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Evaluating 2-[^{18}F]FDG-PET in differential diagnosis of dementia using a data-driven decision model

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ABSTRACT

2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (2-[^{18}F]FDG-PET) has an emerging supportive role in dementia diagnostic as distinctive metabolic patterns are specific for Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD). Previous studies have demonstrated that a data-driven decision model based on the disease state index (DSI) classifier supports clinicians in the differential diagnosis of dementia by using different combinations of diagnostic tests and biomarkers. Until now, this model has not included 2-[^{18}F]FDG-PET data.

The objective of the study was to evaluate 2-[^{18}F]FDG-PET biomarkers combined with commonly used diagnostic tests in the differential diagnosis of dementia using the DSI classifier.

We included data from 259 subjects diagnosed with AD, DLB, FTD, vascular dementia (VaD), and subjective cognitive decline from two independent study cohorts. We also evaluated three 2-[^{18}F]FDG-PET biomarkers (anterior vs. posterior index (API-PET), occipital vs. temporal index, and cingulate island sign) to improve the classification accuracy for both FTD and DLB.

We found that the addition of 2-[^{18}F]FDG-PET biomarkers to cognitive tests, CSF and MRI biomarkers considerably improved the classification accuracy for all pairwise comparisons of DLB (balanced accuracies: DLB vs. AD from 64% to 77%; DLB vs. FTD from 71% to 92%; and DLB vs. VaD from 71% to 84%). The two 2-[^{18}F]FDG-PET biomarkers, API-PET and occipital vs. temporal index, improved the accuracy for FTD and DLB, especially as compared to AD. Moreover, different combinations of diagnostic tests were valuable to differentiate specific subtypes of dementia.

In conclusion, this study demonstrated that the addition of 2-[^{18}F]FDG-PET to commonly used diagnostic tests provided complementary information that may help clinicians in diagnosing patients, particularly for differentiating between patients with FTD, DLB, and AD.

Abbreviations: Aβ42, beta-amyloid 1-42; AD, Alzheimer's disease; API, anterior vs. posterior index; AUC, area under the receiver-operator characteristic curve; bal. acc., balanced accuracy; CERAD, consortium to establish a registry for Alzheimer's disease; CSF, cerebrospinal fluid; DDRC, Danish Dementia Research Centre; DLB, dementia with Lewy bodies; DSI, disease state index; 2-[^{18}F]FDG-PET, 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; p-tau, phosphorylated tau; RAVLT, Rey auditory verbal learning task; ROI, region of interest; SCD, subjective cognitive decline; TBM, tensor-based morphometry; TMT, trail making test; VaD, vascular dementia; VBM, voxel-based morphometry; WMH, white matter hyperintensity

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1. Introduction

The most common causes of dementia are Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD) (Livingston et al., 2017; World Health Organization, 2012). Correct clinical dementia diagnosis is essential to establish proper treatment, support and care (National Collaborating center for Mental Health, 2007).

Clinical decision support systems are emerging to assist clinicians for earlier and accurate diagnosis of dementia by providing a systematic and objective overview of comprehensive patient data (Bruun et al., 2019a; Kawamoto et al., 2005; Klöppel et al., 2008; Mattila et al., 2011).

The use of biomarkers, such as total tau, phosphorylated tau (p-tau) and amyloid beta 1–42 (Aβ42) from cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI), have improved the differential diagnosis of dementia and have been included in the clinical diagnostic criteria (Gorno-Tempini et al., 2011; McKeith et al., 2017; McKhann et al., 2011; Rascovsky et al., 2011; Sachdev et al., 2014). Nevertheless, DLB and FTD remain particularly difficult to identify due to shared clinical and pathological features with other subtypes of dementia, especially AD (McKeith et al., 2016; Mendez et al., 2013; Ossenkoppele et al., 2015; Schneider et al., 2007; Thomas et al., 2018). Most of the previous biomarker studies have focused on the ability to differentiate AD from other dementias, and moreover, biomarkers for other subtypes of dementia are less evolved (Jack et al., 2016).

2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (2-[^{18}F]FDG-PET) imaging is considered a sensitive imaging modality for neuronal degeneration in dementia and has shown potential to support the diagnosis of dementia at an early stage (Bloudek et al., 2011; Hort et al., 2010). Various subtypes of dementia have characteristic patterns of regional hypometabolism (Nobili et al., 2018), and 2-[^{18}F]FDG-PET is included as a supportive biomarker in the diagnostic criteria of AD, DLB, and FTD (Gorno-Tempini et al., 2011; McKeith et al., 2017; McKhann, 2001; McKhann et al., 2011; Rascovsky et al., 2011).

Data-driven diagnostic tools are useful for analysing heterogenous multimodality data of complex diseases such as dementia. Previous studies have demonstrated that a data-driven decision model based on the disease state index (DSI) classifier (Mattila et al., 2012) is a promising method for clinical decision support in the differential diagnosis of dementia by using different combinations of cognitive tests, CSF biomarkers, and automatic and visual MRI quantification features (Bruun et al., 2018; Koikkalainen et al., 2016; Tong et al., 2017). Until now, this model has not included 2-[^{18}F]FDG-PET data.

