Title

Temporoparietal Hypometabolism in Frontotemporal Lobar Degeneration and Associated Imaging Diagnostic Errors

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Temporoparietal hypometabolism is common in FTLD and is associated with imaging diagnostic errors

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Abstract

Objective—To evaluate the cause of diagnostic errors in the visual interpretation of positron emission tomography scans with 18F-fluorodeoxyglucose (FDG-PET) in patients with frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD).

Design—Twelve trained raters unaware of clinical and autopsy information independently reviewed FDG-PET scans and provided their diagnostic impression and confidence of either FTLD or AD. Six of these raters also recorded whether metabolism appeared normal or abnormal in 5 predefined brain regions in each hemisphere – frontal cortex, anterior cingulate cortex, anterior temporal cortex, temporoparietal cortex and posterior cingulate cortex. Results were compared to neuropathological diagnoses.

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Setting—Academic medical centers

Patients—45 patients with pathologically confirmed FTLD (n=14) or AD (n=31)

Results—Raters had a high degree of diagnostic accuracy in the interpretation of FDG-PET scans; however, raters consistently found some scans more difficult to interpret than others. Unanimity of diagnosis among the raters was more frequent in patients with AD (27/31, 87%) than in patients with FTLD (7/14, 50%) (p = 0.02). Disagreements in interpretation of scans in patients with FTLD largely occurred when there was temporoparietal hypometabolism, which was present in 7 of the 14 FTLD scans and 6 of the 7 lacking unanimity. Hypometabolism of anterior cingulate and anterior temporal regions had higher specificities and positive likelihood ratios for FTLD than temporoparietal hypometabolism had for AD.

Conclusions—Temporoparietal hypometabolism in FTLD is common and may cause inaccurate interpretation of FDG-PET scans. An interpretation paradigm that focuses on the absence of hypometabolism in regions typically affected in AD before considering FTLD is likely to misclassify a significant portion of FTLD scans. Anterior cingulate and/or anterior temporal hypometabolism indicates a high likelihood of FTLD, even when temporoparietal hypometabolism is present. Ultimately, the accurate interpretation of FDG-PET scans in patients with dementia cannot rest on the presence or absence of a single region of hypometabolism, but must take into account the relative hypometabolism of all brain regions.

Introduction

Frontotemporal lobar degeneration (FTLD) is the third most common degenerative dementia behind Alzheimer's disease (AD) and dementia with Lewy bodies.[1] FTLD is a heterogeneous disorder with at least 3 recognized clinical presentations,[2] multiple histopathologic subtypes[3, 4] and familial cases associated with mutations in four different genes[5-9] with an additional genetic linkage on chromosome 9p.[10-12]

Despite the existence of consensus clinical diagnostic criteria, patients with FTLD are commonly misdiagnosed as having AD or a psychiatric illness.[2, 13-15] These mistakes are understandable given the insidious, progressive nature of both FTLD and AD and their shared symptomatology.[16] Both illnesses may have prominent behavioral changes, which can overlap symptoms typically seen in psychiatric disorders.[17-19] While amnesia as the initial symptom of a progressive dementing disease strongly favors a diagnosis of AD, it also occurs in some patients with FTLD.[20] FTLD may present with language deficits, but prominent language deficits also occur in AD.[2, 21-24] The difficulty in obtaining a detailed and reliable clinical history in some situations is a further challenge to accurate diagnosis and highlights the value of validated diagnostic biomarkers.

Despite the difficulties, accurate diagnosis is critical because the clinical management of AD and FTLD differ. The FDA currently has approved 5 drugs for the treatment of AD, 4 cholinesterase inhibitors and an NMDA channel modulator.[25] In contrast, no drugs have been shown to be effective in FTLD, although serotonin reuptake inhibitors are often used.[26] Cholinesterase inhibitors can worsen behavioral symptoms in FTLD patients and are generally avoided.[27-29] The treatment of FTLD with memantine has been the subject of a few small trials, but the open label design of these trials prevents definitive conclusions from being drawn.[30-32] The treatment approaches for AD and FTLD will likely diverge even further with the anticipated arrival of specific disease modifying therapies for AD.[26, 33]

