BRAIN REPORT

Astrogliosis marker ^{11}C-SL25.1188 PET in traumatic brain injury with persistent symptoms

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Traumatic brain injury (TBI) is common but little is known why up to a third of patients have persisting symptoms. Astrogliosis, a pathophysiological response to brain injury, may be a potential therapeutic target, but demonstration of astrogliosis in the brain of humans with TBI and persistent symptoms is lacking.

Astroglial marker monoamine oxidase B (MAO-B) total distribution volume (^{11}C-SL25.1188 V_T), an index of MAO-B density, was measured in 29 TBI and 29 similarly aged healthy control cases with ^{11}C-SL25.1188 PET, prioritizing prefrontal cortex (PFC) and cortex proximal to cortical convexity. Correlations of PFC ^{11}C-SL25.1188 V_T with psychomotor and processing speed; and serum blood measures implicated in astrogliosis were determined.

^{11}C-SL25.1188 V_T was greater in TBI in PFC ($P = 0.00064$) and cortex ($P = 0.00038$). PFC ^{11}C-SL25.1188 V_T inversely correlated with Comprehensive Trail Making Test psychomotor and processing speed ($r = -0.48$, $P = 0.01$). In participants scanned within 2 years of last TBI, PFC ^{11}C-SL25.1188 V_T correlated with serum glial fibrillary acid protein ($r = 0.51$, $P = 0.037$) and total tau ($r = 0.74$, $P = 0.001$).

Elevated ^{11}C-SL25.1188 V_T argues strongly for astrogliosis and therapeutics modifying astrogliosis towards curative phenotypes should be tested in TBI with persistent symptoms. Given substantive effect size, astrogliosis PET markers should be applied to stratify cases and/or assess target engagement for putative therapeutics targeting astrogliosis.

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Keywords: astrogliosis; traumatic brain injury; positron emission tomography; monoamine oxidase B; comprehensive trail making test

Received October 14, 2022. Revised June 22, 2023. Accepted July 24, 2023. Advance access publication August 21, 2023

Introduction

With lifetime prevalence of ~20%, traumatic brain injury (TBI) is an important public health problem.[1] Most disability is attributable to persistent, chronic symptoms in approximately one-third of cases, including severe headaches, excessive sensitivity to stimuli, dizziness and cognitive impairment.[1,2] Presently there are no established pharmacological treatments for persistent symptoms.[2] Arguably the main barrier to developing such is a lack of targetable processes broadly identifiable across a high proportion of TBI cases with persistent symptoms.

Astrogliosis is a pathophysiological response to injury for which there are promising therapeutic interventions.[3,4] Unfortunately, it is unknown whether there is astrogliosis in the brain of humans with TBI and persistent symptoms. Post-mortem studies demonstrate astrogliosis in late stage chronic traumatic encephalopathy (CTE)[5] representing 5% of TBI.[1,2] However, about 85% of TBI cases, initially categorized as mild-to-moderate, occur in community settings and involve one to a few injuries with approximately a third of these progressing to severe persistent symptoms.[1,2] Studies of astrogliosis in human TBI are either not representative of this latter group, have concurrent neurological sequelae confounding interpretation, or are too small. For example, the leading investigation of astrogliosis in TBI is observation in surgical tissue of nine severe TBI participants almost all of whom had subdural/epidural hygromas or haematomas.[6] Other data include elevated glial fibrillary acidic protein (GFAP, an astrogliosis marker) immunoreactivity in prefrontal cortex (PFC) of 14 TBI participants with 11 years of repeated brain injury, mostly from college level American football, compared to seven control subjects.[7] One imaging investigation of monoamine oxidase B (MAO-B), a marker of astrogliosis, applied deuterium labelled ^{11}C-l-deprenyl PET in seven TBI cases with persistent seizures and nine control subjects.[8] This study demonstrated feasibility but is inconclusive given the small sample size, uncertain effects of concurrent seizures, and low radiotracer sensitivity (Supplementary material).[9]

