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Neurocenter of Southern Switzerland (NSI)

2. Neurocenter of Southern Switzerland (NSI)

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Introduction

The **Neurocenter of Southern Switzerland (NSI)** hosts the Services of Neurology, Neurosurgery, Neuroradiology, Neuroanesthesia 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 continous excellence of care, the NSI carries out important activities such as the accomplishment of basic and clinical research as well as educational duties. 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.

In 2015, the first PhD title in neurosciences was obtained from the University of Bern by a collaborator working in our "Laboratory for Biomedical Neurosciences".

The main focus of scientific activities at the NSI currently concerns 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 supports NSI investigators for investigator-initiated and sponsor-initiated studies and participated in several studies described below.

The respective projects in basic and clinical research carried out or still ongoing in 2015, are summarized in the following sections.

Main areas of research of the NSI

2.1 Multiple Sclerosis Center

Claudio Gobbi MD PD, Chiara Zecca MD

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

The Multiple Sclerosis Center focuses on three **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 Center has already included 88 of 100 planned patients. 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), Fingolimod (NCT01779934), Siponimod (NCT01665144). Observational trials focus on new drug administration methods (TERIFLO6965, 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 management of MS symptoms aiming at improving the patients' quality of life.**

We collaborate closely with the University Hospital of Basel (Study SMSC, teaching), the Queens Square Hospital London concerning treatment of lower urinary tract symptoms, and for topics involving Neuroradiology with Vita-Salute San Raffaele University, Italy. We also have collaborations with Istituto Neurologico Besta, Milan, Italy and Casa Sollievo Della Sofferenza Istituto Di Ricovero E Cura A Carattere Scientifico, S. Giovanni Rotondo, Italy.

Ongoing research

- *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 MS and migraine and at defining the relationship between functional brain 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 functional brain 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. Correlation between MRI findings and clinical and neuropsychological measures in MS patients with and without migraine, and patients with migraine alone will be established. 51 patients were recruited in 2015.

- *Prevalence and characterization of urinary and sphincter symptoms in patients with multiple sclerosis - a retrospective analysis of clinical practice data (EOC.NSIMS.14.02).*
  Lead investigator: C. Zecca.
  Collaborators: L. Panicari, C. Gobbi, U. Candrian, A. Digesu.

  This is a retrospective analysis of clinical practice data. Patients with multiple sclerosis experience have various sphincter and urinary disturbances due to the underlying neurological disease. The real prevalence of these symptoms and their course related to disease progression is little known. The project aims at estimating the proportion of MS patients with urinary and sphincter disturbances in the Ticino MS population, the prevalence of their various symptoms and their connection to demographic and clinical data. Data of female and male patients, aged 18–80 years old, with urinary and/or sphincter disturbances are analyzed. Urinary and/or sphincter complaints are recorded during ambulatory visits using structured questionnaires, videourodynamics, PTNS treatment, demographic and MS medical history data yielding datasets of 216 patients. Descriptive statistics for demographics, prevalence of urinary symptoms, sphincter dysfunction, Spearman rho correlation test for association of demographics, clinical urinary, and sphincter symptoms will be used.
  The part concerning urinary symptoms was concluded at the end of 2014, but all data were reanalyzed with a different statistical methodology in 2015.

- *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) to provide a detailed characterization 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) to see how the prevalence and the overlaps between fatigue, somnolence, depression and attention dysfunction are influenced by the method of assessment; 3) to better characterize the sleep structure in MS patients with fatigue under both the macro- and microstructural points 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 61 out of 100 planned patients were enrolled and concluded the assessments.

- *A prospective, randomized double-blind, placebo-controlled, parallel-group, single center, phase IV study of oral prednisone taper vs. placebo following intravenous steroids for the treatment of acute relapses of multiple sclerosis within the Ticino cohort (EOC.NC.10.04).*
  Lead investigator: C. Gobbi.
  Collaborators: C. Zecca, U. Candrian, L. Panicari, G. Disanto, V. Pifferini.

  This double-blind, randomized, placebo-controlled, prospective trial aims at comparing the efficacy, tolerability and safety of tapering doses of oral Prednisone and placebo after short-term high-dose i.v. Methylprednisolone on the recovery from an acute relapse in patients with clinically isolated syndrome, relapsing-remitting multiple sclerosis (RR-MS) and primary (PP-MS) or secondary progressive multiple sclerosis (SP-MS) with superimposed relapses. Inclusion criteria are female and male patients with clinically isolated syndrome, RR-MS, PP-MS or SP-MS and experiencing an acute relapse with clinical worsening (>1 point if EDSS ≤4.5 or 0.5 point if EDSS >4.5 or >2 points in one functional system of the Expanded Disability Status Scale (EDSS), EDSS score 0–8, aged 18–80 years. They were treated with Methylprednisolone for 3 days and randomized to receiving either orally decreasing doses of Prednisone for 25 days or placebo. At first 25 patients were enrolled, 24 of them concluded the trial. The study was terminated prematurely in 2015 after inclusion of overall 27 patients, due to recruitment difficulties.

Number of trainees (cand. med.)

1 Master class medical students from the University Hospital of Basel.

Main funding

C. Gobbi
"Pain network and neuropsychological profile in multiple sclerosis and migraine patients - a clinical and Magnetic Resonance Imaging Study (EOC.NSIMS.14.01)": **ABREOC** (hospital competitive internal grant) (year of activation: 2014; duration: 18 months).

"Multidimensional assessment of fatigue in multiple sclerosis – Observational study - Ticino (EOC.NSI.13.02)": **Clara-Miller Stiftung** (Swiss multiple sclerosis Society) (Foundation, private, non competitive) (year of activation: July 2013; duration: 18 months).

C. Zecca
"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** (competitive grant) (year of activation: 2015; duration: 2 years) (amount obtained in 2015: CHF 42,000).

Peer reviewed publications in 2015 (selection)

Agazzi P, Bien CG, Staedler C, Biglio V, **Gobbi C**. Over 10-year follow-up of limbic encephalitis associated with anti-LGI1 antibodies. J Neurol. 2015;262(2):469-470. doi: 10.1007/s00415-014-7540-3.

Hupperts R, Becker V, Friedrich J, **Gobbi C**, Salgado AV, Sperling B, You X. Multiple sclerosis patients treated with intramuscular IFN-β-1a autoinjector in a real-world setting: prospective evaluation of treatment persistence, adherence, quality of life and satisfaction. Expert Opin Drug Deliv. 2015;12(1):15-25. doi: 10.1517/17425247.2015.989209.

Kuhle J, **Disanto G**, Lorscheider J, Stites T, Chen Y, Dahlke F, Francis G, Shrinivasan A, Radue EW, Giovannoni G, Kappos L. Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis. Neurology. 2015;84(16):1639-1643. doi: 10.1212/WNL.0000000000001491.

Kuhle J, Gaiottino J, Leppert D, Petzold A, Bestwick JP, Malaspina A, Lu CH, Dobson R, **Disanto G**, Norgren N, Nissim A, Kappos L, Hurlbert J, Yong VW, Giovannoni G, Casha S. Serum neurofilament light chain is a biomarker of human spinal cord injury severity and outcome. J Neurol Neurosurg Psychiatry. 2015;86(3):273-279. doi: 10.1136/jnnp-2013-307454.

Longoni G, Rocca MA, Pagani E, **Riccitelli GC**, Colombo B, Rodegher M, Falini A, Comi G, Filippi M. Deficits in memory and visuospatial learning correlate with regional hippocampal atrophy in MS. Brain Struct Funct. 2015;220(1):435-444. doi: 10.1007/s00429-013-0665-9.

Rocca MA, Pravatà E, Valsasina P, Radaelli M, Colombo B, Vacchi L, **Gobbi C**, Comi G, Falini A, Filippi M. Hippocampal-DMN disconnectivity in MS is related to WM lesions and depression. Hum Brain Mapp. 2015;36(12):5051-63. doi: 10.1002/hbm.22992.

