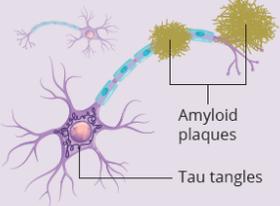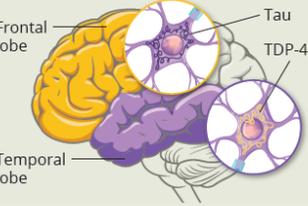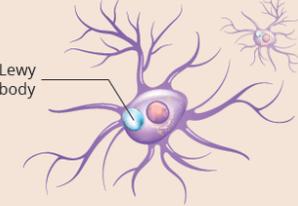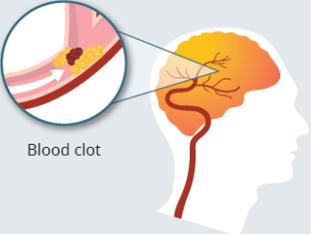# Update on Neuroimaging in Dementia
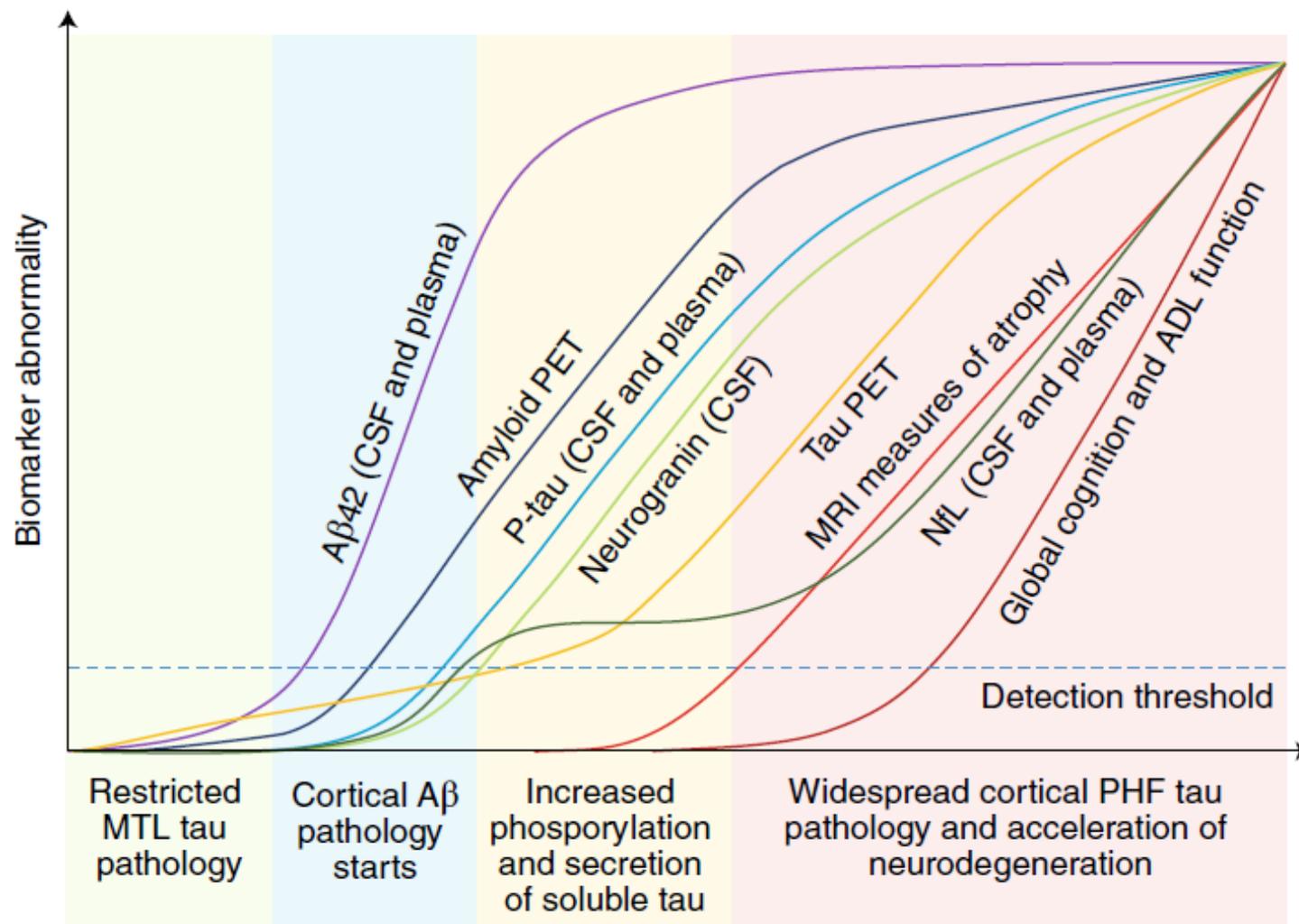
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Department of Psychiatry

