, the between-subject variation is again larger than the between-site variation. This is due to natural variations of tissue T_2^* values from subject to subject (Wansapura et al., 1999).

Diffusion

As shown in Fig. 5, CV values for MD are best for the within-subject measurements and worst for the between-subject measurements. With chaotic flow patterns in the CSF, high variance is seen in both the ventricles and along the pial surface.

Like MD, the CV values for FA are lowest within-subjects and worst for the between-subject measurements, seen in Fig. 6. These results indicate that between-site and cross platform systematic diffusion weighted imaging variations are lower than the natural variations between subjects. Additionally, FA metrics are shown to yield less variance in white matter where diffusion is more well defined.

Functional

The mean REHO map in Fig. 7 clearly shows more homogeneity within the gray matter, which is expected. Like all other metrics, values for REHO are best for the within-subject measurements. In the gray matter compartments, REHO shows very similar CV in between-subject and between-site measurements. In the white matter compartments, which are not typically studied in fMRI analyzes, REHO shows slightly improved stability in the between-site analysis.

Like REHO, the mean fALFF map shows an increase of power in low frequency BOLD oscillations within the gray matter, as expected in Fig 8. Like diffusion metrics, CV values for fALFF are consistently the lowest for the within-subject measurements and worst for the between-subject measurements.

Arterial spin labeling

As expected, the mean rCBF map shows substantially increased flow in the gray matter in Fig. 9. Consequently, the within-subject CV is far better in the gray matter than the other tissue compartments. The between-site CVs are far less than the between-subject CVs in the gray matter compartments. Even with substantial differences between the ASL acquisitions on the two vendor platforms, the subject-specific variations are more substantial than the quantitative platform-specific performance differences.

Region of interest results

Tables providing numerical CV results for all metrics across all ROIs are included as Online Supplements. Figure 10 provides a scatter plot summary of these ROI CV values and displays trends that have been consistently revealed in this work. The following trends are apparent in this plot: relative CBF shows the most systematic variation across all analysis groups, diffusion metrics are more consistent in white matter and yield CVs of less than 15% in within subject gray matter ROIs, and local fMRI metrics (REHO and fALFF) show strong stability in gray matter ROIs. The fMRI metrics also show excellent stability in the white matter, although most other metrics show similar levels of stability (with the exception of rCBF).

Table 5 quantitatively illustrates the observed trends in this stability analysis. For all of the metrics, within-subject CV is the lowest of the analysis groups. In addition, for most of the metrics, between-subject CVs are the largest source of variance. The exceptions to this trend are highlighted in boldface. Of these exceptions, only the underlined cases exhibit statistical significance. Only one of these cases (T_2^* weighted values in the deep gray compartment) is outside of the CSF compartment group. As previously discussed, this result is not surprising, due to the variations of reception coil performance between the different sites. The deep gray compartment will be most effected by this variance. The CSF compartment consistently shows very high CVs, and is clearly not a good compartment for comparison of the metrics analyzed in this work.

Discussion

Coefficients of variation illustrate different levels of variability between scanning sessions within a subject, between platforms, and between subjects. These differences offer insight into the levels of precision available for evaluating concussion exposure and recovery related changes in the imaging data acquired as part of the ARC study.

For each analyzed metric, coefficients of variation are lowest within repeated subjects. This is expected, as anatomical changes over the time scale of the repeated measurements are minimal, and identical hardware is used for each measurement within individual subjects. Despite these fixed parameters, physiologic factors can contribute to the non-zero coefficient of variation within the repeated measures. Such physiological variance is, in fact, the focal point of interest in the larger CARE MRI study. Variance within subjects across time points will be utilized to track the natural history of injury recovery, potential changes associated with exposure to sub-concussive impacts, and the natural variation of the imaged biomarkers associated with participation in high-level athletics.

Between-site coefficients of variation changed substantially for different imaging metrics. Generally, quantitative images (T_2^* , MD, FA, REHO, and fALFF) show lower levels of variation than contrast weighted images (T_1 , T_2 FLAIR, T_2^*). This difference is expected, given the variations of pulse sequences employed by the different scanner vendors.

