Thalamic integrity underlies executive dysfunction in traumatic brain injury

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ABSTRACT

Objective: To quantify the effects of traumatic brain injury on integrity of thalamocortical projection fibers and to evaluate whether damage to these fibers accounts for impairments in executive function in chronic traumatic brain injury.

Methods: High-resolution (voxel size: 0.78 mm × 0.78 mm × 3 mm^3) diffusion tensor MRI of the thalamus was conducted on 24 patients with a history of single, closed-head traumatic brain injury (TBI) (12 each of mild TBI and moderate to severe TBI) and 12 age- and education-matched controls. Detailed neuropsychological testing with an emphasis on executive function was also conducted. Fractional anisotropy was extracted from 12 regions of interest in cortical and corpus callosum structures and 7 subcortical regions of interest (anterior, ventral anterior, ventral lateral, dorsomedial, ventral posterior lateral, ventral posterior medial, and pulvinar thalamic nuclei).

Results: Relative to controls, patients with a history of brain injury showed reductions in fractional anisotropy in both the anterior and posterior corona radiata, forceps major, the body of the corpus callosum, and fibers identified from seed voxels in the anterior and ventral anterior thalamic nuclei. Fractional anisotropy from cortico-cortico and corpus callosum regions of interest did not account for significant variance in neuropsychological function. However, fractional anisotropy from the thalamic seed voxels did account for variance in executive function, attention, and memory.

Conclusions: The data provide preliminary evidence that traumatic brain injury and resulting diffuse axonal injury results in damage to the thalamic projection fibers and is of clinical relevance to cognition. *Neurology*® 2010;74:558–564

GLOSSARY

ACR = anterior corona radiata; **AN** = anterior thalamic nucleus; **bCC** = body of the corpus callosum; **CST** = cortical-spinal tract; **DAI** = diffuse axonal injury; **DM** = dorsomedial nucleus; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **fMaj** = forceps major; **fMin** = forceps minor; **FOV** = field of view; **FSE** = fast spin echo; **gCC** = genu of the corpus callosum; **IC** = internal capsule; **IFOF** = inferior frontal occipital fasciculus; **LOC** = loss of consciousness; **miTBI** = mild TBI; **msTBI** = moderate to severe TBI; **NEX** = number of excitations; **PCR** = posterior corona radiata; **PTA** = posttraumatic amnesia; **PU** = pulvinar; **ROI** = region of interest; **sCC** = splenium of the corpus callosum; **SLF** = superior longitudinal fasciculus; **SS** = sagittal stratum; **TBI** = traumatic brain injury; **TE** = echo time; **TR** = repetition time; **VA** = ventral anterior thalamic nucleus; **VL** = ventral lateral thalamic nucleus; **VPL** = ventral posterior lateral nucleus; **VPM** = ventral posterior medial nucleus.

Traumatic brain injury (TBI) is a serious public health problem with a high incidence[1-3] which can result in structural damage to the cerebrum including contusions, edema, and diffuse axonal injury (DAI).[4] DAI has been demonstrated in all stages and severities[5-7] and is often the only significant pathology in milder injury.[6,8-15] The variable nature of injury mechanism, severity, lesion presence, and location makes the identification and definition of the key cere-

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bral mechanisms which underlie behavioral impairments challenging. Behaviorally, patients with a history of TBI commonly have deficits in cognition, behavior, and mood that load heavily on the executive or frontal lobe functions.[16-20] However, the relationship between measures of frontal lobe structure and shearing within frontal lobe white matter tracts and cognition are generally weak.[7,19,21] This weak relationship between frontal structure and function, coupled with the finding that DAI not only affects local function but can also disrupt critical cortical-subcortical pathways,[22,23] led us to the general hypothesis that damage to cortical-subcortical fibers projecting to and from the thalamus contribute to chronic impairment in cognition and behavior. This hypothesis is supported by the report that thalamic volume is related to 2-year outcome.[24] We tested the hypothesis that damage to thalamic projection fibers underlies executive function impairments using high-resolution diffusion tensor imaging of the thalamus (DTI) in a group of healthy controls and in 2 groups of patients who had sustained a closed-head brain injury.

METHODS

Standard protocol approvals, registrations, and patient consents. The research was conducted in compliance with both institutional (University of Illinois at Chicago) and federal (Department of the Army) human subjects guidelines using standards consistent with the declaration of Helsinki. All subjects provided prospective, written, informed consent.

