STRUCTURAL NEUROIMAGING IN COGNITIVE IMPAIRMENT

ABSTRACT
Structural neuroimaging with CT or MRI in the assessment of people with cognitive impairment has traditionally been used to rule out potentially treatable/reversible causes of cognitive impairment. However, over the last decade, clinical neuroimaging has been used to rule in pathology, to refine the differential diagnosis by identifying subclinical infarcts, to quantify white matter changes and to monitor progression of atrophy. Standardization of MRI sequence acquisition across MRI platforms has facilitated large multi-centre longitudinal cohort studies including the Alzheimer Disease Neuroimaging Initiative (ADNI) and like projects. Longitudinal measurement of signature regions affected by Alzheimer Disease has improved the sensitivity and specificity in differentiating between “normal” and “dementia”. As well, the prediction of progression from mild cognitive impairment (MCI) to dementia continues to improve. For clinical trials, MRI is being used to select subjects who are more likely to meet the new criteria for Alzheimer Disease. MRI can be used to enrich a study sample by identifying people who have MCI that are more likely to progress. Safety in clinical trials with compounds purported to be disease modifying is monitored with repeated MRI after each treatment to detect amyloid-related imaging abnormalities, (ARIA)-E and ARIA-H, and development of new micro-bleeds or hemorrhage. This review begins with the recommendations on structural neuroimaging from the Third Canadian Consensus Conference for the Diagnosis and Treatment of Dementia (CCCDTD) 2006 and considers the evidence for structural neuroimaging in family practice, specialist memory clinics, clinical trials and dementia research over the last 6 years. New recommendations are proposed for the clinical neuroimaging of people with cognitive impairment by Canadian physicians in family practice and cognitive specialists in memory clinics.

INTRODUCTION
The CCCDTD 2006 supported 3 recommendations on structural neuroimaging for patients being assessed for dementia, managed with dementia, or participating in clinical trials.

1. There is fair evidence to support the selective use of CT or MRI scanning in the work-up for dementia per 1999 guidelines (Grade B, Level 2).
2. There is fair evidence to support use of structural neuroimaging to rule in concomitant cerebrovascular disease that can affect patient management (Grade B, Level 2).
3. There is fair evidence to support the use of structural neuroimaging to track the progression of AD in clinical trials, especially if the morphometry is combined with neuropsychological testing (Grade B, Level 2). (Ref. Chow 2007)

The indicators for head CT or MRI as stated from the 1999 CCCDTD were:
A cranial CT scan is recommended if one of more of the following criteria are present:
- Age younger than 60 years
- Rapid (e.g., during 1 to 2 months) unexplained decline in cognition or function
- “Short” duration of dementia (less than 2 years)
- Recent/significant head trauma
- Unexplained neurologic symptoms (e.g., new onset of severe headache or seizures)
- History of cancer (especially in sites and types that metastasize to the brain)
- Use of anticoagulants or history of a bleeding disorder
- History of urinary incontinence and gait disorder early in the course of dementia (as might be found in normal pressure hydrocephalus)
- Any new localizing sign (e.g., hemiparesis or a Babinski’s reflex)
- Unusual or atypical cognitive symptoms or presentation (e.g., progressive aphasia)
- Gait disorder
(Ref. Chow 2007)

METHODS
The literature review used Pub Med, including articles in English, using the terms dementia, Alzheimer Disease, mild cognitive impairment and magnetic resonance imaging and structural magnetic resonance imaging between January 2006 and January 2012. The search identified 416 papers. A separate search used the same parameters for review papers to identify recent evidence based reviews and yielded 63 papers. A 3rd search with the same strategy using head CT instead of MRI yielded 6 papers.

HEAD COMPUTERIZED TOMOGRAPHY (CT)
For the initial assessment of patients presenting with symptoms of progressive memory loss or dementia, guidelines from several countries indicate that structural neuroimaging with CT or MRI is appropriate (Knopman 2001, Musicco 2004, Scottish Intercollegiate Guideline Network
2006, Feldman 2008 CMAJ ) Hort 2010. None of the guidelines differentiate between family physician practice or specialist memory clinic as to whether head CT or MRI is preferred. The usefulness of the Canadian consensus neuroimaging guidelines (Patterson 1999) have been evaluated in a memory clinic (Sitoh 2006). The guidelines would not have missed any space occupying lesions but in the 210 patients would have missed 26 of 120 strokes.

