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Repetitive mild traumatic brain injury induces persistent alterations in spontaneous synaptic activity of hippocampal CA1 pyramidal neurons

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ABSTRACT

Mild traumatic brain injury (mTBI) or concussion is the most common form of TBI which frequently results in persistent cognitive impairments and memory deficits in affected individuals [1]. Although most studies have investigated the role of hippocampal synaptic dysfunction in earlier time points following a single injury, the long-lasting effects of mTBI on hippocampal synaptic transmission following multiple brain concussions have not been well-elucidated. Using a repetitive closed head injury (3XCHI) mouse model of mTBI, we examined the alteration of spontaneous synaptic transmission onto hippocampal CA1 pyramidal neurons by recording spontaneous excitatory AMPA receptor (AMPAR)- and inhibitory $GABA_AR$-mediated postsynaptic currents (sEPSCs and sIPSCs, respectively) in adult male mice 2-weeks following the injury. We found that mTBI potentiated postsynaptic excitatory AMPAR synaptic function while depressed postsynaptic inhibitory $GABA_AR$ synaptic function in CA1 pyramidal neurons. Additionally, mTBI slowed the decay time of AMPAR currents while shortened the decay time of $GABA_AR$ currents suggesting changes in AMPAR and $GABA_AR$ subunit composition by mTBI. On the other hand, mTBI reduced the frequency of sEPSCs while enhanced the frequency of sIPSCs resulting in a lower ratio of sEPSC/sIPSC frequency in CA1 pyramidal neurons of mTBI animals compared to sham animals. Altogether, our results suggest that mTBI induces persistent postsynaptic modifications in AMPAR and $GABA_AR$ function and their synaptic composition in CA1 neurons while triggering a compensatory shift in excitation/inhibition (E/I) balance of presynaptic drives towards more inhibitory synaptic drive to hippocampal CA1 cells. The persistent mTBI-induced CA1 synaptic dysfunction and E/I imbalance could contribute to deficits in hippocampal plasticity that underlies long-term hippocampal-dependent learning and memory deficits in mTBI patients long after the initial injury.

1. Introduction

Traumatic brain injury (TBI) poses a significant health burden in the United States with 2.8 million TBI-related emergency department visits, hospitalizations and deaths in 2013 alone (Taylor et al., 2017). The majority of TBI injuries are mild (mTBI also known as concussion) with the most common form of mTBI in humans as repeated and mild concussive head injuries that are associated with a higher rate of cognitive and memory deficits, social anhedonia, anxiety and mood disorders (Fehily and Fitzgerald, 2017; Mouzon et al., 2014). Hippocampal synaptic dysfunction is shown to underlie learning and memory deficits following mTBI but the majority of the studies have utilized preclinical open skull injury models of mTBI with most using a single injury and have reported changes in hippocampal plasticity and synaptic function at earlier time points (Girgis et al., 2016; Schwarzbach et al., 2006; Almeida-Suhett et al., 2015; Cohen et al., 2007). Emerging TBI research has begun to incorporate more closed head injury models of mTBI where mTBI mostly enhances excitatory synaptic strength while decreasing inhibitory synaptic drive, and induces deficits in hippocampal plasticity in different sub-regions of the hippocampus including CA1 with more persistent impairment of hippocampal long-term potentiation (LTP) in females (White et al., 2017; Logue et al., 2016; Sloley et al., 2021; Griesemer and Mautes, 2007; Witkowski et al., 2019; McDaid et al., 2021; Mei et al., 2018; Friedman-Levi et al., 2021). Specifically,

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the long-term impairment of cognitive function following TBI may be attributable to an imbalance of synaptic transmission following a persistent deficit in extracellular glutamate regulation resulting in prolonged elevated levels of glutamate at synapses (Dorsett et al., 2017). Glutamate/GABA signaling imbalance favoring excitation or inhibition has both been reported in prefrontal cortex, amygdala and hippocampus based on the early versus later stages of mTBI across different brain regions (Guerriero et al., 2015; Reger et al., 2012; Schneider et al., 2016; Feng et al., 2021). Additionally, consistent with earlier findings with mTBI (Almeida-Suhett et al., 2015; Mei et al., 2018; Reger et al., 2012; Pavlov et al., 2011; Gibson et al., 2010; Raible et al., 2012; Selvaraj et al., 2019), our most recent study using a repetitive closed head injury model of mTBI in mice also shows enduring alterations in hippocampal AMPAR, NMDAR and $GABA_AR$ subunit composition/expression following mTBI that could affect postsynaptic glutamatergic and GABAergic synaptic function within the hippocampus (Selvaraj et al., 2021). However, persistent functional effects of this model of mTBI on pre- and post-synaptic transmission and presynaptic E/I balance of hippocampal CA1 neurons were unclear. Therefore, here we sought to explore long-term effects of repeated mTBI in spontaneous neurotransmission of CA1 pyramidal neurons at two-week time point following the injury utilizing a 3× closed head injury (3XCHI) mouse model that we have recently shown to negatively affect working and spatial memory performance assessed by Y-maze spontaneous alternation task and Morris water maze test, where mTBI mice showed significant impairment and deficits in both tests (Selvaraj et al., 2019). We observed persistent alterations in postsynaptic AMPAR- and $GABA_AR$-mediated synaptic transmission with a possible compensatory presynaptic E/I imbalance in hippocampal CA1 pyramidal neurons that may contribute to chronic hippocampal synaptic dysfunction and learning and memory deficits associated with mTBI.

