The Canadian Dementia Imaging Protocol: Harmonizing National Cohorts

Simon Duchesne, PhD,[1,2]* Isabelle Chouinard, MRT,[2] Olivier Potvin, PhD,[2] Vladimir S. Fonov, PhD,[3] April Khademi, PhD,[4] Robert Bartha, PhD,[5] Pierre Bellec, PhD,[6] D. Louis Collins, PhD,[3] Maxime Descoteaux, PhD,[7] Rick Hoge, PhD,[3] Cheryl R. McCreary, PhD,[8] Joel Ramirez, PhD,[9] Christopher J.M. Scott, BScH,[9] Eric E. Smith, MD,[8] Stephen C. Strother, PhD,[10] Sandra E. Black, MD,[9] for the CIMA-Q group and the CCNA group

Background: Harmonized protocols to collect imaging data must be devised, employed, and maintained in multicentric studies to reduce interscanner variability in subsequent analyses.
Purpose: To present a standardized protocol for multicentric research on dementia linked to neurodegeneration in aging, harmonized on all three major vendor platforms. The protocol includes a common procedure for qualification, quality control, and quality assurance and feasibility in large-scale studies.
Study Type: Prospective.
Subjects: The study involved a geometric phantom, a single individual volunteer, and 143 cognitively healthy, mild cognitively impaired, and Alzheimer's disease participants in a large-scale, multicentric study.
Field Strength/Sequences: MRI was perform with 3T scanners (GE, Philips, Siemens) and included 3D T_1w, PD/T_2w, T_2^*, T_2w-FLAIR, diffusion, and BOLD resting state acquisitions.
Assessment: Measures included signal- and contrast-to-noise ratios (SNR and CNR, respectively), total brain volumes, and total scan time.
Statistical Tests: SNR, CNR, and scan time were compared between scanner vendors using analysis of variance (ANOVA) and Tukey tests, while brain volumes were tested using linear mixed models.
Results: Geometric phantom T_1w SNR was significantly ($P < 0.001$) higher in Philips (mean: 71.4) than Siemens (29.5), while no significant difference was observed between vendors for T_2w (32.0 and 37.2, respectively, $P = 0.243$). Single individual volunteer T_1w CNR was higher in subcortical regions for Siemens ($P < 0.001$), while Philips had higher cortical CNR ($P = 0.044$). No significant difference in brain volumes was observed between vendors ($P = 0.310/0.582/0.055$). The average scan time was 41.0 minutes (SD: 2.8) and was not significantly different between sites ($P = 0.071$) and cognitive groups ($P = 0.853$).
Data Conclusion: The harmonized Canadian Dementia Imaging Protocol suits the needs of studies that need to ensure quality MRI data acquisition for the measurement of brain changes across adulthood, due to aging, neurodegeneration, and other etiologies. A detailed description, exam cards, and operators' manual are freely available at the following site: www.cdip-pcid.ca.
Level of Evidence: 2
Technical Efficacy: Stage 2

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Investigators involved in large-scale, multicenter neuroimaging studies face significant harmonization problems, inherent when acquiring data on a host of different scanner platforms. Harmonizing acquisitions matters, as protocol and scanner differences (vendor, model, configuration) will induce systematic biases. Two studies by Schnack et al

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*Address reprint requests to: S.D., Centre CERVO, Institut universitaire en santé mentale de Québec, 2601 rue de la Canardière, F-3582, Québec, QC, Canada, G1J 2G3. E-mail: simon.duchesne@fmed.ulaval.ca

From the [1]Department of Radiology, Université Laval, Québec, Canada; [2]Centre CERVO, Institut universitaire de santé mentale de Québec, Québec, Canada; [3]McConnell Brain imaging Center, Montreal Neurological Institute, McGill University, Montréal, Canada; [4]Image Analysis in Medicine Lab, Ryerson University, Toronto, Canada; [5]Centre for Functional and Metabolic Mapping, Robarts Research Institute, Department of Medical Biophysics, University of Western Ontario, London, Canada; [6]Université de Montréal, Montréal, Canada; [7]Sherbrooke Connectivity Imaging Lab, Université de Sherbrooke, Sherbrooke, Canada; [8]Department of Clinical Neurosciences, University of Calgary, Calgary, Canada; [9]LC Campbell Cognitive Neurology Research, Sunnybrook Research Institute, University of Toronto, Toronto, Canada; and [10]Rotman Research Institute, Baycrest Medical Biophysics, University of Toronto, Toronto, Canada

illustrate this problem. They collected magnetic resonance imaging (MRI) brain scans from volunteers scanned at five research sites with scanners from four different manufacturers running different acquisition protocols. Statistical analyses demonstrated that cerebrospinal fluid / gray matter and gray/white matter contrasts showed an overall significant site effect; a similar conclusion was reached for voxel-based morphometry and cortical thickness analyses.[1,2] In fact, Shinohara et al reported significant remaining systematic biases due to site differences in expert-traced lesion measurements in multiple sclerosis ($P < 0.01$ for both T_1 and T_2 lesion volumes),[3] even *after* ensuring that all sites had a common harmonized protocol. Solutions must therefore be devised to obtain and maintain a validated and calibrated acquisition procedure at all sites, thereby reducing as much as possible this major metrological issue in subsequent analyses on pooled data.

