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Associations between Neuropsychiatric Symptoms and Cerebral Amyloid Deposition in Cognitively Impaired Elderly People

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Abstract.
Background: Neuropsychiatric symptoms, also known as behavioral and psychological symptoms of dementia (BPSD), affect the majority of patients with dementia, and result in a greater cognitive and functional impairment.
Objective: To investigate associations between BPSD and amyloid cerebral deposition as measured by ^{18}F-Florbetapir-PET quantitative uptake in elderly subjects with and without cognitive impairment.
Methods: Participants with cognitive impairment [mild cognitive impairment (MCI) or Alzheimer's disease (AD)] and healthy controls (HC) from the ADNI cohort (Alzheimer Disease Neuroimaging Initiative) who underwent an ^{18}F-florbetapir PET scan between May 2010 and March 2014 were included. Clinical assessments included the Clinical Dementia Rating, the Mini-Mental State Examination (MMSE), and the Neuropsychiatric Inventory. Freesurfer software was used to extract PET counts based on T1-based structural ROI (frontal, cingulate, parietal, and temporal). Spearman's partial correlation scores between BPSD severity and regional amyloid uptake were calculated.
Results: Data for 657 participants [age = 72.6 (7.19); MMSE = 27.4 (2.67)] were analyzed, including 230 HC [age = 73.1 (6.02); MMSE = 29 (1.21)], 308 MCI [age = 71.5 (7.44); MMSE = 28.0 (1.75)], and 119 AD subjects [age = 74.7 (8.05); MMSE = 23.1 (2.08)]. Considering all diagnostic groups together, positive significant correlations were found between anxiety and ^{18}F-florbetapir uptake in the frontal ($r = 0.102$; $p = 0.009$), cingulate ($r = 0.083$; $p = 0.034$), and global cerebral uptake ($r = 0.099$; $p = 0.011$); between irritability and frontal ($r = 0.089$; $p = 0.023$), cingulate ($r = 0.085$; $p = 0.030$), parietal ($r = 0.087$; $p = 0.025$), and global cerebral uptake ($r = 0.093$; $p = 0.017$); in the MCI subgroup, between anxiety and frontal ($r = 0.126$; $p = 0.03$) and global uptake ($r = 0.14$; $p = 0.013$); in the AD subgroup, between irritability and parietal uptake ($r = 0.201$; $p = 0.03$).
Conclusion: Anxiety and irritability are associated with greater amyloid deposition in the neurodegenerative process leading to AD.

Keywords: ADNI, Alzheimer's disease, amyloid, anxiety, behavioral and psychological symptoms of dementia, dementia, cingulate, frontal, irritability, neuroimaging, neuropsychiatric symptoms

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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INTRODUCTION

More than 7 out of 10 demented patients experience at least one behavioral and psychological symptom (BPSD) during the natural course of their illness [1]. Because BPSD significantly increase both morbidity in Alzheimer's disease (AD) patients and stress in caregivers [2], they represent a major concern in the medical community. As AD is commonly viewed as a neurodegenerative disease that affects mainly memory circuits, the associations between BPSD and AD pathology have not been extensively investigated so far.

In the last decades, isotopic neuroimaging procedures, such as cerebral perfusion scintigraphy (single-photon emission computed tomography, SPECT) or ^{18}F-fluorodeoxyglucose (FDG) brain positron emission tomography (PET), have revealed some correlations between BPSD and specific neuronal networks. In 2000, Mega and colleagues were among the firsts to describe an association between hypoperfusion in connected frontal networks and the occurrence of psychotic symptoms in a small population of AD women patients [3]. Specifically, the authors found a significant hypoperfusion in the dorsolateral frontal cortex bilaterally and the left anterior cingulate, as well as in the ventral striatum, pulvinar, and dorsolateral parietal cortex. The involvement of frontal cortical structures in patients with delusions, one of the most prominent psychiatric symptoms in AD patients, has been further described in several studies based on brain perfusion SPECT assessment. For instance, Nakano and colleagues studied a large population of AD patients with delusions, and demonstrated a functional deficit in the frontal lobe with right side dominance, specifically in the prefrontal cortex and in the anterior cingulate gyrus [4]. As previously demonstrated by Benoit and colleagues, anterior cingulate regions are also affected in apathetic AD patients [5], while prefrontal cortex could be involved in depressive patients [6, 7].

Lopez and colleagues demonstrated that specific mood related disorders in three AD patients (depression, apathy, and emotional lability) were associated with a meso-limbic system dysfunction, with a specific involvement of areas usually involved in the modulation of motivation and affect. Relative cerebral blood flow (CBF) was calculated using PET-based time activity data after intravenous bolus injection of ^{15}O-water [8]. All the patients showed a CBF decrease in the prefrontal cortex (left or bilaterally), a result which was further confirmed by SPECT studies [6, 7] and by (a few) FDG PET studies [9].

