Appendix 2: Onderzoekslijnen Center for Neurosciences

Inhoudsopgave

I. Target Driven Drug Discovery

1.1. Neuropeptides and beyond

Neuropeptides appear to be of importance when the central nervous system is challenged, such as during high-frequency firing and/or pathological conditions. Neuropeptides are then released mainly extrasynaptically where their peptide receptors can modulate overall excitability without interfering too much with the fast synaptic neurotransmission. Potential advantages of treatments that target neuropeptide systems in comparison to classical neurotransmitter systems and ion channels revolve consequently around the subject of efficacy as well as the reduced likelihood of side effects, thus making them attractive candidates for the development of new clinical applications for various disorders including epilepsy and epileptogenesis. Indeed, since high frequency firing is the pathological hallmark of epileptic seizures, the search for neuropeptides linked to epilepsy is of utmost interest.

Current neuropeptide projects:

Neuropeptide Y and related neuropeptide receptors
PIs: Ilse Smolders, Jeanelle Portelli
Technical/administrative support: Ria Berckmans, Gino De Smet, Carina De Rijck, Rose-Marie Geens, Gerda De Boeck
Scientific collaboration with Alfred Meurs (UGent), Frederic Simonin (Université de Strassbourg, France), Jean-Jacques Bourgignon (Université de Strassbourg, France), Frederic Bihel (Université de Strassbourg, France)

Neuropeptide Y (NPY or YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY) is a well-established first-in-class antiepileptic neuropeptide in animal models of seizures and epileptogenesis (reviewed by Meurs et al., 2007) with inhibitory actions on excitability via mainly NPY Y2 and Y5 receptors. Our team has contributed to the field by showing that NPY increases extracellular hippocampal dopamine and glutamate levels *in vivo*, the dopamine increase being sigma1 receptor-mediated and contributing to NPY's anticonvulsant action (Meurs et al., 2007), and the glutamate increase being Y1 receptor-mediated without interfering with NPY's anticonvulsant effects (Meurs, Portelli et al., 2012). The role of NPY Y1 receptors in anticonvulsant mechanisms was reassessed using different Y1 receptor ligands, namely two highly selective Y1 receptor ligands (the agonist D-His23-NPY and the antagonist BVD10) and the mixed Y1/FF receptor antagonist BIBP3226. We established that the highly selective Y1 receptor ligands did not affect limbic seizure severity when compared to the control group, whereas BIBP3226 administration significantly attenuated the seizures possibly due to its action on NPFF (FLFQPQRFamide) receptors. This has led us to further investigate the role of NPFF receptors in seizure-modulating effects. NPFF1 and NPFF2 receptors belong to the G protein-coupled receptor (GPCR) family and possess a 30-35% structure homology with NPY receptors.

Ghrelin
PIs: Jeanelle Portelli, Ilse Smolders, Ann Massie
PhD student: Jessica Coppens
Technical/administrative support: Ria Berckmans, Gino De Smet, Carina De Rijck, Rose-Marie Geens, Gerda De Boeck
Scientific collaboration with Paul Boon (UGent), Alfred Meurs (UGent), Kristl Vonck

(UGent), Robrecht Raedt (UGent), Jean-Alain Fehrentz (Université de Montpellier, France)
Ghrelin (GSSFLSPEHQRVQQRKESKKPPAKLQPR, n-octanoylated on Ser-3) is a pleiotropic neuropeptide that has only very recently been introduced into the field of epilepsy (reviewed by Portelli et al., 2012). Animal studies performed to date indicate that ghrelin has anticonvulsant properties; however, there is a great paucity with regard to what mechanism of action is utilized by ghrelin to inhibit seizures. We recently showed that the anticonvulsant effects of ghrelin are mediated via the growth hormone secretagogue receptor (GHSR). To our surprise, however, we found that the GHSR knockout mice had a higher seizure threshold than their wild-type littermates when treated with the chemoconvulsant pilocarpine. Using both *in vivo* and *in vitro* models, we further discovered that inverse agonism and desensitization/internalization of the GHSR attenuate limbic seizures in rats and epileptiform activity in hippocampal slices. This constitutes a novel mechanism of anticonvulsant action, whereby an endogenous agonist reduces the activity of a constitutively active receptor (Portelli et al., 2012). We are now studying the effects of ghrelin and its receptor on inflammation and neuroprotection in chronic epilepsy models.

Somatostatin and cortistatin
PI: Ilse Smolders
PhD student: Najat Aourz
Technical/administrative support: Ria Berckmans, Gino De Smet, Carina De Rijck, Rose-Marie Geens, Gerda De Boeck
Scientific collaboration with Kyriaki Thermos (University of Heraklion)

Somatostatin-14 (SRIF or AGCKNFFWKTFTSC) is a potent anticonvulsant in rodent models of limbic seizures with the hippocampus as major site of action. Moreover loss of SRIF function in the dentate gyrus contributes to epileptogenesis and seizure susceptibility. We contributed to the field by showing that - in rats - the hippocampal sst1 receptor acts as an inhibitory autoreceptor but is not involved in the SRIF-mediated anticonvulsant effects (De Bundel et al., 2010). We also provided the first *in vivo* evidence for potent anticonvulsive properties exerted by intrahippocampal administration of highly selective sst3 and sst4 receptor agonists (respectively L-796,778 and L-803,087). Nevertheless, selective sst2 receptor antagonism prevented these sst3- or sst4 receptor-mediated anticonvulsant effects, suggesting a functional cooperation with rat hippocampal sst2 receptors (Aourz et al., 2011). Rodent cortistatin shares 11 of its 14 amino acids with SRIF and mediates several of its effects via activation of the 5 types of sst receptors. Cortistatin (PCKNFFWKTFSSCK) has also affinity for the ghrelin receptor (GHSR) and the possible existence of a cortistatin-specific receptor has been suggested as well (possibly orphan receptor MRGX2). We are currently investigating which receptor subtypes are involved in the anticonvulsant effects mediated by cortistatin in a rodent limbic seizure model.

Neurotensin/Neuromedins
PIs: Ilse Smolders, Ann Van Eeckhaut
PhD students: Katrien Maes, Yannick Van Wanseele, An De Prins
Technical/administrative support: Ria Berckmans, Gino De Smet, Carina De Rijck, Rose-Marie Geens, Gerda De Boeck
Scientific collaboration with Steven Ballet (VUB), Dirk Tourwé (VUB), Vicky Caveliers (VUB), Bart De Spiegeleer (UGent)

The tridecapeptide neurotensin (NT or pELYENKPRRPYIL) mediates its central and peripheral effects through interaction with three identified receptor subtypes, referred to as NTS1, NTS2 and NTS3 (Sortilin 1). NTS1 and NTS2 belong to the GPCR family, whereas Sortilin 1 is a single transmembrane domain receptor. Cerebral administration of NT can strongly modulate dopaminergic neurotransmission, leads to hypothermia and protects against ischemic stroke, and exhibits naloxone-independent analgesic responses. Glycosylated neurotensin analogues were shown to have also anticonvulsant effects in the 6Hz model of farmacoresistent seizures (Lee et al., ChemMedChem, 2009). Neuromedin N (KIPYIL) is closely related to NT in terms of sequence and activity at NT1S1 and NTS2 receptors. We are currently studying whether whether neuromedin N also plays a role in limbic seizure susceptibility. Finally we are interested in another neuromedin family, containing neuromedin U and neuromedin S. Neuromedin U (FRVDEEFQSPFASQSRGYFLFRPRN) is a highly conserved neuropeptide present in many species. It can activate the HPA axis and is therefore linked to the stress response; it can affect feeding behaviour, blood pressure regulation, pronociception and proinflammatory mechanisms, amongst others. We are currently developing selective NMUR1 and NMUR2 ligands for further *in vivo* proof-of-principle testing.

Other related projects:

Insulin-regulated aminopeptidase, an enzyme with various neuropeptide substrates
PIs: Ilse Smolders, Ann Massie
PhD student: Jessica Coppens
Technical/administrative support: Ria Berckmans, Gino De Smet, Carina De Rijck, Rose-Marie Geens, Gerda De Boeck
Scientific collaboration with Siew Chai (Monash University, Australia), Patrick Vander Heyden (VUB), Dimitri De Bundel (Université de Marseille), Zsolt Csaba (INSERM Paris, France), Pascal Dournaud (INSERM Paris, France)

We have long been intrigued by the biological effects of the hexapeptide angiotensin IV (Ang IV or VYIHPF) and contributed to the field by showing that Ang IV improved spatial memory in a plus maze task (De Bundel et al., 2009) and exerted anticonvulsant effects against pilocarpine-induced seizures (Stragier et al., 2006; for review De Bundel et al., 2009). Nevertheless, to date the exact mechanism of action of Ang IV in these effects remains elusive and is part of our current investigations. An interesting breakthrough was the fact that our Australian colleagues demonstrated that the Ang IV binding site was an enzyme, insulin-regulated aminopeptidase (IRAP) (Albiston et al., 2001), and that Ang IV acts as an IRAP inhibitor but not an IRAP substrate. We could subsequently show that genetic deletion of IRAP can alter the threshold for pentylenetetrazole-induced seizures (Loyens et al., 2011) and that IRAP is required to observe the antidepressant-like effects of one of the IRAP substrates, namely oxytocin (Loyens et al., 2013). Other possible *in vivo* substrates of IRAP that could explain some of the biological effects of IRAP inhibition by Ang IV are SRIF and vasopressin. We are especially focussing at the moment on the link between IRAP and SRIF-mediated actions.

Connexin-mimetic peptides
PI: Ilse Smolders
PhD student: Laura Walrave
Technical/administrative support: Ria Berckmans, Gino De Smet, Carina De Rijck,

Rose-Marie Geens, Gerda De Boeck
Scientific collaboration with Mathieu Vinken (VUB), Luc Leybaert (UGent)

Connexins (Cxs) are the constituents of gap junctions (GJs) and hemichannels (HCs), which mediate intercellular and extracellular communication, respectively. Accruing evidence underscores a key role for Cx43 signalling in hippocampal physiology. The specific involvement of Cx43HCs in *in vivo* hippocampal functioning however remains elusive. In this project, we will use a tool set of Cx43 mimetic peptides that can finally distinguish Cx43GJs and Cx43HCs, and that will unveil for the first time the possible roles of Cx43HCs in *in vivo* hippocampal physiology and dysfunctioning.

1.2. Glutamate transporters

This research theme focuses on the role of glutamate transporters in neurological disorders. The different glutamate transporters that are being studied comprise system xc- or the cystine/glutamate antiporter, the Na+/K+-dependent glutamate reuptake transporters (EAATs) and the vesicular glutamate transporters (VGLUTs).

