Chapter 4

Imaging

Vyara Valkanova and Klaus P. Ebmeier

Exactly 21 years have passed since John Besson's chapter 'Imaging' in the previous edition of these seminars. There has been an amazing proliferation of imaging methods, but very little change in the clinical imaging protocols available to the average UK clinician. X-ray computed tomography (CT) still seems to be the mainstay of assessment in the standard psychiatric memory clinic. Magnetic resonance imaging (MRI) tends to be available, but only as a 'special treat', often mediated by neurologists, and emission tomography, such as single photon emission computerised tomography (SPECT) and positron emission tomography (PET), is only used in highly specialised cases outside a few academic centres. Apart from generic NHS austerity, 'health without mental health', and institutional ageism, what could be the reasons for this?

Introduction

The classical explanation is that brain ageing interferes with the specificity of any diagnosis based on imaging. As we age, our brains shrink, develop microvascular white matter lesions, lose dopamine and accumulate amyloid. The radiologists' phenomenology is usually insufficient to separate pathology from age-related changes that are not directly attributable to illness. Still, three-dimensional imaging, particularly MRI, is now recommended as a biomarker, together with functional imaging (fluorodeoxyglucose [FDG]-PET) and CSF-tau, to aid clinical diagnostic criteria by providing evidence of neuronal injury [1]. However, as the National Institute on Aging/Alzheimer's Association workgroups emphasise, 'All biomarkers are continuous measures, and the diagnostic labels of "positive" or "negative" require that cut-off values be applied to continuous biological phenomena' [1]. This in turn requires the application of quantitative methods beyond the inspection of scans, as well as a large representative normal reference base of scans, so that cut-off values can be determined for strata defined by age, sex and other potential confounding properties [2]. This requires a departure from radiological routine and culture. Very few departments generate reports that comment on the degree of hippocampal atrophy (e.g., using Scheltens scores or even volumes in CT or MRI scans), or white matter changes (e.g., citing Fazekas scores on FLAIR [fluid attenuation inversion recovery]), or indeed associative cortex/primary sensory-motor cortex metabolism ratios using FDG-PET with the relevant reference ranges [3]. While quantitative automated methods have become available, the hardware, software and expertise needed to employ them is usually absent.

The second argument that has prevented the rapid proliferation of quantitative imaging is the presumed absence of convincing therapeutic options. The accepted specific indication of acetylcholinesterase inhibitors in Alzheimer's type and Lewy body dementia (DLB) demonstrates that this argument is losing in strength: being able to exclude patients with

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vascular brain changes that may explain dementia from this treatment protocol makes CT at least, if not MRI, defensible for generic use in all patients attending memory clinics. While incidental finding of new bleeds or infarctions or of tumours may be sufficiently rare to justify withholding routine scans from patients without neurological symptoms or signs, the selection of only a proportion of clinic attenders for treatment and specialist outpatient follow-up sways the cost-benefit balance in favour of scanning.

Imaging Modalities

Commenting in passing on established imaging methods, we will focus on the methods that have developed significantly over the last decade. Some methods are likely to remain of primary research interest, either because of the infrastructure needed (local cyclotron), or because their relevance is limited to specific research questions, usually about mechanisms. Table 4.1 gives an overview of methods of imaging, indicating their specific role, novelty, clinical applicability and current use. The important new developments have taken place in MRI and PET, and it is on the clinical implications of these that we will focus in the following.

The format of this seminar does not lend itself to the technical discussion of imaging methods, or modalities that are more experimental. Readers are advised to refer to a relevant chapter in larger textbooks for this [3,4].

