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Neurocenter of Southern Switzerland (NSI)

2. Neurocenter of Southern Switzerland

Prof. Alain Kaelin MD, PhD
Head of Department and Scientific Director of NSI and Neurosciences

The Neurocenter of Southern Switzerland (NSI) hosts the services of neurology, neurosurgery, neuroradiology, neuroanaesthesia as well as the neuroscience research unit. The goal of the NSI is to confer the highest quality of treatment to the patient with the application and promotion of an inter- and multidisciplinary approach. To ensure a continuous excellence of care, the implementation of basic and clinical research, as well as educational duties, is an important priority for the NSI.

Academic collaboration with local, national and international universities and hospitals including regular teaching activities at the level of the Master of Medicine at the University of Bern and Basel, as well as active participation in PhD programs in neurosciences at the University of Bern, Basel and Zurich are contributing to the success of the NSI.
The main focus of scientific activities at the NSI currently relies on multiple sclerosis, sleep disorders, movement disorders and stroke, even though, active research is also carried out in other fields of clinical neuroscience.

For clinical research, one of the two seats of the Clinical Trial Unit of the Ente Ospedaliero Cantonale (CTU-EOC) is located at the NSI. The Clinical Trial Unit supported the investigators of the NSI for investigator-initiated and sponsor-initiated studies and participated in several studies described below.
The pertaining projects in basic and clinical research carried out or still ongoing in 2016, are summarised in the following sections.

2.1. Multiple Sclerosis Center

Claudio Gobbi MD, PD
Head Doctor of the Neurology Service - Chief of Center
Chiara Zecca MD
Head of the Neurology Service - Chief of Center

Collaborators: Giulio Disanto MD, Isabella Maraffi MD, Emanuele Pravatà MD, Rosaria Sacco MD, Liliane Petrini PhD, Gianna Riccitelli PhD, Mara Gola Study Nurse, Valeria Pifferini Study Nurse, Silvia Tentori Study Nurse

The Multiple Sclerosis Center aims at offering an optimal care for patients with multiple sclerosis (MS) mainly living in the Ticino area. A dedicated team of two senior neurologists, one neuroradiologist, three assistants, one neuropsychologist, and three MS nurses specialised in multiple sclerosis, run the outpatient care service and concomitantly performs research activities. Research contributes to offering alternative and innovative treatments to patients and advancing knowledge in the MS field.

Peer reviewed publications in 2016

Arrambide G, Espejo C, Eixarch H, Villar LM, Alvarez-Cermeño JC, Picón C, Kuhle J, Disanto G, Kappos L, Sastre-Garriga J, Pareto D, Simon E, Comabella M, Río J, Nos C, Tur C, Castilló J, Vidal-Jordana A, Galán I, Arévalo MJ, Auger C, Rovira A, Montalban X, Tintore M.
Neurofilament light chain level is a weak risk factor for the development of MS.
Neurology. 2016;87(11):1076-1084. doi: 10.1212/WNL.0000000000003085. Epub 2016 Aug 12.

Bernardini LR, Zecca C, Clerici VT, Gobbi C, Mantegazza R, Rossi S.
Severe articular and musculoskeletal pain: An unexpected side effect of dimethyl-fumarate therapy for multiple sclerosis.
J Neurol Sci. 2016;369:139-140. doi: 10.1016/j.jns.2016.07.026. Epub 2016 Jul 14.

Disanto G, Benkert P, Lorscheider J, Mueller S, Vehoff J, Zecca C, Ramseier S, Achtnichts L, Findling O, Nedeltchev K, Radue EW, Sprenger T, Stippich C, Derfuss T, Louvion JF, Kamm CP, Mattle HP, Lotter C, Du Pasquier R, Schluep M, Pot C, Lalive PH, Yaldizli Ö, Gobbi C, Kappos L, Kuhle J; SMSC Scientific Board.
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. doi: 10.1371/journal.pone.0152347. eCollection 2016.

Pravatà E, Zecca C, Sestieri C, Caulo M, Riccitelli GC, Rocca MA, Filippi M, Cianfoni A, Gobbi C.
Hyperconnectivity of the dorsolateral prefrontal cortex following mental effort in multiple sclerosis patients with cognitive fatigue.
Mult Scler. 2016;22(13):1665-1675. Epub 2016 Feb 4.

Zecca C, Riccitelli GC, Disanto G, Singh A, Digesu GA, Panicari L, Puccini F, Mattioli M, Tubaro A, Gobbi C.
Urinary incontinence in multiple sclerosis: prevalence, severity and impact on patients' quality of life.
Eur J Neurol. 2016;23(7):1228-1234. doi: 10.1111/ene.13010. Epub 2016 Apr 27.

Main areas of research

The Multiple Sclerosis Center focuses on three long-term research topics

MS epidemiology is endorsed by the participation in the Swiss Cohort of MS patients (SMSC), an innovative project to establish a clinical database and a biological sample collection available for current and future research. Our Multiple Sclerosis Center achieved the goal for inclusion of patients, as 107 patients have already been enrolled. It participates in a sub-study to validate multimodal evoked potentials for prognosis and monitoring the MS disease course in different stages of the disease.

Upcoming MS treatments can be provided to our patients with primary and/or secondary relapsing-remittent MS through our participation in several international trials. Some of them evaluate suitable MS therapeutic compounds such as ocrelizumab (NCT01247324) and siponimod (NCT01665144). Observational trials focus on new drug administration methods (TERIFL06965, NCT02076841, NCT02247310) or gather safety and efficacy data on marketed drugs [fingolimod (CFTY720D2406), natalizumab (NCT02386566), di-methylfumarate (NCT02047097)]. Industry-sponsored research is also performed in migraine indication (NCT02483585).

Investigator-initiated trials focus on the diagnosis and on the understanding of MS symptoms aiming at improving the patients' quality of life.

Ongoing studies

Serum neurofilament light chain levels: a biomarker for prediction of neurological disability in multiple sclerosis.
Lead investigator: C. Zecca.
Collaborators: C. Gobbi, G. Disanto and J. Kuhle (Department of Neurology, University of Basel).

Neurofilaments (Nf) are structural elements of neurones composed of three Nf chains (light (NfL), medium and heavy (NfH)) and α-internexin in the central nervous system (CNS) or peripheral nervous system. Nf are released into the extracellular space following neuronal death and are therefore considered as a candidate biomarker of ongoing neurodegeneration. Levels of neurofilaments are abnormally high in cerebrospinal fluid in patients with MS and correlate with measures of disease severity. Obtaining CSF is a relatively invasive procedure which limits the potential use of Nf as biomarkers in MS in clinical trials. A sensitive electrochemiluminescence (ECL)-based immunoassay for the quantification of NfL in serum was recently developed and showed a close correlation between serum and CSF NfL levels. We investigate the potential role of serum and CSF NfL levels in the prediction of future neurological disability and the correlation between serum and CSF NfL levels in MS patients of the Ticino cohort and their association with different clinical phenotypes. This is a retrospective analysis of biosamples of 200 MS patients and 254 healthy controls. Cox regression models will be used to test the association between baseline serum and CSF NfL with time to reach disability milestones as measured by the EDSS and time to develop new clinical relapses.

Pain network and neuropsychological profile in multiple sclerosis and migraine patients – a clinical and Magnetic Resonance Imaging study (EOC.NSIMS.14.01).
Lead investigator: C. Zecca.
Collaborators: G. Riccitelli, E. Pravatà, A. Cianfoni, C. Gobbi.

This is a prospective, observational, cross-sectional, case-control, three-arm, single-center research project aiming at investigating brain functional and structural substrates of pain network in patients with multiple sclerosis (MS) and migraine and at defining the relationship between brain functional activity, the severity of brain tissue damage and specific neuropsychological profile in MS patients with migraine. Assessments include Magnetic Resonance Imaging data acquisition running 6 different sequences, EDSS score and neuropsychological tests assessing executive functions, attention, memory, and visuospatial abilities. The intrinsic brain functional connectivity from MRI BOLD data obtained at rest will be estimated. The microstructural and

macrostructural brain damage using high field T1 and DTI MRI techniques will be quantified. A correlation between MRI findings and clinical and neuropsychological measures in MS patients with and without migraine and patients with migraine alone will be established.
At present, 84 out of 100 planned patients were enrolled and concluded the assessments.

Multidimensional assessment of fatigue in multiple sclerosis – observational study – Ticino (EOC.NSI.13.02).
Lead investigator: C. Gobbi.
Collaborators: M. Manconi, C. Zecca, L. Panicari, G. Riccitelli, S. Fulda, C. Cartellina.

This cross-sectional, prospective, observational, instrumental investigation seeks to: 1) provide a detailed characterisation of fatigue in a cohort of selected MS patients, including a definition of the boundaries and the overlaps between fatigue, somnolence, mood disorders and attention dysfunction; 2) see how the prevalence and the overlaps between fatigue, somnolence, depression and attention dysfunction are influenced by the method of assessment; 3) better characterise sleep structure in MS patients with fatigue under both the macro- and microstructural point of view. Inclusion criteria are a definite diagnosis of MS (or clinically isolated syndromes according to the current criteria, Expanded Disability Status Scale (EDSS) score < 7.0 and last magnetic resonance imaging (MRI) within previous 12 months. Fatigue, sleep, psychiatric and cognitive assessments will be performed using appropriate questionnaires.
At present, 84 out of 100 planned patients were enrolled and concluded the assessments.

Clinical trials in collaboration with the pharmaceutical industry

EMR200136_597 (NCT02949908): a phase IV, prospective, multicenter, open-label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif® after discontinuing initial first-line treatment.
Sponsor: Merck.

CHE-TYS-12-10341 (NCT02386566): a prospective, multicenter, single-arm phase IV study to assess the correlation of EDSS with quality of life in MS patients treated with natalizumab.
Sponsor: Biogen.

109MS421 (NCT02776072): a multicenter, global, retrospective, observational study to characterize real-world clinical outcomes in patients with relapsing-remitting multiple sclerosis treated with disease - modifying therapies (Tecfidera®, Copaxone®, Aubagio®, or Gilenya®).
Sponsor: Biogen.

105MS401 (NCT02230969): Plegridy™ (peginterferon β-1a) Real World Effectiveness and Safety Observational Program (POP).
Sponsor: Biogen.

109MS401 (NCT02047097): a multicenter, global, observational study to collect information on safety and to document the drug utilization of Tecfidera™ (dimethyl fumarate) when used in routine medical practice in the treatment of multiple sclerosis.
Sponsor: Biogen.

CBAF312A2304 (NCT01665144): exploring the efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis (EXPAND).
Sponsor: Novartis.

CFTY720D2406: long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Sponsor: Novartis.

COMB157G2302 (NCT02792231): a randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis.
Sponsor: Novartis.

WA21092/93 (NCT01247324): a study of ocrelizumab in comparison with interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis.
Sponsor: Roche.

TERIFLO6965: teriflunomide in RRMS patients assessing clinical benefit and patient

reported outcomes in real-life medical practice. TERIFLO6965.
Sponsor: Sanofi-Aventis.

20120297 (NCT02483585): a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AMG 334 in migraine prevention.
Sponsor: Amgen.

CHE-AVX-12-10348 (NCT02076841): tolerability and quality of life in patients with multiple sclerosis switched to intramuscular interferon beta-1a autoinjector (Avonex® PenTM).
Sponsor: Biogen.

The study closed in 2016.

BF1401 (NCT02247310): BETAEVAL Global – The new BETACONNECTTM auto-injector: adherence and EVALuation of MS patients treated with Betaferon®.
Sponsor: Bayer.

The study closed in 2016.

Active internal collaborations

M. Manconi, NSI
Multidimensional assessment of fatigue in multiple sclerosis – observational study
1 ongoing research project.

A. Cianfoni, NSI
Pain network and neuropsychological profile in multiple sclerosis and migraine patients
1 ongoing research project, 1 publication (case report).

A. Reinert, NSI
1 publication (case report).

Active external collaborations

L. Kappos and J. Kuhle, Department of Neurology, University of Basel
Validation of multimodal evoked potentials; Swiss Multiple Sclerosis Cohort-Study; Serum neurofilament light chain levels
1 publication, 1 publication submitted (Annals of Neurology journal).

V. Martinelli, Department of Neurology, San Raffaele Scientific Institute, Milan, Italy
MS treatment with fingolimod
1 publication submitted (Multiple Sclerosis Journal, MSJ).

R. Mantegazza, Neuroimmunology and Neuromuscular Diseases Unit, IRCCS Foundation, "Carlo Besta" Neurological Institute, Milan, Italy
1 publication (case report).

M. Filippi, Neuroimaging Research Unit, San Raffaele Hospital, Milan, Italy
2 publications (original papers).

Main funding

C. Zecca:
Serum neurofilament light chain levels: a biomarker for prediction of neurological disability in multiple sclerosis: ABREOC (internal competitive grant).

Pain network and neuropsychological profile in multiple sclerosis and migraine patients - a clinical and Magnetic Resonance Imaging study (EOC. NSIMS.14.01): Swiss MS Society (external competitive grant; amount obtained in 2015: CHF 42,000; year of activation: 2015; duration: 2 years).

G. Disanto:
Pre-diagnostic presentations of multiple sclerosis in primary care: a case-control study: Swiss MS Society (external competitive grant; amount obtained in 2016: CHF 20,000; year of activation: 2016; duration: 1 year).

C. Gobbi:
Effects of repetitive transcranial magnetic stimulation and cognitive rehabilitation on cognitive functions in patients with multiple sclerosis: an explorative study with structural and functional MRI: Swiss MS Society (external competitive grant; amount obtained in 2016: CHF 35,000; year of activation: 2016; duration: 1 year).

Number of trainees

Two Masterclass medical students (cand. Med) from the University Hospital of Basel (September 2016).

