Abbreviated title page

Title

Neuroimaging in Dementia: more than typical Alzheimer's Disease

Article type

Invited review

Summary

The aim of neuroimaging combined with clinical findings, plasma and CSF biomarkers is to help with early diagnosis of neurodegeneration, ideally before the onset of dementia. Different subtypes and variants of Alzheimer's disease, other dementias and co-existing diseases are important considerations.

Essentials

1. In the age of emerging treatments for Alzheimer's disease (AD), early diagnosis is of increasing clinical importance, as is differentiating AD variants from their mimics.
2. The diagnostic process should consider mixed pathologies and overlap between neurodegenerative and concurrent cerebrovascular diseases, which are frequent in old age.
3. Cerebrovascular diseases share underlying risk factors and have overlapping symptoms with AD; it is vital to consider their contribution to the clinical presentation and the associated treatment options.
4. Developments in neuroimaging, including MRI and PET, data-driven disease models, and genetic analyses provide increasing evidence that not all AD is typical AD.
5. For emerging treatments to be effective, early diagnosis is essential to prevent neuronal loss, yet subtle early findings make early diagnosis challenging.
6. Early diagnosis can probably be achieved only by combination of neuroimaging, clinical findings, plasma and CSF biomarkers

Abbreviations

AD Alzheimer disease

DLB dementia with Lewy bodies

FDG fluorodeoxyglucose

FTD frontotemporal dementia

NPH Normal pressure hydrocephalus

PD Parkinson Disease

Abstract

Alzheimer's disease (AD) is the most common cause of dementia. The prevailing theory of the underlying pathology assumes amyloid accumulation followed by tau aggregation and neurodegeneration. However, the current anti-amyloid and anti-tau treatments show only variable clinical efficacy.

Three relevant points are important for the radiological assessment of dementia. First, besides various dementing disorders (including AD, fronto-temporal dementia, and Lewy body dementia), clinical variants and imaging subtypes of AD include both typical and atypical AD. Second, atypical AD has overlapping radiological and clinical findings with other disorders. Third, the diagnostic process should consider mixed pathologies in neurodegeneration, especially concurrent cerebrovascular disease, which is frequent in old age.

Neuronal loss is often present at the onset of cognitive decline. Thus, for effective emerging treatments, early diagnosis before the onset of clinical symptoms is essential to slow down or stop subsequent neuronal loss, requiring molecular imaging or plasma biomarkers.

Neuroimaging, particularly MRI, provides multiple imaging parameters for neurodegenerative and cerebrovascular disease. With emerging treatments for AD, it is increasingly important to recognize AD variants and other disorders that mimic AD. Describing the individual composition of neurodegenerative and cerebrovascular disease markers while considering overlapping and mixed diseases is necessary to better understand AD and develop individualized, efficient therapies.

Introduction

The currently available therapeutic options for AD, and neurodegenerative diseases in general, are still limited, except for several treatment options for the motor symptoms of Parkinson's Disease (PD). Acetylcholinesterase inhibitor treatment may show transient slowing of cognitive decline or even cognitive improvement in AD. But this beneficial effect is often temporary for 1-2 years; then cognitive decline accelerates.

More recently, clinical trials have evaluated therapeutic strategies targeting amyloid deposits (1). Aducanumab is a human monoclonal antibody and the first approved disease-modifying drug against AD (2). Other similar approaches include gantenerumab (3) or lecanemab (4). The clinical impact of these drugs in clinical trials have been variable, while they frequently cause side effects, notably amyloid related imaging abnormalities (ARIA) which occur in two variants including brain edema or sulcal effusion (ARIA-E) and hemosiderin deposits (ARIA-H) (5, 6). Additional side effects include neuronal disturbance (7) or multiple cerebral hemorrhages related to treatment with a tissue plasminogen activator while receiving anti-amyloid treatment (8).

The low success rate of AD treatment trials is due to a combination of factors. The first factor is late diagnosis. Many clinical trials in AD have focused on the late stages of the disease. Already at the onset of cognitive decline, on average around 50% of neurons of the hippocampus are lost, with significant inter-individual variability (9). Even if an AD treatment is efficient to slow down or even stop subsequent neuronal loss and cognitive decline, it is very unlikely that treatment will repopulate lost neurons. The second factor is not considering the variants and subtypes of AD. Most clinical trials assume a stereotypical AD disease progression, while several AD variants and subtypes exist. The third factor is viewing AD as an isolated disease while ignoring co-existing diseases such as cerebrovascular disease. The coexisting diseases may act as catalysator and accelerate neurodegenerative pathology (10), or both pathologies may interact in their effect on cognitive functioning. The fourth factor is treating AD as having a single cause instead of being a multifactorial disease. The underlying mechanism of AD is still disputed. The prevailing theory suggests misfolded proteins

that aggregate (notably beta-amyloid and tau), leading to neuronal loss (11). Alternative theories include a neuroinflammation pathway. Drugs addressing this theory are fundamentally different from those amyloid hypothesis drugs mentioned above and are still in early phases. Other theories include disease of synapses or mitochondria (12). Even after more than 100 years, to our knowledge, there is no consensus regarding the underlying pathology of AD. This suggests that AD is a multifactorial disease with different disease phenotypes and co-existing diseases. In concert, those observations imply that dementia is more than typical AD and that AD is not a stereotypical single disease but comes in several variants, subtypes, and with other co-existence diseases. Consequently, neuroimaging, in conjunction with laboratory and genetic testing, should aim for early detection before the onset of dementia.

Part 1: AD and its variants

Mechanism of AD

Most available research on AD assumes a stereotypical disease progressing from cognitively healthy to mild cognitive impairment to AD. While the exact mechanism of AD remains unknown, most studies use the amyloid cascade theory as their basis, represented by the amyloid/tau/neurodegeneration (ATN) classification (13). This model assumes initial accumulation of amyloid (A+T-N-), then additional accumulation of tau (A+T+N-) finally leading to neurodegeneration (A+T+N+). This model is also the underlying theory of most current anti-amyloid drug developments. When applying this ATN disease progression model to typical memory clinic visitors with subjective or objective cognitive impairment, 53% would follow the model of A+T-N (16%) to A+T+N- (20%) to A+T+N+ (17%) (14). Among other patterns (eg, A-T+N- (6%) or A-T-N+(9%), 24% would not match this model, thus indicating an alternative disease, such as limbic-predominant age-related TDP-43 encephalopathy (LATE) (below).