Recently, Caroli and colleagues assessed cortical glucose metabolism with FDG PET, and demonstrated that hypometabolism and grey matter tissue loss mapped to similar regions (specifically, the temporoparietal, retrosplenial, and medial temporal regions) Indeed, hypometabolism in depressive AD patients was mainly located in the posterior cingulate cortex (PCC). Consistent with the literature, hypometabolism exceeded grey matter atrophy in PCC, indicating a metabolic depression. On the other hand, the amygdala (mainly on the left side) showed atrophy exceeding hypometabolism, which could be an indicator of a compensation mechanism. The authors suggested that metabolic depression in AD, defined as a mismatch between hypometabolism and atrophy, could be linked to higher amyloid deposition compared to tau deposition in PCC. By modulating synaptic plasticity, amyloid-β (Aβ) proteins may cause synaptic dysfunction even in the absence of detectable atrophy. Then, in PCC, synaptic damage with neuron survival might occur, explaining the metabolic depression concept [10].

In summary, limited evidence exists regarding the effectiveness of isotopic neuroimaging procedures in the assessment of aberrant motor behaviors, nighttime behavioral disturbances, or eating disturbances.

BPSD have been investigated in a few neuropathologic studies. In accordance with neuroimaging findings about frontal structures, in a study on 27 AD patients, psychosis symptoms were associated with significantly increased densities of amyloid plaques and neurofibrillary tangles in the prosubiculum and middle frontal cortex [11]. Neurofibrillary tangle burden in other frontal structures such as the orbitofrontal and the anterior cingulate cortices has also been associated with agitation in AD [12] Also, previous studies found a correlation between apathy—a frequent BPSD symptom of AD—and a greater burden of anterior cingulate neurofibrillary tangles, suggesting that chronic behavioral changes reflect better the disease pathology compared to acute changes [13]. Apathy has also found to be significantly correlated with tau and p-tau but not with $A\beta_{1\text{-}42}$ in cerebrospinal fluid [14]. Apathy is often expressed early in the AD progression, and a recent amyloid imaging study on a small sample of apathetic mild cognitive impairment (MCI) patients argued for a possible role also of amyloid. Specifically, the authors found a significant association between increased apathy (lower Apathy Evaluation

Scale score) and a greater cortical Pittsburg compound-B retention, but no significant association between apathy and regional FDG metabolism, contrary to ever mentioned functional neuroimaging studies [15].

Using the first FDA-approved Aβ PET ligand, ^{18}F-florbetapir (^{18}F-AV-45), a correlation has recently been demonstrated between $A\beta_{42}$ histopathological post-mortem measures and cortical ^{18}F-florbetapir uptake [16]. But, so far, only one recent study screened BPSD and demonstrated a correlation between Aβ prefrontal uptake and apathy in AD [17].

Using quantification of cerebral ^{18}F-florbetapir uptake, here we aimed at testing associations between BPSD and *in vivo* amyloid deposition in specific cortical areas in elderly participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.

MATERIALS AND METHODS

Population

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO.

The population sample of the present study included 657 ADNI participants who received an ^{18}F-florbetapir PET scan between May 2010 and March 2014. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. At the first ADNI2 visit, participants from previous cohorts underwent 1.5 tesla MRI (for ADNI1 participants) or 3T MRI scans (for ADNI-GO participants). Then, on the following day, clinical and cognitive assessments, genetic blood draw and ^{18}F-florbetapir-PET scans were performed. Newly included participants in ADNI2 had a screening visit with a 3T MRI scan and then, with a maximum delay of 28 days, they underwent clinical and cognitive assessments, genetic blood draw and ^{18}F-florbetapir-PET scans.

Before data collection, participants received a diagnosis. In summary, the control group was free of memory complaints with a Clinical Dementia Rating (CDR) scale's score = 0 with memory box score = 0 and a Mini-Mental State Examination (MMSE) score between 24 and 30. Normal memory function was also documented by normal scores obtained at the Logical Memory II subscale (delayed Paragraph Recall) from the Wechsler Memory Scaled - Revised (more than or equal to 9 for 16 or more years of education), as well as by preserved activities of daily living; the MCI group had a subjective memory complaint and a CDR score at 0.5 with memory box score at 0.5, abnormal memory function documented by scores below the education level adjusted cutoff on the Logical Memory II subscale, impaired cognition and activities of daily living which did not match the AD diagnosis criteria. The AD group had a CDR of 0.5 or 1, memory box score = 0.5 or 1, abnormal memory function on the Logical Memory II subscale, MMSE score between 20 and 26, and matched NINCDS/ADRDA criteria for probable AD. For participants under medication, a 12-week stable treatment for cognitive decline (cholinergic inhibitors or memantine) was a requisite for inclusion. Washout from psychoactive medication, (e.g., excluded antidepressants, neuroleptics, chronic anxiolytics, or sedative hypnotics, etc.) for at least 4 weeks prior to screening was done. Only stable doses of antidepressants lacking significant anticholinergic side effects (if patient was not currently depressed and did not have a history of major depression within the past year) were allowed. Complete details regarding inclusion/exclusion criteria can be found at http://www.adni-info.org.

All subjects gave written informed consent; the study was in agreement with the Declaration of

Helsinki and was approved by institutional ethics committees at each site.

