Dynamic contrast enhanced MRI for characterization of blood-brain-barrier dysfunction after traumatic brain injury

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# Background and Purpose
Dysfunction of the blood-brain-barrier (BBB) is a recognized pathological consequence of traumatic brain injury (TBI) which may play an important role in chronic TBI pathophysiology. We hypothesized that BBB disruption can be detected with dynamic contrast-enhanced (DCE) MRI not only in association with focal traumatic lesions but also in normal-appearing brain tissue of TBI patients, reflecting microscopic microvascular injury. We further hypothesized that BBB integrity would improve but not completely normalize months after TBI.

# Materials and Methods
DCE MRI was performed in 40 adult patients a median of 23 days after hospitalized TBI and in 21 healthy controls. DCE data was analyzed using Patlak and linear models, and derived metrics of BBB leakage including the volume transfer constant ($K_{trans}$) and the normalized permeability index (NPI) were compared between groups. BBB metrics were compared with focal lesion distribution as well as with contemporaneous measures of symptomatology and cognitive function in TBI patients. Finally, BBB metrics were examined longitudinally among 18 TBI patients who returned for a second MRI a median of 204 days postinjury.

# Results
TBI patients exhibited higher mean $K_{trans}$ ($p = 0.0028$) and proportion of suprathreshold NPI voxels ($p = 0.001$) relative to controls. Tissue-based analysis confirmed greatest TBI-related BBB disruption in association with focal lesions, however elevated $K_{trans}$ was also observed in perilesional ($p = 0.011$) and nonlesional ($p = 0.044$) regions. BBB disruption showed inverse correlation with quality of life (rho = $−0.51$, corrected p = 0.016). Among the subset of TBI patients who underwent a second MRI several months after the initial evaluation, metrics of BBB disruption did not differ significantly at the group level, though variable longitudinal changes were observed at the individual subject level.

# Conclusions
This pilot investigation suggests that TBI-related BBB disruption is detectable in the early post-injury period in association with focal and diffuse brain injury.

# Keywords
- TBI
- Dynamic contrast-enhanced MRI
- Blood-brain-barrier
- Microvascular injury

# Abbreviations
- TBI, Traumatic brain injury; DCE, dynamic contrast-enhanced; BBB, blood-brain-barrier.

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mechanisms of secondary, slowly progressive brain tissue damage following the initial impact. Chronic neurotoxicity resulting from the inability of endothelial cells and pericytes to limit the entry of plasma-derived proteins, circulating metals, and inflammatory cells into the brain is increasingly recognized in the pathogenesis of several neurodegenerative disorders including Alzheimer Disease (AD) and other AD-related dementias (ADRDs) (Zlokovic, 2011). Thus, there is a strong rationale to determine how BBB dysfunction after TBI may underpin the development of poor long-term cognitive outcomes after TBI as well as TReND (Smith et al., 2019).

TBI-related BBB breakdown is readily detectable radiologically in association with traumatic contusions in the early post-injury period manifested by parenchymal hemorrhage, vasogenic edema, and contrast-enhancement (Kushi et al., 1994; Schweitzer et al., 2019). Pathological and experimental studies also indicate that more subtle and widespread TBI-related BBB dysfunction is frequently present beyond the extent of focal anatomical lesions or hemorrhage, and may persist well into the chronic postinjury phase (Hay et al., 2015; Johnson et al., 2018). This lower-level, chronic elevation in BBB permeability, while occult on conventional neuroimaging sequences, is potentially detectable with dynamic contrast enhanced (DCE) MRI, which quantifies temporal enhancement properties driven by the movement of low-molecular weight MRI contrast agents from the vascular compartment to the extravascular extracellular space. While DCE has most frequently been used for assessing microvascular pathology associated with tumors in neuro-oncological applications, it has also proven useful in characterizing lower-level BBB dysfunction associated with aging, neurovascular, and neuroinflammatory conditions when contrast enhancement is not visibly apparent (Montagne et al., 2015; Chi et al.; Li et al., 2018).