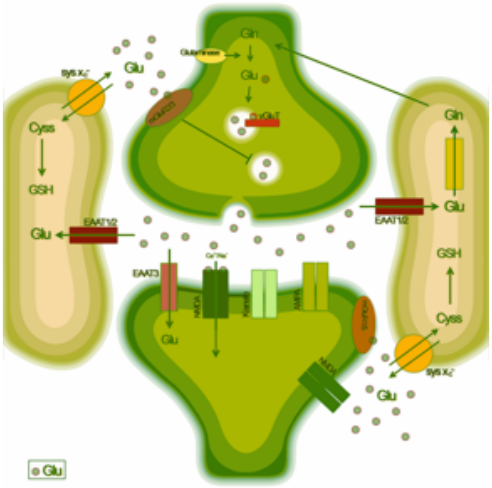


Figure: Glutamate (Glu) is loaded into presynaptic vesicles by vesicular glutamate transporters (VGLUTs). After its release into the synaptic cleft, glutamate is cleared by high-affinity Na+/K+-dependent glutamate transporters (EAATs). Glutamate can be released into the extrasynaptic space via system xc- or the cystine/glutamate antiporter. This antiporter imports one cystine molecule in exchange for one glutamate molecule.

Recently, most of our projects focus on system xc-, with xCT as specific subunit. This antiporter imports one cystine molecule into the glial cell in exchange for one glutamate molecule. Cystine is intracellularly reduced to cysteine, the rate-limiting building block in the synthesis of glutathione. As such, increased activity of system xc- can protect cells against oxidative stress. Yet, this increased uptake of cystine is coupled to increased release of glutamate and can consequently result in toxic extracellular glutamate levels. The involvement of this antiporter in neurological disorders that are commonly characterized by increased oxidative stress as well as excitotoxic damage, can thus be dual.

System xc- in the brain: screening of antibodies
PIs: Ann Massie, Ilse Smolders
PhD student: Joeri Van Liefferinge
Collaborators: Lut Arckens (K.U.Leuven), Niels Danbolt (University of Oslo, Norway),

Joeri Aerts (VUB), Emmanuel Hermans (UCL), Hideyo Sato (Yamagata University, Japan)
It is common knowledge that the antibodies that are being used for the detection of system xc- in immunohistochemistry/immunocytochemistry are not always specifically binding xCT, the specific subunit of system xc-. As such, the regional as well as cellular distribution of system xc- in the brain is still questionable. We therefore decided to screen a large battery of home-made as well as commercial antibodies for their specificity in the most common immunological techniques, i.e. immunohisto(cyto)chemistry, Western blotting and FACS analysis, by using xCT knockout tissue as negative control. Using the appropriate antibody combined with the appropriate protocol, we will perform a regional/cellular distribution study.

System xc- and Parkinson's disease
PIs: Ann Massie, Yvette Michotte
PhD-student: Eduard Bentea
Collaborators: Charles Meshul (Portland VA Medical Center, USA); Veerle Baeckelandt (K.U.Leuven); Hideyo Sato (Yamagata University, Japan)
We recently reported increased expression levels of xCT, the specific subunit of system xc-, in the striatum of the 6-OHDA hemi-Parkinson rat model (Massie et al., 2008). To further understand the functional meaning of this upregulation, we investigated the susceptibility of xCT knockout mice, i.e. mice that do not express functional system xc-, for 6-OHDA-induced neurodegeneration and we observed a significant neuroprotection in these mice compared to wildtype littermates (Massie et al., 2011). These data suggest that inhibition of system xc- might be a neuroprotective strategy for the treatment of Parkinson's disease. Currently, we are using two other mouse models for PD to confirm our observations in the 6-OHDA model, i.e. the chronic, progressive MPTP model and the lactacystin model. Moreover, in the latter model we will be investigating the link between glutamate toxicity and alpha-synuclein aggregation.
All glutamate transporters subtypes as well as the proteins that regulate their expression levels are being studied in tissue of PD patients.

System xc- and epilepsy/epileptogenesis
PI: Ilse Smolders, Ann Massie
PhD student: Joeri Van Liefferinge
Collaborators: Hideyo Sato (Yamagata University, Japan), Jan Lewerenz (University Hospital Ulm, Germany)
We have shown that the threshold for limbic seizures is higher in mice lacking xCT, the specific subunit of system xc-, compared to wildtype littermates. This decreased susceptibility was suggested to be related to the decreased hippocampal extracellular glutamate levels in xCT knockout mice (De Bundel et al., 2011). Moreover, we recently discovered increased xCT expression levels in hippocampal samples of epileptic patients (Lewerenz et al, submitted). Currently, we are investigating whether system xc- might be involved in the process of epileptogenesis by using several rodent models for epilepsy.

System xc- in multiple sclerosis
Co-PI: Ann Massie, Jacques Dekeyser, Bart Rombaut
PhD student: Ellen Merckx
Collaborators: Jan Lewerenz (University Hospital Ulm, Germany), Pam Maher (The Salk Institute, USA), Axel Methner (University of Düsseldorf, Germany), Thomas Michiels (UCL), Emmanuel Hermans (UCL)

Ample evidence points towards an involvement of glutamate excitotoxicity in the pathogenesis of multiple sclerosis (MS). Indeed, the focal lesions in the central nervous system (CNS) are characterized by inflammation, demyelination and infiltration of immune cells. Whereas inflammation and demyelination can be the result of glutamate toxicity, the infiltrating immune cells could be a possible source of glutamate. The aim of this project is to unveil the involvement of system xc- in the pathogenesis of MS. We will thereby distinguish between system xc- present on the glial cells of the CNS and system xc- present on the infiltrating immune cells, as it has been shown that activation of monocytes can induce glutamate release through system xc- (Pampliega et al., 2011).

System xc- in major depression
Co-PI: Ilse Smolders, Ann Massie
PhD student: Thomas Demuyser
Collaborators: Mia Lindskog (Karolinska Institute, Sweden)
In the field of depression, the glutamate hypothesis is currently one of the most exciting avenues. Monoaminergic imbalance is still proposed as a causative factor, whereas the resulting abnormal glutamatergic transmission critically mediates emotional changes. With this project we investigate the possible involvement of glutamate transporters, including system xc-, in depression.

1.3. Bioanalytical research in neuroscience

Neurochemical and neuropharmacological research is strongly dependent on the availability of sensitive analysis methods for neurotransmitters, neuromodulators and drugs in brain microdialysis samples of rats and mice. The development of new, faster and sensitive analysis methods remains challenging for the bioanalyst due to the very low concentrations of these compounds in small volumes of dialysate, coupled to a low microdialysis recovery, in addition to the need for higher throughput.
The research group has ample experience in the development of miniaturized LC methods, coupled to fluorescence, electrochemical or tandem mass spectrometric (MS/MS) detection, for the quantification of neurotransmitters and neuromodulators in microdialysates. In addition, we have a large experience in the development and validation of analytical methods for the determination of drugs in drug products and biological samples with capillary electrophoresis, LC-UV, LC-fluorescence and LC-MS/MS.

Quantification of neuropeptides in microdialysates with nano LC-MS/MS
PIs: Ann Van Eeckhaut, Ilse Smolders, Yvette Michotte
PhD students: Katrien Maes, Yannick Van Wanseele
Technical support: Carina De Rijck, Gino De Smet
Neuropeptides seem to play an important role when the central nervous system is challenged. In order to obtain better insights into the central peptidergic effects, it is essential to monitor their concentration in the brain. Quantification of neuropeptides in dialysates is challenging due to their low extracellular concentrations (low pM range), their low microdialysis efficiencies, the need for acceptable temporal resolution, the small sample volumes, the complexity of the matrix and the tendency of peptides to stick to glass and polymeric materials. The quantification of neuropeptides in dialysates therefore necessitates the use of very sensitive nano LC–MS/MS methods. A number of LC–MS/MS and microdialysis parameters need to be optimized to achieve maximal sensitivity. This project focuses on the peptides of the neuromedin group.

HPLC with electrochemical detection for the simultaneous quantification of glutathione (GSH), glutathione disulfide (GSSG), cysteine and cystine in brain homogenates

PIs: Ann Van Eeckhaut, Ann Massie
PhD student: Katrien Maes
Technical support: Gino De Smet

Glutathione (GSH) is an important thiol tripeptide antioxidant in cells. It exists in two forms, namely reduced as GSH and oxidized as glutathione disulfide or GSSG. GSH is significantly favored over GSSG under healthy physiological conditions. However, pathological conditions causing oxidative stress have been found to result in a decreased GSH/GSSG ratio.

The aim of this project is to develop and validate a HPLC method with electrochemical detection for the simultaneous quantification of both redox couples GSH/GSSG and cysteine/cysteine in brain homogenates. This will provide us valuable information about the total redox state of the cell and will be applied to samples of models for neurological disorders before and after drug treatment, transgenic animals, etc.

UHPLC with electrochemical detection for quantification of monoamines in microdialysates

PI: Ann Van Eeckhaut
PhD student: Jolien Van Schoors
Technical support: Ria Berckmans

In this project, the coupling of an ultra-high pressure liquid chromatography (UHPLC) system with an electrochemical detector (ECD) for the analysis of the low concentrated monoamines in microdialysates will be investigated. The monoamines dopamine, noradrenaline and serotonin are neurotransmitters implicated in several neurological disorders. Monitoring of changes in these neurotransmitter concentrations in the brain using *in vivo* microdialysis sampling is an important tool in neuropharmacological research in the quest for new drug candidates.

Analytical challenges exist both at the level of the chromatography and the ECD. More sensitive methods are needed to allow detection of these monoamines in small brain areas, in smaller laboratory animals or in situations where catecholamine levels are decreased. Furthermore, there is a high demand for faster analysis to increase sample throughput.

For this purpose, the chromatographic parameters (stationary phase, mobile phase, flow rate and separation temperature) will be optimized. In addition, also the detection temperature, filtering of the signal, electrochemical cell type, electrode material and optimal working potential, will be studied. New developments in ECD such as new cell types and electrode material will be investigated in collaboration with Antec (the Netherlands), the manufacturer of amperometric ECD.

Enantioselective LC-method with fluorescence detection for quantification of glutamate and D-serine in biological samples.

PI: Ann Van Eeckhaut, Ilse Smolders
PhD student: Anissa El Arfani, Laura Walrave
Technical support: Carina De Rijck, Ria Berckmans
Scientific collaboration with Mia Lindskog (Karolinska Institutet, Sweden), Emmanuel Hermans (UCL)

We have a large background in chiral separations, especially with capillary electrophoresis. In this project, we adapted our existing LC-fluorescence method for the analysis of amino acids (Van Hemelrijck et al., 2005) to allow chiral separation of D-

serine. D-serine is a physiological co-agonist of the N-methyl D-aspartate (NMDA) type of glutamate receptor which is a key excitatory neurotransmitter receptor in the brain. It binds with high affinity to a co-agonist site at the NMDA receptors and, along with glutamate, mediates several important physiological and pathological processes, including NMDA receptor transmission, synaptic plasticity and neurotoxicity (Wolosker et al., FEBS, 2008). To further elucidate its role, it is important to develop a sensitive analytical method which can detect and quantify D-serine in biological samples. For this purpose, the achiral *thiol mercaptoethanol*used in the derivatization procedure was replaced by N-isobutyryl-L-cysteine, allowing the formation of diastereomeric compounds. After optimization of the mobile phase composition and the gradient profile, the method was validated for the quantification of glutamate and D-serine in brain homogenates. The enantioselective analysis method was applied to analyse D-serine in brain homogenates of Flinders Sensitive Line rats, a rat model for depression (Gomez-Galan et al. 2012). The method is further optimized for quantification of glutamate and D-serine in other biological samples, such as microdialysates, CSF, plasma and cell cultures.

