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SCIENTIFIC REPORT 2013-2014
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Neurology department UCL SAint-luc hospital
Neuromuscular reference centre
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Neuro Imaging
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Physical Medecine & Rehabilitation Department CHU UCL Mont-Godinne

PHD STUDENT DAY

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Our Institute of NeuroScience (IoNS) encompasses more than 250 researchers supported by about 35 technical and administrative staff. Experimental and clinical neuroscience research program are integrated within divisional groupings of Cellular & Molecular Neuroscience, Systems & Cognitive Neuroscience and Clinical Neuroscience allowing our research to span all of the different organisational levels of the nervous system. A specific aim of IoNS is to provide a high quality research environment in which long-term projects can be conducted that have the potential to truly advance our knowledge of normal brain function and enable treatments of neurological and psychiatric diseases.

Jean-Noël OCTAVE, President of the Institute of Neuroscience
OVERVIEW

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IoNS Team building day in the Fagnes (April 2014)
The Cellular and Molecular Neuroscience division consists of nine research groups who use molecular and cell biology, biochemistry, electrophysiology, pharmacology, imaging, and transgenesis to investigate the fundamental bases of development, physiology and pathologies of the nervous system.

Research interests include the characterization of mechanisms involved in neural differentiation, neuronal migration, axon guidance, synaptogenesis, degeneration, and physiology of neurons, astrocytes, and microglia.

At the long run, the aim of the research is to improve diagnosis and treatment of congenital malformations, Alzheimer’s disease, multiple sclerosis and neuro-muscular disorders such as Duchenne muscular dystrophy and Amyotrophic Lateral Sclerosis.
Alzheimer disease (AD), the most frequent neurodegenerative disease in the elderly, is characterized by the presence in the brain of two types of lesions. Intraneuronal neurofibrillary tangles contain the microtubule-associated protein Tau, which is hyperphosphorylated. Extracellular senile plaques contain an amyloid deposit of $\beta$-amyloid peptide ($\beta$-A), the major constituent of senile plaques. In addition, the cleavage of the membrane-bound APP C-terminal fragments (CTFs) by $\gamma$-secretase releases the AICD (APP Intracellular C-terminal Domain), a soluble intracellular protein believed to control APP-dependent signal transduction and nuclear signallng. Together, this strongly supports the view that APP processing and APP function are interconnected and that the $\gamma$-secretase cleavage play a crucial role in the onset and progression of AD.

Dimerization of APP and APP C-terminal fragments might differ due to the presence of the bulky ectodomain in full-length APP. We developed split protein assays (split fluorescence and split luciferase assays) to monitor APP dimerization in living cells. APP dimerization is indeed mainly driven by the correct folding of the Kunitz-type protease inhibitor domain (KPI) present in the extracellular region of non-neuronal APP isoforms (1). KPI folding favours APP dimerization measured in living cells by split fluorescence. Dimerization regulates trafficking along the secretory pathway and is correlated to enhanced non-amyloidogenic processing (Fig. 1).

We also identified the juxtamembrane/transmembrane GxxxG motifs of APP as key determinants of the amyloidogenic processing. The GxxxG (or GxxxG-like) motifs are highly enriched in transmembrane sequences (TM) and known to favour helix-helix interactions. We showed that GxxxG motifs are required for proper orientation and dimerization of the APP transmembrane (TM) domains and promote Aβ release (2) (Fig. 2). However, AICD production appears to be less sensitive to this process, but is allowed by a break in the helical structure of APP transmembrane domain (3). We very recently found that the motifs from TM region are not only involved in dimerization but are key players in conformational changes that have consequences in pathological processing of APP (4). Interestingly, similar molecular determinants are present in highly conserved TM regions of presenilins, the catalytic subunits of the $\gamma$-secretase. Our work gradually provides new structural clues to understand processing events specific to Aβ production and APP function.

APP STRUCTURE, DIMERIZATION AND PROCESSING

C. Marinangeli, M. Decock, L. El Haylani, B. Tasiaux, J.N. Octave, P. Kienlen-Campard

APP is a type 1 transmembrane protein. Its cleavage in the amyloidogenic pathway by $\beta$- and $\gamma$-secretases produces the $\beta$-amyloid peptide ($\beta$-A), the major constituent of senile plaques. In addition, the cleavage of the membrane-bound APP C-terminal fragments (CTFs) by $\gamma$-secretase releases the AICD (APP Intracellular C-terminal Domain), a soluble intracellular protein believed to control APP-dependent signal transduction and nuclear signalling. Together, this strongly supports the view that APP processing and APP function are interconnected and that the $\gamma$-secretase cleavage play a crucial role in the onset and progression of AD.

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ALZHEIMER DEMENTIA: CELLULAR AND MOLECULAR MECHANISMS

Alzheimer disease (AD), the most frequent neurodegenerative disease in the elderly, is characterized by the presence in the brain of two types of lesions. Intraneuronal neurofibrillary tangles contain the microtubule-associated protein Tau, which is hyperphosphorylated. Extracellular senile plaques contain an amyloid deposit of Aβ peptide, which is produced from the amyloid precursor protein APP. The APP juxta-/transmembrane domain is able to homo-dimerize and hetero-dimerize with other membrane proteins. Our group is investigating how these molecular interactions can affect processing of APP. The function of APP remains largely unknown. By over expressing various APP isoforms or down regulating endogenous APP expression, we are investigating the neuronal function of the protein both in vitro and in vivo. Another important issue is to understand the pathophysiological role of protein Tau and to identify Tau-directed therapeutic targets. We are using in vitro to in vivo models in a versatile way for identification and characterization of novel modifiers of Tau.
FUNCTION OF THE AMYLOID PRECURSOR PROTEIN


Although APP processing by secretase activities has been extensively studied, the function of the protein remains largely unknown. APP knockout mice have a normal phenotype with only subtle defects, and particularly a neuromuscular phenotype with reduced grip strength. We initially identified in transcriptome analyzes GDNF (Glial cell-Derived Neurotrophic Factor) to be an APP target gene. The neuromuscular phenotype found in APP KO mice (reduced formation of functional neuromuscular junctions) appears to be related to APP-dependent transcription of GDNF gene in muscle cells.

APP controls the transcription of several genes by mechanisms that could involve epigenetic modifications. We recently observed that APP significantly down regulated Egr1 expression at both mRNA and protein levels. Enrichment of acetylated histone H4 at the Egr1 promoter region was measured in APP-/- neurons, as well as in brain of APP-/- mice, in which increase in Egr1 expression was also measured, demonstrating an important function of APP in the epigenetic regulation of Egr1 gene transcription both in vitro and in vivo (5). Since Egr1 is an immediate early gene involved in memory formation, we wondered whether other early genes involved in memory were regulated by APP and observed that APP down regulates expression of four immediate early genes, Egr1, c-Fos, Bdnf and Arc. Although transcription of these immediate early genes was increased following exposure of APP +/- mice to novelty, such an induction was not possible in APP-/- mice with a high basal level of expression. These results demonstrate that APP-mediated regulation of immediate early genes by different epigenetic mechanisms is needed for their induction during exposure to novelty.

Perturbation of lipid metabolism favours progression of Alzheimer disease, in which processing of APP has important implications. APP cleavage is tightly regulated by cholesterol and APP fragments regulate lipid homeostasis. We observed that expression of APP decreased HMG-CoA reductase (HMGCR)-mediated cholesterol biosynthesis and SREBP mRNA levels, while its down regulation had opposite effects. APP and SREBP1 co-immunoprecipitated and co-localized in the Golgi (Fig. 3). This interaction prevented Site-2 protease-mediated processing of SREBP1, leading to inhibition of transcription of its target genes. A GXXXG motif in APP sequence was critical for regulation of HMGCR expression. Neuronal expression of APP decreased both HMGCR and cholesterol 24-hydroxylase mRNA levels and consequently cholesterol turnover, leading to inhibition of neuronal activity (Fig. 4), which was rescued by geranylgeraniol, generated in the mevalonate pathway. We conclude that APP controls cholesterol turnover needed for neuronal activity (6).
As yet unsuccessful results of anti-amyloid based ‘late’ (post-diagnosis) therapies for AD underscore (i) technical problems associated with these therapies, (ii) the need to identify the exact form of pathological amyloid peptides, and (ii) particularly the need for combined therapeutic strategies aiming at amyloid and ‘late’ targets. A ‘late’ executive role of Tau, in neurodegeneration is corroborated by (i) correlation of tangles with disease progression, (ii) its aggregation in a variety of neurodegenerative disorders ‘Tauopathies’, (iii) clinical mutations in Tau causing certain forms of Tauopathies and (iv) the identification of APP-metabolites as Tau-modifier. We aim at the identification of modifiers of Tau and amyloid-Tau signaling using versatile in vitro to in vivo models, in order to gain insight in their pathological role in Alzheimer’s Disease and related disorders.

We have generated transgenic mice co-expressing mutant APP/PS1 and mutant Tau, which develop a dramatic combined amyloid and tau-pathology (Fig 5), and thereby provide a model recapitulating the pathological hallmarks of AD and a better preclinical model for evaluation of targets for AD therapy (7). In addition, Tau-pathology is dramatically aggravated in these mice compared to the parental Tau transgenic mice (Fig 6). These findings not only strengthen the amyloid cascade hypothesis, but also provide a robust model to study the mechanisms of amyloid-induced Tau-pathology (7). These mechanisms are under investigation in our research group, with particular emphasis on kinase imbalances (GSK3) and following up on previous work (8-9).

We further aim at the identification of novel Tau-modifiers and their validation in mice with combined amyloid and tau-pathology and in mice with tau-pathology only. In view of lack of success of anti-amyloid therapies, therapies aiming at Tau, a centre-staged protein in AD, have gained interest. In collaboration with Johnson&Johnson, a Tau-interactome map has been generated and the Tau-modifying potential of Tau-interacting proteins is under investigation. In this context, increased expression of BIN1 was demonstrated to mediate Alzheimer genetic risk by modulating tau pathology, in collaboration with C. Lambert(10). Further high-throughput screening is combined with in depth analysis to identify novel Tau-modifiers with therapeutic potential.

Finally, we focus on mechanisms involved in spreading of Tau-pathology. Recently, it was shown that spreading of pathology in proteinopathies linked to misfolding of alpha-synuclein, prion protein, Tau, … occurs in a prion-like way. Hence protein misfolding spreads to functionally connected brain regions. In view of the well-defined way of spreading of tau-pathology in Alzheimer’s Disease, we aim at studying mechanisms involved and functional repercussions of spreading of Tau-pathology in AD models.

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- IWT (Government agency for Innovation by Science and Technology)
- PAI (Belspo)
- DIANE (Région Wallonne)

**EQUIPMENT**
- Cell culture facilities
- Calcium imaging
- Quantitative PCR
- ECLIA [Electro-chemiluminescence immuno assay]
- Electrophysiology
- Fluorescent microscopy
- Transgenesis facilities

**AWARDS**
- Prix Aline, fondation Roi Baudoin
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The laboratory of Developmental Neurobiology (DENE) studies genes and proteins that are implicated in neural development, with a particular emphasis on planar cell polarity (PCP) genes Celsr1-3, and on Formins. Mutations in those genes have been induced in mice and their phenotypes are actively investigated using anatomical, biochemical, and cellular techniques, as well as in vitro culture systems. Analysis of the mutant phenotypes provides clear hypotheses on the mechanisms of action of these proteins during neural development. They might at the long run help developing repair strategies for the injured and/or diseased nervous system.
ROLE OF PCP PROTEINS IN EPENDYMA L POLARITY

C. Boutilin, A. Goffinet, F. Tissir

In the nervous system, cilia dysfunction perturbs the circulation of the cerebrospinal fluid, thus affecting neurotransmission and brain homeostasis. Role for planar cell polarity (PCP) signaling in the orientation of cilia (i.e., rotational polarity) and cilogenesis is established. However, whether and how PCP regulates cilia positioning in the apical domain (translational polarity) in radial progenitors and ependymal cells remains unclear. By comparative analysis of a large panel of PCP mutant mice, we show that Celsr1, Fzd3 and Vangl2 position the primary cilium in radial progenitors. In ependymal cells, whereas Celsr2&3 and Vangl2 organize cilia in individual cells, Celsr1, Fzd3 and Vangl2 coordinate different component of polarity at the tissue level. These signals are relayed by distinct cytoskeletal changes. Our data reveal unreported functions of PCP and provide an integrated view on how polarity is acquired by radial progenitors (monocilia) and passed on to ependymal (multiciliated) cells. A manuscript reporting the results of this study is under consideration.

Fig. 1: “En face” view of the ependymal layer lining the lateral ventricle of the adult brain. Green: tight junctions (ZO1); White: basal bodies of motile cilia (gamma-tubulin); Red: cells where inactivation of Celsr1 was induced upon tamoxifen injection.

Fig. 2: Cross section of the lumbar spinal cord at embryonic day 11.5. Motor neurons and their axons projecting into the hindlimb are labeled with Hb9::GFP transgene (green).

CELSR3 IN HINDLIMB INNERVAITION AND LOCOMOTOR CIRCUITRY DEVELOPMENT

G. Chai, A. Goffinet, F. Tissir

Celsr3 regulates the directional growth and targeting of axons in the central nervous system, but whether it acts in collaboration with or in parallel to other axon guidance cues is unknown. Furthermore, the role of Celsr3 in the peripheral nervous system is still largely unexplored. We have shown that Celsr3 plays a key role in pathfinding of motor axons innervating the hindlimb. Celsr3-deficient axons of the peroneal nerve segregate from those of the tibial nerve. However, contrary to control axons, they fail to extend dorsally and stall near the superficial versus deep peroneal nerve branching point. Mutant axons are able to respond to repulsive ephrinA3/EphA forward signaling and to GDNF. In contrast, they are insensitive to the attractive EphA/ephrinA reverse signaling. In transfected cells, Celsr3 co-immunoprecipitates with ephrinA2/5, Ret, GFRα2, and Fzd3. The function of Celsr3 in peripheral axons is Fzd3-dependent but Vangl2-independent. Our results therefore provide the first evidence that Celsr3/Fzd3 interacts with EphA/ephrinA reverse signaling to steer motor axons in the dorsal hindlimb. The data was compiled in a manuscript that is under revision.

Fig. 3: A coronal section of murine cortical wall showing a neural stem cell labelled in green (electroporated GFP). The pial surface is left and the ventricular side is right. Blood vessels are shown in red (Laminin staining).

ROLE OF CELSR1 IN NEURAL STEM CELLS

C. Boucherie, A. Goffinet, F. Tissir

Celsr1 is specifically expressed in neural stem cells (NSC). Those cells extend from the lateral ventricle to the pial surface and display an apico-basal polarity. At early embryonic stages, NSC in the ventricular zones undergo symmetric divisions to produce daughter cells that go back to the cell cycle. Such divisions increase stem cell numbers and lead to lateral expansion of the developing cortical sheet. At the onset of neurogenesis, NSC acquire characteristics of radial glia and begin to divide asymmetrically to form either neurons or inter- mediates progenitors. Signals that cause the adjustment from symmetric to asymmetric division have profound impact on neuronal number, diversity, and position. Those signals regulate the cortical size and architecture but the underlying molecular mechanisms are not fully understood. We are investigating the involvement of Celsr1 in corticogenesis with a specific focus on how this protein regulates interactions between different cell types that control neurogenesis.

Fig. 4: Immunohistochemistry of Celsr1. Green: Celsr1; Red: tight junctions (ZO1); White: basal bodies of motile cilia.

O-FUCOSYLATION AND FRINGE MODIFICATION OF CELSR1

W. Wang, F. Tissir, A. Goffinet

O-fucosylation is a rare post-translational modification catalyzed by Protein O-fucosyl transferase 1 (POFUT1). O-fucose is further modified by Fringe enzymes into important proteins, particularly Notch and Delta, and the role of Fringe is usually considered in relation to Notch signaling. We showed that Celsr1 is O-fucosylated and modified by Fringe and that some phenotypic traits in Celsr1 mice are also present in Fringe mutants. O-fucosylation and Fringe modification hamper secretion of Celsr1, probably by disturbing folding and/or ER to Golgi exit. Current work is focused on understanding the role of Celsr1 O-fucosylation further, by using POFUT1 conditionally mutant mice and the Cre/loxP system to probe the role of POFUT1 in PCP events known to be regulated by Celsr1.

IDENTIFICATION OF CELSR3 AND FZD3 PARTNERS

N. Parmentier, F. Tissir, A.M. Goffinet

A severe limitation to studies of Celsr and Fzd proteins is the lack of high affinity and specific antibodies. We have obtained a guinea-pig anti Celsr1 and two mouse monoclonals against Celsr3, but it remains impossible to visualize Celsr3 in tissues. Based on epitope prediction programs and comparison between different Celsr and Fzd sequences, we have designed peptide and fusion protein sequences cloned in expression vectors. Fusion proteins have been sent to commercial companies for immunization of guinea pigs. Serum has been obtained and polyclonal antibodies are being purified and tested. At parallel, monoclonal antibodies are under production. In addition to their utilization in immunohistochemistry to detect endogenous proteins, those antibodies will be used in co-immunoprecipitation experiments to define partners of Celsr3 using proteomic analysis.

Fig. 5: Immunohistochemistry of Celsr3. Green: Celsr3; Red: tight junctions (ZO1); White: basal bodies of motile cilia.

A. Goffinet, F. Tissir, W. Wang, B. Boucherie, C. Boutilin, C. Tissir

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FORMIN DIAP3 IN CORTICAL DEVELOPMENT

D. Damiani, A. Goffinet, F. Tissir

Formins are a family of proteins that were first identified in 1990 by molecular analysis of the limb deformity locus. All the proteins belonging to the family display the same features, with the presence of the so-called Formin Homology domains FH1 and FH2. 15 members in 7 different groups have been identified to date in mouse and humans. Formin proteins are fundamental actors in the regulation of actin dynamics. They have the capability to interact with the growing (also known as barbed) end of actin filaments and accelerate the polymerization of actin itself increasing both filament nucleation and elongation.

Diaphanous related formins (DRFs), discovered in Drosophila in 1994, can be distinguished from other formins in that they can exist in two different states, active or inactive. Inactivation of DRFs occurs via a mechanism of autoregulation, in which a C-terminal domain, the Diaphanous Autoregulatory Domain (DAD), tightly interacts with the upstream Diaphanous Inhibitory Domain (DID). Activation of Diaphanous formins occurs via binding of RhoGTP to the N-terminal GTPase Binding Domain (GBD) that disrupts the interaction between DID and DAD. DRFs, known in the mouse as Diap1-3, display other crucial cytoskeletal functions, as actin bundling as well as microtubule capping, stabilization and bundling. The function of DRF proteins in the Central Nervous System (CNS) have been already studied in the mouse via targeting of Diap1 and Diap2 genes. Double knock-out (DKO) animals display impaired tangential interneurons and SVZ migration due to inhibition of actin polymerization. Also, DKO mice display disruption of neuroepithelium integrity and severe hydrocephalus.

The role of Diap3 in CNS development has not been studied to date. We have generated a Diap3 mutant allele with a loss of function of the protein. Analysis of the KO mouse revealed that the ventricular zone (VZ) of the cerebral cortex is disrupted at E13.5. The cortical thickness is also greatly reduced. A time point analysis showed a massive loss of neuroepithelial progenitors by embryonic day 10.5 in the mutant cerebral cortex. We are currently trying to understand the precise molecular mechanisms governing this loss.

Fig. 4: Emergence of apoptotic cells in the cortical neuroepithelium of the Diap3 KO mice. Dying cells (TUNEL+, red) don’t appear to be intermediate progenitors, as they are not co-stained with Tbr2 (green). Nuclei are counterstained with DAPI.

ROLE OF CELSR3 IN THE NEUROGENIC TO GLIOGENIC SWITCH

W. Wang, F. Tissir, A. M. Goffinet

From around E15 in mice, telencephalic neural progenitors switch their fate from the production of neurons to that of glial cells. We found that this switch is altered in Celsr3 and Fzd3 mutant mice, in which as excess of neurons are produced at the expense of glial cells. This phenotype is also seen when Celsr3 and Fzd3 are conditionally inactivated in postmitotic neurons but not in progenitors, using Nex-Cre. It is known that postmitotic neurons play a critical role in the neuron-glia switch, via secretion of proteins such as cardiotrophin-1 and activation of JAK-STAT signaling in progenitors, which directs them to the glial fate. We therefore investigate the hypothesis that Celsr3 and Fzd3-mutant postmitotic neurons are unable to provide that feedback to progenitor cells, and examine the possible mechanisms.

Fig. 5: A coronal section of E18.5 embryonic cortex stained with Olig2(Green), Ctip2(Red) and Satb2(Blue). Mutant cortices have more neurons (Ctip2+ & Satb+) and less oligodendrocyte precursor cells (Olig2+) as compared to littermate controls (Ctrl).
**EQUIPMENT**

- Cell culture
- Vibratomes
- Microtomes
- Sliding microtome
- Cryostat
- Fluorescent microscope
- Confocal microscope
- Micro-injection station

**FUNDING**

- Fonds National de la Recherche Scientifique (FNRS)
- Fondation Médicale Reine Elisabeth (FMRE)
- Fédération Wallonie Bruxelles, Actions de Recherches Concertées (ARC)
- pôles d’attraction interuniversitaires (PAI)
- WELBIO

**AWARDS**

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**SELECTED PUBLICATIONS**


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**LABORATORY OF CELL PHYSIOLOGY**

**Role of TRP channels in cell physiology**

Our laboratory studies the mechanisms regulating Ca²⁺ fluxes between intracellular medium, endoplasmic reticulum (ER), mitochondria and extracellular medium. In particular, we focused our research on TRP (Transient Receptor Potential) ion channels. Besides deciphering the gating mechanisms and the pharmacological properties of these channels, we try to understand their involvement in muscle contraction, in cell migration, proliferation and in apoptotic cell death. Recently, we began to investigate their role in brain, in particular in learning and memory processes.

**TRP channels**

TRP cationic channels constitute a large family of almost ubiquitously expressed proteins. The family was designated TRP because of a spontaneously occurring mutation in Drosophila, the photoreceptors of which lacked TRP protein and responded to a continuous light stimulus with a transient receptor potential response. The homologous proteins in mammalian cells seem to mediate cellular responses to a large variety of extracellular signals such as agonists, pheromones, odorant ligands, temperature, pH, osmolarity, oxidative stress… Some isoforms also seem to be activated by depletion of intracellular Ca²⁺-stores. The activation and regulation mechanisms of TRP channels are largely unknown and diverse. On the basis of amino acids homologies, the mammalian TRP channel superfamily can be divided into six subfamilies: TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPA1 (Ankyrin), TRPP (Polycystin) and TRPML (Mucolipin).
TRP CHANNELS AND DUCHENNE MUSCULAR DYSTROPHY

Although all TRPs are nonselective cation channels, their role in Ca$^{2+}$ influx represents their most common and most investigated function. Adult muscle fibres do not exchange much Ca$^{2+}$ with the extracellular medium. In skeletal muscle, research on TRP channels has in fact been initiated and driven by the search of the channel responsible for an abnormal influx of Ca$^{2+}$ observed in Duchenne muscular dystrophy (DMD) [1].

DMD is characterized by a progressive and severe muscle degeneration. It follows a progressive loss of strength which is extremely debilitating. We study a mouse model (mdx) of the disease, which, like the patients suffering from Duchenne dystrophy, is deficient in dystrophin, a cytoskeletal protein. Dystrophin makes a physical link between the extracellular matrix and the actin cytoskeleton. Its absence makes the membrane more fragile. Indeed, dystrophic muscle and is particularly sensitive to eccentric contraction (significant loss of strength during repeated muscle contractions accompanied by a lengthening muscle). We have previously shown that the absence of dystrophin also causes an abnormal control of specific membrane ion channels. This results in an increased entry of calcium into muscle fibres which could result in the activation of Ca$^{2+}$-dependent proteases called calpains, cause mitochondrial dysfunction and thus lead to cell death. We showed that among the abnormally regulated ion channels, two isoforms play a particularly important role.

TRPC1 plays a crucial role in muscle function and regeneration [2, 3]. Indeed, we showed that TRPC1 controls the rate of myoblasts migration and their fusion into myotubes and that it modulates PI3K/Akt pathway during myoblast differentiation and muscle regeneration.

The mechanisms of activation of TRPC1 remain poorly understood. It may be activated by the depletion of intracellular stores of Ca$^{2+}$, by a direct phosphorylation or by binding to a second messenger such as diacylglycerol or arachidonic acid (or one of its derivatives). TRPC1 could also be mechanosensitive.

TRPV2 seems sensitive to membrane stretch; we showed that its inhibition protects dystrophic muscle against damage due to eccentric exercise. It clearly plays a crucial role in the pathophysiology of the disease. It seems also involved in osmosensation (fig. 1). Indeed, upon hypertonic challenge, T-tubules dilate, this activates TRPV2 channels that participate to membrane depolarization, release of Ca$^{2+}$ from the sarcoplasmic reticulum and activation of a regulatory volume increase (RVI).

![Graph showing hyperosmotic shock and Ca$^{2+}$ transient](image)

**Fig. 1: TRPV2 is involved in osmosensation.** In normal muscle fibres (a; membranes stained with di-ANNEPS), hyperosmotic shock induces a fast cell shrinkage (CS) followed by a slow RVI. This is accompanied by a large Ca$^{2+}$ transient. In detubulated fibres (b) or in fibres expressing a mutated dominant negative form of TRPV2 (TRPV2DN), both Ca$^{2+}$ transients and RVI were abolished.
TRP CHANNELS AND CELL MIGRATION, CELL DEATH AND PROLIFERATION

TRP channels have been associated with cell proliferation and aggressiveness in several cancers. In particular, TRPC1 regulates cell proliferation and motility, two processes underlying cancer progression.

**Calcium and directional cell migration.**

Ca\(^{2+}\) imaging has revealed that different patterns of Ca\(^{2+}\) transients and gradients across the cell body may provide directional clue for cell migration. In different cancer cell types (pancreatic ductal adenocarcinoma, glioblastoma, prostate adenocarcinoma, rhabdomyosarcoma), we have observed that agonist stimulation (neotensin, δ1 receptor agonist, androgen) modifies cell migration (and in parallel, cell differentiation and/or sensitivity to apoptosis). Previously, in C2C12 cells, we observed that the influx of Ca\(^{2+}\) through TRPC1 channels played an essential role in cell migration.

We now show that TRPC1 is a crucial determinant of directionality of migration of glioblastoma cells in response to the chemotactic agent PDGFR. Preliminary results suggest that stimulation with PDGFR results in TRPC1 channel localization to the leading edge of migrating glioblastoma cells and to its activation.

**Role of TRPC1 in cell proliferation.**

We observed that siRNA-mediated TRPC1 depletion in non small cell lung carcinoma (NSCLC) cell lines induces G0/G1 cell cycle arrest resulting in dramatic decrease in cell growth. The expression of cyclins D1 and D3 is reduced after TRPC1 knock-down, pointing out the role of TRPC1 in G1/S transition. This is associated with a decreased phosphorylation and activation of EGFR and with a subsequent disruption of PI3K/Akt and MAPK downstream pathways. Stimulation of EGFR by its natural ligand, EGF, induces phosphorylation of p44/p42 by MEK1. In the A549 model of NSCLC, MAPK pathway has a minor role in cell cycle progression directly and PI3K via the adaptor protein Gab1. Triggering of the MAPK pathway requires activation of a transduction cascade leading to phosphorylation of p44/p42 by MEK1. In the A549 model of NSCLC, MAPK pathway has a minor role in cell cycle progression, leading to phosphorylation of p44/p42 by MEK1. In the A549 model of NSCLC, MAPK pathway has a minor role in cell cycle progression directly and PI3K via the adaptor protein Gab1. Triggering of the MAPK pathway requires activation of a transduction cascade leading to phosphorylation of p44/p42 by MEK1. In the A549 model of NSCLC, MAPK pathway has a minor role in cell cycle progression.

**Role of [Ca\(^{2+}\)]\(_{ER}\) in autophagy and apoptosis lesson from a model of prostate cancer.**

Reference treatment of advanced prostate cancer relies on pharmacological or surgical androgen deprivation therapy. However, despite initial efficacy of androgen deprivation (AD), the tumor inevitably adapts to low testosterone environment and becomes hormone-refractory (HRPCa). We recently observed in HRPCa cells, that AD or treatment with the anti-androgen bicalutamide promoted autophagy. This effect was associated with an inhibition of the PI3K/Akt/mTOR pathway and with a disruption of the complex formed by androgen receptor and the regulatory subunit of PI3K-Akt.

Autophagy and apoptosis: lesson from a model of prostate cancer.

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ROLE OF TRP CHANNELS IN LEARNING AND MEMORY

TRP channels are largely expressed in the brain, including in the hippocampus where the understanding of their role only begins to emerge.

