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The Relationship between Delirium Duration, White Matter Integrity, and Cognitive Impairment in Intensive Care Unit Survivors as Determined by Diffusion Tensor Imaging

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Abstract

Objective—Evidence is emerging that delirium duration is a predictor of long-term cognitive impairment (LTCI) in Intensive Care Unit (ICU) survivors. Relationships between (a) delirium duration and brain white matter integrity, and (b) between white matter integrity and LTCI are poorly understood and could be explored using Magnetic Resonance Imaging (MRI).

Design, Setting, Patients—A two-center, prospective cohort study incorporating delirium monitoring, neuroimaging and cognitive testing in ICU survivors.

Measurements—Delirium was evaluated with the Confusion Assessment Method for the ICU (CAM-ICU) and cognitive outcomes were tested at 3 and 12-month follow-up. Following the ICU stay, Fractional Anisotropy (FA), a measure of white matter integrity, was calculated quantitatively using Diffusion Tensor Imaging (DTI) with a 3-Tesla MRI scanner at hospital discharge and three-month follow-up. We examined associations between (a) delirium duration and FA and (b) between FA and cognitive outcomes using linear regression adjusted for age and sepsis.

Results—A total of 47 patients with median age of 50 years completed the DTI-MRI protocol. Greater duration of delirium (3 vs. 0 days) was associated with lower FA (i.e. reduced FA=white matter disruption) in the genu (−0.02; p = 0.04) and splenium (−0.01; p = 0.02) of the corpus callosum and anterior limb of the internal capsule (−0.02; $p = 0.01$) at hospital discharge. These associations persisted at 3 months for the genu (−0.02; $p = 0.02$) and splenium (−0.01; $p = 0.004$). Lower FA in the anterior limb of internal capsule at discharge (−10.35; $p = 0.05$) and in genu of corpus callosum at three months (−8.81; $p = 0.006$) was associated with worse cognitive scores at 3 and 12 months.

Conclusions—In this pilot investigation, delirium duration in the ICU was associated with white matter disruption at both discharge and 3 months. Similarly, white matter disruption was associated with worse cognitive scores up to 12 months later. This hypothesis-generating investigation may help design future studies to explore these complex relationships in greater depth.

Keywords

delirium; Diffusion Tensor Imaging; MRI; ICU; sepsis; neuroimaging; white matter integrity; frontal lobe; critical care; intensive care; mechanical ventilation; aging; geriatrics

Introduction

While the likelihood of surviving a critical illness has increased over the last 50 years, survivors frequently experience significant neurologic morbidity including neuromuscular weakness, cognitive impairments and psychiatric disorders (1–3) that were likely not present prior to critical illness (4, 5). Long-term cognitive impairment (LTCI) associated with critical illness is common in survivors. To date, research regarding specific mechanisms of these impairments is limited. Few studies have used neuroimaging to identify the extent and severity of neurologic injury and its relationship to LTCI following critical illness (6).

Emerging data indicate that delirium may be a risk factor for ICU-associated LTCI. Delirium is linked to longer hospital stays, greater medical costs, untoward ICU clinical outcomes and higher mortality following discharge (7–14). Delirium is also associated with adverse neurologic outcomes. Girard et al.(1) found delirium duration independently predicted cognitive impairment 12 months after critical illness. Studies in non-critically ill

patients with delirium suggest the frontal lobe may be differentially affected by perturbations in blood flow. Yokota (15) and Fong (16) observed reduced regional cerebral blood flow in the frontal and temporal lobes in patients with delirium. Shashar et al.(17) found that patients with delirium and sepsis had white matter abnormalities on MR imaging. In older elective cardiac surgery patients who developed delirium the white matter abnormalities were risk factors for delirium (18). Converging data suggest a relationship between delirium, neurologic injury and LTCI. Studies using emerging neuroimaging techniques, such as Diffusion Tensor Imaging (DTI) Magnetic Resonance Imaging (MRI, together DTI-MRI), will be helpful to initiate our understanding of relationships between critical illness and white matter integrity.