Study methods

Neuropsychiatric Inventory assessment

The Neuropsychiatric Inventory (NPI) is a validated informant-based interview that is widely used in clinical research studies to evaluate BPSD in dementia patients. The NPI is a retrospective (to 1 month) caregiver-informant interview covering 12 neuropsychiatric symptom domains: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, nighttime behavioral disturbances, and appetite/eating disturbances. The NPI includes a screening question for each symptom domain, followed by a list of questions about domain-specific behaviors administered if the screening question is positive. Neuropsychiatric manifestations within a domain are collectively rated by the caregiver in terms of both frequency (1 to 4) and severity (1 to 3), yielding a composite symptom domain score (frequency × severity) [18].

Genetic data

Apolipoprotein genetic status was also considered (APOE) genotyping and sample methods are available on ADNI website).

Neuroimaging protocol and analysis

PET images were acquired 50–70 min following intravenous injection of 370 MBq of ^{18}F-florbetapir. Details on PET scanners used in the study, imaging protocol, and quality control measures have been previously published [19]. Images were spatially aligned, averaged, interpolated to a standard voxel size, and smoothed to a resolution of 8-mm full width at half maximum. Recent MRI scans (1.5 or 3 Tesla) were used to define cortical and subcortical regions of interest (ROI) and the reference region (whole cerebellum), and each ^{18}F-florbetapir scan and corresponding MRI were then coregistered. After segmentation and ROI delineation in native-space MRI scans using Freesurfer v. 4.5.0 (http://surfer.nmr.mgh.harvard.edu/), ^{18}F-florbetapir cortical mean uptake was extracted from four large grey matter-only regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) (see Supplementary Table 1 for subregion's distributions). A semi-quantitative composite ^{18}F-florbetapir cortical index (SUVR) was then calculated by creating a conventional (nonweighted) average across the four main cortical regions and dividing by the whole cerebellum reference region (cortical summary ROI). Preprocessing and postprocessing steps were completed by the ADNI PET core (partial volume correction was not applied to these data (more details are available on the ADNI website). SUVR data were directly downloaded from the ADNI website.

Statistical methods

^{18}F-florbetapir brain PET with Aβ cortical uptake higher than an empirically defined threshold (cortical summary ROI, SUVR >1.11, with the whole cerebellum defined as the reference region) were considered as pathologic (positive PET) [16].

Correlations between BPSD and cerebral ROI were calculated (Spearman's partial correlation considering age, gender, MMSE, education variables altogether), for the whole population and for each diagnostic group (HC, MCI, and AD), considering cerebral amyloid deposition as an independent biological continuum.

As there is not a total clinical progression from one diagnosis group to another, we choose to analyze also a total population subgroup to consider a more objective biomarker continuum point of view. Odds ratios (OR) were calculated for the whole population and for each diagnostic subgroup; then results were sorted according to PET results (positive or negative) and to a NPI subscore >3 for each behavioral domain [20].

Assuming that amyloid deposition in cortical subregions may vary among patients according to NPI symptoms, we additionally compared mean cortical uptake values (globally and regionally) between symptomatic versus asymptomatic patients for each NPI symptom. As the amyloid brain deposition did not follow a normal distribution among the most symptomatic subgroups (i.e., NPI subscores >3), a non-parametric test (Mann-Whitney-Wilcoxon test) was used to compare amyloid deposition between symptomatic and asymptomatic patients.

Concerning the complementary results, group comparisons should be interpreted with caution considering the numerous statistical comparisons performed, potentially increasing the risk of type-1 errors. As this analysis was only exploratory, a significant threshold was defined as 0.05 for p-values, and no correction for multiple tests was applied.

Difference of APOE ε4 prevalence between compared groups was assessed by chi-square tests.

Assuming that variables such as NPI symptoms, age, gender, MMSE score, education level, number of APOE ε4 gene held, and clinical diagnosis could be potentially correlated with the amyloid brain deposition, after a principal component analysis (PCA) performed on NPI symptoms, we assessed by a logistic regression the independent impact of these covariables on the amyloid load (positive or negative) variations. Principal components (PC) were defined as followed: PC1 included agitation, euphoria, apathy, disinhibition, irritability (frontal symptoms); PC2 included sleep and appetite disturbances (instinctual disturbances); PC3 included depression, anxiety, aberrant motor behavior and delusion (mood symptoms unless aberrant motor behavior and delusion); and PC4 included hallucinations. These four PCs could explain more of 50% of the variance of cortical amyloid uptake.

For an eingenvalue >1, after varimax rotation and Kaiser normalization, considering a factor loading threshold >0.4 (relative to previously proposed threshold in literature [21].