Participant characteristics. A total of 24 patients with a history of a single, closed-head type TBI were recruited via advertisements in local newspapers (no patients were recruited from an active clinical practice) and were screened and consented in the order they responded to advertisements. Inclusion criteria for patients and controls included age at study (18–50 years of age included), education (at least 1 year of high school), negative history (prior to TBI) for psychiatric illness, and English as a native language. For patients with TBI, age at injury was required to be after age 16 and at least 12 months prior to study. Patients were classified as having had a mild TBI (miTBI) if they reported either no loss of consciousness (LOC) or a LOC less than 30 minutes and posttraumatic amnesia (PTA) for less than 24 hours. Patients were classified as moderate to severe TBI (msTBI) if they experienced LOC greater than 30 minutes, PTA greater than 24 hours, or a positive MRI or CT study for contusion, edema, or ischemia at the time of injury. Detailed clinical assessments were carried out (M.F.K.) to establish injury severity and extract specific injury variables including mechanism of injury, presence and duration of LOC, neurologic examination, presence of posttraumatic headache, and associated injuries at the time of TBI. See table e-1 on the *Neurology*® Web site at www.neurology.org for details. Estimates of PTA and LOC are presented as the nature and time from injury makes accurate estimates difficult. Subjects were excluded if they were taking any medications used to enhance cognitive function, had significant depressive symptoms, had current or past litigation related to the injury, or had failure on tests of effort and symptom validity. All but 2 of the patients with TBI had returned to work or school following the injury. Of the 2, 1 was unable to return to work and the other dropped out of college. The gross majority of subjects reported a level of function less than prior to the injury (20 of 24) even though more than 14 returned to the same job or matriculated to the next stage of schooling. Of the 24 patients with TBI, all but 3 reported some degree of sustained problems with cognition or sustained alteration in cognitive function at the time of testing. In terms of alterations in behavior, 12 of the 24 reported sustained alterations in behavior following the TBI.

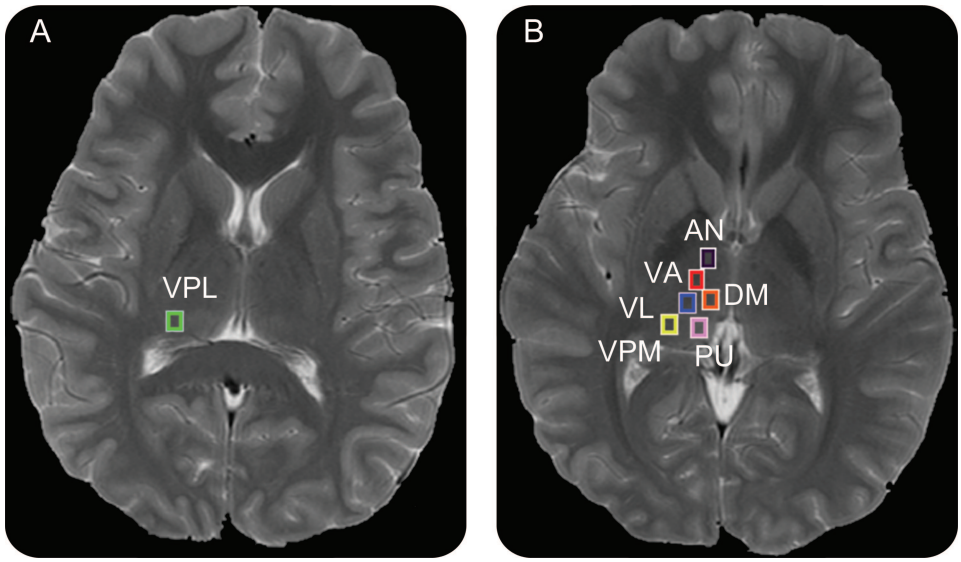
The groups were matched on age and education, with controls reporting 15 years of formal education (mean = 15.4, SEM = 0.6) and age at study of 31 years (mean = 30.8, SEM = 3.04); miTBI reporting16 years of formal education (mean = 16.4, SEM = 0.36) and age at study of 31 years (mean = 31.2, SEM = 2.71); and msTBI reporting 16 years of formal education (mean = 16.1, SEM = 0.60) and age at study of 33 years (mean = 33.3, SEM = 3.20). The miTBI and msTBI were roughly matched for age at injury (miTBI: mean = 27.2 years of age, SEM = 2.4; msTBI: mean = 25.3 years of age, SEM = 2.9). All 3 groups were matched on estimates of premorbid IQ (controls: mean = 112.4, SEM = 3.55; miTBI: mean = 111.2, SEM = 2.78; msTBI: mean = 111.7, SEM = 1.6).

