Dementia Imaging: what the clinician needs to know

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Highlights:

a) ***CT remains the workhorse of dementia imaging, but structural MRI provides valuable additional information on small vessel disease, including white matter hyperintensities and microbleeds.***
b) ***Standardized MRI sequences including high resolution 3D T1 further allow automatic quantification of hippocampal volume and cortical thickness, though this is not routinely used clinically. Furthermore, template-based quantification does not work well for focal atrophy syndromes or cerebrovascular disease associated brain injury from small or large vessel disease.***
c) ***Imaging functional changes in dementia can be achieved in a one-stop shop using arterial spin labelling, cerebrovascular reactivity mapping, task-based and task-free bold fMRI. Nuclear medicine, techniques such as SPECT and PE, if available can also contribute functional insight.***
d) ***However, the game changer in dementia imaging over the last decade has been the arrival of molecular PET which allows visualization of hallmark pathologies of AD- initially amyloid beta, and now tau in development. This is transforming our understanding of aging, prognostication and clinical trial design in the common dementias.***

1) Current clinical imaging methods:

Structural Imaging:

CT scanning continues to be the mainstay modality in the basic work-up for dementia, because of its ready availability, lack of contra-indications (eg pacemakers and claustrophobia), quickness, which is important for frail elderly or agitated patients, and for its utility in acute stroke and in delirium in emergency room, the venue where dementia is sometimes recognized for the first time.

MRI is more sensitive for detecting small vessel disease (SVD), however, and necessary to detect microbleeds, which can influence decision-making in use of antithrombotics.

Through efforts such as the Alzheimer Disease Neuroimaging Initiative (ADNI), standardization of key essential scan acquisitions across vendor platforms at 1.5 and 3.0 Tesla has been achieved in North America and similar protocols are being used in many countries for population and patient studies (1-3)

The typical dementia research protocol includes a high resolution 3D T1 (for atrophy and lacunes), FLAIR (for strokes and SVD), gradient echo or Susceptibility Weighted Imaging (for chronic haemorrhage and microbleeds) and Diffusion Weighted Imaging (DWI) (for acute ischemia). Proton density and T2-weighted sequences are more sensitive to hyperintense lesions in the basal ganglia and thalamus, can help differentiate lacunes from perivascular spaces, and can potentially be useful for more accurate, efficient extraction of brain and sulcal cerebrospinal fluid from the skull and meninges (4-6). Standardized, synoptic reporting using rating scales for global and medial temporal atrophy and other SVD, with appropriate consensus definitions and training, can

improve communication among the multidisciplinary physicians involved in dementia care and would assist health services research for quality improvement and evaluation in jurisdictions that provide access to large healthcare databases.

Vascular imaging is also going beyond the lumen with carotid and intracranial wall imaging [eg (7)], but space does not permit justice to be done to these important developments.

Diffusion Tensor Imaging has yet to be incorporated into clinical dementia protocols, in part due to variability among scanners and scanner upgrades, but in group studies, it can detect microstructural damage, especially in association and projection tracts (8), in correlation with different types of dementia (eg more widespread changes seen in focal atrophy syndromes such as semantic dementia than expected) (9).

Functional Imaging:

Pseudo Continuous Arterial Spin Labelling (PCASL) may be useful in detecting topographical patterns of hypoperfusion in Alzheimer's Disease (AD) that may be responsive to current cholinesterase inhibitors (10)), similar to single photon emission computerized tomography (SPECT) (11) or signature hypometabolic patterns on 18Fdeoxyglucose PET (12)

Characteristic patterns of reduced functional connectivity in the default mode network in AD and in the salience mode in Frontotemporal Degeneration (13, 14) are found consistently across many studies, but the reliability of resting state(rs), task-free fMRI remains a concern, including sleep lapses during collection that may obfuscate findings. Reduced connectivity may be ameliorated by cholinesterase inhibitors after 6 months of use (15)and rest between task engagement also shows some normalization of connectivity(9), suggesting that rs fMRI may be more dynamic than first thought.

2) <u>Computational Analysis: Transitioning to the future</u>

Automatic techniques for cortical thickness estimation and regional parcellation are currently available based on template matching (eg Freesurfer), and can reveal topographical patterns of thinning- a signature for AD that involves the parietal-temporal, posterior cingulate and dorsolateral prefrontal regions (16, 17), and can also be predictive of decline to dementia in the prodromal stages (18).

However, automatic techniques for parcellation and calculating cortical thickness do not work well if there is focal stroke or other structural lesions, or if there are significant volumes of white matter hyperintensity, which usually segments as gray matter and can falsely inflate grey matter volumes, if not taken into account (19). Template matching also does not serve well in detecting focal atrophy syndromes as seen in atypical early onset AD or Frontotemporal Degeneration, especially the temporal variant in which the temporal pole atrophies significantly, causing semantic dementia, a subtype of primary progressive aphasia if the left side shrinks first. These disorders call for a more individualized approach, requiring user editing by a trained observer (5).