The hippocampus is a neural structure that is critical for some forms of memory function. It performs this function through the ability of its neurons to fire patterns of activity that encode information and the ability of synaptic connections between neurons to strengthen or weaken. Long-term potentiation (LTP) and its counterpart long-term depression (LTD) are the major forms of long-lasting synaptic plasticity. They have been largely studied e.g. in the Schaffer collateral-commissural pathway between CA3 and CA1 regions of the hippocampus and at the perforant pathway between enthorinal cortex and the dentate gyrus of the hippocampal formation. LTP is predominantly triggered by the synaptic activation of N-methyl-D-aspartate receptor (NMDAR) and involves CaMKII. However, many other cellular mechanisms seem to be involved and could modulate LTP, such as stimulation of metabotropic glutamate receptors (mGluR) expressed presynaptically (mGluR1) or postsynaptically (mGluR) known to be critical in memory consolidation. This increase of expression was observed in both the cortex and the hippocampus. Interestingly, in TRPC1-/- mice, the expression of Arc and zip268 did not change in the hippocampus but well in the cortex, suggesting an abnormal plasticity in the hippocampal formation. LTP is under study (CA1, CA3 and dentate gyrus).

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AWARDS

Prix Madame veuve André Mathys-Bove
Prix ABMM - Association Belge contre les Maladies neuromusculaires

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We and others have previously shown that there is a selective increase in the proportion of lymphocytes expressing IL-17A during a MS relapse (Muls et al, J Neuroimmunol, 2012). Other proinflammatory cytokines were not upregulated during a relapse (IL-17F, IL-21). However, we observed an upregulation of IL-22 mRNA expression levels in relapsing MS patients (Figure 1).

However, when PBMCs are restimulated polyclonally in vitro, no difference in IL-22 expression was measured by flow cytometry between MS patients during a relapse and healthy controls (data not shown). This suggests that the ability of immune cells to respond to a polyclonal antigenic stimulation does not differ between MS patients and healthy controls.

We did not observe a change in the proportion of T regs between MS patients during a relapse and healthy controls by several techniques (flow cytometry or methylation-specific qPCR for the intron 1 of Foxp3). However, CD39 expression was significantly increased in MS patients. CD39 is an ectonucleotidase expressed at the surface of many immune cell types (> 90% of monocytes, neutrophils and B-cells, but also in lesser proportion of T-cells and Nk cells) (Borsellino G et al., Blood, 2007). It hydrolyzes ATP in AMP. As ATP has a pro-inflammatory effect, CD39 mediates an anti-inflammatory effect. Moreover CD39+ T regs are able to suppress Th17 cells (Fletcher J.M. et al., J Immunol, 2009). By flow cytometry, we have been able to show that the proportion of CD4+ and CD8+ T cells expressing CD39 was increased during the MS relapse (Figure 2). The proportion of T regulatory cells (CD4+CD25hiFoxp3+ cells), expressing CD39 is increased in patients versus controls (58.35% versus 35.93%; p=0.024) (Figure 3).

In conclusion, the increased expression of CD39 suggests that immunoregulatory responses are induced during a MS relapse.
Immune biomarkers following treatment by ivMP, IFNβ, GA or Fingolimod

a. Effect of ivMP

CD39 expression is further increased following administration of ivMP (Fig. 4). This was shown ex vivo both at the mRNA and protein level in PBMCs. By flow cytometry, we could show that the proportion of CD39-expressing Tregs (CD4+CD25hiFoxp3+ cells) was increased following ivMP (Figure 4).

In addition to the induction of the anti-inflammatory cytokines IL-10 and TGF-β, CD39 upregulation is a further mechanism induced by corticosteroids to regulate the immune response during a MS relapse. IL-22 expression was unaffected by ivMP treatment (data not shown). Interestingly, mRNA levels of AHR, a transcription factor involved in the expression of both IL-22 and CD39, are induced following treatment by ivMP (Figure 5).

Fig. 4: Ex vivo proportion of CD39-expressing CD4+CD25hiFoxp3+ T-cells in MS before (MS-A) and after ivMP treatment (MS-B), measured by flow cytometry. * indicates a p-value <0.05.

Fig. 5: Ex vivo relative mRNA expression levels of CD39 and AHR in PBMCs from MS patients during a relapse (MS-A), following ivMP treatment (MS-B), compared to healthy controls (Ctrl), measured by qPCR. Results are expressed relative to the mean of the healthy control patients (Ctrl) set at 1. ** and *** indicate respectively p-values of 0.005 and 0.0001.
b. Effect of IFNβ and Glatiramer Acetate on immune markers of MS disease activity and biomarkers of treatment response

First-line disease-modifying therapies (DMTs) are currently available for the MS patients: IFNβ-1a, IFNβ-1b and glatiramer acetate (GA). IFNβ has demonstrated beneficial effects in decreasing the number of clinical relapses and disease activity measured by MRI. The mechanisms of action by which IFNβ produces its therapeutic effects in MS are not yet fully understood, but likely mediated by IFNβ-responsive genes. Moreover, the expression of IFNβ-responsive genes Jak2, IFI6, IFIT1 and MxA was correlated to disease activity (Brynedal B. et al., Neurobiol Dis, 2010; van der Voort L. et al., Neurology, 2010).

IL-22 mRNA expression was increased following treatment by IFNβ but not by GA (Figure 6). This result is again in concordance with a potential immunoregulatory function of this cytokine. We will further investigate the effects of IFNβ or GA on the expression of the immunoregulatory markers CD39 and AHR.

Fig. 6 (i-M): Ex vivo mRNA levels in PBMC of remitting patients. Box plot shows ex vivo mRNA level of IL-21, IL-22, Tim-1, Tim-3 and Tim-4 relative to ABL. The relative cytokine mRNA levels were calculated with, as reference, the mean of healthy controls set at 1. Whisker intervals correspond to the 2.5 and 97.5 percentiles. * and ** indicate respectively p-values of <0.05 and 0.005 using the Mann-Whitney test.
c. Fingolimod

Fingolimod is a sphingosine-1-phosphate receptor modulator approved in the European Union as second line treatment of relapsing remitting MS. Fingolimod acts by inhibiting lymphocyte egress from secondary lymphoid organs. This results in a significant decrease in circulating naïve and central memory T cells, while conversely the proportion of effector memory T cells is increased.

We analysed cytokine expression in patients under fingolimod therapy for three months. IL-17, IL-22 and Foxp3 mRNA levels were reduced in fingolimod-treated patients, but CD39 and AHR mRNA levels were increased (Figure 7). By flow cytometry, we could show that, although circulating Tregs were decreased in PBMCs, they were relatively enriched within the CD4+ T cell subset. This was also the case for CD39-expressing Tregs (Figure 8).

Fig. 7: Ex vivo cytokine expression, measured by qPCR from PBMCs of MS patients before (t0) and 3 months after initiating treatment by fingolimod (t3), in comparison to a cohort of healthy controls. Results relative to ABL are shown. They are expressed relative to the mean of healthy control patients (HC) set at 1. *, ** and *** indicate respectively p-values of <0.05, <0.005 and <0.001.

Fig. 8: Ex vivo proportion of CD39-expressing CD4+CD25hiFoxp3+ T-cells in MS patients before (t0) and three month after starting fingolimod (t3), compared to healthy controls (HC), measured by flow cytometry. * and ** indicate respectively p-values of <0.05 and <0.005.

Conclusion and perspectives

Our work has up to now identified several promising immunoregulatory markers expressed ex vivo during a MS relapse (IL-22 and CD39). Both corticosteroid treatment of a relapse and disease modifying treatments affect the expression of these markers. ivMP treatment potentiates AHR and CD39 expression. Treatment by IFNβ induces not only the known IFN-responsive genes (MxA, IFI6, IFIT1 and JAK2), but also IL-22. Although considered up to now a pro-inflammatory cytokine, novel immunoregulatory functions of IL-22 are being investigated.

We plan to set up an assay for CD39 activity in order to determine the functional relevance of our results. Secondly, we will continue investigating whether ivMP induces CD39 transcription directly or indirectly through AHR activation. An alternative hypothesis could be that IL-35 is implicated in CD39 upregulation upon ivMP treatment (Kochetkova I et al., J Immunol, 2010).

The evidence provided could be of significance to the understanding of the pathophysiological mechanism involved in dysimmune diseases, such as MS. AHR is a transcription factor activated by a number of different environmental (chemical or dietary) and endogenous agents. AHR is therefore a crucial link between environmental factors and host immune function (Lee J.S. et al., Front Immunol, 2012).

ANALYSIS OF SPECIFIC CSF PROTEINS USING A PROTEOMICS APPROACH

A. Dang, Z. Naur, V. Van Peesch, C. Sindic

By means of a high sensitivity and resolution liquid chromatography-mass spectrometry methodology, it is possible to detect up to 2630 proteins in the normal human CSF; of which 56% are CSF specific, not being found in the plasma (Schutzer et al, PLOS, 2010, 5:e10980). There is a large number of low-abundance proteins, and a protein enrichment technique is required to eliminate the most abundant proteins. The ProteoMiner technique of Biorad has been chosen by M. Rider and D. Vertommen and applied on three groups of CSF samples: a control group (N=28), a MS group (N=31) and an Alzheimer group (N=9). We detected certain proteins specific to each group by PCA or logistic regression (C. Bugli and R. Rousseau, Institut de Statistiques, UCL), or other proteins enriched in the pathological groups as shown by their spectral counts.

Work has focused on the 14-3-3 zeta protein, detected uniquely in the CSF samples of Alzheimer’s disease patients. This protein is an attractive biomarker candidate, as its presence has been demonstrated in the neurofibrillary tangles of Alzheimer’s disease patients (Layfield et al, 1996). This protein is known to interact with a number of proteins among which the Tau protein. The 14-3-3 zeta protein might play a role to facilitate the hyperphosphorylation of Tau through the GSK3β kinase (Yuan et al, 2004; Li et al, 2007; Hashiguchi et al, 2000).

Using an anti-14-3-3 zeta monoclonal antibody produced in the laboratory of Y. Nizet, we have screened a series of different CSF samples (Figure 9). In CSF samples, we could mainly detect a dimeric form of the 14-3-3 zeta protein, as confirmed by protein sequencing of the 55 kDa band. A semi-quantitative analysis from Western Blot was performed using the Fusion imaging platform (Figure 10).

No significant differences were detected between the different groups with the exception of 2 cases of neurosarcoidosis, with higher levels of the 14-3-3 zeta protein in the CSF. We are currently optimising the detection of the 14-3-3 gamma protein in the CSF and of the 14-3-3 zeta protein in the serum.

Through our collaboration within the bio-MSeu network, other proteomic analyses have been performed using CSF samples of MS patients (Published references 9 and 10).
SELECTED PUBLICATIONS


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This project was financially supported by the Belgian Charcot Foundation, Bayer Schering and the Walloon Region “Désordres Inflammatoires dans les Affections Neurologiques” project.
The Reelin signaling pathway is important for cortical organization, dendrite growth and synaptic function. As such, it has been involved in lissencephalies, schizophrenia, epilepsy and Alzheimer’s disease. During embryonic development, absence of Reelin results in improper layering of the cerebral cortex and other structures of the nervous system. Therefore, the reelin-deficient mouse presents a good model in which to investigate the mechanisms of establishment of the precise organization of the cortex. The very first steps of the signaling cascade are already known. Its mechanism of action, however, still remains elusive.

The cortex is composed of different types and sub-types of neurons that accumulate into 6 layers according to their birth date. Excitatory neurons, the major type in the cortex, are born in a region called the ventricular zone (VZ) and migrate first as bipolar cells to reach the intermediate zone (IZ) where they start a multipolar migration (slow and characterized by frequent changes in direction). Then neurons resume a bipolar migration (fast and unidirectional) towards a region of the cortex called the cortical plate (CP) where they form synapses with each other (Fig 1).

Reelin is expressed by cells on top of the CP, where excitatory neurons stop their migration. The current model suggests that Reelin instructs neurons to detach from the radial glia fiber on which they migrate and stop their journey after a final somal translocation. However, our recent work has challenged the current model. We showed that the processing of Reelin produces an active central fragment. This fragment diffuses deep into the tissue to reach and affect neurons at the IZ. Briefly, Reelin mediates a new polarizing function that affects multipolar neurons at the IZ before they reach the CP by regulating Rap1 which in turn regulates N-cadherin. Multipolar cells have to move from the lower part to the upper part of the IZ and Reelin triggers this movement. Yet we do not know how N-cadherin allows the polarization of cortical neurons. One of our projects focus on investigating the molecular and cellular mechanisms involved in this particular type of movement of neurons during development which is important for the correct organization and functioning of the adult brain.

Fig1. Migration of GFP labelled excitatory neurons during embryonic development.
A) A population of neurons was labelled for GFP expression and visualized 1, 3 and 11 days after their birth date.
B) Schematic of the different phases of migration of excitatory neurons. Green cells represent neural stem cells and red cells represent neurons.
C) Example of multipolar neurons polarizing their movement under the control of the Reelin/N-cadherin signal. Purple is the expression of a fluorescent protein and green dots (appearing white in purple cells) is a fluorescent labelling for the Golgi apparatus.
MECHANISMS REGULATING EMBRYONIC NEURAL STEM CELL ADHESION, PROLIFERATION AND DIFFERENTIATION

A. Pire, Y. Jossin

During development, embryonic neural stem cells either self-renew or produce neurons, astrocytes or oligodendrocytes. In the developing brain, they are maintained at the ventricular zone (VZ) through adherens junctions (AJs) and undergo an interkinetic nuclear movement, which is an oscillation of the position of their nuclei during the cell cycle (mitosis at an apical position and S phase at the more basal position). However, the function of this movement is not well understood although it is believed to be important for the regulation of cell fate decision. During differentiation, newly generated neurons detach from the apical surface and exit the cell cycle (fig. 2). A tight regulation of the embryonic neural stem cells self-renewal, interkinetic nuclear movement, cell cycle exit, differentiation and delamination of post-mitotic cells is necessary to produce the right number of neurons and glial cells at the right time. Defects in these signaling pathways have been shown to cause abnormal human cortical development such as periventricular heterotopias (characterized by a gray matter abnormally located near the ventricular space) or microcephalies (characterized by a significant reduction in brain size). An important part of our effort is dedicated to the investigation of signaling pathways that control these processes in the embryonic neural stem cells at a molecular and cellular level.

EQUIPMENT

- Mouse surgery
- In utero DNA transfer
- DNA electrophoresis
- Protein electrophoresis
- Western blotting
- RT-PCR
- Cell culture

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Initiation of movements and control of body posture depend on multiple interconnected neuronal networks located in the cortex and in other regions of the encephalon. The activity of these networks eventually converges toward the primary motor cortex wherein primary motor neurons project to multiple nuclei and to the spinal cord and innervate local spinal motor circuitries. Interestingly, whereas cortical networks ensure the initiation of any motor activity, local spinal circuitries autonomously regulate stereotyped aspects of movement including speed, flexor/extensor alternation, rhythmicity and left/right alternation during locomotion.

Spinal motor circuits are composed of motor neurons and of dozens of different premotor interneuron types located in the ventral horn of the spinal cord. Most of these adult premotor interneuron populations arise during development from 4 cardinal classes of embryonic ventral interneuron populations, which progressively diversify into discrete subsets with specific properties and activity. However, the correspondence between these embryonic populations and the dozens of interneuron types described in the adult spinal cord remains elusive. Therefore, we undertook to characterize novel subsets of ventral interneurons in the embryonic spinal cord.

Using an improved labeling technique on whole-mount spinal cords, we demonstrated that these subsets are non-homogeneously distributed along the anteroposterior axis, likely related to their specific contribution to the motor circuitries (Fig. 1). This comprehensive molecular profiling of ventral interneurons provides an important resource for investigating neuronal diversification in the developing spinal cord and for refining our knowledge of the function of each neuronal subset in motor control (2). We also contributed to the discovery of late subsets of V0 and V2 interneurons (5).

**Fig. 1: Anteroposterior distribution of ventral interneuron subpopulations in the developing spinal cord.** Using whole-mount immunofluorescence, we characterized the relative distribution of all the ventral interneuron populations (6hN) and of specific ventral interneuron subsets (here the V0, V1, V2 and V3 populations) in different portions of the embryonic spinal cord (here in the lumbar region). Immunolabeling for Foxp1, which is present in the lateral motor columns, enable to delineate the brachial and lumbar regions.

Mechanisms of Neuronal Differentiation and Migration in the Developing Spinal Cord

The functioning of the CNS relies on the proper activity of thousands of neuronal circuitries that are established during embryonic development. Setting up these circuitries requires acquisition of a specific neuronal identity, migration of differentiating neurons to a defined location within the nervous system and establishment of proper connections with target cells. Destruction of these circuitries as a result of tissue injury or neurodegenerative disorder results in functional impairment of the nervous system. However, cellular and molecular mechanisms that participate in neural development are reactivated in response to neural injury, suggestive of a possible strategy to restrain deleterious outcomes or to repair injured neural tissue. The goal of our research projects is to characterize molecular and cellular mechanisms that control neuronal differentiation, migration and maintenance during embryonic development and to determine whether these mechanisms may be instrumental in treating lesions of the CNS.
ONECUT FACTORS CONTROL THE DEVELOPMENT OF VENTRAL INTERNEURONS

A. Harris, A. Collin, C. Francius, M. Hidalgo-Figueroa, M. Toch, V. Rucchin and F. Clotman
in collaboration with A. Huber, Helmholtz Zentrum München

The transcription factors of the Onecut family, namely HNF-6, OC-2 and OC-3, are transiently expressed in all neurons at the onset of neuronal differentiation. At later stages, they become restricted to multiple well-defined or diffuse neuronal populations dispersed throughout the encephalon and the spinal cord. In the ventral spinal cord, Onecut factors are present in subsets of motor neurons and of each population of ventral interneurons. We recently observed that Onecut proteins are necessary for the diversification of several ventral interneuron populations. As we previously demonstrated for motor neurons (1,8), indeed, in the absence of Onecut factors, some interneuron subsets are not generated. In addition, we uncovered that these factors are required for proper migration of different interneuron populations (Fig. 2). Current investigations aim at identifying the molecular mechanisms whereby Onecut proteins regulate differentiation and migration in the ventral spinal cord.

Furthermore, we observed that neuronal subsets wherein Onecut factors are not detected in wildtype embryos are altered in Onecut compound mutant embryos. This suggests that these transcription factors control a non-cell autonomous mechanism involved in proper spinal cord development. Conditional inactivations of the Onecut genes are in progress to identify the population(s) that mediate this non-cell autonomous control and to determine the molecular mechanisms implicated in this process.

IDENTIFICATION OF A NOVEL POPULATION OF VENTRAL SPINAL INTERNEURONS

C. Francius, M. Hidalgo-Figueroa, S. Debrulle, B. Pelosi, V. Rucchin and F. Clotman, in collaboration with R. Ghou, University of Victoria; S. Malas, University of Nicosia; M. Xiang, Center for Advanced Biotechnology and Medicine; C. Parnas, Brain and Spine Institute

Our expression studies of the Onecut factors in the developing spinal cord unveiled the existence of a yet uncharacterized population of ventral spinal interneurons. These cells start to be generated at very early stages from the p2 progenitor domain. The size of this population is similar to that of the two other major neuronal subsets that arise from this same progenitor domain, namely V2a and V2b. However, they are distinct from these cells in terms of molecular markers, migration pattern and final location. They were temporarily named V2x interneurons. Furthermore, it has been demonstrated that proper generation of V2a and V2b interneurons depends on a binary cell fate decision mediated by the Notch signaling pathway and on different transcription factors including Ascl1 and Foxn4. In contrast, the production of V2x cells is not altered in Ascl1 or Foxn4 mutant embryos nor in embryos deficient in the Notch pathway. Therefore, the developmental determinants of the V2x cells are different from those involved in the generation of other V2 subsets. Hence, we have discovered a yet unknown population of ventral spinal interneurons.

Fig. 2: Onecut factors control the migration of ventral spinal interneurons.
Top: the location of the V2a interneurons, characterized by the presence of the transcription factor Chx10, is altered in the absence of Onecut factors. Bottom: a Matlab routine has been adapted to analyze the relative position of any neuronal population in the spinal cord from a set of successive sections and to determine whether this distribution is statistically abnormal.

We have identified one specific marker of the V2x interneurons. We are currently generating loss-of-function and gain-of-function models to understand the role of this factor in these cells. In addition, we are using intersectional genetics to specifically target these cells during embryonic development and unravel their progeny, their connectivity, their specific properties and their roles in motor control.

ONECUT FACTORS CONTROL THE DEVELOPMENT OF DORSAL INTERNEURONS

K. Kabayiza, G. Magistrino, V. Rucchin and F. Clotman

As observed in the ventral spinal cord, Onecut factors are also present in the developing dorsal interneurons, most of which eventually colonize the dorsal horn of the spinal cord to constitute primary relays for somatosensory information in their transit from the periphery towards the encephalon while others migrate ventrally to eventually integrate into the premotor circuitries. The distribution of Onecut proteins in the dorsal interneuron populations displays a particular spatial and temporal regulation. Indeed, these factors are absent from the dorsalmost populations while their prevalence increases progressively in more ventral cells. In addition, their expression is transient in dorsal populations but progressively more persistent in ventral cells. This suggests that the expression of Onecut factor might be regulated by morphogen gradients or signaling pathways involved in the spatial and temporal patterning of the developing spinal cord (Kabayiza et al., in preparation).

Furthermore, we uncovered that Onecut factors are involved in multiple aspects of the development of dorsal spinal interneurons. In some subsets, Onecut regulates the size of the neuronal population, likely acting in a non-cell autonomous manner on the exit of these cells from the cell cycle. In other populations, Onecut proteins contribute to the diversification of dorsal interneurons by promoting the differentiation into a particular subpopulation at the expense of the others. Finally, Onecut factors control ventral migration of the premotor interneurons that originate from the dorsal spinal cord (Kabayiza et al., in preparation). Experiments are ongoing to identify the molecular mechanisms whereby Onecut exert these different roles in dorsal spinal interneurons.
HNF-6 contributes to the reorganization of Purkinje cells in postnatal cerebellum development. Thus, the Onecut factor interface between the molecular and the granular layer to reorganize as a regular continuous monolayer at the cells were produced normally but part of them failed to reorganize as a regular continuous monolayer at the interface between the molecular and the granular layer of the cerebellum. Right picture shows abnormal superposition of Purkinje cells in a mutant newborn, whereas these cells where absent in other portions of the monolayer.

**Fig. 3: HNF-6 contributes to proper reorganization of the Purkinje cells at the end of cerebellar development.** In Hnf6 mutants, Purkinje cells were produced normally but part of them failed to reorganize as a regular continuous monolayer at the interface between the molecular and the granular layer of the cerebellum.

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Altered control of glutamate transmission by glial cells is one of the key pathogenic mechanisms of amyotrophic lateral sclerosis. Glutamate-mediated excitotoxicity in the cerebral cortex, the brainstem and the spinal cord causes the degeneration of motoneurons which in turn results in muscle weakness in early stages and paralysis at later stages. The impaired uptake of glutamate by astrocytes has been largely documented in the literature and our group has developed research projects aimed at further characterizing this glial dysfunction (1). As the disease also involves neuroinflammation, we have considered the influence of inflammatory mediators on the expression and activity of glial glutamate transporter subtypes.

Using a transgenic rat model of amyotrophic lateral sclerosis, we have previously demonstrated that the progression of the disease is accompanied by a differential regulation of the glutamate transporters isoforms GLT-1a and GLT-1b in several brain structures. Our recent data indicate that these isoforms are differentially regulated by inflammatory mediators (2) (Figure 1). The shorter splice variant GLT-1b contains a PDZ domain known to interact with the scaffold protein PICK1 and we have shown that this protein is also regulated in the context of amyotrophic lateral sclerosis (3,4).

Our group also considers neurotransmitter receptors present on glial cells as putative molecular targets to pharmacologically modulate the expression and activity of glial glutamate transporter subtypes.

Using a transgenic rat model of amyotrophic lateral sclerosis, we have previously demonstrated that the progression of the disease is accompanied by a differential regulation of the glutamate transporters isoforms GLT-1a and GLT-1b in several brain structures. Our recent data indicate that these isoforms are differentially regulated by inflammatory mediators (2) (Figure 1). The shorter splice variant GLT-1b contains a PDZ domain known to interact with the scaffold protein PICK1 and we have shown that this protein is also regulated in the context of amyotrophic lateral sclerosis (3,4).

Our group also considers neurotransmitter receptors present on glial cells as putative molecular targets to pharmacologically modulate the expression and activity of astrocytic glutamate transporters in the context of the disease. Thus, we have herein demonstrated that a lipophilic analogue of the vasoactive intestinal peptide can promote the expression of GLT-1 and improve the survival of transgenic rats (Figure 2). These observations support the proposed link between neuroinflammation and excitotoxicity in neurodegenerative diseases (Goursaud et al., submitted).
REGULATION OF IMMUNE RESPONSES FOLLOWING NERVE LESIONS AND ITS RELEVANCE FOR THE TRANSITION FROM ACUTE TO CHRONIC PAIN

A. Gallo, B. Michot, A. Steyaert, P. Forget, S. van Gorp, P. Lavand’homme, B. Le Polain De Waroux, E. Veyckemans, M. De Kock, E. Hermans

Within this research theme we, together with our clinical colleagues from the Clinique universitaires Saint-Luc and (inter)national collaborators, aim to understand why postoperative pain can become chronic in some cases (10-50% of surgical patients) but spontaneously resolves in other cases. On the basis of clinical studies and animal models we focus our efforts at the immune system which is activated upon surgery. In particular, we study the immune system in the context of so-called vulnerability factors, which are thought to trigger a dysregulation of immune responses following surgery (5).

We and others have previously shown that nerve trauma in peripheral tissues, which occurs in many types of clinical surgical interventions, elicits immune responses in the central nervous system that are very persistent over time (6) (Figure 3). On the basis of studies on genetically modified rats, we obtained evidence suggesting that an imbalance/amplification of immune responses in the spinal cord resulted, on the long-term, in altered immune markers and higher pain scores (7) (Figure 4). These original data demonstrate the importance of controlling the immune response after surgery, not only to reduce early pain, but also to prevent chronic pain after tissue healing.

Work in progress concerns: (i) validating new animal models to investigate the molecular regulation of immune responses in relation to pain chronification or pain resolution, and (ii) pharmacological and cell-based immune modulatory interventions to attenuate or prevent chronic pain.

REGULATION OF G-PROTEIN-COUPLED RECEPTORS SIGNALLING BY INFLAMMATORY MEDIATORS

B. Basier, P. Doyen, M. Vergouts, R. Deumens, J.-M. Maloteaux, E. Hermans

G-protein coupled receptors constitute the largest family of pharmacological targets, in particular in neurosciences. Our group has contributed to develop the concept that the complexity of cell signalling associated with these receptors is larger than initially proposed. One given receptor can couple to several G-proteins and these couplings are influenced by the activating ligand as well as by the cell and ionic environments (8). We here investigate whether the inflammatory environment may alter the functional response to drugs acting on these receptors. Both in vitro, on cultures of glial cells exposed to inflammatory mediators and in vitro, in the spinal cord of animals with peripheral nerve lesions, we characterize the changes in the expression of the receptor or in the availability of signalling partners.

Our recent studies have demonstrated that the expression of the glial metabotropic glutamate receptors mGlu3 and mGlu5 (that act as sensors of the extracellular glutamate) is strongly regulated in response to soluble inflammatory triggers (9). As these regulations are associated with major changes in the associated signalling in astrocytes, our ongoing studies aim at delineating the physiological consequences on the neuroprotective activities supported by these glial cells.

Similarly, we also study the regulation of signalling pathways associated with the CB1 cannabinoid receptor. While presence of this receptor on astrocytes was recently demonstrated (10), we have evidenced regulation of its expression and other signalling partners in the spinal cord of animals with peripheral nerve lesions. Our work aims at characterizing the consequence of these regulations on the analgesic properties of CB1 receptor ligands.
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VIRAL IMMUNITY AND PATHOGENESIS

The possibility for evolved organisms to survive viral infections depends on the ability of their immune system to eliminate the infectious agent. Therefore, numerous mechanisms, involving different types of immune cells such as cytolytic lymphocytes, T helper and B lymphocytes and macrophages, the molecules that allow these cells to communicate, namely the lymphokines, and the products of those interactions, including antibodies, have been elaborated. On the other hand, viral infections strongly modulate the immune microenvironment of the host which often leads to alterations of responses elicited against non-viral antigens and of concomitant diseases with an immune component. Our project is to analyze, in murine models, some aspects of these relations between viruses and the immune system.

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VIRAL INFECTIONS RESULT IN A DRAMATIC INCREASE IN THE PROPORTION OF IGG2A

Of particular interest is the fact that all antibody responses are not equal. Indeed, depending on their isotype, immunoglobulins display various properties, such as differential affinity for receptors expressed on phagocytes. During the last years, we found that the isotype of antibody responses was influenced by concomitant viral infections. The effect of the virus resulted in a dramatic increase in the proportion of IgG2a, not only in antiviral antibodies, but also in immunoglobulins with an antigenic target unrelated to viral proteins. The modulations of antibody responses was analysed with more details by using a model of infection with lactate dehydrogenase-elevating virus (LDV), a common mouse nidovirus that induces strong and early immune responses (1). We could demonstrate that a dual regulation of antibody responses by gamma-interferon (IFN-γ) and interleukin-6 explains this isotypic bias. IgG2a anti-LDV antibodies were found to be more efficient than other isotypes to protect mice against a fatal polioencephalomyelitis induced by the virus (2). However, the modification of the isotype of antibodies reacting with self antigens could potentially lead to more deleterious autoimmune reactions.

