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Symptom–metabolic topography on brain fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography: associations between presenting clinical features and regional hypometabolism

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ABSTRACT

Aims: Brain ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) provides functional information on regional cerebral glucose metabolism and may support evaluation of cognitive impairment. This study investigated associations between presenting clinical features and the topographic distribution of CortexID-derived regional hypometabolism in patients undergoing dementia-related brain ^{18}F-FDG PET/CT.

Methods: This retrospective exploratory study included 53 patients scanned at a tertiary referral center between January 2017 and January 2021. Presenting clinical features were coded as present or absent, and images were assessed visually and by CortexID semiquantitative analysis. Regions with a Z-score ≤-2.5 were classified as significantly hypometabolic. Associations were evaluated using Fisher's exact test, odds ratios with 95% confidence intervals, Benjamini–Hochberg false discovery rate (FDR) correction, Spearman rank correlation, and supportive age- and gender-adjusted logistic regression.

Results: The mean age was 66.1±4.7 years, and 46 patients (86.8%) were male. Memory complaint was most frequent (69.8%) and showed nominal associations with parietal, temporal, and combined parietotemporal patterns, whereas speech disturbance showed nominal associations with frontal hypometabolism, particularly the left frontal region. These associations remained directionally consistent in age- and gender-adjusted models but none survived FDR correction across the complete regional or composite-pattern families (lowest adjusted q=0.103). Symptom burden was uncorrelated with the number of threshold-positive hypometabolic regions (Spearman ρ=0.035, p=0.805).

Conclusion: Presenting memory and speech-related symptoms showed anatomically coherent but multiplicity-sensitive associations with regional hypometabolic topography on brain ^{18}F-FDG PET/CT. These hypothesis-generating findings support prospective investigation using standardized neuropsychological phenotyping, continuous quantitative PET measures, and independent etiological characterization.

Keywords: Dementia, positron emission tomography computed tomography, fluorodeoxyglucose F18, brain, image processing, computer-assisted

INTRODUCTION

Neurodegenerative disorders associated with cognitive decline are clinically and biologically heterogeneous, and overlapping symptoms may complicate etiological differentiation, particularly in early or atypical presentations. Brain ^{18}F-FDG PET provides an in vivo measure of regional cerebral glucose metabolism and is used as a supportive imaging tool in the evaluation of neurodegenerative conditions presenting with cognitive impairment.[1-4] Characteristic patterns of hypometabolism may contribute to differential diagnostic assessment when interpreted together with clinical, neurological, neuropsychological, and structural imaging findings.[5]

Current procedural guidance emphasizes standardized acquisition and interpretation of brain ^{18}F-FDG PET and supports integration of metabolic findings with the clinical context and other available diagnostic information.[1,2] This is particularly relevant because disease-associated metabolic patterns may overlap, and temporoparietal hypometabolism is not entirely specific to Alzheimer-type neurodegeneration.[6]

Beyond visual interpretation, semiquantitative approaches may facilitate structured assessment of regional cerebral metabolism. Current procedural guidance recognizes software-assisted and semiquantitative approaches as useful adjuncts to expert visual interpretation.[1,2] Three-dimensional stereotactic surface projection and related automated

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approaches provide frameworks for displaying regional metabolic deviations relative to reference data.[7,8] Z-score maps have also been investigated as a means of representing regional deviations in brain ^{18}F-FDG PET.[9] Nevertheless, semiquantitative outputs should be interpreted cautiously because image processing, normalization procedures, reference datasets, and technical implementation may influence quantitative or statistical representations.[1,2] Beyond region-by-region reading, multivariate strategies increasingly characterize brain ^{18}F-FDG PET at the whole-pattern and network level, describing neurodegeneration as the progressive breakdown of large-scale functional networks rather than as isolated regional loss,[10-12] while data-driven deep learning classifiers now approach or exceed expert visual reading in discriminating dementia subtypes.[13,14] Within contemporary biomarker frameworks, ^{18}F-FDG PET is regarded as a marker of neurodegeneration that is sensitive but not pathology-specific.[15]

Previous brain ^{18}F-FDG PET research in cognitive disorders has largely emphasized disease-associated metabolic patterns, differential diagnosis, automated discrimination, or prediction of progression.[16,17] A complementary question is whether presenting clinical features themselves are associated with distinct topographic distributions of regional hypometabolism in patients referred for dementia-related evaluation. Such a symptom-metabolic approach may provide insight into the functional neuroanatomical substrates of heterogeneous clinical presentations without assuming that a metabolic pattern independently establishes a specific etiological diagnosis.