^{11}C-SL25.1188 is a newer PET MAO-B radioligand with outstanding properties, including a very high specific binding to non-displaceable binding ratio (>8), high reversibility, high brain uptake and high selectivity for MAO-B; and no brain penetrant radioactive metabolites.[10,11] The total distribution volume, ^{11}C-SL25.1188 V_T, an index of MAO-B density measured with this method, is highly correlated with MAO-B concentration in post-mortem human brain ($r^2 > 0.90$) and very reproducible.[10] MAO-B is applied as a marker of astrogliosis because MAO-B expression is increased in reactive astrocytes; MAO-B density is highly correlated with other markers of astroglial activation across neuropsychiatric diseases such as GFAP, vimentin and heat shock protein 27; and MAO-B overexpression in astrocytes of transgenic mice creates astrogliosis.[12–15] In addition, MAO-B is mainly located in astrocytes throughout the brain with the chief exception of the midbrain.[16]

The main objective of this study was to compare ^{11}C-SL25.1188 V_T between TBI cases with persistent symptoms and control subjects; and secondarily, to evaluate the relationship of PFC ^{11}C-SL25.1188 V_T to symptoms of psychomotor speed and cognitive processing in TBI. More specifically, it is hypothesized that greater ^{11}C-SL25.1188 V_T is present in the PFC and cortex regions proximal to cortical convexity in a community-based sample of TBI with persistent symptoms, a group typically reporting mild-to-moderate symptoms initially after injury. Although this TBI group lacks investigations of astrogliosis in brain, persistence of symptoms could indicate ongoing injury and/or response to injury; astrogliosis is reported in CTE, severe surgical cases[6] as well as some animal models of machine-induced concussions.[17] The secondary hypothesis is that slowed psychomotor speed is correlated with greater PFC ^{11}C-SL25.1188 V_T. Slowed psychomotor speed is common in chronic TBI and diseases with astrogliosis in PFC.[18] Moreover, transgenic mice with globally greater MAO-B protein expression and associated astrogliosis including PFC demonstrate decreased rates of activity and movement.[15] Among neuropsychological tests of psychomotor speed, the Comprehensive Trail Making Test (CTMT), requiring movement speed in the context of avoiding distractors, is prioritized because it is demonstrably affected in TBI, including separation from malingering.[18] Additional hypotheses are that PFC ^{11}C-SL25.1188 V_T correlates with serum level of proteins often expressed in reactive astrocytes with the primary measure being GFAP and secondarily S100 calcium-binding protein β (S100β) and S100 calcium-binding protein A8 (S100A8) (detailed in the Supplementary material).[19]

Materials and methods

Participants

This study was conducted from 1 December 2018 to 4 February 2022 at CAMH, Toronto, Canada. Fifty-eight participants aged 18 to 66, including 29 participants with TBI and 29 similarly aged control subjects, completed the study (Table 1 and Supplementary material). Participants were recruited from CAMH, Southern Ontario through organizations supporting people with TBI and advertisement (Supplementary material). All participants provided written informed consent. The protocol and informed consent forms were approved by the Research Ethics Board of the CAMH and Health Canada.

Main inclusion criteria for TBI participants were that the last TBI occurred within the past 5 years and that there were continuing symptoms; documented on the Brain Injury Screening Questionnaire (BISQ), Head Injury Questionnaire (HIQ), and a standardized self report of TBI symptoms from a University of Toronto affiliated clinic (for descriptions of questionnaires, see the Supplementary material). Main inclusion criteria for healthy participants were good health based on a structured health questionnaire, no history of TBI and medication-free. Exclusion criteria common to TBI and healthy were no history of neurological disease (except TBI symptoms in the TBI group), current substance use disorder, substance use within the previous month (including marijuana) further verified by urine drug screen, cigarette smoking, and use of an MAO-B inhibitor in the previous 4 weeks (Supplementary material).