In Canada, a collection of studies centered on dementias were scheduled to start acquiring similar data in the 2013–2016 timeframe. Even though there was a strong focus on Alzheimer's disease (AD) as the most common cause of neurodegeneration, they shared different goals than the by now well-known AD Neuroimaging Initiative (ADNI).[4] Among the differences were the emphasis on non-AD etiologies as well as the study of comorbidities, especially vascular contributions to cognitive impairment and neurodegeneration. In their timeline, it was foreseen that all studies would eventually share, or allow access to, their data. Thus, in order to permit the future comparison and statistical analysis of participants' data between studies, there was an opportunity to devise a common, harmonized process for MRI data acquisition, taking advantage of advances in hardware and software technology. This led to the statement of need for harmonizing *every* pulse sequence across *all* vendors; and conforming to the requirements set forth in the "STandards for ReportIng Vascular changes on nEuroimaging" (STRIVE) report[5] regarding the investigation of cerebral vascular lesions, given the emphasis on vascular comorbidities in the aforementioned studies.

Materials a and Methods

Protocol Design

Several organizations and projects have contributed to the development of this protocol: Canadian Alliance for Health Hearts and Minds[6] (cahhm.mcmaster.ca); the Consortium pour l'identification précoce de la maladie d'Alzheimer – Québec (CIMA-Q) (www.cima-q.ca); the O2 study from the Consortium Québécois sur la Découverte du Médicament (www.cqdm.org); the Medical Imaging Trials Network of Canada – C6 (clinicaltrials.gov/ct2/show/NCT02330510); and the Ontario Brain Institute's Ontario Neurodegenerative Disease Research Initiative[7] (ondri.ca). All authors stem from these projects. Various teleconferences and drafts were exchanged during the 2013–2014 time period to establish the final protocol. The requirements were stated as: 1) comprehensiveness of evaluations; 2) compliance with best practices, eg, STRIVE; 3) possibilities for harmonization across vendors, hardware, and software; and 4) compatibility with existing protocols, eg, ADNI. While it was expected that the protocol be used in centers with 3T scanner strength and 12-channel coils (the most prevalent combination available at all participating centers), operating at 1.5T field strength and with other head coils was to be taken into consideration.

Qualification, Quality Control, and Assurance

The group also needed to define and design procedures for quality control and assurance procedures to deploy, qualify, and maintain quality within a multicentric setting. This procedure was to test for compliance using a geometric object ("phantom") as well as a single individual volunteering for multiple observations across the network (SIMON) testing compatibility between vendors and defining all associated procedures. The geometric phantom was a large vessel containing 125 Lego DUPLO bricks made of ABS plastic (Billund, Denmark) assembled inside a polycarbonate Nalgene 8L container and filled with a water solution of 0.15 mM/L MnCL2 and 2.8 g/L NaCL. Lego DUPLO 234 bricks were chosen for the construction in order to have a phantom that can easily be reproduced across multiple sites with minimal cost and with a high degree of accuracy, as manufacturing tolerances for LEGO bricks are 2 lm.23,24 It further includes a vial of T2-contrast agent (0.0654 mM/L MnCL2 and 2.8 g/L NaCL). SIMON (S.D) was a healthy ambidextrous male volunteer with over 20 years education aged 41 years old at the beginning of the study.

For both the geometric phantom and SIMON, signal- or contrast-to-noise ratio (SNR, CNR) was used as a primary outcome to verify protocol implementation. For the geometric phantom, SNR was defined as the difference in the signal inside and outside a contrast agent-filled vial, divided by the signal outside of the vial. We extracted the bulk of the phantom (ie, filled with the liquid) and then used an adaptation of the median absolute deviation estimator in wavelet domain for Rician noise.[8] CNR for the single individual volunteer was measured using voxel intensities from raw T_1-weighted (T_1w) images with the mean of gray matter (GM) and cerebral white matter (WM):

$$CNR = \frac{(GM\ mean - WM\ mean)^2}{(GM\ variance + WM\ variance)}$$

where subcortical and cortical GM and WM volumes were obtained from the aparc and aseg labels derived from automated segmentation using FreeSurfer (v. 5.3 with default

TABLE 1. General Overview of the Core Protocol: Parameters

Sequence	Scanner model	Matrix	Resolution (mm)	# of slices	FOV (mm)	TR (msec)	TE (msec)	TI (msec)	Angle Flip	Acc	Time (min:sec)
T1w	GE	256 × 256	1.0 × 1.0 × 1.0	180 180	256 × 256	6.7	2.9	400	11	2	4:54
	Philips	256 × 248			256 × 248	7.3	3.3	935	9		6:50
	Siemens	256 × 256		192	256 × 256	2300	2.98	—	9		5:21
PD/T2w	GE	256 × 256	0.94 × 0.94 × 3.0	48	240 × 240	3000	11/85	—	125	2	2:43
	Philips	256 × 254					13/100	—	90		5:24
	Siemens	256 × 256					10/91	—	165		5:17
FLAIR	GE	256 × 256	0.94 × 0.94 × 3.0	48	240 × 240	9000	140	2250	125	1	4:32
	Philips	256 × 224			240 × 210		125	2500	150	2	4:12
	Siemens	256 × 256			240 × 240		123	2500	165		4:05
T2Star	GE	256 × 256	0.94 × 0.94 × 3.0	48	240 × 240	650	20	—	20	2	2:15
	Philips							—		2	4:17
	Siemens							—			3:04
DWI 30 directions	GE	128 × 128	2.0 × 2.0 × 2.0	70	256 × 256	9000	85	—	90	2	5:06
	Philips				256 × 256	9970	101	—			5:47
	Siemens				256 × 256	9400	96	—			5:20
BOLD 300 volumes	GE	64 × 64	3.5 × 3.5 × 3.5	40	224 × 224	2500	30	—	70	2	10:38
	Philips					2110		—			11:09
	Siemens					2110		—			11:11