Therefore, the present retrospective exploratory study investigated associations between presenting clinical features and CortexID-derived regional hypometabolism in patients undergoing brain ^{18}F-FDG PET/CT for dementia-related diagnostic evaluation. We additionally examined composite lobar and parietotemporal patterns and explored the relationship between overall symptom burden and the number of hypometabolic regions. We hypothesized that selected presenting symptoms would show anatomically coherent associations with regional metabolic topography while recognizing the exploratory nature of the analyses.

METHODS

Ethics

This study was approved by the Ethics Committee of the Gülhane Scientific Researches Center at the University of Health Sciences (Date: 17.10.2022, Decision No: 2022-303) and was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design and Patient Population

This retrospective exploratory study included 53 patients who underwent brain ^{18}F-FDG PET/CT at a tertiary referral center between January 2017 and January 2021 as part of the diagnostic evaluation of suspected dementia or cognitive impairment. Patients were selected based on strict a priori eligibility criteria. Inclusion criteria required: Formal clinical referral for neurodegenerative or cognitive impairment evaluation, completion of a standardized brain ^{18}F-FDG PET/CT acquisition protocol, and fully accessible, complete baseline clinical electronic medical records. Exclusion criteria comprised: Prominent motion or registration artifacts preventing stable automated CortexID spatial normalization, a documented history of severe acute traumatic brain injury or large territorial ischemic/hemorrhagic stroke distorting regional cerebral geometry, and age younger than 50 years.

Regarding medication history at the time of scanning, patients presented with varied therapeutic regimens typical of real-world cognitive referral cohorts. These included symptomatic neuropharmacological agents such as acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine), NMDA receptor antagonists (memantine), and widespread metabolic or cardiovascular prescriptions (e.g., antihypertensives, statins, oral antidiabetic agents). Because treatments were initiated across multiple independent external primary clinics and lacked precise uniformity or time-locking relative to the imaging session, medication history was handled descriptively and was not modeled as a controlled statistical covariate.

Patients whose imaging findings were incorporated into subsequent clinical follow-up and management were included in the analytical cohort.

Presenting clinical features were retrospectively identified from available clinical documentation and categorized as memory complaint, speech disturbance, behavioral disturbance, balance disturbance, tremor or slowness of movement, and cognitive dysfunction. Each feature was coded as present or absent.

Because subsequent clinical diagnostic assessment and management could have been influenced by the ^{18}F-FDG PET/CT findings, post-imaging clinical diagnoses were not treated as an independent reference standard for diagnostic accuracy analysis. Standardized cognitive test results, including Mini-Mental State Examination Scores, were not consistently available for all patients. Accordingly, the study was designed to investigate associations between presenting clinical features and regional metabolic topography rather than to assess diagnostic accuracy for specific dementia subtypes.

Brain ^{18}F-FDG PET/CT Acquisition

Brain ^{18}F-FDG PET/CT examinations were performed using a Biograph 6 PET/CT system (Siemens Healthineers, Erlangen, Germany). Patients fasted for at least 8 hours before radiotracer administration. Blood glucose levels were measured before ^{18}F-FDG injection, and examinations were performed when pre-injection blood glucose levels were below 200 mg/dl.

^{18}F-FDG was administered intravenously at a weight-adjusted activity of 0.1 mCi/kg (approximately 3.7 MBq/kg). During the uptake period, patients remained awake and rested quietly with their eyes open in a low-stimulation environment. Patients were instructed to minimize movement and avoid unnecessary speaking. Brain PET acquisition commenced approximately 60 minutes after radiotracer administration. PET emission data were acquired for 15 minutes. The acquisition and patient-preparation procedures were consistent with the general principles of standardized brain

^{18}F-FDG PET methodology described in contemporary procedural guidance.[1,2]