2. Methods and materials

2.1. Animals

Male, 8- to 10-week-old C57BL/6J mice were purchased from The Jackson Laboratory (Bar Harbor, ME), subjected to repeated closed-head injuries (mTBI) or sham surgeries one week after arrival in the animal facility, and then sacrificed two weeks later for electrophysiology. All animal procedures were carried out in accord with the guidelines established by the National institutes of Health (NIH) and approved by the Uniformed Services University Institutional Animal Care and Use Committee.

2.2. Repetitive closed head injury of mTBI mouse model

mTBI was performed in mice using an electromagnetic controlled stereotaxic impact device, as described previously (Selvaraj et al., 2019). Briefly, mice were anesthetized with 3% isoflurane before stabilizing the head using ear bars in a mouse stereotaxic frame (Stoelting Co., Wood Dale, IL). A midline sagittal incision was made to expose the skull. The stereotaxic electromagnetic impactor with a 3.0-mm steel tip impounder was used to deliver a single controlled cortical impact, delivered at coordinates of 1.8 mm caudal to bregma and 2.0 mm left to midline with a controlled velocity at 3.0 m/s, an impact depth of 2.0 mm, and a dwell time at 100 ms. Mice with depressed skull fracture or visible hemorrhage were excluded from the study. After impact, the skin was sutured and the animals were allowed to recover from anesthesia and then returned to their home cages. A second and third identical closed head injury procedure was performed after removing the sutures on day 2 and day 3 after the initial injury. The skull fracture rate was less than 2.0% during the surgical procedures. Sham mice underwent the identical surgical procedures (handling, anesthesia, opening of the scalp, and suturing of the skin) as the injured group, but no impact was delivered. At 14 days after repetitive mTBI, coronal slices containing hippocampus were prepared and used for electrophysiological recording of spontaneous excitatory and inhibitory synaptic transmission in hippocampal CA1 pyramidal neurons.

2.3. Slice preparation

For all electrophysiology experiments, mice were anesthetized with isoflurane, decapitated, and brains were quickly dissected and placed into ice-cold artificial cerebrospinal fluid (ACSF) containing (in mM): 126 NaCl, 21.4 NaHCO3, 2.5 KCl, 1.2 NaH2PO4, 2.4 CaCl2, 1.0 MgSO4, 11.1 glucose, and 0.4 ascorbic acid and saturated with 95% O2–5% CO2. Briefly, coronal slices containing hippocampus with all the surrounding tissues (to preserve most of the synaptic inputs) were cut at 250 μm and incubated in above prepared ACSF at 34 °C for at least 1 h prior to electrophysiological experiments. For patch clamp recordings, slices were then transferred to a recording chamber and perfused with ascorbic-acid free ACSF at 28 °C.

2.4. Electrophysiology

Voltage-clamp whole-cell recordings were performed from CA1 pyramidal neurons in hippocampus-containing slices using patch pipettes (3–6 MOhms) and a patch amplifier (MultiClamp 700B) under infrared-differential interference contrast microscopy. Data acquisition and analysis were carried out using DigiData 1440A, pCLAMP 10 (Molecular Devices), Clampfit, and Mini Analysis 6.0.3 (Synaptosoft, Inc.). Signals were filtered at 3 kHz and digitized at 10 kHz.

Whole cell recordings of AMPAR-meditated spontaneous excitatory postsynaptic current (sEPSC) recordings were performed in ACSF perfused with picrotoxin (100 μM) and D-APV (50 μM), and pipettes filled with Cs-gluconate internal solution (117 mM Cs-gluconate, 2.8 mM NaCl, 5 mM MgCl2, 2 mM ATP-Na+, 0.3 mM GTP-Na+, 0.6 mM EGTA, and 20 mM HEPES, pH adjusted to 7.28 using CsOH, osmolality adjusted to 275–280 mOsm). Whole-cell recordings of $GABA_AR$-mediated spontaneous inhibitory postsynaptic currents (sIPSC) were performed in ACSF perfused with AP-V (50uM), DNQX (10 μM), and glycine receptor inhibitor (strychnine, 1 μM). Patch pipettes were filled with KCl internal solution (125 mM KCl, 2.8 mM NaCl, 2 mM MgCl2, 2 mM ATP Na+, 0.3 mM GTP-Na+, 0.6 mM EGTA, and 10 mM HEPES, pH adjusted to 7.28 with KOH, osmolarity adjusted to 275–280 mOsm). For both sEPSCs and sIPSCs, CA1 neurons were voltage-clamped at − 70 mV and recorded over 10 sweeps, each lasting 50 s. The cell series resistance was monitored through all the experiments and if this value changed by more than 10%, data were not included. For the entire study, we recorded 43 cells from 20 mice (5 mice, sham or mTBI, per experiment and only 2–3 cells were recorded from each mouse).