Brain imaging provides an independent, objective, and quantitative measure of disease that complements clinical information and can aid in distinguishing FTLD and AD. Voxel based morphometric analysis of structural MRI can detect differences in regional atrophy between groups of patients with FTLD, FTLD subtypes, AD and controls.[34, 35] However, visual

interpretation of individual MRI scans, while helpful, can be misleading.[36] FDG-PET imaging typically shows sufficient abnormalities that can be used to improve the accuracy of distinguishing AD from FTLD in individual cases.[37] Patients with AD characteristically have reduced activity most prominently in posterior temporoparietal cortex and the posterior cingulate cortex.[38] By contrast, the FDG-PET scans of patients with FTLD have hypometabolism that is most prominent in the frontal cortex, anterior temporal cortex and anterior cingulate cortex.[39] Metabolic abnormalities are not limited to these regions, however. As the severity of dementia increases, the severity and topographic extent of hypometabolism also increases and begins to involve other regions. Likewise, there is considerable heterogeneity in the individual pattern of hypometabolism that reflects the patient's clinical symptoms. Consequently, considerable judgment is required for visual diagnostic interpretation. Analytic techniques such as stereotactic surface projection maps (SSP) that incorporate both metabolic and statistical information further improve diagnostic accuracy of FDG-PET scan interpretation as compared to standard transaxial images.[40]

In a previous study, utilizing the same series of SSP processed FDG-PET scans that are used in this current analysis, individual raters were able to interpret the scans of autopsy confirmed AD patients with a very high degree of sensitivity (97.8%) and confidence. Scans from autopsy confirmed FTLD patients, however, had more variability of interpretation resulting in reduced sensitivity (70%) and confidence, although there remained in FTLD patients a significant positive impact on diagnostic accuracy as compared to clinical assessment alone (positive likelihood ratio = 36.5).[37] We decided to further evaluate the inconsistencies between individual raters for their interpretations of these FTLD PET scans to see what features were associated with inaccurate scan interpretation, and provide guidance to improve diagnosis. In standard clinical settings, a scan will typically be interpreted by a single individual without the benefit of a diagnostic consensus process often used in research. Identifying and describing features commonly found in the FDG-PET scans of FTLD patients that are associated with inaccurate interpretations may improve the diagnostic accuracy of these scans in clinical practice.

Methods

Overview

The data for this analysis came from two different studies that evaluated the utility of FDG-PET to distinguish AD from FTLD. Each study utilized a group of 6 raters who reviewed the same series of FDG-PET scans.[37] In both studies, the raters individually interpreted each scan as being most consistent with either AD or FTLD before any discussion took place and while blinded to all clinical information. This yielded twelve independent interpretations for each scan from which we could observe the degree of discrepancy between the raters. The members of one group also rated each of 10 regions (5 regions on the right and left sides) as normal or abnormal.

To simplify the comparisons, we classified a region as abnormal if it was judged to be abnormal on either the left or right side, yielding 5 regions.

Subjects

A previously described group of 45 dementia patients with FDG-PET scans and subsequent postmortem histopathological diagnoses of either AD or FTLD were used for this study.[37] This group was comprised of all patients meeting the above criteria whose scans were obtained at the University of Michigan between December 1984 and July 1998 and for whom retrievable medical records as well as technically adequate parametric PET scans were available. A summary of the subjects' characteristics is provided in table 1. FTLD is

caused by several distinct pathologies. We did not have the information to categorize each of the pathologies but provide the pathologic classification from the autopsy report. We did not attempt to analyze data based on pathologic subtypes because of inadequate numbers from which to draw statistically valid conclusions. A database of FDG-PET scans from 33 normal elderly patients of a similar age were used for statistical comparison with patient scans as previously described.[37]

Raters

There were two different groups of raters used in this study. Each group consisted of six members for a total of twelve raters. Ten of the raters were neurologists and two were psychiatrists. All had extensive experience in dementia care at eight NIA-funded Alzheimer's Disease Centers. The raters had variable experience with FDG-PET imaging, ranging from expert to novice. Each rated the scans independently, without knowledge of the opinions of the others and blinded to any clinical data.

Image processing

The data used in these analyses were from the interpretation of SSP processed FDG PET Scans. SSP is an automated analysis method that warps images into a common stereotactic space and allows for statistical analysis of individual scans as compared to a control group. This results in six surface projection maps that are displayed as both a metabolic map and as a statistical map showing surface pixel-by-pixel z-scores derived from comparison to a control group. Examples of the maps are shown in figure 1. Please see Foster et al, 2007 for further details.[37]

Rater training

All raters completed a two-hour training session to establish a uniform approach to scan interpretation and to familiarize the raters with the SSP presentation of FDG PET data.[26] Interpretation was based upon the evaluation of five regions of the cerebral cortex in each hemisphere and judging the relative degree of abnormality in regions typically affected in AD (temporoparietal and posterior cingulate cortex) and FTLD (anterior temporal, frontal and anterior cingulate cortex). The raters were not instructed to weigh any particular region more heavily than another, but rather to base their final interpretation on whether the preponderance abnormalities were in AD or in FTLD associated cortical areas. The training utilized 25 scans from clinically diagnosed patients and normal elderly controls (10 AD, 10 FTLD, 5 controls) that were not part of the experimental dataset. The five regions were reviewed to establish consistent interpretation of the anatomical boundaries of each region (fig 1).