Statistical analyses. Neuropsychological test scores were analyzed using a one-way analysis of variance with group membership (controls, miTBI, msTBI) as the between-subjects factor and were corrected for multiple comparisons using the least significant difference post hoc tests. The primary measures of interest were 3 scores which were each a composite of those individual test results which loaded preferentially on executive, memory, and attention domains. Group differences on individual neuropsychological tests were corrected for multiple comparisons using the Bonferroni correction. The primary analyses carried out on the dependent measures extracted from the DTI data were a one-way mixed design analysis of variance with group membership (controls, miTBI, and msTBI) as the between-subjects factor. The primary dependent measure was fractional anisotropy (FA). Data were confirmed to have a normal distribution using the Kolmogorov-Smirnov test. To examine the relative contributions of thalamic and cortical (to include cortico-cortico and corpus callosum white matter) regions of interest, both bivariate correlations and stepwise linear regressions were used.

Neuropsychological testing. Subjects completed a neuropsychological battery comprised of tests known to be sensitive to the cognitive deficits associated with TBI, with a focus on tests of executive function, attention, memory, and processing speed. Additional measures were included to assist in the estimation of premorbid function and to assess effort. Tests and selected scores from the tests are included in table e-2. These test scores were converted to standardized *z* scores (based upon control means) and combined to create 3 cognitive domains (executive, attention, memory).

Image acquisition. In order to reliably perform the FA analysis and fiber tracking in the thalamus, we used a customized high-resolution DTI protocol which relied on a single-shot EPI acquisition[25] together with parallel imaging using an 8-channel phased-array head coil on a GE 3.0 T Signal HDx scanner (Gen-

Figure 1 Thalamic nuclei



Seed regions for the ventral posterior lateral nucleus (VPL) (green), anterior thalamic nucleus (AN) (purple), ventral anterior thalamic nucleus (VA) (red), dorsomedial nucleus (DM) (orange), ventral lateral thalamic nucleus (VL) (blue), ventral posterior medial nucleus (VPM) (yellow), and pulvinar (PU) (pink) overlaid on the T2-weighted images.

eral Electric Healthcare, Milwaukee, WI). The imaging parameters included repetition time (TR)/echo time (TE) = 5,000/64 msec, b = 0,1000 s/mm^2, diffusion directions = 27, field of view (FOV) = 20 × 20 cm^2, matrix = 256 × 256, slice thickness/gap = 3/0 mm, slices = 7, number of excitations (NEX) = 8, and acceleration factor = 2. In order to visualize the thalamus and differentiate the thalamus from surrounding structures, a set of 2D T2-weighted images were acquired (fast spin echo [FSE], axial, TR/TE = 4,000/80 msec, ETL = 8, matrix = 512 × 256, FOV = 20 × 20 cm^2, slices = 7, slice thickness/gap = 3/0 mm). To visualize the dorsomedial nucleus, 3-dimensional inversion recovery spoiled gradient recalled echo (3DIRpSPGR) images were acquired (TR/inversion time/TE = 13.8/600/2.7 msec, flip angle = 25°, matrix = 512 × 192, FOV = 22 × 16 cm^2, slices = 120, slice thickness = 1.5 mm, NEX = 1, bandwidth = ±15.6 kHz).

Diffusion tensor imaging and analysis. DTI is a type of diffusion-weighted imaging that allows the assessment and visualization of large white matter fibers on a millimeter-level multidimensional scale. DTI takes advantage of the diffusivity of water and the restrictions imposed on the diffusion of water by white matter fiber tracts. When fiber tracts are dense the restriction imposed by their density leads to directionally dependent or anisotropic diffusion with the shape of water diffusion occurring preferentially along those tracts. When there is less organization or a lack of aligned and organized fiber structures (i.e., gray matter, CSF, axonal loss, or demyelination) the shape of water diffusion will be more isotropic. Commonly, the degree of alignment and anisotropy is calculated as the FA. FA values range from 0 to 1, where 0 represents isotropic diffusion and 1 represents anisotropic diffusion.