Automatic segmentation of hippocampal volumes has also been available for some years (20-22) based on template matching to hand tracing, but over 10 different tracing protocols have been used. Recently, consensus has been reached on the best hippocampal protocol and is now recommended for future analyses (23, 24)

Automatic quantification procedures, which depend on computational capacity, will need to become more reliable, validated and generalizable across dementia populations to be used clinically, and some efforts are underway to do this (eg Canadian Consortium for Neurodegeneration in Aging http://www.cihr-irsc.gc.ca/e/46475.html).

Personalized Profiling:

Because stroke is a common cause for dementia, often co-exists with Alzheimer pathology, and can be quite variable in size, number and location, rating scales and tracing methods have been traditionally used to quantify focal injury as well as lesion load and topography, to help in the study of brain-behavior correlations (26). Previously, descriptive terms for extent and relationship of focal strokes to vascular territories, their lobar and subcortical locations have been the traditional method of clinical reporting. Quantification of cerebrovascular associated brain injury, such as focal stroke, also requires a more customized pipeline with user-editing and tracing (27). Computational methods for lesion symptom mapping may be useful to discern brain-behavior correlations groups of patients.

Small Vessel Disease is also variable in extent and location, and to address this complexity, a recent consensus process has recommended definitions for reporting SVD, including lacunes, white matter (WMH) or subcortical hyperintensities, perivascular spaces, microbleeds and microinfarcts (25). User interactive methods may also be more effective for quantification of SVD, which is important to take into account as it is common, being reported to some degree in 95% of elders (28). However, there may be a threshold of around 10cc of WMH to discern cognitive effects, usually in executive functions (29).

Similarly, a consensus round-table of the Alzheimer Association US met to define the concept of amyloid-related imaging abnormalities (ARIA), specifically microbleeds and vasogenic edema, which have been reported in association with amyloid-lowering drugs (30). The resulting preliminary recommendations have been adopted by the FDA for testing anti-amyloid therapies with guidelines for exclusion criteria and for stopping experimental treatment now incorporated in clinical trial design. This is still investigational as there are no anti-amyloid disease-modifying drugs currently approved for treatment of AD.

3) <u>Molecular imaging methods</u>:

18F deoxyglucose PET has been available for 30 years to study AD and other dementias, with hypometabolism signatures discernible using statistical parametric mapping and surface projection methods. However, an exciting new development over the last decade has been the arrival of molecular PET imaging. Initially C-11 labelled amyloid PET ligands (Pittsburgh compound B-PIB), and now 18F amyloid radiotracers are available, allowing Alzheimer pathology to be visualized in vivo. This means that patients can be "credentialed" for participation in clinical trials of anti-amyloid disease-modifying therapies. In the NIA-sponsored Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, for example, cognitively normal individuals aged 65 to 85 at risk of AD (most often due to a positive family history) are offered a florbetapir amyloid PET scan. If uptake is seen in the signature regions, the participant can choose to be randomized to an amyloid antibody treatment (solanezumab) vs placebo, infused monthly over 3 years, with the goal of preventing cognitive decline. Similar clinical trials are underway in asymptomatic patients who are carriers of mutations for autosomal dominant AD.

Tau ligands are also in development, enabling for the first time the visualization of tau pathology in AD and Frontotemporal degeneration (31). Synuclein ligands are likewise in the pipeline to identify the spectrum of Lewy Body/Parkinson's Disease, and ligands to detect neuroinflammatory

mechanisms are also being tested in brain disorders (32). Hence it is increasingly possible to identify pathologies in vivo to guide therapeutics, monitor target engagement and evaluate outcomes. However, whether or not these expensive new imaging technologies are revealing targetable pathologies that can be prevented, ameliorated or reversed as new therapeutics develop, remains to be seen. It is too early to tell, but there is no doubt that methods that visualize neuropathologies *in vivo* are becoming a game changer in detection and differential diagnosis of dementia.

How to affordably integrate such neuroimaging advances into clinical care will be challenging. Cost-benefit analyses will need to determine clinical utility if effective disease-modifying therapies have not yet become available (33). However, our ability to document amyloid beta and tau pathology in vivo as it is currently unfolding (or better put, "misfolding"!) is potentially transformative in the field of cognitive aging, cerebrovascular and neurodegenerative disorders.

4) Conclusion:

We are transitioning into an information age when computational analysis will allow routine reporting of indices of brain health and comparisons can be made over time to document brain tissue loss and increase in pathologies that will be objective and can also be used for tracking longitudinal change and as outcome measures for treatment interventions. However, some user interaction will likely be required for quantifying the heterogeneous manifestations for cerebrovascular associated brain injury, such as focal stroke, white matter hyperintensities, perivascular spaces and microbleeds.

Finally molecular imaging will likely find an important niche along the spectrum of prevention, intervention and long term outcomes for the misfolded proteins that accumulate in human aging and disease, spreading through the brain over decades, possibly transynaptically along functionally connected neuronal pathways. If detected early perhaps there is chance for rescue and repair, and hopefully one day we can use the same multimodal methods to track reversal of pathology and re-establishment of network connectivity.

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