Neuroimaging

A 3D high-resolution research tomograph (HRRT; CPS/Siemens) PET scanner system acquired imaging data for 90 min as previously described (Supplementary material).[10] During the emission PET scan, concurrent arterial sampling was done using an automatic blood sampling system and manual sampling. For delineation of regions of interest (ROI), an MRI image (Discovery MR750 3.0T GE scanner) was acquired. ^{11}C-SL25.1188 V_T was calculated using a two-tissue compartment model previously validated for ^{11}C-SL25.1188 PET.[10]

Neuropsychological tests

In addition to the aforementioned BISQ, HIQ and structured questions, participants with TBI completed neuropsychological tests,

Table 1 Demographic/clinical history and traumatic brain injury cases

Characteristics	Patients	Healthy
Age,* mean (SD), y	36 (12)	35 (13)
Sex*, *n* (%)		
Males	4 (14)	10 (34)
Females	25 (86)	19 (66)
Multiple TBIs, *n* (%)	21 (72)	NA
Number of TBIs, mean (SD)	3 (3)	NA
Duration since last TBI, mean (SD), y	2 (1)	NA
Duration since most severe TBI, mean (SD), y	7 (1)	NA
Loss of consciousness[a], *n* (%)[b]		
No loss of consciousness	14 (50)	NA
<1 h	8 (29)	NA
1–24 h	1 (3)	NA
Unknown	5 (18)	NA
Duration of confusion[a], *n* (%)		
None	5 (17)	NA
<1 day	9 (31)	NA
1 day–1 month	5 (17)	NA
>1 month	10 (35)	NA
Cause of injury, *n* (%)[c]		
Sports	17 (59)	NA
Motor vehicle accident	14 (48)	NA
Falling	12 (41)	NA
Pedestrian hit by vehicle	5 (17)	NA
Physical abuse	3 (10)	NA
Fight/assault	1 (3)	NA
Other	7 (24)	NA
Health services used, *n* (%)[d]		
Emergency department	18 (62)	NA
Family doctor	24 (83)	NA
Walk-in clinic	7 (24)	NA
Neurologist	14 (48)	NA
Psychiatrist	7 (24)	NA
Psychologist	10 (34)	NA
Rehabilitation services	15 (52)	NA
Alternative therapies	21 (72)	NA
Other	4 (14)	NA

NA = not applicable; SD = standard deviation; TBI = traumatic brain injury; y = years.
[a]Self-reported from most serious incident.
[b]*n* = 28 able to remember.
[c]The number of injuries surpasses the number of participants because participants endured on average three injuries.
[d]The number of health services visited surpasses the number of subjects because participants each visited multiple services.
*$P > 0.10$.

covering different domains by trained staff (Supplementary material). The prioritized test was the CTMT Trail 1, 2 and 3, items identified in factor analysis, which assess psychomotor speed in the context of varying degrees of distractors.[20]

Serum markers

Blood serum levels of GFAP and NDGR2 were measured with a sandwich ELISA; and S100β, S100A8, MCP-1 and T-tau were measured by a customized multiplex assay (R&D system) using the LUMINEX platform (Supplementary material).

Statistical analyses

Initial analyses compared ^{11}C-SL25.1188 V_T between TBI participants and healthy controls, starting with whole PFC using ANOVA. Additional analyses applied repeated measures ANOVA (rmANOVA) and mixed effects models evaluating group and region as fixed effects; and for mixed effects models, participant as a random effect. Second analyses included cortex regions proximal to cortical convexity including prefrontal, parietal, temporal and occipital cortices; and third analyses included other grey matter regions including hippocampus, anterior cingulate cortex (ACC), ventral striatum, dorsal putamen, thalamus and midbrain. Where significance of rmANOVA and mixed effects models were the same, one result is reported (see the Supplementary material for additional detail).