T HELPER LYMPHOCYTE ACTIVATION AND DIFFERENTIATION

M. Gaignage, J-P Coutelier

This property of viruses to enhance selectively the production of one immunoglobulin isotype could depend on the preferential activation of a subset of T helper lymphocytes. Indeed, different subpopulations of those cells, called Th1 and Th2, respectively, are distinguished in particular by their capability of producing selectively IFN-γ or interleukin-4, which can selectively trigger B lymphocytes to produce IgG2a or IgG1, respectively. We have found that LDV infection results in a suppression of Th2 responses elicited by immunization with an antigen unrelated to the virus. More recently, other populations of Th lymphocytes, such as Th17 cells that are involved in some autoimmune responses, as well as T regulatory lymphocytes that inhibit ongoing responses have been described. Preliminary observations in our group show a dramatic protection of diseases such as autoimmune encephalitis (Figure 1) and graft-versus-host disease in mice acutely infected with LDV. Whether this protective effect of the virus results from a modulation of T helper/ T regulatory cells differentiation remains to be determined. LDV may also impair antigen presentation and therefore activation of T helper lymphocytes. The disappearance of a dendritic cell subset following infection results in impairment of allogeneic responses. This may explain the preventive effect of the virus on graft-versus-host disease.

Fig. 1. Encephalitis progression in control mice and in animals infected with LDV.
ACTIVATION OF NATURAL KILLER CELLS
M. Mandour, J-P. Coutelier

Many of the influences that viruses may have on diverse immune responses can be explained by the production of pro-inflammatory cytokines, including IFN-γ. Therefore, our analysis of the relationship between viruses and the immune system has focused on the activation, by LDV, of cells from the innate immune system that are able to secrete this cytokine, namely the natural killer (NK) cells. Within a few days after infection, a strong and transient NK cell activation, characterized by accumulation of this cell population in the spleen, by enhanced IFN-γ message expression and production, as well as by cytolysis of target cell lines was observed. Two pathways of IFN-γ production have been observed that both involve NK cells. The first pathway, found in normal mice, is independent from type I IFN and from interleukin-12. The second pathway involves interleukin-12, but is suppressed by type I IFN (3). Because NK cells and IFN-γ may participate in the defense against viral infection, we analyzed their possible role in the control of LDV titers, with a new agglutination assay. Our results indicated that neither the cytolytic activity of NK cells nor the IFN-γ secretion affect the early and rapid viral replication that follows LDV inoculation.

Interestingly, NK cell activation results in an increased expression of CD66a (CEACAM-1), an adhesion molecule that display immunoregulatory function on activated T lymphocytes. However, this enhanced expression, that is also found on immature NK cells, results from NK cell stimulation with IL-12 and IFN-γ. This increased susceptibility of LDV-infected mice to endotoxin shock was not mediated by modulation of the expression of membrane receptors for LPS, but correlated with increased levels of soluble LPS receptors (6). In this context, the production of type I IFNs may protect the host against exacerbated pathology by controlling the production of IFN-γ.

Virtually-induced macrophage activation leads also to an enhanced phagocytic activity, with potential detrimental consequences for ongoing autoantibody-mediated autoimmune diseases. LDV infection resulted in moderate thrombocytopenia in normal animals through enhanced spontaneous platelet phagocytosis (7). We have analysed whether a viral infection could modulate an antibody-mediated autoimmune disease induced by mouse immunization with rat platelets (8). In mice treated with anti-platelet antibodies at a dose insufficient to induce clinical disease by themselves, infection with LDV or mouse hepatitis virus was followed by severe thrombocytopenia (9). Similarly, administration of anti-erythrocyte monoclonal autoantibody to mice resulted in the development of a transient hemolytic anemia that was dramatically enhanced by a simultaneous infection with LDV, leading to the death of most animals. This viral infection induced an increase in the ability of macrophages to phagocytose in vitro autoantibody-coated red cells, and an enhancement of erythropagocytosis in the liver (10).

Treatment of thrombocytopenic or anemic mice with clodronate-containing liposomes and with total IgG indicated that opsonized platelets and erythrocytes were cleared by macrophages. Administration of clodronate-containing liposomes decreased also the in vitro phagocytosis of autoantibody-coated red cells by macrophages from LDV-infected animals. The increase of thrombocytopenia triggered by LDV after administration of anti-platelet antibodies was largely suppressed in animals deficient for IFN-γ receptor. Moreover, LDV infection resulted in an increased expression of receptors recognizing the Fc portion of antibodies, which may at least partially leads towards the enhanced phagocytic activity of macrophages. Together, these results suggest that viruses may exacerbate autoantibody-mediated thrombocytopenia and anemia by activating macrophages through IFN-γ production, a mechanism that may account for the pathogenic similarities of multiple infectious agents.

Together, these models may correspond to the development of some auto-immune diseases: a first stimulus triggers the production of autoantibodies, through molecular mimicry. A second stimulus, such as a viral infection, leads to the activation of macrophages and results in the destruction of opsonized target cells.

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Researchers within the Systems & Cognitive Neuroscience division (COSY) of the Institute seek to understand the neural mechanisms underlying perceptual, cognitive and motor processes at the level of the whole organism.

More than 26 senior scientists and a total of about 80 researchers are affiliated to COSY. Our research interests include the neural mechanisms of numerical and social cognition, sensori-motor coordination, motor control, spatial attention, representation of time and expectation, sensory plasticity, impact of early visual defects on late development of cognitive functions, language and gesture understanding and production, semantics, pain, face recognition, the dynamics of object grasping, psychometry, neuro-rehabilitation, biomechanics of locomotion, and neural interfaces.

Our research relies on a wide range of methods and techniques available locally or through national and international collaborative networks: functional magnetic resonance imaging (fMRI), evoked potentials and electroencephalography (ERPs, EEG), transcranial magnetic stimulation (TMS), recordings of eye movements, mental chronometry and electromyography. These methods are complemented by neuropsychological studies of brain-damaged patients.
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ALGOLOGY

Using behavioral measures and non-invasive functional neuroimaging techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), the main objective of our research is (1) to improve the understanding of the physiology and pathophysiology of pain in humans. Progress in understanding the neural representation of pain is not only important for basic neuroscience. Indeed, it is also critical to develop effective strategies for the diagnosis and management of pathological pain conditions, in particular, chronic neuropathic pain. To explore these questions, we have developed a number of novel methods to identify and characterize neural activity specifically related to nociception, such as the recording of steady-state evoked potentials and, more recently, the combination of EEG and fMRI with transcranial magnetic stimulation to characterize activity-dependent changes in cortical excitability and functional connectivity. Building on these methodological developments, we also explore the cortical mechanisms involved in (2) vibrotactile and active touch, (3) olfaction and (4) multisensory integration and sensorimotor synchronization.

NOVEL APPROACHES TO TAG CORTICAL ACTIVITY SPECIFIC FOR NOCICEPTION

E. Colon, A. Mouraux

Studies have shown that the repetition of a stimulus may induce, at certain frequencies of stimulation, a sustained electro-cortical response of corresponding frequency, referred to as steady-state evoked potentials (SS-EPs). Unlike event-related potentials (ERPs), which reflect phasic cortical activity triggered by a transient stimulus, SS-EPs reflect sustained cortical activity triggered by a wave of repetitive stimuli. In other sensory modalities, it has been shown that SS-EPs result from an entrainment of neuronal populations responding to the stimulus at the frequency of stimulation, originating mainly from early, sensory-specific cortices. In this project, we explore and characterize, for the first time, SS-EPs elicited by the rapid periodic stimulation of cutaneous nociceptors. Two different approaches have been developed to generate the required periodic nociceptive input. The first relies on infrared CO2 laser stimulation of heat-sensitive skin nociceptors (Figure 1). The second relies on direct intra-epidermal electrical stimulation of nociceptive free nerve endings using a needle cathode surrounded by a cylindrical anode. We have shown that consistent nociceptive and non-nociceptive SSEPs can be recorded using a wide range of stimulation frequencies (3–43 Hz). The magnitude, scalp topography and temporal dynamics of the obtained responses are distinct from those elicited by non-nociceptive vibrotactile stimulation (Figure 2). Whereas non-nociceptive vibrotactile SS-EPs are maximal over the parietal region contralateral to the stimulated side, nociceptive SS-EPs are maximal at the scalp vertex and symmetrically distributed over both hemispheres. This indicates that nociceptive and non-nociceptive SS-EPs reflect the entrainment of distinct neuronal populations and, hence, that they could constitute a promising mean to study the cortical processes specifically involved in nociception and the perception of pain. Furthermore, because SS-EPs can be used to “frequency tag” the activity elicited by several, concurrently applied streams of sensory stimuli, we are now exploiting this approach to study the interactions and integration of nociceptive and non-nociceptive sensory inputs.

Fig. 1: Rapid periodic stimulation of skin nociceptors can be used to elicit nociceptive steady-state evoked potentials (SS-EPs). Here, CO2 laser stimulation was applied to the hand dorsum. A. In this first setup, a computer-controlled laser targeting system is used to rapidly displace the target of the CO2 laser stimulus after each pulse, such as to avoid skin overheating and nociceptor habituation or sensitization. B. In this second setup, the continuous adjustment of laser power as a function of an online measurement of target skin temperature is used to generate a rapid and controlled oscillation of skin temperature at a given frequency.
QUESTIONING THE FUNCTIONAL SIGNIFICANCE OF THE “PAIN MATRIX”

G. Liberati, V. Legrain, A. Mouraux

Neuroimaging and neurophysiological studies have shown that transient nociceptive stimuli elicit responses in an extensive cortical network including somatosensory, insular and cingulate areas, as well as frontal and parietal areas. A long-standing view in the field of pain research has been that this network, often referred to as the “pain matrix”, represents the neural activity through which pain emerges as a percept. We have performed a number of studies challenging this interpretation. First, we conducted a number of experiments showing that pain intensity can be entirely dissociated from the magnitude of the responses in the so-called “pain matrix”, and that the magnitude of the elicited brain responses are strongly influenced by the context within which the stimulus appears, in particular, stimulus novelty. Second, using EEG (Figure 3) and fMRI (Figure 4), we showed that non-nociceptive stimuli as well as stimuli not perceived as painful can elicit cortical responses having a spatial distribution that is indistinguishable from that of the “pain matrix”. For these different reasons, we proposed an alternative view of the functional significance of the “pain matrix”, in which it would reflect a system involved in detecting, orienting attention towards, and reacting to the occurrence of salient sensory events. Furthermore, we postulated that this cortical network might represent a basic mechanism through which significant events for the body’s integrity are detected, regardless of the sensory channel through which these events are conveyed.
Although there is a general consensus that this is crucial to understand how chronic pathological pain is represented in the human brain, very few studies have explored the cortical responses induced by sustained noxious input. Importantly, the cortical activity elicited by such stimuli could be very different from the cortical activity triggered by the sudden onset of a transient noxious stimulus. Hence, to gain an understanding of the cortical representation of clinically relevant pain, it appears crucial to shift towards novel experimental approaches to characterize, in humans, the cortical activity induced by sustained noxious input. Furthermore, several recent studies have suggested that the perception of pain, like any complex experience, does not result from the activity within a specific brain structure but, instead, emerges from the flow and integration of neural activity within a network of interconnected brain areas. The aim of this project is thus to develop new approaches to characterize the functional connectivity, interdependency and hierarchical organization of the different brain regions responding to noxious input. Recent studies have suggested that the combination of transcranial magnetic stimulation (TMS) with EEG and fMRI could constitute a novel non-invasive tool to measure directly the functional connectivity between two brain regions. Specifically, by delivering a single pulse of TMS over a given brain region and by concomitantly sampling the activity elicited by the TMS pulse in other brain areas using EEG and fMRI, we postulate that it is possible to obtain a direct index of the cortical excitability and effective connectivity between brain regions (Figure 5). In this project, we develop this technique to characterize the changes in brain function induced by sustained experimental pain (e.g. high frequency electrical stimulation) and chronic pathological pain (e.g. chronic post-operative pain).
COGNITIVE ASPECTS OF NOCICEPTION AND PAIN

V. Legrain

Pain is a complex perceptive phenomenon depending not only on physical properties of nociceptive stimulation but also on the emotional and cognitive state of the subject. It is believed that the central nervous system has mechanisms to modulate pain and to detect and respond to external threats. Attention plays a major role in these functions. Focusing attention away from nociceptive input decreases nociceptive processing and pain.

Electroencephalographic studies have shown that focusing attention away from nociceptive input or away from the location where nociceptive input is applied decreases the brain responses elicited by nociceptive stimulation already at very early processing levels in somatosensory cortices (top-down attention). On the other hand, other attentional mechanisms under control of the anterior cingulate cortex allow attention to be involuntarily attracted by pain itself in order to allow reaction to a potential threat (bottom-up attention). The modulation of pain thus appears to be influenced by a fine balance between different cognitive processes. Acting on these processes through psychological manipulations could constitute a novel mean to reduce the experience of pain in patients. For example, we have shown that involving subjects in a task that requires maintaining pain-unrelated information in working memory reduces the perception of pain, probably because the content of working memory defines the aims and the features of the attended information during the achievement of cognitive activities. Furthermore, we have shown that this attentional control of pain requires a high attentional load to narrow attention on the processing of task-relevant information. On the contrary, under low attentional load, information processing is less selective; distractors will also be perceived and their ability to gain control over cognitive activity will depend on the ability of executive functions to inhibit the attentional capture by pain.

MULTISENSORY INTEGRATION, BODY REPRESENTATION AND SPATIAL PERCEPTION

L. Filbrich, D. Torta, A. Mouraux, V. Legrain

The ability to localize nociceptive stimuli is important because it allows the detection of which part of the body is potentially threatened. It is also of primary importance to identify in external space the spatial position of the object that might be the cause of damage in order to prompt and to guide defensive motor responses towards the location of the threat. These considerations underline the importance of coordinating the representation of the body space and the representation of external space. It is believed that the brain takes into account different frames of reference when coding the spatial position of sensory information (Figure 6). One frame of reference is the anatomical reference, based on the existence of a spatial organization of sensory receptors in receptive fields which project to spatially-segregated populations of neurons. For example, the primary somatosensory and motor cortices are somatotopically organized and, thereby, contain a spatially organized representation of the cutaneous surface of the body. However, this frame of reference alone cannot integrate the perception of which part of the body is stimulated and the perception of the position of external objects in contact with the body. In other words, defensive motor responses cannot be spatially guided towards the threat efficiently if the position of nociceptive stimuli is not remapped according to both the position of the stimulated body part and the position of the threatening object in external space. The personal reference frame of reference is of particular interest because it allows integrating the body space and the space surrounding it. Indeed, this frame of reference allows coding the position of somatosensory stimuli on the body space and the position of external stimuli, e.g., visual or auditory stimuli, occurring close to the body. Using behavioural measures and EEG, our project aims to characterize the brain mechanisms underlying the building of a multisensory representation of personal space that integrates nociceptive inputs in order to localize physical threats. Using a neuropsychological approach we also plan to explore how chronic pain affects the representation of the body and personal space, functions to inhibit the attentional capture by pain.

NOVEL APPROACHES TO ASSESS OLFACTORY FUNCTION AND DYS-FUNCTION IN HUMANS

C. Huart, P. Remboux, A. Mouraux

Compared to other sensory modalities, the physiology and pathophysiology of olfaction remains poorly explored in humans. Yet, olfactory disorders are common in the general population, affecting up to 20% of the population. Over the recent years, the recording of ERPs triggered by the transient presentation of odors has been receiving strong and increasing interest. The approach is not only of interest for basic researchers aiming to characterize the cortical representation of odors in humans. Indeed, it is also of great interest for clinicians currently needing objective and robust tools to diagnose disorders of olfaction. Unfortunately, olfactory chemosensory ERPs exhibit a very low signal-to-noise ratio. Hence, although the technique is recognized as having great potential, its current usefulness remains very limited, particularly in the context of clinical diagnosis. In a first study, we hypothesized that the low signal-to-noise ratio of chemosensory ERPs could at least in part be due to an important amount of temporal jitter affecting the brain responses to chemosensory stimulation, itself due to the number of steps required for transduction of the chemosensory stimulus into a neural impulse. Therefore, we developed an approach to reveal olfactory EEG responses that are not strictly phase-locked to the onset of the stimulus, using a method based on the continuous wavelet transform (Figure 7). We found that this approach significantly enhances the signal-to-noise ratio of the elicited responses, and discloses an important fraction of the cortical activity to chemosensory stimulation that is lost by conventional time-domain averaging. By providing a more complete view of how odors are represented in the human brain, this approach could constitute the basis for a robust clinical tool to assess olfaction in humans. In a second study, based on the assumption that early neurodegeneration in Alzheimer’s disease is asymmetrical and that olfactory input is primarily processed in the ipsilateral hemisphere, we assessed whether unihemispheric and electrophysiological assessment of olfactory function can contribute to the diagnostic workup of mild cognitive impairment (MCI). We found that MCI patients exhibit a marked asymmetry of olfactory function, which could serve as a non-invasive biomarker for the early diagnosis of AD.
MUSICAL RHYTHM AND FREQUENCY TAGGING TO STUDY THE NEURAL DYNAMICS OF MULTISENSORY BINDING AND SENSORIMOTOR SYNCHRONIZATION

S. Nozaradan, A. Mouraux

To gather information from the environment, we most often explore it through movement, and these exploratory movements are thought to shape the processing of sensory inflow. Because exploratory movements are often rhythmic in nature, it has been suggested that movement-perception shaping is supported by some form of movement-induced neural entrainment.

In this project, we exploit the unique context of musical rhythm and beat perception to study the neural dynamics of multisensory binding and sensorimotor synchronization in the human brain. Feeling the beat in music refers to the spontaneous and universal ability to extract temporal periodicities from rhythms, i.e. stimuli that are not strictly periodic in reality. Through several models, theorists have hypothesized that beat perception is supported by an entrainment of neuronal populations at the frequency of the beat. This neuronal entrainment would allow the binding of distant cortical areas through synchrony of their activity. To study this phenomenon, we have developed a novel approach based on the recording of SS-EPs. Using this approach, we were able to show that musical beats induce a widespread neuronal entrainment that can be captured directly in the human EEG, in the form of an SS-EP appearing at the frequency of the beat (Figure 8). Furthermore, we showed that temporally-congruent auditory and visual beats, as compared to incongruent auditory and visual beats, elicit markedly enhanced SS-EPs, due to an increased phase coherence of their activities. Finally, we showed that moving to the beat is related to an enhanced synchronization of sensory- and movement-related SS-EPs. In collaboration with Pr. L. Maillard (CHU Nancy), we have recently implemented our approach to intracranial recordings performed in epileptic patients. This allowed us to demonstrate that beat perception involves a selective neural entrainment occurring already in the primary auditory cortex (Figure 9). Taken together, these different studies indicate that the coherent integration of multisensory inputs having matching temporal dynamics, as well as the synchronization of movement to the temporal dynamics of a sensory stimulus is subtended by a « binding by synchrony » of the dynamic activity of distant cortical areas.
sensory and motor activities. In turn, body representa-
tion is shaped by our sensory-motor experiences. Body
representation is a complex theoretical concept as it
embraces many different aspects. However, it has
been shown to be clinically relevant, since clinicians
have been confronted to this complexity through a
large variety of disorders, mostly consecutive to brain
lesions. Recently, it has been shown that chronic situa-
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This project is conducted within the frame of a
multi-partner European project (Marie Curie Initial
Training Network PROTOTOUCH), focusing on the
development of (1) novel techniques to generate tactile
sensations such as the perception of textures (2) novel
approaches to explore the neurophysiological mech-

system and (3) novel signal-processing methods and
computational neuroscience techniques to character-
ize the neural encoding of the tactile input generated
by finger interactions with tactile displays. It is increa-
singly recognized that the active perception of textures
emerges from the vibrations induced by sliding the
finger on the textured surface. Here, we will use a joint
time-frequency analysis of EEG signals to characterize
the temporal dynamics of the brain response induced by
the dynamic exploration of textured surfaces. Methods
based on the recording of steady-state evoked
potentials will be used to isolate and characterize the
cortical activity elicited by simple textures such as gra-
tings in the frequency domain.

BODY REPRESENTATION AND SENSORY-MOTOR FUNCTIONS

S. Hatem, Y. Bleyenheuft, V. Legrain

How we mentally represent our body influences
sensory and motor activities. In turn, body representa-
tion is shaped by our sensory-motor experiences. BODY
representation is a complex theoretical concept as it
embraces many different aspects. However, it has
been shown to be clinically relevant, since clinicians
have been confronted to this complexity through a
large variety of disorders, mostly consecutive to brain
lesions. Recently, it has been shown that chronic situa-
tions affecting sensori-motor functions also modify
cognitive abilities to perceive and represent the body.
The aim of the present project is to determine and
characterize specific deficits of body representation in
various sensori-motor affections such as chronic pain,
hemiparesis and cerebral palsy. The aim of this project
is also to develop a multidisciplinary approach of sen-
sory-motor rehabilitation by defining a common fra-
mework between physiotherapy and neuropsychology.

NOVEL APPROACHES TO STUDY THE CORTICAL REPRESENTATION OF ACTIVE TOUCH AND THE PERCEPTION OF TEXTURES IN HUMANS

A. Klöcker, A. Moungou, J.-L. Thonnard, A. Mouraux

This project is conducted within the frame of a
multi-partner European project (Marie Curie Initial
Training Network PROTOTOUCH), focusing on the
development of (1) novel techniques to generate tactile
sensations such as the perception of textures (2) novel
approaches to explore the neurophysiological mech-

equipment

• High speed 64-channel EEG systems
• Experimental power-regulated CO2 laser with
computer-controlled targeting device to selecti-
vely activate heat-sensitive cutaneous nociceptors
• Experimental MR-compatible CO2 laser stimula-
tor with a built-in high-speed radiometer allowing
an online adjustment of skin temperature at target

Sensory-motor rehabilitation by defining a common fra-
album of activity for each sense

selected publications

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The role of working memory in the attentional control of

SELECTED PUBLICATIONS

FUNDING

• AUL. Marie Curie incoming post-doctoral fel-
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• FNRS
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• Programme CWAListy « NEUROSENSE »
• FWO (Research Foundation Flanders)
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AWARD

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ANTICIPATION AND ITS TROUBLES

My research activity is devoted to the study of anticipatory eye movements. In order to better understand the neuronal bases of anticipation, behavioral and electrophysiological experiments are realized. The role of the cortical region referred to as the ‘Supplementary Eye Field’ in anticipation is investigated with electrophysiological methods (single neuron recordings, EEG). Moreover, we also carry out an important set of behavioral studies in Parkinson’s disease patients. The dual approach consisting in studying fundamental processes in healthy subjects and at the same time doing experiments with Parkinson’s disease patients is particularly fruitful and improves our understanding of anticipation and temporal cognition in health and disease.

DOPAMINE AND TEMPORAL EXPECTATION

I. Ameqrane, M. Missal

The goal of this project is to better understand the role of dopamine in temporal expectation using anticipatory eye movements as a tool. Anticipatory eye movements are analyzed in Parkinson’s disease patients during a task where events can be predicted on the basis of temporal information. In an animal model, injections of dopaminergic agonists and/or antagonists in the dorsal striatum will help us better understand the role of that structure in temporal cognition and anticipation.

NMDA RECEPTORS AND TEMPORAL EXPECTATION

I. Ameqrane, M. Missal

The goal of this project is to better understand the role of NMDA receptors in temporal expectation using anticipatory eye movements as a tool. Anticipatory eye movements are analyzed during a task where events can be predicted on the basis of temporal information. In an animal model, injections of subanaesthetic doses of ketamine will help us better understand the role of NMDA receptors in temporal cognition and anticipation.

Fig. 3. Schematic of the causality paradigms. A.1–4, Time course of experiment 1. At trial onset, the tool octagon appeared (A.1). After 500 ms, the two stationary reaction targets appeared adjacent to the tool, as well as the launcher target which moved inward from the periphery (A.2). After an additional 370 ms the launcher contacted the tool (A.3). Immediately (standard trials) or 100 ms after the collision (delay trials), one of the reaction targets moved toward the periphery at the same speed as the launcher (A.4a,b). In causal trials, the target directly opposite the launcher was the one that moved (A.4a). In noncausal trials, the target orthogonal to the path of the launcher moved (A.4b). Solid arrows indicate a current movement; dashed lines indicate a previous movement. Subjects were instructed to fixate the tool initially, then to track whichever reaction target moved after the collision. B, Stimulus layout used for experiment 2. The launcher target approached at an oblique angle. After the collision, the single reaction target moved in one of the two directions indicated (50% probability for each). There were no time-delay trials, but during no-tool blocks the octagonal tool was not visible. The fixation interval was also slightly longer (750 ms).
causality perception emerges from neuronal activities. Recordings will be performed to better understand how "reaction" target. EEG recordings and single neuron cher impacts a tool to trigger the motion of a second measured while viewing a display in which a laun-
Therefore, eye movements of human observers are measured while viewing a display in which a laun-
ch on the neuron bases of causality perception are unknown. Although est-
lished as a perceptual and linguistic concept, the two events occurred independently. Although es-

When viewing one object move after being struck by another, humans perceive that the action of the first object caused the motion of the second, not that the two events occurred independently. Although est-
sults, the perception of causality can be biased by various factors including perceptual evidence, biomechanical constraints, personal goals, contextual rules or the expected outcome of actions. A number of current projects are concerned with the study of how these factors are integrated during action selection and the role of inhibitory mechanisms during movement planning in this context.

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- FRSM - Fund for Scientific Medical Research

**SELECTED PUBLICATIONS**


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**COGNITION AND ACTION**

Our research mostly focuses on the neural correlates of complex motor behavior in humans. Most daily life situations require making decisions about actions. The fluid and flexible manner with which we make such decisions indicates the operation of a selection process that takes into account multiple factors including perceptual evidence, biomechanical constraints, personal goals, contextual rules or the expected outcomes of actions. A number of current projects are concerned with the study of how these factors are integrated during action selection and the role of inhibitory mechanisms during movement planning in this context.

Besides, another important research topic of our group revolves around the mechanisms by which the brain copes with the limited resources that are available to a living organism, being computational, energetic or otherwise. This encompasses our previous research topics, namely effort-based decision making, which consists in the processes involved in minimizing the cost of our decisions, and especially in the context of Parkinson disease but also mental fatigue, which can be viewed as a consequence of an excess of mental effort investment, visual selective attention, a process dealing with the allocation of limited visual resources to the most potentially relevant information, habitual learning, a process allowing us to learn how to behave in a complex environment while saving computational resources and finally, chunking, a mechanism originally viewed as a strategy aimed at reducing working memory load, but operational in many other behaviors, including sequence learning, language and perception.
INHIBITORY CONTROL OF ACTIONS

P-A Klein, C. Petitjean, J. Duqué

A central idea emerging from our work is that there are two distinct neural inhibitory mechanisms that shape activity of the motor system during the planning of actions. These mechanisms shape neural activity of potential action representations with different computational purposes. The first mechanism is directed at the motor representation of selected actions, helping to prevent the premature initiation of movements. As such, this mechanism referred to as “inhibition for impulse control (IC)”, controls when the execution of a selected response should be released. The second mechanism, referred to as “inhibition for competition resolution (CR)”, is more related to the action selection process. It helps to sharpen competitive selection processes, favoring the suppression of inappropriate action representations. Hence, this second mechanism helps to specify what response should be produced. Recently, we have shown that these two inhibitory mechanisms operate at different levels of the motor pathways, even though they produce similar effects on global measures of CS excitability. IC modulates spinal excitability, allowing cortical preparatory processes to operate without triggering premature movement, whereas CR arises exclusively from cortical interactions. IC and CR also mobilize separate brain regions in the frontal cortex, respectively the premotor and the lateral prefrontal cortex, consistent with their different functional contribution to action planning. Additionally, we have shown that the strength of these motor inhibitory effects varies according to the task demands; they are strengthened when action selection occurs under situations of conflict, probably through top-down influences originating in pre-supplementary motor area (pre-SMA). Finally, because an emerging view in the addiction literature is that impulsivity may be central to the development and aggravation of an addiction and because self-control is thought to rely on the ability to inhibit inappropriate motor responses, we have started to evaluate CR and IC in alcohol-dependent patients. The main working hypothesis of our work is that the compulsive behaviour to obtain drug (e.g. alcohol) that characterizes the state of addiction may be due to a deficit in inhibition and deficient top-down control over these processes, resulting in an inability to resist the urge of highly attractive drug cues.

Fig.1: Schematic representation of two mechanisms of inhibition during selection of a right hand response. Inhibition for competition resolution (CR) reduces activity of non-selected representation at the cortical level, possibly through interhemispheric inhibitory interactions. Inhibition for impulse control (IC) reduces the activity of selected response representations at the spinal level.

