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ORIGINAL ARTICLE

Behavioural disorders in Alzheimer's disease: the descriptive and predictive role of brain ^{18}F-fluorodesoxyglucose-positron emission tomography

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Abstract

Background: Alzheimer's disease (AD) has a high incidence in the elderly. Besides cognitive disorders, patients may also develop behavioural and psychological symptoms of dementia (BPSD), which can be particularly disabling for patients and families. BPSD encompass a wide range of symptoms, among which psychotic symptoms and disruptive behaviours often prompt the first related hospitalization and request for family support. The aetiological mechanism of BPSD has not yet been clarified, and no predictive or risk factors have been identified. The main objectives of our study are to describe the frequency of aggression/agitation and psychotic symptoms, defined 'positive BPSD', in a cohort of 60 AD patients, identify areas of the brain involved in behavioural symptomatology through brain ^{18}F-fluorodesoxyglucose-positron emission tomography (FDG-PET), and investigate a potential predictive role of brain FDG-PET in BPSD development.
Methods: A cohort of 60 AD patients was retrospectively enrolled and regularly followed for at least 3 years. Each subject underwent brain FDG-PET at the time of diagnosis. Patients were divided into three groups based on the presence of behavioural disturbances: present, absent, and developed later.
Results: Of the 60 AD patients in the cohort, 52% had positive BPSD: 17 at baseline and 14 during the 3-year follow-up. FDG-PET identified an association between hypometabolism in the bilateral temporal lobes and the presence of BPSD, and showed initial hypometabolism in the postero-temporal lobes 3 years before symptom onset.
Conclusions: Positive BPSD are frequently manifested in AD. Our study identified the temporal lobes as the neurobiological substrate of positive BPSD and FDG-PET as a potential instument to predict their developement. Temporal lobes are involved in processing facial expression and recognizing emotions; an impairment of these functions could cause delusions and agitated/aggressive behaviour. To confirm the potential predictive role of FDG-PET in the onset of BPSD in AD, further studies are needed.

INTRODUCTION

Alzheimer's disease (AD) is the most frequently occurring neurodegenerative disorder. Its progressive chronic course starts from a phase of mild symptomatology and reaches dementia. The behavioural and psychological symptoms of dementia (BPSD) are a heterogeneous group of symptoms that are common to all types of dementia and that occur in up to 90% of AD patients.[1–4] The frequency of each symptom varies among patients and during the disease course.[5–7] BPSD may include depression, apathy, delusions/hallucinations, and agitation/aggression, which are the most common symptoms, occurring in

20–50% of patients.[8–11] The onset of BPSD is related to patients, caregivers, and environmental factors,[10,11] but predicting their development is an unmet need in the management of AD patients. Many past studies focused on identifying the neurobiological underpinnings of BPSD,[12–30] but their results have been controversial.[31] In particular, there has been no consensus or agreement on symptom definitions.[14,31,32] Among BPSD, aggression/agitation and psychotic symptoms are the most common reason for hospitalization and institutionalization, and they can greatly affect patients' and caregivers' quality of life.[10,11] Moreover, previous studies reported that they often occur together.[2,3]

In the present study we retrospectively assessed the occurrence of agitation/aggression and psychotic symptoms over a 3-year period in a cohort of AD patients. Because of frequent symptom overlap, we have combined these symptoms into a category: 'positive BPSD'. We used brain ^{18}F-fluorodesoxyglucose-positron emission tomography (FDG-PET) to evaluate a possible common metabolic pattern of positive BPSD and to explore whether such a pattern could have a role in predicting their onset.