TR: repetition time; TE: echo time; TI: inversion time; FOV: field of view; Acc: acceleration.
B0 = 3T / Scanners presented: GE: Discovery; Philips: Achieva and Ingenia; Siemens; Tim Trio. Other model exam cards are available on the CDIP website.

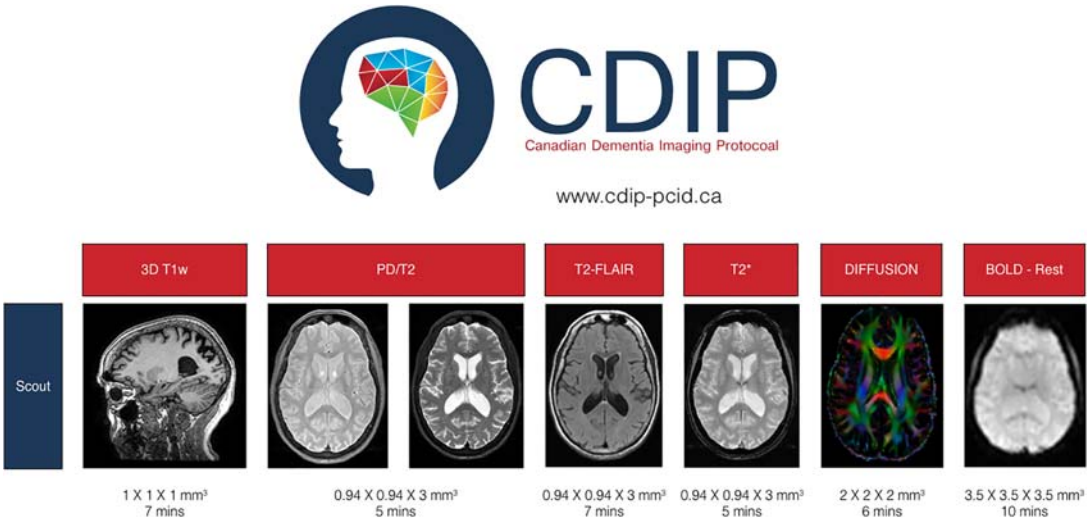

FIGURE 1: Overview of the core protocol

parameters; freesurfer.net). The technical details of FreeSurfer procedures are described in prior publications.[9–14]

In order to compute CNR for T_2w-FLAIR images, the same equation as T_1w was used. However, since there is little contrast between WM and GM classes in T_2w-FLAIR, the first tissue class is called the brain class (which is GM+WM as a whole), and the second tissue class is the cerebrospinal fluid (CSF). In order to compute the mean and standard deviations (SDs) for the brain and CSF tissues, segmentations of these tissues were required. Tissue segmentation was generated using a standardization and segmentation framework for T_2w-FLAIR MRI.[15–17] To ensure that the tissue classes contained pure tissues only, 70% of the middle slices were retained for CNR calculation, ensuring that if the brain extraction algorithm missed any skull at the top or bottom, it would not bias the approach.

For the remaining acquisitions (resting state functional MRI [fMRI] and diffusion MRI), quality control and assurance metrics are dependent on the inherent variability of the outcome of interest. Our group is working on separate articles to report on the stability of the resting state networks across time and vendors,[18] and the comparison of stability in tract reconstruction using two high-dimensional tractography algorithms across vendors (in preparation).

Feasibility

To assess feasibility, the CIMA-Q study (www.cima-q.ca) used the CDIP to scan its entire MRI cohort ($n = 143$) in the time period 2014–2017. Ethics approval was obtained for the CIMA-Q study from the Institutional Review Board of the Institut universitaire de gériatrie de Montréal. Informed consent was obtained from all participants at entry in the study, including SIMON.

Statistical Analyses

All statistical analyses and figures were conducted in python using SciPy,[19] StatsModels,[20] and Seaborn[21] modules. Analyses of variance (ANOVAs) and Tukey post-hoc tests were conducted on all measures to compare between scanner vendors, except volumetric data, which were examined using a linear mixed model with site as a within factor.

Results

Protocol Design

The CDIP is composed of two parts: the first, mandatory, is the core protocol, and is described herewith. The second, optional, consists of site-specific add-on acquisitions. Parameters for each one of these sequences have been harmonized across the three main MRI vendors: General Electric Healthcare (GE, Milwaukee, WI), Phillips Medical Systems (Philips, Best, Netherlands), and Siemens Healthcare (Siemens, Erlangen, Germany). Repetition time (TR), echo time (TE), and other parameters were all chosen to obtain images of similar quality in terms of contrast and resolution. The complete list of parameters is available on the CDIP main website (www.cdip-pcid.ca).