2.5. Statistics

Values are presented as means ± SEM. The threshold for significance was set at $^*p < 0.05$ for all analyses. All statistical analyses of data were performed using Graphpad, Prism 9.2. For all electrophysiological data, n represents the number of recorded cells/mouse. Mini Analysis software was used to detect and measure sIPSCs and sEPSCs using preset detection parameters of IPSCs and EPSCs with an amplitude cutoff of 5 pA. Differences between sham and mTBI mean and cumulative probabilities of sEPSC and sIPSC amplitude, charge transfer, tau decay and frequency were analyzed using 2-tailed unpaired Student-t-tests and Kolmogorov Smirnov tests (KS, $\alpha = 0.05$), respectively. The ratio of excitatory/inhibitory frequency was calculated by dividing the mean sEPSC frequency by the mean sIPSC frequency. Ratios of GluR1/GluR2 were calculated by dividing the previous normalized data set of Western Blot analysis of GluR1 and GluR2 subunit expression values in a recent study from our group using the same mTBI model (Selvaraj et al., 2021) which was not reported. Differences between sham and mTBI GluR1/-GluR2 ratios were analyzed using 2-tailed unpaired Student-t-tests.

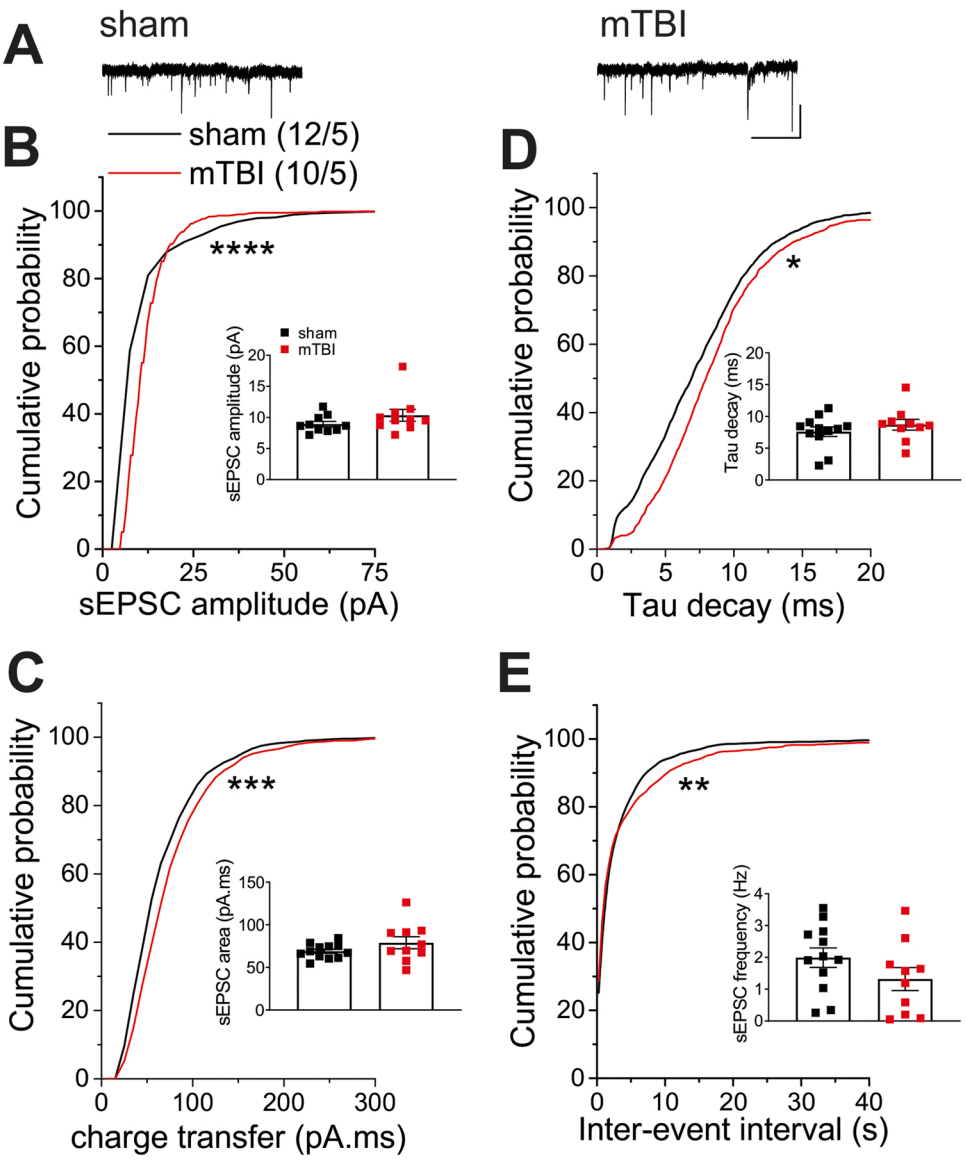

Fig. 1. mTBI alters spontaneous EPSC input on CA1 pyramidal neurons, (A) Representative trace of AMPAR-mediated sEPSC recorded from CA1 pyramidal neuron from sham and mTBI mice. The cumulative probability (CP) and group means (insets) of sEPSC (B) amplitude, (C) charge transfer, (D) Tau decay, and (E) inter-event interval and frequency. Data are shown as means ± SEM for each condition. Group numbers referred to as number of recorded cells/mouse (2–3 cells from each mouse). Unpaired Student's t-test, or KS tests for cumulative distribution curves, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

3. Results and discussion

To test the protracted effects of repeated mTBI in CA1 pyramidal synaptic function, we evaluated AMAPAR- and $GABA_AR$-mediated spontaneous neurotransmission onto CA1 neurons using a 3XCHI model of mTBI that we have recently shown to impair working and spatial memory performance in Y-maze spontaneous alternation task and Morris water maze test (Selvaraj et al., 2019). We pharmacologically isolated and recorded AMPAR-mediated sEPSCs 2 weeks following mTBI or sham injury (Fig. 1). We found that while the