The ability of neuroimaging to detect and characterize frank BBB disruption as well as more subtle BBB leakage therefore holds potential to reveal the natural history of BBB dysfunction after TBI and advance the understanding of the mechanisms driving TReND. This may in turn allow for the development of novel biomarkers for improved patient prognostication, and ultimately reveal new avenues for therapeutic intervention to mitigate progressive neurological deterioration after TBI. Initial investigations of DCE MRI in TBI have suggested that BBB dysfunction is detectable in individuals exposed to repetitive sub-concussive head trauma (Weissberg et al., 2014) and mild TBI (Yoo et al., 2019), and is correlated with serologic markers of BBB damage, providing validation of DCE findings. Nevertheless, there are many unknowns about the frequency and extent of BBB dysfunction after TBI, relationship to focal lesions, and evolution over time. Furthermore, as recent evidence suggests that different approaches to DCE MRI analysis shed light on different mechanisms of BBB leakage (Veksler et al., 2020), we aimed in this preliminary study to characterize patterns of fast and slow contrast leakage in the early post-TBI period and assess their persistence over time.

2. Materials and methods

2.1. Subjects

This study was approved by the Institutional Review Board of the University of Pennsylvania and written informed consent was provided by each participant or their legally authorized representative. Each participant or their representative was informed of the potential for gadolinium retention from the contrast administration as part of the informed consent process. Adult patients with TBI, as defined by the Department of Defense (Management of Concussion/mTBI Working Group, 2009), and were hospitalized (either due to TBI or for other concurrent injuries) were enrolled at the time of hospital admission. Patients were excluded if they had a history of pre-existing serious neurological or psychiatric disease as determined by study personnel, comorbid disabling condition limiting outcome assessment, current pregnancy, or were incarcerated. Healthy control subjects with similar demographics to the TBI patient population were also recruited and were included if they had no history of TBI within the previous 1 year, pre-existing disabling neurological or psychiatric disorders, or current pregnancy.

From an initial cohort of 46 TBI patients and 22 control participants, 6 TBI patients and 1 control participant were excluded due to poor quality DCE data (insufficient volumes acquired, insufficient pre-contrast volumes, or severely degraded by artifacts). TBI patients were imaged at a median of 23 days (range 8–79 days) post-injury. A subset of 18 TBI patients returned for a second MRI at a median of 204 days (range 166–317 days) post-injury, at which time they were also screened for additional head injuries sustained during the follow-up interval. Control subjects underwent a single MRI examination.

Demographic information, medical history, injury characteristics, and other clinical information were collected from the medical record and personal interview. Injury characteristics included the post-resuscitation Glasgow Coma Scale (GCS) score, presence or absence of loss of consciousness (LOC), and presence or absence of acute TBI-related intracranial findings on the initial head CT. Neuropsychological tests were administered within 21 days of the MRI and included the Controlled Oral Word Association Test (COWAT) (Benton et al., 1994), Rey Auditory Verbal Learning Test (RAVLT) for immediate recall (Lezak et al., 2004), Trail-Making-Test parts A and B (MTM-A/B) (Reitan et al., 1985), and the Processing Speed Index (PSI) from the Wechsler Adult Intelligence Scale-IV (WAIS) (Wechsler, 2014). Post-TBI symptoms were assessed with the Rivermead Post-Concussion Symptom Questionnaire (RPQ) (King et al., 1995), Satisfaction with Life Scale (SWLS) (McMahon et al., 2014), and Brief Symptom Inventory-18 (BSI-18). Global functional outcome was assessed using the Glasgow Outcome Scale-Extended (GOS-E) (Jennett et al., 1981).

2.2. Imaging

Brain MRIs were performed on a 3 T scanner (Siemens Prisma) using a product 32-channel head coil. Structural imaging included a sagittal T1-weighted MPRAGE (TR = 2.3 s, TE = 2.94 ms, TI = 900 ms, FA = 9°, resolution = 1 × 1 × 1 mm) as well as a sagittal 3-D FLAIR (TR = 6 s, TE = 90 ms, TI = 2100 ms, FA = 120°, resolution = 1.2 × 0.5 × 0.5 mm). Whole brain DCE imaging was used for assessing microvascular pathology associated with tumors in neuro-oncological applications, it has also proven useful in characterizing lower-level BBB dysfunction associated with aging, neurovascular, and neuroinflammatory conditions when contrast enhancement is not visibly apparent (Montagne et al., 2015; Chi et al.; Li et al., 2018).

