Longitudinal diffusion changes following postoperative delirium in older people without dementia


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David C. Alsop: study concept and design, acquisition, analysis and interpretation of data.

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Michele Cavallari, Long H Ngo, and David C. Alsop performed the statistical analyses.

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SEARCH TERMS
Delirium [299], Cognitive Aging [36], MRI [120], DWI [128].
ABSTRACT

Objective: To investigate the effect of postoperative delirium on longitudinal brain microstructural changes, as measured by diffusion tensor imaging.

Methods: We studied a subset of the larger SAGES study cohort of older adults (≥70 years) without dementia undergoing elective surgery: 113 participants who had diffusion tensor imaging before and one year after surgery. Postoperative delirium severity and occurrence were assessed during the hospital stay using the Confusion Assessment Method and a validated chart review method. We investigated the association of delirium severity and occurrence with longitudinal diffusion changes across one year, adjusting for age, sex, vascular comorbidity and baseline cognitive performance. We also assessed the association between changes in diffusion and cognitive performance across the one-year follow-up period, adjusting for age, sex, education, and baseline cognitive performance.

Results: Postoperative delirium occurred in 25 subjects (22%). Delirium severity and occurrence were associated with longitudinal diffusion changes in the periventricular, frontal, and temporal white matter. Diffusion changes were also associated with changes in cognitive performance across one year, although the cognitive changes did not show significant association with delirium severity or occurrence.

Conclusions: Our study raises the possibility that delirium has an effect on the development of brain microstructural abnormalities, which may reflect brain changes underlying cognitive trajectories. Future studies are warranted to clarify whether delirium is the driving factor of the observed changes or rather a correlate of a vulnerable brain that is at high risk for neurodegenerative processes.
INTRODUCTION

Postoperative delirium is among the most frequent complications of surgery in older patients,¹ and may lead to disabling outcomes, including progressive cognitive decline and dementia.²⁻⁵ The neural correlates of the consequences of delirium are largely unknown. Previous neuroimaging studies suggest that delirium may contribute to the development of brain abnormalities underlying cognitive decline. Duration of delirium was associated with global and regional brain atrophy of the frontal lobe and hippocampus, as well as diffusion tensor imaging (DTI) abnormalities of the corpus callosum at time of hospital discharge in intensive care patients.⁶⁻⁷ Structural magnetic resonance imaging (MRI) abnormalities of the corpus callosum,⁸⁻¹⁰ and changes in network connectivity between the dorsolateral prefrontal cortex and posterior cingulate on resting-state functional MRI¹¹ have been reported during delirium episodes. Due to confounders and lack of baseline neuroimaging assessment associated with the challenge of conducting neuroimaging studies in subjects with delirium,¹² the previous studies were not able to address the key question of whether delirium contributes to brain injury or serves only as an indicator of pre- or co-existing brain abnormalities.

We previously demonstrated regional DTI abnormalities at baseline that predispose to postoperative delirium.¹³ DTI is a sensitive MRI tool for measuring microstructural brain abnormalities by quantifying the mobility of water and its directionality within the brain parenchyma.¹⁴,¹⁵ In the present study, we investigated the effect of postoperative delirium on longitudinal microstructural changes, as measured by DTI before and one year after surgery, in the same cohort of older individuals without dementia undergoing elective surgery. We also investigated the relationship between changes in diffusion and cognitive performance across the one-year follow-up period.
METHODS