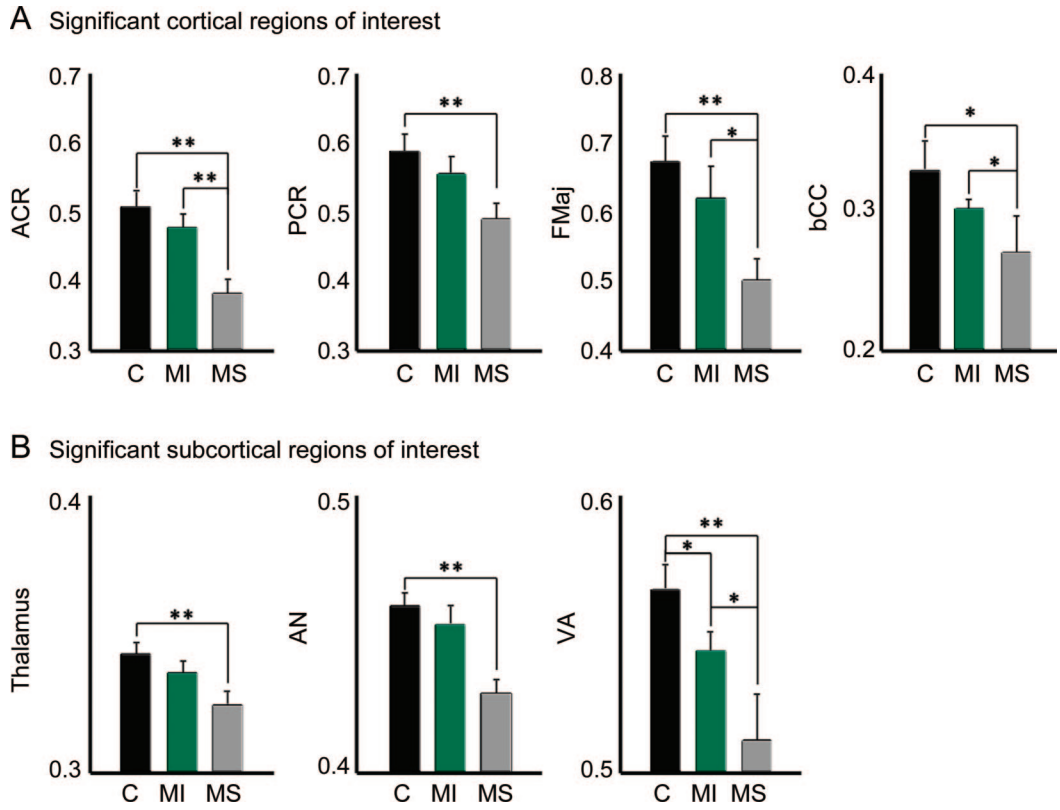
In the present study, the diffusion images were reconstructed and FA calculated using DTI Studio.[26] For each slice, the set of 28 DTI images were examined for image quality. Head movement was required to be within 1 voxel across the image acquisition. Because noise can introduce bias in estimates of the eigenvalues and decrease the signal-to-noise ratio, a background noise level of 125 (MR units) was applied prior to calculation of pixel-wise FA, eigenvectors, and eigenvalues. All region of interest (ROI) analyses were carried out on each individual in original image space.

Effects of trauma on cerebral white matter. To assess the effects of trauma on DTI, 3 analyses were applied. Gross measures of whole brain FA and thalamic FA were extracted. For the whole brain mask, each voxel with a FA greater than 0.2 was included (ensuring only white matter in the calculations). Second, specific ROI were drawn on corpus callosum and cortico-cortico white matter tracts, which have been previously implicated in head injury.[7] These "cortical" ROIs were placed on the cortical-spinal tract (CST), anterior corona radiata (ACR), posterior corona radiata (PCR), forceps minor (fMin) and forceps major (fMaj), sagittal stratum (SS), internal capsule (IC), inferior frontal occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), and in the genu (gCC), body (bCC), and splenium (sCC) of the corpus callosum. Separate ROIs were placed in the left and right hemisphere where appropriate. Details on placement can be found in figure e-1.