Significant differences exist in the utilized approaches to ASL blood-flow estimation on the GE and Siemens platforms. This led to increased coefficient of variation in computed rCBF maps, which is particularly visible in regions of low CBF; e.g. white matter. The majority of the ASL datasets were acquired on the Siemens platform with the 2D-pASL approach; which demonstrated much higher variance than the 3D-pCASL approach. As a specific example, we point to an ROI based in the left postcentral gyrus. The CV of subjects in the GE platform group (N=5) in this ROI was 0.24. In the Siemens platform group (N=17), the CV in this ROI was 0.80. However, even with higher performing 3D-pCASL approach, the rCBF CV values are substantially higher than those of the other metrics analyzed in this study. Preliminary analyzes of ASL metrics in mTBI have shown very large effect sizes that survive this relatively large systematic variation in the measurement (Wang et al., 2016).

Between-subject coefficients of variation are generally found to be higher than all other analyzed data groups, with the single exception of T_2^* weighted imaging.

To our knowledge, this is the first stability analysis of a wide variety of MRI metrics spanning locations, vendors, and subjects. The unique nature of the CARE consortium's longitudinal non-contact sport control population enabled this broad MRI biometric stability analysis. In addition, the deployment of a human phantom to the imaging sites allowed for a more intricate analysis of site to site and cross-vendor differences.

The statistical approach in this study closely followed the TRACK-TBI stability analysis (Palacios et al., 2016). However, the data acquisition approaches for these two stability assessments were different. The TRACK-TBI approach utilized traveling phantom and diffusion-phantom acquisitions to look carefully at diffusion metric stability. This allowed for a limited study of within-subject and between-site variations. With the addition of a longitudinal non-injured control cohort, the current study was able to more carefully examine between-subject variations as well. However, the within-subject and between-site MD and FA stability results presented here are in very close agreement with those reported by the TRACK-TBI study, with white-matter ROIs CVs ranging around a few percent (Palacios et al., 2016). With respect to diffusion metrics, the ARC MRI stability analysis shows that the between-subject FA and MD variations are decisively larger, at roughly twice the CV seen within subjects or between sites.

Conclusions

This study represents a fundamental effort by the CARE Consortium to determine the stability and reproducibility of key MRI metrics in multi-center TBI studies, which is critical to reliably measuring and interpreting the effects of concussion on brain structure and function. The cumulative results of this study have established stability expectations for a broad set of advanced MRI metrics utilized in analyzes of mTBI and neuroimaging in general. This analysis relied upon acquisitions collected on normal controls scanned at longitudinal time points along with traveling human phantom assessments at each of four study imaging sites. Statistical analysis of metric data derived from these datasets has identified an important trend in the data stability: between-subject instability matches or dominates between-site instability. This finding is of substantial importance, in that it

provides confidence in ability to perform collective analysis of all advanced mTBI MRI biomarkers from carefully controlled imaging studies spanning multiple imaging sites and multiple imaging vendors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was funded with support from the Grand Alliance Concussion Assessment, Research, and Education (CARE) Consortium, funded, in part by the National Collegiate Athletic Association (NCAA) and the Department of Defense (DOD). The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702–5014 is the awarding and administering acquisition office. This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Psychological Health and Traumatic Brain Injury Program under Award NO W81XWH-14-2-0151. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense (DHP funds). The authors would like to thank Jenelle E. Fuller, Haley M. Cilliers, Martha Garcia, Sara John, Nana Asiedu, Liga Blyholder, Mike Powers, Morgan Shields, Briana Meyer, Sonal Singh, Zoey Wang, Mania Alexandria, Max Zeiger, Alma Martinez, Douglas Chan, Brennan Delattre, Jonathan Lisinski, Christopher Anzalone, Amber Leinwand, April ‘Nikki’ Jennings, Sharon Bryan, Victor Wright, Jennifer Franco, Issack Boru, Corey Rodrigo, Parker Traugot, Grant Cabell, Erin Grand, Aliza Nedimyer, and Tricia Combs for data acquisition and Brad Swearingen, Lezlie Espana, and Robin Karr for algorithm support.