The different types of dementia

Alzheimer's Disease	Frontotemporal Dementia	Lewy Body Dementia	Vascular Dementia
What Is Happening in the Brain?*			
Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain.	Abnormal amounts or forms of tau and TDP-43 proteins accumulate inside neurons in the frontal and temporal lobes.	Abnormal deposits of the alpha-synuclein protein, called "Lewy bodies," affect the brain's chemical messengers.	Conditions, such as blood clots, disrupt blood flow in the brain.

These changes are just one piece of a complex puzzle that scientists are studying to understand the underlying causes of these forms of dementia and others.

Symptoms			
Mild • Wandering and getting lost • Repeating questions **Moderate** • Problems recognizing friends and family • Impulsive behavior **Severe** • Cannot communicate	**Behavioral and Emotional** • Difficulty planning and organizing • Impulsive behaviors • Emotional flatness or excessive emotions **Movement Problems** • Shaky hands • Problems with balance and walking **Language Problems** • Difficulty making or understanding speech *There are several types of frontotemporal disorders, and symptoms can vary by type.*	**Cognitive Decline** • Inability to concentrate, pay attention, or stay alert • Disorganized or illogical ideas **Movement Problems** • Muscle rigidity • Loss of coordination • Reduced facial expression **Sleep Disorders** • Insomnia • Excessive daytime sleepiness **Visual Hallucinations**	• Forgetting current or past events • Misplacing items • Trouble following instructions or learning new information • Hallucinations or delusions • Poor judgment
Typical Age of Diagnosis			
Mid 60s and above, with some cases in mid-30s to 60s	Between 45 and 64	50 or older	Over 65

Brain changes happen many years before symptom onset :
The ATN framework in AD

Neuroimaging in Dementia: the NICE guidelines

- Use validated criteria to guide clinical judgement when diagnosing dementia subtypes

- Offer structural imaging to rule out reversible causes of cognitive decline and to assist with subtype diagnosis, unless dementia is well established and the subtype is clear

- Only consider further tests (recommendations 1.2.15–28) if:

  - It would help to diagnose a dementia subtype

  - knowing more about the dementia subtype would change management

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Neuroimaging in Dementia: the NICE guidelines on neuroimaging

Further tests if diagnosis unclear:

•**FDG-PET** (fluorodeoxyglucose-positron emission tomography-CT), or perfusion SPECT (single-photon emission CT if FDG-PET is unavailable) **for suspected AD or FTD**

•**CSF** (total tau, p-tau181, Aβ42/40)

•**[123]I-FP-CIT SPECT (DAT scan) if suspected DLB** (or ^{123}I-MIBG cardiac scintigraphy)

•If **vascular** dementia is suspected, use **MRI**

Do you have access to such investigations in your area?

EXPERT REVIEW   **OPEN**

Check for updates

The use of neuroimaging techniques in the early and differential diagnosis of dementia

Leonidas Chouliaras [1,2] and John T. O'Brien [1,3 ✉]