The core protocol includes (Table 1, Figure 1):

1) a 3D isotropic T_1w scan for assessing fine anatomical detail and brain atrophy (voxel size = $1.0 \times 1.0 \times 1.0\,mm^3$) and an acceleration factor of 2 (Siemens: MP-RAGE-PAT: 2; GE: IR-FSPGR-ASSET 1.5; Philips: TFE-Sense: 2);
2) an interleaved proton density/T_2-weighted (PD/T_2w) image for reliable skull stripping and assessment of deep gray structures, with resolution $0.9 \times 0.9 \times 3\,mm^3$, fat saturation, and an acceleration factor of 2;
3) a fluid attenuated inversion recovery (T_2w-FLAIR) image for quantification and assessment of white matter

TABLE 2. Characteristics of Scanner Sites for the CIMA-Q Study Participants

Site	Scanner model	Total scan time in minutes (mean ± SD)	Age (mean ± SD)	Women (%)	Number of participants per group			
					CON	SCI	MCI	AD
BIC	Siemens, TrioTim	41.3 ± 4.0	74.2 ± 6.2	58	6	11	8	6
CHUS	Philips, Ingenia	41.7 ± 3.5	71.8 ± 5.3	55	5	12	1	2
CINQ	Philips, Achieva	42.2 ± 1.5	70.7 ± 4.3	62	5	9	6	1
Douglas	Siemens, TrioTim	40.3 ± 2.3	71.9 ± 4.3	65	1	11	3	2
IUGM	Siemens, TrioTim	43.8 ± 1.8	75.5 ± 5.8	63	13	24	12	5
All	—	41.0 ± 2.8	73.6 ± 5.8	67	30	67	30	16

AD: Alzheimer's disease. BIC: McConnell Brain Imaging Centre. CHUS: Centre hospitalier universitaire de Sherbrooke. CINQ: Consortium d'imagerie en neurosciences et santé mentale de Québec. CON: healthy controls. Douglas: Institut universitaire en santé mentale Douglas. IUGM: Institut universitaire de gériatrie de Montréal. MCI: mild cognitive impairment. SCI: subjective cognitive impairment.

hyperintensities (WMH), with resolution 0.9 × 0.9 × 3 mm^3, fat saturation, and an acceleration factor of 2;
4) a T_2^* gradient echo for the identification of microbleeds, with resolution 0.9 × 0.9 × 3 mm^3 and acceleration factor of 2;
5) a diffusion-weighted image (DWI) for the assessment of white matter microstructural integrity and connectivity, with resolution 2.0 × 2.0 × 2.0 mm^3, a minimum of 30 uniformly distributed directions with $b = 1000$ s/mm^2,[22] (Siemens: EPI-PAT 2–30 directions; GE: EPI-Asset 2–30 directions; Philips: EPI-Sense 2–32 directions; we use the vendor-provided directions set), and acceleration factor of 2. The acquisition asks for three b_0 images, one at the beginning, one in the middle, one at the end; and
6) a task-free, eyes open (resting state) fMRI for the assessment of functional networks and pathways using a T_2^*-weighted blood oxygen level-dependent (BOLD)-sensitive sequence, with resolution of 3.5 × 3.5 × 3.5 mm^3, TR = 2110 msec (GE: 2500 msec), and 300 volumes over time.

The protocol instructions state that the following sequences are all positioned in an identical oblique axial orientation, derived from the sagittal T_1w: PD/T_2-Dual Echo, T_2w-Flair, T_2^*, DTI, and connectivity fMRI.

Qualification, Quality Control, and Quality Assurance

To fully comply with the CDIP entails a site conforming to a three-step procedure that was developed to ensure quality acquisitions across sites and time. The first step is to be successfully qualified. Qualification involves 1) ensuring that the protocol is properly established on the local platform; and 2) acquiring two scans in order to judge the quality of the acquisitions, one of the geometric phantom and one of SIMON. Once acquired, the images are reviewed for quality and conformance to the CDIP acquisition parameter values, and, if deemed acceptable, the site is then qualified. This review verifies the following: anonymization, adherence to protocol parameters, coverage, and presence of artifacts.

The second step is to maintain quality control through time. For this purpose, the same elements are used: 1) the