References

- Andersson JLR, & Sotiropoulos SN (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *NeuroImage*, 125, 1063–1078. [PubMed: 26481672]
- Andersson JLR, Skare S, & Ashburner J (2003). How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *NeuroImage*, 20(2), 870–888. [PubMed: 14568458]
- Ashikaga R, Araki Y, & Ishida O (1997). MRI Of head injury using FLAIR. *Neuroradiology*, 39(4), 239–242. [PubMed: 9144669]
- Bigler ED (2013). Neuroimaging biomarkers in mild traumatic brain injury (mTBI). *Neuropsychology Review*, 23(3), 169–209. [PubMed: 23974873]
- CARE (2015). CARE Consortium homepage. <http://www.careconsortium.net>. Accessed: 2017-02-12.
- Centers for Disease Control and Prevention (2007). Nonfatal traumatic brain injuries from sports and recreation activities—United States, 2001–2005. *MMWR: Morbidity and Mortality Weekly Report*, 56(29), 733–737. [PubMed: 17657206]
- Chen Y, Wang DJJ, & Detre JA (2011). Test–retest reliability of arterial spin labeling with common labeling strategies. *Journal of Magnetic Resonance Imaging*, 33(4), 940–949. [PubMed: 21448961]
- Cox RW (1996). AFNI, Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, 29(3), 162–173. [PubMed: 8812068]
- DeKosky ST, Ikonomic MD, & Gandy S (2010). Traumatic brain injury—football, warfare, and long-term effects. *New England Journal of Medicine*, 363(14), 1293–1296. [PubMed: 20879875]
- Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, & et al. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, 31(3), 968–980. [PubMed: 16530430]
- Detre JA, Leigh JS, Williams DS, & Koretsky AP (1992). Perfusion imaging. *Magnetic Resonance in Medicine*, 23(1), 37–45. [PubMed: 1734182]
- Dodd AB, Epstein K, Ling JM, & Mayer AR (2014). Diffusion tensor imaging findings in semi-acute mild traumatic brain injury. *Journal of Neurotrauma*, 31(14), 1235–1248. [PubMed: 24779720]