The relationship between ^{11}C-SL25.1188 V_T in subregions of PFC with the CTMT Trail 1, 2 and 3, as well as tests corresponding to other domains of cognitive functioning were examined using Pearson correlation analysis (Supplementary material). Serum level of markers associated with astrogliosis and/or astrocytes were correlated with PFC ^{11}C-SL25.1188 V_T applying Pearson correlation analysis (two-tailed, α threshold = 0.05). In addition, since blood level of some markers like GFAP and T-tau vary over 2 to 5 years post-injury,[21] an exploratory sub-analysis of the relationship between blood serum markers and PFC ^{11}C-SL25.1188 V_T was done, including cases who had their last TBI within 2 years of their ^{11}C-SL25.1188 PET scan.

Results

Fifty-eight participants, 29 with TBI and 29 healthy controls were included in the analyses (Supplementary material). Across the TBI and healthy control groups, age was similar and there were no significant differences in sex (Table 1). Symptoms at time of TBI were mild-to-moderate severity.

^{11}C-SL25.1188 V_T in PFC was significantly elevated in TBI compared to control groups [$F(1,56) = 13.10$, $P = 0.00064$] (Fig. 1A and C and Table 2). Consistent with such, ^{11}C-SL25.1188 V_T was greater in TBI than control groups across subregions of PFC [$F(1,56) = 13.40$, $P = 0.00056$] (Fig. 1A and Table 2). ^{11}C-SL25.1188 V_T was also significantly elevated in TBI participants compared to healthy controls in PFC, temporal, parietal and occipital cortices [$F(1,56) = 14.33$, $P = 0.00038$] (Fig. 1A and Table 2). ^{11}C-SL25.1188 V_T in PFC and parietal, temporal and occipital cortices were highly intercorrelated with correlation coefficients $\sim r = 0.90$ (Supplementary material). Group differences were also found in hippocampus, dorsal putamen, thalamus and midbrain [$F(1,56) = 8.14$, $P = 0.0060$] (Fig. 1B and Table 2).

In TBI participants, greater ^{11}C-SL25.1188 V_T in PFC and ACC was associated with slower psychomotor and processing speed measured with mean T-scores of CTMT Trails 1, 2 and 3 (PFC: $r = -0.48$, $P = 0.010$; ACC: $r = -0.52$, $P = 0.0048$) (see Fig. 2A for PFC subregions). ^{11}C-SL25.1188 V_T did not significantly correlate with other test scores inclusive of psychomotor speed or other exploratory tests, except between immediate recall on the Hopkins Verbal Learning Test (HVLT-R) and ^{11}C-SL25.1188 V_T in the ACC ($r = -0.38$, $P = 0.045$) (Supplementary material).

Variation in symptom severity was modest, so exploratory analyses investigated relationships between PFC ^{11}C-SL25.1188 V_T and presence of symptoms reported with the HIQ, showing that PFC ^{11}C-SL25.1188 V_T was associated with presence of verbal aggression [ANOVA, $F(1,27) = 4.32$, $P = 0.047$] and physical aggression [ANOVA, $F(1,27) = 4.82$, $P = 0.037$] (Fig. 2B). In addition, reported loss of consciousness (presence/absence) after a previous TBI was associated with greater PFC ^{11}C-SL25.1188 V_T [ANOVA, $F(1,26) = 4.73$, $P = 0.039$; $n = 28$ able to remember]. There were no significant

