Department of Clinical Neurosciences

Neuroscience Research Center 2015-2016 Presentation

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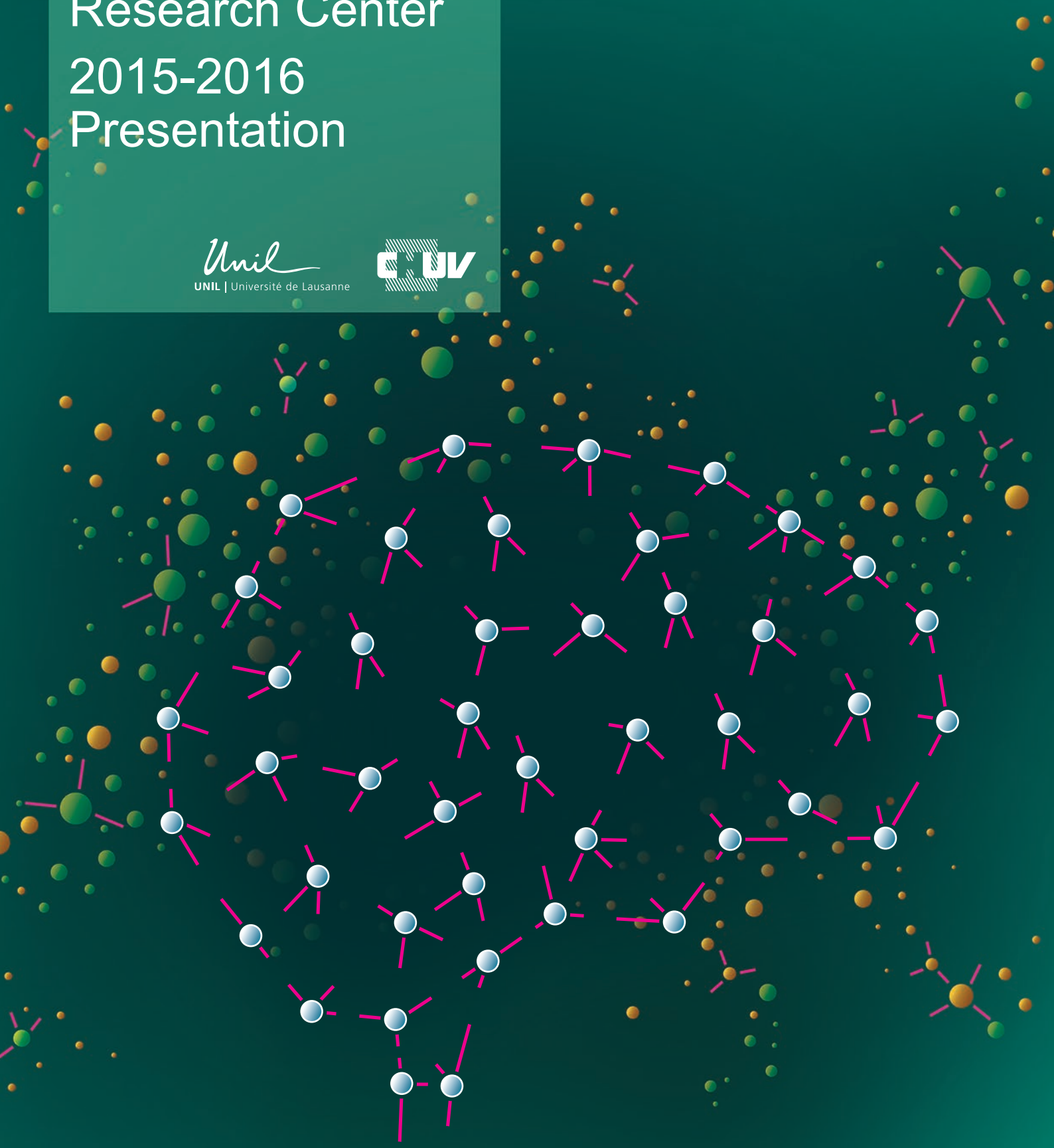
CHUV



Neuroscience Research Center
2015-2016 Presentation

Content

Foreword

The mission of the Neuroscience Research Center (CRN) is to promote patient-oriented interdisciplinary neuroscience research, and to strengthen collaborations, partnerships and training, to improve international visibility, to facilitate interactions with basic biomedical and clinical researchers and, therefore, to favorize translation of scientific knowledge to clinical practice. The center is taking advantage of the unique environment at the Lausanne University Hospital (CHUV) as well as of other major academic institutions in the Lemanic area. Its portfolio offers a large set of platforms and expertise to tackle mechanisms involved in diseases of the central and peripheral nervous system. The CRN is hosting 13 laboratories, encompassing more than a hundred collaborators (>75 FTE). The CRN members are implicated in large national and international initiatives, reflected by >5 millions funding and > 170 articles per year. This excellence has been further recognized with the recruitment in 2016 of two Swiss National Science Foundation professorships.

The CRN neuroscience community has diverse themes of research from understanding to treatment of patients, with a focus on three main axis:

> Neuropathophysiology: deciphering the nervous system in health and disease

Investigators are studying the pathophysiology, epidemiology and, management of epilepsy and disorders of consciousness, environmental factors in multiple sclerosis, mechanisms implicated in cerebral ischemia, gene expression from skin in inflammatory nerve, human brain structures and functions in degenerative disorders, modulation of inflammation in Parkinson's disease, neurophysiology of language and memory in ageing, molecular therapies for Huntington's disease, and genetic and epigenetic alterations in glioma.

> Neuromodulation: brain and spinal modulation

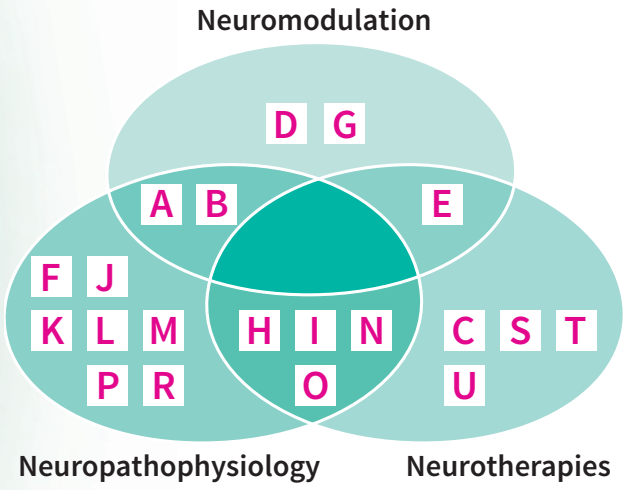
Projects are ongoing on brain and spinal stimulations, motor control, kinematic analysis of movements, and brain spinal interface for spinal cord injury.

> Neurotherapies: protecting the brain, preventing complications and recovering lost function

Several teams are working on improving outcomes of stroke patients, on preventing sudden unexpected death in epilepsy, on the development of neurosensorial approach for acute patient's rehabilitation, on the development of autologous brain cell transplantation in stroke, Parkinson's disease and spinal cord injury, and on multidimensional analyses of molecular profiles of glioma patients treated in clinical trials.

Nicole Déglon

CRN: from understanding to treatment

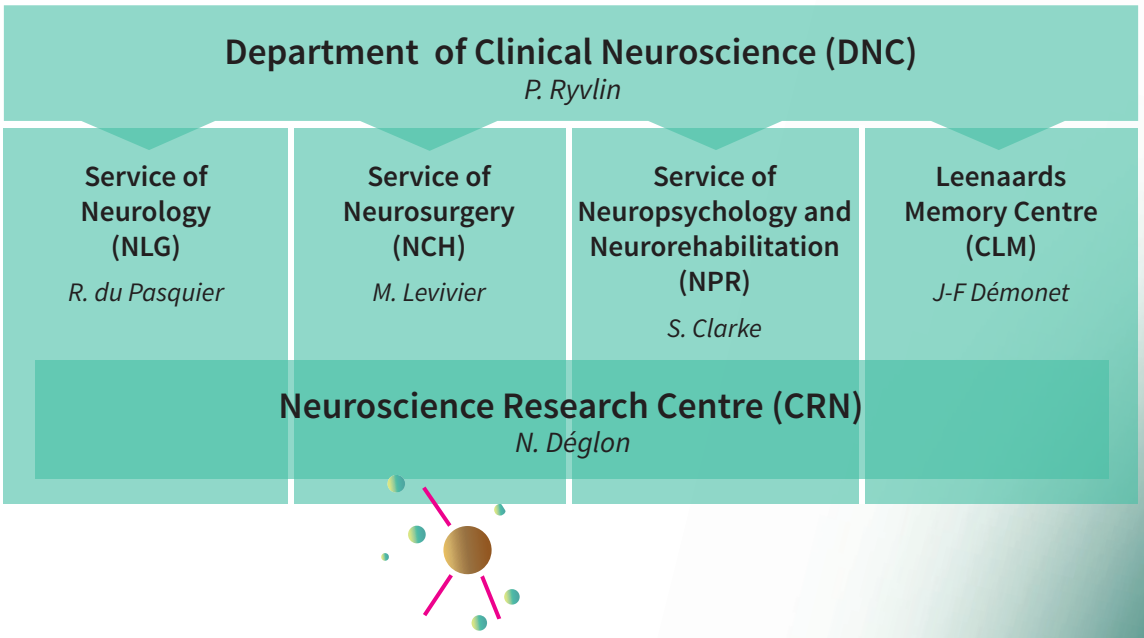


Structure and organization

The CRN is a transversal and cross-disciplinary structure benefiting from a unique environment with four clinical services: Neurology, Neurosurgery, Neuropsychology and Neurorehabilitation, as well as the Leenards Memory Center.

By bringing together laboratories and platforms, and by providing an optimal environment for state-of-the-art neuroscience research, the CRN is seeking to:

> Encourage collaborations, facilitate synergies among the different research groups and promote interactions at all levels at the CHUV and with other institutions
> Foster advances in brain research ranging from diagnosis to innovative therapies
> Develop state-of-the-art platforms.



Additional information

CHUV
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Keywords
Motor system
Movement disorders
Nerve-muscle disorders
Brain stimulation
Neurophysiology
Movement analysis

Laboratory of Clinical Neurophysiology and non-Invasive Brain Stimulation

Laboratory's activity

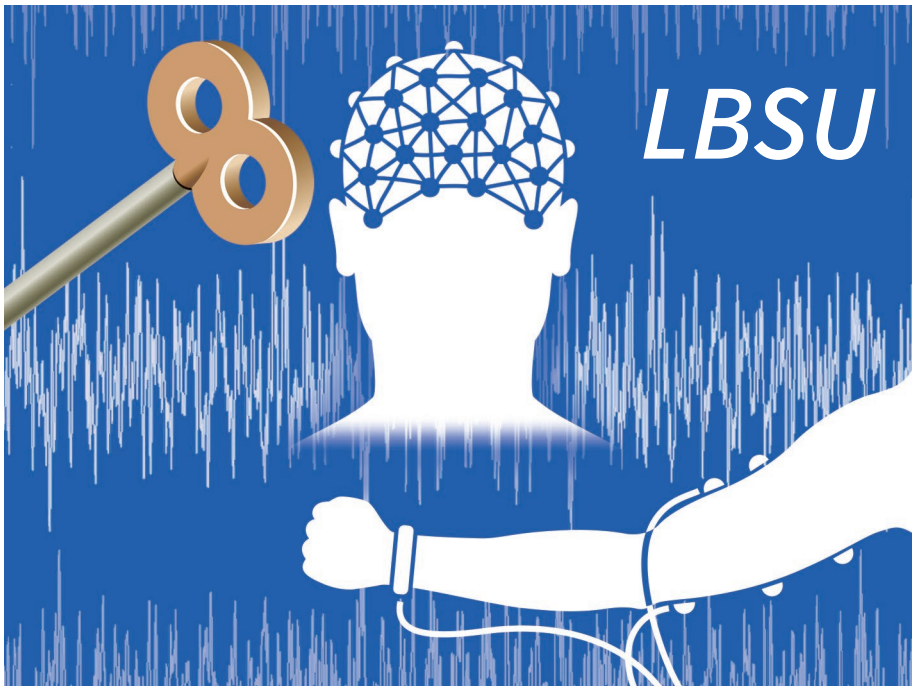
> Randomized controlled therapeutic clinical trial on tDCS for the treatment of the freezing of gait in Parkinson's disease.
> Investigation of the contribution of the cerebellum in rest tremor in Parkinson's disease with TMs.
> Robot-assisted assessment of the rigidity and tremor in Parkinson's disease.
> Investigation of the motor cortex physiology using the triple stimulation technique.
> Investigation of the motor, sensorimotor and plasticity alterations in dystonia associated to a complex regional pain syndrome.
> Investigation of motor fatigue with triple stimulation technique.

Research interests

Our lab is interested in clinical neurophysiology, brain stimulation and the human motor control. The main research work that we currently lead concerns Parkinson's disease, dystonia and normal physiology essentially through transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), electroneuromyography (ENMG), kinematic analysis of movements, and electroencephalography (EEG).

Scientific contributions in 2015-2016

> European Guidelines on Therapeutic Application of Non-invasive Brain Stimulation (rTMS, tDCS)
> cerebellar stimulation for Parkinson tremor
> non-invasive brain stimulation for tinnitus
> combined tDCS-behaviour therapy study for freezing of gait in PD
> CRPS with dystonia.



Our research team mainly uses electrophysiological techniques. Either to record activity: at the cerebral level with electroencephalography (EEG - cap and recording) and muscle level with electromyography (EMG - electrodes and recording); or to interfere or modify ongoing cerebral activity (TMS - coil).

Main publications in 2015-2016

Pal N, Maire R, Stephan MA, Herrmann FR, **Benninger DH**. Transcranial direct current stimulation for the treatment of chronic tinnitus: A randomized controlled study. Brain Stimul. 2015; 8(6):1101-7.

