Biomarkers in the differential diagnosis of dementia
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Chapter 9:

Diagnostic classification following a blinded assessment of combined 11C-Pittsburgh compound B [PIB]-PET and 18F-fluorodeoxyglucose [FDG]-PET in distinct profiles of Dementia; Preliminary results of the ‘Dual PET’ study

F.E. Reesink, A. T. Willemsen, B.M. de Jong, R.A. Dierckx, P. P. De Deyn
Introduction:

Previously, the definite diagnosis Alzheimer Disease (AD) required histopathological confirmation, while the probable clinical diagnosis was based on a cognitive profile, supported by neuroimaging. Neuropathological, AD is characterized by amyloid-β (Aβ) depositions and intracellular neurofibrillary tangles consisting of hyper-phosphorylated tau. The “amyloid cascade hypothesis” postulates that Aβ starts to accumulate, followed by a cascade of neuropathological events such as neurofibrillary tangles formation and neuroinflammation. Since the development of in vivo biomarkers, the pathophysiological process is becoming more important in the clinical diagnosis, also in a prodromal stage, as recommended by the National Institute on Aging-Alzheimer Association in 2011. Recently, this guideline was updated for research purposes, with a proposed ‘A-T-N’ framework founded on a biological definition of AD, with three different labels of biomarker evidence. Firstly, the “A” amyloidosis biomarkers in cerebrospinal fluid (CSF) and amyloid Positron Emission Tomography (PET) imaging (e.g. Pittsburgh compound-B or [11C] PIB). Secondly, “T” Tau-biomarkers in CSF (phosphorylated-Tau levels) and Tau-PET imaging. Thirdly, the “N”-biomarkers of neurodegeneration such as cortical atrophy on structural magnetic resonance imaging (MRI), elevated CSF Total-Tau levels and a “classic” AD fluorodeoxyglucose ([18F] FDG) PET scan. A “classic” AD [18F] FDG-PET scan shows hypometabolism in the temporal-parietal association cortex, more variably also in the prefrontal cortex, but with a relative preservation of metabolism in the primary visual and sensorimotor cortex, striatum, and cerebellum. In the clinical diagnosis of AD, combining molecular imaging biomarker tracers have added value compared to the standard diagnostic criteria for different types of neurodegenerative dementia. Whereas [11C]-PiB PET measures the amyloid deposits in the diagnosis of MCI or AD, compared to [18F]-FDG PET contributes more in patients with low diagnostic certainty and distinguishes between different dementia disorders. A correct clinical diagnosis of dementia is supportive for the patient and caregivers and helps in therapeutic management. Future therapies and medication trials focus on specific proteinopathies, and therefore in vivo biomarkers are becoming important for the clinical diagnosis.

The aim of the ‘dual PET’ study that we designed was to find out how [11C]-PiB and [18F]-FDG PET can contribute to the clinical diagnosis of AD and other types of dementia and how this diagnosis correlates within the clinical differential diagnosis. In this study, 100 subjects are to be included, with a clinical diagnosis of <1> Mild Cognitive Impairment (MCI), <2> probable AD, <3> probable Lewy Body Dementia (DLB), <4> probable Frontotemporal Dementia (FTD) and finally <5> a group of healthy controls. While the ‘dual PET’ study also includes cerebral Magnetic Resonance Imaging (MRI) and formal neuropsychological assessment to further substantiate a final diagnosis, the preliminary analysis reported here had a restricted aim. The objective was to investigate a PET-driven discrimination between different patient groups based on the distinction between PIB positive and negative scans and the subsequent pattern classification of reduced FDG uptake. This analysis thus provided the opportunity to evaluate the match...
between abnormal cerebral amyloid accumulation and the ‘typical’ AD pattern of reduced parietal glucose metabolism. The PET-driven classification further enabled a general comparison with the clinical classification used for inclusion of the participants. The assessment was visually performed by a “blinded” expert, without knowledge of the clinical symptoms.