Statistical analysis

Inter-rater reliability for the six raters judging regional abnormalities was assessed using kappa statistics calculated for all possible rater pairs. The level of agreement based on the kappa statistics was classified as fair (kappa values 0.2-0.39), moderate (0.4-0.59), substantial (0.6-0.79) or almost perfect (0.8-1.0).[41] If four or more of the six raters who rated regional metabolism thought that a region was hypometabolic, then it was considered abnormal. Associations between regional hypometabolism and a pathologically verified diagnosis of AD or FTLD were evaluated using a Chi-square test with Yates correction. Sensitivity, specificity, odds ratios and positive likelihood ratios (+LR) were calculated for hypometabolism in the temporoparietal and posterior cingulate cortices for a pathologic diagnosis of AD, while these same measures were calculated for the frontal, anterior cingulate and anterior temporal cortices for a pathologic diagnosis of FTLD. The +LR incorporates sensitivity and specificity into a single measure: (sensitivity) / (1- specificity).

This represents the probability of a positive test in an individual with the disorder divided by the probability of a positive test in an individual without the disorder. A +LR above 1 means that a positive test is more likely to occur in patients with the disease than in those without the disease.

For the pathologically verified FTLD cases, associations between regional hypometabolism and lack of unanimity among the raters for their overall interpretation were evaluated with the Fisher's Exact test.

Results

Inter-rater reliability for judging individual regions as normal or abnormal was substantial for temporoparietal cortex, and only slightly less for the frontal cortex and the posterior cingulate cortex (table 2). However, inter-rater reliability was only moderate for the anterior cingulate and the anterior temporal cortices, which are typically affected in FTLD.[41] As expected from previous research [38, 42], our raters found hypometabolism in the temporoparietal and posterior cingulate regions much more frequently in AD than FTLD (odds ratios 14.5 and 7.2) (table 3). Nevertheless, 50% of FTLD patients had temporoparietal hypometabolism. Temporoparietal hypometabolism was more sensitive, but posterior cingulate hypometabolism was more specific for AD.

Likewise, our raters found the expected higher frequencies of hypometabolism in frontal, anterior cingulate and anterior temporal regions in FTLD as compared to AD patients (table 4). Despite what might be expected, the presence of frontal hypometabolism alone did not significantly increase likelihood of FTLD (odds ratio 3.3). AD patients with or without frontal hypometabolism did not differ significantly with respect to age (64.6 vs. 66.2, p=0.72). On the other hand, anterior cingulate and anterior temporal hypometabolism were much more likely in FTLD cases. All FTLD scans had hypometabolism in at least one of the typical FTLD areas and all but 1 of the FTLD scans had reductions in the anterior cingulate and/or anterior temporal cortices. Hypometabolism in the anterior cingulate and anterior temporal cortices had higher specificities and higher likelihood ratios for a diagnosis of FTLD than hypometabolism in the temporoparietal cortex had for AD. Even in the presence of temporoparietal hypometabolism, anterior cingulate and anterior temporal hypometabolism were each strongly associated with a diagnosis of FTLD rather than AD (table 5).

The 12 raters who provided an overall interpretation of the scans were unanimous in their decisions 76% (34/45) of the time and all unanimous decisions were also correct. Since non-unanimity would correspond to interpretation errors on the part of some raters, we looked to see what factors, if any, were associated with this subset of misdiagnosed scans (table 6). Of the FTLD scans, 50% had non-unanimous interpretations with a range of 1 – 11 incorrect out of a total of 12 raters (figure 2). In contrast, only 13% of AD scans lacked unanimity demonstrating a strong association of non-unanimous PET interpretation with a diagnosis of FTLD ($p = 0.02$ by Fisher's exact test, Pearson's $\phi = 0.79$). Clearly, raters had more difficulty with FTLD scans. There were only 4 AD scans with non-unanimous decisions and 2 of those had only one discrepant interpretation. In both of the AD cases that had more than 1 discordant interpretation, the posterior cingulate was judged to be normal and at least one FTLD associated area was judged to be abnormal. Because of the small number of these cases, we did not analyze them further. In FTLD cases, hypometabolism in the temporoparietal cortex was significantly associated with non-unanimous interpretations, occurring in 6/7 non-unanimous scans and in only 1/7 unanimously decided scans (table 6). Posterior cingulate abnormalities were not independently associated with non-unanimity beyond the trend level and all FTLD scans that had posterior cingulate hypometabolism also had temporoparietal abnormalities. There were no individual FTLD areas that were

independently associated with unanimity. Five of the FTLD scans had hypometabolism in all 3 FTLD associated areas and all of these had unanimous interpretations.