2.2. Neuromuscolar Unit, Myosuisse Ticino Center

Claudio Gobbi MD, PD
Head Doctor of the Neurology Service - Coordinator of Center (Neurology)
Prof. Gian Paolo Ramelli MD
Head Doctor of the Paediatrics Service - Coordinator of Center (Neuropaediatrics)

Collaborators: Giorgia Melli MD PhD, Paolo Ripellino MD, Massimiliano Tiberti MD, Anna Maria Sury Case Manager

The Neuromuscular Unit is housed in the Myosuisse Ticino Center, which belongs to a network of other Swiss centres specialised in neuromuscular diseases. It provides interdisciplinary and specialised consultancy to patients with neuromuscular diseases, including clinical neurological and instrumental evaluations for accurate diagnosis. The Neuromuscular Unit participates in the Swiss Register of Neuromuscular Disorders (Duchenne dystrophy and other myopathies, myotonic dystrophy, ALS and other rare diseases). Its main research collaborations are established with: the EOC Microbiology Laboratory, "Centre Hospitalier Universitaire Vaudois (CHUV) – (CHUV University Hospital)" of Lausanne, the University Hospital of Basel, the Institute for Research in Biomedicine (IRB) of Bellinzona and several referral centres for neuralgic amyotrophy in England and in the Netherlands collecting European data on neuralgic amyotrophy.
In 2015 we started a prospective pilot study on neurological complications related to hepatitis E in Switzerland.

Main areas of research

Neurological Complications of Acute Virus E infection (NeuroCAVE) (EOC.NSI.MS.1502).
Lead investigator: C. Gobbi.
Collaborator: P. Ripellino.

For the first time, neurological complications related to hepatitis E are studied prospectively. An outbreak in Ticino (due to contaminated meat ingestion) allowed us to follow up 52 acute HEV cases in 2 years (IgM+ and IgG+; PCR+/-). The majority of patients were hospitalised. HEV PCR was positive in 15 cases, and genotype 3 was identified. Overall, 14 patients had Neuralgic Amyotrophy (NA), 19 myalgias and 1 transverse myelitis. NA was bilateral in 9 cases and more common in males, whereas myalgias occurred more frequently in females. 8 cases of NA were confirmed with EMG, showing a predominant upper trunk (C5-C6) involvement. The common findings of CSF analysis, MRI and US in NA patients, and their response to oral Prednisone or IVIg were investigated. The neurological complications of acute HEV genotype 3 infection are frequent (60%) among patients, even with mild hepatitis, and consist mainly in NA and myalgias.

Main funding

ABREOC (internal competitive grant).

2.3. Sleep and Epilepsy Center

Prof. Mauro Manconi MD
Head of the Neurology Service - Chief of Center

The sleep and epilepsy laboratory's scientific mission is to explore brain function during sleep and sleep-related disorders to achieve important pieces of knowledge in the new, intriguing and extremely growing field of sleep research. Our group is internationally recognised for its results in the area of sleep related movement disorders such as restless legs syndrome, periodic limb movement disorders, sleep disorders during pregnancy and the relationship between sleep and stroke.
Two important goals were achieved by the Sleep Center in 2016:

— The official recognition by the Swiss Sleep Society (SSSSC) as a training centre of category A for the sleep medicine expert certificate
— The recognition by the International RLS Foundation as a centre of excellence for the diagnosis and treatment of restless legs syndrome (unique in Switzerland and second in Europe).

In the last five years, thanks to consolidated local and external collaborations, we obtained large competitive grants from the Swiss National Foundation, two of them focused on the impact of sleep disorders on the stroke outcome, one on the effects of sleep related movement disorders on cardiovascular system, one on infraslow oscillation in sleep and the last on sleep disorders and perinatal depression. A further large competitive grant was obtained in 2014 by the Italian Ministry of University to study the efficacy of light therapy on perinatal depression, and the study started in 2015. Other fields of interest, supported by starting competitive local and national grants, include: sleep disorders in Parkinson Disease, sleep disorders in attention deficit hyperactive disorder and infraslow oscillating process in sleeping brain; innovative tools like High-Density EEG will be used in both cases. Educational initiatives such as university masters, European level master courses in sleep medicine, exchanging scholar and fellowship programs and periodic meeting with general population are a further basic pillar of our group's mission.

Peer reviewed publications in 2016

Ferri R, Fulda S, Allen RP, Zucconi M, Bruni O, Chokroverty S, Ferini-Strambi L, Frauscher B, Garcia-Borreguero D, Hirshkowitz M, Högl B, Inoue Y, Jahangir A, Manconi M, Marcus CL, Picchietti DL, Plazzi G, Winkelman JW, Zak RS; International and European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG).
World Association of Sleep Medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms developed by a joint task force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG).
Sleep Med. 2016;26:86-95. doi: 10.1016/j.sleep.2016.10.010. Epub 2016 Nov 7.

Ferri R, Rundo F, Zucconi M, Manconi M, Aricò D, Bruni O, Ferini-Strambi L, Fulda S.
Diagnostic accuracy of the standard and alternative periodic leg movement during sleep indices for restless legs syndrome.
Sleep Med. 2016;22:97-99. doi: 10.1016/j.sleep.2015.11.018. Epub 2015 Dec 18.

Garcia-Borreguero D, Silber MH, Winkelman JW, Högl B, Bainbridge J, Buchfuhrer M, Hadjigeorgiou G, Inoue Y, Manconi M, Oertel W, Ondo W, Winkelmann J, Allen RP.
Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation.
Sleep Med. 2016;21:1-11. doi: 10.1016/j.sleep.2016.01.017. Epub 2016 Feb 23.

Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K, Larramona H, Miano S, Narang I, Trang H, Tsaoussoglou M, Vandenbussche N, Villa MP, Van Waardenburg D, Weber S, Verhulst S.
Obstructive sleep-disordered breathing in 2- to 18-year-old children: diagnosis and management.
Eur Respir J. 2016;47(1):69-94. doi: 10.1183/13993003.00385-2015. Epub 2015 Nov 5.

Miano S, Esposito M, Foderaro G, Ramelli GP, Pezzoli V, Manconi M.
Sleep-Related Disorders in Children with Attention-Deficit Hyperactivity Disorder: Preliminary Results of a Full Sleep Assessment Study.
CNS Neurosci Ther. 2016;22(11):906-914. doi: 10.1111/cns.12573. Epub 2016 Jun 3.

Main areas of research

Sleep-related movement disorders: Restless Legs Syndrome (RLS) and Periodic Limb Movements (PLM).
Lead investigators: M. Manconi, S. Fulda.

The impact of RLS/PLM on cardiovascular function. RLS/PLM as a risk factor for perinatal depression. Respiratory-related limb movements. Time structure of PLM in RLS and other sleep disorders. RLS/PLM in multiple sclerosis and their relationship with fatigue. Treatment and management of long-term complication in RLS, in particular, the augmentation phenomena. Time-structure and dopaminergic response of periodic limb movements during sleep in the spinal lesion.

Sleep and stroke.
Investigators: M. Manconi, S. Miano, L. Ratti, C. Cereda, V. Stojanova.

The impact of sleep disorders on stroke outcome. Efficacy of early CPAP treatment in stroke patients with sleep apnea in improving the stroke outcome.

Infra-slow oscillations.
Investigators: S. Fulda, M. Manconi, C. Prosperetti.

Computation analysis of periodic limb movements during sleep and another infraslow-oscillating process during sleep.

Sleep disorders in pediatrics, hyperactive attention deficit disorder.
Investigators: S. Miano, M. Manconi, V. Pezzoli, GP. Ramelli.
Cycling alternating pattern as a diagnostic marker of hyperactive attention deficit disorder.

Sleep disorders during pregnancy and its relationship with perinatal depression.
Investigators: M. Manconi, C. Garbazza, S. Riccardi, M. Preve, T. Gyr, N. Piazza.

The main aim is to identify early sleep-related markers of perinatal depression, to test the efficacy and safety of light treatment as a preventive and therapeutic strategy for perinatal depression, and to identify possible genetic risk factors for perinatal depression and RLS during pregnancy.

Nocturnal eating disorder.
Lead investigators: M. Manconi, P. Vinai.

Differential diagnosis, polysomnographic and neuropsychological features of sleep-related eating disorder and nocturnal eating disorders.

Sleep and Parkinson Disease.
Investigators: PL. Ratti, A. Kaelin-Lang, N. Amato, S. Miano, S. Hackethal.

Characterisation of the so-called “sleep benefit” (SB) phenomenon, i.e. the spontaneous improvement in motor function referred by some patients with Parkinson’s Disease at awakening.

Active Local Collaborations

A. Auricchio, Cardiocenter TI
RLS/PLM and cardiovascular risk
1 SNSF (Swiss National Science Foundation) grant.

P. Schulz, Science Communication University, USI
Judisky study - Effective empowerment in insomnia
1 SNSF grant.

C. Gobbi, NSI
Sleep/Fatigue in MS
1 paper (review), 1 ongoing study.

S. Galati, NSI
Sleep and Parkinson disease (PD)
1 ongoing study, (ABREOC grant).

C. Cereda, NSI
Sleep-related risk factors for CVD
3 papers.

A. Kaelin, NSI
Sleep and Parkinson disease (PD).

M. Pons, A. Riglietti, Pneumology Service, Regional Hospital of Lugano
Central control of breathing during sleep
2 papers in the process of being printed.

T. Gyr, Gynaecology and Obstetrics Service, Regional Hospital of Lugano
Iron infusion in RLS during pregnancy
1 paper.

M. Preve, Cantonal Psychiatric Clinic of Mendrisio
Life-ON project
1 paper.

Active External Collaborations

S. Clemens, East Carolina University, Greenville, USA
Basic Science (spinal dopaminergic network)
2 papers.

J. Winkelmann, Harvard University, Boston, USA
Sleep-related movement disorders (PLM hypoxia)
2 papers.

R. Ferri, IRCCS Oasi Institute, Italy
Sleep-related movement disorders (PLM/RLS)
36 papers.

C. Bassetti, Bern University, Inselspital, Switzerland
Sleep stroke, pregnancy related RLS
10 papers.

L. Ferini-Strambi, IRCCS San Raffaele, Italy
Sleep/Epilepsy disorders
48 papers.

O. Polo, University of Tampere, Finland
Spinal lesioned model of PLM/RLS
1 paper.

S. Happe, University of Münster, Germany
Computer analysis (LM during sleep)
1 travel grant (ESRS – 2014).

I. Gorayeb, University of Bordeaux, France
Sleep microstructure and PLM in monkeys
2 papers.

F. Fanfulla
Sleep and Stroke
2 papers.

Main funding

M. Manconi (co-applicant), L. Ratti, G. Chiaro:
Sleep loss and sleep disorders and their impact on the short- and long-term outcome of Stroke: Swiss National Science Foundation (SNSF) (amount: CHF 597,000; duration: 2014-2018).

M. Manconi (lead investigator), S. Fulda, A. Auricchio:
Auto-REST Study: Autonomic function and cardiovascular risk in Restless Legs Syndrome: SNSF (amount: CHF 316,000; duration: 2013-2016).

M. Manconi (lead investigator), T. Gyr, C. Garbazza:
Restless Legs Syndrome and Sleep Disorders During Pregnancy and Sleep Related; Risk Factor for Perinatal Depression: MIUR (Italian Department of University Research) Finalised Research, Italian Ministry of University (Italian competitive national grant) (global amount: Euro 901,000; duration: 2015-2019).

S. Fulda (co-applicant):
Sleep Disorder Research. Infra-Slow-Oscillation during Sleep; M. Manconi (Lead investigator): EOC/IBM (funding amount CHF 175,000; started in December 2014; duration 2 years).

T. Gyr, C. Garbazza, M. Preve:

The Life-ON Project: Light-Therapy in Perinatal Depression; M. Manconi (Lead investigator): SNSF (amount: CHF 525,000; duration: 2015-2018).

S. Fulda (lead investigator), C. Prosperetti:
ISO Study: Infra-slow oscillations I: ABREOC (internal competitive grant; duration: 2015-2016).

S. Fulda (lead investigator), M. Manconi, S. Miano; collaboration: S. Vanhatalo, University of Helsinki: Infra-slow oscillations II (NCT02532608): SNSF (amount: CHF 120,000; duration: 2015-2017).

S. Miano, M. Manconi:
A1DHD Study: Markers polisonnografici del disturbo dell'attenzione ed iperattività in età pediatrica e disturbi del sonno (Polysomnographic markers of attention deficit and hyperactivity disorder in paediatric age and sleep disorders): ABREOC (internal competitive grant; duration: 2015-2016).

L. Ratti, A. Kaelin, N. Amato:
Sleep and motor improvement in Parkinson's disease at awakening: an observational home-based study ("Sleep Home & Move"), Sleep, Awake & Move: ABREOC (internal competitive grant; amount: CHF 52,000); Swiss Parkinson Association, (amount: CHF 183,000; duration: 2015-2018).

M. Manconi, C. Garbazza, S. Riccardi, C. Cajochen:
Iron metabolism during pregnancy: Vifor Pharma (unrestrictive grant; amount: CHF 100,000; duration: 2016-2019).

M. Manconi:
Open-label, prospective, interventional pilot study on the efficacy of a novel mandibular advancement device in obstructive sleep apnoea: BVL Investment (amount: CHF 46,000; duration: 2016-2018).

Awards 2016

Manconi M.
Best Poster Award at The 6th Giornata della Ricerca Clinica della Svizzera Italiana 2016 (The 6th Clinical Research Day of Southern Switzerland 2016), Lugano, 18th March 2016
An open-label study of the efficacy and safety of Intravenous Ferric Carboxymaltose in pregnant women with Restless Legs Syndrome.