The ability of neuroimaging to detect and characterize frank BBB disruption as well as more subtle BBB leakage therefore holds potential to reveal the natural history of BBB dysfunction after TBI and advance the understanding of the mechanisms driving TReND. This may in turn allow for the development of novel biomarkers for improved patient prognostication, and ultimately reveal new avenues for therapeutic intervention to mitigate progressive neurological deterioration after TBI. Initial investigations of DCE MRI in TBI have suggested that BBB dysfunction is detectable in individuals exposed to repetitive sub-concussive head trauma (Weissberg et al., 2014) and mild TBI (Yoo et al., 2019), and is correlated with serologic markers of BBB damage, providing validation of DCE findings. Nevertheless, there are many unknowns about the frequency and extent of BBB dysfunction after TBI, relationship to focal lesions, and evolution over time. Furthermore, as recent evidence suggests that different approaches to DCE MRI analysis shed light on different mechanisms of BBB leakage (Veksler et al., 2020), we aimed in this preliminary study to characterize patterns of fast and slow contrast leakage in the early post-TBI period and assess their persistence over time.

2.3. Image analysis

Structural (T1 and FLAIR) images were used for manual segmentation of focal lesions by a neurosurgery resident (S.S.), which were verified and edited as needed by a neuroradiologist (J.W.). Focal lesions were defined as consisting of any parenchymal signal changes determined to represent hemorrhage, contusion, vasogenic edema, or encephalomalacia. The perilesional region was defined as all normal-appearing brain tissue within 10 mm of the focal lesion. Structural image processing was subsequently performed using the Advanced Normalization Tools (ANTs) software package (Avants et al., 2011), which included bias correction, creation of a brain mask, and 6-tissue segmentation. A population-specific anatomical template was created from 20 TBI patients and 20 control subjects selected at random, and T1-weighted images were normalized to the template using the ANTs symmetrical diffeomorphic registration tool (SyN) with B-spline interpolation (Avants et al., 2008). When present, focal lesions were used in
contraining the cost function mask to improve registration accuracy (Andersen et al., 2010; Ripollès et al., 2012).

DCE images were motion-corrected using the tools available in FSL (Jenkinson et al., 2012) and the mean of the corrected DCE timeseries was used to co-register the DCE data with the high resolution structural scan using an affine transformation computed in ANTs (Avants et al., 2008). The resultant inverse registration was then used to transform the structural brain mask into the DCE data space and remove non-brain tissue. Whole-brain T1 maps were created from the variable flip angle images and were used to transform voxel-wise DCE signal intensity data into contrast concentrations using the relaxation of the contrast material used in each subject. For quantitative analysis, brain masks were eroded by 2 voxels to prevent contamination by high values occurring in the meninges and blood vessels just beyond the edge of the brain.

Contrast concentration timeseries data were then analyzed using two methods. First, data were fit to the Patlak model (Patlak et al., 1983) as implemented in the ROCKETSHIP (Barnes et al., 2015) software package, using automated extraction of the vascular input function (VIF) from within a mask drawn over the superior sagittal sinus in each subject. Voxel-wise maps of the volume transfer constant (Ktrans) from within a mask drawn over the superior sagittal sinus in each subject, using automated extraction of the vascular input function (VIF) constraining the cost function mask to improve registration accuracy -images and were used to transform voxel-wise DCE signal intensity data into contrast concentrations using the relaxation of the contrast material used in each subject. For quantitative analysis, brain masks were eroded by 2 voxels to prevent contamination by high values occurring in the meninges and blood vessels just beyond the edge of the brain.

