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# Brain atrophy and white matter hyperintensities are not significantly associated with incidence and severity of postoperative delirium in older persons without dementia

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## Abstract

Postoperative delirium is a common complication in older people, and is associated with increased mortality, morbidity, institutionalization and caregiver burden. Although delirium is an acute confusional state characterized by global impairments in attention and cognition, it has been



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implicated in permanent cognitive impairment and dementia. The pathogenesis of delirium, as well as the mechanisms leading to these disabling consequences, remains unclear.

The present study is the first to address the potential predisposing role of brain morphological changes towards postoperative delirium in a large prospective cohort of patients undergoing elective surgery using state-of-the-art magnetic resonance imaging (MRI) techniques conducted before admission. We investigated the association of MRI-derived quantitative measures of white matter damage, global brain and hippocampal volume with the incidence and severity of delirium.

Pre-surgical white matter hyperintensities (WMH), whole brain and hippocampal volume were measured in 146 consecutively enrolled subjects, ≥70 years old, without dementia who were undergoing elective surgery. These three pre-surgical MRI indices were tested as predictors of incidence and severity of subsequent delirium.

Out of 146 subjects, 32 (22%) developed delirium. We found no statistically significant differences in WMH, whole brain or hippocampal volume between subjects with and without delirium. Both unadjusted and adjusted (age, gender, vascular comorbidity, general cognitive performance) regression analyses demonstrated no statistically significant association between any of the MRI measures with respect to delirium incidence or severity.

In persons without dementia, preexisting cerebral white matter hyperintensities, general and hippocampal atrophy may not predispose to postoperative delirium or worsen its severity.

**Keywords**

Delirium; brain atrophy; hippocampal atrophy; white matter hyperintensities; neuroimaging

## 1. Introduction

Delirium is an acute confusional state marked by global impairments in attention and cognition (Inouye et al., 2014a). Common yet under-diagnosed, postoperative delirium occurs in 11–51% of hospitalized older patients (Inouye et al., 2014a), and significantly increases their risk for death, institutionalization, and dementia (Witlox et al., 2010). Mortality rates among hospitalized patients who develop delirium are as high as those among patients with myocardial infarction or sepsis (Inouye, 2006).

Despite its clinical impact, the pathophysiology of delirium remains poorly understood. It is believed that brain pathology plays an important role. Preexisting cognitive impairment and dementia are important predisposing factors for delirium. In addition, many precipitating factors leading to delirium, such as electrolyte disturbances, malnutrition, infections, anemia, shock, and psychotropic medications have been identified (Inouye, 2006; Inouye et al., 2014a). Many cases of delirium are preventable through management of these precipitating factors.

A pathophysiological role for preexisting brain damage with respect to delirium incidence has been hypothesized. The hypothesis is based upon evidence that primary neurologic diseases (e.g., dementia, stroke, traumatic brain injury) are risk factors for delirium (Inouye, 2006). Neuroimaging studies showing structural and functional magnetic resonance imaging

(MRI) abnormalities in subjects with delirium further support this hypothesis (Alsop et al., 2006; Hughes et al., 2012; Lipowski, 1990; Soiza et al., 2008; Trzepacz, 2000). As long as three decades ago, brain atrophy was found to be associated with delirium in computed tomography studies. Koponen et al. found that delirious patients had more cortical atrophy, wider Sylvian fissures and more prominent ventricular dilatation on computed tomography (Koponen et al., 1989, 1987). Global and regional perfusion abnormalities have been also observed on brain imaging of delirious patients (Fong et al., 2006; Siepe et al., 2011). As neuroimaging advanced, technology has become available to characterize the chronology of structural and functional brain abnormalities related to delirium, and provided clues to the pathogenesis of delirium and associated cognitive decline (Hughes et al., 2012; Saczynski et al., 2012). MRI-derived measures of global and regional brain atrophy, as well as cerebral white matter damage, have been associated with occurrence of delirium (for a systematic review see Alsop et al., 2006). Two small MRI studies found higher cerebral white matter hyperintensity (WMH) burden in subjects who developed delirium after electroconvulsive therapy (Figiel et al., 1990a, 1990b). A few studies suggested a predictive role for multiple brain infarcts (Otomo et al., 2013) and cerebral white matter damage, as measured by WMH burden or diffusion tensor imaging (DTI), for delirium incidence after cardiac surgery (Hatano et al., 2013; Root et al., 2013; Shioiri et al., 2010). In addition, recent resting-state functional MRI findings during and after an episode of delirium suggested that changes in cortical and subcortical functional connectivity underlie the pathogenesis of delirium (Choi et al., 2012). Other neuroimaging studies found associations between MRI abnormalities and delirium features, such as duration of delirium and subsequent cognitive impairment (for a review see Soiza et al., 2008). Recent exploratory research in intensive care unit patients suggests that duration of delirium is associated with brain atrophy, particularly superior frontal and hippocampal, leading to long-term cognitive impairment (Gunther et al., 2012). In a very similar setting, duration of delirium was positively correlated with DTI white matter tract abnormalities at discharge, which persisted at 3 months follow-up (Morandi et al., 2012).

