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An evidence based algorithm for the utility of FDG-PET for diagnosing AD according to presence of medial temporal lobe atrophy

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Abstract

Background

Imaging biomarkers for Alzheimer's disease include medial temporal lobe atrophy (MTLA) depicted on CT or MRI, and patterns of reduced metabolism on FDG-PET.

Aims

To investigate whether MTLA on head CT predicts the diagnostic usefulness of an additional FDG-PET scan.

Methods

Participants had a clinical diagnosis of Alzheimer's disease (AD; n=37), dementia with Lewy bodies (DLB; n=30), or were similarly aged controls (n=30). We visually rated MTLA on coronally reconstructed CT scans and, separately and blind to CT ratings, abnormal appearances on FDG-PET scans.

Results

Using a pre-defined cutoff of MTLA >=5 on the Scheltens (0-8) scale, 0/30 controls, 6/30 DLB and 23/30 AD had marked MTLA. FDG-PET performed well for diagnosing AD vs DLB in the low MTLA group (sensitivity / specificity of 71%/79%), but in the high MTLA subjects, diagnostic performance of FDG-PET was not better than chance.

Conclusions

In the presence of a high degree of MTLA, the most likely diagnosis is AD, and an FDG-PET scan will probably not provide significant diagnostic information. However, in cases without MTL atrophy, if the diagnosis is unclear, an FDG-PET scan may provide additional clinically useful diagnostic information.

Introduction

Dementia affects around 35 million people worldwide, with numbers set to double in the next 30 years. Increasingly, dementia is an international governmental priority, with early and accurate assessment and diagnosis placed at the heart of effective management pathways. The two main causes of degenerative dementia in older people are Alzheimer's disease (AD), responsible for about 65% of all cases, and dementia with Lewy bodies (DLB), responsible for 10-15% of cases in older people.

Most international guidelines for assessment and diagnosis of dementia advocate the use of structural imaging (CT or MR) as a routine, both to exclude other intra-cerebral pathologies and determine the extent of regional brain atrophy [1-3]. Functional imaging methods such as FDG-PET and perfusion SPECT are generally advocated as useful to clarify diagnosis when doubt remains after clinical assessment and structural imaging results.

In the NIA revised diagnostic guidelines [4] proposed for AD clinical diagnosis, three imaging biomarkers for AD are proposed: medial temporal lobe atrophy (MTLA) on structural imaging; temporo-parietal hypometabolism of FDG-PET; and raised amyloid binding on amyloid-PET. The authors suggest that further research is needed "to prioritize biomarkers and to determine their value and validity in practice and research settings". This is important, not only to enable the appropriate sequencing of biomarkers, but also from a health economic and patient perspective to ensure that investigations such as scans are only requested in situations where they will provide useful additional information to inform diagnosis, so that unnecessary cost and inconvenience to subjects is minimised.

Modern multi-slice CT scanners allow assessment of MTLA comparable to T1 weighted MRI, [5] and assessment of MTLA with a visual rating scale [6] can be used to help distinguish AD from DLB [7]. Although there are imaging biomarkers (e.g. FP-CIT [8]) which have good diagnostic properties for the specific question of AD vs DLB, the initial clinical picture is frequently unclear, and scans with more general diagnostic ability such as FDG-PET are often requested in the diagnosis of dementia. The aim of this study was thus to investigate the additional diagnostic utility of FDG-PET following visual rating of MTLA on CT using the question of AD vs DLB as an exemplar. We hypothesised that for more severe MTL atrophy, PET would add little further diagnostic information.

