

Scientific report C4N 2011



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Center for Neurosciences (C4N)

The Center for Neurosciences (C4N) coordinates neuroscience-related research activities, and especially aims a lasting collaborative research program among basic and clinical neuroscientists, allowing research from bench to bed. The Center consists of different research groups, which collaborate in a number of research themes.

Mission

We aim to advance scientific knowledge in the fields of **neuroprotection and neuromodulation**.

- Neuroprotection = the protection of the cells of the nervous system against injury and degeneration.
- Neuromodulation = interventions and factors that modulate functions of the nervous system or how the nervous system modulates other body systems.

Goals

- Coordinate all neuroscience-related research activities at the VUB, and optimize the mutual utilization of infrastructure and technical resources.
- Group interdisciplinary researchers in the area of neuroscience at the VUB.
- Encourage collaborative research among basic and clinical neuroscientists to move discoveries from the laboratory to the patient's bedside and to send questions from the bedside to the laboratory.
- Establish and improve national and international relations with other research groups and industrial partners.

Organisation

The Center consists of different **research groups**, which collaborate in a number of research themes.

- Participating research groups are: **EPHAR, NEUR, MFYS, MICH, CRRG, KINE & COPS**
- Research groups maintain their autonomy
- Researchers can participate in different research themes

Research topics

1. Parkinson's disease

Sophie Sarre, Ron Kooijman, Anja Flamez, Yvette Michotte, Eric Kerckhofs, Eric Soetens, Natacha Deroost, Ann Massie

Neuroprotection

The existing treatment of Parkinson's disease (PD) is purely symptomatic. Neuroprotective strategies are tested in the 6-OHDA model of Parkinson's disease. Different targets and processes, including dopamine receptors, angiotensin receptors (AT1 and AT2), the inflammatory response, neurotrophins, protein aggregation, oxidative stress and excitotoxicity are investigated. Relevant further testing is carried out in transgenic mice where specific proteins associated with PD (a-synuclein, LRRK2, PINK-1) are overexpressed or knocked out.

Deep brain stimulation

High frequency stimulation of the subthalamic nucleus (STN) is considered an important treatment for late stage Parkinson's disease patients with insufficient benefit of pharmacological treatment. A better understanding of the modulation of the neurotransmitter release is considered important in the search for the exact role of the STN and the mechanisms behind the success of its high frequency stimulation. Major depression is a contraindication for Deep Brain Stimulation (DBS) and the treatment in itself can induce depressive-like behaviour. Another line of research relates to the characterization of the 6-OHDA model as a model to study co-morbid depression in Parkinson's disease and to study the effects of antidepressants on the depressive effects of bilateral stimulation of the STN.

External brain stimulation

Dyskinesia is a disabling side effect of current PD therapies, and difficult to manage. The use of repetitive transcranial magnetic stimulation in suppressing dyskinesia is being investigated in patients with PD.

Cognitive dysfunctions

Patients with dysfunctions of the basal ganglia and frontostriatal systems often suffer from executive dysfunctions, memory problems, visuospatial dysfunctions and problems with procedural learning. Cognitive theories and experimental work can contribute to unravel the underlying mechanisms. Actually one research line investigates the capability to learn movement sequences using a serial reaction task paradigm. Another research line examines the neuropsychological profile of Parkinson patients with or without freezing of gait.

Predocctoral researchers: Ben Ampe, Mustafa Varçin, Anissa El Arfani, Jochen Vandenbossche, Jolien van Schoors, Eduard Bentea

Technical support: Ria Berckmans & Gino Desmet.

Collaborations

V. Baekelandt & J. Winderickx (KULeuven), C. Van Broekhoven (VIB,UA), G. Griffioen (reMynd nv, KULeuven), M. O' Neill (Eli Lilly, UK), L. Tenenbaum (ULB), D. Lambert and E. Hermans (Université Catholique de Louvain), P. Vanderheyden (VUB), Y. Temel (U Maastricht), W. Van Den Wildenberg (University of Amsterdam).

2. Epilepsy

Ilse Smolders, Ralph Clinckers, Ann Massie, Ann Van Eeckhaut, Yvette Michotte

Neuropeptides

An increasing number of neuroactive peptides are being identified in the brain. Neuropeptides do not directly interfere with fast synaptic neurotransmission but tend to exert modulatory effects. They are preferentially released at high frequency firing, which typically occurs during epileptic seizures. It is expected that peptidomimetics will have greater efficacy and fewer side-effects compared to current antiepileptic drugs. Neuropeptides and their receptors are considered as promising targets for future anti-epileptogenic or disease modifying treatments. In the ongoing projects, we study, amongst others, angiotensin fragments, cortistatin, ghrelin and neurotensin.