2.4. Movement Disorders Center

Claudio Staedler MD
Head Doctor of the Neurology Service - Chief of Center

Collaborators: Prof. Alain Kaelin MD PhD, Salvatore Galati MD PhD

Research on movement disorders represents one important recent research interest at the Neurocenter of Southern Switzerland. In January 2014, Prof. A. Kaelin joined the movement disorders research group and activities were consolidated in 2015 and 2016. Currently, the priority of the translational research efforts relies on the pathogenesis and potential treatment of dyskinesias, involuntary movements that develop in the course of the long-term levodopa treatment of patients with Parkinson´s disease (PD). Both clinical research and basic research are carried out. All basic research is performed in the "Laboratory for Biomedical Neurosciences" (see paragraph 2.10: Laboratory for Biomedical Neurosciences - LBN).
Other collaborative projects are underway, mainly in collaboration with the University of Bern. In particular, a neurophysiological project financed by the Swiss National Science Foundation and investigating motor system recovery in children after stroke continued in 2016.
In addition, a database of more than 200 patients of Ticino with movement disorders, in particularly PD, was set up and will be useful for the performance of epidemiological and clinical studies and an ambitious translational research project using skin biopsy to diagnose Parkinson's Disease was funded by the Swiss Parkinson Association and is ongoing.

Peer reviewed publications in 2016

Cubo E, Ramos-Arroyo MA, Martinez-Horta S, Martínez-Descalls A, Calvo S, Gil-Polo C; European HD Network (Kaelin A).
Clinical manifestations of intermediate allele carriers in Huntington disease.
Neurology. 2016;87(6):571-578. doi: 10.1212/WNL.0000000000002944. Epub 2016 Jul 8.

Dressler D, Altenmueller E, Bhidayasiri R, Bohlega S, Chana P, Chung TM, Frucht S, Garcia-Ruiz PJ, Kaelin A, Kaji R, Kanovsky P, Laskawi R, Micheli F, Orlova O, Relja M, Rosales R, Slawek J, Timerbaeva S, Warner TT, Saberi FA.
Strategies for treatment of dystonia.
J Neural Transm (Vienna). 2016;123(3):251-258. doi: 10.1007/s00702-015-1453-x. Epub 2015 Sep 14. Erratum in: J Neural Transm (Vienna). 2016;123(3):259. doi: 10.1007/s00702-015-1471-8.

Lönnfors-Weitzel T, Weitzel T, Slotboom J, Kiefer C, Pollo C, Schüpbach M, Oertel M, Kaelin A, Wiest R.
T2-relaxometry predicts outcome of DBS in idiopathic Parkinson's disease.
Neuroimage Clin. 2016;12:832-837. eCollection 2016.

Salvadè A, D'Angelo V, Di Giovanni G, Tinkhauser G, Sancesario G, Städler C, Möller JC, Stefani A, Kaelin-Lang A, Galati S.
Distinct roles of cortical and pallidal β and γ frequencies in hemiparkinsonian and dyskinetic rats.
Exp Neurol. 2016;275 Pt 1:199-208. doi: 10.1016/j.expneurol.2015.11.005. Epub 2015 Nov 10.

Sgroi S, Capper-Loup C, Paganetti P, Kaelin-Lang A.
Enkephalin and dynorphin neuropeptides are differently correlated with locomotor hypersensitivity and levodopa-induced dyskinesia in parkinsonian rats.
Exp Neurol. 2016;280:80-88. doi: 10.1016/j.expneurol.2016.03.024. Epub 2016 Apr 10.

Main areas of research

Role of sleep homeostasis in the development of levodopa-induced dyskinesias in PD patients.

Lead investigator: S. Galati.
Collaborators: A. Kaelin, C. Staedler, A. Salvadè, N. Amato, S. Sarasso (University of Milan).

Levodopa is the most effective treatment for PD, but its therapeutic window becomes narrower in the course of the disease, mainly because of the development of levodopa-induced dyskinesia. Although evidence from animal models of PD suggested a striatal hyper-plasticity underlying the development of dyskinetic movements, their pathogenesis remains not entirely understood. In recent years, slow homeostatic tuning of intrinsic excitability occurring during sleep has been considered fundamental for network stabilisation by sliding plasticity thresholds. Hypothesising an association between these sleep process and dyskinesia, we evaluated the synaptic downscaling during sleep by using high-density EEG, and we are conducting a cross-sectional polysomnographic study in different stages of the disease.
All patients were recruited and the data are now analysed.

Electrophysiological effects of an acute block of the nigrostriatal pathway with respect to the cortico-striatal and cortico-thalamic interplay.

Lead investigator: S. Galati.
Collaborators: A. Kaelin, A. Stefani (University of Rome, A. Salvadè.

Spreading of slow cortical rhythms into the basal ganglia is a well-demonstrated phenomenon in PD. Accordingly, striatal dopamine depletion drives cortical-basal ganglia slow wave coherences in urethane-anesthetised rats. The neuronal basis of this pathological synchronisation was the subject of several investigations, and its behavioural relevance is widely debated. The acute pharmacological inactivation of the SNc-striatal pathway led to a fast developing coherence between cortex and basal ganglia time looked with a significant contralateral akinesia. This procedure offers the advantage of detecting electrophysiological changes irrespectively of chronically developing compensatory mechanisms. This study started in 2015.

Time course of the development of beta ad gamma-band oscillations in the basal ganglia of Parkinsonian rats with and without levodopa-induced dyskinesia.

Lead investigator: S. Galati.
Collaborators: JC. Möller, A. Kaelin, A. Stefani, (University of Rome), A. Salvadè, V. D'Angelo (University of Rome).

The relation between beta and gamma band oscillation and parkinsonian symptoms was based on their identification in local field potential recordings from cortex and basal ganglia of patients affected from PD. Indeed, a direct causative relation of beta band oscillations in PD was inferred by the subtle clinical worsening of akinesia given by stimulating the subthalamic nucleus with the beta band frequency. However, the dissociation of these oscillations and clinical symptoms is also apparent, since it is uncorrelated to the clinical state. To explain these conflicting results between beta band oscillations and clinical motor symptoms in PD we are conducting a closer monitoring of cortical and basal ganglia oscillation in the freely moving parkinsonian animal.
The data collection and analysis have been recently completed and a first article has been published.

Role of lateral habenula in emerging of levodopa-induced dyskinesia.

Lead investigator: S. Galati.
Collaborators: G. Di Giovanni (University of Malta, University of Cardiff), A. Kaelin, A. Stefani, (University of Rome).

The lateral part of habenula (LHb) has been proposed to play a role in both the modulation of sleep and levodopa induced dyskinesia (LID). It is also notable that hyperactivation of the LHb might induce aggravation of LID and sleep disturbance with up-regulation of REM sleep. LHb represents a key structure between the motor and non-motor behaviour receiving inputs from basal ganglia nuclei such as an internal segment of globus pallidus/entopeduncular nucleus (GPi/EPN), and lateral hypothalamus (LH), and projects primarily to the brain stem nuclei.
This project will investigate the effect of LHb lesion on sleep in parkinsonian animal showing LID.

Prevalence and genetics of movement disorders in Ticino - database and biobank.
Lead investigator: S. Galati.
Collaborators: A. Kaelin, C. Städler.

This database was created to capture the spectrum of movement disorders in the population in Ticino. We are currently collecting clinical data as well as additional examinations. The ultimate scope is to capture the mutation frequency of genes involved in these diseases mainly the monogenic forms of PD.

Modulation of striatal gene expression changes in Parkinsonian rats with levodopa-induced dyskinesia.
Lead investigator: A. Kaelin.
Collaborator: S. Sgroi.

This is a PhD thesis of the "Graduate School for Cellular and Biomedical Sciences" of the University of Bern with S. Sgroi as a doctoral student until 2015 and postdoc in 2016 and Prof. A. Kaelin as the thesis supervisor. This project focuses on the role of the endogenous opioidergic neuropeptides in levodopa-induced dyskinesia. Please see "Laboratory for Biomedical Neurosciences" (par. 2.10).

Alpha-synuclein oligomers detection by skin biopsy: a novel early biomarker for Parkinson's disease?
Lead investigator: A. Kaelin.
Collaborator: G. Melli.

This is a translational research project investigating the potential role of skin biopsies in the early diagnosis of Parkinson's Disease and started in 2015. Please see "Laboratory for Biomedical Neurosciences" (par. 2.10).

Cortical Reorganisation of Cerebral Networks after Childhood Stroke: Impact on Outcome.
Lead investigator: M. Steinlin (University of Bern).
Co-investigator at the NSI: A. Kaelin.

This is an important multicenter project using fMRI and Transcranial Magnetic Stimulation for investigating motor recovery after stroke in children. The long-term goal is to develop therapeutic strategies better adapted to children through a better understanding of the mechanisms specifically involved in children. The whole study is performed within the context of the Swiss Neuropaediatric Stroke Registry (SNPSR). The SNPSR is a population-based registry prospectively collecting data on childhood stroke and represents the unique possibility to study children suffering from an ischaemic arterial stroke on a nationwide basis. This multicenter project will strengthen this Swiss initiative and the data of this study will allow us to determine variables that influence the cortical reorganisation and outcome after childhood stroke. The Neurocenter of Southern Switzerland is collaborating on this project mainly thanks to its expertise in Transcranial Magnetic Stimulation of the motor system.
A first article was published.

Main funding

Role of sleep homoeostasis in the development of levodopa-induced dyskinesias in PD patients: ABREOC (internal competitive grant); Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

Electrophysiological effects of an acute block of the nigrostriatal pathway with respect to the cortico-striatal and cortico-thalamic interplay: Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino); Parkinson Schweiz.

Time course of the development of beta ad gamma-band oscillations in the basal ganglia of Parkinsonian rats with and without levodopa-induced dyskinesia: Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

Role of lateral habenula in emerging of levodopa-induced dyskinesia: Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

Prevalence and genetics of movement disorders in Ticino - database and biobank: Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino

(Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

Modulation of striatal gene expression changes in Parkinsonian rats with levodopa-induced dyskinesia: Fondazione Baasch Medicus (Baasch-Medicus Foundation) and Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

Alpha-synuclein oligomers detection by skin biopsy: a novel early biomarker for Parkinson's disease?: ABREOC (internal competitive grant); Swiss Parkinson Foundation.

Cortical Reorganisation of Cerebral Networks after Childhood Stroke: Impact on Outcome: Swiss National Science Foundation (SNSF).

2.5. Stroke Center

Claudio Städler MD
Head Doctor of the Neurology Service - Coordinator of Center
Carlo W. Cereda MD
Head of the Neurology Service - Coordinator of Center

Collaborators: Concetta Manno MD, Vesna Stojanova MD, Jane Frangi Study Nurse

The Stroke Unit EOC (SUN EOC) has been an accredited Comprehensive Stroke Center (since 2014) and therefore recognised as one of the Swiss centres of excellence for the treatment of patients with stroke. The Stroke Center provides optimal care for patients with cerebrovascular diseases. A dedicated and multidisciplinary stroke specialised team takes care of the patients in the acute phase (inpatient unit) and also in a specialised outpatient clinic. The group also performs research activities, mainly focused on 4 topics in clinical research: multimodal imaging and diagnosis of ischaemic cerebrovascular diseases, stroke prevention, stroke epidemiology, and stroke recovery in the acute phase.

Peer reviewed publications in 2016

Cereda CW, Christensen S, Campbell BC, Mishra NK, Mlynash M, Levi C, Straka M, Wintermark M, Bammer R, Albers GW, Parsons MW, Lansberg MG. **A benchmarking tool to evaluate computer tomography perfusion infarct core predictions against a DWI standard.** J Cereb Blood Flow Metab. 2016;36(10):1780-1789. Epub 2015 Oct 19.

Cereda CW, George PM, Inoue M, Vora N, Olivot JM, Schwartz N, Lansberg MG, Kemp S, Mlynash M, Albers GW. **Inter-rater agreement analysis of the Precise Diagnostic Score for suspected transient ischemic attack.** Int J Stroke. 2016;11(1):85-92. doi: 10.1177/1747493015607507.

Wouters A, Lemmens R, Christensen S, Wilms G, Dupont P, Mlynash M, Schneider A, Laage R, Cereda CW, Lansberg MG, Albers GW, Thijs V; **AXIS 2 and DEFUSE 2 study investigators. Magnetic resonance imaging-based endovascular versus medical stroke treatment for symptom onset up to 12 h.** Int J Stroke. 2016;11(1):127-133. doi: 10.1177/1747493015607503.

Main areas of research

Investigator-driven projects

BIO-PREDISC-TIA SWISS cohort study - BIOmarkers and PREDISC diagnostic evaluation for patients with suspected Transient Ischemic Attacks.
Prospective multicenter observational cohort study.
Sponsor-investigator: CW. Cereda.
Collaborators: University of Lausanne (CHUV), University Hospital Inselspital, Bern, University of Basel, University of Zurich, Stanford Stroke Center (Stanford University, CA).

The clinical diagnosis of transient ischaemic attacks (TIAs) shows a significant variability among physicians. PREDISC score is a composite score (clinical and radiological) that has shown to improve inter-rate agreement for the diagnosis of TIA. We conduct a prospective multicenter observational

cohort study, in which we will recruit a total of 56 patients per centre, within 48 hours of onset of transient neurological symptoms (TIA) over a period of 1 year. On admission, the patient will undergo a complete diagnostic work-up, including a clinical neurological examination, determine the ABCD2 score and the Clinical part of the PREDISC SCORE (0-4). In addition, patients will be scanned with MRI as early as possible after symptom onset, but no later than 48 hours from admission. The results of MRI will give the PREDISC Imaging score and determine the final PREDISC Score (1-8). In addition, the serum will be obtained for the analysis of biomarkers (microRNA, Exosomes, PBP and others). The primary objective is to establish whether or not patients with suspected TIA classified by the PREDISC score to be "very likely" to have a true ischaemic event (score 4-8) will have a significantly higher level of a pre-specified biomarker compared to subjects with TIA events classified as "unlikely" to be related to an ischaemic event (PREDISC SCORE 0-1).

Rehabilitation combined with bihemispheric transcranial direct current stimulation in subacute ischemic stroke: a randomized, controlled, double-blind study - The Re.Com.Bi.Ne. (Rehabilitation Combined with Bihemispheric Neuromodulation) post-stroke study.

