

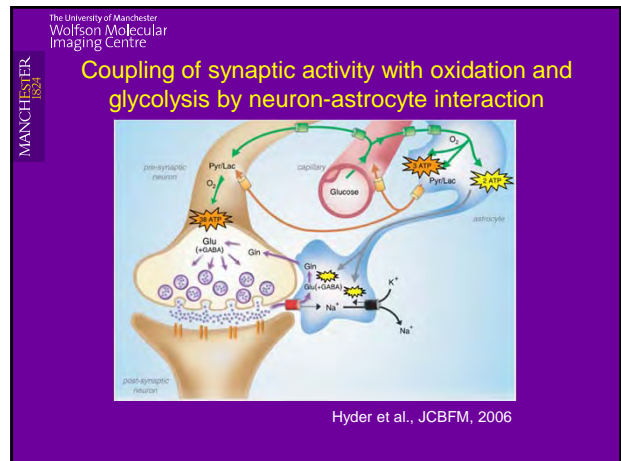
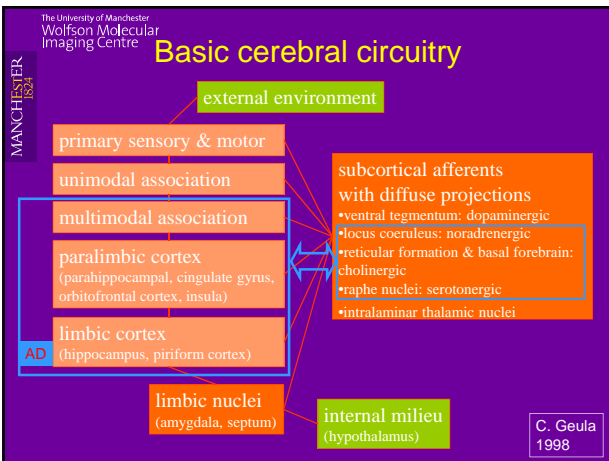
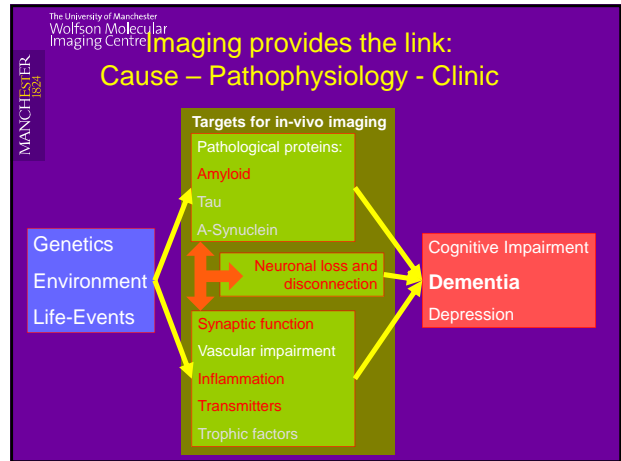


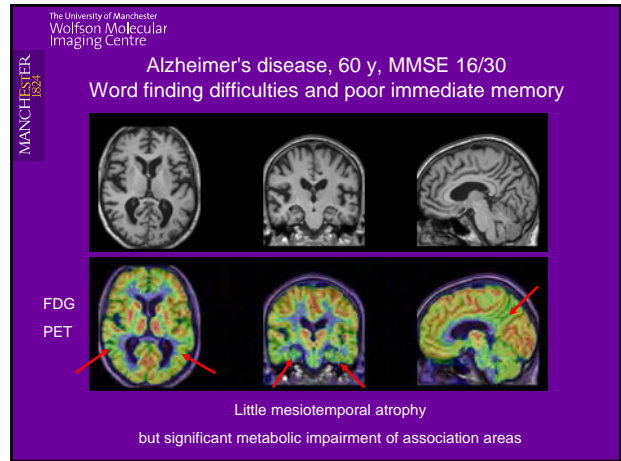
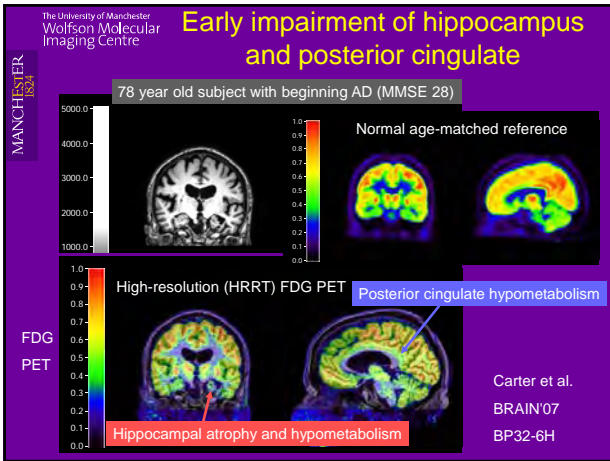
Neurodegenerative diseases