Atypical AD Variants

Besides typical AD, there are several atypical AD variants, determined based on clinical symptoms and neuro-anatomical distribution of pathology. Posterior cortical atrophy is a clinical-radiological variant characterized by posterior atrophy with visuospatial disturbances, found more often in younger patients (15). Behavioral or frontal AD is a variant characterized by symptoms mimicking fronto-temporal dementia and typically with a more frontal atrophy pattern (16). Individuals with behavioral variant AD often have trouble controlling their behavior, clinically overlapping with behavioral variant of frontotemporal dementia (FTD) as discussed below. Language variant AD, for example logopenic variant of AD, is characterized by difficulties in single-word retrieval, repetition of sentences/phrases, and the presence of phonologic errors (17). This variant clinically overlaps with logopenic variant primary progressive aphasia caused by fronto-temporal dementia (FTD) pathology (below).

Clinical use of MRI in typical or classic AD

Typical or classic AD is characterized by memory impairment due to predominant atrophy of the hippocampus and surrounding medio-temporal structures (**Figure 1A**). Atrophy in AD is classified using semi-quantitative visual rating scales, such as the

mesio temporal atrophy (MTA) scale. Alternatively, various image analysis tools exist for automatic volumetry, typically based on volumetric T1 weighted (3DT1) brain MRI. Normal inter-individual variation in hippocampal volume in older controls is in the range of 20%, while the average difference between mild cognitive impairment and healthy controls is in the range of 7%, and AD versus controls is around 12% (18). This indicates that hippocampal volume may discriminate at the group level, yet identification of individual cases of AD is limited notably at initial stages of the disease. In younger patients, the pattern of atrophy might be predominant in the parietal region with less pronounced atrophy of the hippocampus (**Figure 1B**). As there is more inter-individual variability in the volume of the parietal lobe, it can be more challenging to determine the presence of accentuated parietal atrophy using visual assessments such as semi-quantitative rating scales.

Molecular imaging in AD: fluorodeoxyglucose (FDG) PET, Amyloid PET, and tau PET

With regards to molecular imaging, FDG PET is the most established technique in the evaluation of suspected dementia, illustrating brain hypometabolism (19)**.** FDG PET may contribute to the early detection of dementia, as oftentimes hypometabolism precedes brain atrophy. Moreover, FDG PET may with the differential diagnosis of dementia, as different patterns of hypometabolism exist (**supplementary Figure 1).** The typical pattern of hypometabolism in typical AD includes the posterior cingulate cortex and bilateral parietal areas. Due to the metabolic-vascular coupling in the brain, patterns of brain hypoperfusion in arterial spin labeling MRI closely resemble patterns of brain hypometabolism in FDG PET (**supplementary Figure 2).**

While FDG PET measures unspecific brain metabolism, more specific molecular tracers are now available for the diagnosis of AD, especially amyloid PET and tau PET (**Figure 2**). Amyloid PET may be abnormal up to 10 years before disease onset, yet is not specific for AD dementia, as up to 20-30% of cognitively healthy older adults exhibit amyloid deposition. Consequently, amyloid PET is notably good to *rule out* AD. Conversely, tau PET abnormality is more closely related to disease onset and is useful to *rule in* AD. The combination of a positive tau and amyloid PET scan in cognitively unimpaired individual carries a higher risk of future cognitive decline (20).

Imaging-based subtypes of AD based on patterns of brain atrophy

Recently, neuroimaging studies have grouped large data sets with advanced image analysis procedures to define subtypes of AD based on imaging patterns.

A recent study pooled over 1000 cases of amyloid PET in a data-driven analysis with the intention to disentangle disease subtype and disease stage at the same time (22). This study identified 3 pattern subtypes: frontal, parietal, and occipital (**Supplementary Figure 3A**). It might appear contradictory that more recent PET studies suggest subtypes of AD, while previous histopathological studies suggested a more unique and stereotypical AD pattern. Several factors explain this apparent contradiction. First, large data sets allow for clustering analysis, which is necessary to detect such subtypes. Second, the differences between the subtypes are most pronounced at the initial stages of the disease. At later stages, the subtypes converge and it is no longer possible to disentangle them. It is easier to combine large PET datasets across different centers and include pre-symptomatic cases than post-mortem histopathologic grading. The post-mortem grading is usually done in smaller data sets and at later stages of the disease. Third, the analysis is not done specifically to discriminated subtypes (requiring a large data set as discussed) but instead consists of grouped data. If the newly observed subtypes are averaged into one single type, the resulting pattern resembles the established disease pattern known from histopathological studies (**Supplementary Figure 3B**). Of note, there is a certain degree of concordance between clinically-defined AD variants, and imaging-defined AD subtypes, such as frontal dominant AD.

When applying this data-driven stage and type segregation, the results will be close to tau PET which again results in the segregation of subtypes of tau accumulation (23). These 4 subtypes are limbic (typical), mesiotemporal lobe sparing, posterior, and left temporal, reflecting amnestic, behavioral, visuospatial and language variants discussed above**.**

Genetic subtypes and genetic risk factors for AD

An uncommon form of familial early-onset AD, is inherited as an autosomal-dominant gene mutation (the current best-established mutations are amyloid precursor protein, presenilin-1, and presenilin-2). In contrast, in the more common typical late-onset and sporadic AD, genetic mutations are less established. But several identified genetic variants increase the risk of AD and may lead to familial patterns of AD risk. Today,

the most important genetic risk factor for AD is the apolipoprotein E or APOE gene. Each person inherits two APOE alleles, one from each biological parent. APOE3 is the most common allele and carries a neutral risk. APOE4 increases the risk for AD, notably in homozygotes (24, 25). In contrast, APOE2 is relatively rare and is associated with decreased risk of AD (26). In dominantly inherited AD, amyloid deposition in PET is detected 15 years before expected symptoms onset and a decline in amyloid-beta (Aβ)42 in CSF can be detected even earlier (27).

Liquid biomarkers

Recently, substantial progress has been made in liquid biomarkers based on cerebrospinal fluid and blood samples, which will likely change the role of imaging of AD and related diseases in the future. Discussion of those liquid biomarkers is beyond the scope of the current review article, and we refer to a recent review article (28).

Underlying disease, atrophy pattern, or clinical manifestation

There are several ways to classify dementias, including symptom-based, imaging-based, and pathology-based approaches. Different underlying molecular pathologies can lead to similar clinical symptoms and atrophy patterns, which makes the classification of dementias purely based on symptoms and imaging appearances problematic. For example, the underlying pathology of posterior cortical atrophy (below), defined by parietal volume loss and visuospatial symptoms, can be related to AD, dementia with Lewy bodies (DLB) or corticobasal degeneration (29) . Another example is patients presenting with primary progressive aphasia (below) who may have AD or frontotemporal dementia (FTD) as the underlying pathology.

