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Thalamic Functional Connectivity in Mild Traumatic Brain Injury: Longitudinal Associations with Patient-Reported Outcomes and Neuropsychological Tests

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Abstract

Objective—To examine: (1) differences in patient-reported outcomes, neuropsychological tests, and thalamic functional connectivity (FC) between patients with mild traumatic brain injury (mTBI) and healthy controls; (2) the longitudinal association between changes in these measures.

Design—Prospective observational case-control study.

Setting—Academic medical center.

Participants—Thirteen patients with mTBI (mean age = 39.3 years, 4 female) and 11 healthy, age and sex-matched control subjects (mean age = 37.6, 4 female) were enrolled.

Interventions—Not applicable.

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The authors report no conflicts of interest.

Main Outcome Measure(s)—Resting-state FC (3T MRI scanner) was examined between the thalamus and the Default Mode Network (THAL-DMN), Dorsal Attention Network (THAL-DAN), and Frontoparietal Control Network (THAL-FPC). Patient-reported outcomes included pain (Brief Pain Inventory), depressive symptoms (Patient Health Questionnaire-9), post-traumatic stress disorder (PTSD Checklist), and post-concussive (Rivermead Post-Concussion Questionnaire) symptoms. Neuropsychological tests included the D-KEFS Tower test, Trails B, and Hotel task. Assessments occurred at 6 weeks and 4 months after hospitalization for patients with mTBI and at a single visit for controls.

Results—Student's t-tests found increased pain and depressive, PTSD, and post-concussive symptoms, decreased performance on Trails B, increased THAL-DMN FC, and decreased THAL-DAN and THAL-FPC FC in patients with mTBI compared to healthy controls. Spearman correlation coefficient indicated that increased THAL-DAN FC from baseline to 4 months was associated with decreased pain and post-concussive symptoms (corrected $p < 0.05$).

Conclusions—Findings suggest that alterations in thalamic FC occur after mTBI and improvements in pain and post-concussive symptoms are correlated with normalization of thalamic FC over time.

Keywords

brain injuries; functional neuroimaging; magnetic resonance imaging; neuropsychological tests; thalamus

INTRODUCTION

Mild traumatic brain injury (mTBI) affects more than 1 million Americans each year with an incidence as high as 600 per 100,000 individuals.¹ Annual United States healthcare costs for mTBI are estimated at nearly \$17 billion.^{1, 2} Early signs of mTBI are difficult to detect with standard imaging and many patients are under-diagnosed. The long-term physical, emotional, and cognitive impairments caused by mTBI have created a silent epidemic.³ Due to the consequences of mTBI, up to 85% of individuals with chronic symptoms report significant restrictions in their daily lives.^{2, 4}

The thalamus is a central brain region implicated in the pathogenesis of mTBI.^{5–9} The thalamus functions as a sensory relay center with projections to multiple cortical regions.¹⁰ Prior studies show the thalamus is susceptible to injury and can result in decreased volume,^{11, 12} inflammation,¹³ and reduced perfusion.¹⁴ Early magnetic resonance imaging (MRI) studies using fractional anisotropy found associations between the thalamus and TBI symptoms.^{15, 16} Recently, functional MRI (fMRI) has been used for characterizing brain-related changes in conditions like mTBI.^{6, 8} Using fMRI, Iraj et al.⁶ and Sours et al.⁹ found increased functional connectivity (FC) between thalamic and other brain areas in patients with mTBI. These studies offer early evidence that alterations in thalamic FC may be linked to clinical deficits of mTBI.

The connections between the thalamus and the brain's resting state networks, which utilize up to 80% of the brain's resources at rest,^{17, 18} may advance insight into mTBI mechanisms. The current study focused on three networks: the Default Mode Network (DMN),¹⁹ the