RESULTS

Population description

Populations' demographics are presented in Table 1. The sample included 657 participants [age = 72.64 (7.19); MMSE = 27.45 (2.67)], including 230 HC [age = 73.12 (6.02); MMSE = 29 (1.21)], 308 MCI [age = 71.47 (7.44); MMSE = 27.98 (1.75)] and 119 AD [age = 74.75 (8.05); MMSE = 23.11 (2.08)]. The most prevalent BPSD with clinical relevance (NPI-domain subscore >3) were, respectively, apathy (6%, $n = 42$), irritability (4%, $n = 27$), and anxiety (4%, $n = 23$) in the total population; sleep disorders (2%, $n = 5$) and appetite changes (1%, $n = 3$) in the HC subgroup; sleep disorders (10%, $n = 30$), apathy (7%, $n = 21$), and irritability (6%, $n = 17$) in the MCI sub-

Table 1
Population characteristics data are presented as average (standard deviation), for MMSE score [minimum; maximum] and prevalence of neuropsychiatric symptoms presented as percentage (number) in each population according to NPI subscore by behavioral domain and using either NPI >0 or NPI >3 threshold

		Control		MCI		AD		Total	
Population characteristics	N	230		308		119		657	
	Age	73.12 (6.02)		71.47 (7.44)		74.75 (8.05)		72.64 (7.19)	
	Gender ratio M/F	104/126		169/139		72/47		345/312	
	MMSE	29.00 (1.21) [24; 30]		27.98 (1.75) [24; 30]		23.11 (2.08) [19; 26]		27.45 (2.67) [24; 30]	
	Education (years)	16.60 (2.53)		16.38 (2.63)		15.86 (2.58)		16.36 (2.6)	
	NPI total	1.03 (2.63)		4.03 (6.33)		7.83 (9.11)		3.66 (6.45)	
	GDS	0.79 (1.09)		1.80 (1.45)		1.71 (1.52)		1.43 (1.43)	
	APOE ε2	8%		4%		3%		5%	
	APOE ε3	77%		64%		51%		66%	
	APOE ε4	14%		32%		45%		28%	
Mean ^{18}F-florbetapir cortical uptake	frontal	1.29 (0.25)		1.39 (0.29)		1.57 (0.28)		1.39 (0.29)	
	cingulate	1.38 (0.26)		1.47 (0.29)		1.63 (0.27)		1.47 (0.29)	
	parietal	1.30 (0.26)		1.39 (0.29)		1.57 (0.28)		1.39 (0.29)	
	temporal	1.22 (0.23)		1.30 (0.27)		1.47 (0.27)		1.30 (0.27)	
	Cortical summary ROI (SUVR)	1.11 (0.18)		1.22 (0.22)		1.38 (0.21)		1.21 (0.23)	
NPI Scores		>0	>3	>0	>3	>0	>3	>0	>3
NPI Domains	Delusions	0% (0)	0% (0)	2% (5)	0% (1)	8% (9)	4% (5)	2% (14)	1% (6)
	Hallucinations	0% (0)	0% (0)	1% (4)	0% (1)	4% (5)	0% (0)	1% (9)	0% (1)
	Agitation	3% (7)	0% (1)	16% (49)	4% (12)	32% (38)	8% (9)	14% (94)	3% (22)
	Depression	8% (18)	1% (2)	28% (87)	4% (12)	36% (42)	7% (8)	22% (147)	3% (22)
	Anxiety	4% (9)	1% (2)	14% (44)	5% (15)	24% (28)	5% (6)	12% (81)	4% (23)
	Euphoria	0% (0)	0% (0)	2% (6)	0% (1)	2% (2)	1% (1)	1% (8)	0% (2)
	Apathy	3% (7)	0% (0)	15% (47)	7% (21)	41% (48)	18% (21)	16% (102)	6% (42)
	Disinhibition	2% (5)	0% (0)	8% (24)	1% (4)	18% (21)	3% (4)	8% (50)	1% (8)
	Irritability	8% (19)	1% (2)	21% (64)	6% (17)	31% (37)	7% (8)	18% (120)	4% (27)
	AMB	1% (2)	0% (0)	3% (9)	1% (4)	11% (13)	4% (5)	4% (24)	1% (6)
	Sleep disorder	11% (26)	2% (5)	22% (68)	10% (30)	17% (20)	0% (0)	17% (114)	0% (1)
	Appetite changes	3% (6)	1% (3)	7% (22)	3% (10)	23% (27)	8% (9)	8% (55)	3% (22)

Control, healthy control group; MCI, mild cognitive impairment group; AD, Alzheimer's disease group; GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; MMSE, Mini-Mental State Examination; SUVR, standard uptake value ratio; AMB, aberrant motor behavior. Prevalence of each allele type is provided for each of the subsamples.

group; and apathy (18%, $n = 21$), appetite changes (8%, $n = 9$), and agitation (8%, $n = 9$) in the AD subgroup.

Correlation analysis

Significant partial correlations adjusted for age, gender, MMSE, and education level between ^{18}F-florbetapir cortical uptake and BPSD are summarized in Table 2.

As expected, amyloid brain deposition increases along the diagnostic continuum from HC to AD.

Anxiety was correlated with a higher amyloid deposition in the frontal subregions, particularly in patients with MCI, while irritability in AD patients, was correlated with higher ^{18}F-florbetapir cortical uptake in parietal subregions. However, converging with previous findings, we observed that global cortical uptake and regional cortical uptake were strongly intercorrelated (correlation coefficients were systematically higher than 0.7).