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2.4. Statistical analysis

All statistical analysis was performed in R (version 4.1.2). Demographic characteristics were compared between TBI and control groups using t-tests for continuous measures and Fisher’s exact test for categorical measures. DCE data was first analyzed in each subject’s DCE imaging space, where mean Ktrans and NPI values were averaged across the brain (cerebral cortex, white matter, brainstem, and deep grey structures). Furthermore, the extent of elevated BBB permeability in each subject was computed, defined as the proportion of brain tissue voxels exhibiting $K_{trans}$ and NPI values above the 95th percentile value of the control population. These metrics were compared between the control and subacute TBI groups using the nonparametric Mann-Whitney-U test due to the non-normal distribution of these variables. Next, tissue-based analysis was performed in the space of each subacute TBI patient’s TI-weighted structural image. Mean $K_{trans}$ and NPI values were compared between focal lesions, perilesional tissue, and normal-appearing brain tissue using paired Wilcoxon signed-rank tests. To gain insight into the spatial distribution of BBB disruption in the TBI group, a threshold-weighted $K_{trans}$ overlap map was created in template space using a previously described procedure (Seghier and Price, 2016) which quantifies the proportion of subjects showing elevated permeability at each brain voxel unboiled to a single arbitrary threshold. Furthermore, overlap of supraphreshold NPI voxels was also computed in the template space. Next, DCE images exhibiting the largest differences between TBI and control participants were compared with injury characteristics and clinical measures among the TBI group using Spearman’s rank correlation, with p values corrected for multiple comparisons using the false discovery rate (FDR) method. For comparison with outcome, the TBI group was dichotomized based on the GOS-E score into “less disabled” (GOS-E ≥ 7; near or complete return to pre-injury baseline function) and “more disabled” (GOS-E < 7; not returned to pre-injury baseline function) outcome groups. The extent of elevated BBB was compared between outcome groups using the Mann-Whitney-U test. The extent of BBB permeability elevation was examined longitudinally within the subgroup of TBI patients who returned for follow-up scanning using the Wilcoxon signed-rank test for paired samples. Lastly, to investigate the possibility that results may be driven by the few patients with moderate or severe TBI (GCS < 13), a sensitivity analysis was performed in which the above-described analyses were repeated with these subjects excluded.

3. Results

1% Demographic characteristics of the study population are displayed in Table 1. TBI and controls showed no statistically significant group differences in age, sex, or education level. Among the TBI group, 29 (72.5 %) experienced confirmed or suspected loss of consciousness, 22 (55 %) had a trauma-related intracranial abnormality on the initial head CT, and 17 (42.5 %) were found to have a focal TBI-related brain parenchymal lesion on MRI. An example lesion segmentation in a representative patient with a right occipital hemorrhagic contusion along with contrast concentration curves stratified by tissue type is displayed in Fig. 1. While the median GOS-E of TBI group was 7, 46 % of TBI patients had a “more disabled” outcome (GOS-E < 7), and a subset had

| Table 1 | Demographic characteristics of the TBI and control groups, and injury characteristics of the TBI group. |
|---------|-------------------------------------------------------------------------------------------------------------------|
| Age (years)                              | Control (N = 21) | TBI (N = 40) | p value |
| Mean (SD)                                | 33.8 (11.8)      | 35.5 (14.5)  | 0.626   |
| Median [Min, Max]                        | 32.0 [20.0, 59.0] | 30.5 [18.0, 68.0] |          |
| Sex                                       |                   |               |         |
| Male                                      | 11 (52.4 %)      | 30 (75.0 %)  | 0.0909  |
| Female                                    | 10 (47.6 %)      | 10 (25.0 %)  |         |
| Race                                      |                   |               |         |
| White                                     | 10 (47.6 %)      | 13 (32.5 %)  | 0.0166  |
| Black                                     | 6 (28.6 %)       | 25 (62.5 %)  |         |
| Other                                     | 5 (23.8 %)       | 2 (5.0 %)    |         |
| Education Level                          |                   |               |         |
| High School                               | 13 (61.9 %)      | 21 (52.5 %)  | 0.271   |
| School or Equivalent                     | 2 (9.5 %)        | 9 (22.5 %)   |         |
| Less than High School                     | 0 (0 %)          | 3 (7.5 %)    |         |
| Missing                                   | 6 (28.6 %)       | 7 (17.5 %)   |         |
| Positive CT                              |                   |               |         |
| Yes                                       | –                | 22 (45.0 %)  | –       |
| No                                        | –                | 18 (55.0 %)  | –       |
| Glasgow Coma Scale (GCS)                  |                   |               |         |
| Median (25th percentile, 75th percentile) | –                | 15.0 [14, 15] |         |
| Range                                     | –                | 3–15         |         |
| Missing                                   | –                | 2 (5.0 %)    |         |
| GCS Category                             |                   |               |         |
| Mild                                      | –                | 34 (85.0 %)  | –       |
| Moderate                                  | –                | 3 (7.5 %)    | –       |
| Severe                                    | –                | 1 (2.5 %)    | –       |
| Missing                                   | –                | 2 (5.0 %)    | –       |
| Loss of Consciousness                     |                   |               |         |
| Yes (or suspected)                        | –                | 29 (72.5 %)  | –       |
| No                                        | –                | 6 (15.0 %)   | –       |
| Missing                                   | –                | 5 (12.5 %)   | –       |
| Post-Traumatic Amnesia                    |                   |               |         |
| Yes (or suspected)                        | –                | 21 (52.5 %)  | –       |
| No                                        | –                | 9 (22.5 %)   | –       |
| Missing                                   | –                | 10 (25.0 %)  | –       |
| Injury Mechanism                          |                   |               |         |
| Road Traffic Incident                     | –                | 25 (62.5 %)  | –       |
| Fall                                      | –                | 7 (17.5 %)   | –       |
| Other (Non-Intentional Injury, Assault)   | –                | 6 (15.0 %)   | –       |
| Missing                                   | –                | 2 (5.0 %)    | –       |
Persistent posttraumatic symptoms with TBI patients exhibiting a median RPQ score of 14.5 (IRQ 15.74) and a median SWLS score of 25 (IQR 11).