Larger, prospective studies with high power for detecting association between baseline WMH and delirium while controlling for important covariates are lacking. In most studies sample sizes were small, and importantly without baseline pre-delirium imaging performed (Alsop et al., 2006; Soiza et al., 2008). In addition, a number of study participants had diagnosed degenerative dementias or other known structural brain diseases confounding the interpretation of imaging abnormalities (Alsop et al., 2006; Soiza et al., 2008).

Given these limitations, there remains a gap in our knowledge on the relationship between preexisting neuroanatomical changes and delirium. Our study aims to fill this gap using state-of-the-art MRI techniques within a prospective study of post-operative delirium in older persons without dementia. We investigated the association of pre-surgical MRI measures of total WMH volume, global brain atrophy and hippocampal volume with the incidence and severity of postoperative delirium. Our study extended previous work by using state-of-the-art imaging and analysis methods, cognitive and delirium assessments, in a large well-characterized clinical cohort of older individuals without dementia.

## 2. Methods

### 2.1 Study Design and Cohort Assembly

Our study population is a subsample of the Successful AGing after Elective Surgery (SAGES) study, a five-year prospective observational study of postoperative delirium being conducted at Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, and Hebrew SeniorLife in Boston (Massachusetts, USA). The study design and eligibility criteria have been reported in detail previously (Schmitt et al., 2012). Briefly, the elective surgeries included in the study were total hip or knee replacement, laminectomy, lower extremity arterial bypass, open abdominal aortic aneurysm repair, and colectomy. SAGES subjects were recruited through regular review of operating room schedules. Inclusion criteria included: age ≥ 70 years old, English speaking, and undergoing elective surgery at Beth Israel Deaconess Medical Center or Brigham and Women's Hospital. Exclusion criteria included diagnosis of dementia as assessed by initial medical record screening, or reported by the patient during telephone recruitment or enrollment interview; cognitive impairment as defined by a score ≤ 69 or its education-adjusted equivalent on the Modified Mini-Mental State examination (3MS) during the baseline interview (Teng and Chui, 1987); terminal disease; total blindness; severe deafness; and alcohol intake > 5 drinks per day (men) or > 4 drinks per day (women). A subset of approximately one-third of the enrolled SAGES participants was recruited to undergo MRI one month prior to surgery. Additional exclusion criteria for the nested cohort MRI study included contraindications to 3 Tesla MRI, such as pacemakers and certain stents and implants. All study procedures were approved by the institutional review boards at the two surgical sites (Beth Israel Deaconess Medical Center and Brigham and Women's Hospital) and Hebrew SeniorLife, the coordinating center. All subjects gave written informed consent.

### 2.2 Baseline Measures

All the study participants completed a baseline interview about two weeks before surgery. During the baseline interview, the Short Form 12 (SF-12) (Ware et al., 1996), Modified Mini-Mental State examination (3MS), complete neuropsychological test battery (described below), and the Confusion Assessment Method (CAM) (Inouye et al., 1990) were administered. We also assessed presence of depression using the Geriatrics Depression Scale (GDS), which yields a score from 0 to 15 (15 being most depressed). We dichotomized this variable at 5 with an accepted threshold of 5 or above as possibly having depression. Demographic information such as age, gender, vascular comorbidities, ethnicity, years of education and type of surgery planned (orthopedic, vascular, gastrointestinal) were collected.