METHODS

Subjects were patients diagnosed with AD who had been referred to the Neurology Department of Careggi University Hospital (Florence, Italy) between January 2008 and November 2014. Subjects were retrospectively enrolled if they had undergone FDG-PET at the time of clinical diagnosis and had received follow-up treatment for at least 3 years. Patients were diagnosed with AD based on clinical and neuroimaging data according to the National Institute on Aging and the Alzheimer's Assocation workgroup's 2011 criteria[33]; diagnoses made before 2011 were revised, and patients were included only if they met the 2011 criteria.[33]

Clinico-demographic information included gender, age at symptom onset, education, medical history, and family history of dementia. Each subject underwent a brain magnetic resonance imaging (or, when not possible, computed tomography) and FDG-PET at baseline. Neuropsychological assessment included the Mini-Mental State Examination (MMSE),[34] Frontal Assessment Battery,[35] forward and backward digit span test,[36] forward and backward Corsi span test,[36] and logical memory. Positive BPSD were classified as present when a patient scored ≥6 (3 frequent × 2 moderate severity) on at least one item among the psychotic core (delusion and hallucination) and agitation on the Neuropsychiatric Inventory (NPI) or if a patient was currently using antipsychotic drugs.[37,38] At each follow-up, general cognition and BPSD were evaluated by the MMSE and Neuropsychiatric Inventory.[34,37]

Based on the presence of BPSD, the subjects were divided into three groups: (i) AD patients without BPSD (AD-noBPSD); (ii) AD patients with BPSD at the time of FDG-PET (AD-BPSD); and (iii) AD patients who did not have BPSD at the time of FDG-PET but developed symptoms later (AD-BPSD developers).

The study was performed in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki.

FDG-PET brain images

Scans were performed using a Philips Gemini TF16 PET/CT (Philips Medical System, Eindhoven, Netherlands) at the Nuclear Medicine Unit of Careggi University Hospital, Florence. Image acquisition started 30 min after FDG injection (3.7MBq/kg) at rest in a dimly lit and silent room. PET images were subsequently reconstructed using an iterative algorithm (3-D Line of response reconstruction, Field of view: 256, 128 × 128 matrix, 2 × 2 × 2-mm voxel size).

Statistical analysis

Clinico-demographic features of patients' groups were compared with ANOVA for continuous variables; multiple groups were compared for dichotomic variables.

Statistical analyses were performed with SPSS Statistics ver. 20.0 (IBM Corp., Armonk, NY, USA).

Statistical parametric mapping analysis

Voxel-based analyses of FDG-PET were performed with SPM12 software (The Wellcome Centre of Human Neuroimaging, UCL Queen Square Institute of NEurology, London, UK). Multivariate ANOVA routine with post-hoc *t*-contrasts were performed to compare FDG-PET scans of the three group with those of 50 control subjects selected from the Italian Association of Nuclear Medicine FDG-PET normal subject database. Age was set as a nuisance variable. The control subjects consisted of 24 men and 26 women with a mean age of 62.32 ± 13.89 years, a mean education of 11.16 ± 4.29 years, and a mean MMSE

Table 1 Clinico-demographic features of AD patient subgroups by BPSD

	AD-noBPSD ($n = 29$)	AD-BPSD ($n = 17$)	AD-BPSDdeveloper ($n = 14$)	*P*-value
Age (years), mean ± SD	72.2 ± 5.8	74.7 ± 7.1	71.65 ± 9.5	0.40
Male patients, *n* (%)	13 (44.8)	9 (52.9)	5 (35.7)	0.79
Education (years), mean ± SD	7.1 ± 3.67	7.7 ± 4.6	7.1 ± 4.7	0.86
Time from diagnosis to FDG-PET (years), mean ± SD	1.97 ± 1.34	1.88 ± 1.58	2.05 ± 1.14	0.93
MMSE at baseline, mean ± SD	25.44 ± 3.6	20.41 ± 3.7	20.92 ± 3.5	<0.001
Follow-up period (years), mean ± SD	3.75 ± 1.9	2.9 ± 2.3	3.58 ± 2.1	0.45
MMSE at 3-year follow-up, mean ± SD	23.85 ± 8	15.84 ± 7	15.9 ± 6	0.001

AD, Alzheimer's disease; BPSD, behavioural and psychological symptoms of dementia; FDG-PET, ^{18}F-fluorodesoxyglucose-positron emission tomography; MMSE, Mini-Mental State Examination; AD-noBPSD, AD patients without BPSD; AD-BPSD, AD patients with BPSD at the time of FDG-PET; AD-BPSDdeveloper, AD patients who developed BPSD after FDG-PET.