Representative subject DCE examples are displayed in Fig. 2, demonstrating that elevations in BBB permeability are observable in some TBI patients without focal lesions. Group-wise comparisons demonstrated higher mean $k_{\text{trans}}$ ($W = 226, p = 0.0028$, Fig. 3A) as well as a greater proportion of suprathreshold $k_{\text{trans}}$ voxels ($W = 259, p = 0.013$, Fig. 3C) among the subacute TBI group compared to the control group. Mean brain NPI was higher in the TBI group though the difference did not reach statistical significance ($W = 315, p = 0.11$, Fig. 3B). The proportion of suprathreshold NPI voxels was significantly higher among the TBI group compared to the control group ($W = 204, p = 0.001$, Fig. 3B).
Fig. 3. Group-level comparisons between the subacute TBI and control groups demonstrate elevated mean $K_{\text{trans}}$ (A, $p = 0.0028$) and a greater proportion of voxels exceeding the control group 95th percentile $K_{\text{trans}}$ value (B, $p = 0.014$) among the TBI group. There was no statistically significant difference in mean NPI between groups (C, $p = 0.11$), however there was a greater proportion of voxels exceeding the control group 95th percentile NPI value (D, $p = 0.001$) among the TBI group.

Subsequent analysis focused on the mean $K_{\text{trans}}$ and the proportion of suprathreshold NPI voxels. BBB permeability metrics were not significantly correlated with GCS ($\rho = -0.16$, $p = 0.34$ for mean $K_{\text{trans}}$ and $\rho = 0.12$, $p = 0.48$ for suprathreshold NPI voxels). In exploratory correlation analysis with measures of clinical symptomatology and neuropsychological function (Table 2), there were moderate inverse correlations between both metrics and SWLS scores ($\rho = -0.51$, corrected $p = 0.016$ for mean $K_{\text{trans}}$ and $\rho = -0.47$, corrected $p = 0.048$ for suprathreshold NPI voxels). A weak inverse correlation was observed between mean $K_{\text{trans}}$ and RAVLT which was not statistically significant after multiple comparison correction ($\rho = -0.35$, corrected $p = 0.48$) (Fig. 6). BBB permeability metrics were not significantly correlated with other neuropsychological test and symptom scores (Table 2). Furthermore, TBI patients with “less disabled” and “more disabled” outcome (GOS-E $\geq 7$ compared with GOS-E $< 7$) did not show significant differences in BBB metrics mean $K_{\text{trans}}$ ($W = 183$, $p = 0.94$) and proportion of suprathreshold NPI voxels ($W = 200$, $p = 0.57$).