Zecca C, Heldner MR, Kamm CP, **Riccitelli GC**, **Disanto G**, Caporro M, Cianfoni A, Pravatà E, **Gobbi C**. Natalizumab in spinal multiple sclerosis in a daily clinical setting. Expert Opin Biol Ther. 2015;15(5):633-640. doi: 10.1517/14712598.2015.1025046.

Zecca C, Mainetti C, Blum R, **Gobbi C**. Recurrent Nicolau syndrome associated with subcutaneous glatiramer acetate injection--a case report. BMC Neurol. 2015;15:249. doi: 10.1186/s12883-015-0504-0.

2.2 Neuromuscolar Unit, Myosuisse Ticino Center

Claudio Gobbi MD PD

The Neuromuscular Unit is housed in Myosuisse Ticino Center, which belongs to a network of other centres specialized in neuromuscular diseases. It provides interdisciplanary and specialized consultancy to patients with neuromuscular diseases including clinical neurological and instrumental evaluations for accurate diagnosis. The Neuromuscular Unit collaborates with the Microbiology Laboratory of the Ente Ospedaliero Cantonale and the Centre Hospitalier Universitaire Vaudois, Lausanne. New research focusses on neurological complications in patients with suspected hepatitis E infection.

Ongoing research

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

This is an observational retrospective and prospective research project to determine the prevalence of patients with neurological complications of the peripheral type (Guillain-Barré syndrome or neuralgic amiotrofia) and suspected hepatitis virus E infection. A recent hepatitis E epidemic observed in Ticino has suggested gaining more insight on this topic. The neurological characteristics before and after infection will be described and risk factors for developing neurological damage will be identified. It is anticipated to include 50 patients in 2 years. 1 patient was enrolled by the end of 2015.

2.3 Sleep and Epilepsy Group

Mauro Manconi MD

The sleep and epilepsy Group's scientific mission is to explore brain function during sleep and sleep-related disorders in order to achieve important pieces of knowledge in the new, intriguing and incredibly growing field of sleep research. The group is mainly internationally recognized for its results in the field 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. In the last four years, thanks to consolidated local and external collaborations, we obtained 5 competitive large grants from the Swiss National Foundation, two of them focused on the impact of sleep disorders on the stroke's outcome, the first one on the effects of sleep related movement disorders on cardiovascular system, the second one on infraslow oscillation in sleep and the last one on sleep disorders and perinatal depression. A further competitive large 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 sleep related field of interest involve eating disorders during sleep and their connection with obesity, the mechanism of disperception in primary insomnia, and sleep apnea. New emerging areas of research, supported by starting competitive local and national grants, include sleep disorders in Parkinson Disease, sleep disorders in attention deficit hyperactive disorder and an infra-slow oscillating process in sleeping brain, in both of the cases innovative tools like High-Density EEG will be used. Educational initiatives such as European level university master's courses in sleep medicine, exchanging scholar and fellowship programs and periodic meeting with general population are a further basic pillar of the group's mission.

In 2015 **the main projects carried out or still underway** included:

- *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.*
  Lead investigators: M. Manconi, S. Miano, L. Ratti, CW. 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.

- *Infraslow-Oscillations.*
  Lead investigators: S. Fulda, M. Manconi, A. Bernasconi, C. Prosperetti.

  Computation analysis of periodic limb movements during sleep and other infra-slow-oscillating process during sleep.

- *Sleep disorders in Pediatrics, Hyperactive Attention Deficit Disorder.*
  Lead 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.*
  Lead 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 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.*
  Lead investigators: PL. Ratti, A. Kaelin-Lang, N. Amato, S. Miano, S. Hackethal.

  Characterization 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. A. Auricchio (Cardiocenter TI): RLS/PLM and cardiovascular Risk = 1 SNSF (Swiss National Science Foundation) grant.
b. P. Schulz (Communication Science University, USI): Judisky Study (SNSF) Effective Empowerment in Insomnia = 1 SNSF grant.
c. C. Gobbi (Neurocenter): Sleep/Fatigue in MS = 1 paper (review), 1 ongoing study.
d. S. Galati (Neurocenter): Sleep and Parkinson Disease (PD)= 1 ongoing study, (grant ABREOC).
e. CW. Cereda (Neurocenter): Sleep-related risk factors for CVD = 3 papers.
f. A. Kaelin (Neurocenter): Sleep and Parkinson Disease (PD).
g. M. Pons (Pneumology Service, Regional Hospital of Lugano): Central control of breathing during sleep = 2 papers (for print).
h. T. Gyr (Gynaecology and Obstetrics Service, Regional Hospital of Lugano): iron infusion in RLS during pregnancy = 1 paper.
i. M. Preve (Psychiatry Department, Regional Hospital of Mendrisio): Life-ON project = 1 paper.

Active External Collaborations:

a. S. Clemens (East Carolina University, Greenville, US): Basic Science (spinal dopaminergic network) = 2 papers.
b. J. Winkelmann (Harvard University, Boston, US): Sleep Related Movement Disorders (PLM Hypoxia) = 2 papers.
c. R. Ferri (IRCCS Oasi Institute, IT): Sleep Related Movement Disorders (PLM/RLS) = 36 papers.
d. C. Bassetti (Bern University, Inselspital, CH): Sleep Stroke, Pregnancy related RLS = 10 papers.
e. L. Ferini-Strambi (IRCCS San Raffaele, IT): Sleep/Epilepsy Disorders = 48 papers.
f. O. Polo (University of Tampere, Finland): Spinal lesioned model of PLM/RLS = 1 paper.
g. S. Happe (University of Münster, Germany): Computer Analysis (LM during sleep) = 1 travel grant (ESRS – 2014).
h. I. Gorayeb (University of Bordeaux, France): Sleep microstructure and PLM in monkeys = 2 papers.
i. F. Fanfulla = Sleep and stroke = 2 papers.

Main funding

"Sleep loss and sleep disorders and their impact on the short- and longterm outcome of Stroke"; M. Manconi (Co-Applicant), L. Ratti, G. Chiaro:
Swiss National Science Foundation (SNSF) (amount: CHF 597,000. Duration: 2014-2018).

"Auto-REST Study: Autonomic function and cardiovascular risk in Restless Legs Syndrome"; M. Manconi (Lead investigator), S. Fulda, A. Auricchio:
SNSF (amount: CHF 316,000. Duration: 2013-2015).

"Restless Legs Syndrome and Sleep Disorders During Pregnancy and Sleep Related"; "Risk Factor for Perinatal Depression"; M. Manconi (Lead investigator), T. Gyr, C. Garbazza:
MIUR (Italian Department of University Research) Finalized Research, Italian Ministery of University (Italian competitive national grant) (global amount: Euro 901,000. Duration: 2015-2018).

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

"The Life-ON Project: Light-Therapy in Perinatal Depression"; M. Manconi (Lead investigator), T. Gyr, C. Garbazza, M. Preve:
SNSF (amount: CHF 525,000. Duration: 2015-2018).

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

"Infra-slow oscillations II [NCT02532608]"; S. Fulda (Lead Investigator), M. Manconi, S. Miano. Collaboration: S. Vanhatalo, University of Helsinki:
SNSF (amount: CHF 120,000. Duration: 2015-2017).

"A1DHD Study: Markers polisonnografici del disturbo dell'attenzione ed iperattività in età pediatrica"; S. Miano, M. Manconi:
ABREOC (hospital competitive internal grant; duration: 2015-2016).

"Sleep benefit nella malattia di Parkinson"; L. Ratti, A. Kaelin, N. Amato.
Funding:
a. **ABREOC** (hospital competitive internal grant; amount: CHF 52,000);
b. **Swiss Parkinson Association**, "Sleep, Awake & Move" (amount: CHF 183,000. Duration: 2015 - 2018).

Clinical Trials in collaboration with the pharmaceutical industry:

- *SP0994: A multicenter, double-blind, double-dummy follow-up study evaluating the long-term safety of Lacosamide (200 to 600mg/day) in comparison with Carbamazepine (400 to 1200mg/day), used as monotherapy in patients with partial-onset or generalized tonic-clonic seizures (≥16 years) of age coming from the SP0993 study.*
  Ended in November 2014.
  Sponsor: UCB-Pharma.