Finally, fiber tracking was used to assess damage to the fibers projecting from the thalamus. Seed voxels (small ROIs) were placed in 7 thalamic regions (shown in figure 1) including the anterior thalamic nucleus (AN), ventral anterior thalamic nucleus (VA), ventral lateral thalamic nucleus (VL), dorsomedial nucleus (DM), ventral posterior lateral nucleus (VPL), ventral posterior medial nucleus (VPM), and pulvinar (PU). The purpose of these seed voxels is to identify all fiber tracts which run through this region. FA can then be extracted from these fibers identified by the seed voxels and fiber tracking from these seeds. Interrater reliability was greater than 0.94 for placement of AN, VA, DM, VL, and PU seed voxels. Interrater reliability was 0.85 for VPL and VPM. Specific details and rules for placement are included in appendix e-1 and figure e-2.

RESULTS Behaviorally, patients with a history of TBI performed worse on measures of executive func-

Figure 2 Average cortical and subcortical fractional anisotropy (FA)



Mean FA extracted from the anterior corona radiata (ACR), posterior corona radiata (PCR), forceps major (fMaj), and body of the corpus callosum (body of the corpus callosum) as well as from the thalamus and from fibers identified from seed regions in the anterior thalamic nucleus (AN) and ventral anterior thalamic nucleus (VA). Significant post hoc comparisons between groups are indicated (*$p < 0.05$; **$p < 0.01$). Cortical in this figure refers to regions of interest that include cortico-cortico tracts and regions in the corpus callosum.

tion relative to controls [$F(2,36) = 5.15$, $p = 0.011$, $\eta^2 = 0.26$]. Although there were trends for reduced attention and memory performance in TBI, neither of these comparisons reached significance. These findings are consistent with previous work from our group and the literature in general.[7,27-29] A detailed list of performance for each subject group on each test can be found in table e-2.

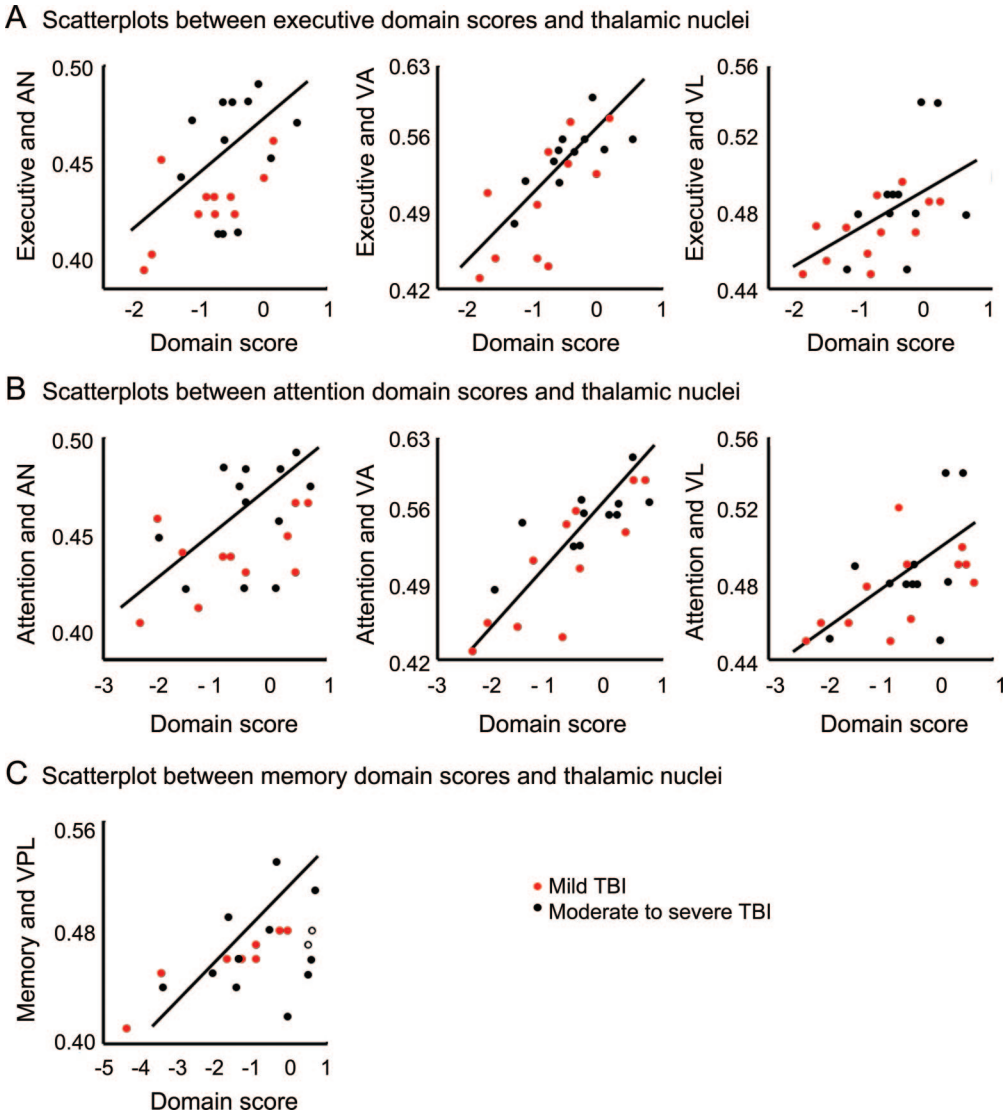
There was an overall effect of subject group (controls, miTBI, msTBI) on FA in the ACR [$F(2,36) = 9.71$, $p < 0.001$, $\eta^2 = 0.0.37$], PCR [$F(2,36) = 3.91$, $p = 0.030$, $\eta^2 = 0.19$], fMaj [$F(2,36) = 5.07$, $p = 0.012$, $\eta^2 = 0.23$], and bCC [$F(2,36) = 4.002$, $p = 0.028$, $\eta^2 = 0.20$], with the greatest differences between controls and those with more severe injury (msTBI; see figure 2A). The patients did not differ from controls in the remaining cortical ROIs (see table e-3 for additional details). Nor did they differ in whole brain FA. There was an overall effect of subject group on thalamic FA [$F(2,36) = 5.40$, $p = 0.009$, $\eta^2 = 0.25$] with controls having higher FA in the thalamus than msTBI. Although there was a trend for the miTBI to show reduced FA relative to controls in thalamic FA, the comparison did not reach significance (see table e-3 for additional details).