Imaging in Dementia

Dementia of Alzheimer Type

Routine neuroimaging is still recommended to exclude some reversible causes of cognitive decline, for example, tumour, subdural haematoma, normal pressure hydrocephalus [5], but the emphasis is now moving to the identification of markers of neurodegeneration that will aid differential diagnosis and prognosis. The best-validated MRI biomarker of Alzheimer's Disease (AD) is localised atrophy of the medial temporal lobe (MTL), including the hippocampus and entorhinal cortex, assessed with T1-weighted MRI [1]. Medial temporal atrophy (MTA) is highly sensitive for AD and is now part of diagnostic criteria, as a topographical marker of neuronal injury [1]. A weakness of this biomarker is its poor specificity to distinguish non-AD causes of cognitive impairment, as it occurs in other dementias, including vascular dementia (VaD) and frontotemporal dementia (FTD) [6]. Its specificity also decreases with age, due to age-related hippocampal atrophy in non-demented people. Importantly, T1-weighted MRI volumetric measures correlate well with the degree of cognitive impairment [7], as well as with the severity and distribution of postmortem neurofibrillary tangles (NFTs) [8]. Atypical presentations might spare the medial temporal regions, especially in younger patients (<65 years) with greater atrophy seen in the parietal regions (e.g., precuneus, posterior cingulate gyrus) [9]. In addition to focal atrophy, patients with AD show accelerated global volume loss.

The Scheltens scale is a clinically validated rating scale for MTA: it uses the width of the choroid fissure, width of the temporal horn and height of the hippocampus, along a 0–4 severity scale (see Figure 4.1) [10].

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Table 4.1 Imaging modalities and uses in old age psychiatry. Only modalities included that do not require a local cyclotron or other highly specialised infrastructure

Modality	Method	Maturity	Clinical use in old age psychiatry
CT	**X-ray tomography**	**Routine protocol for brain structure**	**Routine dementia clinic**
Structural MRI	T1-weighted MRI	Routine protocol for brain structure	Routine use in some dementia clinics (limited by availability)
Structural MRI	FLAIR/T2-weighted MRI	Routine protocol for white matter changes	Routine use in some dementia clinics (limited by availability)
Functional MRI (fMRI)	BOLD MRI	Routine experimental protocol for regional brain activation	No routine use, partially due to cost and lack of standard protocols
Diffusion tensor imaging (DTI)	DTI sequence	Routine protocol for white matter integrity, with incremental improvements (e.g., multiband sequences)	No routine use, partially due to cost and lack of standard protocols
Perfusion MRI	Arterial spin labelling	Experimental use for rCBF measurement	None
Magnetic resonance spectroscopy (MRS)	MRS sequences	Routine research use for limited chemical analysis, but requires special technical procedures (shimming)	None
PET	18F-FDG-PET	Routine protocol for brain metabolism	Available in most centres now as part of oncology service
PET	18F-Florbetaben, 18F-Florbetapir, 18F-Flutemetamol	Routine protocol for imaging Aβ plaques	Licensed for clinical use
PET	18F-FDDNP	Routine experimental protocol for imaging Aβ plaques and NFTs	None
PET	18F-THK5117, 18F-THK5351, 18F-Flortaucipir	Routine experimental protocol for imaging NFTs	None
SPECT	EDT, HMPAO 99mTc-SPECT	Routine protocol	Widely available for perfusion scan
SPECT	FP-CIT 123I-SPECT	Routine protocol	Widely available for scan of dopamine transporter
Electroencephalogram (EEG)	EEG or ERP	Apart from 3-D methods well established	Tend to be specialist neurology applications

Scheltens Score	Width of choroid fissure	Height of lateral temporal horn	Height of the hippocampus
0	Normal	Normal	Normal
1	Slight increase	Normal	Normal
2	Moderate increase	Slight increase	Slight increase
3	Severe increase	Moderate increase	Moderate decrease
4	Severe increase	Severe increase	Severe decrease