- *A randomized, assessor- and patient- blind, multicenter, placebo-controlled study to assess the efficacy and safety of a single administration of Ferric Carboxymaitose in improving outcomes in iron deficient non-anaemic patients with restless legs syndrom.*
  Duration: ongoing.
  Sponsor: Vifor Pharma.

Peer reviewed publications in 2015 (selection)

Bassetti CL, Ferini-Strambi L, Brown S, Adamantidis A, Benedetti F, Bruni O, Cajochen C, Dolenc-Groselj L, Ferri R, Gais S, Huber R, Khatami R, Lammers GJ, Luppi PH, **Manconi M**, Nissen C, Nobili L, Peigneux P, Pollmächer T, Randerath W, Riemann D, Santamaria J, Schindler K, Tafti M, Van Someren E, Wetter TC. Neurology and psychiatry: waking up to opportunities of sleep: State of the art and clinical/research priorities for the next decade. Eur J Neurol. 2015;22(10):1337-1354. doi: 10.1111/ene.12781.

Donfrancesco R, Di Trani M, Porfirio MC, Giana G, **Miano S**, Andriola E. Might the temperament be a bias in clinical study on attention-deficit hyperactivity disorder (ADHD)?: Novelty Seeking dimension as a core feature of ADHD. Psychiatry Res. 2015;227(2-3):333-338. doi: 10.1016/j.psychres.2015.02.014.

Ferri R, Rundo F, Zucconi M, **Manconi M**, Aricò D, Bruni O, Ferini-Strambi L, **Fulda S**. Putting the periodicity back into the periodic leg movement index: an alternative data-driven algorithm for the computation of this index during sleep and wakefulness. Sleep Med. 2015;16(10):1229-1235. doi: 10.1016/j.sleep.2015.05.019.

Fulda S. The Role of Periodic Limb Movements During Sleep in Restless Legs Syndrome: A Selective Update. Sleep Med Clin. 2015;10(3):241-248, xii. doi: 10.1016/j.jsmc.2015.05.013.

Khachatryan SG, **Prosperetti C**, Rossinelli A, **Pedrazzi P**, **Agazzi P**, **Ratti PL**, **Manconi M**. Sleep-onset central apneas as triggers of severe nocturnal seizures. Sleep Med. 2015;16(8):1017-1019. doi: 10.1016/j.sleep.2015.03.019.

Leistner SM, Klotsche J, Dimopoulou C, Athanasoulia AP, Roemmler-Zehrer J, Pieper L, Schopohl J, Wittchen HU, Stalla GK, **Fulda S**, Sievers C. Reduced sleep quality and depression associate with decreased quality of life in patients with pituitary adenomas. Eur J Endocrinol. 2015;172(6):733-743. doi: 10.1530/EJE-14-0941.

Manconi M, Zavalko I, Fanfulla F, Winkelman JW, **Fulda S**. An evidence-based recommendation for a new definition of respiratory-related leg movements. Sleep. 2015;38(2):295-304. doi: 10.5665/sleep.4418.

Picchietti DL, Hensley JG, Bainbridge JL, Lee KA, **Manconi M**, McGregor JA, Silver RM, Trenkwalder C, Walters AS. International Restless Legs Syndrome Study Group (IRLSSG). Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation. Sleep Med Rev. 2015;22:64-77. doi: 10.1016/j.smrv.2014.10.009.

Prosperetti C, **Manconi M**. Restless Legs Syndrome/Willis-Ekbom Disease and Pregnancy. Sleep Med Clin. 2015;10(3):323-9, xiv. doi: 10.1016/j.jsmc.2015.05.016.

Ratti PL, Nègre-Pagès L, Pérez-Lloret S, Manni R, Damier P, Tison F, Destée A, Rascol O. Subjective sleep dysfunction and insomnia symptoms in Parkinson's disease: Insights from a cross-sectional evaluation of the French CoPark cohort. Parkinsonism Relat Disord. 2015;21(11):1323-1329. doi: 10.1016/j.parkreldis.2015.09.025.

Ratti PL, Sierra-Peña M, Manni R, Simonetta -Moreau M, Bastin J, Mace H, Rascol O, David O. Distinctive features of NREM parasomnia behaviors in parkinson's disease and multiple system

atrophy. PLoS One. 2015;10(3):e0120973. doi: 10.1371/journal.pone.0120973.

Silvani A, Martire VL, **Salvadè A**, Bastianini S, Ferri R, Berteotti C, Baracchi F, Pace M, Bassetti CL, Zoccoli G, **Manconi M**. Physiological time structure of the tibialis anterior motor activity during sleep in mice, rats and humans. J Sleep Res. 2015;24(6):695-701. doi: 10.1111/jsr.12319.

Vitelli O, Tabarrini A, **Miano S**, Rabasco J, Pietropaoli N, Forlani M, Parisi P, Villa MP. Impact of obesity on cognitive outcome in children with sleep-disordered breathing. Sleep Med. 2015;16(5):625-630. doi: 10.1016/j.sleep.2014.12.015.

2.4 Movement Disorders Center

Salvatore Galati MD, Claudio Städler MD, Paolo Paganetti PhD, Prof. Alain Kaelin MD PhD

Research on movement disorders represents one important research interest at the Neurocenter of Southern Switzerland. In January 2014, Prof. A. Kaelin joined the movement disorders research group. 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" (please see below). 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 2014.

In addition, a database of more than 200 patients of Ticino with movement disorders, in particularly PD, has been 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 has been funded by the Swiss Parkinson Association and is now starting.

In 2015 **the main research projects** included:

- *Role of sleep homeostasis in the development of Levodopa-induced dyskinesias: electrophysiological and molecular analysis in a Parkinsonian rat model.*
  Lead investigator: S. Galati.
  Collaborators: A. Kaelin, C. Städler, A. Salvadè, S. Sarasso (University of Milan), P. Stanzione (University of Rome).
  Funding: Pharmaceutical company; Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

  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 stabilization by sliding plasticity thresholds. Hypothesizing an association between these sleep process and dyskinesia we measured the synaptic down-scaling during sleep and our results are consistent with an association between synaptic homeostasis and the development of dyskinesias.
  This project was concluded, and the data published in "Neurobiology of Aging" journal in 2015.

- *Role of sleep homeostasis in the development of Levodopa-induced dyskinesias in PD patients.*
  Lead investigator: S. Galati.
  Collaborators: A. Kaelin, C. Städler, S. Sarasso (University of Milan).
  Funding: ABREOC (hospital competitive internal grant); Swiss Parkinson Foundation.

  Based on the findings in rodents mentioned above, the analysis was extended to patients affected by PD. To demonstrate the hypothesis, a cross-sectional high-density polysomnographic study is being conducted at different stages of the disease.
  All patients were recruited and the data are now analyzed.

- *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.
  Funding: 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.

  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-anesthetized rats. The neuronal basis of this pathological synchronization 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 was 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 (Universtity of Rome).
  Funding: Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

  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 by 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, a closer monitoring of cortical and basal ganglia oscillation is conducted in the freely moving parkinsonian animal.
The data collection and analysis have been recently completed and a first article has been published.

- *Prevalence and genetics of movement disorders in Ticino - database and biobank.*
  Lead investigator: S. Galati.
  Collaborators: A. Kaelin, C. Städler, C. Wider (University of Lausanne).
  Funding: Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

  This database was created to capture the spectrum of movement disorders in Ticino population. 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.
  Collaborators: S. Sgroi.
  Funding: Fondazione Baasch Medicus and Fondazione malattie neurodegenerative dell'adulto e dell'anziano Ticino (Foundation for the study of neurodegenerative diseases in adult and elderly people in Ticino).

  This is a PhD thesis of the "Graduate School for Cellular and Biomedical Sciences" of the University of Berne with S. Sgroi as a doctoral student and Prof. A. Kaelin as the thesis supervisor. This project focuses on the role of the endogenous opiodergic neuropeptides in Levodopa-induced dyskinesia. Please see below "Laboratory for Biomedical Neurosciences".

