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The Canadian Dementia Imaging Protocol: a standardized tool for the study of neurodegeneration and aging

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TARGET AUDIENCE – Researchers in neurodegeneration and aging; Researchers in neuroimaging; Radiologists and MR Technicians

PURPOSE – A wealth of studies on *magnetic resonance imaging* (**MRI**) and positron emission tomography has led the U.S. *National Institutes of Aging* to incorporate biomarkers measured with these approaches in the research diagnostic criteria for dementia[1]. However, before using neuroimaging in a clinical setting or multi-centric studies, stringent protocols for acquisition standardization, quality control and assurance must be deployed in order to improve validity, reproducibility and reliability of the acquired data. Similarly, the processing of images after acquisition must be performed in a controlled environment to ensure proper extraction of salient information (e.g. hippocampal volumes; PET FDG metabolism, diffusion metrics) that are now required in the criteria. The *Alzheimer's Disease Neuroimaging Initiative* (**ADNI**)[2] has made huge strides in that direction by implementing and coordinating such procedures at more than 55 sites in the United States and Canada for MRI[3] and PET scanners[4]. Other similar endeavors have since followed worldwide[5]. In every case, the establishment of such a network was shown possible and worthwhile, but represented a non-trivial effort.
A group of physicists, physicians and research coordinators from across Canada, representing a multitude of projects on neurodegeneration and aging, including the Canadian Alliance for Healthy Hearts and Minds (CAHHM; http://fhs.mcmaster.ca/chanchlani/cvcd.html); the Consortium d'Identification de la Maladie d'Alzheimer – Québec (CIMAQ; cima-q.ca); the O2 study from the Consortium Québécois de Découverte du Médicament; the Medical Imaging Trials Network of Canada – C6 (MITNEC; mitnec.org); and the Ontario Brain Institute's Ontario Neurodegenerative Disease Research Initiative (ONDRI; braininstitute.ca), wished to establish a common acquisition, quality control and assurance protocol for purposes of data sharing and results amplification. One major objective was to emphasize the study of vascular co-morbidity and other non-AD etiologies; a second objective was to ensure the clinical applicability of the protocol. Given these emphases, the capacities of new generation scanners, and advances in image acquisition, a new acquisition protocol was needed.

METHODS – Consensus conferences from the investigators of the aforementioned studies were held to develop the *Canadian Dementia Imaging Protocol* (**CDIP**). Rooted in previous protocols such as ADNI and STRIVE[6], it incorporates an acquisition protocol (i.e. specific sequence parameters, harmonized across original equipment manufacturers) as well as a procedure following these steps: (a) site registration; configuration management and tracking is a significant component of quality control and assurance. Each site will be required to register with its parent study. Data regarding current capabilities (e.g. strength, coil) will be collected and maintained, especially through major and minor upgrades to hardware and/or software. Additional quality control will be required after any upgrade that is deemed to have an impact on image quality; (b) site qualification: tests must be performed to qualify a new site, or requalify a site after a major upgrade. These tests include scanning of a geometric phantom, and where possible a human phantom, according to the acquisition protocol; (c) site quality control: to ensure scanner stability and scan quality throughout studies, each site is required to perform monthly quality control scans on the geometric phantom; and (d) site quality assurance: to ensure proper acquisition of data, each subject scan should be individually reviewed for conformity to the acquisition protocol, absence of artefacts, and general image quality.

RESULTS – The protocol includes a series of advanced imaging sequences with high utility across many disease states including but not limited to stroke, dementia, traumatic brain injury, amyotrophic lateral sclerosis and Parkinson's disease. The acquisition protocol includes a high-resolution 3D isotropic T1-weighted scan for assessing fine anatomical detail, an interleaved proton-density/T2 weighted image for reliable skull-stripping and lesion assessment of deep grey structures, a fluid-attenuated inversion recovery image for quantification and assessment of small vessel disease (e.g. white matter hyperintensities), a T2-star gradient echo for identification of microbleeds, >30 directions diffusion MRI to assess white matter diffusion metrics, and resting state blood oxygen level dependent functional MRI for assessment of networks and functional pathways. Parameters have been harmonized across three major vendors (GE Healthcare; Philips Medical Systems; Siemens Healthcare). A single phantom has been selected (LEGO phantom; vsfc.ca). The complete protocol has been deployed at six sites in Quebec as part of CIMAQ and O2; nine sites in Ontario as part of ONDRI; and three other Canadian sites as part of the CAHHM. Compliance is being measured, but tolerability seems acceptable for the targeted population, as the total scan time, including set-up and inter-acquisition calibration, is below 45 minutes. Statistical analysis of the reduction of inter-site variance is being conducted for volumetry and diffusion tensor imaging. Qualitative results of resting state fMRI are given in Figure 1.

DISCUSSION AND CONCLUSION – The need for an updated protocol able to cover a larger scope of primary and secondary morbidities is being addressed by the CDIP. The acquisition design incorporates a core protocol detailed above, and allows for the addition of other acquisitions. While arterial spin labeling for the measurement of regional cerebral blood flow is not part of CDIP, it is used as an add-on for other cohorts such as O2; similarly, CIMAQ is adding a delayed recall fMRI task. Further add-ons are planned to specifically address certain pathologies, e.g. iron imaging in Parkinson's disease. Several other organizations and projects have already committed to adoption of this protocol, notably the Toronto Dementia Research Alliance and the upcoming Canadian Consortium for Neurodegeneration and Aging. Thus, by using the CDIP, these studies will be able to share common core acquisitions, representing a tremendous step forward in the collection and exploitation of significant sample sizes. Widespread usage of CDIP is encouraged: complete parameters, exam cards, terms of use and required acknowledgments are available on www.cdip-pcid.ca.

REFERENCES – 1. McKhann GM et al.,2011; 2.Mueller SG et al., 2005; 3.Jack CR et al. 2008; 4.Jagust WJ et al. 2010; 5.Carrillo MC et al. 2012; 6.Wardlaw JM et al., 2013.

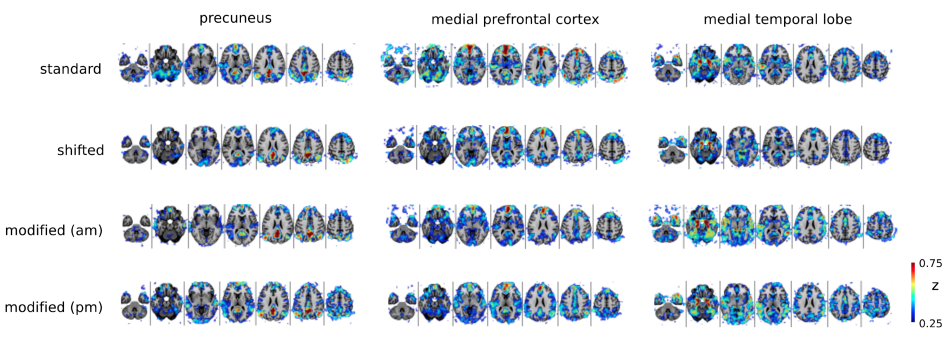

Figure 1 – Qualitative evaluation of reproducibility for BOLD connectivity in functional MRI ("resting state"). Results are presented for the same individual on one scanner in the initial protocol; with rsfMRI early in the sequence, to reduce sleepiness; when scanned first in the morning; and after a full day of scanning. Reliability is strong across major networks, with correlations of 0.61 (precuneus), 0.62 (prefrontal) and 0.58 (medial temporal). Further statistical testing across vendors and sites in on-going.