In longitudinal analysis, there were no significant differences in demographics, injury characteristics, measures of post-concussive symptoms, or outcome between TBI patients who completed the follow up scan and those who did not (Table 3).
Among the follow-up group, there was a decline in mean $K^{\text{trans}}$ (average delta $2.29 \pm 7.9 \times 10^{-4}$ min$^{-1}$) and proportion of suprathreshold NPI voxels (average delta $-0.9\% \pm 11\%$) at the time of follow-up across the TBI group, though which was not statistically significant in paired testing ($V = 105, p = 0.42$ and $V = 104, p = 0.44$ respectively). Decline in BBB metrics over time was greater in lesional patients (delta $K^{\text{trans}} -5.32 \pm 8.2 \times 10^{-4}$ min$^{-1}$ and delta NPI suprathreshold voxels $-5.1\% \pm 7.2\%$) compared to nonlesional patients (delta $K^{\text{trans}} 1.5\% \pm 5.9 \times 10^{-4}$ min$^{-1}$ and delta NPI suprathreshold voxels $6.8\% \pm 12.8\%$).

Inspection of individual trajectories (Fig. 7) showed while some patients with the highest values at the initial scan (due to larger focal lesions) exhibited the largest decreases by the follow-up scan, some were relatively stable while others showed an increase. Trajectories appeared more heterogeneous with the suprathreshold NPI voxel metric than with the mean $K^{\text{trans}}$. In particular, three nonlesional patients (each with a GCS of 15) with lower NPI measures at the initial timepoint showed clear

Fig. 4. Focal traumatic lesions presented as an overlap map (A) exhibited an expected predilection for anteroinferior frontal and temporal lobes, noting 2 patients had right occipital lesions. Threshold-weighted overlap maps displayed on an arbitrary scale in both control (B, provided for reference) and TBI (C) subjects demonstrate TBI-related $K^{\text{trans}}$ elevation in a pattern resembling focal lesions but to a small degree in areas outside of lesioned brain, such as the left temporal-occipital region and high anterior frontal lobes. An overlap map of suprathreshold NPI voxels in the TBI group (D) showed a similar pattern of elevated permeability compared to $K^{\text{trans}}$ again matching the distribution of focal lesions though there are some areas where permeability elevation appears more expansive such as in the high anterior frontal white matter.

Fig. 5. Tissue-based analysis demonstrates highest $K^{\text{trans}}$ values in association with focal lesions ($p < 0.001$), with lower but still elevated $K^{\text{trans}}$ values in the perilesional ($p = 0.011$) and nonlesional ($p = 0.044$) regions in comparison to the control group. NPI values were similarly most elevated in focal traumatic lesions ($p < 0.001$), and to a lesser degree in the perilesional region ($p = 0.011$). NPI in the nonlesional region was not significantly different than the control group ($p = 0.6$). ($^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$).
Table 2

Correlation analysis between clinical measures and the extent of elevated BBB permeability as assessed by $K_{trans}$ (third column) and NPI (fourth column) in the TBI group. * Denotes measures with statistically significant ($p < 0.05$) correlation to imaging metrics.

| Measures                  | N | $K_{trans}$ | p   | NPI | $K_{trans}$ | p   |
|---------------------------|---|-------------|-----|-----|-------------|-----|
| Behavioral Rating Scales: |   |             |     |     |             |     |
| RPQ                       | 38| 0.03        | 0.84|     | –0.04       | 0.8 |
| SWLS*                     | 37| –0.51       | 0.001|    | –0.47       | 0.003|
| BSI-18                    | 37| 0.18        | 0.29|     | –0.06       | 0.71|
| Neuropsychological Tests: |   |             |     |     |             |     |
| PSI                       | 35| –0.25       | 0.14|     | –0.33       | 0.056|
| COWAT                     | 32| –0.12       | 0.5 |     | 0.15        | 0.43|
| RAVLT*                    | 36| –0.35       | 0.03|     | –0.2        | 0.24|
| TMT-A                     | 36| –0.08       | 0.63|     | –0.02       | 0.91|
| TMT-B                     | 36| 0.15        | 0.29|     | 0.04        | 0.8 |

Key: RPQ – Rivermead Post Concussion Symptoms Questionnaire, SWLS – Satisfaction with Life Scale, BSI-18 – Brief Symptom Inventory-18, PSI – Processing Speed Index, COWAT – Controlled Oral Word Association Test, RAVLT – Rey Auditory Verbal Learning Test, TMT – Trail Making Test (parts A/B).

increase by the follow-up timepoint (Fig. 7). Representative individual-subject longitudinal examples are displayed in Fig. 8, including one nonlesional TBI patient who exhibited a multifocal increase in suprathreshold NPI voxels at follow-up.