- *Alpha synuclein oligomers detection by skin biopsy: a novel early biomarker for parkinson disease?*
  Lead investigator: A. Kaelin.
  Collaborators: G. Melli, P. Paganetti
  Funding: Swiss Parkinson Foundation.

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

- *Cortical Reorganisation of Cerebral Networks after Childhood Stroke: Impact on Outcome.*
  Lead investigator: M. Steinlin (University of Berne).
  Co-investigator at the NSI: A. Kaelin.
  Funding: Swiss National Science Foundation (SNSF).

  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 arterial ischaemic 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 NSI is collaborating on this project mainly thanks to its expertise in Transcranial Magnetic Stimulation of the motor system.

Peer reviewed publications in 2015

Galati S, **Städler C**, Möller JC. Parkinsonism and Gorlin-Goltz syndrome: more than an incidental association? J Neuropsychiatry Clin Neurosci. 2015 Winter;27(1):e83-4. doi: 10.1176/appi.neuropsych.13120363.

Galati S, Stefani A. Deep brain stimulation of the subthalamic nucleus: All that glitters isn't gold? Mov Disord. 2015;30(5):632-637. doi: 10.1002/mds.26149.

Galati S, **Salvadè A**, Pace M, Sarasso S, Baracchi F, Bassetti CL, **Kaelin-Lang A**, **Städler C**, Stanzione P, Möller JC. Evidence of an association between sleep and levodopa-induced dyskinesia in an animal model of Parkinson's disease. Neurobiol Aging. 2015;36(3):1577-1589. doi: 10.1016/j.neurobiolaging.2014.12.018.

Kornfeld S, Delgado Rodríguez JA, Everts R, **Kaelin-Lang A**, Wiest R, Weisstanner C, Mordasini P, Steinlin M, Grunt S. Cortical reorganisation of cerebral networks after childhood stroke: impact on outcome. BMC Neurol. 2015;15:90. doi: 10.1186/s12883-015-0309-1.

Magalhães SC, **Kaelin-Lang A**, Sterr A, do Prado GF, Eckeli AL, Conforto AB. Transcranial magnetic stimulation for evaluation of motor cortical excitability in restless legs syndrome/Willis-Ekbom disease. Sleep Med. 2015;16(10):1265-1273. doi: 10.1016/j.sleep.2015.03.018.

Muellner J, **Kaelin-Lang A**, Pfeiffer O, El-Koussy MM. Neurogenic thoracic outlet syndrome due to subclavius posticus muscle with dynamic brachial plexus compression: a case report. BMC Res Notes. 2015;8:351. doi: 10.1186/s13104-015-1317-3.

Rocchi C, Pierantozzi M, **Galati S**, Chiaravalloti A, Pisani V, **Prosperetti C**, Lauretti B, Stampanoni Bassi M, Olivola E, Schillaci O, Stefani A. Autonomic Function Tests and MIBG in Parkinson's Disease: Correlation to Disease Duration and Motor Symptoms. CNS Neurosci Ther. 2015;21(9):727-732. doi: 10.1111/cns.12437.

Stefani A, Olivola E, Liguori C, Hainsworth AH, Saviozzi V, Angileri G, D'Angelo V, **Galati S**, Pierantozzi M. Catecholamine-Based Treatment in AD Patients: Expectations and Delusions. Front Aging Neurosci. 2015;7:67. doi: 10.3389/fnagi.2015.00067.

2.5 Stroke Center

Claudio Städler MD, Vesna Stojanova MD, Carlo W. Cereda MD, Concetta Manno MD, Joe Bontadelli MD, Jane Frangi Study Nurse

The Stroke Unit EOC (SUN EOC) is an accredited Comprehensive Stroke Center (since late 2013) and therefore recognized as a one of the Swiss centres of excellence for the cure of patients with stroke. The Stroke Center offers an optimal care for patients with cerebrovascular diseases. A dedicated and multisciplinary specialized stroke team take care of patients in the acute phase (inpatient unit) and also in a specialized outpatient clinic. The group also performs research activities, mainly focused on 4 topics in clinical research: acute stroke treatment and multimodal diagnosis of stroke, stroke prevention, stroke epidemiology, and stroke recovery in the acute phase.

In 2015 **the main research projects** included:

Investigator driven projects

- *Rehabilitation combined with bi-hemispheric transcranial direct current stimulation in subacute ischemic stroke: a randomised, controlled, double-blind study - The Re.Com.Bi.Ne. (Rehabilitation Combined with Bihemispheric Neuromodulation) post-stroke study.*
  Randomized multicenter interventional trial - NCT 01644929.
  Lead investigators: CW. Cereda, R. Müri.
  Collaborators: Clinica Hildebrand Brissago (CH), University Hospital Inselspital, Berne (CH), Helios Klinik Zihlschlacht (CH).
  Sponsor: EOC.
  Funding: ABREOC (hospital competitive internal grant).

  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 hypothesize that combining bihemispheric tDCS (anodal, excitatory,

of the ipsilesional motor cortex and cathodal, inhibitory, of the contralesional motor cortex) with simultaneous physical/occupational therapy in the subacute phase of ischemic stroke may improve upper limb motor recovery in humans. This study is a randomized, controlled, double-blind, crossover, 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.

- *SWITCH - Decompressive Hemicraniectomy in Intracerebral Hemorrhage.*
  Randomized multicenter interventional trial - NCT 02258919.
  Lead investigator: P. Scarone; Sponsor investigators (SI): CW. Cereda, V. Stojanova.
  Collaborators: Neurosurgery Service, Regional Hospital of Lugano and University Hospital Inselspital, Bern.
  Sponsor: University Hospital, Inselspital, Bern (CH).

  The primary objective of this randomized 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 the best medical treatment only. Secondary objectives are to analyze 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 best medical treatment alone.

- *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: EOC, 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.

  Working hypotheses are that stroke survivors with sleep deficiency and sleep fragmentation due to insomnia, sleep-disordered breathing or restless leg syndrome will present: (1) higher mortality from all causes and higher frequency of new cardio-/cerebrovascular events; and (2) a less favorable 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, CH.

  The three-year cumulative risk of a recurrent stroke, dependent on aetiology, is up to 25 per cent. 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.

Clinical Trials in collaboration with the pharmaceutical industry:

- *SOCRATES – Acute Stroke Or Transient IsChaemic Attack TReated with Aspirin or Ticagrelor and Patient OutcomES.*
  A randomized, double-blind, multinational study - NCT01994720.
  Lead investigators: CW. Cereda; Sponsor investigators (SI): V. Stojanova, C. Manno, M. Schmitt.
  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 ischemic stroke or transient ischemic 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 randomized, double-blind, multinational study - NCT02313909.
  Lead investigators: CW. Cereda; SI: V. Stojanova, C. Manno, M. Schmitt.

  This is a study in patients who recently had an ischemic 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 antitrombotic 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 randomized, double-blind, multinational study - NCT02392120.
  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 Ischemic and Hemorragic Strokes.

Main funding

"The Re.Com.Bi.Ne. (Rehabilitation Combined with Bihemispheric Neuromodulation) post-stroke study": **ABREOC** grant (approval: December 2011; activation: June 2012).

Trainee – Medical Students in 2015

Three medical students (cand. med.) from the Universities of Basel, Zürich and Lausanne (CH).

Peer reviewed publications in 2015

Cereda CW, George PM, Pelloni LS, Gandolfi-Decristophoris P, Mlynash M, Biancon Montaperto L, Limoni C, Stojanova V, Malacrida R, Städler C, Bassetti CL.
Beneficial effects of a semi-intensive stroke unit are beyond the monitor. Cerebrovasc Dis. 2015;39(2):102-109. doi: 10.1159/000369919.

Goeggel Simonetti B, Mono ML, Huynh-Do U, Michel P, Odier C, Sztajzel R, Lyrer P, Engelter ST, Bonati L, Gensicke H, Traenka C, Tettenborn B, Weder B, Fischer U, Galimanis A, Jung S, Luedi R, De Marchis GM, Weck A, **Cereda CW**, Baumgartner R, Bassetti CL, Mattle HP, Nedeltchev K, Arnold M. Risk factors, aetiology and outcome of ischaemic stroke in young adults: the Swiss Young Stroke Study (SYSS). J Neurol. 2015;262(9):2025-2032. doi: 10.1007/s00415-015-7805-5.

