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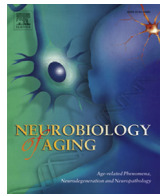
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Association of postoperative delirium with markers of neurodegeneration and brain amyloidosis: a pilot study



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ABSTRACT

The aim of the study was to investigate the association between postoperative delirium (POD) and in vivo markers of Alzheimer's disease pathology in nondemented hip fracture surgery patients. POD was assessed with the Confusion Assessment Method. Amyloid load was quantified on ¹⁸F-Flutemetamol positron emission tomography images as standardized uptake value ratio. Secondary outcome measures were gray matter volumes, white matter integrity, and functional connectivity at rest. All the patients with POD (POD+, N = 5) were amyloid negative (standardized uptake value ratio <0.59), whereas 6 out of 11 patients without POD (POD−) showed brain amyloid positivity. POD+ compared to POD− displayed: lower gray matter volumes in the amygdala ($p = 0.003$), in the middle temporal gyrus and in the anterior cingulate cortex ($p < 0.001$), increased diffusivity in the genu of the corpus callosum and in the anterior corona radiata ($p < 0.05$), and higher functional connectivity within the default mode network ($p < 0.001$). POD patients showed altered gray and white matter integrity in the fronto-limbic regions in absence of brain amyloidosis. Based on this preliminary investigation, delirium pathophysiology might be independent of Alzheimer's disease. Future studies on larger samples are needed to confirm this hypothesis.

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1. Introduction

Delirium is a neurocognitive disorder characterized by acute and fluctuating disturbance in attention and awareness with additional

changes in other cognitive domains (American Psychiatric Association, 2013), and it is commonly reported in elderly patients after major surgery (Inouye et al., 2014). Although delirium is defined by its acute onset, it is now clear that it is associated with subsequent loss of independence, increased risk of mortality, and long-term cognitive decline and dementia, even in the absence of presurgery cognitive impairment (Bellelli et al., 2014; Gleason et al., 2015). The multifactor theory for postoperative delirium (POD) etiology in elderly postulates that vulnerable brain could be less resilient to various stressors, leading to acute brain dysfunctions

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and to further inability to return to the previous levels of functioning (Inouye et al., 2014). However, the specific nature of brain vulnerabilities increasing the risk of POD in elderly and leading to the subsequent long-term cognitive impairment has to be discovered.

Alzheimer's disease (AD) is the most prevalent form of dementia, characterized by extracellular deposition of beta amyloid and intracellular accumulation of tau protein in the brain. These pathophysiological processes can be detected in vivo by surrogate markers using positron emission tomography (PET) or cerebrospinal fluid (CSF) (Scheltens et al., 2016). AD patients furthermore showed impaired structural and functional connectivity within the default mode network (DMN), which involves brain areas early affected by AD pathology such as the posterior cingulate and the precuneus, the parietal cortex, the hippocampus, and the medial prefrontal cortex (Pievani et al., 2014). Amyloid may be present in the brain up to 10–20 years before the onset of clinical symptoms (Villemagne et al., 2013), and around 30% of cognitively normal older individuals show amyloid burden (Sperling et al., 2009); therefore, the presence of cortical amyloidosis in nondemented elderly could represent a major cause of poor brain resiliency. Few studies investigating the predictive value of CSF beta amyloid for POD onset in hip fracture surgery patients led to contrasting results (Witlox et al., 2011; Xie et al., 2014). Furthermore, very recent postmortem studies in oldest-old suggested that the relationship between history of delirium and dementia was not mediated by the typical neuropathological hallmarks of classic dementia, with delirium independently and additively affecting the rate of cognitive decline (Davis et al., 2017). Studies prospectively evaluating the relationship between in vivo AD pathophysiology and POD are needed, in order to improve our understanding of delirium pathophysiology and to further ameliorate the management of patients with cognitive impairment after POD.

Recently, presurgery gray matter (GM) volume decrease in temporal and limbic lobes (Shioiri et al., 2015) and reduced white matter (WM) integrity (Cavallari et al., 2016) were found to increase vulnerability to POD in elective surgery patients. Elective surgery is an ideal approach to investigate the brain vulnerabilities predisposing to POD, since it allows neuroimaging examinations to be performed before surgery. However, individuals after nonelective surgery were a more frail population with increased risk of delirium and adverse long-term outcomes compared to the elective surgery ones, deserving further investigations (Rizk et al., 2016).

The primary aim of the present study was to use in vivo estimation of brain amyloid load and neurodegenerative processes to investigate the association between AD pathology and POD in hip fracture surgery elderly patients. Moreover, we explored the association of markers of brain structural and functional connectivity disruption with POD.

2. Materials and methods

2.1. Participants

Four hundred twenty-six patients with hip fracture were consecutively admitted in 2 Italian Orthopedic Wards (Brescia and Monza) between December 2013 and April 2015 and were screened for inclusion in the study. Eligibility criteria were (1) age over 65 years and (2) no diagnosis of cognitive impairment, dementia, or major stroke. Prefracture cognitive and functional integrity of patients were evaluated by a score: (1) greater than 7 at the New Mobility Score Questionnaire (Parker and Palmer, 1993); (2) lower than 3.9 at the Informant Questionnaire on Cognitive Decline in the Elderly (Cherbuin and Francis Jorm, 2010); and (3) lower than 9 at the Functional Activities Questionnaire (Pfeffer et al., 1982).