Sensitivity analysis after excluding 4 TBI patients with GCS < 13 did not alter the primary results of statistically significant control-TBI group DCE metric differences, tissue-based DCE metric differences, and correlations between DCE metrics and a few of the clinical measures. None of the patients with GCS < 13 returned for the follow-up scan, therefore longitudinal analysis results were unaffected.

4. Discussion

This study examining patients with mild-moderate TBI in the acute post-injury timeframe adds to the emerging literature supporting the use of DCE MRI for the detection and characterization of BBB disruption after TBI. While we observed BBB permeability was most strikingly elevated in association with focal traumatic lesions, elevation of BBB permeability was also detected in otherwise normal-appearing brain tissue surrounding and, to some degree, remote from focal lesions. TBI-related BBB permeability elevation was most frequently observed in anterior and posterior regions of the brain in a spatial distribution resembling that of focal traumatic parenchymal lesions and consistent with anatomical vulnerability to blunt structural brain injuries (Schweitzer et al., 2019). Our current results are in general agreement with previous investigations of DCE MRI which have found that measures of BBB permeability are abnormally elevated after TBI across injury severities (O’Keeffe et al., 2020), including within otherwise radiologically normal-appearing brain tissue (O’Keeffe et al., 2020; Yoon et al., 2021; Tomkins et al., 2011) where permeability elevations are on the order of what has previously been observed in other diseases featuring microvascular pathology (Huisa et al., 2015). In light of recent studies demonstrating correlations between $K_{trans}$ values and elevated serum matrix metalloproteinases (Nichols et al., 2021) and other serologic markers of BBB damage such as S100B (O’Keeffe et al., 2020) after TBI, our results provide further support that DCE abnormalities after TBI reflect loss of BBB integrity.

Our study provides new insights into the evolution of BBB pathology over time and suggests BBB pathology is persistent into the early chronic phase of TBI. Inspection of individual patient trajectories suggests considerable heterogeneity, while TBI patients with larger lesions generally exhibited a decrease in magnitude and extent of BBB disruption by around 6-7 months postinjury, there were some TBI patients showing an increase in BBB disruption. These results, while preliminary, highlight the need to investigate the natural history of BBB disruption on a larger scale to better parse this heterogeneity and ultimately understand its contribution to cumulative neuropathology.

Generally, we found that relationships between BBB disruption and contemporaneous measures of symptomatology, neuropsychological function, and short-term outcome were not strong and appeared weaker than what has previously been demonstrated for traumatic axonal injury and resultant brain network disconnection (Jolly et al., 2021). This is not surprising given the dependence of these outcomes on a range of variables which notably include injury-independent psychosocial factors particularly in patients with mild TBI (Meares et al., 2011), who comprised the majority of our sample. We did, however, observe a moderate inverse correlation between measures of BBB disruption and quality of life scores, suggesting that the magnitude and extent of BBB dysfunction have some relevance to early postruamaic clinical sequelae. This is consistent with previous work demonstrating correlations between BBB disruption and measures of injury severity such as GCS (Winter et al., 2015), as well as with the number and duration of injuries (O’Keeffe et al., 2020), though we are limited by the lack of a more sensitive measure of injury severity. Furthermore, while a weak inverse correlation between BBB disruption and verbal learning was not statistically significant after multiple comparison correction, this relationship has been observed previously among mild TBI patients diagnosed with post-concussive syndrome (Yoo et al., 2019), and warrants further investigation. In light of previous work indicating a relationship between early and persistent BBB damage after a neurological insult and long-term clinical outcome (Lubinski et al., 2019), the most important clinical effects of BBB pathology after TBI may take longer to manifest than the timeframe we have examined. The relevance of BBB disruption to longer-term outcomes after TBI is further supported by its histologic detection years to decades after a TBI (Hay et al., 2015) as well as its colocalization with other late-stage pathological features of chronic traumatic encephalopathy (CTE) (Tagge et al., 2018).