Dorsal Attention Network (DAN),²⁰ and the Frontoparietal Control Network (FPC).²⁰ The DMN is a well-studied network implicated with the thalamus in mTBI symptoms.^{6, 9, 21} The DMN mediates processes related to memory, future thoughts, and attentiveness, and is activated when the brain is at rest and suppressed during directed activity.^{22, 23} While the DMN makes up a “Task Negative Network”, the DAN is part of a more complex system, the “Task Positive Network”.¹⁷ The DAN is activated during goal-oriented tasks, or tasks that require directed attention, such as search and detection.^{24, 25} As anti-correlated networks, a failure by the DAN to deactivate the DMN during tasks could lead to diminished performance.^{26, 27} Lastly, the balance between the DMN and DAN is controlled by the FPC.^{20, 28} The FPC is a task positive network that regulates distributed systems (visual, limbic, motor) during activity.^{25, 29}

Few studies have examined cross-sectional associations between thalamic FC and clinical outcomes in patients with mTBI.^{6, 8} Moreover, there is limited evidence on the longitudinal associations between thalamic FC and clinical outcomes. The purpose of this study was to 1) examine differences in patient-reported outcomes, neuropsychological tests, and thalamic FC between patients with mTBI and healthy controls and 2) determine the longitudinal association between changes in patient-reported outcomes and neuropsychological tests and thalamic FC. Understanding the change in these signals after a brain injury and the subsequent normalization over time may lead to an improved understanding of the mechanisms of mTBI.³⁰

METHODS

Study Design

This was a prospective case-control study conducted at a Level I trauma center of an academic medical institution. Ethical approval was obtained from the Institutional Review Board at the participating center.

Participants

Patients experiencing trauma (e.g., motor vehicle collision or fall) and hospitalized were screened for mTBI from an outpatient clinic after discharge from September 2013 to November 2014. Mild TBI was determined through a medical chart review and patient interview using the American Congress of Rehabilitation Medicine guidelines.³¹ To identify an at-risk sample, eligible participants with mTBI were screened for the presence of cognitive deficits in executive functioning. Deficits were defined as 1 standard deviation (SD) below the norm referenced mean on any 1 of the following neuropsychological tests: Delis-Kaplan Executive Function System (D-KEFS) Tower Test, Trail Making Test B (Trails B), and FAS test.^{32, 33}

Subjects were excluded for the following: (1) evidence of moderate to severe TBI; (2) current alcohol or substance dependence within the last 6 months; (3) preexisting cognitive impairment as determined by a score greater than 3.3 on the short form of the Informant Questionnaire of Cognitive Decline in the Elderly;³⁴ (4) neurological history other than TBI;

(5) history of schizophrenia, psychotic disorder, or suicidal intent; (6) inability to provide a telephone number and stable address, and (7) contraindications for MRI.

Healthy control subjects were recruited through written and electronic advertisement from the medical center and surrounding community. Healthy controls were age and sex-matched to patients with mTBI.

Procedures

At 6 weeks after hospital discharge and after providing written informed consent, patients with mTBI completed an intake assessment (i.e., age, sex, race, marital status, education level, mechanism of injury). Study participants completed patient-reported questionnaires for pain intensity, and depressive, PTSD, and post-concussive symptoms.

Neuropsychological tests were administered after questionnaires and subjects underwent MRI examination. Repeat assessment was completed at a 4-month follow-up visit in patients with mTBI. Healthy control subjects completed all procedures at a single session.

Patient-Reported Outcome Measures

The Brief Pain Inventory (BPI) was used for pain intensity.³⁵ The BPI uses a numerical rating scale (NRS) with 0 meaning “no pain” and 10 meaning, “pain as bad as you can imagine”. Participants rated their pain intensity over 4 conditions and an average obtained: worst pain in the last 24 hours; best pain in the last 24 hours; average pain over the last 24 hours; and current pain. The 9-item Patient Health Questionnaire (PHQ-9) was used for depressive symptoms. Items are scored and summed using a scale from 0 (not at all) to 3 (nearly every day).³⁶ Higher PHQ-9 scores indicate greater depression. The PTSD Checklist-Civilian Version (PCL-C) is a 17-item questionnaire used for PTSD symptoms.³⁷ Subjects rate questions about how much they are bothered by particular symptoms during the past month using a scale from 1 (not at all) to 5 (extremely). The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) is a 16-item questionnaire used for the presence and severity of post-concussive symptoms.³⁸ Items on the RPQ are scored and summed using a scale ranging from 0 (not experienced at all) to 4 (severe problem).