Dementia is a leading cause of disability and death worldwide. At present there is no disease modifying treatment for any of the most common types of dementia such as Alzheimer's disease (AD), Vascular dementia, Lewy Body Dementia (LBD) and Frontotemporal dementia (FTD). Early and accurate diagnosis of dementia subtype is critical to improving clinical care and developing better treatments. Structural and molecular imaging has contributed to a better understanding of the pathophysiology of neurodegenerative dementias and is increasingly being adopted into clinical practice for early and accurate diagnosis. In this review we summarise the contribution imaging has made with particular focus on multimodal magnetic resonance imaging (MRI) and positron emission tomography imaging (PET). Structural MRI is widely used in clinical practice and can help exclude reversible causes of memory problems but has relatively low sensitivity for the early and differential diagnosis of dementia subtypes. ^{18}F-fluorodeoxyglucose PET has high sensitivity and specificity for AD and FTD, while PET with ligands for amyloid and tau can improve the differential diagnosis of AD and non-AD dementias, including recognition at prodromal stages. Dopaminergic imaging can assist with the diagnosis of LBD. The lack of a validated tracer for α-synuclein or TAR DNA-binding protein 43 (TDP-43) imaging remain notable gaps, though work is ongoing. Emerging PET tracers such as ^{11}C-UCB-J for synaptic imaging may be sensitive early markers but overall larger longitudinal multi-centre cross diagnostic imaging studies are needed.
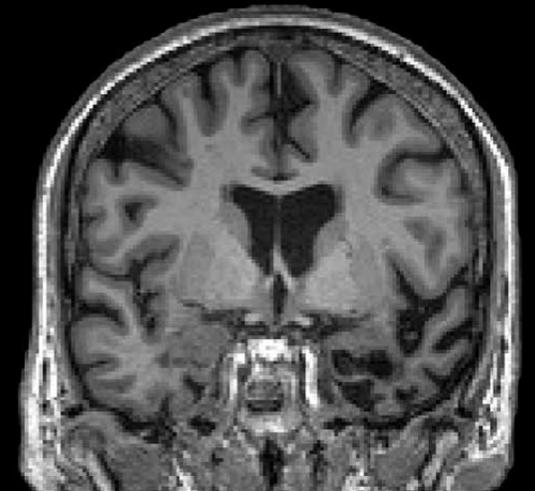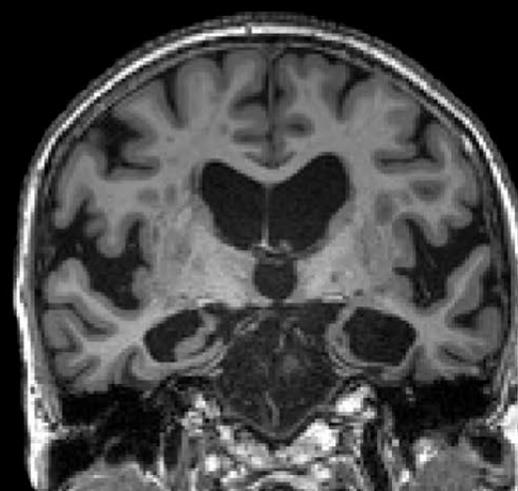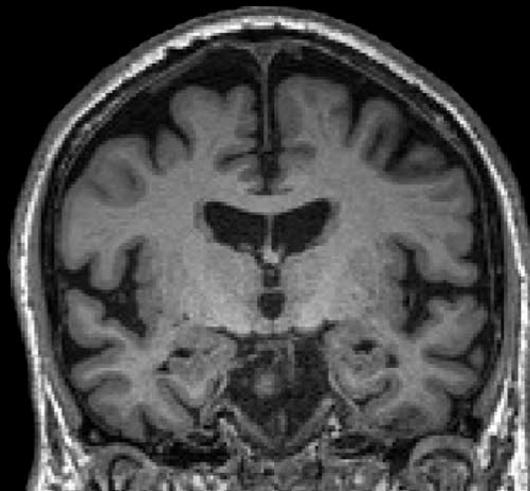
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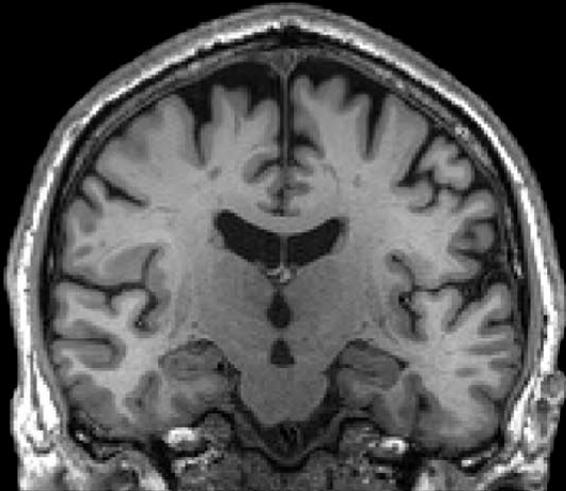# Structural MRI- what do you see here?

Structural MRI

- **Exclude other/reversible causes**

- **Volumetric changes**

    - Visual rating scales → global atrophy (GCA), medial temporal atrophy (MTA) and Koedam (parietal) have high specificity (67-97%)

    - Automated volumetric analyses have improved sensitivity and specificity (70-90%) depending on diagnosis and disease stage

    - Lack of sensitivity in early prodromal stages

    - In older cohorts (85+) sensitivity/specificity drops to 65-75%

- **Serial MRI imaging**

Structural MRI- White matter hyperintensities and microbleeds

- **Lacunes, infarcts, confluent white matters changes (Fazekas scale) are linked with vascular cognitive impairment and dementia**

  - Cardiovascular risk factors

  - White matter changes are not just vascular but can also be tau pathology

- **Cerebral microbleeds and cerebral amyloid angiopathy are common in AD and other dementias**