Posterior cortical atrophy

Posterior cortical atrophy (PCA) consists of predominant parietal atrophy combined with a typical clinical presentation (15). This is a frequent mode of presentation in younger patients, with visuospatial disturbances with lesser degree of hippocampal atrophy (**Figure 3**). Oftentimes, amyloid plaques and neurofibrillary tangles are present, similar to typical AD, yet in a different spatial distribution. Also, APOE4 is less often present in PCA compared to typical AD patients. The differential diagnosis of posterior cortical atrophy includes Lewy body disease (below) with abnormal dopamine transporter imaging of the striatum and corticobasal degeneration with cerebellar atrophy and asymmetric parietal atrophy.

Primary progressive aphasia

Primary progressive aphasia (PPA) is a neurological syndrome characterized by slow progressive impaired language capabilities (30). The commonly used classification distinguishes the clinical subtypes of primary progressive aphasia: (I) Semantic variant svPPA (also still frequently referred to as semantic dementia) (II) Logopenic variant lvPPA and (III) Nonfluent-agrammatic variant (**Figure 4**). It is important to realize that these clinical categories have variable underlying pathology. Whereas AD pathology is frequently associated with the logopenic variant, the semantic and nonfluent-agrammatic variants link to frontotemporal lobar degeneration with primary tau or TDP-43 pathology (31).

PART 2: Other types of dementia that mimic AD

While AD is the most common type of dementia, it is not the only type of dementia. Typical distributions of cases of dementia types in a memory clinic setting (**Figure 5**) show that around 60% of cases are AD, while around 15% are DLB and 5% are FTD. Consequently, the ratio of the clinical diagnosis of AD:DLB is 4:1 and AD:FTD is 12:1. A PubMed search (accessed on December 31, 2022) yielded 218,214 entries for AD since 1913, 9727 for DLB since 1961 and 12,656 for FTD since 1948, which corresponds to rations of AD:DLB of 22:1 and AD:FTD of 17:1 (Supplementary **Figure 4**). These are simplified numbers, yet this illustrates the overrepresentation of AD in scientific research with respect to its clinical prevalence.

The following section discusses the differential diagnosis of other forms of dementia, which may be in the differential diagnoses for AD, either because of overlap in clinical symptoms or in imaging characteristics.

Teaching Point: Hippocampal atrophy is not specific to AD but is a feature of several other forms of dementia. Consequently, focusing on hippocampal volume alone may lead to wrong diagnoses.

LATE

Limbic-predominant age-related TDP-43 encephalopathy (LATE) neuropathological change was recently defined as a TDP-43 proteinopathy in older adults, with or without coexisting hippocampal sclerosis pathology (**Figure 6)** (34). Associated with an amnestic dementia syndrome, this type of dementia mimics an Alzheimer-type dementia clinically and radiologically and distinguishes itself from FTD with TDP-43 pathology as it affects very older adults and has a relatively restricted neuroanatomical distribution of TDP-43 proteinopathy (34). The neuroimaging pattern includes hippocampal atrophy mimicking typical AD but without amyloid deposition on molecular imaging. This dementia is thus a mimic of AD (clinically and radiologically). It is also an example of an entity not following the ATN model discussed above. Assessment of amyloid status (using CSF or PET) is the only safeguard to differentiate AD from LATE/HS.

DLB

Dementia with Lewy bodies (DLB) belongs to the family of synucleinopathies, together with Parkinson disease (PD) and multiple system atrophy (MSA). Characterized by the accumulation of Lewy bodies, this type of dementia shares pathological features with PD. Sometimes, considered as two ends of a DLB spectrum, PD may transition from initial motor symptoms to later cognitive decline while DLB may transition from initial cognitive decline to later motor symptoms. In analogy to other forms of dementia discussed, the DLB / PD spectrum has clinically variable presentations based on overlapping underlying pathology (35). In addition to the extrapyramidal findings most pronounced in PD, typical symptoms include REM-sleep disturbances and visual hallucinations found notably in DLB.

Teaching point: DLB spectrum is common, yet typically has a less obvious atrophy pattern on standard structural imaging (including mild atrophy of parietal regions and hippocampal subregions in structural CT or MRI) and is therefore easily overlooked from a neuroradiological perspective. Dopamine imaging is essential for its diagnosis.

Genetic subtypes and genetic risk factors

Less research has been performed to identify the genetic subtypes and risk factors of DLB compared with AD (36). We know today that DLB shares risk factors with AD, in particular, APOE4. Moreover, as already discussed, DLB overlaps with PD (36).

Structural subtypes and MRI markers

Unlike the hippocampal predominant atrophy in typical AD, DLB and PD are not associated with an obvious pattern of brain atrophy. Compared with AD, DLB has milder hippocampal atrophy, occurring only at later stages, that may have different spatial predominance (eg, preserving cornu ammonis 1 subfield) (37). Sometimes, some mild parietal and occipital atrophy is visible (**Figure 7**). Consequently, standard structural MRI and CT have a blind spot for the diagnosis of DLB and PD. This might be one of the reasons explaining why DLB remains underrecognized at least from a radiological perspective.

Recently abnormal appearance of the nigrosome 1 (also known as swallow tail sign) based on susceptibility-weighted imaging (SWI) was introduced as an MR imaging in PD (38). Abnormal imaging of the nigrosome 1 behaves similar to dopamine imaging in nuclear medicine (the most commonly used technique being 123i-ioflupane SPECT known as DaT-scan). Both MR imaging of nigrosome 1 and nuclear medicine dopamine imaging are abnormal in PD and DLB yet normal in AD or FTD. Consequently, abnormal appearance of the nigrosome 1 in DLB may resolve the blind spot of MRI for the diagnosis of DLB (**Supplementary Figure 5**) (39, 40). Imaging of the nigrosome 1 is without any doubt a challenging sign, which requires an experienced reader and critically depends on appropriate imaging parameters (41). Yet, it is clinically applicable with minimal additional acquisition time and cost without irradiation assuming that most patients with neurodegenerative disease already undergo MRI. Imaging of the nigrosome 1 is probably best applied if the intention is not to replace dopamine imaging, yet to triage patients for subsequent dopamine imaging to improve diagnostic yield (42). Alternative imaging techniques include heavily T1-weighted neuromelanin-sensitive sequences, which is also possible at an individual level and in clinical routine yet might be even more challenging.