Neuropsychological Tests

The D-KEFS Tower Test was used to assess the ability to plan and strategize efficiently and required participants to move discs across 3 pegs until a tower is built using the fewest number of moves.³² Completed D-KEFS Tower Test scores are adjusted for age and converted into a scaled score ranging from 1 to 19, with higher scores reflecting better performance. Trails B is a timed test that measures set shifting and cognitive flexibility.³² Participants are asked to draw a line between a series of alternating number and letters according to a specified sequence and the time taken recorded. The Hotel Task is a measure of planning and organizational ability and involves the participant modeling a real-life multitasking situation as a hotel manager.³⁹ The participant is asked to try and complete five different tasks: compiling bills; sorting charity collection; looking up telephone numbers; sorting conference labels; proof reading the hotel leaflet. In order to complete all five tasks, the participants must distribute their time equally across the total 15-minute allotment. Scoring of the Hotel Task is the total deviation from optimal time allocation.

MR Imaging

Imaging was performed on a 3T MRI scanner (Philips Healthcare, Best, Netherlands) with a 32 channel head coil. Scans included: 1) three-dimensional, T1 weighted high-resolution whole brain image ($1 \times 1 \times 1 \text{ mm}^3$), 2) T2 weighted turbo spin echo, high resolution axial full brain image ($0.5 \times 0.5 \times 2.5 \text{ mm}^3$), 3) two-dimensional, T1 weighted high-resolution axial full brain image ($1 \times 1 \times 4 \text{ mm}^3$) in the same slice locations as the fMRI, and 4) a T2* weighted gradient echo, echo-planar fMRI image series was acquired at rest with eyes closed - matrix 80×80 , FOV = 240 mm, 34 axial slices, TE = 35 ms, TR = 2 sec, slice thickness = 3.5 mm with 0.5 mm gap, 300 volumes (10 minutes). Physiological monitoring of cardiorespiratory signals was performed at 500 Hz using the MRI scanner integrated pulse oximeter and respiratory belt. Conventional MRI sequences were used to assess for preexisting structural and morphological brain abnormalities.

The fMRI images were corrected for slice timing and motion using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). The maximum translation and rotation for each subject was determined and compared between groups. Images were corrected for physiological noise with a RETROICOR protocol⁴⁰ using the measured cardiorespiratory time series. Images were spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed with a $6 \times 6 \times 6 \text{ mm}^3$ full width, half maximum kernel.

For FC, fMRI images were low pass filtered at 0.1 Hz.⁴¹ The T1 weighted, three-dimensional, high-resolution MRI image was segmented into gray matter, white matter and cerebrospinal fluid components using SPM8. Regions of interest (ROIs) were anatomically defined using WFU PickAtlas software.^{42, 43} The ROIs included the left and right thalamus.^{8, 44} Other ROIs were chosen from three defined functional networks including the DMN¹⁹ (left and right hippocampus, precuneus, left and right inferior parietal lobe, bilateral ventromedial prefrontal cortex, bilateral dorsomedial prefrontal cortex), DAN²⁰ (left and right middle temporal area, left and right intra-parietal sulcus), and FPC²⁰ (bilateral anterior cingulate, left and right inferior parietal regions, left and right dorsolateral prefrontal cortex). Each ROI was identified in the gray matter defined by SPM8 tissue segmentation. The preprocessed fMRI time series was averaged across each ROI resulting in 18 time series for each subject. FC was computed as the partial correlation between each pair of regions using the white matter and motion time series as confounds. The correlation coefficient was converted to a Z statistic using the Fisher Z transform.⁴⁵ To test the hypothesis of thalamic FC disruption, four composite thalamic FC measures were calculated. The THAL FC was defined as the average of all pair-wise FC values that included the left or right thalamus. The THAL-DMN, THAL-FPC and THAL-DAN FC were defined as the average of all pair-wise FC values that included one thalamus and one DMN, FPC, or DAN region, respectively.