Comment

Temporoparietal involvement in FTLD that is detectable by both MRI and SPECT has been noted previously, particularly with respect to its association with progranulin mutations.[43-45] CBD, which is part of the FTLD spectrum of disorders, frequently involves the parietal cortex as well[46, 47]. Parietal atrophy has also been demonstrated in patients with microtubule associated protein tau mutations, though it is less than what is seen with progranulin mutations.[48]

In our sample, the presence of temporoparietal hypometabolism on FDG-PET imaging was a common finding in the FTLD cases. This raises concern from a diagnostic standpoint since many use hypometabolism in the temporoparietal region as a reliable sign of AD. While we found the sensitivity of temporoparietal abnormalities to be quite good for AD (93.6%), the specificity was only 50%. This reduced specificity had consequences since temporoparietal hypometabolism had a disproportionate effect on interpretation errors for FTLD subjects. All of the FTLD scans with temporoparietal abnormalities also had hypometabolism in at least 1 or more areas associated with FTLD, and most had abnormalities in at least 2 FTLD regions. This suggests that evidence for AD may have a tendency to “trump” evidence for FTLD in FDG-PET interpretation. Our findings demonstrate, however, that hypometabolism in the anterior cingulate and anterior temporal regions should carry at least as much or more weight for a diagnosis of FTLD as temporoparietal hypometabolism carries for a diagnosis of AD, even when this is seen in the presence of temporoparietal hypometabolism. While we found associations of anterior cingulate and anterior temporal hypometabolism with FTLD, we did not find an association with hypometabolism of the frontal cortex (lateral and dorsolateral) with FTLD. These findings are consonant with other work, which has carefully looked at patterns of atrophy that distinguish FTLD from AD. Atrophy of the paralimbic fronto-insular-striatal network, of which the anterior cingulate is a part, distinguishes FTLD from AD while atrophy of the dorsolateral frontal cortex does not.[49] These findings in turn, mirror the distribution of the von Economo neurons. These neurons are found in the anterior cingulate and anterior insula, and are absent from the dorsolateral frontal lobes. These neurons are preferentially and severely affected early in the course of FTLD and may underlie this specific distribution of atrophy,[50, 51] or in the case of our data, hypometabolism. Our data show that relying more on anterior temporal and especially anterior cingulate hypometabolism for a diagnosis of FTLD would improve the accuracy of scan interpretation.

Ultimately, interpretation of an FDG-PET scan to distinguish between AD and FTLD cannot be based on the presence or absence of hypometabolism in a single region. Instead, over-reliance on findings in a single region of the cortex should be avoided by considering all likely affected regions and determining the relative degree of hypometabolism in each, both in terms of intensity and topographic extent.

There are several limitations to our study. Our sample size was relatively small, particularly with respect to the number of FTLD subjects. Optimally there would be similar numbers of FTLD subjects and AD subjects, however, obtaining such a group of FTLD subjects with both technically adequate PET scans and pathologic confirmation of their diagnosis would be difficult. We used the majority opinion of raters to define the presence or absence of regional hypometabolism. More objective measures of hypometabolism could give different results, but to be clinically meaningful, a finding must be perceptible to an interpreter. We thus believe that our approach provides more practical value for clinical applications. This is a convenience sample, with patients scanned at various points during the course of their

illness. While this study provides some general guidelines for image interpretation, it is possible that different algorithms would be ideal for early diagnosis and when there already are severe deficits. Nevertheless, in current practice determining the cause of dementia is often delayed and patients can be first scanned at any point in their illness.

The findings of this study are particularly relevant given the somewhat recent and growing use of FDG-PET in dementia evaluations. Although recently approved for this use by the Center for Medicare Services in the US, relatively few physicians have been trained to appreciate the complexity of FDG-PET patterns of hypometabolism seen in dementia. This may lead to reliance on an overly simplified interpretation scheme, such as the presence or absence of temporoparietal hypometabolism as the primary deciding factor between AD and FTLD. The results of this study indicate that such an “Alzheimer-centric” approach to FDG-PET interpretation may produce interpretation errors in a substantial proportion of patients with FTLD. The current Medicare guidelines for the use of FDG-PET in dementia recognize it as an appropriate study to distinguish between AD and FTLD when the clinical evaluation cannot. If this criterion is applied correctly by ordering physicians, then the proportion of FTLD patients relative to AD patients will be much larger in the subset of dementia patients receiving PET scans than in the clinical dementia population.

