A new perspective for advanced PET-based molecular imaging in FTD spectrum

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IRCCS and San Raffaele Hospital
**PET in NEURODEGENERATIVE DISEASES:**
glucose metabolism, protein burden, neuroinflammation

Last years are witnessing a rapid transition from a clinical-based to a pathology-based classification of neurodegenerative conditions, largely promoted by the increasing availability of molecular neuroimaging biomarkers.

This implementation promotes a spectrum-approach to neurodegenerative conditions, based on pathology subtypes and clinical endophenotype heterogeneity.

*Perani et al., and IMBI Consortium* Alzh. & Dem., 2019
This approach will enhance efforts to understand both the biology of Alzheimer’s Disease as well as the multifactorial etiology of other dementias, which has been obscured to some extent in the past by equating the PET protein molecular biomarker role to an effective diagnostic tool.

Together with methodological challenges in the production of these tracers, their optimal quantification and standardization procedures, and their evidence-based clinical utility.
Perspective
A new perspective for advanced positron emission tomography–based molecular imaging in neurodegenerative proteinopathies

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Andreas H. Jacobs, MD MD,9,10 on behalf of all partners of the IMBI Project

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8European Institute for Molecular Imaging, University of Münster, Germany
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MOLECULAR PET in vivo IMAGING IN PROTEINOPATHIES

PROTEIN DEPOSITION

Meta-analysis from the relate literature
Color gradients index magnitude of alteration

Perani et al., and IMBI Consortium Alzh. & Dem., 2019
SPECTRUM of PROTEINOPATHIES

- Amyloidopathies
- Tauopathies
- Alpha synucleinopathies
- TAR DNA-binding protein 43 pathology
- Prion protein pathology

Weaknesses

PET TECHNIQUES

- Amyloid PET

Directions/recommendations

- Neuroinflammation PET
- Neurotransmission

Amyloid-PET

Strengths

Directions/recommendations
## Amyloid-PET

<table>
<thead>
<tr>
<th>Amyloid plaques</th>
<th>Tracers</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Technical caveats</th>
</tr>
</thead>
</table>
| • AD dementia  
  • MCI  
  • PDD  
  • FTD  
  • CAA  
  • DLB  
  • DS  
  • TBI  
  • Healthy aging | • [11C]PiB  
  • [18F]Florbetapir  
  • [18F]Florbetaben  
  • [18F]Flutemetamol  
  • [18F]NAV4694 | • In vivo detection of brain deposition of amyloid plaques (amyloidosis) strongly consistent with post-mortem autopsy findings  
• Useful to screen participants in clinical trials  
• Invariantly positive in pathologically-proven dementia due to AD | • Positivity in healthy aging  
• Positivity in non-AD dementias  
• Does not predict progression with high accuracy in MCI and HC  
• Does not correlate with measures of neurodegeneration or clinical impairment  
• Does not detect oligomeric Aβ forms (caveat in clinical trials)  
• Caveats to evaluate amyloid therapies | • SUVR measures are flow-dependent and should not be used for longitudinal evaluations  
• Need for metrics and quantification |

We recommend to **avoid general diagnostic and prognostic practice based solely on amyloid positivity and, even more, for the inclusion in clinical trials**

Eventually, including participants based on their positivity to amyloid protein pathology (a finding that could be incidental or non-AD related) might be dangerous, with the risk of administering potentially harmful, therapies to subjects who are not going to develop AD dementia

It is our belief that **neurodegeneration biomarkers** such as FDG PET or tau-PET should be considered, together with amyloid-PET results, to maximize the accuracy of both early and differential diagnosis
Amy+ HC and Amy+ MCI show a faster cognitive decline

However, 58% of HC and MCI Amyloid+ do not progress clinically during the follow-up

**FOCUSING on FDG-PET**

HC Negative Predictive Value 83% of FDG-negative HC remained stable
MCI Negative Predictive Value 81% of FDG-negative MCI remained stable

Iaccarino, Sala, Perani  Ann ClinTrans Neurology, 2019
Amyloid-PET must be coupled to a measure of neurodegeneration (FGD PET) to avoid enrolment of incident amyloid-positive subjects or other associated ND including FTD.

A certain percentage of FDG PET + subjects had a FTD-like patterns.