Benninger DH, Hallett M. Non-invasive brain stimulation for Parkinson's disease: Current concept and outlook 2015. NeuroRehabilitation. 2015; 37(1):11-24.

Lefaucheur JF, André-Obadia N, Antal A, Ayache SS, Baeken C, **Benninger DH**, *et al*. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2016; 128(1):56-92.

Benninger DH, Sohn YH, Hallett M. Neuromodulation and transcranial magnetic stimulation. Chapter 36. In: Bradley's Neurology in Clinical Practice. 7th Edition. Editors Daroff RB, Jankovic J, Mazziotta JC and Pomeroy SL. Elsevier, Amsterdam. 2015.

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Keywords
Cognitive functions
Neural plasticity
Recovery from brain lesions
Neuropsychology
Auditory cognition
Cerebral cortex

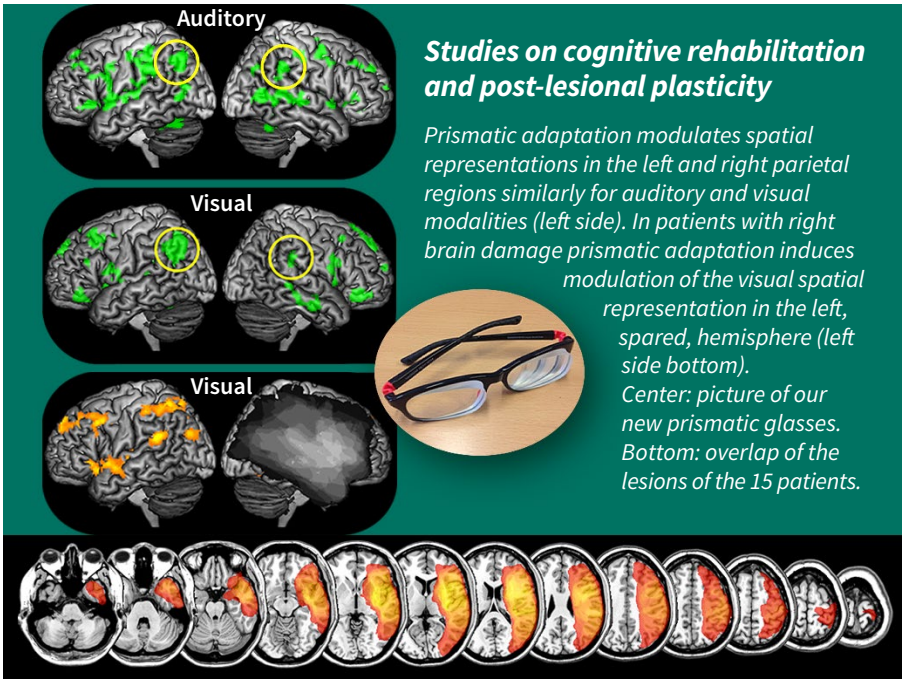
Laboratory of Cognitive Science

Laboratory's activity
We started a new series of investigations "Sound objects in space and time", FNS 159708 (2015-18; CHF 834'000 to S. Clarke). In our daily lives the correct perception of the meaning of a sound needs to be combined with the information about its location and its temporal features. We are investigating these combined representations using psychophysical approaches as well as fMRI and EEG. Understanding how semantic representation is linked to the spatial or temporal characteristics of an object will provide insight into multisensory and object-related representations of space. Better understanding of the underlying mechanisms is likely to focus indications for specific rehabilitation paradigms, which we explore here for neglect, or to help to design new therapies.
Dr. Sonia Crottaz-Herbette investigates the impact of brief therapeutic interventions on recovery of cognitive functions using fMRI paradigms. After her topical study on the effect of prismatic adaptation in neglect, she addresses the mechanisms of working memory recovery.
Dr. Eveline Geiser PD (AMBIZIONE fellow) investigates temporal encoding in the brain using fMRI and EEG paradigms. Her current grant focuses on the mechanisms of global timing perception.

Research interests
With her group Stephanie Clarke carries out research projects that combine investigations of cognitive functions and of the functional organization of the human cerebral cortex, with particular interest in the organization and plasticity of the human auditory cortex.

Scientific contributions in 2015-2016
> Using 7T fMRI, we have demonstrated that the meaning of broad categories of environmental sounds is encoded very early in cortical processing, including in primary auditory cortex.
> In two EEG studies we have shown that high-level expertise in sound recognition depends on temporo-prefrontal regions and hence semantic encoding. First, cortical representation of birdsongs is modulated in these regions by brief training. Second, during cardiac auscultation, successful discrimination depends on the access to these representations. Thus, semantic knowledge is essential when subtle, but complex perceptual differences identify items in a well-known semantic context.

> In three invited reviews we argued key issues on the basis of our previous work:
Existence of a third auditory stream, position-linked representation of sound objects, that is distinct both from the ventral/What and dorsal/Where auditory streams.
Parsimonious explanation for the effect of rightward prismatic adaptation on spatial bias in neglect and on behavioural data in normal subjects, by means of the shift in hemispheric dominance within the ventral attentional system.
Necessity to refine indications for therapeutic cognitive interventions and to stratify clinical trials correspondingly.



(Clarke S, Crottaz-Herbette S, 2016. Modulation of visual attention by prismatic adaptation. Neuropsychologia. 2016.06.022.
Crottaz-Herbette S, Fornari E, Clarke S, 2014. Prismatic adaptation changes visuospatial representation in the inferior parietal lobule. J. Neurosci. 34, 11803–11811.
Tissières I, Fornari E, Clarke S, Crottaz-Herbette S, 2016. Modulation of the auditory and visual space representation by prismatic adaptation. Conference Human Brain Mapping, Geneva.)

Main publications in 2015-2016

De Meo R, Matusz PJ, Knebel JF, Murray MM, Thompson WR, **Clarke S**. What makes medical students better listeners? Current Biology. 2016; 26: 519-520.

Da Costa S, Bourquin NM, Knebel JF, Saenz M, van der Zwaag W, **Clarke S**. Representation of Sound Objects within Early-Stage Auditory Areas: A Repetition Effect Study Using 7T fMRI. PLoS One. 2015; 10(5):e0124072.

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Clarke S, Crottaz-Herbette S. Modulation of visual attention by prismatic adaptation. Neuropsychologia. 2016; 92:31-41.

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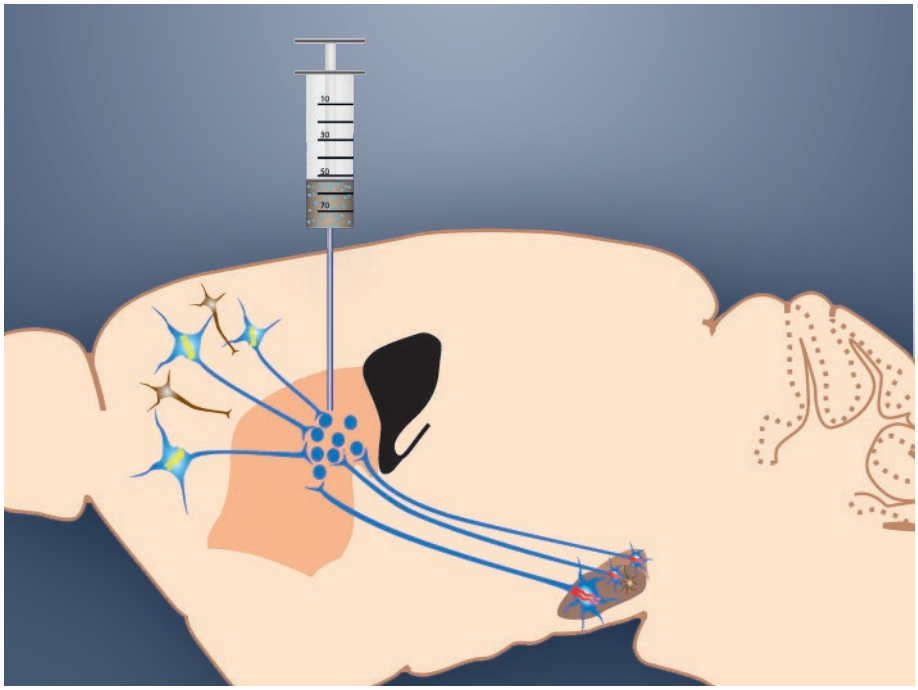
Laboratory of Neurotherapies and Modulation - LNTM

Prof. Nicole Déglon, Head of laboratory

Principal investigators:
Prof. Jocelyne Bloch
Dr Liliane Tenenbaum, Privat Docent



Laboratory's activity
The laboratory's activities are focusing on the development and validation of innovative neurotherapies and neuromodulation strategies. The three principal investigators are focusing on:

> Brain and spinal cord interface and stimulation.
> Autologous cell transplantation for stroke, Parkinson's disease and spinal cord injury.
> Modulation of neuroinflammation and drug-inducible gene therapy of Parkinson's disease.
> Pre-clinical development of molecular therapies for Huntington's disease (HTT lowering and gene editing).
> Cell-type specific gene transfer to investigate spreading of Tau protein in sporadic tauopathies and the contribution of mitochondrial dysfunctions in early Alzheimer's disease.

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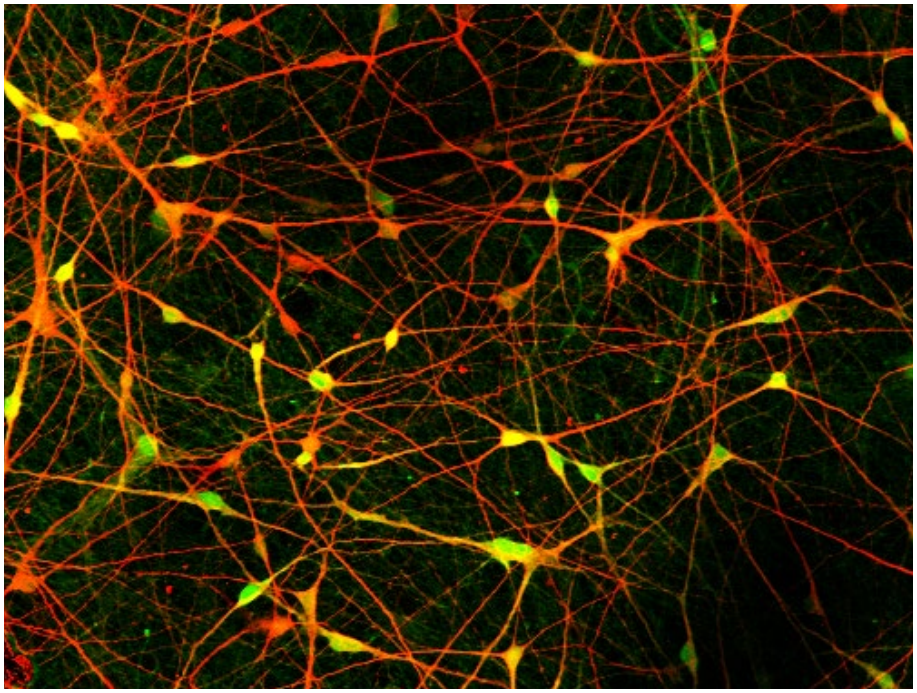
Keywords
Neurodegenerative diseases
Huntington's disease
Tauopathies
Gene therapy
RNA interference
Gene editing

Laboratory of Neurotherapies and Modulation - LNTM

Laboratory's activity
We focus our research work on the development of molecular therapies for neurodegenerative disorders and in particular huntingtin (HTT) lowering strategies and HTT gene editing for Huntington's disease. We have been exploiting the unique features and targeting specificities of viral vectors to deliver therapeutic candidates, generate new models of CNS pathologies or improve our understanding of the pathological mechanisms. In parallel, we are taking advantage of local and cell-type specific overexpression of transgenes in the CNS to investigate spreading of wild-type Tau protein in sporadic tauopathies as well as the contribution of mitochondrial dysfunctions in early Alzheimer's disease.

Research interests
The group has a long-standing experience and expertise in viral gene transfer technology to deliver therapeutic candidates in the brain or to model CNS pathologies by overexpressing disease-causing proteins.

Scientific contributions in 2015-2016
> Pre-clinical validation of HTT lowering strategies by RNA interference.
> Development a self-inactivating CRISPR/Cas9 system for HTT gene editing. We showed that mutant huntingtin was efficiently inactivated in mouse models of Huntington's disease, leading to an improvement in key markers of the disease.
> Development of viral vectors targeting astrocytes to study their contribution in Huntington's disease and the role of JAK/STAT3 pathway as inducer of astrocyte reactivity.
> To study the role of striatal enriched genes and the role of D2short receptor isoform in the selective vulnerability of MSM neurons as well as the neuroprotective effect of AMPK activation in Huntington's disease.
> Use of gene transfer tools to study the correlation between hippocampal connexion 43 levels and antidepressant- and anxiolytic-like activities in mice.



Human differentiated neurons front induced pluripotent stem cells (iPS). Green: MAPP2, red: B-TUB.

Main publications in 2015-2016

Merienne N, Delzor A, Viret A, Dufour N, Rey M, Hantraye P, **Déglon N**. Gene transfer engineering for astrocyte-specific silencing in the CNS. Gene Ther. 2015; 22:830-839.

Francelle L, Galvan L, Gaillard MC, Guillermier M, Houitte D, Bonvento G, *et al*. Loss of the thyroid hormone binding protein Crym renders striatal neurons more vulnerable to mutant huntingtin in Huntington's disease. Hum Mol Genet. 2015; 24:1563-73.

Vázquez-Manrique RP, Farina F, Cambon K, Dolores Sequedo M, Parker AJ, Millán JM, *et al*. AMPK activation protects from neuronal dysfunction and striatal vulnerability across nematode, cellular and mouse models of Huntington's disease. Hum Mol Genet. 2016; 25:1043-1058.