- Eierud C, Craddock RC, Fletcher S, Aulakh M, King-Casas B, Kuehl D, & LaConte SM (2014). Neuroimaging after mild traumatic brain injury: review and meta-analysis. *NeuroImage: Clinical*, 4, 283–294.
- Friedman L, Glover GH, Krenz D, Magnotta V, & The FIRST BIRN (2006). Reducing inter-scanner variability of activation in a multicenter fMRI study: role of smoothness equalization. *NeuroImage*, 32(4), 1656–1668. [PubMed: 16875843]
- Ginsberg MD, Zhao W, Alonso OF, Looor-Estades JY, Dietrich WD, & Busto R (1997). Uncoupling of local cerebral glucose metabolism and blood flow after acute fluid-percussion injury in rats. *American Journal of Physiology-Heart and Circulatory Physiology*, 272(6), 2859–2868.
- Guskiewicz KM, McCrea M, Marshall SW, Cantu RC, Randolph C, Barr W, Onate JA, & Kelly JP (2003). Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA concussion study. *Journal of the American Medical Association*, 290(19), 2549–2555. [PubMed: 14625331]
- Jarrett M, Tam R, Hernández-Torres E, Martin N, Perera W, Zhao Y, Shahinfard E, Dadachanji S, Taunton J, Li DKB, & et al. (2016). A prospective pilot investigation of brain volume, white matter hyperintensities, and hemorrhagic lesions after mild traumatic brain injury. *Frontiers in Neurology*, 7.
- Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, & Smith SM (2012). FSL. *NeuroImage*, 62(2), 782–790. [PubMed: 21979382]
- Just M, & Thelen M (1988). Tissue characterization with t1, t2, and proton density values: results in 160 patients with brain tumors. *Radiology*, 169(3), 779–785. [PubMed: 3187000]
- Kelly JP (1999). Traumatic brain injury and concussion in sports. *Journal of the American Medical Association*, 282(10), 989–991. [PubMed: 10485687]
- Lancaster MA, Olson DV, McCrea MA, Nelson LD, LaRoche AA, & Muftuler LT (2016). Acute white matter changes following sport-related concussion: a serial diffusion tensor and diffusion kurtosis tensor imaging study. *Human Brain Mapping*, 37(11), 3821–3834. [PubMed: 27237455]
- Langlois JA, Rutland-Brown W, & Wald MM (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *The Journal of Head Trauma Rehabilitation*, 21(5), 375–378. [PubMed: 16983222]
- Liu W, Soderlund K, Senseney JS, Joy D, Yeh P-H, Ollinger J, Sham EB, Liu T, Wang Y, Oakes TR, & Riedy G (2016). Imaging cerebral microhemorrhages in military service members with chronic traumatic brain injury. *Radiology*, 278(2), 536–545. [PubMed: 26371749]
- Lu H, Jensen JH, Ramani A, & Helpert JA (2006). Three-dimensional characterization of non-Gaussian water diffusion in humans using diffusion kurtosis imaging. *NMR in Biomedicine*, 19(2), 236–247. [PubMed: 16521095]
- Mayer AR, Bellgowan PSF, & Hanlon FM (2015). Functional magnetic resonance imaging of mild traumatic brain injury. *Neuroscience & Biobehavioral Reviews*, 49, 8–18. [PubMed: 25434880]
- Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, & et al. (2001). A four-dimensional probabilistic atlas of the human brain. *Journal of the American Medical Informatics Association*, 8(5), 401–430. [PubMed: 11522763]
- McCrea M, Guskiewicz KM, Marshall SW, Barr W, Randolph C, Cantu RC, Onate JA, Yang J, & Kelly JP (2003). Acute effects and recovery time following concussion in collegiate football players: the NCAA concussion study. *Journal of the American Medical Association*, 290(19), 2556–2563. [PubMed: 14625332]
- McCrea M, Barr WB, Guskiewicz K, Randolph C, Marshall SW, Cantu R, Onate JA, & Kelly JP (2005). Standard regression-based methods for measuring recovery after sport-related concussion. *Journal of the International Neuropsychological Society*, 11(01), 58–69. [PubMed: 15686609]
- McCrea M, Guskiewicz K, Randolph C, Barr WB, Hammel TA, Marshall SW, & Kelly JP (2009). Effects of a symptom-free waiting period on clinical outcome and risk of re-injury after sport-related concussion. *Neurosurgery*, 65(5), 876–883. [PubMed: 19834399]
- McCrea M, Pritchep L, Powell MR, Chabot R, & Barr WB (2010). Acute effects and recovery after sport-related concussion: a neurocognitive and quantitative brain electrical activity study. *The Journal of Head Trauma Rehabilitation*, 25(4), 283–292. [PubMed: 20611046]