### 2.3 Outcome Measures

The outcomes of interest were post-operative delirium incidence and severity during the hospital stay. To enhance sensitivity we utilized multiple methods to detect delirium. We used both the CAM method and chart review to detect delirium for each patient. If both, or either of the two methods indicated that the patient had delirium, then that patient was defined to have delirium. The CAM method is based on daily structured interview that includes formal neuropsychological testing. Trained interviewers assessed patients daily

during hospitalization for the development of delirium using the CAM (Inouye et al., 1990), a widely used, standardized method for identification of delirium that has high sensitivity, specificity and inter-rater reliability (Wei et al., 2008). The CAM was rated based on information from patient interviews including a brief cognitive screen (e.g., orientation, short-term recall, verbal fluency, digit span) described previously (Schmitt et al., 2012), the Delirium Symptom Interview (DSI) (Albert et al., 1992), and information on mental status changes from nurses or family members. The CAM diagnostic algorithm requires the presence of acute change or fluctuating course, inattention, and either disorganized thinking or an altered level of consciousness to fulfill criteria for delirium. The validated chart review method (Inouye et al., 2005; Saczynski et al., 2014) was performed to enhance sensitivity in detecting delirium episodes that might have fallen outside the time of the CAM assessment; each chart rating was adjudicated by 2 experts. Delirium severity was assessed by the CAM-S Long Form, with scores ranging from 0 to 19 (19 = most severe) (Inouye et al., 2014b). The CAM-S provides an additive score for delirium severity based on the presence of delirium symptoms by the CAM. The CAM-S has been demonstrated to have predictive validity for clinical outcomes associated with delirium severity. Scores of 5 or greater represent severe delirium. Peak CAM-S scores were utilized in our analyses.

### 2.4 Covariates

The following variables were incorporated into our analysis to adjust for potential confounders: age, gender, general cognitive performance (GCP), vascular comorbidity status, and MRI derived intracranial cavity volume (ICV). Age refers to the participant's age (years) at the time of surgery. GCP, a weighted composite to reflect the patient's preoperative cognitive functioning, was based on a battery of neuropsychological tests to assess attention, memory, learning and executive functioning (Jones et al., 2010). The battery included the Hopkins Verbal Learning Test (Brandt, 1991), the Visual Search and Attention Task (Trenerry et al., 1990), the Trail Making Tests A and B (*Trail Making Tests A and B*, 1944), the Digit Symbol Substitution and Copy tests (Wechsler, 1981), the Digit Span forward and backward (Wechsler, 1981), and the 15-item Boston Naming Test (Mack et al., 1992). A higher GCP score indicates better cognitive performance. The GCP scores in SAGES were scaled to reflect population-based norms (Gross et al., 2014) with a mean value of 50 (standard deviation = 10). Thus, a score of 40 on the GCP corresponds to cognitive functioning that is one standard deviation below the mean of the U.S. population. The following conditions were considered to define vascular comorbidity: confirmed or history of myocardial infarction; congestive heart failure; peripheral vascular disease or diabetes (with or without end organ damage); cerebrovascular disease (carotid stenosis or history of stroke or transient ischemic attack); or hemiplegia. The study subjects were categorized in two categories (with vs. without vascular comorbidity), according to the presence/absence of at least one of the pathologic conditions mentioned above. Complications were assessed via chart review by two clinicians and included pneumonia, urinary tract infections, sepsis, surgical wound infection, abdominal abscess, anastomic leak, colitis, gout attack, gout flare, lactic acidosis, leukocytosis.

### 2.5 MRI Acquisition

All subjects were imaged at the Beth Israel Deaconess Medical Center Radiology Department on a 3 Tesla HDxt MRI (General Electric Medical Systems, Milwaukee, WI) scanner using a standard 8-channel head coil. All participants completed a standard clinical screening form for MRI safety and contraindications before the MRI scan.

The MRI acquisition protocol included:

1. High Resolution 3D anatomic imaging – A magnetization prepared fast gradient echo (MPRAGE) 3D T1-weighted sequence with a TR of 7.9 ms, a TE of 3.2 ms, a 15° flip angle and 32 kHz bandwidth, a coronal acquisition plane with 24×19 cm field of view, 0.94 mm in plane resolution, 1.4 mm slices, a preparation time of 1100 ms with repeated saturation at the beginning of the saturation period, and an adiabatic inversion pulse 500 ms before imaging.
2. High Resolution 3D T2-weighted imaging – A 3D fast spin echo sequence (Cube™) was acquired in the sagittal plane with TR 3 s, effective TE 63.6 ms, echo train length 100, bandwidth 62.5, 1 mm in plane resolution, and 128 1.6 mm slices.
3. FLuid Attenuated Inversion Recovery (FLAIR) – An axial acquisition with a TR/TE of 9000/156 and an inversion time of 2250 was employed. Seventy 2 mm slices were acquired with no interslice gap and interleaved acquisition. Nominal in plane resolution was 1 mm.