Lopes C, Aubert S, Bourgois-Rocha F, Barnat M, Rego AC, **Déglon N**, *et al*. Dominant-negative effects of adult-onset huntingtin mutations alter the division of human embryonic stem cells-derived neural cells. Plos One. 2016; 11(2):e0148680.

Meunier C, Merienne N, Jollé C, **Déglon N**, Pellerin L. Astrocytes are key but indirect contributors to the development of the symptomatology and pathophysiology of Huntington's disease. Glia. 2016; 64(11):1841-56.

Blessing D, **Déglon N**. Adeno-associated virus and lentivirus vectors: A refined toolkit for the central nervous system. Curr Opin Virol. 2016; 21:61-66.

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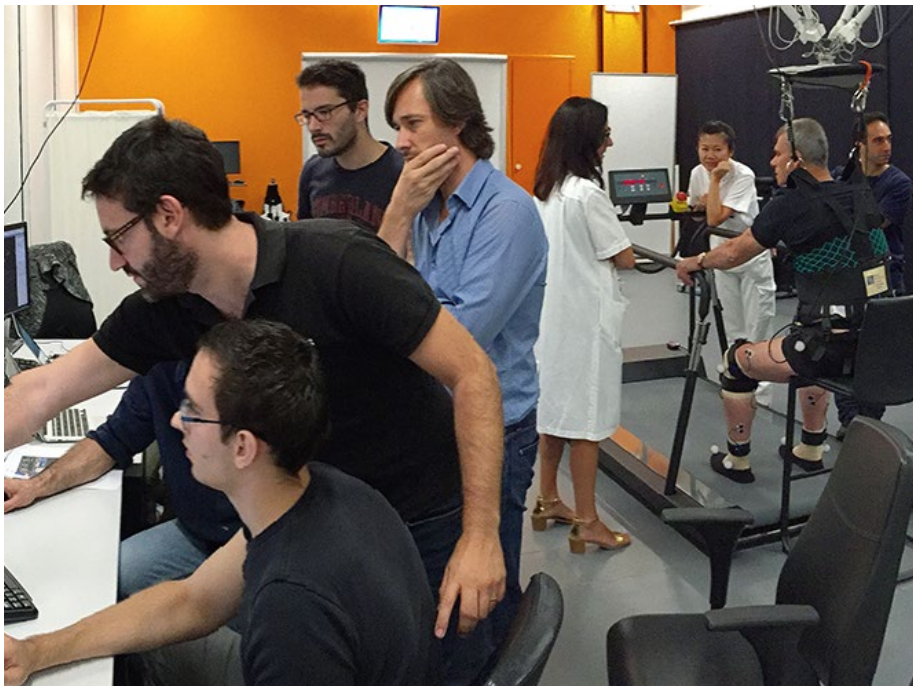
Keywords
Cell therapy
Neuroprosthetics

Laboratory of Neurotherapies and Modulation - LNTM



Rehabilitation session in patients with spinal cord injury

Laboratory's activity
Cell therapy:
> Application of autologous brain cell transplantation in animal models of stroke, Parkinson's disease and Spinal cord injury.
> Collaborative work with the group of Eric Rouiller Physiology Institute of Fribourg, as well as with the EPFL.
Neuroprosthetics:
> Projects with the EPFL groups of Grégoire Courtine and Stéphanie Lacour on spinal cord stimulation and brain spinal interface for spinal cord injury.
> Projects with the EPFL group of José Millan on closed loop deep brain stimulation in Parkinson's disease and brain machine interface.

Research interests
> Cell therapy
> Neuroprosthetics

Autologous brain cell transplantation in an ischemic brain.

Main publications in 2015-2016

Capogrosso M, Milekovic T, Borton D, Wagner F, Martin Moraud E, Mignardot JB, *et al*. A brain-spine interface alleviating gait deficits after spinal cord injury in primates. Nature. 2016; 539:284-288.

Wenger N, Moraud EM, Gandar J, Musienko P, Capogrosso M, Baud L, *et al*. Spatiotemporal neuromodulation therapies engaging muscle synergies improve motor control after spinal cord injury. Nat Med. 2016; 22(2):138-45.

Friedli L, Rosenzweig ES, Barraud Q, Schubert M, Dominici N, Awai L, *et al*. Pronounced species divergences in corticospinal tract reorganization and functional recovery after lateralized spinal cord injury favors primates. Sci Transl Med. 2015; 7(302):302ra134.

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Courtine G, **Bloch J**. Defining ecological strategies in neuroprosthetics. Neuroview Neuron. 2015; 86(1):29-33.

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Keywords
Parkinson's disease
Neuroprotection
Neuroinflammation
Drug- and disease-inducible AAV vectors
GDNF
Tollip

Laboratory of Neurotherapies and Modulation - LNTM

Laboratory's activity

Drug-inducible neuroprotective gene therapy for Parkinson's disease (PD)

On-going gene therapy clinical trials offer efficient but uncontrolled expression of therapeutic transgenes.
Our laboratory uses in-house developed modulatable adeno-associated virus (AAV) to administer glial cell line-derived neurotrophic factor (GDNF) intracerebrally in a rat PD model. Experiments are on-going to demonstrate the therapeutic potential of the vector.

Production of research-grade AAV vectors

Clinical and pre-clinical research raised the questions of the reproducibility of biological products quality and control, necessary to compare data from different teams.
We participated in a study comparing data from several groups who used the same standardized methods for AAV titration and registered standards.
We are producing research-grade AAV vectors characterized using these state-of-the-art methods and reference material.

Modulation of neuroinflammation in the substantia nigra pars compacta (SNpc)

We study the implication of the Tollip gene, a modulator of the NFκB signalling cascade, in response to an inflammatory challenge in the midbrain and using Tollip ko mice as well as viral vectors overexpressing Tollip. Our hypothesis is that Tollip may be a potential actor in neuroprotection.

Research interests

Regulatable neuroprotective gene therapy for Parkinson's disease

> Clinically-acceptable drug-inducible AAV.
> Mechanism of GDNF neuroprotective versus neurochemical effects.

Sensing and reducing brain inflammatory responses

> Inflammation and oxidative stress reporter AAVs.
> Modulators of neuroinflammatory signalling.

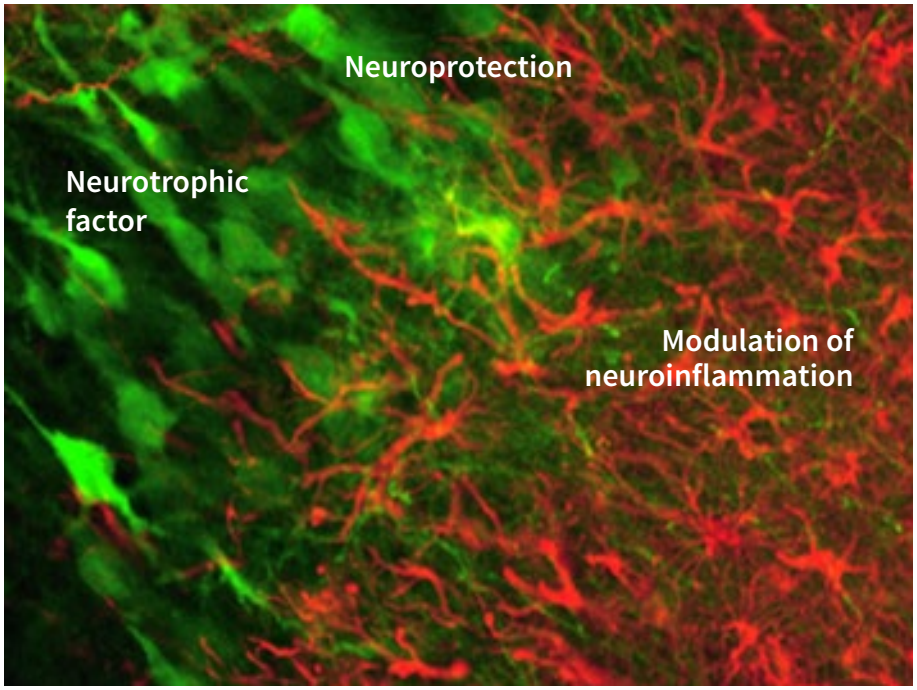
Scientific contributions in 2015-2016

Drug-inducible neuroprotective gene therapy for Parkinson's disease

Using a novel sensitive doxycycline (dox)-inducible AAV vector to administer the GDNF neurotrophic factor in the brain in a controlled manner, we have obtained dox-dose dependent GDNF biological effects . We have demonstrated that GDNF pro- survival effects could be induced at a clinically-acceptable dox dose (approved for long-term treatment of benign inflammatory diseases). In addition, we have shown that the beneficial and undesirable effects of GDNF (such as compensatory neurochemical effects and unbalanced motor effects) only appear in different dose ranges. These data are promising for the use of our vector in controlled clinical settings.

Modulation of neuroinflammation in the substantia nigra pars compacta

We have discovered that the Tollip protein, a modulator of NFκB signalling, was unexpectedly abundant in dopaminergic neurons of the mice *substantia nigra*. We have demonstrated that Tollip deficiency resulted in increased susceptibility to lipopolysaccharide characterized by increased NFκB activation, oxidative and nitrosative stress. Our hypothesis is that Tollip may be a target for neuroprotection in Parkinson's disease.



Our group adresses neuro-degeneration in Parkinson's disease by two complementary approaches: protecting dopaminergic neurons using neurotrophic factors and reducing exaggerated inflam-mation in their environment.

Main publications in 2015-2016

Chtarto A, Humbert-Claude M and Bockstael O, Das AT, Boutry S, Breger L, *et al*. A regulatable AAV vector mediating GDNF biological effects at clinically-approved sub-antimicrobial doxycycline doses. Mol Ther Methods Clin Dev. 2016; 5:16027.

Humbert-Claude M, Duc D, Dwir D, Thieren L, Sandström von Tobel J, *et al*. Tollip, an early regulator of the acute inflammatory response in the substantia nigra. J Neuroinflammation. 2016; 13(1):303.

Das AT, **Tenenbaum L**, Berkhout, B.Tet-On systems for doxycycline-inducible gene expression. Curr Gene Ther. 2016; 16(3):156-67.

Bazewicz M, Draganova D, Makhoul M, Chtarto A, Elmaleh V, **Tenenbaum L**, *et al*. Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines. Neurosci Lett. 2016; 630:209-15.

Barroso-Chinea P, Cruz-Muros I, Afonso-Oramas D, Castro-Hernández J, Salas-Hernández J, Chtarto A, *et al*. Long-term controlled GDNF over-expression reduces dopamine transporter activity without affecting tyrosine hydroxylase expression in the rat mesostriatal system. Neurobiol Dis. 2016; 88:44-54.

Hanna-El-Daher L, Béard E, Henry H, **Tenenbaum L**, Braissant O. Mild guanidinoacetate increase under partial guanidinoacetate methyltransferase deficiency strongly affects brain cell developpement. Neurobiol Dis. 2015; 79:14-27.

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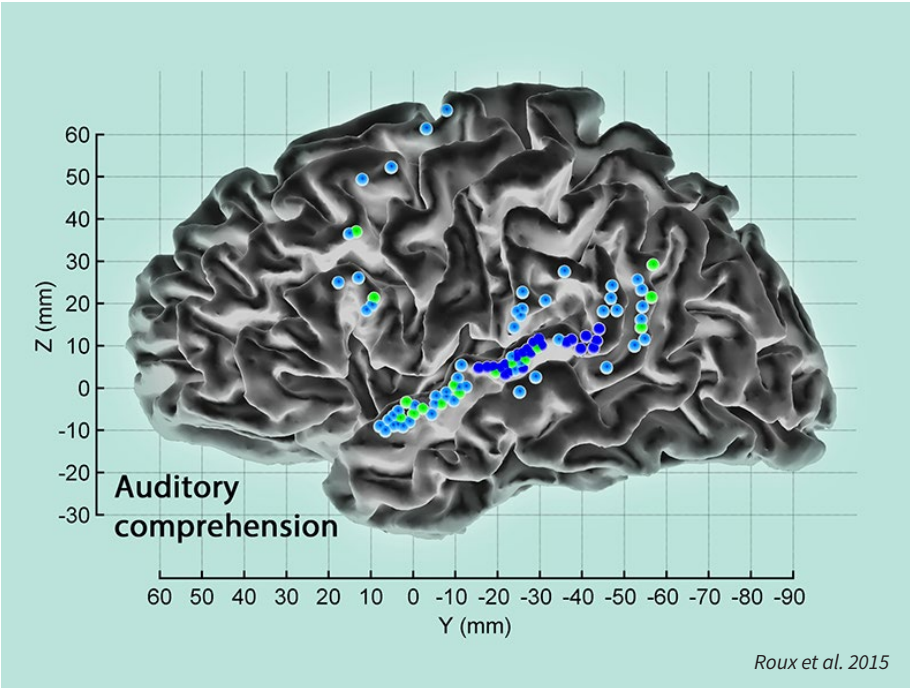
Keywords
Memory
Language
Cognition
Brain imaging
Biomarkers
Neuro-degenerative diseases
Alzheimer's disease
Amnesia
Diagnosis
Treatment

Laboratory for the Exploration of Memory in Neurosciences LEMENS

Laboratory's activity
Laboratory for the Exploration of MEmory in Neuro-Sciences (LEMENS) represents the translational research facet of the Leenaards Memory Centre (www.centrememoire.ch), a Centre devoted to the diagnosis and the care of patients and their families facing the "Ageing-Brain Cognitive Diseases" (the ABCDs), such as Alzheimer's disease and other associated conditions (fronto-temporal dementias, diffuse Lewy body disease, vascular dementia).

Research interests
Our activities involve studying the neurophysiology of language and memory using testing and a variety of brain imaging and function mapping in the broadest sense, from EEG to MRI and direct cortical stimulation. We also try our best to treat patients and support families facing devastating brain diseases affecting cognition and especially neurodegenerative diseases associated with ageing.