Methods:

All subjects included for the present preliminary analysis were recruited from 2013 until 2018 at the memory clinic of the University Medical Center of Groningen (UMCG). Standard dementia screening was performed, including medical history, physical and neurological examinations, screening laboratory tests and T1-weighted MRI scan of the brain. Standard cognitive test battery included Mini Mental State Examination (MMSE)\textsuperscript{15}, Rey Auditory Verbal Learning test (REAVL)\textsuperscript{16}, Visual Association Test (VAT)\textsuperscript{17}, Rey Complex Figure Test (RCFT-IR)\textsuperscript{18}, Immediate Recall Location Learning Test (LLT-IR)\textsuperscript{19}, Delayed Recall (LLT-DR)\textsuperscript{20}, Doors Test A/ B\textsuperscript{21}, Trail Making Test A/B (TMT)\textsuperscript{22}, Semantic Fluency\textsuperscript{23} and Geriatric Depression Scale (GDS)\textsuperscript{24}. CSF samples were collected in polypropylene tubes, transported to the laboratory, centrifuged, and measured or stored at $-80^\circ$C until analysis. The Enzyme-Linked Immuno Sorbent Assays were used, according to the manufacturers’ protocol for the determination of Aβ\textsubscript{42} (INNOTEST® β-AMYLOID (1–42)), t-tau (INNOTEST® TAU Ag) and p-tau (INNOTEST® PHOSPHO-TAU (181P)). CSF biomarkers were considered positive or indicative for AD when CSF Aβ is lower than 500 ng/L, while CSF Tau markers were considered positive when either or both CSF Tau is higher than 350 ng/L and CSF p-Tau higher than 85 ng/L. Clinical diagnosis was established by multidisciplinary team consensus according to the NIA-AA criteria\textsuperscript{25}. Inclusion and exclusion criteria are described in table 1- A and 1- B. The ethics committee of the UMCG approved the study (METc 2014/320). The time between the different investigations was less than 3 months. Demographical and clinical characteristics were compared between groups using chi-square tests and analysis of variance SPSS Statistics version 23.01).
### Table 1- A: Inclusion criteria ‘dual PET’ study

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Age from 50-80 year, sign informed consent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Healthy controls (HC)</strong></td>
<td>MMSE scores between 28-30</td>
</tr>
<tr>
<td></td>
<td>Without subjective memory complaints</td>
</tr>
<tr>
<td><strong>Mild cognitive impairment (MCI)</strong></td>
<td>Diagnosis of MCI assessed by a clinician and neuropsychologist, according to Petersen [26,27], divided in four subtypes:</td>
</tr>
<tr>
<td></td>
<td>Amnestic, Non-amnestic, Multi-domain amnestic, Multi-domain non-amnestic</td>
</tr>
<tr>
<td><strong>Alzheimer’s disease dementia (AD)</strong></td>
<td>Diagnosis of probable AD according to the Alzheimer’s disease and Related Disorders Associations guidelines [28]</td>
</tr>
<tr>
<td></td>
<td>Subtype of primary cortical atrophy [29,30]</td>
</tr>
<tr>
<td></td>
<td>Logopenic progressive aphasia (LPA) due to AD [31]</td>
</tr>
<tr>
<td></td>
<td>Corticobasal Syndrome due to AD [32]</td>
</tr>
<tr>
<td><strong>Dementia with Lewy Bodies (DLB)</strong></td>
<td>Diagnosis of probable DLB according to the fourth DLB consortium [33] with 2 of 4 clinical features: Visual hallucinations, Fluctuations, Parkinsonism, REM sleep behaviour disorder</td>
</tr>
<tr>
<td><strong>Frontotemporal dementia (FTD)</strong></td>
<td>Diagnosis of behavioural variant FTD according to the revised consensus criteria [34]</td>
</tr>
<tr>
<td></td>
<td>Diagnosis of the subtype of FTD of primary progressive aphasia (PPA), divided into semantic dementia (SD), progressive non-fluent aphasia (PNFA) and LPA due to FTD [35,36]</td>
</tr>
</tbody>
</table>

**above. MMSE: mini-mental state examination**
Table 1 –B: Exclusion criteria ‘dual PET’ study

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>History of major psychiatric illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Cerebrovascular disease with cortical infarcts or a Fazekas-score of 2 or higher</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Mentally incompetent to understand full consequence of an informed consent</td>
</tr>
<tr>
<td>Healthy controls (HC)</td>
<td>Abnormal results on neuropsychological tests</td>
</tr>
<tr>
<td></td>
<td>Subjective memory complaints</td>
</tr>
<tr>
<td>All subjects, except healthy controls</td>
<td>Cognitive deficits could be explained by non-neurodegenerative conditions (e.g. stroke, neoplasm, head injury, hydrocephalus or other medical conditions)</td>
</tr>
</tbody>
</table>

A potential subject who meets any of the criteria above was excluded from participation in this study.