- Alzheimer's disease (AD: amyloid, tau)
- Frontotemporal lobar degeneration (FTLD: tau, ubiquitin, TDP43)
 - Frontotemporal dementia
 - Primary progressive aphasia
 - Semantic dementia
 - FTLD with motor neuron disease
- Diseases with Lewy Bodies (α -synuclein)
 - Parkinson's disease (PD)
 - Dementia with Lewy bodies (DLB)
- Transmissible spongiform encephalopathy (TSE: prion)
 - Creutzfeldt-Jakob, Gerstmann-Sträussler, fatal insomnia, Kuru
- Poly-glutamine repeat (polyQ) diseases
 - Huntington's chorea
 - Spinocerebellar atrophy (SCA)

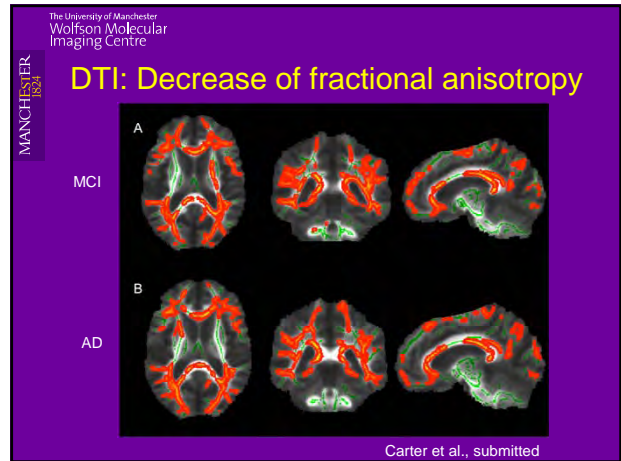
Brain imaging techniques

- Structure and BBB
 - MR morphometry, microanatomy (high-field MR)
 - BBB function (MR: contrast enhancement, PET: pGP function)
- Molecules
 - Pathological proteins (PET, nanoparticles, liposomes)
- Synaptic function
 - Glucose metabolism (FDG PET), CBF (ASL/SPECT/PET)
 - fMRI activation studies
 - EEG, MEG
- Connections
 - MR-DTI & Tractography
 - Resting state fMRI
 - Transmitters/Receptors (PET, SPECT)