Study Design and Cohort Assembly

Our study population is a subsample of the Successful AGing after Elective Surgery (SAGES) study, an ongoing prospective cohort study. The study design and methods have been described previously.16,17 “Eligible participants were age 70 years and older, English speaking, scheduled to undergo elective major non-cardiac surgery at one of two Harvard-affiliated academic medical centers, with an anticipated length of stay of at least 3 days. Eligible surgical procedures were: total hip or knee replacement, lumbar, cervical, or sacral laminectomy, lower extremity arterial bypass surgery, open abdominal aortic aneurysm repair, and colectomy. Exclusion criteria included evidence of dementia, delirium, hospitalization within 3 months, terminal condition, legal blindness, severe deafness, history of schizophrenia or psychosis, and history of alcohol abuse.17” A total of 560 patients were enrolled between June 18, 2010 and August 8, 2013. A subset of 147 study participants was recruited to undergo MRI within one month prior to surgery. One subject was excluded from the study since the baseline MRI protocol was not completed due to non-compliance. Of the remaining 146 subjects scanned at baseline, 126 underwent a follow-up scan one year after surgery: 12 refused to perform the follow-up scan, 2 dropped out the overall study, 5 were unable to perform the follow-up scan due to pacemaker implantation or death following the baseline scan, and 1 could not be scheduled for the follow-up scan during the allowable study time period. Of the 126 subjects who had MRI before and after surgery, 114 had DTI at both time points. DTI failures primarily reflected participant inability to tolerate the full duration of scan (~45 minutes), since DTI was the final sequence of the MRI protocol. The algorithm used for DTI analysis failed in one subject due to
baseline anatomic abnormalities, and this subject was also excluded, yielding a total of 113 subjects for the present study.

**Standard Protocol Approvals, Registrations, and Patient Consents**

Written informed consent was obtained from all participants according to procedures approved by the institutional review boards of Beth Israel Deaconess Medical Center and Brigham and Women’s Hospital, the two study hospitals, and Hebrew SeniorLife, the study coordinating center, all located in Boston, Massachusetts.

**Assessment of Postoperative DeliriumSeverity and Occurrence**

Postoperative delirium severity and occurrence were assessed daily during the hospital stay. Delirium severity was assessed by the Confusion Assessment Method-Severity (CAM-S) Long Form, with scores ranging from 0 to 19 (19=most severe).\(^1\) The sum of all daily CAM-S scores on the daily hospital assessments, regardless of whether or not the patient was delirious, was utilized in the analyses, since it demonstrated the optimal predictive validity for clinical outcomes.\(^2\)

We used both the Confusion Assessment Method (CAM)\(^3\) and a validated chart review method\(^4\) to detect the occurrence of delirium. A patient was deemed to have incident delirium if either or both methods indicated its presence. The CAM is a standardized method for identification of delirium with high sensitivity, specificity and inter-rater reliability.\(^5\) It is based on structured interviews, including formal cognitive testing, administered to patients daily during hospitalization. The validated chart review method\(^6\) was performed to enhance sensitivity in detecting delirium episodes across each 24-hour period, since the daily interview
period with the CAM assessment was brief. Each chart rating was adjudicated independently by
two experts (geriatrician and neuropsychologist) according to pre-specified criteria to determine
possible, probable, definite delirium, or no delirium. A patient was deemed to have delirium if
a rating of definite, probable, or possible delirium was assigned by both raters (any discrepancies
were resolved during a consensus conference).

Assessment of General Cognitive Performance

General Cognitive Performance (GCP) is a weighted composite score based on a battery of
neuropsychological tests administered to assess attention, memory, learning and executive
functioning. The neuropsychological test battery was administered before surgery (median=5,
interquartile range=1–8 days prior to surgery), and one year after surgery (median=376,
interquartile range=365-392 days after surgery). One-year neuropsychological assessment was
administered to 110 out of 113 subjects. The assessment included the Hopkins Verbal Learning
Test, Visual Search and Attention Task, Trail Making Tests A and B, Digit Symbol
Substitution and Copy tests, Digit Span forward and backward, and 15-item Boston Naming
Test. A higher GCP score indicates better cognitive performance. The baseline GCP score was
scaled to reflect population-based norms with a mean value of 50 (standard deviation=10). A
change in 10 units on the GCP score corresponds to a difference in cognitive functioning that is
one standard deviation from the mean of the age-adjusted U.S. population. The GCP score at one
year was adjusted for re-test (learning) effects using an accepted method, which involved
subtracting a correction derived from repeated administrations in a comparison sample of 119
age-matched primary care patients. The difference between re-test adjusted GCP score at one
year and baseline GCP score was used to assess the association of cognitive changes with diffusion changes and delirium.