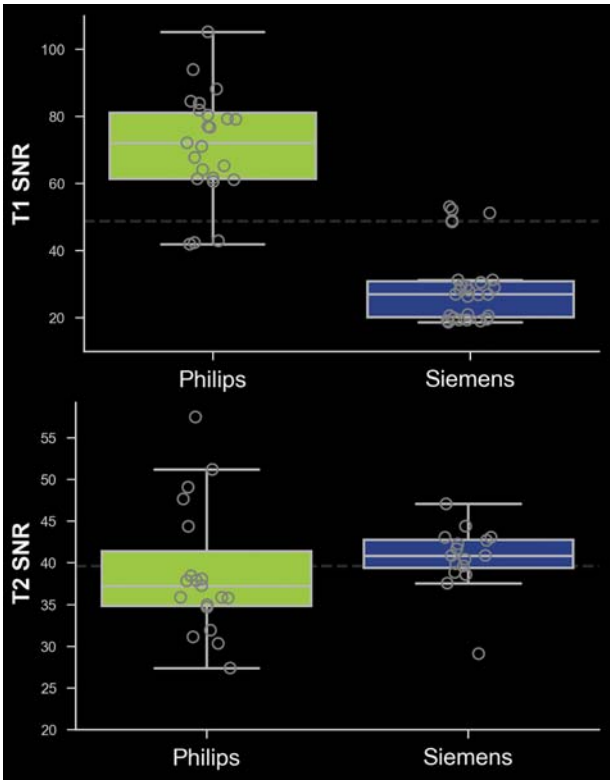

FIGURE 2: Boxplot showing SNR ratio for T_1 ($n = 50$) and T_2 ($n = 35$) weighted MRI of the geometric phantom according to scanner model. Gray circles represent each scan and dashed gray line is the mean. Note that the higher five circles for Siemens T_1 and the lower one for Siemens T_2 are from the Prisma fit.

TABLE 3. Characteristics of CDIP SIMON Scan Sites

Site	Vendors	Scanner model	Number of scans
CHUM	Philips	Achieva	2
CHUS	Philips	Ingenia	3
Cuban Neurosciences Center	Siemens	Allegra	2
Douglas	Siemens	TrioTim	3
Foothills Medical Center	GE	Discovery MR750	1
IUGM	Siemens	TrioTim	7
IUGM	Siemens	Prisma fit	4
McConnell Brain Imaging Centre	Siemens	TrioTim	6
Perform Center	GE	Discovery MR750	2
Peter S. Allen MR Research Center	Siemens	Prisma	1
Quebec	Philips	Achieva	7
Robarts Research Institute	Siemens	Prisma fit	1
Royal University Hospital	Siemens	Skyra	1
Sunnybrook Research Center	Siemens	Prisma	1
UBC	Philips	Intera	1
West Coast Medical Imaging – Uptown	GE	SIGNA Pioneer	1

CHUM: Centre hospitalier universitaire de Montreal. CHUS: Centre hospitalier universitaire de Sherbrooke. Douglas: Institut universitaire en santé mentale Douglas. IUGM: Institut universitaire de gériatrie de Montréal. UBC: University of British Colombia.

geometric phantom is to be scanned once monthly; and 2) SIMON should be scanned at a minimum every second year at each CDIP site. Each acquisition is to be reviewed for ongoing compliance with the protocol and quality.

The last step is to maintain quality assurance, which pertains to the quality of the individual participant's scans. At scan time, technologists should ensure that the protocol is followed, and that images are free of artifacts. Any discrepancy in following the protocol should be reported. To facilitate traceability, it is therefore recommended that a central data repository be used. This further allows for a centralized review of each scan by a highly trained individual (eg, board-certified MR technologist in some jurisdictions) for quality assurance, which should verify the same items through time (anonymization, adherence to protocol parameters, coverage, and presence of artifacts).

In this way, each participating study will ensure that the harmonized protocol is employed, that scans are acquired at the highest possible quality level, and that errors are caught in a timely fashion and immediately corrected. Centralized reading may also allow for a review for incidental findings.

As mentioned, the CIMA-Q study was chosen as the pilot study for the protocol. In total, seven sites were qualified for the study, with all vendors being represented (Table 2). All sites were qualified in 2014; however, due to constraints on the clinical recruitment, only five of those sites scanned participants. Each of those five sites was therefore issued a geometric phantom, which is now being scanned each month and reviewed for stability. Unfortunately, this did not include a GE scanner.

Figure 2 shows the results of the geometric phantom scans in terms of SNR for T_1w ($n = 50$) and T_2w ($n = 35$). An ANOVA ($P < 0.001$) revealed a significantly higher T_1w SNR for Philips (mean: 71.4 ± SD: 15.7) compared to Siemens scanners (29.5 ± 11.0). No significant difference was observed between vendors for T_2w SNR (Philips: 32.0 ± 16.2, Siemens: 37.2 ± 13.9, $P = 0.243$).

SIMON, on the other hand, has been scanned 43 times following the CDIP protocol across 15 sites using 16 different scanners, including three GE scanners (Table 3), as part of the CIMA-Q study as well as the ongoing research endeavors (especially the Canadian Consortium on Neurodegeneration in Aging [CCNA] www.ccna-ccnv.ca). All of these scans have been used to verify this protocol.