INTEGRATION OF REWARD DURING ACTION SELECTION

A. Zénon, P.-A. Klein, A. Alamia, J. Duqué

When people make decisions, they tend to choose actions that are associated with the most rewarding outcome. Starting from this basic observation, we recently examined how this leaning is reflected in the neural pattern of motor activations during action selection. We applied transcranial magnetic stimulation (TMS) over the primary motor cortex (M1) to assess corticospinal (CS) excitability associated with a motor response while the participants performed a task in which they had to select among left and right hand button-presses depending on a visual cue. Each trial was followed by a feedback screen on which a monetary score was displayed. This score was biased to favor one particular button-press. The participants never became aware of this bias but choose the more rewarding option more often and were also faster on these trials. More importantly, CS excitability of the motor response associated with the most beneficial outcome was larger at the onset of the selection process and increased faster from then on. The question remains as to whether this regulation of motor activity is critical for the action selection process itself. A first possibility is that CS excitability of motor representations constitutes the information on the basis of which the choices are made. Following this line of thought, motor decisions would directly emerge from the regulation of motor activity. A second possibility is that the reward-related changes in CS excitability are not critical for the selection process itself: they could serve to pre-activate motor plans, allowing a prompt initiation of selected actions once the decision has been made. These two postulates were recently investigated in a follow-up experiment in which we used a modified version of the above-mentioned task combined with continuous theta burst TMS applied over M1; this procedure allowed us to induce a “virtual lesion” of M1. We hypothesized that, if M1 is critical for decision making, its “virtual lesion” should affect the ability of subjects to make reward-based decisions. Consistent with our hypothesis, we found that a virtual lesion to M1 altered the subjects’ performance, raising stimulating questions on the role of this area for future experiments.

Fig.2: A: Location and orientation of two TMS coils in one of our experiments (Duque et al., 2012). A single pulse transcranial magnetic stimulation (TMS) coil is applied over the primary motor cortex (M1) and the repetitive TMS (rTMS) coil on the dorsal premotor cortex (PMd, left), lateral prefrontal cortex (LPP, middle) or medial postcentral sulcus (PCs, right) in separate sessions on different days. B: Actual MNI (Montreal Neurological Institute) coordinates of the stimulation sites.

A: Schematic illustration of our results in a recent experiment. Motor excitability (as measured using motor-evoked potentials, MEPs) associated with a “to-be-selected” response was up-regulated when this response was associated with a larger reward (biased condition), compared to a neutral situation. B: Illustration of behavioral results in a task used to assess the impact of reward on behaviour and motor excitability. Subjects were instructed to perform left or right key-presses according to the colour (blue or red, respectively) of an imperative signal. The latter was also sometimes ambiguous (greyish circle). Hence, subjects had to respond at “random” on a proportion of trials (ambiguous trials). A monetary reward was provided after each response and was either equal or higher for left than right hand responses (neutral and biased conditions, respectively). Note the significant rightward shift of the sigmoid curve in the biased condition, reflecting an increased preference for left hand responses in that condition compared to the neutral one.
SELECTIVE ATTENTION AND RESPONSE SELECTION DURING MOTOR DECISION MAKING

Klein P-A., Zénon A., Duque J.

On many occasions, multiple stimuli in the environment compete for attention and action. Given this, we continuously have to attend to and act towards stimuli which are the most compatible with the current context, while refraining from selecting less relevant, yet possibly appealing, options. Decision-making involves at least two major interrelated processes. The first one, called “selective attention”, biases competitive interactions between sensory stimuli by favouring processing information that is relevant to specific behavioural goals while ignoring irrelevant stimuli in the environment. The second process, “response selection”, is associated with the accumulation of activity in competing response representations so as to ensure that only activity related to the most beneficial action reaches threshold and is selected. In an ongoing project, we combined a version of the Flanker task (involving congruent and incongruent trials) with the electroencephalography (EEG) methodology to study the interactions between “selective attention” and “response selection” processes. Selective attention and response selection processes were assessed by recording steady-state visual evoked potentials (SSVEP, central and distractor arrows flicked at different frequencies) and current source density (CSD) measures over the contralateral and ipsilateral motor representations. As expected, response times and error rates were larger in incongruent compared to congruent trials. However, this difference was attenuated in a context when the participants had expected conflict to occur between the response alternatives (Mostly Incongruent [MI] blocks, see figure), probably because control mechanisms were recruited in this context to help sharpen selective attention and to facilitate response selection. Our EEG data support this hypothesis. As such, the SSVEPs indicate a larger processing of the central arrow when conflict is expected. This increased selective attention in the MI blocks was associated with specific changes in the CSD signal.
EFFORT-BASED DECISION MAKING

Disrupting the Supplementary Motor Area makes physical work appear less effortful.

Zénon A., Olivier E.

Effort perception, instead of relying on sensory afferences as originally thought, could originate from a copy of the motor command processed by sensory areas. In the current study, we tested this hypothesis and attempted to uncover the precise origin of this efference copy. We disrupted neural activity in the supplementary motor area (SMA) by means of continuous theta-burst transcranial magnetic stimulation (cTBS) while measuring, by different implicit and explicit methods, how participants perceived physical efforts of varying intensities. We found that disruption of the SMA, but not of the primary motor cortex or a visual control site, led to a decrease of all our behavioral and psychophysiological measures of effort perception. These findings indicate that SMA is at the origin of the efference copy involved in effort perception; it also shows that the perception of physical exertion can be non-invasively manipulated.

PUPIL SIZE VARIATIONS CORRELATE WITH PHYSICAL EFFORT PERCEPTION

Zénon A., Olivier E.

It has long been known that the diameter of the pupil increases during mental activities in proportion to the difficulty of the task at hand. However, it is still unclear whether this relationship between pupil size and effort applies also to physical effort. In order to address this issue, we asked participants to perform a power grip task while evaluating their effort both implicitly and explicitly, and monitoring pupil size concurrently. We found that pupil diameter increased during physical effort and that the magnitude of this response reflected the subjects’ perception of the effort intensity. This finding indicates that pupil size signals the level of effort invested in a task, irrespective of whether it is physical or mental. It also helps refining the potential brain circuits involved since this result implies a convergence of mental and physical effort information at some level along this pathway.

THE SUBTHALAMIC NUCLEUS SIGNALS THE VALUE AND COST OF DECISIONS IN PARKINSON’S DISEASE PATIENTS

Zénon A.

Recent studies have suggested that an inadequate evaluation of the cost-benefit ratio of actions in Parkinson Disease (PD) leads to a suboptimal allocation of resources, which would be responsible for bradykinesia. Here, we tried to determine the extent to which variables that are critical to cost-benefit computation can be identified in the neural activity of the Subthalamic Nucleus (STN). We recorded local field potentials in the STN of 12 PD patients implanted with deep brain stimulation electrodes, both ON and OFF dopamine replacement therapy, while they were performing an effort-based decision making task. We found robust responses to the different visual cues in the STN and these responses were strongly modulated by reward, effort and choice variables. Responses in the beta range of frequency were inversely proportional to the probability of choosing to execute the effort whereas gamma range activity signalled the onset of the response execution. Dopamine increased the probability to accept a trial and, accordingly, decreased beta band activity dramatically. In conclusion, signals relevant to effort-based decision making are strongly represented in STN and their modulation by dopamine accounts for its observed behavioural consequences.

DOPAMINE MODULATION OF REWARD- AND EFFORT-BASED DECISION MAKING CIRCUITS

Zénon A., Olivier E.

Cost-benefit computations are known to rely crucially on tonic dopamine levels and on a circuit involving Nucleus Accumbens (NAc) and the dorsal part of the Anterior Cingulate cortex (dACC). However, it remains unclear how these structures interact with each other and how dopamine affects their functioning in humans. In order to address this question, we scanned healthy participants (N=18) in a 3T MRI scanner while they performed an effort-based decision making task. Dopamine manipulations followed a double blind, within-subject protocol, using either placebo, levodopa 125mg or sulpiride 400mg. We found that dopamine increased effort investment in the task and that, conversely, dopamine antagonism led to decreased effort. fMRI data showed that a circuit involving dopaminergic midbrain, NAc, dACC, and dorsal striatum, reflected cost-benefit computations during the task and was modulated by dopaminergic manipulations. These findings provide causal evidence that a circuit involving not only the ventral, but also dorsal basal ganglia, plays a central role in comparing effort costs with reward in order to reach a decision about whether or not to engage in an action.
**Opportunity cost, action selection and response vigor in humans**

Zénon A., Olivier E.

In addition to its associated reward and effort cost, the value of an action is also most likely influenced by its opportunity cost, i.e. the average value of all the other actions that could be executed during the same period of time. To test this hypothesis experimentally, we asked human subjects to participate in different versions of a behavioral task involving effort-based decision making and compared their behavior with different model predictions. Participants had to perform different physical efforts in either a so-called FREE or FIXED condition. In the FIXED conditions, the monetary reward, duration and amount of effort required were determined in advance and participants could simply accept or refuse the trials proposed. In the FREE condition, participants could adjust the level of effort invested in order to decrease the duration of the squeezing. We manipulated opportunity cost by changing the average level of reward and effort required per unit of time. We found that human behavior does not follow model predictions: decisions and responses were much less affected by opportunity cost than predicted. This shows that human subjects, when confronted to choices involving the adjustment of effort and time investment as a function of reward values, do not conform to current theoretical models.

**Dopaminergic modulation of effort-based decision making in healthy humans**

Zénon A., Olivier E.

Dopamine is known to modulate effort-based decision making: increased tonic dopamine levels are associated with an increased willingness to invest more effort. Computational studies have suggested that tonic dopamine levels could in fact signal the opportunity cost of our decisions: the average value per unit of time of all the other possible courses of actions. In order to test this hypothetical function of dopamine experimentally, we asked healthy human participants (N=8) to perform two different effort-based decision tasks. In the “fixed reward task”, subjects had to reach an effort threshold by squeezing a dynamometer and then received a fixed reward indicated at the beginning of each trial. Importantly, they could reach the effort threshold more or less rapidly by squeezing the dynamometer harder or less strongly. In the “fixed duration task”, the duration of the effort was fixed but the amount of reward depended on the effort. In this task, squeezing the dynamometer harder allowed to get more reward but did not allow saving time. We manipulated dopamine by giving to each subject either a 200 mg dose of sulpiride, a 125 mg dose of levodopa, or a placebo, following a within-subject double blind protocol. Preliminary results indicate that the participants chose the effortful actions more often after receiving levodopa, whereas sulpiride had no effect on their choices. Importantly, this effect was similar in the 2 tasks, indicating that dopamine did not affect the opportunity cost computation, but simply increased the willingness to invest effort in actions.

**Mental fatigue leads to implicit compensatory increases in mental effort in neuropsychological patients**

Zénon A.

There is no reliable correlation between the subjective sensation of mental fatigue and its objective consequences on cognitive performance. One hypothesis is that compensatory mechanisms exist, allowing to maintain performance, despite a loss of cognitive resources, at the cost of higher mental effort. We tested this hypothesis by asking neuropsychological patients to perform a demanding singleton visual search, consisting in finding the only item, which was presented alone, among a series of distractors. The reward and difficulty associated to each trial changed pseudo-randomly. The patient had to choose whether he accepted or refused to execute the trial, given its difficulty and associated reward. Mental effort was evaluated in each successive block by different means: subjective analog ratings, measurements of acceptance rate as a function of reward, pupil size, heart rate variability and frontal alpha frequency power. Preliminary results show that behavioral measures of mental effort did not change but that its psychophysiological signatures increased as time passed/over time. Between subjects, the evaluation of mental effort appears to correlate with the subjective feeling of mental fatigue. These results suggest that maintenance of performance in the presence of mental fatigue requires increased mental effort but that these changes are not consciously perceived by the subject.

**Visual selective attention**

Zénon A., Alamia A., Olivier E.

During saccadic eye movements, the processing of visual information is transiently interrupted by a mechanism known as “saccadic suppression” that is thought to ensure perceptual stability. If, as proposed in the premotor theory of attention, covert shifts of attention rely on sub-threshold recruitment of oculomotor circuits, then saccadic suppression should also occur during covert shifts. In order to test this prediction, we designed two experiments in which participants had to orient towards a cued letter, with or without saccades. We analyzed the time course of letter identification score in an “attention” task performed without saccades, using the saccadic latencies measured in the “saccade” task as a marker of covert saccadic preparation. Visual conditions were identical in all tasks. In the “attention” task, we found a drop in perceptual performance around the predicted onset time of saccades that were never performed. Importantly, this decrease in letter identification score cannot be explained by any known mechanism aligned on cue onset such as inhibition of return, masking, or microsaccades. These results show that attentional allocation triggers the same suppression mechanisms as during saccades, which is relevant during eye movements but detrimental in the context of covert orienting.
FCHUNKING AND SEQUENCE LEARNING

Alamia A., Olivier E., Zénon A.

Many motor functions have been assigned to the basal ganglia (BG) but they all remain debated. Amongst those is the storage and recall of overlearned sequential skills. However, this view has been questioned by recent studies in non-human primates showing that a lesion of the main BG output structure - the internal part of the Globus Pallidus (GPi) - leads to very subtle motor deficits, and to no particular deficits in recalling overlearned sequences; a comparable finding was reported in patients with a Parkinson disease (PD) following a pallidotomy. Growing evidence suggests that the BG, instead of being involved in the retention and recall of motor skills, play a causal role in learning such skills. Along these lines, several studies have established that the BG are specifically involved in implicit (unconscious) sequence learning and that implicit sequence learning is correlated with the density of dopamine D2 receptors in the striatum. Additionally, a recent study has shown that the putamen, a part of the striatum, is recruited during motor chunking, a mechanism allowing to split complex actions into sub-units, which can then be merged together to form a meaningful action. One hypothesis that we are currently testing is that BG are centrally involved in motor chunking and that different BG circuits play different roles in this function, some being involved in the splitting operation whereas others being responsible for the merging of the split sequences of actions. This function might provide a unified theory to clarify the contribution of BG to motor learning. Interestingly, recent studies also suggest that motor chunking is a dopamine-dependent process but this hypothesis still requires further investigations.

DYNAMIC ALLOCATION OF VISUAL ATTENTION DURING STATISTICAL LEARNING

Zénon A., Alamia A., Olivier E.

The dynamic world we experience in everyday life presents recurrent patterns, in which stimulus occurrences can be predicted from past events. Here we investigated how attentional allocation takes advantage of this predictability to optimize visual information gathering. We asked human participants to report the occurrence of a target color stimulus. The stimuli consisted of two streams of colored shapes, on either side of the screen center. In the first-order condition, some stimuli were more frequent than others, whereas in the second-order condition, some stimuli predicted, with different levels of probability, the next stimulus. Participants were free to look anywhere on the screen and we analyzed their eye movements by means of an eyetracker. We found that both the first- and second-order statistics of the stimuli affected the RT very early during the course of the experiment. In addition, overt attention was allocated preferentially to the most frequent and most predictive stimuli. This preferential attentional allocation accounted for all the RT advantage in the second-order condition only. In conclusion, these results indicate that both first- and second-order statistics are used to speed up reaction time; this advantage relies on increased attentional allocation only for the second order statistics, whereas first-order statistics biases response selection in addition.

EQUIPMENT

- COSY technical support unit (informatics, programming, electronics, etc.)
- Fully-equipped TMS and EEG lab (single pulse, bistim and repetitive TMS Magstim devices, TMS-compatible EEG system)

AWARD

Fondation Médicale Reine Elisabeth (Zénon & Olivier)

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SELECTED PUBLICATIONS


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Christine DETREMBLEUR, PhD

Our goal is to understand the pathophysiology of the gait to better guide the therapeutic choice. We tried to understand the origin of the increase in energy cost in the disabled person including the amputees, children with cerebral palsy, stroke patients, patients with an osteoarthritis. We have also validated the impact of different therapies on the energy cost and the locomotor mechanism showing that gait analysis is a valuable tool of clinical research to improve the quality of care and validate new treatment. We have validated the effect of neuromuscular block of botulinum toxin and surgery of equine foot in children with cerebral palsy for example. We have better integrated our assessment in the OMS model by simultaneously evaluating the impact of multisite and multimodal treatment on disability, activity and patient quality of life.

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GAIT
LONG-RANGE AUTOCORRELATIONS IN WALKING AND CYCLING PATTERNS OF PARKINSON’S DISEASE: ARE THERE RELATIONS BETWEEN THE LONG-RANGE AUTOCORRELATIONS AND THE NEUROLOGICAL IMPAIRMENTS, WALKING ABILITIES AND THE PRACTICE OF PHYSICAL EXERCISE?

T. Warlop

Parkinson disease (PD) is one of the most common neurodegenerative disorders. Impaired locomotion has been considered to be one of the cardinal symptoms of PD, along with bradykinesia, hypokinesia, rest tremor, rigidity and postural instability (1). These neurological impairments often restrict walking abilities, functional independence in daily living activities and quality of life of parkinsonian patients. Therefore, the functional improvement of locomotion is one of the main goals of the therapeutic interventions. In order to deepen the knowledge of motor control in healthy and pathological walking, the project has two aims. Our first aim is to study the magnitude (CV and SD) and the dynamics (long-range autocorrelations) of cycle duration variability in gait and cycling in parkinsonian patients and their relations with the functional assessment. Our second aim is to assess by a controlled, randomized, single blinded clinical study, the effect of physical exercise on stride duration variability, neurological impairments and walking abilities (Fig.1).

Fig. 1: An example of an ‘on-off’ signal (A). Upward lines correspond to heel strikes, downward lines to heel-off. The time between each upward line, corresponding to the precise stride duration, is automatically computed to determine the fluctuation dynamics of the whole walking trial (B).

KINEMATIC OUTCOMES MEASURES OF TRUNK IN LOW BACK PAIN

B. Hidalgo

The second project develops a standardised, reliable, valid spine model of active trunk movements that accurately discriminates kinematic patterns of patients with chronic non-specific low back pain from those of healthy subjects. This tool can be used clinically to diagnose chronic non-specific low back pain, manage treatment, and as quantitative outcome measures for clinical trial interventions (Fig.2).

Fig. 2: Flexion task from a seated position (A, B) to the end of the range of motion (C, D). (A, B) Photograph and schematic illustration of marker placement on a seated subject. The shoulder and pelvic girdles are represented by two triangles, where the pelvis is delimited by S2 and the anterosuperior iliac spines (ASISs), and the shoulders are delimited by C7 and the acromioclavicular (Ac) joints.

ROBOT DESIGNED TO REHABILITATE THE STROKE PATIENTS

M. Gilliaux

For several years, our team is working on the development of a robot designed to rehabilitate the stroke patients. With this tool, the current recommendations such as movements oriented towards a more functional task, the intensity of the completed exercises, the stimuli rich environment, frequently feedback are respected. This therapy is designed to improve the functional recovery of brain-damaged adults, and therefore their quality of life (Fig.3).

Fig. 3: View of the ReaPLAN robot. 1: distal effector; 2: visual interface of the subject; 3: physiotherapist’s interface.

RE-EDUCATION IN SUPPORT OF URINARY DISORDERS IN THE PATIENT WITH MULTIPLE SCLEROSIS

L. Gaspard

The objective of this thesis is to assess the place of the re-education in support of urinary disorders in the patient with SEP and assess the effectiveness of different treatment.

Fig. 4: General principle of the method to quantify the efforts during gait.

EQUIPMENT

- Gait was assessed using a three-dimensional motion analysis, including synchronous kinematic, electromyographic, mechanical and energy measurements. All data were simultaneously acquired on a motor driven treadmill (Mercury LTmed, HP Cosmos®, Germany).
- A digital video-based motion analysis system analyses the kinematic part of locomotion. The system is composed of 8 infrared cameras tracks (Elite - 200 Hz) and records the trajectories of passive reflective markers (typically small spheres covered with reflective tape) positioned on the skin in relation to anatomical or bony landmarks to define body segments.
- A force platform composed of four 3D strain-gauge force transducers located under the tread-mill simultaneously measures the ground reaction forces.
- Energy expenditure is measured indirectly, based on the rate of oxygen consumption by the individual (VO2) using an ergospirometer (Medisoft).
- An electrical activity muscle is recorded by a Wifi EMG system (16 channels – 1000 Hz Wifi, BTS, Italy) with surface or indwelling electrodes (Fig 1).

FUNDING

- Fondation St Luc: M Gilliaux et T Warlop

AWARD

Pfizer Educational Grant
SELECTED PUBLICATIONS


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NEURAL MECHANISMS OF HUMAN FACE RECOGNITION

The overarching goal of our research is to understand how the human brain recognizes people by their face. Face recognition is probably the most frequent and complex visual recognition task of the human brain, and can serve as an excellent model for understanding human visual recognition in general. Understanding face recognition has social and clinical implications because face recognition is fundamental for the quality of social interactions. Difficulties in face recognition are more prevalent in the normal population than initially thought and are often found following right posterior brain damage, cortical visual impairment, fronto-temporal dementia or neuropsychiatric disorders. A wide network of distributed cortical areas, with a dominance of the right hemisphere, subtends face recognition. We use a wide variety of methods: psychophysics, human electrophysiology (ERP, EEG), neuroimaging (fMRI), eye movement recordings, intracerebral recordings in humans, studies of brain damaged-patients (prosopagnosia), developmental studies (infants, children).

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Andrea CONTE, Programmer
FACE RECOGNITION IMPAIRMENTS FOLLOWING BRAIN DAMAGE (PROSOPAGNOSIA)

T. Busigny, G. Van Belle, M. Ramon, R. Laguenss, K. Torfs, B. Rossion

Following brain damage (trauma, stroke ...), some people may present with great difficulties in recognizing familiar faces and encode new faces in memory. This condition is termed prosopagnosia. Studying cases of prosopagnosia can be particularly interesting, for two reasons:

1. They can help us understanding better the location and the critical role(s) of the brain areas involved in normal face recognition (Figure 1);

2. The kind of visual cues that these patients still can or cannot extract and remember on faces may help us understanding better how normal people recognize faces (what kind of information/processes are particularly important).

Fig. 1. Brain damage in the ventral part of the occipito-temporal cortex may cause prosopagnosia, an impairment in face recognition. Despite extensive posterior brain-damage, we reported face-selective activation in a right occipito-temporal area ("right FFA") in the patient PS’s brain, supporting the view that this face-selective response originates from inputs coming from low-level visual areas (Rossion et al., 2003; Schiltz et al., 2006).

NEUROIMAGING OF FACE PERCEPTION (FMRI)

F. Gentile, J. Jonas, B. Rossion

In collaboration with colleagues of the neighbour university of Maastricht (R. Goebel) but also in Stanford (K. Weiner, K. Grill-Spector) and Nancy (L. Maillard, G. Hossu) we use fMRI to clarify the neural basis of face perception (Figure 2). Studies are performed in normal humans and brain-damaged patients with prosopagnosia.

Fig. 2. In the same brain area as depicted in Figure 1, normal observers show a sensitivity to visual illusion known as the composite face illusion: two top halves of a face are perceived as different if they are aligned with different bottom halves. Consequently, a release from adaptation to face identity is observed in this area for this condition of stimulation compared to other conditions.

ERP STUDIES OF FACE PERCEPTION

C. Jacques, S. Caharel, B. Rossion

To understand the time-course of face perception, we have investigated in depth the response properties of the earliest event-related potential associated with face perception, the occipito-temporal N170. Among other observations, we have demonstrated that individual faces are coded at the level of that component (below 200 ms; Figure 3) and characterized the nature of these early perceptual face processes.

EYE-MOVEMENT RECORDINGS DURING FACE PERCEPTION

G. Van Belle, B. Rossion

Recording of eye movements during face perception is informative about the cues and processes involved. In collaboration with Philippe Lefèvre (UCL), we use gaze-contingency - literally stimulating observers depending on where they look - to study the nature of face perception (Figure 4).
Fig. 3. The N170 is the first face-selective electrophysiological response observed on the human scalp. Here its amplitude is reduced when the exact same face is repeated, showing that the human brain is sensitive to differences between individual faces as early as 160-170 ms.

Fig. 4. While typical observers recognize a face in 1 or 2 fixations located in the middle of the face, slightly below the eyes, patients with acquired prosopagnosia tend to rather fixate specific elements of the face, the mouth in particular. That is, normal observers perceive faces holistically while patients with prosopagnosia analyze a face element by element.

**STEADY-STATE VISUAL EVOKED POTENTIALS STUDIES OF FACE PERCEPTION**

A. Boremanse, J. Liu, G. Vertongen, G. Van Belle, D. Nemrodov, A. Lochy, A. Conte, T. Retter, M. Dzhelyova, B. Rossion

Since 2010, we have launched a full research program on fast periodic visual stimulation, leading to steady-state visual evoked potentials (SSVEPs) during face perception (Figure 5). We take advantage of the high signal-to-noise ratio of the method to understand the sensitivity of the face perception system to various facial properties, and to provide objective signatures of integration of facial parts. This project is funded by a new ERC starting grant (2012-2017).

Fig. 5: An electrophysiological response obtained on the human scalp after 1 minute of stimulation with different faces or an identical face at 3.5 Hz.

**UNDERSTANDING THE NEURAL BASIS OF FACE PERCEPTION IN THE MONKEY BRAIN: fMRI AND NEUROPHYSIOLOGY**

J. Taubert, J. Badler, G. Van Belle, B. Rossion

In collaboration with R. Vogels and W. Vanduffel (KUL), we are developing a research project combining fMRI (to localize face-selective areas in the monkey brain) and single-cell physiology (to study the response properties of neurons in these areas).

**DEVELOPMENT AND PLASTICITY DURING READING ACQUISITION AND FACE PERCEPTION**

A. de Heering, G. Dormal, S. Peykarjou, A. Lochy, B. Rossion

We study the development of the face processing system as well as its plasticity during development or at adulthood using behavioral and neuroimaging methods. Part of this project also concerns the plasticity of the face processing system during reading acquisition, in a collaborative project with R. Kolinsky and P. Peigneux (ULB), and another part concerns the development of visual expertise for nonface objects, in collaboration with Q. Vuong (Newcastle University, UK).
HUMAN INTRACEREBRAL RECORDINGS OF FACE PERCEPTION PROCESSES

J. Jonas, J. Liu, C. Jacques, G. Vertongen, R. Rossion

In collaboration with the Université de Lorraine in Nancy (France), we study the neural basis of face perception and memory by means of intracerebral recordings in patients with epileptic seizures refractory to medication (Figure 6).

![Figure 6: Intracerebral electrical stimulation of a face-selective area of the right hemisphere during the presentation of famous faces leads to a transient inability to recognize the faces (prosopagnosia).](image)

**EQUIPMENT**

- 2 eyetracking recording systems (eyelink 2000, SR-research)
- 1 EEG recording system 160 channels (Biosemi)
- 1 EEG recording system 64 channels (ANT)
- 1 digitalizer for recording of electrodes’ positions (Polhemus)
- Lab space equipped for EEG, eyetracking and behavioral studies
- Access to small population of brain-damaged patients with prosopagnosia
- Access to a Siemens 3T scanner for fMRI research at Maastricht University
- Access to epileptic patients with implanted intracerebral electrodes at the CHU Nancy (Université de Lorraine)

**FUNDING**

- FNRS (individual grants, FRSM 2012-2016)
- ERC starting grant 2012-2017
- PAI-BELSPO (2013-2018) with ULB, KUL, UGent

**SELECTED PUBLICATIONS**


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Our investigations are focusing on sensory plasticity in humans. More particularly, research activities of the Neural Rehabilitation (COSY-Gren) laboratory relate to the investigation of brain plasticity and perception in sensory deprived humans. Do blind persons develop “supernormal” abilities in using their other senses, i.e. audition, touch, proprioception, olfaction, to perceive, to localize, to recognize or to mentally represent objects or scenes? Which are the neural substrates for these abilities in the absence of vision? Is the early-deprived occipital cortex functionally recruited in these tasks the same way as in sighted subjects? Using behavioral tests and functional imaging techniques, in the frame of projects supported by FRSM grants, we wish to get better insight into these questions. The cognitive aspects of sensory substitution are also studied in subjects affected by early deafness, in subjects who suffer from acquired tinnitus as well as in control subjects.

Anne G. DE VOLDER, Principal Investigator
Laurent RENIER, Postdoctoral Fellow
Rodrigo ARANEDA, PhD Student
Elodie LERENS, PhD Student
Isabel CUEVAS, PhD (back to Valparaiso, Chile, in 2011; still collaborating with us)
Paula PLAZA, PhD (currently at Georgetown University; still collaborating with us)
Fernando BERMEJO, Visiting researcher

In Collaboration with:
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Naima DEGGOUJ, MD, PhD (ENT Dept., St. Luc)
Pierre PHILIPPOT, PhD (IPSY)
Yves VANDERMEEREN, MD, PhD (NEUR Dept., CHU Dinant Mont-Godinne)

In early blind adults, affected by pregeniculate lesions from birth or in the first years of life, rates of glucose metabolism measured in primary and association visual cortex are unusually high, reaching a level comparable to that of sighted subjects studied with the eyes open. It has been suggested that early blind individuals develop superior abilities in the use of their remaining senses to compensate for their lack of vision, hypothetically due to this cross-modal reorganization of deafferented visual brain areas to process non-visual information such as sounds or tactile stimuli. While auditory and tactile functions have been investigated for long, little is known about the effects of early visual deprivation on olfactory processing. However, blind humans make an extensive use of olfactory information in their daily life. We investigated olfactory discrimination and identification abilities in early blind subjects and age-matched sighted controls, by means of several olfactory tests, including the clinical Sniffin's Sticks Test, and provided evidence that early blind subjects significantly outperformed the controls in odor discrimination, free-identification and categorization (Figure 1).