Data Analysis

Patient-reported, neuropsychological, and FC data were analyzed using Stata statistical software, release 12.1 (StataCorp LP, College Station, TX). Baseline comparisons were made between patients with mTBI and control subjects for pain intensity (BPI), depressive (PHQ-9), PTSD (PCL-C), and post-concussive symptoms (RPQ), D-KEFs Tower Test, Trails B, the Hotel Task, and the four thalamic FC measures using unpaired Student's t-tests.

Change scores (4-month – baseline) were computed in patients with mTBI for patient-reported outcomes, neuropsychological tests, and thalamic FC. Associations were examined between change scores using Spearman's correlation coefficients with Bonferroni adjustment for multiple comparisons. Correlation values between 0.1 and 0.3 were low, between 0.3 and 0.5 were moderate, and greater than 0.5 were high.⁴⁶

RESULTS

Study Participants

Thirteen patients with mTBI resulting from a fall or motor vehicle collision (mean $\pm$ SD age = 39.3 ± 14.0 years, 4 females) and 11 healthy control subjects (mean $\pm$ SD age = 37.6 ± 13.3 years, 4 females) were enrolled (Table 1). Structural MRI evaluation at baseline showed some patients with complicated mTBI (i.e., meeting mTBI criteria, but showing trauma-related structural abnormalities) (Table 1). In total, 7 patients did not show abnormalities on MRI. Follow-up rate at 4 months for patients with mTBI was 85% ($n=11$) for patient-reported outcomes and neuropsychological tests and 62% ($n=8$) for MRI imaging. There was no statistical difference in demographics between patients with complete and incomplete follow-up data. There was no statistical difference in translation or rotation in the fMRI data between the patients with mTBI and control subjects.

Baseline Comparison of Patient-Reported and Neuropsychological Data

The mTBI group reported higher pain intensity, and depressive, PTSD, and post-concussive symptoms compared to controls ($p < 0.001$) (Table 2). Patients with mTBI also performed poorer on the Trails B test compared to controls ($p = 0.002$).

Baseline Comparison of Thalamic Functional Connectivity

An increase in THAL FC ($p = 0.002$) and THAL-DMN FC ($p = 0.001$) was noted in patients with mTBI compared to controls (Table 2). There was a decrease in THAL-DAN FC ($p = 0.009$) and THAL-FPC FC ($p = 0.01$) when compared to controls.

Change Scores in Patients with mTBI

Across the group of patients who returned, 4-month change scores demonstrated improvement trends for patient-reported outcomes and neuropsychological tests, except for PTSD symptoms (Table 3). THAL FC decreased at 4 months compared to baseline toward normalization. THAL-DMN FC increased and moved away from normalization at 4 months compared to baseline. THAL-DAN FC and THAL-FPC FC increased and moved toward normalization at 4 months compared to baseline.

Correlation between Changes in Patient-Reported Outcomes, Neuropsychological Tests, and Thalamic Functional Connectivity

Correlations were found between pain and THAL-DAN FC and between post-concussive symptoms and THAL-DAN FC (Table 4). As THAL-DAN FC normalized, pain and post-concussive symptoms improved (Figures 1 and 2). Correlations were high between

depressive symptoms and THAL-DAN FC ($r = 0.74$; $p = 0.04$) and between pain and THAL-FPC FC ($r = -0.71$; $p = 0.05$), but were not statistically significant.

DISCUSSION

The aims of this study were to examine thalamic FC longitudinally in patients with mTBI during the early recovery period and determine the relationship to patient-reported outcomes and neuropsychological tests. Patients with mTBI reported worse symptoms and cognitive functioning and showed FC alterations compared to controls. Improvements in pain and post-concussive symptoms were associated with normalization in THAL-DAN FC. These findings advance evidence on brain-related changes and implicate FC alterations as a factor underlying mTBI recovery.