### 2.6 MRI Analysis

Three quantitative MRI indices were extracted through image analysis for this study: 1) WMH volume, as a measure of cerebrovascular damage; 2) Brain Parenchymal Volume (BPV), as a measure of global brain atrophy; 3) hippocampal volume, as a measure of regional atrophy of the hippocampus. Deep WMH were also rated by a single, blinded rater (MC) using the visual semi-quantitative Fazekas score (Fazekas et al., 1987), ranging from 0–3 with increasing severity (0 = absence of WMH, 1 = punctate foci of WMH, 2 = early confluent WMH, 3 = confluent WMH).

Total WMH volume was obtained by a semi-automated image segmentation method based on three channels: T1-weighted, T2-weighted and FLAIR images. Bias-field correction to account for field inhomogeneities and automated spatial co-registration of T1-weighted, T2-weighted and FLAIR images was performed using the 3DSlicer software (www.slicer.org). Intracranial cavity (ICC) masks were segmented from T2-weighted images using the Brain Extraction Tool (Smith, 2002), and subsequently visually assessed and manually corrected by a single, blinded reviewer (TTH). A second rater (MC) reviewed and manually corrected ten ICV masks independently to assess inter-rater reliability. These ICC masks include the brain parenchyma as well as ventricular and cortical cerebrospinal fluid (CSF). The ICC was used as a mask to exclude non-brain/CSF voxels from the subsequent tissue class segmentation, and as intracranial cavity volume (ICV) reference to correct for head size. Tissue class segmentation of grey matter (GM), white matter (WM), and CSF from T1-weighted images occurred in a custom pipeline using FreeSurfer (version 5.2) (Fischl et al., 2002). This segmentation was corrected by use of heuristic constraints based on the FLAIR

image, thereby accounting for misclassifications due to the presence of WMH. The final WMH segmentation was then obtained by a custom version of a 3-channel (T1-weighted, T2-weighted, FLAIR) Expectation Maximization (EM) algorithm, classifying lesions as outliers from the normal tissue intensity distributions (Van Leemput et al., 2001). The initial Freesurfer segmentation was used as the starting point for automated EM segmentation. The EM result is a set of probability maps that provide the likelihood for each image pixel to be part of a lesion (WMH) or one of the other tissue classes. The WMH maps were reviewed and thresholded by a neuroimaging expert (MC) to obtain binary WMH masks using FLAIR images as reference. Total WMH volume, measured using the binary WMH masks, was included in the statistical analysis.

Based on the automated output of FreeSurfer, we measured BPV and hippocampal volume as follows. No manual editing was performed at any stage of the processing workflow (Wenger et al., 2014; Mulder et al., 2014). All the brain structures segmented by FreeSurfer and included in the brain parenchyma (i.e. all of the FreeSurfer labels except the cortical and ventricular CSF, and the choroid plexi) were summed to obtain a measure of the whole BPV. Hippocampal volume measurement was based on the automated parcellation of this structure by FreeSurfer. The average volume of the left and right hippocampus was included in the statistical analysis. Post-hoc quality assessment of the hippocampal volume measures was performed by examining the degree of concordance between the left and right measurement of the hippocampal volumes within each patient. We expected the average within-patient correlation of these two measurements to be no lower than 0.60 (considered to be in the range of a good correlation). We used two measures to assess this correlation: a nonparametric Spearman correlation, and an intra-class correlation obtained from a linear mixed-effects model where the correlation was measured by the compound symmetry structure of the variance-covariance matrix of the two hippocampal volumes. We obtained a Spearman correlation of 0.69 (p-value $< 0.0001$), and an intra-class correlation of 0.61 (p-value $< 0.0001$).

Baseline T2-weighted images were not available for 14 study subjects. T2-weighted images from follow-up scans obtained at one-year following surgery were used to obtain the ICC masks and WMH probability maps in these subjects. While ICV should remain constant at the age of our study subjects, WMH measures may be perceived as biased (false positive) due to the temporal separation. However, the relative weight of the T2-channel in the workflow that classifies WMH was minimal relative to that of the FLAIR channel, and – more importantly – the final expert-driven thresholding of the resulting WMH maps was performed based on the FLAIR images of the relevant time-point. In addition, visual expert review of the 14 follow-up scans did not reveal substantial increase in WMH burden for any of the 14 subjects. The neuroimaging experts who performed the processing and analysis of the images were completely blinded to the clinical data and delirium status.

MRI volumes were all controlled for the effect of subject head size (ICV) by regression. This was achieved by including ICV as a covariate in all statistical models tested. Controlling for ICV by ratio normalization was not used as a primary approach because of potential limitations (Arndt et al., 1991; Curran-Everett, 2013; Sanfilipo et al., 2004).

Parallel analyses with the ratio method were performed but no qualitatively different results were found and they are not reported here.