In order to define the neural substrates for these improved perceptual abilities in early blind subjects, we developed a non magnetic, fMRI-compatible odor delivery system that allows a timely presentation of different odors, producing the expected activation in the olfactory cortex. Using this device, we were able to demonstrate that there is an involvement of the reorganized occipital cortex in the processing of odors in early blind subjects (Figure 2). We currently extend this line of research in a collaborative project (ISCT grant «Visiodor») carried out in collaboration with Pascal Barone (UMR5549, Toulouse, France).

![Fig. 1: Top: When compared to blindfolded sighted controls, blind people are better in odor detection and also tend to differentiate two odors more accurately. However, no group difference is observed for the multiple choice identification component of the Sniffin's Sticks Test, nor in the main available clinical tests (adapted from Cuevas et al., 2010). Bottom: We developed a battery of psychophysical tests in order to be able to show up the potential supernormal abilities of blind people in odor identification. In olfactory tasks with high attention load, blind subjects score better than controls. This is specially the case for free identification and semantic categorization of odors (adapted from Cuevas et al., 2009).](image-url)
FUNCTIONAL SPECIALIZATION OF SENSORY BRAIN AREAS AND SENSORY SUBSTITUTION, INCLUDING IN EARLY BLIND PEOPLE

P. Plaza, E. Lerent, L. Renier, A. G. De Volder

Blind people face specific difficulties in spatial tasks, hypothetically due to the absence of a visual reference framework, which would facilitate, in sighted subjects, the multimodal perception of distal space. However, after having learned how to use a Prosthesis that Substitutes Vision with Audition (PSVA), the blind subjects quickly learn to infer the more or less distant position of an object according to monocular depth cues; they subsequently use accurately the rules of visual depth perception in order to grasp objects (Figure 2). Using functional magnetic resonance imaging (fMRI), we tried to clarify further the role of the dorsal visual pathway during the use of the PSVA, by comparing two spatial tasks (Figure 4). Location and orientation detection with the device induced a similar recruitment of frontoparietal brain areas in blindfolded sighted subjects as the corresponding tasks using the same stimuli in the same subjects in vision. We observed a similar preference of the right superior parietal lobule for spatial localization over orientation processing in both sensory modalities. This provides evidence that the parietal cortex activation during the use of the prosthesis is task related and underlines the existence of common processes controlling both the normal vision and the perception by sensory substitution. In the frame of our collaborative project with Prof. J.P. Rauschecker (Georgetown University), we used fMRI to compare the neural networks of loco-
tion and discrimination as the covariate. Brain regions with a positive covariation were superimposed on the coronal, sagittal and transversal views of a normalized MRI brain of a representa-
tive subject. We used a threshold of p<0.001, uncorrected, and a cluster size threshold correction of p<0.05 based on Monte Carlo simulation. An activation focus was found in the right fusiform gyrus (in orange-yellow: 380 voxels, center of gravity: x: 24, y:-26, z:-13). The graph at the lower part of the Figure shows the strong correlation between brain activity (beta weights) in the right fusiform gyrus during odor processing (white region) and the individual performance in a variety of odor recognition tests (averaged score, %) in the whole group of subjects (n=16): r=0.80; p<0.001. The red lines indicate the confidence interval (95%). So, the level of right fusiform gyrus activation during the olfactory conditions was highly correlated with individual scores in odor recognition, indicating that the additional occipital activation observed in early blind subjects may play a functional role in odor processing (adapted from Renier et al., 2010). Later, the multimodal perception of distal space. However, after having learned how to use a Prosthesis that Substitutes Vision with Audition (PSVA), the blind subjects quickly learn to infer the more or less distant position of an object according to monocular depth cues; they subsequently use accurately the rules of visual depth perception in order to grasp objects (Figure 6). Here we demonstrate that, in the absence of visual input, nonvisual sensory modalities colonize the “visual” cortex and this cross-modal reorganization of occipital brain areas does not occur at random: the dorsal / ventral visual streams seem to develop their designated functional role in processing stimulus location / stimulus recognition independently of visual experience.

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**Fig. 2:** Relationship between olfactory performance and brain activity during odor processing (fMRI study). Brain activation maps were obtained from an analysis of covariance on olfactory conditions plotted together in 16 subjects (8 early blind subjects) using the averaged performance in odor identification, categorization and discrimination as the covariate. Brain regions with a positive covariation were superimposed on the coronal, sagittal and transversal views of a normalized MRI brain of a representative subject. We used a threshold of p<0.001, uncorrected, and a cluster size threshold correction of p<0.05 based on Monte Carlo simulation. An activation focus was found in the right fusiform gyrus (in orange-yellow: 380 voxels, center of gravity: x: 24, y:-26, z:-13). The graph at the lower right part of the Figure shows the strong correlation between brain activity (beta weights) in the right fusiform gyrus during odor processing (white region) and the individual performance in a variety of odor recognition tests (averaged score, %) in the whole group of subjects (n=16): r=0.80; p<0.001. The red lines indicate the confidence interval (95%). So, the level of right fusiform gyrus activation during the olfactory conditions was highly correlated with individual scores in odor recognition, indicating that the additional occipital activation observed in early blind subjects may play a functional role in odor processing (adapted from Renier et al., 2010). Later, the multimodal perception of distal space. However, after having learned how to use a Prosthesis that Substitutes Vision with Audition (PSVA), the blind subjects quickly learn to infer the more or less distant position of an object according to monocular depth cues; they subsequently use accurately the rules of visual depth perception in order to grasp objects (Figure 6). Here we demonstrate that, in the absence of visual input, nonvisual sensory modalities colonize the “visual” cortex and this cross-modal reorganization of occipital brain areas does not occur at random: the dorsal / ventral visual streams seem to develop their designated functional role in processing stimulus location / stimulus recognition independently of visual experience.

**Fig. 3:** (a) The prosthesis for substitution of vision with audition or PSVA (Capelle & al, 1998) used in the experiment. A head-mounted micro camera (attached to glasses) allows online translation of visual patterns into sounds that are transmitted to the user through headphones. (b) Schematic representation of the PSVA. The image acquired by the head-mounted video camera (attached to black covered goggles) is divided into pixels according to a two-resolution artificial retina scheme. A single sinusoidal tone is assigned to each pixel of the multi-resolution image (here, a vertical bar is explored at the middle-upper part of the artificial forest). (c) View of the 3D display used in the experiment where blind subjects and blindfolded controls had to replace, by hand, and object previously localized using the PSVA. The perceived size, the height in the field of view, and the geometrical perspective induced by the poles can be used as depth cues to estimate the egocentric distance of the white cube. Twenty positions of the target were pre-selected and are displayed here for reference, as they could not be detected by touch or with the PSVA. The arrows indicate the width and the depth axes of the scene. (d) Error rates as a function of dimension, group, and time. For each dimension (depth and width), the scores are expressed as the percentage of error in object localization (high scores refer to worse results). Error bars are one standard deviation. As expected, sighted subjects spontaneously used their knowledge about visual depth to perform the task with the PSVA, indicating a cross-modal transfer, while blind subjects were affected by their lack of visual experience and were significantly less accurate in depth evaluation. However, a brief learning phase (three sessions of practicing) sufficed to enable blind subjects to acquire the rules of visual depth and to use them efficiently with the device (adapted from Renier et al., 2010).
Fig. 4: Blindfolded sighted volunteers used a prosthesis substituting vision with audition to compare either the position or the orientation of simple “visual” stimuli encoded into sounds and presented in pairs. Location and orientation detection with the device induced a similar recruitment of frontoparietal brain areas as the corresponding tasks performed in vision by the same subjects in a separate experiment using the same stimuli. There was a massive recruitment of the dorsal visual pathway, with a similar preference of the right superior parietal lobule for spatial localization (a) over orientation processing in both sensory modalities (adapted from Plaza et al., 2012).

Fig. 5: On these pictures from collaborative work with Prof. J.P. Rauschecker, one observes in orange-yellow the brain areas that were activated more in early blind subjects than in blindfolded sighted controls during auditory identification and localization tasks, whereas the blue-green zones are those that are more recruited in sighted subjects performing the same auditory processing tasks on the same stimuli. Activation maps are resulting from a RFX between-group comparison with a threshold of q < 0.05 corrected for multiple comparisons. The color-gradient scale codes the t value (adapted from Renier et al., 2010).

Fig. 6: In subjects who are blind from birth the brain adapts itself and it “re-uses” cortical areas, which are normally devoted to visual abilities, in order to develop auditory and tactile abilities. During fMRI, subjects were provided with sounds or vibrotactile stimuli and were requested to identify, to localize or simply detect them. The task comparison shows that the occipital cortex of blind subjects, devoid of visual function from birth, does reorganize itself to process these stimuli and the cortical reorganization follows the same architecture as the one of sighted subjects. In particular, the right middle occipital gyrus is recruited to localize the stimuli, whatever auditory or tactile, in early blind subjects whereas the same region is only recruited to localize visual stimuli in sighted subjects (adapted from Renier et al., 2010).
Several behavioral and fMRI experiments are planned in collaboration with the team of Pierre Philippot, with the goal to identify the role of cognitive control in sensory perceptions and phantom sensations and to define the potential involvement of the prefrontal cortex and sensory brain areas in tinnitus. The potential therapeutic effect of transcranial direct current stimulation (tDCS) will be assessed in the frame of a collaboration with Yves Vandermeeren. This project will benefit from the know-how acquired by Mr. Laurent Renier, candidate Research associate, in the frame of our ongoing collaboration with Prof. J.P. Rauschecker, worldwide expert in acoustic processing and brain plasticity in hearing troubles.

EQUIPMENT

Our main equipment consists in multisensory stimulation systems compatible with the magnetic resonance imaging (MRI) environment, including following devices (Figure 7):

- a) Two new versions of a visual-to-auditory sensory substitution device, the so-called PSVA that was developed in the laboratory, each equipped with an fMRI-compatible joystick.
- b) A vibrotactile stimulation material for behavioural and fMRI study, providing vibrotactile stimulation of the index fingers via piezo-electric stimulators.
- c) & d) Two versions of a fully automated computer-controlled system for delivering four different odors in synchrony with MRI sequences and participant’s inspiration phase.
- e) Each of these systems is portable and connected to a laptop equipped with a user-friendly programming interface developed in LabVIEW, allowing each system to be used reliably in a wide range of experimental paradigms, ensuring that there is no time shift between fMRI data acquisition and stimulus delivery and with the ability to record participants’ responses via a response button pad.

FUNDING

- FRSM 3.4502.08 (Belgium)
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- Conicyt Becas Chile Dec 2011 (Chile)
- Innoviris BB2B 2010-1-09 (Belgium)
- ISCT grant 2012 Visiodor (Toulouse, France)
- NIH grant to J.P. Rauschecker (GU, USA)


PROCESSING MAGNITUDES WITHIN THE PARIETAL CORTEX

M. Andres, V. Dorme, S. Grade, N. Masson, M. Pesenti

Human beings constantly process numerosity, space and duration to regulate and adapt their behaviour to the external world. It has been suggested that these fundamental adaptive abilities rely on a common magnitude processing system hosted by the parietal cortex. In recent neurotranscripts, we have demonstrated the presence of symmetry (between numerosity and length) and asymmetric (between numerosity and duration) facilitation and interference effects and we have proposed a gradient of automaticity in processing magnitudes, with numerosity as the most and duration the least automatically processed dimension. We have also studied how healthy adults are able to estimate and produce numerosities, and we have modelled the processes going from internal numerosities to symbolic notations. The validity of this model has been tested in early blind adults to assess the role of visual experience in building number meaning.

Using fMRI, we have shown that the areas around the intraparietal sulcus (IPS) host both common and partially distinct and specific representations and mechanisms for numerosity (Figure 1), space and duration processing, and we have also shown how these parietal areas interact with frontal areas of the brain to achieve these functions. Then, using TMS, we have demonstrated that the parietal area critically involved in numerosity processing is not involved in duration processing, revealing at least one cerebral site to assess the role of visual experience in building number meaning.

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Similarly, we have shown that the integrity of the right IPS is a necessary condition not only for discriminating numerosities but also for performing accurate judgements of lengths, confirming that these two processes rely on a common representation and/or mechanism in the right IPS. Finally, we have studied the similarity and specificity in processing each magnitude in various brain-damage populations known to exhibit impairments in processing one magnitude (e.g., spatial neglect, Parkinson disease). [see 3, 4, 5, 6, 9]

EMBODIMENT OF NUMBER SEMANTICS IN SENSORY-MOTOR PROCESSES

M. Andres, S. Di Luca, S. Grade, N. Michaux, M. Pesenti

Finger control and numerical cognition have been shown to share common areas in the parietal and premotor cortices. This common ground for finger movements and numerical processing may be a developmental trace of the use of fingers when learning to count, calculate, represent numerical magnitudes on fingers and communicate them to conspecifics. In this project, our group has demonstrated that the link between numbers and fingers deeply contribute to building number semantics. We have studied the impact of counting strategies on finger numeral configurations and have shown that even educated adults rely on mechanisms involved in the perception and execution of finger movements to process and represent numerosities. This finding led us to propose that the finger configurations corresponding to prototypical counting habits acquire a specific status in long-term memory and activate a place coding representation, as other symbolic notations.

We have also discovered that numbers and fingers interact through goal-directed actions implying the computation of a magnitude estimate, such as the hand conformation to object size. We have shown that processing small- or large-magnitude numbers primes grip closing or grip opening, respectively, and that numerical magnitude influences the judgement of actions towards objects (e.g., estimating whether rods of various length could be grasped between the index finger and the thumb after processing a small- or a large-magnitude number; Figure 2) without actually performing the action. Interestingly, action observation also influences numerical processing: perceiving a grip closing posture slows down the processing of large-magnitude numbers, whereas perceiving a grip opening does not produce any priming or interference effect.

In a final stream of research, we have investigated the links and interactions between spatial, numerical and motor cognition with the aim of providing novel insights into how the motor system is recruited for space perception (how action simulation contributes to space perception), and how a generalized magnitude system may give rise to reciprocal influences between these different cognitive domains.

Thanks to this series of studies we have demonstrated that the way we express physically numerical concepts, by raising fingers while counting, by using grip aperture to describe a magnitude, or by performing pointing or reaching actions with the hands and fingers leads to embodied representations of numbers in the adult brain and supports the idea that number semantics may evolve from the sensory-motor processes on which they are grounded. [see 1, 7, 10]

A NEUROFUNCTIONAL ARCHITECTURE FOR MENTAL ARITHMETIC

M. Andres, S. Di Luca, N. Masson, N. Michaux, M. Pesenti

A main challenge in numerical cognition research is to identify the cerebral processes involved in solving elementary arithmetical problems. To date, the behavioural and neurofunctional data do not provide a clear answer to this question and the involvement of verbal, visuo-spatial and/or motor representations and processes is still under debate. This project aims at identifying the cognitive architecture of mental calculation by specifying the respective contribution of the visual, visuo-spatial and motor systems and the critical role played by the underlying cerebral areas.

We use behavioural studies with a dual-task paradigm to investigate the interactions between each of these systems and the resolution of additions, subtractions and multiplications. For example, we have recently shown that moving the fingers but not the feet while calculating induces a selective time cost in the solving of addition and subtraction problems, whereas multiplication problems remain unaffected. Then, we use fMRI to identify the cerebral areas involved in each arithmetical operation and to determine their overlap with the verbal, visuo-spatial and motor networks. We have found that subtraction and multiplication both rely on areas in the IPS and in the posterior part of the parietal lobules (PSPL) with additional activations in the superior temporal gyrus for multiplication (Figure 3). As predicted by our hypothesis that the use of fingers for learning to count leads to a common substrate for numbers and fingers (see previous section), the parietal areas involved in mental arithmetic also showed increased activity during a finger discrimination task. Finally, a lesional approach using TMS is applied to determine within the identified areas those that are causally involved in each operation. We have found that applying TMS over the left and right IPS but not the PSPL increases response latencies in all operations and error rates in multiplication, which demonstrates the critical role of the IPS in mental arithmetic. We further investigated the hypothesis that mental arithmetic is performed by shifting attention along an internal representation of numbers, conceptualized as a visuospatial medium where numbers are represented from left to right. To do so, we analyzed how processing numerical stimuli influences the allocation of numerical representations.
of visuo-spatial attention and, conversely, how shifting attention with lateralized cues influences number processing and arithmetic problem solving, both in healthy participants and in brain-damage populations known to exhibit impairments in attention orientation (e.g., spatial neglect). [see 1, 2, 8]

Fig. 3: A. In this fMRI experiment, a wooden block was placed in each hand of the participant, with half of the fingers extended over the bumps of the block and the other half flexed in the holes. B. In the finger discrimination task, the participants viewed hand drawings with one finger coloured red. They had to decide whether their matching finger was flexed or not, without visual feedback about hand posture. In arithmetic tasks, they had to multiply the Arabic digit by three or four, or subtract it from 11 or 13. C. Arithmetic tasks induced increased activity in the same intraparietal areas (IPS) as those involved in finger discrimination (red). A selective increase of activity was found in the middle and superior temporal gyri during multiplication only (blue). In this experiment, no overlap was observed in the primary motor (M1) and somatosensory (S1) cortex contralateral to the tested hand (green) (adapted from [2]).

EQUIPMENT
• Eye-tracker
• tDCS
• fMRI (Radio-diagnosis Unit, St-Luc Hospital)
• TMS (CoAction Lab, COSy, IoNS)

FUNDING
• FNRS - Fonds de la Recherche Scientifique

SELECTED PUBLICATIONS


7. Grade, S., Lefèvre, N., & Pesenti, M. Influence of left-right vs. up-down gaze observation on random number generation. Experimental Psychology, 2013, 60 (2), 122-130.


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The field of research of our lab is the physiology and the biomechanics of terrestrial locomotion and analysis of movements in sports (particularly in gymnastics and in track and field).

At first glance, there are many different modes of terrestrial locomotion: some vertebrates move on Earth on two legs while others use four. They walk, amble, trot, pace, canter, gallop, hop, etc. Intrinsic factors (morphology, development, pathologies...) or extrinsic factors (slope or softness of the terrain, carrying a load, obstacles, gravity ...) may modify the pattern of locomotion (stride length, step frequency, muscular activity, ...). The aim of our research is to understand how the human system adapts to these particular situations.

### Physiology and Biomechanics of Locomotion

**Left:** Fig.1. Subject jumping (squat jump) in micro-gravity during the 55th ESA campaign flight.

**Right:** Fig. 2. Subject landing after the opening of the trap door mechanism during the 59th ESA campaign flight. Subject Loading System incl. harness, EMG surface electrodes and several markers can be seen.
BIOMECHANICAL AND PHYSIOLOGICAL ASPECTS OF JUMPING OVER AN OBSTACLE WHILE RUNNING IN HUMAN

G. Mauroy (Supervision: B. Schepens and P.A. Willems)

When leaping a barrier, the runner increases the vertical velocity of its centre of mass (COM) at take off to augment the amplitude and duration of the aerial phase over the obstacle. The purpose of the project is to determine whether and how the bouncing mechanism of running and the stiffness of the lower-limb muscles are adjusted, while running to and jumping over an obstacle.

In the first part of the study, the modification of the bouncing mechanism of running are analysed during the running steps preceding the jump over a barrier. The approaching speed varies between 9 and 21 km h⁻¹. The forces exerted by the feet on the ground are measured by a 13 m-long force platform. The movements of the COM are evaluated by time-integration of the forces and the overall stiffness of the bouncing system by computer simulation. The running mechanism is modified during the two steps preceding the hurdle. During the contact period before last, the overall leg-spring stiffness decreases; consequently, the COM is lowered and accelerated forwards. Then during the contact period preceding the obstacle, the overall leg-spring stiffness increases and the COM is raised and accelerated upwards, whereas its forward velocity is reduced. During this phase, the leg-spring acts like a pole, which stores elastic energy and changes the direction of the velocity vector to release this energy in a vertical direction. This mechanism allows saving mechanical energy during the step preceding the jump.

In a second part of the study, the muscular power and the stiffness generated separately at each lower-limb joint are measured. The leg-spring’s stiffness and the net muscular moment and power, generated at each joint are calculated from the force exerted on the ground and the movements of the lower limb segments. The effect of the barrier height and the approaching speed is studied.

In a third part of this study, we analyse how trained hurdle athletes modify the strategy described in normal subjects. Two questions arise from the results on the normal subjects. First, do athletes optimize the trajectory of the COM to reduce its vertical excursion and limit the loss in the speed of progression? Second, are trained athletes able to maintain the magnitude of the velocity vector during the last contact before the jump?

THE EFFECT OF A PERTURBATION WHEN RUNNING AND ITS MOTOR CONTROL

M. Schier (Supervision: B. Schepens and D. De Jaeger)

The goal of this project is to investigate the adaptations made by the running subject after a dorsiflexion of unexpected timing.

Running is one of the most popular recreational activities. In the real world runners must negotiate various perturbations and little is known about the way they do it. In our protocol, the subject is asked to run on a treadmill at a speed of 2.8 m·s⁻¹ while wearing regular running shoes and equipped with a powered exoskeleton on his right leg. This exoskeleton allows only dorsi-plantar movements and is designed to deliver a defined perturbation to the right ankle joint while the subject is running on the treadmill. The perturbation is evoked at different phases of the running cycle to test whether the adjustments are modulated as a function of the perturbation timing.

To investigate the adjustments made by the subject to maintain his stability, the angular position of the ankle, the ground reaction forces and the muscular activity of lower limb muscles are measured.

Left: Fig. 4. Powered exoskeleton designed to deliver a perturbation to the right ankle joint during running. Two carbon fiber shells around the foot and the lower leg are linked by a hinged joint pivoting at the centre of rotation of the ankle. EMG surface electrodes can be seen.
Right: Fig. 5. Subject running with the exoskeleton on the equipped treadmill. The actuator can be seen at the back.

Fig. 3. Subject running on the force platform and jumping over an obstacle.
THE DOUBLE CONTACT PHASE IN WALKING
G. Meurisse (Supervision: G. Bastien & B. Schepens)

The aim of this study is to understand how the double contact influences walking. Human walking is characterized by the occurrence of a double contact phase (DC), when both feet are on the ground, separating periods of single contact when a lower limb is swung forward. The DC is the step-to-step transition with the transfer of body weight from the rear foot to the front foot.

The quantification of the components of ground reaction force under each foot is necessary to study the mechanics of the double contact when walking, especially the muscular mechanical work done by one foot against the other. However, it requires either sophisticated apparatus such a split-belt treadmill or to place each foot on separate plates when using fixed force platform. Moreover, the subject walks unnaturally with these devices.

In the first part of the study, a method for detecting the limits of the double contact and calculating the 3-D forces under each foot from simple equipment such as a force platform (a measure of the sum of forces) will be developed. This method may have a general utility in gait laboratory. In the second part of the study, we will examine various parameters of double contact, such as mechanical work and the stability of the walking pattern, in healthy adults and subsequently in the elderly.

In order to quantify the quality of the reconstruction, the reconstructed vertical GRFs is compared with the forces measured with individual force plates. An absolute mean difference of 1.76% (±0.77%, max=4.72%, n=374, walking speeds from 0.83 to 1.94 m s⁻¹) is observed.

Fig. 6 and 7. Typical trace of the reconstruction of the vertical GRFs.
Top: Vertical ground reaction forces (GRFs) as a function of time. The bold continuous lines present the real GRFs measured under the front and back legs (respectively Fvfront et Fvback) when using two force platforms, whereas the dashed lines present the reconstructed GRFs. Note that the dashed line is sometimes hidden the continuous line. The thin continuous line presents the sum of front and back legs for the vertical GRF (Fvtot). Bottom: Corresponding time evolution of the relative error calculated as:

\[ \text{Relative Error} = \frac{|\text{FvReconstructed} - \text{FvReal}|}{\text{FvReal}} \times 100\% \]

SELECTED PUBLICATIONS


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The long-term goal of the research described herein is to unravel the sensory-motor mechanisms that control manipulation while handling and stabilizing objects within one's grasp. We are especially interested in expanding knowledge in the domain of the complex interactions between feed-forward and feedback mechanisms in the control of dexterous manipulations. We are studying these mechanisms in patients with neurological disturbances as well as in normal subjects under unusual environmental conditions, such as microgravity. Moreover, we are using the Rasch model to develop and validate new outcome measures in rehabilitation, such as ABILHAND (1), a manual ability scale, and ACTIVLIM (2, 3), a measure of activity limitations (http://www.rehab-scales.org).

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SENSORY-MOTOR CONTROL MECHANISMS OF DEXTEROUS MANIPULATION

Motor actions result from a complex combination of motor commands that control muscular contractions to produce the desired movements. To reliably achieve satisfactory motor actions, one must have an internal knowledge of movement dynamics and must also continuously compensate for external forces acting on the body, including omnipresent gravitational forces. Evidence for an internal representation of such dynamics can be found in the literature. However, the role that gravity plays in internal models of dynamics has yet to be clarified. In this research project, we are using experimental and modelling approaches to elucidate the role of gravity in sensorimotor coordination. Motor prediction has been shown to be sufficiently processed in hypergravity and microgravity conditions, though human subjects perform better in the former than in the latter. That is, predictions in hypergravity have been reported to be very good (4), whereas anticipatory grip force modulation in 0 × gravity (g) are associated with greater uncertainty (5) (Fig.1). Confidence in the prediction, and thus motor control performance, may be impaired in the absence of gravity (e.g., 0 g) as such an environment provides no calibration signal for setting force levels and joint torques. We plan to perform a series of human subject experiments involving dexterous manipulations during exposure to hyper- (1.8 g), micro- (0 g), Lunar (0.16 g) and Martian (0.38 g) gravity induced by parabolic flight (Fig.3). Furthermore, our experiment to be launched in the International Space Station in 2014 will enable us to study the long-term effects of microgravity on dexterous manipulation.

Fig. 1. Average trajectories in 1 g (black) and during the early exposure to 0 g (gray) from one representative subject. Shaded areas represent the SE, computed at each time step. A and B show the elevation angle and the angular velocity as a function of time for upward movements. C and D show the same plots for downward movements. Pooled subjects' data, showing the effect of 0 g on the peak angular acceleration and movement duration, are shown in E and F, respectively. In E and F, the vertical bars indicate the intersubject SE. The shift in speed–accuracy trade-off supports that the uncertainty affects the control strategy and the trial-to-trial variability. The corresponding movements lasted longer, had lower peak velocities, and were performed with velocity profiles that were asymmetric. Subjects also increased their tendency to undershoot the target. In addition, overall endpoint variability increased in 0 g.
Fig. 2. A: raw values of maximum and static grip force at the beginning of the experiment, at the end of the first series of 60 trials, and at the end of the second series. The bars indicate 1 SD, and the dots are the minimum and maximum values across subjects. B: time course of the maximum grip force across trials (mean ± SD across the 8 subjects). C: time course of the static grip force across trials (mean ± SD). For each individual subject, the values were normalized to the last 10 trials of the series with 100-g off-centered mass. B and C: the black lines represent the first-order exponential fit.

ADAPTATION OF GRIP FORCE TO COMPENSATE FOR STATIC AND DYNAMIC TORQUES DURING OBJECT MANIPULATION

T. Giard, D. Cordova Bulens, J-L. Thonnard and P. Lefèvre in collaboration with F. Crevecoeur, Laboratory of Integrative Motor Behaviour, Queen’s University, Kingston, Canada; J. McIntyre, CNRS–Université Paris Descartes, Paris, France.

Our research group recently initiated the study of the adaptive control of grip force in the compensation for static and dynamic torques during object manipulation (6). This paradigm, which includes tangential torques, provides a powerful tool with which to extract the adaptive component of grip control during object manipulation (Fig.2). In the present project, we will further investigate the control strategy employed by subjects manipulating an object with a centre of mass off the grip axis during point-to-point movements, rhythmic oscillations, and collisions. These experiments are being conducted on Earth (1 g), while interacting with robots, as well as during parabolic flights producing 1.8 g and 0 g environments (Fig.3). These investigations are designed to focus on grasp force modulation, upper limb movement control, and eye-hand coordination.

THE NEURAL ORGANIZATION OF DEXTEROUS MANIPULATION IN HEALTHY SUBJECTS AND IN CEREBRAL DAMAGED PATIENTS

E. Guillery, A. Mouraux, V. Legrain, J-L. Thonnard

Grasping an object between the thumb and index finger requires precise coordination between grip force and tangential load force; this coordination is impaired in children with congenital hemiplegia and adult stroke patients. Deficits in predictive and reactive control of the paretic hand have been described in such patients previously (7). Functional brain imaging is a powerful tool that may help reveal the neural organization of grip forces during object manipulation. Therefore, we designed an experimental setting in which we can concurrently record functional magnetic resonance imaging, grip-lift forces, and electromyography (EMG) data enabling us to directly correlate EMG and fingertip forces with the functional cortical network. In further studies, assuming that grip requires supervision by high-level cognitive controls, we will investigate the contribution of cognitive factors in grip control using a dual task paradigm (Fig.4). We will compare patterns of brain activity elicited by a grasping task between healthy participants and cerebral damaged patients performing a cognitively demanding task. We will then assess the effects of a functional neuro-rehabilitation program that targets grip precision. Differences in behaviour and brain activity patterns will be assessed before, during, and after completion of the rehabilitation program. A complementary aim will be to estimate the cognitive load needed to perform the grip task, before versus after completion of the rehabilitation program.