After recovery period, patients performed: clinical and neuropsychological evaluation, ^{18}F -Flutemetamol PET and magnetic resonance imaging (MRI) scans. The study was approved by the local ethical committees. The consent to participate in the study was collected for all patients before surgery, which took place within 24–48 hours from hospital admission.

Fig. 1 displays the flowchart of the study. Among the 151 eligible patients, 58 accepted to participate in the study. After recovery period, lasting 3–5 months, 16 participants completed the study. One patient withdrew from the scanner before the resting-state functional MRI (rs-fMRI) and diffusion tensor imaging (DTI) sequences could be acquired.

2.2. Detection of delirium and clinical and neuropsychological evaluation

POD occurrence was assessed daily for 3 days after surgery using the Confusion Assessment Method and using the review of nursing staff during the day and night shifts (Inouye et al., 1990). The assessors interact daily with nurses to confirm the delirium diagnosis, and the presence of delirium was further confirmed by identifying key words associated with delirium in daily medical and nursing notes, such as delirium, mental status change, inattention, disorientation, hallucination, agitation, inappropriate behavior, and confusion (Inouye et al., 2005).

Patients underwent a comprehensive clinical and neuropsychological evaluation, 3 months after surgery (see [Supplementary Methods](#) for details).

2.3. ^{18}F -Flutemetamol PET images acquisition and processing

Images were acquired and postprocessed using standard procedures on PET/computed tomography scanners: Siemens Biograph mCT for Brescia and GE Discovery 600 Series for Monza. Each patient received an intravenous dose of ^{18}F -Flutemetamol injection

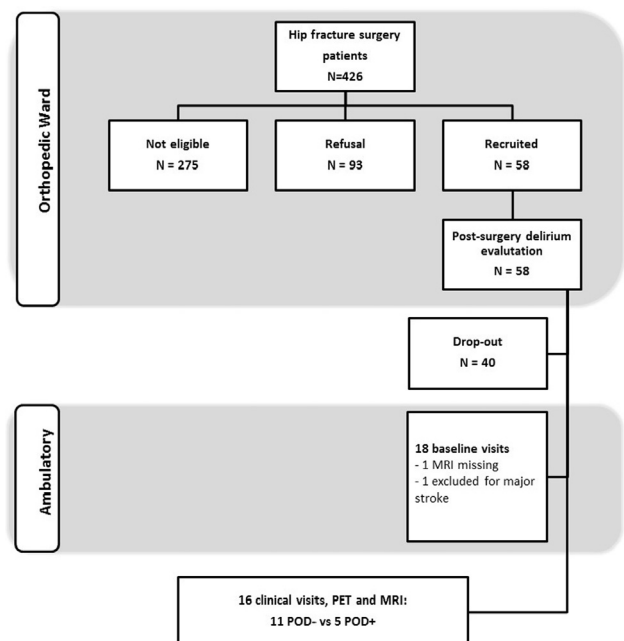


Fig. 1. Flowchart of case selection. Eligible cases were patients admitted at 2 Italian Orthopedic Wards from December 2013 to April 2015 undergoing nonelective hip fracture surgery. Reasons for noneligibility were anamnestic diagnosis of cognitive impairment or dementia. Dropouts were mainly due to prolonged recovery period.

with approximate activity of 185 MBq $\pm$ 10%. The duration of the PET imaging was 20 minutes beginning approximately 90 minutes after ^{18}F -Flutemetamol administration. Images were reconstructed iteratively on a 256×256 matrix with a 1-mm Gaussian post-reconstruction smoothing filter.

An adaptive template registration method was used to spatially normalize ^{18}F -Flutemetamol images to Montreal Neurological Institute space (Lundqvist et al., 2013). Standardized uptake value ratios (SUVRs) with pons as reference region were calculated in predefined volumes of interest: frontal, parietal, lateral temporal, anterior cingulate, precuneus, and posterior cingulate. The cortical composite region, composed of the 5 individual volumes of interest, was computed as a measure of global amyloid load. Based on previous validation on autopsy cohort, amyloid positivity was defined by SUVR greater than 0.59 (Thurfjell et al., 2014).

2.4. MRI image acquisition and processing

MRI images were acquired on 1.5 T scanner: GE Signa HDxt for Brescia and Philips Achieva for Monza. The MRI acquisition protocol was harmonized between scans according to the standardized procedures used in the Italian and European Alzheimer's Disease Neuroimaging Initiative (Cavedo et al., 2014) and included the following sequences: (1) anatomical 3D T1-weighted; (2) fluid attenuation inversion recovery; (3) DTI; and (4) rs-fMRI. Briefly, all the modalities were preprocessed by the following procedures (see [Supplementary Methods](#) for details) to investigate the pattern of neurodegeneration markers in the sample:

1. GM atrophy: Cortical reconstruction and volumetric segmentation was performed on 3D T1-weighted images with the FreeSurfer pipeline (version 5.3.0, <http://surfer.nmr.mgh.harvard.edu>) to perform segmentation of the subcortical WM and deep GM volumetric structures (including hippocampus, amygdala, caudate, putamen, and ventricles) and to obtain cortical volumes in the predefined regions of interest (ROIs) of the Desikan-Killiany atlas (Dale et al., 1999; Desikan et al., 2006). The segmentation outputs were visually inspected to confirm that no major errors were present. One subject was excluded by the ROI analysis since segmentation failed due to large regions of periventricular hypointensities. No manual edits were done on the other outputs. Right and left subcortical volumes were averaged, while the volumes of the 33 cortical ROIs per hemisphere were appropriately combined to obtain measures representing WM and GM cortical volumes of the whole brain and of the frontal, parietal, temporal, and occipital lobes (<https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation>). Subcortical and cortical volumes were proportionally normalized to the estimated Total Intracranial Volume (TIV). 3D T1-weighted images were further processed using Statistical Parametric Mapping 12 (SPM12, <http://www.fil.ion.ucl.ac.uk/spm>) running on MATLAB R2012a (MathWorks, Natick, MA, USA) to performed optimized voxel-based morphometry analysis (Ashburner, 2007; Ashburner and Friston, 2005).
2. White matter hyperintensities (WMHs) segmentation was performed using LesionTOADS software (www.mipav.cit.nih.gov) on intensity inhomogeneity-corrected fluid attenuation inversion recovery. Lesion segmentation was visually inspected and manually edited when appropriate. Lesion volumes were computed using FSLstats (version 5.0, <http://www.fmrib.ox.ac.uk/fsl/>).
3. WM microstructure alterations were measured by voxelwise analysis of DTI data, carried out using TBSS (Smith et al., 2006) (Tract-Based Spatial Statistics), part of FSL (version 4.1, <http://www.fmrib.ox.ac.uk/fsl/>). All subjects' fractional anisotropy,

mean diffusivity (MD), radial diffusivity, and axial diffusivity ($a \times D$) data were projected onto a mean tract skeleton.

4. DMN functional connectivity: rs-fMRI images were realigned, normalized to Montreal Neurological Institute space, and smoothed with a 6-mm full-width at half maximum isotropic Gaussian kernel with SPM8, to perform independent component analysis (ICA) with the Group ICA toolbox (Calhoun et al., 2001) (GIFT v3.0a, <http://mialab.mrn.org/software/gift/index.html>) and the FastICA approach (Hyvärinen et al., 1997). The estimated number of independent components was 39, a dimension determined using the minimum description length criteria. A back-reconstruction step was then used to compute the individual maps from the group maps. The estimated spatial maps were then converted into Z scores. The DMN was identified with a template matching spatial correlation procedure using a previously published DMN template (Shirer et al., 2012).

2.5. Statistical analysis

Statistical analysis was performed using SPSS 19 statistical software (IBM, Armonk, NY, USA). Two-tailed independent sample *t*-test for continuous variables and Fisher's exact test for dichotomous variables were used to compare patients who completed the study ($N = 16$) with those who dropped out ($N = 40$).

Mann-Whitney Test and Fisher's exact test were performed when appropriate to compare sociodemographics and clinical features, SUVR values, WMHs volumes, whole-brain, lobar, and subcortical volumes between POD-positive (POD+; $N = 5$) and POD-negative (POD-; $N = 11$) patients.

Voxelwise GM volume differences between groups were investigated with 2 sample *t*-tests using SPM12. TIV computed with FreeSurfer and scanner type were entered in the model as nuisance covariates. Statistical threshold was set at $p < 0.001$ uncorrected, with a spatial threshold of 50 voxels.

DTI voxelwise statistic was performed to compare groups controlling for scanner, using a permutation-based inference tool for nonparametric statistical thresholding, with 5000 permutations (Nichols and Holmes, 2002). The threshold was set at $p = 0.05$, corrected for multiple comparisons at the cluster level using the threshold-free cluster enhancement option.

One-sample *t*-test was performed on the DMN component to extract the group mean spatial map from the whole sample, using a threshold of $p < 0.005$ corrected for multiple comparisons with false discovery rate (FDR) and with a spatial threshold of 100 voxels. The resulting map was used as inclusive mask for the subsequent voxelwise 2 sample *t*-test group comparisons. *T*-threshold was set at $p < 0.001$ uncorrected, with a spatial threshold of 20 voxels.

3. Results

3.1. Clinical and sociodemographic features

Sociodemographics and presurgery clinical status were comparable between the study sample ($N = 16$) and the drop-out patients ($N = 40$) ([Supplementary Table 1](#)). Thirty-one percent of patients who completed the study developed delirium after surgery. POD+ ($N = 5$) and POD- ($N = 11$) patients showed similar sociodemographics features, physical comorbidity, and independence in daily activities, although POD+ showed reduced Informant Questionnaire on Cognitive Decline in the Elderly score ([Table 1](#)). There were no differences between groups in surgery procedures: the majority of patients in both groups underwent arthroplasty instead of internal fixation (73% in POD- group, 60% in POD+ group,

respectively, $p = 1.00$ at Fisher's exact test), all POD+ patients underwent spinal anesthesia, while 2 out of 11 POD– patients underwent general anesthesia ($p = 1.00$ at Fisher's exact test).

After recovery period, POD+ compared to POD– showed impaired global cognition and reduced verbal long-term memory and verbal fluency (Table 1).