effects of mTBI on group mean sEPSC measurements (amplitude, charge transfer, Tau decay, and frequency) did not reach statistical significance, there were significant effects of TBI on cumulative probability (CP) analysis across each parameter. Specifically, there were significant rightward shifts in the amplitude (Kolmogorov-Smirnov [KS] test, $p < 0.0001$, Fig. 1B), charge transfer (KS test, $p < 0.001$, Fig. 1C), and Tau decay (KS test, $p < 0.05$, Fig. 1D) of sEPSC CPs in mTBI treated mice. The rightward shifts in the amplitude and charge transfer sEPSC CPs reflect an increase in post-synaptic AMPAR function that could be due to an increase in the number or conductance of AMPARs in the synapse following mTBI. Moreover, the slower decay kinetics of AMPARs and the increase in charge transfer may indicate a change in postsynaptic AMPAR subunit composition (Chater and Goda, 2014) where more slow calcium-impermeable GluA2-containing AMPARs with longer decay and charge transfer are inserted at glutamatergic synapses by mTBI. In fact, recent evidence suggest that almost half of glutamatergic synapses onto CA1 pyramidal neurons express slow AMPARs that exhibit reduced desensitization (Pampaloni et al., 2021). Consistently, in our recent study (Selvaraj et al., 2021), we observed changes in AMPAR subunit composition following mTBI at 8 and 32 days post-injury using Western blot analysis of whole hippocampal tissue. We found that mTBI reduced the expression of GluR1 and GluR2 AMPAR subunits, however further analysis of the ratio of GluR1/GluR2 subunits from the same normalized data set revealed that mTBI also significantly reduced GluR1/GluR2 ratios at both time points (GluR1/GluR2 ratio; 8 days post-injury values of sham: 1 ± 0.09 and mTBI: 0.64 ± 0.08, unpaired Student's t test, $t_8 = 2.78$, $p < 0.05$; 32 days post-injury values of sham: 0.99 ± 0.08 and mTBI: 0.52 ± 0.09, unpaired Student's t test, $t_8 = 4.548$, $p < 0.01$). This also supports the possible insertion of GluR2-containing AMPARs with slower decays in mTBI animals. In spite of mTBI-induced potentiation of AMPAR function in CA1 pyramidal neurons, we found a rightward shift in inter-event interval of sEPSC CPs (KS test, $p < 0.01$, Fig. 1E) in mTBI treated mice compared to sham mice suggesting a possible homeostatic decrease in presynaptic glutamate release in response to mTBI-induced