Scientific contributions in 2015-2016
Brain correlates of language processing dynamics of reading consciousness study with MEG, role of posterior and anterior regions of the superior temporal cortex in comprehension, and role of the superior premotor cortex in handwriting
> Study of the neural correlates of the attention training in the elderly using ERP
> Futility of use of CT-scan in transient global amnesia
> Follow up of war veterans: the impact of brain lesion on caregivers.



Mapping through direct cortical stimulation of language comprehension. In dark blue: audio-phonological impairments, in light blue: semantic disorders.

Main publications in 2015-2016

Levy J, Vidal JR, Fries P, **Démonet JF**, Goldstein A. Selective neural synchrony suppression as a forward gatekeeper to piecemeal conscious perception. Cerebral Cortex. 2016; 26(7):3010-22.

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Guevara AB, **Démonet JF**, Polejaeva E, Knutson KM, Wassermann EM, Grafman J, Krueger F. Association between traumatic brain injury-related brain lesions and long-term caregiver burden. J Head Trauma Rehabil. 2016; 31(2):E48-58.

Guevara Brioschi A, **Démonet JF**, Polejaeva E, Knutson KM, Wassermann EM, Krueger F, Grafman J. Association between long-term cognitive decline in Vietnam veterans with TBI and caregiver attachment style. J Head Trauma Rehabil. 2015; 30(1):E26-33.

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Keywords
Coma
Disorders of consciousness
Prediction
Acute neurorehabilitation
Neurosensorial approach
DOC
BCI
Robotic neurovegetative disorders
Virtual reality
Spasticity

Laboratory of Acute Neurorehabilitation - LNRA

Laboratory's activity

Research interests

> To improve the evaluation of different states of consciousness and thus to also improve the prediction of recovery and the choice of therapeutic approach with the goal of reducing false diagnoses of different states of arousal, and improve communication with non-responding patients via direct interaction between the brain and external computer devices.

> To demonstrate the risks of prolonged bed rest on the autonomic nervous system and spasticity in impairing patient outcome and increasing complications.

> To evaluate the effectiveness of training a paralyzed limb following unilateral brain injury using a virtual reality approach using the brain activity recorded by simultaneous EEG.

> To assess the impact of a neurosensorial approach on the patient's rehabilitation and duration of hospital stay. The aim is to develop new approaches for acute neurorehabilitation, as a pilot interdisciplinary unit in Switzerland.

Research interests

To correlate the clinical findings of prediction of coma with the neurophysiology and functional imagery and to begin the acute neurorehabilitation as early as possible.

Scientific contributions in 2015-2016

> identification of a new tool to diagnose the phase of coma and to predict its evolution (MBT Tool, Plos one 2016).

> Demonstration that acute mobilisation for patients with severe neurological lesion with robotic (Erigo) is safe and stabilises the blood pressure. It regulates the catecholamine secretion.

Main publications in 2015-2016

Mézier H, Zambelli PY, Bonnard Ch, Raffoul W, Vuadens Ph, **Diserens K**. Retrospective analysis of treatment indicator of conservative treatment and intervention of surgery of spasticity of upper and inferior limb of an interdisciplinary neuro-orthopedic spasticity consultation. Neuroscience Rehab J. 2016; 4:3.

Pignat JM, Mauron E, Jöhr J, Gilart de Keranflec'h C, Van De Ville D, Pretie MG, *et al*. Outcome prediction of consciousness disorders in the acute stage based on a complementary motor behavioural tool. PLoS One. 2016; 11(6):e0156882.

Rocca A, Pignat JM, Berney L, Jöhr J, Van de Ville D, Daniel RT, *et al*. Sympathetic activity and early mobilization in patients in intensive and intermediate care with severe brain injuries: a preliminary prospective randomized study. BMC Neurol. 2016; 16:169.

Hottinger A, Moura B, Pellet C, Levivier M, Berney L, Giannelli M, *et al*. First Swiss integrated multidisciplinary neurorehabilitation programme for neuro-oncologic in-patients. 2016; SNO in press.

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Laboratories of Neuroimmunology

Laboratory of Neuroimmunology/Multiple Sclerosis - LNIS
Prof. Renaud Du Pasquier, Head of laboratory, Principal Investigator

Laboratory of Experimental Neuroimmunology - LNIE
Prof. Caroline Pot Kreis, Head of laboratory, Principal Investigator

Multiple sclerosis (MS) is an auto-inflammatory disease of the central nervous system, where all components of the immune system, innate and adaptive, are involved. In addition to genetic factors, environmental ones play a crucial role in triggering this complex disease. In the Laboratories of neuroimmunology, we examine how environmental factors, among which Epstein-Barr virus, gut microbiome or cholesterol metabolites support autoreactivity of B and T cells. To tackle our hypothesis, we use different approaches, including animal models, namely the experimental autoimmune encephalomyelitis, human samples analysis (blood, cerebrospinal fluid, urine, soon stools) of MS patients and a human *in vitro* model of MS brain, using induced pluripotent stem cells (iPCS).

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Service of immunology and allergy (LIA)

Keywords
Neuroimmunology
Multiple sclerosis
$CD8^+$ T cells
Induced pluripotent stem cells (iPSC)
Epstein-Barr virus
HIV

Laboratory of Neuroimmunology/Multiple Sclerosis - LNIS

Laboratory's activity

Our Laboratory has a long-standing experience in studying the cellular immune response in multiple sclerosis (MS). We have previously shown that the $CD8^+$ T cell response against Epstein-Barr virus, an environmental factor of MS, was dysregulated in this disease. However, it was impossible to examine whether those cells did recognize auto-antigens in the central nervous system (CNS) since the latter compartment is not accessible in humans. Recently, we established the technology of induced pluripotent stem cells (iPSC), which now allows obtaining CNS cells and thus recapitulating mini-brains of MS patients. This tool opens fascinating perspectives in our research, including the possibility to examine whether peripheral virus-activated T cells can cross-react with auto-antigens in the CNS.

With its background on viral-specific cellular immune response, our Lab also tries to understand why, infrequently, treatments used in MS are able to trigger progressive multifocal leukoencephalopathy, a fearful CNS infection caused by JC virus.

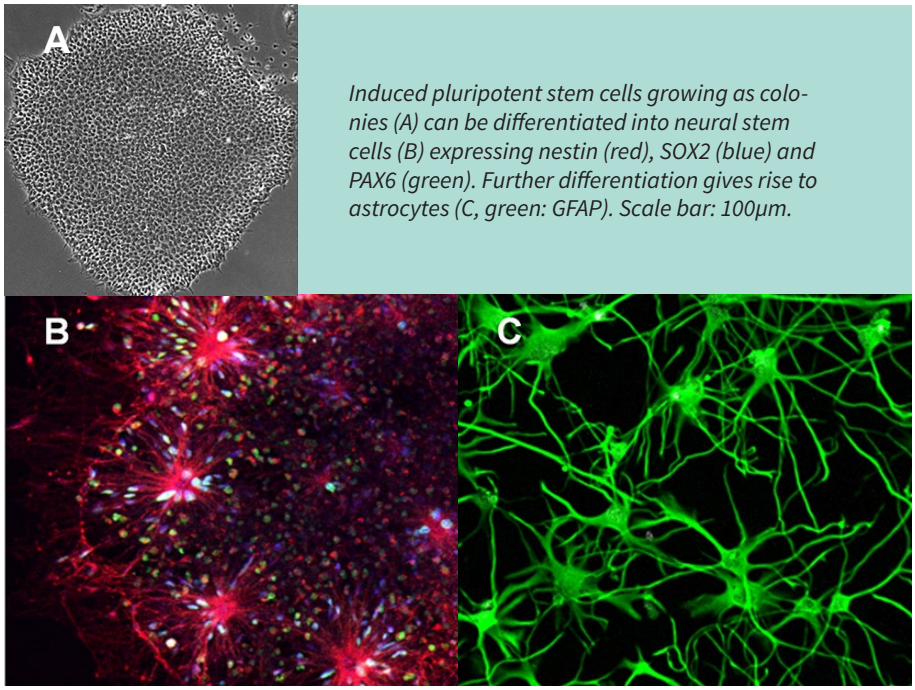
Finally, together with clinicians, the Laboratory holds a research programme dealing with the neurocognitive disorders in HIV^+ patients.

Research interests

Our research work is driven by the desire to better understand the pathogenesis of inflammation in the brain, in particular in the field of multiple sclerosis. Only such an understanding will lead to breakthrough treatments.

Scientific contributions in 2015-2016

> Perriot S, Perriard G, Mathias G, Canales M, Merienne N, Déglon N, Du Pasquier R. iPSC-derived astrocytes are functional and respond to multiple sclerosis-relevant cytokines stimulation. ISNI, Jérusalem, September 29 2016.
> Mathias A, Perriot S, Canales M, Gaubicher C, Engelhardt B, Schluep M, Du Pasquier R. Impact of fingolimod treatment on T cell migration to the CNS: a four-year observational study. ECTRIMS, London, September 16, 2016.
> Perriot S, Perriard G, Mathias A, Canales M, Merienne N, Déglon N, Du Pasquier R. Generation of iPSC-derived astrocytes to study the effects of multiple sclerosis relevant cytokines on the CNS . ARSEP, Paris, May 27, 2016.
> Perriot S, Du Pasquier R. New *in vitro* CNS model to study the pathogenicity of T cells in Multiple Sclerosis. Young Investigator Meeting in Multiple Sclerosis Research, Grindelwald, March 11-13, 2016.
> Mathias A, Perriard G, Canales M, Vuilleumier F, Perrotta G, Schluep M, Du Pasquier R. Fingolimod favors the migration of T cells toward the CNS without interfering with their anti-viral properties. ECTRIMS, Barcelona, October, 7-10, 2015.



Induced pluripotent stem cells growing as colonies (A) can be differentiated into neural stem cells (B) expressing nestin (red), SOX2 (blue) and PAX6 (green). Further differentiation gives rise to astrocytes (C, green: GFAP). Scale bar: 100µm.

Main publications in 2015-2016

Mathias A, Perriard G, Canales M, Vuilleumier F, Perrotta G, Schluep M, **Du Pasquier RA**. The VZV/IE63-specific T cell response prevents herpes zoster in fingolimod-treated patients. Neurol Neuroimmunol Neuroinflamm. 2016; 3(2):e209.

Spatola M, **Du Pasquier R**, Schluep M, Regeniter A. Serum and CSF GQ1b antibodies in isolated ophthalmologic syndromes. Neurology. 2016; 86(19):1780-4.

Perriard G, Mathias A, Enz L, Canales M, Schluep M, Gentner M, Scharen-Wiemers N, **Du Pasquier RA**. Interleukin-22 is increased in multiple sclerosis patients and targets astrocytes. J Neuroinflammation. 2015; 12(1):119.

Bale J, **Du Pasquier R**. Relapse in *Herpes Simplex* Virus Encephalitis: It's not just about the virus. Neurology. 2015; 85(20):1730-1.

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Keywords
Neuroimmunology
Experimental autoimmune encephalomyelitis
Multiple sclerosis
Immunometabolism
Lipidic pathways
Gut-Brain Axis

Laboratory of Experimental Neuroimmunology - LNIE

Laboratory's activity

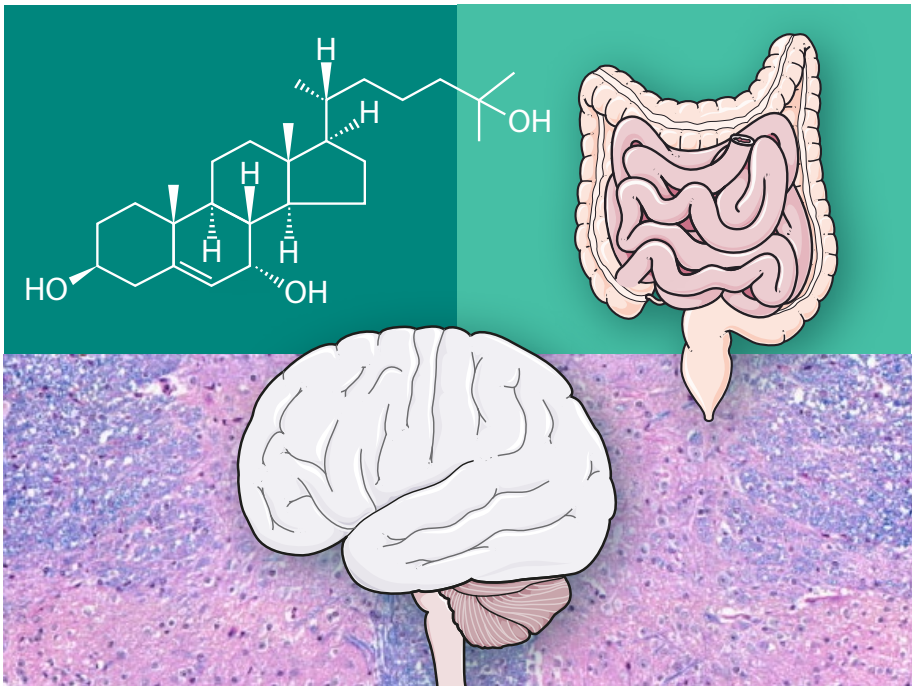
Multiple sclerosis (MS) is a common autoimmune disorder affecting young patients. MS and its animal model, the experimental autoimmune encephalomyelitis (EAE), are characterized by inflammatory cell infiltrates and demyelination of the central nervous system (CNS). The development of this disease is under the control of both genetic and environmental factors. While risk factors such as viral infections or smoking are well established, the role of cholesterol metabolism, intestinal immune responses, and gut microbiota remains unclear.
In our laboratory, we are interested in understanding the role of lipid metabolism and of the gut-brain axis during neuroinflammation using the EAE model. Interest in the field of immunometabolism has been accelerated by the actual obesity epidemic and by the observation that obesity promotes inflammation that drives chronic diseases. Our ongoing work focuses on understanding the role of oxysterols, oxidized forms of cholesterol, during autoimmunity. We further examine the impact of oxysterols on gut homeostasis and gut flora during CNS inflammation using dietary approaches and mouse deficient for oxysterols.