### 2.7 Statistical Analysis

Student's t-test or Kruskal-Wallis test was used to assess differences in continuous demographic, clinical and MRI variables between subjects who developed delirium and subjects who did not, according to the distribution of the data. Chi-Square or Fisher's exact tests were used to assess differences in categorical demographic, clinical and MRI variables between subjects who developed delirium and subjects who did not, as appropriate. Bivariate correlations between MRI indices were assessed using the nonparametric Spearman correlation coefficient (rho). Generalized linear modeling was used to estimate the predictive power of the MRI indices with respect to delirium incidence and severity. Log link and Poisson error distribution were used for the binary delirium incidence outcome (Zou, 2004). Delirium severity was analyzed with and without logarithm transformation, and the results were not different in terms of the significance of the p-values. For ease of interpretation of the model coefficients (the slopes in relations to MRI parameters), we chose to report the non-transformed scale of delirium severity. For each MRI variable, both unadjusted and adjusted analyses were conducted. For unadjusted analyses, only ICV was included in the model to control for head size effects according to the normalization by regression method. For adjusted analyses, the following covariates were included in the model: ICV, age, gender, GCP and vascular comorbidity. According to formal power analysis prior to the study, the available sample of 146 provided a power of at least 0.80 to detect a population odds ratio of 2.0 per one standard deviation difference in hippocampal volume under the assumption that the incidence of delirium in this sample was 20%, and the association in terms of odds ratio between delirium incidence and each of the four covariates (age, GCP, gender, vascular comorbidity) in the model was at least 1.05. Complications were coded as binary (presence/absence) and were included in the regression models in post-hoc analysis to investigate first if there was a significant effect on delirium incidence or severity, and second if the MRI effect estimates would change in the presence/absence of complications. As a test of MRI data quality, generalized linear modeling was also performed to assess the dependence of MRI variables on these covariates for comparison with prior studies. Type-I was set to 0.017 (a Bonferroni correction of 0.05 for the 3 MRI variables tested). SAS software version 9.3 (SAS/STAT User's Guide, Version 8, SAS Institute, Cary, N.C., 2000) was used for all statistical analyses in this paper.

## 3. Results

Of 147 subjects who had MRI prior to surgery, 1 did not complete the entire MRI protocol, and therefore was excluded from this study. Demographic and baseline clinical characteristics of the 146 subjects included in this study are summarized in Table 1. Of 146 subjects, 32 (22%) developed delirium during hospitalization. Delirium was diagnosed in 23 subjects by both the CAM interview and chart review method, and in 9 subjects by chart review alone. No significant differences were found between subjects with and without delirium in age, gender, or 3MS (Table 1). Subjects with delirium had lower GCP (55 ± 7 vs. 59 ± 7, $p = 0.002$, Student's t-test), and lower SF-12 Physical composite scores (32 ± 10

vs. 37 ± 10, p = 0.016, Student's t-test). Subjects with delirium consistently scored higher on delirium severity rating as compared to those without delirium (Table 1). We found no statistically significant difference in delirium incidence between subjects with and without depression. Proportion of delirium was 19% (4/21) in subjects with depression, and 22% (28/125) in those without depression.

WMH volume, BPV and hippocampal volume properties are summarized in Table 2. BPV and hippocampal volume were normally distributed, whereas WMH volume showed kurtosis and skewness. BPV showed a significant association with hippocampal volume (rho = 0.62, $p < 0.001$, Spearman's correlation). As expected, WMH volume correlated with Fazekas score (rho = 0.71, $p < 0.001$, Spearman's correlation). WMH volume did not show significant association with BPV or hippocampal volume (Spearman's correlation). GCP showed no significant correlation with BPV, hippocampal volume and WMH volume (Spearman's correlation). Generalized linear modeling of MRI variables showed significant dependence on age with slopes −5.15 ml/year ($p < 0.001$), −0.02 ml/year (p = 0.004), and 0.52 ml/year (p = 0.003) for BPV, average hippocampal volume, and WMH volume, respectively. Significant dependence of 5.9 ml greater WMH volume for females was also found (p = 0.004). Coefficients of variation of the residuals were 6% for BPV, 11% for hippocampal volume, and 78% for WMH volume.