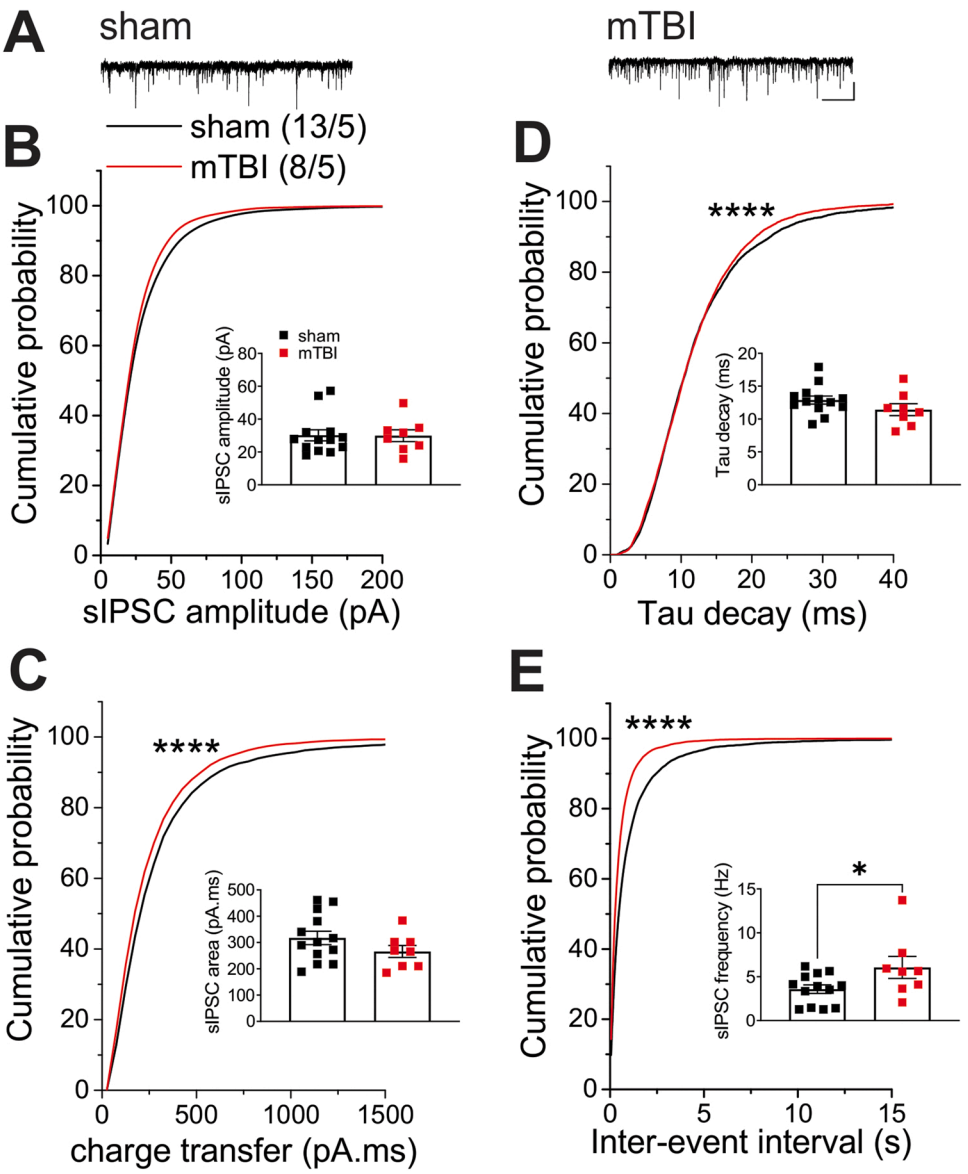

Fig. 2. mTBI alters spontaneous IPSC input on CA1 pyramidal neurons. (A) Representative trace of $GABA_AR$-mediated sIPSC recorded from CA1 pyramidal neuron from sham and mTBI mice. The cumulative probability and group means (insets) of sIPSC (B) amplitude, (C) charge transfer, (D) Tau decay, and (E) inter-event interval and frequency. Data are shown as means ± SEM for each condition. Group numbers referred to as number of recorded cells/mouse (2–3 cells from each mouse). Unpaired student t-test, or KS tests for cumulative distribution curves, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