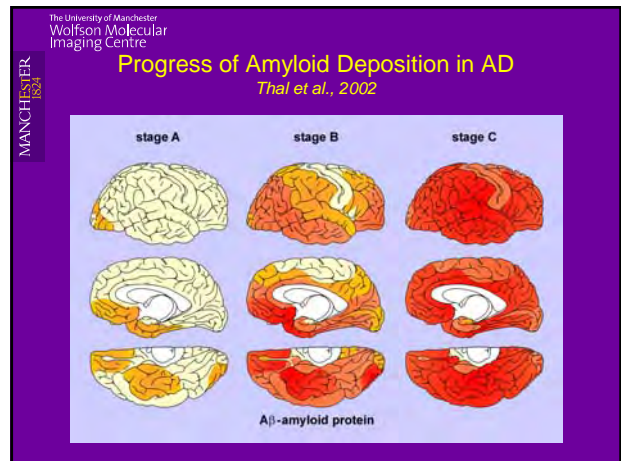


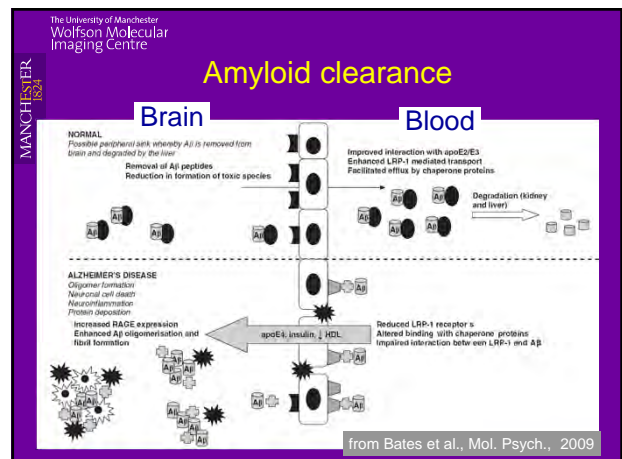
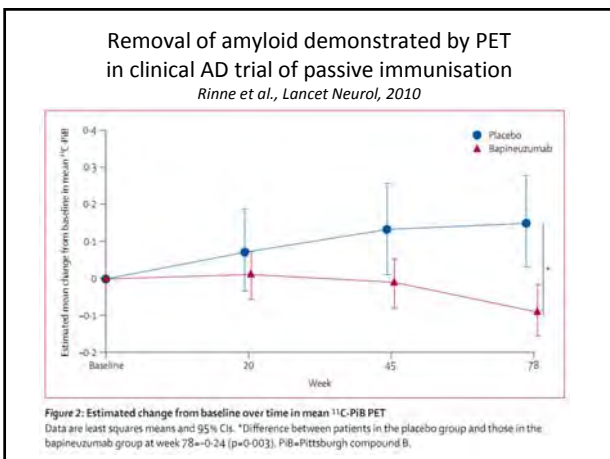
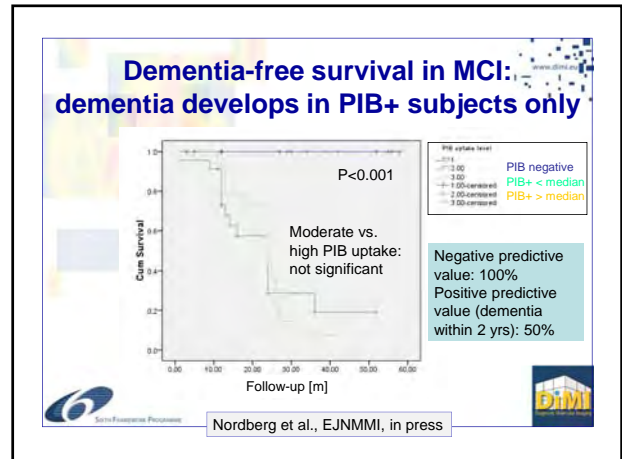
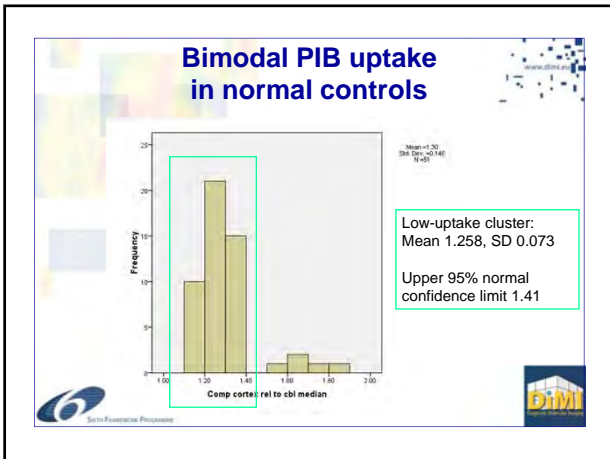
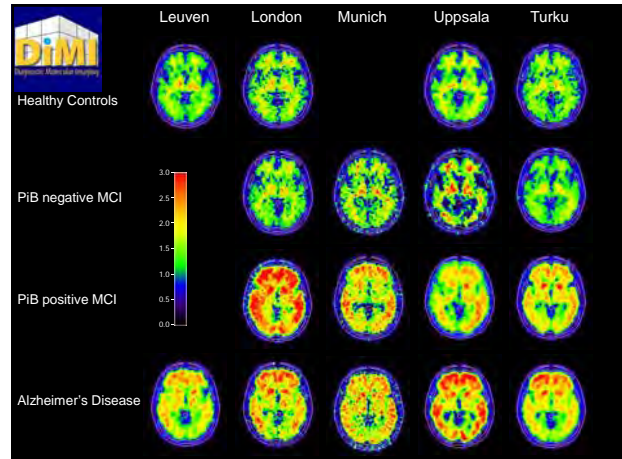
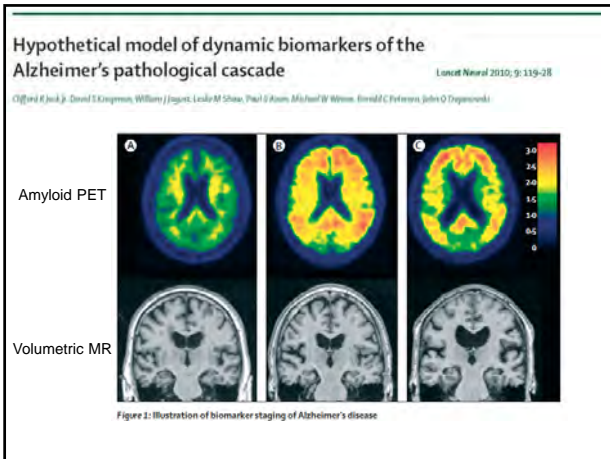


