Plasticity of callosal neurons in the contralesional cortex following traumatic brain injury

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Traumatic brain injury (TBI) represents a significant cause of disability worldwide. It creates a vast array of damaging macro- and microscopic changes in the affected brain area(s), ranging from neuronal cell death, changes in structural spine integrity and dynamics to axonal injury and overall neuronal circuit disruption, ultimately leading to functional and cognitive deficits in both humans and animal models (Nudo, 2013).

Several studies in humans and animals have shown that this loss of function can often be recovered (in part) and compensated for by circuit and cellular plasticity in the brain (Nudo, 2013). Suggesting that the brain possesses an important potential for innate plasticity and can thus mediate some form of recovery. In this regard, studies have often implicated the intact contralesional cortex as an important player in recovery processes after unilateral brain injury, indicating that disrupted but intact neurons are plastic and could be able to compensate for the loss of function of the injured areas and the neighboring penumbra.

What mechanisms, and more precisely which neuronal populations, facilitate such a degree of plastic changes in the brain is still not fully understood. In this perspective, we will briefly recapitulate the current understanding on the role of the contralesional cortex following brain injury and reveal which neuronal cell types adapt in response to injury.

The role of the contralesional cortex following brain injury: Aside from the plasticity that occurs in the adjacent, intact motor cortex after focal injury, the reaction of the contralesional cortex has been extensively studied over the years. Clinical studies have used functional magnetic resonance imaging to show activity changes in the contralesional cortex following brain injury with or without rehabilitation indicating an important contribution of the contralesal hemisphere to recovery (Dodd et al., 2017).

Many experimental reports also point to rapid contralesional changes, such as hyperexcitability, that can occur as early as 1 hour after injury. Although continuous contralesional hyperexcitability can be detrimental for recovery, a subset of well-recovered patients shows contralesional motor activity and decreased functional capability upon contralesional hemisphere inhibition (Dodd et al., 2017). Both sensory and motor representations also rapidly expand in the contralesional cortex indicating a strong level of structural plastic adaptation following brain injury. Functional plasticity has also been documented. For example, upregulation of N-methyl-D-aspartic acid receptors, downregulation of γ-aminobutyric acid receptors, and changes in gene expression, in particular of neuronal circuit disruption, ultimately leading to functional and cognitive deficits in both humans and animal models (Nudo, 2013). Structural plasticity under the form of axonal or dendritic sprouting has also been reported following cortical lesions both clinically and experimentally (Napieralski et al., 1996; Ueno et al., 2012; Dancause et al., 2015; Jones, 2017). We recently were able to show a significant general decrease of spine density in the contralesional cortex early after TBI. Analysis of spine dynamics of newly formed spines over eliminated spines, suggesting some recovery of spine density through changes in spine plasticity after traumatic cortical injury (Empl et al., 2022; Figure 1).

To date, it is not clear which specific neuronal populations adapt in the contralesional cortex and becomes plastic following cortical injury. Only a few studies have reported on the plasticity of specific neuronal populations following cortical injury. One early study reported on the sprouting of corticostriatal input from the spared contralesional cortex following cortical lesion (Napieralski et al., 1996). Ueno et al., (2012) also reported that the contralesional corticospinal neurons can react to a cortical lesion by sprouting fibers into the denervated cervical spinal cord and by making new contact with interneurons. They also pointed out that this newly formed contact mediates recovery and is dependent on brain-derived neurotrophic factor. While such rearrangements are often key to functional recovery, it was also shown that the contralesional adaptations of cortico-reticulospinal connections might preserve low motor control at the cost of fine motor function (McPherson et al., 2018). Our latest study shows a selective sensitivity of callosal neurons to TBI, but also their potential for adaptive circuit plasticity and recovery of function after unilateral TBI, as opposed to other non-callosal neuronal populations in the intact contralesional hemisphere. We describe specific responsiveness in callosal neurons following TBI using an extensive toolbox of techniques spanning from longitudinal in vivo two-photon imaging of spine dynamics, retrograde tracer and viral labeling, mono-synaptic circuit tracing, tissue clearing and in vivo calcium imaging to reveal the specific and time-dependent adjustment of contralesional callosal neurons to injury (Empl et al., 2022; Figure 1).