In the total population, positive significant correlations were found respectively between anxiety and ^{18}F-florbetapir cortical uptake (global: $r = 0.099$, $p = 0.010$; frontal: $r = 0.102$, $p = 0.009$; cingulate: $r = 0.083$, $p = 0.034$); between irritability and ^{18}F-florbetapir cortical uptake (global: $r = 0.093$, $p = 0.017$; frontal: $r = 0.089$, $p = 0.022$; cingulate: $r = 0.085$, $p = 0.029$; parietal: $r = 0.087$, $p = 0.025$); and between hallucinations and ^{18}F-florbetapir cortical uptake (global: $r = 0.078$, $p = 0.044$; frontal: $r = 0.077$; $p = 0.049$; cingulate: $r = 0.079$, $p = 0.042$), parietal: $r = 0.081$, $p = 0.038$).

In the MCI subgroup, anxiety was also significantly correlated with amyloid deposition (^{18}F-florbetapir cortical uptake: global: $r = 0.14$, $p = 0.013$; frontal: $r = 0.126$, $p = 0.027$). No other significant correlations were found with other BPSD.

In the AD subgroup, irritability was correlated with parietal amyloid deposition ($r = 0.201$, $p = 0.029$), while we did not observe any correlation between ^{18}F-florbetapir global cortical uptake and irritability.

No significant correlations were found with other BPSD in the HC subgroup.

Groups comparison

Significant odds ratios were found between anxiety and ^{18}F-florbetapir cortical uptake in the total population (OR = 4.19, CI = [1.37, 17.12]) and in the MCI subgroup (OR = 4.19, CI = [1.37, 17.12]) (see Table 2).

In the total population, participants with NPI-anxiety subscore >3 ($n = 23$) had more frontal (1.38 ± 0.29 versus 1.5 ± 0.25), cingulate (1.46 ± 0.29 versus 1.59 ± 0.27), temporal (1.3 ± 0.27 versus 1.39 ± 0.25), and global ^{18}F-florbetapir uptake (1.21 ± 0.23 versus 1.32 ± 0.2) (see Table 3); participants with a NPI-Irritability subscore >3 ($n = 120$) had a more global (1.19 ± 0.22 versus 1.28 ± 0.25) and regional uptake (frontal: 1.37 ± 0.28 versus 1.47 ± 0.33; cingulate: 1.45 ± 0.28 versus 1.54 ± 0.33; temporal: 1.37 ± 0.28 versus 1.47 ± 0.32; parietal: 1.29 ± 0.26 versus 1.36 ± 0.29).

Using a NPI-domain subscore >0, subjects with depression ($n = 147$) had significantly higher global 18F-florbetapir uptake (1.2 ± 0.22 versus 1.25 ± 0.24).

In the MCI subgroup, subjects with NPI-anxiety subscore >3 ($n = 15$) had a significant increase of global cerebral ^{18}F-florbetapir uptake (1.21 ± 0.22 versus 1.33 ± 0.19).

Among the 4 principal components derived from the 12 NPI symptoms, SUVR variations were statistically correlated with PC3 (1,125; 95% CI [1,004; 1,269]). Amyloid brain deposition was also statistically correlated with APOE $\varepsilon 4$ gene status, MMSE score, age, gender, and clinical stage (see Table 4).

Table 2
Partial Spearman's correlations coefficients between neuropsychiatric inventory symptoms score and ^{18}F-florbetapir standard uptake value ratio (SUVR) in cerebral regions of interest in each population. Correlation coefficient are presented with p value in brackets with "*" for significant results

^{18}F-florbetapir cortical uptake	Frontal	Cingulate	Parietal	Temporal	Cortical summary index (SUVR)
Total population					
NPI hallucination	0.077 (0.049)*	0.079 (0.042)*	0.081 (0.038)*	0.09 (0.020)*	0.078 (0.044)*
NPI anxiety	0.102 (0.009)*	0.083 (0.034)*	0.072 (0.064)	0.073 (0.061)	0.099 (0.010)*
NPI irritability	0.089 (0.022)*	0.085 (0.029)*	0.087 (0.025)*	0.076 (0.051)	0.093 (0.017)*
MCI group					
NPI anxiety	0.126 (0.027)*	0.104 (0.070)	0.094 (0.101)	0.074 (0.196)	0.14 (0.013)*
AD group					
NPI irritability	0.175 (0.059)	0.175 (0.058)	0.201 (0.029)*	0.117 (0.209)	0.149 (0.109)

Table 3
Comparison of mean florbetapir standardized uptake value ratio (SUVR) between NPI anxiety subscore >3 and non-anxious participants in total population and in mild cognitive impairment (MCI) population. Comparison of mean florbetapir standardized uptake value ratio (SUVR) between NPI irritability subscore >0 and non-irritable participants in total population