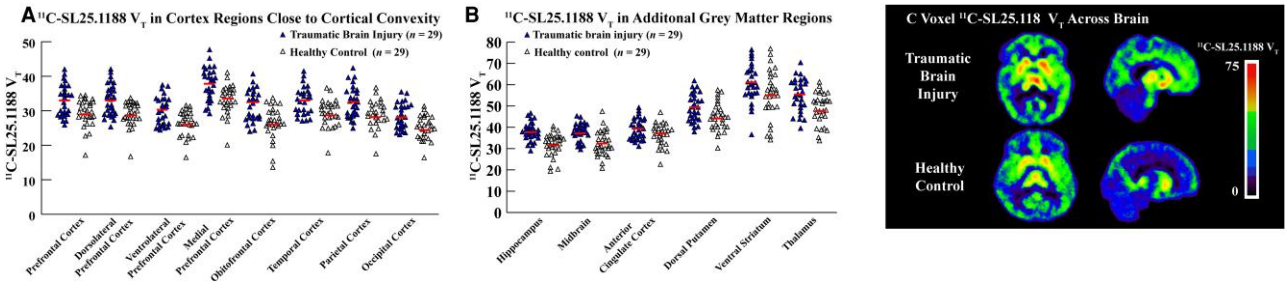

Figure 1 Comparison of ^{11}C-SL25.1188 total distribution volume in traumatic brain injury and healthy controls. (**A**) Plots of ^{11}C-SL25.1188 total distribution volume with group means in cortical and prefrontal regions. A bar represents a group mean. Prefrontal cortex (PFC): $F(1,56) = 13.10$, $P = 0.00064$; PFC subregions: $F(1,56) = 13.40$, $P = 0.00056$; cortex regions (PFC, temporal cortex, parietal cortex and occipital cortex): $F(1,56) = 14.33$, $P = 0.00038$. (**B**) Plots of ^{11}C-SL25.1188 total distribution volume with group means in subcortical regions (hippocampus, midbrain, anterior cingulate cortex, dorsal putamen, ventral striatum and thalamus): $F(1,56) = 8.14$, $P = 0.0060$. A bar represents a group mean. (**C**) Parametric maps of ^{11}C-SL25.1188 total distribution volume of one representative participant from each group. MAO-B = monoamine oxidase B; V_T = total distribution volume.

Table 2 Comparing regional ^{11}C-SL25.1188 V_T between patients with TBI and healthy controls

ROI	^{11}C-SL25.1188 V_T[a]		Effect size[b]	Per cent difference[c]	Mean difference (95% CI)	*P*-value[d]
	Patients ($n = 29$)	Healthy ($n = 29$)				
PFC	33.06 (4.48)	29.00 (3.91)	1.03	14.00	4.07 (1.81–6.32)	0.00064
DLPFC	33.20 (4.58)	29.37 (3.64)	1.05	13.04	3.83 (1.66–6.01)	0.00084
VLPFC	30.03 (4.04)	26.76 (3.67)	0.89	12.22	3.27 (1.24–5.30)	0.0021
MPFC	37.65 (4.80)	33.67 (4.36)	0.91	11.82	3.98 (1.57–6.40)	0.0017
OFC	31.49 (4.51)	26.92 (4.84)	0.94	16.98	4.57 (2.11–7.03)	0.00046
Temporal cortex	32.68 (4.01)	28.89 (3.78)	0.98	13.12	3.79 (1.71–5.87)	0.00058
Parietal cortex	32.38 (4.45)	28.69 (3.87)	0.93	12.86	3.69 (1.50–5.89)	0.0014
Occipital cortex	28.38 (3.62)	24.51 (3.33)	1.14	15.79	3.87 (2.02–5.73)	0.00010
Hippocampus	37.90 (4.37)	32.24 (5.64)	1.00	17.56	5.66 (3.01–8.32)	<0.0001
Midbrain	37.66 (4.20)	32.70 (5.90)	0.84	15.17	4.96 (2.26–7.65)	0.00051
ACC	39.28 (5.01)	36.82 (5.12)	0.48	6.68	2.46 (–0.21–5.12)	0.070
Dorsal putamen	49.21 (6.83)	45.53 (6.63)	0.56	8.08	3.38 (0.14–7.22)	0.042
Ventral striatum	60.24 (9.15)	56.47 (11.59)	0.33	6.68	3.77 (–1.73–9.26)	0.18
Thalamus	55.19 (7.80)	49.05 (7.41)	0.83	12.52	6.14 (2.14–10.15)	0.0033

ACC = anterior cingulate cortex; CI = confidence interval; DLPFC = dorsolateral prefrontal cortex; MPFC = medial prefrontal cortex; OFC = orbitofrontal cortex; PFC = prefrontal cortex; ROI = region of interest; TBI = traumatic brain injury; VLPFC = ventrolateral prefrontal cortex; V_T = total distribution volume.
[a]Mean (standard deviation, SD).
[b](Mean of patients with TBI – Mean of healthy controls) / SD of healthy controls.
[c][(Mean of patients with TBI – Mean of healthy controls) / Mean of healthy controls] × 100.
[d]ANOVA.

correlations of PFC ^{11}C-SL25.1188 V_T (Fig. 2B); or parietal, temporal or occipital cortices with duration since injury.