DTI-MRI may be an excellent tool by which to study the types of injuries hypothesized to be present in ICU survivors considering the cognitive domains most commonly impaired in ICU follow-up cohort studies to date. DTI-MRI allows for quantitative assessment of the integrity of white matter and white matter tracts (19), and it is more sensitive to white matter injury than conventional MR imaging (20–23). The myelin sheath and axonal cell membranes are responsible for myelin integrity, which helps direct the movement of water molecules along the nerve fibers and is referred to as anisotropic diffusion (24). DTI characterizes the direction of movement of water molecules, which is normally parallel to the long axis of the neuron fiber, but which becomes perpendicular after white matter injury. That is, DTI in brain-injured white matter reveals an altered pattern of water movement that can be measured using a technique called fractional anisotropy (*FA*). FA range from 0 to 1, with 0 (very abnormal) representing completely isotropic diffusion as in plain water (i.e., abnormal in that there is a loss of directional preference, with water flowing perpendicular rather than parallel to the nerve fiber axis) and 1 (normal) representing diffusion restricted to one direction (i.e., parallel to the nerve fiber axis and referred to as anisotropic diffusion) (25). To restate this technique, higher FA values approaching 1 indicate axonal integrity (white matter integrity) whereas lower values represent axonal injury (26). Following traumatic brain injury (25) and anoxic brain injury (19), FA is often decreased indicating axonal injury and compromised neuronal transmission, potentially contributing to LTCI (27–29).

Therefore, we sought to determine if FA was altered in white matter areas of the brain (e.g., corpus callosum, internal capsule) that might help elucidate the relationships between acute brain injury and long-term cognitive impairment in ICU survivors such as executive function, memory and attention. This pilot study was designed to investigate the relationships between (a) delirium duration and brain white matter integrity, and (b) between white matter integrity and LTCI. To do this, we enrolled ICU patients from the surgical and medical ICUs at two medical centers who were at high risk for delirium by virtue of being on mechanical ventilation and/or in shock, and followed them with DTI-MRI and cognitive testing.

Methods

Study Design and Population

"The VISIONS (VISualizing Icu SurvivOrs Neuroradiological Sequelae) study was a prospective, convenience sample neuroimaging study that was nested within an ongoing prospective cohort study evaluating the role of delirium in LTCI in patients with respiratory failure or shock. Patients eligible for the VISIONS study were >18 years of age, surviving the ICU admission in the medical, surgical or cardiac ICUs at Vanderbilt University Medical Center (Nashville, TN) or Saint Thomas Hospital (Nashville, TN) between June 2006 and December 2009. We enrolled consecutive patients, except when study staff performing the VISIONS enrollment were unavailable." Study exclusion criteria were presence of

neurological disease with known brain lesions, traumatic brain injury, history of severe dementia or anoxic brain injury that would confound the diagnosis of delirium, blindness, deafness, non-English speaking, cardiopulmonary bypass within 3 months of ICU admission (to avoid potential bypass-related cognitive impairment), and presence of delirium at hospital discharge. Additional MRI exclusion criteria were patient weight >300 pounds (lb) as per MRI couch limits, claustrophobia, and technical MRI contraindications (e.g., pacemakers or other implanted metal incompatible with MRI).

The institutional review boards at Vanderbilt University and Saint Thomas Hospital approved the study protocol. Written informed consent was obtained from surrogates for collection of the demographic and in-hospital data, including delirium evaluation; patients were self-consented prior to MRI imaging once free of delirium.

Baseline and Demographic Characteristics

Baseline clinical and demographic data were collected at study enrollment. Pre-hospitalization baseline cognitive abilities were assessed through surrogate interview using the validated Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-SF) (30). The IQCODE-SF has good sensitivity (75–100%) and specificity (68–86%) as a screening test for dementia. Patients were considered cognitively impaired if the total IQCODE-SF score was >4 (30). If a patient score was 4 or higher, then further evaluation was performed with the Clinical Dementia Rating Scale (CDR) (31, 32). Patients with a CDR score of 3, indicating a severe preexisting dementia, were excluded from the study. Severity of illness was measured using the Acute Physiology and Chronic Health Evaluation II score (APACHE II)(33) and the Sequential Organ Failure Assessment (SOFA) score (34).

Exposure, Covariates and Outcomes

Research nurses assessed delirium twice daily up to 28 days after study enrollment using the Confusion Assessment Method for the ICU (CAM-ICU) (35, 36). Sedation level was measured via the Richmond Agitation-Sedation Scale (RASS) (37–39). Delirium duration was defined as the total number of days a patient had delirium during the hospital stay (up to 28 days). Sepsis on a daily basis throughout the ICU stay was defined by the presence of two systemic inflammatory response criteria and suspected infection, according to international standardized criteria (40).

Cognitive assessment was conducted at three and twelve month follow-up. Subjects were administered the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (41). The RBANS was chosen *a priori* to assess a wide range of neuropsychological functioning for areas believed to be impacted by critical illness. The RBANS provides five domain-specific Index Scores that include the Immediate Memory Index (List Learning and Story Memory subtests), Visuospatial/Constructional Index (Figure Copy and Line Orientation subtests), Language Index (Picture Naming and Verbal Fluency subtests), Attention Index (Digit Span and Coding subtests), and Delayed Memory Index (List Recall, List Recognition, Story Recall, and Figure Recall subtests) as well as a Total Scale Index. The RBANS is a sensitive and reliable method for assessing cognitive function and differentiating individuals with and without brain injury (42). The Language Index of the RBANS was used to define verbal fluency. Executive functioning was assessed using the Trail Making Test Part B.