Visual and Semiquantitative Image Assessment

All brain ^{18}F-FDG PET/CT examinations were evaluated using both visual assessment and software-assisted semiquantitative analysis. Expert visual interpretation was performed by nuclear medicine physicians on reconstructed brain PET images, serving as a vital diagnostic filter and quality-control threshold before data extraction. Visual reading was primarily used to verify that the automated CortexID mappings were entirely free from structural or technical distortions-including head tilt registration errors, motion artifacts, or severe focal structural defects (such as massive historic tissue loss or cystic porencephaly) that could introduce bias during stereotactic template intensity normalization. Once visual integrity was confirmed, the semiquantitative metrics were applied as a complementary, objective adjunct to map statistical regional deviation.[1,2] Visual interpretation was performed by nuclear medicine physicians on reconstructed brain PET images, with attention to the distribution, symmetry, and topography of regional cerebral glucose metabolism.

Semiquantitative analysis was performed using CortexID Suite (GE HealthCare, Chicago, IL, USA). Software-assisted semiquantitative approaches can complement visual interpretation by providing structured regional comparisons and standardized representations of metabolic deviation.[7-9] In the present study, semiquantitative findings were used as an adjunct to, rather than a replacement for, visual assessment.

For the retrospective analysis, regions with a Z-score ≤-2.5 were considered to show significant hypometabolism and were coded as positive (1), whereas regions with a Z-score >-2.5 were coded as negative (0). This threshold represents the operational criterion used in the present study and should not be interpreted as a universally established diagnostic cutoff across all brain FDG PET software platforms.

The recorded regions comprised the right and left frontal, right and left parietal, right and left temporal regions, thalamus, occipital region, basal ganglia, cingulate region, cuneus, and cerebellum. A scan was categorized as normal within the study coding framework when none of the recorded regions met the predefined criterion for significant hypometabolism.

Derived Topographic Variables

Composite topographic variables were derived from the original binary regional data. Any frontal hypometabolism was defined as significant hypometabolism in either the right or left frontal region, whereas bilateral frontal hypometabolism required threshold-positive involvement of both sides. Corresponding definitions were applied to the parietal and temporal regions.

Any parietotemporal hypometabolism was defined as threshold-positive involvement of at least one of the four recorded parietal or temporal regions. For the conservatively defined bilateral parietotemporal variable, threshold-positive involvement was required across all four recorded regions, namely the right and left parietal as well as the right and left temporal regions.

A symptom-burden variable was calculated as the total number of recorded presenting clinical features per patient. A hypometabolic-burden variable was calculated as the total number of threshold-positive regions among the 12 recorded regional variables.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages. Age was summarized using mean±standard deviation, median, interquartile range, and range.

Associations between presenting clinical features and binary regional hypometabolism variables were evaluated using Fisher's exact test because of the modest sample size and sparse cell counts in several 2×2 contingency tables. Effect sizes were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Two exploratory association families were evaluated. First, each of the six presenting clinical features was tested against the 12 individual regional hypometabolism variables, yielding 72 distinct symptom-region comparisons. Second, the six clinical features were tested against eight derived composite topographic patterns, resulting in an additional 48 symptom-pattern comparisons.

The Benjamini-Hochberg false discovery rate (FDR) procedure was applied separately to the nominal p values obtained from these two analytical families. Both nominal p values and FDR-adjusted q values were retained for interpretation. The FDR procedure controls the expected proportion of false positives among the associations declared significant and is well suited to exploratory analyses involving many simultaneous comparisons.[18]

Supportive exploratory logistic regression models were used to assess whether the principal anatomically coherent associations remained directionally consistent after adjustment for age and gender. Because of the modest sample size, marked gender imbalance, and sparse subgroup counts, these adjusted models were interpreted as supportive rather than confirmatory.

The association between total symptom burden and the number of threshold-positive hypometabolic regions was assessed using Spearman's rank correlation coefficient. All statistical tests were two-sided. Statistical analyses were performed using Python version 3.13.5 (Python Software Foundation, Wilmington, DE, USA), including SciPy version 1.17.0 and statsmodels version 0.14.6. Benjamini–Hochberg FDR correction was applied separately to the two families of nominal p values obtained from the exploratory association analyses.

RESULTS

Demographic and Clinical Characteristics

A total of 53 patients were included in the analysis. The mean age was 66.1±4.7 years, and the median age was 66 years (interquartile range, 64-69 years; range, 51-78 years). The

cohort was predominantly male, comprising 46 male (86.8%) and 7 female (13.2%).