Glutamate transporters

System xc⁻ exchanges intracellular glutamate for extracellular cystine molecules. This property makes this glial antiporter crucial for maintaining intracellular levels of the antioxidant glutathione but also makes it a non-negligible player in regulating glutamatergic neurotransmission. The functional role and mechanisms of action of system xc⁻ in acute or chronic recurrent seizures remains elusive. This glial system xc⁻ is - in view of the well-established neuron-glia communication - an innovative and unconventional approach in the field of epilepsy.

Antidepressants

We have several years of experience with the involvement of antidepressant drugs as possible treatment option for epilepsy. We demonstrated anticonvulsant efficacy of several clinically used antidepressants in acute seizure models but now study their potential impact on the processes of epileptogenesis. In view of translation of interesting results to the clinical setting, a minimum of effort is needed since all drugs tested are marketed antidepressant drugs.

Predocctoral researchers: Najat Aourz, Ellen Loyens, Jeanelle Portelli, Katrien Maes, Joeri Van Liefferinge, Katia Vermoesen, Jessica Coppens

Technical support: Gino De Smet, Carina De Rijck

Collaborations:

P. Boon, K. Vonck, A. Meurs, R. Raedt (UGent), P. De Witte (KULeuven), P. De Deyn, D. Van Dam (UA), M. Danhof, Rob Voskuyl, Elizabeth de Lange, Oscar Della Pasqua (Universiteit Leiden), E. Aronica (Academic Medical Center Amsterdam), P. Dournaud, Zsolt Zsaba (INSERM U676 Paris), F. Simonin, J.J. Bourguignon (Université de Strassbourg), Z. Bortolotto, G. Collingridge (University of Bristol), H. Sato (Yalagata University Japan), S. Chai, A. Albiston (Monash University Australia)

3. Neurovirology

Bart Rombaut, Ilse Smolders, Ann Massie, Bert Thys

Poliovirus

Research mainly focuses on the replication of poliovirus, and more specifically on the first steps (adsorption and uncoating) and the last step (morphogenesis) of the viral replication cycle. Research involves basic insights of the replication cycle of the virus, and on the development of antiviral compounds and new poliovirus vaccines. Different Nanobodies® are being developed with antiviral activity against poliovirus. Research should determine whether these small antibody fragments could be used as antiviral drugs against poliovirus.

Viruses and demyelinating disease

Both Theiler's murine encephalomyelitis virus (TMEV) and canine distemper virus cause a demyelinating disease that resembles multiple sclerosis (MS). The aim is to investigate how these viruses modulate cells in the central nervous system, and how this results in MS-like pathology. Furthermore, the design of a pan viral chip is ongoing. The lab wants to trace viral sequences of MS patients in body fluids to make a correlation between viral infections and MS.

Viruses and epilepsy

Contrary to other mouse strains, 50% of C57Bl/6 mice infected with TMEV display acute behavioural seizures. After a latent period, these mice start developing spontaneous seizures, making them a valuable tool for studying the correlation between infection, acute seizures and subsequent development of epilepsy. We focus on the involvement of glutamate transporters in this virus-induced form of epileptogenesis and we are interested in their differential regulation by TMEV-infection in mice developing MS, mice developing epilepsy and mice not showing any signs of one of these disorders.

Predocctoral researchers: Hadewych Halewyck, Ellen Merckx, Lise Schotte

Technical support: Monique De Pelsmacker, Solange Peeters, Frank Van Der Kelen

Collaborations:

E. Wimmer (Stony Brook University, NY, USA; Microarray Facility VIB, KULeuven, Belgium), Johan Neyts (Rega Institute, KULeuven, Belgium), Thomas Michiels (Christian de Duve Institute, UCL, Belgium), Petri Susi (University of Turku, Turku, Finland), Serge Muyldermans & Reza Hassanzadeh-Ghassabeh (CMIM, VUB, Belgium), Soile Blomqvist (National Institute for Health and Welfare (THL), Helsinki, Finland), Jim Hogle (Harvard Medical School, Boston, Massachusetts, USA) Koen Andries (Johnson&Johnson, Pharmaceutical Research & Development, Beerse, Belgium), and the WHO, Geneva, Switzerland.