All subjects underwent a dynamic $[^{11}\text{C}]$ PIB and a static $[^{18}\text{F}]$ FDG scan on the same day under standard resting conditions with eyes closed. Siemens Biograph 40 and 64 mCT PET/CT scanners were used. Radiotracers were manufactured at the radiopharmacy facility of the nuclear medicine department and synthesized according to the Good Manufacturing Procedure, and administered intravenously. Approximately 30 patients were scanned in 60 minutes. Advancing insight and the expert opinion lead to the decision to change the scanning time to 70 minutes. Additionally, 10 patients (5 AD and 5 HC) underwent a sensitivity analysis (comparable with other PET centres and literature) and therefore, scanned for an interval of 90 minutes. Longer scanning gives more stable kinetic analysis, because the longer timeframe shows better reversible tracer kinetics. The dynamic $[^{11}\text{C}]$ PIB data acquisition was started at the time of tracer injection (387 ±18 MBq). The static $[^{18}\text{F}]$ FDG PET was acquired 30 minutes after $[^{18}\text{F}]$ FDG injection (208 ±8 MBq); there were at least 90 minutes between $[^{18}\text{F}]$ FDG injection and $[^{11}\text{C}]$ PIB injection. For the preliminary analysis reported here, the “blinded” expert was unaware of the clinical symptoms. The $[^{11}\text{C}]$ PIB PET scans were assayed in order of inclusion date and visually classified as PIB-positive or PIB-negative, based on the presence of cortical tracer accumulation, which is generally associated with the disappearance of a radial PIB white matter pattern characterizing PIB negative scans. Subsequently, the corresponding $[^{18}\text{F}]$ FDG -PET scans were assayed by annotating the severity of reduced FDG uptake (scaled ‘none’ to ++++) with specification of particularly
The assessment of all FDG scans, the patterns of reduced uptake were classified as (1) “classic” AD pattern with temporal-parietal hypometabolism, (2) variable or non-specific pattern of hypometabolism and (3) normal metabolism. Afterwards, the patients in these PET-based categories were compared to the initial clinical diagnosis and, if available, the ‘A-T-N’ classification with i.e. CSF amyloid-β (Aβ) and Tau biomarkers.

**Results:**

For the visual analysis presented here, 89 participants of the ‘Dual PET’ study were included. Regarding the $[^{11}C]$ PIB-PET scans, 44 were categorized as amyloid positive (49%) while the other 45 $[^{11}C]$ PIB-PET scans (51%) were amyloid negative. The visual assessment of the associated $[^{18}F]$ FDG PET scans resulted in a classification which is specified in Table 2. Examples of $[^{18}F]$ FDG-PET patterns in subjects with positive $[^{11}C]$ PIB-PET scans are illustrated in Figure 1.

**Figure 1:**

Examples of $[^{18}F]$ FDG-PET patterns in subjects with positive $[^{11}C]$ PIB-PET scans.

Transversal brain sections of PET images obtained from example subjects representing the six groups that resulted from the classification by the expert blinded assessment. This classification resulted in $[^{11}C]$ PIB positive and negative PET images with subsequent distinction of three specific $[^{18}F]$ FDG patterns for the two PIB groups, i.e. (i)
a classic pattern compatible with AD, (ii) regionally decreased FDG uptake with an atypical or non-fitting AD distribution or (iii) an FDG pattern classified as normal. Between brackets [ ] the diagnosis is added after final evaluation, including clinical course (see also Table 4)
PIB = Pittsburgh compound-B,  FDG = Fluor deoxyglucose,  AD = Alzheimer disease, DLB = Dementia of Lewy body disease, PPA = primary progressive aphasia, HC = healthy control.