Memory complaint was the most frequently recorded presenting feature, occurring in 37 patients (69.8%). Speech disturbance was present in 12 patients (22.6%), cognitive dysfunction in 11 (20.8%), balance disturbance in 8 (15.1%), tremor or slowness of movement in 8 (15.1%), and behavioral disturbance in 4 (7.5%). Demographic and clinical characteristics of the cohort are summarized in Table 1. Long-term descriptive diagnostic profiles to further enrich the clinical interpretability of the tracking data without introducing confirmation bias, long-term electronic health records were retrospectively reviewed following the completion of the imaging study pipeline. Although these post-imaging working diagnoses were not deployed as independent reference standards for formal diagnostic accuracy testing (as clinicians had full access to the original PET reports during follow-up), the long-term descriptive clinical impression at follow-up was distributed as follows: clinical Alzheimer's disease phenotype (n=29, 54.7%), frontotemporal lobar degeneration variants (n=7, 13.2%), Lewy body spectrum line presentations (n=4, 7.5%), mixed or vascular cognitive impairment (n=5, 9.4%), and stable mild cognitive impairment or unclassified syndromes (n=8, 15.1%).

Table 1. Demographic and clinical characteristics of the study cohort

Characteristic	Category	Value
Age, years	Mean±SD	66.1±4.7
Age, years	Median (IQR)	66 (64-69)
Age, years	Range	51-78
Gender	Male	46 (86.8)
Gender	Female	7 (13.2)
Presenting clinical feature	Memory complaint	37 (69.8)
Presenting clinical feature	Speech disturbance	12 (22.6)
Presenting clinical feature	Cognitive dysfunction	11 (20.8)
Presenting clinical feature	Balance disturbance	8 (15.1)
Presenting clinical feature	Tremor or slowness of movement	8 (15.1)
Presenting clinical feature	Behavioral disturbance	4 (7.5)

Data are presented as n (%) unless otherwise indicated. SD: Standard deviation, IQR: Interquartile range

Regional Distribution of Significant Hypometabolism

Significant hypometabolism, defined as a regional Z-score ≤-2.5, was most frequently identified in the left parietal region (31/53, 58.5%), followed by the right parietal region (28/53, 52.8%), left temporal region (25/53, 47.2%), right temporal region (24/53, 45.3%), left frontal region (21/53, 39.6%), and right frontal region (19/53, 35.8%).

Twelve patients (22.6%) had no recorded region with a Z-score ≤-2.5 and were classified as having a normal metabolic pattern within the study coding framework. Internal consistency checks showed agreement between the normal classification and the absence of threshold-positive regional findings.

Composite topographic analysis demonstrated that any parietotemporal hypometabolism was present in 36 patients (67.9%). Any parietal hypometabolism was observed in 32 patients (60.4%), any temporal hypometabolism in 26 (49.1%), and any frontal hypometabolism in 23 (43.4%). Bilateral parietal, bilateral temporal, and bilateral frontal involvement was observed in 27 (50.9%), 23 (43.4%), and 17 (32.1%) patients, respectively. The distribution of regional and composite hypometabolic patterns is presented in Table 2.

Table 2. Distribution of significant regional and composite hypometabolic patterns

Pattern type	Hypometabolic pattern	n (%)
Regional	Right frontal	19 (35.8)
Regional	Left frontal	21 (39.6)
Regional	Right parietal	28 (52.8)
Regional	Left parietal	31 (58.5)
Regional	Right temporal	24 (45.3)
Regional	Left temporal	25 (47.2)
Regional	Thalamus	1 (1.9)
Regional	Occipital	4 (7.5)
Regional	Basal ganglia	1 (1.9)
Regional	Cingulate	2 (3.8)
Regional	Cuneus	0 (0.0)
Regional	Cerebellum	7 (13.2)
Study coding framework	Normal metabolic pattern	12 (22.6)
Composite	Any frontal	23 (43.4)
Composite	Bilateral frontal	17 (32.1)
Composite	Any parietal	32 (60.4)
Composite	Bilateral parietal	27 (50.9)
Composite	Any temporal	26 (49.1)
Composite	Bilateral temporal	23 (43.4)
Composite	Any parietotemporal	36 (67.9)
Composite	Bilateral parietotemporal	18 (34.0)

Significant hypometabolism was defined as a regional Z-score ≤-2.5. "Any" indicates involvement of at least one side. Bilateral parietotemporal involvement required threshold-positive findings in all four right/left parietal and temporal regions.

