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
  - Spino-cerebellar 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, nonparticles, liposomes)
- Synaptic function
  - Glucose metabolism (FDG PET), CBF (ASL/SPECT/PET)
  - IMRI activation studies
  - EEG, MEG
- Connections
  - MR-DTI & Tractography
  - Resting state fMRI
  - Transmitters/Receptors (PET, SPECT)

C. Geula 1998

Coupling of synaptic activity with oxidation and glycolysis by neuron-astrocyte interaction

Hyder et al., JCBFM, 2006
Alzheimer's disease subtypes

- Amnestic (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)

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)
Bimodal PIB uptake in normal controls

Low-uptake cluster:
Mean 1.258, SD 0.073
Upper 95% normal confidence limit 1.41

Dementia-free survival in MCI: dementia develops in PIB+ subjects only

P<0.001
Moderate vs. high PIB uptake: not significant
Negative predictive value: 100%
Positive predictive value (dementia within 2 yrs): 50%

Removal of amyloid demonstrated by PET in clinical AD trial of passive immunisation

Rinne et al., Lancet Neurol, 2010

Amyloid clearance

Brain
Blood

Nordberg et al., EJNMMI, in press
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

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

Tau paired helical filaments: first deposits in hippocampus

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

from: Mandelkow, 2007

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

Tolboom et al., JNM, 2009

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)

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

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

Brain:
- Basal forebrain
- Pedunculopontine tegmental neurons
- Striatal interneurons
- Cranial nerve nuclei
- Vestibular nuclei

Spinal cord:
- Preganglionic neurons
- Motor neurons

E. Perry, 1999

Tracers for the cholinergic system

- 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:
  - Novel tracers for a7 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

Cortical cholinergic degeneration

Normal control

Mild AD (MMSE 21)

Preservation of basal forebrain nuclei

Heholz et al., Neuroimage, 2004

Microglia

- 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

Results

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

FDG decreases

CIA, Gerhard, Imp. Coll.
Relation between systemic inflammation and microglial activation

C. Drake et al., Brain, Behavior, and Immunity (2011)

High and Low-affinity TSPO Binding Sites: Genetic Ala147Thr polymorphism

Kreisl et al., Neuroimage, 2010
Kreisl et al, Neuroimage, 2010
Difference in binding not observed with C-11-PK11195

Regulation of transcription by histones

Chuang et al., TINS 2009

18F-FAHA PET in Monkey: Cerebral HDAC activity and inhibition by SAHA

Yeh et al., Neuroimage, in press

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

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