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FDG-PET and Neuropsychiatric Symptoms among Cognitively Normal Elderly Persons: The Mayo Clinic Study of Aging

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Abstract. One of the key research agenda of the field of aging is investigation of presymptomatic Alzheimer's disease (AD). Furthermore, abnormalities in brain glucose metabolism (as measured by FDG-PET) have been reported among cognitively normal elderly persons. However, little is known about the association of FDG-PET abnormalities with neuropsychiatric symptoms (NPS) in a population-based setting. Thus, we conducted a cross-sectional study derived from the ongoing population-based Mayo Clinic Study of Aging in order to examine the association between brain glucose metabolism and NPS among cognitively normal (CN) persons aged > 70 years. Participants underwent FDG-PET and completed the Neuropsychiatric Inventory Questionnaire (NPI-Q), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). Cognitive classification was made by an expert consensus panel. We conducted multivariable logistic regression analyses to compute odds ratios (OR) and 95% confidence intervals after adjusting for age, sex, and education. For continuous variables, we used linear regression and Spearman rank-order correlations. Of 668 CN participants (median 78.1 years, 55.4% males), 205 had an abnormal FDG-PET (i.e., standardized uptake value ratio < 1.32 in AD-related regions). Abnormal FDG-PET was associated with depression as measured by NPI-Q (OR = 2.12; 1.23–3.64); the point estimate was further elevated for APOE ε4 carriers (OR = 2.59; 1.00–6.69), though marginally significant. Additionally, we observed a significant association between abnormal FDG-PET and depressive and anxiety symptoms when treated as continuous measures. These findings indicate that NPS, even in community-based samples, can be an important additional tool to the biomarker-based investigation of presymptomatic AD.

Keywords: Agitation, Alzheimer's disease, anxiety, apathy, cognitively normal persons, depression, FDG-PET, neuroimaging, neuropsychiatric symptoms

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INTRODUCTION

Abnormal brain changes precede cognitive outcomes by several years or decades [1–3]. Accordingly, the field of cognitive research is increasingly emphasizing the importance of investigating the presymptomatic phase of Alzheimer's disease (AD) using biomarkers such as fluorodeoxyglucose-positron emission tomography (FDG-PET) [4, 5]. Furthermore, given the extensive and reciprocal neuronal connections between structures that mediate emotion and the epicenter of cognition [6], it is critical to investigate the associations of neuropsychiatric symptoms (NPS) with FDG-PET, a marker of synaptic dysfunction, among cognitively normal participants [7, 8].

We addressed this knowledge gap by utilizing the research setting of the ongoing, population-based Mayo Clinic Study of Aging. We conducted a cross-sectional study to examine the association between brain glucose metabolism as measured by FDG-PET and NPS among cognitively normal participants.

METHODS

Setting and study design

This cross-sectional study was conducted in the setting of the Mayo Clinic Study of Aging (MCSA). Details of the study procedures have been reported elsewhere [9]. Briefly, the MCSA is an ongoing population-based study of normal cognitive aging and mild cognitive impairment (MCI) in Olmsted County, Minnesota. The sample for the current study consisted of 668 cognitively normal (CN) individuals aged 70 years and above on whom FDG-PET, APOE genotyping, and NPS data were available.

The study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center, and informed consent for participation was obtained from every participant.

Cognitive evaluation

Participants underwent three face-to-face evaluations: 1) risk factor ascertainment (including Neuropsychiatric Inventory Questionnaire (NPI-Q [10]) and baseline evaluation (including Clinical Dementia Rating Scale [11]) performed by a nurse or study coordinator; 2) neurological evaluation including a neurological interview, Short Test of Mental Status [12], and neurological examination performed by behavioral neurologists; 3) neuropsychological evaluation of four cognitive domains – memory (delayed recall trials from the Auditory Verbal Learning Test [13] and the Wechsler Memory Scale-Revised [14], Logical Memory and Visual Reproduction subtests); language (Boston Naming Test [15] and category fluency); visuospatial (Wechsler Adult Intelligence Scale-Revised [16], Picture Completion and Block Design subtests); and executive function (Trail Making Test Part B [17] and the Wechsler Adult Intelligence Scale-Revised, Digit Symbol subtest).

All tests were administered by psychometrists who were supervised by neuropsychologists. An expert consensus panel of physicians, neuropsychologists, and nurses or study coordinators reviewed the data and made a diagnosis of normal cognition, MCI, or dementia based on published criteria.