**MRI Acquisition**

Study participants were imaged before surgery (median=7, interquartile range=4–13 days before surgery) and one year after surgery (median=378, interquartile range=364–407 days after surgery) at the Beth Israel Deaconess Medical Center Radiology Department on a 3-Tesla HDxt MRI scanner (General Electric Medical Systems, Milwaukee, WI) using a standard 8-channel head coil. The complete MRI acquisition protocol included 3D T1-weighted imaging, 3D T2-weighted imaging, 2D fluid-attenuated inversion recovery, and arterial spin labeling. Diffusion-weighted echoplanar imaging was performed using a double echo diffusion preparation sequence: TR=16000 ms, TE=84.4 ms, acquisition matrix=96x96, Flip Angle=90°, field of view=240x240 mm, slice thickness=2.6 mm, in plane resolution=2.5x2.5 mm. Whole brain images were acquired with a b value of 1000 s/mm² at each of 25 optimized diffusion directions.

**DTI Analysis**

TRACULA in FreeSurfer 5.2 was used to process the diffusion-weighted images and extract the fractional anisotropy (FA) and mean diffusivity (MD) maps. We ran multiple iterations (n=6) of a nonlinear normalization routine in SPM-8 (http://www.fil.ion.ucl.ac.uk/spm) to align the individual resampled 1x1x1 mm diffusion maps to the average map obtained from all individual diffusion maps. In successive iterations, FA and MD images were alternately used for the normalization to improve spatial alignment across subjects, using a higher than default 1.5 cm cutoff for spatial warping. After normalization, differential diffusion maps for each subject
were obtained by subtracting the baseline from the follow-up signal of the FA and MD maps. The differential diffusion maps were then smoothed using a Gaussian kernel of 6 mm FWHM to improve voxel correspondence. Voxel-wise analysis of the whole brain (including both the gray and white matter) was performed using statistical parametric mapping (SPM-8) (http://www.fil.ion.ucl.ac.uk/spm). Statistical non-parametric mapping (SnPM-13) (http://warwick.ac.uk/snpm) and a region of interest (ROI) approach were used to confirm the main findings obtained by SPM. For ROI analysis, we used an atlas-based method to measure FA and MD changes of the medulla oblongata, pons, midbrain, anterior cerebellum, posterior cerebellum, subcortical/basal ganglia region, occipital lobe, limbic lobe, parietal lobe, temporal lobe, frontal lobe, and frontal-temporal boundary.

MRI analyses were performed by operators (MC, WD, DCA) who were strictly blinded to all demographic and clinical data, including delirium outcomes.

**Statistical Analysis**

Student’s, Kruskal-Wallis, Chi-Square or Fisher’s exact test was used to assess differences in baseline variables between subjects who developed delirium and subjects who did not, according to the distribution of the data.

For our primary analysis, we investigated the voxel-wise association between longitudinal DTI changes and delirium severity in our 113 study subjects. We performed multiple linear regression adjusting for age, sex and vascular comorbidity. Age refers to the participant’s age (years) at the time of surgery. For vascular comorbidity, the subjects were sub-divided in two categories according to the presence or absence of at least one of the following pathologic conditions: confirmed or history of myocardial infarction, congestive heart failure, peripheral
vascular disease, diabetes (with or without end organ damage), cerebrovascular disease (carotid stenosis, history of stroke or transient ischemic attack), or hemiplegia. In secondary analysis, we included additional covariates to the regression model to factor into our analysis preoperative levels of cognitive functioning, as well as preoperative MRI-derived measures of brain abnormalities. We performed separate multiple linear regression analyses, adjusting for baseline GCP, baseline white matter hyperintensities volume, or regional diffusion values associated with delirium at baseline (in addition to age, sex, and vascular comorbidity). Baseline white matter hyperintensities volume was taken from our previous study on the relationship between preoperative MRI abnormalities and delirium in the same cohort. To account for baseline diffusion abnormalities, we used scalar values of a region that showed highly significant association with delirium (i.e., MD of the right parietal lobe) in our previous report on preoperative diffusion abnormalities associated with delirium in the same cohort. In addition, we investigated the voxel-wise association between longitudinal DTI changes and delirium occurrence in separate multiple linear regression models, using the same analysis framework and covariates employed for delirium severity analyses. To assess the spatial distribution of DTI changes across one year regardless of delirium status, we used multiple linear regression adjusted for delirium severity, age, sex, vascular comorbidity, and preoperative GCP. The voxel-wise association between GPC changes and DTI changes across one year, as well as the association of GPC changes with delirium severity and occurrence, was assessed in the 110 subjects who completed the neuropsychological assessment at one year. We performed multiple linear regression analyses, adjusting for age, sex, years of education, and baseline GCP. To investigate the effect of delirium on the relationship between GCP and DTI changes, we also
performed multiple linear regression adjusting for delirium severity, as well as age, sex, education, and baseline GCP.