Figure 3 displays CNR for SIMON T_1w images ($n = 43$). The mean CNR for T_1w images were 1.50 (SD: 0.33) and 6.89 (0.88) for subcortical and cortical areas, respectively. ANOVAs indicated significant differences for subcortical (F: 9.81, $P < 0.001$) and cortical (F: 4.5, $P = 0.017$) CNR across vendors. Siemens had a significantly higher subcortical CNR (mean: 1.65 ± SD: 0.34) than

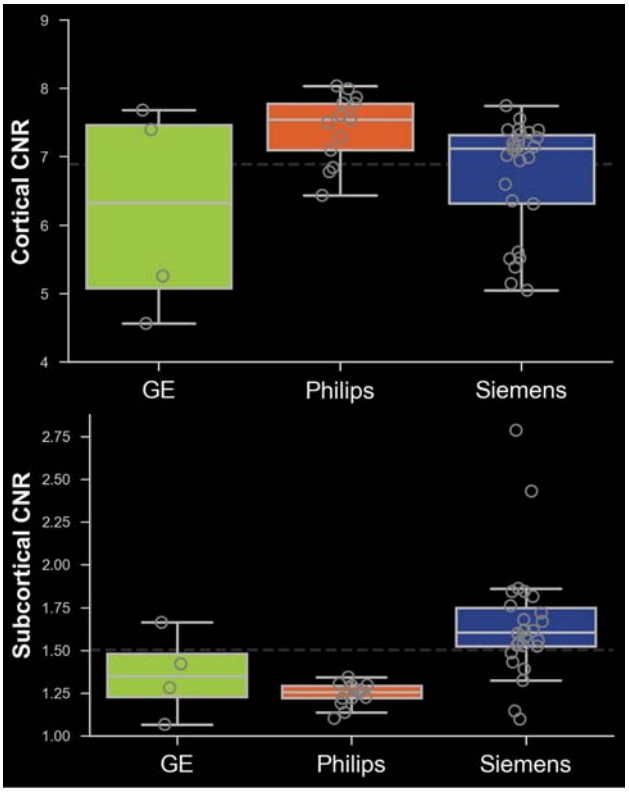

FIGURE 3: Boxplot showing SIMON T_1w CNR for cortical and subcortical brain areas according to scanner vendors. Gray circles represent each scan and dashed gray line is the mean. Note: The two subcortical Siemens circles higher than the other are from two measurements of the same, unique Siemens Allegra system at the EEE site with an 8-channel coil.

Philips (1.24 ± 0.07; $P < 0.001$), but not GE (1.36 ± 0.22; $P = 0.138$), while Philips had significantly higher cortical CNR (7.42 ± 0.48) than both Siemens (6.72 ± 0.81; $P = 0.044$) and GE (6.22 ± 1.34; $P = 0.039$). When interpreting these results, it is important to note that only four GE single individual volunteer scans were available.

Figure 4 shows the CNR for SIMON FLAIR images ($n = 42$). The mean CNR for T_2w-FLAIR images (F: 50.8, $P < 0.001$) was significantly lower for Siemens scanners (335.9 ± 201.0) compared to Philips (945.1 ± 69.7; $P < 0.001$) and GE scanners (938.1 ± 300.6; $P < 0.001$).

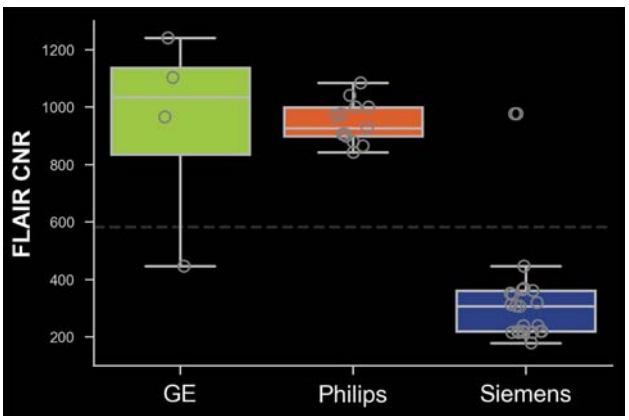

FIGURE 4: Boxplot illustrating T_2w-FLAIR CNR for SIMON. Gray circles represent each scan and dashed gray line is the mean.

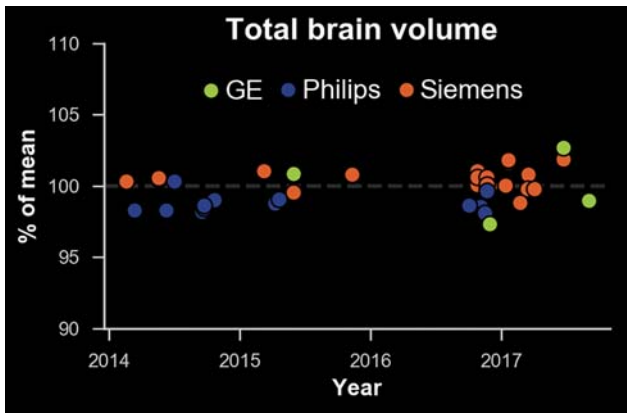

FIGURE 5: Total brain volume from SIMON CDIP scans according to vendors across time. Dashed gray line represents the mean.

Figure 5 shows the variability of total brain volume across SIMON CDIP scans. The range of total brain volume across scans was 1,115,713–1,177,228 mm^3, which was not invariant but minimal. In percentage of the mean of all scans, the range was between 97.3% and 102.7%. No significant difference of total brain volume between vendors was observed (Philips/GE: $P = 0.310$; Siemens/GE: $P = 0.582$; Siemens/Philips: $P = 0.055$).

Feasibility

By design, half of CIMA-Q participants, if MRI-compatible, were sent for scanning and completed the protocol. In total, 143 study participants were scanned, with a mean age of 73.6 years. Of these participants, 30 were cognitively health controls, and 67% were female (see Table 2 for full details).