Iaccarino, Sala, Perani  Ann ClinTrans Neurology, 2019
Maruyama et al. Neuron 2013

Chiotis et al. 2016
Conclusions: 18F-flortaucipir in patients with FTD and predicted tauopathy or TDP-43 pathology demonstrated limited sensitivity and specificity. Further postmortem pathological confirmation and development of FTD tau-specific ligands are needed.
in bvFTD

MAPT mutation carriers
Conclusions: The distribution of THK retention in the bvFTD patients was mainly in the frontal, insula, anterior temporal, and striatum regions which are known to be the brain regions corresponding to the clinical symptoms of bvFTD. Our study suggests that 18F-THK5351 PET imaging could be a supportive tool for diagnosis of bvFTD.

<table>
<thead>
<tr>
<th>Tau aggregates</th>
<th>Tracers</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Technical caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD MCI D LB CBD PSP CTE DS Genetic FTD Healthy aging</td>
<td>[11C]PBB3 [18F]Flortaucipir [18F]THK family</td>
<td>• In vivo detection of brain deposition of neurofibrillary tangles in AD, consistent with post-mortem autopsy findings • Tight relationships with ND and cognitive impairment in AD • Track AD disease progression • Evaluate tau therapies in clinical trials</td>
<td>• Presents non-specific binding in choroid plexus and neuromelanin-containing tissue • Pathologies characterized by predominant 4R tau and TDP-43 present weaker binding increases when compared to AD tauopathy • Medial temporal lobe tau accumulation is present in healthy aging • [18F]THK5351, non-specific binding to MAO-B</td>
<td>• Seems not to reach steady state in 100 minutes • Semi-quantified measurements are needed</td>
</tr>
</tbody>
</table>
PET in NEURODEGENERATIVE DISEASES: glucose metabolism, protein burden, neuroinflammation
In Vivo Detection of Microglial Activation in Frontotemporal Dementia

Cagnin et al., 2004

MICROGLIAL ACTIVATION IN CORTICOBASAL DEGENERATION

In Vivo Imaging of Microglial Activation With $^{11}$C/J6-TACR1-PK11195 PET in Corticobasal Degeneration

Alexander Gerhard, MD,1,2 Joelle Watts, MS,1,2
Stefan Gerhard, MD,1
Fedelico Teichner, PhD,3 Richard B. Basrai, MD,1
Katja Blum, MD,1 and David J. Brooks, MD, DSc1

Movement Disorders, Vol. 19, No. 10, 2004
MICROGLIAL ACTIVATION IN PROGRESSIVE SUPRANUCLEAR PALSY

In Vivo Imaging of Microglial Activation With $^{11}$C-(R)-PK11195 PET in Progressive Supranuclear Palsy

Alexander Gerhard, MD,1
Ish Tewfik-Gerhard, MD,1
Fredéric Turkheimer, MD,1 Nuel P. Ounis, MD,1
Kalich P. Bhatia, MD,1 and David J. Brooks, MD1

Movement Disorders, Vol. 21, No. 1, 2006

$^{11}$C-(R)-PK11195-PET and $^{18}$F-FDG-PET in MCI

Multidomain MCI, 72 yrs, FTD converter

Perani D, personal data
There is very little activation of microglia in preclinical phase. The involvement of thalamic and limbic structures might indicate a role for microglia activation in these key pathologic regions, known to show the most significant neuronal loss.
Iaccarino et al. 2017

CJD cases

IMBI Working Group

Neuroinflammation

<table>
<thead>
<tr>
<th>Tracers</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Technical caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11C]PK11195</td>
<td>- In-vivo detection of microglia and astrocytes reaction to immunological agents, consistent with preclinical and in-vitro evidence</td>
<td>- Strongly sensitive to immune responses in traumatic brain injuries</td>
<td>- 2nd generation tracers suffer from a genetic polymorphism altering binding affinity</td>
</tr>
<tr>
<td>[18F]DPA-714</td>
<td>- Significant TSPO over-expression described in key pathology regions across different conditions,</td>
<td>- Evaluation of neuroinflammation as driving player in neurodegenerative conditions</td>
<td>- TSPO is homogeneously expressed across the whole-brain, is also associated with endothelial expression</td>
</tr>
<tr>
<td>[18F]DPA-713</td>
<td>- In clinical trials to assess the outcome of anti-inflammatory or immunomodulatory therapies.</td>
<td>- TSPO is homogeneously expressed across the whole-brain, is also associated with endothelial expression</td>
<td>- Need of quantification</td>
</tr>
<tr>
<td>[18F]GE180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[11C]deprenyl</td>
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</table>