In voxel-wise analyses, we determined empirically the cluster size that provided significant results (p-value < 0.05 after correction for multiple comparison within each cluster) using a one-tailed p-value threshold of 0.05 or lower at the voxel level, in line with our overarching hypothesis of a deleterious effect of delirium towards accrual of brain microstructural abnormalities associated with increase in MD and decrease in FA over time.\textsuperscript{14,15} In order to improve accuracy in localizing the diffusion changes over one year regardless of delirium status we used a one-tailed p-value threshold of 0.01 or lower at the voxel level.

Since one-tailed p-values are prone to type I error (false positive results), to verify the robustness of our findings we supported the results of the voxel-based analysis obtained through general linear modeling in SPM, with non-parametric randomization/permutation testing (n permutations=1000) in SnPM-13, as well as by a ROI-based approach, using the identical multivariable approaches used in SPM analyses.

JMP Pro version 12 (\url{www.jmp.com}) was used for all non-voxel-based statistical analyses. The threshold for statistical significance was set to \(p < 0.05\) for all analyses.

\textbf{RESULTS}

Baseline demographic and clinical characteristics of the 113 study subjects are summarized in Table 1. The subsample investigated in the present study presented no overall differences in the baseline characteristics with respect to the whole cohort of subjects who underwent MRI at baseline, on which we reported previously.\textsuperscript{34} While the 33 subjects who did not contribute to the
present study were on average slightly older than the 113 subjects who did contribute (mean±SD age=77±4 vs. 76±5 years; Wilcoxon rank-sum test p=0.03), and showed higher prevalence of vascular comorbidity (58% vs. 35%; Chi-Square test p=0.02), we found no differences in sex distribution (58% vs. 60% female; Chi-square test p=0.79), GCP (mean±SD= 58±8 vs. 59±7; Student’s t-test p=0.71), or delirium incidence (21% vs. 22%; Chi-Square test p=0.91) between the two groups. No differences in the baseline characteristics were found between subjects with and without delirium, with the exception of GCP, which was lower in subjects with delirium (Table 1). Postoperative delirium occurred in 25 out of 113 subjects (22%) during hospitalization.

Our primary analysis showed association of delirium severity with longitudinal diffusion changes controlling for age, gender and vascular comorbidity (Figure 1). Delirium was associated with longitudinal decrease in FA and increase in MD, predominantly in the cerebral white matter of the frontal, parietal, and temporal lobes, slightly more prominent in the right hemisphere (Figure 1). MD increase was also detected in periventricular areas, inside the lateral ventricles, and in the lower brainstem (Figure 1). The observed associations and spatial patterns did not change with addition of baseline GCP as a covariable (Supplementary Figure 1). Analyses adjusted for preoperative MRI abnormalities, as measured by either white matter hyperintensities volume or diffusion (in addition to age, sex, vascular comorbidity, and baseline GCP), also showed similar results.

Delirium occurrence showed association with DTI changes over 1 year with a similar spatial pattern (Supplementary Figures 2 and 3), although delirium severity showed a broader spatial pattern and more prominent association with the diffusion changes. FA and MD changes over 1 year regardless of delirium status were distributed throughout the cerebral white matter, with
more prominent involvement of the periventricular and frontal regions (Figure 2). The confirmatory, non-parametric voxel-wise and ROI analyses showed qualitatively similar results.