Exploratory analyses found significant correlations between MCP-1 ($r = –0.41$, $P = 0.03$) and T-tau ($r = 0.39$, $P = 0.042$) with PFC ^{11}C-SL25.1188 V_T (Supplementary Fig. 1). In those who had their last injury within 2 years of scanning, there were significant correlations between PFC ^{11}C-SL25.1188 V_T with GFAP ($r = 0.51$, $P = 0.037$; Supplementary Fig. 1); and T-tau ($r = 0.74$, $P = 0.001$; Supplementary Fig. 1).

Discussion

This is the first study to detect strong evidence of astrogliosis in the brain of TBI with persistent symptoms from a community-based sample and this has key implications for developing therapeutics, including using astrogliosis based imaging for target engagement. ^{11}C-SL25.1188 V_T was significantly elevated with almost half of TBI participants having a greater level than the range of healthy controls in PFC; cortex regions proximal to cortical convexity; as well as hippocampus. Although participants were sampled up to 5 years after their last TBI, the ^{11}C-SL25.1188 V_T marker of astrogliosis was still elevated. Since most TBI are consequent to mild-to-moderate severity events, this study has broad clinical relevance.

While astrogliosis is heterogeneous with a mix of protective and pathological roles, in chronicity, pathological roles tend to be more concerning[4] and it is plausible that amidst possible protective roles, there is ongoing harm from astrogliosis labelled with MAO-B. MAO-B is a major source of hydrogen peroxide in astrocytes; and astrogliosis associated with greater MAO-B level and/or activity, whether transgenically induced, stimulated with lipopolysaccharide, or sampled from tissue adjacent to amyloid plaques, is associated with greater production of hydrogen peroxide and