  - Lobar microbleeds are associated with amyloid pathology

  - deep/basal ganglia microbleeds are associated with hypertensive small vessel disease

  - higher in number in APOE ε4 carriers

- In unimpaired populations, **high microbleed number (>3–4)** is associated with an increased risk of cognitive deterioration and dementia
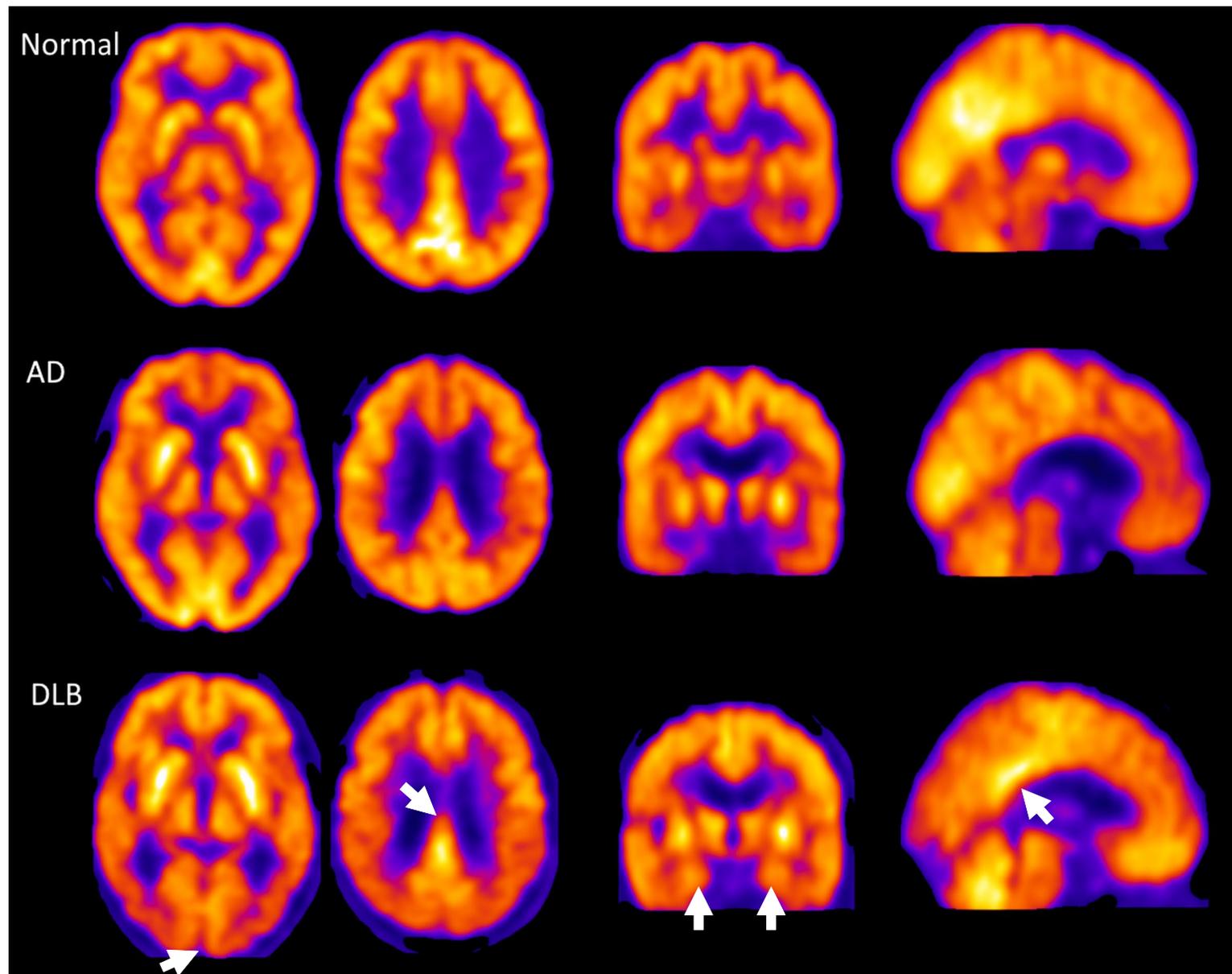
Diffusion weighted imaging (DWI)

- Diffusion tensor imaging (DTI) provides information on the orientation and integrity of white matter tracts through measuring parameters associated with diffusion of water molecules in the brain

- Generates measures of **fractional anisotropy (FA) and mean diffusivity (MD)** of water molecules in a region of interest→lower FA and higher MD in dementia

- Research studies show biologically plausible differences between dementia subtypes and predict progression from MCI to dementia

- Modest sample sizes, from single research sites with no clearly established cutoffs or harmonised, validated methods limit the ability for DTI to be used in clinical practice.