- McCrory P, Johnston K, Meeuwisse W, Aubry M, Cantu R, Dvorak J, Graf-Baumann T, Kelly J, Lovell M, & Schamasch P (2005). Summary and agreement statement of the 2nd international conference on concussion in sport, prague 2004. *British Journal of Sports Medicine*, 39(4), 196–204. [PubMed: 15793085]
- McCrory P, Meeuwisse W, Johnston K, Dvorak J, Aubry M, Molloy M, & Cantu R (2009). Consensus statement on concussion in sport: the 3rd international conference on concussion in sport held in zurich, november 2008. *Journal of Athletic Training*, 44(4), 434–448. [PubMed: 19593427]
- McCrory P, Meeuwisse WH, Aubry M, Cantu B, Dvořák J, Echemendia RJ, Engebretsen L, Johnston K, Kutcher JS, Raftery M, & et al. (2013). Consensus statement on concussion in sport: the 4th international conference on concussion in sport held in Zurich, November 2012. *British Journal of Sports Medicine*, 47(5), 250–258. [PubMed: 23479479]
- McCrory P, Meeuwisse W, Dvorak J, Aubry M, Bailes J, Broglio S, Cantu RC, Cassidy D, Echemendia RJ, Castellani RJ, Davis GA, Ellenbogen R, Emery C, Engebretsen L, Feddermann-Demont N, Giza CC, Guskiewicz KM, Herring S, Iverson GL, Johnston KM, Kissick J, Kutcher J, Leddy JJ, Maddocks D, Makdissi M, Manley GT, McCrea M, Meehan WP, Nagahiro S, Patricios J, Putukian M, Schneider KJ, Sills A, Tator CH, Turner M, & Vos PE (2017). Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. *British Journal of Sports Medicine*. 10.1136/bjsports-2017-097699, <http://bjsm.bmj.com/content/early/2017/04/28/bjsports-2017-097699>.
- Meier TB, Bellgowan PSF, Singh R, Kuplicki R, Polanski DW, & Mayer AR (2015). Recovery of cerebral blood flow following sports-related concussion. *JAMA Neurology*, 72(5), 530–538. [PubMed: 25730545]
- Mori S, Wakana S, Van Zijl PCM, & Nagae-Poetscher LM (2005). *MRI atlas of human white matter*. Elsevier.
- Muir JK, Boerschel M, & Ellis EF (1992). Continuous monitoring of posttraumatic cerebral blood flow using laser-doppler flowmetry. *Journal of Neurotrauma*, 9(4), 355–362. [PubMed: 1291695]
- Palacios EM, Martin AJ, Boss MA, Ezekiel F, Chang YS, Yuh EL, Vassar MJ, Schnyer DM, MacDonald CL, Crawford KL, Irimia A, Toga AW, Mukherjee P, & TRACK-TBI Investigators (2016). Toward precision and reproducibility of diffusion tensor imaging: a multicenter diffusion phantom and traveling volunteer study. *American Journal of Neuroradiology*.
- Penny WD, Friston KJ, Ashburner JT, Kiebel SJ, & Nichols TE (2011). *Statistical parametric mapping: the analysis of functional brain images*. Cambridge, MA: Academic Press.
- Shenton ME, Hamoda HM, Schneiderman JS, Bouix S, Pasternak O, Rathi Y, Vu MA, Purohit MP, Helmer K, Koerte I, Lin AP, Westin CF, Kikinis R, Kubicki M, Stern RA, & Zafonte R (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging and Behavior*, 6(2), 137–192. [PubMed: 22438191]
- Stevenson VL, Parker GJM, Barker GJ, Birnie K, Tofts PS, Miller DH, & Thompson AJ (2000). Variations in t1 and t2 relaxation times of normal appearing white matter and lesions in multiple sclerosis. *Journal of the Neurological Sciences*, 178(2), 81–87. [PubMed: 11018698]
- Tan CO, Meehan WP, Iverson GL, & Taylor JA (2014). Cerebrovascular regulation, exercise, and mild traumatic brain injury. *Neurology*, 83(18), 1665–1672. [PubMed: 25274845]
- Vidorreta M, Wang Z, Rodríguez I, Pastor MA, Detre JA, & Fernández-Seara MA (2013). Comparison of 2d and 3d single-shot ASL perfusion fMRI sequences. *Neuroimage*, 66, 662–671. [PubMed: 23142069]
- Wang Y, Nelson LD, LaRoche AA, Pfaller AY, Nencka AS, Koch KM, & McCrea MA (2016). Cerebral blood flow alterations in acute sport-related concussion. *Journal of Neurotrauma*, 33(13), 1227–1236. [PubMed: 26414315]
- Wansapura JP, Holland SK, Dunn RS, & Ball WS (1999). NMR Relaxation times in the human brain at 3.0 Tesla. *Journal of Magnetic Resonance Imaging*, 9(4), 531–538. [PubMed: 10232510]
- Wu W-C, Fernández-Seara M, Detre JA, Wehrli FW, & Wang J (2007). A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. *Magnetic Resonance in Medicine*, 58(5), 1020–1027. [PubMed: 17969096]

- Yamakami I, & McIntosh TK (1989). Effects of traumatic brain injury on regional cerebral blood flow in rats as measured with radiolabeled microspheres. *Journal of Cerebral Blood Flow & Metabolism*, 9(1), 117–124. [PubMed: 2910893]
- Yue JK, Vassar MJ, Lingsma HF, Cooper SR, Okonkwo DO, Valadka AB, Gordon WA, Maas AIR, Mukherjee P, Yuh EL, & et al. (2013). Transforming research and clinical knowledge in traumatic brain injury pilot: multicenter implementation of the common data elements for traumatic brain injury. *Journal of Neurotrauma*, 30(22), 1831–1844. [PubMed: 23815563]
- Zang Y, Jiang T, Lu Y, He Y, & Tian L (2004). Regional homogeneity approach to fMRI data analysis. *NeuroImage*, 22(1), 394–400. [PubMed: 15110032]
- Zou Q-H, Zhu C-Z, Yang Y, Zuo X-N, Long X-Y, Cao Q-J, Wang Y-F, & Zang Y-F (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *Journal of Neuroscience Methods*, 172(1), 137–141. [PubMed: 18501969]