Randomised multicenter interventional trial - NCT 01644929.
Lead investigators: CW. Cereda, R. Müri.
Collaborators: Clinica Hildebrand Brissago (CH), University Hospital, Inselspital, Bern (CH), Helios Klinik Zihlschlacht (CH).
Sponsor: EOC.

Rehabilitation after stroke improves motor functions by promoting plastic changes and transcranial direct current stimulation (tDCS), a form of non-invasive brain neuromodulation, is a promising tool for improvement of motor function by either up-regulating excitability of the affected cortex or down-regulating excitability in the intact one. In this study, we hypothesise that combining bihemispheric tDCS (anodal tDCS excitatory of the ipsilesional motor cortex, and cathodal tDCS inhibitory of the contralesional motor cortex) with simultaneous physical/occupational therapy in the subacute phase of ischaemic stroke may improve upper limb motor recovery in humans. This study is a randomised, controlled, double-blind, cross-over, multicenter, clinical trial. Outcome measures are functional motor scores (Fugl-Meyer Assessment Upper Extremity, the extended Barthel Index, the Ashworth scale, the Test of Upper Limb Apraxia, the grip strength evaluated by the Jamar Hydraulic Hand dynamometer). This study is designed to provide a class I evidence of the possible adjunctive restorative effect of bihemispheric tDCS combined with physical/occupational therapy in the subacute phase after stroke.

SSR- Swiss Stroke Registry.

Prospective multicenter observational registry.
Lead investigator: L. Bonati; Steering Committee: CW. Cereda.
Collaborators: University Hospital of Lausanne (CHUV), University Hospital, Inselspital, Bern, University Hospital of Basel, University Hospital of Geneva (HUG), University Hospital of Zürich (USZ), CH.
Sponsor: University of Basel (CH).

This project is the largest and more comprehensive Swiss nation-wide prospective stroke registry with data from the acute phase of stroke to long-term outcome measures.

Sleep deficiency and stroke outcome - Sleep deficiency and sleep fragmentation and their impact on the short- and long-term outcome of ischemic stroke and transient ischemic attacks.

Bicenter prospective observational cohort study - NCT 02559739.
Lead investigators: M. Manconi, C. Bassetti.
Sponsor: Inselspital Bern, CH.

The working hypotheses are that stroke survivors with sleep deficiency and sleep fragmentation due to insomnia, sleep-disordered breathing or restless legs syndrome will involve: (1) higher mortality from all causes and higher frequency of new cardio-/cerebrovascular events; and (2) a less favourable clinical outcome. Outcomes will be compared between patients with and without sleep deficiency and fragmentation.

The BIOSIGNAL-Study - Biomarker Signature of Stroke Aetiology Study.

Prospective multicenter observational study - NCT 02274727.
Lead investigators: M. Katan, CW. Cereda.

Sponsor: University Hospital of Zürich (USZ), CH.
Collaborators: Columbia University, NY, USA; University Hospital of Lausanne (CHUV); University Hospital of Basel; University Hospital of Geneva (HUG); University Hospital of Zürich (USZ); University Hospital, Inselspital, Bern.

The three-year cumulative risk of a recurrent stroke, dependent on aetiology, is up to 25 percent. At present, preventing recurrence relies on a broad approach to reduce risk factors associated with atherosclerosis, heart disease and metabolic disorders. However, more specific interventions, such as anticoagulation and surgery or stenting, need aetiologic information. BIOSIGNAL aims at determining where the most promising biomarkers can help identify stroke aetiology and also predict recurrent stroke. In addition, the insights gained into the processes underlying different stroke subtypes may lead to more targeted diagnostic tools.

PRESS - Predictive Swallowing Score.

Prospective multicenter cohort study.
Lead investigators: G. Kägi, CW. Cereda.
Sponsor: G. Kägi, Cantonal Hospital St Gallen.
Collaborators: Department of Neurology, Kantonsspital St. Gallen; Department of Neurology, Inselspital, Bern; Department of Otorhinolaryngology, Kantonsspital St. Gallen, Switzerland.

Guidelines recommend early tube feeding in stroke patients with impaired oral intake for ≥ 7 days. However, early tube feeding should start within 72 hours after stroke onset. Hence, clinicians need to anticipate the clinical evaluation of dysphagia in their stroke patients. Nevertheless, validated prognostic risk scores of the impairment of oral intake are not available. Predictive Swallowing Score (PRESS) is an easily applicable prognostic risk score of impaired oral intake after stroke. We will conduct a prospective multicenter cohort study in five Swiss stroke centers. The study duration will be 2 years. We will include acute stroke patients with a severe initial impairment of oral intake. They will receive a baseline visit with neurologic, logopedic and radiologic assessments, as well as two follow-up visits after 7 and 30 days. The main aim of this multicenter study is to internally and externally validate the PRESS score in five Swiss stroke centers. The secondary objective is to develop and validate a late prognostic risk score (Late-PRESS), which shall be assessed after 7 to 10 days in patients with persistent impairment of oral intake.

ECST-2: the 2nd European Carotid Surgery Trial.

Prospective multicenter, randomised, controlled, open clinical trial - NCT: 97744893.
Lead investigator: MM. Brown, Professor of Stroke Medicine, UCL Institute of Neurology.
Sponsor: University College London.
Collaborators: Swiss lead investigator: Leo Bonati, University Hospital of Basel.

Randomised trials established the benefit of revascularisation by carotid endarterectomy (CEA) for moderate and severe carotid stenosis. However only patients with a high risk of stroke under medical therapy benefited from CEA. For a wide range of patients, there was neither clear benefit nor harm from CEA. Medical therapy for stroke prevention has improved since these original trials. Therefore CEA may not be beneficial in many patients with carotid stenosis treated by modern optimised medical therapy (OMT).
We hypothesise that in patients with carotid stenosis at low and intermediate risk for stroke, OMT alone is as effective in the long-term prevention of cerebral infarction and myocardial infarction (MI) as revascularisation and OMT combined. ECST-2 is a multicenter, randomised, controlled, open, prospective clinical trial with blinded outcome assessment. We will use a risk model based on clinical characteristics to calculate a 5-year Carotid Artery Risk (mCAR) score, which will stratify patients as at high risk (≥15%), intermediate risk (7.5-15%), or low risk (<7.5%) of future stroke. Patients with symptomatic or asymptomatic atherosclerotic carotid artery stenosis will be included (>50%, NASCET criteria), suitable for revascularisation with CAR score indicating low or intermediate risk. Patients will be randomly allocated in equal proportions to be treated by immediate carotid revascularisation with OMT or OMT alone. The planned duration of follow-up is a minimum of 5 years up to a maximum of 10 years. The primary outcome measure for the full trial is any stroke at any time, plus non-stroke death occurring within 30 days of revascularisation. For the safety MRI analysis: the combined 2-year rate of cerebral infarction, cerebral haemorrhage, MI or periprocedural death after randomisation as assessed by

follow-up MRI and screening for MI.

SWITCH - Decompressive hemicraniectomy in intracerebral hemorrhage.
Randomised multicenter interventional trial - NCT 02258919.
Sponsor-Investigators: CW. Cereda, V. Stojanova.
Local lead investigator: P. Scarone;
Collaborators: Neurosurgery Service, Regional Hospital of Lugano and University Hospital Inselspital, Bern.
Sponsor: University Hospital, Inselspital, Bern (CH).

The primary objective of this randomised controlled trial which started in 2015, is to determine whether decompressive surgery and best medical treatment in patients with spontaneous ICH will improve outcome compared to best medical treatment only. Secondary objectives are to analyse mortality, dependency and quality of life. Safety endpoints are to determine the cause of any mortality and the rate of medical and surgical complications after DC compared with the best medical treatment alone.

Clinical trials in collaboration with the pharmaceutical industry

SOCRATES – Acute Stroke Or Transient IsChaemic Attack TReated with Aspirin or Ticagrelor and Patient OutcomES.
A randomised, double-blind, multinational study - NCT01994720.
Sponsor-Investigators: V. Stojanova, C. Manno, M. Schmitt.
Local lead investigator: CW. Cereda;

The primary objective of the study is to compare the effect of 90-day treatment with ticagrelor vs. aspirin for the prevention of major vascular events (composite of stroke, myocardial infarction [MI], and death) in patients with acute ischaemic stroke or transient ischaemic attack (TIA).

NAVIGATE ESUS – Rivaroxaban versus aspirin in secondary prevention of stroke and prevention of systemic embolism in patients with recent Embolic Stroke of Undetermined Source (ESUS).
A randomised, double-blind, multinational study - NCT02313909.
Sponsor-Investigators: V. Stojanova, C. Manno, M. Schmitt.
Local lead investigator: CW. Cereda;

This is a study in patients who recently had an ischaemic stroke and in whom no clear cause of the stroke could be identified. These strokes are likely due to a proximal blood clot (from Hearth or Aorta) and therefore, can be called embolic stroke of undetermined source. The abbreviation is ESUS. The study will compare 2 antithrombotic regimens. Patients will be randomly assigned to either rivaroxaban 15 mg or aspirin 100 mg and the study is intended to show if patients given rivaroxaban have fewer vascular events.

RE-SPECT ESUS - Dabigatran etexilate for secondary stroke prevention in patients with Embolic Stroke of Undetermined Source.
A randomised, double-blind, multinational study - NCT022392120.
Lead investigators: CW. Cereda; SI: V. Stojanova, C. Manno, M. Schmitt.

The study addresses to patients who recently had a brain attack (stroke) "with embolic characteristics" with no clear cause of the stroke (ESUS). The study will compare 2 secondary prevention therapies. Patients will be randomly assigned to either dabigatran 150 mg bid or aspirin 100 mg and the study is intended to show the secondary prevention effect of dabigatran in preventing ischaemic and haemorrhagic strokes.

Main funding

BIO-PREDISC-TIA SWISS cohort study - BIOmarkers and PREDISC diagnostic evaluation for patients with suspected Transient Ischaemic Attacks: Fondazione Svizzera di Cardiologia (Swiss Foundation of Cardiology), Swissheart (external competitive grant; activation: 2016; amount: 70,000; duration: 2 years).

The Re.Com.Bi.Ne. (Rehabilitation Combined with Bihemispheric Neuromodulation) post-stroke study: ABREOC (internal competitive grant).

Number of trainees

Five medical students (cand. med) from the universities of Basel, Zurich, Ulm (Germany), Berlin (Germany) and Varese (Italy).

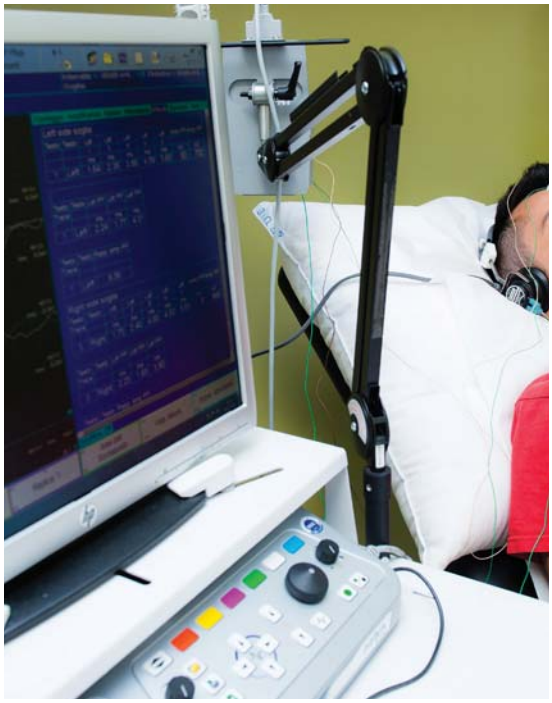
2.6. Neuropsychology Service

Leonardo Sacco MD
Head of Service

The Neuropsychology and Behavioural Neurology Laboratory provides a comprehensive assessment of adult patients with cognitive or behavioural symptoms. Neuropsychological assessment involves a systematic evaluation of higher cognitive abilities: intelligence, executive functions, attention, memory, language and visuospatial functions.
The case studies include suspected memory problems and dementia cognitive and behavioural deficit resulting in various neurological and neurosurgical conditions, such as stroke, epilepsy, Parkinson's disease, multiple sclerosis, brain tumours, traumatic brain injury, learning and developmental disorders. A dedicated team of a senior neurologist and six neuropsychologists run the outpatient Laboratory and concomitantly perform research activities. The topic of the research is the early diagnosis of dementia. The research activity involves local and national participations. We are participating in an international study to test the efficacy of a human antibody against amyloid in mild Alzheimer's disease.

Peer reviewed publications in 2016

Tiraboschi P, Corso A, Guerra UP, Nobili F, Piccardo A, Calcagni ML, Volterrani D, Cecchin D, Tettamanti M, Antelmi L, Vidale S, Sacco L, Merello M, Stefanini S, Micheli A, Vai P, Capitanio S, Gabanelli SV, Riva R, Pinto P, Biffi AM, Muscio C; SCILLA Working Group.
(123) I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission computed tomography and (123) I-metaiodobenzylguanidine myocardial scintigraphy in differentiating dementia with lewy bodies from other dementias: A comparative study.
Ann Neurol. 2016;80(3):368-378. doi: 10.1002/ana.24717. Epub 2016 Aug 2.



Main areas of research

Neurocognitive assessment in the metabolic and ageing cohort "The NAMACO study".
Investigators: M. Cavassini, S. Simioni, F. Schöni-Affolter, S. Clarke, A. Calmy, M. Michel, D. Fasel, U. Kunsel, A. Cusini, K. Gutbrot, C. Di Benedetto, R. Pignatti, P. Vernazza, H. Kovari, P. Brugger, R. Du Pasquier.

This study is included into the metabolic and ageing cohort whose importance was acknowledged by the scientific board and external reviewers. The overall purpose of this investigation is to expand the current knowledge about HIV-associated neurocognitive disorders (HAND) in the HIV ageing population. The current proposal aims at clarifying the global

scope and practical issues of the study and only requires the financial support of the neurocognitive assessment of non-complaining patients, as well as the financial support of the neurological, MRI and CSF assessment of control patients. We are going on with longitudinal evaluations after two years.

