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"Traumatic Brain Injury induces aberrations in dentate gyrus adult-born granule cell maturation and circuit integration"

By

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Tuesday, May 24th, 2022
4:00 P.M.
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ABSTRACT

Traumatic brain injury (TBI) is associated with altered neurogenesis in the adult neurogenic niche of the hippocampal dentate gyrus. However, how immature and mature adult-born granule cells (abGCs) generated after trauma impact the circuit and the timeline for their circuit effects are not known. This study examined how a birth dated cohort of abGCs born immediately after concussive brain injury mature and integrate into the hippocampal dentate circuit. Experiments were conducted in 8 to 10 week old wild-type or tamoxifen inducible Nestin-creERT2-ChR2-YFP mice subject to sham or moderate concussive fluid percussion injury (FPI). The data demonstrate an increase in ectopic migration of doublecortin-positive immature abGCs to the outer 2/3rd's of the granule cell layer at three days post-injury. Both the number of BrdU labeled cells as well as co-expression of NeuN, a marker for mature neurons, with BrdU were increased one week after FPI, suggesting increased production and accelerated maturation of young abGCs. In whole cell recordings from mature granule cells (mGCs), optically activating abGCs born after injury consistently evoked monosynaptic excitatory currents in slices from FPI mice as early as one-week post-injury but not in SHAM controls. The amplitude of optically-evoked, 1 week old abGC-mediated IPSCs, observed in both SHAM and FPI groups, was significantly increased in brain injured mice. In vivo stimulus evoked local field potentials revealed an increase in excitability one week after FPI which was selectively suppressed by optical activation of injury-induced abGCs sin FPI mice but not in sham controls. Mature abGCs examined 8-10 week old after FPI showed reduced dendritic complexity ad an increase in frequency of synaptic inhibitory inputs compared to SHAM controls. Additionally, 8 to 10 week old abGCs contributed to direct synaptic signaling on mGCs in both groups and exhibited an increase in excitatory drive of mGCs injured animals. These results identify aberrant maturation and circuit integration of abGCs generated after injury that continues throughout their development and may suggesting a role for injury-induced abGCs in posttraumatic dentate gyrus pathology.