NEUROIMAGING OF COGNITIVE DISORDERS

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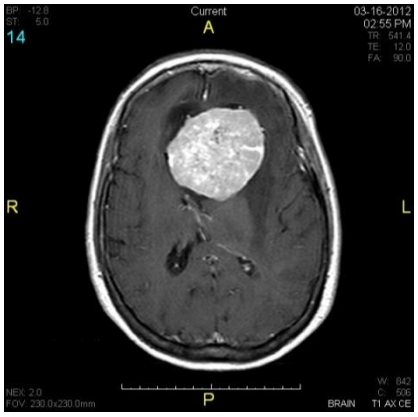
Overview

Cognitive dysfunction is a common reason for presenting for a neurological assessment, especially in the elderly. It was estimated that 44 million people worldwide were living with dementia in 2013 and that the number will rise to over 135 million by the year 2050 (1). There are roughly 5.4 million Americans who have Alzheimer's disease, the most common cause of dementia in the United States. The risk of Alzheimer's disease increases steeply with age. About 1 in 9 people over 65 are estimated to have Alzheimer's, and this increases to 1 in 3 over the age of 85 (2).

With the development of newer imaging techniques, neuroimaging is playing a progressively more important role in the evaluation of patients with cognitive disorders. Historically, neuroimaging was used primarily if not exclusively to rule out reversible causes of cognitive impairment, such as hydrocephalus and mass lesions (Image 1). While this continues to be a valuable role for neuroimaging, only a small minority of patients presenting to a memory clinic with cognitive dysfunction are found to have surgically amenable lesions (3).

Image 1. Meningioma presenting as a degenerative dementia. Contrast enhanced T1W axial MRI demonstrating a large midline enhancing mass consistent with a meningioma.



More recently, neuroimaging is being used in the clinical and research setting to confirm the mechanism of degenerative and other non-surgical disorders of cognition. Novel tracers, in particular with affinity for beta amyloid, have transitioned from the preclinical arena into the pharmaceutical industry and even into limited clinical practice. There are many tau tracers under investigation, and with time they may see a similar trajectory into the clinical arena.

Alzheimer's Disease

Alzheimer's Disease (AD) is the leading cause of dementia in the United States. Due to the aging of society, the prevalence of Alzheimer's is expected to rise significantly in the coming decades, to 7.1 million Americans in 2025 and 13.8 million in 2050 (2). Fortunately, some recent studies suggest that an individual's lifetime risk of Alzheimer's may be declining in the United States and other Western countries. This has been attributed to factors such as increased success in managing cardiovascular risk factors and rising levels of education (4). Alzheimer's disease is characterized by the progressive accumulation of amyloid plaques and neurofibrillary tangles. With time, these changes result in synaptic dysfunction, neuron loss, and ultimately cognitive impairment. It is now widely assumed that these characteristic neuropathological findings, in particular amyloid plaques, may start to accumulate years if not decades prior to the onset of cognitive symptoms. Some of the

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earliest pathological changes of Alzheimer's occur in the medial temporal lobes, and with time the disease spreads to diffuse regions of the brain. Macroscopically, this is manifest by relatively early medial temporal lobe atrophy (5) followed later by more generalized atrophy.

The primary neuroimaging tools currently available for routine clinical use in the assessment of patients with suspected Alzheimer's disease are magnetic resonance imaging (MRI) and positron emission tomography (PET). Although computed tomography (CT) is also commonly utilized in the assessment of patients with dementia, MRI demonstrates superior spatial resolution and other benefits which make it the preferred structural imaging modality.

MRI

MRI is the preferred imaging modality for routine clinical use in the assessment of most patients with suspected Alzheimer's Disease, if not cognitive impairment in general. MRI is extremely sensitive for symptomatic mass lesions, hydrocephalus, and vascular burden. Thus, MRI has been historically used to "rule out" these lesions in a patient who otherwise is suspected to have Alzheimer's Disease or another degenerative process. However, MRI is starting to be used more commonly to identify characteristic patterns of atrophy as well as other findings suggestive or supportive of Alzheimer's. Sometimes, these findings are visible without additional image post-processing or other advanced imaging manipulations, such as profound parieto-occipital atrophy in the posterior cortical atrophy variant of AD, or cerebral microbleeds which are commonly associated with Alzheimer's (6). Hippocampal atrophy can sometimes be appreciated by routine observation, but it commonly requires quantitative or semi-quantitative assessment for confirmation. Formal volumetric assessments are particularly valuable to provide an imaging marker of disease progression. Additional MRI techniques being investigated for use in Alzheimer's disease include arterial spin labeling, diffusion tensor imaging, and resting state functional MRI (fMRI) (7).