Differences in WMH volume, BPV and hippocampal volume between subjects who developed later delirium during their hospital stay and subjects who did not were not statistically significant (Table 2). Both unadjusted and adjusted generalized linear model analyses demonstrated no statistically significant effects for any of the MRI indices with respect to delirium incidence or severity as measured by the CAM-S Long Form (Tables 3 and 4). GCP score was a significant covariate of delirium incidence ($p < 0.01$) and severity ($p < 0.001$) in both multivariable models. The prevalence of complications was 13% (19/146). The main effect of complications was not statistically significant for delirium incidence (p = 0.874 for BPV; p = 0.789 for hippocampal volume; p = 0.808 for WMH; generalized linear model), and significant for delirium severity (p = 0.020 for BPV; p = 0.019 for hippocampal volume; p = 0.014 for WMH; general linear model). The estimates of the MRI parameters in the presence of the significant effect of complications showed little changes, and still remained not statistically significant.

## 4. Discussion

We investigated the predictive role of MRI-derived measures of brain damage with respect to delirium incidence and severity within a prospective study of older subjects without dementia undergoing elective surgery. Incidence of delirium in our study sample (22%) is in line with data reported in the literature (Inouye et al., 2014a). We used WMH volume, BPV and hippocampal volume as established MRI indicators of cerebrovascular damage, global and regional brain atrophy, respectively. None of these three MRI indices of brain damage was significantly associated with delirium incidence or severity in both unadjusted and adjusted analysis in our study.

This finding appears to be in contrast with recent studies that showed MRI correlates of white matter damage and brain atrophy in subjects with delirium. However, most of these studies had methodological limitations inherent in studying the difficult problem of delirium (Alsop et al., 2006; Soiza et al., 2008), such as a retrospective study design (Hatano et al., 2013; Root et al., 2013), lack of a control group or no baseline pre-delirium imaging (Gunther et al., 2012; Morandi et al., 2012). Recently, a large prospective study (153 subjects aged 60 years or older, of which 16 developed delirium) reported a positive association between multiple brain infarcts on pre-surgical MRI and delirium occurrence after cardiac surgery (Otomo et al., 2013). However, the frequency of pure existing single brain infarcts was higher in the non-delirium group, and there was no association between incidence of delirium and WMH burden as measured by the Fazekas score. A number of the studies were also underpowered to establish a robust cause-effect link between preexisting brain pathology and delirium (Figiel et al., 1990a, 1990b). In some of these studies, subjects with underlying neurological or neurodegenerative diseases that may contribute to confounding MRI abnormalities were included (Alsop et al., 2006; Otomo et al., 2013; Soiza et al., 2008). Furthermore, the heterogeneity of underlying medical conditions in the cohorts examined – surgery, critical care (e.g., sepsis, respiratory failure, mechanical ventilation), and general medical illness – may limit the generalizability of the neuroimaging findings in these previous studies. A DTI study showed that microstructural abnormalities of the cerebral white matter and thalamus, as detected by pre-surgical MRI, predicted occurrence of delirium in 19 of 116 elective cardiac surgery patients (Shioiri et al., 2010). Similar to our study, the authors mentioned (without reporting the results) no quantitative differences in MRI measures derived from T1- and T2-wighted images between subjects with and without delirium. Although DTI might be more sensitive than WMH volume to detect subtle structural abnormalities, analysis of the difference in diffusion parameters were not adjusted for relevant potential confounders showing higher prevalence in the delirium group, such as hypertension, hemodialysis and blood transfusion.

The strength and validity of our results lie in the prospective study design and robust means of pre-evaluation and follow-up of a study population that is part of the larger SAGES study (Schmitt et al., 2012). Our study has the largest sample size yet investigated to study the relationship between structural brain damage and delirium using state-of-the-art MRI indices of neurodegenerative and cerebrovascular injury.

Accuracy of the MRI-derived measures employed in this study is further supported by our secondary findings of association of age with WMH volume, GCP and BPV, as well as residual coefficients of variation that are consistent with previous literature (Atwood et al., 2004; Jack et al., 1992; Whitwell et al., 2001; Coffey et al., 1992; Convit et al., 1995; Poggesi et al., 2011; Wu et al., 1981). The observed significant association between GCP score and delirium incidence and severity is also in line with previous literature, which shows that lower cognitive function is among the leading predisposing factors for delirium (Inouye, 2006; Inouye et al., 2014a, 1993; Marcantonio et al., 1994).

Several important limitations of the study are worthy of comment. Since subjects with clinically evident dementia were excluded, the generalizability of our findings to this important population of subjects requires further study. Moreover, since this study was

based on an elective surgical population in a single geographic area, future studies will be needed to verify the findings in other settings and populations, such as general medical, intensive care, and post-acute settings.