Space occupying lesions, usually neoplasms or subdural hematomas, can be detected and they may present with progressive cognitive impairment they are uncommon estimated at 3.3% (Sitoh 2006) or 3.1% (Freta 1998). In the elderly, following one or more falls, subacute or chronic, single or bilateral, subdural hematomas or intracranial epidural hematomas can also cause cognitive impairment or worsening of established cognitive impairment. (E Ishikawa 2002, A Hamlat 2005). The mini mental state examination score and functioning may improve in half of people with existing dementia after surgical drainage (E Ishikawa 2002).

The use of head CT in dementia has recently been reviewed describing its use in routine clinical investigation and in research (Pasi 2011). Head CT imaging takes less time per subject at a lower cost per scan and requires less technical skill than MRI. Claustrophobia, cardiac pace makers, head and neck iron containing tattoos, and iron filings in the eye are contra-indications for MRI that can be accommodated by head CT. As well, head CT scan is more widely available including in smaller community centres in Canada. For restless patients who may only lie still for a short period to rule out a subdural hematoma, head CT scan is more likely to yield a readable scan. A systematic review of Neuroimaging in Dementia reported that in 1.9% to 10.4% of cases did CT reveal causes of dementia with only some being potentially treatable (Gifford 2000).

**STRUCTURAL MAGNETIC RESONANCE IMAGING**

Since its introduction 30 years ago, Structural Magnetic Resonance Imaging has become a powerful research modality to image, in vivo, the progression of neuro-degenerative diseases, in particular Alzheimer's Disease (AD). Alzheimer’s Disease being the most prevalent and well characterized dementia pathologically, has undergone the greatest scrutiny. Several recent review papers on SMRI in Alzheimer’s Disease have been published (M Wattjes 2011, G Frisoni 2010, C Jack 2011), with broader reviews on MRI in Alzheimer's Disease (S Lehéricy 2007),
and neuroimaging in Dementia (O’Brien 2007, M Tartaglia 2011) and neuroimaging in cognitive impairment (Small 2008).

The characteristic neuro-pathological progression described by Braak and Braak (Ref. Acta Neuropathol 1991), typically results in associated atrophy of the anterior parahippocampal gyrus, hippocampus, amygdala followed by the temporal, parietal and frontal association sub-regions. Atrophy of the medial temporal lobe was initially measured by MRI semi-quantitatively using visual rating scales comparing normal elderly and people with probable AD (Ref. Scheltens 1992). Visual rating scales are still valid and can be used in clinical settings where MRI is readily available. Manual tracing to quantify hippocampal volume and, thereby, atrophy when repeated over time, is labour and time intensive (Ref. Jack 1997). However, manual tracing remains the research gold standard for hippocampal volume measurement (Ref. Frisoni 2011). Early cross-sectional and longitudinal approaches to measure atrophy conducted by single research groups with relatively small samples have been reviewed (Ref. Atiya 2003). More recently a prospective SMRI study with atrophy correlation confirmed that medial temporal lobe atrophy differentiates Alzheimer’s Disease from dementia with Levy bodies and vascular cognitive impairment (Burton Brain 2009).

Alzheimer’s Disease Neuroimaging Initiative

Structural neuroimaging in mild cognitive impairment (MCI) and AD took a major step forward in 2004 with the funding and start of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (Ref. Weiner 2010). As the core imaging modality, structural MRI is combined with PET, CSF and blood biomarkers in this longitudinal research study of elderly controls, subjects with MCI and subjects with AD. ADNI recognizes, but is not dependent on, the amyloid cascade hypothesis. The hypothesis begins with progressive accumulation of amyloid (Aβ) in the brain followed by hyperphosphorylated tau protein, loss of synaptic function, neuro-degeneration, neuronal loss and atrophy, cognitive changes and behavioural changes.