postsynaptic effects. We also tested the effects of mTBI on spontaneous inhibitory GABAergic transmission onto CA1 neurons. mTBI did not significantly alter group mean sIPSC amplitude (Fig. 2B) nor group mean of the charge transfer (Fig. 2C) compared to sham controls. Although, mTBI did significantly increased mean sIPSC frequency (Student's t-test, $t(19) = 2.15$, $p < 0.05$, Fig. 2D) as well as a significant leftward shift in the CP of sIPSC inter-event interval (KS test, $p < 0.0001$, Fig. 2E), indicating TBI-induced increases in presynaptic GABA release. In spite of the mTBI-induced presynaptic GABAergic potentiation, we observed a significant leftward shift of the CP of sIPSC charge transfer (KS test, $p < 0.0001$, Fig. 2D), and Tau decay (KS test, $p < 0.0001$, Fig. 2C) suggesting a possible decrease in the number or conductance of $GABA_ARs$ but most likely a change in postsynaptic $GABA_AR$ subunit composition where mTBI increases the insertion of $GABA_ARs$ at inhibitory synapses in CA1 pyramidal neurons that exhibit decreased charge transfer and faster decay. Consistently, $GABA_AR$ subunit expression has been shown to be altered by TBI ranging from acute to chronic (months) after injury (Pavlov et al., 2011; Gibson et al., 2010; Raible et al., 2012). Importantly, our recent study (Selvaraj et al., 2021) also found that mTBI affects $GABA_AR$ subunit expression following mTBI at 8 and 32 days post-injury using Western blot analysis of whole hippocampal tissue. We found that mTBI reduced the expression of $GABA_AR$ subunits of α1, β2,3 and γ2 in mTBI. Given that the faster functional kinetics of $GABA_ARs$ upon the loss of β3 subunits unmasking the faster decay of α1 subunit of $GABA_ARs$ (Nguyen and Nicoll, 2018), we can speculate that a greater decrease in β subunits (specifically β3) may contribute to the faster kinetics of $GABA_ARs$ in mTBI animals. The limitation of the Western blot analysis of AMPAR and $GABA_AR$ subunit composition in this study is the lack of cell-type and region-specificity as well as confinement of receptors in synaptic compartments which can be pursued in the future studies.

We also calculated the mean sEPSC/sIPSC frequency ratio to assess presynaptic E/I balance. The sEPSC/sIPSC frequency ratio from CA1 neurons of sham animals was 0.56 while those from TBI animals were 0.22, indicating that CA1 pyramidal neurons of TBI animals receive 34% fewer excitatory currents per inhibitory currents. This suggest that the E/I balance in hippocampal CA1 cells may be shifted towards inhibition following mTBI due to a higher frequency of IPSCs per EPSCs following mTBI-induced postsynaptic modifications at AMPAR and $GABA_AR$ synapses. Interestingly, a somewhat similar mTBI 3XCHI injury is shown to induce alterations in synaptic transmission as well as neuronal excitability of hippocampal CA1 pyramidal neurons and potentiates CA1

long-term potentiation (LTP) at one week following the injury (Logue et al., 2016). Although the findings of mTBI-induced changes in spontaneous GABAergic transmission onto CA1 neurons were similar to our findings, their findings of sEPSCs were opposite to what we reported here. Besides the subtle differences in TBI protocol and earlier time point of study, in the study reported by Logue and colleagues (Logue et al., 2016) no synaptic blockers were used to specifically isolate postsynaptic AMPAR- and $GABA_AR$-mediated spontaneous synaptic transmission onto CA1 neurons (note that the change in the frequency and inter-event intervals of sEPSCs are not affected by synaptic blockers). In fact, our finding of possible mTBI-induced potentiation of postsynaptic AMPAR function by increases in the amplitude, charge transfer and slower decay of sEPSC CPs were corroborated with the miniature EPSC recordings in CA1 neurons in Logue and colleagues (Logue et al., 2016). Although they found an increase in presynaptic glutamate release in mEPSC recordings following mTBI one week-post injury which is opposite to our finding of presynaptic glutamate release. Given that the change in the sEPSC/sIPSC frequency ratio following mTBI indicates that CA1 pyramidal neurons receive fewer excitatory currents per inhibitory currents, our data further suggest a possible mTBI-induced decrease in the excitability of presynaptic glutamatergic neurons projecting to CA1 neurons. Overall, our results suggest mTBI-induced changes in postsynaptic AMPAR and $GABA_AR$ synaptic function in CA1 pyramidal neurons that triggers a presynaptic imbalance in excitatory to inhibitory inputs as a compensatory adaptation. While mTBI-induced postsynaptic potentiation of AMPARs and reduction in $GABA_AR$ function could promote CA1 hyperexcitability following mTBI as shown with closed head injury models of mTBI at earlier time points (Logue et al., 2016; Griesemer and Mautes, 2007), it is also possible that the enhanced inhibitory drive from GABAergic inputs to CA1 neurons is the main synaptic dysregulation that could prevent hippocampal CA1 synaptic plasticity and underlie chronic cognitive and memory deficits following mTBI. We have recently found that the selective elevation of endocannabinoids (eCB) could reverse the memory impairments, neuroinflammation, and changes in glutamatergic and GABAergic receptor expression associated with our mTBI model (Selvaraj et al., 2019; Selvaraj et al., 2021). However, it is yet to be known how mTBI affects eCB regulation of glutamatergic and/or GABAergic inputs and E/I balance to CA1 pyramidal neurons as well as in CA1 GABAergic interneurons. A recent study using high frequency head impacts to model the human contact sport has provided convincing evidence for the role of hippocampal synaptic glutamate dysfunction in chronic mTBI-induced cognitive deficits (Sloley et al., 2021) and urges the field to further explore synaptic mechanisms that are targeted following mTBI and contribute to long-term behavioral and cognitive deficits in more translationally relevant preclinical models of mTBI. Moreover, given the apparent sex differences in TBI pathogenesis, behavioral outcomes, functional profiles and synaptic plasticity in both human and animal studies where mTBI-related deficits could be more pronounced in one sex compared to the other (White et al., 2017; Gupte et al., 2019; Krukowski et al., 2020; Hehar et al., 2015), the inclusion of females in future experimental mTBI studies are also warranted.