Lansberg MG, **Cereda CW**, Mlynash M, Mishra NK, Inoue M, Kemp S, Christensen S, Straka M, Zaharchuk G, Marks MP, Bammer R, Albers GW; Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE 2) Study Investigators. Response to endovascular reperfusion is not time-dependent in patients with salvageable tissue. Neurology. 2015;85(8):708-714. doi: 10.1212/WNL.0000000000001853.

Mishra NK, Christensen S, Wouters A, Campbell BC, Straka M, Mlynash M, Kemp S, **Cereda CW**, Bammer R, Marks MP, Albers GW, Lansberg MG; DEFUSE 2 Investigators. Reperfusion of very low cerebral blood volume lesion predicts parenchymal hematoma after endovascular therapy. Stroke. 2015;46(5):1245-1249. doi: 10.1161/STROKEAHA.114.008171.

2.6 Neuropsychology

Leonardo Sacco MD

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 visuo-spatial 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 senior neurologists 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 on an international study to test the efficacy of an human antibody against amyloid in mild Alzheimer's disease.

In 2015 **the main studies** included:

- *A-beta 42, tau and phosphorylated-tau liquor alterations in patients with mild cognitive impairment (CDR: 0.5) reflect amyloid accumulation and neuronal damage. Are a semantic memory, ecological memory, and dual-task tests coherent with the neurodegeneration?*
  Lead investigators: L. Sacco, S. Rossi, R. Pignatti.
  Funding: ABREOC (hospital competitive internal grant).

  The purpose 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 determine to which neuropsychological tests better allow discrimination between MCI subjects with AD markers (MCI CSF AD+) and MCI subjects without AD markers (MCI CSF AD-). The secondary purpose of the study is to compare at T1, after one-year follow-up, the proportion of subjects that

convert into AD (CDR≥1) and subjects with stable cognitive status (CDR=0.5) in the two groups (MCI CSF AD+ and MCI CSF AD-).

- *Neurocognitive assessment in the metabolic and aging 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.
  Funding: SHCS 2012 (external financial support).

  This study is included in the metabolic and aging cohort whose importance has been 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 aging 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 starting with longitudinal evaluations after two years.

- *Neuropsychologic outcome after aneurysmal subarachnoid haemorrhage – a new implementation of the prospective multicenter Swiss SOS study.*
  Lead investigators: M. Stienen, R. Weisshaupt, D. Valsecchi, M. Arrighi, M. Reinert, DE. Kuhlen, S. Rossi, L. Sacco.
  Funding: Registre Suisse Hemorragie Sousarachn.

  In the first step, we include all patients with aneurysmal subarachnoid haemorrhage (aSAH). The aim is the prospective implementation of a widely employed, standardized 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 improve the detection of neuropsychological deficits, depression, anxiety, and fatigue; following aSAH in Switzerland; assess the HrQoL in aSAH patients in Switzerland; 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 BiibO37 in subjects with early symptomatic Alzheimer's disease.
Lead investigator: L. Sacco.
Raters: S. Rossi, R. Pignatti, M. Lissi, S. Rocchi.
Funding: Biogen (external financial support).

Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β amyloid (A), including soluble Aβ oligomers and deposited fibrillar Aβ. 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 with placebo in subjects with early Alzhemier's disease (AD), including mild cognitive impairment due to AD and a subset of mild AD.

Trainees in neuropsychology

Three students from the universities of Milano - Bicocca and Geneva.

Peer reviewed publications in 2015

Lucca U, Tettamanti M, Logroscino G, Tiraboschi P, Landi C, **Sacco L**, Garrì M, Ammesso S, Bertinotti C, Biotti A, Gargantini E, Piedicorcia A, Nobili A, Pasina L, Franchi C, Djade CD, Riva E, Recchia A. Prevalence of dementia in the oldest old: the Monzino 80-plus population based study. Alzheimers Dement. 2015;11(3):258-270.e3. doi: 10.1016/j.jalz.2014.05.1750.

Zweifel-Zehnder AE, Stienen MN, Chicherio C, Studerus-Germann A, Bläsi S, **Rossi S**, Gutbrod K, Schmid N, Beaud V, Mondadori C, Brugger P, **Sacco L**, Müri R, Hildebrandt G, Fournier JY, Keller E, Regli L, Fandino J, Mariani L, Raabe A, Daniel RT, Reinert M, Robert T, Schatlo B, Bijlenga P, Schaller K, Monsch AU; Swiss SOS study group. Call for uniform neuropsychological assessment after aneurysmal subarachnoid hemorrhage: Swiss recommendations. Acta Neurochir (Wien). 2015;157(9):1449-1458. doi: 10.1007/s00701-015-2480-y.

2.7 Neurosurgery

Prof. Michael Reinert MD

Research priorities of the Neurosurgery Service are in the field of spinal and neurovascular neurosurgery as well as in neuro-oncology. Neuro-oncology is one of the key domains of the NSI and the collaboration between the IOSI has a longstanding tradition. In 2015, clinical and translational research in neuro-oncology was further developed. The scope is to improve the understanding of neuro-oncological biomolecular pathways to ameliorate patient outcome. 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 Institut of Pathology, ICP). RAMAN spectromicroscopy is used to develop a new intraoperative online tumour- and tumour stage recognition. By a collaboration with the FHNW (Fachhochschule Nordwestschweiz) and UNIBAS (University of Basel), the necessary nanoparticles are specifically conceptualized and produced by our PhD students. Differences of RAMAN signal of tumour in cell cultures and tumour exposed to nanoparticles are studied in the LBN by our PhD students and collaborators. Furthermore, in an in-vivo mouse animal model tumour, the effect of using anti-brain tumour coated nanoparticles is studied upon completion of tumour resection and through online tumour cell recognition, please see below "Laboratory for Biomedical Neurosciences" (Prof. Dr. Michael Reinert).

These are **the main projects performed or still ongoing** in 2015:

- *Neurovascular Research is focused on clinical registration of vascular malformations and of patient outcome.*
  Lead investigators: T. Robert, D. Valsecchi, M. Reinert, A. Cianfoni.

  A 3D modeling project for clinical pretreatment visualization is under development.

- *Spinal Research.*
  Lead investigator: P. Scarone.

  This is a clinical research project in collaboration with the Neuroradiology Service. Trojection and microdiscectomy for the treatment of lumbar disc herniations. This a prospective randomized study that aims at comparing ozone injection (Trojection: Ozone) 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® with surgical discectomy.

- *Studio AIRO: vertebral arthrodesis with pedicular screws: retrospective comparison between intraoperative CT and cone-beam CT associated with spinal navigation.*
  Lead investigator: P. Scarone.

  This is a retrospective cohort study on spinal navigation aiming at comparing two different spinal navigation techniques, one associated with a true intraoperative CT (AIRO system, available at our Service since October 2014) and the other with a Cone-beam CT (O-arm system, available at our Service 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. The secondary objectives are the duration of surgery, clinical results, the position of the screws in different groups of patients, and the radiation exposure with different techniques.

- *SWITCH study: Swiss trial of decompressive craniectomy versus best medical treatment of spontaneous supratentorial intracerebral hemorrhage: a randomized controlled trial.*
  Lead investigator: P. Scarone.
  Collaborators: CW. Cereda, V. Stojanova, D. Valsecchi, T. Robert.
  Funding: Inselspital, Bern, CH.

  Swiss trial of decompressive craniectomy versus best medical treatment of spontaneous supratentorial intracerebral haemorrhage (SWITCH): a randomized controlled trial. The primary objective of this randomized controlled trial in collaboration with the neurovascular group (see above) is to determine whether decompressive surgery and best medical treatment in patients

with spontaneous ICH will improve outcome compared to best medical treatment only. The secondary objectives are to analyze 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 with best medical treatment alone. The first patient was enrolled in 2015.

- *Functional Neurosurgery and Neuromonitoring.* Lead investigator: L. Valci.