The clinician will ultimately have to reconcile clinical, laboratory and imaging data to make a final, accurate diagnosis. FDG-PET improves diagnostic accuracy in dementia, but this effect is, in turn, dependent on accurate scan interpretation. Understanding the moderate specificity of temporoparietal hypometabolism for AD and the relatively high specificity and +LR of anterior cingulate cortex, as well as anterior temporal cortex, hypometabolism for FTLD may improve FDG-PET scan interpretation and therefore maximize the positive impact of these studies on diagnostic accuracy.

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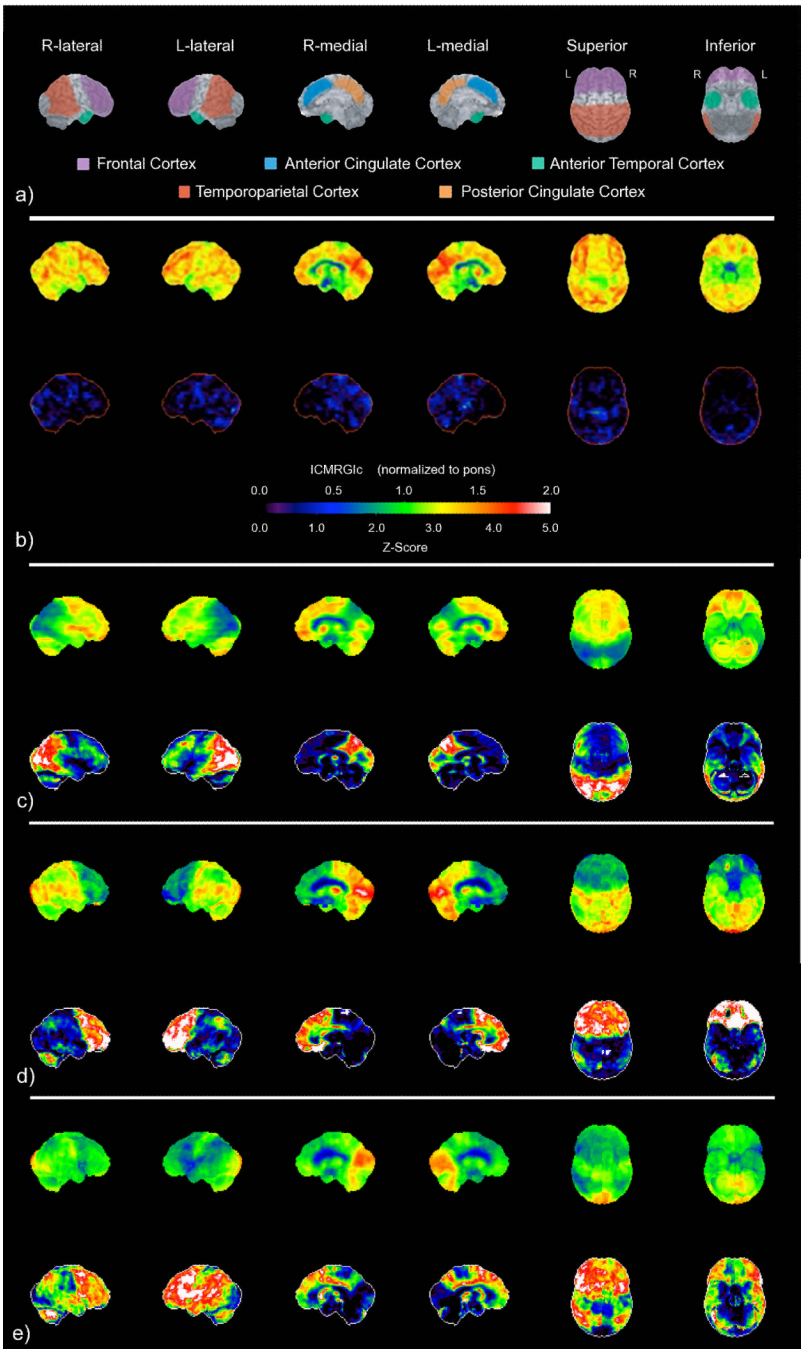

Figure 1.

Localization key and SSP images of 4 example PET scans with activity maps on the top row and z-maps showing deviation from a normal control cohort on the second row a) localization key of brain regions as used by the raters b) scan of a 66 y/o normal control subject and the color scale used for all PET images in the study. The local cerebral metabolic rate of glucose utilization (ICMRGlc) is indicated by the numbers along the top of the color scale and the *z*-score values are represented by the numbers across the bottom of the scale. c) scan of an AD subject with unanimous interpretations d) scan of an FTLD subject with unanimous interpretations e) scan of an FTLD subject with non-unanimous interpretations (Votes: 7 FTLD, 5 AD)