Neuropsychological markers of conversion from Mild Cognitive Impairment to Alzheimer's disease: a 5 years follow-up study.
Lead investigator: L. Sacco.
Co-investigator: S. Rossi.

The aim of the study is to determine which neuropsychological markers (semantic memory, executive functions, memory-ecological test) better reflect the neurodegenerative damage in patients with mild cognitive impairment (MCI). The primary objective is to prove that some specific neuropsychological tests administered at T0 to MCI subjects are predictive of a probable conversion to AD, during the period of the study (5 years). The secondary objective of the study is to analyse the time of conversion and the influence of some sociodemographic variables in our sample. Patients are currently screened and involved in the research.

Neuropsychologic outcome after aneurysmal subarachnoid haemorrhage – a new implementation of the prospective multicenter Swiss SOS study.
Investigators: M. Stienen, R. Weisshaupt, D. Valsecchi, M. Arrighi, M. Reinert, D.E. Kuhlen, S. Rossi, L. Sacco.

In the first step, we include all patients with aneurysmal subarachnoid haemorrhage (aSAH). The aim is the prospective implementation of a widely employed, standardised neuropsychological and (Health-related Quality of Life) HrQoL outcome battery of high quality. Such efforts may help identify subtle but important treatment effects, which may otherwise go unnoticed. The Swiss SOS-NPsych study was designed to: (a) improve the detection of neuropsychological deficits, depression, anxiety, and fatigue; (b) follow aSAH in Switzerland; (c) assess the HrQoL in aSAH patients in Switzerland; (d) develop and validate a neuropsychological testing battery, which may be used for future studies on this subject.

Clinical trial in collaboration with the pharmaceutical industry

Engage and Emerge study: efficacy and safety Of Biib037 in subjects with early symptomatic Alzheimer's disease.
Lead investigator: L. Sacco.
Collaborators: S. Rossi, R. Pignatti, M. Lissi, S. Rocchi.

Aducanumab is a human monoclonal antibody that recognises aggregated forms of β amyloid (A), including soluble Aβoligomers and deposited fibrillar A β. Interim analyses of the ongoing multiple dose study (Study 221AD103) demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-Sum of Boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab treated subjects. This is a Phase 3 study (221AD301 and 221AD302), which will assess the efficacy and safety of aducanumab compared to placebo in subjects with early Alzheimer's disease (AD), including mild cognitive impairment due to AD and a subset of mild AD.

Main funding

Neurocognitive assessment in the metabolic and ageing cohort "The NAMACO study": Swiss HIV Cohort Study (SHCS) (external competitive grant; 2012).

Neuropsychological markers of conversion from Mild Cognitive Impairment to Alzheimer's disease: a 5 years follow-up study: ABREOC (internal competitive grant).

Neuropsychological outcome after aneurysmal subarachnoid haemorrhage – a new implementation of the prospective multicenter Swiss SOS study: Registre Suisse Hemorragie Sousarachnoidale (Swiss Registry of Subarachnoid Haemorrhage).

Engage and Emerge study: efficacy and safety Of Biib037 in subjects with early symptomatic Alzheimer's Disease: Biogen (external grant).

Number of trainees

Two students in neuropsychology from the universities of Milano-Bicocca and Fribourg.

2.7. Neurosurgery vService

Prof. Michael Reinert MD
Head Surgeon

Research priorities of the Neurosurgery Service are in the field of neuro-oncology, neurovascular and spinal neurosurgery. Neuro-oncology is one of the key domains of the NSI and the collaboration with the IOSI has a longstanding tradition. In 2015 and 2016 we initiated the field of experimental research with cell cultures and animal models of glioblastoma. The scope is to improve the understanding of neuro-oncological biomolecular pathways to ameliorate patient outcome. Thereby, new innovative surgical techniques can be developed. Furthermore, by using new preoperative diagnostic non-invasive strategies (MR-spectroscopy study for IDH detection) focused tumour resection can be achieved. These findings can then be correlated with intraoperative findings (NSI Brain tumour Data Bank) and post-operative brain tumour processing (Laboratory for Biomedical Neurosciences, LBN and Cantonal Institute of Pathology, ICP Locarno).

Peer reviewed publications in 2016

Andereggen L, Gralla J, Andres RH, Weber S, Schroth G, Beck J, Widmer HR, Reinert M, Raabe A, Peterhans M.
Stereolithographic models in the interdisciplinary planning of treatment for complex intracranial aneurysms.
Acta Neurochir (Wien). 2016;158(9):1711-1720. doi: 10.1007/s00701-016-2892-3. Epub 2016 Jul 14.

Robert T, Blanc R, Botta D, Ciccio G, Smajda S, Redjem H, Fahed R, Piotin M.
Management of multiple cerebral arteriovenous malformations in a non-pediatric population.
Acta Neurochir (Wien). 2016;158(6):1019-2105. doi: 10.1007/s00701-016-2785-5. Epub 2016 Apr 6.

Robert T, Weil AG, Obaid S, Al-Jehani H, Bojanowski MW.
Supracerebellar transtentorial removal of a large tentorial tumor.
Neurosurg Focus. 2016;40 Video Suppl 1:2016.1.FocusVid.15445. doi: 10.3171/2016.1.FocusVid.15445.

Stienen MN, Netuka D, Demetriades AK, Ringel F, Gautschi OP, Gempt J, Kuhlen D, Schaller K.
Neurosurgical resident education in Europe--results of a multinational survey.
Acta Neurochir (Wien). 2016;158(1):3-15. doi: 10.1007/s00701-015-2632-0. Epub 2015 Nov 17.

Stienen MN, Netuka D, Demetriades AK, Ringel F, Gautschi OP, Gempt J, Kuhlen D, Schaller K.
Residency program trainee-satisfaction correlate with results of the European board examination in neurosurgery.
Acta Neurochir (Wien). 2016;158(10):1823-1830. doi: 10.1007/s00701-016-2917-y. Epub 2016 Aug 12.

Neuro-oncology

Brain Tumour Research Group
(see also paragraph 2.10: Laboratory for Biomedical Neurosciences - LBN)
Prof. Michael Reinert MD
Group Leader

Collaborators: M. Sarti, D. Piffaretti, F. Burgio, E. Pravatà, U. Pieles (FHNW, Basel), L. Mariani (University of Basel), E. Vassella (University of Bern), R. Wiest (University of Bern)

Neuro-oncology is one of the key domains at the NSI and the collaboration with the IOSI has a long-standing tradition. The scope of the research project is to improve the understanding of neuro-oncological biomolecular pathways to improve patient outcome. By using new preoperative diagnostic non-invasive strategies (MR-spectroscopy study for IDH detection), focused tumour resection can be achieved. These findings can then be correlated with intraoperative findings (NSI Brain tumour Data Bank) and post-operative brain tumour processing (LBN and Cantonal Institute of Pathology, Locarno). RAMAN spectro-microscopy is used to develop a new intraoperative online tumour- and tumour stage recognition. By a collaboration with the FHNW and UNIBAS the necessary nanoparticles are specifically conceptualised and produced by our PhD students. Differences of RAMAN signal of tumour in cell culture and tumour exposed to nanoparticles are studied at the LBN. Furthermore, in an in vivo tumour model in mice, the effect of anti-brain tumour-coated nanoparticles is studied upon completion of tumour resection and online tumour cell recognition. In this last study, the long-term scope is to develop a new surgical microscope, which permits immediate intraoperative tumour recognition.

Main areas of research

RAMAN guided resection of glioma using nanoparticles targeted cell recognition in the mouse model.
Investigators: M. Reinert, F. Burgio and D. Piffaretti.

This project aims at using Raman technology to better recognise and differentiate brain tumour areas from normal, non-invaded areas during in vivo surgical resection. To increase Raman sensitivity, and to specifically target brain tumour cells, antibody-conjugated, surface enhanced Raman scattering (SERS) gold nanoparticles (GNPs) are used. A protocol for GNPs surface functionalisation was defined and optimised. It involves three main steps including the attachment of a Raman active molecule, a polyethene glycol shell to increase gold colloidal stability, and the conjugation with anti-EGFR antibodies. Successful GNPs surface functionalisation was confirmed, and currently the functionality of the conjugate is under investigation. GNPs selectivity for EGFR is analysed in vitro in cultured human brain tumour cell lines expressing different EGFR levels. As such, GNPs selection will be defined by testing their ability to cross an artificial Blood Brain Barrier before performing in vivo analysis in a xenograft mouse model.

Hydroxyglutarate detection in wild-type and mutant IDH glioma cells by Raman spectroscopy.
Investigators: D. Piffaretti, F. Marchi, AO. Fontana, F. Burgio, AB. Faia-Torres, M. Reinert.

The new 2016 World Health Organisation Classification of Tumours of the Central Nervous System makes a revolution compared to its 2007 predecessor. In addition to the histology, for the first time, biomolecular parameters were included in order to help understand the real nature of SNC tumours better. Among the different molecular markers, we can find ATRX and TP53 mutations, 1p/19q co-deletion, WNT activation, EGFR amplification or EGFR variant III mutation and IDH mutations. Isocitrate dehydrogenase (IDH) is an enzyme that catalyses the conversion of isocitrate to a-ketoglutarate (α-KG). In eukaryotes, there

are three isozymes of IDH, the cytoplasmic/peroxisomal IDH1 and the mitochondrial IDH2 and IDH3. IDH1 and IDH2 mutations resulting in neomorphic enzymatic activity are found in certain cancers such as glioma and glioblastoma, acute myeloid leukaemia, and colon cancer. This neoactivity shows a change in the substrate specificity resulting in the conversion of a-ketoglutarate to 2-hydroxyglutarate (2- HG). Clinically, since the first paper on IDH was published, IDH mutant gliomas seem to have a better prognosis in particular regarding the overall survival. Moving from the possibility of detection of 2-Hydroxyglutarate with our RAMAN spectroscopy, the objective of our study is to differentiate IDH mutant and wild-type glioma. The final purpose of the project will be the intraoperative detection of IDH mutant and wild-type tumour cells, giving an extremely helpful information which can guide the surgeon during the resection of the tumour.

Swiss Glioma Network: patient data collection and analysis.
Lead investigators: F. Marchi, M. Reinert.

The Swiss Glioma Network is a nationwide initiative launched to intensify the collaboration of specialities involved in the care and research of intrinsic brain tumours. The objective is to improve and foster care and research by coordinating joint activities of therapeutic disciplines - neurosurgery, neuro-oncology, including paediatric neuro-oncology, radiation oncology – as well as diagnostic disciplines - neuroradiology, nuclear medicine and neuropathology. The registry was developed in collaboration with the Institute of Social and Preventive Medicine (ISPM) of the University of Bern and is hosted on its MEMdoc portal.

Spinal Neurosurgery

Main areas of research

Studio AIRO: vertebral arthrodesis with pedicular screws: retrospective comparison between intraoperative CT and cone-beam CT associated with spinal navigation.
Lead investigator: P. Scarone.
Collaborators: G. Vincenzo, D. Distefano, S. Presilla, M. Reinert.

This is a retrospective study on spinal navigation aiming at comparing two different spinal navigation techniques, one associated with a true intraoperative CT (AIRO system, available at our centre since October 2014) and the other with a Cone-beam CT (O-arm system, available at our centre since 2008).
The primary objective is to evaluate the difference between the two groups in the number of misplaced pedicular screws, which is a measure of accuracy.

Triojection Study: post-marketing confrontation study between Triojection and microdiscectomy for the treatment of lumbar disc herniations (see below, neuroradiology).
Lead investigator: A. Cianfoni.
Collaborators: P. Scarone, P. Maino.

This a prospective randomised study that aims at comparing ozone injection (Triojection) to lumbar microdiscectomy to treat patients with lumbar disc herniations which do not respond to standard medical treatments and steroid injections. The primary objective of this study is to compare the early clinical outcomes following non-surgical treatment with Triojection® to surgical discectomy. Early is defined as less than or equal to 6 months. The primary outcome measure will be the amount of improvement in leg pain after treatment. This will be determined by taking the difference between the baseline score and the average of the post-treatment scores at 1 week, 1, 3 and 6 months. The secondary objective is the number of patients having a subsequent injection and/or surgeries. Other secondary objectives include the duration of surgery, the clinical results, the position of screws in different groups of patients, and the radiation exposure with different techniques. Our centre is actually one of the few neurosurgical services in the world, which has these two techniques available. The results of this study show a high accuracy with spinal navigation associated with intraoperative CT in pedicle screw positioning, confirming the results of previous studies. Moreover, we found a lower rate of intraoperative screw repositioning with iCT AIRO compared to O-arm.

Patient radiation-dose during spinal surgery with intraoperative CT.
Lead investigator: P. Scarone.
Collaborators: S. Presilla, D. Gaudino, G. Fumagalli ("Università degli Studi dell'Insubria" (University of Insubria) of Como and Varese, Como, Italy).

In this in-vitro study, we measured the effective doses to different organs using an anthropomorphic phantom in conjunction with thermoluminescent dosimeters.

Comparison between percutaneous versus open dorsal stabilization in spinal surgery.
Lead investigator: N. Porz.

A prospective study comparing two operation techniques for transpedicular screw placement and stabilisation in the lumbar and thoracic spine surgery.

Vascular Neurosurgery

Main areas of research

SWITCH - Decompressive hemicraniectomy in intracerebral hemorrhage.
Sponsor-Investigators: CW. Cereda, V. Stojanova.
Local lead investigator: P. Scarone;
Collaborators: D. Valsecchi, C. Cereda, M. Reinert.
In collaboration with the Stroke Center, see above.