Key to the advances from ADNI has been standardization and validation of structural MRI acquisition across the most common clinical research MRI platforms at 1.5 and 3 Tesla magnetic field strengths. Three factors have been important for the success of ADNI. Firstly, with standardization of MRI image acquisition, consistent images were acquired every 6 months on a prospective cohort of approximately 200 normal controls, 70 years and over, 400 subjects with Mild Cognitive Impairment (MCI), and 200 subjects with Alzheimer Disease (AD). The
emphasiz of ADNI has been on MCI to capture the clinical transition from MCI to dementia and the associated imaging, CSF and blood biomarkers that reflected the progressive neuro-pathological process. Ongoing recruitment to the extensions of ADNI I (ADNI-Go and ADNI 2) has focused on a new cohort of subjects, in particular, those with early MCI (eMCI), more elderly controls over the age of 65, as well as further subjects with late MCI (lMCI).

Secondly, the unprecedented sharing of all the ADNI “cores” (clinical, MRI, PET, biomarker, genetics, neuro-pathology, biostatistics, and informatics) hosted on secure websites has made the data available to any researcher in the world. Researchers can download cross-sectional and longitudinal data to test their own approaches to image analysis. Thirdly, in parallel, ADNI-like projects have developed in Australia (Ref. Ellis 2009), Europe (Geroldi 2008), Japan (Iwatsubo 2010), based on principles of standardized acquisition shared data and international collaboration. From these international neuroimaging initiatives, the exponential growth of publications, particularly in structural MRI, has produced a new understanding of the progression of MRI biomarkers, alone and in combination with other biomarkers, from normal aging through MCI to AD.

Measurement of atrophy

Medial temporal lobe atrophy predicts progression from MCI to AD (Ref. Scheltens 1992, Korf 2004, DeCarli 2007, Duara 2008). Most of the studies measuring hippocampal volume have reported that hippocampal volume loss was asymmetric. A meta analysis of 14 cross sectional studies published between 1998 and 2007 measuring hippocampal volume found that, compared to controls, the average volume reduction was 12.9% and 11.1% in the left and right hippocampus in MCI and 24.2% and 23.1% in the left and right hippocampus respectively in
subjects with AD (Ref. Shi 2009). This evidence of hippocampal volume loss in MCI being less than in AD supports the concept that MCI is a transitional stage from normal to AD.

**Longitudinal studies of atrophy**

A longitudinal study using MRI automatic segmentation of hippocampal volume, at three time points over 10 years on over 500 normal controls, showed that declining hippocampal volume predicted onset of clinical dementia (Ref. den Heijer 2010). As well, decline in hippocampal volume preceded and paralleled subjects who declined in delayed recall but who remained free of dementia. Longitudinal studies of structural MRI aim to characterize the earliest regions affected by AD, its subsequent neuropathological progression and rate of change, as new regions of the neocortex are involved (Ref. Chetelat 2005, Nestor 2004, Fox 2007, Whitwell 2007, Chan 2003, Schott 2003, Tondelli 2011, Hall 2008, Li 2011). Using an open access structural imaging series (OASIS), Li et al selected 150 subjects, half of whom where normal healthy controls and the rest with varying degrees of dementia. MRI had been repeated for up to 7 years. Voxel Based Morphometry was used to identify abnormal brain regions. Absolute atrophy rate in these abnormal regions was determined by a regression methodology. Having identified the hippocampus and the medial temporal gyrus (MTG) as regions of early changes, they explored the cause and effect relationship over time between these regions based on grey matter concentration. They found the earliest signs of AD were in the hippocampus and entorhinal cortex, followed by the MTG. In the causality analysis, there was little difference between the subjects with AD and the age matched healthy controls in hippocampal atrophy rates. There were larger differences in the MTG in the AD subjects. They concluded that there was a greater rate of atrophy in the hippocampus in the years closer to illness onset and suggested that the underlying pathological process in AD amplified progressive changes that were evident in normal aging.