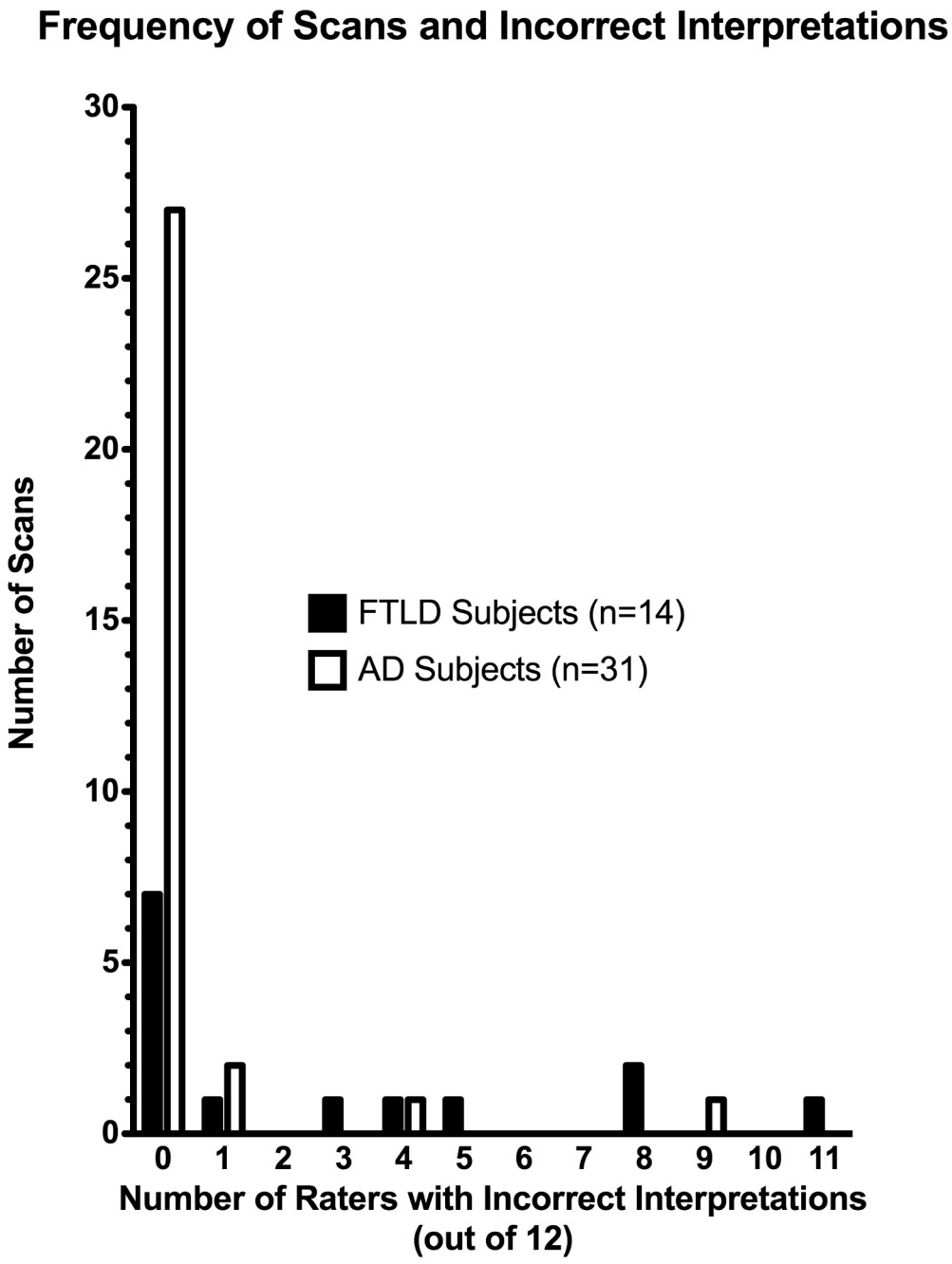

Figure 2.

Histogram of the number of scans and the degree of unanimity in the interpretation. 0 raters with incorrect interpretations indicates unanimous interpretations. Only 50% of the FTLD scans had unanimous, correct interpretations. 87% of the AD scans had unanimous, correct interpretations. Of note, 2/4 AD scans with non-unanimous interpretations had only 1/12 raters in error.