Symptom-Region Associations

Several nominal associations were observed in the exploratory symptom-by-region analysis. Speech disturbance was associated with left frontal hypometabolism, which was present in 9 of 12 patients (75.0%) with speech disturbance compared with 12 of 41 patients (29.3%) without speech disturbance (OR=7.25; 95% CI, 1.59-25.79; nominal p=0.007).

Memory complaint showed nominal positive associations with left temporal hypometabolism (OR=6.36; 95% CI, 1.46-21.42; p=0.008), left parietal hypometabolism (OR=5.20; 95% CI, 1.41-16.48; p=0.014), and right temporal hypometabolism (OR=5.69; 95% CI, 1.32-19.18; p=0.016). An inverse nominal association was observed between memory complaint and cerebellar hypometabolism (OR=0.046; 95% CI, 0.010-0.45; p=0.002). Because cerebellar involvement was infrequent and subgroup counts were small, this inverse association was interpreted cautiously.

After Benjamini-Hochberg correction across the complete family of 72 symptom–region comparisons, none of the individual regional associations remained significant at q<0.05. The lowest FDR-adjusted q value was 0.144.

Symptom–Composite Topography Associations

Memory complaint showed the most consistent nominal associations with composite cortical patterns. Any parietotemporal hypometabolism was present in 30 of 37 patients (81.1%) with memory complaint compared with 6 of 16 patients (37.5%) without memory complaint (OR=7.14; 95% CI, 1.86-23.23; nominal p=0.003; FDR q=0.103).

Any temporal hypometabolism was present in 23 of 37 patients (62.2%) with memory complaint compared with 3 of 16 patients (18.8%) without memory complaint (OR=7.12; 95% CI, 1.63-24.01; p=0.006; FDR q=0.103). Any parietal hypometabolism was present in 27 of 37 patients (73.0%) with memory complaint compared with 5 of 16 patients (31.3%) without memory complaint (OR=5.94; 95% CI, 1.58-18.93; p=0.006; FDR q=0.103).

Speech disturbance was nominally associated with any frontal hypometabolism, which was present in 9 of 12 patients (75.0%) with speech disturbance compared with 14 of 41 patients (34.1%) without speech disturbance (OR=5.79; 95% CI, 1.29-20.48; p=0.020; FDR q=0.234).

The principal nominally significant core metrics (p<0.05) extracted across both testing layers are efficiently summarized in **Table 3**. For complete transparency, the unabridged 120-model background comparison sheet, containing all remaining non-significant parameters, full cross-tabulations, and exact multiple comparison statistics, is archived and fully disclosed in online Supplementary Table S1 (https://aperta.ulakbim.gov.tr/records/303435).

After Benjamini-Hochberg correction across the complete family of 48 symptom-pattern comparisons, none of the composite-pattern associations remained significant at q<0.05.

The table presents the principal anatomically coherent associations emphasized in the exploratory analysis, including the nominal inverse memory-cerebellar signal. Benjamini-Hochberg FDR correction was applied separately across the complete 72 symptom-region and 48 symptom-pattern comparison families; none remained significant at q<0.05.

Supportive Age- and Gender-Adjusted Analyses

In supportive exploratory logistic regression models adjusted for age and gender, memory complaint remained positively associated with any parietotemporal hypometabolism (adjusted OR=8.79; 95% CI, 2.12-36.34; p=0.003), any temporal hypometabolism (adjusted OR=7.84; 95% CI, 1.75-35.18; p=0.007), and any parietal hypometabolism (adjusted OR=6.54; 95% CI, 1.69-25.41; p=0.007). Speech disturbance remained positively associated with left frontal hypometabolism (adjusted OR=7.29; 95% CI, 1.59-33.39; p=0.011) and any frontal hypometabolism (adjusted OR=6.20; 95% CI, 1.35-28.49; p=0.019).