The objective of the study was to evaluate 2-[^{18}F]FDG-PET biomarkers combined with commonly used diagnostic tests (cognitive tests, CSF and MRI biomarkers) in the differential diagnosis of dementia using the DSI classifier.

2. Methods

2.1. Study population

We included data from 259 subjects diagnosed from 2009 to 2018 with either AD, DLB, FTD, VaD, or subjective cognitive decline (SCD) from two independent study cohorts (a subgroup from the PredictND study cohort and a Danish Dementia Research center (DDRC) cohort). The subjects were eligible for inclusion if a 3D T1-weighted MRI sequence with a slice thickness < 2 mm and 2-[^{18}F]FDG-PET images were available.

The PredictND study cohort consisted of 779 prospectively enrolled subjects from four European memory clinics (Bruun et al., 2019b). We included a subgroup from the PredictND study cohort consisting of 119 subjects from the Copenhagen Memory Clinic, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark and 25 subjects from the Section of Gerontology and Geriatrics, University of Perugia and "S. Maria della Misericordia" Hospital of Perugia, Perugia, Italy.

The DDRC cohort consisted of 115 retrospectively identified subjects from the clinical database at the Copenhagen Memory Clinic, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

All diagnoses were confirmed by experienced dementia specialists according to the following established diagnostic criteria: the NIA-AA criteria for AD (McKhann et al., 2011), the DLB consortium criteria for DLB (McKeith et al., 2005), the work group on FTD and Pick's Disease criteria for FTD (Gorno-Tempini et al., 2011; McKhann, 2001; Rascovsky et al., 2011), and the NINDS-AIREN criteria for VaD (Román et al., 1993). Subjects were diagnosed with SCD when the cognitive complaint was present without confirmed objective cognitive impairment, and the criteria for mild cognitive impairment and dementia were not met (Albert et al., 2011; McKhann et al., 2011).

The study was approved by the local Medical Ethical Committees: The Regional Committee on Medical Research Ethics of the Capital Region of Denmark (Approval no.: H-1–2014–126) and Italy (Approval no.: CEAS 2381/14).

2.2. Clinical assessment and auxiliary investigations

All subjects were referred to the memory clinics due to suspicion of a neurodegenerative disease. At baseline, all subjects were assessed with a standard diagnostic dementia program including medical history, physical and neurological examinations, cognitive testing, routine blood screening, and MRI. On a clinical diagnostic indication, the standard diagnostic dementia program was supplemented with diagnostic tests such as CSF biomarkers, 2-[^{18}F]FDG-PET, dopamine transporter single photon emission computed tomography, and amyloid PET.

As a minimum all included subjects had an MRI with 3D T1-weighted sequence, an 2-[^{18}F]FDG-PET scan, and a mini-mental state examination (MMSE) test. Sixty-seven percent had additional cognitive test data other than MMSE, 51% percent had CSF biomarkers of Aβ42, total tau, and p-tau, and 98% had an MRI with fluid-attenuated inversion recovery (FLAIR) sequence (distribution of the diagnostic test for each diagnostic group are listed in Table A.1 in Supplementary material).

2.3. Cognitive tests

The standard cognitive test battery consisted of the MMSE test for assessment of global cognitive functioning, the consortium to establish a registry for Alzheimer's disease (CERAD) test or the Rey auditory verbal learning task (RAVLT) test for assessment of episodic memory, and the trail making test (TMT) A and B, and the animal fluency test for assessment of language and executive functioning.

To compare the episodic memory test scores, we standardized the CERAD test to the RAVLT test using z-scoring as previously described (Bruun et al., 2018).

2.4. Cerebrospinal fluid biomarkers

The CSF biomarkers, Aβ42, total tau, and p-tau, were analysed with enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Innotest, Fujirebio, Europe, Ghent, Belgium).

2.5. Magnetic resonance imaging

MRI were performed on clinical 1.0, 1.5, or 3.0 Tesla scanners. We derived the volumetric and morphometric biomarkers from the 3D T1-weighted MRI sequence (Koikkalainen et al., 2016; Lötjönen et al., 2010). The volumes of 133 brain regions were defined using a multi-atlas segmentation method (Lötjönen et al., 2010) based on the manually segmented Neuromorphometric atlases (Neuromorphometrics Inc, Massachusetts, USA) (Region of interests for MRI are listed

in Table B.1 in Supplementary material).

Ten MRI biomarkers of clinically relevant regions were extracted from the volumetric features, together with the anterior vs. posterior index (API-MRI), defined as a z-scored ratio between the volumes of temporal and frontal lobe regions, and the volumes of parietal and occipital lobe regions (Bruun et al., 2019c).

