

Involvement of Lateral Habenula Dysfunction in Repetitive Mild Traumatic Brain Injury-Induced Motivational Deficits

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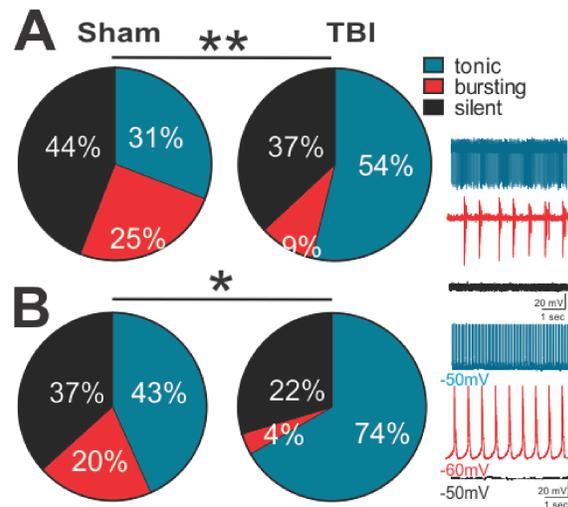
Introduction

- While the majority of traumatic brain injury cases are classified as mild (mTBI), many mTBI patients display persistent post-concussion related symptomatology often associated with affective and motivational deficits.
- The lateral habenula (LHb) is a key brain region implicated in guiding risk/reward decision-making through its negative regulatory effects on midbrain dopaminergic and serotonergic systems.
- The role of LHb in long-term effects of experimental brain injuries on dysregulation of motivated self-efficacious behavior has not been previously explored.

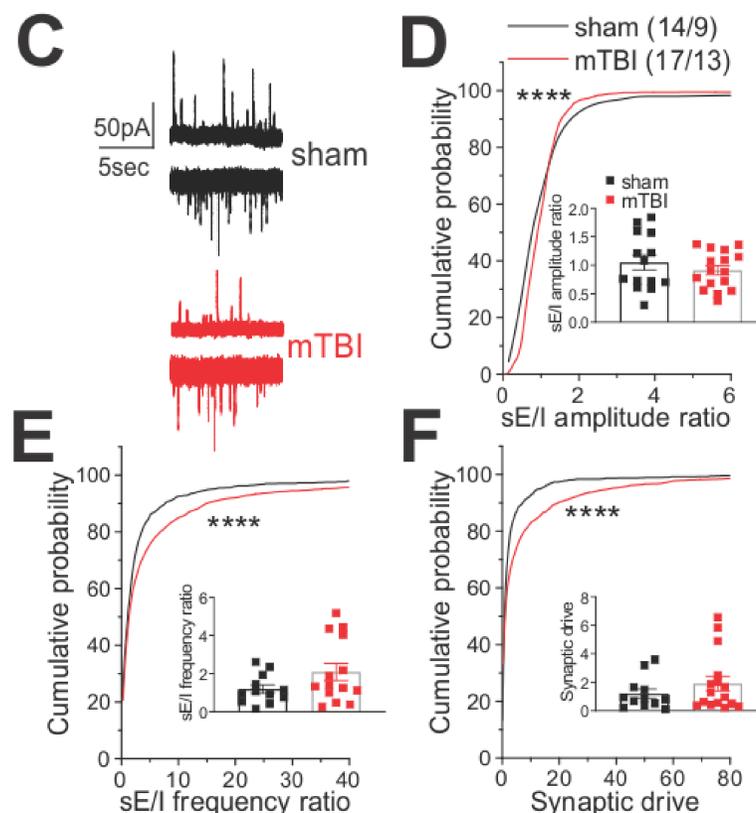
Methods

- Stereotaxic Injection; Viral-mediated DREADD expression:** Three weeks prior to behavioral assessment C57BL/6 (~PN42) received bilateral LHb injections (AP:-1.45 ML: ±0.5 DV: -3.2) of AAV8-CaMKII-hM4Di-mCherry or control AAV8-CamKII-mCherry.
- mTBI model:** Five closed head impacts delivered approximately to bregma via Controlled Cortical Impact device separated by 24-h intervals under isoflurane anesthesia. SHAM surgery consisted of identical procedures without delivery of impact.
- Sucrose Splash Test:** Conducted at 10- and 12-days following final mTBI. 30-min prior testing, DREADD-ligand JHU37160 or Saline was injected (i.p.). Drug exposure was cross-balanced between test days. Following a 10-min acclimation period to the test arena mice were sprayed twice with a 10% sucrose solution on the dorsal coat, then monitored for an additional 5-min. Delay to initiate grooming after splash and total grooming was scored by a blinded observer.
- Ex vivo slice electrophysiology.** Cell-attached and whole cell current clamp recordings were made using a potassium gluconate-based internal solution to determine firing pattern of LHb neurons, and classified into three categories (tonic, bursting, silent). To assess spontaneous synaptic activity, a cesium methylsulfonate internal solution was used, allowing for excitatory/inhibitory ratio to be calculated for each cell. Cells were voltage clamped at -55mV for sEPSC and +10mV for sIPSC recordings in drug-free aCSF.

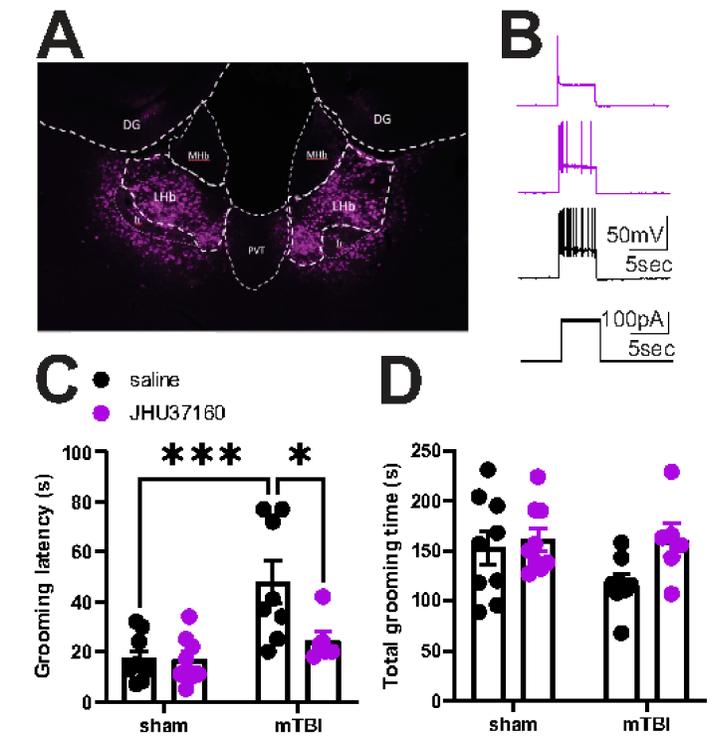
mTBI increases spontaneous tonic neuronal activity within LHb



mTBI shifts LHb Excitation/Inhibition balances toward excitation



Chemogenetic Inhibition of LHb neurons rescues mTBI induced motivational deficits



Highlights

- mTBI in mice results in a change of the firing pattern of LHb neurons. The proportion of bursting neurons was decreased, while more tonic firing cells were observed.
- mTBI alters spontaneous synaptic transmission within the LHb resulting in an increase excitatory synaptic drive onto LHb neurons.
- mTBI decreases motivation toward self-care as observed by increased latency to self-grooming following sucrose splash.
- Chemogenetic inhibition of LHb excitatory neurons is sufficient to reverse mTBI-induced motivational deficits in Sucrose Splash Test



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