Methods

Subjects

Subjects were part of a study investigating the relative performance of FDG-PET vs perfusion SPECT in the diagnosis of AD and DLB. Main results from the study have been reported elsewhere [9]. The study subjects were recruited prospectively from people aged over 60 with mild to moderate dementia (MMSE>12) referred to clinical services in North-East England, together with healthy

controls of similar age, who were recruited from spouses of participants with dementia (N=9), along with those who had previously indicated a willingness to participate in research (N=22). Subjects were recruited between June 2010 and June 2012. Control subjects had no symptoms of dementia, and patients met criteria for probable AD [10] or probable DLB [11]. The study was approved by Newcastle and North Tyneside Research Ethics Committee (REF 09/H0906/88), and all participants (or nominated Independent Mental Capacity Advocate where participant lacked capacity) gave informed consent before participating.

Clinical diagnosis was made by consensus between 3 experienced clinicians. Neither FDG-PET nor the MTLA ratings from CT were used to inform the diagnosis; the only information regarding CT available to the diagnostic raters was from a previous clinical CT report providing information about the extent of any vascular pathology present and confirmation that no space occupying lesion was present. All subjects had to have sufficient command of English and adequate visual and auditory acuity to allow cognitive and neuropsychological testing. Exclusion criteria were a) past history of alcohol or drug dependence; b) contraindications for FDG-PET scanning (e.g. inability to lie flat); c) fasting blood glucose level > 180 mg / dL. All subjects meeting in/exclusion criteria who consented to take part were included in the study. We recruited 102 subjects, of whom three withdrew before completing both scans, and two were excluded due to scanner technical problems. A total of 37 people with AD, 30 with DLB and 30 controls were successfully scanned with FDG-PET-CT.

Subjects underwent detailed neuropsychiatric investigation including the Cambridge Cognitive Examination (CAMCOG)[12], and the Rey Auditory Verbal Learning Test (AVLT) [13]. The Cornell scale for depression in dementia [14] was used to assess mood, and for dementia participants, we performed the Neuropsychiatric inventory (NPI)[15], and the Clinician Assessment of Fluctuation (CAF) scale[16]. Parkinsonian motor features were assessed in all subjects using the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS III)[17].

Scanning

Scans were performed at Newcastle University using a Siemens Biograph-40 Truepoint FDG-PET-CT. CT scans were obtained using the 40 slice CT with 0.6mm slices, pitch 0.8, 200 mAs, 120 kV, imaging time 12s. FDG-PET head scans were done over 10 min starting 30 min after iv administration of 250 MBq F-18 FDG. Siemens software was used for iterative reconstruction with scatter and attenuation correction based on the CT scan data obtained immediately before the FDG-PET scan.

Visual Rating

The CT scans were viewed and rated separately, by different observers to the PET scans. All ratings were performed blind to diagnosis, and to the other images from the same subject.

CT

All CT scans were reconstructed as 3mm thick coronal sections oriented perpendicular to the long axis of the hippocampus by the same operator. Visual rating was performed with a standardized scale (Scheltens scale) to rate right and left MTLA separately [6]. The scale rates atrophy on a 5-point scale (0 = absent, 1 = minimal, 2 = mild, 3 = moderate and 4 = severe) based on the height of the

hippocampal formation and the width of the CSF spaces. For the purpose of analysis the left and right scores were summed to give a combined MTLA score (maximum score 8). All scans were assessed by consensus between two experienced raters (SC and RB) blinded to diagnosis. Figure 1 shows example CT scans.

FDG-PET

Visual rating of the scans was performed blind to diagnosis and any clinical information by three imaging specialists (MJF, EDW, JJL) experienced in analysing and reporting nuclear medicine brain scans.

To facilitate consistency in reporting, the imaging features associated with AD and DLB were set out in a document – key points were a) reduced uptake in precuneus and lateral parietal lobes in both AD and DLB; b) relative preservation of posterior cingulate in DLB; c) occipital loss more likely in DLB d) reduced uptake in temporal and frontal lobe more likely in AD.

Each reader independently rated each scan on a 5-point scale for the degree of confidence in overall abnormality typical of dementia. For all scans not considered to be 'definitely normal', the match to AD or DLB was also rated, again using a 5-point scale. After individual ratings were completed, the imaging team met to compare and review all their ratings and to produce a set of consensus ratings for each scan. Each scan was also given a tripartite consensus classification of normal, AD or DLB.