Fig. 3. Manipulation of the object with the centre of mass off the grip axis during point-to-point movements performed in 0 g environment.

Fig. 4. The grip-lift movement performed during a cognitively demanding task.
The aims of this project are to study the mechanical interactions between the fingertip and a touched surface during haptic exploration of textured surfaces as well as during dexterous object manipulation. Fingertip skin is a multi-layered tissue that contains numerous mechanoreceptors and sweat glands. In a recent study, we characterized skin mechanical deformation at the interface between the fingertip and a glass surface (Fig.5). This investigation indicated that moisture content strongly influences skin properties (8, 10). Furthermore, during object manipulation, fingertip moisture was found to be optimally modulated to maximize friction and minimize the grip force (9, 10). We recently acquired a new experimental set-up that is composed of a robot, a high-speed camera system, and an integrated real-time measurement of fingertip moisture (Fig.6). This equipment enables us to measure and model the mechanical deformations that are induced actively or passively in the fingertip skin during haptic exploration. We will examine whether these mechanical deformations can predict responses from skin mechanoreceptors during object manipulation and haptic exploration. Elucidation of these mechanisms could have important implications in the development of realistic sensory feedback mechanisms for prosthetic-hand users.

**Fig. 5. Image processing using the optical flow technique. By comparing two images, a gradient of displacement was estimated for each pixel. Black corresponds to zero displacement and grey levels correspond to the displacement magnitude (lighter colour indicates greater magnitude). Time course of the normal and tangential force components in a typical trial, associated frames and ‘optical flow images’. During the tangential preloading period (grey box), the tangential force component increased until the slip occurred (black arrow, top). Frames were selected during the preloading phase and were compared to obtain the optical flow images. The contact area is not correlated to the tangential force. The stuck area (dark grey) decreased when the tangential force component increased.**

**Fig. 6. The experimental set-up composed by a robot, a high-speed camera system and an integrated real-time measurement of fingertip moisture.**

**INTENSIVE INTERVENTION FOR CHILDREN WITH CEREBRAL PALSY: NEW PSYCHOMETRIC TOOLS & NEUROPHYSIOLOGICAL CHANGES**

Y. Bleyenheuft, JL Thonnard, A. Renders in collaboration with C. Arnauld, Haute École Louvain en Haïtis, K. Friel & AG Gordon, Columbia University, NY, USA.

Considering the growing evidences in scientific literature for intensive rehabilitation efficiency, this research project aimed to integrate new measurements in the course of HABIT-ILE interventions (Hand and arm bimanual intensive therapy including lower extremity) recently developed. The first part of the project focused on the measurement of upper and lower extremity activity limitations through a new scale called ACTIVLIM-CP. This instrument, calibrated on the basis of 220 children with the Rasch model, will allow targeting the activity limitations in every-day life including activities combining both upper and lower extremities, a concept that was lacking until now in the assessment of children with cerebral palsy. The second part of this project aimed to measure the changes in manual ability that could be delineated during intensive training for children with cerebral palsy with different instruments, including the ABILHAND-Kids questionnaire. We showed in a sample of 100 children an excellent responsiveness of the ABILHAND-Kids questionnaire, especially in young children. The specificity of this questionnaire allows providing standard error of the measure for each patient, which in turn gives access to individual approaches, providing an idea on the amount of change and its clinical significance. Finally we are investigating the neurophysiological changes that can be noticed at a cortical level during intensive rehabilitation (HABIT-ILE intensive sessions) using MRI, DTI, fMRI and TMS cortical mapping. In short term these measure will allow measuring cortical plasticity induced by the neurorehabilitation process. In long term, this could help defining predictors for responsiveness to the treatment and a better targeting of interventions to each child.

**INTERLIMB COORDINATION IN CHILDREN WITH CEREBRAL PALSY**

D. Ebner, Y. Bleyenheuft, JL Thonnard

In the context of the new evidences encouraging combined training of upper and lower extremity in children with cerebral palsy (HABIT-ILE training), a major interest is directed to the interlimb coordination of upper and lower extremity in children with CP.

Interlimb coordination activities are ubiquitous in everyday life, in tasks such as carrying items, opening a door, etc... Although there are a few studies on the coordination between the upper and lower limbs during rhythmic lower limb tasks – typically walking -, there is little information about this interlimb relationship during discrete movements of the lower limb, such as holding an object while passing an obstacle. The objective of this project is to study these limitations of interlimb coordination in the context of discrete movement of the lower limb. In addition a randomized controlled study will allows us to compare changes induced by conventional therapy and intensive therapy (HABIT-ILE) in the interlimb control.
PERCEPTION AND NEURAL CODING OF NATURAL AND VIRTUAL TEXTURES

D. Gueorguiev & A. Monogen, A. Moreaux and J-L. Thonnard, in collaboration with M. Adams, School of Chemical Engineering, University of Birmingham, Birmingham, UK; V. Hayward, UPMC Univ Paris 06, Institut des Systèmes Intelligents et de Robotique, Paris, France.

This project is being conducted within PROTOTOUCH, a European Commission Seventh Framework Project. The project aims to develop a new generation of tactile displays that will recreate the perception of touching shapes and textures. In order to achieve that goal, knowledge of how the texture information is transmitted and coded by the mechanoreceptors and the nervous system is essential. In the psychophysical part of the project, we will modulate tactile stimuli in order to extract the most relevant features of the sensation of touch (active touch, passive touch, proprioceptive modulation).

We will start by evaluating everyday textures. At a later stage of the project, the stimuli will be generated by TDs developed by the partners. Our aim is to understand how physical characteristics influence the perception of textures and to evaluate the performance of TDs at replicating these characteristics. Central neural coding will be investigated through new approaches that isolate and characterize the cortical activity elicited by the mechanical interaction between the contacting finger pad and textured surfaces. Specifically, we examine whether the sustained cortical activity generated by the mechanical interaction between the finger pad and a grated texture can be captured in the form of a steady-state evoked potential (SS-EP) in the EEG signal. During the recording, passive scanning of the right index fingertip across three aluminum gratings whose spatial period (SP) is between 0.4 mm (smooth surface) and 1.6 mm (rough surface). The movement of the gratings is achieved using a robot with feedback force sensors (Figure 7). A constant normal force (1.5 N) and two constant exploration velocities were used (v1 = 1.76 cm/s, v2 = 4.80 cm/s). Depending on the SP, we expect that these dynamic stimuli will elicit SS-EPs at frequencies ranging between 11 and 120 Hz and, possibly, their harmonics.

SELECTED PUBLICATIONS


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Fig. 7. This figure illustrates the robotic device that will be used in the PROTOTOUCH project. The subject’s hand will be stabilized in order to allow easy stimulation of the index fingertip through aluminium plates having different toughness levels. The friction between the fingertip skin and the aluminium plates will be regulated through the normal force generated by the robot.
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SOCIAL COGNITIVE NEUROSCIENCE (SPRINGLAB)

We investigate the cognitive and neural underpinnings of perspective taking in relation to Theory of Mind and moral cognition. To address this, we use several methods including brain activity measurements (fMRI, EEG), mental chronometry and eye movement recordings (classic experimental psychology approach) and the study of the effects of brain lesion (neuropsychological approach) and brain stimulation (tDCS) on performance.

THE COGNITIVE AND NEURAL BASIS OF VISUAL PERSPECTIVE TAKING

A. Surtees, H. Bukowski, A.-A. Beck, D. Samson

Understanding what other people see plays a fundamental role in our social interactions. It is a first step from which we can infer more complex information such as what other people are talking about, what they like and dislike, what they intend to do and what kind of knowledge they form about the world. We showed that we automatically compute which objects are seen by someone else, an ability usually referred to as level 1 visual perspective taking (Samson et al., 2010). This automatic computation of the other person’s point of view means that we need to engage the fronto-parietal attentional control brain network to ignore the other person’s point of view and focus on our own point of view (Qureshi et al., 2010; Ramsey et al., 2013; see Fig. 1). In ongoing projects, we explore further the automaticity of these level 1 visual perspective taking abilities (as part of A.A. Beck’s PhD project in collaboration with B. Rossion) and how these abilities are affected by people’s emotional state and personality (as part of H. Bukowski’s PhD project). We also showed that computing “how” the object is seen from the other person’s perspective, an ability referred to as level 2 visual perspective taking, is not automatic and only occurs spontaneously when we are actively engaged in a social interaction. In order to solve level 2 visual perspective taking problems, we mentally rotate our body to the position of the other person, literally putting ourselves in the other person’s shoes (Surtees et al., 2013a; Surtees et al., 2013b). Such mental body rotation is however not used to solve level 1 visual perspective taking problems (Surtees et al., 2013a).

Fig. 1: In this study, participants were asked on half of the trials to judge their own perspective in a situation in which the self and the other perspectives were consistent (CS) or inconsistent (IS). On the other half of the trials, participants were asked to judge the avatar’s perspective in a situation in which the self and the other perspectives were consistent (CO) or inconsistent (IO). Activation in the dorsolateral prefrontal cortex (PFC), left posterior intraparietal sulcus (IPS) and the left temporo-parietal junction (TPJ) known to sustain controlled attentional processes, was found to be least recruited when participants had to judge the avatar’s perspective in the CO condition, suggesting that people effortlessly computed what the avatar saw. Adapted from Ramsey et al. (2013).
At the neural level, brain imaging studies have shown that understanding what other people think, want or feel (an ability referred to as “Theory of Mind”) relies on a network of brain areas, including the medial prefrontal cortex, the dorsolateral prefrontal cortex, the temporoparietal junction, the posterior cingulate cortex and the temporal poles. Through neuropsychological studies, we aim to further understand the functional role of these various brain areas (see Fig. 2). We showed that the right lateral prefrontal cortex allows us to resist interference from our own perspective (Samson et al., 2005). We also showed that the left temporoparietal junction plays a causal role in allowing us to monitor the environment to find relevant cues to infer the content of other people’s mental states (Michel et al., 2013). Ongoing projects aim at further characterizing the functional role of the various areas involved in the “Theory of Mind” network (as part of A. Biervoye’s PhD project in collaboration with A. Ivanou and L. Dricot). As a direct clinical application of this line of work, we are designing new diagnostic tools to better identify the specific deficits that patients may have following acquired brain lesions (such as following a stroke, a head injury or a neurodegenerative brain disease). We also started to investigate how excessive alcohol consumption affects the functioning of the “Theory of Mind” brain network (as part of F. Maurage’s PhD project in collaboration with Ph. De Timary). At the cognitive level, we showed that even healthy adults who have a fully-fledged Theory of Mind are not flawless when they explicitly reason about mental states (Wang et al., 2014; Liberati et al., in preparation). Such difficulties contrast with other evidence showing that adults and children automatically and implicitly process other people’s mental states (for a discussion see, Samson & Apperly, 2010). This suggests that there may be two types of “Theory of Mind” processes: those engaged in implicit reasoning and those engaged in explicit reasoning. Ongoing studies aim at systematically investigate differences between these two types of processes.

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THE PSY-NAPS

The Psy-NAPS laboratory is run by Martin Edwards investigates the relationships between perception and action in the disciplines of psychology, neuroscience and neuropsychology. The three main aims of the research are: (i) understand how the brain processes perception and action behaviours; (ii) develop assessments or diagnostic measures for perception and action behaviours; and; (iii) develop exercise/re-education activities to improve perception and action behaviours. A variety of methods are used including motion analysis, eye-tracking, virtual reality, dexterity and cognitive testing, neural stimulation and brain imaging with normal aged and brain injured participants. More specific details of the research activities by the laboratory are provided on the website http://psy-naps.org/. The details of six example projects are provided below.

EYE-TRACKING AND COGNITION: MEASURES OF IMPLICIT PROCESSES IN PERCEPTION AND ACTION

M. Edwards, C. Letesson

The project uses eye-tracking technology in order to investigate what visual features participants attend to during a task, without the need for the participant to make an overt explicit response. In perception and action, we are interested in the finding that action observation can moderate the performance of action execution. Here, we investigate what visual features in the observed action moderate subsequent performance, and we attempt to determine whether there are different components of what is observed that influence different specific components of action performance (e.g., speed, error, timing etc.). Furthermore, we explore the relationships between what is observed (through eye-tracking), what brain activity occurs, and what final action response is made (and measured) (Figure 1).

Fig 1: Here, participants first observed an action, and then executed an action. The actions that were observed were of a person sat opposite to the participant, and reaching either a small or large object on the left or right (all possible). We manipulated these observed actions by eye-gaze and action cue information. In a FULL condition, both cues were presented, whereas in the ACTION condition, only the action was presented (and the eyes were covered) and in a GAZE condition, only the eye-gaze information was presented (and there was no action). The cues could have an eye-gaze and/or action to the same spatial location (relative to the actor or the participant) and/or the same target object as that which the participant had to grasp in the second phase of the trial (spatial congruence and object congruence). After observation, the participant had to grasp the small or large object on the left or right (and the object to grasp was indicated with an auditory cue). For the observation of the ACTION condition, the results replicated previous data (e.g., Edwards et al 2003), showing that object congruency and spatial incongruency (equivalent to kinematic congruency) caused a reduction in the time to peak grasp aperture. However, in the FULL cue condition, the presence of the eye-gaze cue caused a retention of the observer’s perspective to that of the actor, causing specific priming only for the object congruent and spatial incongruent (kinematic congruent) condition. When the condition was spatial congruent (kinematic incongruent), there was more interference to the subsequent action execution. These data show that both cues are important in action observation, and there appears to be a combination effect of the cues leading to precise action planning prime effects.
EXPLORING SPATIAL PERCEPTION AND ACTION IN REAL AND VIRTUAL ENVIRONMENTS

M. Edwards, S. Grade, M. Pesenti, C. Van Brussel, B. Macq, Y. Coello

Recent research suggests that the perception of space boundary is determined from the simulation of action execution. Our research investigates whether observed and executed action in real and virtual space can modulate simulation and subsequently, the participant’s perception of space boundary. Using motion analysis and virtual reality technology, we test whether observing actions performed by models that have different arm lengths than that of the participant, or whether moderations to the participants own arm length in virtual reality can influence the participant’s perception of space boundary (See Figure 2 for an example of one the experiments in the research programme).

![Reachability judgment: Can you reach the object?](image1)

![Distance estimation: How far away is the object?](image2)

![Length estimation: What is the distance between the objects?](image3)

**Fig.2**: In the task presented here, we wanted to test whether action processes were necessary for different types of spatial perception. We asked participants to make perceptual judgments of reachability, distance estimation of an object relative to the self, and distance estimation between two objects. Participants either performed the task normally, or they responded to the different perceptual judgments while performing a hand-ball squeezing or arm biceps-curl dual task. The aim of the dual task was to test whether the concurrent action caused interference to the speed that participants were able to make the perceptual judgment (indicating that action is necessary for the perception). The results showed that only the hand-grasping action slowed perceptual judgments. This was demonstrated with an overall significant interference effect for the distance estimation of an object relative to the self, and a significant interference effect for reachability judgments for targets close to the edge of reach space. Based on these results, we can say that action must be used in egocentric spatial perception (space relative to the self), but that there may be different mechanisms underlying the different types of space perception. Furthermore, we interpret the hand-grasping dual task interference perhaps being linked to goal centered action processes.

VIRTUAL REALITY FOR SIMULATED USE

M. Edwards, E. Pasqualotto

The project develops technology that allows participants to make actions in virtual reality through the use of a brain computer interface. The proposed project builds on research in human computer interaction and brain computer interfaces and has three main objectives: (i) to combine brain computer interfaces with virtual reality technology; (ii) to understand recorded EEG brain activity in relation to action planning so that EEG activity can later be used to make virtual actions, and; (iii) to apply the research findings to clinical rehabilitative research.

ACTION OBSERVATION AND IMAGERY FOR THE TREATMENT OF BRAIN-DAMAGED COGNITION

M. Edwards, Y. Vandermeeren, T. Lejeune

Research shows that action observation and action imagery can be used to moderate or improve action performance. In the current project, we investigate how action observation and action imagery can be used to improve the perception and action performance of brain-damaged participants with specific cognitive impairments. We have three main projects, all of which measure cognitive perception and action, before and after action observation and / or action imagery, and in comparison to a control condition. For now, the project focuses on the development of treatments for action impaired hemiparesis, attention impaired hemineglect, and speech action / production impairments. We hope to add to the understanding of how action observation and action imagery can be used for the treatment and recovery of cognitions in brain-damaged participants.
THE IMPACT OF VESTIBULAR DEVELOPMENT ON VISUO-SPATIAL FUNCTIONS IN DEAFNESS

M. Edwards, E. Lacroix, N. Deggouj, A. De Volder, P. Rombaux, M-P. Noël

Recent research suggests that vestibular development dysfunction in deafness may lead to general deficits in cognitive development, such as visuospatial memory disorders, increased errors in orientation and reduced IQ. However, the full extent of the cognitive impairments, or the interactions with different types of deafness (and treatment), is not yet fully understood. In this project, we investigate the behavioural lives and neuropsychological functioning of deaf participants using a variety of different cognitive measures and testing equipment. The main aim is to develop a better understanding of these relationships in perception and action, in brain-damaged participants with hemiparesis, and in participants with moderated action capability induced by robot interaction. In addition, we investigate the relationship between spatial perception and action, and the perception of brain-damaged participants with hemiparesis, and in participants with moderated action capability induced by robot interaction. In this project, we investigate the relationship between action capability and spatial perception in brain-damaged participants with hemiparesis, and in participants with moderated action capability induced by robot interaction. In this example, we develop new tests battery of visuo-spatial cognition (Figure 3).

ROBOTIC INTERACTIONS IN PERCEPTION AND ACTION

M. Edwards, M. Alamour, V. Montedoro, T. Lejeune, B. Dehez, J. Sapin

Research has proposed independent neural processes for perception and action, yet action capability can influence spatial perception, and the perception of action (observation or imagery) can influence action performance. In this project, we investigate the relationship between action capability and spatial perception in brain-damaged participants with hemiparesis, and in participants with moderated action capability induced by robot interaction. In addition, we investigate the relationship between spatial perception and action, and the perception of brain-damaged participants with lateral biases in spatial attention, and in modified virtual-reality and robot-interfaced scenarios. From the understanding of these relationships in perception and action, we develop new exercises for the treatment of perception and action behaviours for brain-damaged participants.

EQUIPMENT

- Motion analysis (Polhemus 240HZ)
- Eye tracking (EyeLink 1000HZ)
- Reaction time (ePrime, PsychoPy and PsyScope)
- Simple Dexterity & Neuropsychological Tests
- Neuronal Stimulation (tDCS)
- EEG and Brain-Computer interface

FUNDING

- Programme Wallonie-Bruxelles Health Exercise 2013
- Marie Curie Actions of the European Commission
- Fonds de la Recherche Scientifique - FNRS
- Fonds Speciaux de Recherche (FSR)

SELECTED PUBLICATIONS


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The Clinical Neurosciences division of the IoNS is composed of eight research groups from Cliniques Universitaires UCL Saint-Luc and CHU Dinant-Godinne UCL. Research is closely interconnected with the clinical activities and utilizes a broad technological repertoire.

NEUR aims at understanding clinical, physiopathological, biochemical, cognitive and neuropharmacological aspects of various nervous diseases, e.g.:

- **Neurological diseases**: stroke (acute management, brain plasticity, non-invasive brain stimulation for therapeutic purpose), inflammatory diseases (in relation with the CSF analysis), neuromuscular disorders, Parkinson’s disease (deep brain stimulation), Alzheimer’s disease (early diagnosis by cognitive evaluation and biomarkers), refractory epilepsy, chronic pain, childhood neurometabolic disorders.

- **Neuro-otology** (cochlear implant induced plasticity, tinnitus) and the chemosensitive platform (neuropsychology, imaging, psychophysics)

- **Neurological aspects in neurooncology**, neurovascular disorders, epilepsy surgery (including invasive EEG)

- **Eye movement**, oculomotor as well as neurosensory disorders

- **Emotional, visual and musical recognition in various psychiatric disorders**: schizophrenia, bipolar disorder, alcohol dependency.

- The neuroimaging group occupies a central position to many research projects including: brain perfusion imaging, preoperative MRI in neuro-oncology, functional MRI, thermography, cerebral pathophysiology of stroke, etc.
NEUR DIVISION'S MEMBERS

The clinicians affected or affiliated to NEUR are engaged in several types of researches:
- Researches on clinical topics: patient series, case reports
- Sponsored research on new tools for diagnostic and treatment
- Collaborative research with other research groups belonging to COSY and CEMO.
Given the diversity of situations and collaborations only some selected projects are detailed in this report.

SAINT-LUC HOSPITAL

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Mélanie BRION
Eric CONSTANT
Philippe DE TIMARY
Fabien D’HOND'T
Magali LAHAYE
Sophie LECLERCQ
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Charline MARBAIX
Pierre MAURAGE
Nicolas MORETTI
Marie PONCIN
Audrey SCHMETS
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NEURO IMAGING
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Jacques GRISART
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Etienne MASQUELIER
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NEURO IMAGING
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Emilie VERRECKT
Maral YEGANEH DOOST

NEUROSURGERY
Claude GILLARD
Thierry GUSTIN
Aleksandar JANKOVI

REHABILITATION & PHYSICAL MEDICINE
Corinne BLEIYENHEUFT
Thierry DELTOMBE
Philippe HANSON
The Institute of Neuroscience, IoNS, provides an outstanding opportunity for the team of clinicians, especially the physicians of the Hospital, to develop their research projects, to collaborate with the other members of the Institute and heatedly work to progress in the knowledge and understanding of the nervous system.

The neurology department at Brussels Saint Luc university hospital provides a wide range of services for all varieties of neurological diseases. Areas of specialty include the Neuromuscular Reference Center (Resp. Professor P. VandenBergh), the Neuropsychology Center (Head Prof. Ivanoiu), clinical neurolinguistics (Professor M-P de Partz) or Epilepsy reference Center (Dr. Fernao Santos & Dr. El Tahry).

Research activities are of course mainly conducted in collaboration with colleagues from other departments (genetics, neuromaging, psychology, psychiatry, rehabilitation, …). Specific collaborations have been developed with the Oncobiochemistry group (Head Pr. Rombaux) and the Human Genetics Centre (Prof. Dr. Yves SZNAJER).

Academic research projects are conducted by most of the neurologists in their field of interest and strong collaborations do exist with research groups involved in more fundamental work. These last fifteen years have been characterised by many new therapeutic possibilities in neurological degenerative diseases but also multiple sclerosis, epilepsy and more recently acute stroke. The neurology department is one of the five most active of the hospital in clinical trials that may lead to new treatments.

Other important activities which will not be developed here, include specific research on multiple sclerosis and inflammatory disorders (see Laboratory of Neurochemistry report, CEMO), Parkinson’s disease and movement disorders, disorders of higher cortical functions, migraine, sleep disorders, stroke, pain ...

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**Neurology Department**

UCL Saint-Luc Hospital

All the members of the Neurology Department are working both as clinicians in the University hospital and as research clinicians in the IoNS Institute. Some of them participate in fundamental research projects in neurosciences. The neurology department from Brussels Saint Luc university hospital provides a wide range of services for all varieties of neurological diseases. Areas of specialty include the Neuromuscular Reference Center (Resp. Professor P. VandenBergh), the Neuropsychology Center (Head Prof. Ivanoiu), clinical neurolinguistics (Professor M-P de Partz) or Epilepsy reference Center (Dr. Fernao Santos & Dr. El Tahry).

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The key medical team of the Neuromuscular Reference Centre is assisted by a multidisciplinary team of medical specialists: cardiology (Anne-Catherine POULEUR), respiratory medicine (Prof. Dr. Giuseppe LISTRO, Dr. Benny MWENGUE, Dr. Véronique GODDING), orthopedics (Dr. Maryline MOUSNY, Prof. Dr. Thibaut LÉEMRIJSE), ENT (Prof. Dr. Gaetien DESUTER), ophthalmology (Prof. Dr. Antoinella BOSCHI), gastroenterology (Prof. Dr. Hubert PIESSEVAUX), neurosurgery (Prof. Dr. Chantal LEFEBVRE), oncology (Prof. Dr. Renier OPSOMER), intensive care (Prof. Dr. Philippe HANTSON), obstetrics (Prof. Dr. Pierre BERNARD), dermatology (Prof. Dr. Dominique TENNSTEDT), psychiatry (Prof. Dr. Eric CONSTANT), radiology (Dr. Thiery DUPREZ, Dr. Frédéric LECOUVET).
CRITERIA AND MANAGEMENT OF INFLAMMATORY Demyelinating Neuropathies

F. Pieret, V. Van Parijs, Y. Rajabally, S. Kawahara, P. Van den Bergh

Electrodiagnosis plays an important role in the early detection and characterization of inflammatory demyelinating polyradiculoneuropathies because timely treatment reduces morbidity and disability. As existing electrodiagnostic criteria for GBS and CIDP were either too non-specific or poorly sensitive, we have developed very sensitive electrodiagnostic criteria for GBS and CIDP in our EMG laboratory. These criteria in our hands are 100% specific with regard to other conditions such as diabetic polyneuropathy and ALS (Van den Bergh and Pieret, 2004).

Our electrodiagnostic criteria for CIDP have been validated in a multi-centre European study, which we have coordinated (Rajabally et al., 2009) and have played a major role in the development of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (Van den Bergh et al., 2016). The study of distal CMAP duration for refinement of the EFNS/PNS electrodiagnostic criteria for CIDP is ongoing as an European-Japanese collaborative project (S Mitusama, et al., The Japanese-European CIDP Electrodiagnosis Study Group, in preparation).

EFNS/PNS guidelines for the management of CIDP, MMN, and paraproteinemic demyelinating neuropathies have been published by an international task force. P. Van den Bergh leads the CIDP task force and is a member of the MMN and paraproteinemic demyelinating neuropathy task forces. The 3 guidelines have been published recently (P. Van den Bergh et al., 2010, R. Hadden et al., 2010, I. van Schaik et al., 2010).

Peter Van den Bergh is a member of the GBS Guideline Task Force, which was created in July 2013 and aims to publish a GBS diagnosis and management guideline in 2016. A retrospective study on the nosological characteristics, the diagnostic criteria, prognosis and treatment of all GBS patients admitted to the Cliniques universitaires St-Luc between 1987 and 2014 is ongoing (Nikolaj TOMAGOVA, Nikolaos TA-GLENT, Peter VAN DEN BERGH). As part of the GBS guideline project, a proposal for new diagnostic criteria and classification of GBS will be evaluated and hopefully validated (Wakerley et al., submitted).
PSYCHOMETRIC PROPERTIES OF ACTIVLIM IN 2-YEAR CROSS SECTIONAL RECORDS OF THE BELGIAN NEUROMUSCULAR DISEASE REGISTRY

C.S. Batcho, P. Van den Bergh, Ph. Vandenauwe, A. Roy, M. Pesas, for the BNMDR scientific committee

ACTIVLIM is a Rasch-built measure of activity limitations in children and adults with neuromuscular disorders. This study aims to investigate its psychometric properties as used in clinical practice in the Belgian Neuromuscular Disease Registry (BNMDR).

A sample of 2986 consecutive patients (56% male, 92% adult over 16 years, and 85% Dutch speakers) was assessed at least once in the BNMDR over years 2011 and 2012 in 6 reference centers across the three main regions in Belgium, leading to 4146 records. The dataset was analyzed with the Rasch rating scale model in order to determine the difficulty of each item (i.e., the calibration) and their targeting to the ability of the patients on a unidimensional and linear scale, to investigate item and person fit and item invariance across demographic and clinical sub-groups, to determine the reliability in this dataset, to compare the BNMDR item difficulty hierarchy with the original scale calibration and to measure the patients change in activity (t-score) over one year (n=1128).

The BNMDR ACTIVLIM data showed excellent fit to a unidimensional scale. The reliability index was 0.95 in the BNMDR and the items were well targeted for 87% of the patients. Invariant item difficulties were observed across age, gender, language, regions, centers, chronicity, item presentation orders and over time. Slight clinically meaningful variations in item difficulty hierarchy were observed across diagnoses. The item calibration was similar to the original publication but with a 3-fold accuracy. A slight but significant deterioration in activity (t=-0.39±1.70; p<0.001) was observed over one year for all diagnoses, except for Amyotrophic Lateral Sclerosis showing a stronger deterioration (t=-1.68±2.1; p=0.001) and for Chronic Inflammatory Demyelinating Polyneuropathy showing a more stable condition (t=-0.49±1.65; p=0.1).

The ACTIVLIM records in the BNMDR demonstrated very good psychometric properties.