MRI Parameters

Patients were scanned in a Philips Achieva 3T MRI scanner (Philips Medical Systems, Inc., Best, The Netherlands) at two time points, hospital discharge and 3-month follow-up. Diffusion weighted images were acquired using echo-planar, pulsed gradient spin echo

imaging sequence with a *b* value of 1000 s/mm^2 along 32 non-collinear weighting directions, acquired at 112×112, FOV = 256 mm then reconstructed at 128×128, FOV = 256 × 256 × 120 (TE = 60 ms, TR = 10 sec, 2 mm thickness, 0 mm gap, sense factor = 2 in the A/P direction, EPI factor = 59).

MRI image processing and Outcomes—Diffusion-weighted images were processed using Philips PRIDE workstation MRI Studio version 4.1R2 (Philips Healthcare, Best, The Netherlands) and Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) (43, 44). Investigators who processed DTI image data were blind to patient identity and all medical information. Diffusion-weighted images were co-registered within subject using an affine algorithm to align them all with the unweighted (b=0) image. All images were visually inspected for major artifacts such as ghosting, motion, or distortion. A diffusion tensor fit was then calculated based on the 32 directionally weighted images, excepting any with major artifacts. Fractional anisotropy (FA) was calculated from the eigen values of the diffusion tensor, and a FA image was created for each subject. The FA images were nonlinearly registered to the MNI atlas space (Montreal Neurological Institute) using a two-step procedure: first, each subject's FA image was registered to each other subject's image. Second, the most representative subject's images were aligned to the MNI atlas space and the appropriate resulting transformations applied to all subjects. The result was a FA map for each subject in MNI space such that generic regions of interest could be applied.

Based on prior imaging research in survivors of critical illness (27–29), the following brain regions were chosen *a priori* and investigated as the key white matter regions of interest: genu, body and splenium of the corpus callosum, fornix (column and body of fornix), anterior limb of internal capsule right, posterior limb of internal capsule, retrolenticular part of internal capsule, external capsule, the anterior cingulum (projection to the cingulate gyrus) and the cingulate hippocampus (white matter fibers that project into the enthorinal cortex a major input pathway to the hippocampus). The corpus callosum contains the largest collection of commissural fibers in the brain and it plays an important role in the interhemispheric functional integration and transfer of auditory, visual, sensory, and motor information.

Regions of interest were derived from the International Consortium for Brain Mapping- DTI (ICBM-DTI)-81 white matter labels atlas (45–47); this atlas was created based on hand segmentation of diffusion tensor maps of 81 subjects. For each subject, a single FA value was derived for each region of interest. This value was the 95th percentile of the FA values of all voxels within the region, chosen to represent the maximal FA within the relevant white matter region while being robust to outlier voxels and edge effects.

Statistical Analyses

Descriptive statistics are presented using medians and interquartile ranges for continuous variables and proportions for categorical variables. To examine the association between duration of delirium with FA in each ROI, we used separate linear regression models for each ROI, adjusting for age at study enrollment and presence of sepsis at any time during the ICU stay. We limited the choice of covariates to age and the presence of sepsis in order to avoid overfitting (i.e., increasing the chance of obtaining a significant result due to random error or noise). The regression coefficient estimates the change in each brain region FA by increasing delirium duration from the 25th to the 75th percentile.

The association between FA in each region of the brain and cognitive outcomes (i.e., executive functioning, attention, verbal fluency, and visual-spatial construction) was also evaluated in separate linear regression models –adjusting for age at study enrollment, and presence of sepsis at any time during the ICU stay – separately at three and twelve-month

follow-up. The differences in the cognitive outcomes were analyzed comparing the 25th to the 75th percentile for each brain region FA. Only regions that showed independent relationships between FA and delirium were examined for their association with cognitive outcomes. This included the corpus callosum and anterior limb of the internal capsule.

To strengthen the understanding of the relationship between delirium duration and FA, we conducted a sensitivity analysis adjusting for the presence of preexisting cognitive function (IQCODE-SF scores). If patients had significant reductions in FA due to prior cognitive impairment, then the IQCODE-SF would theoretically be an independent predictor of FA reduction. R version 2.11.1 was used for all analyses (48

Results

Baseline Demographics

A total of 335 patients were screened between June of 2007 and December of 2009; 10 refused consent, 142 met MRI exclusions, 20 died before being discharged, 60 were delirious at hospital discharge, and 41 were discharged before being consented. A total of 62 patients were enrolled in the current imaging study. Of those enrolled 12 experienced either physical or psychological discomfort in the scanner and were unable to tolerate or complete scanning procedures. The remaining 50 patients were able to complete anatomical MRI imaging. DTI data were not analyzed from 3 subjects at hospital discharge due to scanning error (1 subject) and artifacts (2 subjects). Of the 50 patients, 47 had complete DTI data from at least one visit: 40 at hospital discharge, and 38 at three- month follow-up.