Quantitative analysis

We also performed region of interest analysis on the PET scans. Full details are given elsewhere [9] but briefly, the PET scans were normalised to standard space in SPM8 (www.fil.ion.ucl.ac.uk/spm), and mean intensity within standard regions-of-interest (ROIs) were calculated for each scan. ROIs were taken from the AAL atlas [18] for medial temporal lobe, (hippocampus + parahippocampal gyrus) and medial occipital lobe (calcarine + lingual gyrus).

Statistics

Demographic and clinical rating data were analysed with SPSS 19.0 (SPSS, Chicago, IL). Continuous variables were compared using independent Student t tests or ANOVA. Chi squared tests were used to compare categorical data. ROC analysis was performed in SPSS. The diagnostic statistics (sensitivity etc) were calculated for AD vs DLB using R (http://www.r-project.org/ version 2.14.1) on those with a clinical diagnosis of dementia. For visual rating, the PET AD positive cases were those with consensus visual rating of definitely or probably AD, and PET AD negative cases were all other cases (visual rating of normal scan, unclear, probably or definitely DLB). For the ROI analysis, those with a medial temporal / occipital lobe uptake ratio of < 0.7 were classed as PET AD positive, otherwise negative. The diagnostic classification tables from which the statistics were calculated are available in the supplementary material.

Results

Table 1 shows the subject demographics. The groups were well matched for age, years of education, sex and duration of dementia. There were no significant differences between AD and DLB in CAMCOG score. As expected, the DLB group had more parkinsonian symptoms as demonstrated by significantly higher scores on the UPDRS, whilst the AD group had poorer memory performance on the Rey AVLT. The NPI score was not different between groups, but the DLB patients had more fluctuations of consciousness as measured by the CAF.

All of the control subjects had a MTLA < 5. Table 2 shows the characteristics of the patients with dementia according to MTLA. Those subjects with high MTLA score were older than those with lower score, but there were no other significant differences.

Figure 1 shows typical CT scans, and figure 2 shows the MTLA rating scores by group. In our previous examination of MTL atrophy, we found that a cut off of >=5 optimally distinguished AD from DLB and vascular dementia [7]. With this cutoff, none of the control subjects, 6/30 DLB, and 23/37 AD had marked MTL atrophy. So a high MTLA was a good test for excluding non-dementia and most DLB cases, with a positive predictive value of 79%, but a lower sensitivity (62%) for detecting all AD cases.

Table 3 presents the results of the FDG-PET visual rating consensus classification. PET performed generally very well at distinguishing controls from dementia at all levels of MTLA, with 24/30 (80%) of control scans being classed as normal and 61/67 (91%) of dementia cases as abnormal. For cases with MTLA < 5, visual rating of PET had a sensitivity / specificity of 71%/79% for diagnosis of AD vs DLB (table 4). However for those subjects with a MTLA >=5, visual inspection of PET performed poorly for distinguishing AD from DLB, with a sensitivity of 52%.

Table 5 presents ROC analysis of AD vs DLB for both the visual rating (5 point scale) and the ratio of uptake in the medial temporal to occipital lobe, which we found to have good distinguishing ability in the whole cohort [9]. Visual rating and ROI analysis had similar values of AUC in both low and high MTLA groups. For the high MTLA group, the AUC was 0.69 for visual rating and 0.72 for ROI analysis, neither of which were significantly greater than chance ($p>0.1$). For low MTLA , both the visual rating and ROI analysis were significant ($p < 0.001$) with AUC of 0.83 for visual rating, indicating good diagnostic ability. One factor influencing the less good diagnostic performance of PET at high MTLA is the increased variability, seen as higher SD for the AUC in the ROC analysis, and the ratio of MTL / occipital lobe FDG uptake, (table 3) where the variance is higher in the MTLA >= 5 group, significantly so in AD (SD 0.069 vs 0.032 , $F_{22,13} = 0.22$, $p =0.006$).