Furthermore, we derived two morphometric indices by comparing specific volumetric patterns between two study groups (Koikkalainen et al., 2016). The voxel-based morphometry (VBM) index was estimated using measures of the local concentration of gray matter (Ashburner and Friston, 2000), whereas the tensor-based morphometry (TBM) index was estimated using measures of changes in the local volume (Ashburner et al., 1998).

The region of interest (ROI) based grading was estimated by measuring the similarities of intensities of the T1-weighted image within the ROIs to an image database of subjects with known diagnoses (Tong et al., 2013)

The vascular burden from FLAIR images was estimated from the summed volume of white matter hyperintensity (WMH), cortical infarcts, and the weighted volume of lacunar infarcts by a segmentation method described in (Koikkalainen et al., 2016; Wang et al., 2012).

2.6. 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography

The 2-[^{18}F]FDG-PET images were acquired using GE Medical, Philips, and Siemens PET scanners. The 2-[^{18}F]FDG-PET image was co-registered to the segmented MRI to generate uptake values from the segmented brain regions on 2-[^{18}F]FDG-PET, i.e. 2-[^{18}F]FDG-PET ROIs. The mean uptake value of each 2-[^{18}F]FDG-PET ROI was normalized to the cerebellum.

We selected 12 clinically relevant regions (anterior cingulate gyrus, calcarine cortex, middle cingulate gyrus, posterior cingulate gyrus, precuneus, precentral gyrus, frontal cortex, temporal cortex, parietal cortex, occipital cortex, medial temporal cortex, and whole cortex) as 2-[^{18}F]FDG-PET biomarkers based on previous 2-[^{18}F]FDG-PET studies demonstrating characteristic patterns of hypometabolism which have been well documented in patients with AD, FTD, and DLB, respectively (Davison and O'Brien, 2014; Dukart et al., 2011; Gorno-Tempini et al., 2011; Herholz et al., 2002; Jagust et al., 2009; McKeith et al., 2017; McKhann, 2001; McKhann et al., 2011; Minoshima et al., 2001; Rascovsky et al., 2011; Rice and Bisdas, 2017).

Moreover, three 2-[^{18}F]FDG-PET biomarkers were derived from the segmented 2-[^{18}F]FDG-PET image. The API-PET was defined as a z-scored ratio between the mean uptake in frontal and temporal lobe regions, and the mean uptake in parietal and occipital lobe regions, and is similar to and uses the same regions as the API-MRI (Bruun et al., 2019c). The occipital vs. temporal index was derived as the uptake in occipital lobe region divided by the uptake in temporal lobe region. The biomarker was proposed to improve differentiating between AD and DLB, where the temporal region is often affected in AD and the occipital region is often affected in DLB, respectively (McKeith et al., 2017; McKhann et al., 2011). Cingulate island sign is a supportive DLB biomarker on 2-[^{18}F]FDG-PET (Lim et al., 2009; McKeith et al., 2017). In our analyses, we included the cingulate island sign ratio defined as the uptake in posterior cingulate cortex divided by the sum of the uptake in precuneus and cuneus.

2.7. Disease state index classifier

The DSI classifier is composed of two components: fitness and relevance (Mattila et al., 2012). Fitness is calculated for a biomarker or test result of the subject as $f(x) = FN(x)/(FN(x) + FP(x)$, where FN is the false-negative error rate, and FP is the false-positive error rate in the reference data when using the biomarker or test result value x as a cut-off value in classification. Relevance defines the goodness of a biomarker or test result as sensitivity + specificity-1. A DSI value is calculated as a weighted average of fitness values: DSI = Σ (relevance · fitness)/Σ relevance. DSI is a value measuring the similarity of the subject's data to two diagnostic groups, a reference and study groups. The DSI value zero indicates a perfect similarity to the reference group while the value one a perfect similarity to the study group.

2.8. Data analysis

Differences between groups were tested with one-way ANOVA tests followed by post-hoc Bonferroni tests, Kruskal-Wallis tests followed by post-hoc Bonferroni corrected Mann-Whitney tests, or Chi-square tests followed by post-hoc Bonferroni tests, where appropriate.

The 10-fold cross-validation approach was applied using the whole study population data ($n = 259$). The differentiation between the diagnostic groups was evaluated through pairwise comparisons. The accuracy of each individual diagnostic test and each or combined diagnostic test group for pairwise comparisons was reported as balanced accuracy (bal. acc.) and area under the receiver-operator characteristic curve (AUC) based on the DSI values. The bal. acc., calculated as the average of sensitivity and specificity for pairwise comparison, was computed to adjust the results for the imbalance in the size of the study groups in the dataset (Brodersen et al., 2010).

When an individual or combined group of diagnostic tests was used, we only included a subset of relevant diagnostic tests and excluded the redundant or irrelevant diagnostic tests, for each pairwise comparison by a feature selection method. The diagnostic tests with the highest accuracy were added one by one until the overall AUC did not increase as previously described (Bruun et al., 2018). The feature selection was first performed using complete cross-validation to produce un-biased classification results. After that, the feature selection was applied to all data without cross-validation to produce single optimal feature set to show which features typically were selected.

