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Brain Volume Predicts Behavioral and Psychological Symptoms in Alzheimer's Disease

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Abstract.
Background: Behavioral and psychological symptoms of dementia (BPSD) are frequent and troublesome for patients and caregivers. Considering possible preventive approaches, a better understanding of underlying neural correlates of BPSD is crucial.
Objective: The aim is to assess whether brain regional volume predicts behavioral changes in mild AD.
Methods: This work took part from the PACO study, a multicenter and prospective study that included 252 patients with mild AD from 2009 to 2014. Fifty-three patients were retained. Forty healthy matched control subjects from the ADNI cohort were included as controls. Voxel-based morphometry analysis was conducted to assess regional brain volume using baseline MRI scans as a predictor of future behavioral changes over a period of 18 months. Behavior was assessed at baseline and longitudinally at 6-month intervals using the shortened form of the Neuropsychiatric Inventory (NPI).
Results: The volume of 23 brain structures in frontal, temporal, parietal, occipital, subcortical regions and cerebellum predicted the evolution of NPI scores. Frontal volume was the most powerful predictor with frontal gyri, anterior cingulate cortex, and orbital gyri being particularly involved.

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[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://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: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Conclusion: To our knowledge, this is the first study assessing regional brain volumes as predictors of behavioral changes considered at earlier stages of AD. Up to 23 brain structures were associated with an increased risk of developing BPSD. Frontal lobe volume was the strongest predictor of future evolution of NPI. The involvement of multiple structures in the prediction of behavior suggests a role of the main large-scale networks involved in cognition.

Keywords: Alzheimer's disease, behavioral and psychological symptoms of dementia, Neuropsychiatric Inventory, magnetic resonance imaging, neuroimaging

INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) affect more than 80% of patients over the course of Alzheimer's disease (AD) [1]. BPSD are often the triggering events for negative outcomes and complications like emergency room consultations, psychotropic prescriptions, motor disability resulting in an excess of dependency, and increased nursing home admission rates [2]. BPSD are present at the earliest clinical AD stages [3] and their severity exponentially increases over the course of the disease [4]. To date, no curative treatment is available for AD. Therefore, a better knowledge of the hitherto poorly understood pathophysiological correlates of BPSD in AD would facilitate the development of innovative strategies targeted at prevention and care.

Anatomical magnetic resonance imaging (MRI) provides crucial clues to consider regional neurodegeneration by disclosing related cortical/subcortical structure volume decrease. A recent review of neuroimaging correlates of BPSD in AD highlighted associations between BPSD and frontal structural and metabolic changes, with a participation of diffused neural networks rather than specific brain regions. However, almost all previous studies have disclosed cross-sectional data and only considered specific BPSD. Moreover, an approach favoring the evaluation of all brain region volumes as possible predictors of all main BPSD in AD is not documented in the scientific literature [5].

Thus, the aim of this study was to assess whether regional brain volumes of the whole brain would predict behavioral changes at the mild stages of AD by using a longitudinal design.

METHODS

Study participants

The inclusion criteria were as follows: patients with a probable AD at prodromal or mild dementia stage; Mini-Mental State Examination (MMSE) score superior or equal to 20; age over 50 years; being able to complete the clinical and neuropsychological evaluations; presence of a caregiver close enough to the patient to report the onset of behavior changes; no BPS other than mild symptoms of depression, anxiety, apathy, eating disorders, sleep or eating disorders, these manifestations occurring with high prevalence at the early stage of AD.

The diagnosis of AD was based on neuropsychological evaluation and MRI biomarkers according to the Dubois et al. criteria [6]. The distinction between AD stages relied on Clinical Dementia Rating (CDR) score measured as 0.5 for prodromal stage and 1 for mild stage. This study took part in the published PACO protocol for which a complete description of the study design is available in a previous paper [7].

Two hundred and fifty-two patients were recruited between 2009 and 2014 at memory centers in Lyon, Saint Etienne, Grenoble, Nice, Saint Chamond University hospitals and Lyon psychiatric hospital and diagnosed by a neurologist or a geriatrician specialized in neurocognitive disorders. Fifty-three patients were retained for this study: 60 out of 252 underwent MRI examination due to the refusal of patients to undergo MRI scan (MRI examination was optional and most of patients had already MRI in routine care) and 7 out of 60 provided non-exploitable data.

Forty healthy control subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort took part in this study. 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 MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. We only selected controls who were age-matched, scored 30 at the MMSE, scored 0 at the baseline and the follow-up

Neuropsychiatric Inventory (NPI), and whose MR images were acquired on a 1.5 Tesla scanner. Forty ADNI subjects matched these criteria.

Informed consent and ethical consideration

All data were anonymized prior to the study. Informed written consent is obtained from both subject and caregiver before baseline assessment takes place. The study protocol has been reviewed and approved by an ethics committee (Comité de Protection des Personnes Lyon Sud Est III). All procedures are in accordance with the declaration of Helsinki. The PACO study has been registered in the clinical trials (Current Controlled Trials NCT01297140).

Study design

Patients and controls were assessed at 6-month intervals over a period of 18 months (longer for ADNI controls but not used for this study). The follow-up time period for measuring was in place in 2015. At baseline visit, the patients underwent behavioral examination and a brain MRI. If inclusion was confirmed, the patients underwent behavioral examination followed at 6-month intervals over a period of 18 months.