Perani et al. JPND IMBI Consortium Alzh & Dem, 2019
This consensus review of PET molecular techniques provides neurologists and researchers with a new vision on the use of PET-based tools for detecting and measuring neuropathology in vivo in different neurodegenerative conditions.

The adoption of a pathology-based spectrum approach for the classification of neurodegenerative conditions influences the application of PET molecular imaging techniques, which can play a unique and leading role in the in vivo assessment of brain pathology using appropriate PET tracers.

**PET in ND: glucose metabolism**
Role of PET imaging in diagnostic practice

More than 20 years of research in FDG PET molecular imaging provides specific metabolic patterns for the different neurodegenerative disorders.

The importance of quantification
solute or parametric measures

CRITICAL ISSUES
VOXEL-BASED SEMI-QUANTITATIVE ANALYSIS

Tools:
- NeuroQ (Syntermed)
- NeuroClick (Hermes)
- PMOD software
- SPM
- W-score Maps
- Multivariate analysis

Common denominator is a normal database
Greater sample sizes in normal database provide more accurate results

THE NEED FOR METRICS

Summary of sensitivity for FDG measures:
- 0.86 for Early Diagnosis (MCI)
- 0.90 for Differential Diagnosis

DIAGNOSTIC CHALLENGES

FTD spectrum

Seelaar et al., 2013

FDG PET SPM MAPS in BEHAVIORAL VARIANT FTD  SINGLE SUBJECT

Cerami et al. Cortex, 2016
bvFTD 59 years old

MRI T2 Flair

FDG-PET SPM Map

FWE-Corrected
Statistical Comparison
1 vs 112 Subjects

BEHAVIORAL VARIANTS OF FTD SINGLE SUBJECT

VOXEL-BASED SPM ANALYSIS

Frontal bvFTD

Temporal-limbic bvFTD

Cerami et al., Cortex 2016, Sala et al. 2019
Neuropsychological profiles

<table>
<thead>
<tr>
<th></th>
<th>FRONTAL</th>
<th>TEMPOROLIMBIC</th>
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<tbody>
<tr>
<td>Number of subjects</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>11/14</td>
<td>12/15</td>
</tr>
<tr>
<td>Age in years (mean±sd)</td>
<td>85.9±7.90</td>
<td>72.8±7.083</td>
</tr>
<tr>
<td>Education (mean±sd)</td>
<td>11.1±4.61</td>
<td>10.7±4.81</td>
</tr>
<tr>
<td>GDS sum of boxes (mean±sd)</td>
<td>4.9±2.06</td>
<td>5.4±3.57</td>
</tr>
<tr>
<td>Disease duration (mean±sd)</td>
<td>26.8±13.94</td>
<td>34.8±27.15</td>
</tr>
<tr>
<td>MMSE/csw score (mean±sd)</td>
<td>22.0±4.76</td>
<td>22.6±7.74</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Behavior n=16</td>
<td>Behavior n=11</td>
</tr>
<tr>
<td>Language n=0</td>
<td>Behavior n=10</td>
<td>behavior n=11</td>
</tr>
<tr>
<td>Bipolar syndrome or depression in anosognosia</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Behavioral distribution (n. of cases)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Apathy or inertia (n. of cases)</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Both disinhibition and apathy (n. of cases)</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Use of empathy or sympathy (n. of cases)</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Perseverative, stereotyped, or compulsive/ritualistic behaviors (n. of cases)</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Hyperactivity and dietary changes (n. of cases)</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Executive deficits (n. of cases)</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Immediate recall memory impairments (n. of cases)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Delayed recall memory impairments (n. of cases)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Both immediate and delayed recall memory impairments (n. of cases)</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>No immediate and delayed recall memory impairments (n. of cases)</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