PET

Positron emission tomography is a nuclear medicine imaging modality of increasing significance in the assessment of cognitive dysfunction. Since 2004, FDG PET has been a Medicare-reimbursable study to distinguish between dementia due to Alzheimer's and Frontotemporal disease. With the advent of the first amyloid-binding tracer, Pittsburgh Compound-B (PIB), PET imaging is able to indirectly identify the presence of intracerebral beta-amyloid. Subsequently, the FDA has approved for clinical use multiple novel amyloid binding tracers with significantly longer half-lives than PIB. While amyloid-PET is not commonly utilized in routine clinical assessments, it is more widely employed in academic centers and in industry-sponsored trials of anti-amyloid agents.

There are a number of limitations to the routine clinical use of amyloid-PET imaging. First, a significant percentage of otherwise normal elderly are shown to demonstrate the presence of amyloid on PET imaging. A related observation, supported by autopsy data, is that the burden of amyloid does not closely correlate with the degree of cognitive impairment in Alzheimer's patients. This has led to interest in the development of tau-PET tracers, as tau much more closely correlates with cognitive dysfunction. Presently, there are multiple tau-PET tracers which are being investigated.

<u>Frontotemporal Dementia</u>

Frontotemporal dementias (FTDs) represent a heterogeneous set of degenerative disorders primarily characterized by language and/or behavioral symptoms (Table 1) (8). Although rare in the elderly population, FTD syndromes approach the prevalence of AD in demented individuals under the age of 65 years. The two general categories of FTD are the behavioral and language variants.

Behavioral variant FTD (bvFTD) is characterized by a progressive decline in behavior, including disinhibition, apathy, loss of sympathy, and perseverative behaviors. The language variants of FTD are semantic variant primary progressive aphasia (PPA) and nonfluent agrammatic variant PPA. The semantic variant is characterized by impaired speech comprehension, often manifest by fluent but empty speech with prominent anomia. In contrast, patients with the nonfluent agrammatic variant generally maintain speech comprehension in the early stages of disease, but present with prominent nonfluency, agrammatic errors, and often demonstrate apraxia of

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speech (8). Due to its frequent association with beta-amyloid deposition, the logopenic variant of primary progressive aphasia is now generally considered to be a subtype of Alzheimer's Disease rather than a subtype of FTD (9).

Classic imaging findings associated with the FTD syndromes are asymmetric lobar atrophy and hypometabolism, best visualized with MRI and FDG PET respectively. While demonstration of focal lobar involvement on neuroimaging is not always confirmed, it is considered a supportive feature in the diagnostic criteria for bvFTD (10). Relevant imaging abnormalities are also often seen in the semantic variant of PPA. In contrast, imaging abnormalities are often less conspicuous in the nonfluent agrammatic variant using routine imaging modalities.

Table 1. Clinical and Anatomic Features of FTD Syndromes

	Primary Symptoms	Anatomic correlation
bvFTD	Disinhibition Apathy Loss of sympathy Perseverations	Primarily nondominant frontal and/or anterior temporal lobes
Semantic variant PPA	Impaired word comprehension Anomia	Primarily dominant anterior temporal lobe
Nonfluent agrammatic variant PPA	Nonfluent speech Speech apraxia Comprehension spared early	Dominant perisylvian cortical regions

Numerous genetic mutations and associated abnormal protein depositions have been implicated in the various FTD syndromes. Abnormal TDP-43 deposition is demonstrated in about half of pathologically proven FTD subtypes, whereas abnormalities in tau are seen in some cases of familial FTD as well as in a variety of other disorders (11). Tau imaging holds promise for further characterization of these non-AD syndromes associated with abnormalities in tau protein. For example, a recent case series has demonstrated strong correlation between tau imaging findings and regional tau neuropathology in patients with MAPT mutations (12).

Other Dementing Disorders

Neuroimaging abnormalities are commonly seen in a variety of other dementing disorders (Table 2). In the cases of vascular dementia and Creutzfeldt-Jakob disease, neuroimaging and MRI in particular play a critical role in the diagnosis of these conditions. In contrast, while abnormal MRI findings are not uncommon in several movement disorders (such as Huntington's Disease, Multiple System Atrophy, and Progressive Supranuclear Palsy), an accurate diagnosis can often be achieved based on the clinical picture in the absence of identification of characteristic imaging findings. Finally, in certain common dementing disorders such as Lewy Body Disease, routine neuroimaging is often normal.

Table 2. Characteristic MRI Findings in Other Dementias

	Characteristic Finding
Vascular Cognitive Impairment	Strategic ischemic or hemorrhagic infarct(s) and/or extensive white matter disease
Creutzfeldt-Jakob Disease	Sporadic CJD: FLAIR or DWI hyperintensity in the subcortical nuclei (thalamus, caudate, putamen) and/or cortical ribbon Variant CJD: FLAIR or DWI hyperintensity in the medial thalamus and pulvinar ("hockey stick" sign)
Multiple System Atrophy	Atrophy of pons, cerebellum, middle cerebral peduncle, other structures. Linear pontine T2 hyperintensity ("hot-cross bun" sign)
Progressive Supranuclear Palsy	Midbrain atrophy ("hummingbird" sign)
Huntington's Disease	Atrophy of caudate head

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