  The focus is on developing new intraoperative standards for reducing artefacts and reducing motion using the the D-Wave and preoperative localization of eloquent areas using navigated transcranial magnetic stimulation.

Peer reviewed publications in 2015 (selection)

Cianfoni A, Raz E, Mauri S, Di Lascio S, **Reinert M**, Pesce GF, Bonaldi G. Vertebral augmentation for neoplastic lesions with posterior wall erosion and epidural mass. AJNR Am J Neuroradiol. 2015;36(1):210-218. doi: 10.3174/ajnr.A4096.

Hsieh K, Stein K, Mono ML, Kellner-Weldon F, Verma RK, Weisstanner C, Andereggen L, **Reinert M**, Gralla J, Schroth G, El-Koussy M. In-vivo phase contrast magnetic resonance angiography of the cerebrovascular system: a comparative study with duplex sonography. Swiss Med Wkly. 2015;145:w14155. doi: 10.4414/smw.2015.14155.

Krähenbühl AK, Gralla J, Abu-Isa J, Mordasini P, Widmer HR, Raabe A, **Reinert M**. High-flow venous pouch aneurysm in the rabbit carotid artery: A model for large aneurysms. Interv Neuroradiol. 2015;21(3):407-411. doi: 10.1177/1591019915582381.

Kurzbuch AR. Does size matter? Decompressive surgery under review. Neurosurg Rev. 2015;38(4): 629-640. doi: 10.1007/s10143-015-0626-2.

Reinert M, **Valci L**, **Dalolio M**, Reyes V, D'Auria J. Anterior communicating artery aneurysm clipping using standard small fronto-pterional approach, clipping with 3 Lazic clips. Neurosurg Focus. 2015;38(VideoSuppl1):Video6. doi: 10.3171/2015.V1.FOCUS14541.

Robert T, Blanc R, Ciccio G, Gilboa B, Fahed R, Redjem H, Pistocchi S, Bartolini B, Piotin M. Angiographic factors influencing the success of endovascular treatment of arteriovenous malformations involving the corpus callosum. J Neurointerv Surg. 2015;7(10):715-720. doi: 10.1136/neurintsurg-2014-011271.

Robert T, Blanc R, Ciccio G, Redjem H, Fahed R, Smajda S, Piotin M. Anatomic and angiographic findings of cerebellar arteriovenous malformations: Report of a single center experience. J Neurol Sci. 2015;358(1-2):357-361. doi: 10.1016/j.jns.2015.09.361.

Schucht P, Banz V, Trochsler M, Iff S, Krähenbühl AK, **Reinert M**, Beck J, Raabe A, Candinas D, **Kuhlen D**, Mariani L. Laparoscopically assisted ventriculoperitoneal shunt placement: a prospective randomized controlled trial. J Neurosurg. 2015;122(5):1058-1067. doi: 10.3171/2014.9.JNS132791.

2.8 Neuroradiology

Alessandro Cianfoni MD, Emanuele Pravatà MD

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 2015, three visiting radiology residents joined the team, and received both theorethical and practical traning in neuroradiology, by attending lectures and cooperating in case reporting together with the senior members. Furthermore, the neuroradiology scientific activity increased in 2015, both in terms of design and initiation of original projects, and of cooperation and support provided to other Neurocenter services, as well as with external Institutions. The first research project "High-resolution post-contrast imaging at 3 Tesla: a comparison of three different techniques" received funding approval by a competitive internal grant (ABREOC), and is presently ongoing. Other two new starting projects - regarding CT accuracy in the acute stroke setting and the accuracy comparison of two different spine surgery implant techniques- were initiated in cooperation with the Stroke Center and the Neurosurgery Service, respectively (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, a collaboration with Dr. Mattia Cattaneo and Prof. Augusto Gallino's cardiology research team in Bellinzona also started, resulting in a research grant obtained from the Swiss Heart Foundation to investigate the MRI brain functional correlates of the Tako-Tsubo and X-syndrome cardiac diseases.
Other active collaborations continued during 2015 with the Inselspital of Bern, and the San Raffaele Hospital in Milan through the Multiple Sclerosis Center, in the field of advanced neuroimaging. The cooperation with the Siemens Medical for the development of new work-in-progress MRI sequences, also continued.

These are **the main ongoing projects** in 2015:

- *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.

  Obtaining Gadolinium-enhanced magnetic resonance images (MRI) increases accuracy in the detection and characterization of neoplastic and multiple sclerosis (MS) brain lesions. We hypothesize 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 lesions (CELs) detectability, volume, conspicuity (a qualitative judgment of how clearly CELs appear), and artefacts assessed by two independent neuroradiologists (E.P., D.D.) blind to clinical data. Current status: Data acquisition in progress (April 2015-November 2016). Until 31st December 2015, 122 patients recruited. Of these, 111 participated (47, tumours; 64 MS). 11 did not provide informed consent. Preliminary data inspection showed 40 with at least one CEL, of whom 35 tumours and 5 MS.

- *Post marketing non-inferiority study comparing Triojection to Discectomy for Lumbar Disc Herniation.*
  Investigators: A. Cianfoni (Co-Investigator), P. Scarone (Co- Investigator), P. Maino, G. Bonaldi (Co- Investigator, Ospedali Riuniti of Brescia, 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 has been 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 randomized controlled international multicenter 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.
  We aim at reviewing the prevalence of stroke-mimic conditions in our Center and investigating the ability of our diagnostic protocol (consisting of brain CT+angiography CT+perfusion CT) to discriminate ischemic stroke from stroke like conditions in the acute/hyperacute phase.
  Patients with imaging studies performed from January to December 2015 for clinical suspicion of acute ischemic 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.

  Preliminary findings: 163 patients fulfilled the inclusion criteria. The prevalence of stroke-like conditions was 7.4%, including 6 cases of seizure, 3 brain tumours, 2 migraines and 1 arteriovenous fistula. The CT-angio CT-perfusion CT protocol was able to differentiate "stroke mimic" from ischemic stroke in all cases.

- *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 stabilization 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 stabilization. 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 16 months. Ethical committee authorization request for this retrospective assessment is being submitted.

Active Internal and External Collaborations

a. P. Scarone (Lead investigator), Neurosurgery Service (NSI): 1 Research Project submitted to the Ethical committee for approval: "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 stabilization with pedicle screws: a retrospective comparative study between two neuronavigation techniques: intraoperative computed tomography and cone beam tomography associated with spinal navigation).

b. M. Cattaneo (Lead investigator), A. Gallino, Cardiovascular Research Center, Regional Hospital of Bellinzona and Valli and University of Zürich: 1 Swiss Heart Foundation (SHF) grant: "Tako-Tsubo Cardiomyopathy and Cardiac Syndrome X: a study on the brainheart interactions in two orphan cardiac diseases".

Main funding

A. Cianfoni
"High-resolution post-contrast imaging at 3 Tesla: a comparison of three different techniques" (EOC. NEURORAD.1501): **ABREOC** (hospital competitive internal grant; approved: 2015; activation: 2016; duration: 24 months).

Peer reviewed publications in 2015

Catteruccia M, Sauchelli D, Della Marca G, Primiano G, Cuccagna C, Bernardo D, Leo M, Camporeale A, Sanna T, **Cianfoni A**, Servidei S. "Myo-cardiomyopathy" is commonly associated with the A8344G "MERRF" mutation. J Neurol. 2015;262(3):701-710. doi: 10.1007/s00415-014-7632-0.

Cianfoni A, Raz E, Mauri S, Di Lascio S, Reinert M, Pesce G, Bonaldi G. Vertebral augmentation for neoplastic lesions with posterior wall erosion and epidural mass. AJNR Am J Neuroradiol. 2015;36(1):210-218. doi: 10.3174/ajnr.A4096.

Rocca MA, **Pravatà E**, Valsasina P, Radaelli M, Colombo B, Vacchi L, Gobbi C, Comi G, Falini A, Filippi M. Hippocampal-DMN disconnectivity in MS is related to WM lesions and depression. Hum Brain Mapp. 2015;36(12):5051-5063. doi: 10.1002/hbm.22992.