Table 2 Clusters of significant hypometabolism in AD-noBPSD patients as compared to controls

Cluster extent	X	Y	Z	Localization	BA	T	Z-score
199	−26.0	−35.0	0.0	Left hippocampus	Hippocampus	3.81	3.74
789	0.0	−41.0	32.0	Left cingulate gyrus	31	4.16	4.08
	6.0	−62.0	36.0	Right precuneus	7	4.11	4.02
	−8.0	−63.0	31.0	Left precuneus	7	3.73	3.66
38	−44.0	−52.0	43.0	Left inferior parietal lobule	40	3.68	3.62

AD-noBPSD, patients with Alzheimer's disease without behavioural and psychological symptoms of dementia; BA, Brodmann areas; T, T-score.

Table 3 Clusters of significant hypometabolism in AD-BPSD patients as compared to controls

Cluster extent	X	Y	Z	Localization	BA	T	Z-score
3919	46.0	−59.0	32.0	Right superior temporal gyrus	39	7.25	6.84
	57.0	−45.0	−10.0	Right inferior temporal gyrus	20	5.45	5.26
	61.0	−41.0	0.0	Right middle temporal gyrus	21	5.42	5.24
3964	−61.0	−35.0	−3.0	Left middle temporal gyrus	21	6.39	6.10
	−46.0	−61.0	29.0	Left middle temporal gyrus	39	6.00	5.75
	−50.0	−53.0	19.0	Left superior temporal gyrus	22	5.80	5.58
2637	−6.0	−55.0	29.0	Left cingulate gyrus	31	5.75	5.53
	8.0	−47.0	32.0	Right precuneus	31	5.56	5.36
	6.0	−59.0	34.0	Right precuneus	7	5.17	5.01
244	−46.0	11.0	−11.0	Left superior temporal gyrus	38	3.71	3.65
	−51.0	0.0	−2.0	Left superior temporal gyrus	22	3.51	3.45
73	−44.0	−19.0	10.0	Left superior temporal gyrus	13	3.69	3.63
30	50.0	0.0	−7.0	Right superior temporal gyrus	38	3.17	3.12

AD-BPSD, patients with Alzheimer's disease and behavioural and psychological symptoms of dementia; BA, Brodmann areas; T, T-score.

score of 29.23 ± 0.94; each control subject had had a follow-up assessment of cognitive status after at least 1 year. Further, the three patient group were compared, with age and MMSE as the nuisance variables. FDG-PET scans were adjusted for the global mean by proportional scaling. Results were examined at $P < 0.001$, uncorrected (cluster extent ≥20 voxels). The anatomic location of brain regions showing significant effects was described with Talairach and Tournoux coordinates.

RESULTS

A sample of 60 AD subjects (27 men, 33 women) was collected; their average age was 72.9 years, and their mean MMSE was 22.9 at baseline. With respect to the presence of BPSD, 29 AD-noBPSD, 17 AD-BPSD, and 14 AD-BPSDdeveloper were identified. The three groups were comparable in terms of age, gender, education, and family history of dementia. AD-noBPSD had a higher MMSE score at baseline and during the 3-year follow-up than AD-BPSDdeveloper and

Table 4 Clusters of significant hypometabolism in AD-BPSDdeveloper patients as compared to controls