<75 years: score of 2 or more is abnormal

>75 years: score of 3 or more is abnormal

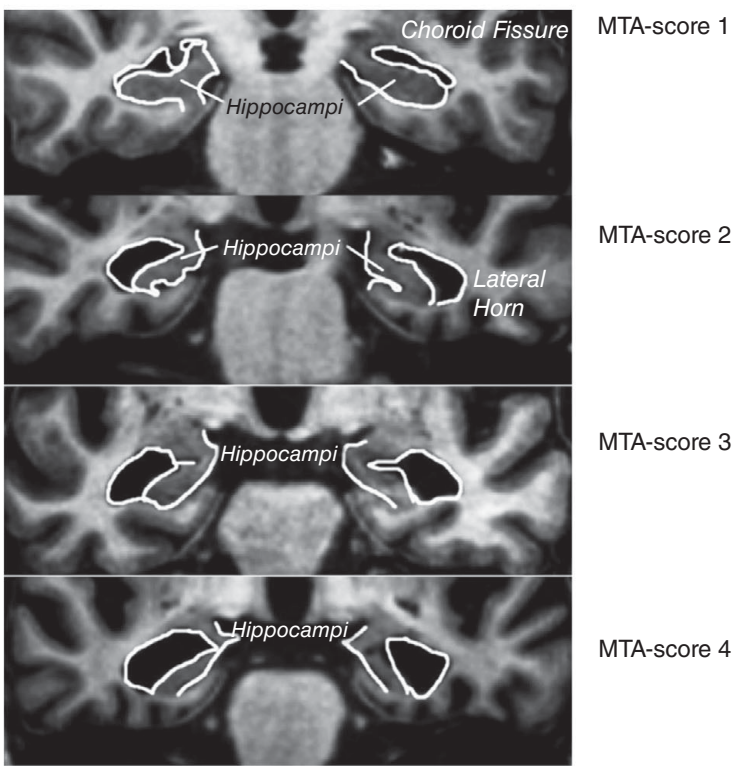

Figure 4.1 Scoring of Scheltens Scale for medial temporal atrophy and example images. Images supplied courtesy of Prof Philip Scheltens, Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam.

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Visual inspection differentiates mild AD from normal ageing with a sensitivity and specificity of 80–85% [9]. Clinicians easily learn the visual scoring of MTA, but particularly with less experienced raters, automated volumetric analysis may give higher reliability [6].

More advanced MRI imaging techniques, such as diffusion tensor imaging (DTI) and perfusion imaging typically appear in the research context. DTI can determine the integrity of white matter tracts in vivo, and reveals decreased fractional anisotropy (FA) and increased mean diffusivity (MD) in widespread regions in AD compared with controls, indicating the presence of white matter damage [3]. Arterial spin labelling (ASL) uses magnetically labelled water molecules in the blood as an endogenous contrast agent to provide a measure of cerebral blood flow; the ASL pattern observed in AD is similar to that of FDG-PET hypometabolism. Functional MRI studies in AD demonstrate decreased functional connectivity between precuneus, posterior cingulate cortex, medial prefrontal cortex and hippocampus, which are part of the resting state default-mode network [3].

Changes in brain function typically occur earlier than atrophy detectable by structural imaging. AD is characterised by abnormal perfusion or metabolism in temporo-parietal association cortex, with the posterior cingulate, precuneus and angular gyrus affected early in the disease course. Frontal association areas may be involved in advanced disease, while primary sensory-motor cortex is relatively well preserved [11].

FDG-PET is more sensitive than SPECT in detecting AD, and has been included as a topographical diagnostic marker in recent diagnostic criteria [1,11]. Both FDG-PET and HMPAO-SPECT, however, are more specific than clinical criteria and are recommended by the National Institute for Health and Care Excellence (NICE) when the differential diagnosis is in doubt [5]. Although FDG-PET is at a more advanced stage of validation compared to other AD biomarkers, there is insufficient evidence on how covariates such as cortical atrophy or APOE genotype affect hypometabolism in AD [6].

Advances in molecular PET imaging, such as amyloid and tau imaging, allow visualising Alzheimer's type pathology in the brain directly. The use of 11C-compounds (e.g., Pittsburgh compound B) is limited to centres with an on-site cyclotron [18]. F-fluorinated tracers with longer half-life (110 min) allow geographically central production and distribution to more remote centres. Three compounds have a licence for clinical use. Increased amyloid cortical tracer uptake in regions associated with Alzheimer-type pathology is a pathophysiological marker of AD [1]. Important applications of PET Aβ imaging agents include diagnosis, stratification of subjects for therapeutic trials and assessment of the efficacy of experimental anti-Aβ therapeutics.