Research interests

The aims of Caroline Pot's research is to fine-tune immune responses in regards to environmental factors and metabolic pathways. This could lead to novel therapeutics and contribute to scientific re-evaluations of life-changes thus promoting personalized medical approaches for MS patients.

Scientific contributions in 2015-2016

> Annual meeting of the Swiss Neurology Society 2015, Bern, 29-30.10.2015. Oral presentation "Oxysterols and human memory T lymphocytes: an attractive story".
> Joint SSORL/SSIA meeting 2016, Montreux, 28-29.04.2016: Poster presentation "The oxysterol/EBI2 interaction and memory lymphocytes: attractive hosts in the world of multiple sclerosis"
> 10th World Immune Regulation Meeting (WIRM), Davos, 16-19.03.2016. Poster presentation "Oxysterols and human memory lymphocytes, intriguing actors on the scene of multiple sclerosis". Won the Poster Prize Award of Nature Reviews Immunology.
> 2nd Congress of the EUROPEAN ACADEMY OF NEUROLOGY (EAN), Copenhagen, 28-30.05.2016: Poster presentation "Oxysterols, human memory lymphocytes and multiple sclerosis: a peculiar team".



Schematic drawing illustrating the interplay between lipid metabolism, gut immune response and inflammation of the central nervous system during multiple sclerosis.
We study the interactions between oxysterols, oxidized forms of cholesterol (depicted on the left) and gut homeostasis/ gut flora (right) to assess their contributions in driving autoimmunity in the central nervous system (bottom).

Main publications in 2015-2016

Peters A*, Fowler K*, Chalmin F, Merkler D, Kuchroo VK, **Pot C**. IL-27 Induces Th17 differentiation in the absence of STAT1 signaling. J Immunol. 2015 ; 195(9):4144-53.

Disanto G, Benkert P, Lorscheider J, Muller S, Vehoff J, Zecca C, *et al*. The Swiss Multiple Sclerosis Cohort-Study (SMSC): A prospective Swiss wide investigation of key phases in disease evolution and new treatment options. PLoS One. 2016; 11(3):e0152347.

Chalmin F, Rochemont V, Lippens C, Clottu A, Sailer AW, Merkler D, Hugues S, **Pot C**. Oxysterols regulate encephalitogenic CD4$^+$ T cell trafficking during central nervous system autoimmunity. Journal of Autoimmunity. 2015; 56:45-55.

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Laboratory for Research in Neuroimaging - LREN

Assoc. Prof. Bogdan Draganski, Head of laboratory

Principal investigators:
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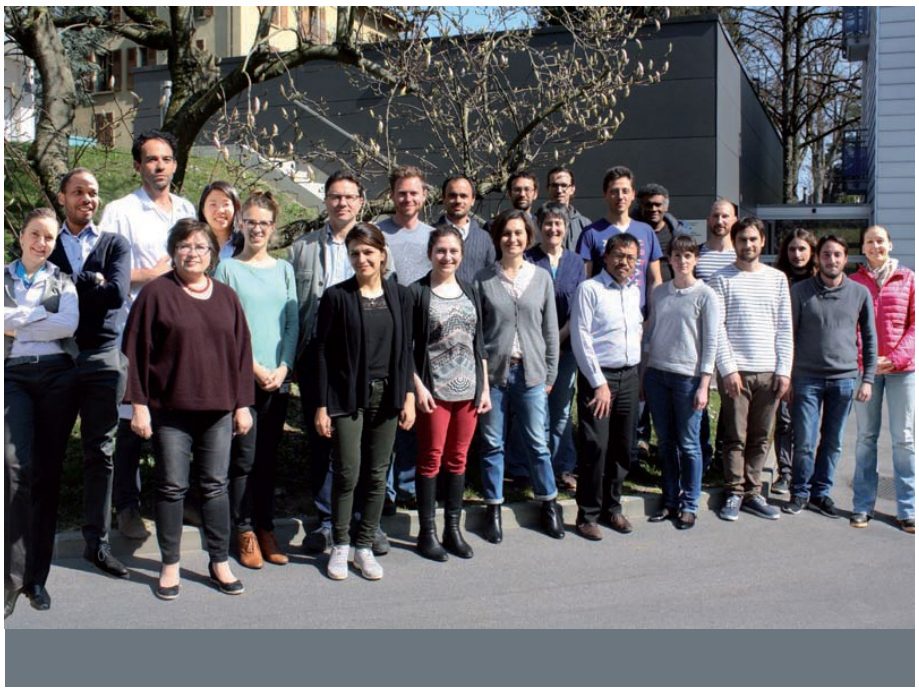
Marzia De Lucia, Senior Researcher, Privat Docent, Senior Lecturer (MER)
Antoine Lutti, Senior Researcher, Privat Docent, Senior Lecturer (MER)



Laboratory's activity

LREN is a neuroimaging laboratory where clinical and basic neuroscientists study human brain structure and function relevant to neurological disorders and normal cognition. We develop and apply non-invasive neuroimaging methods - magnetic resonance imaging and electro-encephalography to investigate topics including use-dependent brain plasticity, rehabilitation of lost function, and neurodegeneration.

LREN is responsible for a state-of-the-art neuroimaging platform featuring high-end research-only Siemens Prisma 3T MRI scanner, sophisticated MRI compatible neurophysiological equipment, and high-density EEG machines.

LREN's main goal is to translate basic research findings into clinical applications for early diagnosis of disease and for prediction of clinical outcome.

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Keywords
Imaging neuroscience
Human Brain Project

Laboratory for Research in Neuroimaging - LREN

Research interests
> Brain plasticity
> Preclinical neuroscience.

Main publications in 2015-2016

Accolla EA, Herrojo Ruiz M, Horn A, Schneider GH, Schmitz-Hübsch T, **Draganski B***, Kühn AA*. Brain networks modulated by subthalamic nucleus deep brain stimulation. Brain. 2016; 139(Pt9):2503-15. *Equal contribution.

Freund P, Friston K, Thompson AJ, Stephan KE, Ashburner J, Bach DR, *et al*. Embodied neurology: an integrative framework for neurological disorders. Brain. 2016; 139(Pt6):1855-61.

Lorio S, Kherif F, Ruef A, Melie-Garcia L, Frackowiak R, Ashburner J, *et al*. Neurobiological origin of spurious brain morphological changes: A quantitative MRI study. Hum Brain Mapp. 2016; 37(5):1801-15.

Lorio S, Fresard S, Adaszewski S, Kherif F, Chowdhury R, Frackowiak RS, *et al*. New tissue priors for improved automated classification of subcortical brain structures on MRI. Neuroimage. 2016; 130:157-66.

Accolla EA, Aust S, Merkl A, Schneider GH, Kühn AA, Bajbouj M, **Draganski B**. Deep brain stimulation of the posterior gyrus rectus region for treatment resistant depression. J Affect Disord. 2016; 194:33-37.

D'Angelo D, Lebon S, Chen Q, Martin-Brevet S, Snyder LG, Hippolyte L, *et al*. Cardiff University Experiences of Children With Copy Number Variants (ECHO) Study, the 16p11.2 European Consortium, and the Simons Variation in Individuals Project (VIP) Consortium. Defining the Effect of the 16p11.2 Duplication on Cognition, Behaviour, and Medical Comorbidities. JAMA Psychiatry. 2016; 73(1):20-30.

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Keywords
Imaging neuroscience
Human Brain Project

Laboratory for Research in Neuroimaging - LREN

Research interests
> Disease outcome prediction
> Predictive analytics.

Main publications in 2015-2016

Lorio S, **Kherif F**, Ruef A, Melie-Garcia L, Frackowiak R, Ashburner J, Helms G, Lutti A, Draganski B. Neurobiological origin of spurious brain morphological changes: A quantitative MRI study.Human brain mapping. 2016; 37:1801-1815.

Orio S, Fresard S, Adaszewski S, **Kherif F**, Chowdhury R, *et al*. New tissue priors for improved automated classification of subcortical brain structures on MRI. NeuroImage. 2016; 130:157-166.

Maillard AM, Ruef A, Pizzagalli F, Migliavacca E, Hippolyte L, *et al*. The 16p11.2 locus modulates brain structures common to autism, schizophrenia and obesity. Molecular Psychiatry. 2015;20:140-147.

Twomey T, Waters D, Price CJ, **Kherif F**, Woll B, Mac Sweeney M. Identification of the regions involved in phonological assembly using a novel paradigm. Brain and Language. 2015; 150:45-53.

Cui J, Zufferey V, **Kherif F**. *In-vivo* brain neuroimaging provides a gateway for integrating biological and clinical biomarkers of Alzheimer's disease. Current Opinion. 2015; 28:351-357.

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Keyword
Imaging neuroscience

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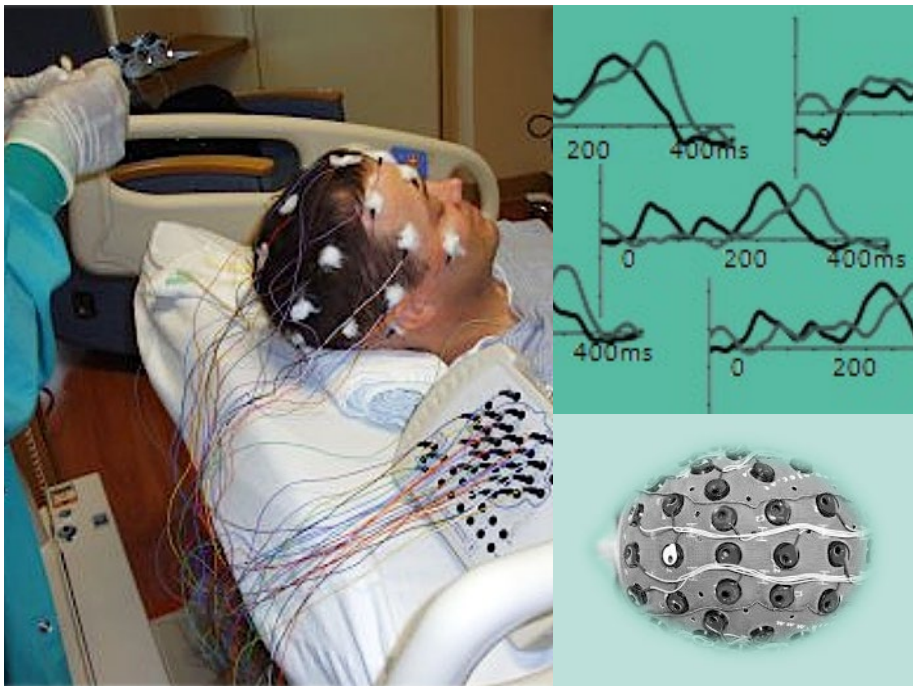
Research interests
Disorders of consciousness.



Sensory processing during loss of consciousness.

Main publications in 2015-2016

Juan E, Nguissi NA, Tzovara A, Viceic D, Rusca M, Oddo M, Rossetti AO, **De Lucia M**. Evidence of trace conditioning in comatose patients revealed by the reactivation of EEG responses to alerting sounds. Neuroimage. 2016; 141:530-41.

Tzovara A, Chavarriaga R, **De Lucia M**. Quantifying the time for accurate EEG decoding of single value-based decisions. J Neurosci Methods. 2015; 250:114-25.

De Lucia M, Tzovara A. Decoding auditory EEG responses in healthy and clinical populations: A comparative study. J Neurosci Methods. 2015; 250:106-13.

Juan E, **De Lucia M**, Tzovara A, Beaud V, Oddo M, Clarke S, Rossetti AO. Prediction of cognitive outcome based on the progression of auditory discrimination during coma, Resuscitation. 2016; 106:89-95.

Tzovara A, Rossetti AO, Juan E, Suys T, Viceic D, Rusca M, Oddo M, **De Lucia M**. Prediction of awakening from hypothermic post anoxic coma based on auditory discrimination. Annals Neurology. 2016; 79:748–757.

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Keywords
Imaging neuroscience Human Brain Project

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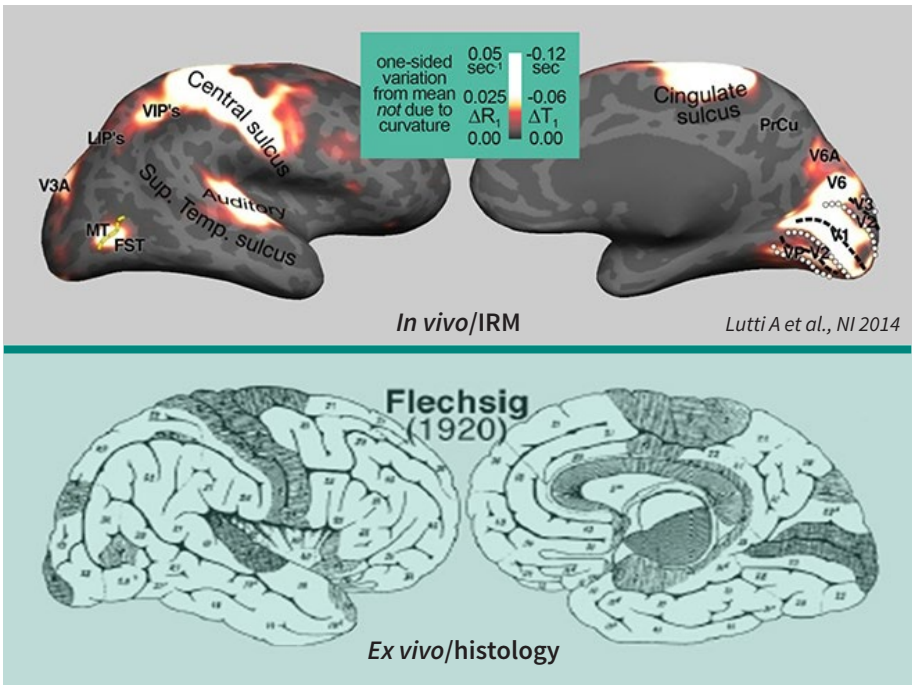
Research interests
In vivo histology using MRI.