Comparisons between groups on FA extracted from the seed regions in the thalamic nuclei are presented in figure 2B. There was an effect of subject group only in fibers extracted from the AN [$F(2,36) = 5.82$, $p = 0.007$, $\eta^2 = 0.26$] and VA [$F(2,36) = 4.82$, $p = 0.015$, $\eta^2 = 0.23$] seed voxels. Post hoc comparisons among controls, miTBI, and msTBI are also indicated on figure 2B.

To examine the relationship between cognition and fiber tract integrity, a series of bivariate correlations were conducted. All of the ROIs were included and examined relative to the neuropsychological domain scores for executive function, memory function, and attention. Correlations were conducted for the control and TBI separately so as not to bias the correlation simply because patients show lower FA than controls.

For controls, there was a statistical relationship between the executive domain score and FA of the gCC ($r = 0.685$, $p = 0.014$) as well as FA of fibers identified with the VL seed voxel ($r = 0.586$, $p =$

Figure 3 Relationship between thalamic fractional anisotropy (FA) and cognition



Scatterplots of FA from thalamic seed voxels relative to executive (A), attention (B), and memory (C) domain scores for traumatic brain injury (TBI) patients. Best-fit lines are indicated in black.

0.045). The attention domain scores were also correlated with FA from the VL ($r = 0.668$, $p = 0.018$) and VPL ($r = 0.639$, $p = 0.025$). Memory function in controls was associated with FA in the genu of the gCC ($r = 0.667$, $p = 0.018$) and inferior frontal occipital fasciculus ($r = 0.605$, $p = 0.037$).

Scatterplots of the significant correlations between neuropsychological function and FA for the TBI are presented in figure 3. In the TBI groups, there were no correlations between any cortical or corpus callosum ROIs with executive function, attention, or memory performance. There was a relationship between the attention domain and FA in the gCC ($r = 0.506$, $p = 0.012$). For thalamic seed voxels, executive function was related to FA extracted from seed voxels in the AN ($r = 0.497$, $p = 0.014$), VA ($r = 0.741$, $p < 0.001$), and VL ($r = 0.540$, $p = 0.006$). Similar relationships were also found between the attention domain score and integrity of fibers from the AN ($r = 0.489$, $p = 0.015$), VA ($r = 0.786$, $p < 0.001$), and VL ($r = 0.523$, $p = 0.009$). In contrast, memory function was associated with integrity of VPL fibers ($r = 0.540$, $p = 0.006$). Integrity of DM was not associated with memory function. Correlations between individual neuropsychological tests and ROIs can be found in table e-4.