1.4. Neurovirology

Fundamental and applied research on poliovirus:

Development of antiviral compounds against poliovirus as a help in the last steps of poliovirus eradication (C. Jensen, L. Schotte)

WHO as well as CDC have concluded that in the late stage of poliovirus eradication, antiviral agents are necessary to eradicate the disease. In collaboration with other colleagues of the VUB (Serge Muyldermans), nanobodies were developed as candidate antivirals. Under supervision of the WHO , and in collaboration with the REGA institute (KULeuven) and Harvard Medical School (USA) these nanobodies are further tested.

Research on the replication cycle of poliovirus (L. Schotte)

Fundamental research on the first (adsorption, internalization) and last stage of the replication cycle of poliovirus is still going on. This knowledge is used to unravel the target of antiviral compounds (collaboration with REGA institute KULeuven)

Development of separation techniques for viral particles (H. Halewijck)

New separation techniques for viral particles are developed in collaboration with the Research Group FABI (VUB)

Relationship between neurological diseases and viruses:

TME Virus as a model for Multiple Sclerosis (E. Merckx, A. Massie)

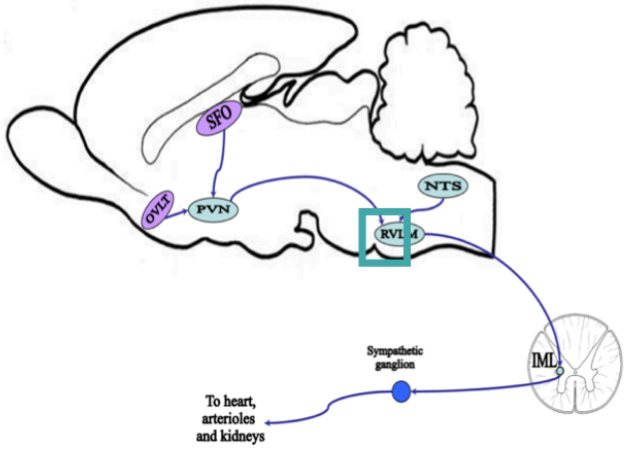
Infection of mice with TME Virus is used as a model to study MS.

1.5. CNS and blood pressure controle

Role of brain angiotensin peptides in the regulation of sympathetic tone and blood pressure: interaction with glutamate, GABA and NO

PI: Alain Dupont

PhD student: Sofie Brouwers



There is increasing evidence that brain angiotensin peptides, glutamate, GABA and NO interact 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 this central regulation of blood pressure and sympathetic tone in normotensive and spontaneous hypertensive rats. We study the interactions of the local renin-angiotensin system and different neurotransmitters such as glutamate, GABA and NO within the rostral ventrolateral medulla (RVLM) and the paraventricular nucleus of the hypothalamus (PVN) of the brain. Blood pressure is monitored and neurotransmitters are measured in the PVN and RVLM under different conditions using microdialysis, and after local administration of several compounds interacting with different components of the renin-angiotensin system and of receptors agonists and antagonists as well as enzyme inhibitors. In addition we also aim to document the effect of brain angiotensin peptides on renal hemodynamics and of renal damage on the central control of blood pressure.

1.6. Neuro-inflammation, neurotrophic factors and neuroprotection

The role of astrocyte-neuronal interactions in multiple sclerosis
PIs: Jacques De Keyser, Ron Kooijman, Ann Massie
PhD students: Frauke Demol, Guy Laureys
Post-doc: Cathy Jensen

Astrocytes are the main cellular targets of noradrenergic terminals in the brain. Stimulation of astrocytic glycogenolysis is mediated by noradrenaline acting on ß2 adrenergic receptors (ß2AR), a process that appears to be modulated by a variety of neuropeptides (e.g. VIP). Increases in ß2AR-mediated cAMP are involved in the synthesis of a variety of trophic factors, suppression of immune-inflammatory responses through inhibition of the transcription factor NF-kB, and inhibition of astrocyte proliferation (astrogliosis), pointing out that the astrocyte ß2AR-cAMP pathway might serve as novel target for neuroprotective therapies. A dysfunction of this pathway is suspected to play an important role in the pathophysiology of MS, since our group has discovered that astrocytes in MS are deficient in ß2Ars.

The major research questions are: how can we obtain *neuroprotective* effects by modulating the astrocytic noradrenergic/cAMP system, and what is the role and cause of the loss of astrocytic ß2ARs in MS?
- What is the neurobiochemical, behavioral and pathological phenotype of our recently developed astrocyte-selective ß2AR KO mouse (astroß2AR KO)? Could this

represent a new animal model for MS? Can the deficit and disease manifestations be restored by ß2AR gene therapy?
• What is the role of the astrocytic ß2AR-cAMP signaling pathway in astrocyte metabolism, cerebral perfusion, and immune modulation in vivo in animal models and in patients?
• What other transmitter systems activate or influence the astrocytic cAMP-signaling pathway, for example to compensate for the loss of the astrocytic ß2AR observed in MS? Is the PKA or EPAC signaling pathway involved?
• Is a viral infection of astrocytes responsible for the loss of astrocytic ß2ARs in MS, and what is the underlying mechanism?
• Can we improve the disease course of MS by activating or modulating the ß2AR/cAMP-signaling pathway (in MS through the cAMP signaling pathway) and can we identify neuroprotective compounds that can be used in the clinic?

Neuroprotection by administration of neurotrophic factors in animal models for ischemic stroke
PIs: Ron Kooijman, Jacques De Keyser
PhD students: Wendy Stoop, Ann De Smedt

Stroke is the most common cause of adult disability and ischemic stroke represents about 85% of all cases. Until now, the only approved acute treatment of ischemic stroke is reperfusion by tissue-plasminogen activator, but only 10-15% of the patients benefit from this treatment. On the other hand, we have provided proof-of-principle for neuroprotection by post-stroke systemic administration of recombinant human (rh)IGF-I or estradiol in a rat model of ischemic stroke. Furthermore, we showed that systemically administered rhIGF-I passes the blood brain barrier in normal rats leading to physiologically relevant concentrations of rhIGF-I in the brain (1.2 ng/mg protein and 0.6-4.5 ng/ml in the extracellular space as assessed by microdialysis). Using an IGF-I receptor antagonist, we also provided evidence that intravenously injected rhIGF-I acts directly through interaction with its receptors in the brain. Furthermore, both rhIGF-I and estradiol affect the activation/differentiation of microglia after stroke.

The major research questions are: What are the basic mechanisms of neuroprotection by IGF-I and estradiol in ischemic stroke and how can we optimize the treatment protocol for neuroprotection?
• Which events of the ischemic cascade (excitotoxicity, neuroinflammation, oxidative stress, different forms of neuronal cell death) are modulated by systemic administration of IGF-I?
• What is the role of microglia in neuroprotection?
• Insight into the working mechanism will support the development of combination therapies with drugs exerting complementary actions on the ischemic cascade.
• Do IGF-I and estradiol act in synergy in the ischemic brain as observed in models for epilepsy and Parkinson's disease?
• Can we stimulate IGF-I transport to the brain or the local expression of endogenous IGF-I in astrocytes?
• Does long term expression of IGF-I in the brain through injection of adeno associated virus-based vectors lead to neuroprotection or recovery?

Neuroprotection by hypothermia in ischemic stroke
PIs: Ron Kooijman, Said Hachimi-Idrissi, Ilse Smolders, Jacques De Keyser
Post-doc: Joline Goossens

We have shown that a short post-stroke treatment protocol for hypothermia inhibits apoptosis and decreases infarct size which correlates well with a decreased sensorimotor impairment. These effects are maintained for up to one week and go along with a decrease in neuroinflammation at three days after the insult and an increase in neuroinflammation at one week after stroke. Furthermore, by differential display we have identified proteins of which the expression levels are corrected by hypothermia.

We will focus on the working mechanism of neuroprotection and the development of biomarkers

- Are the effects of hypothermia on neuroinflammation beneficial or detrimental?
- Are proteins of which the expression levels are restored by hypothermia involved in neuroprotection?
- Is it possible to obtain neuroprotection by a more specific and direct regulation of these proteins?
- Can we develop biomarkers predicting the efficacy of hypothermia for different patients?

II. Clinical Research and Disease

2.1. Multiple Sclerosis and related disorders

The role of astrocytes

Several lines of evidence point to a dysfunction of astrocytes, which are involved in controlling immune responses, energy metabolism and perfusion of the CNS.
Key findings in astrocytes of MS patients:

- downregulation of beta2 adrenergic receptors [supposed to play a role in facilitating immune responses, reduced axonal energy metabolism, and reduced trophic support (BDNF)]
- reduced PCr metabolism due to reduced brain creatine kinase (CK-B) levels (might be involved in reduced glutamate uptake and excitotoxicity)
- increased expression of endothelin-1 in reactive astrocytes in MS plaques (likely responsible for the decreased cerebral perfusion in MS)

Pathophysiological mechanisms related to these findings are studies in cell cultures, postmortem MS brain samples, microdialysis in small rodents and genetic mouse models (e.g. astrocyte selective beta2 AR KO mouse), MR spectroscopy and perfusion studies in patients with MS.
Findings are further evaluated in proof-of-concept studies, which may lead to clinical trials with new therapeutic approaches. A current study evaluates the effect of fluoxetine and prucalopride in CNS energy metabolism and perfusion (CAME study). A clinical trial using fluoxetine (FLUOX-PMS) in progressive MS is ongoing.
New studies will target the endothelin-1 system with the aim of improving CBF in patients with MS.

Factors that influence the disease course

By investigating factors that influence the course of the disease we intend to find clues of pathophysiological mechanisms that protect MS patients against new lesion formation and the axonal degeneration responsible for the progressive phase. Interesting findings are further investigated in proof-of concept studies in animal models of MS and patients with MS. A new area of interest that is being studied is the role of the gut microbioma and balance of the autonomic nervous system in MS.

2.2. Management of Stroke

Improving acute stroke management

A number of topics are being studied:

Prehospital care

PIs: Raf Brouns, Jacques De Keyser
PhD student: Laetitia Yperzeele
Collaborators: Robbert-Jan Van Hooff, Alexis Valenzuela Espinoza, Koen Putman, Liesbet De Wit, Guy Nagels, Ives Hubloue, Andre Convents, Rohny van de Casseye
The goal of the Prehospital Stroke Study at Universitair ziekenhuis Brussel (PreSSUB) is to develop and apply a telemedicine system for providing specialized care to stroke patients during ambulance transportation to the hospital.