My work aims at the development of MRI markers of the brain microstructure allowing in vivo histological analysis of brain tissue ("in vivo histology").

Main publications in 2015-2016

Todd N, Josephs O, Callaghan MF, **Lutti A**, Weiskopf N. Prospective motion correction of 3D echo-planar imaging data for functional MRI using optical tracking. Neuroimage. 2015; 113:1-12.

Lambert C, Zrinzo L, Nagy Z, **Lutti A**, Hariz M, Foltynie T, *et al*. Do we need to revise the tripartite subdivision hypothesis of the human subthalamic nucleus (STN)? Response to Alkemade and Forstmann. Neuroimage. 2015; 110:1-2.

Callaghan MF, Helms G, **Lutti A**, Mohammadi S, Weiskopf N. A general linear relaxometry model of R1 using imaging data. Magn Reson Med. 2015; 73(3):1309-14.

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Keywords
Brain tumours
Tumour genetics and epigenetics
Translational research
Predicitive biomarkers
PDX-mouse models
High resolution magnetic resonance spectroscopy

Laboratory of Brain Tumour Biology and Genetics

Laboratory's activity

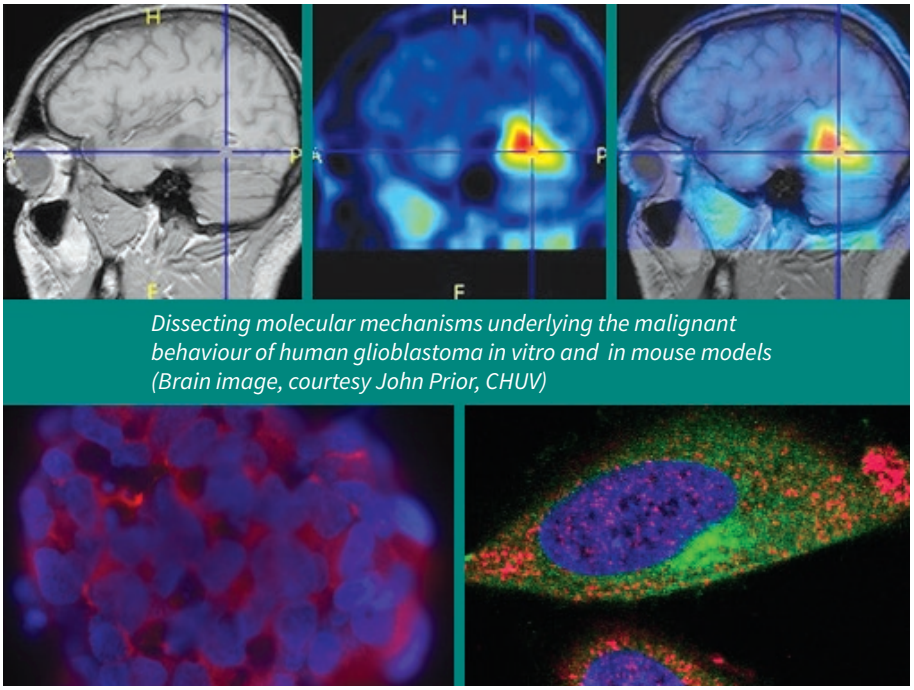
We work at the interphase of clinical and basic cancer research, analyzing multidimensional molecular profiles of glioma from patients treated in clinical trials. We aim at identifying predictive factors for response to therapy and new druggable targets, with a particular focus on tumour epigenetics. We have completed the methylome from over 500 glioma of patients treated in 3 clinical trials for low and high grade glioma. Epigenetic changes contribute substantially to the malignant behaviour of tumours, but may constitute a druggable "Achilles-heel", as we have shown for the repair gene MGMT, that when epigenetically silenced renders glioblastoma sensitive to alkylating chemotherapy. Identified candidate genes/pathways are followed up with experimental studies *in vitro* and *in vivo* to evaluate molecular mechanisms and potential clinical utility. An additional topic is the development of rational combination therapies including epigenetic drugs using a systems medicine approach. In an interdisciplinary DNC/SIB/CIBM-EPFL project, we establish patient-derived xenografts for glioblastoma that are compared to their human counterparts using high resolution magnetic resonance spectroscopy and molecular profiling to identify metabolic patterns for the design of translational clinical trials.

Research interests

> Genetic and epigenetic alterations in glioma, their relevance for tumour biology, tumour classification and response to therapy.
> Experimental follow-up of underlying mechanisms and evaluation of potential interest for new therapeutic approaches.
> Translation of findings into clinical trials for glioma patients.

Scientific contributions in 2015-2016

> Loss of expression of the Wnt Inhibitory Factor 1 (WIF1), a soluble inhibitor of WNTs, is associated with increased migration and invasion and shorter survival as we determined in an orthotopic glioma mouse model. Mechanistically, these effects were mediated through the WNT-pathway, involving WNt5a and the long non-coding RNA *MALAT1*.
> Diffuse invasion is a characteristic feature of glioblastoma prohibiting complete resection and resulting almost invariably in tumour recurrence. Using high resolution Magnetic Resonance Spectroscopy (14 Tesla; collaboration with CIBM-EPFL) distinct temporal migratory patterns of gliomas developing from transplanted patient-derived glioma spheres were detectable in the mouse brain. This provides a valuable tool for preclinical studies.
> Identification of a predictive factor for sensitivity to an mTOR inhibitor in a randomized phase 2 trial for glioblastoma. The marker will be used for patient selection in a basket trial for glioblastoma patients.
> Molecular subgroups of low grade glioma revealed to be predictive for progression free survival of patients treated in a randomized phase 3 trial with either temozolomide or radiotherapy.



Dissecting molecular mechanisms underlying the malignant behaviour of human glioblastoma in vitro and in mouse models (Brain image, courtesy John Prior, CHUV)

Main publications in 2015-2016

*Baumert B, ***Hegi ME**, van den Bent MJ, von Deimling A, Gorlia T, Hoang-Xuan K, *et al*. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. Lancet Oncol. 2016; 17(11):1521-1532. *equal contribution

Wick W, Gorlia T, Bady P, Platten M, van den Bent MJ, Taphoorn MJ, *et al*. Phase II study of radiotherapy and temsirolimus versus radiochemotherapy with temozolomide in patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation (EORTC 26082). Clin Cancer Res. 2016; 22:4797-4806.

Bady P, Delorenzi M, **Hegi ME**. Sensitivity analysis of the MGMT-STP27 model and impact of genetic/epigenetic context to predict the MGMT methylation status in gliomas and other tumours. J Molec Diagn. 2016; 18(3):350-61.

Vassallo I, Zinn P, Lai M, Rajakannu P, Hamou MF, **Hegi ME**. WIF1 re-expression in glioblastoma inhibits migration through attenuation of non-canonical WNT signalling by downregulating the lncRNA MALAT1. Oncogene. 2016; 35(1):12-21.

Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, *et al*. Maintenance therapy with tumour-treating fields plus temozolomide *vs* temozolomide alone for glioblastoma: A Randomized Clinical Trial. JAMA. 2015; 314(23):2535-2543.

Kurscheid S, Bady P, Sciuscio D, Samarzija I, Shay T, Vassallo *et al*. Chromosome 7 gain and DNA hypermethylation at the HOXA10 locus are associated with expression of a stem cell related HOX-signature in glioblastoma. Genome Biol. 2015; 27:16:16.

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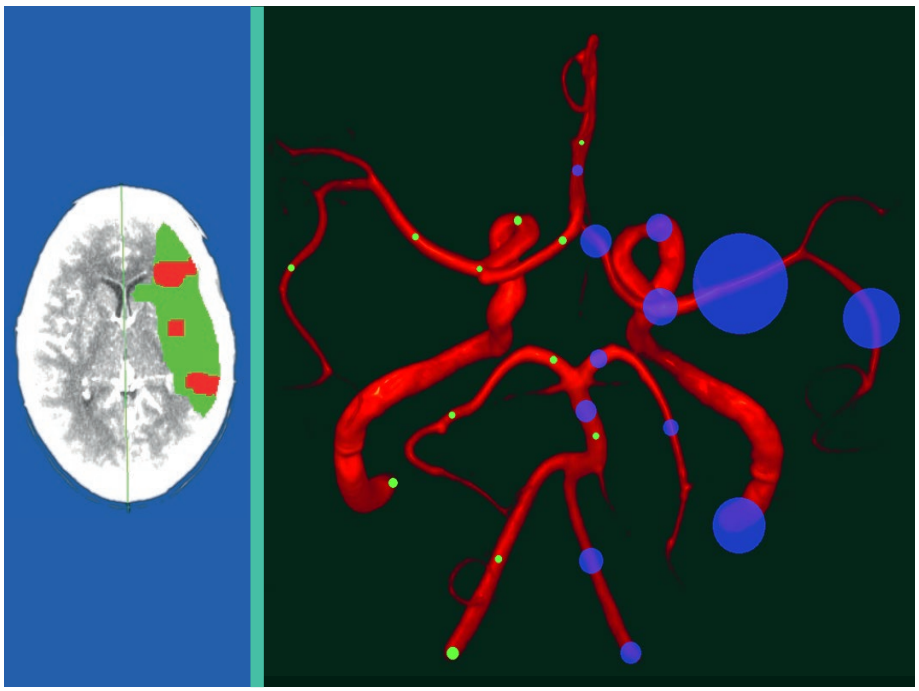
Laboratories of Stroke Research - LMCV

Prof. Lorenz Hirt, Head of laboratory

Laboratory of Stroke Research
Prof. Lorenz Hirt, Head of laboratory, Principal Investigator

Laboratory of Clinical Stroke Research Unit
Prof. Patrik Michel, Head of laboratory, Principal Investigator



Cerebral perfusion and arterial occlusions in acute ischemic stroke.
Left: *perfusion CT of a patient with acute left hemispheric stroke, predicting irreversible tissue damage (red) and potential for tissue survival with optimal treatment (green).*
Right: *CT angiography of cerebral and cervical arteries in 2209 stroke patients, displaying the relative frequency of occlusions (blood clots) that cause stroke symptoms (blue dots) and that are asymptomatic (green dots).*
*(**Sources:** left: Neuroradiology, Department of Medical Radiology, CHUV - Right: Rotzinger D; Mosimann PJ; Meuli RA; Maeder P; Michel P. American Journal of Neuroradiology 2017)*

The Stroke Research branch in the CRN has a wide fundamental research activity including neuroprotection, neuroradiological analyses, and clinical stroke research. It is well known that experimental lab and clinical registries contribute to the understanding of stroke mechanisms as well as to the advancement of acute and chronic treatment of stroke victims. Both the Stroke Laboratory and the Clinical Stroke Research teams are well connected through local, national and international collaborations and welcome international researchers.

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Keywords
Stroke
Cerebral ischemia
Lactate
Neuroprotection

Laboratory of Stroke Research

Laboratory's activity

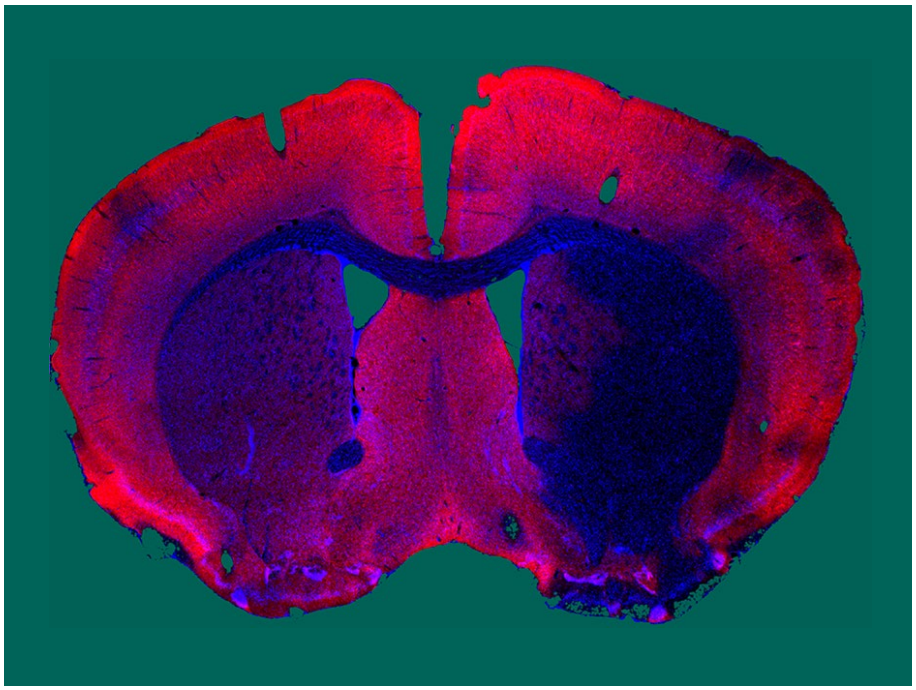
The stroke laboratory is studying mechanisms of cell death after cerebral ischemia using experimental models both *in vivo* (mouse middle cerebral artery occlusion) and *in vitro* (oxygen and glucose deprivation in organotypic hippocampal slice cultures). We are studying lactate as a neuroprotective agent as well as neuroprotective mechanisms involving its receptor and transporters. We have shown that lactate's mode of action is dual, both metabolic and as a signalling molecule. Lactate is known to be involved in angiogenensis and we are currently investigating the effect of lactate on pericytes, endothelial cells as well as the blood brain barrier after stroke. We are characterizing neuroinflammatory changes in the brain parenchyma after ischemia and, in a collaborative project, have studied the role of the scaffolding protein Homer1 in calcium signaling in astrocytes. Two new SNF projects are starting, one on caveolin-1 in cerebral ischemia, the other on the use of hyperpolarized substrates to characterize brain metabolism and brain perfusion and neuroprotection after stroke in the mouse. Lab members are Lara Buscemi PhD; Melanie Price, PhD; Ximena Castillo MD-PhD; Camille Blochet, MSc.