Nuclear medicine

Unlike the unspecific structural CT and MRI findings, nuclear medicine has a vital role in the diagnosis of DLB/PD (43)

Dopamine imaging

Dopamine imaging is the most established and specific nuclear medicine technique for DLB/PD (44). ^{123}I ioflupane SPECT also known as DaTscan is the best-known technique, yet other dopamine tracers and techniques do exist. As a simplification, the normal dopamine uptake in the striatum has a bilateral comma shape pattern. In DLB and PD, the tracer uptake of the putamen decreases, which results in a loss of the typical comma-shaped striatal appearance. Dopamine imaging is abnormal in DLB and PD (and atypical parkinsonian syndromes) but normal in AD and FTD.

Alternative PET tracers

Standard FDG PET typically shows a specific pattern of hypometabolism in DLB involving the bilateral parietal and occipital areas while sparing the posterior cingulate (giving rise to the cingulate island sign). In contrast, the typical pattern of FDG PET

hypometabolism in AD spares the occipital areas but involves bilateral parietal and occipital areas. Typical FDG hypometabolism in FTD also spares the occipital region and involves fronto-parietal areas.

A certain amount of β-Amyloid (Aβ) pathology is also found in patients with DLB and amyloid PET may therefore be positive. However, in a study with pathologically proven diagnoses, 11CPittsburgh compound B(PiB) uptake on PET was lower in DLB than in AD (45).

Frontal dementias

Representing a heterogeneous group of dementias, FTD is part of the larger entity referred to as frontotemporal lobar degeneration, which also includes other disorders such as progressive supranuclear palsy and corticobasal degeneration, depending on the classification system used (46).

These dementias have variable underlying pathology, atrophy patterns, and clinical presentations. The latter can be broadly categorized into language-led presentations (primary progressive aphasias PPA) and behavior-led presentations (disintegration of personality, sometimes misdiagnosed as psychiatric disorders) (31, 47). Usually presenting at a younger age than AD, FTD is more frequently associated with gene mutations, especially in familial cases. In addition, they can be associated with other neurological conditions, such as parkinsonism or motor neuron disease. A detailed discussion of frontotemporal lobar degeneration goes beyond the scope of this review article. We, therefore, focus on the most common subtypes relevant in the current context and which may mimic AD: behavioral variant frontotemporal dementia (bvFTD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD).

Teaching point: hippocampal atrophy, oftentimes asymmetric, is a typical feature of frontotemporal lobar degeneration. This might mimic the diagnosis of AD when focusing only on hippocampal atrophy.

Clinical use of MRI for differentiation of frontotemporal dementias

Behavioral variant frontotemporal dementia

Behavioral variant frontotemporal dementia (bvFTD) is the most common subtype of FTD and is characterized by predominant fronto-temporo-parietal atrophy, typically

with an anterior to posterior gradient. Mesiotemporal atrophy is oftentimes associated, though typically quite asymmetric (**Figure 8**).

Progressive non-fluent aphasia

Progressive non-fluent aphasia (PNFA) is a form of frontotemporal dementia characterized by word production problems, effortful and non-fluent speech but language comprehension remains intact. Imaging shows asymmetrical focal atrophy of the inferior frontal gyrus and peri-insular region, most frequently on the left side. (**Figure 9)**. There are, however, wide variations in severity and posterior extension of the atrophy.

Semantic dementia

A disorder affecting language comprehension (losing the meaning of words and images), semantic dementia (SD) is characterized by focal atrophy of the temporal pole and, in particular, the fusiform gyrus, classically on the left side. Asymmetric mesio-temporal atrophy is typical but as the disease progresses the contralateral side usually also gets involved (**Figure 10 A, B**).

Right-lateralized semantic dementia

Right-lateralized frontotemporal dementia is characterized by mirror-symmetric right-dominant temporal pole atrophy. This type of dementia is much rarer than semantic dementia (**Figure 10, C, D**). It remains controversial whether right-sided FDT is less common than left-lateralized typical semantic dementia; speculations include that in most individuals the left hemisphere is dominant and predominantly involved in language processing and therefore might degenerate faster. Alternatively, right-lateralized FTD might be underdiagnosed as affection of the non-dominant right hemisphere results in less evident clinical dysfunction.

Genetic subtypes and genetic risk factors for FTD

Most cases of genetic FTD are due to mutations in one of the three following genes: C9ORF72, MAPT, or GRN. Rarely, is genetic FTD caused by a mutation in the following genes: TARDBP, VCP, CHMP2B, SQSTM1, UBQLN1, or TBK1. Different mutations have different patterns of atrophy and clinical presentations, and different ages of presentation (31, 47).

Normal pressure hydrocephalus (NPH) configuration spectrum, glymphatic system

The classic description of NPH includes the clinical triad of dementia, gait disturbance, and urinary incontinence. NPH is presumably related to impaired cerebrospinal fluid dynamics. The radiological findings associated with NPH include : a dilated ventricular system with high-convexity tight sulci, trans ependymal transudation of cerebrospinal fluid, dilation of the Sylvian fissure, corpus callosum in a V-shaped angle in the coronal plan, posterior cingulate sulcus sign, and others. The iNPH Radscale, a grading scale for the imaging findings of idiopathic NPH, summarizes key imaging findings. (48). In some patients with suspected dementia, only some radiological findings are suggestive of NPH, yet without the full clinical picture of NPH **(Figure 11)**. It was recently suggested that radiological NPH configuration, notably high-convexity tight sulcus, represents a subgroup of non-AD pathophysiology associated with cognitive impairment, which may confound clinical and biomarker interpretation in AD clinical trials (49). This NPH configuration is therefore a potential explanation for cases not matching the ATN model discussed above. If NPH configuration relates to impaired cerebrospinal fluid dynamics and thus an impaired glymphatic system, we could speculate that NPH configuration is a surrogate marker of an impaired glymphatic system. As the glymphatic system is the garbage system of the brain, an impaired glymphatic system dynamic could result in an increased concentration of toxic substances around the brain, explaining the catalysator effect on brain degeneration.

Teaching point: neuroradiologic NPH configuration does not imply complete clinical picture of NPH (dementia, gait disturbance, and urinary incontinence) yet might be an imaging marker of impaired cerebrospinal fluid flow and indicate a higher risk of subsequent cognitive decline. Likewise, moderate white matter hyperintensities do not imply the diagnosis of vascular dementia, yet imply an increased risk of vascular cognitive impairment and risk of cognitive decline.

It has been suggested that dilated Virchow-Robin spaces can also be considered as markers of impaired cerebrospinal fluid flow and a surrogate marker of glymphatic system impairment. This hypothesis that NPH configuration (and dilated Virchow-Robin spaces) might represent a neuroimaging marker for impaired cerebrospinal fluid dynamics, which in turn indicates an impaired glymphatic system as a risk factor for neurodegeneration is currently quite speculative and needs further investigation.