At ICU admission, patients were severely ill with a median APACHE II score of 27 [interquartile range (IQR), (20, 32)] and a median SOFA score of 10 (7.5, 12). From the time of enrollment, patients were mechanically ventilated for a median of 1.53 (0.73, 3.70) days. The patients' median age was 58 (48, 65) years (see Table 1). Only two patients had preexisting cognitive impairment as defined by a score of >4 on the IQCODE-SF. These 2 patients were then further assessed for cognitive impairment using the CDR; both had CDR scores of 0.5, reflecting mild cognitive impairment (32). Of the patients 68% experienced delirium during their critical illness and 25% were delirious for 3 or more days.

Delirium duration and white matter integrity

After adjusting for age and sepsis, longer duration of delirium was independently associated with white matter disruption, as expressed with lower FA values. Models for duration of delirium and FA are shown in Table 2. Increased duration of delirium was associated with lower FA in the genu of the corpus callosum at discharge, such that compared to a patient who experienced no delirium (25th percentile of delirium duration), a patient who experienced three days of delirium (75th percentile) had an FA 0.02 lower on average [95% confidence interval, CI (−0.03, 0.0); p = 0.04]. Similar results were found for the splenium of the corpus callosum [FA point estimate= −0.01 (−0.02, 0.0); p = 0.02] at hospital discharge. Each of these relationships remained significant at three-month follow-up. These changes in the genu and the splenium of the corpus callosum are clinically significant given that the typical decrease in FA associated with aging is 0.03 (from age 52–71) (49). Finally, a significant association between delirium duration and white matter integrity was detected for the body of the corpus callosum at three-month follow-up [−0.02 (−0.04, −0.01); p= 0.006] but not at discharge [FA= −0.02 (−0.03, 0.0); p= 0.08].

Duration of delirium was independently associated with decreased FA in the anterior limb of the internal capsule at discharge [FA = −0.02 (−0.03, −0.01); p = 0.01], while a trend for an association was noted at three-month follow-up [FA = −0.01 (−0.03, 0.00); p = 0.06].

A sensitivity analysis was conducted to account for preexisting cognitive function, measured by the IQCODE-SF that did not nullify the relationship between delirium duration and the brain regions mentioned above.

White matter integrity and Neuropsychological Outcomes

White matter disruption (i.e., lower FA) in several brain regions of interest was significantly associated with worse cognitive outcomes. As stated in the introduction, FA value closer to 1 is indicative of white matter integrity, while FA value closer to 0 is indicative of white matter damage. At hospital discharge, lower FA in the splenium of the corpus callosum was associated with worse verbal fluency scores at three-month follow-up. A patient who had a FA in the splenium of the corpus callosum of 0.79 (25^{th} percentile) compared to a patient with an FA of 0.83 (75^{th} percentile of FA in the splenium) had an average verbal fluency 5 points lower [−5.37 (95% CI −10.44, −0.3,); p = 0.05]. Lower FA in the genu of the corpus callosum at three months was also associated with worse attention scores at 12-month follow-up [−10.35 (−20.1, – 0.59; p= 0.05)]. Finally, lower FA in the anterior limb of the internal capsule at discharge was associated with lower attention scores at three-month follow-up [−8.81 (−14.65, −2.97); p = 0.006].

Discussion

While we want to emphasize that this study is hypothesis-generating and not definitive in explaining a cause-and-effect relationship between delirium and brain injury acutely or long250 term, it is the first study to our knowledge using DTI-MRI in general medical and surgical ICU patients to examine the relationships between an early clinical marker (delirium), brain integrity (FA values), and a long-term clinical marker of injury (cognitive testing). Duration of delirium was associated with reduced FA values – demonstrating compromised white matter integrity – in areas of the brain involved in interhemispheric connectivity as the genu, splenium and body of the corpus callosum and the anterior limb of the internal capsule at hospital discharge and three256 month follow-up. The second finding of this investigation was that lower FA values were also associated with attention and verbal fluency that are frequently impaired in ICU survivors and represent important cognitive components critical for executive functioning. Specifically, lower FA values in the splenium of the corpus callosum were associated with worse verbal fluency, while lower FA values in the body of the corpus callosum and anterior limb of the internal capsule were associated with lower attention scores.