Consistent with existing literature, patients with mTBI reported higher pain, and depressive, PTSD, and post-concussive symptoms.^{6, 47–52} These symptoms are expected in individuals who experience trauma and correspond to a biopsychosocial impact. Deficits in executive functioning have also been demonstrated in some patients with mTBI.^{4, 7, 53} One reason for the cognitive deficit findings in the current study may be related to the inclusion criteria of high-risk patients demonstrating cognitive impairment at discharge. The cross-sectional fMRI results from the current study are consistent with studies by Iraj et al.⁶ and Tang et al.⁸ who showed increased THAL-DMN FC in patients with mTBI in the acute (7 days) and subacute (22 days) phases of recovery. Studies of patients with Alzheimer's disease,⁵⁴ schizophrenia,⁵⁵ and cognitive decline⁵⁶ also highlight the relevance of between-network connectivity for a global investigation of brain plasticity. For example, decreased THAL-FPC FC has been found in patients with schizophrenia.^{57, 58} In the current study, THAL-DMN FC was increased, while THAL-DAN and THAL-FPC FC were decreased compared to controls. These findings are not surprising as activity of the DMN and task positive networks are anti-correlated, with the FPC responsible for this relationship.²⁰

Findings from the longitudinal analysis demonstrated movement toward clinical improvement and FC normalization, except for PTSD symptoms and THAL-DMN FC. Persistent PTSD symptoms can complicate mTBI recovery.^{59, 60} However, less is known about changes in THAL-DMN FC. Mayer et al.⁵³ saw no longitudinal changes in FC between the DMN and other brain regions. In patients with Alzheimer's disease, Cai et al.⁶¹ observed increased FC over time between the thalamus and precuneus, a main ROI in the DMN, which converges with the current findings. Additional support linking the DMN and PTSD is found in a study by Yin et al.⁶² that noted increased THAL-DMN FC in trauma patients diagnosed with PTSD eight months after experiencing a major traumatic event.

Correlations were noted between changes in THAL-DAN FC and pain intensity. The thalamus is involved in pain modulation and is a key region within the "pain neuromatrix".^{63, 64} Thalamic FC has been a focus of studies investigating pain processing with recent emphasis on thalamus FC to broader networks.^{65–67} Studies using acute pain models have found decreased thalamic FC to multiple pain-related brain regions that were associated with reductions in clinical pain.^{66, 67} Additional studies in chronic pain conditions such as fibromyalgia have implicated thalamic FC changes as a potential

underlying feature of chronic pain.^{68–70} Ichresco et al.⁶⁸ noted increased THAL-DMN FC was associated with increased pain in patients with chronic pain. Cauda et al.⁷¹ reported a link between chronic neuropathic pain and the DAN which coincides with findings from the current study.

Changes in THAL-DAN FC and post-concussive symptoms were also correlated, which is consistent with preliminary evidence.^{8, 44, 72} Tang et al.⁸ found an association between post-concussive symptoms and thalamic voxel symmetry in patients with mTBI. Additionally, Messe et al.⁷² showed that patients with subacute mTBI and post-concussive symptoms had significant thalamic changes compared to mTBI patients without post-concussive symptoms and healthy controls. A link between post-concussive symptoms and thalamo-cortical connectivity has been observed in patients with subacute mTBI. Notably, Zhou et al.⁴⁴ showed that post-concussive symptoms were correlated with thalamic connectivity (coherence) to brain regions associated with the DAN such as the temporal and parietal areas.

Study Limitations

The sample size was small and precluded definitive analytical strategies to examine change or explore subgroup effects (i.e., age-related). Despite the low number of subjects, strong associations were observed after correcting for multiple comparisons. Larger studies are needed to validate the current findings. All subjects were recruited and screened for mTBI at an outpatient clinic. Thus, specific details regarding the severity or extent of mTBI was not collected at the time of admission to the hospital. Outcomes, including MR imaging, were measured at 4 months after the baseline visit in the patient group only. Comparisons to longitudinal change in the control group were unable to be conducted. Future studies should examine the utility of FC changes in predicting longer-term outcomes. Follow-up fMRI data were not available for five patients. However, statistical comparison noted no difference between patients with and without follow-up data.

CONCLUSION

The current study examined FC between the thalamus and resting-state networks in patients with mTBI. The findings suggest thalamic FC, especially with the DAN, is disrupted after mTBI and a potential underlying factor for mTBI recovery. Future studies should aim to validate these findings and examine whether thalamic FC can be used as an objective biomarker to evaluate specific therapies in mTBI.