Table 2: Global visual judgement of blinded Dual PET- scans in categories

<table>
<thead>
<tr>
<th>[¹¹C]PIB POSITIVE (%)</th>
<th>'Classic' AD</th>
<th>'Variable'</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 (77)</td>
<td>6 (14)</td>
<td>4 (9)</td>
<td></td>
<td>44 (100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>[¹¹C]PIB-NEGATIVE (%)</th>
<th>'Classic' AD</th>
<th>'Variable'</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 (35)</td>
<td>7 (16)</td>
<td>22 (49)</td>
<td></td>
<td>45 (100)</td>
</tr>
</tbody>
</table>

Total 50 13 26 89


In the group of 44 [¹¹C]PIB-positive PET scans, 34 subjects (77%) showed a ‘classic’ AD pattern on their [¹⁸F]FDG PET scan, 6 subjects (14%) had a variable or non-specific FDG pattern with focal (frontal) or strongly lateralized hypometabolism, while in 4 subjects (9%) the [¹⁸F]FDG PET was considered normal. Particularly in group of the non-specific FDG pattern (n=6), more restricted focal asymmetric cortical PIB accumulation was seen. See further Table 3, which also highlights the diagnosis at inclusion, and Table 4A, which specifies the diagnosis after final evaluation.

In the group of 45 [¹¹C] PIB-negative PET scans, 22 subjects (49%) had a normal pattern on [¹⁸F] FDG-PET scan. This concerned 11 healthy controls at inclusion and 11 subjects that were included with cognitive impairment and a probable dementia syndrome, but eventually turned out to have complaints due to an alternative psychiatric diagnosis (see Table 4B). However, in 16 subjects (35%) with a [¹¹C]PIB-negative scan, a ‘classic AD’ FDG pattern of hypometabolism was found. The majority of this group concerned DLB patients (n=5). One of the initially diagnosed AD patients appeared to be affected from Creutzfeldt Jacob Disease(CJD) as post-mortem confirmed. Another initially diagnosed AD subject had dementia with unknown cause. Three subjects had an initial diagnosis of MCI, but a likely alternative cause of cognitive dysfunction was found such as medical side effects, psychiatric symptoms and obstructive sleep apnea syndrome (OSAS), respectively. Two subjects had an initial diagnosis FTD, which remained a clinically confirmed diagnosis of behavior variant FTD. The four healthy controls without cognitive deficits were assessed to have only slightly reduced parietal FDG uptake.

Table 3: Summary of demographics, according to initial clinical diagnosis
AD: Alzheimer’s Disease, MCI: Mild Cognitive Impairment, FTD: Frontotemporal dementia, DLB: Lewy Body dementia, HC: healthy control. MMSE: Mini Mental State examination. Age and MMSE in mean (standard deviation). PIB: Pittsburgh compound-B or [11C] PIB PET scan, + is positive and – is negative. FDG: fluorodeoxyglucose ([18F] FDG) PET scan, AD is a “classic” AD pattern with temporal-parietal hypometabolism, VAR is: variable or not-specific pattern of hypometabolism and NORM is: normal metabolism.

Taking in account that 20 subjects with an initial clinical diagnosis of AD were included, the diagnosis was confirmed with a positive [11C]PIB PET scan in 18 subjects, of which 3 did not show a ‘classic’ AD pattern on [18F] FDG PET and 1 subject was even judged as having a visual normal FDG pattern. As described above, these variable patterns on the [18F] FDG PET scan did correlate with clinically atypical presentations of AD such as CBS and PPA. In 13 subjects with MCI diagnosed at inclusion (8 ‘pure’ and 5 ‘multi-domain’ amnestic), Dual PET imaging provided support for the diagnosis MCI due to prodromal AD. The other 5 subjects were confirmed clinical AD. In 4 subjects with an initial clinical diagnosis of probable FTD, dual PET imaging changed the diagnosis to AD or mixed pathology. The initial diagnosis of DLB appeared to be associated with a variable combination of [11C]PIB and [18F]FDG uptake, ranging from normal on both (n=6) to a profile of mixed pathology with AD (n=3). In case of regionally reduced FDG uptake, this exclusively concerned the parietal cortex. In table 4 A and B the diagnosis after ‘dual PET’ study with [11C]PIB-positive PET scans (A) and [11C]PIB-negative PET scans are described.