Cluster extent	X	Y	Z	Localization	BA	T	Z-score
7862	−46.0	−59.0	32.0	Left superior temporal gyrus	39	7.30	6.88
	6.0	−53.0	30.0	Right cingulate gyrus	31	7.11	6.71
	−4.0	−55.0	27.0	Left cingulate gyrus	31	6.18	5.92
231	−59.0	−37.0	−10.0	Left middle temporal gyrus	21	4.39	4.28
275	−36.0	−49.0	−1.0	Left parahippocampal gyrus	19	3.85	3.78
	−36.0	−28.0	−10.0	Left parahippocampal gyrus	36	3.21	3.16

AD-BPSDdeveloper, patients with Alzheimer's disease who developed behavioural and psychological symptoms of dementia after ^{18}F-fluorodesoxyglucose-positron emission tomography; BA, Brodmann areas; T, T-score.

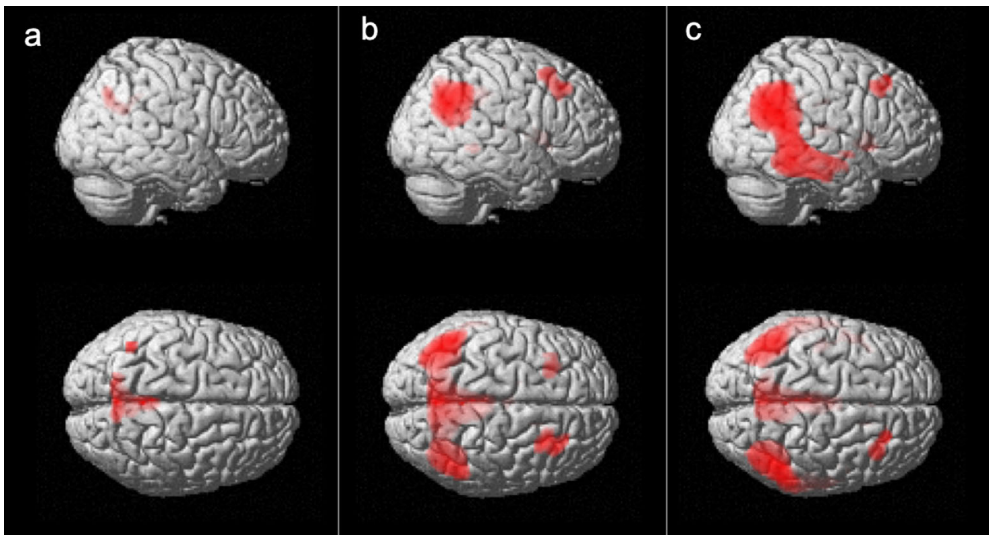

Figure 1 Areas of significant hypometabolism in AD-noBPSD, AD-BPSDdeveloper, and AD-BPSD as compared to controls. (a) AD-noBPSD: PCC, precuneus, bilateral medial temporal and parieto-temporal cortices; (b) AD-BPSDdeveloper: PCC, precuneus, bilateral medial temporal and parieto-temporal cortices, superior temporal gyri and left parahippocampal gyrus; (c) AD-BPSD: PCC, precuneus, bilateral medial temporal and parieto-temporal cortices, and bilateral superior, middle, and inferior temporal gyri. AD, Alzheimer's disease; BPSD, behavioural and psychological symptoms of dementia; FDG-PET, ^{18}F-fluorodesoxyglucose-positron emission tomography; AD-noBPSD, AD patients without BPSD; AD-BPSD, AD patients with BPSD at the time of FDG-PET; AD-BPSDdeveloper, AD patients who developed BPSD after FDG-PET; PCC, posterior cingulate cortex.