Discussion

Using a predetermined cutoff of >=5 on the MTL atrophy visual rating scale on 3mm slice CT for diagnosing AD (compared to DLB), we found a sensitivity of 62% and a specificity of 80%. The cutoff also excluded all of the normal control subjects and had good positive predictive value for AD (79%). Analysis of PET scans in the high MTLA subjects did not significantly improve diagnostic

discrimination. In the group with low MTLA (14 AD, 23 DLB), PET performed well for identifying controls, and also had a sensitivity and specificity of 71% and 79% for distinguishing AD from DLB.

Visual rating of the hippocampus can be performed fairly quickly by a trained person, with good reliability, and studies have shown it to be comparable to volumetric measurement for assessment of the hippocampus in AD [19]. CT scans are quick and relatively cheap to perform, and are frequently done for suspected dementia to exclude space occupying lesions or vascular disease. Alternatively, if coronal MRI head scans are available, MTLA could be rated from those. We suggest that rating of MTLA should form a standard part of the examination report, since our data suggest that when there is a high degree of medial temporal lobe atrophy present, then the most likely diagnosis is Alzheimer's disease, and it is unlikely that a FDG-PET scan will provide significant additional diagnostic information. In cases where MTL atrophy is absent or mild, and the diagnosis is unclear, then a FDG-PET scan may provide additional information. Our results are consistent with those of Ossenkoppole et al [20] who found that PET imaging contributed most to diagnosis when there was greater diagnostic uncertainty before considering the scan results. In the case where AD is still suspected, but there is absent MTL atrophy, testing levels of Aβ42 in CSF may be appropriate, as this has good sensitivity for detecting AD. [21]

Reduction in FDG uptake in the posterior cingulate cortex (PCC) is one of the characteristic features of AD. Previous work has shown that this is associated with disconnection between the PCC and the medial temporal lobe [22, 23]. It is thus likely that the presence of severe MTLA on a CT scan will be accompanied by Alzheimer-like features on the FDG-PET scan due to this disconnection. This partly explains the relative lack of additional diagnostic information from FDG-PET in high MTLA. In the case of uncertain diagnosis in subjects with high MTLA, then a PET/SPECT scan examining a different neural system may be more useful (e.g. with an FP-CIT SPECT scan for detecting dopaminergic deficit associated with DLB [8]).

Subjects with high MTLA were older. Even in healthy subjects, MTLA tends to increase with age, [24] there is an age related decrease in FDG-PET uptake, [25] and subjects with later onset AD have previously been reported to have less pronounced FDG deficits [26]. The poorer diagnostic performance of FDG-PET in the high MTLA may thus have been in part due to lower and less distinct FDG uptake patterns in older subjects. It is also possible that the DLB subjects with high MTLA may have had some degree of AD pathology present.

Caveats are that we only investigated AD and DLB in this study. Evaluation of MTLA in cases of mild cognitive impairment has good predictive value for development of AD [27] and studies are needed as to how best combine this with other biomarkers such as PET. Patients with fronto-temporal dementia commonly have hippocampal atrophy, and it is difficult to differentiate FTD from AD on the basis of MTLA [28-30]. In the case of suspected FTD, more detailed examination of structural scans may help the diagnosis, since the pattern of structural atrophy is different to that seen in AD [31, 32]. On FDG-PET scans, patients with FTD typically have greater frontal and temporal hypometabolism than AD [33] and studies have found generally good diagnostic differential ability for AD vs FTD [33-35] though with, in general, lower reported sensitivity (53-72%) for FTD than specificity (95-99%).

We have previously shown that MTLA also discriminates AD from vascular dementia [7], and other studies have also found MTLA in VaD to be intermediate between controls and AD [36, 37] and hence the higher the MTLA score, the less likely there is VaD. Examination of MRI scans for presence of vascular lesions is most likely to be of use to identify/exclude cases of VaD [38].