	Anxiety Results							Irritability Results			
	Total Population			MCI Population				Total Population			
NPI Anxiety score	NPI<=3	NPI >3	*p*	NPI<=3	NPI >3	*p*	NPI Irritability score	NPI=0	NPI >0	*p*
N	634	23		293	15			537	120	
Age	72.64 (7.16)	72.5 (8.25)	0.9042	71.49 (7.4)	71.08 (8.38)	0.9042		72.39 (7.23)	73.71 (6.94)	0.0856
Gender ratio M/F	1.09	1.56	0.4098	1.17	2.75	0.1407		0.94	2.43	<1e-04*
MMSE	27.48 (2.65)	27 (2.94)	0.4672	27.97 (1.76)	28.2 (1.66)	0.6829		27.68 (2.54)	26.5 (2.98)	<1e-04*
Education (years)	16.4 (2.58)	15.22 (2.83)	0.0503	16.45 (2.6)	15 (3.07)	0.0766		16.37 (2.57)	16.33 (2.75)	0.9789
GDS	1.42 (1.43)	1.78 (1.51)	0.2102	1.8 (1.45)	1.73 (1.62)	0.7525		1.4 (1.42)	1.57 (1.48)	0.1927
APOE ε2	5%	7%	0.7006	4%	3%	0.6922		6 %	3%	0.3326
APOE ε3	40%	48%	0.4227	41%	40%	0.9154		45 %	65%	0.0597
APOE ε4	6%	46%	<1e-04*	7%	57%	<1e-04*		10 %	32%	6e-04*
NPI domain score										
Delirium	0.05 (0.49)	0.96 (2.46)	>1e-04*	0.02 (0.24)	0.47 (1.55)	2e-04*		0.07 (0.61)	0.17 (0.94)	0.0022*
Hallucination	0.02 (0.24)	0.09 (0.42)	0.211	0.03 (0.32)	0 (0)	0.6548		0.02 (0.19)	0.07 (0.42)	0.0413*
Agitation	0.33 (1.07)	1.48 (2.39)	2e-04*	0.33 (1.03)	1.47 (2.23)	0.0043*		0.19 (0.79)	1.19 (1.92)	<1e-04*
Depression	0.42 (1.05)	1.61 (1.8)	>1e-04*	0.49 (1.1)	1.93 (1.91)	1e-04*		0.35 (0.97)	0.93 (1.49)	<1e-04*
Anxiety	0.15 (0.52)	5.3 (1.55)	>1e-04*	0.15 (0.51)	5.47 (1.6)	>1e-04*		0.21 (0.94)	0.85 (1.61)	<1e-04*
Euphoria	0.04 (0.44)	0 (0)	0.5898	0.05 (0.44)	0 (0)	0.5806		0.02 (0.29)	0.12 (0.8)	0.0195 *
Apathy	0.49 (1.51)	1.87 (2.51)	>1e-04*	0.47 (1.49)	1.47 (2.36)	0.0054*		0.32 (1.2)	1.53 (2.46)	<1e-04*
Disinhibition	0.14 (0.71)	0.61 (1.75)	0.0091*	0.14 (0.71)	0.67 (2.06)	0.0702		0.1 (0.63)	0.43 (1.18)	<1e-04*
Irritability	0.44 (1.28)	1.61 (2.13)	1e-04*	0.49 (1.32)	1.53 (2.13)	0.0061*		0 (0)	2.64 (2.01)	<1e-04*
AMB	0.11 (0.67)	0.48 (1.12)	4e-04*	0.08 (0.5)	0.4 (1.12)	0.0147*		0.08 (0.5)	0.31 (1.23)	0.0025 *
Sleep disorder	0.64 (1.76)	1.52 (2.86)	0.0224*	0.89 (2.16)	1.8 (3.3)	0.0975		0.51 (1.49)	1.36 (2.72)	1e-04*
Appetite changes	0.33 (1.4)	1.65 (3.28)	1e-04*	0.25 (1.17)	0.93 (2.25)	0.0444*		0.24 (1.2)	0.99 (2.41)	<1e-04*
Amyloid SUVR										
Frontal	1.38 (0.29)	1.5 (0.25)	0.0166*	1.39 (0.3)	1.49 (0.24)	0.0721		1.37 (0.28)	1.47 (0.33)	0.0022*
Cingulate	1.46 (0.29)	1.59 (0.27)	0.0153*	1.46 (0.29)	1.59 (0.28)	0.056		1.45 (0.28)	1.54 (0.33)	0.004*
Parietal	1.39 (0.29)	1.48 (0.24)	0.0531	1.39 (0.29)	1.45 (0.23)	0.1929		1.37 (0.28)	1.47 (0.32)	0.0027*
Temporal	1.3 (0.27)	1.39 (0.25)	0.0426*	1.3 (0.27)	1.37 (0.24)	0.1743		1.29 (0.26)	1.36 (0.29)	0.007*
Global	1.21 (0.23)	1.32 (0.2)	0.0141*	1.21 (0.22)	1.33 (0.19)	0.0307*		1.19 (0.22)	1.28 (0.25)	0.0016*

Mean is presented with standard deviation. "*" indicates significant difference for p value <0.05. GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; MMSE, Mini-Mental State Examination; AMB, aberrant motor behavior; APOE, apolipoprotein E.