AD-BPSD (Table 1). In contrast to the controls, all AD patients had a typical AD pattern on FDG-PET imaging, with significant hypometabolism in the bilateral posterior cingulate cortex, precuneus, and bilateral medial temporal and parieto-temporal cortices (Table 2). In addition to having the prototypical AD pattern, AD-BPSDdeveloper had further involvement of the superior temporal gyri and the left parahippocampal gyrus (Table 3), whereas AD-BPSD had involvement of the bilateral superior, middle, and inferior temporal gyri (Table 4). The hypometabolic pattern of each group in comparison to control subjects is shown in Figure 1. We also compared FDG-PET imaging among the three AD groups. Compared to AD-noBPSD, AD-BPSD showed significant hypometabolism in the bilateral superior, middle, and inferior temporal gyri, but compared to AD-BPSDdeveloper, AD-BPSD showed hypometabolism in the middle and inferior temporal gyrus (Table 5). Compared to AD-noBPSD, AD-BPSDdeveloper had significant hypometabolism only in the bilateral superior temporal gyrus (Table 5, Fig. 2). No other clusters of significant hypometabolism were found in the between-group analysis.

DISCUSSION

In the present cohort of 60 AD patients, 52% presented positive BPSD: 17 at baseline and 14 during the 3-year follow-up period. BPSD were associated both with mild AD at baseline and with moderate AD when they developed during the follow-up period. In the literature, the frequency of BPSD in AD patients ranges from 30%

Table 5 Comparisons of clusters of significant hypometabolism

Cluster extent	X	Y	Z	Localization	BA	T	Z-score
AD-BPSD < AD-noBPSD							
1463	63.0	−43.0	−3.0	Right middle temporal gyrus	21	4.25	3.93
	55.0	−1.0	−12.0	Right middle temporal gyrus	21	3.79	3.56
	46.0	17.0	−11.0	Right superior temporal gyrus	38	3.77	3.54
150	42.0	−57.0	30.0	Right superior temporal gyrus	39	4.03	3.75
AD-BPSD < AD-BPSDdeveloper							
52	57.0	−1.0	−13.0	Right middle temporal gyrus	21	3.33	3.17
32	50.0	6.0	−32.0	Right middle temporal gyrus	21	3.33	3.17
AD-BPSDdeveloper < AD-noBSDS							
192	−42.0	−55.0	30.0	Left superior temporal gyrus	39	4.26	3.94
71	42.0	−57.0	30.0	Right superior temporal gyrus	39	3.91	3.66

AD, Alzheimer's disease; BPSD, behavioural and psychological symptoms of dementia; FDG-PET, ^{18}F-fluorodesoxyglucose-positron emission tomography; AD-noBPSD, AD patients without BPSD; AD-BPSD, AD patients with BPSD at the time of FDG-PET; AD-BPSDdeveloper, AD patients who developed BPSD after FDG-PET; BA, Brodmann areas; T, T-score.

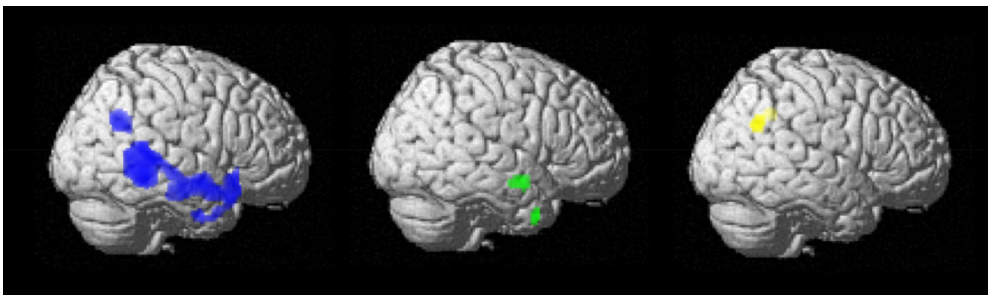

Figure 2 Areas of significant hypometabolism in (left) AD-BPSD as compared to AD-noBPSD (blue): bilateral superior, middle, and inferior temporal gyri; (centre) AD-BPSD as compared to AD-BPSDdeveloper (green): middle and inferior temporal gyrus; and (right) AD-BPSDdeveloper as compared to AD-noBPSD (yellow): bilateral superior temporal gyrus. AD, Alzheimer's disease; BPSD, behavioural and psychological symptoms of dementia; FDG-PET, ^{18}F-fluorodesoxyglucose-positron emission tomography; AD-noBPSD, AD patients without BPSD; AD-BPSD, AD patients with BPSD at the time of FDG-PET; AD-BPSDdeveloper, AD patients who developed BPSD after FDG-PET.