Data from all subjects in the study population were used in the analysis because the DSI classifier can operate with missing data (Rhodius-Meester et al., 2016).

The volumetric imaging biomarkers were corrected for intracranial volume, age, and sex (Buckner et al., 2004; Cole and Green, 1992), while the other features were corrected for age and sex (Cole and Green, 1992).

Statistical analysis was performed using SAS Studio software, version 9.4 (SAS Institute Inc., Cary, NC, USA). A MATLAB toolbox was used in the DSI analyses (Cluitmans et al., 2013). The analyses were performed in MATLAB, version R2015b (MathWorks, Natick, MA).

A two-sided p-value < 0.05 was considered indicative of statistical significance.

3. Results

3.1. Subjects

The baseline demographics are presented in Table 1. There were fewer women in the DLB group as compared to the AD group. The subjects with SCD were younger and performed better on MMSE than the dementia groups. The AD group had higher tau values, and together with the DLB group lower Aβ42 values than the other groups (Additional details of baseline demographics are shown in Table C.1 in Supplementary material).

3.2. Diagnostic tests and diagnostic test groups

The performance of the individual diagnostic tests for each pairwise comparison is shown in Table 2. Overall, the episodic memory tests had a high classification accuracy for differentiating subjects with SCD from the dementia groups (bal. acc. ranging from 71%-91%), whereas CSF biomarkers had a good accuracy for differentiating AD from the other groups (bal. acc. ranging from 73%-84%), except Aβ42 for AD vs. DLB

Table 1
Baseline demographics.

	AD	DLB	FTD	VaD	SCD	Group-wise comparison when significant
Subjects, n	90	41	37	25	66	
Female, n (%)	50 (56%)	10 (24%)	17 (46%)	10 (40%)	34 (52%)	DLB < AD
Age, mean years ± SD	73.2 ± 7.9	72.5 ± 8.6	68.7 ± 9.5	74.8 ± 8.7	64.5 ± 9.8	SCD < AD, DLB, VaD
MMSE, median score (IQR)	25 (23–27)	27 (23–29)	25 (21–28)	26 (24–28)	30 (29–30)	SCD > All
CSF Aβ42, median concentration pg/mL (IQR)	507 (425–596)	531 (413–685)	896 (670–1006)	927 (762–1121)	1021 (797–1170)	AD, DLB < FTD, VaD, SCD
CSF total tau, median concentration pg/mL (IQR)	556 (427–728)	346 (170–407)	254 (190–333)	248 (188–395)	237 (186–352)	AD > All
CSF p-tau, median concentration pg/mL (IQR)	83 (62–97)	54 (29–73)	36 (30–42)	38 (29–46)	40 (36–50)	AD > All

Abbreviations: Aβ42: amyloid beta 1–42; AD: Alzheimer's disease; CSF: cerebrospinal fluid; DLB: dementia with Lewy bodies; FTD: frontotemporal dementia; IQR: interquartile range; MMSE: mini mental state examination; n: number; p-tau: phosphorylated tau at threonine 181; SCD: subjective cognitive decline; SD: standard deviation; VaD: vascular dementia.

with a bal. acc. of 50%. As expected, the MRI biomarkers of vascular burden were the most valuable diagnostic tests to differentiate VaD from the other groups (bal. acc. ranging from 80%-89%). The 2-[^{18}F]FDG-PET biomarker occipital vs. temporal index had a high accuracy for distinguishing AD vs. DLB compared to the two supportive biomarkers for DLB, occipital hypometabolism and cingulate island sign (bal. acc.: occipital vs. temporal index: 79% vs. occipital hypometabolism: 62% vs. cingulate island sign: 67%). For AD vs. FTD, the CSF biomarkers and API-PET had a high accuracy, whereas API-MRI had a lower accuracy (bal. acc.: CSF biomarkers: 79-83% vs. API-PET: 76% vs. API-MRI: 64%). The performance of additional diagnostic tests for each pairwise comparison is shown in Table D.1 in Supplementary material.

The accuracies of the individual and combined groups of diagnostic tests for pairwise comparison are presented in Table 3. The addition of 2-[^{18}F]FDG-PET biomarkers to cognitive tests, CSF and MRI biomarkers considerably improved the classification accuracy for all pairwise comparisons of DLB to other dementias (bal. acc.: DLB vs. AD from 64% to 77%; DLB vs. FTD from 71% to 92%; and DLB vs. VaD from 71% to 84%). Furthermore, 2-[^{18}F]FDG-PET biomarkers combined with CSF and MRI biomarkers had a high performance for distinguishing FTD from the other dementia groups (bal. acc. ranging from 83% − 92%), whereas combined 2-[^{18}F]FDG-PET and MRI biomarkers were useful to distinguish VaD from the other dementia groups (bal. acc. ranging from 80% − 90%).