Assessment of blood flow and perfusion using MRI

- Contrast agents or magnetically labelling blood → arterial spin labelling (ASL)

- Blood flow closely matches the patters of hypometabolism on FDG-PET due to the close coupling between perfusion and metabolism in brain

- ASL was shown to be comparable to FDG-PET in identifying AD compared to controls

- Great potential for the early detection of neurodegeneration

- FDG-PET seems to outperform methods for MRI cerebral blood flow and is more widely adopted.

FDG-PET

FDG-PET is widely used for the differential diagnosis of dementia

- Readout of the local **cerebral metabolic rate of glucose consumption**, correlates with **synaptic activity** and **neurodegeneration**

- Meta-analytic evidence suggests that FDG-PET has 90% sensitivity and 75-89% specificity in diagnosing AD from controls

- In young onset AD, hypometabolism on FDG-PET can be detected as early as 10 years before symptom onset

- Large range in the sensitivity (56–100%) and specificity (24–100%) in predicting conversion from MCI to dementia

- PSP, autoimmune encephalitis, chronic schizophrenia, alcohol related brain damage and late onset psychiatric disorders may also be associated with patterns of hypometabolism on FDG-PET

- inversely affected by brain glycaemia → caution in diabetic patients

Imaging synucleopathies (DLB and PDD)

- Brain **dopamine transporter imaging** using ^{123}I-Ioflupane (FP-CIT) SPECT or cardiac sympathetic nerve imaging using ^{131}I-Metaiodobenzylguanidine myocardial scintigraphy (MIBG)

- High sensitivity and specificity in **DLB**$\rightarrow$ indicative biomarkers as part of the current International Consensus diagnostic criteria for DLB

- FP-CIT SPECT differentiated DLB from AD with 78% sensitivity and 91% specificity in a large multi-site study

- An autopsy study showed that FP-CIT has accuracy of 86% (sensitivity 80%, specificity 92%) compared to neuropathological diagnosis of DLB

- Dopaminergic imaging can be **abnormal in other neurodegenerative disorders** where dopaminergic transmission is affected, such as FTD, CBD, PSP and MSA

Amyloid PET

- Early, specific and unbiased diagnosis of AD

- young onset AD vs. other dementias, e.g. bvFTD

- ^{11}C-Pittsburgh compound–B (PiB), ^{18}F-flutemetamol, ^{18}F-florbetaben, ^{18}F -florbetapir that image Aβ plaques and have been validated through autopsy studies

- Visual rating or standard update value ratio (**SUVR**) or the **centiloid** scale

- More sensitive (89% vs 73%) but less specific (83% vs 98%) compared to FDG-PET for the differential diagnosis between AD and FTD

- Does not correlate with symptom onset and disease severity

- Cannot predict time of onset of dementia syndrome

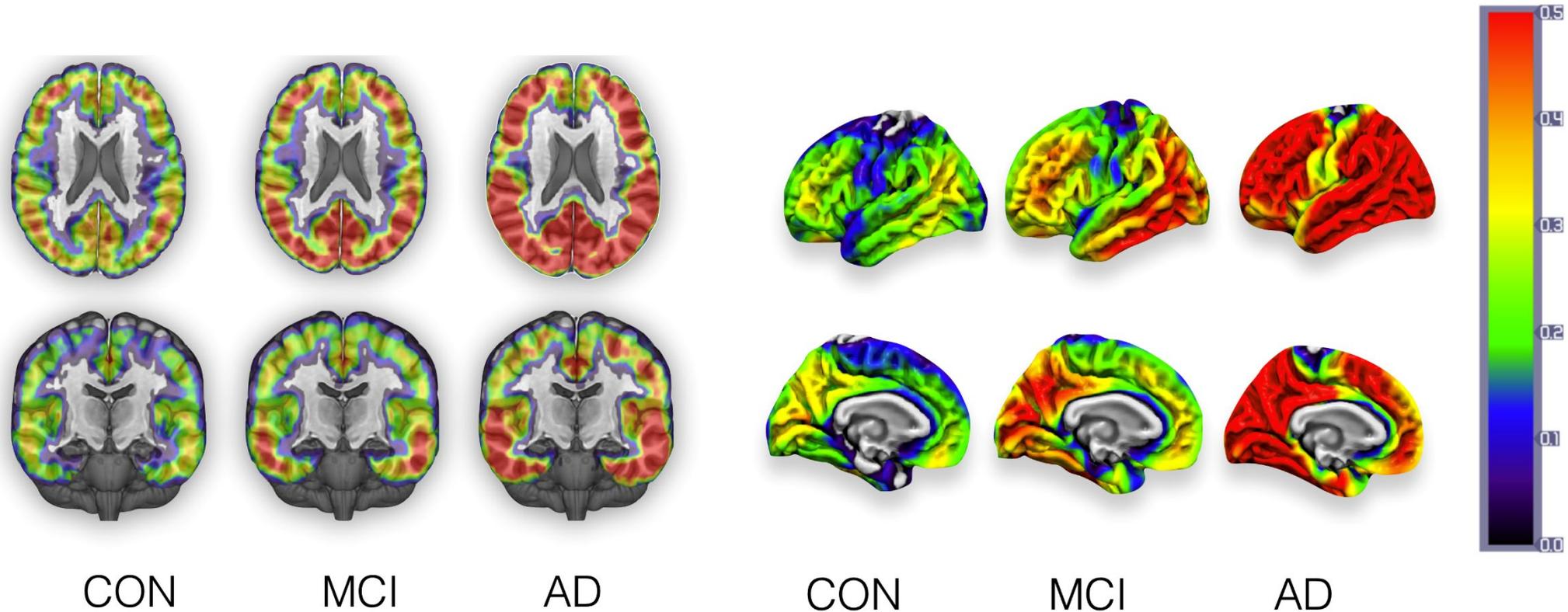- Amyloid pathology is prevalent in a lot of asymptomatic older people