MRI procedures

For both patients and healthy subjects, brain MRI scans were obtained on a 1.5T MRI machine. For volumetric analyses, 1 mm isotropic 3D T1 sequences without contrast injection were performed.

For AD patients, brain MRI scans were performed at the time of diagnosis or no later than 3 months after the inclusion. A research engineer set up the exact same MR imaging protocol at each site to ensure that acquisition parameters were identical. Due to the multicenter design of the study, three brands of MRI scan were used to examine the patients.

For the healthy group, data MRI scans were downloaded from the ADNI public database (http://www.loni.ucla.edu/ADNI).

For the analyses, the same work of pre-processing for patients and controls was conducted.

Behavioral assessment

BPSD were assessed longitudinally during the initial and at each subsequent consultation with the patient. The shortened form of the Neuropsychiatric Inventory (NPI-Q) was used. The NPI-Q [8] is a questionnaire designed to collect information on neuropsychiatric problems in patients with cerebral disorders. It is an assessment questionnaire administered to the caregiver. It was designed to evaluate the severity of symptoms and their effect on the caregiver, not their frequency. Each symptom's score can range from 0 to 3 and the total NPI-Q score ranges from 0 to 36. In this study, only severity of symptoms, scored from 0 to 3, was collected. Twelve BPSD categories are covered by the questionnaire: delusions, hallucinations, agitation/aggressiveness, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, and problems with eating and sleeping. The maximum score of NPI-Q for each category of the 12 BPSD from baseline to 18 months was retained to assess brain volume.

For the healthy control group, only subjects who scored 0 at the follow-up NPI were selected.

Characteristics of the population

Descriptive data were analyzed using R (R Foundation for Statistical Computing, Vienna, Austria). Characteristics of the overall population were expressed as mean and standard deviation for continuous variables and as number of subjects and percentage for categorical variables. The cohort did not follow a normal distribution after checking by the Kolmogorov-Smirnov test. Therefore, a Wilcoxon rank sum test was applied to test age, sex, and MMSE score significance between patients and controls.

MRI analysis: voxel-based morphometry (VBM)

Regional volume differences between groups were assessed using SPM12b (Statistical Parametric Mapping, V.12b; http://www.fil.ion.ucl.ac.uk/spm) running in Matlab V.R2014b (uk.mathworks.com/products/matlab/). We followed the recommendations for designing robust VBM analyses [9]. The converted NIfTI images of the T1 MPRAGE were segmented through unified segmentation. The images were visually inspected for artifacts, bias-corrected, and tissue classified (gray matter (GM), white matter, cerebrospinal fluid (CSF) segments).

Gray matter data were spatially normalized and warped in DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) method [10], and transformed to Montreal Neurological Institute (MNI) space

(http://www.mni.mcgill.ca/). Images were then Jacobian scaled (similar tomodulation) to ensure that relative volumes of GM were preserved following the spatial normalization procedure and then smoothed with an 8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. After spatial pre-processing, the smoothed, modulated, normalized GM datasets were used for statistical analysis.

The imaging data were assessed by applying the general linear model between AD patients and healthy subjects to investigate the effects of gray matter loss associated to the risk of developing BPSD between baseline and follow-up visit. For the NPI score of the follow-up visit, the maximum score was considered among the NPI scores of 6, 12, or 18 months to reach the behavior changes of the patient.

A two-sample *t*-test was conducted to test regional GM volume differences between the AD patients and healthy subjects.

Significant effects were assessed using a threshold of $p \leq 0.001$, without correcting for multiple comparisons but with a minimum cluster size of 100 voxels.

The anatomical location was then determined using atlas from the BSPMView program version 3 (http://www.bobspunt.com/bspmview), an intuitive and customizable user interface for exploring statistical images (e.g., spmT*), including instant anatomical labeling.

Sex, age and type of MRI (e.g., GE, Phillips, Siemens) for both, ADNI controls and patients were included in the design matrix as nuisance covariates in all VBM analyses.

Total intracranial volume of each participant was calculated by summing the total tissue probability of GM, white matter, and CSF from probability maps generated during the initial segmentation step.

RESULTS

Population characteristics

Characteristics of the included participants are presented in Table 1. The median age (interquartile range) of the sample ($n = 93$) was 78 years (74–81). The mean age (SD) was 77.4 (4.8). There were 56 women (60%) and 37 men (40%). There was no difference between the AD group and the controls with regard to age and sex, and there was a significant difference in the two groups regarding MMSE ($p < 0.01$).

Descriptive BPSD

Distributions of each of the symptom domains from the NPI-Q are shown in Table 2. Anxiety and Apathy were the most prevalent BPSD during the period of follow-up (75.3% and 73.6%, respectively). Hallucinations were the least prevalent (<1%).