Measurement of neuropsychiatric symptoms (depression, anxiety, agitation, apathy)

NPS were measured using the NPI-Q. The NPI-Q is a shorter version of the Neuropsychiatric Inventory, a validated clinical instrument [10]. We considered the NPI-Q an appropriate screening instrument because it assesses a broad variety of NPS and was also selected by the Uniform Data Set Initiative of the National Institute on Aging [18]. It was administered as a structured interview to an informant, usually the spouse. The NPI-Q is designed to obtain information on 12 emotional behaviors (i.e., agitation, delusion, hallucination, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep, and eating/appetite).

As reported previously [19, 20], delusions, hallucinations, and euphoria are extremely rare events thus no meaningful analyses could be made regarding these symptoms.

Measurement of anxiety and depression using BAI and BDI

Anxiety symptoms were measured using the Beck Anxiety Inventory (BAI) [21]. The BAI is a validated, self-administered questionnaire consisting of 21 items that are assessed over the last week. The severity of each symptom is rated ranging from 0 to 3 with a total score ranging from 0 to 63.

Depressive symptoms were measured using the validated, self-administered Beck Depression

Inventory-II (BDI-II) which is a sensitive instrument in elderly individuals [22]. Similar to the BAI, the BDI-II is an ordinal measure that consists of 21 items that are assessed over the last two weeks and are rated in severity ranging from 0 to 3. Thus, the total scores can range from 0 to 63.

FDG-PET measurement

366-399 MBq of ^{18}FDG was injected intravenously to all study participants followed by an uptake period of 30 min. During this time, the participants were left undisturbed in a darkened room and instructed to rest quietly without activity with their eyes open. Afterwards participants were imaged with their eyes open for an 8-min image acquisition consisting of four 2-min dynamic frames. Also, a CT image was obtained for attenuation correction.

Quantitative image analysis for FDG PET was performed using our in-house fully automated image processing pipeline [23, 24]. Statistics on image voxel values were extracted from automatically labeled cortical regions of interest (ROIs) using an atlas [25] modified in-house. There were 19 regions of interest after combining the left and right regions from the atlas. The meta-region of interest consisted of bilateral angular gyrus, posterior cingulate/precuneus, and inferior temporal cortical regions from both hemispheres and was identified as AD signature ROI elsewhere [26–28]. The ratio of this AD signature ROI and the pons as well as the cerebellar vermis is referred to as the standardized uptake value ratio (SUVR). These two regions of references were chosen because they have preserved glucose metabolism in AD [29]. We defined an abnormal FDG-PET ratio as SUVR less than 1.32 [30, 31].

APOE genotyping

Blood was drawn from the study participants after obtaining informed consent. Then, APOE ε4 genotypes were determined from DNA using a polymerase chain reaction amplification [32]. The laboratory technicians were blinded to other study variables.

Statistical analysis

Categorical analysis

We conducted multivariable logistic regression analyses to examine the association between brain metabolism as measured by FDG-PET and the odds of having NPS (defined as presence or absence of anxiety, depression, apathy, agitation as measured by NPI-Q). We computed odds ratios (OR) and 95% confidence intervals (95% CI) and adjusted for age (continuous variable), sex, and education (continuous variable). OR (95% CI) were used to compare the odds of having NPS between two groups: 205 participants with an abnormal FDG-PET versus 463 participants with a normal FDG-PET. We also conducted a stratified analysis by APOE ε4 carrier status.

Continuous analysis

We calculated linear regression analyses and Spearman rank-order correlations between FDG-PET ratio (as continuous variable) and Beck Anxiety Inventory as well as Beck Depression Inventory (as continuous variables) and adjusted for age, sex, and education. Statistical testing was done at the conventional 2-tailed alpha level of $p < 0.05$. Statistical analyses were performed using SAS System, version 9.3 software (SAS Institute, Cary, NC).

RESULTS

Baseline demographic characteristics

The demographic characteristics of the sample are summarized in Table 1. Two hundred five participants had an abnormal FDG-PET and 463 participants had a normal FDG-PET. The two groups differed significantly in age and sex. However, the comparison of NPS between the two groups was done after adjusting for age, sex, and education.

Categorical analysis of NPS based on NPI-Q

Depression was the most common symptom, affecting 31 (15.2%) of participants with an abnormal FDG-PET and 33 (7.3%) of participants with a normal FDG-PET. Participants with an abnormal FDG-PET were more than twice as likely to have depression as compared to participants with normal FDG-PET (OR = 2.12; 1.23, 3.64). Additionally, the point estimates were elevated for anxiety (OR = 1.61; 0.76-3.42), and agitation (OR = 1.21, 0.38–3.79) but none reached statistical significance. Additional adjustment for history of depression did not alter the results. Details of the findings are displayed in Table 2.