Table 4
Results of logistic regression using factors from principal component analysis

	Odds ratio	95% confidence interval	*p* value
PC 1 (agitation, euphoria, apathy, dishinibition, irritability)	0.969	[0.910; 1.031]	0.321
PC 2 (sleep and eating disturbances)	0.927	[0.857; 1.002]	0.056
PC 3 (depression, anxiety, AMB, delusion)	1.125	[1.004; 1.269]	0.047*
PC 4 (hallucinations)	2.860	[0.788; 71.133]	0.339
Age	1.063	[1.035; 1.093]	<1e-04*
Gender (female)	2.031	[1.353; 3.072]	7e-4*
Education level (years)	0.959	[0.888; 1.035]	0.282
MMSE	0.865	[0.764; 0.978]	0.022*
MCI (clinical stage)	2.117	[1.378; 3.267]	6e-4*
AD (clinical stage)	4.403	[1.671; 12.087]	0.003*
APOE $\varepsilon 4$ gene (number held)	4.869	[3.466; 6.967]	<1e-04*

PC, principal component; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; APOE $\varepsilon 4$, apolipoprotein E $\varepsilon 4$; AMB, aberrant motor behavior. "*" indicates a statistically significant result.

DISCUSSION

The present study investigated the relationship between BPSD and cerebral amyloid uptake using data from the ADNI cohort. Our main finding was a positive partial correlation between amyloid cortical deposition and some specific BPSD, such as anxiety and irritability. Specifically, our results suggest the existence of a positive correlation between anxiety severity and frontal, cingulate, and global amyloid deposition, and between irritability severity and frontal, cingulate, parietal and global amyloid deposition, across the diagnostic spectrum (from HC to AD).

Anxious MCI patients (NPI-anxiety subscore greater than 3) showed the highest (frontal) amyloid cerebral deposition in group comparison testing, while only irritable AD patients may specifically demonstrate the highest amyloid (parietal) cerebral deposition. However, as global and regional cortical ROI uptake measures were strongly inter-correlated, our results do not allow us to conclude on any specific pattern. Nevertheless, our findings indicate a trend deserving further investigation. One of the limitations of the present study relies on the inclusion of mild to moderate AD participants, without AD patients in the severe stages. The prevalence and typology of BPSD is known to change according to the disease severity; our study is then not fully representative of BPSDs across the full dementia spectrum [1]. Associated psychotropic medications were not added as a covariate due to lack of homogenous information in the ADNI database for concurrent medications at baseline and during follow-up. It therefore constitutes an additional limitation in our analysis.

Anxiety

After adjustment for age, gender, education and MMSE, we observed that anxiety in our total population (including patients and HC) correlated with the level of amyloid cortical deposition. (see Table 3).

More specifically, in the MCI subgroup we found a positive significant partial correlation (adjusted for age, gender, education, and MMSE) between anxiety severity and amyloid deposition, as well as a significant association between anxiety (NPI-anxiety subscore >3) and global uptake in comparison testing relative to a non-anxious group (NPI-anxiety subscore $\leq$3). In a previous FDDNP-PET study with a limited number of MCI participants, anxiety was associated with amyloid and/or tau binding in the posterior cingulate region only [22]. The presence of anxiety was also associated with abnormal CSF $A\beta_{42}$ and t-tau concentrations in a population comprising 268 MCI patients [23]. We also observed a trend between anxiety and high level of amyloid deposition in frontal and cingulate cortical grey-matter areas.

Due to the inclusion criteria, depressive symptoms should have been less represented ($n = 147$, $n = 22$ for NPI >3). Anxiety was also well represented, with $n = 81$, $n = 23$ for NPI >3. Concerning the PC analysis, factor loading of anxiety (0.548) was superior to the depressive symptoms factor loading (0.424) in PC3. Hallucination ($n = 9$, $n = 1$ for NPI >3), delusion ($n = 14$, $n = 6$ for NPI >3), and aberrant motor behavior ($n = 24$, $n = 6$ for NPI >3) were rare symptoms. Apart from PC3, Table 4 shows also other significant results from the logistic regression (for age, gender, MMSE, diagnosis, APOE $\varepsilon 4$ status) corresponding to ever identified predictive variables of amyloid burden.

Specific volumetric and functional neuroimaging data for anxiety in dementia are currently lacking. BPSD may result from an interruption in corticostriatal circuits (cortico-striato-pallido-thalamic loops) previously described by Alexander et al. [24]. More specifically, disruptions in the 'limbic' loop comprising the anterior cingulate (anterior cingulate-ventral striatum including ventromedial caudate, ventral putamen and nucleus accumbens-ventral pallidum-medial thalamus and back to anterior cingulate) and orbitofrontal (orbitofrontal cortex-ventromedial caudate and ventral striatum-internal pallidum and pars reticulate-thalamus and back to orbitofrontal cortex) loops have been associated with affective disturbances [25]. Generalized anxiety disorder studies provide an insight in emotional processing brain structures. Patients with generalized anxiety disorder show hyperactivation and greater volume of the amygdala, disturbed emotional regulation involving the ventral lateral prefrontal cortex and the anterior cingulate cortex [26]. A hyperactivated prefrontal cortex failing to trigger the emotional regulatory regions was also described [27]. One diffusion tensor imaging study investigating anxiety showed anomalies in the connectivity between prefrontal and cingulate structures and the amygdala [28]. In the present study, anxiety was associated with greater amyloid SUVR in frontal and cingulate regions, suggesting the potential role of amyloid deposition in the disruption of the 'limbic' loop within the cortical areas. As suggested by Stein and colleagues, emotional disturbances could involve both the ventral and dorsal regions of the prefrontal cortex [25]. Amyloid-related disruptions within the striatal grey matter regions leading to increased levels of anxiety are probably more debatable as ^{18}F florbetapir is typically not very pronounced in nigrostriatal regions.