4. Multiple Sclerosis

Jacques De Keyser, Ralph Clinckers, Ron Kooijman, Ann Massie, Véronique Bissay

The role of astrocytes

Several lines of evidence point to a dysfunction of astrocytes in multiple sclerosis (MS), which may explain many of the pathological features of the disease: the occurrence of relapses associated with inflammatory responses in the CNS, apoptosis of oligodendrocytes, and axonal degeneration that underlies the progressive deterioration. Key findings from previous research include the absence of beta2 adrenergic receptors on astrocytes in MS lesions and normal appearing white matter, and reduced brain creatine kinase (CK-B) levels resulting in a decreased PCr metabolism. The role of astrocytes is studied in cell cultures, postmortem MS brain samples, in vivo microdialysis in mouse, and in an astrocyte selective beta2 adrenoreceptor KO mouse. Preclinical studies are performed to investigate how therapies that may restore astrocyte functions may be translated to the clinic. Energy metabolism and cerebral perfusion are studied in different MS subgroups, and these parameters are used to evaluate possible new therapies for MS in proof-of-concept studies.

Natural history and factors that influence the disease course

The clinical course of MS is heterogeneous, and about 25% has a relatively benign course. By investigating factors that alter the course of the disease we hope to find clues of pathophysiological mechanisms that protect MS patients against focal injury and axonal degeneration. Interesting findings will be further investigated in proof-of-concept animal models of MS.

Neuroprotective therapy of relapses

Relapses are currently treated with high dose corticosteroids, but recovery is incomplete in many patients, and this contributes to the cumulative disability. We aim to investigate therapies that not only resolve symptoms but also protect cells in the CNS threatened by the inflammatory attacks. We intend to investigate modulation of the insulin-growth factor system as a possible protective therapy.

Post-doc: Cathy Jensen (Australia)

Predocctoral researchers: Marie D'Hooghe, Guy Laureys, Frauke Demol, Melissa Cambron, Miguel D'Haeseleer

Technical support: Anke Desmedt (preclinical), Annick Van Meirhaegen-Wieleman (clinical)

Collaborations:

M. D'hooge and G. Nagels (MS Center Melsbroek), N. Wilczak and D.J. Heersema (Groningen, The Netherlands), J. Mostert (Arnhem, The Netherlands) A. Arutjunian (St. Petersburg, Russia), E. Frohman (Texas, US), H. Tremlett (British Columbia, Canada).

5. Brain ischemia

Ron Kooijman, Sophie Sarre, Sylvie De Raedt, Raf Brouns, Said Hachimi-Idrissi, Yvette Michotte, Jacques De Keyser

Hypothermia

Hypothermia represents one of the most effective neuroprotective strategies of brain injury. The effects of mild hypothermia are investigated in the endothelin-1 rat model for focal transient cerebral ischemia. Currently, the effect of hypothermia on the inflammatory response after stroke is being studied. Identification of other important markers that can explain the protection is carried out using 2D-gel electrophoresis (in collaboration with Prof. Arckens of the KULeuven). Clinically relevant markers/strategies (glucose, neuron-specific enolase (NSE), therapeutic window) are investigated to facilitate the translation of this treatment to the clinic.

Insulin like-growth factor-I

The effects of insulin like-growth factor (IGF-I) as a neuroprotective agent in focal cerebral ischemia are studied in endothelin-1 induced focal cerebral ischemia in conscious rats with hypertension as a relevant comorbidity factor. At the moment, we study the effects of clinically feasible ways of IGF-I administration and their windows of opportunity for treatment. We have already shown that subcutaneous administration in normal rats after the insult reduces infarct volume. A second study addresses the working mechanisms of IGF-I in neuroprotection with special reference to neuroinflammation and oxidative stress. In the clinic, we will investigate ways to increase IGF-I levels in acute stroke patients.

Improving acute stroke management

We assess the role of different factors that can influence stroke severity, progression and outcome. We investigate factors that influence the outcome of thrombolysis. An important area of research is investigating the possibilities of starting neuroprotection in the pre-hospital setting.

Acute stroke is associated with several factors that worsen outcome, including hypertension, hyperglycemia, hyperthermia and arrhythmias. The relationship between autonomic nervous system dysregulation and these factors will be studied both in patients admitted at the stroke unit and in animal models to assess therapeutic interventions.

Predocctoral researchers: Tine Zgavc, Deborah De Geyter, Wendy Stoop, Sylvie De Raedt, Ann Desmedt, Robbert-Jan Van Hooff, Christine Minnekeer

Technical support: Ria Berckmans and Peggy Verdood (preclinical), Rita Van Dijck (clinical).