**Automation**

Various groups have proposed automated methods to classify people with AD and MCI using structural MRI T1 weighted images. These automated approaches are aided by advances in statistical learning and new machine-learning algorithms to manage the wealth of data from MRI images. These approaches can be broadly categorized as voxel based or region of interest based (Ref. Cuingnet 2011). Using the ADNI database and ten methods (5 voxel based, 3 on cortical thickness and 2 based on the hippocampus) (Ref. Cuingnet et al 2011) examined longitudinal data over 18 months from 81 normal controls, 67 people with MCI who did not
convert, 39 people with MCI who converted and 69 with AD. For the comparison between AD and cognitively normal subjects, whole brain methods (voxel based or cortical thickness based) achieved high accuracies of up to 81% sensitivity and 95% specificity. However, the sensitivity to detect the difference between cognitively normal and people with MCI varied between 71% to 51%. The specificity for three of the methods was high at 85%. When comparing MCI non-converters with converters, only 4 of the 10 methods managed to predict conversion slightly more accurately than random chance. The authors concluded that most of the techniques accurately classified normal controls and subjects with AD. However, these methods had lower sensitivity in diagnosing prodromal AD. They suggested that structural MRI combined with other biomarkers and/or clinical and neuropsychological knowledge could improve the accuracy to predict prodromal AD.

**Hippocampal Harmonization**
ADNI and ADNI-like initiatives have standardized the acquisition of structural MRI. Manual segmentation to measure hippocampal volume is recognized as the gold standard. However, in the literature, at least 56 different protocols have been described for the manual segmentation of the hippocampus. An international collaboration established a task force which first met in July 2008, to reduce heterogeneity of the anatomic landmarks of the hippocampus and work towards a harmonized protocol (Ref. Frisoni 2011, Jack 2011). If there are to be future drugs which alter the progression of AD, it will be imperative to have valid measurements of the target region of the brain as an MRI surrogate outcome measure. The initial survey of the 12 most cited manual segmentation protocols revealed a 2.5 fold volume measurement difference (Ref. Boccardi 2011). Steps to standardize the measurement of hippocampal volume as a biomarker of clinical trials and also a diagnostic criteria for AD have been described (Ref. Jack 2011). Using the standardized definition of anatomic hippocampal boundaries on MRI arising from the European Alzheimer’s Disease Centres – ADNI, Hippocampal Organization, is the first step towards a reference standard. A publically available reference standard dataset such as a sample of subjects from ADNI with manual measurements of the hippocampus will need to be available. It is anticipated that new automated measurements of the hippocampal volume can then have their metrics compared to the manual benchmark. Automated validated measures of hippocampal volume will help select appropriate subjects for clinical trials. It can also be used as inclusion/exclusion criteria to enrich the sample of the trials to improve therapeutic efficiency, and reduce the sample size (Ref. Hampel 2010, McEvoy 2010).
Subregional atrophy
Sub-regional hippocampal atrophy has been explored in a longitudinal study using a small sample of normal elderly subjects who remained normal and cognitively normal subjects who were diagnosed with MCI. The investigators used a technique known as hippocampal radial distance mapping using 3D hippocampal maps, applied to 1.5 tesla MRI images 3 years apart. This pilot study suggested that excess CA1 subicular atrophy is present in cognitively normal persons who will progress to amnestic MCI. Atrophy spreading further to the CA2-3 sub-field in persons with amnestic MCI, predicts a future diagnosis of AD (Apostolova 2010). A small cross sectional study of normal controls people with MCI and with Alzheimer’s disease at 4 Tesla showed that compared to controls people with AD had smaller volumes of the entorhinal cortex, subiculum CA1 and CA1-2 regions in total hippocampal volumes. People with MCI had smaller C 1-2 volumes (S Mueller 2010).

Structural MRI and evolving Alzheimer Disease definitions
In parallel with the steps to standardize biomarkers, new definitions of AD have been proposed that include biomarkers along with clinical symptoms seen in predementia and dementia syndromes. Biomarkers have been categorized reflecting the underlying neuropathology (Ref. (Dubois 2007, Dubois 2010). The research criteria for AD requires evidence of both specific memory changes and in vivo markers of AD pathology and can include CSF amyloid β (Aβ), total tau and phospho tau, retention of specific PET amyloid tracers, medial temporal lobe atrophy on MRI, and/or temporal parietal hypometabolism on FDG PET scans. Likewise, prodromal AD requires clinical symptoms of episodic memory loss of the hippocampal type (free recall deficit on testing not normalized with cueing), without impairment of activities of daily living (ADL), and biomarker evidence on CSF or imaging that is supportive of the presence of AD pathological changes.