Only two subjects did not complete the protocol within a session: one exited before completing the resting state acquisition, while another completed the protocol in two sessions over as many days. Average total scan time

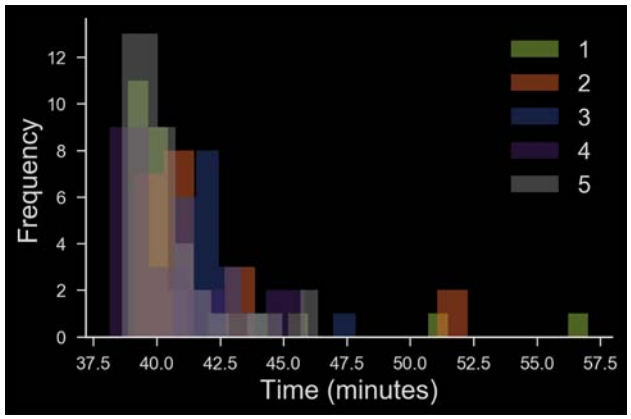

FIGURE 6: Distribution of total scan time of the CDIP according to scan sites.

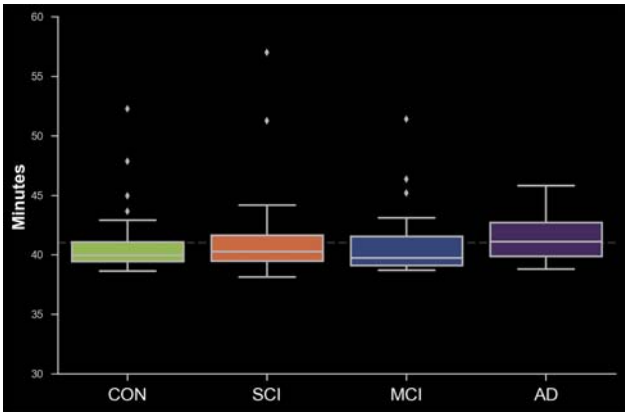

FIGURE 7: Total scan time of the CDIP according to groups. CON: controls, SCI: subjective cognitive impairment, MCI: mild cognitive impairment, AD: Alzheimer's disease. Diamonds represent outliers defined beyond the 1.5 interquartile range of the low and high quartiles extending plot whiskers.

(defined as the time between the start of the first CDIP sequence to the end of the last core protocol sequence, separated from any additional sequence that may be performed) across sites was 41.0 minutes (SD: 2.8, range: 38.1–57.0), which was close to the mean total scan time for 29 scans of SIMON (mean: 39.9 minutes, SD: 2.1, range 37.0–43.6). As shown in Figs. 6 and 7, scan length was not significantly different between sites (F: 2.22, $P = 0.071$) and groups (F: 0.26, $P = 0.853$), respectively.

Visual review of all scans was performed by a trained technologist (I.C.) and no scans were excluded at quality control due to artifacts. Parameter compliance with the CDIP was automatically controlled upon uploading of the data in the LORIS databasing system.[25] In this study group, nine readings for incidental findings were requested, of which only three (2% of total scans) revealed an actual pathology necessitating a clinical follow-up.

Discussion

The harmonized Canadian Dementia Imaging Protocol has been developed to suit the needs of a number of co-occurring Canadian studies. The protocol is designed to ensure the acquisition of high-quality MRI data for the measurement of brain anatomical, vascular, and functional changes across adulthood, due to aging, neurodegeneration, and other etiologies. According to the STRIVE recommendations, it is especially designed to properly assess neuroimaging markers of cerebrovascular disease.

The need for harmonization has been identified for a number of years. Bartzokis et al had shown early on how clinically available MRI methods (2D acquisition; inversion recovery and calculated T_2 images; 3 mm contiguous slices) that could optimize image contrast, quality, and resolution, together with standardized positioning protocols, could maximize the in vivo accuracy (test–retest reliability) of brain volume measurements.[26] Quality control and assurance using centralized database tools has also been around for more than a decade; for example, with the LORIS system built for the National Institutes of Health (NIH) MRI study of normal brain development.[27]

Within the field of dementias, ADNI (www.ADNI-info.org) made a significant contribution when proposing harmonized neuroimaging procedures for both MRI and positron emission tomography. These were implemented, starting in 2005, across more than 50 sites in Canada and the U.S.[28] Thus, the ADNI project has been instrumental in pushing the concept of harmonization forward as multiple studies worldwide have adopted their approach and/or standards. This widespread acceptance rests on the early decision to share both the acquisition protocol and the data openly with the general scientific/clinical research community. The CDIP follows in these footsteps.

Compatibility with other protocols such as ADNI is clear, insofar as many of the parameters chosen were largely based on the Jack et al protocol,[4] except in cases where enhancements were possible and desired. This was especially true of acceleration, now available for multiple contrasts. Thus, overall and o-going compatibility including with ADNI-3[29] is expected but remains to be thoroughly tested.

The protocol is of course immediately applicable to any other study using similar vendor's hardware/software combinations. While complete CDIP compliance requires following all steps, it is understood that some investigators may choose to implement only a select number of the harmonized sequences for their own studies.