to 90%,[1–4] and positive BPSD are described with similar frequency both in mild and moderate–severe AD stages.[5–7] The three subgroups—AD-noBPSD, AD-BPSD, and AD-BPSDdeveloper—were comparable in terms of age, gender, education, and family history of dementia, but there were differences in MMSE score at baseline, with AD-noBPSD having the highest score.

Our analysis of FDG-PET showed an association between brain hypometabolism in the temporal cortex and the presence of BPSD in AD. Moreover, we demonstrated that temporal cerebral metabolism was already reduced 2–3 years before the onset of BPSD in the superior regions. However, the study of the anatomical basis of BPSD, in literature data, has provided inconsistent results. Most data have indicated that temporal lobe dysfunction is associated with aggressive behaviour,[13,14,39] but associations with the orbito-frontal area,[12,14,40] insula region, and cingulate region have been also suggested.[15] The discrepancies in the results are due to the heterogeneity among studies in terms of the definition of neuropsychiatric symptoms, symptom severity, and type of neuroimaging analysis. In our study, most AD patients presented a physically agitated behaviour, as defined by Banno *et al.*,[14] who, like us, described an association between these symptoms and the right superior temporal sulcus on brain perfusion single-photon emission computer tomography.

The superior temporal cortex has been recognized as having a fundamental role in the processing of facial expressions, which is crucial for social behaviour and the recognition of emotion.[41–43] Functional magnetic resonance imaging studies conducted on healthy subjects showed an activation of the bilateral superior temporal sulcus during the coding of different facial movements with social and emotional meaning.[43] Face and emotion perception are impaired in patients with schizophrenia, and investigations have typically found a reduction in the volume of the medial,

superior, middle, and inferior temporal lobe and the fusiform regions in those patients, as compared to controls.[44,45] Schizophrenic patients also show aberrant activity in the superior temporal sulcus during social cognition, indicating that impaired perceptions of emotions and intentions could contribute to the development of delusions.[46] Similarly, the temporal hypometabolism identified in our patients with positive BPSD could indicate impairment in understanding facial expressions and in perceiving and communicating emotions, thus resulting in delusions and agitated and aggressive behaviour.

Although the statistical parametric mapping analysis was corrected for the severity of cognitive decline, we cannot completely rule out the influence of AD severity on the differing hypometabolic patterns in the three groups. In fact, AD-noBPSD patients had a higher MMSE score at baseline and after 3 years' follow-up than AD-BPSD and AD-BPSDdeveloper patients. AD-BPSD and AD-BPSDdeveloper had the same severity of cognitive impairment at baseline. However, they had different regional hypometabolism on PET imaging, which supports the hypothesis that the varying hypometabolic patterns was not due to AD severity.

The present study highlighted and confirmed the association between hypometabolism in the temporal lobe area and the presence of BPSD symptoms in AD patients. To our knowledge, no other studies have evaluated the role of FDG-PET imaging in the prediction of BPSD development. Our data suggest that hypometabolism in the superior temporal lobes can be identified 3 years before the onset of positive BPSD. However, no previous studies have evaluated aggression/agitation and psychotic symptoms together, and their correlation needs to be confirmed.

This is the first study to identify a possible common predictor of the development of aggression/agitation and psychotic symptom in AD patients, and it provides a starting point for further research. Because of the limited sample size, larger replicative studies are required. This may lead to a deeper understanding of these disorders in the future, hence contributing to better patient management or even the development of prevention strategies.

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