Table 1
Characteristics of population

	AD	Control	*p*
N	53	40	
Age			ns
mean (SD)	78 (5)	77 (4)	
median (interquartile)	79 (74–81)	75 (74–79)	
Sex			ns
F n (%)	30 (56,6)	26 (65)	
M n (%)	23 (43,4)	14 (35)	
MMSE (mean (SD))	24 (2)	30 (0)	<0.01 (2.2^{-16})
NPI score (Severity (0–3)) (Mean)			
Agitation item score	0.01	0	
Depression item score	0.22	0	
Anxiety item score	0.47	0	
Apathy item score	0.36	0	
Irritability item score	0.34	0	
Sleep disorder item score	0.15	0	
Appetite disorder item score	0.22	0	
NPI Total score (Severity (0–36)) (Mean (SD))	1.81 (1,36)	0	<0.01
CDR (mean)	0,7	0	
Type of MRI			
Phillips (n)	48	5	
GE (n)	1	15	
Siemens (n)	4	20	

Table 2
Numbers of patients presenting with BPSD from baseline to the 18 months follow-up period

NPI score severity at each period	At baseline				At 6 months				At 12 months				At 18 months			
BPSD	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Anxiety	28	25	0	0	28	16	8	1	30	11	12	0	33	7	12	1
Apathy	34	19	0	0	28	14	8	3	32	10	10	1	33	6	12	2
Irritability	35	18	0	0	32	13	8	0	32	11	8	2	31	15	7	0
Depression	40	13	0	0	39	9	5	0	35	9	9	0	40	5	8	0
Appetite disorder	41	12	0	0	42	8	3	0	46	3	3	1	45	4	4	0
Sleep disorder	45	8	0	0	42	8	3	0	42	10	1	0	45	6	2	0
Agitation	52	1	0	0	45	6	2	0	40	6	6	1	43	4	6	0
Elation	53	0	0	0	49	4	0	0	48	4	1	0	48	2	3	0
Delusions	53	0	0	0	51	0	1	1	50	1	1	1	51	0	2	0
Disinhibition	53	0	0	0	50	2	1	0	50	2	1	0	51	2	0	0
Aberrant motor behavior	53	0	0	0	52	1	0	0	52	0	0	1	51	1	1	1
Hallucinations	53	0	0	0	52	1	0	0	52	0	1	0	53	0	0	0

For the healthy control group, only subject scored 0 from the baseline to the follow-up NPI were selected.

VBM results: Brain volume as predictor of BPSD

Brain volumes that predict the occurrence of BPSD from baseline to 18 months are presented in Table 3.

Up to 23 structures predicted the occurrence of significant BPSD during the period of follow-up. The frontal cortical volume was the most powerful predictor of BPSD, especially the frontal gyrus (Fig. 1).

The BPSD for which the most structures were involved are anxiety, depression, hallucinations, and aberrant motor behavior. There was no significant structure predicting sleep disorder.

A global brain pattern proposed in Fig. 2 supports the frontal, temporal, parietal, occipital, subcortical and cerebellum volumes as predictors of incident BPSD during the 18-month follow-up period.

DISCUSSION

To our knowledge, this is the first study assessing neuroimaging brain changes as predictors of behavioral changes in mild AD. The baseline volume of up to 23 brain structures in frontal, temporal, parietal, and occipital lobes, as well as subcortical regions and cerebellum predicted the risk of future global and specific domain NPI scores changes.

Cortical volume of frontal structures was the best predictor of most of behavioral impairments. More precisely, the frontal gyrus (middle, superior, and inferior), the anterior cingulate cortex (ACC), and the orbito-frontal cortex (OFC) were particularly associated with the development of apathy, depression, anxiety, irritability, agitation, delusions, hallucinations, aberrant motor behavior, and appetite disorder. These prospective findings are consistent with several previous cross-sectional studies [5].

The middle frontal gyrus was found to be associated with the risk of developing apathy, agitation, and appetite disorder. A recent study found a correlation between apathy score and the middle frontal gyrus that represents a core structure of the Central Executive Network (CEN) [11]. The CEN is a frontoparietal system which is crucial for actively maintaining and manipulating information for decision making in the context of goal-directed behavior [12]. The association of its atrophy and the risk prediction of apathy are thus particularly relevant. The middle frontal gyrus is a structure that has shown strong connectivity with the ACC [13] which is included in the Salient Network (SN) and was found to be associated with the risk of developing hallucinations, delusions, and aberrant motor behavior in this study. The SN is a cingulate-frontal system anchored in the ACC and frontoinsular cortex, associated with the processing of emotional information [12] and with the identification of the most relevant stimuli (internal and external) to guide behaviors [14]. The ACC acts as an interface between emotions and intentional and motivated behavioral responses. An alteration of the SN has been suspected to participate to the genesis of some BPSD [15] that may explain ACC involvement in emotional behavior [14]. Indeed, agitation, disinhibition, irritability, euphoria, and aberrant motor behavior were related to enhanced connectivity in SN nodes such as the ACC [16]. The OFC, also included in the SN, was found to be associated with hallucinations and aberrant motor behavior in the present study that is in line with literature disclosing an association between OFC alteration and socially inappropriate behavior