Author contribution

FN and YZ were responsible for the study concept and design. LL, PS and SG contributed to the acquisition of animal data. FN, LL, and SS assisted with data analysis and interpretation of findings. FN, LL, SS and YZ wrote the manuscript. All authors critically reviewed content and approved final version of manuscript for submission.

Declaration of Competing Interest

The authors have no competing interests to declare.

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References

Almeida-Suhett, C.P., Prager, E.M., Pidoplichko, V., Figueiredo, T.H., Marini, A.M., Li, Z., Eiden, L.E., Braga, M.F., 2015. GABAergic interneuronal loss and reduced inhibitory synaptic transmission in the hippocampal CA1 region after mild traumatic brain injury. Exp. Neurol. 273, 11–23.

Chater, T.E., Goda, Y., 2014. The role of AMPA receptors in postsynaptic mechanisms of synaptic plasticity. Front. Cell. Neurosci. 8, 401.

Cohen, A.S., Pfister, B.J., Schwarzbach, E., Grady, M.S., Goforth, P.B., Satin, L.S., 2007. Injury-induced alterations in CNS electrophysiology. Prog. Brain Res. 161, 143–169.

Dorsett, C.R., McGuire, J.L., DePasquale, E.A., Gardner, A.E., Floyd, C.L., McCullumsmith, R.E., 2017. Glutamate neurotransmission in rodent models of traumatic brain injury. J. Neurotrauma 34 (2), 263–272.

Fehily, B., Fitzgerald, M., 2017. Repeated mild traumatic brain injury: potential mechanisms of damage. Cell Transplant. 26 (7), 1131–1155.

Feng, Y., Li, K., Roth, E., Chao, D., Mecca, C.M., Hogan, Q.H., Pawela, C., Kwok, W.M., Camara, A., Pan, B., 2021. Repetitive mild traumatic brain injury in rats impairs cognition, enhances prefrontal cortex neuronal activity, and reduces pre-synaptic mitochondrial function. Front. Cell. Neurosci. 15, 689334.

Friedman-Levi, Y., Liraz-Zaltsman, S., Shemesh, C., Rosenblatt, K., Kesner, E.L., Gincberg, G., Carmichael, S.T., Silva, A.J., Shohami, E., 2021. Pharmacological blockers of CCR5 and CXCR4 improve recovery after traumatic brain injury. Exp. Neurol. 338, 113604.

Gibson, C.J., Meyer, R.C., Hamm, R.J., 2010. Traumatic brain injury and the effects of diazepam, diltiazem, and MK-801 on GABA-A receptor subunit expression in rat hippocampus. J. Biomed. Sci. 17 (1), 38.

Girgis, F., Pace, J., Sweet, J., Miller, J.P., 2016. Hippocampal neurophysiologic changes after mild traumatic brain injury and potential neuromodulation treatment approaches. Front. Syst. Neurosci. 10, 8.

Griesemer, D., Mautes, A.M., 2007. Closed head injury causes hyperexcitability in rat hippocampal CA1 but not in CA3 pyramidal cells. J. Neurotrauma 24 (12), 1823–1832.

Guerriero, R.M., Giza, C.C., Rotenberg, A., 2015. Glutamate and GABA imbalance following traumatic brain injury. Curr. Neurol. Neurosci. Rep. 15 (5), 27.

Gupte, R., Brooks, W., Vukas, R., Pierce, J., Harris, J., 2019. Sex differences in traumatic brain injury: what we know and what we should know. J. Neurotrauma 36 (22), 3063–3091.

Hehar, H., Yeates, K., Kolb, B., Esser, M.J., Mychasiuk, R., 2015. Impulsivity and concussion in juvenile rats: examining molecular and structural aspects of the frontostriatal pathway. PLOS One 10 (10), e0139842.

Krukowski, K., Nolan, A., Frias, E.S., Grue, K., Becker, M., Ureta, G., Delgado, L., Bernales, S., Sohal, V.S., Walter, P., Rosi, S., 2020. Integrated STress Response Inhibitor Reverses Sex-dependent Behavioral and Cell-specific Deficits after Mild Repetitive Head Trauma. J. Neurotrauma 37 (11), 1370–1380.