Their role in diagnosis, however, is exclusionary, as several lines of evidence suggest that Aβ deposition is a necessary but insufficient correlate of AD. First, there is a poor association between brain Aβ load and the severity of cognitive symptoms in AD. Second, cross-sectional and longitudinal amyloid PET studies demonstrate that by the time cognitive symptoms appear, amyloid load has already reached a plateau. Finally, many cognitively healthy older people show higher cortical binding, with an age-related increase in amyloid positivity [12].

In summary, a negative amyloid scan makes Alzheimer pathology as a cause of cognitive impairment very unlikely. Amyloid imaging is more useful in younger patients, when the a priori risk of amyloid deposits is lower. It is also helpful in differentiating AD from dementias without amyloid deposition, such as FTD. Amyloid imaging, however, is less informative for distinguishing AD from DLB because the latter can be associated with amyloid deposition [13]. The average cortical binding in DLB is lower than in AD, but higher than in controls. Cortical amyloid-beta deposition may be a factor in the

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development of cognitive impairment in Lewy body disorders, as binding appears to be normal in patients with Parkinson's disease (PD) without dementia [13].

Unlike amyloid, tau deposits are present mainly intracellularly, and until recently, they could only be studied postmortem using immunohistochemistry. In AD, tau-specific PET tracers demonstrate tau accumulation in temporo-parietal cortices [12]. Furthermore, a distinct tau retention pattern has been observed across a spectrum of clinical AD phenotypes (e.g., amnestic variant, visual variant and language variant), consistent with pathological findings [14].

In contrast to amyloid imaging, tau-PET is suitable as a marker of disease progression. It correlates with cognitive measures, including global cognition, episodic memory, visuospatial domain and language. Tau-PET reflects neurodegeneration, as measured by cortical and hippocampal atrophy, and hypometabolism on FDG-PET [12]. While this is a considerable advance, a number of caveats exists. The available tracers have shown differential affinity to different subtypes of tau and significant non-specific binding, particularly to subcortical structures [14]. The binding properties of tau ligands remain to be fully characterised, but the use of tau-imaging agents is likely to lead to a greater understanding of the pathophysiology of AD and other proteinopathies. The relationship between amyloid and tau-pathology requires further elucidation. Although a significant body of research demonstrates that amyloid deposition is the initial phenomenon that triggers tau-aggregation, there is evidence to suggest that a subset of cognitively healthy older people may present with tau-driven neurodegeneration prior to abnormalities in Aβ markers [15].

Mild Cognitive Impairment and Prognosis towards Dementia

In people with mild cognitive impairment (MCI), imaging provides information about the possible underlying pathology and prognosis. MRI evidence of hippocampal atrophy, temporo-parietal hypometabolism or an amyloid positive scan suggest underlying Alzheimer's type pathology and can indicate an increased risk of progression.

Among the three biomarkers, FDG-PET by itself is the strongest predictor of progression from MCI to AD [16]. A Cochrane systematic review of 14 FDG-PET studies found 82% specificity and 76% sensitivity in predicting conversion from MCI to AD [17]. While amyloid PET is very sensitive (96%), it has low specificity (56%); for every 100 subjects with a negative scan, only one will develop dementia, but 28 of 100 subjects with high amyloid retention will not progress [18]. Combining amyloid and neurodegeneration biomarkers achieves higher accuracy [16]. A positive result for one amyloid marker and one neurodegeneration marker indicates a high likelihood that the MCI syndrome is due to AD; it is also strongly associated with clinical progression over time and the development of disability and dementia within five to seven years [1,6]. Nevertheless, the utility of imaging biomarkers in the clinic remains unclear, because of a substantial overlap between patients and controls, which makes conclusions at an individual level difficult. In vascular cognitive impairment, structural MRI shows evidence of vascular pathology. Mixed pathologies are common, and the presence of vascular lesions does not exclude other possible pathologies.

Vascular Dementia

Evidence from structural neuroimaging is obligatory for a diagnosis of vascular dementia (VaD). Diagnostic criteria require vascular changes not only to be present but also to be clinically

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and temporarily relevant to cognitive decline. VaD may be the result of large vessel disease, small vessel disease (SVD) or strategic infarcts. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a rare, genetic form of VaD.