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Tau PET

- Approved by the FDA for the in vivo assessment of tau in people with AD

- **^{18}F-AV1451/flortaucipir,** ^{18}F-THK family and ^{11}C-PBB3, ^{18}F-MK6240, ^{18}F-R0948, ^{18}F-PI260, ^{18}F-GTP1, and ^{18}F-JNJ-64326067

- Binds to cortical tau tangles but also non-specific binding in subcortical structures suggesting it is not suitable for non-AD tauopathies

- Correlates with patterns of tau pathology deposition (Braak) and shows strong correlations with cognitive function, even in cognitively normal older people

- Longitudinal deposition in tau PET is associated with baseline levels tau and Aβ deposition is a necessary antecedent for spread of tau beyond the temporal lobe in AD
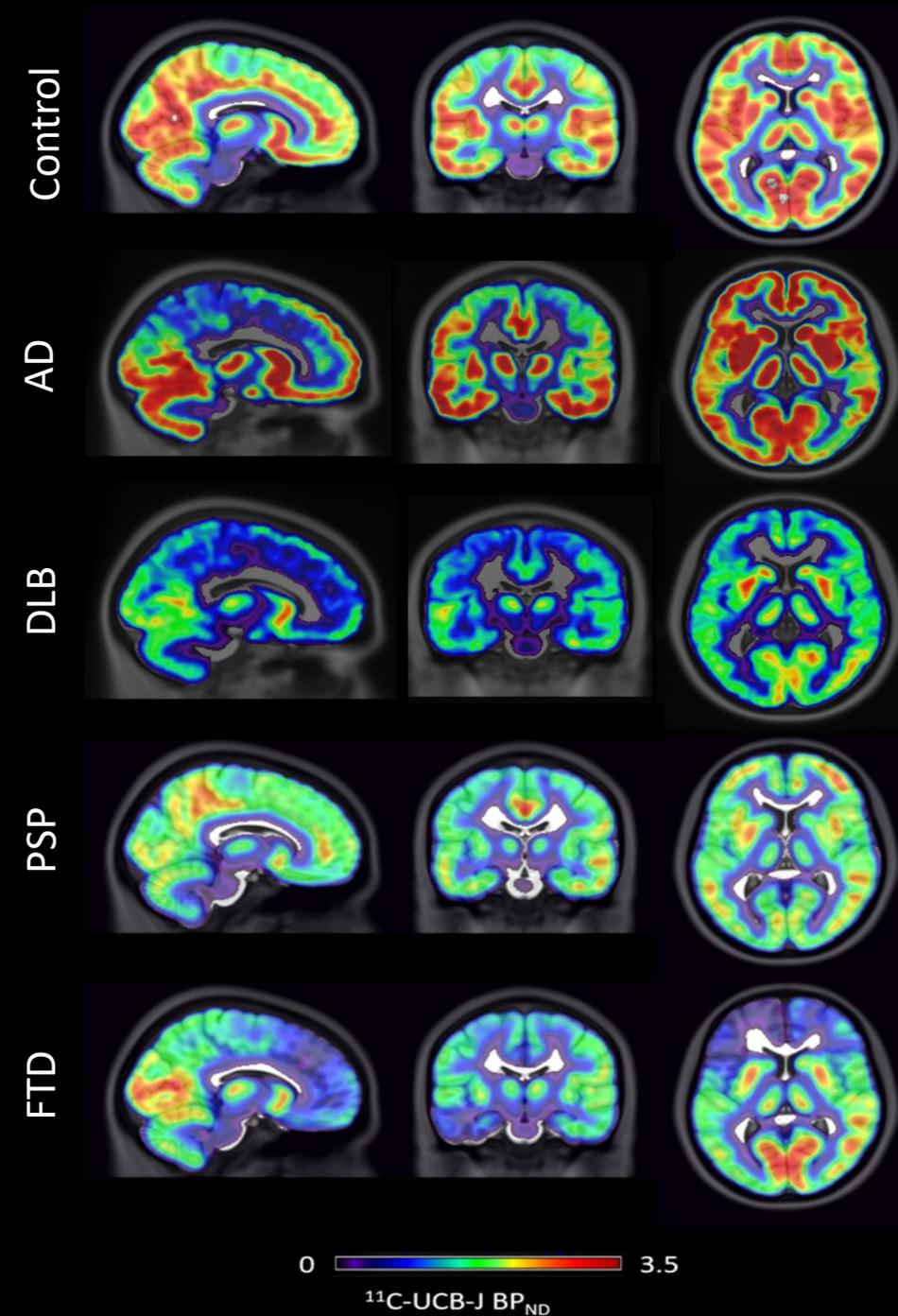
Tau PET progression in the Alzheimer's continuum

