

● PERSPECTIVE

## How the brain can rewire itself after an injury: the lesson from hemispherectomy

Does a post-lesional rewiring exist in the central nervous system (CNS)? Whereas neuroimaging and neuromodulation techniques illustrate the extensive cortical reshaping after a brain injury, the remodeling of ascending and descending neuronal pathway is more difficult to be investigated. Here, we discuss how the studies dealing with hemispherectomy (HS) can provide interesting information about the functional and anatomical reorganization which take place after an extensive unilateral lesion. Indeed, studies in humans and animal models of HS clearly illustrate that the brain is capable of a widespread rewiring between the contralesional cortices and the subcortical structures as well as the medullary segments linked to the affected side of the body.

**HS techniques are effective to treat unihemispheric epilepsy:** HS actually refers to a group of surgical disconnection procedures performed to treat selected cases of epileptic patients, whose seizures are secondary to unihemispheric pathologies. The earlier performed anatomical HS was abandoned in the 1960s, and less invasive techniques have since been developed. The hemidecortication and the functional HS, which involve more disconnection rather than resection of brain structures, are now valuable therapeutic options in selected cases of perinatal strokes, or in the Rasmussen encephalitis, an immune-mediated chronic unihemispheric inflammatory disease, as well as in malformations of cortical development, which include the focal cortical dysplasias and the hemimegalencephaly, a unilateral hemispheric malformation. Also, the Sturge-Weber syndrome, a disorder characterized by venous capillary abnormalities of the leptomeninges, can benefit this technique. HS is highly effective for treating refractory epilepsy in the pediatric age group, as the seizure freedom occurs in 73% of patients. The neurological improvement in HS patients is often substantial, and is not limited to the seizure reduction. Indeed, many patients show improvement of the motor performance, increased somatosensory discrimination capabilities, or improvement in the motor and somatosensory evoked potentials, compared to their pre-operative capabilities (Shimizu et al., 2000; Pilato et al., 2009; Hu et al., 2016).

**Experimental HS triggers extensive anatomical and functional rearrangement:** Preclinical studies in animal models provide compelling evidence of an extensive plastic reorganization of the CNS, which underlies the post HS improvement. This anatomical and functional reorganization has been shown for several neuronal pathways within the CNS, and involves motor, somatosensory and visual pathways, as well as circuitries linking cerebral cortex or deep cerebellar nuclei to basal ganglia or other deep structures. Neuronal circuitries originating from both the ipsilesional and the contralesional hemisphere can rearrange after HS, to such a great degree that normally uncrossed structures become able to decussate, and *vice versa*. How can this extensive rewiring take place? Diverse neuronal pathways that are decussating in the adult brain can have had an ipsilateral component, which was deactivated during the developmental process, but can be reactivated through new functional demand. Alternatively, novel functional pathways have been described, as the remodeling of already present anatomical connection, which can give origin to new axonal collaterals.

These plastic changes have been shown in different models and species, and demonstrate how the entire CNS undertake a long-term morphological remodeling after HS, which is substantial in neonatal lesioned animals, in contrast with a reduced remodeling potential in the adult life. These results illustrate how each hemisphere has the latent capacity to be linked with both the ipsilateral and the contralateral limbs, and thus the ability of HS to induce a complete rear-

range of the relative role of the two hemispheres (Sebastianelli et al., 2017). For instance, in hemiparetic animals the motor function of the affected limbs can be controlled by descending pathways originating from the contralesional, and hence ipsilateral, cortex. Two distinct mechanisms have been described: the reinforcement of the ipsilateral corticospinal tract (iCST), and the axonal sprouting from the intact contralesional corticospinal tract, which could send axonal collaterals to the denervated side at the medullary level.

Physiological execution of skilled motor tasks requires the interaction of several neuronal pathways, well beyond the corticospinal tract (CST). Takahashi et al. (2009) investigated how this interplay can be altered after HS in a comprehensive anatomical work in the rat model. These authors show that the contralesional cortex could project to multiple nuclei, which receive no more afferents by the lesioned cortex, but are necessary for a complete movement control: ipsilesional superior colliculus, ipsilesional red nucleus, ipsilesional pontine nuclei, ipsilateral dorsal column nucleus and ipsilateral gray matter of the cervical spinal cord. Furthermore, the corticostriatal pathway, which is the main cortical projection toward the ipsilateral basal ganglia, can project also contralaterally after neonatal HS in rats (Kolb et al., 1992).

The corticotectal pathway, which ipsilaterally links visual cortex to superior colliculus to control saccadic ocular movements, shows functional and anatomic changes after both adult and neonatal HS, although the rewiring capacity is more pronounced in neonatal lesioned animals. Indeed, a decussated pathway linking the contralesional superior colliculus to visual cortex can be observed in neonatal HS cats (see for review Sebastianelli et al., 2017).

After neonatal hemicerebellectomy in kittens, neurons from the intact cerebellothalamic pathway can send axonal collaterals also to the ipsilateral thalamus, as well as the normally innervated contralateral thalamus (Kawaguchi et al., 1979).

**Medically required HS in humans also alters the interplay between lesional and contralesional hemisphere:** Clinical data in the field of HS techniques are provided mainly by single case reports, small case series and single-center retrospective analyses. Nonetheless, there is consistent evidence that a significant functional and anatomical reorganization may occur in human subjects, although a better recovery potential is a feature of the lesions sustained in early childhood, regardless of the severity or the etiology. Therefore, also the human CNS can react to extensive injuries by reorganizing its structures, despite this capability might be underestimated given the difficulty of systematically studying HS in human infants and children.