Teaching point: dilation of the temporal horns is a feature of NPH configuration. Notably, in the case of the co-existence of AD-related hippocampal atrophy and NPH configuration, the dilation of the temporal horns as a feature of NPH configuration may lead to an overestimation of the risk of hippocampal atrophy.

Other rare mimickers of AD

Not each case of hippocampal atrophy is equivalent to AD. In addition to LATE discussed above, several other rare diseases exist, which may lead to hippocampal atrophy. One example is a chronic stage after auto-immune encephalitis (limbic encephalitis) (50), which can be due to a variety of para-neoplastic (**Figure 12)** and non-para-neoplastic etiologies. Careful analysis of past medical history may provide clues in such cases.

PART 3: Mixed and overlapping disease

Many instances of cognitive decline are related to a co-existence of diseases rather than an isolated neurodegenerative disease. The most common combination is AD-type neurodegeneration and cerebrovascular disease, particularly in old age (51). With advancing age, both pathologies may develop **(Figure 13).** Yet, co-existent cerebrovascular disease is not always appreciated and is further discussed below.

Cerebrovascular disease, vascular cognitive impairment, vascular dementia

Isolated vascular dementia exists but is uncommon. More frequently, neurodegeneration and cerebrovascular disease co-exist in older adults. Both diseases share risk factors such as hypertension or high cholesterol. Importantly, if neurodegeneration and cerebrovascular disease co-exist, the effect may be additive, meaning that one disease will function as a catalysator and accelerate the other (10).

Teaching point: while vascular dementia in the strict definition is rare, it is very common to have a mixed disease with a cerebrovascular disease component in addition to a neurodegenerative disease component.

Criteria of cerebrovascular disease, vascular cognitive impairment, and vascular dementia

The term vascular cognitive impairment is an umbrella term that includes the entire spectrum of vascular contributions to cognitive decline (52). The most severe degree, called vascular dementia, is at the extreme end of the vascular cognitive impairment spectrum (**Supplementary figure 6**). This presentation of patients with vascular cognitive impairment may differ from amnestic mild cognitive impairment, which often heralds AD.

Several criteria have been proposed for the definition of vascular dementia, the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) NINDS-AIREN being the most specific one (53). Common to the various criteria is the objective of clinical research. Moreover, the definition of vascular dementia is in general strict. Those criteria were initially not intended for daily clinical use, and the threshold for the definition of vascular dementia is high while definitions for earlier

stages of cerebrovascular disease within the vascular cognitive impairment spectrum are lacking. This might be one of the reasons for the lack of appreciation of cerebrovascular disease in suspected dementia or cognitive impairment.

MRI markers of cerebrovascular disease

MRI has the advantage of providing several markers of cerebrovascular disease in one imaging session (54). This advantage of MRI might also be a weakness. An individual case typically has various MRI markers of cerebrovascular disease. It is difficult to decide what burden of vascular disease contributes to cognitive impairment, given that vascular pathology such as white matter hyperintensities are common in 'normal' brain aging. Consequently, there is a large variability in the radiological reporting of the various MRI markers of cerebrovascular disease.

Cerebrovascular disease subtypes

There is a substantial individual variability / variable pattern of cerebrovascular disease including cerebral small vessel disease, cerebral large vessel disease, single or multiple lacunes (small, cystic cavities of the brain substance as chronic stage of an ischemic infarction), and in the expression of MRI markers of cerebrovascular disease. In analogy to the other forms of dementia discussed, those different patterns might be considered as cerebrovascular disease subtypes.

White matter hyperintensities

White matter hyperintensities are markers of cerebral small vessel disease (**Figure 14 A**). They are oftentimes semi-quantitatively described using the Fazekas score (55) ranging from 0-3, generally increasing with age and indicating a higher risk of stroke and cognitive decline. After the age of 40, the majority of individuals (> 90%) will harbor some degree of white matter pathology, which when low in burden does not necessarily lead to cognitive deficits. Apart from white matter hyperintensity burden, there is increasing evidence of an association between the location of white matter hyperintensities and functional outcomes. In the future, one expects that age- and sex-specific reference curves and strategic lesion location maps will better inform clinical practice on the impact of white matter hyperintensities on the clinical presentation, including vascular cognitive impairment and mixed disease.

Microbleeds

Cerebral microbleeds are small punctiform lesions best appreciated on susceptibility weighted-imaging (41) (**Figure 14 B)**. They are associated with aging and cognitive decline, with a deep location might suggesting hypertension, while a superficial lobar distribution is indicative of cerebral amyloid angiopathy, often in the context of AD (56). However, lobar cerebral microbleeds are only found in 20-30% of AD cases and their absence does not rule out AD.

Enlarged perivascular spaces

Enlarged perivascular spaces (EPVS), also know as dilated Virchow-Robin spaces, recently emerged as a potential marker of cerebrovascular disease (**Figure 14 C)**. Possible underlying mechanisms include hypertension, obstruction, and inflammation (57). Dilated Virchow-Robin spaces are also associated with cerebral amyloid angiopathy (58–60). At a group level, EPVS probably represent an emerging cerebrovascular marker. However, there is normal inter-individual variability with frequent observation of EPVS also in the younger adults. Thus, it remains unclear how important this probable cerebrovascular disease marker is at an individual level in the context of cognitive decline.

Etat criblé

Etat criblé refers to a special type of EPVS at the level of the basal ganglia (**Figure 14 D)**. In contrast to the general EPVS (typically of the hemispheres) discussed above, état criblé is probably a more direct and important cerebrovascular disease marker and almost invariably associated with confluent white matter hyperintensities.

Strategic lacunes

According to NINDS-AIREN (53), strategic lacunes are lacunes in the basal ganglia (**Figure 14 E).** T2-weighted MRI sequences can better visualize strategic lacunes in the thalami than T2 fluid-attenuated inversion recovery (FLAIR) sequences. The lacunes are often missed with the FLAIR sequence in this location (61).