Table 1

Subject characteristics and scan interpretation data

Case #	Pathologic diagnosis	Age at onset	Age at PET	Symptom duration at PET	MMSE at PET	Clinical syndrome and prominent features	Scan Interpretation 12 raters FTLD/AD	Temproparietal	Posterior Cingulate	Frontal	Anterior Cingulate	Anterior Temporal
1	AD	67	72	5	10	Typical AD	0/12	Abnl	Abnl	Abnl	Nl	Nl
2	AD	59	62	3	NA	CBD	0/12	Abnl	Abnl	Abnl	Nl	Nl
3	AD	76	79	3	20	Aphasia	1/11	Abnl	Nl	Nl	Nl	Abnl
4	AD	72	75	3	23	Typical AD	0/12	Abnl	Abnl	Nl	Nl	Abnl
5	AD	65	71	6	11	Typical AD	0/12	Abnl	Abnl	Nl	Nl	Nl
6	AD	64	70	6	NA	Typical AD	0/12	Abnl	Abnl	Nl	Nl	Nl
7	AD	57	62	5	NA	Aphasia	0/12	Abnl	Abnl	Abnl	Nl	Nl
8	AD	32	35	3	NA	Typical AD	0/12	Abnl	Abnl	Nl	Nl	Nl
9	AD	74	77	3	11	Typical AD	0/12	Abnl	Nl	Nl	Nl	Nl
10	AD	47	54	7	NA	Typical AD	0/12	Abnl	Abnl	Abnl	Nl	Nl
11	AD	72	79	7	27	Slow course	0/12	Nl	Nl	Nl	Nl	Nl
12	AD	68	71	3	0	Typical AD	1/11	Abnl	Abnl	Abnl	Nl	Abnl
13	AD	61	68	7	2	Aphasia	4/8	Abnl	Nl	Abnl	Nl	Nl
14	AD	55	57	2	24	Parkinsonism	0/12	Abnl	Abnl	Nl	Nl	Nl
15	AD	46	51	5	15	Typical AD	0/12	Abnl	Abnl	Nl	Nl	Nl
16	AD	74	76	2	23	Typical AD	0/12	Abnl	Abnl	Nl	Nl	Nl
17	AD	33	34	1	0	Typical AD	0/12	Nl	Abnl	Nl	Nl	Nl
18	AD	49	64	15	3	Typical AD	0/12	Abnl	Abnl	Abnl	Nl	Nl
19	AD	54	57	3	NA	CBD	0/12	Abnl	Abnl	Nl	Nl	Nl
20	AD	65	71	6	19	Visuospatial deficits	0/12	Abnl	Abnl	Nl	Nl	Abnl
21	AD	64	66	2	24	Typical AD	0/12	Abnl	Nl	Nl	Nl	Nl
22	AD	57	61	4	5	Typical AD	0/12	Abnl	Abnl	Abnl	Nl	Nl
23	AD	62	71	9	5	Typical AD	0/12	Abnl	Nl	Nl	Nl	Nl
24	AD	58	68	10	1	Aphasia	0/12	Abnl	Abnl	Abnl	Abnl	Abnl
25	AD	64	68	4	20	Aphasia	0/12	Abnl	Abnl	Nl	Nl	Nl
26	AD	69	77	8	20	Slow course	0/12	Abnl	Abnl	Nl	Nl	Nl
27	AD	65	68	3	22	Typical AD	9/3	Abnl	Nl	Abnl	Abnl	Nl

Case #	Pathologic diagnosis	Age at onset	Age at PET	Symptom duration at PET	MMSE at PET	Clinical syndrome and prominent features	Scan Interpretation 12 raters FTLD/AD	Temproparietal	Posterior Cingulate	Frontal	Anterior Cingulate	Anterior Temporal
28	AD	58	61	3	19	Typical AD	0/12	Abnl	Abnl	Abnl	Nl	Nl
29	AD	58	61	3	12	Visuospatial deficits	0/12	Abnl	Abnl	Nl	Nl	Nl
30	AD	69	75	6	13	Typical AD	0/12	Abnl	Abnl	Nl	Nl	Abnl
31	AD	68	73	5	20	Typical AD	0/12	Abnl	Nl	Nl	Nl	Nl
32	FTLD (Mesocorticolimbic degeneration)	74	81	7	18	Typical AD	4/8	Abnl	Abnl	Abnl	Nl	Abnl
33	FTLD (DLDH)	58	61	3	NA	Aphasia	12/0	Nl	Nl	Nl	Nl	Abnl
34	FTLD (Pick's disease)	60	63	3	20	Aphasia	12/0	Nl	Nl	Abnl	Abnl	Abnl
35	FTLD (Progressive subcortical gliosis)	58	59	1	NA	PSP	11/1	Nl	Nl	Abnl	Nl	Nl
36	FTLD (Pick's disease)	60	62	2	24	Behavior	12/0	Nl	Nl	Abnl	Abnl	Abnl
37	FTLD (DLDH)	59	64	5	23	Behavior and aphasia	8/4	Abnl	Nl	Nl	Nl	Abnl
38	FTLD (DLDH)	58	65	7	0	Behavior	4/8	Abnl	Abnl	Nl	Abnl	Abnl
39	FTLD (DLDH)	57	64	7	NA	Typical AD	1/11	Abnl	Abnl	Nl	Nl	Abnl
40	FTLD (DLDH)	66	69	3	0	PSP	12/0	Abnl	Nl	Abnl	Abnl	Abnl
41	FTLD (Pick's disease)	60	61	1	24	Behavior	12/0	Nl	Nl	Abnl	Abnl	Abnl
42	FTLD (CBD)	65	67	2	14	Behavior and aphasia	12/0	Nl	Nl	Abnl	Abnl	Nl
43	FTLD (FTDP-17T)	54	64	10	9	Behavior	12/0	Nl	Nl	Abnl	Abnl	Abnl
44	FTLD (Pick's disease)	63	69	6	23	Behavior and aphasia	9/3	Abnl	Nl	Nl	Abnl	Abnl
45	FTLD (CBD)	59	69	10	NA	Behavior	7/5	Abnl	Abnl	Abnl	Abnl	Nl