3.3. Optimal combination of diagnostic tests

The optimal combination of diagnostic tests for each pairwise comparison is presented in Table 4. The optimal sets of diagnostic tests included diagnostic tests from more groups, most commonly MRI and 2-[^{18}F]FDG-PET biomarkers, except for the AD vs. FTD comparison with only CSF biomarkers. In general, CSF biomarkers combined with imaging biomarkers obtained the highest accuracy for differentiating AD from the other groups. The API-PET was included in the optimal combination of diagnostic tests for FTD, whereas the MRI biomarker of vascular burden was included in the optimal combination of diagnostic tests for VaD. The optimal diagnostic tests to differentiate DLB from the other groups included 2-[^{18}F]FDG-PET biomarkers with different combinations of cognitive tests, CSF and MRI biomarkers.

4. Discussion

This study evaluates the performance of 2-[^{18}F]FDG-PET biomarkers combined with commonly used diagnostic tests (cognitive tests, CSF and MRI biomarkers) in the differential diagnosis of dementia using a DSI classifier in two mixed memory clinic cohorts.

First, we found that the 2-[^{18}F]FDG-PET biomarkers, particularly API-PET and occipital vs. temporal index, improved the classification accuracy for both FTD and DLB, especially as compared to AD. Second, different combinations of diagnostic tests were valuable for distinguishing specific subtypes of dementia. And third, the CSF biomarkers were useful to differentiate AD from the other groups, the MRI biomarker of vascular burden was useful to differentiate VaD from the other groups, and cognitive tests were highly useful to differentiate subjects with SCD from the dementia groups. The latter finding is in line with previous studies using the DSI classifier (Bruun et al., 2018; Rhodius-Meester et al., 2016; Tolonen et al., 2018).

Previous studies have demonstrated the usefulness of the DSI classifier in the differential diagnosis of dementia using automatic MRI quantification features (Koikkalainen et al., 2016) and various combinations of cognitive tests, CSF biomarkers, and automatic and visual MRI quantification features (Bruun et al., 2018; Tolonen et al., 2018; Tong et al., 2017). Comparison of the classification results obtained in this study to two other DSI classifier studies using exclusively cognitive tests, CSF biomarkers, and automatic MRI quantifications, showed that our classifier had a considerable lower accuracy (bal. acc. ranged from 64% − 94% (Table 3) vs. 77% − 97% in (Bruun et al., 2018) vs. 80% − 98% in (Tolonen et al., 2018)), with the lowest accuracies for detecting DLB and FTD. However, our study population may have included patients with a more uncharacteristic presentation due to selection bias, where 2-[^{18}F]FDG-PET likely was used as a supplemental diagnostic test for patients with an uncertain diagnosis after disclosure of standard diagnostic tests such as MRI and cognitive tests. Furthermore, the two previous studies had a larger study cohort with a greater proportion of AD patients and subjects with SCD and moreover, the studies did not include 2-[^{18}F]FDG-PET.

Previous DSI classifier studies without 2-[^{18}F]FDG-PET biomarkers reported the diagnostic sensitivity for FTD and in particular DLB as suboptimal with many cases being misclassified as AD (Bruun et al., 2018; Koikkalainen et al., 2016; Tolonen et al., 2018; Tong et al., 2017). This issue is to some extent due to the paucity of specific disease biomarkers for FTD and DLB, but also a result of the clinical heterogeneity in both FTD and DLB together with the clinical and pathological overlap with AD (McKeith et al., 2017; Neary et al., 1998). In particular, many DLB patients have coexisting Aβ pathology (Merdes et al., 2003). This is corroborated by the low accuracy of 50% for the CSF Aβ42 biomarker in differentiating DLB and AD in our study (Table 2). In addition, FTD represents various clinical syndromes including primary progressive aphasia and behavioural variant of FTD, of which the latter often seemed difficult to differentiate from AD (Mendez et al., 2013; Neary et al., 1998).

We added 2-[^{18}F]FDG-PET biomarkers to the DSI classifier to improve the classification accuracy, particularly for DLB and FTD as compared to AD, as 2-[^{18}F]FDG-PET is a supportive biomarker for AD, DLB, and FTD (Gorno-Tempini et al., 2011; McKeith et al., 2017; McKhann, 2001; McKhann et al., 2011; Rascovsky et al., 2011). We found that the addition of 2-[^{18}F]FDG-PET biomarkers to cognitive tests, CSF and MRI biomarkers improved the accuracies of DLB and FTD with most substantial improvement for the pairwise comparison of AD vs. DLB (from 64% to 77%, Table 3).

Table 2
The pairwise comparison of individual diagnostic tests.