We recruited control subjects from a similar demographic to the dementia participants. Controls had the highest mean years of education of any group, but there were no significant differences between the groups in age, sex or years of education. Our diagnosis was based on clinical assessment, without the aid of neuroimaging or CSF biomarkers, an approach which has been been validated in our group both against autopsy and other imaging markers and is a standard now accepted by regulatory authorities [8]. Although there may be some mistaken clinical diagnoses, we believe that they are unlikely to affect our main conclusion that a FDG-PET scan will probably not help the diagnosis of AD in the presence of MTL atrophy on CT.

Many countries, including the UK, have initiatives aimed at raising the profile of dementia and increasing the numbers diagnosed, with some research estimating that currently, less than half the people with dementia receive a formal diagnosis [39]. There will also be a substantial increase in the numbers of patients with dementia over the next 40 years, due to increases in lifespan[40]. Neuroimaging services will be an important part of providing diagnoses to these increasing numbers. However, FDG-PET remains a relatively expensive option and involves a rather lengthy procedure for the patient compared to a CT scan. Therefore, to maximise health care resources, and minimise unnecessary investigations for people with dementia, FDG-PET will have to be used only as part of an evidence based diagnostic pathway. Based on our results, a suggested algorithm for considering neuroimaging, dependent on both the CT results and the clinical question, is presented in Figure 3. Future work should seek to incorporate other imaging biomarkers into this algorithm, for example amyloid-PET.

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Conflicts of interest

MF reports grants from National Institute for Health Research, KH reports grants and personal fees from Lilly/Avid Radiopharmacuticals, personal fees from GE Healthcare, Cytox, and Elan, other from Herholz Consulting GmbH, outside the submitted work, JOB report grants and other from GE Healthcare, grants and other from Lilly, other from Bayer Healthcare, other from TauRx, other from Cytox, outside submitted work.

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Tables

Table 1 Subject demographics. Values are mean (SD) [range]

	Control (N=30)	AD (N=37)	DLB (N=30)	
Age	76.3 (6.6)	75.8 (7.6)	76.5 (5.8)	$F_{2,94}$= 0.11, p=0.9
Female:Male	10:20	15:22	7:23	X^2= 2.2, p=0.3
Education (years)	11.9 (2.8)	11.5 (2.6)	10.6 (2.3)	$F_{2,94}$=1.97, p=0.15
Duration of dementia (months)	-	44.1 (23.2) [12 – 132]	38.1 (27.3) [9 – 120]	t_{65} = 0.97, p=0.3 §
MMSE	28.9 (1.1) [26 – 30]	20.9 (3.7) [15 – 28]	21.8 (4.2) [14 – 28]	t_{65} = -0.95, p=0.3 §
CAMCOG	98.4 (4.0)	71.5 (11.7)	72.6 (13.1)	t_{65} = -0.35, p=0.7 §
Rey total	70.3 (12.3)	25.1 (9.6)	33.4 (12.1)	t_{65} = -3.1, p=0.002 §
Cornell	1.8 (1.8)	4.5 (2.8)	8.1 (3.8)	$F_{2,94}$ = 35.9, p<0.001
CAF total	-	1.5 (2.5)	6.0 (4.7)	t_{64} = -4.7, p<0.001 §
NPI total	-	14.8 (14.6)	19.7 (15.6)	t_{64} = -1.3, p=0.2 §
UPDRS	2.6 (2.7)	3.7 (3.3)	25.5 (11.9)	$F_{2,94}$= 104, p<0.001
MTLA >=5	0 (0%)	23 (62 %)	6 (20%)	X^2 = 32.6; p<0.001