Different hypotheses have been postulated to explain the pathogenesis of delirium (16, 50–53), including the role of large neutral amino acid perturbation, systemic inflammation, sedatives or analgesics. Nonetheless, a definitive understanding of the mechanisms or how brain perturbations can predispose to or be associated with delirium remains to be determined. Two studies, have investigated the role of cerebral perfusion impairments in a total of 33 patients with delirium showing reduced cerebral blood flow in the frontal and temporal lobes (15, 16), neural regions in which we found compromised white matter integrity. These two studies used different neuroimaging techniques (i.e. single photon emission computed tomography, xenon-enhanced computed tomography) and only Yokota and colleagues enrolled in their study ICU patients, including patients with traumatic brain injury. Different from these studies in our investigation we sought to focus on white matter abnormalities - as be detected through DTI-MRI exploring 1) their association with delirium and 2) with neurocognitive deficits.

White matter abnormalities are reported in critically ill patients with delirium (17, 54). Recently, Shiori and colleagues (18) evaluated white matter integrity in a group of elderly patients with postoperative delirium using DTI techniques with FA. FA values in delirious

patients were significantly lower in the left frontal lobe, in the splenium of the corpus callosum, and bilateral thalamus. These findings of reduced FA values in the frontal lobe and corpus callosum are linked to the cardinal features of delirium, inattention and altered level of consciousness. As suggested by Shiori et al. (18) white matter integrity is required to control consciousness and attention, which are impaired in patients with delirium and these neural messages are transmitted through the thalamus to the cortex. In our study we found an association between delirium duration and FA values in the corpus callosum and anterior limb of the internal capsule. The corpus callosum is essential for interhemispheric communication and alterations in its white matter integrity might also be explanatory of the duration of delirium.

White matter abnormalities are also reported to be associated with cognitive impairment (55) but their role and significance in critically ill patients remains unclear. White matter lesions as a result of a traumatic event can be responsible for cognitive impairments in domains of executive functioning, working memory, and attention (56–59). These neurocognitive deficits are also common in ICU survivors (1, 4, 60–64) though white matter abnormalities due to trauma may involve different mechanisms such as metabolic, hypoxic, and microvascular damage. Our preliminary data showed an association between reduced FA in the genu of the corpus callosum and the anterior limb of the internal capsule -white matter pathways associated with attention-, and the splenium - associated with verbal fluency. These findings are in line with recent studies in TBI patients which have reported an association between lower FA values and adverse neurocognitive outcomes (21, 27–29, 65, 66). Finally, we did not detect an association between FA values and memory domains, potentially due to small sample size. Palacios and colleagues (67) has reported that a diffuse white matter damage are associated with working memory impairments (frontal lobe function), while declarative memory deficits seem to be the result of more local disruption of the cerebral activity in temporal lobe structures.

Previous findings in TBI coupled with our preliminary investigation suggest that acute disruption of neuronal transmission and alteration of white matter integrity –may be as a result of longer duration of delirium– may play a role in the development of LTCI. Further investigation is required to assess the hypotheses that 1) delirium is associated with white matter integrity; 2) white matter integrity is associated with cognitive impairment, and 3) delirium is associated with cognitive impairment. Our and others findings of the association of DTI with delirium and LTCI have the potential to integrate, in clinical settings, the use of white matter integrity as a predictor of brain injury and development of LTCI. Our findings suggest that delirium is not just a marker of temporary neurologic changes but may be a marker of permanent neurologic injury and LTCI. Thus, interventions that prevent or treat delirium in millions of ICU survivors across the world are needed.

Our study has important strengths and limitations that warrant attention. Important strengths include the prospective cohort design of the study, protocolized MRI scans at two time points, delirium assessment performed daily by research nurses with a validated and reliable delirium assessment tool (CAM-ICU) (35, 36) and use of a validated sedation scale (RASS) (37–39). Additionally, assessors of brain imaging and FA values were blinded to the clinical characteristics and duration of delirium.

The population included in this study represents a limitation to our study because it represents a convenience sample of patients admitted to the ICUs during the study period.” Another important limitation is the sample size, which has limited our ability to include the severity of illness in the statistical models, though we were able to adjust for important covariates as age and sepsis. Also, this is the first study evaluating medical and ICU survivors with DTI and the number of patients included in this investigation is comparable

to other studies investigating the role of FA in TBI (range of patients number from 8 to 48) (21, 27, 29, 65, 66). The absence of pre-ICU admission MRI scans limit the interpretation of these preliminary data and precludes us from assigning directionality to our findings (a point for a future study). In fact the reduced FA could pre-exist ICU admission, however it is unlikely as we excluded individuals with prior neurologic disease or injury. The absence of pre-ICU MRI scans is also reflective of the nature of the population who are emergently admitted to an ICU, making pre-ICU scans difficult or impossible to obtain. Finally, we used specific predefined brain region of interest to investigate potential associations between delirium duration and white matter integrity. This approach was driven by previous clinical investigations, which underlined impairments in specific neurocognitive domains (i.e., attention, memory, executive function) in ICU survivors. Other approaches for example using tract-based spatial statistics (TBSS –a method to perform a whole-brain voxelwise analysis) should be investigated in future studies as this method could allow for better model fitting and inferences.