Table 3
Voxel-based morphometry results

BPSD	Cluster location and laterality		Peak voxel MNI coordinate	Number of voxels in cluster (k)	Cluster-level *p* value with 0.001 unc.	Peak voxel *t*-value
Anxiety	Precentral gyrus	R	[37 –26 65]	2071	<0.001	4.23
	Cuneus	L	[–4 –105 20]	327	0.088	4.17
			[–5 –88 24]	262	0.122	3.58
	Precuneus	L	[–3 –57 76]	1147	0.004	4.04
	Middle occipital gyrus	L	[–33 –102 4]	229	0.147	4.02
	Calcarine gyrus	L	[3 –90 –1]	168	0.210	3.51
Apathy	Middle frontal gyrus	L	[–33 43 39]	127	0.274	3.8
Irritability	Superior frontal gyrus	L	[–20 31 50]	178	0.198	3.97
Depression	Precentral gyrus	L	[–29 –15 72]	317	0.092	4.12
	Superior parietal lobule	L	[–21 –73 50]	532	0.035	4.91
			[–21 –61 75]	167	0.211	3.94
	Postcentral gyrus	R	[20 –40 67]	341	0.082	3.51
	Angular gyrus	L	[–43 –73 37]	164	0.215	3.99
Appetite disorder	Middle frontal gyrus	L	[–32 3 67]	126	0.277	3.59
	Cerebellum	R	[16 –56 –50]	524	0.036	5.15
		L	[–20 –59 –49]	938	0.008	4.14
Agitation	Superior frontal gyrus	R	[18 5 70]	200	0.173	4.22
	Middle frontal gyrus	R	[31 39 40]	199	0.174	4
	PMFC	L	[4 –4 64]	376	0.069	3.73
	Middle cingulate cortex	L	[–2 –16 51]	487	0.042	3.93
	Precuneus	L	[–11 –58 72]	272	0.116	3.72
Elation	Middle temporal gyrus	L	[–62 –63 3]	146	0.241	3.91
Delusions	ACC	R	[11 42 27]	168	0.21 1	3.72
Disinhibition	Inferior occipital gyrus	R	[45 –74 –8]	1853	<0.001	5.11
	Inferior temporal gyrus	R	[64 –61 –6]	265	0.119	4.18
	Cerebellum	R	[30 –62 –53]	460	0.046	4.15
Aberrant motor behavior	ACC	R	[8 42 28]	392	0.065	4.45
			[6 48 15]	110	0.309	3.58
	OFC	R	[22 37 –20]	150	0.236	3.76
	Inferior frontal gyrus	R	[54 26 8]	135	0.266	3.93
			[44 25 17]	104	0.323	3.77
			[49 39 7]	179	0.197	3.66
	Rectal gyrus	L	[–6 49 –21]	889	0.009	4.15
	Superior medial gyrus	L	[–11 56 35]	206	0.168	3.74
Hallucinations	Middle frontal gyrus	R	[41 43 27]	217	0.159	3.87
	ACC	R	[7 39 31]	104	0.325	3.77
	OFC	R	[41 53 –7]	190	0.186	4.28
		L	[–37 57 –1]	113	0.304	3.77
		L	[–15 25 –23]	1483	0.001	5.99
	Superior medial gyrus	L	[–8 45 48]	244	0.137	3.92
	Middle temporal gyrus	L	[–65 –18 –17]	100	0.334	4.01
	Thalamus	R	[9 –19 9]	1296	0.002	4.26
	Caudate nucleus	R	[21 10 18]	616	0.025	3.97
	Inferior frontal gyrus	L	[–53 23 8]	112	0.307	3.84

Clusters that survive a height threshold $p < 0.001$ (uncorrected) and an extent threshold of 100 voxels are reported. ACC, anterior cingulate cortex; OFC, orbito-frontal cortex; PMFC, posterior medial frontal cortex.

[17]. Previous studies have shown that OFC, ACC [12, 14], and superior frontal gyrus [18] are involved in the regulation of social and emotional behavior and that the middle frontal gyrus is involved in social and sexual behavior [19].

The involvement of frontal-limbic circuits in pathogenesis of main BPSD is consistent with findings of abnormalities in prefrontal areas but also in temporal and sub-cortical areas. In this study, these structures were found to be associated with the risk to develop hallucinations, disinhibition, and euphoria. Regarding networks involvement, in addition to frontal structures, the SN also includes subcortical structures which are important for detecting emotional and reward saliency [12]. In line with our study, hallucinations were found to be associated with brain changes in the basal ganglia [20] and medial temporal lobe [21]. Also, a recent systematic review is in