Table 2 Subject demographics by MTLA for the patients with dementia

	AD MTLA < 5 (N=14)	AD MTLA >=5 (N=23)		DLB MTLA < 5 (N=24)	DLB MTLA >=5 (N=6)	
Age	71.0 (7.1)	78.7 (6.4)	T=3.3,p=0.002	75.3 (5.4)	81.0 (5.7)	T=2.3,p=0.031
Female:Male	7:7	8:15	X^2=0.8, p=0.5	5:19	2:4	X^2=0.4,p=0.6
Duration of dementia (months)	39.7 (17)	46.7 (26)	T=0.9,p=0.4	38.0 (26)	38.0 (35)	T=0.0,p=1.0
MMSE	21.1 (4.2)	20.8 (3.5)	T=-0.3,p=0.8	22.5 (4.0)	19.0 (3.8)	T=-1.9,p=0.06
CAMCOG	74.0 (12)	70.0 (11)	T=-1.0,p=0.4	74.1 (11)	66.5 (19)	T=-1.3,p=0.2
UPDRS	3.6 (4.1)	3.7 (2.7)	T=0.2, p=0.9	24.3 (12)	30.0 (11)	T=1.0,p=0.3

Table 3 Consensus visual rating from 3 observers of PET scans by different groups and MTL atrophy severity. Values in shaded cells represent correct diagnoses. Ratio of FDG-PET uptake in medial temporal lobe to occipital lobe ROIs also shown.

		PET visual rating consensus				PET MTL / Occipital ROI ratio mean (SD)
MTLA		Def/Prob normal	Def/ Prob AD	Unclear AD v DLB	Def/ Prob DLB	
	AD					
0-4	14	1 (7%)	10 (71%)	3 (21%)	0	0.647 (0.032)
5-8	23	1 (4%)	12 (52%)	6 (26%)	4 (17%)	0.631 (0.069)
	DLB					
0-4	24	4 (17%)	5 (21%)	1 (4%)	14 (58%)	0.751 (0.080)
5-8	6	0	1 (17%)	3 (50%)	2 (33%)	0.711 (0.123)
	Controls					
0-4	30	24 (80%)	1 (3%)	3 (10%)	2 (7%)	0.681 (0.039)
5-8	0					

Table 4. Diagnostic statistics for identifying AD (vs DLB). 95% confidence interval in brackets. PET ROI is the MTL / occipital uptake ratio. The CT & PET visual rating figures are obtained by following the diagnostic flowchart in figure 3, i.e. an AD diagnosis is given via either MTL atrophy on CT, or AD positive FDG-PET scan following normal MTL on CT.

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy	Likelihood ratio for positive result
CT rating	0.62 (0.45-0.77)	0.80 (0.61-0.92)	0.79 (0.60-0.91)	0.63 (0.46-0.78)	0.70 (0.58-0.80)	3.11 (1.46-6.64)
PET visual rating, all cases	0.59 (0.42-0.75)	0.80 (0.61-0.92)	0.79 (0.59-0.91)	0.62 (0.45-0.76)	0.69 (0.56-0.79)	2.97 (1.39-6.38)
CT <5, PET visual rating	0.71 (0.42-0.90)	0.79 (0.57-0.92)	0.67 (0.39-0.87)	0.83 (0.60-0.94)	0.76 (0.59-0.88)	3.43 (1.47-8.00)
CT >=5, PET visual rating	0.52 (0.31-0.73)	0.83 (0.36-0.99)	0.92 (0.62-1.00)	0.31 (0.12-0.59)	0.59 (0.39-0.76)	3.13 (0.50-19.5)
CT & PET visual rating	0.89 (0.74-0.96)	0.63 (0.44-0.79)	0.75 (0.59-0.86)	0.83 (0.60-0.94)	0.78 (0.65-0.87)	2.43 (1.50-3.94)
PET MTL/Occipital ROI	0.89 (0.74-0.96)	0.80 (0.61-0.92)	0.85 (0.69-0.94)	0.86 (0.66-0.95)	0.85 (0.74-0.92)	4.46 (2.16-9.20)
CT <5, PET ROI	0.93 (0.64-1.00)	0.83 (0.62-0.95)	0.76 (0.50-0.92)	0.95 (0.74-1.00)	0.87 (0.71-0.95)	5.57 (2.25-13.8)
CT >=5, PET ROI	0.87 (0.65-0.97)	0.67 (0.24-0.94)	0.91 (0.69-0.98)	0.57 (0.2-0.88)	0.83 (0.64-0.93)	2.61 (0.83-8.18)
CT & PET ROI	0.97 (0.84-1.00)	0.67 (0.47-0.82)	0.78 (0.63-0.89)	0.95 (0.74-1.00)	0.84 (0.72-0.91)	2.92 (1.75-4.86)