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- ### Alzheimer's disease subtypes
- Amnesic (hippocampal dysfunction)
 - Most frequent
 - Onset predominantly after age 65
 - ApoE4 is risk factor
 - Neocortical dysfunction
 - Onset predominantly before age 65
 - Posterior cortical atrophy
 - Logopenic aphasia
 - Autosomal genetic
 - Early onset
 - Mutations of APP, PSEN1, PSEN2
 - Atypical clinical features (e.g., motor symptoms)



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- ### Posterior Cingulate Gyrus & Precuneus
- Most prominent region with reduced FDG uptake already before onset of dementia (Minoshima et al., 1997, Reiman et al. 2001)
 - Linked with Papez circuit (memory deficit) and neocortical association areas (cognitive deficits) via cingulate fibres
 - Central hub of default-mode network
 - High metabolic rates in normal subjects at resting state
 - Reduction of glucose metabolism associated with loss of cytochrome oxidase (Valla et al., 2010) and deposition of amyloid (Cohen et al., 2009)
 - Impairment can be compensated by cognitive reserve in highly educated subjects (Garibotto et al., 2008)





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Proteins involved in A-beta removal

- Insulin-like growth factor (IGF-1)
- Insulin degrading enzyme
- Neprilysin
- Receptor for advanced glycation end products (RAGE)
- *Alpha-2 macroglobulin*
- *Clusterin (aka apolipoprotein J)*
- *Complement component (3b/4b) receptor 1*

Ref: Bates et al., 2009, Lambert et al., 2009

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Neurofibrillary tangles in AD: stages and age-distribution in autopsy series
Braak et al. 1999

Case count of tangles (n = 774)

Stages I and II (n = 158)

Stages III and IV (n = 137)

Stages V and VI (n = 205)

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Tau paired helical filaments: first deposits in hippocampus

Highly variable domains
Variable splicing
Intracellular deposits often hyperphosphorylated
Increased in CSF

from: Mandelkow, 2007

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Neocortical PIB (amyloid) versus hippocampal FDDNP (tau) in Alzheimer's

