**PET ligands and metabolic brain imaging**

Prof. Karl Herholz

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**Positron-Emission-Tomography (PET)**

- Short-lived positron emitting isotopes produced by cyclotron
- Isotopes coupled to minute (typically microgram) amounts of biomolecules – tracer
- Tracer injected intravenously into patient
- Coincidence events caused by pairs of 511 keV γ-rays (originating from electron-positron annihilation) detected by PET camera
- Local metabolic rates and binding potentials calculated from kinetics of in vivo tracer biodistribution

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PET images in this lecture, unless indicated otherwise, are from Max-Planck-Institute for Neurological Research, Cologne, Germany.
**Frequent neurodegenerative diseases with characteristic PET findings**

- Alzheimer's disease
- Frontotemporal dementia (Pick complex)
- Dementia with Lewy bodies
- Parkinson's disease
- Multiple system atrophy
- Huntington's disease
- Amyotrophic lateral sclerosis

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**Imaging of Local Brain Function**

- Neuronal function
  - Ion gradients
  - Transmitter synthesis and recycling
- Energy consumption: FDG-PET
- Blood flow: PET, SPECT, fMRI

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**FDG-PET:** Normal cerebral glucose metabolism
FDG-PET:
Progression of early-onset Alzheimer Disease

14 months later

mild dementia

First symptoms: "Mild cognitive impairment"

Progression of early-onset Alzheimer Disease

Posterior cingulate impairment in Alzheimer's disease

Posterior Cingulate and Precuneus in Normal Subjects

Function (seen in activation studies):
- Episodic memory, esp. Retrieval
- "The mind's eye": Imagery in episodic recall
- Integrating current input with background knowledge
- Autobiographical memory retrieval

Resting glucose metabolic activity
- related to education
- slightly reduced in ApoE4 carriers

From: Herholz et al., NeuroPET, Springer-Verlag, 2004
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Diagnostic Accuracy of FDG PET for detection of Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All probable AD vs. controls</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td>Very mild AD (MMSE &gt;= 24) vs. controls</td>
<td>84%</td>
<td>93%</td>
</tr>
<tr>
<td>Earliest AD vs. controls (matched by MMSE 27-29)</td>
<td>83%</td>
<td>82%</td>
</tr>
</tbody>
</table>


Automatic detection of abnormal metabolism and regions that are typically affected by AD

T-statistics compared to European network (NEST-DC) normal database and correction for scanner resolution and patient age

Herholz et al. Neuroimage 2002

Software by: PMOD Technologies Inc.
Late vs. early onset AD

The selective metabolic impairment in temporo-parietal and posterior cingulate cortex is more pronounced in familial AD with early onset than in late-onset AD, which is mostly sporadic. Overall cortical impairment is similar, however...

Vascular dementia also shows mostly global metabolic impairment without much regional selectivity.

Multifactorial etiology, which is common in late onset dementia, is related to widespread cerebral metabolic impairment.

Progressive prosopagnosia

In most cases (Tung-Wai et al, Neurology 2004) “posterior variant of Alzheimer’s disease”

Frontal brain areas show reduced glucose metabolism in depression

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Anosognosia in AD: Metabolic changes related to patients' self assessment
E. Salmon et al., Human Brain Mapping, In press

Anosognosia in AD: Metabolic changes related to patients' self assessment
E. Salmon et al., Human Brain Mapping, In press

Metabolic impairment in FDG PET predicts clinical deterioration or mild cognitive impairment ('possible Alzheimer's disease')

EC Multicenter Study: 52 patients with MMSE >= 24

Frequency (%) of deterioration within 2 years

FDG PET abnormality at entry

Prospective study of FDG PET in MCI (anchisi et al., Arch Neurol, in press)

