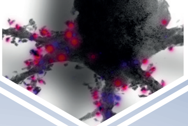

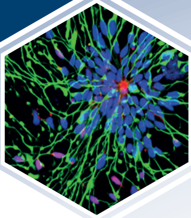

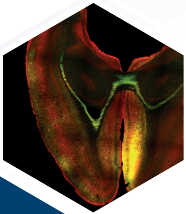

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Network of European
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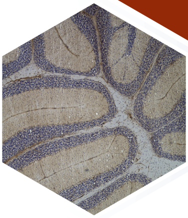
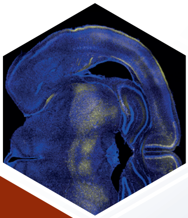
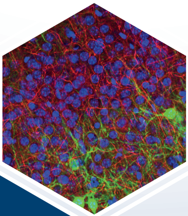
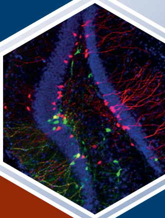


Mid-Term Symposium

External Insults to the Nervous System
JTC2016







Content

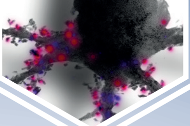
Posters of Consortia

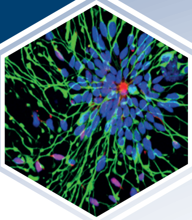
Introduction

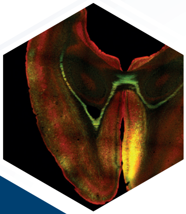
The ‚Network of European Funding for Neuroscience Research' (NEURON) has been established under the ERA-NET scheme of the European Commission, and its aim is to co-ordinate research efforts and funding programmes of its partner countries in the field of disease related neuroscience. That is because maintenance, improvement and restoration of human health are of fundamental importance and worldwide priority. Biomedical and health research provide an important basis for the improvement of healthy living. Disorders of the brain are globally major causes of morbidity, mortality and impaired quality of life, and therefore, neuroscience research and its translation into diagnostic and therapeutic outcomes are fundamental.

In 2016, under the umbrella of NEURON, a joint transnational call (JTC 2016) was launched together with the European Commission in the field of 'External Insults to the Nervous System'. 23 funding organizations had agreed to fund the joint call for multinational research projects in this scientific area. The aim of the call was to facilitate multinational, collaborative research projects that address important questions relating to physical insults to the central nervous system, i.e. traumatic brain injury (TBI) and spinal cord injury (SCI). These insults often cause permanent disability and constitute a heavy burden for patients and their families. 19 research consortia were selected for funding on the basis of ambitious scientific goals, research excellence, and clear demonstration of an added value from working together. More than 75 principal investigators from the funded projects of this JTC2016 gathered at the MidTerm meeting in Bonn, Germany, in January 2019 to discuss progresses and challenges of their research efforts. As a dedicated support measure, NEURON invited PhD students and postdocs to display a poster on their work within the projects. 55 early career researchers followed this invitation and submitted abstracts, accordingly. The ERA-NET NEURON promotes young excellent neuroscientists in early stages of their careers through a devoted set of activities. These activities are promoted to increase the attractiveness of brain research for early-career neuroscientists as well as to enhance the possibilities for methodological training, networking and mobility in the context of the scientific research funded in the NEURON joint transnational calls.

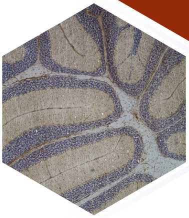
The meeting schedule comprised, besides the scientific symposium poster sessions, a best poster award, the award ceremony for the 'Excellent Paper in Neuroscience Award' (EPNA), which has a long NEURON tradition. As a novum, the workshop on “Quality assurance and reproducibility of results” was held in conjunction with the EU-funded European Brain Research Agenda (EBRA) project.

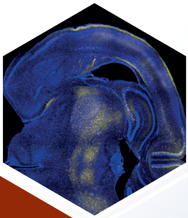


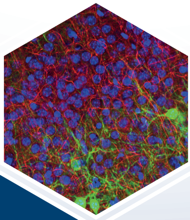


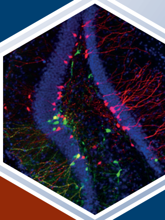


Consortia









Altered Chloride homeostasis in Reactive plasticity upOn BrAin Trauma (ACRoBAT)

Traumatic brain injuries are the main injury-related causes of permanent disability, and are the third leading cause of mortality in Europe. Worldwide, more than 10 million people are affected every year. Post-traumatic epilepsy is the most common cause of new-onset epilepsy in young adults; following penetrating brain wounds, the likelihood of developing epilepsy is more than 50%. 30 to 40% of patients with post-traumatic epilepsy have seizures that are incompletely controlled with currently available medication. Moreover, unnecessary treatment with currently available antiepileptic drugs may then impair neurorehabilitation after brain trauma. It is evident that this field desperately needs new therapeutically relevant targets. In order to find them, we need to understand in detail the mechanisms engaged upon brain trauma. In this proposal, five European groups, with expertise ranging from cellular to systems Neuroscience, will pursue a common aim: **to disclose the mechanisms and impact of trauma-induced changes in inhibitory neurotransmission in the cortex.**

Our preliminary results allow us to propose a working hypothesis in which **a major component of altered inhibitory neurotransmission upon brain trauma is the malfunction of proteins involved in chloride transport in neurons.** Subsequent abnormalities in neuronal chloride regulation not only perturb inhibitory signals, but appear to be crucial for post-traumatic neuronal survival and proliferation, leading to altered activity of neuronal networks. Thus, the multifaceted impact of chloride transport malfunction in neurons makes it a particularly promising target with strong potential for innovative therapeutic strategies to improve rehabilitation of brain trauma patients in the future.

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Spinal cord repair: releasing the neuron-intrinsic brake on axon regeneration (AxonRepair)

After SCI, the connections between nerve cells in the brain and in the spinal cord are lost and fail to grow back. In patients with SCI this results in permanent disability, including paralysis below the level of the injury, and loss of sensory, bladder and sexual function.

There are two major obstacles to the regeneration of nerve fibers (referred to as axons) of central nervous system (CNS) neurons. First, CNS nerve cells do not switch on the necessary machinery for vigorous regrowth of axons. Second, a nerve cell has to deliver the necessary components for growth to the tip of the nerve fibre, which may be quite far as the axon can extend a long way from the cell body. Many CNS nerve cells fail to transport growth proteins into their axons after injury. These proteins are essential for nerve fiber regeneration through the hostile terrain of a spinal lesion. In AxonRepair we aim to promote axon regeneration in the spinal cord by 1. Activating the gene program required for nerve fiber extension, and by 2. Overcoming the transport block of growth-promoting proteins into injured axons.

To achieve aim 1 our approach takes advantage of know-how collected by our consortium on the powerful regenerative abilities of peripheral nerve cells. Peripheral nerve cells do regenerate successfully because they have a kind of ‘switch’ which turns on a robust regenerative machinery, and because they do not exclude growth-related molecules from their axons. We have identified key molecular components of this switch and aim to use these to activate the regeneration program in neurons after a spinal cord lesion. Previous attempts to do this have focused on individual molecules, which can be considered individual parts of the switch. In AxonRepair we are attempting a novel strategy where we target multiple collaborating elements of the switch at the same time.

Many mature CNS neurons have a specialized structure at the transition zone between their cell body and their axon that acts as a molecular barrier for transport of pro-regenerative proteins. It has recently been recognized that this molecular barrier plays a major role in the failure of axon regeneration: following an injury certain proteins (e.g. integrins) required for axon regeneration are excluded from the nerve fibers. Aim 2 of AxonRepair is therefore to “dissolve” the transport barrier allowing transport of essential pro-regenerative proteins into injured axons. At the completion of AxonRepair we expect to have developed an intervention strategy to promote robust axon regeneration and functional recovery after injury to long spinal cord axon tracts. The results obtained in the context of AxonRepair will provide the basis for a potential therapeutic strategy for SCI.

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Frank Bradke, German Center for Neurodegenerative disease, BMBF, Bonn, Germany
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Developing and validating blood and imaging BIOmarkers of AXonal injury following Traumatic Brain Injury (BIO-AX-TBI)

Traumatic brain injury (TBI) occurs when the brain is physically damaged, for example after a car crash. It is common and survivors often have major ongoing problems. It is very difficult to predict how patients will do after TBI. One reason for this is that we are unable to measure all the effects of TBI. An important factor is that the connections between nerve cells are damaged by the impact on the brain of an injury (axonal injury). This damage has been difficult to measure in the past, but new ways to scan the brain and more sensitive ways of picking up the effects of this injury in the blood could change this. In other parts of medicine tests of this type have had a dramatic effect on how we treat patients. For example, the products of heart muscle damage that have leaked into the blood can be used identify a heart attack and guide treatment. We need similar tests to be available in TBI. This should be possible as the products of axonal injury also leak into the blood and we have a sensitive way to pick this up. An accurate test for axonal injury would guide treatment choices and allow us to predict how patients will recover. We have brought together an international team who have been working on different aspects of this problem for many years. Together we will conduct a large study to identify the best measures of axonal injury. We will carefully test whether these measures help us predict outcomes and will study where the blood markers come from using a safe method to measure the effects of axonal injury directly from the brain. The work links into some large projects that have already started and will use a standard way to assess patients after their injury. This is important because it will allow us to share results across studies. We hope the work will allow us to identify a blood marker for TBI that could be widely used to quickly identify the presence of axonal injury. We will also show what brain imaging measure is best at picking up axonal injury and how best to combine the measures to best predict how patients recover. This will allow doctors to diagnose problems after TBI more accurately choose the right treatments and give patients and their families accurate advice about what will happen after discharge from hospital.

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Non-invasive electrical stimulation of the cervical spinal cord to facilitate arm and hand functional recovery in incomplete traumatic cervical spinal cord injured patients (CERMOD)

Injury to the spinal cord is irreparable. There are no current treatments that promote the reconnection between the brain and the spinal cord neurons below the injury. Over the last years several strategies have focused on promoting the regeneration of the damaged spinal axons across the injury. Although several treatments have shown promising results in experimental animal models, none of them are yet available for treating human patients. A novel approach, which has opened great expectations, is the development of bioengineering technologies. The development of bio-electronic devices is intended to modulate the preserved connections between the brain and the spinal cord or to further restitute the damaged nervous tissue in more severe neurological conditions. Along this line, experiments in which electrical current has been delivered to the spinal cord through implantable electrodes have facilitated hind limb function in both animal models and human patients. However, it is unknown whether or not the same technology can be applied to the cervical spinal cord to facilitate recovery of arm and hand function.

In the present proposal, we have designed a set of experiments both in animal models and in human patients to obtain a proof of principle of the utility of non-invasive transcutaneous electrical stimulation to facilitate arm and hand recovery. To achieve this objective, we have built an international consortium of leading laboratories, which employ a complementary set of penetrating experimental techniques and animal models. To achieve its objectives, the proposal is divided into 4 work packages (WP), which will be individually developed in each of the consortium laboratories.

In WP1 we will identify the best stimulation parameters to facilitate reaching and grasping recovery in cervical contused rats and identify the cervical spinal neurons involved in this motor task.

In WP2, we will study in transgenic mice the relationship between the plasticity of the spinal inhibitory system and the recovery generated by the electrical stimulation.

In WP3, we will evaluate and optimize in non-human primates the acute and long term facilitation (or inhibition) of spinal cord function generated by electrical stimulation, and finally in WP4, we will Implement a technology recently developed in the US to deliver painless non-invasive transcutaneous stimulation of the spinal cord, beginning with stimulation parameters that have been shown to activate lumbar spinal networks in humans. We will then optimize the stimulation parameters using as a reference the results obtained in the animal model studies.

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Emergence of a spinal micturition reflex after SCI: abolition by silencing of hyperexcited C-fiber bladder afferents by gene therapy to restore continence and micturition (ELPIS)

This program aims to develop a gene therapy to treat neurogenic detrusor overactivity (NDO) and ultimately to restore urinary continence and voluntary micturition, which remains an unmet medical need in spinal cord injured patients who are currently emptying their bladder by intermittent catheterization. NDO is a severe disabling disorder caused by spinal cord injury (SCI) and characterized by involuntary bladder contractions, resulting in urinary incontinence, recurrent urinary infections and, if untreated, renal failure, which can be fatal. The role of the bladder is to store urine excreted by the kidneys. When the bladder is full, micturition occurs consisting in bladder emptying by contraction of the bladder muscle and opening of the urethral sphincter. Bladder function is controlled by a reflex organized as a neural loop, constituted of nerves from the bladder to the spinal cord (bladder afferents) and back from the spinal cord to the bladder (bladder efferents) and the urethral sphincter, with the spinal cord being under the control of the brain. After SCI, bladder afferents send aberrant information to the spinal cord resulting in chaotic bladder contractions. There is also a loss of brain control on the spinal cord responsible for a lack of voluntary control on micturition. Current NDO treatments comprise oral antimuscarinics or botulinum toxin (BoNT) injections into the bladder, both of which inhibit bladder contractions by blocking bladder efferents, consequently paralyzing the bladder. Intermittent bladder catheterization (5-6 times a day) is therefore mandatory for bladder emptying, which is responsible for recurrent urinary infections and for a significant decrease in quality of life by increasing disability.

We aim to design an original gene therapy to inhibit the transmission of aberrant information from the bladder to the spinal cord via bladder afferents to treat NDO without bladder paralysis. We will design herpes simplex virus-based vectors to be injected into the bladder to silence bladder afferents neurons. By infecting bladder afferents, these vectors, will blunt their intracellular machinery for neurotransmission by expressing relevant intracellular transgenes. Vectors will be tested and selected in a variety of assays, including SCI rats with NDO to assess their therapeutic effect and safety. The neural command of micturition will thus remain available for on-demand electrical stimulation by an implantable stimulator (already available in humans) to elicit micturition without bladder catheterization. Ultimately, this should revolutionize the management of NDO in SCI patients.

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Understanding the mechanisms of atrophy associated with spinal cord injury: the application of MRI-based in vivo histology and ex vivo histology (hMRIofSCI)

Spinal cord injuries (SCI) are mainly caused by traumatic events, such as traffic and sports accidents and violence. Paraplegia (legs paralysed) and tetraplegia (both legs and arms paralysed) permanently, severely and dramatically reduce the quality of life of the affected person as well as their ability to remain a member of the workforce. These negative consequences arise because functional recovery following SCI remains limited and the majority of patients are left with severe impairments in the longer term. While rehabilitative training can improve clinical outcome following SCI, which is a major benefit to the patients‘ quality of life, the degenerative processes as well as the mechanisms underpinning any neurological and functional recovery are not well understood. Recent advances in the field of magnetic resonance imaging (MRI) have vastly improved how we can visualize and interrogate the structural organisation and functioning of the central nervous system. Notable among these advances is the emerging ability to investigate “microscopic” changes in the human central nervous system. This includes distinguishing white and grey matter – two fundamental divisions of structure in the spinal cord, brainstem, and brain.

Using microscopic MRI protocols we have shown that structural changes occur over time following a specific spatial and temporal pattern. In fact these changes occur early after the injury and happen both in the cord and in the brain. However so far, the range of biological changes that may underlie the observed changes cannot be disentangled. By means of in vivo histology using MRI (hMRI) - an emerging field in MRI - we aim to establish the missing link between measured MRI signals and changes in the underlying tissue microstructure, which will help us to explain and better understand the disease processes associated with spinal cord injury.