A ¹¹C-PIB

B MRI

C ¹⁸F-FDDNP

Control AD

Tolboom et al., JNM, 2009

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Alpha-synuclein

- Deposits are hallmark of Parkinson's disease (midbrain) and Lewy-Body-Dementia (cortex)
- No significant affinity for C-11-PIB (Ye et al., 2008)
- Labelling by benzoxazole compounds (18F-BF-227, Fodero-Tavoletti et al., 2009)

PD Substantia nigra

α -syn

BF227

Ap

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Imaging the dopaminergic deficit: PD & Dementia with Lewy Bodies (DLB)

- Dopamine precursors
 - 6-[18F]fluoro-m-tyrosine: Tyrosine hydroxylase
 - 6-[18F]fluoro-L-dopa (F-DOPA): Synthesis and storage
- Vesicular monoamine transporter 2 (VMAT2)
 - 11C-dihydrotetrabenazine (Koeppel et al., 2005)
 - 18F-FP-DTBZ (AV-133) (Kung et al. 2008)
- Catecholamine transporter
 - 11C-methyphenidate (Doudet et al., 2005)
- Dopamine transporter
 - 123I-FP-CIT SPECT, 18F-FE-PE2I (Varrone et al., 2011)

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Cholinergic systems

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brain
 basal forebrain
 pedunclopontine
 tegmental neurons
 striatal interneurons
 cranial nerve nuclei
 vestibular nuclei

spinal cord:
 preganglionic neurons
 motor neurons

E. Perry, 1999

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Tracers for the cholinergic system

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- ChAT: none
- Vesicular acetylcholine transporter:
 - I-123-iodobenzovesamicol, F-18-vesamicol analogue
- Muscarinic receptors:
 - M1: C-11-N-methyl-4-piperidylbenzilate (NMPB)
 - M2: F-18-FP-TZTP (agonist)
- Nicotinic receptors:
 - A4b2: I-123-A85380, F-18-FA-85380, F-18-flubatinid
 - Novel tracers for $\alpha 7$ under development
- Choline esterase:
 - AChE: acetylcholine analogue
C-11-N-methyl-4-piperidyl-acetate /-propionate (MP4A, MP4P)
 - BChE: C-11-N-methyl-4-piperidyl-butyrate (MP4B)
 - Labeled AChE-inhibitors

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Cortical cholinergic degeneration

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Local AChE activity by C-11-MP4A PET

Normal control

Mild AD (MMSE 21)

Reduction of cortical AChE

Preservation of basal forebrain nuclei

Herholz et al., Neuroimage, 2004

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Microglia

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- resident immune cells of the CNS

Microglial Activation

- Detected in inflammatory, degenerative, vascular and infective CNS diseases
 - potential to increase neuronal damage
 - might also contribute to amyloid removal
- Expression of Translocator Protein (TSPO), also known as peripheral benzodiazepine receptor

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Glucose Metabolism and Microglial Activation in MSA

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Results

11C-PK11195 increases (basal ganglia, brainstem, cerebellum, cortical regions)

FDG decreases

C/f A. Gerhard, Imp. Coll.

normal MSA

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Microglial activation in neurodegenerative disease