Table 1
Demographic characteristics of study participants

Variable	Abnormal FDG-PET ($N = 205$)	Normal FDG-PET ($N = 463$)	p p
Male Gender, n (%)	125 (61.0)	238 (51.4)	0.023
Age at visit date (years)[a]	80.3 (76.7, 84.1)	77.2 (73.8, 82.0)	<0.001
70–79, n (%)	96 (46.8)	309 (66.7)	
80–95, n (%)	109 (53.2)	154 (33.3)	
Education (years)[a]	14.0 (12.0, 16.0)	14.0 (12.0, 16.0)	0.673
>12 years, n (%)	131 (63.9%)	302 (65.2%)	0.792
APOE ε4+, n (%)[b]	57 (27.8)	112 (24.2)	0.327

[a]Median (interquartile range), [b]4 patients missing APOE ε4 status.

Table 2
NPS and FDG-PET

NPS	Abnormal FDG-PET ($N = 204$) n (%)	Normal FDG-PET ($N = 454$) n (%)	OR (95% CI)
Agitation	5 (2.5)	9 (2.0)	1.21 (0.38–3.79)
Depression	31 (15.2)	33 (7.3)	**2.12 (1.23–3.64)***
Anxiety	13 (6.4)	19 (4.2)	1.61 (0.76–3.42)
Apathy/Indifference	9 (4.4)	20 (4.4)	0.86 (0.37–1.97)

*$p \leq 0.05$. Note: Neuropsychiatric data were missing for 1 participant with an abnormal FDG-PET and 9 participants with a normal FDG-PET. In this analysis, we only included participants in which NPS (agitation, depression, anxiety, and apathy as measured by NPI-Q) were present.

Measurement of depressive and anxiety symptoms on a continuous scale

Even though BDI and BAI are ordinal scales, we treated the data as continuous. FDG-PET ratios were significantly associated with both, BDI score (–0.0036, SE = 0.0012, $p = 0.004$) and BAI score (–0.0033, SE = 0.0015, $p = 0.030$) in a linear regression analysis that was adjusted for age, sex, and education. Similarly, when we calculated Spearman correlations, the correlation between FDG-PET ratio and BDI score ($r = –0.10$, $p = 0.007$) as well as BAI score ($r = –0.11$, $p = 0.007$) was significant.

Categorical analysis of NPS: Stratified by APOE ε4

We conducted a stratified analysis by APOE ε4 genotype (any versus none) among participants with an abnormal FDG-PET for additional understanding of the data. As expected, the point estimates of having NPS were consistently higher for APOE ε4 carriers than APOE ε4 non-carriers with the exception of anxiety. Participants who were APOE ε4 carriers and had an abnormal FDG-PET, had double the odds of having depression, even though the association was marginally significant (OR = 2.59; 1.00–6.69; $p = 0.050$). The point estimate was also elevated though not significant in APOE ε4 non-carriers who had an abnormal FDG-PET (OR = 1.86; 0.97–3.57; $p = 0.063$).

Secondary analysis: Specific regions of interest

We ran additional multiple regression analyses to investigate the association between depression, anxiety and specific regions of interest. We adjusted the models for age, sex, education, depression medication, medical comorbidities, and global cognition. We did not observe any significant associations and the point estimates were very small as expected. However, we observed a tendency of an inverse relationship between the point estimates and the regional glucose uptake, i.e., the higher the depressive or anxiety symptoms, the lower the glucose uptake. Please refer to Table 3.

DISCUSSION

Here we report a population-based cross-sectional study that investigated the association between brain metabolism as measured by FDG-PET and neuropsychiatric symptoms among cognitively normal elderly persons after adjusting for age, sex, and education. The study was driven by our desire to understand whether brain glucose metabolism as measured by FDG-PET was associated with neuropsychiatric symptoms in cognitively normal persons and thereby

Table 3
Depression, anxiety, and regions of interest

ROI	BDI ($N = 655$)	p	BAI ($N = 655$)	p
Anterior Cingulate	–0.0014 (–0.0033, 0.0005)	0.14	–0.0015 (–0.0038, 0.0008)	0.20
Prefrontal	–0.0015 (–0.0040, 0.0011)	0.26	–0.0013 (–0.0044, 0.0018)	0.41
Temporal	–0.0006 (–0.0026, 0.0013)	0.52	–0.0000 (–0.0023, 0.0023)	0.99
Caudate	–0.0015 (–0.0036, 0.006)	0.15	–0.0019 (–0.0044, 0.0006)	0.13
Insula	–0.0011 (–0.0028, 0.0006)	0.21	–0.0009 (–0.0029, 0.0012)	0.40
Medial Temporal	–0.0001 (–0.0013, 0.0011)	0.86	–0.0000 (–0.0014, 0.0014)	1.00
Parietal	–0.0012 (–0.0041, 0.0017)	0.42	–0.0008 (–0.0042, 0.0027)	0.67
Thalamus	–0.0004 (–0.0024, 0.0015)	0.66	–0.0009 (–0.0033, 0.0014)	0.44

increase our understanding of the preclinical phase of AD [4].