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LIST OF ABBREVIATIONS

BPI Brief Pain Inventory

DAN	Dorsal Attention Network
D-KEFS	Delis-Kaplan Executive Function System
DMN	Default Mode Network
fMRI	functional magnetic resonance imaging
FPC	Frontoparietal Control Network
MRI	magnetic resonance imaging
mTBI	mild traumatic brain injury
NRS	numeric rating scale
PCL-C	PTSD Checklist-Civilian Version
PHQ-9	Patient Health Questionnaire-9
PTSD	post-traumatic stress disorder
ROI	region of interest
RPQ	Rivermead Post-Concussion Symptoms Questionnaire
SD	standard deviation
THAL	thalamus

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FIGURE 1. Correlation between changes in pain intensity and thalamus to DAN functional connectivity for patients with mTBI ($r = -0.93$, $p = 0.001$).

FIGURE 2.

Correlation between changes in post-concussive symptoms and thalamus to DAN functional connectivity for patients with mTBI ($r = -0.86$, $p = 0.007$).

Table 1

Demographic and clinical characteristics of enrolled subjects.

Group	ID	Age/Sex	Race	Marital	MRI Findings
<i>Mild TBI</i>	1	40/M	White	Married	Moderate area of cystic encephalomalacia and hemosiderin staining in R frontal lobe, B/L temporal lobes. Evolution of encephalomalacia on follow-up imaging.
	2	40/M	White	Married	Mild cystic encephalomalacia and volume loss within inferior R frontal lobe. No change on follow-up imaging.
	3	56/M	White	Divorced	Negative
	4	47/F	White	Married	Evolving small L anterior temporal contusion, trace L SDH, and CSVID. No change on follow-up imaging.
	5	41/M	White	Married	CSVID. No change on follow-up imaging.
	6	26/M	White	Single	Small amount of SDH along falx and L tentorium. Resolution of SDH on follow-up imaging.
	7	18/M	White	Single	Negative
	8	21/F	White	Single	Negative
	9	23/F	Black or African American	Living with Partner	Negative
	10	43/F	White	Divorced	Negative
	11	52/M	White	Single	Negative
	12	64/M	Black or African American	Divorced	Evolving SDH over L inferior frontal (9mm) and temporal lobes (5mm) and CSVID. Near complete resolution of SDH on follow-up imaging.

Group	ID	Age/Sex	Race	Marital	MRI Findings
	13	40/M	White	Married	Negative
<i>Control</i>	1c	42/M	White	Single	Negative
	2c	39/M	White	Living with Partner	Negative
	3c	57/M	White	Married	Negative
	4c	47/F	Black or African American	Married	Negative
	5c	42/M	White	Living with Partner	Negative
	6c	26/M	White	Living with Partner	Negative
	7c	18/M	White	Single	Negative
	8c	21/F	White	Single	Negative
	9c	24/F	White	Living with Partner	Negative
	10c	42/F	White	Married	Negative
	11c	52/M	White	Married	Negative

Abbreviations: B/L = bilateral; CSVID = chronic small vessel ischemic disease; L = left; MOI = mechanism of injury; MVC = motor vehicle collision; R = right; SDH = subdural hematoma

Table 2

Baseline comparison of patient-reported outcomes, neuropsychological tests, and thalamic functional connectivity between patients with mild TBI and healthy controls.

	Mild TBI (n = 13)	Control (n = 11)	p
<i>Patient-Reported Outcomes</i>			
Pain	4.3 ± 1.93	0.3 ± 0.42	< 0.001 *
Depressive symptoms	12.3 ± 6.20	1.5 ± 2.62	< 0.001 *
PTSD symptoms	37.9 ± 11.15	21 ± 6.46	< 0.001 *
Post-concussive symptoms	29.9 ± 11.58	6.2 ± 5.74	< 0.001 *
<i>Neuropsychological Tests</i>			
D-KEFS Tower Test	9.5 ± 2.14	12.2 ± 5.36	0.12
Trails B	42 ± 11.40	58.3 ± 10.39	0.002 *
Hotel Task	502.2 ± 360.8	271.2 ± 164.8	0.07
<i>Thalamic Functional Connectivity</i>			
THAL	2.0 ± 1.0	0.3 ± 1.3	0.002 *
THAL-DMN	2.6 ± 1.5	0.3 ± 1.4	0.001 *
THAL-DAN	0.7 ± 1.8	3.2 ± 2.6	0.009 *
THAL-FPC	0.4 ± 1.5	2.3 ± 2.0	0.01

* Statistically significant after Bonferonni correction.