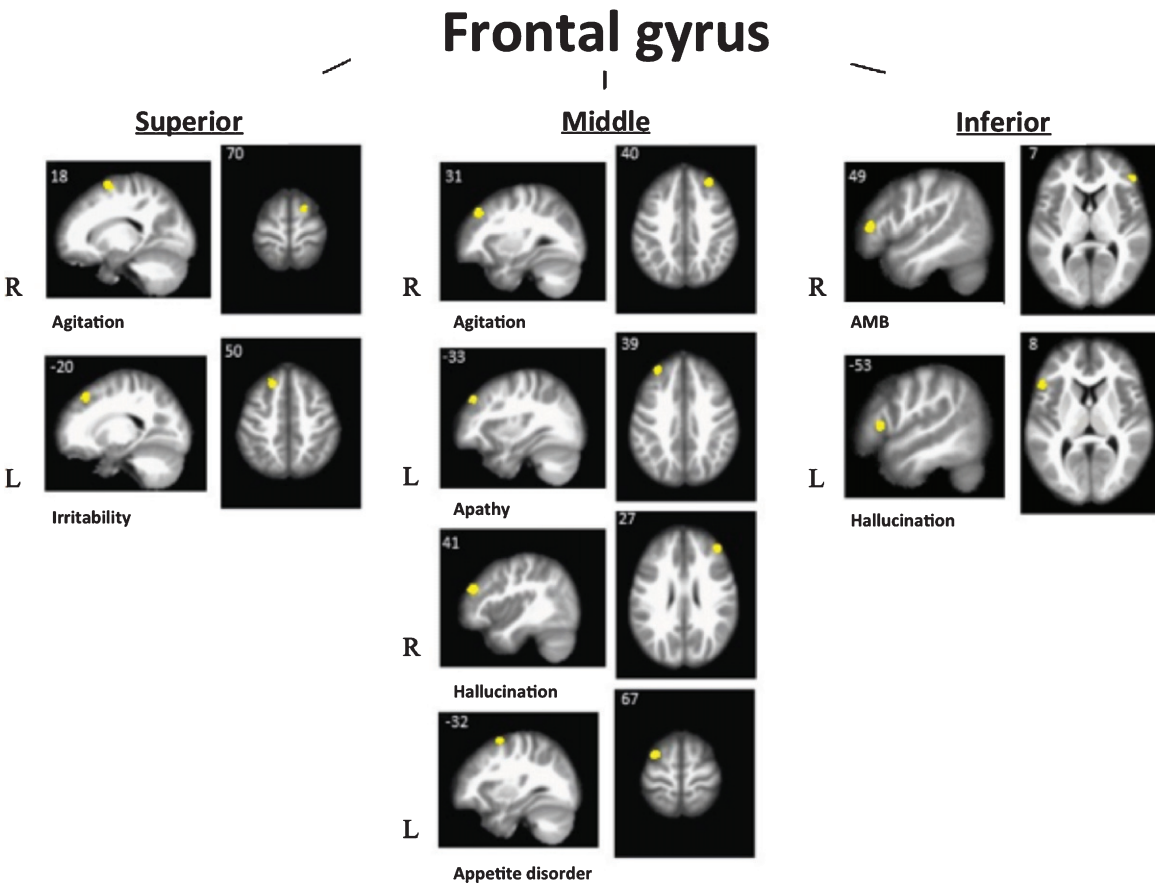

Fig. 1. Frontal gyrus volume predicts several BPSD. Numbers are X and Z coordinates of MNI Space. Yellow spots are brain volume (threshold $p < 0.001$ (uncorrected) and extent threshold of 100 voxels). AMB, aberrant motor behavior.

keeping with our results and has demonstrated that psychotic symptoms are associated in most of the studies with either a volume reduction or a decreased metabolism in OFC, ACC, and temporal lobes [22]. Harding et al. found that visual hallucinations in Lewy body disease were related to the quantity of Lewy bodies found in the temporal lobe [23].

The medial temporal lobe, associated with the risk of developing euphoria and hallucinations in the present study, was shown to be a robust predictor of AD progression [24]. Prominent nodes in the medial temporal lobe are part of the default mode network (DMN) which is associated with emotion regulation [25].

The present study also showed parietal and occipital cortical volume predicting some NPI domain changes like anxiety, depression, agitation, and disinhibition. Cross-sectional studies have found associations between agitation, anxiety, and depression and brain changes in parietal lobes [5]. Interestingly, in addition to a prediction by the volume of the parietal lobe, these three BPSD domains were found to be predicted by frontal lobe volume. More precisely in this study, depression and anxiety were both found to be predicted by precentral gyrus volume. Li et al. found that depression was associated in MCI patients with frontal and parietal structures that are included in DMN [26]. In AD, agitation was associated with neurodegeneration affecting the anterior SN that may reduce capacity to process and regulate behaviors properly [27]. Agitation, depression, and anxiety seem to be associated with changes in the same anatomical structures, corroborating some sharing of common pathophysiological mechanisms and usual coexistence [28].

Occipital structures predicting anxiety and disinhibition in the present study was an unexpected finding. This contrasts with a number of prior cross-sectional studies in which anxiety and disinhibition were never associated with occipital structures and in which visual hallucinations were more associated with occipital region [5]. However, other prior cross-