Cerami et al., Cortex 2016

RESEARCH DIAGNOSTIC CRITERIA including FDG PET

LEWY BODY DISEASE

FRONTOTEMPORAL DEGENERATION SPECTRUM
Heterogeneous clinical phenotypes are associated with the PPA (nf-PPA, sem-PPA, lv-PPA), and recent review studies refer to Alzheimer disease (AD), corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP)

The topography of FDG PET brain hypometabolism represents the major signature of the clinical PPA phenotype

Gorno-Tempini et al., Neurology 2011

Cerami et al., JAD 2016
SEMANTIC PPA VARIANT OF FTD        SINGLE SUBJECT

Iaccarino et al., PLOS ONE  2015
Cerami et al., JAD  2016

FRONTAL TEMPORAL DEGENERATION SPECTRUM


RESEARCH DIAGNOSTIC CRITERIA including FDG PET

LEWY BODY DISEASE

The Parkinsonian Disorders (APD) frequently overlap in clinical presentations, making the differential diagnosis challenging, particularly in the early stages.

Low dopamine transporter uptake at SPECT is present in all the parkinsonian syndromes making its role in the differential diagnosis of APD not possible.

The dysfunctional brain patterns revealed by FDG PET represent biomarkers of local synaptic dysfunction associated with disease-specific alterations characterizing APD conditions.

**Progressive supranuclear palsy**

- [18F]FDG-PET SPM Single-subject Analysis
- [18F]FDG-PET SPM Commonality Analysis

Metabolic reductions in:
- Upper brainstem
- Thalami
- Caudate
- Frontal opercula
- Middle frontal cortex
- Anterior cingulate gyrus

Caminiti et al., EJN 2017

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**Corticobasal degeneration (CBD)**

- [18F]FDG-PET SPM Single-subject Analysis
- [18F]FDG-PET SPM Commonality Analysis

Asymmetric reductions in:
- Thalamus
- Striatum
- Precentral gyrus
- Frontoparietal areas
- Middle cingulate gyrus

Caminiti et al., EJN 2017
FDG PET SPM showed an almost 20% increase in overall accuracy compared to initial clinical classification.

Caminiti et al., EJN 2017

SPM maps of significant FDG-PET hypometabolism at the single-subject level in CBS subjects with by different language profiles: a) nfv-PPA (nfv-PPA/CBS); b) language dysfunctions not fulfilling PPA criteria (LANG-CBS); c) no language dysfunctions (i.e., NOL-CBS).

Dodich et al. NI Clin 2019
These results strongly suggest the inclusion of FDG-PET imaging in the diagnostic algorithm of individuals with CBS clinical phenotype in order to early identify functional metabolic signatures due to different neuropathological substrates, thus improving the diagnostic accuracy.

Cerami et al. submitted

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**INDIVIDUAL BRAIN METABOLIC SIGNATURES IN CORTICOBASAL SYNDROME**

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**LEWY BODY DISEASE**

**FRONTOTEMPORAL DEGENERATION SPECTRUM**
PRE-DEMENTIA PHASE

FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicenter MCI cohort

80 MCI

FDG-PET-SPM classification the most accurate biomarker, able to provide disease-specific hypometabolism patterns in the prodromal MCI phase
Alternative pathological conditions, such as AGD, primary age-related tauopathy or age-related TDP-43 proteinopathy, known to spread throughout the medial temporal lobe and limbic system structures

Cerami et al., Alzh Res Ther 2018
A recently recognized disease entity, limbic-predominant age-related TDP-43 encephalopathy (LATE) is a common TDP-43 proteinopathy, associated with an amnestic dementia syndrome that mimics Alzheimer’s-type dementia.

MRI atrophy

Biomarkers based definition of limbic predominant long-lasting amnestic Mild Cognitive Impairment

Perani et al. submitted
Clinical demographic features of the whole long-lasting aMCI cohort