Large vessel disease is more likely to be associated with cognitive impairment, if it presents with multiple infarcts (multi-infarct dementia). Strategically placed infarcts, such as bilateral thalamic or fornix infarcts, are associated with severe memory deficits.

SVD is the most common cause of VaD and is characterised by lesions involving more than a quarter of white matter. It results from damage to the cerebral microcirculation. Wardlaw and colleagues describe the imaging features of SVD on MRI in detail: they include white matter hyperintensities (WMH), recent small subcortical infarcts, lacunes, prominent perivascular spaces, cerebral microbleeds and atrophy [19]. All imaging features of SVD also occur in healthy older people, but they are strongly associated with vascular risk factors and cognitive impairment [20].

WMH clearly appear on T2-weighted or FLAIR MRI sequences as bright, bilateral, often symmetrical signal areas. They are predominantly supratentorial in distribution, although can be seen in the pons, and have a predilection for the frontal lobes [21]. WMH are not specific to VaD and occur in a wide range of inflammatory and autoimmune conditions. The severity of white matter damage can be quantified using rating scales or automated segmentation methods. In clinical practice, the Fazekas scale can be used [22]. It rates deep and periventricular WMH separately on FLAIR MRI images, with large confluent and irregular lesions typical of VaD (Table 4.2). On structural imaging, CADASIL is characterised by extensive confluent WMH, lacunar infarcts and involvement of the anterior temporal lobes and external capsule [19].

Table 4.2 Fazekas rating scale for severity of white matter lesions (see also [22])

Fazekas score	Periventricular white matter lesions	Deep white matter lesions
0	**absence**	**absence**
1	Caps or pencil thin lining	Punctate foci
2	Smooth halo	Beginning confluence of foci
3	Irregular periventricular hyperintensities extending to the deep white matter	Large confluent areas

Advanced MRI techniques, such as DTI, demonstrate reduced white matter integrity in patients with VaD. VaD has been conceptualised as a 'disconnection syndrome', and disrupted cortical-subcortical connections due to white matter tract damage are likely to underlie the cognitive symptoms. If this is the case, DTI may be a more sensitive marker than structural MRI of the pathological changes in VaD. DTI studies have found that patients with subcortical ischaemic VaD have reduced white matter integrity in anterior subcortical areas, periventricular areas, frontal and parietal white matter, the genu of the corpus callosum and the superior longitudinal fasciculus [23].

Functional imaging demonstrates areas of hypoperfusion or hypometabolism, often asymmetrical, distributed in a vascular territory and involving cortical and subcortical structures [4].

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Vascular pathology is common with advancing age, and often coexist with neurodegenerative brain changes. VaD and AD have common risk factors and a synergistic relationship; therefore, even when the imaging is suggestive of extensive vascular damage, the presence of mixed pathology cannot be excluded.

Lewy Body Dementia

Structural imaging techniques contribute little to the early diagnosis of Lewy body dementia (DLB) because they are non-specific and difficult to assess at an individual level. DLB is associated with diffuse atrophy, which is greater than in controls, but less severe than in AD. Relative sparing of the MTA on structural imaging supports a diagnosis of DLB, rather than AD. On functional imaging (FDG-PET or HMPAO-SPECT), DLB is characterised by reduced occipital activity, including the primary visual cortices, as well as a relative preservation of posterior or mid-cingulate metabolism on FDG-PET ('cingulate island sign') [24]. These features, however, are not specific to DLB, as they occur in posterior cortical atrophy, a variant of AD. Similar to AD, parieto-temporal reductions in metabolism are seen in DLB also [24].

The only imaging feature included in the diagnostic criteria for DLB is reduced dopamine transporter (DAT) uptake in basal ganglia, demonstrated by FP-CIT SPECT [24]. A DAT scan is also recommended by NICE, when the diagnosis is in doubt [5]. Clinical symptoms generally appear after significant striatal neurodegeneration has occurred; therefore, the difference between a normal and abnormal scan is usually clear and visual interpretation is sufficient for clinical evaluation.