3.2. Brain amyloid load

Based on global SUVR threshold, all POD+ were amyloid negative, while 45% of POD– were amyloid positive. POD+ patients had regional SUVR values always below or close to the threshold (Fig. 2). Mean SUVR values were not different between POD+ and POD– (Supplementary Table 2).

3.3. GM atrophy

Supplementary Table 3 describes whole-brain, lobar, and subcortical volumes comparisons between groups: POD+ compared to POD– showed a significant reduction of GM volumes in temporal lobes (POD– = 87.3 ± 5.3 , POD+ = 75.1 ± 6.8 ; $p = 0.014$) and in the amygdala (POD– = 1.3 ± 0.2 , POD+ = 1.0 ± 0.2 ; $p = 0.003$).

Table 1

Sociodemographic and presurgery clinical features were comparable between postoperative delirium positive (POD+) and negative (POD–) patients, except for IQCODE scores denoting greater informant-reported cognitive decline in POD+

Clinical and neuropsychological features of the sample	POD–, N = 11	POD+, N = 5	p
Presurgery			
Sociodemographics			
Age, y	78 ± 7	82 ± 2	0.156
Sex, females	10	3	0.214
Education, y	8 ± 4	9 ± 4	0.341
Physical comorbidity (CIRS)			
Comorbidity index	2.2 ± 1.2	2.2 ± 0.8	0.953
Severity index	1.4 ± 0.2	1.4 ± 0.1	0.512
Cognitive and functional performance			
New Mobility Score Questionnaire	8.7 ± 0.5	8.6 ± 0.5	0.622
Informant Questionnaire on Cognitive Decline in the Elderly	3.1 ± 0.1	3.3 ± 0.0	0.017
Functional Activities Questionnaire	1.0 ± 1.5	2.8 ± 2.2	0.113
After recovery period			
Time from surgery (d)	88 ± 45	112 ± 60	0.533
Risk of falling (Tinetti scale)			
Balance	12 ± 3	10 ± 3	0.389
Gait	9 ± 2	8 ± 3	0.318
Neuropsychological tests ^a			
Mini–Mental State Examination	28 ± 3	23 ± 6	0.045
Clock-drawing test	3 ± 2	4 ± 1	0.056
Word list learning	50 ± 8	36 ± 13	0.036
Word list delayed recall	11 ± 3	7 ± 4	0.047
Logical memory	13 ± 4	8 ± 5	0.047
Complex figure copy	29 ± 9	21 ± 18	0.671
Complex figure recall	16 ± 6	9 ± 4	0.066
Trail Making Test part A (s)	46 ± 28	95 ± 70	0.176
Trail Making Test part B (s)	192 ± 242	390 ± 172	0.116
Category fluency	40 ± 8	25 ± 4	0.002
Letter fluency	33 ± 9	19 ± 9	0.027
Behavioral and affective symptoms			
Neuropsychiatric Inventory	9 ± 23	17 ± 17	0.053
Geriatric Depression Scale	4 ± 3	3 ± 1	0.357

Values denote mean ± standard deviation for continuous variables or counts for dichotomous variables. p values indicate statistical significance Mann-Whitney Test for continuous variables or Fisher's exact test for dichotomous variables. Bold values indicate significant differences ($p < 0.05$).

Key: CIRS, comorbidity index rating scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

^a Age and education adjusted neuropsychological tests scores are displayed.

POD+ compared to POD– showed reduced GM volume in the right middle temporal gyrus and in the anterior cingulate cortex at voxel-based morphometry analysis (Fig. 3). No significant differences were found for the opposite contrast (POD+ > POD–). No clusters survived with corrections for multiple comparisons using FDR.

3.4. WM alterations

WMH volumes (cc) did not differ between groups (POD– = 17.9 ± 25.8 , POD+ = 19.9 ± 19.4 ; $p = 0.692$ at Mann-Whitney Test).

Voxelwise tract-based analysis showed no significant differences between groups in fractional anisotropy. However, POD+, compared to POD–, showed altered diffusivity in several regions: higher MD, radial diffusivity, and $a \times D$ in the genu of the corpus callosum and in the anterior corona radiata, higher MD and $a \times D$ in the body of corpus callosum and the superior corona radiata, increased MD in the left posterior thalamic radiation, and increased $a \times D$ in the anterior limb of internal capsule, the cingulum, and the superior longitudinal fasciculus of the right hemisphere (Fig. 4).

3.5. DMN functional connectivity

POD+ compared to POD– showed increased connectivity within the DMN, bilaterally in the superior parietal cortex (Fig. 5). No significant differences were found for the opposite contrast (POD+ < POD–). No clusters survived with corrections for multiple comparisons using FDR.

4. Discussion

This is the first study investigating in vivo markers of AD in patients with POD. Our results show a pattern of reduced GM volumes and WM integrity in the right temporal and bilateral medial frontal areas, in the absence of cortical amyloidosis.

These preliminary findings suggest that brain amyloidosis is unlikely to be a major cause of poor brain resiliency increasing the risk of POD after nonelective surgery.