Changes in GCP over one year were associated with diffusion changes, predominantly in the posterior temporal, parietal, and occipital white matter (Figure 3). Specifically, we observed a positive association between FA and GCP changes, and a negative association between MD and GCP changes. Longitudinal GCP changes were not associated with delirium severity or occurrence in multivariate analysis, adjusting for age, sex, education, and baseline GCP.

**DISCUSSION**

Our main finding was the association between postoperative delirium and longitudinal brain microstructural changes as measured by DTI mainly in the periventricular, frontal, and temporal white matter. As the study participants were imaged shortly before and then one year after surgery, with incident delirium occurring in 22%, the finding raises the intriguing possibility that delirium may contribute to the development of the observed brain microstructural abnormalities.

Development and accrual of these abnormalities might result from neurodegenerative phenomena, which may coexist with or result from delirium. Moreover, delirium may represent either the result of or serve as a mediator of many factors, such as anesthesia, surgery, psychoactive drugs, which may initiate inflammatory or neurotoxic cascades that lead to the observed diffusion changes at one year. Our ability to establish a causal relationship between delirium and the observed diffusion changes is limited by our own previous finding of presurgical DTI abnormalities predisposing to delirium in the same cohort. While not completely overlapping, the spatial pattern of pre-existing diffusion abnormalities that we
observed in our previous study\textsuperscript{13} included brain areas that also showed longitudinal diffusion changes associated with delirium in the present study (e.g., the frontal, parietal, and temporal white matter). The secondary analysis adjusting for preoperative diffusion abnormalities predictive of delirium\textsuperscript{13} further supports that delirium may have an effect on the development of subsequent brain microstructural abnormalities. Since our study design includes only one MRI data point before surgery, we are unable to estimate premorbid trajectories of diffusion changes and therefore to establish whether the occurrence of delirium had \textit{per se} a deleterious effect.

In the present study, only the association between MD and delirium severity was robust throughout the different analysis approaches, including non-parametric and ROI-based analyses. This finding suggests that the effect of delirium on subsequent diffusion changes is relatively mild. This is further supported by comparison of t-values between the observed diffusion changes over one year regardless of delirium status (Figure 2; t-values ranging from 2.4 to 9) and the delirium-associated diffusion changes (Figure 1; t-values ranging from 1.7 to 5). Our relatively healthy population of highly educated, elective surgery patients without dementia at baseline may explain the proportionately modest effect of delirium on diffusion changes over one year observed in our study.

Notably, the observed diffusion abnormalities do not seem to be related to major focal cerebrovascular events, as we observed no major MRI signs of occurrence of \textit{de novo} ischemic lesions at one year. Rather, the observed diffusion changes likely represent accrual of more diffuse damage to the cerebral white matter. This is further supported by the secondary analysis adjusting for white matter hyperintensities volume, which showed an association between diffusion changes and delirium, similar to our primary analysis (adjusted for age, sex, and vascular comorbidity only). Although we did not find an association between white matter
hyperintensities and delirium in our previous study, the DTI abnormalities observed in watershed areas may reflect diffuse white matter damage of vascular origin. The diffusion changes observed around and within the lateral ventricles likely reflect expansion of the cerebrospinal fluid compartment associated with brain atrophy, similar to previous observations in normal aging. Since this is an ongoing study, we plan additional structural MRI analysis (e.g., voxel-based morphometry, cortical thickness) to investigate more in depth whether measures of brain atrophy are associated with delirium in our cohort.

We found an association between diffusion and cognitive changes over one year. The finding may reflect both improved structural connectivity associated with improvements in cognitive performance and impaired structural connectivity associated with preclinical trajectories of cognitive decline that may lead to subsequent cognitive impairment and dementia. The observed association between diffusion and cognitive changes seems to reflect predominantly the effect of aging, hospitalization, and surgery, since we found no association between longitudinal cognitive changes and delirium severity or occurrence in our imaging cohort. This is further supported by the observed association between diffusion and cognitive changes when adjusting for delirium severity (in addition to age, sex, education, and baseline GCP). However, since analysis of the larger cohort from which this imaging cohort was derived, and other studies did show a deleterious effect of delirium on longer term cognitive decline, the lack of association between cognitive changes at one year and delirium may be explained by the relatively short follow-up of the present study, exclusion of subjects with dementia, smaller sample size of the MRI subcohort, as well as by the higher sensitivity of MRI measures in capturing pre-clinical cognitive changes. As this is an ongoing study, and we are still acquiring and analyzing
longitudinal cognitive data, we will investigate the long-term effect of delirium and the associated diffusion changes on cognitive trajectories in future studies.