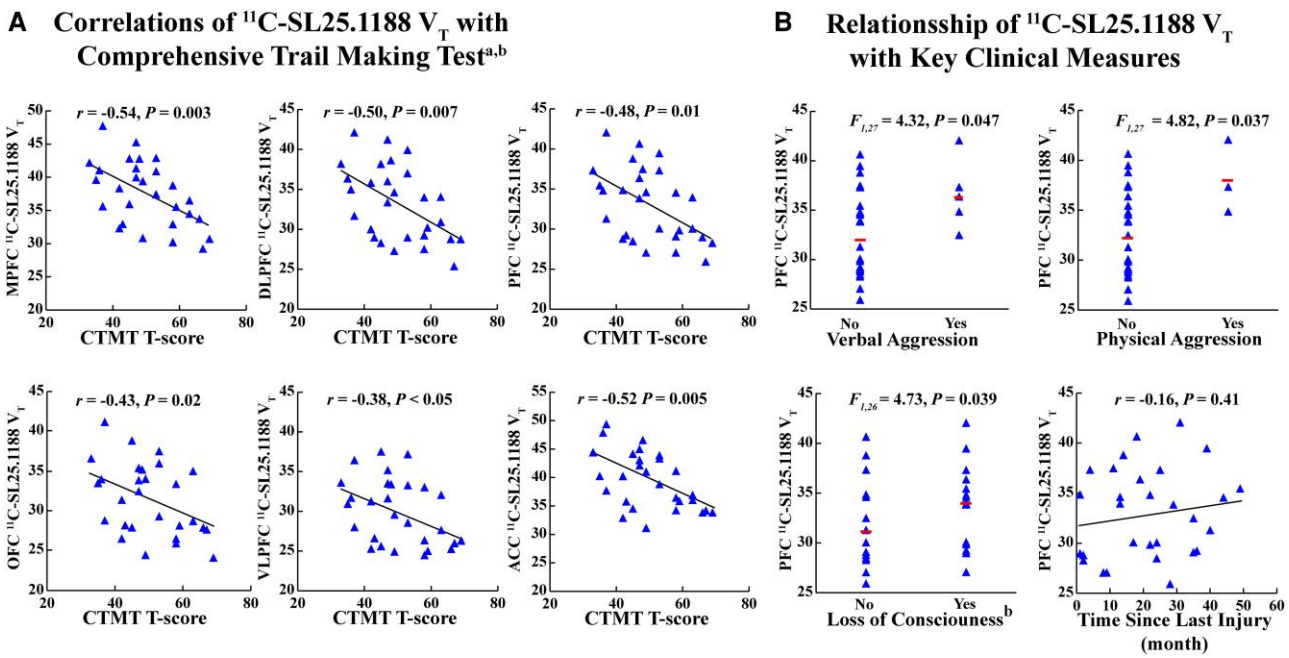

Figure 2 Associations between ^{11}C-SL25.1188 total distribution volume and cognitive and clinical measures. (**A**) Associations between T-scores of CTMT and ^{11}C-SL25.1188 V_T in the entire PFC, PFC subregions and ACC. (**B**) Associations between clinical measures including verbal and physical aggression, loss of consciousness, and time since last injury (month) and PFC ^{11}C-SL25.1188 V_T. ACC = anterior cingulate cortex; CTMT = Comprehensive Trail Making Test; DLPFC = dorsolateral prefrontal cortex; MAO-B = monoamine oxidase B; MPFC = medical prefrontal cortex; OFC = orbitofrontal cortex; PFC = prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; V_T = total distribution volume.[a]Mean T-Scores of CTMT Trail 1, 2, and 3.[b]$n = 28$.

reactive oxygen species.[15,22,23] Widespread astrogliosis associated with overexpression of MAO-B in rodents causes adverse behavioural sequelae of reduced speed, activity and exploratory behaviour, as well as induction of Parkinson's disease pathology.[15] Furthermore, MAO-B labelled astrocytes are implicated in fostering greater amyloid accumulation based on their location, presence and timing.[13,24,25] In the present study, the distribution of ^{11}C-SL25.1188 V_T elevation encompasses regions affected by astrogliosis in Alzheimer's disease and Parkinson's disease, raising the possibility that one mechanism through which TBI creates risk for these diseases is via MAO-B labelled astrogliosis. Moreover, greater MAO-B density itself is implicated in pathological events like production of aldehydes, impairment of mitochondrial function, and creation of neurotoxic metabolites.[9,15,16,22]

There are a number of examples of pathological roles of astrogliosis associated with greater expression of MAO-B, but there may be other roles of such astroglia that are helpful and that only through testing astroglial targeting medications would the risk-benefit profile of such interventions be ascertained in TBI with persistent symptoms. Potential approaches to ascertain whether targeting aspects of astrogliosis in chronically symptomatic TBI has therapeutic benefit includes reducing potentially harmful functions like overexpression of MAO-B through MAO-B inhibition with medications like KDS2010 or rasagiline. Targeting other downstream effects like production of reactive oxygen species and more generalized inflammatory sequelae via antioxidant medications like *n*-acetylcysteine or celecoxib could also be studied.[3,26] Enhancing curative roles of astroglial function like increasing extracellular glutamate clearance to avoid neurotoxicity, such as with riluzole, is another potential direction. Whereas most clinical trials for TBI address acute injury,[26] these interventions would be for chronically persistent symptoms. Moreover, the prominent elevation of cortex ^{11}C-SL25.1188 V_T, with an effect size ~1, represents a breakthrough for astrogliosis PET neuroimaging to assess target engagement of novel therapeutics. Therapeutics assessed could include those that directly lower astrogliosis labelled with MAO-B or those that reduce ongoing injury that indirectly elicits such astrogliosis. Although ^{11}C-SL25.1188 has outstanding radioligand qualities, other potential astroglial PET imaging agents include imidazoline-2 receptor binding ^{11}C-BU99008[25] and MAO-B binding ^{18}F-SBMT-1.[27]