4.1. Brain amyloid load

The analysis of ¹⁸F-Flutemetamol scans revealed SUVR values below the threshold of positivity in all the patients who manifested POD. Previous investigations on the relationship between AD biomarkers and risk of POD in humans found no association between presurgery levels of CSF beta amyloid concentration and risk of POD in older patients (Witlox et al., 2011; Xie et al., 2014). Conversely, when amyloidosis and neurodegeneration markers were jointly considered, an association between lower CSF beta amyloid to tau ratio and increased risk of POD was found (Xie et al., 2014). Furthermore, recent postmortem investigations on oldest-old found that delirium act independently and additively to AD neuropathologic process (Davis et al., 2012, 2017). Our study is partially in line with these findings, showing a lack of association between POD and in vivo AD pathophysiology by amyloid PET.

4.2. Regional GM atrophy

POD-positive patients displayed a 30% of atrophy in the amygdala and decreased GM volumes in the right middle temporal gyrus and in the dorsal anterior cingulate cortex. Previous studies found no association between hippocampal volumes and POD (Cavallari et al., 2015), while the fusiform gyrus and the middle temporal gyrus showed moderate accuracy in predicting delirium (Shioiri et al.,

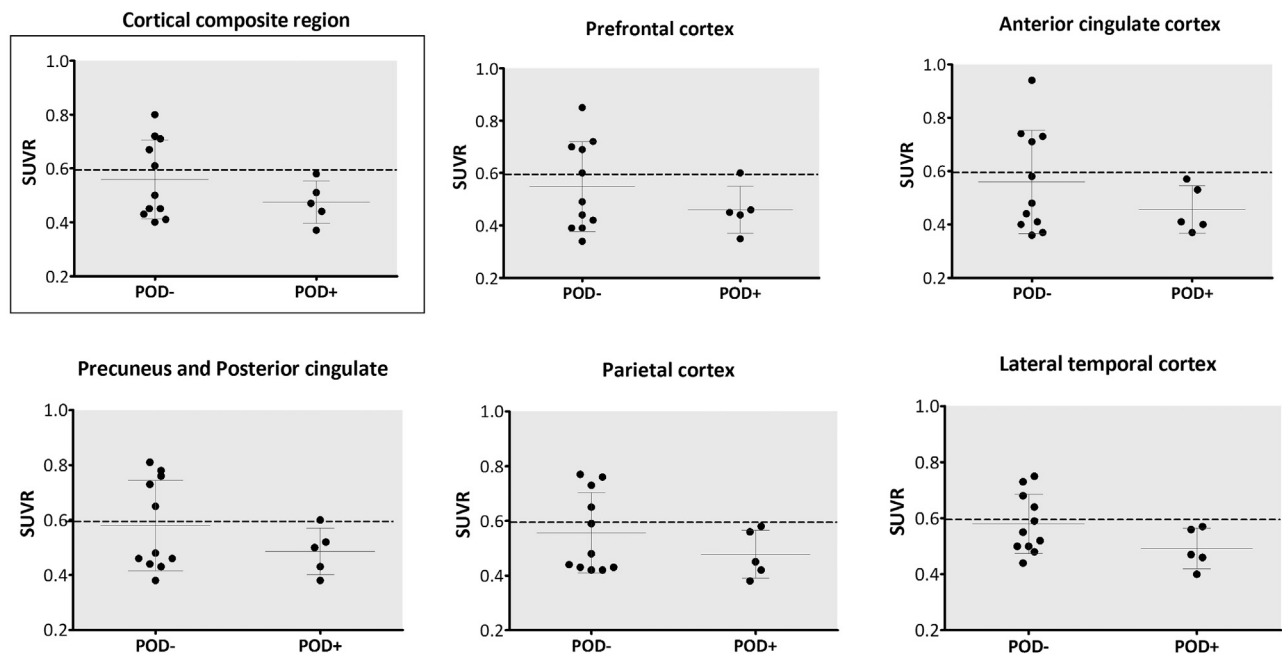


Fig. 2. Composite and regional standardized uptake value ratio (SUVR) denoting brain amyloid load under the threshold of positivity in all postoperative delirium positive (POD+) patients. Dotted line denotes the SUVR threshold for positivity (0.59). POD–: postoperative delirium negative. Cortical composite region is a measure of global amyloid load, composed of the relevant 5 individual cortical regions displayed.

2015). These latter findings are in line with our results describing a significant GM reduction in the right middle temporal gyrus.

4.3. WM microstructure alterations

We found comparable WMHs in POD-positive and POD-negative patients, in line with previous findings on a large sample of non-demented patients older than 70 years, showing that WMHs

volumes were not associated with POD incidence after elective surgery (Cavallari et al., 2015).

Our POD+ patients showed reduced WM microstructure integrity in medial frontal area and in the right fronto-temporal tracts. Specifically, alterations in all the diffusion indexes were found in the genu of the corpus callosum and in the anterior corona radiata, while increased axial diffusivity was found in the cingulum and in the superior longitudinal fasciculus. Furthermore, increased mean

