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Altered neocortical cellular and network function after mild traumatic brain injury

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Traumatic brain injury (TBI) is a growing international problem and may be the largest cause of death and disability by 2020, according to the World Health Organization. The large majority of injuries occur in the mild range, typically causing concussion. While some symptoms subside within weeks, cognitive difficulties can last years and even decades. Neuronal structural alterations after mild (m) TBI are well known, including diffuse axonal injury. Treatments have largely focused on ameliorating axonal disconnection, with less focus on possible damage to neurons with intact axons. Using a well described rodent model of mild (m) TBI combined with the YFP-H transgenic strain of mice, we are able to identify the axonal status of layer V pyramidal neurons as axotomized or intact, prior to whole cell patch clamp recordings. We have demonstrated that both axotomized and intact neurons undergo functional changes within two days of injury. These alterations include not only intrinsic cellular changes, but also modified synaptic input. The axotomized and intact neurons follow independent courses of modification identified as early as one day after injury and as late as 40 days after injury. Using the second derivative analysis of the action potential, the current density at axon initial segment (AIS) can be separated from that at the soma. We have recently published data showing that this current density is reduced at the AIS of intact neurons two days after injury. For axotomized neurons, there is a complete loss of the action potential at the AIS. Surprisingly, at one day after injury, 40% of intact neurons also show a loss of the action potential at the AIS. These intrinsic neuronal modifications likely alter the pattern of output from intact neurons, effectively rewiring cortical functional networks. Field potential recordings show that this rewiring contributes to a consistent increase in network excitability even one month after injury. While most studies have concentrated on the excitatory network, we have recently extended our focus to include damage of neocortical inhibitory interneurons. We have found that inhibitory interneuron subtypes are differentially altered, with many parvalbumin inhibitory cells (PV) showing axonal disconnection. This likely contributes to loss of inhibitory control over the AIS and cortical networks via PV interneurons. Utilizing optogenetics with channel rhodopsin inserted into somatostatin inhibitory interneurons, we demonstrate an enhanced output from this type of inhibitory cell. One result of this enhancement is an increased inhibition of other inhibitory interneurons, contributing to network disinhibition. Overall we demonstrate that the neocortical gray undergoes complex network alterations after a mild injury lacking contusion and that some of these modifications persist for at least one month. This profound change to the neocortical gray matter may underlie persistent cognitive difficulties in mild TBI patients for which there are currently no methodologies for identification through clinical imaging.

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