Neurostimulation to treat brain injury?

VALORIZATION ADDENDUM

SOCIETAL RELEVANCE

Animal models of human pathology are still used to investigate processes impossible to be studied *in vitro*; however, the disease symptoms shown by the model organism may differ overtly from the human situation[1]. Therefore, the methods to measure functional impairment and improvement need to be sensitive and species-specific[2] to increase the translational value of the results. In other words, choosing the right behavioral tests increases the probability that preclinical results will lead to the development of new treatment opportunities. In Chapters 4 and 5, we compared and reviewed several motor tests that are well-suited to detect motor impairments in rodents.

Despite the use of prevention measures, traumatic brain injury (TBI) still affects millions of individuals worldwide leading to death or long-lasting disability in numerous cases[3]. TBI affects individuals from all age groups: young people are prone to TBI[4] due to an increased willingness of risk taking, engaging in physical activities that might lead to head injury, whereas in older people falls occur frequently[5] due to problems with balance and coordination.

Much effort is spend on improving the preventive measures to decrease the incidence of TBI; however, these measures can only decrease the number of new TBI cases, but do not help patients that already suffer from disabilities. Therefore, new treatment opportunities to restore functions after TBI are necessary. Long-lasting consequences of TBI exert a substantial strain on the patients' quality of life and take away their independence, which creates an immense socioeconomic burden[6]. Effective therapies would recover functions and independence of the patients, thereby increasing their quality of life and reducing the costs spend on patient care. Motor cortex stimulation (MCS), or in other words electrical stimulation of the motor cortex through intracranial

electrodes[7], is a more invasive intervention compared to drugs or physical rehabilitation therapy. However, if functional recovery could be achieved with MCS, it would not only benefit the present patient population, but also pave the way for research into less invasive forms of stimulation, such as transcranial direct-current stimulation (tDCS) or transcranial magnetic stimulation (TMS). In Chapter 2 and 3 we have reviewed and shown cellular changes induced by electrical stimulation, which might form a basis for MCS to be used as a therapy[8, 9].

TARGET GROUPS

The results presented in this dissertation address various target groups. First, in Chapters 4 and 5 we tested and evaluated a number of rodent motor tests based on their applicability for a certain animal model together with advantages and disadvantages. Our own experiences, described in Chapter 4, and our recommendations how to choose the best behavioral tests, described in Chapter 5, should help fellow scientists who plan research using animal models with a motor impairment and may help to reduce the number of experimental animals.
Second, research on the regenerative potential of MCS is relevant to patients suffering from motor dysfunction after cortical damage. We conducted studies using either healthy rats, to study basic mechanisms[8], or a rat model of severe TBI. The findings obtained from the latter may also be interesting to stroke research, since the lesion area and resulting symptoms are comparable between the two conditions. Third, the development of an effective treatment to improve motor functions would be a major relief to caregivers, partners or family members that are closely interacting with the patient. Finally, achieving

rehabilitation of patients and increasing their quality of life would lower the socioeconomic burden caused by healthcare and social costs.

ACTIVITIES AND PRODUCTS

We focused on two main objectives: First, the validation of a standardized rat model of TBI combined with suitable behavioral testing methods and second, elucidating the effects of MCS on the brain and testing its potential for functional regeneration after TBI. In general, a successful product is developed after positive findings have been obtained during a previous thorough testing phase. MCS as a novel approach to treat brain injury seemed promising to us after we discovered its cellular effects in healthy rats in Chapter 3. However, application of MCS in rats with severe TBI did not lead to any functional improvement in our experimental paradigm, as described in Chapter 6. We cannot exclude that the experimental design was responsible for the absence of a therapeutic effect; therefore, we cannot draw any conclusion about the use of MCS to treat brain injury at this point.

Nevertheless, we made a valuable contribution to the scientific community and lastly also to the patient population by presenting a number of rodent behavioral tests that are sensitive enough to measure motor impairment resulting from severe TBI in Chapter 4. In Chapter 5 we present numerous motor tests and we conclude with recommendations on how to choose tests to measure motor impairment in rodents. The latter should be used to refine future experimental designs to comply with the '3Rs' (replacement, reduction and refinement) of animal experiments[10] and improve the quality of the scientific outcomes. Good quality results do not only benefit the scientific community, but also society by having a high predictive validity; they may increase the likelihood that a given

therapeutic approach that has been successful in a preclinical setting, will be beneficial in the clinical population as well.

INNOVATION

Two main innovative findings resulted from the experiments conducted in the scope of this dissertation. First, we needed an animal model with a long-lasting motor impairment to test neurostimulation as a novel treatment for cortical injury. In addition, motor tests were necessary that measure the initial deficits and their improvement. In Chapter 4 we showed, which behavioral tests were sensitive enough to detect long-term forelimb motor impairment in rats and, equally important, which tests were not[11]. We detected a species-specific difference in the overt manifestation of motor impairment following TBI when using the CatWalk XT to measure gait-related deficits. Gait-related deficits after mechanical damage to the motor cortex have been reported after a corresponding lesion in mice[12, 13]. Surprisingly, we could not detect any gait-related deficits following TBI in rats, which strengthens the notion for a careful selection of the behavioral testing methods. To conclude; choosing the right behavioral testing methods will enable researchers to investigate the therapeutic potential of neurostimulation while preventing unnecessary experiments that result in the unjustifiable use of experimental animals and potentially negative data due to a suboptimal methodological design.

Second, in Chapter 3 we described the effect of MCS on cortical tissue at the cellular level[8]. In healthy rats, we found a profound effect of MCS on endogenous neural stem and progenitor cells (NSPCs) and, based on these results, we suggested a migration of these NSPCs guided by the electrical current *in vivo*. The ability of attracting endogenous stem cells to a certain area

inside the brain bears a great potential to restore damage in the central nervous system while bypassing the numerous disadvantages inherent to grafted stem cells[14].

However, we were unable to detect functional improvements caused by MCS treatment in a rat model of severe TBI, although there might be the possibility that substantial changes in the experimental setup would lead to positive results in the future. In our experiments the use of neurostimulation did not lead to functional recovery after TBI, but the profound effects of electrical current on brain cells *in vivo* as detected in Chapter 3, might not only occur when using MSC, but also in other clinically applied forms of neurostimulation, such as deep brain stimulation (DBS)[15]. With the results obtained in this dissertation we want to make researchers and clinicians aware of neuroplastic changes that may result after the delivery of electrical current to the brain. These neuroplastic changes are probably different from the intended clinical mechanism of action, but might also bear a certain therapeutic potential.

IMPLEMENTATION

From the studies described in this dissertation, we gained valuable knowledge about the methodology to conduct preclinical research on motor impairment after cortical damage. Furthermore, we investigated the mechanism of action of MCS together with its potential to restore motor impairments after cortical damage. This knowledge has and will be shared with fellow researchers, clinicians and health care organizations through presenting data at international conferences and by publishing the results in scientific journals. The findings described in this dissertation should add to the refinement of preclinical studies

on motor impairment in rodents and the potential use of neurostimulation to restore it.

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