<table>
<thead>
<tr>
<th>Patients sample</th>
<th>n=80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male ratio</td>
<td>32/48</td>
</tr>
<tr>
<td>Age at the first evaluation (mean ± SD)</td>
<td>74.28 ± 5.4</td>
</tr>
<tr>
<td>Age at the follow-up (mean ± SD)</td>
<td>78.78±5.26</td>
</tr>
<tr>
<td>Years of education (mean ± SD)</td>
<td>13.76 ± 4.41</td>
</tr>
<tr>
<td>Disease duration at the first evaluation (mean ± SD)</td>
<td>4.05±2.44 (Range: 2-12 years)</td>
</tr>
<tr>
<td>Years of follow-up (mean ± SD)</td>
<td>4.40±1.90 (Range: 2-12 years)</td>
</tr>
<tr>
<td>MMSE adjusted score at the first evaluation (mean ± SD)</td>
<td>25.73±2.06</td>
</tr>
<tr>
<td>MMSE adjusted score at follow-up (mean ± SD)</td>
<td>25.05±2.58</td>
</tr>
<tr>
<td>CDR at the first evaluation (mean ± SD)</td>
<td>0.5±0.0</td>
</tr>
<tr>
<td>CDR at follow-up (mean ± SD)</td>
<td>0.56±0.34</td>
</tr>
<tr>
<td>IADL at the first evaluation (mean ± SD)</td>
<td>6.77±1.31</td>
</tr>
<tr>
<td>IADL at follow-up (mean ± SD)</td>
<td>6.33±1.13</td>
</tr>
<tr>
<td>FAQ at the first evaluation (mean ± SD)</td>
<td>4.14±5.98</td>
</tr>
<tr>
<td>FAQ at follow-up (mean ± SD)</td>
<td>6.85±8.83</td>
</tr>
<tr>
<td>CSF Aβ42 pathological (n° of subject)</td>
<td>43</td>
</tr>
<tr>
<td>CSF t-Tau high (n° of subject)</td>
<td>40</td>
</tr>
<tr>
<td>CSF p-Tau high (n° of subject)</td>
<td>51</td>
</tr>
<tr>
<td>T-tau/Aβ42 ratio pathologic (n° of subject)</td>
<td>56</td>
</tr>
<tr>
<td>P-tau/Aβ42 ratio pathologic (n° of subject)</td>
<td>63</td>
</tr>
</tbody>
</table>
**AT(N) classification**

AT(N) non-Alzheimer’s disease spectrum (46.30%):
- A-T+(N+): 23.80%
- A-T-(N+): 22.50%

AT(N) Alzheimer’s disease spectrum (53.80%):
- A+T+(N+): 40%
- A+T-(N+): 13.80%

**Single-subjects hypometabolic pattern**

Images A to H and I to R show different hypometabolic patterns in various regions of the brain.
MCI amnestic patient

Age: 74
MMSE score, baseline: 26
MMSE score, last follow up: 27
Disease duration: 8 Years

CSF:
Aβ pathologic
Ttau pathologic
Ptau pathologic
Single Subject

MCI amnestic patient

Age: 77
MMSE score, baseline: 26
MMSE score, last follow up: 24
Disease duration: 9 Years
CSF: Aβ pathologic
Ttau pathologic
Ptau pathologic

Single Subject

MCI amnestic patient

Age: 79
MMSE score, baseline: 26
MMSE score, last follow up: 24
Disease duration: 7 Years
CSF: Aβ negative
Ttau negative
Ptau negative
Argyrophilic grain disease (AGD), a 4-repeat tauopathy associated with memory deficits and behavioural disturbances in the elderly, characterized by the presence of argyrophilic grains in the medial temporal lobe which may also overlap with neuropathology changes of Alzheimer’s disease (Rodriguez et al., 2016);

Primary age related tauopathy (PART), a tauopathy affecting aged individuals presenting progressive deposition of neurofibrillary tangles, comparable to Alzheimer’s disease, involving medial temporal lobe structures, in the absence of cortical amyloid load (Crary et al., 2014)

These complementary results suggest that the selective limbic brain metabolic pattern is associated with clinical stability and makes progression to Alzheimer’s dementia or other dementia very unlikely. These findings underline the key role of $[^{18}\text{F}]$FDG-PET metabolism pattern as a fundamental biomarker in the diagnosis and prognosis of amnestic mild cognitive impairment population.
Future of Multi-modal MI in Personalized Medicine


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- S.P. Caminitti
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- G Tondo
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THANK YOU
FOR YOUR ATTENTION

Imaging imagination. Shown is part of the engraving, "The Physician Curing Fantasy," by Mathaus Greuter (1564–1618).