In healthy subjects, DAT scans of the lenticular nuclei demonstrates two symmetric comma-shaped regions of activity. Age-related degeneration affects these structures equally, while in PD and DLB posterior putamen loses dopaminergic terminals earlier and to a greater degree, giving the appearance of dot-shaped regions of activity. DAT concentrations are decreased in DLB, PD and atypical parkinsonian syndromes (APS), hence DAT scan can help distinguish these syndromes from drug-induced parkinsonism (antipsychotics bind to the postsynaptic D2 receptors, not DAT) and essential tremor, which have normal dopaminergic presynaptic binding. However, DAT scans cannot differentiate DLB from APS or between APS because all these conditions demonstrate abnormal but overlapping patterns of dopamine input to the basal ganglia [25].

DAT imaging is very good at differentiating DLB from AD, with sensitivity 78% and specificity 90% [24]. Abnormal DAT uptake is less useful in differentiating DLB from FTD or VaD because a proportion of these patients have abnormal scans. Vascular parkinsonism may show asymmetric striatal binding, in regions affected by infarction as demonstrated by structural defects on MRI imaging.

Frontotemporal Dementias

Imaging biomarkers, such as a specific pattern of grey matter atrophy or reduction in brain metabolism/perfusion detected by PET/SPECT, are part of the guidelines for making a diagnosis of 'probable' FTD in addition to a clinical diagnosis [26,27].

FTD is a heterogeneous group of clinical-anatomical subtypes with various underlying pathologies, divided into behavioural variant frontotemporal dementia (bvFTD) and language associated syndromes (primary progressive aphasia, or PPA).

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On T1-weighted MRI, bvFTD is associated with atrophy in the frontal and temporal lobes, as well as the anterior cingulate cortex and insula [28]. Later in the disease course, subcortical structures are involved as well [28]. Three PPA syndromes have been described: semantic variant PPA (svPPA), non-fluent variant PPA (nfvPPA) and logopaenic variant PPA (lvPPA). In PPA, the atrophy is often asymmetrical, with the left side being more affected. SvPPA is associated with antero-inferior temporal lobe atrophy, nfvPPA with perisylvian and insular atrophy, and lvPPA with involvement of the posterior temporal cortex. In a large proportion of cases, the logopaenic variant is associated with AD pathology. Assessment of atrophy using visual rating scales and performed by experienced clinicians showed a specificity of 81% in the discrimination of FTD from AD [28].

Up to 20% of all FTD cases have a genetic cause, resulting largely from mutations in three genes: MAPT (encoding microtubule-associated protein tau), GRN (progranulin) and C9orf72. Highly asymmetric fronto-temporo-parietal atrophy has been associated with mutations in the progranulin gene, MAPT mutations are associated with relatively symmetrical involvement of anteromedial-temporal and orbitofrontal lobes, while a C9orf72 gene expansion shows a predominantly symmetrical and widespread pattern of atrophy with involvement of the thalamus [28].

DTI has shown decreased white matter integrity in the respective regions affected depending on the clinical phenotype; the changes in white matter are more widespread compared to AD, with particular damage to anterior tracts. The frontal-insula-anterior cingulate are suggested to be part of a structurally and functionally connected network (a salience network), which demonstrates decreased connectivity during resting state fMRI, although normal or increased connectivity has been reported as well [28].

FDG-PET reflects the pattern seen on structural scans, but the changes are visible earlier, sometimes years before patients meet clinical criteria for a diagnosis of probable FTD [28].

Rare Dementias (Neurological Dementias)

Table 4.3 shows the neuroimaging features of the less common dementias.

Imaging in Other Psychiatric Conditions

Depression (Late Onset vs. Early Onset)

Neuroimaging is not part of the routine clinical assessment of late-life depression, but it has contributed to our understanding of illness mechanisms. Unlike early-onset depression (EOD), structural brain abnormalities are hypothesised to play a key role in the pathophysiology of late-life depression (LLD) and particularly late-onset depression (LOD), defined as age of onset >60 years.