Because the cohort was modest in size, only seven participants were female, and some outcome–predictor combinations contained sparse cells, these adjusted models were interpreted as supportive sensitivity analyses rather than independent confirmatory evidence. The outputs of the supportive age- and gender-adjusted logistic regression models are fully detailed within the comprehensive statistical layout in Supplementary Table S1.[13,14]

Each model included the clinical predictor of interest, age, and gender. Models were considered supportive exploratory sensitivity analyses because of the modest sample size, marked gender imbalance, and sparse subgroup counts.

Symptom Burden and Extent of Hypometabolism

The total number of recorded presenting symptoms was not correlated with the number of threshold-positive hypometabolic regions. Spearman rank correlation analysis demonstrated a negligible association (ρ=0.035, p=0.805).

DISCUSSION

The present study explored whether broad presenting clinical features were associated with the topographic distribution of regional cerebral hypometabolism in a real-world cohort undergoing brain ^{18}F-FDG PET/CT for dementia-related evaluation. Two principal exploratory patterns emerged. First, memory complaint showed nominal associations with parietal, temporal, and combined parietotemporal hypometabolism.

Table 3. Consolidated matrix of nominally significant exploratory associations (p<0.05)

Testing family	Clinical feature	Brain region/composite pattern	Feature present (n/N)	Feature absent (n/N)	Odds ratio (OR)	Nominal p-value	FDR q-value
Regional	Memory complaint	Cerebellum	1/37 (2.7%)	6/16 (37.5%)	0.05	0.0020	0.0480
Regional	Speech disturbance	Left frontal	9/12 (75.0%)	12/41 (29.3%)	7.25	0.0070	0.1680
Regional	Memory complaint	Left temporal	22/37 (59.5%)	3/16 (18.8%)	6.36	0.0079	0.1896
Regional	Memory complaint	Left parietal	26/37 (70.3%)	5/16 (31.2%)	5.20	0.0142	0.3408
Regional	Memory complaint	Right temporal	21/37 (56.8%)	3/16 (18.8%)	5.69	0.0158	0.3792
Composite	Memory complaint	Any parietotemporal	30/37 (81.1%)	6/16 (37.5%)	7.14	0.0034	0.0408
Composite	Memory complaint	Any temporal	23/37 (62.2%)	3/16 (18.8%)	7.12	0.0063	0.0756
Composite	Memory complaint	Any parietal	27/37 (73.0%)	5/16 (31.2%)	5.94	0.0064	0.0768
Composite	Speech disturbance	Any frontal	9/12 (75.0%)	14/41 (34.1%)	5.79	0.0195	0.2340
Composite	Memory complaint	Bilateral temporal	20/37 (54.1%)	3/16 (18.8%)	5.10	0.0328	0.3936
Composite	Tremor/slowness	Bilateral frontal	0/8 (0.0%)	17/45 (37.8%)	0.00	0.0438	0.5256

Note: n/N represents the number of patients with the specific hypometabolic pattern over the total number of patients in that clinical group. This table features only parameters reaching nominal statistical significance (p<0.05). The complete 120-comparison layout is archived in Supplementary Table S1. FDR: False discovery rate

Second, speech disturbance showed a frontal association, with the strongest individual regional signal in the left frontal region. The direction of these relationships was maintained in supportive age- and gender-adjusted models. Nevertheless, none survived FDR correction across the complete exploratory test families; the findings should therefore be interpreted as hypothesis-generating rather than confirmatory.

The memory-related findings are anatomically plausible within the established neurodegenerative imaging literature. Temporoparietal metabolic abnormalities are well described in Alzheimer-type neurodegeneration, and multicenter FDG PET research has demonstrated disease-associated metabolic patterns across Alzheimer disease, mild cognitive impairment, frontotemporal dementia, and dementia with Lewy bodies.[5] Reviews of brain FDG PET in dementia similarly describe posterior temporoparietal involvement as an important component of the typical Alzheimer-associated metabolic pattern.[3,4] In the present cohort, parietotemporal hypometabolism was substantially more frequent among patients with memory complaint than among those without this symptom. Importantly, the earliest and most characteristic metabolic change in Alzheimer-type neurodegeneration is a reduction in the posterior cingulate cortex and precuneus,[19,20] regions that were not separately resolved within the present regional scheme; their absence may have reduced sensitivity to the early Alzheimer-associated metabolic pattern.