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Project Partners: Jan Klohs, University of Zurich AND ETH Zurich, Institute for Biomedical Engineering, SNSF, Zurich, Switzerland
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International Collaboration On Neuroinflammation in Traumatic Brain Injury (ICON-TBI)

Traumatic brain injury (TBI) is commonly thought of as an acute self-limited problem. However, in many patients, it can result in chronic disability. In a sizeable minority, such disability can be progressive. Indeed, we now know that either a single severe TBI, or repeated mild TBI, can substantially increase the risk of late dementia. It is believed that a substantial part of these late effects of TBI may be driven by brain inflammation. Indeed, we have known for a long time that patients who suffer a severe TBI have significant acute inflammation in the brain. However, there is increasing evidence that this process may also be important in milder forms of TBI, and that it can become a chronic process. Intriguingly, there are suggestions from animal models of TBI that some of this chronic inflammation may be because the body develops an immune response against the brain, but it is not clear whether this process is beneficial or harmful to patients.

We plan to investigate this issue by studying 175 patients with a range of TBI severity. We will look at the levels of inflammatory cells and molecules in both blood and brain fluids, and compare this with a technique called positron emission tomography (PET), which uses small doses of radioactive tracers to image brain inflammation, and with serial magnetic resonance imaging to map the impact of such inflammation. These clinical studies will be underpinned by a portfolio of animal studies which will obtain more detailed information on the types of brain inflammation that occur after TBI, understand what drives it to produce harm or benefit, and investigate the effect of novel drugs in improving this process. We believe that our research may allow us to identify patients who develop chronic inflammation, differentiate those who experience harm from those who benefit from this process, and provide drugs that might be used to control this process in specific subgroups of patients. This holds the promise that we may be able to identify drugs that act more precisely, and match them to the needs of specific patients. This would represent a substantial advance on the present context, where we use drugs that have very wide actions on inflammation across an entire population of patients, and run the risk that many of these patients may not experience any benefit from the drug, but still be at risk of harm from its side effects.

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Karen Barlow, University of Calgary, Cummings School of Medicine, CIHR, Calgary, AB, Canada

Paediatric Brain Monitoring with Information Technology: Using Information Technology (IT) Innovations to Improve Childhood Traumatic Brain Injury Intensive Care Management, Outcome, and Patient Safety (KidBrainIT)

Brain trauma (TBI) is the main cause of death in children older than 1 year of age. We know 5.6 children per 100,000 population in Britain will sustain life-threatening brain trauma requiring intensive care. The majority of children surviving a life-threatening brain trauma have new disabilities that affect how they function throughout the rest of their lives. This also has great impact on their careers and supporting community. Currently the best option to improve survival and recovery of children with life-threatening brain trauma is to improve their early intensive-care as none of the new experimental therapies tested in the laboratory are useful in clinical practice.

In the early hospital treatment of children with life-threatening brain trauma, often much of the routine bedside monitoring data that is available for clinical interpretation is not fully used. Vital information from this data is discarded rather than being used to help clinicians improve treatments. Multicentre data collection and analysis of such ‘big-data’ in adult brain trauma have been shown to generate new research ideas and analysis methods. A good example of successful ‘big-data’ initiatives in adult brain trauma is the adult BrainIT group. No-one has attempted to setup a similar approach in children with brain trauma.

Using such ‘big-data’ from two children’s intensive-care-units (PICU) and working with the adult BrainIT group, we know that new research ideas, and treatment improvement measures are possible which can lead to huge advances in children’s brain trauma treatment. In this proposal, we are setting up a new childhood brain trauma ‘big-data’ initiative (KidsBrainIT) that uses high-quality data from TBI patients recruited in 10 PICU from 4 countries. Use of this data is expected to improve current treatment, patient safety and outcome.

Intensive-care treatment of brain trauma aims to treat a patient’s abnormal physiology that often follows a brain injury (i.e. secondary insults like low blood pressure or increased brain pressure). In this application, we will focus on improving treatments to two of these physiological insults: increase in pressure from brain swelling (raised ICP) and brain perfusion pressure (CPP).

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New therapeutic strategies in the treatment of traumatic brain injury by targeting the LEctin Activation Pathway of complement (LEAP)

Traumatic Brain Injury (TBI) is a leading cause of death and of permanent disability worldwide. New approaches holding potential for novel therapies are urgently needed. Within minutes following the primary, biomechanical, irreversible trauma, TBI induces the activation of several injurious cascades that develop over time and account for the majority of brain damage. Among these, the Lectin complement activation Pathway (LP) has been identified to contribute to the detrimental outcome of TBI. This LP senses “danger signals” presented by damaged cells and is aimed at setting the body towards a state of alert and of clearing debris and dead or dying cells from the area of injury, thus fostering recovery. This response, however, can be too strong and result in the death of otherwise healthy cells, thus leading to further injury and worsening the overall clinical outcome of trauma pathology.

The LEAP project is aimed at blocking specifically this injurious mechanism. The LEAP programme will first qualify and quantify this mechanism activated following TBI, studying both a mouse model of TBI and the disease events inTBI patients. LEAP will then test a few molecules and drugs that can block or modulate this pathway thus making it less injurious. Previous data obtained by the applicants in other pathological conditions have shown the therapeutic potential of these tools. LEAP will study their therapeutic properties in order to reduce TBI related morbidity and mortality.

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Cortical microcircuitry after traumatic brain injury: molecules to Networks (Micronet)

Traffic accidents, accidental falls and violent attacks may result in the damage to a person’s brain: the ability to move, feel, speak, form memories and judgments can be lost at once. Repairing this damage is often beyond our current therapeutic abilities. Nerve cells become disconnected following the impact and parts of the brain become unable to communicate with each other. Yet some cells manage to establish new contacts and some level of recovery can arise although it is never complete.

Which nerve cells are important for recovery? What happens to those disconnected cells, and why some do some succeed and others fail at making new connections? Are memories, movements, and feelings lost beyond repair, or can we restore lost functions? We have to answer these questions to improve the condition of those patients for whom there are few treatment options.

In this project, we will use the most advanced technologies available for visualizing how and when nerve cells lose connections after trauma and regain the ability to communicate with each other. We will develop new methods, bringing together scientists from computer science, medicine and biology to understand which nerve cells need to be stimulated for recovery to happen. Then, we will look for ways to promote such recovery. We will screen for drugs that have a positive regenerative effect on damaged neural cells and can therefore be used in the treatment of traumatic brain injuries. We will also study new ways to predict how successful the recovery will be. Our long-term goal is to funnel all this information into a coherent rehabilitation program aimed at severely impaired patients and help them to regain integrity of brain and mind.

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Spinal cord repair from endogenous stem cells in the spinal niche (NEURONICHE)

Spinal cord injury in humans leads to permanent loss of function. This is despite the presence of stem cell like cells in the spinal cord. In contrast, the zebrafish regain full swimming capacity after a lesion and its spinal stem cells make new neurons that contribute to the repair.

Here we plan to identify the signals acting on the stem cells in the fish to then use them to improve the reaction of stem cells of humans (in a dish) and spinal cord repair in rat models. In the course of the project, we will develop tools that will aid our research, but also contribute to the work of our colleagues in the community: We will develop small proteins that can be used to drive stem cells into a repair type, we will adapt a new microscopy technique to monitor repair in live fish and rats as it happens, and we will develop new stem cell lines directly from human spinal cord material.

This project will identify repair factors that could then be taken into clinical trials. Our team comprises colleagues from the UK, Germany, Belgium, France and Poland, among them basic neuroscientists and neurosurgeons.

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Project Partners: Jean-Philippe Hugnot, INSERM, U1051- Université de Montpellier Institute for Neurosciences of Montpellier, ANR, Montpellier, France
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Repurposing Acute Therapies for Enhanced Recovery after Spinal Cord Injury (RATER SCI)

Profound sensorimotor deficits are the hallmark of damage in the central nervous system (CNS). Among the more difficult to manage are muscle paralysis and neuropathic pain. The combination of these deficits is particularly cruel: burning or dysthesia in areas of the body that are otherwise numb and incapable of volitional movement. The economic burden to the individual, caregivers, and European and Canadian societies are enormous.

The proposed research project will evaluate the effectiveness of pharmacological and rehabilitation interventions to increase motor function and/or relieve neuropathic pain. Our aims are to determine:
1) if existing treatment options already used to manage neuropathic pain can be repurposed to improve motor function and
2) whether an existing rehabilitation intervention to improve locomotion can be repurposed to relieve neuropathic pain.

Research will be carried out in Canada, Switzerland, Germany, and Spain, and involve research in humans and animal models of spinal cord injury. An investigation into pain medications will be primarily focused on the use of anticonvulsants. These are a particular class of drug that is commonly administered for neuropathic pain after spinal cord injury. Two rehabilitation therapies will be investigated for their potential to resolve neuropathic pain and increase muscle strength. In Spain, a research project will incorporate the use of electrical stimulation applied to the brain as a strategy to improve hand function. Parallel studies in Canada will investigate if gait training reduces pain whilst improving how people walk. At the end of the proposed research project, our goal is to understand the relationship between pain and the recovery of muscle strength, and develop new strategies to enhance neurological recovery in humans with SCI.

Project Coordinator: John Kramer, The University of British Columbia, International Collaboration on Repair Discoveries (ICORD), CIHR, Vancouver, Canada

Project Partners: Armin Curt, University Hospital Balgrist, Spinal Cord Injury Center, In-kind, Zurich, Switzerland
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Catherine Mercier, Center for Interdisciplinary Research in Rehabilitation and Social Integration, University of Laval, FRQS, Hamel, Canada
Soler Dolors, Institut Guttmann, ISCIII, Badalona, Spain

Induction of Reactive Neural Stem Cells by Traumatic Brain Injury in the Adult Hippocampus (REACT NSCs)

Traumatic brain injury (TBI) is a major health problem affecting more than 8 million European and becoming a challenge for the health systems. Patients affected by TBI show serious neurological disorders such as decision-making and memory deficits, depression or aggressive behavior. Several of the important brain functions affected by TBI depend on the hippocampus, a brain structure very important for memory and learning that is highly vulnerable to this kind of injury. After an episode of TBI, the hippocampus suffers atrophy and alterations in synaptic transmissions. In addition, adult hippocampal neurogenesis, the generation of new neurons from neural stem cells (NSCs), a process involved in memory, learning and control of anxiety, is impaired. We hypothesize that TBI induces long-term changes in both NSCs and newborn neurons subsequently impairing hippocampal and brain functioning.

This project highlights the importance of considering NSCs and new neurons as novel targets in developing innovative strategic therapies against brain damage. We aim to understand what particular changes are induced in NSCs and newborn neurons by TBI, and what is the actual impact on brain functioning and behavior of these changes. Then, we will be able to preserve the properties of NSCs and newborn neurons to fight against the neurogenesis-related symptoms of TBI, and thus contributing to improve the quality of life of millions of TBI patients worldwide.

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Repetitive Subconcussive Head Impacts – Brain Alterations and Clinical Consequences (RepImpact)

Concussion occurs from an impact to the head that results in rotation and acceleration forces that stretch the brain tissue. It is a very common injury that affects millions of people every year worldwide. The harmful long-term effects that range from chronic cognitive symptoms to progressive neurodegenerative diseases are now acknowledged. However, even more common than concussions are subconcussive blows to the head, which usually don't result in acute symptoms. Subconcussive blows to the head are observed in millions of people who participate in sports, who are in the military service, or who experience medical conditions such as head banging in children with autism. Because there is often no evidence of immediate clinical symptoms, subconcussive blows to the head are generally considered to be harmless among athletes, parents, coaches, and even physicians.

Until recently, technical limitations have made it nearly impossible to detect subtle brain alterations following repetitive subconcussive brain trauma. Using highly sensitive neuroimaging techniques, we have now demonstrated for the first time alterations in the brain's microstructure in soccer players who are at high exposure to repetitive subconcussive impacts. This finding is not only very alarming given the more than 250 million soccer players worldwide, but, and most importantly, it suggests that even repetitive subconcussive blows to the head may lead to long-term alterations of the brain's structure and function.

The overarching aim of this project is to detect and to characterize alterations in the brain's structure, function and connectivity due to exposure to repetitive subconcussive brain trauma and to identify the role of risk factors. We propose a multidisciplinary (e.g., neuroradiologists, computer scientists, neuroscientists, physicists), longitudinal study, which follows young professional youth soccer players over time, and uses cutting-edge neuroimaging and biochemical techniques. By focusing on soccer as an example of a sport where subconcussive blows are commonly observed, we can begin to understand the risks of repetitive subconcussive blows to the head, and, most importantly, we can begin to understand which factors determine recovery versus those factors that lead to persistent symptoms, cognitive impairments, and brain alterations. The results of this project will dramatically change our understanding of the effects of subconcussive brain trauma and it will lead to a new understanding of underlying causes and risk factors. This knowledge will, in turn, lead to new horizons of research for the early diagnosis, treatment, and prevention of long-term consequences of brain injury, and thus change the landscape of global health.

Project Coordinator: Inga Koerte, Ludwig-Maximilians-Universität München, Klinik und Poliklinik für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie, BMBF, München, Germany

Project Partners: Stephan Swinnen, K. U. Leuven, Onderzoeksgroep Bewegingscontrole en Neuroplasticiteit, Faculteit Bewegings- en Revalidatiewetenschappen, Groep Biomedische Wetenschappen, FWO, Heverlee, Belgium
Nir Sochen, Department of Applied Mathematics, Tel Aviv University, MOH, Tel Aviv, Israel
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Peter Filipcik, Institute of Neuroimmunology, Slovak Academy of Science, SAS, Bratislava, Slovakia
Alexander Leemans, PROVIDI Lab, Image Sciences Institute, University Medical Center Utrecht, NWO, Utrecht, The Netherlands

Identification of novel bioactive mediators of tissue scarring, inflammation and extracellular matrix remodeling after spinal cord injury (SCI-NET)

Spinal cord injury (SCI) can have a devastating impact on the life of affected individuals. It is usually the result of severe trauma following road traffic accidents, occupational and sporting accidents and acts of violence. SCI often results in partial or complete paralysis, limiting the patients' ability to perform simple daily functions independently (such as eating, washing and dressing) as well as loss of bladder, bowel and sexual function. Despite this, there are still no adequate therapies for SCI. Pathologically, SCI is characterized by chronic inflammation at the site of injury and tissue damage that does not heal or regenerate. The lack of healing causes drastic changes in the tissue structure, which becomes fibrotic scar tissue.

We have recently discovered that there is a link between the molecules (or proteins) involved in tissue scarring and chronic inflammation, and that proteins that make up the scar tissue can cause and amplify inflammation. This leads to a long term inflammatory reaction and does not allow positive tissue regeneration and healing. Unfortunately, the molecules that are responsible for this problematic response are not yet known and the mechanism is not understood.

Here, our consortium of leading international experts in the field of SCI will collaborate in order to understand this pathological process and will test a therapeutic approach that aims to block this unceasing local inflammation and promote positive wound healing. To do so, we will use rodent animal models that accurately replicate the pathological characteristics of human SCIs and precious clinical human samples from SCI patients. In our pre-clinical animal models we will test the therapeutic approach and identify the molecules and mechanisms that drive inflammation and scarring. The human samples will be used to discover new diagnostic markers of disease and possible therapy targets focusing on the disruption of perpetual inflammation and fibrosis. To maximize our chances for discovery we will use different variations of a high-end technology called proteomics, based on stateof- the-art analytical instruments that can identify and quantify thousands of proteins, the key molecules that make up our tissues and are massively altered after injury.

Our approach is very innovative and we expect to make new discoveries that will change our understanding of the pathology of SCI and processes involved in repairing the spinal cord, and ultimately this data may lead to new therapies for improving functional outcome for spinal injured patients.