It has been postulated that vascular disease compromises the integrity of the frontal-subcortical circuits involved in mood regulation (the vascular depression hypothesis) [29]. In contrast to depression in younger adults, LOD is associated with more severe WMH, subcortical lacunes and microinfarcts, as well as grey matter atrophy, mainly within frontal lobe and hippocampus [30]. A meta-analysis of DTI studies demonstrates reduced white matter integrity within fronto-striatal (dorsolateral prefrontal cortex) and limbic networks

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Table 4.3 Neuroimaging features of the less common dementias

Diagnosis	Imaging
Idiopathic normal pressure hydrocephalus (CT/MRI)	• Ventricular enlargement (Evan's index* >0.3), not caused by atrophy, significant cerebrovascular disease or congenital enlargement • No macroscopic obstruction to CSF flow
Huntington's disease (MRI)	• Caudate atrophy, generalised cortical atrophy
Multiple sclerosis (T2/FLAIR MRI)	• Multiple hyperintense white matter lesions, particularly if periventricular, ovoid in shape, 5 mm or larger, involving corpus callosum, brainstem, cerebellum • Enhancement after contrast in acute lesions • Differential diagnosis: small vessel disease
Dementia in Parkinson's disease (DAT scan)	• Abnormal DAT scan
Progressive supranuclear palsy (MRI, DAT scan)	• Midbrain atrophy (axial diameter <7 mm, 'humming bird sign'; involvement of pons, thalamus, superior cerebellar peduncle, striatum) • Abnormal DAT scan
Corticobasal degeneration (MRI/FDG-PET, DAT scan)	• Asymmetrical frontoparietal cortical atrophy • Hypometabolism mirrors the pattern seen on structural imaging • Abnormal DAT scan
Multiple system atrophy (MRI, DAT scan)	• Atrophy of putamen, middle cerebellar peduncle, pons and/or cerebellum • 'Hot cross bun sign' (cruciform hyperintensity on T2-weighted MRI in an atrophied pons) • Abnormal DAT scan
Prion diseases (T2/FLAIR/diffusion weighted imaging MRI)	• Hyperintensities within the basal ganglia, thalamus and cortex ('cortical ribboning') • 'Pulvinar sign': hyperintensities in the posterior thalamus is thought to be indicative of vCJD† and is included in the diagnostic criteria
Limbic encephalitis (T2/FLAIR MRI)	• High-intensity changes in the medial temporal lobes

* Evan's index = greatest width frontal horns of the lateral ventricles/maximum internal width of the skull.
† vCJD = variant Creutzfeldt-Jacob disease.

(uncinate fasciculus) of patients with LLD, which are considered the key neural pathways for the pathology of LLD [31].

Lack of specificity of findings, heterogeneity in the anatomy of results reported, as well as the uncertain value current imaging markers add beyond clinical assessment, make their translation into clinical practice difficult [3]. For the same reasons, neuroimaging studies in other psychiatric disorders (bipolar affective disorder, schizophrenia) are not part of routine clinical practice.

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Future Developments

The future of neuroimaging will involve incorporating new modalities into clinical practice. A multidisciplinary task force has proposed a framework to aid the translation of AD biomarkers from research into clinic [6]. Future priorities include the standardisation of biomarkers and defining the normative values, which require research in representative samples, rather than select patient groups from highly specialised centres. To achieve that, large-scale prospective epidemiological studies like the Human Connectome Project, UK Biobank, Lifebrain and the Whitehall-II Imaging substudy have been set up [32–35]. They include healthy populations and aim to accumulate data using advanced neuroimaging methods, complemented by sophisticated software, as well as to link these data with a wide range of social, behavioural and biological variables. Several disease-based cohorts have been established, for example the Canadian Consortium on Neurodegeneration in Aging [2]. Other research priorities include the evaluation of biomarker performance in detecting early disease and studying their performance in combination (using multimodal imaging, but also integration with blood tests or neuropsychological tests). Finally, clinical guidelines for the appropriate use of biomarkers in memory clinics need to be developed [6]. There will be ethical issues around the use of biomarkers in pre-dementias.

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