The primary objective of this randomised controlled trial is to determine whether decompressive surgery and the best medical treatment in patients with spontaneous ICH will improve outcome compared to the best medical treatment only.
The secondary objectives are to analyse mortality, dependency and quality of life.
The safety endpoints are to determine the cause of any mortality and the rate of medical and surgical complications after decompressive craniectomy compared to the best medical treatment alone.
Thirty-six patients were randomised until now in more than 20 hospitals in Europe.
Our centre is one of the main contributors with 2 randomised patients (one randomised to decompressive craniectomy and the other randomised to the best medical treatment).

Modified WFNS study.
Lead investigators: D. Valsecchi, T. Robert.

The "Modified WFNS" is a study that aims at demonstrating how the actual WFNS score (World Federation of Neurological Surgeons Grading System for Subarachnoid Hemorrhage) does not allow you to define, with adequate accuracy, the clinical status in those patients, affected by aneurysmal SAH, with poor GCS at the onset. Therefore, a retrospective study (carried out by the Neurosurgery of Inselspital of Bern), showed how the early signs of brain herniation, in addition to the WFNS score, seemed to be more effective to determine the clinical status and its prognostic value. In December 2015, this multicenter prospective, not randomised study began. The aim is to recruit 250 patients, throughout Switzerland, with SAH and poor grade of WFNS score, and to evaluate the correlation between their clinical outcome and the signs of brain herniation at the onset (hWFNS score).

Swiss SOS (subarachnoid haemorrhage).
Lead investigators: D. Valsecchi, T. Robert.
Collaborators: A. Venier, M. Reinert.

The Swiss SOS is a nationwide, multicenter clinical study in patients with aneurysmal subarachnoid haemorrhage. Initiated in 2008, it evolved to be a prospective, institutional-review-board approved continuous database, currently containing anonymous information on > 1700 patients. The aims of the Swiss SOS are: (a) to serve as a tool for disease monitoring in Switzerland, (b) to measure and control the quality of aSAH treatment in Switzerland, (c) to foster clinical research and collaboration between eight Swiss neurovascular centers, d) to guide the future direction of aSAH management in Switzerland. Lugano joined the study in 2013 and in 2014, all the retrospective data about SAH treated in our Hospital from 2009 to 2013 were provided. The website (www.swiss-sos.ch) is currently online.
In February 2016, we hosted the "Swiss SOS" annual meeting.

Somatosensory evoked potentials during clipping of unruptured middle cerebral artery aneurysms: new signal processing techniques for prevention of brain ischemia.

Lead investigator: L. Valci.
Collaborators: F. Tecchio, F. Cecconi, E. Colamartino.

This is a prospective, observational, single-center research project, which aims at analysing the somatosensory evoked potential (SSEP) signal for the prevention of cerebral ischaemia during operations for intracranial aneurysms. The primary goal is the construction of a device capable of reading and interpreting the SSEP signal and of sending an alarm in visual form (light signal) directly into the eyepiece of the operating microscope, once ischaemia is suspected; the secondary endpoint is the search for an electrophysiological index, that is more sensitive than the SSEP amplitude, to detect cerebral ischaemia. The study will continue for three years and is intended to include 30 patients with unruptured middle cerebral artery aneurysm. This study is conducted by the Intra-operative electrophysiology group that consists of two medical doctors and four technicians.
This research team for intraoperative electrophysiology was created in 2015 and collaborates with the CNR (National Research Council) of Rome.

Other clinical cohort studies in the field of vascular neurosurgery
Lead investigator: T. Robert.

- Anatomic and angiographic analyses of ophthalmic artery collaterals in Moyamoya disease
- Clinical outcome after an aneurysmal SAH without preventive treatment of cerebral vasospasm
- Clinical and angiographic improvement of cerebral vasospasm after intracisternal injection of papaverine during clipping surgery in an aneurysmal SAH population presenting with symptomatic vasospasm
- Using cisterns to minimise brain retraction: the example of a posterior oriented anterior communicating artery aneurysm. How I do it
- Thrombosis of Venous Outflows of the Cavernous Sinus: Possible Aetiology of the Cortical Venous Reflux in case of Indirect Carotid-Cavernous Fistulas
- Does the recanalisation of the inferior petrosal sinus during the endovascular treatment of a carotid-cavernous fistula represent an independent factor of sixth nerve palsy or worsening?
- Does tamoxifen treatment promote the occurrence of dural arteriovenous fistulas?
- A proposed grading system to evaluate the endovascular curability of deep-seated arteriovenous malformations.

Intra-Operative Neurophysiology Group (IONG): somatosensory evoked potentials during clipping of unruptured middle cerebral artery aneurysms: new signal processing techniques for prevention of brain ischemia.
Lead investigator: L. Valci.

Intra-operative electrophysiology allows safeguarding of the main functions of the central and peripheral nervous system during surgery by using the fundamental principle of the nervous system itself, i.e., the electrical current flow. At present, this group is composed of two medical doctors and four technicians. A research team for intraoperative electrophysiology was created in 2015. Its purpose is to understand the working mechanisms of the central nervous system and to study the techniques that allow the protection of nervous structures during neurosurgical operations. Currently, the group collaborates with the CNR (National Research Council) of Rome on the project "Somatosensory evoked potentials during clipping of unruptured middle cerebral artery aneurysms: new signal processing techniques for prevention of brain ischemia".

Main funding

M. Reinert (lead investigator):
Neuro-oncology projects: neurosurgical funds (amount: CHF 500,000; started: 2015 - duration: 2018; type of fund: non-competitive, two PhD student positions, fellowship in neuro-oncology).

Intra-Operative Neurophysiology Group (IONG): somatosensory evoked potentials during clipping of unruptured middle cerebral artery aneurysms: new signal processing techniques for prevention of brain ischemia: ABREOC (internal competitive grant).

2.8. Neuroradiology Service

Alessandro Cianfoni MD, PD
Deputy-Head
Emanuele Pravatà MD
Research Coordinator

The Neuroradiology Service of the NSI provides a comprehensive array of state-of-the-art morphological and functional advanced diagnostic neuroimaging, advanced innovative image-guided minimally invasive spine interventions as well as endovascular diagnostic and therapeutic procedures.
During 2016, several ongoing research projects continued in both the diagnostic and interventional neuroradiology fields. In particular, data acquisition continued for the project "High-resolution post-contrast imaging at 3 Tesla: a comparison of three different techniques", and other two projects regarding CT accuracy in the acute stroke setting and the accuracy comparison of two different spine surgery implant techniques were carried out in cooperation with the Stroke Center and the Neurosurgery department, respectively (see below). New interventional research projects in the field of spine minimally invasive procedures for vertebral stability also started, one of them with the external cooperation of the Polytechnic Institute of Milan and Ospedali Riuniti Hospital of Bergamo, Italy (see below).
The Interventional Neuroradiology is also actively involved, along with Neurosurgery and the Pain Center, in the "Post-marketing non-inferiority study comparing Triojection to Discectomy for Lumbar Disc Herniation" multicenter international clinical trial, comparing minimally-invasive disc herniation treatment with surgery. Finally, an fMRI research project, regarding MRI brain functional correlates of the Tako-Tsubo and X-syndrome cardiac diseases, in cooperation with Dr. Mattia Cattaneo and Prof. Augusto Gallino's cardiology research team in Bellinzona, continued.
Other active collaborations with the Inselspital of Bern and the San Raffaele Hospital in Milan through the Multiple Sclerosis Center continued in the field of advanced neuroimaging research in 2016.
Since 2016, the Neuroradiology Service has been a co-investigator site for MRI data acquisition in a multicenter phase 3 clinical trial testing the efficacy of Aducanumab monoclonal antibody sponsored by Biogen, for the treatment of AD-related MCI, locally coordinated by Dr. Sacco's Neuropsychology team.

Peer reviewed publications in 2016

Pravatà E, Tavernier J, Parker R, Vavro H, Mintzer JE, Spampinato MV.
The neural correlates of anomia in the conversion from mild cognitive impairment to Alzheimer's disease.
Neuroradiology. 2016;58(1):59-67. doi: 10.1007/s00234-015-1596-3. Epub 2015 Sep 23.

Pravatà E, Zecca C, Sestieri C, Caulo M, Riccitelli GC, Rocca MA, Filippi M, Cianfoni A, Gobbi C.
Hyperconnectivity of the dorsolateral prefrontal cortex following mental effort in multiple sclerosis patients with cognitive fatigue.
Mult Scler. 2016;22(13):1665-1675. Epub 2016 Feb 4.

Prodi E, Grassi R, Iacobellis F, Cianfoni A.
Imaging in Spondylodiskitis.
Magn Reson Imaging Clin N Am. 2016;24(3):581-600. doi: 10.1016/j.mric.2016.04.005.

Spampinato MV, Langdon BR, Patrick KE, Parker RO, Collins H, Pravata' E;
Alzheimer's Disease Neuroimaging Initiative. Gender, apolipoprotein E genotype, and mesial temporal atrophy: 2-year follow-up in patients with stable mild cognitive impairment and with progression from mild cognitive impairment to Alzheimer's disease.
Neuroradiology. 2016;58(11):1143-1151. Epub 2016 Sep 2.

Ventura E, Manno C, Gobbi C, Vitale VA, Cianfoni A.
MR neurography of a vagal neuropathy.
Neurology. 2016;87(2):234-235. doi: 10.1212/WNL.0000000000002838.

Main areas of research

High-resolution post-contrast imaging at 3 Tesla: a comparison of three different techniques.

Investigators: A. Cianfoni, L. Danieli, D. Distefano, E. Prodi, E. Ventura, GC. Riccitelli, C. Zecca, C. Gobbi, E. Pravatà.

Acquisition of gadolinium-enhanced magnetic resonance images (MRI) increases accuracy in detection and characterisation of neoplastic and multiple sclerosis (MS) brain lesions. We hypothesise that potentially relevant diagnostic differences exist between 3 available gadolinium-enhanced MRI techniques ("MPRAGE", "VIBE" and "SPACE"). Patients scheduled to undergo brain MRI for known or suspected tumours or MS. Test sequences consecutively and randomly acquired during a single examination per patient, after intravenous administration of 0.1mmol/Kg of gadobutrolum.
Contrast-enhancing lesion (CELs) detectability, volume, conspicuity (a qualitative judgment of how clearly CELs appear), and artefacts were assessed by two independent neuroradiologists (E. P., D. D.) blind to clinical data.
Current status: Data acquisition in progress (April 2015-May 2017).

Post-marketing non-inferiority study comparing Triojection to discectomy for lumbar disc herniation.

Lead Investigator: A. Cianfoni.
Co-investigators: P. Scarone, P. Maino, G. Bonaldi (Papa Giovanni XXIII Hospital of Bergamo, Italy).

Lumbar disc herniation can cause radicular pain. When conservative non-invasive treatment fails and pain persists, surgical discectomy is commonly performed. The use of ozone injection in the disc was reported in non-controlled series to be of benefit in such patients. Ozone intradiscal injection is a minimally invasive image-guided intervention, performed as an outpatient procedure.
This randomised controlled multicenter international trial (3 centres in Europe) aims at comparing surgical discectomy versus a single intradiscal ozone injection in patients with radicular pain without neurological impairment caused by a lumbar disc herniation, resistant to conservative treatment.

Stroke and stroke "mimics" in the acute setting: a one year experience in our centre.

Investigators: E. Prodi, L. Danieli, E. Pravatà, C. Manno, CW. Cereda, A. Cianfoni.

Stroke can be mimicked by non-vascular clinical syndromes that are sudden and focal.
In our centre, we aim at reviewing the prevalence of stroke-mimic conditions and investigating the ability of our diagnostic protocol (consisting in brain CT + angiography CT + perfusion CT) to discriminate ischaemic stroke from stroke-like conditions in the acute/hyperacute phase.
Patients with imaging studies performed from January to December 2016 for clinical suspicion of acute ischaemic stroke were included. We will compare the results of the first CT examination with the findings of the follow-up assessment (CT and/or MRI and/or angiography) and with the final clinical diagnosis at discharge.

Vertebral body stenting and cement augmentation to restore structural stability in extreme spinal osteolysis.

Investigators: A. Cianfoni, D. Distefano, P. Scarone, V. Espeli, GF. Pesce, G. Bonaldi.

Vertebral augmentation can be used in neoplastic vertebral lesions for pain palliation and/or stabilisation of collapsed or at-risk-of-collapse vertebral bodies. Osteolysis widely involving cortical margins of the vertebral body pose a risk of cement leakage and can ultimately limit the amount of bone cement that can be injected, resulting in insufficient stabilisation. We want to retrospectively assess technical feasibility, clinical effectiveness and complications of the cement augmentation of vertebral bodies affected by extreme osteolysis by the use of implantable vertebral body stents, to provide stability and bone cement containment.
The procedures have been performed at NSI in the last 28 months. Follow-up has terminated. Amendment to an existing approved Ethical Committee authorisation is being requested for this retrospective assessment.

Pedicular screw-anchored vertebral body stenting and cement augmentation to restore structural stability in extreme spinal osteolysis.

Investigators: A. Cianfoni, D. Distefano, P. Scarone, V. Espeli, GF. Pesce, G. Bonaldi.

Vertebral augmentation can be used in neoplastic vertebral lesions for pain palliation and/or stabilisation of collapsed or at-risk-of-collapse vertebral bodies. Osteolysis widely involving cortical margins of the vertebral body pose a risk of cement leakage and can ultimately limit the amount of bone cement that can be injected, resulting in insufficient stabilisation. We want to retrospectively assess technical feasibility, clinical effectiveness and complications of the cement augmentation of vertebral bodies affected by extreme osteolysis by the use of implantable vertebral body stents, to provide stability and bone cement containment. A novel technique, using percutaneous fenestrated pedicular screws to anchor the vertebral body stents to the posterior elements of the vertebra, ensures safer stabilisation of the implants, preventing hardware mobilisation, and should provide further 360-degree stabilisation of the vertebra. The procedures have been performed at NSI in the last 16 months. Amendment to an existing approved Ethical Committee authorisation is being requested for this retrospective assessment.