Research interests

Our research aims at finding additional options to improve the outcome of stroke patients. Experimentally, we are investigating the neurovascular unit, neuroinflammation, angiogenesis and metabolism after stroke. In clinical research, we are exploring our newly established large retrospective Doppler US database.

Scientific contributions in 2015-2016

> Progress in research in different fields leading to 11 publications.
> Obtained two FNS grants with national and international collaborations and 1 Biaggi-Juchum grant.
> One person obtained a Lemanic Neuroscience PhD in the lab.
> Established a large retrospective Doppler database.
> Several invitations for lectures and symposia, both national and international.



A transient 30-minute occlusion of the left middle cerebral artery in the mouse induces an ischemic stroke shown here after 48h. The loss of red labelling (MAP2) illustrates the neuronal damage. (Courtesy of L. Buscemi)

Main publications in 2015-2016

Castillo X, Rosafio K, Wyss MT, Drandarov K, Buck A, Pellerin L, Weber B, **Hirt L**. A probable dual mode of action for both l- and d-lactate neuroprotection in cerebral ischemia. J Cereb Blood Flow Metab. 2015; 35:1561-1569.

Rosafio K, Castillo X, **Hirt L**, Pellerin L. Cell-specific modulation of monocarboxylate transporter expression contributes to the metabolic reprograming taking place following cerebral ischemia. Neuroscience. 2016; 317:108-120.

Buscemi L, Ginet V, Lopatar J, Montana V, Pucci L, Spagnuolo P, Zehnder T, Grubisci V, Truttmann A, Sala C, **Hirt L**, Parpura V, Puyal J, Bezzi P. Homer1 scaffold proteins govern ca^{2+} dynamics in normal and reactive astrocytes Cerebral cortex. 2016; pii:bhw078.

Papavasileiou V, Milionis H, **Hirt L**, Michel P. Strokes and tias during and after carotid artery doppler: Cause or coincidence? Ultrasound Med Biol. 2015; 41:418-422.

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Keywords
Stroke
Thrombolysis
Thrombectomy
CT angiography
CT perfusion

Laboratory of Clinical Stroke Research Unit

Laboratory's activity

Since 2003 the Clinical Stroke Research team proactively maintains the ASTRAL registry (Acute STroke Registry and Analysis of Lausanne). It contains >4'000 acute stroke patients, each with >300 variables that include demographic, clinical, comorbidity, multimodal imaging, etiological, metabolic, and outcome data. CT angiography and CT perfusion data are collected and analysed in a detailed manner. We also study frequent and rare stroke mechanisms and syndromes, prognostic marker for good outcome and complications, as well as the influence of acute revascularisation treatments in different situations. The team participates in multiple national and international randomized trials for acute stroke treatment and secondary prevention.

Research interests

Patrik Michel's research interests concern clinical stroke syndromes, acute stroke management, CT-based perfusion and arterial imaging, and stroke prognosis. He and his collaborators have derived the ASTRAL-prognostic, the ASTRAL-occlusion, the ASTRAL-recanalisation and the ASTRAL recurrency scores. Publications on stroke syndromes concern rare stroke causes (air embolism, Doppler-related stroke, floating arterial thrombi, hair-dresser strokes), stroke mimics and chameleons, stroke severity, and early worsening. Regarding prognosis, he has investigated the influence of specific patient features (cardiac failure, haematological values, PFO, insurance type), acute metabolic values (early blood pressure dynamics, hyperglycemia), and of early neuroimaging. In the area of acute stroke treatment, research is performed on the response to thrombolysis in different populations (stroke severity, renal failure, body weight, arterial occlusion status) and treatment of hyperglycemia. Further research interest includes acute arterial occlusion patterns, predictors of recanalisation with and without treatment, impact of collateral, and of brain perfusion imaging. He collaborates with several international teams on the methods and the clinical value of acute perfusion-CT imaging, thrombolysis, PFO-related stroke and basilar artery occlusion.

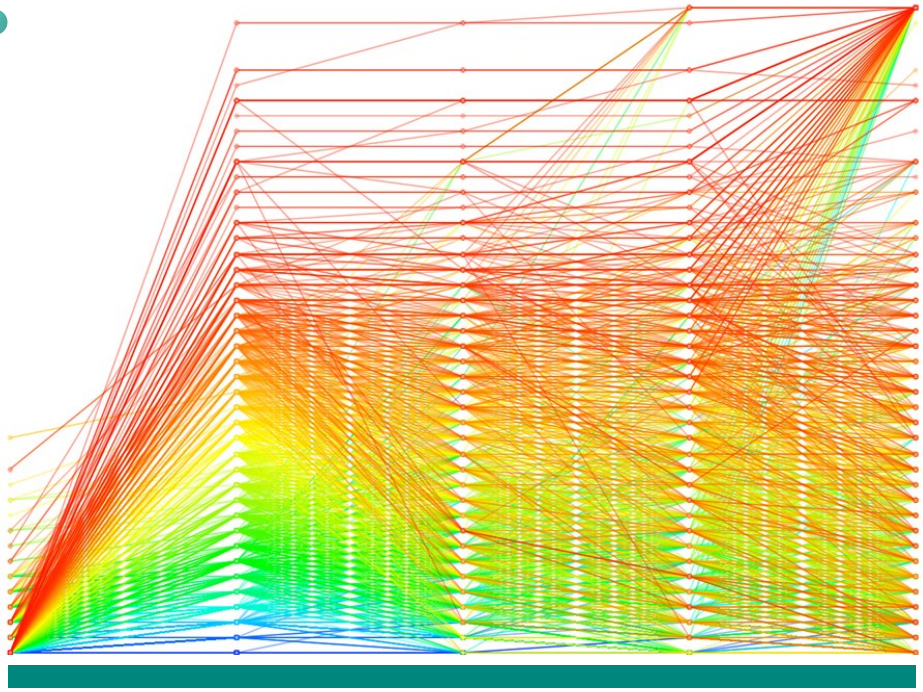
Scientific contributions in 2015-2016

> Clinical stroke syndromes: we have contributed to the understanding of missed stroke («chameleons»), strokes in vertebrobasilar dolichoectasia, strokes during carotid artery Doppler examination, embolic stroke of undetermined source (ESUS) and during hair-dresser visits.

> Acute stroke management: we have identified predictors of arterial recanalisation in acute ischemic stroke (with and without treatment) and developed a score predicting arterial occlusion (ASTRAL-occlusion score) and recanalisation with thrombolysis (ASTRAL-recanalisation score). We have contributed to the understanding of thrombolysis response in men and women, patients with prestroke handicap, different body mass indices, on novel oral anticoagulants, with previsous thrombolysis, with and without acute arterial occlusions, and with floating arterial thrombus. We also have also examined reasons for non-thrombolysis in acute stroke.

> CT-based perfusion and arterial imaging: we have analyzed the clinical value of multimodal CT imaging in acute stroke and the predictive values of CT-perfusion in predicting haemorrhagic transformation after thrombolysis.

> Regarding stroke prognosis, through our work, we have found that various prognostic scores perform better than physicians and that neuroimaging influences prognosis in several ways.



Severity of neurological deficits in 3'443 consecutive ischemic stroke patients from the ASTRAL registry (Acute STroke Registry and Analysis of Lausanne) at 5 time points (from left to right): before the stroke, on arrival at the CHUV, at 6 hours, 24 hours and 7 days later.

Main publications in 2015-2016

Medlin F, Amiguet M, Vanacker P, **Michel P**. Influence of arterial occlusion on outcome after intravenous thrombolysis for acute ischemic stroke. 2015; 46(1):126-31.

Vanacker P, Heldner M, Seiffge D, Mueller H, Eskandari A, Ntaios G, Mosimann PJ, Sztajzel R, Mendes Pereira V, Cras P, Engelter S, Lyrer P, Fischer U, Lambrou D, Arnold M, **Michel P**. ASTRAL-R score predicts non-recanalization after intravenous thrombolysis in acute ischemic stroke. Thromb Haem 2015: 113(5): 1121-6.

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Vanacker P, Lambrou D, Eskandari A, Mosimann PJ, Maghraoui A, **Michel P**. Eligibility and Predictors for Acute Revascularization Procedures in a Stroke Center. Stroke 2016; 47: 1844-1849.

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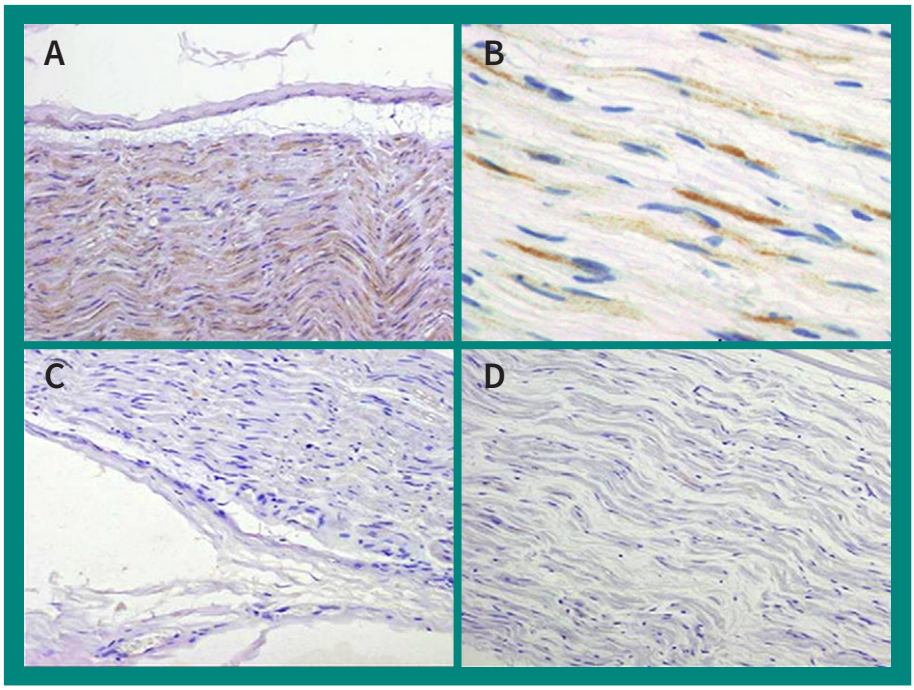
Keywords
Muscle diseases
Peripheral nerve disorders
Gene expression in skin punch biopsies
Electrophysiology in animal models
Clinical Neurophysiology

Laboratory of Nerve-Muscle Unit - NMUL

Laboratory's activity
The Lab is specialized in studying gene expression from skin in inflammatory nerve or degenerative disorders, in quantifying skin denervation by histology and studying axon reflex reaction. The other activities include assessement of nerve-muscle disorders by clinical neurophysiology (large and small nerve fibers), muscle whole body MRI studies, and clinometric measures of muscle function.

Research interests
> Gene expression from skin in inflammatory nerves (CIDP and Guillain-Barré syndrome)
> Quantitative skin denervation by histology
> Clinical neurophysiology
> New tools to assess muscle function.

Scientific contributions in 2015-2016
> Developed a standardized semi-automated quantification of density of Intra-Epidermal Nerve Fibers (IENF) in skin biopsies independent of the observer.
> Acquired skills in analyzing gene expression changes from skin in inflammatory neuropathies.



MSRV-Env is expressed in peripheral nerves biopsies from CIDP patients. Representative immunohistological analysis showing that MSRV-Env immunoreactivity (brown) is found in the cytoplasm of Schwann cells (low magnification: A; high magnification: B). No staining is observed in the corresponding serial section of the same biopsy incubated with a non-relevant isotype antibody (C) or in a biopsy from a control neuropathy (D). Scale bar: 0.5 μm. *(In: EBioMedecine. 2016 Apr;6:190-8. doi: 10.1016/j. ebiom.2016.03.001. Human Endogenous Retrovirus and Neuroinflammation in Chronic Inflammatory Demyelinating Polyradiculoneuropathy)*

Main publications in 2015-2016

Faucard R, Madeira A, Gehin N, Authier FJ, Panaite PA, Lesage C, *et al*. Human Endogenous Retrovirus and Neuroinflammation in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. EBioMedicine. 2016; 6:190-8.

Tsouni P, Panaite PA, Puttini S, **Kuntzer T**, Steck AJ. Intravenous Immunoglobulins Lower Inflammatory Gene Expression in Skin Biopsies of Chronic Inflammatory Demyelinating Polyradiculoneuropathy Patients. European Neurology. 2016; 75(5-6):290-1.

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Laboratory of Cortical Excitability and Arousal Disorders - LE²C

Prof. Philippe Ryvlin, Head of laboratory

Principal investigators:
Dr Jan Novy
Dr Andrea Rossetti

Laboratory's activity

Our laboratory's activities are focusing on clinical research in patients with epilepsy or disorders of consciousness of various origin, including status-epilepticus and post-anoxic coma.

In epilepsy, six main research objectives are being developed:

> Pathophysiology and prevention of Sudden Unexpected Death in Epilepsy Patients (SUDEP)
> Seizure detection in ambulatory patients using mobile health technology
> Optimisation of pre-surgical evaluation and epilepsy surgery
> Point-of-care testing of antiepileptic drugs plasma dosage
> Pharmacogenomic/biomarkers of the disease
> Epidemiology and management of status-epilepticus.

In disorders of consciousness, our current research primarily focuses on outcome prognostication of acute coma, particularly after cardiac arrest.

The methods used in our laboratory include clinical neurophysiology (scalp-EEG, intra-cerebral EEG, evoked potentials), neuroimaging (MRI, functional MRI, PET), biology (dosage of AEDs, genomic), epidemiology and randomized controled trials.