The role of biomarkers in stroke
PIs: Raf Brouns, Jacques De Keyser
PhD student: Laetitia Yperzeele
Collaborators: Dirk Hendriks (UA), Ingrid De Meester (UA), Robert Verkerk (UA), Sebastiaan Engelborghs (UA)
The diagnostic and prognostic value of biochemical parameters reflecting key processes underlying cerebral ischemia is evaluated in patients presenting with acute stroke.

The role of dysautonomia in stroke
PIs: Raf Brouns, Jacques De Keyser
PhD students: Sylvie De Raedt, Aurelie De Vos, Laetitia Yperzeele
Collaborators: Yori Gidron
Stroke is often associated with disturbances of the autonomic nervous system. We assess the potential relation between cardiovascular autonomic dysfunction and stroke characteristics.

The effects of surface cooling in stroke
PIs: Raf Brouns, Robbert-Jan Van Hooff, Jacques De Keyser
PhD students: /
Collaborators: Ives Hubloue
Hyperthermia is an independent predictor of poor outcome in stroke patients. We assess the effects of mild therapeutic hypothermia through surface cooling in patients with acute stroke.

Factors associated with the efficacy and safety of thrombolysis and neuroprotective interventions
PIs: Raf Brouns, Jacques De Keyser
PhD students: Laetitia Yperzeele, Ann De Smedt
Collaborators: Guy Nagels, Robbert-Jan Van Hooff

Using the UZ Brussel Stroke Registry, which is a prospective and blinded patient database, we investigate efficacy and safety parameters of interventions with regard to acute stroke care and secondary cerebrovascular prevention.

Improving secondary prevention
COACH (COunseling, Advice and Consolidation of Health promoting actions in stroke patients)
Optimization of long-term care is one of the cornerstones for improving outcome in stroke survivors. This requires patients' adherence to medical treatment and lifestyle adjustments, which we attempt to improve through patient empowerment based on personalized information and coaching.
PIs: Raf Brouns, Jacques De Keyser
PhD students: Ann De Smedt
Collaborators: Koen Putman, Liesbet De Wit

2.3. Neuromodulation of disease

The role of the vagus nerve in cancer
PI: Yori Gidron
PhD student: Marijke De Couck
Collaborators: Jacques De Greve and Denis Schallier (VUB, Belgium), Raphael Marechal and Jean-Luc Van Laethem (ULB, Belgium), Paul Boon (UZ Gent, Belgium), Samuel Ariad (Ben-Gurion Univ., Israel), Luca Vannucci (Prague, Czech Republic), Boris Mravec (Bratislava, Slovac Republic).

Recent studies show that the autonomic nervous system modulates tumor progression. Our work focuses on the effects and mechanisms of vagal nerve modulation of tumors. This happens due to vagal modulation of multiple key processes etiological to carcinogenesis including inflammation, oxidative stress and sympathetic hyperactivity. We are testing this topic in 3 levels: 1. The relationship between vagal nerve activity (indexed by heart-rate variability) and cancer prognosis; 2. Can activating the vagus nerve affect tumors in rats and the underlying mechanisms; 3. Can activating the vagus nerve improve prognosis in patients with advanced cancer, and the underlying mechanisms. This work has scientific implications for neuroimmunomodualtion of diseases and could have clinical implications for introducing new ways for possibly treating cancer.

The role of the vagus nerve in obesity
PIs: Yori Gidron & Olivier Luminet (UCL, Belgium)
Post-Doc: Renata Cserjesi
Collaborators: Brigitte Velkeniers, Nancy van Wilders, Marijke De Couck (UZ Brussles, VUB, Belgium), Philip De Timary & Jean-Paul Thiessen (UCL, Belgium).

Overweight and obesity is a global epidemic of severe health consequences for diabetes, cardiac diseases and several cancers. A main challenge is to target multiple risk factors of obesity. However, often, health providers target only one obesity cause or use multiple ways to target several risk factors. The vagus nerve modulates or is related to multiple obesity risk factors (e.g., inflammation, food-preference, sympathetic activity, brain functions and mood modulation). Thus, it may be more efficient to increase vagal nerve activity to reduce weight via modulating multiple risk factors of obesity. This two-center RCT will examine the effects of various modes of vagal nerve activity and the mechanisms, on weight in obese people.

Effects of hemispheric lateralization (HL) on infectious diseases
PI: Yori Gidron
PhD students: Tereza Killianova (VUB), Sebastien van Eycken (VUB), Olga Ferreira (Portugal)
Collaborators: Chris Baeken (UZ Gent, Belgium), Patrick Lacor and Rembert Mertens (UZ Brussel, VUB, Belgium), Gabriella Berg (Univ of Buenos Aires, Argentina).

During the past two decades, research has shown that the left hemisphere activates immunity while the right hemisphere inhibits it. The mechanisms of such effects are still under investigation. In these studies, we first try to understand the basic properties of hemispheric lateralization (HL). Second, we examine whether HL predicts infectious disease onset and prognosis. Finally, we plan to also examine whether activating the left

hemisphere increases immunity and reduces the risk of such infectious diseases or improves their prognosis. Our research will investigate whether activity or functional measures of HL are related to infectious diseases. This research has scientific implications for neuroimmunomodulation and clinical implications for preventing such common public health outcomes as the common cold.

The role of the left hemisphere in daily mood
PI: Yori Gidron
PhD student: Dana Herzog (VUB, from Israel)
Collaborators: Filip Germeys (HUB, Belgium)

During the past decades, studies have shown a complex modulation of mood by the two hemispheres, with the left side involved in "approach" emotional states (positive mood, anger) and the right side in "inhibitory" emotional states (anxiety, depression). This line of research first examined the role of the left hemisphere in moderating the effects of adverse stressful events on distress. Second, we will examine whether performing cognitive exercises that activate left prefrontal regions increase daily positive affect. This work has scientific implications for understanding neuromodulation of daily mood and clinical implications for people's self-regulation of their distress.

2.4. Mental diseases

The main research objectives here are within the neurobiological field of Affective and Addictive Disorders, with a focus on psychiatry Imaging. The major goals are to gain more insight in the underlying mechanisms of emotional brain processes in the 'healthy' as well as in the 'mentally affected' human brain. Brain-imaging paradigms (MRI, fMRI, (S)PET,….) are used with or without the combination of neuromodulation techniques, such as repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS). The acquired neurobiological and neuropsychological knowledge of these combinations should not only increase our insight in the implicated neurocircuitries, but it should also result in appropriate treatment paradigms for patients suffering from Affective and Addictive Disorders.

2.5. Neuroophthalmology

Research of the unit neuroophthalmology centres around four clusters: i) binocularity ii) neuropeptides and proteomics iii) multiple sclerosis iv) population screening

i) Binocularity
Development of an eyetracker that combines measurement of stereopsis and visual acuity in preverbal children.
Investigator: Dr Anne Cees Houtman (PhD student)
Promotor: Prof. dr. Marcel ten Tusscher

Infantile esotropia (IE) is a distinct clinical entity in the field of strabismus. Its onset is typically between 3 and 5 months of age. IE is incompatible with normal binocular vision because the visual axes are not aligned. There is no correlation between the (monocular) visual signals from the eyes in the visual cortex. Therefore patients do not develop stereopsis (or "3D vision"). IE can delay the development of visuomotor skills, it has an impact on psychosocial development and professional requirements may hamper a patient's career ambitions.

Stereopsis emerges around the age of 10-12 weeks of age in normal infants and can be demonstrated by so-called Forced Choice Preferential Looking (FCPL) assessment in 60% of children around that age. Interestingly this can also be demonstrated in 60% of infants who will later develop IE. The majority of the latter subsequently lose their stereopsis.
There is a controversy regarding the timing of surgical treatment of IE, i.e. early or late. Theoretically it makes sense to offer very early surgery (to realign the visual axes) to those infants who have demonstrable stereopsis but testing for stereopsis in preverbal children is cumbersome and practically never used in a clinical setting.
The Stereotracker combines an autostereoscopic screen and an eye-tracker to make an automated FCPL assessment of stereopsis or visual acuity in preverbal children . The Stereotracker should ultimately help in identifying those patients that will benefit from (very) early treatment. But it may also be a vision screening tool by combining tests for visual acuity and stereopsis.
A prototype of the Stereotracker has been developed in the first stage of this project. Preliminary studies have indicated that the concept of the Stereotracker is valid but refinements will need to be made before the device can be put to a clinical test. Currently the performance of the eye tracker appears sufficient to test adults but not preverbal children. Solutions may be found in improving the software component or replacing the eye tracker by a more robust system.

The origin of strabismus
Investigator: Prof. dr. M ten Tusscher

The sensory cause and motor aspects of infantile strabismus, fusion and binocularity are studied with functional MRI.
A closer look at the evolution of the eye and the brain provides a possible explanation for both the origin of infantile esotropia and its motor characteristics. In the course of evolution the eyes have moved from a lateral to a frontal position. Consequently the monocular visual fields started to overlap resulting in a binocular visual field. In lateral-eyed animals the retinae project to the contralateral visual cortices only. These projections are also found in binocular mammals and birds with binocular visual fields but in addition there are uncrossed projections from the temporal retinae to the visual cortex. The partial chiasmal decussation and the corpus callosum provide the necessary structure that allows binocular vision to develop.
Disruption of normal binocular development causes a loss of binocularity in the primary visual cortex and beyond. Beyond the primary visual cortex the contralateral eye dominates while the temporal retinal signal appears to lose influence. Loss or absence of binocular vision in infantile esotropia may be caused by inadequate retinotopic matching between the nasal and temporal retinal signals like in albinism with an abnormal or asymmetric chiasmal decussation, or agenesis of the corpus callosum.
Dominance of the crossing retinal signal might also explain the motor characteristics of infantile esotropia (asymmetric OKN, latent nystagmus, DVD). A normal binocular cortical signal will predominate over the evolutionary older, originally non-binocular, retinal projections to the superior colliculi (CS) and the accessory optic system (AOS). A suppressed temporal retinal signal paves the way for the re-emergence of eye movements driven by one eye, as in lateral eyed non-binocular animals.

ii) Neuropeptides and proteomics
Investigator: Dr. Peter Raus (PhD student)
Shared promotorship: Prof. dr. P Verhaert, Delft technical university/ Prof. dr. M ten

Tusscher

There are an estimated 285 million people with visual impairment worldwide, of whom 39 million are blind. The pathogenesis of many eye diseases remains poorly understood. Proteomics may provide key insight into the biological pathways of disease. We try to identify new biomarkers for eye diseases using proteomics. Recent advances in proteomics now allow the identification of hundreds of proteins in eye fluids. The large repertoire of investigative proteomic tools has great potential to transform vision science and enhance understanding of physiology and disease processes that affect sight.
Dr Raus is interested in Sjogren syndrome en dry eye pathology. He investigates tear fluid peptides in order to find biomarkers for Sjogrens disease and diagnose and possibly treat dry eye disease.
Together with the diabetes department of the VUB eye fluids of patients will be investigated in order to try and find biomarkers for ischemic diabetic ocular disease.
In another arm the effect of refractive corneal surgery on neuropeptides secretion will be studied.