Within 1 year:
- Alzheimer's disease
- no progression

Positive predictive value
- CVLT 48%
- PET 93%

Negative predictive value
- CVLT 93%
- PET 93%
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Fronto-temporal Dementia (FTD)
Changes of personality and executive function, aphasia
Apathy or disinhibited, bizarre behavior
Fronto-temporal "lobar" atrophy
Mostly sporadic
rarely autosomal dominant (tau gene at 17q21-22)
Various inconstant histopathological changes
(astrogliosis, neuronal loss, Pick bodies, basophilic inclusion bodies,
ubiquinonated tau-negative non- eosinophilic inclusions)

Frontotemporal Dementia
asymmetric frontotemporal atrophy and functional impairment

Impairment of Ventromedial Frontopolar Cortex in Fronto-temporal Dementia

From: Herholz et al., NeuroPET, Springer-Verlag, 2004

**Proposed functions of frontomesial cortex in activation studies**

- "Theory of mind" (Fletcher et al., 1995)
- Self-referential mental activity (Maguire et al., 1999)
- Self-initiated, intentional thoughts (McGuire et al., 1996)
- Subjective emotional responses (Lane et al. 1997)

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**Frontotemporal Dementia with Amyotrophic Lateral Sclerosis**

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**Frontotemporal Lobar Atrophies**

- Often with pathological protein tau deposits ("tauopathy"), similar to fronto-temporal dementia
  
  **Primary progressive aphasia**
  
  Nonfluent progressive aphasie
  
  Mostly left inferior frontal and temporal metabolic impairment and atrophy
  
  **Semantic dementia**
  
  Severe progressive disturbance of semantic memory
  
  Mostly left temporal (and frontal) metabolic impairment and atrophy
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Corticobasal Degeneration

Mild reduction of CMRglc and FDOPA uptake in left striatum
Severe atrophy and metabolic impairment of left parietal cortex

From: Herholz et al., NeuroPET, Springer-Verlag, 2004

Progressive supranuclear palsy

Mild gait disorder, no definitive clinical diagnosis
7 years later: supranuclear palsy, severe falls, parkinsonism

CMRglc deviation from normal

From: Herholz et al., NeuroPET, Springer-Verlag, 2004

Chorea Huntington

Normal control

From: Herholz et al., NeuroPET, Springer-Verlag, 2004
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**FDG PET Metabolic Signatures**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Brain regions with reduced FDG uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease (AD)</td>
<td>Temporoparietal association cortex, posterior cingulate cortex and precuneus, variable also frontaltemporal association cortex</td>
</tr>
<tr>
<td>Dementia with Lewy bodies (DLB)</td>
<td>As in AD, plus primary visual cortex (POVRA is abnormal, in contrast to AD)</td>
</tr>
<tr>
<td>Frontotemporal dementia (FTD)</td>
<td>Predominantly frontomesial, also frontotemporal and anterior part of temporal lobe</td>
</tr>
<tr>
<td>Parkinson disease (PD)</td>
<td>FDG PET usually normal except from atrophy effects, but cortical impairment similar to LBD is possible in later stages of the disease</td>
</tr>
<tr>
<td>Dementia with cerebellar atrophy</td>
<td>Putamen, brainstem, cerebellum, often also cerebral cortex</td>
</tr>
<tr>
<td>Frontotemporal degeneration</td>
<td>Putamen</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Frontal, basal ganglia and midbrain</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Mainly parietal, central and frontotemporal cortex, striatum and thalamus, often very asymmetric (contralateral to side of clinical symptoms)</td>
</tr>
<tr>
<td>Spinocerebellar degeneration</td>
<td>Variable, probably depending on subtype, may be similar to HD</td>
</tr>
<tr>
<td>Olivo-ponto cerebellar atrophy</td>
<td>Putamen, putamen, frontal, lateral, and anterior part of temporal lobe</td>
</tr>
</tbody>
</table>

From: Herholz et al., NeuroPET, Springer-Verlag, 2004

**Imaging cerebral amyloid**

Pittsburgh Compound-B (PIB)