Research interests

Our primary research interests are the pathophysiology and prevention of sudden unexpected death in epilepsy (SUDEP), seizure detection in ambulatory settings, and optimisation of epilepsy surgery. All three topics are driven by the development of novel technologies and mobile health.

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Keywords
Epilepsy
Sudden unexpected death in epilepsy
Neuroimaging
Intracerebral EEG
Seizure detection
Neurotechnologies
Pharmacology
Epidemiology
Biomarkers
Genetic

Laboratory of Cortical Excitability and Arousal Disorders - LE²C

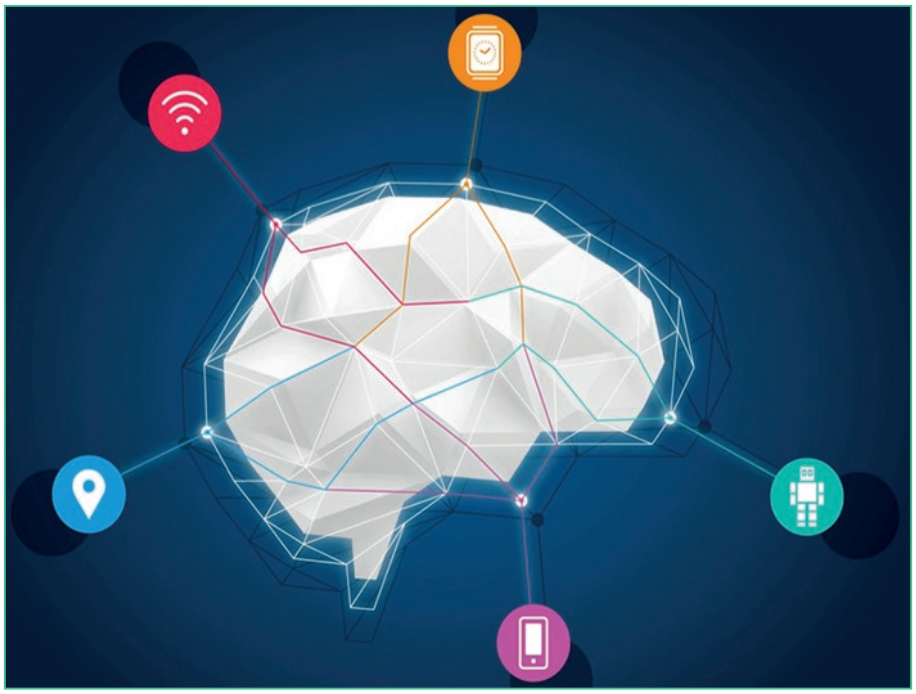
Scientific contributions in 2015-2016

> We estimated the cost-effectiveness of epilepsy surgery in France in comparison to medical treatment alone and showed that direct medical costs became significantly lower in the surgical group the third year after surgery, and that the latter became cost-effective between 9 and 10 years after surgery. This would be significantly earlier if indirect costs were taken into account as well.

> We showed that temporal plus epilepsy, an original concept we developed some years ago, was one of the main predictors of temporal surgery failures. Distinguishing this syndrome from temporal lobe epilepsy proper is thus instrumental for optimal epilepsy surgery.

> We demonstrated that the risk of Sudden Unexpected Death in Epilepsy (SUDEP) is decreasing over time in patients treated with vagus nerve stimulation (VNS), with an overall 25% reduction between years 1-2 and years 3-10 post-VNS implant (submitted to publication).

> We participated to several reviews on epilepsy (Lancet), epilepsy surgery (Current Opinions in Neurology), and research priorities in epilepsy (Epilepsia).



The NeuroTech Platform provides an infrastructure dedicated to the evaluation of the medical and medico-economic impact of novel technologies in clinical neurosciences.

Main publications in 2015-2016

Barba C, Rheims S, Minotti L, Guénot M, Hoffmann D, Chabardès S, Isnard J, Kahane P, **Ryvlin P**. Temporal plus epilepsy is a major determinant of temporal lobe surgery failures. Brain. 2016 Feb;139(Pt 2):444-51.

Beniczky S, Neufeld M, Diehl B, Dobesberger J, Trinka E, Mameniskiene R, Rheims S, Gil-Nagel A, Craiu D, Pressler R, Krysl D, Lebedinsky A, Tassi L, Rubboli G, **Ryvlin P**. Testing patients during seizures: A European consensus procedure developed by a joint taskforce of the ILAE - Commission on European Affairs and the European Epilepsy Monitoring Unit Association. Epilepsia. 2016 Sep; 57(9):1363-8.

Ryvlin P, Rheims S. Predicting epilepsy surgery outcome. Curr Opin Neurol. 2016 Apr; 29(2):182-8.

Baulac M, de Boer H, Elger C, Glynn M, Kälviäinen R, Little A, Mifsud J, Perucca E, Pitkänen A, **Ryvlin P**. Epilepsy priorities in Europe: A report of the ILAE-IBE Epilepsy Advocacy Europe Task Force. Epilepsia. 2015 Nov; 56(11):1687-95

Moshé SL, Perucca E, **Ryvlin P**, Tomson T. Epilepsy: new advances. Lancet. 2015 Mar 7; 385(9971):884-98.

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Keywords
Epilepsy
Sudden unexpected death in epilepsy
Neuroimaging
Intracerebral EEG
Seizure detection
Neurotechnologies
Pharmacology
Epidemiology
Biomarkers
Genetic

Laboratory of Cortical Excitability and Arousal Disorders - LE²C

Scientific contributions in 2015-2016

> We explored the causes of mortality in people with epilepsy in general population, and its relationships with the disease.

> We set up the randomised trial assess therapeutic drug monitoring in epilepsy (collaboration with the laboratory and the division of clinical pharmacology, Profs L. Decosterd and T. Buclin).

> We set up several studies assessing the relationship between drug levels and clinical response in chronic epilepsy, as well as in status epilepticus.

> We explored the phenotype of several rare genetic condition involving cortical excitability.

Main publications in 2015-2016

Keezer MR, Bell GS, Neligan A, **Novy J**, Sander JW. Cause of death and predictors of mortality in a community-based cohort of people with epilepsy. Neurology. 2016; 23:704-712.

Bell GS, Neligan A, Giavasi C, Keezer MR, **Novy J**, Peacock JL, *et al*. Outcome of seizures in the general population after 25-years: a prospective follow-up, observational cohort study. J Neurol Neurosurg Psychiatry. 2016; 87: 843–850.

Leu C, Balestrini S, Maher B, Hernandez-Hernandez L, Gormley P, Hämäläinen E, *et al*. Genome-wide Polygenic Burden of Rare Deleterious Variants in Sudden Unexpected Death in Epilepsy. EBioMedicine. 2015; 2(2):1063-70.

Jaffer F, Avbersek A, Vavassori R, Fons C, Campistol J, Stagnaro M, *et al*. Faulty cardiac repolarization reserve in alternating hemiplegia of childhood broadens the phenotype. Brain. 2015; 138:2859-2874.

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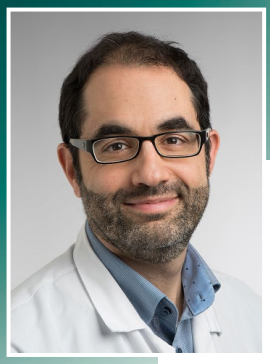

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Keywords
Epilepsy
Status epilepticus
Coma prognostication
EEG
Evoked potentials

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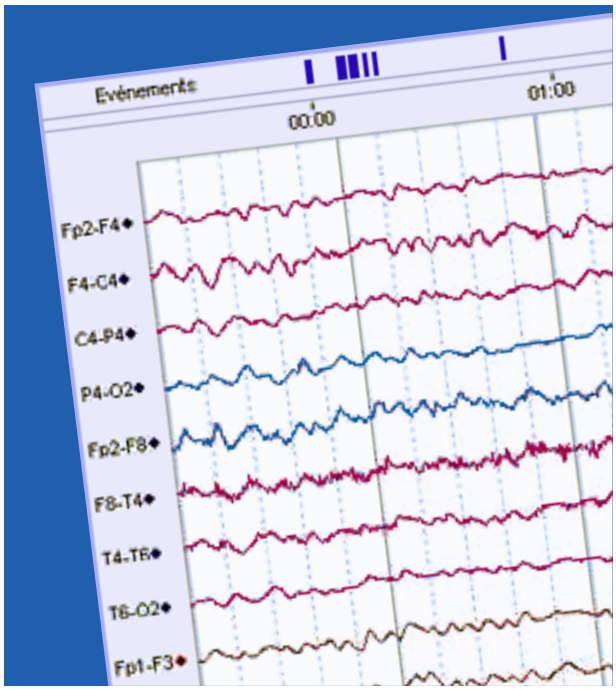

Laboratory's activity
Studies on osology and treatment of status epilpeticus prognostication of acuta coma; EEG monitoring in intensive care unit.

Research interests
Nosology and treatment of status epilpeticus prognostication of acuta coma; EEG monitoring in intensive care unit.

Main publications in 2015-2016

Marchi NA, Novy J, Faouzi M, Stähli C, Burnand B, **Rossetti AO**. Status epilepticus: impact of therapeutic coma on outcome. Crit Care Med. 2015; 43(5):1003-1009.

Spatola M, Novy J, Du Pasquier R, Dalmau J, **Rossetti AO**. Status epilepticus of inflammatory etiology: a cohort study. Neurology. 2015; 85:464-470.

Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome patients in coma after cardiac arrest. Lancet Neurology. 2016; 15:597-609.

Juan E, De Lucia M, Tzovara A, Beaud V, Oddo M, Clarke S, **Rossetti AO**. Prediction of cognitive outcome based on the progression of auditory discrimination during coma. Resuscitation 2016; 106:89-95.

Alvarez V, Lee JW, Westover MB, Drislane FW, Novy J, Faouzi M., Marchi NA, Dworetzky BA, **Rossetti AO**. Therapeutic coma for status epilepticus: differing practices in a prospective multicenter study. Neurology. 2016; 87(16):1650-1659.

Tzovara A, **Rossetti AO**, Juan E, Suys T, Viceic D, Rusca M, Oddo M; De Lucia M. Prediction of awakening from hypothermic post anoxic coma based on auditory discrimination. Ann Neurol. 2016; 79:748-757.

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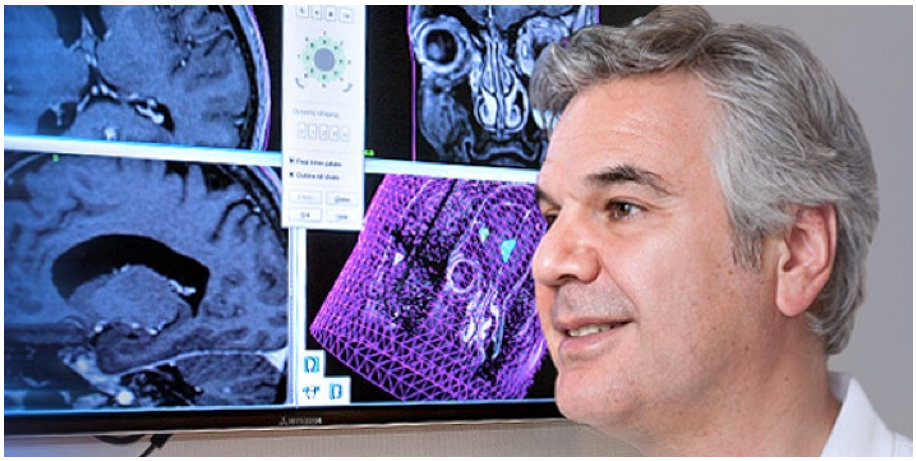
Gamma Knife Center

Prof. Marc Levivier, MD, PhD
Head of the Neurosurgery Service
Head of the Gamma Knife Center



The Gamma Knife Center in the CHUV started its clinical activity in July 2010 and on a regular basis treats patients with a large spectrum of neurosurgical conditions. The indications are multiple and Gamma Knife radiosurgery can be proposed as an alternative to a classical microsurgical excision, as a complement of the former, or when surgery is not possible. More than 1200 patients have been treated as of today. Since June 2016, our Gamma Knife Center is equipped with the latest model and newest functionalities of the Leksell Gamma Knife ICON.
The research activity is an integrated part of the Gamma Knife Center's usual activities.

Research activity involves two main aspects:
> Clinical (in partnership with the Neurosurgery Service in the CHUV, but also with other university hospitals, including those from Marseille, London, Oxford or Lille)
> Fundamental (mainly in partnership with the Swiss Federal Institute of Technology, EPFL, University of Geneva and the Timone Hospital in Marseille)

Our clinical research focuses on the study of clinical outcomes related to functional neurosurgery (in particular pain, as in trigeminal or glossopharyngeal neuralgia), as well as the optimization of functional results after Gamma Knife treatment in benign tumours, such as vestibular schwannomas (hearing preservation, treatment of the acute effects, combined approaches with microsurgery), meningiomas (multicentric studies, place of hypofractionation) or vascular malformations (study of the predictive factors for obliteration). Collaboration with London and Oxford is currently evaluating the possibility of establishing complex algorithms for dose prescription, allowing increasing the efficacy and diminishing the toxicity of certain radiosurgical procedures.

Our fundamental research focuses on the study of structural and functional brain connectivity by using 3 Tesla or higher (7 Tesla) MRI. The purpose is to ameliorate the management of patients with essential tremor, thanks to multiple aspects, allowing optimizing the targeting and also better understanding the clinical response after Gamma Knife thalamotomy. This is mainly evaluating the therapeutic response in function of different phenotypes of the disease. This integrated research work takes the format of an MD-PhD and PhD programme. Radiophysical fundamental research (dosimetric comparisons) is realized also with the Radiophysical Institute in Lausanne. Welcome to the scalpel of the 21st Century.

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Neuroscience Research Center

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Lausanne, 29th March 2017

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Project Coordinator: Valérie Taylor (CRN's Strategic Missions Officer)
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