Tau PET deposition mirrors the progression of AD pathology, correlates with disease severity and in that respect it is hypothesised that will become one of the most important tools for the differential diagnosis between AD and non-AD dementias

CON   MCI   AD   CON   MCI   AD

Other PET

- A number of studies have used the binding potential of ^{11}C-UCBJ PET which binds to the synaptic vesicle protein 2a (SV2A) as a marker of synaptic density

- PET-imaging of neuroinflammatory processes using ^{11}C -PK11195 (PK-PET) which binds to the 18-kDA translocator protein (TSPO), a mitochondrial membrane protein that is upregulated in activated microglia

- PK-PET is increased in the entorhinal, temporal, parietal and cingulate cortex in AD, in the frontotemporal regions in FTD, while PSP shows increased PK-PET binding in the thalamus, putamen and pallidum, showing differential distribution of neuroinflammatory processes in different types of dementia

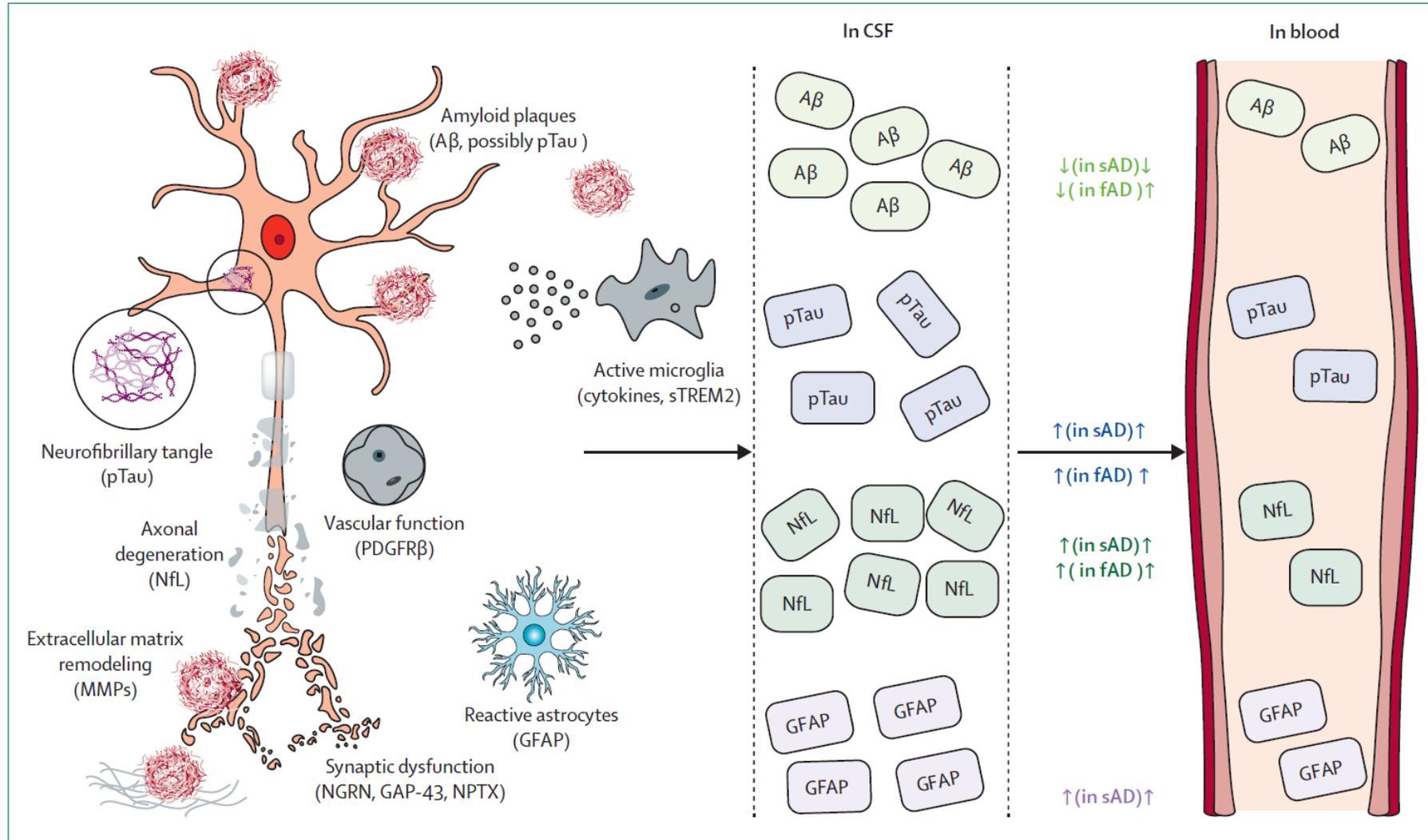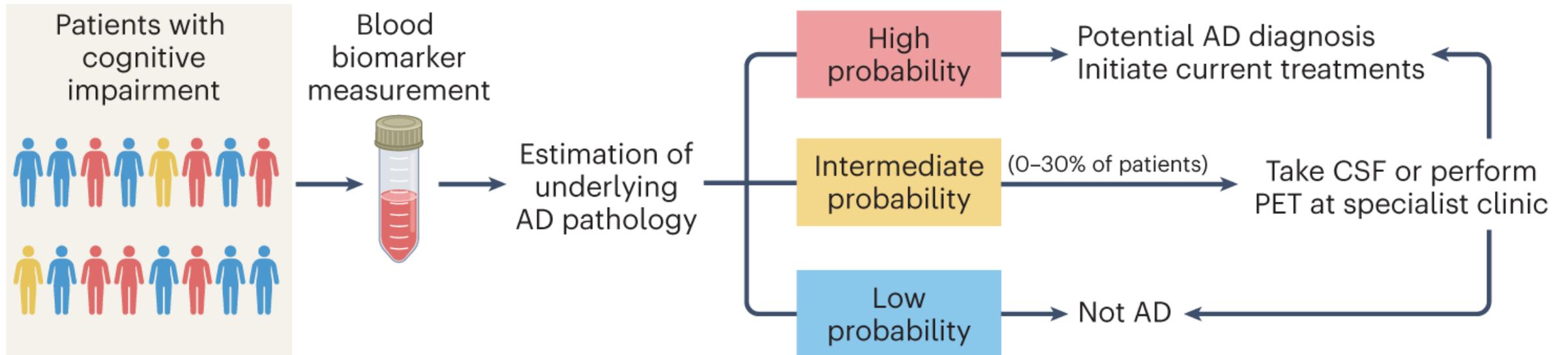UNIVERSITY OF CAMBRIDGE

Blood Biomarkers in Alzheimer's Disease and neurodegeneration

Figure 1: Pathological mechanisms involved in Alzheimer's disease and their associated biofluid-based biomarkers

Teunissen et al Lancet Neurol, 2022

Suggested blood-based biomarker-based workflow for Alzheimer's disease diagnostics

Summary

1. Brain imaging is key for the early, accurate and differential diagnosis of dementia

2. An expert consensus has recommended three pathways in situations where further testing is warranted for the clinical diagnosis of dementia

   1. **Amyloid** PET or **CSF** if **AD** is suspected.

   2. **FDG-PET** could be used when the initial workup suggests a **non-AD dementia**

   3. **When** cognitive problems present with **a movement disorder** then **a FP-CIT SPECT or MIBG** could be used

3. Importantly, brain imaging is increasingly used as means for stratification of participants for clinical trials and as a marker of treatment response in disease modifying therapeutic trials.

Acknowledgements

Cambridge Centre
for Parkinson-Plus

Dementia Researchers
Running for Dementia
Research

@ChouliarasL

Thank you