Recovery of retinal terminal fields after traumatic brain injury: evidence of collateral sprouting and sexual dimorphism

Athanasios S. Alexandris,[1] Jaeyoon Yi,[1] Chang Liu,[1] Joseph Belamarich,[1] Zahra Alam,[1] Abhishek Vats,[2] Anthony Peng,[1] Derek S. Welsbie,[2] Donald J. Zack,[3-6] Vassilis E. Koliatsos[1,7,8]

[1] Department of Pathology, Johns Hopkins University School of Medicine, MD, USA.
[2] Viterbi Family Department of Ophthalmology and Shiley Eye Institute, University of California San Diego, La Jolla, USA
[3] Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[4] Department of Molecular Biology and Genetics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[5] Department of Neuroscience Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[6] Department of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[7] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
[8] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Keywords: collateral sprouting, reactive synaptogenesis, regeneration, diffuse axonal injury, sex differences

Corresponding authors
A. S. Alexandris (aalexa27@jh.edu)
V. E. Koliatsos (koliat@jhmi.edu)

Conflicts of interest
None to declare

Acknowledgments
We are grateful to Dr. Alex Kolodkin, Professor of Neuroscience (Johns Hopkins University), and Dr. Constantine Frangakis, Professor of Biostatistics (Johns Hopkins University), for insightful discussions. We thank Dr. Victoria Neckles for assistance with optomotor response testing. We also acknowledge Ms. Georgia L. Lawlor and Mr. Sadid Khan for their help in setting up pattern visual evoked potential recordings.

Funding
This research was supported by funding from the National Eye Institute (RO1EY028039) and the National Institute of Neurological Disorders and Stroke (R01NS114397) to VEK, and from the Department of Defense (TH94252310589) to DJZ and VEK. Imaging was performed using the MICA Leica microscope in the Division of Neuropathology, supported by the Johns Hopkins Alzheimer's Disease Research Center (ADRC; P30 AG066507), and support was also provided by P30 EY001765. In all cases, the funding agencies were not involved in the acquisition, analysis, interpretation, and/or presentation/reporting of data.

Abstract

The central nervous system is characterized by its limited regenerative potential, yet striking examples of functional recovery after injury in animal models and humans highlight its capacity for repair. Little is known about repair of pathways/circuits after traumatic brain injury (TBI), which results in disruption of connectivity. Here we utilize a mouse model of diffuse traumatic axonal injury (Impact-acceleration TBI) in order to explore, for the first time, the evolution of structural and functional changes in the terminal fields of the injured visual system. Retinal ganglion cell (RGC) axons and synapses were genetically labeled via AAV transduction, while anterograde and transsynaptic tracers were used to mark terminals and postsynaptic cells. Functional connectivity and visual integrity were assessed by monitoring c-Fos expression following light stimulation and visual evoked potentials (VEPs). Our findings demonstrate that, although TAI results in approximately a 50% loss of RGC axons and terminals, surviving RGCs generate collateral sprouting, a form of compensatory branching of surviving axons, that restores terminal density to pre-injury levels. Transsynaptic tracing and c-Fos mapping confirmed the reestablishment of connectivity, which was also associated with significant improvements in visual function as measured by pVEPs. Interestingly, the recovery process exhibited sexual dimorphism, with female mice showing delayed or incomplete repair. Moreover, collateral sprouting proceeded normally in Sarm1 knockout mice, evidence of some independence from Wallerian degeneration. Our findings show that collateral sprouting may be an important mechanism of circuit repair in TAI independent of Wallerian degeneration and may represent a promising target for therapeutic interventions.

Significance

Homotypic collateral sprouting -the process by which uninjured axons from the same neuronal source extend new branches to reinnervate targets deprived of their original connections- is a fundamental yet understudied mechanism for CNS repair following injury. Unlike heterotypic sprouting, involving sprouting from unrelated pathways, homotypic sprouting offers potential to restore circuit architecture after partial lesions. Here, we employed a model of diffuse axonal injury in the mouse visual system to examine this mechanism. Our research demonstrates surviving retinal ganglion cell axons can re-establish terminal fields, achieving structural and functional connectivity. Importantly, we discovered significant sex differences: female mice showed delayed/incomplete recovery compared to males. These findings provide evidence of repair of brain circuits perturbed by TBI and the role of homotypic sprouting.