Zecca C, Heldner MR, Kamm CP, Riccitelli GC, Disanto G, Caporro M, **Cianfoni A**, **Pravatà E**, Gobbi C. Natalizumab in spinal multiple sclerosis in a daily clinical setting. Expert Opin Biol Ther. 2015;15(5):633-640. doi: 10.1517/14712598.2015.1025046.

2.9 Neuroanaesthesia

Paolo Maino MD

The EOC Pain Management Center promotes the highest possible quality of life for patients with persistent pain, providing accurate diagnosis and direct interventions to reduce, eradicate or manage the pain and provide support particularly about management of pain problems of high medical and psychological complexity, and about the use of controlled drugs, minimal invasive interventions and neuromodulation. The ambulatory service which is present in all 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. In 2015, academic cooperations with the University of Maastricht and the VUMC University Medical Centre of Amsterdam were formalised. The collaboration will be with Prof. Dr. Bert A. Joosten in Maastricht, who has broad expertise in pain research within the theme of Neuropathic Pain and with Prof. Roberto Perez in Amsterdam.

The Neuroanesthesia Service is responsible for the anesthetic care of patients undergoing neurosurgical procedures, including craniotomies for brain tumours, aneurysms and arteriovenous malformations, carotid endarterectomies, posterior fossa surgeries, epilepsy surgeries, complex spinal surgery, and stereotactic and interventional neurovascular techniques. Neuroanesthesia locations include multiple MRI-equipped operating rooms plus advanced neurovascular interventional suites.

The research activity of our team mainly focused on:

- *Neuromodulation RELIEF STUDY (A7007), a global registry to evaluate long-term effectiveness of neurostimulation therapy for pain.*
  Lead investigator: P. Maino.
  Sponsor: Boston Scientific International SA.

- *Intrathecal pump refill: reservoir fill port identification by palpation versus ultrasound, a mono-centre prospective comparison study in patients undergoing regular intrathecal pump refill.*
  Lead investigator: P. Maino, E. Koetsier.

  Intrathecal drug therapy with implantable intrathecal pumps is being utilized increasingly

for the treatment of chronic refractory pain and spasticity. However, performing the regular refill procedures of the pumps with the commonly performed "blind" technique carries the potential risk of medication injection into the subcutaneous tissue, which can lead to an overdose. The primary purpose of this study is to assess the accuracy of the ultrasound-guided technique for the refill procedure compared to the blind technique in subjects undergoing regular refills of their intrathecal pumps for the treatment of chronic non-malignant pain or spasticity.

- *Dorsal root ganglion stimulation for the management of painful intractable non-diabetic small fibre neuropathy in the lower limbs: a prospective case series.*
  Lead investigators: P. Maino, E. Koetsier, C. Gobbi, A. Kaelin.

  Background: small fiber neuropathy (SFN) is a disorder of the peripheral nerves that affects thinly myelinated A Delta and unmyelinated C nerve fibers whose painful symptoms typically affect the limbs in a distal-to-proximal gradient. Treatment of the painful symptoms frequently fails. Spinal cord stimulation (SCS) is used to treat chronic, intractable pain when conventional therapies have failed and has been shown to be effective in patients having a variety of neuropathic pain syndromes including diabetic polyneuropathy. However, achieving good pain-paresthesia overlap of the feet is noted to be challenging with conventional spinal cord stimulation.
  Spinal cord stimulation of the dorsal root ganglion (DRG-SCS) is a relatively new mode of SCS with promising results and has demonstrated pain relief for groin pain, complex regional pain syndrome and chronic, intractable neuropathic pain of the limbs and trunk.
  The purpose of this study is to assess the effectiveness of DRG-SCS in alleviating the painful symptoms in patients with non-diabetic small fiber neuropathy in the feet. The secondary objectives are to assess neuropathic pain components, pain and paresthesia distributions, central sensitization, efficacy of DRG-SCS on the quality of life, physical functioning, mood, global improvement, and the progression of SFN assessed by biopsy.

- *Comparative evaluation of clinical outcome of degenerative disc disease treated with a new nucleus augmentation device.*
  Lead investigators: P. Maino, E. Koetsier, R. Perez.

  Degenerative Disc Disease (DDD) is one of the most common spinal pathologies, affecting up to 10-15% of adults. The degeneration is associated with diminished water-binding capabilities of the nucleus pulpous leading to disc dehydration, volume reduction, changes in cellular activity, biomechanical changes and painful symptoms. Patients are initially treated with non-surgical pain-management techniques, such as anti-inflammatory medications and physical therapy, but these treatments often provide only temporary relief. When non-surgical intervention fails, fusion or total disc arthroplasty are often prescribed, both of which are highly invasive surgeries with significant associated morbidity. Clearly, a meaningful solution for the treatment gap existing between conservative care and invasive surgical intervention is needed.
  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 primary objective of this study is to quantify the reduction in lumbar pain.

Main funding

"Dorsal root ganglion stimulation for the management of painful Intractable small fibre neuropathy: a prospective case": **ABREOC** (hospital competitive internal grant; approval: 2015; activation: 2015; duration: 24 months).

Peer reviewed publications in 2015

Canet J, Sabaté S, Mazo V, Gallart L, de Abreu MG, Belda J, Langeron O, Hoeft A, Pelosi P; PERISCOPE group (**Maino P**). Development and validation of a score to predict postoperative respiratory failure in a multicentre European cohort: A prospective, observational study. Eur J Anaesthesiol. 2015;32(7):458-470. doi: 10.1097/EJA.0000000000000223.

Codipietro L, **Maino P**. Aseptic arachnoiditis in a patient treated with intrathecal morphine infusion: symptom resolution on switch to ziconotide. Neuromodulation. 2015;18(3):217-220; discussion 220. doi: 10.1111/ner.12201.

Maino P, Koetsier E, Perez RS. The Accuracy of Template-Guided Refill Technique of Intrathecal Pumps Controlled by Fluoroscopy: An Observational Study. Neuromodulation. 2015;18(5):428-432. doi: 10.1111/ner.12212.

2.10 Laboratory for Biomedical Neurosciences (LBN)

Prof. Alain Kaelin MD PhD, Paolo Paganetti PhD

The Laboratory for Biomedical Neurosciences (LBN) is committed to discovering new treatments and diagnostics methods for patients affected by neurodegenerative disorders, a family of debilitating and irreversible disorders that significantly affect the life of patients and caregivers.
The integration of the LBN within the NSI offers the unique opportunity for a reciprocal fostering between clinician-initiated basic research and the translation of new findings into effective therapies to prevent and treat disease, as well as innovative early diagnostic measures. Basic, translational and clinical investigations are complementary branches of biomedical sciences. Our translational research strategy aims at filling the traditional gap between basic research discoveries and medical applications. The vision of the LBN is to improve the understanding of neurodegenerative disorders at the functional and molecular level. The LBN has 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 of other neurodegenerative disorders also defined as proteinopathies. The LBN research platform is a comprehensive approach based on electrophysiology, behavioural analysis, histology, flow cytofluorometry, confocal microscopy, and modern techniques in cellular and molecular biology, in order to analyze cellular and animal models of disease. Understanding the pathophysiology of Parkinson's disease and the search for novel therapeutics based on counteracting aberrant protein levels by targeting protein modification, misfolding and toxicity, are our everyday life. Research by Dr. Paolo Paganetti takes a molecular and cellular approach to investigate the causes of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Huntington's disease. The research groups of Prof. Dr. Kaelin and Dr. Galati successfully created and implemented animal models for Parkinson`s disease, which are tailored to behavioural and histopathological investigations (Prof. Dr. Kaelin) as

well as for electrophysiological studies (Dr. Galati). These research models were implemented to understand the pathological mechanisms underlying these brain disorders and as experimental models to test new therapeutic interventions. In 2015, the LBN was fruitfully broadened by a new group led by Prof. M. Reinert researching brain tumours.