REFERENCE VALUES OF THE DISTAL COMPOUND MUSCLE ACTION POTENTIAL DURATION FOR DIAGNOSIS OF CIDP: A JAPANESE-EUROPEAN MULTICENTER PROSPECTIVE STUDY


The distal compound muscle action potential (DCMAP) duration is a useful parameter to detect axonal demyelination in the distal nerve segments, and currently employed in the electrodiagnostic criteria of CIDP (EFNS/PNS, 2010). However, the cut-off values in the criteria are provided using only 20 Hz low-cut filtering, whereas DCMAP durations are substantially influenced by low-cut filter settings. We aimed to establish widely available reference values of DCMAP duration with a number of low-cut filters. We prospectively measured DCMAP duration of the median, ulnar, peroneal and tibial nerves in 59 typical CIDP patients and 147 normal controls in a multicenter population of Europe (Belgium, UK) and Japan. The low-cut filter setting was set as 2 Hz, 5 Hz, 10 Hz, and 20 Hz. The cut-off values were calculated as the point with 98% specificity by plotting ROC curves between CIDP patients and normal controls. Low cut filter settings significantly affected DCMAP durations both in CIDP and normal controls; the use of lower filters was associated with the shorter DCMAP duration in all 4 nerves. We provided the cut-off values of each nerve under each low-cut filter settings. Using these cut-off values, the sensitivity was 56-77% and the specificity was 95-98%. We confirmed the effects of the low cut filters on DCMAP duration and established, in the four nerves tested, the cut-off values for each low-cut filter settings: 2 Hz, 5 Hz, 10 Hz, and 20 Hz. The reference values can be widely used for diagnosis of CIDP.
SELECTED PUBLICATIONS


COGNITION IN NEURODEGENERATIVE DISORDERS

Humans have the capacity of learning at a single exposure and later recalling complex information made of disparate elements that are held together into a same unit in a specific temporo-spatial context. This ability is called relational, associative or contextual memory and was found to depend on the hippocampus. Amnestic mild cognitive impairment patients (aMCI), putative predemential Alzheimer’s disease (AD), constitutes an experimental model particularly well suited to study these aspects since relational memory impairment is the core of their deficit and these patients show hippocampal morpho-functional changes. Previous research from our group already showed that:

- aMCI patients are more sensitive to interference and this deficit is not only related to the competition between items at the recall phase but, specifically and contrary to healthy elderly, it is present since the encoding phase.
- patients with aMCI have an abnormal activation of their temporal lobes in fMRI in a paradigm of associative memory and this is related to atrophic changes, predominant in the anterior temporal lobes.
- Patients with aMCI have a specific pattern of atrophy in the hippocampal subfields (more atrophic CA3 and subiculum when compared to healthy elderly).
- multimodal imaging -including magnetic resonance imaging (MRI) and positron emission tomography (PET)- improves the classification of patients attending Memory Clinics. A combination of various imaging techniques and memory testing appears the best way to distinguish worried-well from early AD patients.
Amnestic mild cognitive impairment (aMCI) is a condition characterized by an isolated episodic memory deficit without impairment of daily life activities. Many, although not all aMCI patients evolve to Alzheimer's dementia in a few years. However, healthy ageing is also characterized by a memory decline. Therefore, a distinction between the memory deficit related to an incipient AD and the one apparent with ageing is necessary. Surrogate markers are under study today in order to better recognize early stages of AD. The main goal of the present study is to evaluate with a multi-marker approach the mild cognitive impairment patients consulting at the Memory Clinic in Saint Luc Hospital.

This project has been approved by our local Ethics Committee. Ninety-one subjects have been included, 31 of them are healthy elderly volunteers, the other 60 are patients recruited from those consulting the Memory Clinic. All participants underwent a detailed neuropsychological examination, a volumetric brain MRI, a 18FDG PET scanner, a 18flutemetamol PET scanner and an ApoE genotyping. The specific interest of this study was to create a common database for all surrogate markers.

This study has proved that a combination of volumetric brain MRI, 18FDG PET scanner and 18flutemetamol PET scanner was the best way to disclose early AD patients, before dementia and even before memory impairment for some of them. Other analyses are still ongoing, mainly concerning regional patterns of cortical atrophy and hypometabolism in amyloid-positive patients. We are also interested in comparing patients with worried-well subjective complainers and healthy elderly. Furthermore, we just obtained authorization to continue the study and include a longitudinal follow-up of patients up to three years (end of study expected in 2017). In this second part of the study, we will add resting-state functional MRI to the other imaging techniques already performed by our group.

Fig.1: 18F-flutemetamol scan of a healthy volunteer (left) and a patient presenting mild cognitive impairment due to Alzheimer's disease (right). Amyloid deposits appear in red.

Fig.2: Cortical thickness analysis between amyloid-positive MCI (AP-MCI; n=28), neurodegenerative only MCI (NO-MCI; n=19) and biomarker negative subjective complainer (BN-SVI; n=13).

Comparing PET Scan-18FDG and Resting-State FMRI in Preclinical Alzheimer Disease

B. Hanseeuw, A. Ivanoiu, RA. Sperling

In October 2014, B. Hanseeuw will join Prof. Sperling lab at Harvard Medical School. He will work there on longitudinal FDG-PET and resting-state data in amyloid-positive asymptomatic elderly (preclinical AD). He will also have the opportunity to discover tau-imaging. This new international collaboration will be highly valuable to improve the ability of our group to analyse longitudinal functional imaging data together with molecular imaging of preclinical AD patients. This project is supported by a grant from the Belgian American Education Foundation.
Our aim is to investigate the relational aspects of memory for words and faces in older adults and without pre-demential Alzheimer’s disease (AD). Learning complex information implies establishment of relationships between the disparate elements that compose this piece of information and a specific temporal-spatial context. Neuro-anatomically, this ability referred to as relational, associative or contextual memory was found to depend on the hippocampus, cerebral substrate subjected to morpho-functional changes in AD since the early stages of the disease. In our first study, we inquired about the contiguity/asymmetry effects through a behavioral paradigm measuring the probability of recalling words in a recently studied list according to their distance into the list. The contiguity effect refers to the fact that the successive recall of nearby items into the initial list is more probable than the successive recall of items that are spaced into the list. The asymmetry effect refers to the fact that the recall in the direction of the list is more likely than the recall in the opposite direction. Results showed that the contiguity effect was reduced in patients with positive AD biomarkers compared to healthy controls (Figure 1). On the contrary, the asymmetry effect was similar across groups. These findings suggest that patients with positive AD biomarkers have difficulties to process the contiguity of events and the commonality of context between events, which could contribute to their general deficit in episodic memory. In a second study, we will investigate other effects described in the context of the relational memory: the pattern separation/completion effects through behavioral, functional and volumetric paradigms that will use new vs. old faces as stimuli. We hypothesize that patients with positive AD biomarkers will show reduced performance compared to healthy elderly, irrespective of the items presentation modality (verbal vs. visual) and the type of relationship among items (temporal vs. spatial). The theoretical interest of the current project is to highlight qualitative differences in relational memory between healthy elderly and patients with predemential AD, related to different lesional patterns and brain activation.

**AWARD**

B. Hanseeuw received in 2013 the Belgian Neurological Society prize for the best young research investigator.

**FUNDING**

- Belgian American Education Foundation
- La Plateforme pour l’Education et le Talent
- Fondation Saint-Luc
- L’oeuvre du Calvaire Malte
- General Electric Healthcare (Flutemetamol provider)
- FNRS

**SELECTED PUBLICATIONS**

1. Ivanou A, Dricot L, Gilis N, Grandin C, Lhomme R, Quenon L, Hanseeuw B. Classification of nondemented patients attending a Memory Clinic using the new diagnostic criteria for Alzheimer’s with disease-related biomarkers. – submitted (under revision).


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AFFECTIVE AND SOCIAL NEUROSCIENCE OF ADDICTIONS, SCHIZOPHRENIA AND OTHER PSYCHIATRIC DISORDERS

Our main research interest is the exploration of the brain correlates of alcohol-related problems by means of a multidisciplinary approach combining neuropsychological, electrophysiological neuroimaging and biological tools. We propose a developmental perspective exploring these impairments in alcohol-dependence but also at earlier stages of the pathology (e.g. binge drinking). We are also interested in the influence of biological factors involved in addictions (e.g. stress, inflammatory factors and gut permeability). Our research group is part of the Laboratory for Experimental Psychopathology (LEP), which is specialized in the elucidation of the psychological processes involved in the development and maintenance of addictive behaviours and emotional disorders, as well as in the development of psychological interventions targeting these processes. This experimental psychopathology approach is inspired by complementary theoretical backgrounds and methodologies (e.g., social and affective neurosciences, cognitive and behavioural psychology, neuropsychology, cognitive psychopathology).

Besides these aspects related to addictions, we also develop other research topics that explore cognitive and emotional dimensions of different psychiatric diseases, in particular in schizophrenia and Huntington disease.

PHILIPPE DE TIMARY, MD, PhD (Head of the Alcohol-dependence Unit in academic hospital Saint-Luc)
Pierre MAURAGE, PhD, Research Associate at the Fonds National pour la Recherche Scientifique Eric CONSTANT, MD, PhD (Head of Adult Psychiatry Department in academic hospital Saint-Luc)

Fabien D’HONDT, Postdoctoral Fellow
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Sophie LECLERCQ, PhD Student
Lahaye MAGALI, PhD Student
Marie PONCIN, PhD Student
Audrey SCHMETS, PhD Student

PHILIPPE DE TIMARY, MD, PhD
Pierre MAURAGE, PhD
Eric CONSTANT, MD, PhD

EMOTIONAL AND INTERPERSONAL PROCESSES IN ALCOHOL-DEPENDENCE

P. Maurage, P. de Timary, M. Brion

During the last decade, the rise of socio-affective neuroscience has led to major changes in the research topics and strategies in social psychology, psychology of emotion, and neuropsychology. Extending this renewal to psychiatric populations would not only markedly revitalize knowledge about psychopathology but also about healthy socio-affective functioning. This project aims at taking part in this development of social and affective neuroscience of psychopathology, by exploring emotional and interpersonal processes in alcohol-dependence (AD), where socio-affective impairments are omnipresent and play a central role in relapse. We have indeed already conducted several studies showing that AD is characterized by massive emotional processing impairments. Capitalizing on these earlier results, this project aims at (1) building an integrative model of AD: AD research and models have focused on cognitive functions and have neglected emotional-interpersonal impairments. The present project thoroughly explores these impairments, to lead to an integrative model of cerebral, cognitive, emotional and interpersonal deficits in AD. This model will allow switching from the current models (focused on cognitive and frontal dysfunctions) to multi-level theoretical proposals offering a large description of AD impairments and thus broadening experimental perspectives and renewing therapeutic proposals in AD; (2) Shedding new light on social and affective neuroscience in healthy individuals: studying clinical populations has traditionally improved the understanding of normal functioning in (neuro)psychology. As AD leads to massive socio-affective difficulties, exploring them will clarify crucial questions in social and affective neuroscience, notably concerning the specific characteristics of ‘social mind’ and ‘social brain’. Following these aims, recent works conducted in our group notably allowed to determine the brain correlates of emotional (Figure 1) and interpersonal (Figure 2) impairments in alcohol-dependence in more ecological situations using innovative neuroscience paradigms.

Fig.1: Contrast results showing the activity of crossmodal (in red) and unimodal areas (in blue) during the specific processing of emotional face-voice pairs (as compared to isolated face or voice processing). This figure illustrates the massive reduction of the brain activations related to crossmodal emotional processing in alcohol-dependence. p < .05 corrected for multiple comparisons at cluster size. Error bars indicate standard deviations.
EMOTION-VISION INTERACTIONS IN ALCOHOL-DEPENDENCE

P. Maurage, P. de Timary, F. D'Hondt

This project explores the neurophysiological substrates of emotional deficits in alcohol-dependence, with a twofold aim: (1) determining whether these deficits are due to impaired emotional processing per se or, at least partly, to a more basic visual impairment; (2) testing, in a clinical population, the validity of the «affective prediction» model (Figure 4), which offers a totally new perspective on vision-emotion interactions. Indeed, emotional decoding deficits have been widely described among alcohol-dependent individuals (ADI) and are classically considered as indexing a genuine emotional impairment. However, recent evidence suggests that visual deficits might play a role in these emotional alterations. Determining the interactions between visual and emotional processes thus appears crucial as it might lead to a deep reinterpretation of earlier studies exploring emotional processing among ADI. At a more general level, the question of whether emotional processing arises in reaction, in parallel or is intrinsically linked to visual processing is still an open issue. The recent «affective prediction» model proposes that visual and emotional processes are closely related. This model is based on previous works showing that the brain guesses the identity of a visual stimulus from a coarse impression of visual inputs, which relies on low spatial frequency (LSF) information more slowly conveyed. In this context, the affective content is an essential part of visual prediction prioritizing relevant information for survival and well-being. While heuristic, this recent model is still in need of experimental support. As alcohol-dependence may be associated with both altered LSF pathways and OFC but overall preserved HSF pathways and ITC, this population offers dissociation between the two pathways postulated by the affective prediction hypothesis, and thus constitutes a relevant psychopathological model to test it. Following the model's predictions, emotional dysfunction among ADI could rely on altered affective prediction at early stages of visual processing. By exploring this hypothesis, this ongoing project offers a better understanding of the roots of emotional deficits among ADI and tests for the first time the affective prediction model in a clinical population.
We propose that emotional deficits in alcohol-dependence might be the consequence of impaired early emotion-vision interactions (in yellow) based on the identification of the affective value on the basis of coarse (low spatial frequency, LSF) processing by the dorsal visual stream (orbitofrontal cortex, OFC and parahippocampal gyrus, PHC) ending in the infero-temporal cortex (ITC).

Besides the importance of social interaction in AD that has been described above, Hull and colleagues have also described the importance of the relation to the self. In its self-awareness theory of drinking, he had shown that ADI had a strong tendency to relapse in situations where the self was threatened. In keeping with this hypothesis, we observed that self-consciousness (i.e. the tendency to focus on the self or the way the self is perceived by others) was a strong moderator of the relation between affects and alcohol craving (9). We are currently developing a new project in collaboration with professor Vermeulen from the institute of psychology where we will test various dimensions of the self (body awareness, feeling of agency, autobiographic memory) as possible determinants involved in the development of alcohol-dependence, by testing this hypothesis both in binge drinkers and in ADI. We will also evaluate whether these dimensions are related to biological markers that could somehow alter the sense of self.

**THE ROLE OF SELF-CONSCIOUSNESS AND BODY AWARENESS IN THE TENDENCY FOR DRINKING IN ALCOHOL-DEPENDENCE**

M. Poncin, P. Maurage, P. de Timary, S. Leclercq

Besides the importance of social interaction in AD that has been described above, Hull and colleagues have also described the importance of the relation to the self. In its self-awareness theory of drinking, he had shown that ADI had a strong tendency to relapse in situations where the self was threatened. In keeping with this hypothesis, we observed that self-consciousness (i.e. the tendency to focus on the self or the way the self is perceived by others) was a strong moderator of the relation between affects and alcohol craving (9). We are currently developing a new project in collaboration with professor Vermeulen from the institute of psychology where we will test various dimensions of the self (body awareness, feeling of agency, autobiographic memory) as possible determinants involved in the development of alcohol-dependence, by testing this hypothesis both in binge drinkers and in ADI. We will also evaluate whether these dimensions are related to biological markers that could somehow alter the sense of self.

**BIOLOGICAL MARKERS OF ALCOHOL-DEPENDENCE**

S. Leclercq, P. de Timary

Besides its psychological and social dimensions, the development of alcohol-dependence also involve important changes at the level of biological markers. Most biological studies so far have focussed on neurotransmitter disequilibrium to explain the development of the addiction. Our group has focussed on changes in biological markers that occur out of the brain. We have first tested the hypothesis that while becoming dependent, besides changes occurring at the level of the brain, there is also an adaptation of energy balance. The conclusions from that metabolic and endocrine study was that for a fraction of ADI, alcohol drinking induces a large acceleration of energy metabolism that is related to a decrease in body weight and fat mass and a decrease in the production of leptin, a physiological brake to energy intake. Altogether, this decrease in the regulation of energy intake in heavy drinking ADI subjects leads to a large increase in total energy intake (food and drinks), despite the fact that these subjects remain lean (10). A second hypothesis that we have tested in collaboration with the team of nutrition of Professor Nathalie Delzenne, is the possibility of alterations in gut permeability in ADI, and that these changes might induce changes in behaviour, through a communication between the gut and the brain. We indeed have observed a large increase in intestinal permeability in ADI at the beginning of alcohol withdrawal and that this increase was related to a rise in bacterial fragments in the blood and to the development of an inflammation that was related to psychological dimensions of alcohol (11). More recently, we have described into details the nature of the inflammatory pathways stimulated in polymorphonuclear cells by alcohol-dependence and came to the conclusion that these pathways were essentially stimulated at the level of the gut (12). We are currently investigating the nature of the changes occurring at the level of the gut microbiota, and are planning to correlate these aspects with brain alterations in ADI.
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Fig. 5: Model for disruption of energy balance in ADI. In alcoholics drinking « low alcohol » quantities, alcohol mainly serves as a fuel and the alcohol related energy intakes are compensated for by a decrease in food intakes. This balance is probably due to a rise in anorexigenic peptides including leptin, PYY, a stimulation of the hypothalamo-pituitary-adrenal axis and a decrease in orexigenic peptide ghrelin. In those drinking « high alcohol » quantities, alcohol mainly acts to accelerate metabolism, and induces a decrease in fat mass and in plasma leptin, which disrupts leptin regulated balance in energy intakes. Hence, the excessive alcohol related energy intakes are no-longer compensated for by a decrease in food intake and total intakes largely exceed norms.

Fig. 6: Schematic representation of inflammatory signaling pathways observed in Polymorphonuclear cells of ADI. Alcohol induces an increase in gut permeability, a rise in lipopolysaccharides (LPS) and peptidoglycans (PGN), which are fragments from the gut bacteria. These will induce a stimulation of specific inflammatory pathways within polymorphonuclear cells in the blood that lead to the secretion of cytokines. The circulating levels of these cytokines are correlated to the quantity of alcohol drunk per day by ADI and to alcohol craving, suggesting that inflammation it might play a role the pathophysiology of alcohol-dependence.

TOWARDS A DEEPER AND CLOSER TO REAL LIFE INVESTIGATION OF EMOTIONAL IMPAIRMENTS IN HUNTINGTON’S DISEASE

Labaye M., P. Maurage, C. Markais, E. Constant

Huntington’s disease (HD) is a genetic neurodegenerative disorder characterised by progressive cerebral atrophy, primarily affecting basal ganglia before expanding through the brain. While originally described as a chorea, thus focusing on the motor symptoms, it progressively appeared that this pathology also leads to non-motor symptoms like cognitive alterations (concerning executive functions, attention or memory) and psychiatric disturbances (mainly depression, suicidal ideation and anxiety).

This project is a first exploratory step offering the first insights concerning unexplored topics in HD: (1) The subtle emotional processing; (2) The processing of non-facial emotional stimulations; (3) The crossmodal processing of emotional stimuli. If results are promising, they will be extended in a more ambitious project combining behavioural, electrophysiological and neuroimaging techniques to precisely explore emotional deficits in HD, following the example of the studies we conducted in other clinical populations. This project will thus lead to theoretical implications (e.g. concerning the specificity of the emotional deficit for disgust, the brain correlates of this deficit and its generalisation to real-life situations), but also to therapeutic propositions, by allowing the development of clinical programs focusing on these deficits’ rehabilitation (e.g. ‘FaceTales’, recently developed in our group: http://www.ipsp.ucl.ac.be/recherche/projets/FaceTales/en/Home.htm), and thus improving quality of life in HD.

INVESTIGATION OF THE GENERALIZATION AND THE SPECIFICITY OF THE IMPAIRMENT OF EMOTIONAL DECODING IN SCHIZOPHRENIA

E. Constant, P. Maurage, C. Mangellinckx, J-B Belge

Decoding impairments of emotional facial expressions are observed in schizophrenia, but several questions remain unanswered concerning the specificity of this deficit for the emotional characteristics of faces and on the potential generalization of this deficit in other social stimuli or in situations closer to the daily life. The present study aims at exploring these questions, and in particular at testing three hypotheses:

1. The specificity of the deficit for the emotional aspects of faces, by testing if this deficit is specific for emotions or also present for other complex facial treatments, independent from emotions (for example judgment of age or gender).

2. The generalization of this deficit to more elaborated interpersonal skills, and in particular in capacities of theory of mind and empathy such as estimated by Reading the Mind in the Eyes Test (RMET).

3. The evolution of this deficit in situations closer to real situations of social interaction, in particular during the treatment of crossmodal emotional stimuli involving simultaneously the processing of emotional faces and voices.
Among the deficits present in schizophrenia, numerous authors have studied the presence of impaired skills in the theory of mind, and this, already from a first psychotic episode. The theory of mind consists of the capacity of human beings to predict or to explain the behavior of others allowing that the latter possesses mental contents different from ours. Those deficits were defined as being important predictors of social functioning in schizophrenia.

In the led studies, it would seem that the subjects suffering from important negative symptoms present a deficit significantly more important than the subjects having a lower level of negative symptoms.

This present study aims to explore more finely the results obtained by every patient, and so, to be able to reveal if a consensus exists concerning skills in theory of mind in schizophrenic patients. We will use in this study two tasks of false beliefs exploring the behavioral capacities of inhibition of the subjects by involving requests of inhibition of high-level but also low-level.

### Equipment

- EEG-ERPs
- tDCC
- fMRI (Radio-diagnosis Unit, St-Luc Hospital)

### Funding

- FNRS - FSR
- FRIA
- UCL

### SELECTED PUBLICATIONS


My research interests include assessment of language in neurologically adult patients with acquired focal or degenerative lesions, relationship between assessment and language therapy, and development of treatments from a current cognitive approach.

Consistent with current cognitive theories, our clinical research aims at developing a language battery for adult French patients who present neurologically acquired (focal or degenerative) lesions. This language battery would enable the clinician to detect variety of language disorders, to assess the overall severity of aphasia, to elucidate the nature of the language impairment(s) and to indicate what aspects of language performance are most appropriate for treatment. Moreover, we will try to inform more precisely (and earlier) of the heterogeneous forms of language disorders in patients who presented primary progressive aphasia.

CLINICAL NEUROLINGUISTICS

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**ASSESSMENT OF LANGUAGE IN NEUROLOGICALLY ADULT PATIENTS**


M. Boisson, C. Gentile, M-P. de Partz

The FLAA-18 is conceived to be a theoretically screening assessment of language disorders in the French speaking adult population (Belgian and French). It includes 18 subtests for the assessment of both comprehension and production of oral and written language. In the whole battery, different variables (word frequency, grammatical class, concept familiarity, semantic subcategories, age of acquisition, lexicality, regularity of spelling, length, etc.) which are known to have significant influence on performance, were tested or controlled. Identical stimuli are included in some tests to be administered across different modalities (verbal and non-verbal), enabling the clinician to detect differential impairments across these domains of input/output.

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Normative data in relation to age, level of school and gender are obtained from a large sample of neurologically healthy adults subjects (from 35-89 years and from four educational levels). At this stage, the whole battery was administered to a total of 144 neurologically healthy adults aged from 40 to 69 years with no history of neurological or psychiatry disorders, alcohol or drug, visual or hearing deficits or learning disability. The sample of population is composed of 62 men and 82 women (68 Belgians and 76 French). Subdivisions within the age and education groups are as follow: three age subgroups (40-49; 50-59; 60-69) and four education subgroups: level 1 (< 9 years of formal education), level 2 (between 12-14 years), level 3 (15 years) and level 4 (university education). Each cell is composed of 12 subjects. Qualitative analyses of error types are also reported.

Among the results, and according to the literature, we retain a significant age effect in different tasks: picture naming, fluency index in oral and written narrative tasks, oral (but not written) comprehension of complex sentences. Education effect is reported in reading and writing irregular words, in oral and written comprehension of unfrequented words and in production of syntacical complex sentence. A gender effect is retrieved in some semantic subcategories. On the whole sample, we note that names are easier to treat than verbs. Contrary to the literature, none interaction is found between age and educational level in oral naming, due likely to a lack of sensitivity of the naming test.
In the following phase of this clinical research, a final version of the battery with minor revisions will be conducted and the normalization of the FLAA-18 will be completed. Data will be collected in a sample of 30 stroke aphasic patients and in 30 primary progressive aphasia to test the sensitivity of the battery of language tests. Test-retest reliability and inter-rater validity will be also provided.

3. **Quantitative and qualitative analysis of narrative and connected speech in aphasic patients and in primary progressive aphasia**

A-C. Berlier, I. Léopold, M-P. de Partz, in collaboration with Professor Agnese Pillon (IPSY)

Careful analyses of connected and narrative speech can provide valuable information about patients' language capacities. In this study, we set out to determine whether the same analysis could be carried out in order to assess progressive recovery of language abilities in acute aphasic patients or their decline in neurodegenerative aphasia. For that purpose, we will use the method described by Rochon and coworkers (Rochon et al., 2000 and Fraser et al., 2013) to analyze patients discourse. We will extract detailed measurements of semantic, lexical, morphological and syntactic characteristics of patients' discourse from transcriptions of connected speech and narrative speech (tasks 1 and 2 of the FLAA) for three groups: acute aphasic patients, primary progressive aphasia and healthy controls. We assume that the analysis of the influential features will be sensitive to the change encountered in the two groups of patients. In the same time, we would expect to observe test-retest reliability in healthy controls.

3. **“The cognitive profile of the bilingual brain: A unifying framework”**

M-P. de Partz, in collaboration with Professor Arnaud Smalac and Lise Van der Linden (FNRS) (IPSY)

It is now widely accepted that bilinguals differ from monolinguals in a wide range of cognitive processes. In the linguistic domain, numerous foreign-word-learning studies consistently find that bilinguals outperform monolinguals in language acquisition skills. However, the cognitive mechanisms that underlie this advantage remain poorly understood. In the non-linguistic domain, there is ample evidence that bilinguals have marked advantages in executive control functions, like inhibitory control or resistance to interference. This executive control advantage is assumed to result from the continuous requirement to resist (inhibit) interference from one language when speaking in a second language. Interestingly, although both bilingual advantages originate from the same (bilingual) language experience, both areas of research have developed independently from each other and it remains unclear whether and how these advantages may be accommodated within a single, unifying theoretical framework. The current research project attempts to integrate these two co-existing lines of research on bilingualism under the hypothesis that improved executive control capacities are directly responsible for superior language acquisition skills in bilinguals.

The above hypothesis will be tested by using experimental research designs, in both adult and developmental samples of mono- and bilinguals, taken from normal and pathological populations. Two lines of research will be developed. The first line of research investigates the main question, i.e. to know to which extent bilinguals’ executive control benefits may also be responsible for their improved word-form acquisition skills. Within this unifying framework, the second line of research is then aimed to investigate how impaired executive control functions may affect language acquisition and processing in bilingual stuttering and bilingual aphasia.

**AWARD**

17/02/2014: Raymond Bassem Prize managed by the Rotary Club North-Brussels (4.000€) for the master dissertation entitled « LAB-15 normative data in relation to age, gender and level of school education in 144 neurologically healthy French patients. » (Marjolaine Boisson, Clothilde Gentile & Marie-Pierre de Partz).

4/12/2013: Gert Noël Prize winning project - 30.000 € (2013) managed by King Baudouin Foundation for « The Information to patient relatives of aphasic patients’ group » (Marie-Pierre de Partz, Caroline Detry, Bénédicte Léonard & Pauline Meys).

**FUNDING**

- FNRS

**SELECTED PUBLICATIONS**


**CONTACT**

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The department of Otorhinolaryngology of the Cliniques universitaires Saint-Luc offers a wide range of services for all otorhinolaryngological diseases. Within the department, the units of Rhinology and Otology are affiliated to the Institute of Neuroscience (IoNS). Research activities are mainly conducted in collaboration with colleagues from other departments (Algology, Medical imaging, Neurology, Neural Rehabilitation, PSY-NAPS...). In Otology, research activities focus on the development of implantable hearing devices, the rehabilitation of patients with cochlear implants and tinnitus, and the study of the vestibular functioning in children with developmental delays. In Rhinology, research activities focus on chemosensory function (taste, smell and trigeminal functions). The IoNS offers the opportunity for our team of clinicians to develop their research projects in parallel to the clinical activity and in collaboration with other colleagues of the institute.

LONGITUDINAL EVALUATION OF TEMPORAL FINe STRUCTURe'S COding BY PATIENTS WITH UNILATERAL COCHLear IMPLANT: 2 SUBTESTS FROM A§E ANd TEMPORAL FINE STRUCTURE

F. Ngo, J.Wathour, N. Deggouj

A temporal fine structure coding information is mainly mediated by phase locking mechanisms. Temporal fine structure (TFS) disturbances will have a negative impact on speech discrimination in a quiet and noisy environment. Cochlear implanted patients receive limited TFS information and are very disturbed in noisy environment.

The just noticeable difference (JND) of dysharmonic A§E test is frequently presented as a useful test to study the TFS functioning.

A study is going on the JND measures done in cochlear implanted subjects to verify if this measure correlates effectively with their speech perception abilities in a noisy and quiet environment.

VSAD: A NEW BATTERY FOR THE EVALUATION OF VISUOSPATIAL ABILITIES IN DEAFNESS

E. Lacroix, N. Deggouj, M. G. Edwards

People that are deaf or are hard of hearing particularly rely on visuospatial perceptual and action abilities, not least for communication using sign language. Unfortunately, hearing loss can lead to vestibular function deficits that may impact cognitive and visuospatial behaviors.