Bal. acc./AUC	AD vs. DLB	AD vs. FTD	AD vs. VaD	AD vs. SCD	DLB vs. FTD	DLB vs. VaD	DLB vs. SCD	FTD vs. VaD	FTD vs. SCD	VaD vs. SCD
Cognitive tests										
MMSE	59/58	39/36	55/54	85/89	56/59	56/54	71/79	52/53	79/88	83/89
Episodic memory (learning)	48/59	62/62	50/46	91/97	43/39	61/63	88/93	71/60	90/90	87/94
Episodic memory (recall)	64/68	66/67	59/58	89/96	51/51	56/49	85/92	64/54	84/89	81/90
CSF										
Aβ42	50/50	79/82	78/86	83/89	79/77	75/81	81/84	57/57	60/63	57/55
Total tau	77/80	83/84	80/83	84/88	58/56	61/55	61/58	29/27	33/35	35/33
p-tau	73/76	83/90	82/88	78/88	63/66	69/63	64/57	11/4	51/62	20/21
MRI										
Frontal cortex	59/62	55/58	57/59	71/74	63/69	68/69	59/64	41/34	70/78	72/77
Temporal cortex	57/64	46/43	66/71	84/90	56/61	52/56	75/82	54/64	75/85	74/76
Medial temporal cortex	58/61	51/51	60/66	80/91	45/51	38/38	80/85	54/56	75/84	75/83
Parietal cortex	48/48	56/63	54/58	68/74	59/67	50/48	68/74	68/72	62/65	76/81
Occipital cortex	59/65	52/45	60/61	61/63	59/64	46/51	68/75	49/49	51/55	60/65
API-MRI	62/63	64/70	56/58	61/64	76/79	41/35	44/43	72/78	74/82	34/32
Vascular burden	45/46	51/50	82/89	63/69	59/59	80/85	64/70	83/89	67/69	89/93
2-[^{18}F]FDG-PET										
Frontal cortex	47/43	58/59	42/40	74/79	58/63	44/41	72/78	55/56	76/85	72/77
Temporal cortex	56/57	55/58	61/67	80/86	45/42	56/60	80/86	56/58	76/80	67/73
Medial temporal cortex	62/62	63/69	57/59	75/83	76/80	66/71	82/89	55/57	68/71	70/72
Parietal cortex	72/74	65/67	38/36	66/70	78/86	73/80	80/89	65/60	39/36	63/64
Occipital cortex	62/68	58/58	59/67	70/78	71/76	44/37	63/62	68/74	74/81	62/62
API-PET	75/81	76/86	59/62	47/43	92/97	83/90	82/87	74/80	79/88	60/61
Occipital vs. Temporal index	79/85	54/60	63/65	70/75	83/90	70/76	63/71	64/74	73/83	62/60
Cingulate island sign ratio	67/79	54/51	62/63	71/77	71/77	64/70	57/59	55/61	75/77	67/68

Abbreviations: Aβ42: amyloid beta 1-42; AD: Alzheimer's disease; API: Anterior vs. posterior index; AUC: area under the receiver operating characteristic curve; bal. acc.: balanced accuracy; CSF: cerebrospinal fluid; DLB: dementia with Lewy bodies; FTD: frontotemporal dementia; MMSE: mini mental state examination; MRI: magnetic resonance imaging; p-tau: phosphorylated tau at threonine 181; ROC: receiver operating characteristic; SCD: subjective cognitive decline; VaD: vascular dementia; 2-[^{18}F]FDG-PET: 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography;
The colours correspond to the bal. acc. for the pairwise comparison. Bal. acc. 85%–100% are highlighted in dark green. The gradually lighter shades of green indicate lower bal. acc. with white being at or below 50. Both bal. acc. and AUC are reported as percentage values (%).

Furthermore, we evaluated three 2-[^{18}F]FDG-PET biomarkers in the differential diagnosis of dementia with focus on their ability to differentiate DLB and FTD as compared to AD.

The API-PET was included to demonstrate a specific pattern of reduced metabolism in frontotemporal regions and relative preserved metabolism in posterior region as seen in many FTD patients (Bohnen et al., 2012; Neary et al., 1998; Rascovsky et al., 2011). The API-PET is similar to and uses the same regions as API-MRI, which has demonstrated a good classification accuracy for differentiating between FTD and AD (Bruun et al., 2019c, 2018). When comparing the API-PET and the API-MRI for differentiating FTD from the other groups, the API-PET had higher bal. acc. ranging from 74% to 92% in comparison to the API-

Table 3
The pairwise comparison of individual and combined groups of diagnostic tests.