Although our findings do not support the utility of MRI-derived indices of global WMH volume and whole-brain or hippocampal atrophy for predicting delirium, we cannot rule out a potential role for regional WMH burden, volumes of specific brain regions or other measures of brain pathology with regards to delirium incidence. This study examined only the role of pre-delirium (baseline) neuroimaging markers for the prediction of delirium; examination of the impact of delirium on subsequent neuroimaging measures could not be examined in the present study. MRI correlates of brain damage may still prove to be useful in monitoring subjects following delirium. For example, quantitative MRI indices of cerebral white matter damage and atrophy may have prognostic value for predicting and monitoring disabling sequelae of delirium, such as cognitive decline. In addition, interval change in these volumetric brain indices may have significant correlation with delirium incidence or severity. These represent important areas for future research.

Delirium is a morbid yet common condition, with significant impact on the outcome and long-term prognosis of older patients. This study raises the intriguing possibility that delirium incidence in elective surgery patients may not be strongly related to underlying generalized or hippocampal atrophy, or WMH, at least in a population without dementia at baseline.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A list of participating personnel of the SAGES Study can be found online as supplementary material.

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## Abbreviations

| | |
|---|---|
| **(BPV)** | Brain Parenchymal Volume |
| **(CSF)** | Cerebrospinal Fluid |
| **(CAM)** | Confusion Assessment Method |
| **(DSI)** | Delirium Symptom Interview |
| **(DTI)** | Diffusion Tensor Imaging |
| **(FLAIR)** | Fluid Attenuated Inversion Recovery |

| | |
|---|---|
| **(GCP)** | General Cognitive Performance |
| **(ICC)** | Intracranial Cavity |
| **(ICV)** | Intracranial Volume |
| **(MRI)** | Magnetic Resonance Imaging |
| **(MPRAGE)** | Magnetization Prepared Fast Gradient Echo |
| **(MDAS)** | Memorial Delirium Assessment Scale |
| **(3MS)** | Modified Mini-Mental State Examination |
| **(SF-12)** | Short Form 12 |
| **(WMH)** | White Matter Hyperintensity |

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## Highlights

- Prospective study of the association between MRI and postoperative delirium
- Powered study of delirium using state-of-the-art MRI indices of structural brain damage
- Pre-surgical white matter hyperintensities, brain and hippocampal volume were measured
- Out of 146 consecutively enrolled subjects, 32 (22%) developed delirium
- None of the three MRI indices was associated with delirium incidence or severity

## Table 1

Baseline characteristics of study participants

| | All Subjects | No Delirium | Delirium | p-value |
|---|---|---|---|---|
| **Number of Subjects** (n, %) | 146 | 114 | 32 | - |
| **Age** (years, mean ± SD) | 76 ± 4 | 76 ± 5 | 77 ± 4 | 0.467[a] |
| **Female Gender** (n, %) | 87 (60%) | 65 (57%) | 22 (69%) | 0.232[c] |
| **Non-white or Hispanic** (n, %) | 14 (10%) | 11 (10%) | 3 (9%) | 1.000[d] |
| **Education** (years, mean ± SD) | 15 ± 3 | 15 ± 3 | 14 ± 3 | 0.188[a] |
| **3MS Score** (0–30, 0 most severe; mean ± SD) | 26 ± 2 | 26 ± 1 | 26 ± 2 | 0.159[a] |
| **GCP Score** (externally scaled, mean ± SD) | 58 ± 7 | 59 ± 7 | 55 ± 7 | 0.002[a] |
| **SF-12 Physical Composite** (T-score, mean ± SD) | 36 ± 10 | 37 ± 10 | 32 ± 10 | 0.016[a] |
| **Vascular Comorbidity** (n, %) | 58 (40%) | 45 (39%) | 13 (41%) | 0.906[c] |
| • Cardiovascular disease | 28 (19%) | 18 (16%) | 10 (31%) | 0.049[c] |
| • Congestive Heart Failure | 3 (2%) | 2 (2%) | 1 (3%) | 0.527[d] |
| • Peripheral vascular disease | 11 (8%) | 8 (7%) | 3 (9%) | 0.706[d] |
| • Hemiplegia | 0 | - | - | - |
| • Diabetes | 28 (19%) | 20 (18%) | 8 (25%) | 0.344[c] |
| • Diabetes w/end organ damage | 5 (3%) | 4 (4%) | 1 (3%) | 1.000[d] |
| **Surgery** (n, %) | | | | |
| • Orthopedic | 120 (82%) | 92 (81%) | 28 (88%) | 0.782[d] |
| • Vascular | 8 (5%) | 7 (6%) | 1 (3%) | |
| • Gastrointestinal | 18 (12%) | 15 (13%) | 3 (9%) | |
| **Delirium Severity** (mean ± SD) | | | | |
| • CAM-S Long (0–19, 19 most severe) | 3.59 ± 3.2 | 2.37 ± 1.6 | 7.94 ± 3.8 | <0.001[b] |
| **Fazekas Score** (0–3, 3 most severe; n, %) | | | | |
| • 0 | 10 (7%) | 9 (8%) | 1 (3%) | 0.358[d] |
| • 1 | 97 (66%) | 72 (63%) | 25 (78%) | |
| • 2 | 39 (27%) | 33 (29%) | 6 (19%) | |
| • 3 | 0 | - | - | |