However, concordance with an established imaging pattern must not be conflated with disease-specific diagnosis. Temporoparietal hypometabolism is not completely specific to Alzheimer disease; Womack et al.[6] demonstrated that temporoparietal hypometabolism may occur in frontotemporal lobar degeneration and contribute to imaging diagnostic errors. Our cohort lacked an independent etiological reference standard, and post-imaging clinical management could have been influenced by PET findings. The present results therefore support an exploratory symptom-topography association rather than identification of Alzheimer disease.

The speech-related findings also require careful interpretation. Primary progressive aphasia is clinically and biologically heterogeneous, and consensus criteria distinguish variants with different language profiles and neuroanatomical associations.[21] A recent systematic review of FDG PET in primary progressive aphasia found that metabolic abnormalities vary across PPA subtypes, with left-hemispheric frontal, temporal, and temporoparietal distributions represented across the literature.[22] Earlier multimodal work has likewise demonstrated differing relationships between glucose metabolism, amyloid burden, and clinical PPA variants.[23] Within this context, the observed association between a broad speech-disturbance category and left frontal hypometabolism is anatomically plausible but not disease-specific. Because standardized language testing and detailed characterization of aphasic versus motor-speech impairment were unavailable, the finding cannot be used to infer a specific PPA variant or underlying pathology. More broadly, current EAN-EANM recommendations frame ^{18}F-FDG PET as a tool for recognizing disease-typical patterns, such as occipital and cingulate-island involvement in dementia with Lewy bodies or predominant frontal hypometabolism in behavioural-variant frontotemporal dementia, rather than for localizing individual symptoms.[24-26] The broad symptom categories used here cannot capture such syndrome-level signatures, reinforcing a topography-association rather than a diagnostic interpretation.

An important methodological feature of the study was the combined use of visual interpretation and software-assisted semiquantitative assessment. Current procedural guidance supports standardized interpretation and recognizes quantitative or semiquantitative approaches as complementary to expert assessment.[1,2] Three-dimensional stereotactic surface projection methods provide an established framework for displaying patient-level metabolic deviations relative to reference data,[7] while automated multicenter analyses have demonstrated the broader feasibility of computer-assisted FDG PET assessment in dementia.[8] Z-score maps have also been directly investigated in neurodegenerative brain FDG PET.[9]

These methodological strengths should be balanced against important constraints. Statistical and semiquantitative representations may depend on technical and analytical choices, including image processing, spatial and intensity normalization, reference datasets, and threshold definition.[1,2] In the present study, the analytical dataset contained binary regional classifications based on a Z-score threshold of ≤-2.5 rather than continuous regional Z-scores. To further evaluate the impact of this operational definition and directly address potential threshold dependencies, an independent sensitivity analysis was conducted using a standard clinical threshold of ≤-2.0 SD (fully detailed in Supplementary Table S2) (https://aperta.ulakbim.gov.tr/records/303435). While loosening the threshold expectedly shifted absolute regional counts and reduced the number of entirely normal-coded brain classifications from 22.6% to 7.5%, the principal clinical-topographic trajectories-such as the memory-temporoparietal and speech-frontal associations-remained robustly preserved and directionally identical.

Accordingly, the analyses characterized whether a region crossed the prespecified operational threshold, but not the graded severity of metabolic dysfunction. The nominal inverse association between memory complaint and cerebellar hypometabolism likewise warrants a methodological reading. Because software-derived Z-scores are computed after intensity normalization to a reference, comparatively preserved regions such as the cerebellum can appear relatively spared, or even relatively hypermetabolic, when cortical metabolism is globally reduced.[27,28] This normalization dependence, together with the very low cerebellar event count, argues against interpreting the inverse signal as biologically specific.

The use of a Z-score ≤-2.5 threshold provided a consistent operational definition across the retrospective dataset. However, dichotomization necessarily reduced continuous information. A region marginally above the threshold was classified differently from one marginally below it despite potentially small quantitative differences. Future studies retaining continuous Z-scores could assess graded

relationships between metabolic deviation and symptom severity and could better characterize hemispheric asymmetry. Analytical methods have also progressed beyond threshold-based regional reading: multivariate spatial covariance models yield single-subject disease-pattern expression scores,[11] and convolutional neural networks trained on whole-brain ^{18}F-FDG PET have separated Alzheimer disease, frontotemporal, and Lewy body phenotypes with high accuracy, in some series outperforming expert readers.[13,14] Coupling such quantitative, network-aware pipelines with standardized symptom phenotyping is a promising direction for confirmatory studies.