Logue, O.C., Cramer, N.P., Xu, X., Perl, D.P., Galdzicki, Z., 2016. Alterations of functional properties of hippocampal networks following repetitive closed-head injury. Exp. Neurol. 277, 227–243.

McDaid, J., Briggs, C.A., Barrington, N.M., Peterson, D.A., Kozlowski, D.A., Stutzmann, G.E., 2021. Sustained hippocampal synaptic pathophysiology following single and repeated closed-head concussive impacts. Front. Cell. Neurosci. 15, 652721.

Mei, Z., Qiu, J., Alcon, S., Hashim, J., Rotenberg, A., Sun, Y., Meehan, W.P., Mannix, R., 2018. Memantine improves outcomes after repetitive traumatic brain injury. Behav. Brain Res. 340, 195–204.

Mouzon, B.C., Bachmeier, C., Ferro, A., Ojo, J.O., Crynen, G., Acker, C.M., Davies, P., Mullan, M., Stewart, W., Crawford, F., 2014. Chronic neuropathological and neurobehavioral changes in a repetitive mild traumatic brain injury model. Ann. Neurol. 75 (2), 241–254.

Nguyen, Q.A., Nicoll, R.A., 2018. The GABA(A) receptor β subunit is required for inhibitory transmission. Neuron 98 (4), 718–725 e3.

Pampaloni, N.P., Riva, I., Carbone, A.L., Plested, A., 2021. Slow AMPA receptors in hippocampal principal cells. Cell Rep. 36 (5), 109496.

Pavlov, I., Huusko, N., Drexel, M., Kirchmair, E., Sperk, G., Pitkänen, A., Walker, M.C., 2011. Progressive loss of phasic, but not tonic, GABAA receptor-mediated inhibition in dentate granule cells in a model of post-traumatic epilepsy in rats. Neuroscience 194, 208–219.

Raible, D.J., Frey, L.C., Cruz Del Angel, Y., Russek, S.J., Brooks-Kayal, A.R., 2012. GABA (A) receptor regulation after experimental traumatic brain injury. J. Neurotrauma 29 (16), 2548–2554.
Reger, M.L., Poulos, A.M., Buen, F., Giza, C.C., Hovda, D.A., Fanselow, M.S., 2012. Concussive brain injury enhances fear learning and excitatory processes in the amygdala. Biol. Psychiatry 71 (4), 335–343.
Schneider, B.L., Ghoddoussi, F., Charlton, J.L., Kohler, R.J., Galloway, M.P., Perrine, S. A., Conti, A.C., 2016. Increased cortical gamma-aminobutyric acid precedes incomplete extinction of conditioned fear and increased hippocampal excitatory tone in a mouse model of mild traumatic brain injury. J. Neurotrauma 33 (17), 1614–1624.
Schwarzbach, E., Bonislawski, D.P., Xiong, G., Cohen, A.S., 2006. Mechanisms underlying the inability to induce area CA1 LTP in the mouse after traumatic brain injury. Hippocampus 16 (6), 541–550.
Selvaraj, P., Wen, J., Tanaka, M., Zhang, Y., 2019. Therapeutic effect of a novel fatty acid amide hydrolase inhibitor PF04457845 in the repetitive closed head injury mouse model. J. Neurotrauma 36 (10), 1655–1669.
Selvaraj, P., Tanaka, M., Wen, J., Zhang, Y., 2021. The novel monoacylglycerol lipase inhibitor MJN110 suppresses neuroinflammation, normalizes synaptic composition and improves behavioral performance in the repetitive traumatic brain injury mouse model. Cells 10 (12), 3454.
Sloley, S.S., Main, B.S., Winston, C.N., Harvey, A.C., Kaganovich, A., Korthas, H.T., Caccavano, A.P., Zapple, D.N., Wu, J.Y., Partridge, J.G., Cookson, M.R., Vicini, S., Burns, M.P., 2021. High-frequency head impact causes chronic synaptic adaptation and long-term cognitive impairment in mice. Nat. Commun. 12 (1), 2613.
Taylor, C.A., Bell, J.M., Breiding, M.J., Xu, L., 2017. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. MMWR Surveill. Summ. 66 (9), 1–16.
White, E.R., Pinar, C., Bostrom, C.A., Meconi, A., Christie, B.R., 2017. Mild traumatic brain injury produces long-lasting deficits in synaptic plasticity in the female juvenile hippocampus. J. Neurotrauma 34 (5), 1111–1123.
Witkowski, E.D., Gao, Y., Gavsyuk, A.F., Maor, I., DeWalt, G.J., Eldred, W.D., Mizrahi, A., Davison, I.G., 2019. Rapid changes in synaptic strength after mild traumatic brain injury. Front. Cell. Neurosci. 13, 166.