Bal. acc./AUC	AD vs. DLB	AD vs. FTD	AD vs. VaD	AD vs. SCD	DLB vs. FTD	DLB vs. VaD	DLB vs. SCD	FTD vs. VaD	FTD vs. SCD	VaD vs. SCD
Cognitive tests	56/60	62/58	47/51	94/97	57/60	53/62	84/88	58/59	83/89	82/87
CSF	76/78	90/94	85/84	85/93	79/80	68/75	81/82	28/32	55/51	47/49
MRI	62/69	74/78	80/86	83/90	65/73	76/83	78/83	73/86	85/91	84/89
2-[^{18}F]FDG-PET	76/84	76/87	63/72	82/87	92/97	83/90	80/90	72/75	77/90	75/80
Cognitive tests + CSF	70/73	90/94	85/84	94/97	74/75	66/71	84/88	58/59	83/89	82/87
Cognitive tests + MRI	50/54	68/79	80/85	94/97	74/76	73/79	85/89	73/85	84/91	92/92
Cognitive tests + 2-[^{18}F]FDG-PET	78/84	77/87	64/68	94/97	92/97	87/89	86/88	63/71	80/88	82/87
CSF + MRI	70/73	90/94	84/82	87/93	75/81	75/80	83/89	73/85	85/91	86/88
CSF + 2-[^{18}F]FDG-PET	80/88	90/94	85/84	85/93	92/97	83/88	84/89	70/74	77/90	75/80
MRI + 2-[^{18}F]FDG-PET	77/85	78/86	80/88	85/93	92/97	82/90	85/91	83/86	86/93	90/90
Cognitive tests + CSF + MRI	64/64	90/94	84/82	94/97	71/75	71/77	85/89	73/84	84/91	92/92
Cognitive tests + CSF + 2-[^{18}F]FDG-PET	76/85	90/94	85/84	94/97	92/97	87/91	86/88	64/71	80/88	82/87
Cognitive tests + MRI + 2-[^{18}F]FDG-PET	80/83	80/86	80/86	94/97	92/97	82/90	86/89	83/85	80/90	92/92
CSF + MRI + 2-[^{18}F]FDG-PET	75/85	90/94	81/81	92/94	92/97	82/90	85/91	83/86	86/93	89/88
Cognitive tests + CSF + MRI + 2-[^{18}F]FDG-PET	77/87	90/94	81/81	94/97	92/97	84/90	86/89	83/85	80/90	92/92

Abbreviations: AD: Alzheimer's disease; AUC: area under the receiver operating characteristic curve; bal. acc.: balanced accuracy; CSF: cerebrospinal fluid; DLB: dementia with Lewy bodies; FTD: frontotemporal dementia; MRI: magnetic resonance imaging; ROC: receiver operating characteristic; SCD: subjective cognitive decline; VaD: vascular dementia; 2-[^{18}F]FDG-PET: 2-[^{18}F]fluoro-2-deoxy-D glucose positron emission tomography;
The colours correspond to the bal. acc. for the pairwise comparison. Bal. acc. 85%–100% are highlighted in dark green. The gradually lighter shades of green indicate lower bal. acc. with white being at or below 50. Both bal. acc. and AUC are reported as percentage values (%).

Table 4
The optimal sets of diagnostic tests for each pairwise comparison.

Pairwise comparison	Cognitive tests	CSF	MRI	2-[^{18}F]FDG-PET
AD vs. DLB		p-tau	Lateral ventricles	Occipital vs. temporal index
AD vs. FTD		Aβ42, p-tau		
AD vs. VaD		Aβ42	Medial temporal cortex, frontal cortex, temporal cortex, parietal cortex, vascular burden	Parietal cortex
AD vs. SCD	Episodic memory (learning), episodic memory (recall)	p-tau		
DLB vs. FTD	Animal fluency			API-PET
DLB vs. VaD	Animal fluency	Aβ42	Frontal cortex	API-PET, middle cingulate gyrus
DLB vs. SCD	Episodic memory (learning), TMT-B		Temporal cortex	Occipital cortex
FTD vs. VaD			Parietal cortex, vascular burden	API-PET, middle cingulate gyrus
FTD vs. SCD	MMSE		Global VBM	API-PET
VaD vs. SCD	Episodic memory (learning)		Vascular burden	

Abbreviations: Aβ42: amyloid beta 1–42; AD: Alzheimer's disease; API: anterior vs. posterior index; CSF: cerebrospinal fluid; DLB: dementia with Lewy bodies; FTD: frontotemporal dementia; MMSE: mini mental state examination; MRI: magnetic resonance imaging; p-tau: phosphorylated tau at threonine 181; SCD: subjective cognitive decline; TMT: trail making test; VaD: vascular dementia; VBM: voxel-based morphometry; 2-[^{18}F]FDG-PET: 2-[^{18}F]fluoro-2-deoxy-D glucose positron emission tomography.

MRI with bal. acc. ranging from 64% to 76% (Table 2), suggesting that in the present study 2-[^{18}F]FDG-PET outperformed MRI with regards to specific FTD patterns. Additionally, the API-PET was included in the optimal sets of diagnostic tests for differentiating FTD from DLB, VaD, and SCD, respectively (Table 4). However, the performance of the API-MRI for differentiating FTD from the other groups was lower in our study than in a previous study (Bruun et al., 2019c). Differences in patient populations with more atypical atrophy patterns (Bruun et al., 2019c; Ranasinghe et al., 2016) in our sample could potentially explain the lower performance of API-MRI, if these patterns do not affect 2-[^{18}F]FDG-PET to the same degree.