Fig. 1. T1 weighted image mean, first row, within-subject CV, second row, between-site CV, third row, and between-subject CV, fourth row

Fig. 2. FLAIR image mean, first row, within-subject CV, second row, between-site CV, third row, and between-subject CV, fourth row

Fig. 3.

$T2^*$ weighted image mean, first row, within-subject CV, second row, between-site CV, third row, and between-subject CV, fourth row. The black arrowhead in left column represents between-site CV changes that are due to reception coil differences between sites. The white arrowhead shows between-subject CV changes in the frontal lobe, which are due to variations in sinus-cavity geometry and composition across subjects

Fig. 4. Computed T2* image mean, first row, within-subject CV, second row, between-site CV, third row, and between-subject CV, fourth row

Fig. 5. Mean diffusivity image mean in mm^2/s , first row, within-subject CV, second row, between-site CV, third row, and between-subject CV, fourth row

Fig. 6. Fractional anisotropy image mean, first row, within-subject CV, second row, between-site CV, third row, and between-subject CV, fourth row

Fig. 7. Regional homogeneity of low BOLD fluctuations image mean, first row, within-subject CV, second row, between-site CV, third row, and between-subject CV, fourth row

Fig. 8. Fractional amplitude of low frequency fluctuations image mean, first row, within-subject CV, second row, between-site CV, third row, and between-subject CV, fourth row

Fig. 9. Relative cerebral blood flow image mean, first row, within-subject CV, second row, between-site CV, third row, and between-subject CV, fourth row

Fig. 10.
Coefficients of variation across all subjects in brain regions of interest for each modality

Table 1
Numbers of subjects for each imaging acquisition that were included in the stability analysis at each imaging site

Site	T ₁	T ₂	FLAIR	T ₂ [*]	Diff.	BOLD	ASL
Within-Subject							
UCLA	6	6		5	6	4	6
UNC	10	11		10	11	12	9
UW	6	6		5	6	6	5
VT	6	7		5	7	7	NA
Totals	28	30		25	30	29	20
Between-Subject							
UCLA	6	6		5	6	8	6
UNC	11	11		11	12	14	11
UW	6	6		5	6	6	5
VT	7	7			7	7	NA
Totals	30	30		26	31	35	22

The ASL pulse sequence was not available at the VT MRI system

Table 2

Hardware and software used for MRI acquisitions at each site

Site	Vendor	Model	Software	Coil	T ₁	T ₂ FLAIR	T ₂ [*]	Diff.	BOLD	ASL
UCLA	Siemens	Trio	VB17	12, 32-ch	S1	S2	S3	S4	S5	S6
UNC	Siemens	Trio	VB17	12, 32-ch	S1	S2	S3	S4	S5	S6
UW	GEHC	MR750	DV25	32-ch	G1	G2	G3	G4	G5	G6
VT	Siemens	Trio	VB17	8-ch	S1	S2	S3	NA	S5	S6

Each acquisition is labeled according to ‘GX’ for GE site and ‘SX’, which is used to distinguish the protocols outlined in Tables 3 and 4, which provide respective acquisition protocols utilized on the Siemens and GE vendor platforms

Table 3
Acquisition parameters for each deployed imaging protocol on the Siemens Trio platform