Project Coordinator: Elizabeth Bradbury, King's College London, MRC, London, United Kingdom

Project Partners: Samuel David, Research Institute of the McGill University Health Centre, CIHR, Montreal, Quebec, Canada
Jan Schwab, Charité - Universitätsmedizin Berlin, Department of Neurology & Experimental Neurology, BMBF, Berlin, Germany
Ralph Schlapbach, Eidgenössische Technische Hochschule Zürich/Swiss Federal Institute of Technology (ETH Zurich), Functional Genomics Center Zurich, SNSF, Zurich, Switzerland

Spinal Cord Injury-induced Systemic Maladaptive Immune Response and Autoimmunity to Central Nervous System Antigens - European Network Approach (SILENCE)

Traumatic spinal cord injury represents a lifelong disease, for which there is no consistent therapy for restoration of lost neurological function. The variability of the limited natural recovery after spinal cord injury is insufficiently explained. A maladaptive systemic immune response (MSIR) occurs early after spinal cord injury and is characterized by at least two hallmarks: i) an emerging immune reaction against components of the central nervous system and ii) an immune deficiency, which is related to central nervous system injury.

In this project, we use specimen and data collections from recent and upcoming trials conducted for characterization of the MSIR after spinal cord injury and combine them with experimental methods. We address the questions whether
i) autoimmunity against spinal cord and brain tissue is extending over time,
ii) the targets of the autoimmunity are relevant for the function of the central nervous system,
iii) the autoimmunity can be linked to clinical outcome of the patients, and
iv) whether autoimmunity is also present after other injuries to the central nervous system such as traumatic brain injury.
An international consortium of experts in different research fields such as the immune system, proteins, neurological injuries and disease mechanisms as well as diagnosis, treatment and rehabilitation of spinal cord injury will investigate distinct patterns of autoimmunity in experimental as well as clinical studies. The results of these studies can be linked to long-term recovery of the patients' functional abilities such as self-care and walking. Based on data from pilot studies, we will challenge the hypothesis whether patients with poor response to rehabilitative treatment differ from normal rehabilitation responders in terms of distinct autoimmunity patterns. To characterize spinal cord injury patients by the occurrence and severity of the MSIR can be used for the definition of patient subgroups as a basis for the development of new individualized treatment concepts after spinal cord injury

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Giorgio Scivoletto, IRCCS Fondazione S. Lucia, MOH, Rome, Italy

Seeing-Moving-Playing: Early Rehabilitation utilizing visual and vestibular technology following traumatic brain injury (SiMPLyReha)

Traumatic brain injuries (TBI) are among the most commonly occurring injuries internationally.

Dizziness and difficulty with balance and vision may occur following a TBI. Many people recover in the initial weeks following injury, but in some cases symptoms and difficulty functioning continues and may require treatment.

There is little research evaluating the effects of treatment in this area. There is some research showing that balance and vision treatment may help with recovery after a TBI. Thus, the aim of this research program is to bring together an international group of researchers with knowledge in TBI of all types to: 1) Evaluate potential problems with vision, inner ear-eye reflexes and deficits of processing eye information that occur following TBI; and 2) Evaluate treatment programs for individuals with eye and inner ear problems that persist for greater than 10 days following injury. This study will include 465 youth and young adults (aged 6-30 years old) who sustain a TBI of any severity. An initial evaluative phase using the best available technology to evaluate eye and inner ear function will be performed, and compared with typical tests that are used in the clinic. If symptoms and functional problems remain 10 days after injury, participants will be randomly placed into a treatment group (including eye movement, inner ear-eye reflex and attention exercises as per our pilot studies) or a control group (typical rehabilitation).

We will measure success in terms of return to sport (mild TBI), achievement of goals (moderate and severe TBI) and quality of life. It is expected that this program will inform clinical practice and future research leading to a treatment program in TBI that includes multiple components. Ultimately, this program will lead to better health care delivery and decreased public health burden from TBI.

Project Coordinator: Isabelle Gagnon, Research Institute of the McGill University Health Center, CIHR, Westmount, Quebec, Canada

Project Partners: Kathryn Schneider, Sport Injury Prevention Research Centre, CIHR, Calgary, Canada
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Michal Katz-Leurer, Tel Aviv University, CSO-MOH, Tel Aviv, Israel

A New Traumatic Axonal Injury Classification Scheme based on Clinical and Improved MR Imaging Biomarkers (TAI-MRI)

Traumatic injuries to the head can cause differing degrees of damage to the brain, ranging from none to mild, moderate or severe traumatic brain injury (TBI). The management of patients with TBI depends on the severity of the injury and in the diagnostic work-up the primary imaging modality is still CT (computer tomography) in the acute phase. But today we know that CT may only show the "tip of the iceberg" of the actual injuries to the brain following trauma, and in some instances the scan miss injuries altogether. In particular, traumatic axonal injury (TAI) is difficult to detect by CT. In the last decade, different MRI (magnetic resonance imaging) techniques therefore have been increasingly used in the early time period following TBI. This imaging technique can detect TAI, but also other more subtle brain injuries, with a much higher sensitivity than that observed for CT.

In TAI-MRI, we aim to develop a classification system that can better describe severity of TAI and predict the outcome of injuries. The current classification system is based on neuropathological studies from 1980s (looking at the tissue directly in the microscope) and has been extrapolated to classify also injuries on MRI in surviving patients. This classification system has shown limitation in reflecting the actual burden of axonal injuries, and thus its prognostic value is questionable. A classification system that better reflects the distribution of axonal injuries and that also takes into account the prognostic significance of the different TAI lesions would help both doctors and health care professionals as well as patients and their families to understand the effects of brain injury and also what prognosis can be expected during the first months or year. To develop such an important and reliable classification system, researchers from four different countries will collaborate and data from three different studies including almost 1400 patients will be included and analyzed. MRI methods have been continuously developed during the last couple of decades, and new promising technological advances enable us to analyze MRI data in a more automated way. The results of this project should improve the care of patients with TBI in the near future.

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David, Menon, University of Cambridge, Department of Medicine, Division of Anaesthesia, MRC, Cambridge, United Kingdom

Time dependent Remote Alteration after Injury to the Nervous System (TRAINS)

Injury to the brain or the spinal cord results in **long-term functional deficits** in affected patients which mainly affect **sensation** and **motor function**. Traditionally it was believed that these impairments are solely caused by the initial local brain damage. However, an increasing body of evidence now indicates that in addition to the acute local changes also **distant areas of the brain** connected to the primarily injured area are also **critically involved in this process**. The **aim of the current project** is therefore to **unravel the mechanisms** resulting in these remote changes and to **develop novel therapeutic strategies** aimed to prevent long-term functional deficits after CNS injury. This will occur by **establishing a consortium of internationally recognized experts** in the field of brain and spinal cord injury and using **newly developed in vivo and ex vivo CNS imaging technologies** together with state-of-the-art treatment and drug development approaches.

Project Coordinator: Jerome Badaut, CNRS, Institut des Neurosciences Cognitives d'Aquitaine, ANR, Bordeaux, France

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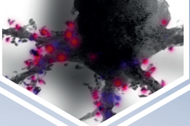
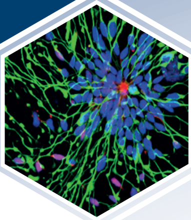
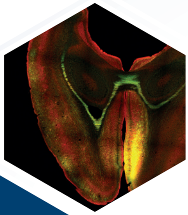

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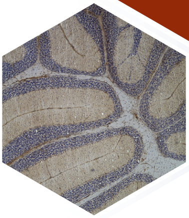
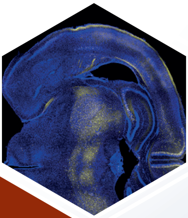
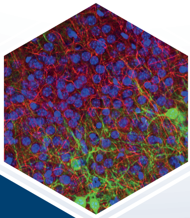
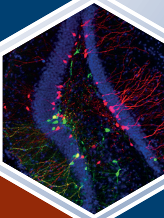

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ACRoBAT

Marine Tessier

Role of NKCC1 and Cl- homeostasis in TBI induced microglia activation in the frontal cortex

Brain trauma triggers a cascade of deleterious events leading to enhanced incidence of drug resistant epilepsies, depression and cognitive dysfunctions. Particularly, a Traumatic Brain Injury (TBI) triggers and imbalance in the functional expression of the chloride transporters NKCC1 and KCC2 in favor of NKCC1 expression suggesting impaired chloride homeostasis. One contribution to post traumatic increased excitability could be the increase of parvalbumin interneuron apoptosis. Our objective is to investigate whether the inflammation caused by trauma is involved in the mechanism leading to these alterations. Using controlled-cortical impact (cci) as experimental model of brain trauma in adult mouse we assess the temporal relations between inflammation and other parameters e.g. social interaction behavior, Grid-EGG over both hemispheres and intracortical multichannel in vivo recordings and FACT analysis of experiments performed in the CX3CR1-EGFP transgenic mice. Using high-density EEG recordings in freely moving mice we found an overall reduction of theta power with some asymmetric reorganization of EEG signals in TBI versus Sham-operated animals. Our preliminary results show that microglial activation is increased in the ipsilateral side at 3, 5- and 7-day post CCI. Treatment with the NKCC1 inhibitor Bumetanide induces phasic temporal changes in microglia activation with different ipsilateral and contralateral profiles that have interesting correlations with a preliminary analysis of the in vivo electrophysiology data as well as behavior. At the poster we will present a comprehensive analysis of the data obtained.

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AxonRepair

Veronika Cubinkova

Combined delivery of transcription factors with active alginate to improve the spinal cord injury recovery

Spinal cord injury (SCI) is a serious multicomplex neurological disorder that causes temporary or permanent disability. Spinal cord repair is negatively affected by the loss of the integrity of neurons to regenerate axons, by blocking the transport of pro-regenerative proteins to the lesion site and by the highly repulsive environment. Currently no effective therapy is available for SCI and that is why new therapeutic strategies are necessary. The goal of our project is to study synergy between enhancement of the intrinsic growth capacity of injured CNS neurons and environmental stimulation of axon regeneration. The strategy is to create a combinatory treatment, with overexpression of key pair of transcriptional factors with an active alginate releasing growth factors in the rat model of traumatic SCI.

Firstly, we injected the lumbar L4 and L5 dorsal root ganglions (DRGs) with the AAV5 with fluorescent protein (GFP) and we observed efficient transduction in corresponding DRGs. Secondly, we have involved diffusion tensor imaging that is more sensitive than conventional MRI in detecting SCI and predicting the severity of injury. DTI parameters including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated, and diffusion tensor tractography (DTT) in the injury site was reconstructed. Our final study will include the combination of the gene therapy (via DRGs) and alginate (at the lesion site) with DTT in balloon compression SCI model in order to improve the regenerative capacity of axons. Acknowledgements: supported by ERANET- AxonRepair and APVV 15-0613.

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AxonRepair

Matthew Mason

Expressing transcription factors combinations to drive regeneration-associated gene expression and promote axon regeneration

A complex gene expression program that drives axon regeneration is activated by axotomy in dorsal root ganglion neurons. The transcriptional control of this program is not well understood although many transcription factors are up-regulated. Using bioinformatics to identify key TFs followed by combinatorial in vitro screening, we identified the combinations KLF7/MEF2 and KLF7/MEF2/ATF3 as potent promoters of neurite outgrowth in vitro. In vivo, in a dorsal column spinal cord injury model, overexpression of KLF7/MEF2 in DRG neurons, but not KLF7/MEF2/ATF3, promoted significant functional recovery, sprouting at the lesion site, and reduced retraction. Both groups induced collateral sprouting in the caudal intact spinal cord. To further understand the actions of these TF combinations, we carried out a gene expression profiling study. AAV vectors expressing each TF with a unique fluorophore were delivered to the DRG and using laser dissection microscopy we selectively dissected large diameter neurons expressing individual TFs or the above combinations of 2 or 3 TFs. These samples were processed for RNASeq. In parallel we also generated gene expression profiles of axotomised large diameter DRG neurons to compare TF-induced gene expression with the regeneration-associated gene (RAG) program. Fold-change correlation analysis and Weighted Gene Co-expression Network Analysis (WGCNA) showed that all TFs/combinations except MEF2 by itself induced axotomy-like changes in gene expression, in 40% of strongly regulated RAGs. Furthermore a large number of weakly regulated RAGs are specifically induced by KLF7/MEF2. This dataset will allow the further development of TF combinations to drive RAG expression.

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AxonRepair

Bart Nieuwenhuis

Phosphoinositide 3-kinases promote axon regeneration in the central nervous system

Traumatic injury of the central nervous system (CNS) has devastating consequences because adult axons do not regenerate. We hypothesize that a developmental decline of phosphoinositide lipids in the axon contributes to restricted regeneration. The objective of this study is to explore whether overexpression of phosphoinositide 3-kinases (PI3K), which synthesize the phosphoinositide lipid PIP3, can stimulate axon regeneration. Immunocytochemistry revealed that the PIP3 levels in the soma and growth cone are significantly lower in maturing neurons (17 days in vitro, DIV) compared to developing cortical neurons (3 DIV). Expression of constitutively activated PI3K increased axonal growth in developing neurons, and overexpression in matured neurons resulted in more complex dendritic morphology and doubling of the soma size. As expected, PI3K increased PIP3 signaling in the transfected neurons. Laser axotomy was used to investigate axon regeneration in vitro. Mature cortical neurons had a limited capacity for axon regeneration and expression of PI3Ks increased the success rate of regeneration. We recently investigated whether PI3K promotes regeneration after optic nerve crush in vivo. Activation of PI3K resulted in significantly increased axon regeneration beyond the injury site compared to controls. In conclusion, mature neurons have little axonal PIP3 signaling which contributes to the failure of axon regeneration. Expression of PI3Ks restores PIP3 signaling and promotes axon growth and regeneration. We are currently investigating the effect of PI3K on axonal transport of regeneration-associated receptors as potential mechanism for regeneration.

B. Nieuwenhuis[1,2]; R. Evans[1]; C.S. Pearson[1]; A.C. Barber[1]; J. Fuchs[3]; B.J. Eickholt[3]; K.R. Martin [1]; R. Ev [1]; J.W. Fawcett [1,4]

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AxonRepair

Veselina Petrova

Protrudin enhances axon regeneration through multiple mechanisms

One reason why adult CNS axons have poor regenerative capabilities is that a developmental change occurs where growth-promoting molecules such as integrins become excluded from axons. Integrins are normally transported along axons in Rab11-positive recycling endosomes by motor proteins/adaptor complexes. However, this transport decreases with maturation leading to a regenerative capacity decline. Protrudin, a membrane-associated protein, when phosphorylated, preferentially binds to Rab11-GDP, an association required for neurite outgrowth and for anterograde movement. We hypothesised that increasing the phospho-protrudin/Rab11 interaction would result in anterograde transport of growth-promoting molecules to the tip of injured axons enabling regeneration of primary cortical neurons after laser axotomy. To test this, two phosphomimetic forms of protrudin were created at phosphorylation sites implicated in its association with Rab11. We found that both constitutively phosphorylated protrudin forms and also wild-type protrudin increased the proportion of regenerating axons compared to control. Live-cell imaging experiments confirmed that the increase in regenerative capacity is likely a result of increased anterograde transport of integrins. In order to unpick protrudin's mechanisms of action on regeneration, five mutants were tested for their effects on regeneration - each targeting a specific region of the protein important for its involvement in various molecular pathways. Protrudin was found to promote regeneration through multiple mechanisms, some of which, such as ER function have not previously been associated with axon regeneration. Protrudin's ability to promote regeneration was also confirmed in vivo in a mouse model optic nerve crush.

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BIO-AX TBI

Adriano Bernini

Safety and feasibility of an advanced combined brain-blood-MRI approach to monitor post-traumatic axonal damage in patients with traumatic brain injury.