Table 5 Values from ROC analysis based on the consensus rating and the ratio of regions of interest in the occipital / medial temporal lobe. Values are AUC (SE) and sensitivity/specificity for identifying AD.

MTL rating	PET AD vs DLB Consensus visual rating (N=67)	PET ROI MTL/Occipital (N=67)
	AUC (SE)	AUC (SE)
0-4	0.83 (0.07)***	0.85 (0.07) ***
5-8	0.69 (0.13)	0.72 (0.15)

*** p<0.001

Figure 1 CT of DLB with (left) high (MTLA=8) and (right) low (MTLA=2) MTLA score. Greater medial temporal atrophy (arrowed) is clearly visible in the left hand scan.

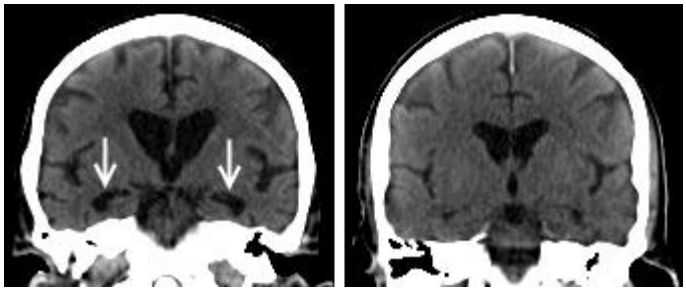


Figure2 Medial temporal lobe atrophy rating (L+R) for all subjects. Horizontal bar shows group means.