Contralesional callosal neurons have a unique vulnerability and adaptability to brain injury: Callosal neurons connect the two hemispheres of the cortex via their axons that form the corpus callosum. They primarily mediate interhemispheric communication and are responsible for higher order information processing, such as attention and language in a lateralized manner, and sensorimotor processing as a whole (Hinkley et al., 2016). As neuronal structures spanning both hemispheres, they are either directly affected by a brain injury in the case of the callosal neurons located in the ipsilesional hemisphere or directly anatomically connected to the site of a brain injury through their axons for the populations whose cell bodies are located contralesionally. In our recent paper (Empl et al., 2022), we have demonstrated the unique vulnerability and adaptability of contralesional callosal neurons to cortical injury. Using GFP-M mice, retrograde tracing of callosal neurons and confocal microscopy, our study showed an initial spine loss early after injury on contralesional callosal neurons. The loss in spine density and changes in spine dynamics in callosal neurons following TBI may preserve low motor control at the cost of fine motor function (McPherson et al., 2018). Our latest study shows a selective sensitivity of callosal neurons to TBI, but also their potential for adaptive circuit plasticity and recovery of function after unilateral TBI, as opposed to other non-callosal neuronal populations in the intact contralesional hemisphere. We describe specific responsiveness in callosal neurons following TBI using an extensive toolbox of techniques spanning from longitudinal in vivo two-photon imaging of spine dynamics, retrograde tracer and viral labeling, mono-synaptic circuit tracing, tissue clearing and in vivo calcium imaging to reveal the specific and time-dependent adjustment of contralesional callosal neurons to injury (Empl et al., 2022; Figure 1).

Figure 1 | Contralesional changes in spines and in circuit structure and function following traumatic brain injury. (A) Selective spine dynamics & morphology in callosal and non callosal neurons. (i) Schematic of the imaging performed in the contralesional cortex to investigate changes in spine dynamics and morphology. (ii) Schematic of the spine density in callosal (top) and non callosal (bottom) neurons following injury. (iii) Schematic of the quantification of spine density following injury. (iv) Schematic of the quantification of spine morphological subtypes following injury. (v) Schematic of the persistence index of the callosal and non callosal neurons. (B) Structural and functional circuit adaption of callosal neurons after injury. (i) Schematic of the imaging performed to determine structural adaptation of pre-synaptic input to newly activated pre-synaptic input at early and late time injury time points. (ii) Functional adaptations of callosal neurons following traumatic brain injury. (vi) Pie chart showing the activity history of callosal neurons. Unpublished data.

NEURAL REGENERATION RESEARCH | Vol 18 | No. 6 | June 2023 | 1257
density was followed by its recovery at later time points. Interestingly, these plastic changes in spine density were specific to callosal neurons, as non-callosal neurons were stable over the whole study period. Furthermore, these changes were mirrored by alterations in spine morphology. The number of mushroom spines, that are thought to regulate mature synaptic function, significantly decreased early after injury before recovering at later time points while immature spines, stubby spines, transiently increased following cortical lesion.

After two-photon microscopy, those distinct findings were not affected, indicating that those changes are specific to the callosal population. This likely indicates that less stable and immature spines are formed in response to the injury and could lead to the establishment of mature and more stable spines, reinstating "normal" spine density. To understand this, we tracked single spines using two-photon microscopy in callosal, as well as non-callosal neurons. To perform in vivo two-photon imaging, spines were visualized with a retrograde adenosine triphosphate expressing enhanced green fluorescent protein. Here, we could show that newly formed spines on callosal neurons were more stable than those that form on non-callosal neurons according to the idea, that while spine density may be significantly decreased in callosal neurons shortly after injury, an abundance of newly formed spines in callosal neurons, that transiently contacts, is able to re-establish initial spine number or even lost circuit connections. The implication of callosal neurons in the brain injury, as also been demonstrated in different systems and injury paradigms. For example, following visual cortical injury the intact cortex and the corpus callosum can compensate the visuo-motor function (Celeghin et al., 2017). Plasticity of callosal inputs has also been implicated in cortical takeover following unilateral peripheral lesion under the form of brain injury. Neural Regen Res 18(6):1257-1258.

In our own work and that of others therefore point to a specific vulnerability and plasticity of callosal projection neurons following brain injury. As they are directly anatomically linked to the lesion site in unilateral cortical lesions, contralesional callosal neurons may compensate for the loss in spine number, changes in morphology and activity by a temporary increase in the number of newly formed spines after injury, which in turn are able to persist longer and thereby re-establish functional connection to their formerly lost pre-synaptic partners. This way this particular neuronal population might help in triggering recovery. Taken together this puts callosal neurons, and their resilient potential for circuit adaption following brain injury, on the map as a new possible therapeutic target. One possibility to specifically target these neurons could be to use adeno-associated viruses-based gene therapy delivered to layer 2/3 cortical neurons using stereotaxic surgery combined to the use of specific promoters targeting neurons such as a hyn promoter. As callosal neurons seem to play a crucial role in previously reported processes of functional recovery after brain injury, they may also very well be an appropriate point of research in other injury paradigms such as stroke or other neurological disorders.

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