Introduction: We describe a novel approach that combines bedside brain tissue interstitial (BTI) and blood biomarkers' sampling with advanced MRI imaging, to monitor axonal injury in patients with TBI.

Methods: Advanced brain monitoring consisted of intra-cerebral microdialysis, using specifically conceived large (100 KDa) cut-off cerebral microdialysis catheter (CMA 71, MDialysis AB, Stockholm, Sweden; perfusion rate 0.3 μL/min, using newly available Dextran-containing fluid to maximize protein recovery). Hourly assessment of regional BTI biomarkers of axonal injury, including Tau and Neurofilament (NFL) proteins, was performed at the patient bedside during the early phase of TBI (first 7 days). Patients underwent simultaneous paired blood tau/NFL sampling, and repeated advanced diffusion tensor magnetic resonance imaging (10 days-6 weeks; 6 months; 12 months after TBI) for longitudinal axonal injury analysis.

Results: A total of 21 TBI patients (3 females and 18 males) admitted to the Department of Intensive care medicine, Lausanne University Hospital, was included over a 6-months recruitment period; 17 had advanced MRI and blood sampling, and 4 comatose TBI patients had complete MRI-blood-brain assessment. Longitudinal MRI follow-up was completed in all six subjects. No complications were reported related to BTI monitoring; one patient needed repetition of the early phase advanced MRI because of agitation during the first procedure.

Conclusions: We conclude that a novel approach for combined brain-blood-MRI tracking of post-traumatic axonal injury in humans is safe and feasible. Our current recruitment rate should provide necessary information to advance the knowledge of post-traumatic axonal injury in the near future.

A. Bernini[1]; S. Abed-Maillard[1]; JP. Miroz[1]; S. Magnoni[2]; G. Bertolini[2]; H. Zetterberg[3]; D. Sharp[3]; M. Oddo[1]
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BIO-AX-TBI

Elena Garbero

BIO-AX-TBI follow-up protocol: the conceptual framework

The BIO-AX-TBI follow-up protocol was developed to assess outcomes of patients with moderate-to-severe traumatic brain injury (TBI) admitted to critical care. For the sake of feasibility, the package was designed to be easily administered by attending physicians and/or nurses, and to be relatively brief - bearing in mind staff time constraints and TBI patients' reduced capacity for concentration. With a view to sustainability, the protocol was conceived to eventually be introduced into routine practice since it can add significant value to clinical care delivery, adding a human element and helping to personalise the TBI-patient care pathway. The package was modelled on the WHO/ICIDH concepts of impairment (temporary or permanent loss or abnormality of a body structure or function, whether physiological or psychological), disability (loss of functional capacity resulting from impairment), handicap/participation (sociocultural consequences of an impairment or disability that restrict or prevent the fulfilment of a role considered normal), and quality of life (self-perceived morbidity in relation to own goals, expectations, standards and concerns). The approach to patient follow-up is holistic. Patients are followed-up in the short- and medium-term (at 6 months by telephone interview, at 6 and 12 months in the outpatient setting), and over the longer term using a remote internet-based system at home. Outcome assessment focuses on brief objective measures of structural and functional impairment (motor, cognitive and behavioural), administrable by non-experts. Patients' subjective view of participation and quality-of-life are broadly evaluated by the QOLIBRI and Glasgow Outcome Scale Extended, also used to subdivide patients into outcome categories.

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BIO-AX-TBI

Amanda Heslegrave

Diagnostic and prognostic fluid based biomarkers for traumatic brain injury.

Diagnostic and prognostic fluid based biomarkers for traumatic brain injury (TBI) remain a major unmet clinical need where intense research is being conducted. The presentation will give an update on the literature on fluid biomarkers for neuronal axonal, oligodendrocytic, astroglial and blood-brain barrier injury, as well as markers for neuroinflammation and metabolic dysregulation, in. The context of TBI, post concussion syndrome and chronic traumatic encephalopathy. We will also discuss technical and standardisation issues and potential pathways to advance the most promising biomarker candidates into clinical laboratory practice.

A. Heslegrave[1]; H. Zetterberg[2]

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BIO-AX-TBI

Federico Moro

Harmonization of the magnetic resonance imaging protocol in the BIOAXTBI study

Aim: To harmonize the MRI protocols across scanners at the hospitals participating in the BIO-AX-TBI study.

Methods: 7 MRI scans are used in the study, 4 of them are 3T (3 Siemens and 1 Philips) and 3 are 1.5 T (1 Siemens, 1 Philips and 1 GE). The MRI protocol includes: 3D T1 weighted images (3D-T1WI), diffusion tensor imaging (DTI), resting state fMRI (rsfMRI), FLAIR and susceptibility weighted images. Two centers have also advanced sequences in their protocol: Neurite Orientation Dispersion and Density Imaging (NODDI) and MP2RAGE. Two traveling volunteers and a n-tridecane phantom were used to compared scan characteristics. The variability of DTI data were assessed calculating the coefficient of variation (CoV) of the mean fractional anisotropy (FA) values in selected white matter regions of interest (ROIs).

Results: The protocols were successfully tested in all centers. The voxel sizes of the 3D-T1WI (1x1x1 mm), rsfMRI (3x3x3 mm), and DTI (2x2x2 mm) were harmonized across centers. In all centers DTI sequences have the same b-value (1000 s/mm2) and 64 diffusion directions. For both volunteers the CoV of the mean FA values in all ROIs were always below 5%. In each center one n-tridecane phantom was leaved for longitudinally assessment of the DTI sequence.

Conclusions: In order to successfully use medical imaging biomarkers is crucial to encompass the instrumentation differences to provide reproducible measurements. Despite the great variability of the MRI scans used in our study these results suggest the feasibility of standardizing imaging parameters in a multicentric study.

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BIO-AX-TBI

Karl Zimmerman

A multicentre analysis of diffusion tensor imaging and blood biomarkers of axonal injury after traumatic brain injury (TBI)

Aims: to investigate the utility of advanced diffusion MRI measures and blood based biomarkers in detecting axonal injury after TBI in a multicentre study.

Methods: Diffusion-weighted volumes were acquired using a 64-direction protocol (64 slices, 2mm isotropic, TR = 9500ms, TE = 103ms, b-value = 1000mm2.s-1) in 6 centres; Imperial College (London), CHUV (Lausanne), Policlinco (Milan), Niguarda (Milan), Careggi (Florence) and UMC (Ljubiana). Four non-diffusion weighted images were also acquired (b-value = 0mm2.s-1). Diffusion data are being acquired at 2 timepoints; 10 days-6 weeks and 6 months after injury. Diffusion weighted imaging will be pre-processed following the DTIFIT pipeline, and images co-registered and aligned using the DTITK toolkit. Fractional anisotropy (FA) values will be extracted in selected regions of interest. Aliquots of plasma will also obtained at the date of MRI and analysed for levels of neurofilament light and other plasma biomarkers. A small sample of controls were also scanned at each center for inter-site comparisons.

Analysis plan: 100 moderate-severe TBI patients are expected to be recruited by the time of presentation. Cross-sectional differences between patients and control FA's in selected regions of interest will be investigated, along with a comparison of FA between hyperacute and acute time points. FA values will also be correlated with plasma neurofilament levels and other plasma biomarkers.

K. Zimmerman[1]; F. Moro [2]; M. Yanez-Lopez[1]; A. Jolly[1]; N. Bourke[1]; EJ. Mallas[1]; N. Graham[1]; D. Sharp[1]
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CERMOD

Thomas Guiho

Epidural and transcutaneous spinal cord stimulation facilitates descending inputs to upper-limb motoneurons

In recent years, interest in spinal cord stimulation (SCS) has been renewed following reports of significant gains of voluntary motor function in spinal cord-injured patients after SCS-assisted rehabilitation. Although not fully elucidated, the mechanism behind this effect is believed to be a potentiation of spinal network excitability that unmasks spared but weakened descending pathways from the brain. We performed a series of transcutaneous and epidural stimulations in anaesthetized, neurologically intact monkeys in order to better characterize SCS and elucidate its impact on corticospinal excitability. Spatial selectivity of SCS was delivered using an 8-contact ring electrode placed epidurally around the cervical spinal cord while electromyogram (EMG) signals were recorded from upper-limb muscles. In separate experiments we delivered transcutaneous stimulation using a high carrier frequency through electrodes on the skin. We assessed the interaction between cortical inputs and subthreshold SCS by delivering intracortical microstimulation to the hand area of primary motor cortex during trains of epidural or transcutaneous SCS (at frequencies of 10, 20, 50 and 100 Hz). Cortical-evoked motor potentials were reliably facilitated by dorsal stimulation, although the effect was more pronounced for epidural versus transcutaneous SCS. Facilitation was maximal for the stimulus frequency of 50 Hz. These results can be explained by a simple model whereby dorsal stimulation activates afferent inputs to motoneurons, raising their excitability, but also presynaptically inhibits subsequent afferent input. We further suggest that the facilitation of cortical-evoked responses could be used to optimise patient-specific stimulation parameters prior to SCS-assisted rehabilitation.

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[1]University of Newcastle

ELPIS

Charles Joussain

Emergence of an abnormal spinal micturition reflex after spinal cord injury (SCI): abolition by silencing of hyper-excited C-fiber bladder afferents by gene therapy to restore continence and micturition.

Neurogenic detrusor overactivity (NDO) is a severe disabling condition caused by SCI, characterized by involuntary bladder contractions, resulting in urinary incontinence, recurrent urinary tract infections and, if untreated, renal failure. We are developing a highly selective and long-lasting bladder deafferentation by molecular neurosurgery to treat NDO by intradetrusor delivery of herpes simplex virus type 1 (HSV1) non-replicative vectors. Preliminary HSV-1-derived amplicon vectors were constructed to assess efficacy of therapeutic transgenes and selectivity of bladder afferents-specific promoters. Amplicons expressing botulinum toxin light chains (BoNT LC) A to F, driven by HCMV promoter, were evaluated in primary cultures of rat embryonic sensory neurons and in organotypic cultures of rat dorsal root ganglia (L6-S1) (DRG). These vectors cleaved their respective SNARE proteins and decreased release of neurotransmitters, though with different potency. Vectors expressing luciferase, driven by various sensory neuron-specific promoters (TRPV1, ASIC3, advillin, CGRP) were assessed for selectivity of expression in organotypic cultures of DRG, GPC (parasympathetic ganglia) and SCG (sympathetic ganglia). All promoters displayed selective expression for DRG, with different levels of efficacy. Based on these data, we selected the best transgenes (BoNT-A and F) and the best promoters (advillin and CGRP) to generate transcription cassettes that were introduced in the LAT region of recombinant defective HSV1 vectors to evaluate selective and long-term therapeutic expression in vivo. These constructions have been already completed, and the vector genomes were sequenced. Further experiments are ongoing to assess functional activity of the vectors in a relevant model of rat NDO.

C. Joussain[1]; A. Aranda Muñoz[1]; O. Le Coz[1]; A. Pichugin[1]; A. Aka[1]; P. Marconi[2]; F. Lim[3]; M. Sicurella[2]; S. Gomez[3]; F. Wandosell[3]; F. Montorsi[2]; F. Giuliano[1]; A. L. Epstein[1]
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hMRIofSCI

Yael Balbastre

Learning brain and neck tissue probability maps from heterogeneous MR images

Voxel-based morphometry (VBM) and quantification (VBQ) enable the study of brain macro- and microstructure by performing voxel-wise statistical analyses of tissue volume and physical properties. This allows investigation of the effect of different variables on an organ's structure, without a priori spatial assumptions. While they have been used to characterise the impact of spinal cord (SC) injury in the brain (Grabher et al., 2015), numerous challenges make VBM and VBQ difficult to extend to the SC itself, e.g., its small size, weak grey/white matter contrast, or ill-adapted coils. Furthermore, most tissue probability maps (TPMs), that encompass prior knowledge about tissue location, lack the neck region and SC.

Recently, Blaiotta et al. (2018) generated TPMs that do include the neck region, enabling the SC to be studied as a whole. While this adds value, these TPMs do not distinguish between spinal grey and white matter, precluding the study of patterns specific to these sub-regions. To address this, we seek to further develop the framework of Blaiotta et al. by incorporating data that better delineate grey and white matter within the SC. Unfortunately, it is rare that high spatial resolution images cover both brain and spine and achieve good contrast throughout. However, it may be possible to bring all of these features together by combining different imaging data into the same framework. Therefore, we propose to extend the probabilistic model so that it may learn population priors from heterogeneous datasets (different contrast and resolution). This will allow us to build brain and neck TPMs from a combination of low-resolution brain scans and high-resolution SC scans, bringing us closer to the goal of objective, voxel-wise analyses in the brain and cord.

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hMRIofSCI

Zsofia Kovacs

Ex vivo validation of SCI-related changes with hMRI and NODDI-DTI in the brain and cervical spinal cord

Histological magnetic resonance imaging (hMRI) has been proposed to provide more specific neuroimaging read-out of spinal cord injury (SCI)-associated changes than the more quantitative (MPM, DTI) and conventional (voxel based morphometry) MRI biomarkers. Applying these sophisticated MRI analytic tools to rodent models of SCI is crucial in order to understand how changes in microstructure and tissue composition affect the biophysical properties and, thus, the generated hMRI maps. To replicate the functionality and morphology of the common form of SCI, incomplete transection of the spinal cord (SC) was performed on the thoracic (T8) level in adult Lewis rats. High-resolution MRI data of ex vivo brain and cervical SC samples have been obtained at a small animal 9.4T MR scanner using a cryogenic RF coil. So far, region-of-interest-based analysis of cervical SC samples revealed significantly lower T1 and T2 signal intensities at the brain stem of injured SC and no difference in the relaxation time constants T1 and T2 and the DTI metrics FA and MD. We will extend the analysis to tissue areas closer to the lesion and the brain. In addition, we will create MPMs using MATLAB tools and analyze diffusion MRI data with novel NODDI-DTI tools. Statistical analysis of these data will be performed in the SPM framework using SPM mouse. We also aim to verify tissue composition and cellular changes in normal and pathological tissue with gold standard histology, immunohistochemistry and chemical element imaging, as well as test the effect of chemical fixation on the measured MRI parameters.

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hMRIofSCI

Sebastian Papazoglou

Testing the validity of the biophysical NODDI-DTI model in SCI

Most clinical studies today using diffusion MRI rely on the DTI model, which is difficult to interpret in terms of underlying microscopic changes. Our model NODDI-DTI (Edwards et al., Front. Neurosci. 2017) provides analytical relations for DTI invariants such as fractional anisotropy (FA) and axial diffusivity (AD) to microscopic features of white matter, such as fibre dispersion tau and neurite density nu. However, the extent to which this simplified biophysical model remains valid in presence of spinal cord injury has not yet been investigated. To approach this question, we revisited previously published data (Brennan et al., NI 2013), including ex vivo histology and DTI in injured mouse spinal cords using NODDI-DTI to predict the measured DTI data from ex vivo histology. We modelled the DTI invariants as a function of neurite density and used a fixed tau = 0.7 (Sepehrband et al. HBM 2015), assuming that changes in DTI were mainly due to Wallerian degeneration. To calculate neurite density from histology, we used the neurofilament staining (NF200) data of Brennan et al. 2013, using intercept and slope as calibration constants with nu = C x NF200 + b. While NODDI-DTI fails to predict the observed AD values, very good agreement between measured and predicted FA was found for nu between 0.4-0.9. This indicates that the model assumptions of NODDI-DTI are invalid for AD, whereas for FA they break down below 0.4. Our results imply that the NODDI-DTI model cannot be applied in SCI without further adjustment of the underlying biophysical model.