Several clinical measures correlated with greater PFC ^{11}C-SL25.1188 V_T, including decrements in psychomotor functioning with visual scanning on the CTMT as well as greater problems with verbal and physical aggression. Correlations do not prove causality but it is established that injury to PFC is associated with CTMT impairment and predisposes to aggressive behaviour, which could account for these changes and elevated in ^{11}C-SL25.1188 V_T. Also, exploratory analyses found relationships between regional ^{11}C-SL25.1188 V_T and level of several serum blood markers, including a positive association with serum T-tau, a negative correlation with MCP-1, and in a subset of participants, whose previous TBI was within 2 years of scanning, a positive correlation with GFAP (and T-tau) (see Supplementary material regarding speculative mechanisms). These symptom measures and blood markers could be considered for stratifying in future clinical trials of astrogliosis targeting interventions for TBI, applying cut-offs corresponding to PFC ^{11}C-SL25.1188 V_T outside the range of health.

Some limitations should be addressed. First, as is standard with PET imaging studies, ^{11}C-SL25.1188 V_T reflects radioligand binding to MAO-B plus non-displaceable binding. However, based on blocking studies in humans, non-displaceable binding in the cortex is less than 15%[10] and unlikely to account for a mean ~15% elevation in cortex ^{11}C-SL25.1188 V_T as this would require elevations in non-displaceable binding exceeding 150%. Second, while MAO-B is mainly found in astrocytes within regions sampled, the midbrain

is an exception because of substantial contributions of MAO-B from cell bodies of serotonergic neurons of the raphe and dopaminergic neurons in the substantia nigra.[16] Third, TBI is heterogeneous so the best interpretation of elevated ^{11}C-SL25.1188 V_T may be that about half of TBI participants exhibit much more highly elevated cortical ^{11}C-SL25.1188 V_T (~30% to 40%) diluted by TBI participants with lesser change, rather than the interpretation that all TBI cases on average have elevated ^{11}C-SL25.1188 V_T. Finally, although not statistically significant, there were more females in the TBI than control group; however, sex was not a significant predictor of ^{11}C-SL25.1188 V_T and even if sex were added as a covariate, group differences were similarly significant.

In summary, strong evidence for elevated gliosis in TBI with persistent symptoms in a community-based sample is presented with greater ^{11}C-SL25.1188 V_T in PFC, cortices proximal to cortical convexity, as well as hippocampus, thalamus and midbrain. Given the potentially adverse effects of MAO-B labelled astrocytes and implication of ongoing injury, this argues for testing therapeutic candidates that reduce harmful aspects of astrogliosis and/or shift astrogliosis towards curative roles in TBI with persistent symptoms. Moreover, astroglial-based PET imaging should be applied as markers of target engagement for novel therapeutics that impact MAO-B labelled astrogliosis.

Data availability

Data will be made available for each figure that contains the main findings (Supplementary material).

Acknowledgements

Infrastructure support included the Azrieli Foundation for radiochemistry laboratories; and the Canadian Foundation for Innovation and the Ontario Ministry for Innovation for PET scanner, MRI scanner, and cyclotron infrastructure. The authors acknowledge the invaluable contributions of the study participants as well as research staff at Centre for Addiction and Mental Health.

Funding

Primarily, Canadian Institutes of Health Research; some from the Canadian Institute for Military and Veteran Health Research. Data collection for this project and dissemination of the data presented in this manuscript was supported primarily by a Project Grant funded by the Canadian Institutes of Health Research and partially by the Canadian Institute for Military and Veteran Health Research. N.V., I.B. and J.H.M. were supported by the Canada Research Chair program. J.B. was supported by a Doctoral Award funded by the Canadian Research Institutes of Health Research.

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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