Interesting data can be obtained by comparing pre- and post-surgical data, even if in single patients. In these cases, extensive pre-HS cortical rewiring in the contralesional hemisphere has been observed, which would have begun immediately after the onset of the initial pathology. For instance, after extensive perinatal stroke, pre-HS functional magnetic resonance imaging (fMRI) indicate that both nonparetic and paretic motor hand function are controlled by the contralesional primary motor cortex (M1). Accordingly, transcranial magnetic stimulation (TMS) of the contralesional central area can elicit motor responses in both hands. This extensive preoperative cortical rewiring is thought to be at the basis of the post-HS behavioral improvement (Rutten et al., 2002). Nonetheless, further adaptive changes occur after HS in the motor cortex excitability and cortical map representation (Pilato et al., 2009), which can explain the improvement of motor performance. fMRI and TMS reveal a reshaping of motor cortical representation, as well as a significant reduction of cortical silent period, which reflects intracortical inhibitory mechanisms. It has been therefore hypothesized that the inhibitory transcallosal interactions might play a maladaptive role before HS, as the lesioned hemisphere may exert unphysiological inhibition toward the contralesional one. Shimizu et al. (2000) documented this kind of interaction in a series of three cases. By using TMS and positron emission tomography (PET), the authors found that the transection of the corpus callosum in the HS procedure results in a disinhibition of the motor and premotor cortices of the contralesional hemisphere. These phenomena suggest a strong post-HS neuroplastic reorganization, which leads to the improvement after the operation.

HS is only rarely performed in adult patients, and the published

data are discouraging. Serious adverse outcomes are reported, including aphasia, hemiparesis, visual field deficits and memory impairment. In pediatric subjects, a longer duration of epilepsy correlates negatively with developmental and behavioral outcomes after HS (Spencer and Huh, 2008).

**HS offers unique opportunities to study the cortical rewiring and the interplay between lesioned and unlesioned hemisphere in brain injuries:** Neurophysiological, behavioral and functional imaging data indicate the functional rearrangement in human patients as much more complex than that in the animal models. In preclinical experiments, HS is generally the first ever lesion, from which the animal should recover. Conversely, in cases of medically required HS in human subjects, a large lesion previously existed, and generally preceded the HS by many years. As shown in several patients, the neural reorganization begins prior to surgery and is mediated by extensive functional rearrangement and rewiring of the contralesional hemisphere. However, the potential role of these plastic changes cannot be translated completely into improved functional performance, until the diseased hemisphere continues to exert its negative effects. When the lesioned hemisphere is removed, a rapid reorganization takes place in the remaining hemisphere, and the post-lesional and the post-HS functional reorganization becomes clinically evident.

Uncrossed pathways descending from the contralesional hemisphere play a key role in this reorganization process. In healthy children, the ipsilateral corticospinal connections remain functional until around 10 years of age. Ipsilateral motor evoked potentials (iMEPs) can directly assess the function of these pathways, and can also be recorded in healthy adults, even if they require higher thresholds, have longer latencies and different cortical map representation. The strengthening of the iCST can take place also after lesions occurring in the adult life, through a new functional demand (Ziemann et al., 1999). Nonetheless, in patients with later acquired brain damage, also the cortico-reticulospinal pathways may play a dominant role in ipsilateral motor control. The evoked responses elicited through the stimulation of the M1 and premotor cortex (PMC) may thus result from two distinct pathways that may serve ipsilateral function, both containing fast-conducting fibers: the iCST, which mainly originates from M1, and the cortico-reticulospinal pathway, which take origin principally by the PMC (Holloway et al., 2000).

The behavioral improvement after HS is reminiscent of the so called "Sprague effect" described in animal studies, in which a second lesion of the brain may lead to the recovery of deficits which were acquired following an initial brain lesion.

**Conclusions:** HS studies provide evidence that, after extensive unilateral brain injuries, the contralesional hemisphere can assume several of the functions of the affected side, quite likely also in the adult life. This complex reorganizational process is the result of a widespread rewiring between the contralesional cortex and subcortical nuclei as well as spinal cord segments functionally and anatomically linked with the affected side of the body.

The cortical rewiring and the interplay between lesioned and unlesioned hemisphere is a main topic in the neurorehabilitation of brain injuries. Indeed, different patterns of plastic changes can be observed depending from the extent of the injury: small lesions induce mainly ipsilesional rearrangement, whereas larger lesions involve the contralesional hemisphere in the functional reorganization (Staudt et al., 2002). After an extensive unilateral stroke, homologous motor areas of the contralesional hemisphere can be engaged in the movement of ipsilateral limbs early after the onset, and underpin the functional recovery. However, in stroke patients having a small subcortical lesion, the activity of the contralesional hemisphere can also be regarded as maladaptive, and this view is the basis of treatments aimed at reducing the activity of the contralesional hemisphere, and thus at rebalancing the activity of the two hemispheres, for instance by means of inhibitory repetitive TMS.

HS studies illustrate the remarkable resilience of the brain to extensive unilateral lesions, which is sustained by a complex anatomical and functional rearrangement. Furthermore, clinical studies describe a peculiar transcallosal interaction between the lesioned and the intact hemisphere. That makes HS an interesting model to

study the post-lesional brain plasticity.

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**Open peer review report:**

Reviewer: Gregory Wohl Kirschen, Stony Brook University, USA.

Comments to authors: In this article, the authors discuss the various rewiring mechanisms that take place following experimental or therapeutic hemispherectomy. These changes generally facilitate functional recovery, although they may be maladaptive under certain circumstances. The article summarizes important information in this field, and is generally well-written.

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