Conclusions

In this pilot investigation, delirium duration in the ICU was associated with white matter disruption at both discharge and 3 months. Similarly, white matter disruption was associated with worse cognitive scores up to 12 months later. The use of neuroimaging techniques as diffusion tensor imaging (DTI) with FA can potentially provide the clinicians with important tools to identify white matter injury not detected with conventional MRI. These preliminary data provide important information for a hypothesis that connects white matter integrity with delirium duration and long-term cognitive impairment in ICU survivors. Further investigation is required to develop this hypothesis and provide clinicians with new tools to predict patients at higher risk of LTCI and potentially develop interventions to reduce the burden of this public health concern.

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ABBREVIATIONS

ALIC	anterior limb of internal capsule
APACHE II	Acute Physiology and Chronic Health Evaluation II score
CAM-ICU	Confusion Assessment Method for the ICU
CDR	Clinical Dementia Rating Scale
CHF	congestive heart failure
COPD	Chronic Obstructive Pulmonary Disease
DTI	diffusion tensor imaging
DTI-MRI	diffusion tensor imaging-magnetic resonance imaging
DAI	diffuse axonal injury
FA	fractional anisotropy
ICBM	International Consortium for Brain Mapping

ICU	intensive care unit
IQCODE-SF	Short Informant Questionnaire on Cognitive Decline in the Elderly
IQ	Intelligence quotient
LTCI	long-term cognitive impairment
MI	myocardial infarction
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SOFA	Sequential Organ Failure Assessment score

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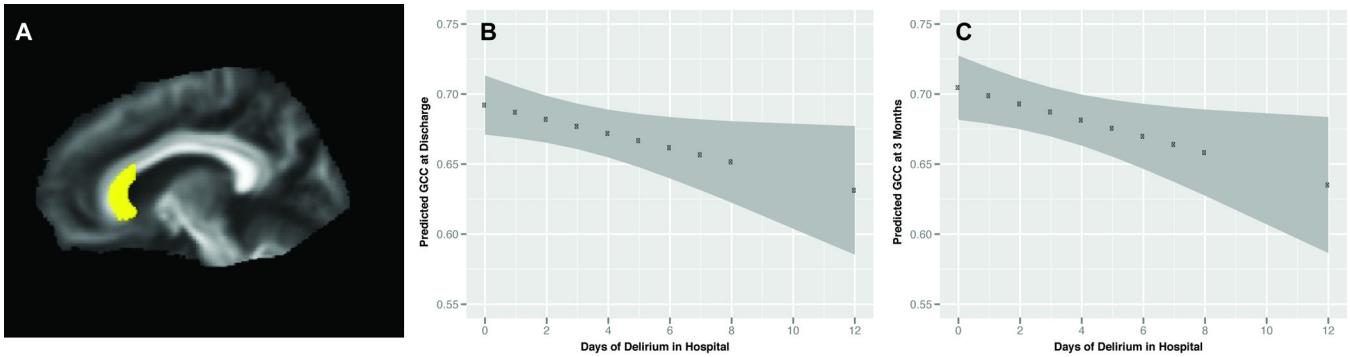

Figure 1. Delirium Duration and Fractional Anisotropy in the Genu of the Corpus Callosum

The Figure1A shows a sagittal section of the average of all subjects' FA images; white matter is therefore bright, while gray matter and CSF are dark. The genu of corpus callosum region of interest is overlaid in yellow. Increased duration of delirium was independently associated with reduced FA both at hospital discharge (Figure 1B) and at three-month follow-up (Figure 1C), after adjusting for age and presence of sepsis. FA is shown on the y-axis of figures 1a and 1b. The x-axis for all figures represents the duration of delirium measured in days. In Figure 1B and 1C, the circles show the point estimate of the association between FA and cognitive outcomes, and the dashed lines indicate the 95% confidence intervals.