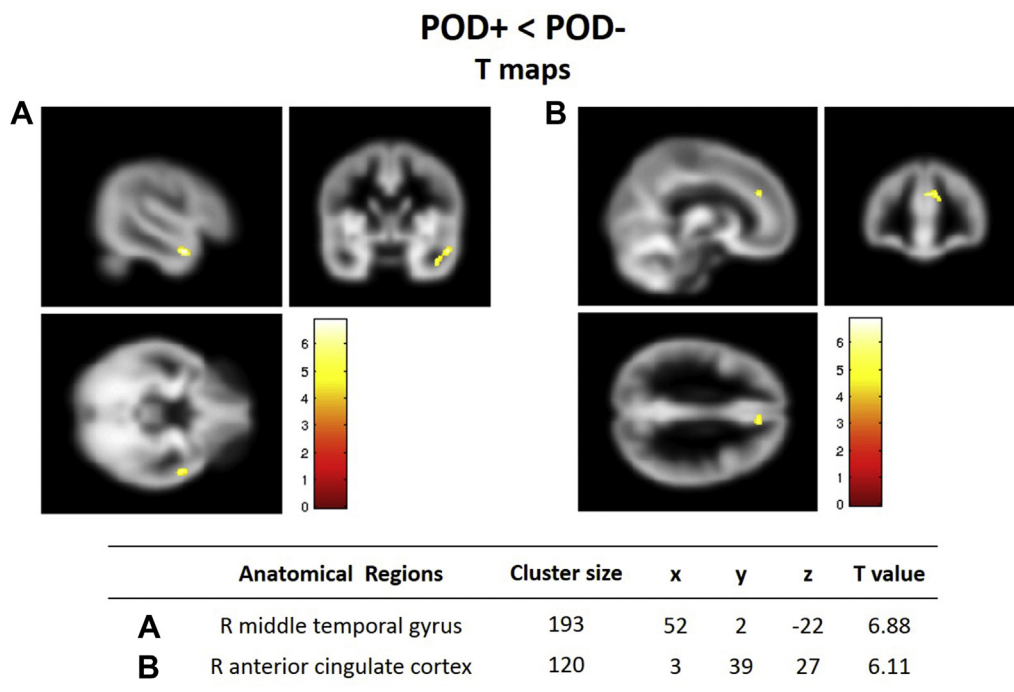


Fig. 3. Results from the VBM DARTEL analysis showed reduced gray matter volumes in the right temporal and cingulate cortices in postoperative delirium positive (POD+) patients compared to postoperative delirium negative (POD–) ones. Statistical parametric maps are overlaid on the study-specific GM template. Statistical significance is set at $p < 0.001$ uncorrected with cluster size > 50 voxels. Data refer to the whole study population of 11 POD– and 5 POD+. Abbreviation: VBM, voxel-based morphometry.