Another important objective of the LBN is **training and education** of young scientists to foster their careers 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 specialized 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 state of the art infrastructure and 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 will participate in the corresponding programs provided 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 organized 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 PhD students hosted by the LBN in 2015 were affiliated with the University of Bern, the University of Zürich or the University of Basel. In dicember 2015, Stefania Sgroi obtained her PhD at the University of Bern, being the first completed PhD in neuroscience of the LBN.

Since 2014, Dr. Paolo Paganetti and Prof. A. Kaelin have redefined the strategy of the LBN. Thanks to the new laboratory space occupied in March 2014 at the Swiss Institute for Regenerative Medicine (SIRM) in Torricella-Taverne, the LBN has considerably grown. From the first four scientists, the LBN was hosting at the end of 2015 eithteen scientists in four research groups. This included four practicants, five PhD doctoral students, and three post-doctoral fellows. So far, the LBN received substantial financial support from competitive research grants, charitable organizations and benevolent donors. This external financial support for research activities planned for the period 2015-2017 covers 43% of the total LBN expenses in addition to financing provided by the EOC, two-thirds of the external support are through competitive grants.

Parkinson Disease Research Group

Group Leader: Prof. A. Kaelin MD PhD.
Collaborators: S. Sgroi, G. Melli, W. Song, A. Salvadé, V. Biemmi, V. Tettamanti, P. Paganetti, S. Galati.

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder with most cases occurring after the age of fifty. The motor symptoms of PD result from the loss of dopaminergic neurons in specific regions of the brain. A pathological characteristic of PD is the deposition of the protein alpha-synuclein in Lewy bodies whose number and distribution directly relates to the clinical symptoms. Prolonged use of dopamine-replacement therapies may lead to a complication called dyskinesia. Levodopa-induced dyskinesia is characterized by abnormal involuntary movements (dystonia, chorea, athetosis).

Research at the LBN focus on the development of new animal models of the disease, e.g. to understand the pathophysiology of Levodopa-induced dyskinesia. Molecular studies aim at understanding the molecular mechanisms inducing alpha-synuclein-mediated toxicity. The purpose is also to use alpha-synuclein analysis on the skin as an early disease marker (see also above, **Movement Disorders Center**).

Main funding

"Alpha synuclein oligomers detection by skin biopsy: a novel early biomarker for parkinson disease?": **Swiss Parkinson Foundation.**
Lead investigator: Prof. A. Kaelin MD PhD.
Amount: CHF 327,627.
Started: 2014 - duration: 2017.
Type of fund: competitive.

"Corticostriatal plasticity and Parkinson's Disease: Investigating the role of the striatal opioidergic system in parkinsonian rats":
SNSF (IBRO fellowship).
Lead investigators: A. Kaelin, W. Song.
Amount: CHF 55,000.
Started: February 2015, international postdoc visit for 1 year.
Type of fund: competitive.

Basal Ganglia Pathophysiology Research Group
Group Leader: S. Galati MD.
Collaborators: G. Orban, G. Di Giovanni, V. Trendafilov, A. Salvadé, M. Sarti, S. Pinton, A. Kaelin.

The scope of the research is to understand the control mechanisms of movement. The project is aimed at defining the activity of some deep regions of the brain, the basal ganglia. They play a critical role in the pathogenesis of various movement disorders such as Parkinson's and Huntington's diseases. Recent studies have indicated that the neural networks of the basal ganglia-thalamo-cortical loop participate in everyday complex behaviors that require coordination between cognition, motivation, and movements. The investigation is therefore aimed at understanding the role and way of action of the basal ganglia-thalamo-cortical loop in normal behaviour and pathological states, such as Parkinson's disease and Levodopa-induced dyskinesia.
The research group creates animal models that reproduce the clinical characteristics of early and advanced stages of Parkinson's disease. The group can record the simultaneous extracellular and intracellular activity of several neurons in the basal ganglia with local field potential, in anesthetized and awake, normal, parkinsonian and dyskinetic rat models.

Key Research Areas:

- Experimental dopamine-depleted animal models.
- Mechanisms underlying neuronal network activity in the basal ganglia.
- The role of oscillations in cortico-basal ganglia-thalamic loop function and dysfunction.
- The role of homeostatic plasticity in processing of cortical input by the basal ganglia.

Main funding

"Role of motor thalamus in parkinsonian state":
Swiss Parkinson Foundation.
Lead investigator: S. Galati.
Amount: CHF 342,923.
Started: 2014 - duration: 2017.
Type of fund: competitive.

Neurodegeneration Research Group
Group leader: P. Paganetti PhD.
Collaborators: C. Foglieni, S. Papin, S. Pinton, A. Salvadé, A. Stuerchler, G. Ulrich.

The discovery of disease mutations in the genes encoding for the proteins that form brain deposits in patients affected by neurodegenerative disorders has established a link between the sporadic and hereditary disease forms. Most importantly, this demonstrates the role of these aberrant protein forms of proteins in causing cell loss and the neurodegenerative process. 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 characterizing post-translational modifications and subcellular localization of the proteins involved in the pathogenesis of neurodegenerative disorders. To this end, in the first year the research group developed the necessary research tools and implemented multiple genetic, molecular and cellular techniques. In 2015, several research projects started in parallel to a consolidation effort characterized by scientific collaborations with local (CCT/Dr. Barile, role of exosomes in neurodegeneration, IRB/Prof. Molinari, analysis of cellular stress pathway associated with aging), national (University of Zürich/Prof. Polymenidou, protein homeostasis and proteotoxicity; University of Zürich/Prof. Aguzzi, new treatment for Alzheimer's disease), and international (Los Angeles/CHDI, immune assays to study huntingtin biology) institutes.

Main funding

"Difetti nel metabolismo proteico come causa della malattia di Alzheimer" (Defects in protein metabolism as a cause of Alzheimer's disease):

Gelu Foundation.
Lead investigator P. Paganetti.
Amount: CHF 750,000.
Started: 2015 - duration: 2017.
Type of fund: competitive, one senior scientist position, five practicants.

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

NN.
Lead investigator P. Paganetti.
Amount: CHF 50,000.
Started: 2015 - duration: 2016.
Type of fund: non competitive, research consumables and equipment.

Brain Tumor Research Group
Group Leader: Prof. M. Reinert MD.
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, ICP).
RAMAN spectromicroscopy 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 conceptualized 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 nanoparicles is studied upon completion of tumour resection and through online tumour cell recognition.
In this last study, the longterm scope is to develop a new surgical microscope, which permits immediate intraoperative tumour recognition.

Main funding

Neurosurgical Funds.
Lead investigator: M. Reinert.
Amount: CHF 500,000.
Started: 2015 - duration: 2018.
Type of fund: non competitive, two PhD student positions.

Neurocenter of Southern Switzerland (NSI) Awards 2015

Best Poster 2015 **Joint Neurosurgery and Neuroradiology Annual Meeting**, Lucerne, 11th September 2015: **Pravatà E**, Sestieri C, Caulo M, **Riccitelli G**, **Zecca C**, **Cianfoni A**, **Gobbi C**.
"Brain intrinsic resting-state functional connectivity modulation induced by mental effort in multiple sclerosis patients with fatigue".

Fulda S.
Award **FNT Fondazione Neuroscienze Ticino** for the Best Clinical Neuroscience Publication:
"An Evidence-Based Recommendation for a New Definition of Respiratory-Related Leg Movements". Sleep. 2015;38(2):295-304. doi: 10.5665/sleep.4418.

Galati S.
Award **FNT Fondazione Neuroscienze Ticino** for the Best Translational Neuroscience Publication: "Evidence of an association between sleep and levodopa-induced dyskinesiain an animal model of Parkinson's disease". Neurobiol Aging. 2015;36(3):1577-1589. doi: 10.1016/j.neurobiolaging.2014.12.018.

Cereda CW.
Prize **Quinta Giornata della Ricerca Clinica della Svizzera Italiana 2015** (The 5th Clinical Research Day of Southern Switzerland 2015) for the Best Original Pubblication as a researcher from 35 to 45 years of age: "Beneficial Effects of a Semi-Intensive Stroke Unit are Beyond the Monitor, Cerebrovascular Diseases". Cerebrovasc Dis. 2015;39(2):102-109. doi: 10.1159/000369919.