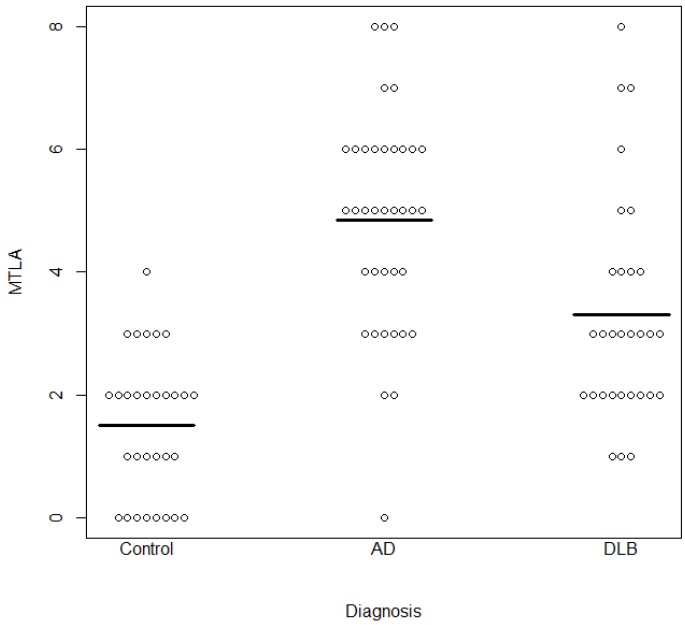
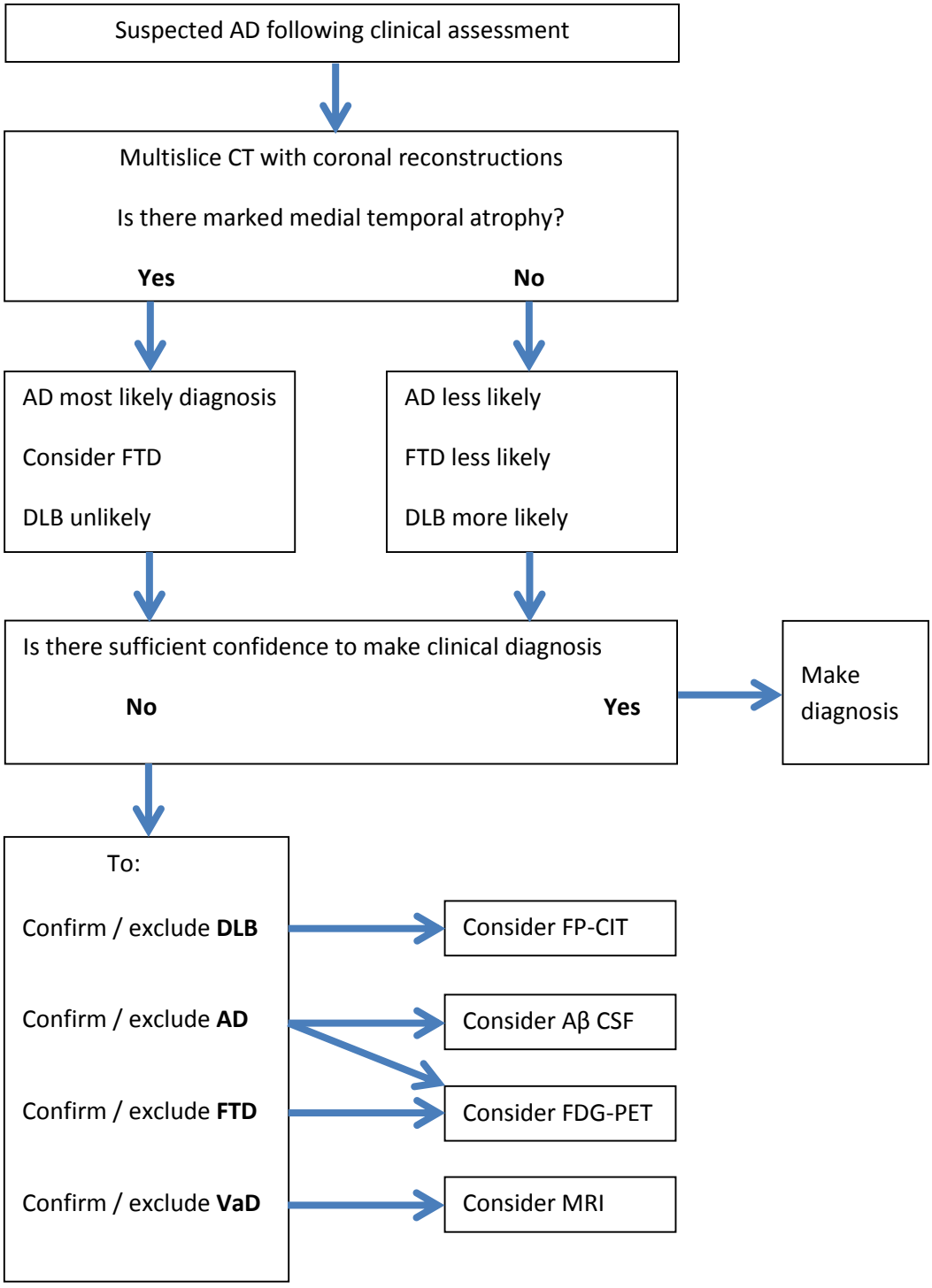


Figure 3 Evidence based imaging algorithm for FDG PET use



Abbreviations

AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; FTD = Fronto-temporal dementia; FP-CIT = SPECT with FPCIT (dopamine transporter) ligand; CT = computed tomography; FDG-PET = fluorodeoxyglucose PET (positron emission tomography); VaD = Vascular Dementia; Aβ Amyloid-beta; CSF = Cerebrospinal fluid

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