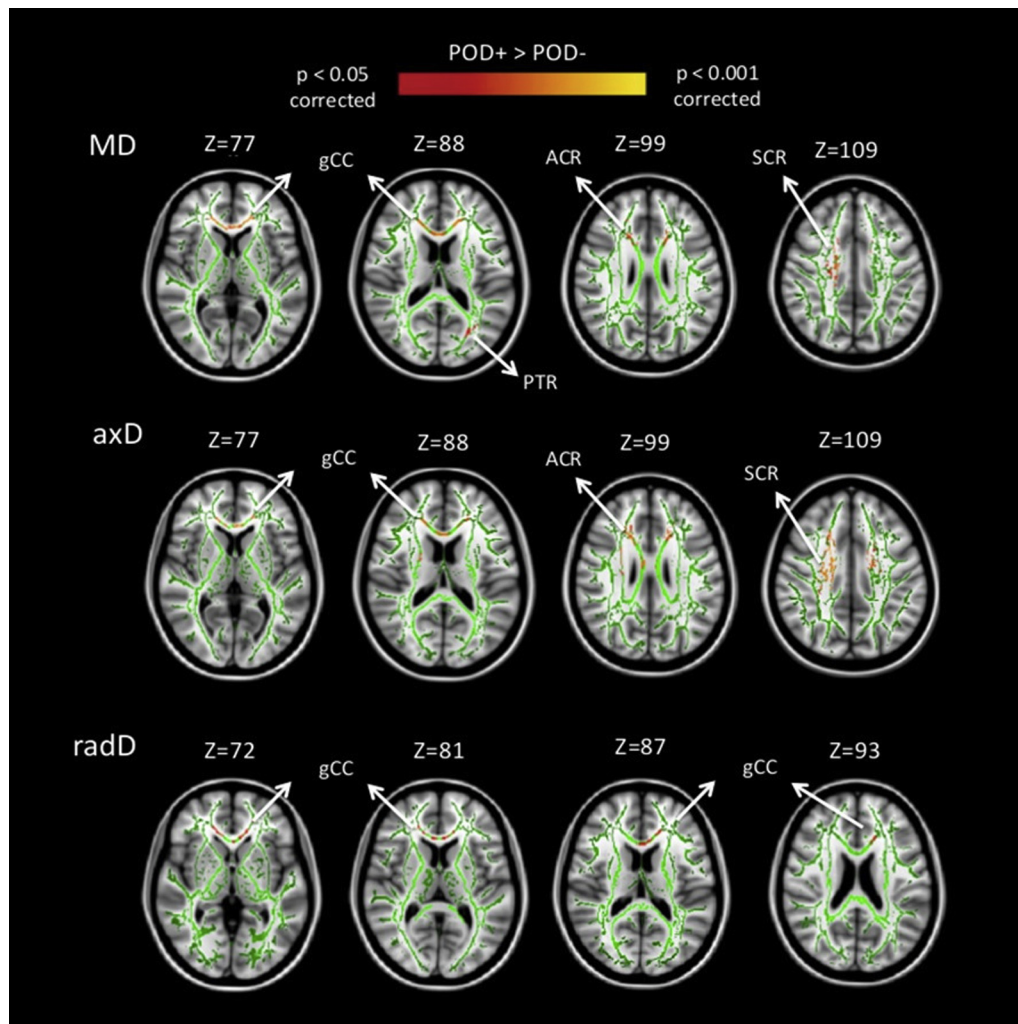


Fig. 4. Results from TBSS analysis showed higher mean (top row), axial (middle row), and radial diffusivity (bottom row) in the genu of corpus callosum and anterior corona radiata in postoperative delirium positive (POD+) patients compared to POD-. The most representative slices are shown. Results are overlaid onto the standard MNI template and significant differences ($p < 0.05$ corrected for multiple comparisons with TFCE) are shown in orange. The FA skeleton is shown in green. Images are in the radiological convention (left of image is right of brain). One POD+ patient withdrew from the scanner before the DTI sequence could be acquired. Abbreviations: ACR, anterior corona radiata; gCC, genu of corpus callosum; POD-, postoperative delirium negative; PTR, posterior thalamic radiation; SCR, superior corona radiata; TBSS, Tract-Based Spatial Statistics; TFCE, threshold-free cluster enhancement. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

diffusivity was found in the left posterior thalamic radiation. These findings are coherent with a previous study describing an association between presurgery DTI abnormalities and POD incidence, specifically affecting the interhemispheric, fronto-thalamo-cerebellar, limbic, and memory WM tracts (Cavallari et al., 2016).

4.4. DMN functional connectivity

POD patients, compared to controls, showed higher functional connectivity within the parietal nodes of the DMN at rest, in contrast with the pattern of decreased functional connectivity largely observed in AD patients (Pievani et al., 2014). The differences observed in the present sample, could be reasonably attributed to reduced DMN connectivity of POD- compared to POD+ individuals, due to the higher prevalence of amyloid positivity found in this group (45% and 0%, respectively) (Sperling et al., 2009). This finding further supports the lack of association with POD and AD-like brain abnormalities in our sample. Only 1 previous study investigated functional connectivity using rs-fMRI in delirious patients compared to controls, reporting increased

connectivity between the posterior cingulate and the dorsolateral prefrontal cortex and between the precuneus and the posterior cingulate cortex, key nodes of the DMN (Choi et al., 2012). Emerging interest recently arose on the investigation of brain functional connectivity during delirium using different techniques (Haggstrom et al., 2017). Owing to the heterogeneity in key features of study designs, such as timing of functional connectivity evaluations, methods used, and clinical settings, direct inferences between our findings and the ones described in previous studies are limited.

4.5. Neurodegeneration without amyloidosis

Taken together our results, although preliminary, seem concordant with the majority of previous MRI studies on delirium populations and suggest a peculiar pattern of structural gray and white matter alterations, in the absence of brain amyloidosis. This biomarker profile has been recently defined as suspected non-Alzheimer disease pathophysiology (SNAP) (Jack et al., 2016). SNAP patients with cognitive impairment showed increased risk of

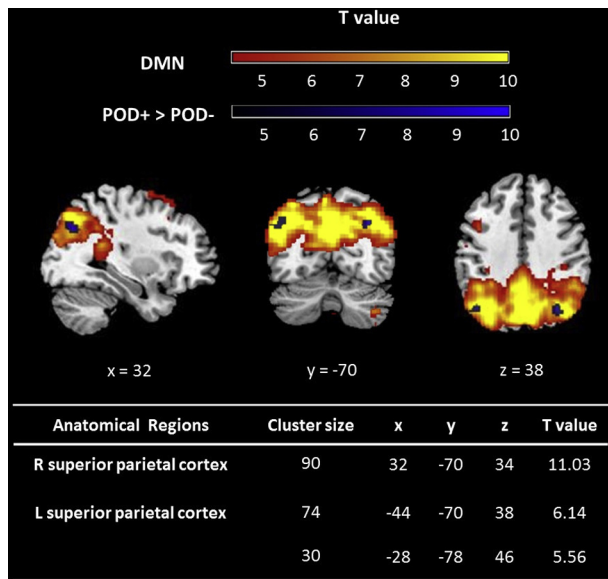


Fig. 5. Results from rs-fMRI analysis showed higher connectivity in the bilateral superior parietal cortex within the posterior portion of the default mode network (DMN) in postoperative delirium positive (POD+) patients. Results are overlaid on the DMN spatial map (red to yellow scale) extracted from the entire sample with 1-sample *t*-test. POD-: postoperative delirium negative. Statistical significance was set at $p < 0.001$ uncorrected, cluster size > 20 voxels. One POD+ patient withdrew from the scanner before the fMRI sequence could be acquired. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

cognitive deterioration compared to biomarker negative or amyloid only positive patients (Caroli et al., 2015). Moreover, they displayed less AD-specific hypometabolism and CSF signature compared to typical AD (Landau et al., 2016) and limbic-predominant atrophy compared to controls, characterized by subtle atrophy and hypometabolism mainly restricted to the retrosplenial, orbitofrontal, and dorsomedial prefrontal cortex (Chételat et al., 2016). However, the mechanism underlying neurodegeneration in SNAP patients is still unknown (Jack et al., 2016), as well as the pathophysiological processes underlying POD and leading to the subsequent cognitive impairment and dementia.