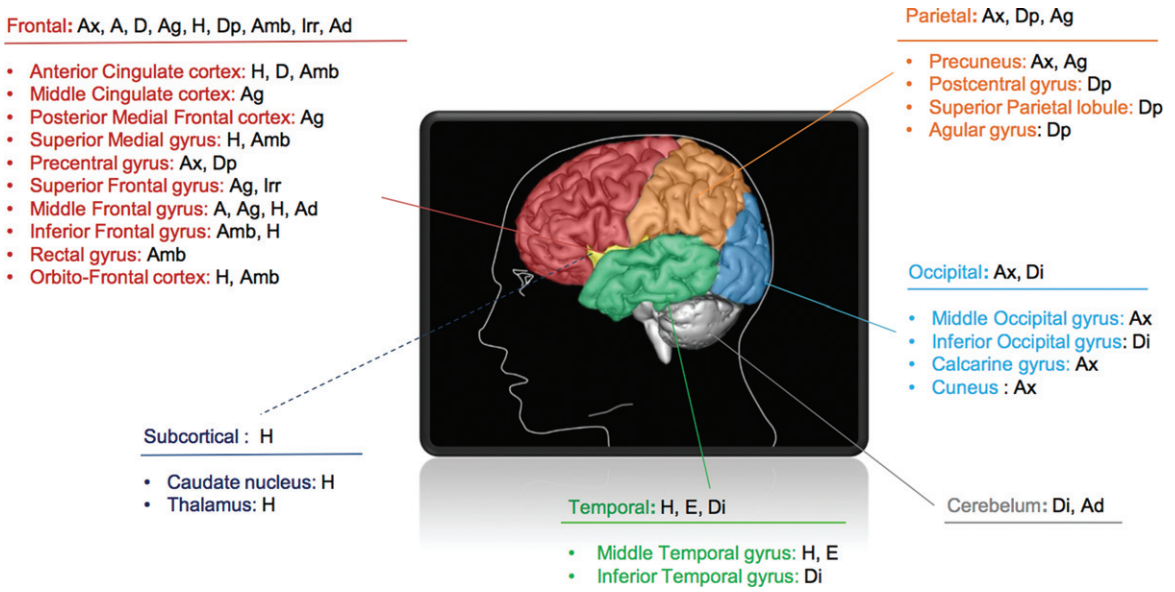

Fig. 2. Brain volume as predictor of BPSD. Up to 23 structures predicted the occurrence of significant BPSD. D, delusions; A, apathy; Dp, depression; Ag, agitation; H, hallucinations; Ax, anxiety; Amb, aberrant motor behavior; Di, disinhibition; Irr, irritability; Ad, appetite disorders; E, euphoria; S, sleep disorders.

sectional studies did not find a relationship between hallucinations and brain changes in occipital structures [29]. Hallucinations typically occur later in AD, whereas in this study patients were considered at mild stages of AD. The absence of long-term follow-up could thus underestimate any relationship between occipital neurodegeneration and risk of hallucination.

The present data disclose the cerebellum as being a predictor of disinhibition and appetite disorders. The risk of developing disinhibition was also associated with the subcortical and temporal region. Very few studies reported the cerebellum being associated with some BPSD [30]. A strong and sustained reciprocal connection between the deep cerebellar nuclei to the thalamus and then on to the (prefrontal) cerebral cortex, called the cerebello-thalamic-cortical pathway [31], neuroanatomically accounts for the cerebellum's role in numerous behavioral processes [32]. Consistent with our findings, in healthy individuals, the cerebellum is involved in feeding control via autonomic and visceral control [33]. Also, a higher increase in sensitivity to appetitive stimuli was observed in cerebellum in schizophrenic patients [34]. The effect of AD pathology on neurochemical alterations in the cerebellum requires further examination due to its possible underestimated role in the pathophysiology of BPSD.

Most of the structures found to predict BPSD are among those that represent components of the three networks SN, DMN, and CEN [35]. These results suggest that the dynamic interaction between functional state of SN, DMN, and CEN, may be associated with the risk of developing BPSD in neurodegenerative conditions. To understand the association between the risk of developing these BPSD and each region of the brain, we have to overcome a modular vision and understand how neural networks are involved. The SN plays a crucial role in switching between the CEN and the DMN [35].

Also, Stern et al. investigated the presence of a single network as a likely candidate for a generic cognitive reserve network which was shown to be centered in the right and left superior frontal (BA 10), left medial frontal (BA 9), right medial frontal (BA 6 and 8), and left middle frontal (BA 8) gyri [36]. Interestingly, these brain structures illustrated in the present study by the decrease of the cortical volume are demonstrated as being particularly associated with the risk of developing some BPSD. Furthermore, AD is marked by changes in behavior associated with an impairment in executive functions subserved by the frontal lobes [37]. Early dysfunction and neurodegeneration of frontal lobe region may lead to a decline of cognitive functions subserving behavioral control and thus, to a "behavioral reserve" associated to social insertion. Further studies are needed to disclose an association between cogni-

tive reserve and the risk of developing BPSD in light of brain volume changes.

The present study has strengths. All included AD patients were clinically and behaviorally well characterized from the inclusion thanks to standardized inclusion criteria. Prior studies differed from these analyses by focusing on smaller samples constituted solely of patients at later stages of AD. Studies including a control group are under-represented. This study examined longitudinal data unlike most of studies assessing cross-sectional data. There are also limitations to the present study. The absence of long-term follow-up could underestimate the links between regional brain volumes and BPSD that are rarely observed in mild AD. Some therapeutics have been shown to modify the natural characteristics of some BPSD. The influence of drugs was not considered in this study. However, patients taking any neuroleptic or psychotropic medication were not included at baseline. Also, it is difficult to conclude with reliability about delusion, disinhibition, aberrant motor behavior, and hallucinations since they based on less than 10% of patients suffering from these BPSD.

Multiple comparisons correction was not performed in the VBM analyses. We attempted to overcome the chance factor in keeping only a minimum cluster size of 100 voxels. We have also used a threshold of $p \leq 0.001$ (and not 0,05) as usually used in the VBM study when multiple comparison correction is not applicable [38]. Also, mixed effect model would be more appropriate. But, this requires a larger study. Thus, this work has to be considered as a pilot study.