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hMRIofSCI

Shubhajit Paul

Ultra high resolution diffusion and anatomical imaging for investigations into spinal cord injury

Understanding mechanisms of and changes due to spinal cord injury calls for non-invasive high-quality measurements of brain microstructure, particularly the cortical spinal tract and somatomotor areas. As a part of the hMRIofSCI consortium we develop novel diffusion weighted imaging (DWI) and quantitative anatomical imaging methods with unprecedented resolution at 7T and on a 3T Connectom MRI (Siemens, Erlangen) equipped with high-performance gradients for maximal DWI quality. We implemented DWI with z-gradient modulated spiral trajectories and through-slice acceleration using simultaneous multi-slice (SMS) to obtain high spatial resolution DWI in both gray and white matter with very short echo-time (25 ms) and acquisition time (based on Herbst et al. 2017, MRM). It is complemented by magnetic field monitoring using a clip-on camera system (Skope, Zurich) and 23-channel flexible surface-coil (Kirilina et al. 2018, ISMRM) for improved signal-to-noise and image quality (0.8 mm). Their use were enabled by newly developed field camera probe-inserts and extension of the scanner patient table. Advanced reconstruction for spiral raw-data integrated with field camera data (Chen et al. 2013, NeuroImage) are currently being developed for high spatial resolution, high quality images, reducing phase errors and artifacts originating from physiological noise. The DWI data will be complemented by quantitative ultra high resolution multi-parameter mapping (MPM) with 400 um resolution acquired at 7T (Trampel et al. 2017, NeuroImage), to obtain additional different information about the underlying microstructure, which will be central to understanding of pathological changes in spinal cord injury.

B. Nieuwenhuis[1,2]; R. Evans[1]; C.S. Pearson[1]; A.C. Barber[1]; J. Fuchs[3]; B.J. Eickholt[3]; K.R. Martin [1]; R. Ev [1]; J.W. Fawcett [1,4]

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hMRIofSCI

Przemyslaw Podgorski

Assessing microstructural damage in areas of atrophy in chronic SCI patients: a prospective cross-sectional study

WP6 started in September 2018 and is currently on track. It's deliverables are planned in 2020. We plan to assess the extent of degeneration in the chronic phase of injury within the brain and cervical cord and also within the lumbar spine below the level of injury. Finally we aim to investigate whether these changes relate to clinical outcome measures of locomotion, neurophysiological measures of myelination and axonal integrity. We have already recruited 20 patients with chronic SCI meeting all criteria and healthy volunteers. We will apply the same hMRI sequences developed in WP1 for brain and cervical spine assessment. In addition we will acquire high-resolution volumetric and dMRI sequences at the level of the lumbar cord. These include T2* weighted structural scan with 0.25x0.25x2.5 mm3 resolution using an optimized multi-echo gradient echo Siemens product sequence (3D MEDIC) for volumetric data and a diffusion tensor imaging sequence at 0.5x0.5x5 mm3 resolution with four multi-directional diffusion tensor imaging scans (cardiac gated) for microstructural data above, at and below the level of spinal cord injury. We will use the same voxelbased approach developed in WP1&3 to assess spinal cord grey and white matter changes above, at and below the level of injury. To identify relationships between the level of impairment and magnitude of electrophysiological measures of myelin and axon integrity in patients with the amount structural changes of qMRI sensitive readouts of myelin and axon density and g-ratio, we will use regression models.

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hMRIofSCI

Maryam Seif

Outcome prediction in acute SCI using hMRI biomarkers

Traumatic spinal cord injury (SCI) leads to permanent disability due to the mechanical disruption of major spinal pathways. After traumatic SCI, extensive upstream morphometric (cord and brain atrophy) changes occur throughout the first year post-injury, the magnitude relating to the degree of disability (Freund et al 2013). However, the pathophysiological processes underlying the observed atrophic changes and its relation to the severity of injury and clinical impairment are not yet well understood. In this work package thus, we will use hMRI of white matter of the spinal pathways and grey matter in the sensorimotor cortices to improve our understanding of the pathophysiological processes leading to cord and brain atrophy in acute SCI. Within a pilot study, we applied high-resolution hMRI in SCI to reveal the immediate extent of trauma-induced neurodegenerative changes of spinal tracts rostral to the lesion and determine the predictive clinical value of hMRI biomarkers following injury. A high-resolution diffusion-MRI (David et al 2017) and a T2*-weighted scan were acquired at the cervical cord in 13 acute SCI and 13 controls to predict clinical outcome at one-year post-injury. Patients were clinically assessed based on ISNCSCI protocol one-year post-injury.

At baseline, the cord- (by -7%, $p<0.04$), white matter area (by -9%, $p<0.03$), and fractional-anisotropy (FA) (by -5%, $p=0.055$) decreased in SCI patients compared with healthy controls. FA and Axial-Diffusivity are associated with sensorimotor outcomes at one year ($R=0.69$, $p<0.05$). Our findings suggest neurodegenerative changes rostral to the lesion occur early in SCI and hMRI biomarkers at baseline are predictive of recovery.

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ICON-TBI

Erik Fraunberger

Chronic Alterations of Cerebellar Inflammatory Networks and Glial Cell Activation in a Rat Model of Pediatric Mild Traumatic Brain Injury

Post-TBI inflammation is a well-documented but poorly understood phenomenon, especially at chronic time points and in brain areas other than the cortex. The cerebellum, important for motor and cognitive functioning, represents an area of the brain affected by TBI that is seldom evaluated despite its connection to chronic deficits after injury. In the context of TBI and inflammation, studies tend to be done using severe TBI in adult males, to the detriment of applicability to pediatric and/or mild, closed head TBI. Our study addresses this gap by profiling cerebellar inflammation over time in the juvenile male and female rat brain following a mild, closed head-weight drop injury. At 24h, 72h, 7d, and 21d post-mTBI, animals were subjected to behavioural testing to evaluate TBI effects over time. Alongside behavioural assessments, inflammatory profiling using multiplex ELISA revealed increased inflammatory markers, including CXCL1, IL-5, and VEGF, in the blood plasma at 24h/72h and in the cerebellum at 72h post-injury. Network analysis of ELISA data also showed increased dependency between multiple mediators at all time points, emphasizing the persistent changes to inflammatory networks after mTBI. Transcripts of microglia activation markers, including Iba1 and CX3CR1, increased at 7d post-injury in both sexes with a large increase in females at 21d, suggesting chronic activation of immune cells in the cerebellum up to 3 weeks post-mTBI. Characterizing the evolution of cerebellar inflammation in pediatric mTBI provides insight into potential mechanisms of chronic changes that could modify susceptibility to accelerated neurodegeneration and impairment over time.

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ICON-TBI

Edward Needham

Autoantibody Responses Following Traumatic Brain Injury

Introduction Traumatic Brain Injury (TBI) is a leading cause of death and disability. Significant unexplained heterogeneity in outcome occurs, with prognostic models accounting for only around one third of variation. Differential immunological responses to TBI represent a potentially therapeutically modifiable factor. We hypothesise that a proportion of TBI patients develop autoantibodies to brain antigens, which associate with poor outcome. Methods We developed a protein microarray to detect autoantibodies against brain antigens in TBI patients at day 0, day 7 and 6-9 months post-injury, and compared immunological responses with clinical outcome. Results The development of IgM and IgG autoantibodies was seen in around two-thirds of patients by day 7, and a similar proportion of patients demonstrated persisting IgG autoantibodies at 6-9 months. There was marked inter-individual variation, with a distinct subset demonstrating a tendency to autoimmunity. The presence of both IgM and IgG autoantibodies provided significant independent prognostic predictive value when combined in a multivariable regression model with the IMPACT prognostic score, increasing R2 against GOSE from 0.14 (IMPACT alone) to 0.404 (combined model; $p = 0.02$). IgG responses appear to be driven largely by magnitude of protein release (GFAP autoantibody vs GFAP protein: $R2 = 0.812$, $p = < 0.0001$). IgG Responses are markedly attenuated by treatment with recombinant IL1RA (mean IgG hits 0.1 vs 0.6; $p = 0.04$). Conclusions Autoantibodies to brain antigens develop after TBI in a subset of patients and appear to correlate with poor outcome. Their development can be arrested using IL1RA.

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ICON-TBI

Gloria Vegliante

Aged mice have increased susceptibility to traumatic brain injury associated with white matter damages

Aims: to assess the susceptibility of aged and young mice to different degrees of traumatic brain injury (TBI) by behavioural and MRI studies.

Methods: young adult (8 weeks old) and aged (18 months old) mice were subjected to sham, mild (m) or severe (s) TBI by controlled cortical impact. Sensorimotor deficits were longitudinally assessed by simple neuroassessment of asymmetric impairment (SNAP) up to 6 weeks post-TBI. Contusion volume was measured using T2-weighted MRI. White-matter (WM) integrity was evaluated by diffusion tensor imaging (DTI).

Results: Aged TBI mice showed greater sensorimotor deficits than young mice at all time points, with mTBI in the elderly producing a degree of functional impairment similar to that observed in young sTBI mice. Contusion volume at 6 weeks was 11.4±3.4 mm3 and 18.4±4.4 mm3 after mTBI and sTBI respectively, with no age effect. A high correlation between SNAP score at 1 week and contusion volume in both young (r2=0.74) and aged (r2=0.43) mice was observed. In contrast SNAP score at 6 weeks only correlated with contusion volume in aged mice (r2=0.69), suggesting a higher recovery potential in the young. DTI analysis showed a decreased fractional anisotropy in the ipsi-lateral (il) corpus callosum and external capsule (il-EC) with an injury-severity dependent effect both in young and aged mice. Interestingly axial, radial and mean diffusivity in the il-EC were increased only in aged sTBI mice.

Conclusions: aged TBI mice show higher WM damage with ongoing micro-structural abnormalities possibly contributing to a worse functional outcome compared to young mice

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LEAP

Agata Ciechanowska

Comparisons of Changes in mRNA Level of Some Interleukins in Brain Structures (Cortex, Hippocampus, Thalamus Andstriatum) induced by Traumatic Brain Injury in Mice

Traumatic brain injury (TBI) - affliction caused by rapid violation of central nervous system is very dangerous and deadly – it's kind of epidemic incident nowadays. Management is hard, expensive and insufficient. Inflammatory reaction initiated and regulated by interleukins may play some role in TBI progression. We have analyzed the pattern of proinflammatory interleukins expression (IL-1, IL-18, IL-6) in mouse model of TBI at day 4th and 7th after injury. mRNA levels were measured using qRT-PCR in four brain structures (cortex, hippocampus, thalamus and striatum) which are one of the most damaged in disease progression. The level of mRNA of all investigated interleukins was elevated in hippocampus and striatum. We observed strong up-regulation of IL-1, IL-6 mRNA but not IL-18, in cortex. In thalamus only level of IL-1 mRNA was importantly increased. Expression of tested factors have different, time- and structure-dependent pattern of activation. It prove important possibility to control TBI proceeding by inhibition these well known, important proinflammatory factors or by blocking their receptors. To summarize the observed growth of IL-1, IL-18, and IL-6 after TBI make them an attractive targets for future therapies. Acknowledgments: Supported by the NCBiR grant ERA-NET NEURON-COFUND/1/LEAP/15/17

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LEAP

Stefania Ippati

Identification of peripheral biomarkers following brain injury in mice

Traumatic brain injury (TBI) has been recognized as one of the major public health issues that leads to devastating neurological disability. TBI causes persistent and progressive symptoms and currently, reliable diagnostic methods such as biomarkers are lacking. Animals models of TBI have been developed to replicate the various aspects of human TBI, to better understand the underlying pathophysiology and to explore new therapeutic agents. Therefore, validation of TBI biomarkers in mice represents an essential tool for the development and testing of new treatments that can be translated into clinic. Here we evaluate the use of different innate immunity and brain-derived markers found in mouse plasma applied to the controlled cortical impact (CCI) injury mouse model, that mimics several pathophysiological aspects of TBI found in humans. We found an increase in the acute post-injury phase in the circulating levels of the SNC-derived glial fibrillary protein (GFAP), measured by ELISA. Newly, we found a time dependent increase at the protein levels, measured by Western Blot (WB) analysis, of the complement components C4 and C3 in TBI mouse plasma with a peak at 48 hours. Other components of the classic and lectin pathway of complement such as C1q, MBL-A and MBL-C showed specific changes over time. Furthermore, we measured the protein plasma levels by WB, of the anti-inflammatory lectin-like shedded protein domain (sTM) of thrombomodulin (TM), founding a significant reduction persistently at 1 week after brain trauma. Finally, our results provide an outline of different potential biomarkers in mice following traumatic brain injury, which may represent novel indicators of assessment of brain damage and therapeutic treatment in patients.

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LEAP

Katarzyna Pawlik

Comparisons of changes in mRNA level of some chemokines in brain structures (cortex, hippocampus, thalamus and striatum) induced by Traumatic Brain Injury in mice

Every year, millions of people suffer from various forms of Traumatic Brain Injury (TBI) and there for a new approaches holding potential for novel therapies are urgently needed. TBI is a damage caused by external factors like accidents, violence or sports injuries. There is still a problem with effective recognition and treatment. Within minutes following the primary, biomechanical, irreversible trauma, TBI induces the activation of several injurious cascades that develop over time and account for the majority of brain damage. In our opinion, chemokines seems to play also an important role in TBI progression. Therefore, in our research we analyzed the pattern of expression of selected chemokines: CCL2, CCL9, XCL1 in murine pneumatic model of TBI on the day 4th and 7th after injury. mRNA was measured in structures of: cortex, striatum, hippocampus and thalamus by using qRT-PCR technique. We observed strong up-regulation of CCL2 and CCL9 mRNA in all subjected brain areas. Pattern of XCL1 mRNA level was differential - elevated only at 4th day (cortex, striatum) or at 7th day (thalamus). In hippocampus we did not observe expression of XCL1. To sum up, we noticed that expression of chemokines is simultaneously structure-and time-dependent. After TBI there is significant increase of expression of CCL2, CCL9 and XCL1 that is why this chemokines seems to be interesting targets for future investigations. Acknowledgments: Supported by the NCBiR grant ERA-NET NEURON-COFUND/1/LEAP/15/17.

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LEAP

Jordi Pedragosa

Role of MBL in Neutrophil Infiltration after TBI

Questions: Traumatic Brain Injury (TBI) is a leading cause of death and permanent disability worldwide. Following the primary biomechanical damage, leukocyte infiltration and the complement cascade are recognized as critical mechanisms involved in secondary brain damage. Several studies show that the Lectin Pathway (LP) is activated in brain ischemia and pharmacological targeting of mannose-binding lectin (MBL) is protective. Stroke patients carrying genetic MBL deficiency present smaller infarctions and better outcomes. The objective of this study is to investigate the involvement of LP in the inflammatory response in a mouse model of TBI. For comparative purposes we used a model of cerebral ischemia. We focused on the innate immune response leaded by neutrophil infiltration to the damaged brain tissue.

Methods: Wild-type mice and MBL-deficient were subjected to controlled cortical impact as a model of TBI, or permanent middle cerebral artery occlusion for induction of ischemia. Paraffin and cryostat brain sections were obtained and specific staining for neutrophils was carried out at different time points after brain injury. Cell counting was performed with a stereological microscope. We studied neutrophil infiltration, specific location in vascular or parenchymal compartments, and studied signs of formation of neutrophil extracellular traps.

Results: MBL-deficient mice show reduced tromboinflammation and better outcomes after ischemia. Both stroke and TBI caused neutrophil infiltration to the injured brain tissue. Neutrophil infiltration was reduced in MBL-deficient mice versus wild-type mice after ischemia, and we are evaluating the results for TBI. The results support that MBL promotes neutrophil infiltration after acute brain injury.