Studio biomeccanico a supporto dell'utilizzo di stent vertebrali, cemento e viti peduncolari nel trattamento di pazienti con metastasi spinali con lisi ossea estrema (Biomechanical study supporting the use of vertebral stents, cement and pedicular screws in the treatment of patients with spinal metastases with extreme osteolysis).

Investigators: A. Cianfoni, D. Distefano, L. Labarbera, G. Bonaldi, T. Villa.

Spinal osteolytic metastatic lesions are often associated with a severe reduction in quality of life due to associated pain, instability risk, fractures and, in the most severe cases, neurological symptoms caused by compression of nerve structures. Vertebral soma lesions, which reduce the strength of the load bearing front column, are responsible for the highest risk of vertebral fracture and instability. Different therapeutic actions can be directed to preservation of neurological functions, pain relief and mechanical stabilisation. Posterior stabilisation surgery is a proven and effective method of restoring spinal stability: it can be carried out using different techniques, with open or percutaneous surgery, but should always be accompanied by front column stabilisation with partial or total corpectomy and placement of autologous bone, cage or bone cement grafts. However, stabilisation surgery operations, are not always feasible in neoplastic patients due to numerous factors, such as age, life expectancy, patient's clinical status, frequent multilevel pathology or poor bone quality. In particular, the operation of corpectomy is particularly invasive and burdened by high rates of morbidity and long hospitalisation times, especially in this category of patients.
This study aims at providing the biomechanical basis for the use of an innovative mini-invasive technique, based on the use of metal stents, bone cement and pedicular screws, not necessarily coupled with posterior fixation, in patients with metastatic spinal lesions with extreme osteolysis at risk of fracture of the vertebral soma. This technique is intended to provide mechanical support and stability, reduce hospitalisation and postoperative complications linked to the invasiveness of traditional surgical procedures, thus resulting in a significant improvement in life quality of the treated patients. To this end, comparative analysis of the finished elements, highlighting the biomechanical advantages deriving from the use of the new technique on the remaining parts of the backbone, will be performed.
This study is carried out by the biomechanical engineers of the Polytechnic Institute of Milan.

Minimally invasive spinal hardware rescue with cement augmentation.

Investigators: K. Huscher, L. Roccatagliata, A. Cianfoni.

Surgical spinal instrumentation used to treat traumatic and porotic fractures, instability and deformities, might be complicated at short- or long-term by insufficiency spinal fractures at treated or adjacent levels, bone resorption, painful mobilisation, or pull-out of screws. These complications often require major corrective surgical intervention. Minimally invasive percutaneous image-guided vertebral cement augmentation (cement rescue) might represent an alternative option in selected patients.

This study retrospectively reviews clinical, imaging and procedural charts of a consecutive series of patients who underwent a cement augmentation procedure for spinal hardware complications.
Ethical committee authorisation is being requested for this retrospective assessment.

Active Internal and External Collaborations

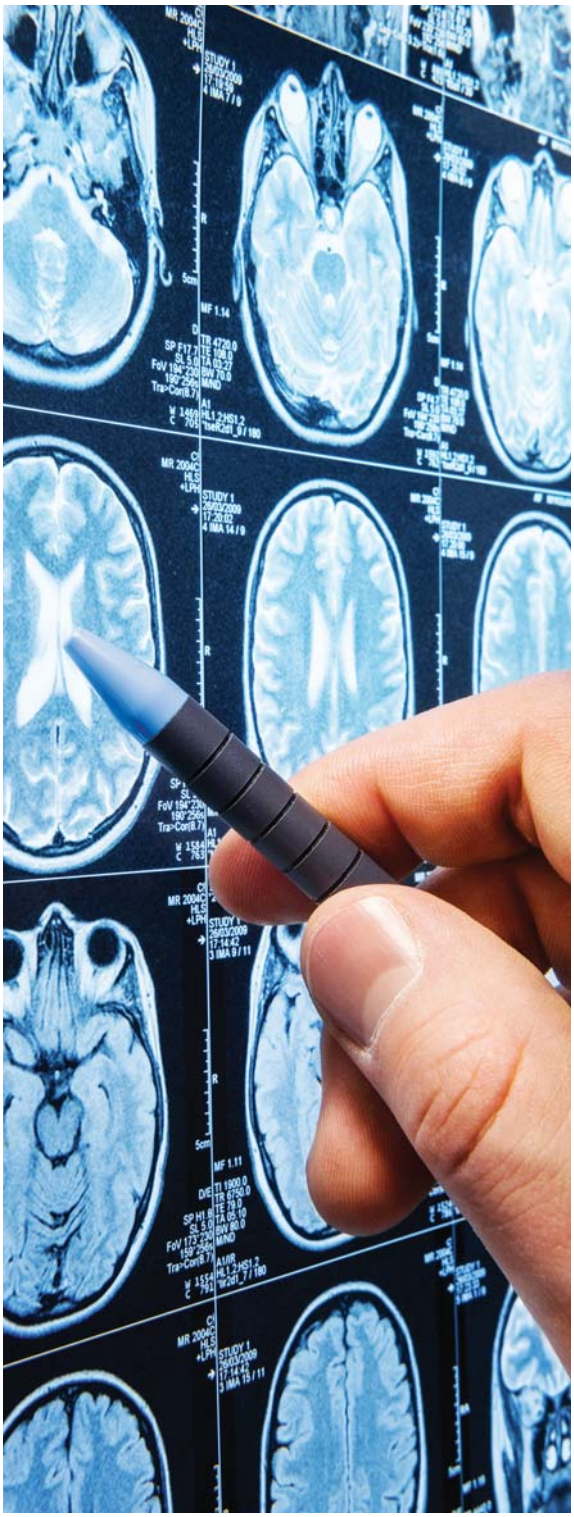
P. Scarone (lead investigator), Neurosurgery Service (NSI)
Stabilizzazione vertebrale con viti peduncolari: studio retrospettivo comparativo tra due tecniche di neuronavigazione: tomografia computerizzata intraoperatoria e tomografia a fascio conico associate a navigazione spinale (Spinal stabilisation with pedicular screws: a retrospective comparative study between two neuronavigation techniques: intraoperative computed tomography and cone beam tomography associated with spinal navigation)
1 ongoing study.

T. Villa, Laboratory of Biological Structure Mechanics, Chemistry, Material and Chemical Engineering Department "Giulio Natta", Polytechnic Institute of Milan
Studio biomeccanico a supporto dell'utilizzo di stent vertebrali, cemento e viti peduncolari nel trattamento di pazienti con metastasi spinali con lisi ossea estrema (Biomechanical study supporting the use of vertebral stents, cement and pedicular screws in the treatment of patients with spinal metastases with extreme osteolysis)
1 ongoing study.

Main funding

High-resolution post-contrast imaging at 3 Tesla: a comparison of three different techniques (EOC. NEURORAD.1501): ABREOC (internal competitive grant).

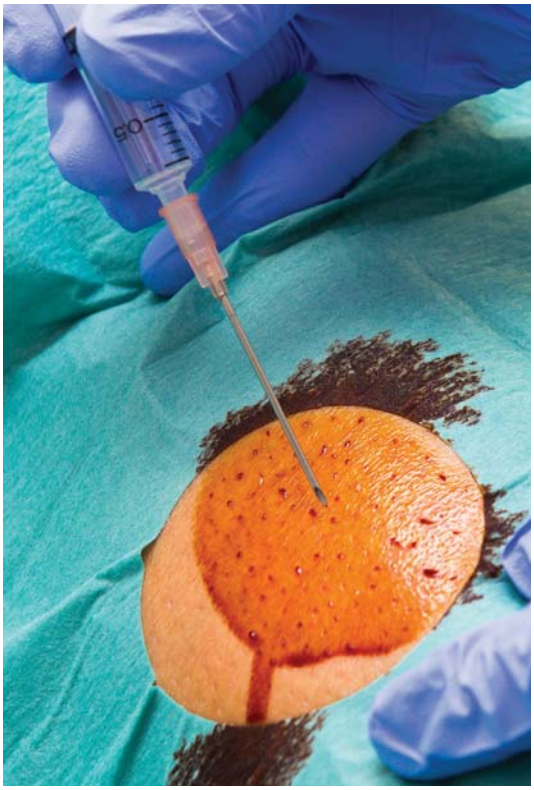
Studio biomeccanico a supporto dell'utilizzo di stent vertebrali, cemento e viti peduncolari nel trattamento di pazienti con metastasi spinali con lisi ossea estrema (Biomechanical study supporting the use of vertebral stents, cement and pedicular screws in the treatment of patients with spinal metastases with extreme osteolysis): fondazione scientifica FROM (FROM scientific foundation), Bergamo, Italy (duration: 12 months; amount: Euro 12,000).



2.9. Neuroanaesthesia Service

Paolo Maino MD
Deputy-Head

The EOC Pain Management Center promotes the highest possible quality of life for patients with persistent pain, by offering accurate diagnosis and direct interventions to reduce, eradicate or manage the pain and provide support particularly around the management of pain problems of high medical and psychological complexity, and around the use of controlled drugs, minimal invasive interventions and neuromodulation. The outpatient Service which is present in all the EOC Hospitals has the mission of providing specialist consultations, evidence-based and the most up to date treatments to all chronic pain patients in Ticino.
Since 2015, academic cooperations with the University of Maastricht and the VUMC University Medical Center of Amsterdam have been formalised. The collaboration with Prof. Dr. Bert A. Joosten in Maastricht is related to research projects investigating the effects of dorsal root ganglion stimulation for treatment of diabetic neuropathy. The collaboration with Prof. Roberto Perez at the VUMC in Amsterdam is related to investigating technical aspects to improve safety and efficacy in pain therapy. New research collaboration also started with Prof. Marco Barbero from the Rehabilitation Research Laboratory of the University of Applied Sciences and Arts of Southern Switzerland.



Peer reviewed publications in 2016

Zanini C, Maino P, Möller JC, Gobbi C, Raimondi M, Rubinelli S.
Enhancing clinical decisions about care through a pre-consultation sheet that captures patients' views on their health conditions and treatments: A qualitative study in the field of chronic pain.
Patient Educ Couns. 2016;99(5):747-753. doi: 10.1016/j.pec.2015.11.029. Epub 2015 Dec 3.

Zecca C, Panicari L, Disanto G, Maino P, Singh A, Digesu GA, Gobbi C.
Posterior tibial nerve stimulation in the management of lower urinary tract symptoms in patients with multiple sclerosis.
Int Urogynecol J. 2016;27(4):521-527. doi: 10.1007/s00192-015-2814-6. Epub 2015 Aug 6.

The accuracy of the Ultrasound-guided versus the blind conventional Refill Technique of Intrathecal Pumps, a prospective comparison study.

Investigators: P. Maino, RSGM. Perez, E. Koetsier.

The purpose of this study is to assess the accuracy and safety of the US-guided refill technique compared to the blind conventional refill technique in subjects undergoing regular refills of their MedStream programmable infusion systems for the treatment of chronic pain or spasticity. 19 patients were enrolled. Two pain physicians will complete the blind technique once and twice the US-guided technique each, within the same patient on consecutive refill procedures. The primary endpoint is the number of attempts to enter the RFP with the needle comparing the US-guided technique versus the blind technique. The secondary endpoints are the number of skin punctures, the time to enter the RFP with the needle and patient discomfort in order to assess user friendliness. 19 patients were enrolled from January to April 2015. The refills were performed over a period of 24 months. At the moment, we are analysing the results of this study.

Radiation dose exposure for lumbar Transforaminal Epidural Steroid Injections and facet joint blocks under CT versus fluoroscopic guidance: a retrospective comparison study.

Investigators: P. Maino, S. Presilla, P. Colli, RSGM. Perez, E. Koetsier.

The purpose of this study is to compare patient radiation dose for lumbar TFESIs and facet joint blocks under CT fluoroscopic guidance versus guidance. The primary endpoint is the difference between the mean estimated effective dose (ED) of CT guidance and fluoroscopic guidance for TFESIs and facet joint blocks. We retrospectively reviewed a series of CT-guided and fluoroscopy-guided lumbar TFESIs and facet joint blocks on 42 patients (18 men, 24 women; mean age, 60 ± 14 years; range, 30 – 90 years). These patients collectively underwent a total of 100 procedures. At the moment, we are analysing the results of this study.

Dorsal Root Ganglion Stimulation for the management of intractable painful polyneuropathy: a prospective case series.

Investigators: P. Maino, G. Melli, RSGM. Perez, E. Koetsier.

A prospective, single-arm, single-center pilot study to obtain preliminary information on the ability of Dorsal Root Ganglion Stimulation (DRGS) in relieving the painful symptoms in patients with polyneuropathy. The primary outcome will be the change in pain intensity assessed by Numeric Rating Scale at baseline and 6 months post-DRGS implant. Secondary outcomes involve the assessment of: changes in neuropathic pain aspects, sensory perception improvement measured by Quantitative Sensory Testing, changes in health-related quality of life, changes in mood, global improvement of change, changes in the impact of pain on physical functioning, satisfaction with stimulation, evolution of the SFN assessed by repeated biopsies. At the moment, we are recruiting patients for this study.

A randomized, double-blind, placebo-controlled, multicenter efficacy study of the Gelstix™ device to treat chronic discogenic low back pain.

Investigators: P. Maino, RSGM. Perez, A. Cianfoni, E. Koetsier.