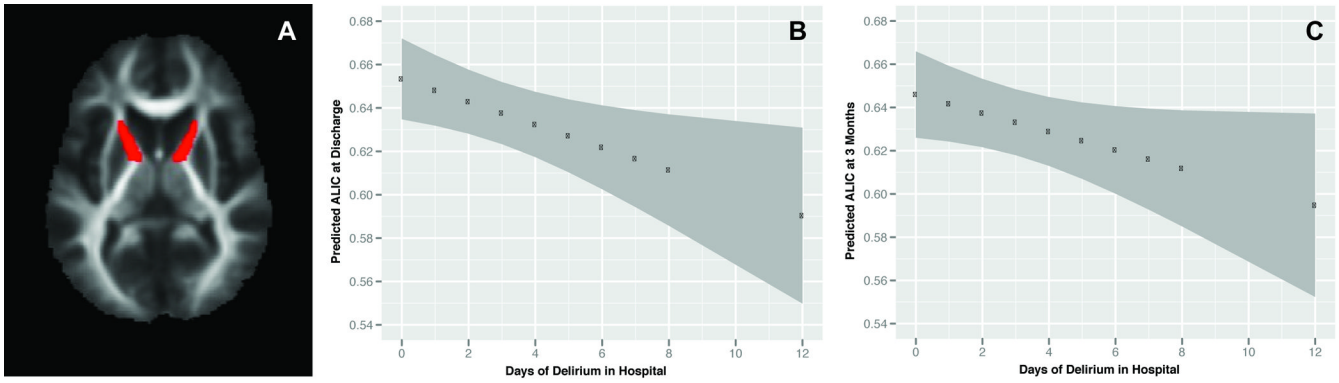

Figure 2. Delirium Duration, and Fractional Anisotropy in the Anterior Limb of the Internal Capsule

The image in Figure 2A shows an axial section of the average of all subjects' FA images; the anterior limb of the internal capsule region of interest is overlaid in red. Duration of delirium was independently associated with reduced FA in the anterior limb of the internal capsule (ALIC) at discharge (Figure 2B) and at three-month follow-up (Figure 2C), after adjusting for age and presence of sepsis. Brain FA values are shown on the y-axis. The x-axis is duration of delirium measured in days. In Figures 2B and 2C, the circles show the point estimate of the association between FA and cognitive outcomes, and the dashed lines indicate the 95% confidence intervals.

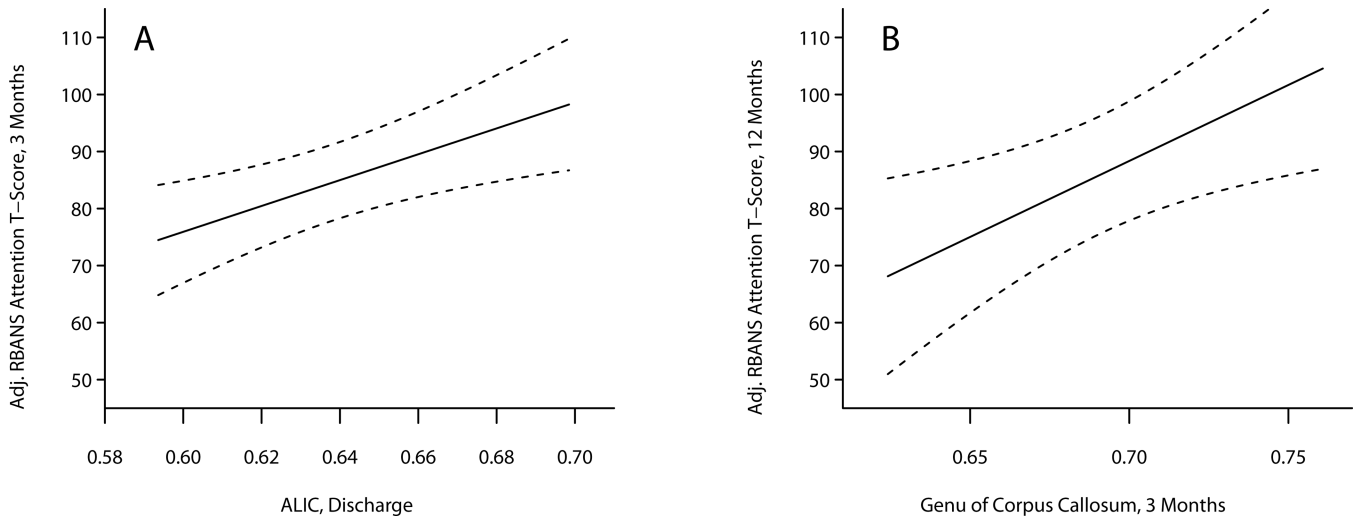

Figure 3. Fractional anisotropy (FA) and cognitive outcomes

Figure 3A) Lower FA in the anterior limb of the internal capsule (ALIC) (indicative of white matter disruption) at discharge was associated with worse attention scores at 3-month follow-up, after adjusting for age and presence of sepsis. Figure 3B) Lower FA (indicative of white matter disruption) in the genu of the corpus callosum (GCC) at 3-month was associated with better attention scores at 12-month follow-up, after adjusting for age and presence of sepsis. The solid black line shows the point estimate of the association between FA and cognitive outcomes, and the dash line indicates the 95% confidence interval.