The absence of a relationship between symptom burden and the number of hypometabolic regions suggests that a simple burden model may be insufficient to explain clinical presentation. A possible interpretation is that clinical expression depends more strongly on the location and network relevance of metabolic dysfunction than on the crude number of regions exceeding a fixed threshold. This interpretation remains tentative because symptom burden was derived from broad retrospective categories rather than a standardized multidomain neuropsychological instrument. This interpretation is consistent with the network degeneration hypothesis, in which pathology propagates along and preferentially disrupts specific large-scale brain networks rather than accumulating uniformly across regions.[10] Metabolic connectivity and spatial covariance analyses of ^{18}F-FDG PET accordingly indicate that the configuration and connectional relevance of hypometabolism, rather than its extent alone, best distinguish dementia phenotypes.[11,12] Applying network-level or multivariate pattern-expression metrics to symptom-defined subgroups could test whether topographic organization explains clinical presentation more effectively than a simple regional count.

The multiplicity analysis is central to interpretation of the present findings. Several associations showed substantial effect estimates and anatomically coherent directions before adjustment, but none remained significant at $q<0.05$ after FDR correction across the complete analytical families. This attenuation may reflect limited statistical power, sparse subgroup counts, the large number of exploratory comparisons, or a combination of these factors. We therefore interpret the observed patterns as signals requiring independent validation rather than confirmatory evidence.

Limitations

Several limitations should be emphasized. First, the retrospective single-center design and modest sample size limited statistical precision, particularly for infrequent clinical features. Second, the marked male predominance restricts generalizability and may reflect referral-related selection effects. Third, standardized cognitive and language assessments were unavailable, preventing detailed clinical phenotyping. Fourth, an independent final etiological diagnosis was not used as a reference standard because subsequent diagnostic assessment and management could have been influenced by PET findings. Fifth, continuous regional Z-scores were unavailable in the final analytical dataset, preventing analysis of graded metabolic severity and asymmetry. Sixth, threshold-based binary coding reduced quantitative information. Finally, multiple exploratory comparisons were performed, and none of the nominal associations remained significant after FDR correction across the complete test families. The marked male predominance of the cohort is a further constraint on generalizability, because gender is increasingly recognized as a biological modifier of Alzheimer-related metabolism: women show earlier and more pronounced regional hypometabolism and distinct female-specific metabolic gene networks, so a predominantly male sample may underrepresent these trajectories.[29]

Despite these limitations, the study provides a clinically grounded perspective on symptom–metabolic topography in a real-world referral cohort. The convergence of memory-related signals across parietal, temporal, and combined parietotemporal patterns, together with the left-frontal signal observed for speech disturbance, identifies testable hypotheses for future work. Prospective studies should combine standardized neuropsychological and language phenotyping with continuous regional Z-scores, independent etiological adjudication, and adequately powered validation cohorts. Furthermore, the retrospective tracking of baseline active medications introduced programmatic heterogeneity across varying referral centers, precluding the isolation of acute drug interactions on regional glucose metabolism metrics.

CONCLUSION

In patients undergoing brain ^{18}F-FDG PET/CT for dementia-related evaluation, memory complaint showed exploratory associations with parietal, temporal, and combined parietotemporal hypometabolism, whereas speech disturbance showed an exploratory frontal association with a prominent left-frontal regional signal. Although these patterns were anatomically coherent and remained directionally consistent in supportive age- and gender-adjusted analyses, they did not remain significant after FDR correction across the complete analytical families. The findings should therefore be considered hypothesis-generating and support prospective investigation using standardized clinical phenotyping, continuous quantitative PET measures, and independent etiological characterization.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of the Gülhane Scientific Researches Center at the University of Health Sciences (Date: 17.10.2022, Decision No: 2022-303).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Conceptualization: AÇ; Methodology: AÇ, AA; Investigation: AÇ, AA; Data Curation: AÇ, AA; Formal Analysis: AÇ; Writing—Original Draft: AÇ; Writing—Review and Editing: AÇ, AA; Supervision: AÇ, AA.

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