In 26 of the 44 subjects with [11C]PIB-positive PET scans CSF was available. According to the ‘A-T-N’ classification, we found in 14 of 26 subjects (54%) a concordance in ‘A’
(amyloid) classification with positive PIB imaging and decreased CSF Aβ (‘A’) biomarker, and in 12 of these 26 subjects (46%) also concordance was found in ‘T’(tau) classification of AD with increased CSF p-Tau biomarker results. ‘N’ (neurodegeneration) classification is based on an increased CSF Tau in 20 of 26 subjects (77%) and decreased [18F]FDG-PET hypometabolism (‘classic’ and ‘variable’ pattern of hypometabolism) in 40 of 44 (91%). CSF biomarkers that were available for 14 of 45 negative [11C]PIB-PET subjects and were all normal, except from 1 subject with an isolated decreased Aβ.

Table 4- A: Diagnosis after ‘dual PET’ study with [11C]PIB-positive PET scans

<table>
<thead>
<tr>
<th>[11C]PIB POSITIVE (44)</th>
<th>Diagnosis after 'Dual PET'</th>
</tr>
</thead>
<tbody>
<tr>
<td>[18F]FDG-PET Pattern</td>
<td></td>
</tr>
<tr>
<td>‘Classic’ AD (34)</td>
<td>AD with dementia (14), AD with amnestic MCI (8), AD with multi-domain MCI (5), AD with FTD-phenotype (4), Mixed diagnosis AD and DLB (3)</td>
</tr>
<tr>
<td>‘Variable’ (6)</td>
<td>Probable AD, AD-CBS, AD-PPA, AD-FTD phenotype (3)</td>
</tr>
<tr>
<td>Normal (4)</td>
<td>Probable AD, FTD-phenotype, PPA, AD-DLB mixed diagnosis</td>
</tr>
</tbody>
</table>

Table 4- B: Diagnosis after ‘dual PET’ study with [11C]PIB-negative PET scans

<table>
<thead>
<tr>
<th>[11C]PIB NEGATIVE (45)</th>
<th>Diagnosis after 'Dual PET'</th>
</tr>
</thead>
<tbody>
<tr>
<td>[18F]FDG-PET Pattern</td>
<td></td>
</tr>
<tr>
<td>‘Classic’ AD (16)</td>
<td>Dementia unknown cause, CJD, behavior variant FTD(2), probable DLB(5), MCI with causes of cognitive dysfunction, i.e. medical side effects, psychiatric symptoms and OSAS, HC (4)</td>
</tr>
<tr>
<td>‘Variable’ (7)</td>
<td>FTD (5), MCI, HC</td>
</tr>
<tr>
<td>Normal (22)</td>
<td>HC (10), alternative psychiatric diagnosis(11), (3 years non-progressive) MCI.</td>
</tr>
</tbody>
</table>

fluorodeoxyglucose PET scan, AD is a “classic” AD pattern with temporal-parietal hypometabolism, VAR is: variable or not-specific pattern of hypometabolism and normal: normal metabolism.

Discussion:

The aim of the Dual PET study is to investigate how PET imaging with the combination of $^{11}$C PIB binding and expressed pattern of $^{18}$F FDG uptake contributes to the clinical diagnosis of AD and differential diagnosis of non-AD dementia (MCI, DLB and FTD) and healthy controls. The results presented here of 89 participants (out of a planned number of 100) represents a preliminary analyses in which the starting point was the distinction between PIB-positive and negative scans followed by the classification of associated patterns of reduced FDG uptake. This analysis, based on the visual assessment of a single expert, without knowledge of the clinical symptoms, resulted in a clear distinction between PIB positive and negative scans, while the additional assessment of FDG scans resulted in a fruitful classification of 6 categories. At the time of analysis, the clinical inclusions were not finally completed and future analysis will include all diagnostic and neuropsychological data in a multimodal, multitracer and multivariate analysis to demonstrate regional and voxelwise correlations.

The results obtained here underscore that the diagnosis of specific subtypes of dementia remains a challenge. Following the ‘A-T-N’ framework, $^{11}$C PIB-PET scans confirmed a biological definition of AD or Alzheimer’s pathological changes. However, there seems to be various subgroups of AD; the majority of PIB positive scans with a classic FDG pattern of reduced parietal uptake concerned AD patients at inclusion, followed by MCI due to AD, the remaining various types of reduced FDG patterns indeed appeared to correspond with non-classic AD presentations, including e.g. PPA. $^{18}$F FDG PET is a non-AD-specific (“N”) biomarker of neurodegeneration, and disease-specific patterns of hypometabolism are described in MCI, AD, FTD and DLB. $^{18}$FFDG PET correlates with CSF Tau biomarker concentrations and seems to ‘mirror’ neurodegenerative Tau pathology, as observed with the PET tracer $^{18}$FAV 14517. Combining a $^{18}$FFDG PET and a $^{11}$C PIB- PET scan, could therefore improve the differential diagnosis of dementia, also in case of AD subgroups and concomitant (mixed) non-AD pathology.