Limitations of our study include generalizability of our findings since our study sample included an elective surgical population of older subjects without dementia in a single geographic area. Future studies are needed to confirm the findings in different settings (e.g., general medicine, intensive care, and post-acute settings), as well as other populations (e.g., subjects with dementia). In prioritizing adjustment for relevant baseline covariates and avoiding over-controlling given the limited number of outcome events, we did not account for other potential confounders, such as perioperative factors related to the surgical procedure. Future studies using more advanced acquisition technologies, and different analysis approaches targeting both the white and grey matter (e.g., DTI tractography, voxel-based morphometry, cortical thickness, perfusion, and resting-state fMRI measurements) are also warranted to improve the anatomical detail of the observed association between brain changes and delirium, and to assess the effect of delirium on specific brain networks. Future studies with longer follow-up and more MRI data points before surgery are also warranted to assess whether delirium may accelerate the trajectory of diffusion changes reflecting brain microstructural abnormalities.

We observed a modest yet significant association between delirium and brain microstructural changes in our cohort of older individuals without dementia undergoing elective non-cardiac surgery. The observed diffusion changes may reflect diffuse damage to the cerebral white matter, consistent with the global pathophysiology of delirium. Our findings raise the possibility that delirium, or the underlying neuropathology, has an effect on the development of brain microstructural abnormalities.
ACKNOWLEDGMENTS

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

References


Table 1. Characteristics of the study participants

<table>
<thead>
<tr>
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<th>All Subjects</th>
<th>Delirium</th>
<th>No Delirium</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Number of Subjects</strong></td>
<td>113</td>
<td>25</td>
<td>88</td>
<td>–</td>
</tr>
<tr>
<td><strong>Age (years, mean ± SD)</strong></td>
<td>76 ± 5</td>
<td>76 ± 4</td>
<td>75 ± 5</td>
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<td><strong>Female Sex (n, %)</strong></td>
<td>68 (60%)</td>
<td>18 (72%)</td>
<td>50 (57%)</td>
<td>0.16c</td>
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<tr>
<td><strong>Non-white or Hispanic (n, %)</strong></td>
<td>10 (9%)</td>
<td>2 (8%)</td>
<td>8 (9%)</td>
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<tr>
<td><strong>Education (years, mean ± SD)</strong></td>
<td>15 ± 3</td>
<td>14 ± 2</td>
<td>15 ± 3</td>
<td>0.29b</td>
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<tr>
<td><strong>Baseline 3MS Score</strong> (0–30, 0 most severe; mean ± SD)</td>
<td>26 ± 2</td>
<td>26 ± 2</td>
<td>26 ± 1</td>
<td>0.19b</td>
</tr>
<tr>
<td><strong>Baseline GCP Score</strong> (externally scaled, mean ± SD)</td>
<td>59 ± 7</td>
<td>55 ± 5</td>
<td>59 ± 7</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td><strong>GCP Score at 1 Year</strong> (retest adjusted, mean ± SD)*</td>
<td>61 ± 7</td>
<td>56 ± 6</td>
<td>60 ± 7</td>
<td>0.02a</td>
</tr>
<tr>
<td><strong>GCP Score Changes Across 1 Year</strong> (retest adjusted, mean ± SD)*</td>
<td>0.86 ± 3.46</td>
<td>1.21 ± 3.74</td>
<td>0.75 ± 3.39</td>
<td>0.58a</td>
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<tr>
<td><strong>Vascular Comorbidity (n, %)</strong></td>
<td>39 (35%)</td>
<td>10 (40%)</td>
<td>29 (33%)</td>
<td>0.52c</td>
</tr>
<tr>
<td><strong>Surgery (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Orthopedic</td>
<td>95 (84%)</td>
<td>23 (92%)</td>
<td>72 (82%)</td>
<td>0.58d</td>
</tr>
<tr>
<td>• Vascular</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
<td></td>
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<tr>
<td>• Gastrointestinal</td>
<td>15 (13%)</td>
<td>2 (8%)</td>
<td>13 (15%)</td>
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</tbody>
</table>

P-values refer to group comparison no delirium vs. delirium by (a) Student’s t-test, (b) Wilcoxon rank sum test, (c) Chi-Square test or (d) Fisher’s exact test.