Three further working groups from the National Institutes on Aging – Alzheimer’s Association, have proposed new diagnostic guidelines for AD (Reference McKhann 2011), MCI (Reference Albert 2011) and the preclinical stage of AD (Sperling 2011). The five most widely studied biomarkers of AD were incorporated into the diagnostic criteria by each of the working groups since the biomarkers reflect the underlying pathology and can act as proxies. For Aβ accumulation, the biomarkers are tracer retention on amyloid PET imaging and low CSF Aβ42. The biomarkers of neuronal degeneration or injury are elevated CSF Tau, decreased fluorodeoxyglucose uptake on PET and the temporal parietal cortex and atrophy on structural
MRI of the medial basal and lateral temporal lobes and medial and lateral parietal cortices. It is hypothesized that amyloid PET imaging and CSF Aβ may first become abnormal as long as 20 years before the first clinical symptoms appear. CSF, Tau and FDG PET follow, with structural MRI as the last biomarker to become abnormal (References Jack 2011, Jack 2010). Structural MRI has been used in AD randomized controlled trials (RCTs) for exclusion of subjects with strokes, lacuna infarcts (in particular, strategic infarcts) and extensive white matter changes. A relatively new phenomenon is the recognition of micro-bleeds. These are small dot-like lesions seen in T2* images representing deposition of hemosiderin. More than 4 micro hemorrhages have become exclusion criteria for RCTs of compounds that are potentially disease modifying.

In clinical trials, using compounds to lower amyloid, vasogenic edema and micro hemorrhages have been detected on MRI after treatment with these compounds. These 2 phenomenons have recently been renamed amyloid-related imaging abnormalities (ARIA)-E and ARIA-H respectively (Sperling et al 2011). In a memory clinic, the prevalence of micro-bleeds in AD has been reported as high as 20% (Ref. Cordonnier 2006 Frisoni 2010). The micro-hemorrhages may have prognostic significance and together with atrophy may predict mortality in the memory clinic population (Ref. Henneman 2009).

**Neuroimaging in memory clinics**

The added value of neuroimaging in a memory disorders clinic has been evaluated in a retrospective study of 193 consecutively referred patients with cognitive impairment. All subjects had an MRI scan and SPECT scan. The MRI scans were evaluated for micro and macro vascular disease (Fazekas Scale; Mild, Moderate or Severe) and morphological abnormality, e.g. lobar atrophy and ventricular enlargement. Specific clinical diagnosis, using neuroimaging, was suggested in 72% of cases and in 26%, an abnormal/not diagnostic pattern was noted. Only 2% had entirely normal scans. Neuroimaging confirmed, clarified or contradicted the initial clinical diagnosis in more than 80% of patients. In 60% of the subjects indicators of cerebrovascular disease were present. However this was not predicted by the presence of vascular risk factors alone. Of the cases clinically thought to be caused by a single process, imaging suggested complex dementia etiology in 21%. In contrast, of the complex clinical differential diagnosis, the use of neuroimaging suggested a single cause pattern in 46% (Ref. Borghesani 2010). Comparison between MRI and 64-detector row CT has been made on patients seen in a memory clinic. (Wattjes MP 2009). The intraobserver agreement between
CT and MRI was excellent on global cortical atrophy with substantial overall agreement on white matter changes.

**Clinical application**
In the United States, most clinical radiology units acquire and interpret 2D MRI data for qualitative visual inspection of images to allow higher patient throughput. 3D volumetric acquisitions require longer scan times, more data to be stored and a quantitative interpretation (Brewer 2009). Spatial distortion may arise from differing positioning in the scanner. Subject motion also affects the quality of scan for volumetric measurement. Normative values from healthy patients, other than hippocampal volumes, are limited (Brewer 2009). The subjects volunteering for ADNI are highly selected, have a higher level of education and are not representative of the general population. Other disorders besides AD can cause hippocampal atrophy but despite these challenges, one group has described a fully automated volumetric MRI of normative ranges and are attempting to make the translation from clinical research to clinical practice (Ref JB Brewer 2009). In their paper, they describe coordination between the radiology and neurology departments so that the additional steps can be accommodated with their clinical work flows. The software they used was Neuro Quant (Ref. Brewer 2009, Kovacevic 2009). They used the ADNI sequences for their General Electric 1.5T scanners and produced a clinical volumetric MRI report and a normative chart by age and volume for the hippocampus and a separate chart for the inferior lateral ventricle. Forty-three of forty-five scans passed quality checks. The report also had coronal, sagittal and axial images which were clinically helpful to the referring physician in educating patients and their families.