There were no issues of compliance, as the 143 MRI compatible CIMA-Q participants selected for this procedure completed all acquisitions at all sites. The sole exception, a participant with mild cognitive impairment, did not complete the connectivity fMRI sequence, but fulfilled all other sequences. It was found that the protocol was well tolerated for an aging population, the individuals in the study ranging from 65–84 years old (67% females; mean age = 73.6; SD = 5.8), with no aborted procedure. The total protocol time was sufficiently short to allow for the inclusion of other site-specific acquisitions, beyond those required by the core group. For example, the CIMA-Q study added an fMRI delayed recall task better suited to the study of early memory decline due to Alzheimer's disease.

The protocol is already in use as the core protocol for the CIMA-Q study (143 participants; four sites), and the Ontario Brain Institute's Ontario Neurodegenerative Disease Research Initiative (~600 participants, start date: April 2013; 11 sites). It serves as the basis for the core protocol of the Canadian Alliance for Health Hearts and Minds, whereas the core protocol (~7000 participants) includes both T_1w and FLAIR acquisitions, and the extended version is the complete CDIP (~1500 participants; eight sites) (start date: 2014). Additionally, it has been used in the O2 study

from the Consortium Quebecois de découvert de medicament, the Medical Imaging Trials Network of Canada – C6, and by groups such as the Toronto Dementia Research Alliance. It has been deployed at more than 19 sites in Canada as part of the CCNA (start date: 2017), and has now reached beyond Canadian shores at the Cuban Neuroscience Center's Human Brain Mapping Unit. Together, these studies plan on recruiting well over 10,000 participants, across adulthood and a range of cognitive conditions.

The protocol was designed in 2013, and at the time newer scanning options were not available; nor were all options available across vendors, and even if they were, not all sites could upgrade or acquire the required software packages to perform state-of-the-art acquisitions. The CDIP was intended as a multicentric protocol that could be applied across the country, and therefore tended to revert to a lower-common-denominator approach. It is different from other protocols that may cater by design to a smaller number of high-end, research-dedicated scanners, and therefore elect to choose the state-of-the-art in image acquisition. This underlies some of the choices, eg, the number of directions for diffusion imaging, set at the vendor's default; or 3D acquisitions for T_2w and T_2w-FLAIR scans.

On-site MR technicians are asked to verify the quality for all acquired sequences, including fMRI and DWI. However, the large number of images slices and brain volumes collected during fMRI and DWI sequences make it difficult to detect between slice or volume motion issues visually on a scanner. While some vendors (eg, GE BrainWave RT) do provide an estimation of 3D motion in mm during the acquisition, setting a specific threshold of acceptable motion is difficult.

Offline postprocessing methods are widely available for both eddy current and motion correction; the postprocessed images can be reviewed for uncorrected motion issues, which we have done separately in this work. All SIMON validation data were run through postacquisition rigid body motion estimation, and these scans were found of appropriate quality. In group analyses however, volumes with excessive motion are typically excluded, with some requirement on the minimal number of remaining timepoints (100 or more). The specific choice of motion threshold and number of required volumes after exclusion will vary depending on the question of interest, as older subjects and certain patient populations move more and may require less stringent thresholds than healthy young adults. Detailed reporting on these quality metrics will be included in the CDIP fMRI validation article, currently in preparation.

A website has been established (www.cdip-pcid.ca) to collect all information regarding the protocol. Dissemination is free and only requires acknowledging the current effort. On the site, visitors can find 1) the full protocol, with all harmonized parameters detailed for each vendor; 2) exam cards or PDF output for all tested scanners to date from the three major vendors, ready for upload in a similar machine; and 3) a complete operator manual for MR technologists, complete with descriptions of the procedure to scan the geometric phantom, SIMON, and any study participant. It also includes a list of common acquisition artifacts with sample images, and pointers to help individual sites in overcoming any quality issues they may encounter.

Slice timing is one area of harmonization that we failed to catch when designing the protocol, and was not specified. To make matters worse, it is not consistently stored in the DICOM header, if at all, and even when it is stored, the interpretation may be vendor-specific (eg, interleaved) and interact with the way data are stored as a matrix. Future revision of the protocol will likely be revised to sequential ascending, as it is consistently implemented across vendors and software versions. Interleaved sequences are defined differently by different vendors, and introduce an additional risk of error.

In conclusion, the protocol is designed to evolve, as scanning experience, advances in acquisition hardware/software, and new research needs invariably surface. Yet any change will be accepted only if it both maintains harmonization (longitudinally, and in a multicentric setting) and reaches the highest imaging quality possible. Other acquisitions are being discussed (eg, arterial spin labeling); a comprehensive and evidence-based upgrade strategy must be devised; and further, we aim to propose a web-based system using the data collected in this study to automatically test the aforementioned quality metrics for both geometric phantom and SIMON, offering statistical comparisons to quantify compliance with the protocol. Finally, SIMON data should be released to the MR community as a dataset useful for testing longitudinal stability of image-processing algorithms. This dataset keeps on expanding as the quality control procedure for studies CIMA-Q and CCNA remain active and are envisioned to continue until 2024 at the very least.

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