* One-year data available for 110 out of 113 study participants.

Abbreviations: GCP – General Cognitive Performance; 3MS – Modified Mini-Mental State Examination.
Figure Legend

Figure 1. Longitudinal diffusion changes associated with delirium severity in multiple linear regression analysis adjusted for age, sex and vascular comorbidity. Areas showing decrease in fractional anisotropy (FA) and increase in mean diffusivity (MD) are overlaid to canonical T1-weighted images. Colors refer to T-values of significant DTI changes (one-tailed p < 0.05 after correction for multiple comparison within each cluster, cluster size ≥ 10000) on a scale of 1.7 (red) to 5 (yellow).

Figure 2. DTI changes over 1 year regardless of delirium status in multiple linear regression analysis adjusted for delirium severity, age, sex, vascular comorbidity, and baseline general cognitive performance (GCP). Areas showing decrease in fractional anisotropy (FA) and increase in mean diffusivity (MD) are overlaid to canonical T1-weighted images. Colors refer to T-values of significant DTI changes (one-tailed p < 0.05 after correction for multiple comparison within each cluster, cluster size ≥ 5000) on a scale of 2.4 (red) to 9 (yellow).

Figure 3. Diffusion changes associated with cognitive changes across one year in multiple linear regression analysis adjusted for age, sex, education, and baseline general cognitive performance (GCP). Areas showing decrease in fractional anisotropy (FA) and increase in mean diffusivity (MD) are overlaid to canonical T1-weighted images. Colors refer to T-values of significant DTI changes (one-tailed p < 0.05 after correction for multiple comparison within each cluster, cluster size ≥ 10000) on a scale of 1.7 (red) to 5 (yellow).
Supplementary Figure Legend

**Supplementary Figure 1.** Longitudinal diffusion changes associated with delirium severity in multiple linear regression analysis adjusted for age, sex, vascular comorbidity, and baseline general cognitive performance (GCP). Areas showing decrease in fractional anisotropy (FA) and increase in mean diffusivity (MD) are overlaid to canonical T1-weighted images. Colors refer to T-values of significant DTI changes (one-tailed $p < 0.05$ after correction for multiple comparison within each cluster, cluster size $\geq 10000$) on a scale of 1.7 (red) to 5 (yellow).

**Supplementary Figure 2.** Longitudinal diffusion changes associated with delirium occurrence in multiple linear regression analysis adjusted for age, sex and vascular comorbidity. Areas showing decrease in fractional anisotropy (FA) and increase in mean diffusivity (MD) are overlaid to canonical T1-weighted images. Colors refer to T-values of significant DTI changes (one-tailed $p < 0.05$ after correction for multiple comparison within each cluster, cluster size $\geq 10000$) on a scale of 1.7 (red) to 5 (yellow).

**Supplementary Figure 3.** Longitudinal diffusion changes associated with delirium occurrence in multiple linear regression analysis adjusted for age, sex, vascular comorbidity, and baseline general cognitive performance (GCP). Areas showing decrease in fractional anisotropy (FA) and increase in mean diffusivity (MD) are overlaid to canonical T1-weighted images. Colors refer to T-values of significant DTI changes (one-tailed $p < 0.05$ after correction for multiple comparison within each cluster, cluster size $\geq 10000$) on a scale of 1.7 (red) to 5 (yellow).
Diffusion Changes Over 1 Year Regardless of Delirium
(delirium severity, age, sex, vascular comorbidity, baseline GCP)
GCP Changes Over One Year
(age, sex, education, baseline GCP)