Fig. 6. Scatter plots depicting inverse correlations between the mean $K_{trans}$ and satisfaction with life score (SWLS) (A), and between the proportion of elevated NPI voxels and RAVLT score (B).
DCE MRI is not a novel technique, however optimal methodology for quantitative BBB leakage assessment and in particular detection of low-level BBB dysfunction remains an active area of research. While highly relevant to the study of TBI as well as other neurovascular, neurodegenerative, and neuroinflammatory conditions, interstudy generalizability of low-level BBB leakage measurements have been hampered by variations in acquisition and analysis strategies. In this study we employed both the Patlak model, which has been suggested as the most suitable for detection of low-level permeability disturbances (Barnes et al., 2016; Heye et al., 2016), as well as linear dynamic analysis which may have greater sensitivity for slower mechanisms of BBB leakage (Veksler et al., 2020). We also employed a DCE acquisition duration (15 min) which, while clinically feasible, is substantially longer than typically used for clinical brain tumor imaging. In order to account for the inherent spatial heterogeneity of neuropathology expected to occur in TBI, whole brain imaging is required, necessitating compromises in spatial and temporal resolution which in turn reduce accuracy of vascular input function estimation and subsequent pharmacokinetic modeling (Raja et al., 2018). Nevertheless, we could still observe significant differences in normal-appearing brain between TBI and control participants. Encouragingly, results obtained with both methods were generally convergent, though some differences were apparent. Most notable was a longitudinal increase in BBB permeability observed in a few patients with the linear dynamic method which was not clearly apparent in $K_\text{trans}$. In the context of prior work demonstrating a correlation between linear dynamic analysis and a trans-cellular molecular transport mechanism across the BBB (Veksler et al., 2020), the current longitudinal results may suggest this mechanism plays a greater role in the chronic phase, at least in some patients. Nevertheless, further research into the longitudinal course of BBB disruption after TBI and validation of these results are needed before firm conclusions can be drawn.

Other limitations of this study include the small sample size, particularly for longitudinal analysis, as well as missing data from some of the TBI participants which reduced statistical power for examining neuropsychological and clinical correlates of BBB disruption. Furthermore, the use of a convenience sample which may not be entirely representative of the TBI population at large may limit the generalizability of these results, particularly the observed longitudinal trends given high rate of loss to follow-up. Variable time-from-injury for the initial and follow-up scans limits the ability to draw definitive conclusions about the time course of BBB dysfunction after TBI, but our results should encourage the undertaking of larger follow-up studies to address these issues. While concern remains over the potential for neurotoxicity related to retained gadolinium after intravenous administration of gadolinium-based contrast agents (GBCA) in patients with a compromised blood–brain barrier, research to date has not identified any associated adverse health effects, and accumulating evidence suggests that the use of macrocyclic agents minimizes deposition (Mathur et al., 2020). Ultimately the use of GBCA in research is guided by risk–benefit analysis, which in the case of TBI and related neurological conditions is informed by mounting evidence for the pathogenic role of BBB dysfunction and where improved understanding may lead to new and much needed avenues for diagnosis and therapy.

5. Conclusion

We found evidence of abnormally elevated BBB permeability within and to a lesser degree outside of focal lesions in patients with subacute TBI. These findings suggest that hospitalized TBI is associated with low-level BBB disruption in otherwise normal-appearing brain tissue which can be detected with DCE-MRI. This also encourages additional research using DCE to determine the natural history of this potentially important pathology and to better understand its contribution to long-term outcomes of chronic TBI.

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CRediT authorship contribution statement

Jeffrey B. Ware: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Funding acquisition. Sauarbh Sinha: Data curation, Software, Formal analysis, Writing – review & editing. Justin Morrison: Data curation, Investigation, Project administration. Alexa E. Walter: Formal analysis, Writing – review & editing.
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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