We also examined the injury variable duration of loss of consciousness relative to FA measures and relative to domain scores. Accurate ranges of LOC were collected for 19 of 24 subjects. The remaining subjects reported LOC but did not have a witness present. Duration of LOC was negatively correlated with the executive domain ($r = -0.460$, $p = 0.048$) and memory domain ($r = -0.500$, $p = 0.029$).

LOC also correlated with FA from the bCC ($r = -0.661$, $p = 0.002$).

Because of a significant amount of shared variance between nuclei, a series of linear regressions were applied to the TBI data with the executive function domain score as the dependent variable. In the first stepwise linear regression, the frontal lobe ROIs including the ACR, fMin, and gCC were entered. This model did not account for the executive domain variance ($r^2 = 0.19$, $p = 0.236$). Because the white matter tracts are not contained within the frontal lobe, we expanded this regression to include any ROIs which have fiber projections to or from the frontal lobes. This model was expanded to include not only the ACR, fMin, and gCC but also the CST, SS, and IFOF. Although this model accounted for more variance than the first model, it still did not reach significance ($r^2 = 0.322$, $p = 0.291$). This same strategy was applied to the fiber projections from the thalamic nuclei. The projections from the AN, VA, VL, and DM were entered into a linear regression with executive function as the dependent measure. This model did account for variance in the executive domain ($r^2 = 0.674$, $p < 0.001$). Within this model, the only unique predictor was FA from the VA seed voxels ($p = 0.001$) with VA accounting for 26% of the unique variance. Duration of LOC was also added into the regression models. Although it accounted for additional variance in the subcortical model ($r^2 = 0.701$, $p < 0.001$), LOC on its own was not a significant unique predictor.

DISCUSSION The present study presents preliminary support for a thalamic hypothesis as a central mechanism of injury and resultant cognitive impairment in TBI. The thalamus, although not located near the skull and therefore less susceptible to direct contusion, is likely differentially sensitive to shear and strain injury because of the corticospinal fibers which extend from the spine to the cortex. Within the thalamus, incoming sensory, motor, and cognitive processing pathways are organized and integrated within distinct nuclei. Following this integration, various thalamic nuclei send diffuse and specific efferent projections to cortical, cerebellar, and subcortical regions. The thalamus is also known to gate and mediate many cognitive, sensory, motor, and behavioral functions and damage to these projection fibers can result in widespread functional impairments.[30,31] Overall, thalamic lesions are associated with a decrease in executive function with larger lesions associated with greater deficits.[32,33] In the case of frontal lobe functions, impairments in executive function could be accounted for by damage to the fiber projections to and from the dorsomedial nucleus or anterior thalamic or ventral anterior thalamic nuclei rather than the frontal lobes per se.

However, because the thalamus is a relay center for the majority of cortical fiber projections, characterization of thalamic damage must include assessments of the integrity not only of thalamus proper but also for fibers entering or exiting the thalamic nuclei. The fiber tracking methods employed here with the spatial resolution provided by the sequences used allow this concern to be addressed. These projection fibers may in fact be even more susceptible to TBI than the thalamus itself because of the sharp turning angles of the cortical-subcortical fibers both as they leave the thalamus and again as they enter the cortex.[22,23]

The present data reaffirm the presence of executive dysfunction in TBI and suggest that executive dysfunction is correlated with cortical-subcortical damage rather than simply due to damage to the cortical frontal lobe structures, cortico-cortico tracts, or corpus callosum alone. This conclusion is supported both by the presence of correlations between executive function and FA in thalamic nuclei and also by the absence of correlations with FA in the measured cortical regions. The data do not, however, identify the location of damage within these fiber tracts. The primary damage to these fibers could occur at the boundary of the thalamus as the fibers exit the thalamus or it could occur at the junction of gray and white matter as the fibers enter the cortex.

Although these conclusions are based upon a relatively small sample (n = 24), the data suggest that thalamic integrity may be a central mechanism in TBI and provide initial evidence that damage to thalamic projection fibers, especially those involved in frontal-thalamic circuitry, is of great importance in understanding executive dysfunction following TBI. Furthermore, the findings support the need for further investigation into the applicability of these measures in other populations which demonstrate executive dysfunction.

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