iii) Multiple sclerosis
Investigator: Dr. Michel van Lint (PhD student)
Promotor: Prof. dr. M. ten Tusscher

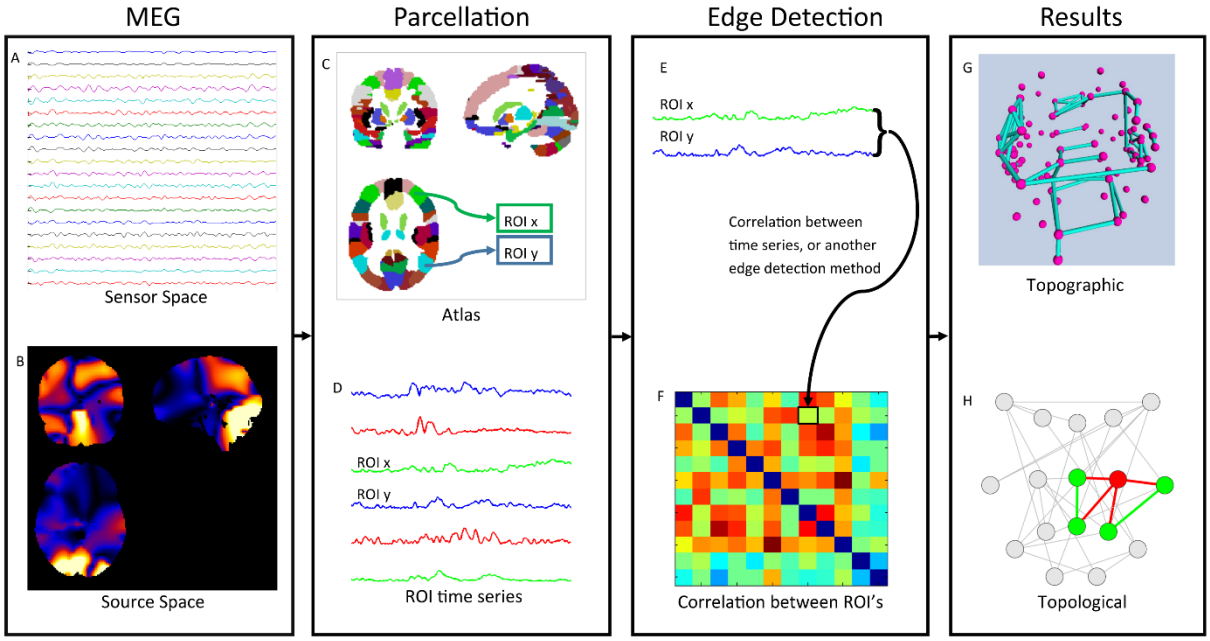
The retina is the most approachable part of the brain. Recent studies of the retina in patients with multiple sclerosis (MS) demonstrated neuronal and axonal loss besides macular oedema. The human retina promises to be a window into the health of a patient with multiple sclerosis. A clear view of the retina in-vivo, with high resolution detail, could give the vital detail that may enable clinicians to make early and accurate diagnosis of the disease and possibly shed light on its aetiology which until now remains elusive. Neuronal loss in MS can be severe and occurs throughout the brain and is already demonstrated in patients presenting with their first clinical attack of MS. This reduction is still present one year later and was independent of whether the patients had progressed to develop MS. MS patients demonstrated an average of 46 per cent faster thinning of the ganglion cell nerve layers in their retinas compared to the healthy patients. These data suggest that quantification of axonal thickness in the retina by optical coherence tomography provides concurrent information about MRI brain abnormality in MS. In addition macular microcystic edema in MS patients was described recently.
Adaptive optics with optical coherence tomography and confocal microscopy allows retinal analysis at the molecular level. The present study may help in identifying those patients that will develop multiple sclerosis or benefit from early treatment.

iv) Population screening
Investigator: Dr. Zahra Javdani
Promotor: Prof. dr. M. ten Tusscher

Preventable and treatable eye diseases are found to occur very often in the elderly. Often the individual with such a disease is unaware of it. A population study will be undertaken to quantify the incidence of unknown ocular pathology and low vision. Another objective of this study will be a comparison between a questionnaire with some simple tests and high-tech imaging devices.

2.6. Cognition & Modelling

The Cognition and modelling group focuses on the characterisation of cognitive decline in several neurological disorders with a specific emphasis on multiple sclerosis. The functioning of the degenerative brain is assessed by different neuroimaging modalities (EEG, MEG, fMRI) and these data are subsequently used as input features for artificial intelligence techniques (support vector machines, artificial neural networks) in order to develop biomarkers for neurological disorders.



This figure illustrates how graphs or networks are extracted from raw data. The first panel shows MEG data, but the process works just as well starting with EEG or fMRI data. We then use information from a brain atlas (C) to perform parcellation, dividing the brain into different regions of interest (ROI), the nodes. Another option to perform parcellation (not shown) is Independent Component Analysis (ICA). Data from the regions of interest is then summarised into a single time series per ROI (D). The data from the ROIs will then be used to perform edge detection (E), for example by calculating the correlation between ROI time series. Edges are collected in a correlation matrix (F) where the axes show all ROIs and the colour of the squares represents the correlation, or edge value, between two ROIs. Finally, the last panel shows the results of the analysis. The brain network can be shown in a topographic view (G), where the pink spheres represent the nodes and the blue cylinders the edges; or topological data can be shown (H), like the degree or clustering coefficient.

Projects:

Cognitive impairment in MS – Statistical and Neurophysiological aspects
PIs: Guy Nagels, Jacques De Keyser, Marie B D'hooghe
PhD student: Jeroen Van Schependom

Cognitive impairment is an important aspect of multiple sclerosis affecting about half of the MS population. In this project we have analysed clinical neuropsychological data collected during the period 2000-2014 at the National MS Center Melsbroek. By constructing survival curves for different cognitive tests, we were able to show the importance of information processing speed. Furthermore, we have demonstrated the

value of the Symbol Digit Modalities Test in detecting general cognitive impairment (cross-validated sensitivity of 90 % at a specificity of about 60 %).
Electrophysiological data allow us to assess the functioning of the brain at a timescale determined largely by the electronics used (typically well above 100 Hz). Clinical EEG data were analysed and substantial differences in network topology were found between a group of cognitively intact and cognitive impaired MS patients. In a follow-up study, we are collecting MEG data on a small group of MS patients.

A biomarker for cognition in multiple sclerosis, based on graph theoretical analysis of neurophysiological measurements
PIs: Guy Nagels, Jacques De Keyser, Marie B D'hooghe
PhD student: Jeroen Gielen

Reduced cognition is both hard to measure and hard to treat. We want to improve our ability to measure the impairment, in hopes of gaining a better understanding of what happens to the brain during the disease and being able to improve treatment. To do this we will gather brain scans from patients and look for regions that are more active during tasks concerning cognition, and how these regions interact with each other. This way we can visualise a brain network of interconnected regions. These networks will have certain properties, like the amount of connections the regions have or how many regions you would have to pass through to get from one region to another. We will summarise these properties in a biomarker.
We are currently analysing brain scans of a group of students that performed two stimulus frequencies and modalities (auditory and visual) of Paced Serial Addition Testing (PSAT). Results show a lower effect of modality compared to stimulus frequency. This would imply that visual testing will be sufficient in cognitive testing over auditory testing, as it is also the preferred form of testing by patients.

Pattern classification techniques to improve the value of neurophysiological measurements for individual patients
PI: Guy Nagels
PhD student: Jorne Laton

Using electrophysiological measurements and machine learning we investigate classification and symptom estimation of individual patients suffering from neurological disorders. Classification algorithms are mainly suited for yes/no problems and are therefore useful for diagnosis and prognosis. Regression algorithms generate a continuous value, which is useful for estimating symptom severity, like fatigue and cognition. The data are EEG and MEG measurements, which can be analysed at sensor level, extracting features from the electrode signals or correlating these signals with each other. A 3D model can be generated from the 2D EEG/MEG data with source reconstruction, which allows to further analyse the data at source level.
The focus of this project is mainly on schizophrenia and EEG, but a new study has been set up involving multiple sclerosis patients and MEG. In another study the effects of electroconvulsive therapy are to be estimated by comparing EEG measurements before and after therapy. In the first stage of the schizophrenia study, we have been able to show a reasonably high accuracy of 84% in separating patients from healthy controls. Next stages in this particular study are sensor space localisation of differences between the two groups and 3D source reconstruction to improve classification results.

III. Cognition, Behavior and Health Impact

3.1. Cognitive dysfunctions in Parkinson's disease

PIs: Eric Kerckhofs, Natacha Deroost

Apart from the typical motor symptoms, it has become evident in the last decennia that patients with Parkinson's disease (PD) suffer from non-motor impairments including cognitive dysfunctions. Our research team, linking together the laboratories of cognitive psychology (N. Deroost) and neurological rehabilitation (E. Kerckhofs), investigates motor learning in patients with PD bridging those two domains. More concretely the capacity for (implicit) learning of motor sequences is examined in relation to the progression of the disease. Also the effect of brain modulation by transcranial direct current stimulation on implicit sequence learning is studied. In a large interuniversity research program the role of cognitive impairment in freezing of gait was examined (PhD study of Dr. Jochen Vandenbossche).

3.2. Exercise and the Brain in Health and Disease

The research in the dept. of Human Physiology is focused on 'Exercise and the Brain in Health & Disease' where the interaction of exercise on neurochemistry and neurophysiology is explored. The research is concentrated at 3 different levels:
Fundamental – Physiological research. At this fundamental level, animal and human experiments are combined, with measurements of neurotransmitters and the hormonal output from the brain during different manipulations. We perform fundamental research on the limits of fatigue, mechanisms of thermoregulation, and the positive effects of exercise on neurogenesis. Also, the effects of exercising in a polluted environment on the brain also include animal studies.

The Applied – Clinical research aims at examining the value of the study findings of the fundamental research at the applied/clinical level. Again, all studies are within the area of 'Exercise and the Brain in Health & Disease'. In general, the applied – clinical research is focused on studying exercise and training in different patient populations such as cardiovascular disease, obese, diabetes patients, sports injuries. Recently, the effects of exercise and pollution on health are integrated into the applied – clinical cluster. Linking brain research with pathologies such as obesitas, diabetes, and cardiovascular disease is established in collaboration with dr. Luc Van Loon (*University of Maastricht, The Netherlands*). This collaboration results in research on cognition, neurogenesis in diabetics, and the elderly person. The ongoing collaboration with dr. Elsa Heyman (*University of Lille, France*) is in full support of this project, looking at cognitive aspects in type 1 diabetics.