P-values refer to group comparison no delirium vs. delirium by (a) Student's t-test, (b) Kruskal-Wallis test, (c) Chi-Squared test or (d) Fisher's exact test.

Abbreviations: CAM-S – Confusion Assessment Method - Severity; GCP – Global Cognitive Performance; MDAS – Memorial Delirium Assessment Scale; 3MS – Modified Mini-Mental State Examination; SF-12 – 12-item Short Form.

## Table 2

Quantitative pre-surgical MRI measures of brain parenchymal damage

| | All Subjects (n=146) | No Delirium (n=114) | Delirium (n=32) | p-value |
|---|---|---|---|---|
| **WMH Volume** (cc) | 11.27 ± 9.46 | 11.55 ± 9.94 | 10.24 ± 7.59 | 0.710[b] |
| **BPV** (cc) | 1013.91 ± 113.11 | 1018.71 ± 114.32 | 996.79 ± 108.68 | 0.334[a] |
| **Hippocampal Volume** (cc) | 3.24 ± 0.43 | 3.23 ± 0.43 | 3.25 ± 0.47 | 0.862[a] |
| **ICV** (cc) | 1416.71 ± 158.51 | 1417.88 ± 163.73 | 1410.05 ± 138.23 | 0.805[a] |

Data are expressed as mean ± SD.

P-values refer to group comparison no delirium vs. delirium by (a) Student's t-test or (b) Kruskal-Wallis test.

Abbreviations: BPV – Brain Parenchymal Volume; ICV – Intracranial Cavity Volume; WMH – White Matter Hyperintensities.

## Table 3

Effect of pre-surgical MRI indices of brain damage on postoperative delirium incidence

| | Relative Risk (per cc unit change) | 95%-C.I. | p-value |
|---|---|---|---|
| **WMH Volume** | | | |
| *Adjusted for ICV only* | 0.987 | 0.947 – 1.029 | 0.549 |
| *Fully adjusted model*[*] | 0.966 | 0.919 – 1.016 | 0.178 |
| **BPV** | | | |
| *Adjusted for ICV only* | 0.997 | 0.992 – 1.002 | 0.251 |
| *Fully adjusted model*[*] | 0.997 | 0.992 – 1.003 | 0.367 |
| **Hippocampal Volume** | | | |
| *Adjusted for ICV only* | 1.160 | 0.453 – 2.973 | 0.757 |
| *Fully adjusted model*[*] | 1.371 | 0.494 – 3.799 | 0.545 |

Generalized linear model with log link and Poisson error distribution.

[*] The fully adjusted model includes the following covariates: ICV, age, gender, global cognitive performance and vascular comorbidity.

Abbreviations: BPV – Brain Parenchymal Volume; ICV – Intracranial Cavity Volume; WMH – White Matter Hyperintensities.

## Table 4

Effect of pre-surgical MRI indices of brain damage on delirium severity as assessed by the Confusion Assessment Method - Severity test Long Form

| | Estimate (per cc unit change) | 95%-C.I. | p-value |
|---|---|---|---|
| WMH Volume | | | |
| *Adjusted for ICV only* | −0.032 | −0.087 – 0.024 | 0.262 |
| *Fully adjusted model*[*] | −0.055 | −0.107 – −0.002 | 0.045 |
| **BPV** | | | |
| *Adjusted for ICV only* | −0.006 | −0.014 – 0.002 | 0.136 |
| *Fully adjusted model*[*] | −0.002 | −0.009 – 0.006 | 0.686 |
| **Hippocampal Volume** | | | |
| *Adjusted for ICV only* | −0.494 | −1.892 – 0.904 | 0.490 |
| *Fully adjusted model*[*] | 0.178 | −1.160 – 1.515 | 0.795 |

General linear model.

[*] The fully adjusted model includes the following covariates: ICV, age, gender, global cognitive performance and vascular comorbidity.

Abbreviations: BPV – Brain Parenchymal Volume; ICV – Intracranial Cavity Volume; WMH – White Matter Hyperintensities.