Occipital hypometabolism on 2-[^{18}F]FDG-PET is considered a supportive biomarker for DLB, particularly for differentiating DLB from AD (McKeith et al., 2017). Notably, we found a moderate accuracy for occipital cortex on 2-[^{18}F]FDG-PET for pairwise comparison of DLB vs. AD (AUC 68%). This finding was somewhat unexpected as previous 2-[^{18}F]FDG-PET studies have found accuracies between 70%−92% for occipital hypometabolism in differentiating DLB from AD using various quantitative methods (Caminiti et al., 2019; Ishii et al., 2007; Lim et al., 2009). The variability in accuracy may be explained by differences in operating procedures (Frisoni et al., 2013). The fully automated analysis had lower accuracies ranging from 68% to 78% (Kono et al., 2007; Lim et al., 2009) with the lowest accuracy in this study compared to computer-aided visual read by experienced neuroimaging physicians with accuracy of 92% (Caminiti et al., 2019). Moreover, the differences in the study cohorts may also have an impact on the accuracy, and as previously mentioned our study cohort include patients with a more uncharacterised presentation. We intended to optimize the DLB feature by proposing the occipital vs. temporal index, especially to improve differentiating of DLB from AD. This 2-[^{18}F]FDG-PET biomarker was the diagnostic test with the highest accuracy for differentiating between DLB and AD (bal. acc. of 79%, Table 2) and was included in the optimal sets for pairwise comparison of AD vs. DLB, suggesting that 2-[^{18}F]FDG-PET disease specific biomarkers have an impact on the accuracy for differentiating AD and DLB.

Likewise, we included the cingulate island sign ratio, which has been suggested to support the diagnosis of DLB (Kantarci et al., 2012; Lim et al., 2009; McKeith et al., 2017). The cingulate island sign ratio differentiated DLB from AD with a moderate AUC (79%) in comparison to a previous study with an AUC of 92% (Kantarci et al., 2012). The lower accuracy in our study may reflect a more heterogenous study population with more dual pathology in our study, as the presence of cingulate island sign has been reported to be associated with less concurrent AD pathology (McKeith et al., 2017).

The strength of our study is that the model was developed and validated using commonly used diagnostic tests and 2-[^{18}F]FDG-PET biomarkers in a relatively large cohort with diagnoses confirmed by experienced dementia specialists.

One of the limitations of this study is the possibility of circularity considering that the clinical reference diagnosis was supported and reinforced by all available diagnostic tests, consistent with established diagnostic criteria (Gorno-Tempini et al., 2011; McKeith et al., 2005; McKhann, 2001; McKhann et al., 2011; Rascovsky et al., 2011; Román et al., 1993). Moreover, we used both cohorts for cross validation due to the limited availability of FTD and DLB cases. However, the derived automatic neuroimaging biomarkers were not used for clinical diagnosis. Furthermore, the objective of the study was to investigate the clinical impact of commonly used diagnostic tests and 2-[^{18}F]FDG-PET biomarkers in the differential diagnosis of dementia and obtain information about their relative performance, and not to get precise accuracy estimates.

Another limitation for this study and other similar studies is the absence of pathological validation diagnosis.

In conclusion, this study demonstrated that the addition of 2-[^{18}F]FDG-PET biomarkers to commonly used diagnostic tests using the DSI classifier increased the classification accuracy for FTD and DLB, especially as compared to AD. Moreover, specific combinations of diagnostic tests were valuable to differentiate each subtypes of dementia.

This study provides support for the addition of 2-[^{18}F]FDG-PET in diagnosing dementia. The additional information from the 2-[^{18}F]FDG-PET may support clinicians in the differential diagnosis of dementia. Future research studies should evaluate the clinical diagnostic value and the cost-effectiveness of the diagnostic tests using the DSI classifier in a prospective multi-center study to optimize the use of diagnostic tests in clinical practice.

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Declaration of competing interest

Juha Koikkalainen and Jyrki Lötjönen are shareholders in Combinostics Oy. The other authors declare no competing interests.

CRediT authorship contribution statement

Le Gjerum: Conceptualization, Formal analysis, Data curation, Writing - original draft. **Kristian Steen Frederiksen:** Conceptualization, Writing - review & editing. **Otto Mølby Henriksen:** Writing - review & editing. **Ian Law:** Writing - review & editing. **Marie Bruun:** Data curation, Writing - review & editing. **Anja Hviid Simonsen:** Data curation, Writing - review & editing. **Patrizia Mecocci:** Data curation, Writing - review & editing. **Marta Baroni:** Data curation, Writing - review & editing. **Massimo Eugenio Dottorini:** Data curation, Writing - review & editing. **Juha Koikkalainen:** Conceptualization, Data curation, Writing - review & editing. **Jyrki Lötjönen:** Conceptualization, Data curation, Writing - review & editing. **Steen Gregers Hasselbalch:** Conceptualization, Data curation, Writing - review & editing, Supervision.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2020.102267.

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