In order to bring applied research in line with the Exercise & Brain research we created the 'Lotto Sport Science Chair'. In a PhD project several aspects of performance and recovery are examined, focusing on brain mechanisms of fatigue and recovery. These experiments are linked with the control experiments from the Antarctica mission (2011-2012), and the project focusing on sleep & recovery, and the underlying neurophysiological aspects of recovery and (over)training. Most of the applied sports research is in collaboration with the *Australian Institute of Sports* looking at training & recovery, and the *Royal Military Academy (VIPER)*. Sports Injury Prevention especially neuromuscular aspects of injury prevention are run together with dr. Evert Verhagen

(*University of Amsterdam, the Netherlands*) and integrating sports injuries with fatigue, recovery and underlying neuromuscular mechanisms. ECSS-ACSM consensus statement on Overtraining was published in 2013. This is the 'standard' publication which is now accepted by the two largest sports science societies in the world (European College of Sport Science & the American College of Sports Medicine).

Policy making research. The 'Commuter Cycling' research line investigates the effect of cycling for transportation on health in a broad prospective. In collaboration with *VITO* we examine the balance between the health enhancing effects of commuting by bicycle and exercising in busy traffic (polluted air). Bicycle accidents are analyzed into detail in adult and adolescent populations in order to advise policy makers how to create to safer and healthier environment.

Running projects:

Central fatigue during exercise in different environmental circumstances
PIs: Prof. Dr. Romain Meeusen, Prof. Dr. Bart Roelands
Collaborators: Prof. Dr Phil Watson, Prof Dr. MF Piacentini, Prof.Dr. Nathaly Pattyn, dept. of Applied Biology of the Université Libre de Bruxelles ULB, Dr. Luk Buyse.
Fatigue during prolonged exercise is caused by a complex interplay between peripheral and central processes in the human body. Besides the accumulation of waste products and lack of energetic sources, as abundantly described in the 20th century, the brain and central nervous system have shown to be involved in the onset of fatigue. Environmental circumstances such as heat and altitude further emphasize the role of central fatigue.

Cycling performance, recovery and brain functioning – (Lotto Cycling Chair)
PI: Prof. Dr. Romain Meeusen
PhD student: Drs. Kevin De Pauw
Collaborators: Prof. Dr. Bart Roelands, Prof. Dr. MF Piacentini
The emphasis of the Lotto project is on the post-exercise recovery period after a prolonged, intensive cycling performance in a thermoneutral (20°C) and hot (30°C) environment. Experiments were conducted with the aim to determine the effect of different post-exercise recovery interventions on a subsequent cycling performance, physiological parameters and brain functioning.

Physical activity, air pollution and the brain
PI: Prof. Dr. Romain Meeusen
Post-doc: Dr. Inge Bos
Collaborators: VITO
Physical activity benefits the brain. However the enhanced ventilation rate during exercise results in an increased inhalation of air pollution. Air pollution has been linked to adverse effects on the brain. In this project we investigate the effect of air pollution exposure during exercise on the brain.

Diabetes Associated Cognitive Decline, Can Exercise Help?
PIs: Prof. Dr. Romain Meeusen, Dr. Elsa Heyman
PhD student: Dra. Cajsa Tonoli
Collaborators: Prof. Dr. Serge Berthoin, Université Lille Nord de France, Prof. Dr. Bart Roelands, Dr Luk Buyse.
Patients with Type 1 Diabetes (T1D) show a modest, but significant decline in their

cognitive function compared to healthy controls. It is however well-known that physical exercise has beneficial effects on the cognitive function in humans with Alzheimer disease, dementia, elderly … The effects of exercise on diabetes-associated cognitive decline are not yet established. Therefore, this is investigated in this research line.

Human Performance under extreme conditions
PIs: Prof. Dr. Romain Meeusen, Prof. Dr. Nathalie Pattyn
PhD student: Drs. Helio Fernandez
Collaborators: Prof. Dr. Xavier Neyt VIPER (Royal Military Academy), Prof. Dr. Bart Roelands, Prof Dr. MF Piacentini, VITO – Sport University Köln – VIPER – University of Rome (Foro Italico)

Periodic breathing (PB) is a form of sleep-disordered breathing (SDB) characterized by instability in the respiratory pattern that shows an oscillatory behavior. PB is correlated with higher levels of mortality and can be found, e.g., in subjects with damaged respiratory centers, who are exposed to acute hypoxia or suffering from chronic heart failure.
To further explore PB, we conducted an experiment at the Concordia station in the framework of the European Space Agency's Life Science campaign. In this experiment, that took part during the 2012 winter over, 13 healthy male participants were monitored using a wireless polysomnography. Because of its altitude, at approximately 3800 meters, Concordia provides a unique environment for the study of PB. This is to our knowledge the longest duration study about adaptation to hypoxia ever done. Therefore, the results from this study will provide new insights on the evolution of PB over time.

Sleep-wake regulation - effects of time-on-task on sustained attention using behavioural and electrophysiological recordings
PIs: Prof. Dr. Romain Meeusen, Prof. Dr. Nathalie Pattyn
Post-doc: Dr. Gregory Collet
Collaborators: *VIPER* – Prof. Dr. Xavier Neyt,
Gregory Collet is studying the effects of time-on-task on sustained attention using behavioural and electrophysiological recordings. He also try to identify variations in cognitive performance and sleep during the Antarctic overwintering period and to investigate the effect of exercise on sleep quality, circadian desynchronization and mood at the behavioural and molecular level.

'Strategic Research Program' @ VUB Assessment of Human Robot Interaction
PI: Prof. Dr. Romain Meeusen
PhD student: Dra. Kristel Knaepen
Collaborators: Prof. Dr. Dirk Lefeber (R&MM), Prof. Dr. Bram Vanderborght (R&MM), Dr Grégory Collet – see also ALTACRO, CYBERLEGS
Until today, it is not entirely clear how humans interact with robotic devices and how we can, based on that interaction, maximize the effectiveness of exoskeletons during rehabilitation. This research line focusses on assessing the human-robot interaction by looking at physiological parameters and the brain in order to improve robot-assisted rehabilitation.

Commuting to school & Health
PIs: Prof. Dr. Bas de Geus, Prof. Dr. Romain Meeusen

PhD student: Drs. Jef Van Parijs
Collaborators: VITO
Despite the well-established health benefits associated with regular physical activity, many young people do not meet the WHO & ACSM recommended level. Physically active commuting to school (PACS) has important health implications, because it holds the potential of being physically active on a regular basis. Stimulating cycling or physical activity in general at young age is important as it will increase the probability of being physically active during adulthood.

We-bike: promoting a physically active lifestyle
PI: Prof. Dr. Romain Meeusen
PhD student: Dra Tine Torbeyns
Collaborators: Prof. Dr. Bas de Geus, Prof. Dr. Nathalie Pattyn
The purpose of this project is to examine the effects of daily cycling on a We-bike on several parameters of general health, cognition and quality of life. We will examine this in secondary school students, office workers and elderly people. For the different age groups respectively, the effects on learning performance and focus (students), productivity and absenteeism (office workers) and cognitive decline and independent functioning (elderly) will be studied. Besides the health aspects, also produced power and the accompanying savings will be measured.

Cognitive and physical strain during sustained military operations
PIs: Prof. Dr. Romain Meeusen, Prof. Dr. Nathalie Pattyn
PhD student: Dra Susan Vrijkotte
Collaborators: Prof. Dr. Bart Roelands, Prof. Dr. MF Piacentini, Dr. Luk Buyse
Soldiers are exposed to sustained operations during which they need to be active for more than 72 hours without time to rest. The cognitive and physical sustainability of these soldiers will be affected. At the moment, there is no objective tool that can predict soldier's sustainability.

Central aspects of Sports injury prevention
PI: Prof. Dr. Romain Meeusen
PhD student: Drs. Jo Verschueren
Collaborators: Dr Luk Buyse, Dr. Evert Verhagen
Sports injury prevention is becoming increasingly important in organised sports. This domain has evolved rapidly in the last decades, leading to a better understanding of peripheral risk factors and injury mechanisms. This research focuses on the central aspects of sport injuries and sports injury prevention.

Sports injury prevention
PIs: Prof. Dr. Romain Meeusen, Dr. Evert Verhaegen
PhD student: Dra Inne Aerts
Collaborators: Dr Elke Cumps, Dr. Luk Buyse
Current information seems inconclusive as to the exact factors that predispose athletes to greater lower extremity injury risk; yet preliminary information leads us to believe that biomechanical landing patterns are associated with increased knee injury risk. It is important to prevent these injuries to diminish the consequence for the athlete (missing training, games high costs,…)

Collaborations – partnerships:

Of special interest is the collaboration with *the R&MM research group of the faculty of Engineering (VUB)*. This collaboration started with the ALTACRO project in which a substantial grant from the VUB goes to the building of a 'rehabilitation robot'. It is the purpose to convert and integrate this project into the 'Exercise & Brain' program. A first accomplishment is the recent successful EU grant application (FP7-ICT-2011-7) 'Cyberlegs'. In this new project R&MM and MFYS are the VUB partners in building a 'cognitive' orthesis – a project that fully underscores the 'Exercise and the Brain, in Health & Disease' research line.

This ongoing collaboration resulted in the *'Strategic Research Program' @ VUB*. 'Exercise and the Brain in Health & Disease: The Added Value of Human-Centered Robotics' focuses at integrating the expertise of the two VUB groups so that the specific multidisciplinary research can be performed. Furthermore, it will allow us to cross the conventional research borders, and develop an unique joint expertise within the consortium. A 'SBO grant' was obtained (KUL-VUB-UCL) 'MIRAD' (An integrated methodology to bring intelligent Robot Assistive Devices to the user).

The *Royal Military Academy (VIPER)* is also a prominent partner, especially Dr. Nathalie Pattyn, who is an expert in psychophysiological aspects of stress, sleep and cognition. The study on confinement has led to an ESA grant 'Mars 500' on long duration isolation and the effect of exercise. This international project is run together with the *University of Rome – Foro Italico* and the *Sport university of Köln*. The ESA-BELSPO sponsored 'Antarctica project' integrates the collaboration between several groups such as *VITO – Sport University Köln – VIPER – University of Rome (Foro Italico) - MFYS VUB*.

The close collaboration with the *laboratory of pharmacology FASC (VUB)* within the *Centre for Neuroscience* for the animal studies has proven to be an important factor in the research. An international collaboration with a Japanese group (*University of Hiroshima*) is established.

Exploring brain mechanisms of fatigue not only involves neurotransmission but also supraspinal pathways, this is examined together with the dept. of Applied Biology of the *Université Libre de Bruxelles (ULB)*.

MFYS involves all levels of research in its projects (from fundamental physiological, through applied clinical research to policy making research). The first interuniversity spin-off between VUB & UGent Spartanova is a company that is specialized in bringing sport science technology (training & testing, injury prevention, training monitoring) from academia to end users (sport scientist, sport physiotherapists, trainers, coaches and athletes).

3.3. Education and the brain

This research is focused on educational aspects of brain research often but not exclusively oriented towards multilingual education or content and language integrated learning (CLIL). Below is a description of the status of current projects related to C4N. August 2014.