Interestingly, the pattern of neurodegeneration found in our exploratory analysis on POD patients, suggests an involvement of WM tracts and GM structures of the fronto-limbic pathway: the dorsal anterior cingulate cortex exert a regulatory function on affective reactions through inhibitory connection with the amygdala (Stein et al., 2007); the genu allows interhemispheric communication between medial prefrontal cortex, while the cingulum connects temporal regions with orbitofrontal cortex, which all are cortical regions involved in emotion regulation and stress response and highly interconnected with the amygdala (Kim et al., 2011). During stress condition, the physiological response of the stress signaling pathways affect the interplay between amygdala and prefrontal cortex, leading to a bottom-up control exerted by the amygdala, with a detrimental effect on prefrontal cortex functioning (Arnsten, 2009). Intriguingly, in the context of delirium research, hyper-responsiveness of these pathways in response to an external stressor has been suggested as a possible pathophysiological basis accounting for the cortical dysfunction and behavioral alterations observed during a delirium episode (Cunningham and MacLullich, 2013). In this view, presurgery structural abnormalities within the fronto-limbic pathway could possibly reduce the resilience against external stressors, such as

surgery, accounting both for the immediate and the long-term sequelae of delirium episodes. However, future studies should explore this hypothesis by combining multimodal MRI with biological measures possibly involved in fronto-limbic pathways' hyper-responsiveness.

4.6. Limitations

Several limitations of this study should be discussed. The major limitation of this study is the reduced sample size, due to difficulties in the enrollment phase. Indeed, informed consent was collected before emergency surgery leading to high refusal rate (62% of eligible patients), and after discharge, patients underwent prolonged recovery period, leading to even higher attrition rate (69% of enrolled patients). This limitation reduces the generalizability of our results and conclusions. However, the clinical and sociodemographical features of the sample collected are comparable to the ones found in the majority of patients who underwent the same surgery (results reported in [Supplementary Table 1](#)). Second, due to the unpredictable nature of hip fracture and to the short time interval between hospital admission and surgery, cognitive assessment, and neuroimaging examinations were performed after surgery, preventing from clear interpretation on the direction of causality between the brain vulnerabilities found and POD onset. Brain amyloid deposition and morphometric alterations are very slow phenomena that take place over decades (Villemagne et al., 2013); therefore, we considered these measures as proxies for presurgery brain status, possibly decreasing brain resilience against external stressors. Indeed, the 2 groups were comparable for several predisposing and precipitating factors for delirium (Inouye et al., 2014): age, comorbidity indexes (see [Table 1](#)), urgent admission, and surgery procedures. However, delirium itself affect brain integrity and cognition (Fong et al., 2015), and without a presurgery evaluation, it is impossible to rule out that part of the brain abnormalities found were directly driven by POD itself. Future investigations on nonelective hip fracture surgery patients should be designed to allow all the visits and examinations to be completed within the recovery period, in order to prevent the elevated postdischarge attrition rate observed in this study and to further clarify the temporal relationship between brain alterations, surgery, and POD.

5. Conclusion

This is the first study directly addressing the association between in vivo AD pathophysiology and POD, showing the absence of pathologic amyloid load in POD patients. The main strength of the present study is the use of a multimodal imaging approach by different imaging techniques, resulting in a peculiar pattern of gray and white matter brain structural abnormalities in POD patients, affecting regions and networks largely involved in the fronto-limbic pathway, related to affective regulation and stress response. The present study is underpowered to drive firm conclusions on delirium pathophysiology, but the novelty of the methods used and our preliminary results could lead to new questions and hypothesis on the pathophysiology of delirium. New promising imaging techniques should be used to investigate pathophysiological mechanisms underlying POD such as tau imaging to assess the in vivo formation of neurofibrillary tangles (Villemagne et al., 2015), and [^{11}C]UCB-J PET to assess the synaptic density of alternative brain pathways involved in POD, such as the fronto-limbic pathway (Finnema et al., 2016).

Furthermore, long-term clinical and neuropsychological follow-up to investigate the specific clinical features of cognitive impairment and dementia subsequent to POD are needed. A deeper

understanding of POD pathophysiology and of its clinical course is urgently needed to improve the clinical management of this population.

Disclosure statement

Dr Cunningham has received speaker's honoraria from Eli Lilly. Dr Guerra taught courses for fees to GE Healthcare and Eli Lilly personnel. Dr Buckley is an employee of GE Healthcare who performed a blinded SUVr analysis of the [¹⁸F]flutemetamol images. Dr Frisoni has served as a paid member of advisory boards for Roche, Lilly, BMS, Bayer, Lundbeck, Elan, AstraZeneca, Pfizer, Taurx, Wyeth, GE Healthcare, and Baxter. He received research grants from Wyeth Int, Lilly Int, Lundbeck Italia, GE Healthcare, Avid/Lilly, Roche, Piramal, and the Alzheimer's Association. In the last 2 years he received speaker honoraria from Lundbeck, Piramal, GE Healthcare, and Avid/Lilly. The other authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2017.09.020.

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