**Bridging the research to clinical practice gap**
There are major gaps between the precision of ADNI and ADNI-like structural MRI neuroimaging research protocols and clinical practice in specialist clinics or family practice. In Canada at present, it is unlikely that any specialist memory clinic presently uses more than one neuroimaging modality on all subjects for their initial assessment, and most often it is MRI or head CT scan. With MRI, it is likely that no more than 6 specialist centres apply volumetric measurement and only in selected cases. However, with 5 centres in Canada participating in the ADNI study and at least 1 or more using ADNI sequences, standardization of MRI images of clinical patients could be acquired using an agreed upon standardized dementia workup sequences. As well, in the future, standardization could be expanded to other interested
specialist centres. With the appropriate consent, these clinical images could be stored in a Canadian neuroimaging database and be more representative of clinical patients seen in Canadian specialist clinics. To be meaningful, the corresponding core clinic and neuropsychological data would need to be electronically stored as well and able to be collated with the image(s). This data would be more generalizable to patients seen in Canadian clinical practice. This could become a Canadian equivalent to the Alzheimer’s Disease Cooperative Study and National Coordinating Centre that is already well established in the United States (Ref. Beekley DL 2007, Morris 2006).

In Canada, specialist clinical trials centres are primarily members of the Consortium for Canadian Centres for Cognitive Research (C5R). Those that have the training and expertise may be selected by pharmaceutical companies to participate in randomized controlled trials (RCT) to assess new compounds purported to offer symptomatic or, alternatively, disease modifying treatments. In the latter case, the RCT protocols use MRI for safety monitoring. Between trials there is some variability in the MRI sequences required. However, each site is able to acquire the protocol mandated sequences. Standardization of sequences acquired trials will naturally expand the number of Canadian sites with the capability to acquire standardized images. If trials agree to common standards across trials, images, from not only the treatment cohorts but the placebo cohorts, could be compared. Therefore, collaboration between cognitive specialists (neurologists, geriatricians, geriatric psychiatrists) in memory clinics with local radiologists/neuroradiologists will be important in the future for the consistent acquisition of MRI images using ADNI-like sequences for people undergoing cognitive assessment.

An even wider gap exists for patients seen in family practice where the present clinical standard is a MRI or head CT scan, depending on urgency, availability and exclusion factors for MRI. However this gap has been narrowed by the development of a new model of memory assessment clinics within Family Health Teams with the lead family physician being supported by a cognitive specialist (Linda Lee et al JAGS 2010).

RECOMMENDATIONS

1. For the initial assessment of a person presenting with cognitive impairment, structural neuroimaging with head CT scan or MRI is recommended to rule out potentially reversible causes such as subdural hematomas neoplasia and normal pressure...
hydrocephalus and rule in specific patterns of atrophy and concomitant cerebrovascular disease/changes (Grade A, Level 2).

2. Head MRI 1.5 or 3 Tesla, is preferred when a radiologist/neuroradiologist and/or a cognitive specialist (neurologist, geriatrician, or geriatric psychiatrist) can interpret the scan to provide the added diagnostic and predictive value from an MRI (Grade B, Level 2).

3. A head CT scan is recommended when MRI or 1.5 Tesla or 3 Tesla is not available or contraindicated (pacemaker, claustrophobia, iron containing head and neck tattoos or cranial metal (Grade A, Level 2).

4. Standardization of clinical acquisition of core MRI dementia sequences is recommended in Canadian centres that have radiologists and cognitive specialists with expertise in assessing cognitive disorders, particularly when repeat MRI images can provide additional diagnostic information, or predict progression to dementia, or provide safety information regarding treatment options (Grade B, Level 2).

5. When available in the clinic, cognition specialists may use the computer images of the brain to educate a person with cognitive impairment and family members about changes in the brain. This knowledge may reinforce adherence to vascular risk factor management and to lifestyle modification to improve brain health (Grade C, Level 3).


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