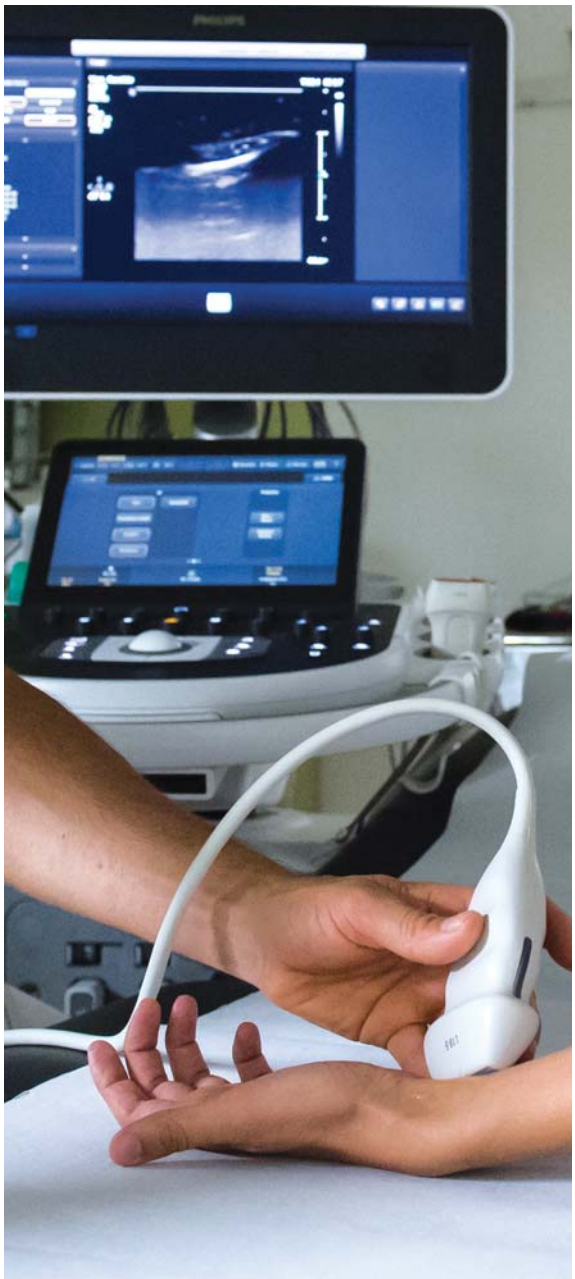
Double-blind, prospective, randomised, placebo-controlled, outcome study. The purpose of this study is to evaluate the efficacy of treatment with the GelStix™ device in a patient population that had no benefit from conservative care. The total expected number of patients to be randomised is 72. At the moment, we are recruiting patients for this study.

Spinal cord stimulation of the L5 dorsal root ganglion for the treatment of experimental painful diabetic polyneuropathy.

Investigators: E. Koetsier, G. Franken, RSGM. Perez, EA. Joosten, P. Maino.

The goal of this study is to develop the technique of experimental DRG-SCS and gain a first insight into the effect of L5 DRG-SCS in female PDP

Sprague-Dawley rats. Diabetes was induced by intraperitoneal injection of streptozotocin. Animals are tested for mechanical hypersensitivity using Von Frey hindlimb withdrawal testing at baseline, and once a week for 4 weeks following streptozotocin injection, to select animals that develop PDP. Subsequently, animals are implanted with a DRG-SCS electrode at L5 and stimulated for 30 minutes at 2 and 3 days following implantation. Immediately before stimulation, 15 and 30 minutes during stimulation, and 15 and 30 minutes after stimulation, animals were tested for mechanical hypersensitivity. First data indicate a successful reduction in mechanical hypersensitivity upon DRG-SCS in PDP rats. Further analysis in more animals is following.



Main funding

Dorsal Root Ganglion Stimulation for the management of intractable painful polyneuropathy: a prospective case series: ABREOC (internal competitive grant).

Spinal cord stimulation of the L5 dorsal root ganglion for the treatment of experimental painful diabetic polyneuropathy: St. Jude Medical (non-competitive grant; amount: CHF 60,000).

P. Maino:
Neuromodulation RELIEF STUDY (A7007), a global registry to evaluate long-term effectiveness of neurostimulation therapy for pain: Boston Scientific International SA (non-competitive grant; amount: CHF 37,000).

2.10. Laboratory for Biomedical Neurosciences (LBN)

Prof. Alain Kaelin MD, PhD
Scientific Director
Paolo Paganetti PhD
Chief of LBN

The Laboratory for Biomedical Neurosciences (LBN) is committed to discovering therapies and innovative diagnostics measures for patients affected by neurodegenerative diseases, a family of debilitating and irreversible disorders that significantly affect the life quality of patients and caregivers.
Basic, translational and clinical research are complementary disciplines of biomedical sciences. The integration of the LBN into the NSI offers the unique opportunity for translational research that is reciprocally fostered by clinicians and biologists. Our science aims at filling the traditional gap between discoveries in basic research and their applications in medicine. The vision of the LBN is to improve the understanding of neurodegenerative disorders at the functional and molecular levels. To do so, we established a research platform enabling a comprehensive approach based on cellular and animal models of disease coupled with innovative, functional analysis and state of the art molecular and genetic methodologies.
The studies focus on the elucidation of the molecular mechanisms involved in the initiation, progression and consequences of motor disorders such as Parkinson's disease or other neurodegenerative disorders collectively defined as proteinopathies. To analyse cellular and animal models of disease, we offer a wide range of technologies such as electrophysiology, behavioural analysis, histology, flow cytofluorometry, confocal microscopy, as well as modern methods in cellular and molecular biology.

The team of Dr. Paolo Paganetti (see also page 87: **Neurodegeneration Research Group**) takes a molecular and cellular approach to investigate the causes of neurodegenerative diseases such as frontotemporal dementia, Parkinson's disease, Alzheimer's disease, and Huntington's disease. The search for novel therapeutics is based on counteracting aberrant protein levels by targeting protein modification, misfolding and toxicity, which also define new diagnostic markers.

The research groups of Prof. Dr. Alain Kaelin and Dr. Salvatore Galati (see also paragraph 2.4: **Movement Disorders Center**) successfully created and implemented animal models for Parkinson`s disease, which are tailored to behavioural and histopathological investigations as well as electrophysiological studies. These research models were implemented to understand the pathological mechanisms underlying these brain disorders and as experimental models to test new therapeutic interventions. An additional project seeks markers of Parkinson's disease in human skin.

The team led by Prof. Michael Reinert (see also paragraph 2.7: **Neurosurgery**) focuses research on brain tumours with particular emphasis on methods aimed at improving the surgical intervention.

Another important objective of the LBN is training and education of young scientists to foster their career in basic and clinical research. As part of the scientific community, the LBN advocates the exchange of know-how and data among national and international research teams and the dissemination of our rationale and results through specialised and general communication channels. Education and training at the LBN for young scientists, interested in a career in basic and translational research, is granted by a state of the art infrastructure and an excellent supervision which help achieve an academic degree (master student, PhD student) or by widening and deepening their scientific knowledge (postdoctoral and visiting fellows). With the envisaged integration into the Faculty of Biomedical Sciences and Master School of Human Medicine of the University of Southern Switzerland, the LBN will have the ability to assign a PhD degree. In the meantime, PhD and Master students hosted at the LBN participate in the corresponding

programs offered by national and international academic institutions, whilst absolving their practical work within the LBN research facilities as well as actively participating in lectures, seminars and courses organised by the LBN or by the LBN in collaboration with other research institutes located in Ticino. PhD and Master students pursue their research projects under the mentorship of experienced group leaders and learn modern research technologies and how to conduct a scientific research project independently.

The five PhD students hosted by the LBN in 2016 were affiliated with the University of Bern, the University of Zurich and the University of Basel.

Our Laboratory exists thanks to a substantial financial support received by competitive research grants, charitable organisations and donors. For the years 2015-2017, the support provided by the EOC was supplemented with a total amount of CHF 3.1 million that we received until the end of 2016, which has already covered 51% of the total LBN expenses. The competitive grants provide about 60% of the external support.

Neurodegeneration Research Group

Paolo Paganetti PhD
Group leader

Collaborators: C. Foglieni, S. Papin, G. Pedrioli, S. Pinton, A. Salvadé, G. Ulrich

The discovery of disease mutations in gene encoding for the proteins that build up brain deposits in patients affected by neurodegenerative disorders established a link between the sporadic and the hereditary disease forms. Most importantly, this demonstrates that these aberrant protein species initiate the neurodegenerative process and cause cell loss. The research group studies the molecular processes that regulate protein misfolding, deposition and toxicity in cellular models of disease. In particular, we are interested in characterising post-translational modifications and subcellular localisation of the proteins involved in the pathogenesis of neurodegenerative disorders.
In 2016 our work enabled us to win several prestigious and highly competitive national research grants, which will allow us to advance our sciences further as well as to establish alliances and collaborations with well-known research groups in Switzerland and Europe. Several research projects have already started or are about to start. Moreover, a major US-based translational research foundation has selected our group to validate a new diagnostic marker for Parkinson's disease.

- Project 1: Modification of tau as function of subcellular distribution.
  (Giorgio Ulrich, in collaboration with Prof. Paola Picotti, ETHZ)
  We are studying the modification of the protein tau, which is associated with frontotemporal dementia, Parkinson's and Alzheimer's disease, when located in the nucleus and other subcellular sites. Protein mislocation and modification are assumed to be key determinants of tau-induced neuronal cell loss and represent disease biomarkers
- Project 2: Structural and cellular determinants regulating TDP-43 multimerization in health and disease.
  (Chiara Foglieni, in collaboration with Prof. Magdalini Polymenidou, Uni ZH)
  We are studying the formation of homo and hetero protein complexes composed of the protein TDP-43, which is associated with frontotemporal dementia and amyotrophic lateral sclerosis. At least three different forms of TDP-43 aggregates with very different activity, physiological oligomers involved in RNA and DNA metabolism, cytosolic granules forming during cellular stress and the pathological aggregates observed in the disease were described. The complementation technology we implemented to study TDP-43 biology is also used to study the protein tau as well as the huntingtin protein involved in Huntington's disease

— Project 3: Extracellular vesicles involved in disease spreading and transmission in the brain.
(Giona Pedrioli, in collaboration with Prof. Anne Spang, Biocenter, Uni Basel)
We are studying extracellular vesicles such as exosomes for their role in transporting proteins from neurone to neurone, in particular for proteins associated with neurodegenerative disorders. Transcellular transport of proteins may represent the key molecular process at the basis of disease progression. For this project that has recently started, we are establishing protocols and evaluating markers to study if and how an intracellular protein can reach the interior of a receiving cell

— Project 4: Measuring pathological protein forms as markers of Parkinson's disease.
(Dr. Stéphanie Papin, in collaboration with the Michael J Fox Foundation)
We are implementing and validating a test to measure pathological forms of proteins associated with Parkinson's disease. The aim of this study is to develop a test for the diagnosis, the analysis of progression and as a therapeutic read-out of disease

— Project 5: Nuclear Tau in health and disease.
(Dr. Stéphanie Papin)
The main function of the protein tau is in the regulation of microtubules. Nevertheless, tau was also found in the nucleus where it can bind and protect DNA. The main objective of our project is to investigate the function of nuclear tau further. In particular, we will assess the role of tau in the DNA damage response, in chromatin modification and epigenetic regulation of gene expression, and identify mechanisms mediating the nuclear translocation and function of tau.

Peer reviewed publications in 2016

Chopra V, Quinti L, Khanna P, Paganetti P, Kuhn R, Young AB, Kazantsev AG, Hersch S.
LBH589, A Hydroxamic Acid-Derived HDAC Inhibitor, is Neuroprotective in Mouse Models of Huntington's Disease.
J Huntingtons Dis. 2016;5(4):347-355.

Devraj K, Poznanovic S, Spahn C, Schwall G, Harter PN, Mittelbronn M, Antoniello K, Paganetti P, Muhs A, Heilemann M, Hawkins RA, Schrattenholz A, Liebner S.
BACE-1 is expressed in the blood-brain barrier endothelium and is upregulated in a murine model of Alzheimer's disease.
J Cereb Blood Flow Metab. 2016;36(7):1281-1294. doi: 10.1177/0271678X15606463. Epub 2015 Oct 13.

Kroth H, Sreenivasachary N, Hamel A, Benderitter P, Varisco Y, Giriens V, Paganetti P, Froestl W, Pfeifer A, Muhs A.
Synthesis and structure-activity relationship of 2,6-disubstituted pyridine derivatives as inhibitors of β-amyloid-42 aggregation.
Bioorg Med Chem Lett. 2016;26(14):3330-3335. doi: 10.1016/j.bmcl.2016.05.040. Epub 2016 May 13.

Main funding

Gelu Foundation
Lead investigator P. Paganetti.
Amount: CHF 750,000. Started: 2015 - duration: 2019 (five years). Type of fund: competitive, one senior scientist position, five trainees.

Gabriele Charitable Foundation
Lead investigator: P. Paganetti.
Amount: CHF 300,000. Started: 2014 - duration: 2016 (three years). Type of fund: non-competitive, two PhD student positions.

NN
Lead investigator: P. Paganetti.
Amount: CHF 50,000. Started: 2015 - duration: 2020 (five years). Type of fund: non-competitive, research consumables and equipment.

AILA/OIL
Lead investigator: P. Paganetti; Co-investigator: A. Salvadè.
Amount: CHF 100,000. Started: 2016 - duration: 2016 (single contribution). Type of fund: non-competitive, research equipment.

Swiss National Foundation (SNF)
Lead investigator: P. Paganetti.
Amount: CHF 210,000. Started: 2016 - duration: 2019 (three years). Type of fund: competitive, one PhD student, research consumables.

Swiss National Foundation (SNF Sinergia)
Co-investigator: P. Paganetti.
Lead investigators: B. Schuler and M. Polymenidou (Uni ZH), F. Allain and G. Jeschke (ETHZ).
Amount: CHF 2,600,000. Started: 2017 - duration: 2020 (four years). Type of fund: competitive, one PhD student, research consumables.

Michael J Fox Foundation
Co-investigators: P. Paganetti and G. Sancesario (Università di Roma Tor Vergata – University of Rome "Tor Vergata").
Lead investigator: L. Petricca (IRBM Science Park Rome).
Amount: USD 112,300. Started: 2017 - duration: 2017 (one year). Type of fund: competitive, laboratory technician, research consumables.

Synapsis Foundation
Lead investigator: P. Paganetti; Co-investigator: S. Papin.
Amount: CHF 298,600. Started: 2017 - duration: 2020 (three years). Type of fund: competitive, Postdoc, research consumables.