Current projects:

Functional and Structural Plasticity in the Bilingual Brain
Researcher: Esli Struys
In this fMRI and DTI driven research it is shown how the brains' functionality and connectivity changes in multilingual children and adults. Specifically, the variability within multilingual populations was examined. Multilingual speakers who speak different languages on a daily basis show cognitive advantages compared to other multilinguals and monolinguals.

Advanced MRI of Bilingualism-related differences in brain development
Researcher: Ghazal Mohades
It is shown how bilingual brains differ in brain development especially regarding white matter.

Cognition, CLIL and Mathematics
Researcher: Jill Surmont
Cognitive or rather cognitional differences between CLIL learners and non-CLIL learners are examined at secondary school level.

Implicit Learning and Its Cognitive and Brain Effects on Language Learning With Special Reference to Implicit Music Learning
Researcher: Marie-Eve Joret
The cognitive or cognitional effects of early implicit learning of language and music in young children is examined.

Chinese and Western Mathematics in Secondary Schools
Researcher: Liu Chang
Chinese and western learners approach mathematical processing differently. How differently the brains work is examined by means of an fMRI study.

Amygdala, Emotion and Language Use
Researcher: Nour Soudabeh
The involvement of amygdala on emotional language use is the focus of attention

Less Dyslexia in CLIL Schools. An fMRI study
The number of dyslexic children in CLIL schools is far below average. It is hypothesized that this might be due to the implicit learning process and the role of the cerebellum hereby

3.4. Experimental psychopathology

Clinical Experimental Psychology focuses on the experimental study of psychopathology. Our main research topics are cognitive dysfunction in neurodegeneration and affective disorders.

Collaborators
Head
- Natacha Deroost

PhD students

- Mieke Beckwé
- Koen Homblé

Postdoctoral researchers

- Daphné Coomans
- Jochen Vandenbossche

Implicit learning

We investigate the role of selective attention and attentional control in implicit learning processes as well as the representations (perceptual or motor) underlying implicit sequence learning. Another line of research focuses on the consolidation of implicit sequence knowledge. We also address the development of explicit knowledge during implicit sequence learning.

Cognitive decline in neurodegenerative disorders: deficits in automaticity and control

In collaboration with Eric Kerckhofs of the Department of Neurological Rehabilitation and Eva Dierckx of the Department of Developmental and Clinical Psychology

Our aim is to develop an integrative empirical model that predicts the development of cognitive decline in neurodegenerative disorders using a fine-grained analysis of cognition. More particularly, we focus on how disturbances in automaticity and control contribute to cognitive deterioration in Parkinson's disease, Multiple Sclerosis and Alzheimer's disease. Our long-term goal is to identify evidence-based predictors for cognitive rehabilitation based on innovative compensation strategies and neurostimulation.

Affective disorders: role of attentional control and repetitive negative thought

In collaboration with Rudi De Raedt and Ernst Koster of the Psychopathology and Affective Neuroscience (PAN) Lab of the Department of Experimental Clinical & Health Psychology of Ghent University.

We investigate how repetitive negative thought (RNT) and impaired attentional control contribute to affective symptoms. Another line of research determines the role of developmental psychological risk factors associated with anxiety and depression from childhood to adolescence. We also address the therapeutic effects of Cognitive bias modification on RNT and depressive complaints.

3.5. The neural and behavioral underpinnings of (conscious or unconsious) cognitive control

This research theme focuses on studying the neural and behavioral underpinnings of cognitive control and the role that consciousness plays in this. Until recently, it was assumed that cognitive control requires consciousness. However, a few recent studies (cf. Desender et al., 2013) have shown that cognitive control can also be exerted unconsciously under certain circumstances. Within this research theme, two projects can be situated.

Cognitive control: Conscious, unconscious, proactive, and reactive

PIs: Eva Van den Bussche & Tom Verguts (UGent)

PhD student: Bart Aben

Consciousness remains a mysterious topic which receives massive attention from psychologists, philosophers and neuroscientists. Despite the long research tradition, the function of consciousness remains unclear. One way to investigate which processes critically require consciousness, is to compare conscious versus unconscious processing. A promising domain to implement this approach is *cognitive control*. Cognitive control entails our abilities to plan a new strategy, evaluate it, control its execution, and correct possible errors. This has often been exclusively associated with consciousness, although recent data suggest otherwise. Cognitive control therefore provides a fruitful domain to explore this debated issue. Two types of cognitive control can be distinguished. Reactive control occurs in direct response to an encountered problem or error, whereas proactive control entails planning ahead of possible problems. In the current project, we first, and for the first time, rigorously test at the behavioral level whether unconscious reactive control is possible and contrast it to conscious reactive control. Second, we examine whether proactive control is also possible at an unconscious level. Third, we investigate the neural correlates of reactive and proactive control, again making sure we clearly distinguish conscious from unconscious trials.

Unconscious cognitive control
PIs: Eva Van den Bussche & Filip Van Opstal (UGent)
PhD student: Kobe Desender

In order to define the borders of unconscious processing, it has been argued that cognitive control is a set of strategic operations exclusively associated with consciousness. The prefrontal cortex is known to play a crucial role in cognitive control, and consequently, most theories state that this brain area cannot be activated by an unconscious task. However, in this project, we adopt a more significant role for unconscious processing, and examine whether cognitive control can also be exerted unconsciously. To address this question, we will study a specific form of cognitive control, namely context effects. A paradigm which circumvents theoretical and methodological problems demonstrated for previous studies will be used. In a first part, it will be tested whether an unconscious context can be created at all. We will examine whether the influence of unconscious ambiguous stimuli on response behavior can be altered depending on the context created by other stimuli presented in the experiment. In a second part, it will be tested whether subjects are also able to use these unconscious contexts to improve responding. We will create one context with mainly congruent and one with mainly incongruent trials, and look whether subjects can adapt to these contexts. In a third part, a functional MRI study will be conducted, to investigate whether, contrary to predictions of current theories, the prefrontal cortex is involved in the adaptation to unconscious contexts.

The familial transmission of pain: the role of observational learning in the parent-child dyad
PIs: Eva Van den Bussche, Liesbet Goubert (UGent), Gethin Hughes (University of Essex)
PhD student: Elke Van Lierde

Although research has demonstrated that chronic pain tends to run in families, the underlying mechanisms are still unclear. In this project, we will focus on psychological processes that can make children of chronic pain sufferers more vulnerable to develop chronic pain themselves. According to the fear-avoidance model, three processes are

considered to be pivotal in the development and sustainment of chronic pain in adults and children: pain catastrophizing (i.e., the tendency to exaggerate the threat value of pain and perceived inability to cope with pain), pain-related fear (i.e., an emotional fear reaction to pain-related stimuli) and hypervigilance (i.e., heightened selective attention) to pain. Extensive research has shown that a vicious cycle of pain, catastrophizing, fear, attention to pain and disability is involved in chronic pain. We aim to investigate how these processes develop in children. In particular, we will study the influences of observing important social models (i.e., parent) on children's responses to pain. This way, we will extend preliminary research results demonstrating the role of observational learning in the context of pain. The aims of this project are to investigate how observing a parent's pain can (1) induce pain-related fear, (2) heighten vigilance to pain and (3) alter the processing and experience of pain in children. In addition, moderating influences of pre-existing pain catastrophizing and pain-related fear on these effects are studied.

The recruitment dynamics of cognitive control in insomnia

PIs: Eva Van den Bussche, Olivier Mairesse (VUB), Gethin Hughes (University of Essex)
PhD student: Charlotte Muscarella

Insomnia patients report severe deficits in cognitive functioning. However, both behavioral and neurological research on these complaints remains remarkable scarce and inconclusive. The Dual Mechanisms of Control theory proposes that reduced cognitive efficiency might be caused by changes in the temporal dynamics of the neural recruitment of cognitive control mechanisms. Cognitivecontrol reflects our ability to plan a new strategy, evaluate it, control its execution and correct possible errors. More specifically, it is hypothesized that insomnia patients have difficulty maintaining task goals to anticipate and prevent interference before it occurs. Based on this theory, we use a more dynamic approach in the current project in order to shed light on how insomniacs recruit cognitive control and under which circumstances its efficiency fails. Furthermore, our project aims to explore whether these biased patterns of neural activation are reversible and can be trained. By incorporating a cognitive strategy training, we will examine whether a shift towards a more efficient cognitive control recruitment can be established in insomniacs. With this project we aim to increase our understanding of the recruitment dynamics of cognitive control in insomniacs and its flexibility. Consequently, these insights can provide promising indications with regards to cognitive interventions in clinical practice.

3.6. The social brain

Our major research interest is currently social neuroscience, or the neurological underpinning of the psychology on social behavior. In particular, we focus on person impression formation involving traits, goals, attributions and affective states of others.

The last decade has witnessed an upsurge of social neuroscientific approaches exploring the social aspects of the human mind and human behavior by applying novel neuroimaging techniques. This has resulted in several new areas of social psychological study including social and affective neuroscience.

Many social processes that look quite similar from the surface, may in fact appear very much different if explored from a neurological perspective and methodology. Our lab

asks novel questions about underlying neurological processes of social and affective processes by using state-of-the-art imaging methods such as fMRI (functional magnetic resonance imaging) and ERP (event-related potentials). As such, the study of social processes may not only become much more fine-grained, but ultimately also more accurate in its understanding of underlying processes and prediction of social and emotional behavior.

One of our interests in social neuroscience is spontaneous social inferences. We explore the question of whether earlier social neuroscience findings in which participants make such inferences explicitly, generalize to the case where these inferences are made implicitly. We also explore the similarities and differences between different judgments about other's such as goals, beliefs, traits and so on. We also investigate how social context, groups, norms and affective factors impact on these inferences, and which brain areas are involved and when.

Another interest refers to construal level theory. This theory claims that the level at which social and non-social events are construed and defined, strongly determines how we interpret these events. We hypothesize that the construal level also determines which brain areas are involved in social judgment. Construals of the here-and-now tend to recruit the brain areas involved in temporary judgments. In contrast, construals at a larger psychological distance (other persons instead of me, hypothetical or future events instead of the present, person traits rather than situational inferences) tend to implicate brain areas involved in inferring enduring characteristics.

Another recent interest is the memory representation or “code” of social judgments: traits, of the agents that engage in trait-implying behaviors and of the goals that they pursue. For this we use a methodology known as fMRI adaptation.

3.7. The affective brain

Emotion Regulation in the Recovery from Emotional Stressful Life-Events, Sleep and Psychopathology
PI: Marie Vandekerckhove
Researcher: Iris Van Tieghem
Is an experiential emotion regulation strategy effective to process emotional stressful life-events and to recover from them? How does that affect well-being as well as quality of sleep?

Experiential emotion regulation and affective dynamics
PI: Marie Vandekerckhove
Researcher: Margo Verhasselt
How does the training of an experiential emotion regulation approach versus a more analytical emotion regulation approach affect
daily affective and associated physiological dynamics of negative and positive emotion within healthy individuals?