Collaborations:

G.J. Luijckx (UMC Groningen, The Netherlands), P. Boon (UGent), C. Kessler (University of Greifswald, Germany), L. Arckens (KULeuven), T. Lahoutte (VUB)

6. Central regulation of systemic disorders

Yori Gidron, Alain Dupont, Maarten Moens, Jean D'Haens

Neuroimmunomodulation systems and peripheral diseases

The CNS and immune system are in constant bidirectional communication, and the inflammatory response plays major roles in oncogenesis and coronary artery disease. This line of research spans across three main topics related to neuromodulation of illnesses:

1. The role of the vagus nerve in possible tumor modulation
2. The effects of hemispheric lateralization and left prefrontal activation on the common cold
3. The effects of prefrontal cognitive exercises on mood.

CNS and blood pressure control

There is increasing evidence that brain angiotensin peptides, glutamate, GABA and NO interact within the rostral ventrolateral medulla (RVM) and paraventricular nucleus (PVN) to control sympathetic tone and blood pressure and may be important in the pathogenesis of many forms of hypertension.

This project aims to improve our understanding of the regulation of the PVN-RVLM axis and their contributions in hypertension.

Chronic pain

Chronic neuropathic pain is a very complex entity and often difficult to treat. Despite many efforts of pharmaceutical and instrumental companies, the pathophysiology behind well-known medical and interventional treatments remains unclear. Understanding the cerebral correlates of acute and chronic pain perception has increased significantly since the advent of neuroimaging. Clinical research deals with methods for detection of functional and neurobiological cerebral alterations after treatment with neuromodulation devices and/or medication. We hope to detect new mechanisms involving these treatment options in order to improve the understanding of the pathophysiological mechanisms and provide better therapies.

Predocctoral researchers :

Marijke De Couck, Tereza Killianova, Sofie Brouwers, Sylvie De Raedt, Dana Herzog (Univ of Tilburg)

Technical support: Wim Vanhecke, Rita Van Dijck

Collaborations:

Oncology, cardiology and psychiatry, UZ; Bordet hospital, Brussels; Univ of Tilburg, The Netherlands, B. Nuttin (KULeuven)

7. Mental disorders and cognitive decline

Chris Baeken, Ilse Smolders

Repetitive transcranial magnetic stimulation

This clinical research unit investigates the neurobiological impact of rTMS on the underlying neurocircuitry of emotion in affective disorders: in 'normal' emotion, unipolar and bipolar depression, schizophrenia, alcohol dependency, and borderline personality disorder.

Pharmacological approaches

Within the preclinical research unit, we study the mechanisms of action underlying the spatial memory improving effects or the antidepressant-like effects of various neuropeptides (e.g. angiotensin IV, oxytocin). Moreover, the functional role of the cystine-glutamate antiporter in hippocampus-related physiological memory tasks is investigated. A computer controlled video tracking system is available to thoroughly analyze rodent behavior during preclinical tests for antidepressant-like activity (e.g. mouse tail suspension, mouse forced swim test) and spatial memory tasks (e.g. Morris water maze, continuous and delayed spontaneous alternation in a Y maze) .

Predocctoral researchers: Liesbeth Santermans, Ellen Loyens

Collaborations: UGent (psychology), UIA (CAPRI), UZ Leuven (genetics), UMC Utrecht, University Munster, University Lyon, University of Melbourne, University of Brighton.

8. Exercise and the Brain

Romain Meeusen, Guy Nagels, Nathalie Pattyn, Jo Nijs

The interaction of exercise on neurochemistry, neurophysiology and neuroplasticity is explored. Animal and human experiments are combined, with measurements of neurotransmitters and the hormonal output from the brain during different manipulations. We explore the limits of fatigue, mechanisms of thermoregulation, and the positive effects of exercise on neurogenesis.

This research theme also deals with the influence of exercise and training on cognition and brain activity in different patient populations, including those with cardiovascular disease, obesity, diabetes mellitus and sports injuries. Peripheral and central mechanisms of chronic pain and chronic fatigue are investigated in conditions like fibromyalgia, chronic fatigue syndrome, chronic whiplash, and chronic low back pain. The effects of exercise and pollution are studied to find out whether health-enhancing effects of 'commuter cycling' outweigh the effects of air pollution, especially the effects on cognition. The ALTACRO (Automated Locomotion Training using an Actuated Compliant Robotic Orthosis) is a project in collaboration with the Faculty of Engineering. The major purpose of the ALTACRO project is to build a rehabilitation robot, and will link CNS aspects with neurophysiologic mechanisms of locomotion.