The selection of our study control population and the relatively small sample size of our study limit the generalizability of our findings. Therefore, our findings will need to be confirmed in a larger population-based cohort.

Our findings support an emerging framework disclosing early neuroanatomical brain changes, especially frontal changes affecting the SN, DMN, and CEN as a predictor of BPSD. The SN has been proposed as a key target for neuromodulation treatments across a variety of psychiatric illnesses [39]. With respect to SN nodes and their downstream regulatory loops, both invasive and non-invasive brain stimulation techniques appear capable of modulating the activity of these circuits by imposing long-term changes in cortical nodes that cascade through the SN loop. These changes are accompanied by alterations in affect and behavior in the patient receiving treatment [40]. Longitudinal and prospective approaches in AD may help to better define the population that would benefit from prevention programs targeting specific BPSD and tailored to the patient's profiles.

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REFERENCES

[1] Youn JC, Lee DY, Jhoo JH, Kim KW, Choo IH, Woo JI (2011) Prevalence of neuropsychiatric syndromes in Alzheimer's disease (AD). *Arch Gerontol Geriatr* **52**, 258-263.

[2] David ND, Lin F, Porsteinsson AP, Alzheimer's Disease Neuroimaging Initiative (2016) Trajectories of neuropsychiatric symptoms and cognitive decline in mild cognitive impairment. *Am J Geriatr Psychiatry* **24**, 70-80.

[3] Serra L, Perri R, Cercignani M, Spanò B, Fadda L, Marra C, Carlesimo GA, Caltagirone C, Bozzali M (2010) Are the behavioral symptoms of Alzheimer's disease directly associated with neurodegeneration? *J Alzheimers Dis* **21**, 627-639.

[4] Fernandez-Martinez M, Molano A, Castro J, Zarranz JJ (2010) Prevalence of neuropsychiatric symptoms in mild cognitive impairment and Alzheimer's disease, and its relationship with cognitive impairment. *Curr Alzheimer Res* **7**, 517-526.

[5] Boublay N, Schott AM, Krolak-Salmon P (2016) Neuroimaging correlates of neuropsychiatric symptoms in Alzheimer's disease: A review of 20 years of research. *Eur J Neurol* **23**, 1500-1509.

[6] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P (2007) Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. *Lancet Neurol* **6**, 734-746.

[7] Rouch I, Dorey J-M, Boublay N, Henaff M-A, Dibie-Racoupeau F, Makaroff Z, Harston S, Benoit M, Barrellon M-O, Fédérico D, Laurent B, Padovan C, Krolak-Salmon P, PACO group (2014) Personality, Alzheimer's disease and behavioural and cognitive symptoms of dementia: The PACO prospective cohort study protocol. *BMC Geriatr* **14**, 110.

[8] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology* **44**, 2308-2314.

[9] Celle S, Delon-Martin C, Roche F, Barthélémy J-C, Pépin J-L, Dojat M (2016) Desperately seeking grey matter volume changes in sleep apnea: A methodological review of magnetic resonance brain voxel-based morphometry studies. *Sleep Med Rev* **25**, 112-120.

[10] Ashburner J (2007) A fast diffeomorphic image registration algorithm. *Neuroimage* **38**, 95-113.

[11] Joo SH, Lee CU, Lim HK (2017) Apathy and intrinsic functional connectivity networks in amnestic mild cognitive impairment. *Neuropsychiatr Dis Treat* **13**, 61-67.

[12] Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* **27**, 2349-2356.

[13] Guo Z, Liu X, Jia X, Hou H, Cao Y, Wei F, Li J, Chen X, Zhang Y, Shen Y, Wei L, Xu L, Chen W (2015) Regional coherence changes in Alzheimer's disease patients with depressive symptoms: A resting-state functional MRI study. *J Alzheimers Dis* **48**, 603-611.

[14] Zhou J, Seeley WW (2014) Network dysfunction in Alzheimer's disease and frontotemporal dementia: Implications for psychiatry. *Biol Psychiatry* **75**, 565-573.

[15] Uddin LQ (2015) Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci* **16**, 55-61.

[16] Balthazar MLF, Pereira FRS, Lopes TM, da Silva EL, Coan AC, Campos BM, Duncan NW, Stella F, Northoff G, Damasceno BP, Cendes F (2014) Neuropsychiatric symptoms in Alzheimer's disease are related to functional connectivity alterations in the salience network. *Hum Brain Mapp* **35**, 1237-1246.

[17] Mega MS, Cummings JL (1994) Frontal-subcortical circuits and neuropsychiatric disorders. *J Neuropsychiatry Clin Neurosci* **6**, 358-370.

[18] Phillips ML, Ladouceur CD, Drevets WC (2008) A neural model of voluntary and automatic emotion regulation: Implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry* **13**, 829, 833-57.

[19] Bramham J, Morris RG, Hornak J, Bullock P, Polkey CE (2009) Social and emotional functioning following bilateral and unilateral neurosurgical prefrontal cortex lesions. *J Neuropsychol* **3**, 125-143.

[20] Palmqvist S, Sarwari A, Wattmo C, Bronge L, Zhang Y, Wahlund LO, Nägga K (2011) Association between subcortical lesions and behavioral and psychological symptoms in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* **32**, 417-423.