Cortical microinfarcts

Cortical microinfarcts have recently emerged as a cerebrovascular disease biomarker and when recent, can be detected as incidental findings on diffusion imaging (**Figure 14 F1, F2**). If imaging is performed when restricted diffusion is not present, it may be difficult or even impossible to detect such cortical microinfarcts (**Figure 14 F3).** While

the detection rate of chronic cortical microinfarcts is good at 7T, a substantial number of chronic cortical microinfarcts remain undetected at 3T in a clinical setting. (62, 63)

Hippocampal microinfarcts

Hippocampal microinfarcts are a subtype of cortical microinfarcts (**Figure 14 G)**. From histopathology, hippocampal microinfarcts are quite common in older adults and may be associated with cognitive decline, mimicking AD. It is notoriously difficult to detect hippocampal microinfarcts. For example, a recent study compared post-mortem MRI at 3T (with imaging parameters equivalent to clinical MRI) observed an accuracy of 2% of MRI to detect hippocampal microinfarcts (64). This might explain why this important cerebrovascular disease marker is likely highly underestimated.

Other forms of overlapping/mixed disease

Another important overlap is between AD and cerebral amyloid angiopathy, recently defined in the Boston 2.0 criteria (60). Both diseases are linked to amyloid accumulation, although it is not the same type of amyloid and not the same compartment of accumulation (65). Nevertheless, there is a co-existence of AD and cerebral amyloid angiopathy which clearly exceeds chance, indicating an interaction between the two diseases, with the APOE 4 allele increasing the risk for both. This is in particular important in view of the previously mentioned side effects of newly emerging anti-amyloid therapies (ARIA-E and ARIA-H), which are thought to occur more often in individuals who also harbor vascular amyloid pathology (e.g. as evidenced by presences of multiple lobar microbleeds). While the overlapping/mixed disease of AD and cerebrovascular disease and AD and cerebral amyloid angiopathy are important examples, other co-existences of neurodegenerative and cerebrovascular disease(s) exist (66–68) (**Figure 5B**). Thus, it is important to avoid trying to force a single disease label on an individual patient, as this deprives them of receiving adequate prognostic counseling, symptom-reducing treatment, or, in the case of cerebrovascular disease, preventive management. Given the frequent co-existence of vascular pathology and neurodegenerative pathologies, the radiologists have a key role to signal dual pathology. It is also important to highlight that sometimes, due to the coexistence of several imaging markers suggesting overlapping/mixed disease, it may be impossible to establish a firm diagnosis based on radiological assessment (**Figure 15**).

Other diseases

A variety of other diseases and conditions may cause cognitive decline and dementia. These include subdural hematoma, neoplasm, infection/inflammation such as Creutzfeldt–Jakob disease, neurodegeneration with brain iron accumulation, and metabolic or toxic diseases. Such conditions are not neurodegenerative diseases in strict sense and are out of the scope of the current review article.

Differential diagnosis based on imaging findings and clinical symptoms

The various forms of dementia discussed above have partially overlapping and partially distinct patterns of atrophy and clinical presentations. Simplified differential diagnoses based on imaging patterns are summarized in **Table 1.** Simplified differential diagnoses based on key clinical findings are summarized in **Table 2**

Conclusion

Dementia is more than typical AD, and AD is more than a single and stereotypical process of neurocognitive decline. Each patient will have a personal blend of different components of neurodegenerative and cerebrovascular diseases. Neuroimaging, in concert with genetic and laboratory testing, should aim for early diagnosis ideally before the onset of frank dementia, subtyping of AD, and other forms of dementia while considering co-existing disease. This will be the fundamental basis to better understand the mechanisms of AD, and to aid the development of individualized and efficient therapies.

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Table 1

Hippocampal atrophy		
Imaging finding	**Associated findings**	**Most likely diagnosis**
Predominant hippocampal atrophy	ABNORMAL amyloid (amyloid PET, CSF or blood markers)	Typical AD
Predominant hippocampal atrophy	NORMAL amyloid (amyloid PET, CSF or blood markers), older (>90) and Tau-markers	LATE
Asymmetric hippocampal atrophy and other, more pronounced atrophy	Predominant frontal atrophy including hippocampal atrophy	bvFTD
Asymmetric hippocampal atrophy and other, more pronounced atrophy	Predominant temporal pole atrophy (oftentimes asymmetric) and hippocampal atrophy	SD (classic left, atypical right)
Asymmetric hippocampal atrophy and other, more pronounced atrophy	Predominant peri-insular atrophy including hippocampal atrophy	PNFA
Temporal horn enlargement mimicking hippocampal atrophy	Prominent ventricular system, crowding of sulci of vertex, corpus callosum in “V” configuration, cingulate sulcus sign, dilation of sylvian fissure	NPH configuration
Hippocampal atrophy and vascular imaging markers	Hippocampal atrophy and white matter hyperintensities, microbleeds, microinfarcts, strategic infarcts, dilated VRS	Mixed disease AD and vascular
Hippocampal atrophy and vascular imaging markers, notably lobar distribution of microbleeds	Hippocampal atrophy, lobar distribution of microbleeds notably parieto-occipital, superficial siderosis, White matter signal anomaly	Mixed disease AD and CAA
Hippocampal atrophy and signal abnormality	-	Hippocampal sclerosis
Hippocampal atrophy and signal abnormality	-	Status post limbic encephalitis

Predominant frontal atrophy		
Imaging finding	**Associated findings**	**Most likely diagnosis**
Predominant frontal atrophy	Anterior to posterior gradient of atrophy, NORMAL amyloid (amyloid PET, CSF or blood markers)	bvFTD
Predominant frontal atrophy	ABNORMAL amyloid (amyloid PET, CSF or blood markers)	Frontal variant AD
Predominant frontal atrophy – temporal pole	Predominant temporal pole atrophy (oftentimes asymmetric) and hippocampal atrophy	SD (classic left, atypical right)
Predominant frontal atrophy – notably peri-insular	Predominant peri-insular atrophy including hippocampal atrophy	PNFA

Predominant parietal atrophy / PCA pattern		
Imaging finding	**Associated findings**	**Most likely diagnosis**
Predominant parietal atrophy	ABNORMAL amyloid (amyloid PET, CSF or blood markers)	Parietal variant AD

Predominant parietal atrophy	ABNORMAL dopamine nuclear medicine or ABNORMAL nigrosome 1	DLB
Predominant parietal atrophy	ABNORMAL dopamine nuclear medicine or ABNORMAL nigrosome 1, cerebellar atrophy, movement disorder	CBD
Predominant parietal atrophy	-	Normal variant

Table 1: Simplified differential diagnoses based on imaging patterns

AD Alzheimer disease
bvFTD behavioral variant frontotemporal dementia
CAA cerebral amyloid angiopathy
CSF cerebrospinal fluid
DLB dementia with Lewy bodies
LATE Limbic-predominant age-related TDP-43 encephalopathy
NPH normal pressure hydrocephalus
PET positron emission tomography
PNFA progressive non-fluent aphasia
SD semantic dementia

Table 2:

Predominant memory loss	
Associated imaging findings	**Most likely diagnosis**
Hippocampal atrophy, ABNORMAL amyloid (amyloid PET, CSF or blood markers)	Typical AD
Hippocampal atrophy, NORMAL amyloid (amyloid PET, CSF or blood markers), older (>90)	LATE
Predominant frontal atrophy including hippocampal atrophy	bvFTD
Vascular imaging markers (white matter hyperintensities, strategic infarcts etc(	VCI / VaD
Prominent ventricular system, crowding of sulci of vertex, corpus callosum in “V” configuration, cingulate sulcus sign, dilation of sylvian fissure	NPH
Hippocampal microinfarcts – oftentimes undetected by clinical MRI	Oftentimes missed diagnosis (sensitivity of clinical MRI is low)
Mixed imaging findings	Mixed disease

Predominant behavioral and executive function presentation	
Associated imaging findings	**Most likely diagnosis**
Predominant frontal atrophy with anterior to posterior gradient including hippocampal atrophy, NORMAL amyloid (amyloid PET, CSF or blood markers)	bvFTD
Predominant frontal atrophy with anterior to posterior gradient including hippocampal atrophy, ABNORMAL amyloid (amyloid PET, CSF or blood markers)	Frontal variant AD

Predominant language impairment	
Associated imaging findings	**Most likely diagnosis**
Dominant left temporal pole atrophy, including asymmetric hippocampal atrophy	SD
Dominant peri-insular atrophy, including asymmetric hippocampal atrophy	PNFA
Dominant anterior peri-insular atrophy with anterior to posterior gradient, may include asymmetric hippocampal atrophy	Non-fluent / agrammatic PPA
Left-dominant peri-insular atrophy extending into parieto-occipital junction, may include asymmetric hippocampal atrophy	Logopenic variant PPA

Table 2: Simplified differential diagnoses based on key clinical findings
AD Alzheimer disease
bvFTD behavioral variant frontotemporal dementia
CSF cerebrospinal fluid
LATE Limbic-predominant age-related TDP-43 encephalopathy
NPH normal pressure hydrocephalus
PET positron emission tomography
PNFA progressive non-fluent aphasia
PPA primary progressive aphasia
VaD vascular dementia
VCI vascular cognitive impairment

Figure Legends

NOTE : in order to have the correct consecutive numbering of the references in the figure captions, I moved the figure captions into the main body of the MARKED version. Below are only the figure captions of the online supplementary figures.

Figure 1: Upper panel: Images in an 83-year-old male with typical AD with predominant atrophy of the hippocampus (coronal T1 weighted image, A), associated with hypoperfusion of the posterior cingulate cortex on arterial-spin labeling (ASL) (B) known as (absent) light bulb sign. In a healthy individual, the perfusion at rest of the posterior cingulate cortex should be as least as high as the grey matter of the insular region. Lower panel: Images in a 65-year-old male with predominant parietal atrophy suggestive of an atypical, parietal variant of AD (C). The parietal variant of AD oftentimes affects younger patients and can be asymmetric. Corresponding ASL (D) shows associated hypoperfusion, which is likely overestimated by the atrophy/partial volume effect.

Figure 2: Normal patterns of amyloid PET show uptake notably in white matter, while uptake in grey matter decreased. Amyloid PET is useful notably to rule out AD. Normal uptake of tau PET is very minimal, while abnormal tau PET uptake is typically most pronounced in the temporal regions. Tau PET is notably good to rule in AD. Normal FDG PET shows homogeneous uptake in superficial and deep grey matter. Typical pattern of hypometabolism in FDG PET in AD includes hypometabolism in posterior cingulate cortex (PCC) and bilateral parietal regions.
FDG: Fluorodeoxyglucose
Adapted and reprint with permission (21)

Figure 3: Images in a 61-year-old female with posterior cortical atrophy (PCA) with impaired visual-spatial integration. Axial T2 (A) and coronal T1 (B) weighted images show predominant atrophy in right-dominant parietal area associated with hypoperfusion on ASL (C).

Figure 4: Upper panel: Non-fluent /agrammatic primary progressive aphasia (PPA) is characterized by word production problems, effortful and non-fluent speech. Typical atrophy pattern shows left-dominant peri-insular atrophy with anterior-to-posterior gradient in as demonstrated in left (A) and right (B) sagittal T1 weighted images. Lower panel: Logopenic variant of PPA is characterized by word findings difficulties, slow speech, but preserved understanding. Typical atrophy pattern is left-dominant peri-insular and extends posterior into parieto-occipital cortex in axial (C) and coronal (D) T1 weighted images.

Figure 5: The classic distribution of dementias (A) in a memory clinic setting shows that most cases are AD (60%) (32)**. Although AD contributes to be the majority, 40 % are not AD. More recent studies suggest that within the AD group, less than half of the cases are isolated AD, while more than half of cases are various combinations of mixed pathologies including AD** (33). **Reprinted, with permission, from** (32, 33)

Figure 6: Example case of a 86-year-old female A-T-N+ who was diagnosed during life as suspected non-Alzheimer's pathology (SNAP). Autopsy within a year confirmed LATE-NC. Note that the predominant hippocampal atrophy mimics AD, and in the absence of amyloid and tau PET imaging LATE may be indistinguishable from AD.
Reprinted, with permission, from (34)**.**

Figure 7: Images in a 79-year-old female with Lewy Body Dementia. Standard MRI sequences including axial T2 (A) and sagittal T1 (B) typically show only minor structural abnormalities, most commonly mild parietal atrophy. FDG PET or ASL (C) typically show preserved metabolism (FDG PET) or perfusion (ASL) in posterior cingulate cortex known as cingulate island sign, yet reduced metabolism (FDG PET) or perfusion (ASL) in the parieto-occipital region.
FDG **fluorodeoxyglucose**, ASL arterial spin labeling

Figure 8: Images in a 79-year-old male with progressive cognitive decline. Coronal T2 FLAIR (A, B), shows predominant frontal atrophy and to a lesser degree mesio-temporal atrophy (MTA 1) suggestive of bvFTD. There are a few cerebral microbleeds (example SWI, C), mild white matter pathology (Fazekas 1) and a cortical microinfarct (D, T2 FLAIR) suggesting cerebrovascular disease component. In total, this suggests mixed disease FTD and vascular.
FLAIR fluid-attenuated inversion recovery, bvFTD behavioral variant frontotemporal dementia

Figure 9: Images in a 76-year-old female with early progressive non-fluent aphasia (PNFA). Mild asymmetric left-dominant atrophy is present in the peri-insular region on coronal T1 weighted image(A). This is associated with slight hypoperfusion in left-dominant peri-insular and to a lesser degree fronto-parietal regions on ASL (B).
ASL arterial spin labeling