Values are mean ± SD unless otherwise indicated.

Abbreviations: PTSD = post-traumatic stress disorder; THAL = thalamus; THAL-DAN = thalamus to DAN; THAL-DMN = thalamus to DMN; THAL-FPC = thalamus to FPC

Table 3

4-month outcome data and change from baseline for patients with mild TBI.

	4 month	Change from Baseline (95% CI)	Direction
<i>Patient-Reported Outcomes (n = 11)</i>			
Pain	3.8 ± 1.5	−0.7 (−2.0; 0.7)	<i>Improvement</i>
Depressive symptoms	8.8 ± 5.7	−2.1 (−7.5; 3.3)	<i>Improvement</i>
PTSD symptoms	40.0 ± 12.1	3.5 (−3.9; 11.0)	<i>Worsening</i>
Post-concussive symptoms	25.3 ± 10.7	−4.5 (−12.2; 3.1)	<i>Improvement</i>
<i>Neuropsychological Tests (n = 11)</i>			
D-KEFS Tower Test	11.5 ± 4.1	1.6 (−1.2; 4.5)	<i>Improvement</i>
Trails B	51.3 ± 16.2	6.8 (−3.2; 16.8)	<i>Improvement</i>
Hotel Task	441.5 ± 259.3	−101.9 (−276.5; 72.7)	<i>Improvement</i>
<i>Functional Connectivity (n = 8)</i>			
THAL	1.8 ± 1.7	−0.3 (−1.8; 1.1)	<i>Toward Normalization</i>
THAL-DMN	3.4 ± 1.8	0.7 (−0.5; 1.9)	<i>Away from Normalization</i>
THAL-DAN	2.2 ± 3.0	1.8 (−1.2; 4.7)	<i>Toward Normalization</i>
THAL-FPC	1.9 ± 2.3	2.0 (−0.6; 4.5)	<i>Toward Normalization</i>

4-month values are mean ± SD.

Abbreviations: PTSD = post-traumatic stress disorder; THAL = thalamus; THAL-DAN = thalamus to DAN; THAL-DMN = thalamus to DMN; THAL-FPC = thalamus to FPC

Table 4

Correlation between 4-month change scores for patient-reported and neuropsychological variables with thalamic functional connectivity for patients with mild TBI.

	THAL	THAL-DMN	THAL-DAN	THAL-FPC
Pain	0.49	0.24	-0.93 *	-0.71
	<i>0.21</i>	<i>0.56</i>	<i>0.001*</i>	<i>0.05</i>
Depressive symptoms	0.41	0.18	-0.74	-0.63
	<i>0.31</i>	<i>0.67</i>	<i>0.04</i>	<i>0.10</i>
PTSD symptoms	0.41	-0.11	-0.57	-0.59
	<i>0.32</i>	<i>0.80</i>	<i>0.14</i>	<i>0.13</i>
Post-concussive symptoms	0.36	-0.09	-0.86 *	-0.69
	<i>0.39</i>	<i>0.82</i>	<i>0.007*</i>	<i>0.06</i>
D-KEFS Tower Test	-0.61	-0.12	0.42	0.44
	<i>0.11</i>	<i>0.78</i>	<i>0.30</i>	<i>0.27</i>
Trails B	-0.52	-0.5	-0.05	-0.02
	<i>0.18</i>	<i>0.21</i>	<i>0.91</i>	<i>0.95</i>
Hotel Task	-0.43	-0.07	0.14	0.59
	<i>0.29</i>	<i>0.87</i>	<i>0.74</i>	<i>0.12</i>

* Statistically significant after Bonferonni correction.

Values are Spearman rho correlation coefficients.

p-values are indicated by italics.

Abbreviations: PTSD = post-traumatic stress disorder; THAL = thalamus; THAL-DAN = thalamus to DAN; THAL-DMN = thalamus to DMN; THAL-FPC = thalamus to FPC