Especially in early stages of disease as in MCI, and in clinically ambiguous cases, the clinical utility of $^{11}$C PIB-PET imaging appears to provide an important contribution. Abnormal CSF Aβ (although limited available) was in concordance with abnormal $^{11}$C PIB- PET scans in 64 %, which is in line with former literature. Although CSF biomarkers have a better diagnostic performance in combination with increased CSF Tau and p-Tau, $^{11}$C PIB- PET scans perform better than CSF biomarkers in confirming the diagnosis of AD.

This first ‘blinded’ visual assessment, further generated a preliminary global overview of the included subjects of the Dual PET study, when specifically taking into account the
pattern of regional hypometabolism identified by $^{[18F]}$FDG PET. As stated above, the classic bilateral parietal FDG reduction associated with PIB-positive scans clearly correspond with clinical ‘classic’ AD. On the other hand, in 35 % of $^{[11C]}$PIB-PET negative subjects, a ‘classic AD’ $^{[18F]}$FDG PET pattern was observed associated with the clinical diagnosis of DLB, FTD, other dementia and obstructive sleep apnea syndrome (OSAS). The pattern of reduced FDG uptake thus provides a fair marker for regional impairment of cerebral function, but not necessarily due to AD pathology. Therefore, $^{[18F]}$FDG PET scans may not be optimally specific as an AD marker, however it has a high negative predictive value and has thus at least the added value of excluding dementia.

In a variable pattern, predominant focal and lateralized hypometabolism is observed in the $^{[18F]}$FDG PET scan, distinctive from an AD pattern. In our $^{[11C]}$PIB-PET negative subjects, most subjects with a variable FDG PET pattern were clinically diagnosed as FTD. On the other hand, a ‘variable’ $^{[18F]}$FDG PET pattern in our $^{[11C]}$PIB-PET positive cases is observed in clinically ambiguous cases. This variation reflects the fact that AD is a multifactorial and heterogeneous disorder consisting of various subgroups of AD, i.e. Corticobasal syndrome (CBS), Primary progressive aphasia (PPA) and Posterior cortical atrophy (PCA) each with its, potentially distinctive, pattern. It is suggested that Tau-rather than Amyloid- pathology may be driving disease manifestation and might thus correlate better with clinical symptoms. Unfortunately, Tau-imaging is not yet used in clinical practice but it promises to be of additional diagnostic value in different subgroups of AD and clinically ambiguous cases. In what extent a Tau PET marker will provide a more accurate diagnosis than the combined $^{[11C]}$PIB- and $^{[18F]}$FDG PET has to be elucidated.

Only a small amount of subjects (9 %) had a normal metabolism at $^{[18F]}$FDG PET and a positive $^{[11C]}$PIB PET scan. The initial clinical diagnosis of these cases were early stage dementia, with clinical phenotype of AD, FTD (2) and DLB. This is consistent with the assumption that amyloid deposition is an earlier sign of disease, and may thus be detectable before cerebral metabolic disruption can be quantified. On the other hand, PIB PET imaging alone is not adequate since amyloid accumulation in the brain is associated with older age and does not always lead to cognitive complaints, although overall it is associated with cognitive declines.

To conclude, the ‘blind’ visual assessment by an expert of the ‘Dual PET’ scans resulted in a classification of six groups of participant, which was of additional value to the initial clinical diagnosis of HC, AD, MCI, DLB and FTD, in such a way that (1) unmistaken support for AD pathology could be provided, also in the clinical stage of MCI, (2) support was obtained for distinct AD subtypes and (3) the issue of mixed pathology in the clinical ambiguous cases came to the forefront in a series particularly consisting of DLB patients. Future analysis will follow.

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36. Harris JM, Gall C, Thompson JC, et al. Classification and pathology of primary