Figure 10: Images in a 73-year-old female with progressive cognitive decline including semantic difficulties. Coronal T2 FLAIR (A, B), shows predominant atrophy of the left temporal pole, including also the asymmetric hippocampal

atrophy suggestive of semantic dementia. There is only very minor cerebrovascular disease.
Images in a 63-year-old male with progressive cognitive decline and trouble recognizing faces. Coronal T2 FLAIR (C, D), shows predominant of the right temporal pole, including the asymmetric right-dominant hippocampal atrophy suggestive of right-hemispheric FTD. There is only very minor cerebrovascular disease.
FLAIR fluid-attenuated inversion recovery

Figure 11: Images in a 73-year-old female with progressive cognitive decline. With respect to a previous MRI 14 years prior (A), coronal T2 FLAIR illustrates progressive hippocampal atrophy suggesting AD neurodegeneration. There is additional appearance of NPH configuration including dilated ventricular system, slight transependymal transudation, crowding of sulci at the vertex, V-shaped corpus callosum and enlargement of sylvian fissure. Note that dilation of temporal horns is a feature of NPH configuration and might lead to over-estimation of hippocampal atrophy. Moreover, there are progressive signs of vascular disease including progressive white matter hyperintensities on axial T2 (C, D) and a new cerebellar micro-infarct in proximity to pre-existing cerebellar micro-infarcts. In total, this suggests a mixed disease including AD type neurodegeneration, NPH configuration and a cerebrovascular component. Note there are some imaging features of NPH configuration, yet not the full radiological signs of NPH nor the typical clinical presentation of NPH.
NPH normal pressure hydrocephalus, FLAIR fluid-attenuated inversion recovery

Figure 12: Coronal T1 weighted image (A) and coronal T2 FLAIR (B) in a patient with testicular germinoma demonstrate T2 FLAIR abnormality in bilateral hippocampi suggestive of auto-immune encephalitis (limbic encephalitis). One year later, coronal T1 weighted image (C) and coronal T2 FLAIR (D) illustrate hippocampal volume loss without vascular component. If only the follow-up imaging was available, the hippocampal volume loss could have been misinterpreted as AD.

Figure 13: Images in a 81-year-old female without cognitive complaints (A, B, C). At the age of 81 (A, B, C), there is no significant atrophy of the hippocampus, and only beginning white matter hyperintensities. 13 years later, there was evidence of atrophy most pronounced in right-dominant hippocampus suggesting a component of typical AD-type neurodegeneration, associated with progressive white matter hyperintensities and two minor infarcts of the left basal ganglia indicating a cerebrovascular component (D, E, F). In concert, this is a typical example of mixed neurodegenerative and cerebrovascular disease.
A, D coronal T1 weighted, B, E coronal T2 FLAIR, C, F axial T2 weighted

Figure 14: Summary figure of various MRI markers of cerebrovascular disease. White matter hyperintensities / white matter lesions on T2 FLAIR (A), cerebral microbleeds on SWI (B), état criblé of the basal ganglia on T2 weighted image

(C), dilated perivascular spaces / Virchow Robin spaces on axial T2 weighted image (D), strategic lacune in the left thalamus on T2 weighted image (E), cortical microinfarct as incidental finding on diffusion weighted imaging with b=1000 (F1) and T2 weighted image (F2) which is virtually invisible on follow-up imaging after 3 months T2 weighted image (F3), hippocampal microinfarct on T2 weighted image (G).
FLAIR fluid-attenuated inversion recovery, SWI susceptibility weighted imaging,

Figure 15: Images in 67-year-old female with progressive cognitive decline. Axial T2 (A) and coronal T1 (B) weighted images demonstrate left-dominant frontal atrophy. Coronal T1 weighted image (C) also shows several signs of NPH configuration including prominent ventricular system, insular enlargement, crowding of convexity sulci. There is also beginning hippocampal atrophy as feature of frontal dementia, but this analysis is confounded by co-existing temporal horn enlargement as feature of NPH configuration. This example illustrates that it is not always possible to establish a firm radiological diagnosis.
NPH normal pressure hydrocephalus

Supplementary figure 1: typical patterns of brain FDG PET hypometabolism with respect to a control cohort (violet) for the most common forms of dementia.
Adapted with permission (69)
AD Alzheimer disease, DLB dementia with Lewy Bodies, FTD frontotemporal dementia, CBD corticobasal degeneration, PCA posterior cortical atrophy.

Supplementary figure 2: Due to the metabolic-vascular coupling in the brain, patterns of hypometabolism of FDG PET closely correspond to patterns of hypoperfusion in MRI ASL. First and fourth column represent raw ASL perfusion and FDG PET metabolism. The individual case is compared with a matched reference group, and only those regions that differ from the mean are illustrated. Note the good correspondence of regions with ASL hypoperfusion in axial (second column) and sagittal (third column) plane compared with corresponding FDG PET hypometabolism (fifth and sixth columns)
Reprinted, with permission, from (70)
FDG fluorodeoxyglucose, ASL arterial spin labeling,

Supplementary figure 3: Three different pattern subtypes (frontal, parietal, occipital) of amyloid accumulation identified in a large set of 1000 cases using a data-driven analysis, looking for disease stage and disease type at the same time (A). Differences between the types are most pronounced at early stages and converge at later stages. Of note, if the algorithm is forced to merge all 3 subtypes into a single subtype, the classic pattern of amyloid accumulation appears (B).
Reprinted, with permission, from (22)**.**

Supplementary figure 4: Number of PubMed citations using the terms "Alzheimer dementia", "Lewy dementia" and "frontal dementia" accessed on 2022-12-31.

Supplementary figure 5: axial susceptibility images at the level of the mesencephalon demonstrate the nigrosome 1 at the posterior aspect of the substantia nigra is abnormal, i.e. black in DLB (A, B). In contrast, the nigrosome 1 is normal (bright) in both AD (C) and FTD/FTLD (D).
DLB dementia with Lewy bodies, AD Alzheimer disease, FTD fronto-temporal dementia, FTLD frontotemporal lobar degeneration
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Supplementary figure 6: Schematic illustration of AD pathology (top): Mild cognitive impairment (MCI) is a precursor state of AD, i.e. patients can have either MCI (mild) or AD (advanced) stage. In contrast, the lower part illustrates that vascular cognitive impairment (VCI) is an umbrella term that also includes

the most severe form i.e. vascular dementia (VaD). In other words, a patient can have VaD and VCI, but not AD and MCI.