(N-methyl-{11C}L)-2-(4'-methylaminophenyl)-6-hydroxybenzothiazole

Klunk et al. (2005) In: Herholz, Perani & Morris: The dementias (Dekker)

**Tracers for the Dopaminergic System**

**Pre-synaptic:**
- Dopaminergic Axon
  - Dopamin-Synthesis: \(^{18}F\)-fluorodopa
  - Vesicle transporter (VMAT2): \(^{123}I\)-iodoamphetamine

**Post-synaptic:**
- Striatal Neuron
  - Reuptake Receptors: \(^{11}C\)-carfentanil, \(^{18}F\)-fallypride
  - Vesicle transporter (VMAT2): \(^{123}I\)-iodoamphetamine

\(^{11}C\)-carfentanil, \(^{18}F\)-fallypride, \(^{123}I\)-iodoamphetamine
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Anatomy of the Dopaminergic System

Mild Parkinson's disease (HY2)
FDG
Dopamine synthesis impaired in striatum, most severely in right caudal putamen
D2 receptors upregulated in right caudal putamen, but slightly reduced in caudate

FDOPA
Progression of impairment of dopamine synthesis

RAC
D2 receptors similar to first study

CMRglc intact in striatum and cortex

From: Herholz et al., NeuroPET, Springer-Verlag, 2004

Progression of Parkinson's disease

Hiller et al., Arch Neurol., 2005

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Striatonigral degeneration (SD) compared to Parkinson's disease (PD)

Pre- and postsynaptic Changes

Cholinergic systems
brain:
basal forebrain
pedunculopontine
tegmental neurons
striatal interneurons
cranial nerve nuclei
vestibular nuclei

spinal cord:
preganglionic neurons
motor neurons

From: Herholz et al., NeuroPET, Springer-Verlag 2004
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PET Tracers for the cholinergic system

Acetylcholine esterase (AChE)
- C-11-N-methyl-4-piperidyl-acetate (MP4A)
- C-11-N-methyl-4-piperidyl-propionate (MP4P)

Muscarinic receptors
- C-11-N-methyl-4-piperidylbenzilate (NMPB)

Nicotinic receptors
- F-18-fluoro-A-85380
- C-11-nicotine

C-11-MP4A (C-11-N-methyl-4-piperidyl-acetate) Kinetic Model (Namba et al., 1994)

Blood

Brain

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AChE activity measured by C-11-MP4A

$k_3$ Parametric images of hydrolysis rates

C-11-MP4A PET in mild to moderate AD:
Preservation of AChE in Nucleus basalis Meynert
(Herholz et al., Neuroimage, 2004)

Cortical AChE activity in MCI is associated with progress to dementia

Herholz et al., Neureport, 2005

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**Dementia with Lewy Bodies (DLB)**

- Essential symptoms (2 of 3) for clinical diagnosis
- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations that are typically well formed and detailed
- Spontaneous motor features of parkinsonism

McKeith et al., 1996

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**Transmitter Deficits in Lewy Body Dementia:**

- **MMPA:** Reduction of cortical AChE activity
- **F-DOPA:** Dopaminergic deficit in striatum

From: Herholz et al., NeuroPET, Springer-Verlag, 2004

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**Cholinergic but not dopaminergic deficit differentiates between Parkinson’s disease (PD) and Dementia with Lewy bodies (LBD)**

- Mean cerebral AChE activity
- Dopa influx Putamen

LBD IPS Control

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Systems Impairment in Degenerative Dementia

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>Subsystem impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer dementia</td>
<td>Function: FDG</td>
</tr>
<tr>
<td></td>
<td>Cholinergic: MP4A</td>
</tr>
<tr>
<td></td>
<td>Dopaminergic: FDOPA</td>
</tr>
<tr>
<td>Posterior cingulate/precuneus, angular gyrus</td>
<td>cortical</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>similar to AD, plus visual cortex</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Frontomesial, with variable extension to frontotemporal and anterior temporal cortex</td>
</tr>
</tbody>
</table>