In the categorical analysis based on data from the NPI-Q, we observed that depression was associated with an abnormal FDG-PET among cognitively normal elderly persons. Participants with an abnormal FDG-PET were twice as likely to have depression as compared to individuals with a normal FDG-PET. Additionally, we also observed that depressive and anxiety symptoms were associated with abnormal FDG-PET when treated as continuous variables as derived from BDI and BAI. To investigate whether the findings could be biased by concomitant use of medications, we compared medication intake (e.g., SSRI/SNRIs) between participants with a normal versus abnormal FDG-PET. We did not observe any significant differences between the two groups for either class of medications.

In a secondary analysis, we examined the association between regions of interest that are reported in the literature to be associated with major depressive disorder [33] and anxiety disorders [34]. We sought to investigate if these ROI were also associated with subsyndromal depressive and anxiety symptoms. Indeed, we observed a small inverse yet non-significant relationship between depressive and anxiety symptoms and specific regions of interest. This was expected given that our participants are community-dwelling, cognitively normal elderly individuals. Therefore, on average, they are less likely to have clinically significant depressive and anxiety symptoms. In previous studies, hippocampal atrophy was reported in severe recurrent depression in clinical samples [35]. However, we did not observe this in our sample.

To our knowledge, only one study investigated the association between FDG-PET and depressive symptoms in normal aging [36]. Investigators from Massachusetts General Hospital analyzed FDG-PET data on a volunteer sample of 248 community-dwelling older adults. They measured depression using the Geriatric Depression Scale (GDS). Consistent with our finding they reported that depression was associated with FDG-PET hypometabolism, even though their effect size is smaller. However, they also reported a significant association between FDG-PET hypometabolism and apathy, which we did not observe in our data. The differences in our findings could be attributable to various factors. These factors could include the difference in the measurement of depressive symptoms as we used NPI-Q and BDI and they used GDS. Another possible explanation for the differences could be the way in which study participants were recruited. The investigators from Boston used a volunteer sample of community-dwelling older adults whereas we had a randomized, population-based sample of elderly individuals.

In the past, few studies have investigated the association between NPS and FDG-PET in MCI and clinical AD samples [37–42]. However, those studies were not directly relevant to our study because our study participants were cognitively normal persons.

As APOE ε4 genotype is a well-known genetic risk factor for AD, we also examined its role in influencing the association between NPS and brain glucose metabolism by conducting a stratified analysis. We observed that APOE ε4 carriers who had an abnormal FDG-PET were more than twice as likely to have depression as compared to non-carriers, even though this association was marginally significant. Previous studies found an association between APOE ε4 genotype and reduced brain glucose metabolism [43, 44], but there is essentially no study available on the association between NPS and FDG-PET as stratified by APOE ε4 genotype among cognitively normal persons.

Our findings should be interpreted in the context of the strengths and limitations of this study. The strength of our study pertains to the large, population-based sample size. In addition, all study participants underwent numerous face-to-face evaluations including FDG-PET scans. They were classified as cognitively normal or having MCI or dementia

based on a consensus panel at a center with a well-established track record in the field of aging and MCI. Furthermore, our study could be one of the few that investigated the association between depression, anxiety and specific AD-related brain regions among cognitively normal elderly persons.

Our study also has limitations. As in any cross-sectional study, it is not possible to determine the direction of causality between the exposure of interest (i.e., neuropsychiatric symptoms) and the outcome of interest (i.e., FDG-PET). Another limitation pertains to the use of the NPI-Q, which is an informant-based assessment and may therefore be prone to recall bias. However, it must be noted that the NPI-Q is a validated and common tool to assess neuropsychiatric symptoms that has been used in a variety of other large-scale studies in the field. Also, one of the limitations of the study was that we were not able to examine the association of neuropsychiatric symptoms with regions of interest stratified by hemisphere (right versus left); such an approach would have required twice as much power. A future, much larger sample that specifically seeks to test an a priori hypothesis of laterality can address this question.

The current key research agenda of the field of aging is a biomarker-based investigation of presymptomatic AD. This may be one of the first studies to address this research question in the context of emotional behaviour. We observed that depression and anxiety are associated with an abnormal FDG-PET. Our findings suggest that interventions that target biomarkers of presymptomatic AD may need to account for depressive and anxiety symptoms. Our study finding may also be relevant to the construct of mild behavioral impairment (MBI). Based on our findings, we hypothesize that MBI subjects with an abnormal FDG-PET may constitute a subset of MBI that may need to be followed to determine if they are at higher risk for clinical AD. However, our finding should be considered as preliminary until confirmed by a cohort study.

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