AD: Alzheimer's Disease; CBD: Corticobasal degeneration; DLDH: Dementia lacking distinctive hystology; FTDP-17T: Frontotemporal dementia with parkinsonism associated with a chromosome 17 tau mutation; FTLD: Frontotemporal lobar degeneration; MMSE: Mini Mental State Examination; PSP: Progressive supranuclear palsy

The last 5 columns show the regional metabolic data summarized as either normal (Nl) abnormal (Abnl). Abnl was designated if ≥4 of the 6 raters judged the region to be hypometabolic.

Table 2

Interrater Reliability by Region

Cortical region	Right	Left
Frontal	0.59	0.6
Temporoparietal	0.73	0.68
Anterior temporal	0.47	0.36
Anterior cingulate	0.47	0.48
Posterior cingulate	0.61	0.56

Kappa statistics calculated for all possible pairs of raters

Table 3

Association of Hypometabolism in Typical AD regions with Pathological Diagnosis

Cortical region	AD (n=31)	FTLD (n=14)	*p*	OR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	+LR
Temporoparietal	94% (29)	50% (7)	0.003	14.5 (2.5 – 86)	93.6% (79 – 99)	50% (23 – 77)	1.87
Posterior cingulate	74 (23)	29 (4)	0.01	7.19 (1.8 – 30)	74.2 (55 – 88)	71.4 (42 – 92)	2.6

OR: Odds Ratio for a diagnosis of AD

+LR: Positive likelihood ratio for a diagnosis of AD

Table 4

Association of Hypometabolism in Typical FTLD regions with Pathological Diagnosis

Cortical region	AD (n=31)	FTLD (n=14)	*p*	OR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	+LR
Frontal	35% (11)	64% (9)	0.14	3.27 (0.88 – 12)	64.3% (35 – 87)	64.5% (45 – 81)	1.82
Anterior cingulate	6 (2)	64 (9)	< 0.001	26.1 (4.3 – 158)	64.3 (35 – 87)	93.6% (79 – 99)	9.96
Anterior temporal	19 (6)	79 (11)	<0.001	15.3 (3.2 – 73)	78.6 (49 – 95)	80.7% (63 – 93)	4.06

OR: Odds Ratio for a diagnosis of FTLD

+LR: positive likelihood ratio for a diagnosis of FTLD

Table 5

Association of Anterior Cingulate and Temporoparietal Hypometabolism with FTLD in the Subset of Scans with Temporoparietal Hypometabolism

Cortical Regions	AD (n=29)	FTLD (n=7)	*p*	OR for FTLD	Sensitivity	Specificity	+LR
Temporoparietal + anterior cingulate	7.4% (2)	57% (4)	0.008	18.0 (2.3 – 143)	57% (18 – 90)	93% (77-99)	8.29
Temporoparietal + anterior temporal	20.7 (6)	85.7 (6)	0.016	7.67 (1.5 – 40)	67 (30 – 93)	79 (60 – 92)	3.22

OR: Odds Ratio for a diagnosis of FTLD

+LR: Positive likelihood Ratio for a diagnosis of FTLD

Table 6

Association of Regional Hypometabolism with Non-unanimous FDG-PET Scan Interpretation in subjects with FTLD

Cortical Region with Hypometabolism	Non-unanimous (7)	Unanimous (7)	*p-value*	OR (95% CI)
Temporoparietal	86% (6)	14% (1)	0.03	36.0 (1.8 – 719)
Posterior cingulate	57 (4)	0	0.07	19.3 (0.800 – 467)
Frontal	43 (3)	86 (6)	0.27	0.125 (0.009 – 1.67)
Anterior Cingulate	43 (3)	86 (6)	0.27	0.125 (0.009 – 1.67)
Anterior temporal	71 (5)	86 (6)	0.60	0.417 (0.030 – 6.07)