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LEAP

Katarzyna Popiolek-Barczyk

Time-dependent changes in cerebral C1qa and Ptx3 mRNA level induced by Traumatic Brain Injury in mice

Traumatic brain injury (TBI) is a complex disease with multifaceted pathogenesis. An essential contributor to the secondary injury induced by TBI is an inflammatory reaction, where the complement system plays a substantial role. In our preclinical studies we have used an animal model of TBI, controlled cortical impact (CCI), which accurately reflects neurological and histopathological changes in humans. Using RT-qPCR we analyzed the expression of genes (elements of the classic and lectin complement pathway)in four brain structures (cortex, hippocampus, thalamus and striatum) of mouse exposed to CCI. The tissues were collected on day 4th and 7th after TBI and from control (sham-operated) animals. We observed strong expression of the classical pathway of complement activation initiator, C1qa molecule, both on day 4th and 7th after damage. We showed a statistically significant decrease in C1qa expression on day 7th compared to day 4th in cortex and striatum. Examination of pentraxin 3 (Ptx3), a molecules related to activation of the lectin complement pathway, showed an increase of expression at both tested time points in cortex, hippocampus and striatum, in thalamus only at day 4th. In cortex and striatum on day 7th Ptx3 expression was significantly reduced compared to day 4th. To summarize, our preliminary data showed strong activation of members of classic and lectin complement pathways, which expression have similar pattern of activation. Our results suggest that the complement system plays an important role after brain damage, therefore, further studies should be continued.

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Micronet

Jacob Kjell

Remodeling of the brain extracellular matrix after traumatic brain injury

CNS trauma may cause both early and persistent changes to the extracellular environment. Changes in the extracellular matrix (ECM) are known to govern plasticity and affect recovery. We have recently identified a key role of invading monocytes using the CCR2-/- mouse model in promoting scar formation and inhibiting reactive astrocyte proliferation. Here we investigate the ECM changes at the basis of this effect and compare stab wound injury and blunt-head trauma in mice using proteomics. ECM architecture is important to its function and these changes are invisible for protein measurements. Thus, we also used a new proteomics-optimized method to assess various diffusible grades from the entirely un-soluble ECM. We find that some of the early changes in ECM persist and investigating the persistent ECM change in CCR2-/- mice allow us to determine them to be associated to invading monocytes.

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Micronet

Piotr Majka

A computational infrastructure for managing and processing high-resolution 3D imaging datasets

Recent advances in experimental, imaging, and computational techniques have enabled routine acquisition of images of entire brains at cellular resolution resulting in a surge in demand for tools for managing and analyzing voluminous imaging data. Yet, adequate methods are still absent. We present a solution, comprising a data model for efficient storage and retrieval of imaging data, and a pipeline, for intra- and cross-modal registration of whole brain light sheet fluorescence microscopy (LSFM) images as well as images of other modalities. The data model is found on the Hierarchical Data Format 5 (HDF5) which facilitates handling large datasets. The container is capable of storing multichannel acquisitions of a single or multiple individuals, affine and dense spatial transformations, imaging metadata, and can be easily extended to accommodate additional information. Images are organized as a multi-resolution pyramid, enabling rapid access to subsets of image volume at different scales, for instance, for the purpose of atlas-based segmentation, analyzes such as cell counting, or accessing the image with popular 3D image viewers. Further extensions of the infrastructure include machine learning-based methods for image segmentation and object (e.g. cells and axons) detection. The project is supported by ERA-NET NEURON grant from the National Centre for Research and Development (ERA-NET-NEURON/17/2017), and by the G2631 grant from the National Science Center.

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Micronet

Laura Masullo

Light sheet microscopy to study neural circuits in clarified whole-brain samples

A key question in neuroscience research is to understand how neural networks are structurally and functionally organized and connected. In the past decades, the development of novel molecular methods has paved the way to systematic classification of cell types, providing genetic access to different neuronal types for studies of connectivity and neural substrates of behavior. Although the development of molecular and genetic tools applied to neuroscience has been prosperous, there is a need to develop technologies that would allow us to systematically identify and quantitatively analyze neuronal populations at the circuit level within an organism. Recent developments in whole-organ clearing and imaging technologies with single-cell resolution has enabled high resolution fluorescence imaging of large tissue volumes. When combined with selective labelling of genetically defined neuronal populations, these technologies have the potential to establish correspondence between cell types and complete morphology and projection patterns.

Here we established a pipeline of work for whole-brain clarification of adult mouse tissue combined with light sheet fluorescence microscopy imaging. The system allows up to five acquisition channels and it is capable to accommodate an entire clarified brain. The system uses double-sided light sheet illumination for optimal acquisition and mesoscale imaging. Multiple clarification protocols have been tested and we are now deciding a standard, optimal solution for the project; The two alternatives being considered are Cubic and iDisco+. In collaboration with the Wojcik team we have begun optimizing the acquisition procedures in light of the following volumetric reconstruction effort (WP2). Output form this collaborative effort will weigh in favour of one of the two clarification methods. The infrastructure for data storage and transfer is also in progress.

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Micronet

Michael Miller

Primary Somatosensory Parvalbumin Microcircuitry in Motor Recovery After Traumatic Brain Injury

Acute disconnection and degeneration of neuronal circuits after traumatic brain injury leads to the onset of severe motor, sensory and cognitive dysfunctions. Even though spontaneous functional improvements can occur after injury, the extent of recovery remains limited. Furthermore, it is currently unknown how changes in neural circuit connectivity rearrangements and activity lead to functional deficits and recovery. Given that functional contributions of parvalbumin-positive (PV+) neurons are implicated in various types of learning processes including motor learning, we hypothesized that PV+ interneurons similarly contribute to circuit rearrangements and recovery after a traumatic brain injury. Here, we implemented a closed blunt brain trauma model at the forelimb region of the primary somatosensory (S1) cortex of the mouse to study the PV+ circuit functions and rearrangements that underlie motor impairment and recovery after injury using a goal-oriented forelimb pellet-retrieval task. Traumatic brain injury in the S1 cortex causes immediate deficits in forelimb movement followed by a spontaneous, yet limited improvement in motor control. Using mouse genetics, virus-mediated tracing techniques, high-resolution confocal imaging and unbiased three-dimensional kinematic analyses, we are starting to uncover connectivity changes from PV+ interneurons to layer V pyramidal neurons within the S1 cortex that parallels spontaneous motor recovery. Furthermore, this project aims to modulate PV+ neuronal activity to link neurocircuit reconfiguration and functions of a specific neuronal population that contribute to motor recovery in a skilled forelimb task after a closed blunt brain trauma.

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Micronet

Rida Rehman

Large scale signaling architecture reveals translational targets for therapy in blunt Traumatic Brain Injury at acute time point

Traumatic Brain Injury (TBI) is a highly complex pathology involving multiple events occurring simultaneously including, but not limited to, inflammation, blood brain barrier disruption, apoptosis and alterations in neuronal signaling. Most studies targeted individual protein effect limited to single event with little progress in managing the pathology. In order to understand this complexity of signaling proteins and identify therapeutically targetable entry points, we focus on mapping large scale signaling architecture, at therapeutically effective time point, originating from key regulators of multiple signaling events (such as cell proliferation, differentiation, apoptosis); Receptor Tyrosine Kinases (RTKs). Due to cellular specificity of RTKs, understanding their signaling architecture would make them interesting translational therapeutic targets thereby providing control over biologically meaningful modules. We opted for an advanced unbiased approach to explore the spatial and temporal dynamics of different tyrosine kinase receptors in TBI. Initial investigation of temporal activation revealed that most signaling events initiate at 3-hour time point limiting our therapeutic window. Establishing the temporal significance and spatial relevance of the RTKs with therapeutic insight, we did a large scale in-depth analysis of activated signaling precursors at the same time point and prioritized proteins showing significant differences compared to controls to identify distinct signaling modules. We also inhibited therapeutically significant modules in different cell types to explore the changes in the downstream signaling and its effect on cognitive and functional restoration.

R. Rehman; M. Mulaw; F.Roselli

NEURONICHE

Anna Bejrowska

Catecholaminergic components of locomotor recovery induced by intraspinal grafting of embryonic brainstem in adult paraplegic rats

Intraspinal grafting of the embryonic (E14) brainstem area containing serotonergic (5-HT) neurons restores plantar stepping (PS) in paraplegic rats that is mediated by 5-HT2A and 5-HT7 receptors. Here we asked whether neurons of other phenotypes contribute to the recovery. We found a number of catecholaminergic (CA) neurons in the grafts, and 5-HT and CA axons of graft origin innervated different host spinal cord structures. The 5-HT fibers of graft origin innervated areas of the dorsal and ventral horns, central canal and intermediolateral zone. 5-HT fibers were found 20 mm caudal to the graft. The CA fiber distribution was limited to the areas around the central canal and in the intermediolateral zone. The most caudal CA innervation was detected 7 mm below the graft. The spinal cord of control spinal rats without a graft was devoid of any 5-HT and CA innervation. In order to investigate the role of CA innervation we analyzed locomotor performance of control and grafted paraplegic rats after i.p. application of α2-adrenergic receptor agonist (Clonidine) or antagonist (Yohimbine). PS was significantly impaired by Clonidine resulting in a lack of body weight support and hindlimb dragging. Yohimbine increased the regularity and lengthening the episodes of sustained PS. In control spinal rats the application of either drug did not change their limited locomotor performance. Our results indicate that in addition to the undeniable role of 5-HT innervation, CA innervation plays a potent role in locomotor hindlimb movement enhanced by intraspinal grafting of brainstem embryonic tissue in paraplegic rats.

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NEURONICHE

Valeria Hansberg-Pastor

A subpopulation of PDGFRA-Sox10 mouse spinal cord stem cells identified in vitro: a role for Desert hedgehog signalling?

In the adult mice spinal cord (SPC), the central canal harbors a niche of stem cells known as the ependymal zone (EZ). Due to the cell diversity observed in the EZ, the signals that regulate a particular cell fate remain elusive. In this work, we aim to characterize these progenitor cells using the PDGFRA-GFP transgenic mice. FACS analysis of a subventricular zone (SVZ) and spinal cord neurospheres culture shows a 10% of GFP-positive cells. However, sorted GFP-negative cells gain GFP expression after a few days in culture. IF for different oligodendrocyte progenitor cell markers (Olig1/2, Sox10, Nkx2.2, and PDGFRA) show that 80% of the GFP cells are positive, while the Sox10 expressing cells are restricted to the GFP-positive cell population. An Affymetrix transcriptome analysis of spheres grown under proliferation versus differentiation conditions indicates that the expression levels of Olig1/2 and Nkx2.2 are reduced upon differentiation, while PDGFRA increases, and Sox10 is not modified. Remarkably, we found that Desert hedgehog (Dhh) is reduced after differentiation but not Sonic or Indian hedgehog (Shh/Ihh). Dhh was detected by RT-qPCR and IF in the cultured cells. WT spinal cord cells transfected with a plasmid carrying a Gli-binding sequence (GBS-GFP) indicate that a subpopulation of cells has functional Gli1/2 proteins. Also, the number of cells is reduced upon treatment with cyclopamine (10 μM), an inhibitor of the Hedgehog pathway. Our data show that in vitro, a subpopulation of SVZ and spinal cord cells are PDGFRA and Sox10 positive and might respond to Dhh signaling.

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NEURONICHE

Volker Kroehne

Oligodendrocyte progenitor cells (OPCs) and remyelination after injury of the adult zebrafish spinal cord

Adult zebrafish can functionally regenerate the central nervous system, in contrast to mammals. A major component of the loss of axonal function after spinal cord injury (SCI) in mammals is the death of oligodendrocytes and consequent loss of myelin sheaths that are essential for proper axonal signal transduction. Therefore, we decided to study de- and consequent remyelination using the regeneration permissive adult zebrafish spinal cord as a model. Using a spinal cord transection lesion paradigm we find that mature oligodendrocytes and myelin sheaths are lost around the site of injury within 3 days after lesion, followed by a proliferation response of oligodendrocyte precursor cells that results in the reestablishment of the normal myelination pattern. To study the cellular and molecular basis of remyelination we developed a novel, easy-to-use, inexpensive and highly reproducible OPC culture system based on spinal OPCs from adult zebrafish that enables in vitro analysis. Zebrafish OPCs are robust, can easily be purified with high viability and taken into cell culture. This method enables to examine why zebrafish OPCs remyelinate better than their mammalian counterparts, identify cell intrinsic responses, which could lead to pro-proliferating or pro-differentiating strategies, and to test small molecule approaches. Finally, we demonstrate that zebrafish OPCs differentiate into Myelin Basic Protein (MBP)-expressing OLs when co-cultured with human iPSC-derived motor neurons. This shows that the basic mechanisms of oligodendrocyte differentiation are conserved across species. Understanding the mechanisms of remyelination in zebrafish could help to develop novel therapeutic strategies for the diseased or injured human spinal cord.

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RATER-SCI

Charline Dambreville

Recruitment of the corticospinal tract during a complex locomotor task in humans

INTRODUCTION. After incomplete spinal cord lesion, gait control is often compromised and neuropathic pain can develop. New training methods enhancing voluntary drive from motor cortex to the spinal cord might improve current gait rehabilitation and reduce pain. Animal models have shown that corticospinal drive is augmented during complex gait tasks (e.g. ladder walking, obstacle avoidance). The aim of this pilot study was to measure if a complex walking task would lead to similar increases in corticospinal excitability in humans.

METHODS. Sixteen healthy participants walked on a treadmill facing a large screen during regular walking (‘simple’ condition) and while stepping onto virtual targets projected on the screen (‘complex’ condition). To assess corticospinal excitability, motor evoked potentials (MEPs) induced by single pulse transcranial magnetic stimulation during walking were recorded from the tibialis anterior and compared across conditions.

RESULTS. MEP size increased in all participants during the complex task (increase of 93 +/- 72% $p<0.01$). In addition, performance improved between the beginning and end of the test (of the complex task), from 79.7% to 92.6 % target hits. Also, while the last 10 MEPs where smaller than the first 10, they remained significantly above baseline ($p<0.05$).

CONCLUSION. As hypothesized, the complex gait task was associated with a stronger corticospinal drive in healthy participants. This complex gait task is now being tested in individuals with incomplete spinal cord injury to quantify effect size, potential training feasibility, and whether this approach can contribute to improvement in gait and to a decrease in neuropathic pain.

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RATER-SCI

Catherine Jutzeler

Pharmacological Management of Secondary Complications After Spinal Cord Injury - An Observational Study

Background: Spinal cord injury (SCI) is often immediately coupled with various secondary health conditions including infections, spasticity, and the development of neuropathic pain. These conditions necessitate the administration of a range of drugs (e.g., antibiotics, analgesics). To date, a comprehensive evaluation of the drugs administered in the acute phase of SCI is missing.

Objectives: To determine the types of drugs commonly administered, alone or in combination, in the acute phase of SCI.

Methods: We completed a secondary analysis of a cohort of adult patients with traumatic SCI who participated in the multi-centre randomized controlled clinical trial. Concomitant medication use (non-randomized medications), including dosage, timing and reason for administration, was tracked through the duration of the one-year trial. Descriptive statistics (means, percentages, standard deviation, confidence intervals, etc.) were used to describe the drugs administered. Patterns of poly-pharmacy was determined using network analysis.