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Elderly control subject

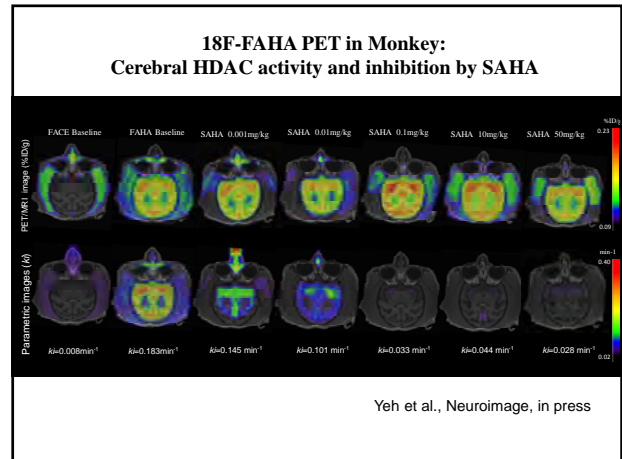
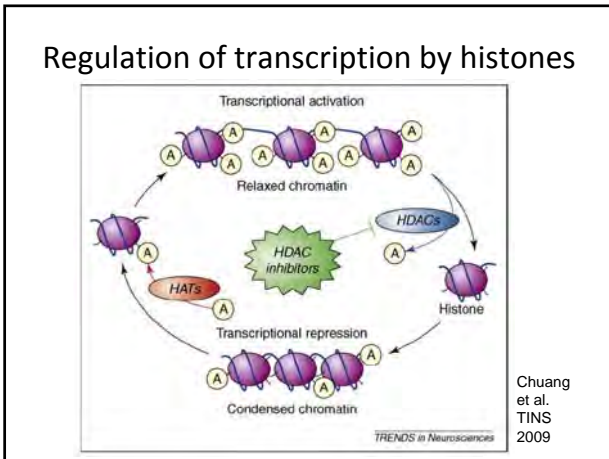
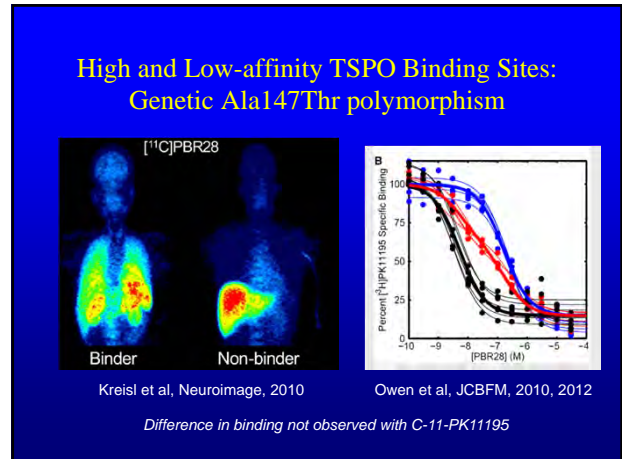
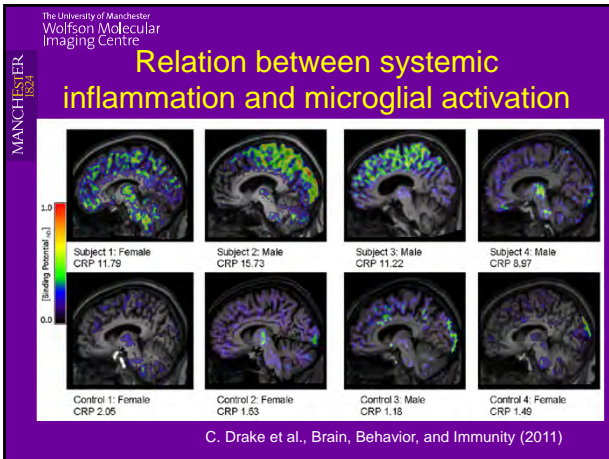
Mild cognitive impairment (MCI) patient

[¹¹C]PK11195 binding potential

0 0.5

Coronal view Sagittal view Transverse view

Gerhard, Karim, et al., manuscript in preparation



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- ### Clinical research & imaging in AD
- Longitudinal multimodal imaging to study in-vivo pathophysiology and the effects of intervention
 - AD subtypes: continuum or distinct diseases?
 - Dynamics of β -amyloid formation, including vascular factors (perfusion, endothelial transport)
 - Shared mechanisms with other neurodegenerative diseases
 - Inflammation
 - Synaptic plasticity and dysfunction
 - Brain resilience/reserve
 - Tau deposition, axonal transport
 - Oxidative/mitochondrial damage
 - Impairment of translation and transcription

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- ### Pathophysiology & Imaging: Comprehensive multidimensional research
- Practical systems biology:
 - Specific molecular changes in specific brain regions
 - Networks: interactions between brain regions
 - Functional and structural downstream effects
 - Perform longitudinal studies with targeted intervention