The neurophysiological aspects of recovery and (over)training are examined, including several aspects of performance and (neuromuscular) recovery. The link between performance, recovery and the brain is also explored in a research project sponsored by the European Space Agency. In this project the effects of exercise on sleep, performance and cognitive functioning is studied at the Concordia basis in Antarctica.

Post-docs : Bas de Geus, Bart Roelands, Mira Meeus

Predoctoral researchers : Kristel Knaepen, Jessica Van Oosterwijck, Vinciane Fontenelle, Kevin De Pauw, Inge Bos, Cajsja Tonoli, Jo Verschueren, Susan Vrijkotte, Kelly Ickmans

MD : Luk Buyse, Guido Van Gent, Luc Itterbeek

Collaborations:

Dr. E. Heyman (University of Lille), Prof. Dr. L. Van Loon (University of Maastricht), MS kliniek Melsbroek, Royal Military Academy, Prof. B Keymeulen (Diabetes Center), The German Sport University Koln & VITO

Appendix

MD/PhD dissertations 2011

23/08/2011

Maike Goekint – Exercise and brain-derived neurotrophic factor: an exploratory study on acute exercise, training and neurotransmission

Promotor: Prof. dr. Romain Meeusen

06/07/2011

Anneleen Schallier - Discovery of glutamate transporters as novel drug targets for epilepsy and Alzheimer's disease

Promotor(s): Prof. dr. Ilse Smolders, Prof. dr. Ann Massie

Co-promotor: Prof. dr. Yvette Michotte

19/09/2011

An-Gaëlle Ceulemans - The effect of mild hypothermia on the neuroinflammatory response in experimental stroke

Promotor(s): Prof. dr. Yvette Michotte, Prof. dr. Sophie Sarre

Co-promotor(s): Prof. dr. Said Hachimi-Idrissi, Prof. dr. Ron Kooijman

04/11/2011

Bert Thys - New antiviral tools targeting the capsid of poliovirus for use in late stage poliomyelitis eradication strategies

Promotor: Prof. dr. Bart Rombaut

Publications 2011

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Seminars 2011

06/10/2011

Tine Zgavc - Proteomic analysis of the global protein changes in the endothelin-1 rat model for cerebral ischemia: effect of mild hypothermia

Deborah De Geyter - IGF-I as a treatment in a rat model for focal cerebral ischemia

27/10/2011

Jolien Van Schoors - UHPLC with electrochemical detection for in vivo neurochemical research

Eduard Bentea - Modeling Parkinson's disease by inhibiting the ubiquitin-proteasome system: relevance to human pathogenesis and opportunities for disease intervention

10/11/2011

Frauke Demol - Involvement of astrocytic B2 receptor deficiency on MS

Guy Laureys - Astrocytic beta2-adrenergic receptors: key players in neuroinflammation and metabolic cerebral homeostasis

24/11/2011

Najat Aourz - Rodent models for initial validation of small molecules with proconvulsant /anticonvulsant properties, screened in zebrafish

Katia Vermoesen - Research towards the anticonvulsant and antiepileptogenic properties of antidepressants in the kainic acid-induced post-status epilepticus model

08/12/2011

Lise Schotte - The development of nanobodies as an anti-polioviral drug

Hadewych Halewyck - Capillary electrophoresis of poliovirus particles

22/12/2011

Inge Bos - Impact of exposure to particulate matter and physical activity on cognition

Vinciane Fontenelle - Neurophysiology of fatigue

Contact

Directors:

Prof. dr. Jacques De Keyser
UZ Brussel
Department of Neurology
Head of Department
Laarbeeklaan 101
1090 Brussel
Phone: +32-(0)2-477 64 10
E-mail: Jacques.DeKeyser@uzbrussel.be

Prof. dr. Yvette Michotte
Vrije Universiteit Brussel
Department of Pharmaceutical Chemistry and Drug Analysis
Laarbeeklaan 103
1090 Brussel
Phone: +32-(0)2-477 47 48
E-mail: Yvette.Michotte@vub.ac.be

Scientific coordinator:

Lies Van Cauwenbergh
Vrije Universiteit Brussel
Laarbeeklaan 103
1090 Brussel
Phone: +32-(0)2-474 92 64
+32-(0)485-97 58 07
E-mail: Lies.Van.Cauwenbergh@vub.ac.be