Results: Of 797 patients included in our analysis (mean age at injury: 34 years; 83% male), 75% were injured at the cervical level. A total of 640 drugs from 49 different drug classes were administered within 90 days after injury. The average number of drugs given to one patient in the first month was 30 [range 1-66]. The highest prevalence was found for analgesics (acetaminophen [92.6%], morphine [75.4%]), coagulants (heparin [68.3%]), and antibiotics (cefazolin [52.4%]). The most frequent drug-combination was acetaminophen and heparin [68.4%]).

Conclusions: Our study reveals important findings regarding the types and prevalence of drugs administered (alone or in combination) to patients sustaining a traumatic SCI.

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REACT NSCs

Pascal Bielefeld

Controlled Cortical Impact Induces a Shift in Hippocampal Neural Stem Cell Fate Leading to Increased (Reactive) Astrogenesis.

Traumatic brain injury (TBI) is associated with long-term cognitive deficits that are often dependent on hippocampal functioning. Even when not directly mechanically affected by the trauma, the hippocampus undergoes atrophy, gliosis and synaptic alterations. Furthermore, neural stem cells (NSCs) in the hippocampus, which are crucial for adult hippocampal neurogenesis, may be affected. Here we aim to identify the effect of cortical TBI on different subpopulations of astrocytes and NSCs. To this aim we make use of the controlled cortical impact (CCI) model of TBI, in combination with a Nestin-GFP NSC reporter mouse line. Our data indicates that TBI affects the hippocampus and its NSCs shortly after a CCI. Severe astrogliosis can be seen in the hippocampus 3 days post CCI, as well as an increase in potentially astrogenic NSC populations, the Type B NSCs and the reactive NSCs. We are currently undertaking single cell RNA sequencing studies to further map the changes in astrocyte and NSC populations after CCI, and to identify potential genetic mechanisms underlying the changes in NSC fate we observed.

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REACT NSCs

Esteve Irene Durá

Traumatic Brain Injury-induced alterations in adult hippocampal neurogenesis

Several important cognitive functions affected by Traumatic Brain Injury (TBI) depend on the hippocampus, where new neurons are born throughout life. Adult hippocampal neurogenesis is a process involved in memory, learning and control of anxiety, cognitive functions which result impaired after TBI. We hypothesize that TBI induces long-term changes in both neural stem cells (NSCs) and newborn neurons, subsequently altering hippocampal and brain functioning. We aim to understand what particular changes at the cellular, molecular an electrophysiological level are induced in NSCs and newborn neurons by TBI using a model of controlled cortical impact (CCI), and what is the behavioral consequences of these changes and their manipulation. NSCs have been the focus of regenerative medicine because of their potential to replenish the neurons lost by injury or disease. We are here proposing and different view that NSCs can be actually contributing to hippocampal dysfunction. Our results suggest that the most affected hippocampal area after TBI is the dorsal blade of the dentate gyrus, where we have observed anatomical anomalies, thickening and a long-lasting- increase in the number of abnormal newborn neurons (enlarged soma and anomalous arborization) with altered migration. In addition we have found that NSCs turn into a reactive-like phenotype, similar to the one induced by seizures. The biological consequences of the TBI-induction of reactive-NSCs is currently under way.

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REACT NSCs

Chris Van den Haute

Viral vectors as a tool for gene transfer

Viral vectors, derived from different families of viruses are an excellent tool to target different cell types. Lentiviral vectors (LV) from lentiviruses and adeno-associated viral vectors (AAV) are commonly used. The integration capacities of LV makes them very useful for gene transfer in dividing cells while high titer AAV vectors are valuable for non-dividing cells in vivo. Larger cloning capacities might favor the choice for LV. We have built up expertise in producing viral vectors overexpressing transgenes or short interfering RNA's to suppress expression. Combining different AAV serotypes with cell-specific promoters allows us to target specific cell populations. However, the choice of the serotype or promoter should be evaluated experimentally. Different AAV serotypes show great differences in transduction efficiency while so-called cell specific promoters might show aspecific expression in a viral vector context. Our research group has experience with more than 10 different AAV serotypes (2/1, 2/2, 2/5, 2/6.2, 2/7, 2/8, 2/9, 2/ShH10, PHP.B and mutants of these serotypes). Combined with a set of universal (CMV, EF1a) and more specific promoter (Synapsin, CaMKII, GFABC1D, MAG, MBP, TH, somatostatin, DLX) we have a wide portfolio of viral vectors to generate cellular or animal models for different research questions.

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RepImpact

Alberto De Luca

Acquisition and automated processing of a multi-modal MRI protocol to investigate the effect of repetitive head impacts on the brain.

Repetitive head impacts (RHI) in contact sports may lead to cumulative brain injury. Within the RepImpact project, we designed a multi-disciplinary examination protocol, including Magnetic Resonance Imaging (MRI), to elucidate the underpinnings between RHI and cumulative brain damage in young professional soccer players. In this work, we present our multi-modal protocol and an automated analysis approach to integrate results from different MRI sequences. To date, 103 subjects underwent a 3T MRI in three international sites, Munich (DE), Leuven (BE), and Oslo (NO). The acquisition included a high-resolution T1 weighted sequence, multi-shell diffusion MRI (dMRI) (13 diffusion weightings) and resting-state fMRI (RS-fMRI). Additionally, Magnetic Resonance Spectroscopy was collected and co-registered to T1 images. The T1 weighted data was processed with FreeSurfer to label the cortical surfaces, which were registered to the dMRI and RS-fMRI space for ROI based analysis. Diffusion MRI and RS-fMRI were corrected for subject motion and deformations, to achieve high accuracy to the structural image space. Thanks to its design, dMRI data allowed to fit simultaneously four models. Diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) provide metrics related to microstructural organization. The intra-voxel incoherent motion (IVIM) provides maps showing the relative amount of perfusion, intra cellular and extra cellular diffusion. Finally, spherical deconvolution maps the individual connectome for structural connectivity investigation. In conclusion, we have developed a multi-modal acquisition protocol providing a comprehensive description of tissue organization within one-hour acquisition time, as well as a processing pipeline for its analysis with minimum user interaction.

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RepImpact

Jolien Gooijers

Potential effects of repetitive heading on postural control in elite youth soccer

Athletes participating in contact-sports frequently experience concussions. However, more often they experience subconcussive head impacts that occur in short succession. Such subconcussive head impacts occur repeatedly during soccer heading and are often considered harmless. Since a decrease in balance performance is common in concussed athletes and balance tests are known to have a high sensitivity for concussion diagnosis[1], we expect that balance tests may also be sensitive to detect subtle changes in postural stability following repetitive heading. Therefore, we perform a longitudinal study examining youth soccer athletes and controls from three study sites at three timepoints: a baseline evaluation pre-season, a follow-up post-season, and a second follow-up after a between-season break. At each time point, assessments include balance testing on the Balance-Tracking-System (BTrackS). Participants are instructed to stand still on the BTrackS force plate with eyes closed, hands on the hips and feet shoulder-width apart. The protocol consists of three trials on a firm and three trials on a compliant surface (20-seconds each). Postural steadiness is determined by advanced metrics capturing size, consistency, and speed of center of pressure. Regarding the longitudinal component of the study, we hypothesize that both soccer and control athletes will improve balance performance, but that soccer athletes relative to controls might show less improvement over time. As play season of the athletes is ongoing, we will mainly present cross-sectional findings for soccer athletes (N=80) and controls (N=44) at baseline. Note that the present study is part of a large-scale multimodal project investigating the effects of repetitive heading on brain structure/function and clinical impairments.

[1] Goble, D.J., Manyak, K.A., et al. An initial evaluation of the BTrackS Balance Plate and Sports Balance Software for Concussion Diagnosis. Int. J. Sports Phys. Ther. 2016; 11(2): 149-155.

J. Gooijers[1]; C. Seer[1];R. Bahr[2]; A. Leemans[3]; O. Pasternak[4]; N. Sochen[5]; P. Filipcik[6]; I. Koerte[7]; SP. Swinnen[1]

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RepImpact

Sandmo Stian Bahr

Evaluation of an in-ear Sensor for quantifiying Head Impacts in Youth Football

Our purpose was to test the validity of an in-ear sensor for quantifying head impacts in youth football. First, the sensor was mounted to a Hybrid III headform (HIII) and impacted with a linear impactor or football. Peak linear acceleration (PLA), peak rotational acceleration (PRA) and peak rotational velocity (PRV) were obtained from both systems; random and systematic error were calculated using HIII as reference. Then, six youth football players wore sensors and performed a structured training protocol including heading and non-heading exercises; they also completed two regular football sessions. For each accelerative event recorded, PLA, PRA and PRV outputs were compared to video recordings. Receiver operating characteristic curves were used to determine the sensor's discriminatory capacity in both on-field settings, determining cut-off values for predicting outcomes. For the laboratory tests, the random error was 11% for PLA, 20% for PRA and 5% for PRV; the systematic error was 11%, 19% and 5%, respectively. For the structured training protocol, heading events resulted in higher absolute values (PLA=15.6±11.8g) than non-heading events (PLA=4.6±1.2g); the area under the curve (AUC) was 0.98 for PLA. In regular training sessions, AUC was >0.99 for PLA. A 9g cut-off value yielded a positive predictive value of 100% in the structured training protocol vs. 65% in regular football sessions. In conclusion, the sensor displayed considerable random error and overestimated head impact exposure substantially. While on-field accuracy for discriminating headings from other accelerative events was excellent, secondary means of verifying events are still necessary.

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SCI-NET

Isaac Francos-Quijorna

Molecular and cellular responses of immune cells following therapeutic targeting of the extracellular matrix after spinal cord injury

Spinal cord injury (SCI) causes irreversible axonal damage and neuronal death, resulting in permanent disability. In addition to the initial mechanical injury, a wide range of secondary cellular and molecular events occurs after SCI which lead to further tissue damage and consequently, functional impairments. One major contributor to this pathological cascade is the inflammatory response which is aggressive and unresolved. The factors that impede the clearance of immune cells after the injury have not been fully characterized and several lines of evidence imply a role for altered extracellular matrix (ECM) in SCI inflammation. However, the mechanisms that underlie immunomodulatory effects of ECM after SCI are not yet understood. To evaluate whether ECM alteration modulates the inflammation after SCI we performed a large-scale digestion of inhibitory scar matrix by Chondroitinase-ABC enzyme delivered via lentiviral vector (LV-ChABC) after thoracic SCI in adult rats. By flow cytometry, we assessed the number of microglial cells, macrophages and neutrophils within the injury epicentre. Our results show that ECM digestion by LV-ChABC promotes inflammatory resolution after SCI revealed by accelerated clearance of neutrophils and reduced accumulation of macrophages and microglial cells compared with control animals (LV-GFP). These data suggest that ECM alteration after SCI impedes the inflammatory resolution, contributing to tissue damage and functional impairments. Furthermore, we are assessing changes in cytokine and chemokine expression and potential signalling pathways involved in ECM-immune interactions. Understanding the cellular and molecular mechanisms underlying ECM-mediated modulation of the inflammatory response may lead to more effective therapies to treat SCI.

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SCI-NET

Leonarda Serdani

Soluble alarmins after human spinal cord injury

Chronic dysregulated inflammation, tissue scarring and maladaptive changes in the extracellular matrix contribute to the failure of tissue repair and functional recovery after spinal cord injury (SCI). Embedded in the SCI-NET consortium, we assess alarmins with diagnostic and therapeutic potential for SCI in human serum and cerebrospinal fluid (CSF). Sera from patients (n=68) enrolled in the longitudinal, prospective SCIentinel trial (Kopp et al., 2013, BMC Neurol. 13:168) are analyzed in part 1 of the project. In part 2 (SCIentinel-prolong trial), serum and CSF samples will be combined to identify alarmin pathways specific for the central nervous system (CNS). Comparing three groups: motor complete SCI, motor incomplete SCI and vertebral fracture (control without SCI), we measure a panel of alarmins, including HMGB1 as associated with both, tissue inflammation and necrosis (Yang et al. 2013, J Leukoc Biol. 93:865-73). The non-parametric Kruskal-Wallis-test followed by Dunn's pot-hoc test was used for multiple comparisons. Results indicate differences in serum HMGB1 levels [median, (interquartile range)] between vertebral fracture and SCI patients 10 weeks post-injury, which are not present in the first or second week. Compared to vertebral fracture [7.7 (5.0-13.1) ng/ml] significantly higher levels were detected in motor incomplete SCI [18.8 (15.9-28.8); p= 0.024)], but not in motor complete SCI [12.0 (5.2-18.1); p= 0.79]. The observed higher serum HMGB1 developing at the sub-acute stage in subgroups of SCI patients, support our hypothesis of its association with tissue remodeling and an interaction with SCI-induced immune dysregulation. Regarding CNS-specificity, the preliminary findings will undergo validation in CSF.

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SILENCE

Christian Blex

The SCIentinel-prolong trial, deciphering humoral post-traumatic autoimmunity: study concept and protocol

The SCIentinel-prolong study provides an integrative approach to define the imprint of the maladaptive systemic immune state (Schwab et al., 2014 Exp Neurol, 258:121-9) after acute spinal cord injury (SCI). Its main objective are signatures of post-traumatic humoral autoimmunity developing against CNS and PNS antigen, their interrelation with the spinal cord injury-induced immune deficiency syndrome (SCI-IDS) and impact on neurological outcome in SCI patients. The prospective, multicenter SCIentinel-prolong study recruits 81 Patients of 3 equally sized groups i) SCI AIS A, ii) SCI AIS B-D, and iii) vertebral fracture without SCI. The primary endpoint is the prevalence of autoantibodies against CNS and PNS antigens identified by combining cell- and tissue-based assays with protein microarrays using CSF and sera collected 3 months post injury. Clinical outcomes comprise neurological classification, physical independence, walking, pain and neuroelectrophysiology. Protein microarray pilot data indicate a pattern of 108 differentially elevated autoantibodies in sera 3 months after SCI compared to age- and gender-matched control patients. Antibodies against potassium channels have been characterized to result in acquired channelopathies affecting immune cell and neuronal function (Schattling, et al., 2014, Exp Neurol 262 Pt A:28-36) with potential effects on disease development and progression. The SCIentinel-prolong trial to decipher post-traumatic "de-novo"autoimmunity and concurrent pathogenetic effects of autoantibody patterns after SCI aims at complementing the understanding of the maladaptive systemic immune response after SCI and identifying functionally relevant autoimmune targets for patient specific immune-modulatory treatments as a precision medicine approach.

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SILENCE

Carmen Schwaiger

The role of auto-antibodies in spinal cord injury-induced maladaptive immune response and autoimmunity

Background: Up to 7 million patients worldwide live with the debilitating consequences of spinal cord injury (SCI). Poor neurologic and functional recovery may be associated with a maladaptive systemic immune response (MSRI) such as post-traumatic autoimmunity against CNS-neo-antigens or SCI-induced immune deficiency syndrome.

Objective: To determine the frequency and clinical relevance of autoantibodies in patients with SCI.

Methods: We evaluated IgG antibodies in serum of 73 patients with SCI and isolated vertebral fracture without neurological deficit and 14 healthy individuals. Blood samples were collected 1 week and 10 weeks after the trauma. All samples were screened on an in-house tissue based assay (TBA) of post-fixed rat spinal cord. The reactivity of antibodies with surface antigens was examined with live neuronal immunofluorescence staining of primary cultures of dorsal root ganglia cells. All samples were analyzed blinded to the clinical diagnoses by two investigators (RH and CS).

Results: Among the 73 patients studied with TBA, 14 showed a synaptic staining pattern in the lamina II of the dorsal horn. In 5 of these patients the reactivity was detectable in week 1 and in 9 in week 10 after trauma. The healthy controls were negative. All patients positive in TBA and 43 randomly selected negative patients were subsequently stained on live primary cultures of ganglia cells. 13/14 positives and 1/43 negatives showed a dot-like membrane labeling of ganglion cells.