Emotion Regulation and Neuronal Correlates
PI: Vandekerckhove, M.
Researcher: Kris Baetens
Emotion regulation strategies encompass multiple psychological processes (direction of attention, executive processes, interoception etcetera). Existing research often

compares highly specific emotion regulation conditions (e.g., “downregulate emotion by distancing yourself from the stimulus”) with quite loosely defined baseline conditions (e.g., “maintain the emotion” or “experience naturally”) which involve unspecified and uncontrolled subprocesses. A challenge is therefore to dissociate subprocesses involved in emotion regulation. In the present study, we investigate the functional correlates of two important factors which differ between emotion regulation strategies: an internal versus external focus of attention on the one hand, and a descriptive versus an interpretative stance on the other.

High-level and Low-level processing interactions on the emergence of affective consciousness. A neurophysiological approach
PI: Vandekerckhove, M., Van Overwalle, F., & Mariën, P.
Researcher: Luis Carlo Bulnes
The main goal of this research project is to understand how affective conscious experience is shaped by the dynamics between low-level subcortical (bottom-up) and high-level (top-down) cortical interactions in the emergence of affective consciousness based on a dynamic facial emotion recognition paradigm with fMRI, lesion studies and TMS.

Affective Memory, Consciousness and the Brain
PI: Vandekerckhove, M.
This line of research concerns the analysis of evolutionary levels of memory and associated consciousness, with a focus on anoetic (without knowledge) forms of consciousness as the basis of noetic (knowledge-based) and autonoetic (higher reflective mental) functions that permit conscious awareness. These anoetic (raw perceptual and affective) forms of consciousness can be elaborated by brain networks that are subcortical and thus can function without neocortical involvement.

3.8. Neurocognitive and psychosocial outcome of childhood brain tumor survivors

Learning difficulties and related environmental problems have not been systematically listed in Belgian childhood brain tumor survivors (CBTS). Management strategies are being formulated internationally for some groups of children at high risk for neurodevelopmental problems (e.g., very low birth weight infants). However, no specific strategies for screening and management of learning problems in CBTS have been developed. Moreover, little is known about care trajectory-related patient and parental experiences in CBTS. While a great deal of research is focused on finding a cure for brain tumors, quality of life is often overlooked.

Ongoing project:
Care and educational trajectories of childhood brain tumor survivors: inventory and exploration of possible management strategies.
PI: Philippe Paquier
Co-I: Anna Jansen, Johan Bilsen, Lieve Peremans, Patrick Van Bogaert (ULB)
Collaborators: Jutte Van Der Werff Ten Bosch, Inge Gies, Eva Cloet, Reginald Deschepper, Elke Van Hoof, Eric Sariban (ULB), Danielle Balériaux (ULB), Olivier De Witte (ULB), Daniel Devriendt (ULB), Paul Meijnders (UA)
PhD students: Stephanie Vanclooster, Sophie Genin (ULB)

This multi- and transdisciplinary research project jointly led by the Vrije Universiteit

Brussel (VUB) and the Université Libre de Bruxelles (ULB) aims at optimizing the care trajectory and the management of learning difficulties and related environmental problems in CBTS, in order to allow these children to catch up with their peer group as early as possible after their medical treatment, to reintegrate school in optimal conditions, and to have a good quality of life. The project consists of two interrelated parts which are being carried out in parallel, with the following aims: (Part I - ULB) to make an inventory of learning difficulties and related environmental problems in CBTS, and to assess the factors which influence the implementation of a potential management package based on the existing practice for learning difficulties, and (Part II - VUB) to identify key events in the care trajectory following surgery for childhood brain tumor, and to qualitatively analyze how patients and parents experience care-related decisions, with special attention directed to the interactions between patients and parents, and care professionals. The findings of this pilot project in CBTS treated at VUB-UZ Brussel and ULB-Hôpital Erasme might later on be verified in a larger, multi-university context and, so, constitute a starting point for an outcome study. This in-depth analysis is aimed at (a) delivering recommendations for early screening of learning difficulties and related environmental problems, and their follow-up, and (b) optimizing the care trajectory by identifying the key events in post-surgery and rehabilitation care based on the patients' and parents' experience, in order to develop an explanatory model for care-related decisions that allows for optimal care trajectory counseling.

3.9. Mental Health and Wellbeing

The World Health Organisation (WHO) defines mental health as a state of general emotional, mental and social wellbeing, and considers this as a fundamental prerequisite for health in general ('No health without mental health'). In recent years, one becomes more and more convinced of the important role mental health plays in global health. In Europe, mental health is even considered to be one of the greatest public health challenges for the coming decades. The WHO estimates that at present each year at least one third of the European population deals with mental health problems. According to the 'Global Burden of Disease Report 2012' of the WHO, about 19% of the global disease burden can be attributed to these health problems. This is not only detrimental to the individual, but it obviously has a very severe social impact, which is also formally recognized in several declarations and action plans within the WHO and Europe, such as the 'European Pact for Mental Health and Wellbeing 2008 ', and the recent 'WHO Comprehensive Mental Health Action Plan 2013-2020', signed in 2013 by ministers of 194 countries. However, we see that mental health is still receiving poor attention compared with "somatic" health care, both in terms of public interest, treatment options, prevention initiatives, released budget, etc ... This is partly due to the still existing stigma of having psychological problems and to incomprehension, but is also largely due to a lack of evidence-based insights because of the shortage of solid scientific research in this area.

Aims and focus of the research group 'MENT'

The Mental Health and Wellbeing Research Group (MENT) conducts primarily social scientific research (quantitative-epidemiological as well as qualitative) in the field of mental health and general well-being, clearly starting from a holistic bio-psycho-social health / disease model. The research is situated in different sub-domains:
-factors associated with good mental health and general well-being
-frequency of various problems in the field of mental health and general well-being

-risk factors and determinants of such health
-prevention of these problems and promoting mental health and general well-being; coping mechanisms
-therapeutic interventions in this area
-healthcare (health services research) and policies (health policy research) regarding mental health and general well-being

The research focuses on both the broad population and certain sub-populations or risk groups in terms of mental health, such as:
-children, youth, school children (child mental health)
-elderly subjects, residents of nursing homes (elderly mental health)
-people in difficult working conditions (occupational mental health)
-people with severe somatic diseases, the chronically ill, terminally ill
-psychiatric patients, people with intellectual disabilities, people with dementia
-immigrants and other minority groups
-people in extreme dependency situations, eg. prisoners, hospitals, …
-people in deprivation, poverty
-singles
-people with different sexual orientation
-. ...

A broad range of relevant topics related to mental health and wellbeing in these various fields and populations can be studied, such as: depression, anxiety, addiction, suicide, sexuality, burnout, stress, happiness, pain, life, self-determination and dependency, stigma, etc ... The research can be quite varied in nature, but it has always the same finality in mind: scientific insight in and promoting the mental health and well-being (as defined by the WHO) of populations.

Within the Center for Neurosciences (C4N) the Mental Health and Wellbeing Research Group (MENT), as part of the section “Behavior & Cognition and Health Impact”, will predominantly contribute to the epidemiological and psycho-social aspects of the mainly basic and clinical (neuro)scientific research of the other members.

Current research projects

1) Psychosocial needs and coping strategies of single cancer patients (VLK, promotor: Prof. R. Deschepper, co-promotors: Prof. J. Bilsen and Prof. M. Grypdonck)

2) Sexuality in people with incurable chronic diseases (FWO, promotor: Prof. J. Bilsen, co-promotors: Prof. P. Enzlin, Prof. L. Peremans and Dr. V. Cocquyt)

3) Psychosocial problems and stigma among immigrant SSA women with AIDS in Belgium (VUB, promotor: Prof. R. Deschepper, co-promotor: Prof. J. Bilsen)

4) Critical medical decision making in an increasingly multicultural context of health care providers and patients (FWO, promotor: Prof. J. Bilsen, co-promotors: Prof. W. Distelmans and Prof. L. Huyghens)

5) Autonomy and rights of people in extreme dependency situations (HOA-VUB, promotor: Prof. S. Snacking, co-promotors: Prof. W. Distelmans, Prof. S. Gutwirth, Prof. P. De Hert and Prof. J. Bilsen)

6) Neurocognitive and psychosocial outcome of childhood brain tumor survivors (KBS, Promotor: Philippe Paquier, co-promotors: Anna Jansen, Johan Bilsen, Lieve Peremans, Patrick Van Bogaert)

7) Suicide Attempts in the Brussels-Capital Region: characteristics and care of suicide attempters in the emergency departments of hospitals in Brussels (Prospective Research for Brussels in 2013, promotor: Prof. J. Bilsen)

8) Assessment of pain and stress experiences in incompetent, sedated patients (VUB, promotor: Prof. R. Deschepper, co-promotor: Prof. J. Bilsen).

9) (Sexual) Cross-border behavior in mental healthcare (VUB, promotor: Prof. J. Bilsen)

Multidisciplinary group of researchers

Research on such a broad field, and starting from a bio-psycho-social model of health and disease can only be done properly by a multidisciplinary research team. The current team of researchers consists of: social health scientists, nurses, anthropologists, a sexologist, a sociologist, an ethicist, a lawyer, a public health physician, a master in health education and promotion, youth health physician, occupational health physician, neurologist, psychologists, and a psychiatrist. There is also a wide network of national and international cooperation in the field of public health and mental health, e.g. with several members of the 'Word Federation for Mental Health' and of the 'Workgroup Mental Health of the European Public Health Association' and the 'Belgian Association of Public Health'.

3.10. Cognition and aging

Early detection of Alzheimer's Disease

Nowadays, the early diagnosis of Alzheimer's disease (AD) becomes a major challenge in psychogeriatric medicine, as disease-modifying pharmacological treatments for AD are currently under development. Patients might benefit from cognition-enhancing or disease-modifying drugs It is generally assumed that these treatments will have the greatest efficacy early in the course of dementia. Despite considerable progress with regard to the diagnostic work-up of dementia, the early diagnosis of AD remains an important challenge since it is still difficult to discriminate early dementia from depression on clinical and neuropsychological grounds. Similar cognitive and affective problems can occur in both mild AD and so-called "depressive pseudodementia" or "dementia syndrome of depression".

Besides depression and AD, which are considered to be among the most prevalent and disabling mental disorders among elderly, nowadays a lot of attention is paid to the concept of Mild Cognitive Impairment (MCI). MCI is defined as a boundary area between normal aging and dementia. However, although MCI is regarded as a precursor to dementia, not all people diagnosed with MCI will develop dementia. Some will go on to develop dementia or AD in particular (and are in fact prodromal AD patients), while others remain stable or even improve. In the light of an early diagnosis of AD, the importance of an early detection of preclinical/prodromal AD among MCI patients becomes obvious.

Taken all this together, it appears that, in the early detection of AD, not only the differentiation between AD and elderly depression is important, but it also becomes an

important challenge to psychogeriatricians to recognize AD in its preclinical/prodromal stage among so called MCI-patients.