Label	S1	S2	S3	S4	S5	S6
Contrast	MPRAGE	T2 FLAIR	T2*	Diff	BOLD	ASL
Plane	Sagittal	Sagittal	Axial	Axial	Axial	Axial
Slices	176	80	56	60	45	36
Matrix	256 × 256	256 × 256	384 × 240	90 × 90	70 × 70	64 × 64
TE (ms)	2.98	390.00	10.00 [†]	98.00	27.00	13.00
TR (ms)	2300.0	5000.0	45.0	7800.0	2250.0	3204.6
T1 (ms)	900	1800	NA	NA	NA	700
FOV (cm)	25.6	25.6	25.6 × 16.0	24.3	24.5	25.6
Thickness (mm)	1.0	2.0	3.0	2.7	3.5	4.5
Volumes	1	1	1	54	265	109
b-Value	NA	NA	NA	1000	NA	NA
(s/mm ²)				2000		
b-Directions	NA	NA	NA	30	NA	NA
Label Time (ms)	NA	NA	NA	NA	NA	1800.0
Label Delay (ms)	NA	NA	NA	NA	NA	1600.0

All times are in ms. Labels are in accordance with the site definitions identified in Table 2.

[†]:Biopolar multi-echo T2* sequence acquired 4 echoes with an echo spacing of 4.75 ms. The 1st echo is indicated in the table

Table 4
Acquisition parameters for each deployed imaging protocol on the GEHC MR 750 platform

Label	G1	G2	G3	G4	G5	G6
Contrast	BRAVO	T2 FLAIR	T2*	Diff	BOLD	ASL
Plane	Sagittal	Sagittal	Axial	Axial	Axial	Axial
Slices	164	160	70	50	36	36
Matrix	256 × 256	256 × 256	384 × 240	80 × 80	64 × 64	128 × 128
TE (ms)	2.91	65.65	13.53 [†]	67.00	33.00	10.54
TR (ms)	6.62	6500.00	58.70	5250.00	2000.00	4632.00
T1 (ms)	450.0	1913.0	NA	NA	NA	1525.0
FOV (cm)	25.6	25.6	25.6 × 16.0	24.3	25.6	25.6
Thickness (mm)	1.0	2.0	3.0	3.0	4.0	3.0
Volumes	1	1	1	64	180	2
b-Value	NA	NA	NA	1000	NA	NA
(s/mm ²)				2000		
b-Directions	NA	NA	NA	30	NA	NA
Label Time (ms)	NA	NA	NA	NA	NA	1450.0
Label Delay (ms)	NA	NA	NA	NA	NA	1520.0

All times are in ms. Labels are in accordance with the site definitions identified in Table 2.
[†]: T₂* sequence acquired 5 echoes with an echo spacing of 11 ms. The 1st echo is indicated in the table

Table 5

Average CVs across all gray matter, white matter, deep gray matter, and cerebrospinal fluid ROIs for within subject, between site, and between subject comparisons

	T1	T2	FLAIR	T2* - T2	Wt	T2*	MD	FA	REHO	FALFF	rCBF
Gray Matter											
Within Subject	0.052	0.060		0.059		0.100	0.089	0.140	0.052	0.031	0.190
Between Site	0.106	0.157		0.171		0.193	0.149	0.175	0.177	0.076	0.227
Between Subject	0.151	0.156		0.175		0.284	0.218	0.329	0.171	0.081	0.732
Deep Gray											
Within Subject	0.043	0.046		0.048		0.094	0.040	0.064	0.051	0.029	0.224
Between Site	0.049	0.095		0.203		0.172	0.071	0.086	0.149	0.054	0.257
Between Subject	0.058	0.074		0.102		0.222	0.101	0.145	0.144	0.066	0.547
White Matter											
Within Subject	0.039	0.040		0.040		0.050	0.035	0.029	0.050	0.026	0.554
Between Site	0.039	0.069		0.108		0.082	0.032	0.055	0.134	0.048	-3.579
Between Subject	0.038	0.051		0.066		0.115	0.069	0.080	0.134	0.06	0.819
CSF											
Within Subject	0.055	0.100		0.058		0.197	0.132	0.158	0.061	0.037	1.035
Between Site	0.123	0.402		0.203		0.372	0.377	0.221	0.159	0.058	-0.548
Between Subject	0.176	0.342		0.191		0.493	0.259	0.332	0.188	0.086	0.503

Cases where between subject CVs are lower than between site CVs are bolded, and cases where the difference is statistically significant are underlined. Of note, regions where between site CVs are greater than between subject CVs are areas where the measurements are well known to have low signal-to-noise ratios. Negative CVs in rCBF measurements arise from measurement noise in regions of minimal blood flow where the tag images had greater intensity than control images