Conclusion: Preliminary findings indicate that a sub-group of SCI patients may develop auto-antibodies against surface antigens of the dorsal horn of the spinal cord.

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SiMPLyReha

Adrienne Crampton

Monitoring oculomotor and vestibulo-ocular function after mild traumatic brain injury in children and adolescents.

Background: Dizziness and visual complaints are commonly reported post-TBI, with persistent symptoms and functional limitations often requiring treatment. Current literature evaluating injury to the visual and vestibular systems is limited. Emerging evidence suggests that rehabilitative strategies that include ocular and vestibular rehabilitation could be beneficial following mild TBI, but high level evidence is lacking on how to best evaluate deficits in children and adolescents. Our primary objective is to describe the post-injury characteristics and recovery of primary oculomotor, vestibulo-ocular and dynamic visual attention function that occur over the first 6 months post-mTBI in children and youth, using multimodal assessments (clinical and technology-based). Methods: This study will include 150 youths (aged 6-17 yrs) who sustained a mTBI. Participants will be seen within 10 days of injury for initial assessment, 8 weeks later, and 6 months post-injury. At each time-point, assessments will include clinical and computerized tests of oculomotor and vestibulo-ocular function, and global markers of overall recovery. Results to date: 15 children (mean age 13.9) were seen on average 11 days post-injury, for initial assessment in the Montreal site. The assessment protocol was feasible. Approximately 20% of participants presented with difficulties in one of the clinical oculomotor tests, while almost 25% had difficulties with dynamic visual acuity, representing difficulties with vestibulo-ocular function. Updated results from all 4 enrolment sites and those obtained with computerized assessments will be presented. Conclusion: Preliminary results to date confirm that oculomotor and vestibulo-ocular deficits are common in pediatric and adolescent populations post-mTBI.

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SiMPLyReha

Aurélie Garat

Oculomotor and vestibulo-ocular disorders after moderate or severe TBI in children and adults : are they present and how severe are they?

Traumatic brain injury (TBI) is a major public health concern worldwide, and represents the main cause of mortality and acquired disability, with major social and economic consequences. Oculomotor and vestibulo-ocular dysfunctions are common following mild TBI, with deleterious consequences on everyday life, as they allow one to maintain balance while moving around, to keep a stable and clear image when the head is moving? Much less is known on the incidence, severity and consequences of those deficits following moderate to severe TBI, as motor and cognitive disorders are often predominant and more routinely assessed and managed. Given the greater severity of brain lesions, one can suspect the existence of more severe deficits following moderate/severe TBI, that would probably require targeted interventions. The aims of the study were to assess initial oculomotor, vestibulo-ocular and dynamic visual attention function, and changes that occur over 6 months following childhood or adulthood moderate/severe TBI using multimodal assessments (clinical and technology-based). Secondary aims include comparisons of the clinical and instrumental assessments. According to the results, recommendations could be made about assessment and management of those deficits in clinical practice. Currently, 8 patients have been assessed in France (one child; ages 14-51 years), and 15 are expected in the next weeks. To date, it appears that patients with moderate/severe TBI often have convergence disorders, lack of stereoscopic vision, and deficits in smooth pursuit and saccades. In Bonn, detailed results will be presented following statistical analyses performed with patients included on the different sites (Israel, Canada, France).

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SiMPLyReha

Heather Shepherd

Ocular-Motor Consequences of Sport-Related Concussion in Children and Adults

Background: Concussion is a common injury in sport. Blurred vision and difficulty reading are commonly reported following concussion. Emerging literature suggests that alterations in oculomotor function may occur following SRC. However, minimal literature has evaluated changes in oculomotor function following SRC.

Objective: The objectives of this study are to 1) Describe the oculomotor consequences of sport-related concussion (SRC) in children and adults (ages 13-50) using clinical tests and technological measures; 2) Compare technological and clinical measures of oculomotor function in the early time period following an SRC.

Methods: This is part of an ERA-NET Neuron funded study SiMPLy Rehab. Subjects who are seen at the Acute Sport Concussion Clinic and are diagnosed with an SRC who are between 10-21 days post injury will be invited to participate. Symptom reports, oculomotor clinical tests and the Vestibular Ocular Motor Screen (VOMS) will be completed. Technological tests (ICS Impulse oculomotor test battery) will also be completed. Test scores will be summarized using descriptive statistics. Linear regression modeling will be used to evaluate the association between clinician administered tests and the paired technological measure. The regression model will include co-variates such as age, sex, time since injury, and concussion history.

Significance: The results of this study will identify potential oculomotor deficits that occur following SRC using the best available technology. In addition, the ability of clinical tests to identify deficits found on the current best available measures will inform future work to optimize clinical tests interpretation and development, ultimately informing rehabilitation strategies.

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SiMPLyReha

Gilad Sorek

The Association between Vestibular and Autonomic Impairment post moderate-severe Traumatic Brain Injury

Outcomes of traumatic brain injury (TBI) are varied both in the level of damage within systems and in the variety of systems that are impaired. The autonomic system is frequently impaired and presents a hyper sympathetic function. The prevalence of vestibular impairment post moderate/severe TBI is less known. These two systems have some functional interaction. First, during position changes both associate with blood pressure regulation. Secondly, dizziness due to vestibular impairment may cause anxiety and hyper sympathetic states. The aim of the current abstract is to present preliminary results related to the level of impairment of these two systems and the association between the function of these systems in young adults post moderate/severe TBI and in healthy controls. Methods: 12 healthy young adults and five post moderate/severe TBI participated, their age between 13-28 years, 20-120 days post injury. Heart rate and Heart rate variability, using time and frequency measures, were assessed at rest, during tilt, grip and breathing tests. The vestibular tests were performed as well. A-parametric statistic tests were performed. Results: There was a significant difference between the groups in autonomic regulation to different stimulus- the responses in the study group were significantly smaller. All the post TBI participants demonstrated vestibular impairments. An association between vestibular dysfunctions and blood pressure deregulation due to position changes was noted in the TBI group. Conclusion: In this small sample, impairments were presented in both the autonomic and the vestibular systems, and a tendency towards association between these two systems' dysfunction was observed.

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TAI-MRI

Kevin Koschmieder

Brain Extraction in Susceptibility-Weighted MR Images using Deep Learning

Brain extraction methods in MRI have so far been exclusively developed for T1- and T2- weighted images. A deep neural network is presented to segment the brain tissue in susceptibility-weighted images (SWI) in healthy individuals and patients with traumatic brain injury (TBI).

MRI scans from 33 patients with moderate to severe TBI and 18 healthy controls were collected. SWIs (27ms TR, 20ms TE, 15° flip angle, and $0.98 \times 0.98 \times 1.00 mm^3$ voxel size) were acquired on a 3T Siemens Magnetom MRI scanner.

The reference standard were brain masks, which were semi-automatically obtained with an existing brain extraction method for T1-weighted images (SPM12). The brain masks were visually inspected and manually corrected for the test set.

We implemented a 2D-U-Net, which predicts brain extraction masks given axial slices. The U-Net architecture allowed the model to utilize both local and contextual information.

The 2D-U-Net was able to produce accurate brain masks. On a test set of 20 pathological and 10 healthy subjects, the model predictions achieved a dice score of 0.98±0.002 and a modified Haussdorf distance of 0.93±0.11mm per volume. Visual analysis showed that the model was able to ignore failures, e.g. under-segmentations and holes, in the reference standard during its training process.

SWI is the best modality to determine the number of cerebral microbleeds in TBI patients, which can give the clinician insight into the extent of a patient’s traumatic axonal injury. Brain extraction in SWI is the first step in the development of computer-aided systems detecting these microbleeds

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TAI-MRI

Hans Kristian Moe

The prospective Trondheim TBI studies: Traumatic axonal injury and level of consciousness in the early phase for patients with mild, moderate and severe traumatic brain injury

AIM: This prospective study explored the association between traumatic axonal injury (TAI) on MRI and level of consciousness as measured by the Glasgow Coma Scale (GCS) score in traumatic brain injury (TBI) patients.

METHODS: Patients with mild (GCS 14-15, n=161), moderate (GCS 9-13, n=98) and severe TBI (GCS 3-8, n=132) with MRI within 6 weeks at 1.5 or 3T were included (mild TBI: median 2 days [IQR 2-3]; Moderate-severe TBI: median 8 days [IQR 4-19]). GCS scores were registered before intubation, or at admission. Patients with evacuated hematoma or non-evacuated hematoma>25ml were excluded (n=48). The MRI protocol consisted of T2*weighted gradient echo or susceptibility weighted imaging, fluid attenuated inversion recovery (FLAIR) and diffusion weighted imaging. TAI lesions were evaluated in a blinded manner according to sequence, volume and location.

RESULTS: TAI was present in 47% of patients (165/354), and the prevalence differed between mild (8%), moderate (66%), and severe TBI (90%, Chi-square test: p<0.001). 67% of those with GCS 13 (24/36) had TAI, compared to 19% of those with GCS 14 (5/27, p<0.001). GCS scores were lower in patients with TAI in the brain stem (n=58, median 6 [IQR 3-8] vs 14 [IQR 10-15]) or thalamus (n=36, median 6 [IQR 3-8] vs 13 [IQR 8-15]) than those without such lesions (p<0.001). Total FLAIR TAI lesion volume correlated with GCS scores (Spearman's rho=-0.67, p<0.001).

CONCLUSION: The location and lesion load of TAI in early clinical MRI was related to level of consciousness in this large prospective study of TBI patients.

H.K. Moe[1]; T. Follestad[2]; A. Håberg[1,3]; S. Abel-Grüner[3]; E. Saksvoll[4]; Ø.Olsen[4]; A-M. Holte Flusund[1,5]; T. Skandsen[1,6]; N. Andelic [7,8]; C. Røe[7,9]; O. Sandrø[1]; T. E. Wanvik Farnes[1]; K-A. Kvistad[3]; A. Vik*[1,10]; K. Gøran Moen*[1,4]

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TAI-MRI

Virginia Newcombe

Towards a new classifcation system for traumatic axonal injury

Traumatic brain injury (TBI) constitutes a major cause of death and disability worldwide. TBI is not one single disease entity but includes a very heterogeneous and complex spectrum of pathologies, ranging from TAI (or diffuse axonal injury) to focal hemorrhages and contusions to extra-cerebral hematomas. TAI often explains the reduced level, or temporary loss, of consciousness and results from acceleration deceleration or rotational forces, which typically occur in high energy traffic accidents and sports injuries. Standard clinical MRI assessment of TBIs, including T2*GRE/SWI, FLAIR and DWI, can be used to classify TAI. The most commonly used classification system (Gentry) was based on original autopsy studies. We have manually annotated all lesions on 125 patients with moderate-to-severe TBI. All had MRI within 1 week of injury while sedated and ventilated. Sequences acquired included FLAIR, T2*GRE or SWI. This poster will present preliminary results of developing a new classification system using advanced MRI.

V. Newcombe[1]; S. Winzek[1]; E. Kornaropoulos[1]; B. Glocker[2]; M. Correia[3]; J. Simpson[1]; A. Kane[1]; F. Mathieu[1]; G.W. Williams[4]; D. Menon[1]

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TRAINS

Tifenn Clément

Spatiotemporal astroglial evolution following juvenile mild traumatic brain injury

Pediatric mild-TBI (mTBI) represents ~80% of all emergency room visits and results in higher probability to develop long-term cognitive disorders. To date, molecular and cellular mechanisms underlying the post-TBI cognitive dysfunction are unknown. Astrogliosis is a process that generates significant changes in astrocyte properties following brain injury. Astrocytic alterations have never been investigated after juvenile mTBI (jmTBI) in various brain regions, over time and in parallel with neuroimaging changes.

A closed-head injury model was used for jmTBI on postnatal day 17 in C57BL6 wild-type mice and Nestin x CreERT2 mice. Astrogliosis was studied using GFAP, vimentin and Nestin immunolabeling in somatosensory cortex (SSC), dentate gyrus (DG), amygdala (AMY) and infralimbic area (ILA) of prefrontal cortex in both ipsi- and contralateral hemispheres from 1 to 30 days post-injury (dpi). In-vivo T2-weighted magnetic resonance imaging (T2WI) and diffusion tensor imaging (DTI) was acquired at 30dpi to examine tissue level alterations.

Increased GFAP-labeling was observed in the ipsilateral SSC up to 30 dpi, corresponding to the site of the impact but contrasts to vimentin and nestin, which did not show changes in their level of expression. The morphology of GFAP positive cells was significantly altered in the SSC, DG, AMY and PFC over 7dpi. Within these brain regions T2WI and DTI values were significantly altered at 30dpi, in particular within regions distant from the impact site.

Astrogliosis process is induced spatiotemporally with distinct changes in astrocytic morphology after jmTBI. The presence and time course of astrogliosis could contribute to pathophysiological process.

T. Clément[1]; JB. Lee[2]; A. Ichkova[1]; B. Rodriguez-Grande[1]; M.-L. Fournier[1]; J. Aussudre[1]; M. O. Ogier[3]; F. Canini[3]; M. Koehl[4]; D. N. Abrous [4]; A. Obenaus[2,5]; J. Badaut[1,2]

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TRAINS

Gundega Stelfa

The effects of R-phenibut in experimental model of fluid percusion injury

Our previous results have shown that in rats R-phenibut significantly improves recovery of tactile and proprioceptive stimulation and histological outcome after transient middle cerebral artery occlusion. The aim of the present study was to evaluate the effects of R-phenibut on neurobehavioral and histological outcomes following TBI. Mice were subjected to lateral fluid percussion (lFP) TBI. Two hours after the trauma, animals received an intraperitoneal injection of R-phenibut at doses of 10 and 50 mg/kg. After that R-phenibut was administered daily for an additional 7 days. The neurobehavioral status of SW mice was assessed on post-TBI days 1, 3 and 7 by the neurological severity score (NSS) testing. Nissl (cresyl violet) staining was used to assess the neuronal injury. Nissl-stained dark neurons (N-DNs) were investigated in the cerebral neocortex at the level of the cortical impact at day 7 after the lFP brain injury. TBI induced significant functional deficits in TBI control mice as compared with sham-operated mice. The average NSS in TBI control group and sham-operated mice was 5.0 ±0.6 and 2.4±0.4, respectively. R-phenibut treatment at a dose of 50 mg/kg significantly ameliorated functional deficits and the average NSS in R-phenibut treated animals was 3.5 ±0.3 on the post-injury day 7. Histological analysis showed that R-phenibut treatment at a dose of 50 mg/kg significantly reduced the number of N-DNs in neocortex after TBI. Our results provide evidence that R-phenibut reduces early neuronal injury, improves functional recovery and it might be used in clinical therapy in the acute phase after TBI.

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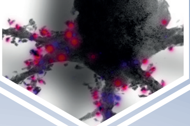

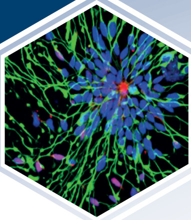

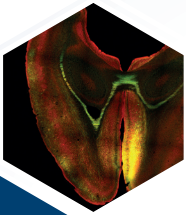

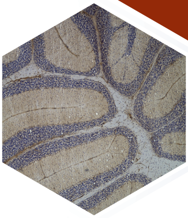

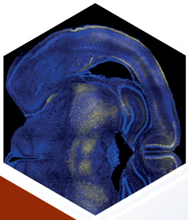

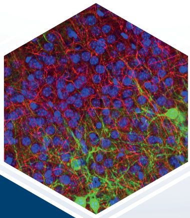

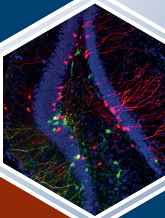

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