Irritability

Our second main finding concerns irritability. After adjustment for age, gender, education, and MMSE, we observed that irritability in our total population (including patients and HC) correlated with the level of amyloid cortical deposition (Table 2). In group comparisons, however, despite increased male prevalence in the NPI-irritability >0 subgroup in the total population, we found increased uptake in all ROIs (including the cingulate cortex). This is partly in agreement with results from previous studies. For instance, an imaging study on 127 patients with subcortical vascular cognitive impairments found that global cerebral PiB retention was associated with higher odds of delusions and irritability among all the BPSD of the NPI scale, regardless of their small vessel disease impact [29]. An exploratory analysis on a small sample of MCI and AD subjects found that lower anterior cingulate fractional anisotropy, indicative of worsened white matter integrity in this area, was associated with higher odds of irritability [30]. Current models of irritability argue for a dysfunction of medial orbitofrontal cortex, failing to down-regulate amygdala activity [31]. In the AD subgroup, a significant positive partial correlation between parietal uptake and irritability was found. Using a simple Spearman's correlation, however, a significant negative correlation was found between all ROIs and age indicating unexpected characteristics for our AD sample and so a possible population sampling bias. The parietal lobe among subjects with irritability may be involved in attention tasks to maintain emotional and/or behavioral response in frustrating conditions as seen among preclinical Huntington disease patients [32] and children with irritability [33].

There is limited literature on irritability and functional brain imaging. Irritability is often considered a component of aggressive behavior or agitation. Cluster analysis on BPSD constantly associated irritability with agitation, and often disinhibition and euphoria giving a clue for an anterior brain dysfunction [17, 34]. Our study showed the possible role of frontal and cingulate amyloid deposition in irritability along cognitive decline.

APOE status

Prevalence and distribution of APOE genotypes in the ADNI cohort are consistent with previous epidemiologic data. All participants with a NPI subscore >0 or >3 had an increased prevalence in APOE ε4 genotypes. APOE ε4 allele is known for increasing the amyloid burden; nevertheless, the association between APOE genotypes and BPSD in AD appears to still remain unclear [35]. APOE ε4 genotype has already been associated in the ADNI cohort with higher frontal uptake [36]. This result is also confirmed by the results of our logistic regression, where APOE ε4 was found to be the best predictor of global cortical amyloid load (OR = 4,87; 95% CI = [3,47; 6,97]).

Future directions

To our knowledge, this is the first study investigating correlations between BPSD severity and cerebral

amyloid ^{18}F-florbetapir uptake in a large population comprising elderly subjects with or without cognitive impairment (from MCI to AD). Geda and colleagues previously conducted an exploratory analysis on the ADNI 1 cohort between the Neuropsychiatric Inventory–Questionnaire (NPI short version) scores and PiB uptake; after adjusting for age, gender, and education, a weak correlation was found between global PiB uptake and total NPI-Q scores, but significance was lost after adjusting for MMSE [as cited in 33]. The use of a large sample, combined with a validated ^{18}F-florbetapir PET imaging method [7], and the accuracy of a clinically relevant threshold for BPSD severity assessment are important a strengths of the present study. This study is limited, however, by its cross sectional design and the limited number of subjects with clinically relevant BPSD relative to the population sample size.

We found an increasing trend between anxiety severity and frontal, cingulate, and global amyloid deposition levels across diagnostic groups. Interestingly, anxiety severity in the MCI population showed an increased tendency with frontal and global amyloid deposition that is also supported by comparison results yielding a positive odd ratio for global deposition and anxiety. We also found an increased tendency between irritability and frontal and global amyloid deposition in the total sample, and specifically in the AD population between irritability and parietal uptake. Irritability is often included in anxiety associated to dementia definitions [23]. The DSM-V includes irritability symptoms in general anxiety disorder diagnosis criteria, irritability is cited as temper outbursts manifested verbally or behaviorally in the disruptive mood dysregulation disorder criteria's list, and still as a symptom belonging to several diagnosis [37]. The current cluster analyses of BPSD demonstrated a reliable association of irritability and agitation [20, 38], but the association with anxiety is still controversial: clusters comprising depression, agitation, anxiety, and irritability were found in two studies [38, 39]. Anxiety is consistently clustered with depression. Our results should help to explain the clinical confusion between anxiety and irritability arguing for partial overlap in physiopathologic pathways, as frontal and cingulate lobes seem to be involved in both symptoms. Data on BPSD and amyloid uptake in dementia are still lacking and specific amyloid deposition topographic patterns for each BPSD are still to be determined. A clear consensual definition of cerebral topography is also required to obtain a better comparability between studies as cortical regional boundaries often change. Previous studies on BPSD have been often based on smaller samples and showed some inconsistent results.

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SUPPLEMENTARY MATERIAL

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