[21] Lopez OL, Smith G, Becker JT, Meltzer CC, DeKosky ST (2001) The psychotic phenomenon in probable Alzheimer's disease: A positron emission tomography study. *J Neuropsychiatry Clin Neurosci* **13**, 50-55.

[22] Alves GS, Carvalho AF, de Amorim de Carvalho L, Sudo FK, Siqueira-Neto JI, Oertel-Knochel V, Jurcoane A, Knochel C, Boecker H, Laks J, Pantel J (2017) Neuroimaging findings related to behavioral disturbances in Alzheimer's disease: A systematic review. *Curr Alzheimer Res* **14**, 61-75.

[23] Harding AJ, Broe GA, Halliday GM (2002) Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain* **125**, 391-403.

[24] Weiner MW, Aisen PS, Jack CR Jr, Jagust WJ, Trojanowski JQ, Shaw L, Saykin AJ, Morris JC, Cairns N, Beckett LA, Toga A, Green R, Walter S, Soares H, Snyder P, Siemers E, Potter W, Cole PE, Schmidt M (2010) The Alzheimer's Disease Neuroimaging Initiative: Progress report and future plans. *Alzheimers Dement* **6**, 202-211.e7.

[25] Etkin A, Egner T, Kalisch R (2011) Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci* **15**, 85-93.

[26] Li Y, Jing B, Liu H, Li Y, Gao X, Li Y, Mu B, Yu H, Cheng J, Barker PB, Wang H, Han Y (2017) Frequency-dependent changes in the amplitude of low-frequency fluctuations in mild cognitive impairment with mild depression. *J Alzheimers Dis* **58**, 1175-1187.

[27] Trzepacz PT, Yu P, Bhamidipati PK, Willis B, Forrester T, Tabas L, Schwarz AJ, Saykin AJ, Alzheimer's Disease Neuroimaging Initiative (2013) Frontolimbic atrophy

is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement* **9**, S95-S104.e1.

[28] Kataoka K, Hashimoto H, Kawabe J, Higashiyama S, Akiyama H, Shimada A, Kai T, Inoue K, Shiomi S, Kirike N (2010) Frontal hypoperfusion in depressed patients with dementia of Alzheimer type demonstrated on 3DSRT. *Psychiatry Clin Neurosci* **64**, 293-298.

[29] Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, O'Brien JT (1999) Medial temporal lobe atrophy on MRI in dementia with Lewy bodies. *Neurology* **52**, 1153-1158.

[30] Fischer CE, Ting WK-C, Millikin CP, Ismail Z, Schweizer TA, Alzheimer Disease Neuroimaging Initiative (2016) Gray matter atrophy in patients with mild cognitive impairment/Alzheimer's disease over the course of developing delusions. *Int J Geriatr Psychiatry* **31**, 76-82.

[31] Schmahmann JD (1996) From movement to thought: Anatomic substrates of the cerebellar contribution to cognitive processing. *Hum Brain Mapp* **4**, 174-198.

[32] Russo-Neustadt A, Cotman CW (1997) Adrenergic receptors in Alzheimer's disease brain: Selective increases in the cerebella of aggressive patients. *J Neurosci* **17**, 5573-5580.

[33] Zhu J-N, Wang J-J (2008) The cerebellum in feeding control: Possible function and mechanism. *Cell Mol Neurobiol* **28**, 469-478.

[34] Stip E, Lungu OV, Anselmo K, Letourneau G, Mendrek A, Stip B, Lipp O, Lalonde P, Bentaleb LA (2012) Neural changes associated with appetite information processing in schizophrenic patients after 16 weeks of olanzapine treatment. *Transl Psychiatry* **2**, e128.

[35] Menon V (2011) Large-scale brain networks and psychopathology: A unifying triple network model. *Trends Cogn Sci* **15**, 483-506.

[36] Stern Y, Zarahn E, Habeck C, Holtzer R, Rakitin BC, Kumar A, Flynn J, Steffener J, Brown T (2008) A common neural network for cognitive reserve in verbal and object working memory in young but not old. *Cereb Cortex* **18**, 959-967.

[37] Perri R, Monaco M, Fadda L, Caltagirone C, Carlesimo GA (2014) Neuropsychological correlates of behavioral symptoms in Alzheimer's disease, frontal variant of frontotemporal, subcortical vascular, and Lewy body dementias: A comparative study. *J Alzheimers Dis* **39**, 669-677.

[38] Shen S, Sterr A (2013) Is DARTEL-based voxel-based morphometry affected by width of smoothing kernel and group size? A study using simulated atrophy. *J Magn Reson Imaging* **37**, 1468-1475.

[39] Downar J, Blumberger DM, Daskalakis ZJ (2016) The neural crossroads of psychiatric illness: An emerging target for brain stimulation. *Trends Cogn Sci* **20**, 107-120.

[40] Di Filippo M, Picconi B, Tantucci M, Ghiglieri V, Bagetta V, Sgobio C, Tozzi A, Parnetti L, Calabresi P (2009) Short-term and long-term plasticity at corticostriatal synapses: Implications for learning and memory. *Behav Brain Res* **199**, 108-118.