Table 1

Baseline Demographics and Clinical Characteristics[a]

Characteristic	Cohort (n=47)
Age at enrollment, y	58 (48, 65)
Female, % (n)	38% (18)
Education, years	12 (12, 14)
IQCODE-SF	3 (3, 3.06)
Baseline Cognitive impairment, % (n/total)[b]	4% (2)
APACHE II at enrollment	27 (20, 32)
SOFA at enrollment	10 (7.5, 12)
Mechanical ventilation, % (n)	94% (44)
Days in the ICU	3.8 (2.0, 6.0)
Days in the hospital	9.1 (6.6, 13.0)
Admission diagnoses, % (n)	
Sepsis/acute respiratory distress syndrome	30% (14)
Hepatobiliary/pancreatic Surgery	23% (11)
CHF/MI/Cardiogenic shock	13% (6)
COPD/Asthma	9% (4)
Acute respiratory distress syndrome without infection	6% (3)
Other	17% (9)
ICU Delirium	
Prevalence, % (n)	68% (32)
Patients with 1 day of delirium, % (n)	21% (10)
Patients with 2 days of delirium, % (n)	13% (6)
Patients with 3 days of delirium, % (n)	15% (7)
Duration, days	1 (0, 3)

[a] All results expressed as median (interquartile range), or % (n/total).

[b] Patients with a IQCODE-SF score ≥ 4 were considered to have mild-moderate preexisting cognitive impairment; patients with severe dementia preventing them from living independently were excluded from enrollment.

Abbreviations:
IQCODE-SF, Short Informant Questionnaire of Cognitive Decline in the Elderly; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, Intensive Care Unit; COPD, Chronic Obstructive Pulmonary Disease; ARDS, Acute Respiratory Distress Syndrome; Myocardial infarction;CHF, Congestive Heart Failure; SOFA, Sequential Organ Failure Assessment; MI, Myocardial Infarction; Other diagnoses include colonic surgery, ENT surgery, gastric surgery, vascular surgery neurological disease, pulmonary other, renal failure, seizures/status epilepticus and transplants (excluding liver).

Table 2

Relationship between Brain White Matter Integrity and Duration of Delirium[a]

Anatomical Region	Average FA at Hospital D/C	Average FA Three-months	Discharge 3 vs. 0 Days Delirium Point Estimate (95% CI)	P value	Three-months 3 vs. 0 Days Delirium Point Estimate (95% CI)	P Value
Corpus Callosum						
- Genu	0.687	0.700	−0.02 (−0.03, 0.0)	0.02	−0.02 (−0.03, 0.0)	0.02
- Body	0.703	0.716	−0.02 (−0.04, 0.0)	0.03	−0.03 (−0.04, −0.01)	0.001
- Splenium	0.813	0.815	−0.01 (−0.02, 0.0)	0.006	−0.01 (−0.02, −0.01)	0.004
Fornix	0.52	0.57	−0.02 (−0.06, 0.01)	0.23	−0.04 (−0.08, 0.0)	0.06
Internal Capsule						
- Retrolenticular part	0.642	0.641	0.0 (−0.02, 0.01)	0.82	0.0 (−0.02, 0.01)	0.66
- Anterior limb	0.650	0.646	−0.02 (−0.03, −0.01)	0.008	−0.01 (−0.03, 0.0)	0.03
- Posterior limb	0.708	0.697	0.0 (−0.01, 0.01)	0.44	0.0 (−0.01, 0.01)	0.67
External capsule	0.464	0.454	−0.01 (−0.02, 0.0)	0.07	−0.01 (−0.02, 0.0)	0.29
Anterior cingulum	0.620	0.621	−0.01 (−0.02, 0.0)	0.12	−0.02 (−0.03, 0.0)	0.06
Cingulate hippocampus	0.496	0.482	0.0 (−0.02, 0.01)	0.53	−0.01 (−0.02, 0.01)	0.33

[a]All results adjusted for age and presence/absence of sepsis.

White matter integrity is determined using diffusion tensor imaging (DTI). DTI measures fractional anisotropy (FA), the efficiency of water flow through axons. FA is value between 0 and 1 with higher values representing greater efficiency of flow and preserved white matter integrity. The point estimate (95% confidence interval) represents differences in fractional anisotropy (FA) for each region of interest in patients who have 3 days of delirium versus those who had 0 days of delirium. For example, patients who experienced three days of delirium had, on average, an FA value that was −0.02 lower than a patient who had no delirium (i.e., lower FA = reduced white matter integrity) at hospital discharge and −0.03 lower at three-month follow-up in the body of the corpus callosum.

Abbreviations: fractional anisotropy = FA

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