With the support of the “Fondation Saint-Luc”, we have the opportunity to start the creation of a new battery of tests for the evaluation of Visuo-Spatial Abilities in Deafness (VSAD). The VSAD will use computerized tests presented on a WACOM tablet, developed with DiagnoseIS software (Metrisquare Company). The main functions that we propose to evaluate with this battery include visual perception, selective visual attention, visuospatial working memory, mental rotation and reproductive abilities (two dimensions). We propose that the use of new computerized technology for the tests will allow greater precision and reduced variance in the different measures, as well as additional dependent variables such as reaction time and response efficiency, not possible in traditional paper and pencil tests. In addition, the simplification of the tasks (recording and automatic correction of the
data), will improve contact between the patient and the practitioner, and provide more time to the practitioner for listening to the patient, and qualitatively understanding the patients various difficulties. The test will also provide economic savings (with time in report writing, and increasing the ability of the clinician to handle more evaluations).

THE SUBCUTANEOUS CARINA MICROPHONE IN COCHLEAR IMPLANTS: CLINICAL STUDY – PHASE 1

J-M. Gérard, N. Verhaert (KUL)

Cochlear has been working towards the advancement of implantable microphone such subcutaneous and intra-mastoid devices to address the needs of totally implantable device development, improvement of microphone sensitivity and quality to improve functional hearing results, the quality of life and cosmetic.

People who suffer from moderate to profound hearing loss wear classical hearing aids or cochlear implants. Those aids offer sufficient gain but other problems arise such occlusion effect, feedback, chronic skin conditions of the external canal, poor speech understanding in noise, sound localization problem, practical and cosmetic impacts.

For the patients indicated above, a new implantable microphone called Tubemic was developed by Cochlear in close collaboration with specialists in microtechnology and otological microsurgery. It works on the principle of a numeric microphone incorporated in a titanium tube which also include a mechanical sound amplifier system. The Tubemic is coupled via a rod to the ossicular chain to record the natural mechanical vibration of the ear.

NEW COUPLINGS WITH THE CODACS ACOUTIC IMPLANT

J-M. Gérard, N. Verhaert (KUL)

Direct transfer function of an acoustic stimulator can be measured using Laser Doppler Vibrometry (LDV) on a third window on the scala tympani (with intact endosteum) created using a robotic drill. We want to investigate the functional results of the Codacs stimulation on the round window (RW), Lateral semicircular canal (LSCC), stapes, footplate and develop the surgical and coupling techniques.

FEEDBACKS IN ACTIVE TBAHA AND CODACS IMPLANTS

J-M. Gérard, N. Verhaert (KUL)

We study the feedback signal picked up by the microphone of the Sound processor on the behind the ear of active implanted device such the tBAHA and Codacs. The active tBAHA measurements consisted of three tested conditions such:

- The transducer at BAHA reference position and touching the strain relief of the BTE cable close to the ear canal.
- The transducer at BAHA reference position without touching the strain relief.
- The transducer is close to the ear.

The two non-compensated stimuli were:

1. Exponential Sine Sweep
2. MaximumLength Sequence

For the Codacs measurements, the stimuli we used were the same as before.

TUBEMICROPHONE R AND D

J-M. Gérard, N. Verhaert (KUL)

A sensor or microphone is a crucial component of a fully implantable hearing system. A sensor coupled to the middle ear ossicles benefits from the natural directivity and amplification of the pinna, ear canal and ossicles. To ensure optimal performance, a mobile middle ear is essential since the sensitivity of the sensor is proportional to the movement of the ossicles. However, the sensor inherently affects the mobility of the chain. A correct impedance matching is therefore vital. In this study, a middle ear sensor and its influence on the mobility of the ossicular chain is modeled. The model is validated using fresh frozen cadaver heads and is used to optimize the design parameters of the sensor.

RHINOLOGY

The main focus of our research group is human chemosensation (taste, olfaction and trigeminal chemosensory function). Since 2004 we have developed a high expertise in the field of human chemosensation, particularly olfaction, and an increasing number of patients with olfactory dysfunction are referred to our department. Since 2004 we have evaluated almost 1000 patients complaining of olfactory dysfunction.

We dispose of a full equipment to assess human chemosensory function, based on psychophysical and electrophysiological testing. Of note, we are the only hospital in Belgium having an olfactometer. This device is mandatory to deliver chemosensory stimuuli in a controlled manner, a prerequisite for the recording of chemosensory (olfactory and trigeminal) event-related potentials.

Our current researches involve: (1) the assessment of olfactory bulb volume as a prognosis factor, (2) the development of new psychophysical methods to assess olfactory and trigeminal function, (3) the development of new electrophysiological methods to assess olfactory and trigeminal function, and (4) the evaluation of the usefulness of olfactory testing for the early diagnosis of Alzheimer’s disease.

Researches are performed in collaboration with Prof André Mouraux (COSY pole) and Prof Adrian Iwatsuo (NEUR pole) of the IoVS, and with international collaborators (Prof Thomas Hummel, Dresden, Germany).

PROGNOSTIC VALUE OF THE OLFAC-TORY BULB VOLUME MEASURE-MENT FOR RECOVERY IN POSTIN-FECTIOUS AND POSTTRAUMATIC OLFACTORY LOSS

Ph. Rombaux, C. Huart C., N. Deghouj, T. Duprez, T. Hummel

Olfactory dysfunction is thought to affect up to 20% of the general population and severely impact quality of life. Because treatments are lacking, scientific community agree that a complete clinical work up procedure is necessary to assess olfactory function and propose a prognosis of recovery to patients. Several prognostic factors influencing the recovery from olfactory dysfunction have been described. The olfactory bulb is a highly plastic structure whose volume reflects olfactory function. The aim of this study was to investigate whether olfactory bulb volume could be used as a new predictor of olfactory recovery in postinfectious and posttraumatic olfactory loss.

A cohort of patients with postinfectious and posttraumatic olfactory loss was investigated. Assessment of olfactory function was performed using psychophysical olfactory tests, at the time of the diagnosis (t1) and 15 months later (t2). All patients were examined on magnetic resonance imaging, and the olfactory bulbs volume was assessed using planimetric contouring at the time of the diagnosis (t1).

Our results showed a significant correlation between changes in olfactory functions and initial measurement of the total olfactory bulb volume; with larger volumes relating to higher improvement of olfactory function. Finally, we found that none of the patients with a total olfactory bulb volume of 40 mm3 or less exhibited recovery of olfactory function.

Our conclusion was that olfactory bulb volume seems to be a predictor of olfactory recovery in patients with postinfectious and posttraumatic olfactory loss.

Currently, we are continuously collecting MRI data from patients in order to better understand the morphological variations of olfactory-related brain structures in the context of olfactory deprivation and/or recovery.

These studies could significantly improve our understanding of the plasticity of the human olfactory system.
We developed a new psychophysical approach to specifically assess the trigeminal contribution to chemosensory perception. Our test shares similarities with the well-known and validated Sniffin’ Sticks Test to assess the olfactory function. Instead of using sticks impregnated with substances that preferentially activate olfactory afferents, we have used a number of substances previously shown to preferentially activate trigeminal afferents (menthol, allyl isothiosulfate, ethanol, propanol, eucalyptol, and camphor). The psychophysical test comprises the following four steps: (1) estimation of the detection threshold to trigeminal; (2) assessment of the discrimination performance; (3) evaluation of the ability to identify different types of trigeminal chemosensory stimuli; (4) assessment of the ability to localize lateralized trigeminal chemosensory stimuli. At present, the experimental setup is finalized (conception and development of the trigeminal felt tip pens, etc.) and we have started to collect normative data by testing a population of healthy normosmic subjects. Furthermore, we have started to test patients presenting with smell disorders in order to validate its clinical usefulness.

**Fig. 1:** Time-frequency representation of the non phase locked EEG responses to olfactory and trigeminal stimulation (CWT-SINGLE) in the normosmic, hyposmic and anosmic groups of patients.

Non phase-locked EEG responses were identified by performing across-trial averaging in the time-frequency domain, enhancing both phase-locked and non phase-locked EEG responses. Signal amplitude (group-level average, olfactory stimulation: electrode Fz vs. A1A2; trigeminal stimulation: electrode Cz vs. A1A2) is expressed as a percentage increase or decrease relative to baseline (-0.4 to -0.1s) (ER%). After olfactory stimulation, normosmic patients exhibit a clear and long-lasting increase of signal amplitude at low frequencies, referred to as OLF-TF1. In hyposmic patients, the magnitude of OLF-TF1 is reduced. In anosmic patients, this increase cannot be identified. Also note that trigeminal stimulation does not only elicit a phase-locked EEG response (TRI-TF1) but also induces a long-lasting desynchronization of the alpha-band EEG rhythms (8-12Hz) and a non phase-locked increase in EEG signal amplitude peaking approximately 350 ms after stimulus onset and centered around 10-15Hz.
Fig. 2: Receiver Operating Characteristic (ROC) analysis. ROC curves were computed to estimate the discrimination performance of each of the different measures of the EEG response to olfactory stimulation identified using across-trial averaging in the time-domain (OLF-N1 and OLF-P2) and across-trial averaging in the time-frequency domain (OLF-TF1). The shaded areas represent the 95% confidence interval of the obtained curves.

Fig. 3: Correlation between psychophysical olfactory performances (TDI score) and the magnitude of the OLF-TF1 response to olfactory stimulation identified in the CWT-SINGLE transform. Note the significant positive correlation between the TDI score and the OLF-TF1 magnitude (r=0.64, p=0.0001).

EVALUATION OF NORMAL OLFACTORY FUNCTION IN A POPULATION OF SOUTH-KIVU (CONGO) AND IMPACT OF ENDEMIC DISEASES ON OLFATORY FUNCTION

P. Balungwe, C. Huart, Ph. Rombaux

The aim of this work is to evaluate olfactory function in different populations of adult living in South-Kivu (Democratic Republic of Congo). First, (1) we will evaluate in healthy subjects if psychophysical tests of olfactory performances used in Europe are culturally adapted to Congolese population. Based on the results of this first study, (2) we will adapt the test to the Congolese population. Then, (3) we will assess olfactory function in different group of patients suffering from olfactory disorders in order to evaluate whether the frequency of these disorders are similar to those observed in Europe. Finally, (4) we will study olfactory function of patients suffering from diseases endemic to this region of the world (i.e. HIV, malaria, tuberculosis).

MRI AND SMELL

C. Huart, A. Mouraux, Th. Duprez, Ph. Rombaux

The aim of this study is to assess the usefulness of structural MRI in patients suffering from smell disorders. Attention is paid to morphological variations observed in patients with acquired or congenital anosmia, as well as to the prognostic value of MRI. Using MRI, we aim to evaluate the correlation between olfactory function and the trophicity of brain structures known to be associated with olfactory perception in controls and patients with olfactory disorders, as well as the correlation between olfactory function and trophicity of brain structures known to be associated with Alzheimer’s disease pathology. This study is expected to bring new insights on the understanding of the olfactory system and its interaction with cognition.

FUNDING

• FNRS (Clinicien Chercheur Doctorant)
• Fondation Saint-Luc (développement technologique, Lacroix)
• Cochlear Technology Centre, Belgium
• Medtronic Europe

AWARD

Award of the German Working Group Olfactory/Gustology 2013 (C. Huart – 2014)
Pfizer Educational grant (C. Huart – 2013)
**SELECTED PUBLICATIONS**


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**NEURO IMAGING**

The Radiodiagnostic Unit (IMAG) aims at participating to the technological run-up in Magnetic Resonance Imaging (MRI) and computing methods to advance the medical research and improve the practice in Radiology.

MRI is a highly interdisciplinary research area. Projects developed within IMAG draw on an opened technical platform (three 1.5T MRI scanners plus one 3T MR surgical suite for intraoperative cerebral and spinal studies) as well as on knowledge in several fields such as neuroimaging, abdominal and thoracic imaging, musculoskeletal imaging, pediatric imaging, vascular and interventional imaging, women’s imaging, physics, animal experimentation, signal and image processing, and statistics.

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**Thierry Duprez, MD**
3T MR SURGICAL SUITE
Intraoperative cerebral and spinal studies

F-MRI STUDIES
central platform for various protocols

MULTIMODALITY IMAGING
linking MRI (1.5T vs 3T), PET (Met, Cho, FDG, H2O), bone-scintigraphy, CT, echography.

ANIMAL AND HUMAN studies

NEW MR TECHNIQUES
sequences optimization; image processing; data modelling

TARGETED CONTRAST AGENTS
for tracking transplanted cells

DIFFUSION MRI
DTI in congenital hemiplegia, atlas of white matter fiber tracks, profound fiber tracks. QSI in experimental tumors, acute stroke, steroid treatment, head & neck tumors.

WHOLE BODY MRI
Intraoperative cerebral and spinal studies

PERFUSION (DCE/DSC)
brain tumors, bone, kidney, liver

MR ELASTOGRAPHY
in steatohepatitis fibrosis, cirrhosis

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NEURO-VESTRAL PATHOLOGY (ACUTE STROKE TREATMENT, STROKE PREVENTION)

P. Laloux, Y. Vandermeeren

The treatment of acute stroke is a challenge and a moving target that requires both technical developments and knowledge (such as modern imaging methods with MRI or emergency intra-arterial interventions) and expert skills; the development of structured Stroke Units is becoming a mandatory requirement for assuring optimal care. The Stroke Unit of the Neurology Department is involved in such development and quality processes and takes part in multicentre national and international trials, initiated by pharmaceutical industries or academic centres. All consecutive stroke patients are recorded in a prospective registry. The research projects which are ongoing at the present time are the following:

- WAKE-UP: Efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomized, double-blind, placebo-controlled trial.
- Microbleeds: Clinical and radiological features and outcome (joint research with the department of neurologist Queen Square Hospital, UCL Institute, London, UK).

The Stroke Unit is actively participating in national and international trials aiming at the secondary prevention of stroke. The ongoing research projects are presented below:

- Socrates: Acute Stroke Or transient Ischemic attack treated with Aspirin or Ticagrelor and patient outcome. A Randomised, Double-Blind, Multinational Study to Prevent Major Vascular Events (stroke, MI & death) with Ticagrelor Compared to Aspirin (ASA) in Patients with Acute Ischaemic Stroke or TIA.
COGNITIVE DISORDERS AND DEMENTIA

E. Mormont

Although the disclosure of the diagnosis of Alzheimer’s disease (AD) is recommended by several guidelines, many clinicians do not announce the diagnosis to their patient. One of the main arguments against disclosure is the fear of a depressive reaction. Few studies have evaluated the modification of mood, the incidence of depression or the emotional impact of a disclosure of AD or dementia.

In a retrospective study using a structured questionnaire, we reported the experience and agreement of 108 patients and their caregivers regarding the disclosure of the diagnosis of AD. The disclosure of AD was a painful experience in about a third of patients, responsible for anxiety or sadness, especially for the patients who could remember their diagnosis. However, these negative feelings seem to persist only in a minority of patients, not more than 15% of the whole sample. Only 5% of our patients and 4% of the caregivers regretted that the AD diagnosis was disclosed or would have chosen to refuse this disclosure, whatever the patient’s remembrance of the diagnosis.

In a prospective study, we evaluate the modification of anxiety and depressive symptoms three months after the disclosure of the diagnosis of AD to 100 consecutive newly diagnosed mild or moderate AD patients. The symptoms of depression and anxiety were assessed with the Zung Self-Rating Depression Scale (Zung SDS) and the depression item (NPI-d) and the anxiety item (NPI-a) of the Neuropsychiatric Inventory. At three months, there was no significant change of the mean NPI-d (p=0.87) and Zung SDS (p=0.18) and a significant reduction of the NPI-a (p=0.05). The caregivers rated the global effect of the disclosure as negative in 8%, neutral in 71%, and positive in 21% of cases. None of the patients or their proxies reported suicide attempts or catastrophic reactions. We conclude that the disclosure of AD is safe in most cases and may improve anxiety. Symptoms of depression or catastrophic reaction should not prevent clinicians to disclose the diagnosis of AD.

HEMINEGLIGENCE AND RECOVERY OF MOTOR DISABILITY IN PHYSIOTHERAPY AFTER STROKE

C. Coils, S. Mabiat, M. Leewerck, F. Peret, N. Vandenbroucke, R. Collard, P. Hansen, Y. Vandermeeren, P. Laloux

The identification of a unilateral neglect syndrome after stroke is one of the most pejorative prognosis for the recovery of the patient autonomy for most activities of daily life.

Our goal is to demonstrate that early neuropsychological monitoring of hemineglect during hospitalization of stroke patients with movement disorders is essential for the functional evolution of the patient. The neuropsychological monitoring will consist of a battery of cognitive and spatial assessments as well as physiotherapy testing. This prospective study is funded by the “Fondation Mont-Godinne”.

MULTIPLE SCLEROSIS

P. Laloux, S. Dorban, M. Oueemann, L. Rohaye

The MS Unit is devoted to the neurological and interdisciplinary care of patients suffering from multiple sclerosis, oversees the monitoring of complex new treatments, provides information about the disease and medications.

Various clinical research projects are underway: testing of new drugs and new procedures, scientific registries, ...

- PASSAGE: Long term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with Fingolimod once daily or treated with another approved disease-modifying therapy.

- MOBILE: Exploratory Study to Assess the Effect of Fampridine on Walking Ability and Balance in Patients With Multiple Sclerosis.

- MS TeleCoach: Evaluating the effect of enhanced physical activity and energy management on fatigue in patients suffering from MS.

- CONFIDENCE: Assessment of COgnitioN. Fatigue, Depression, anxiety, adherENCE in Relapsing Remitting Multiple Sclerosis patients treated with Rebif in real life settings.

PLASTICITY AFTER STROKE: STUDY WITH FMRI AND THERAPEUTIC MODULATION WITH NON-INVASIVE BRAIN STIMULATION

Y. Vandermeeren, S. Lefebvre, M. Veganeh Doont, P. Laloux

Understanding how cerebral plasticity supports motor recovery after a stroke and how to improve recovery by means of non-invasive brain stimulation are among our main research themes.

In a first experiment, we explored the capacity of transcranial direct current stimulation (tDCS), applied over the primary motor cortex, to improve paretic hand motor performance as well as in precision grip than in digital dexterity in 19 chronic stroke patients. Compared to sham, real tDCS significantly improved dexterity (+38%) and several parameters of the precision grip performed with the paretic hand (Fig.1).

Motor learning plays a central role in daily life and in neurorehabilitation. We explored the fMRI brain activation related to learning a complex motor skill with the non-dominant hand in 20 healthy volunteers. The supplementary motor area (SMA) was to be the key area underlying the achievement of early successful motor skill learning (shift of the speed/accuracy trade-off) (Fig. 2).
After a stroke, patients need to (re-)learn to use their paretic upper limb. We used a motor skill learning task ("Circuit game", Fig.3) to evaluate the impact of 30 min of tDCS during motor learning in 18 chronic stroke patients. tDCS improved on-line motor skill learning (44% with real tDCS versus 4% with sham; rmANOVA p=0.001). Furthermore, the performance at the retention test (one week later) was greater after real tDCS (44%) than after sham (3%) (p<0.001) (Fig.4).

The neural mechanisms underlying stimulation-enhanced motor skill learning involving a paretic upper limb have not been resolved. With functional magnetic resonance imaging (fMRI), we explored the neural substrates underlying the effects of dual-tDCS upon continued motor skill learning one week after intervention. 19 chronic stroke patients participated in 2 separate motor skill learning sessions (circuit game, 30 min) under real/sham dual-tDCS, each followed by a fMRI session one week later. Real (1 mA, 30 min) & sham dual-tDCS were applied over the two primary motor cortices (M1) in a double-blind & cross-over fashion. The circuit game consisted of moving a cursor with a MR-compatible mouse held by the paretic hand along a circuit as quickly & accurately as possible. Motor skill learning evolution was quantified by a Learning Index (LI) expressing % change of SAT compared to baseline. Multi-subject & random effect (RFX) analyses compared the brain areas involved in continued learning one week after real/sham dual-tDCS. External Pearson correlation analyses were performed between the beta weights (GLM) & LI in the regions of interest.
During continued motor skill learning one week after sham, there were 6 non-learners. One week after real dual-tDCS, there were only 3 non-learners. Non-learners were excluded from fMRI analyses. During continued motor skill learning after sham, activation (RFX t12=2.23, p<0.05) was observed in the bilateral M1, damaged hemisphere: S1_damH (primary sensory cortex), PPC_damH & IPC_damH (posterior & inferior parietal cortices), and undamaged hemisphere: SMA (supplementary motor area). Statistically significant positive correlations were found in the bilateral M1, PPC_damH, IPC_damH and S1_damH. One week after real dual-tDCS, activation (RFX t15=2.23, p<0.05) was observed in M1_damH, SMA_damH, PMd_damH (dorsal premotor cortex), & cerebellum ipsilateral to the paretic hand; with a positive correlation exclusively in PMd_damH. Dual-tDCS applied during the first session enhanced continued learning with the paretic limb 1 week later relative to the sham series. This lasting behavioural enhancement was associated with more efficient recruitment of the motor skill learning network, that is, focused activation on the motor-premotor areas in the damaged hemisphere, especially on the PMd, compared to the widespread activation found after sham. Dual-tDCS applied during motor skill learning with a paretic upper limb resulted in prolonged shaping of neural efficiency, which supported behavioural enhancements in chronic hemiparetic stroke patients.

FUNDING
• FRIA
• Fondation Mont-Godinne
• FSR, FRSM
• Belgian Neurological Society (BNS)
• Clinical Research Grant

AWARD
Prix Fernand Depelchin 2013: UCL

SELECTED PUBLICATIONS

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http://www.uclouvain.be/282209.html
Development of new psycho-physical assessment and therapeutics aspects of patients with neuropathic pain, chronic regional pain syndrom (CRPS) and chronic widespread pain with a bio-psycho-social lecture.

Many patients with fibromyalgia and neuropathic pain feel to response to the available treatment: there is an enormous clinical need for the development of new therapeutic approach for this condition.

Therapy that directly modulates brain activity in specific neural network might be particularly relevant to release chronic pain.

Among the method of central neurostimulation, two of them, rTMS (repetitive transcranial magnetic stimulation) and tDCS (transcranial direct current stimulation) are particularly appealing as they can change brain activity in a non-invasive, painless and safe way. These methods are associated with a significant elevation of quality of life in fibromyalgia and neuropathic pain syndrom.

In FMS patients, we would like to confirm the long-term effectiveness of rTMS or tDCS, understand the mechanism underlying the analgesic effect and assure combination with exercises of cognitive therapy.

The laser-evoked potentials (LEP) reflects the functional state of the nociceptive pathway which is related to the neural processing of pain perception.

The aim of this retrospective study is to examine if FMS patients have a dysfunctional thermonociceptive system based on LEP recording as suggested by previous studies. LEP abnormalities could be linked to clinically distinct subgroups of FMS.

Our project in the future is to associate CO2 laser evoked potential and functional assessment with thermal QST in FMS patients.
RESEARCH ABOUT THE EFFICACY OF SPECIFIC EXERCISES OR DRUGS ON MUSCULO-ARTICULAR STIFFNESS IN FMS PATIENTS OR OTHER CHRONIC PAIN PATIENTS

E. Masquelier, C. Detrembleur, F. Dierick, J. D’Haeyer

We have observed recently and for the first time that younger and middle-aged female subjects with fibromyalgia have a significant increase of passive elastic and viscous stiffness of ankle. The results also suggest a premature increase of passive elastic stiffness of ankle in FMS subjects.

How can we explain these results ?

The significant increase of muscular-articular stiffness in FMS patients can be explained by different factors : alteration of the collagen metabolism, dysfunction of the autonomic nervous system or the gamma feedback loop hypothesis.

In the next future, we have the plan to compare this population with other chronic pain patients and with sedentary people. We would develop research studies about the efficacy of specific exercises, drugs or rTMS on muscular-articular stiffness.

RESEARCH PROJECT IN COLLABORATION WITH POLE CEMO

E. Herman, P. Forget, R. Deumens, A. Abdilki, E. Masquelier

Research about animal model of chronic widespread pain and the determination of the degree of involvement of glial cells and immune system mediators in the pathophysiology of FMS and CRPS.

Animal model of FMS would be very helpful to advance an understanding of the basis of this condition. FMS is a unique pain syndrome because it is diagnosed by symptoms, not actually by underlying pathology. There are several animal models of FMS: biogenic amine depletion, repeated intramuscular injection of acidic saline, intermittent cold stress, exposure to unpredictable sound stress….

Each model is unique and may be useful for understanding different aspects of the disease process. Recently, activation of glial cells has been implicated in the development, mechanism and amplification of chronic pain.

The activation of glial cells could be implicated in the altered pain modulation in FMS patients. Markers for glial cell activation in the CNS, like a CSF level of cytokines, begin to be study in FMS patients or CRPS patients. We have the plan to assess intrathecal concentrations of pro-inflammatory substance in fibromyalgia and to observe the modulation by pharmacological of non pharmacological treatment.

SELECTED PUBLICATIONS


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Spasticity, a velocity-dependent increase in muscle tone, is a frequent condition among patients suffering from an upper motor neuron lesion such as stroke, traumatic brain injury, spinal cord lesion and multiple sclerosis. Spasticity treatment may improve gait and hand function, pain and quality of life. However, available treatments are multimodal including neuro-rehabilitation, orthosis, botulinum toxin injections, tendon transfer and lengthening surgery as well as functional neurosurgery (neurotomy and intra-thecal baclofen therapy). Our challenge is to promote an interdisciplinary approach of the spasticity treatment by means of practical guidelines.

DIAGNOSTIC NERVE BLOCK WITH ANAESTHETICS AS AN ASSESSMENT TOOL

T. Delombe, T. Gustin

Diagnostic nerve blocks with anaesthetics performed at the level of the motor nerve branches innervating spastic muscles allow us to evaluate the functional improvement expected from a spasticity treatment. The predictive value of these nerve blocks is suspected according to clinical experience and studies with a small number of patients. Our first project tended to demonstrate it with a prospective study with a larger number of patients.

ISOKINETIC ASSESSMENT OF THE SPASTICITY

L. Etienne, M. Leeuwerck, T. Delombe

Spasticity is usually evaluated with clinical scales such as Ashworth and Tardieu scales. Even if the inter and intra rater reliability of such scales seems to be acceptable, both are non-linear scale and does not provide objective data. Isokinetic dynamometer (Cybex) are usually used for muscle strengthening but can be used in passive mode to assess muscle resistance to passive movement which is the definition of spasticity. The aim of this project is to determine the reliability of the isokinetic dynamometer in the assessment of the quadriceps spasticity.

NEURO-ORTHOPOAEDIC TREATMENT OF THE SPASTIC FOOT

T. Delombe, T. Gustin, P. De Cloedt, F. Peret

This project evaluates the beneficial effect of a neuro-orthopaedic surgical treatment (selective tibial neurotomy and orthopaedic tendon surgery) of the spastic equinovarus foot among stroke patient according to the International Classification of Functioning (ICF) of the World Health Organization (WHO). Patients are prospectively assessed by means of body function and structure (spasticity, strength and range of motion), activities (FAQ, FWC, ABILOCO) and quality of life (Satispart, SF 36) scales. ClinicalTrials.gov N° NCT012655238

Equinus foot in stroke patient
RECTUS FEMORIS TENOTOMY AS A TREATMENT OF THE STIFF KNEE GAIT IN STROKE PATIENTS

T. Deltombe, P. De Cloedt, C. Detrembleur

Stiff knee gait is defined as the lack of knee flexion in the swing phase of gait. It’s a frequent condition among stroke patients responsible for low gait speed and high energy expenditure. Botulinum toxin injections at the rectus femoris muscle is the treatment of choice. However, the effect is transient necessitating repeated injections supporting the need for a permanent solution such as rectus femoris proximal tenotomy. The aim of this study is to perform an RCT with assessor-blinded evaluation to compare the effect of botulinum toxin and tenotomy in stiff knee gait using gait analysis.

AWARD

Fondation Mont-Godinne for the project “Rectus femoris tenotomy as a treatment of the stiff knee gait in stroke patients”

SELECTED PUBLICATIONS


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PROGRAM OF THE THIRD PhD STUDENTS DAY

8h30 - 9h30  Registration

9h30 – 11h00  Introduction & first session of oral presentations
Anne Klöcker. Physical factors influencing pleasant touch during tactile exploration.
Vergouts Maxime. Altered regulation of mGluR5 signalling in astrocytes derived from a rat model of amyotrophic lateral sclerosis.
Gambelli Clément. Effects of simulated hyper-gravity on the Motor control of landing from a jump.

11h00 – 11h15  Coffee break

11h15 – 12h00  First posters session
Anne-Sophie Lambert. Bouncing elephants
Sébastien Lobet. Impact of functional deficit of the ankle on the energetic and mechanical of gait: the case of haemophilic arthropathy
Anne Klöcker. Rasch built measure of pleasant touch elicited through active exploration

12h00 – 12h30  Second session of oral presentations
Van den Broeke Emanuel. Increasing the gain of pain: how we become more sensitive to pain
Kon Elif. Control of Neuronal Positioning by N-Cadherin in the Developing Cerebral Cortex

12h30 – 13h30  Lunch

13h30 – 14h30  Third session of oral presentations
Lochy Aliette. Visual discrimination of words as evidenced by rapid periodic stimulation
Decock Marie. Role of the membrane GXXXG motifs in the association of the beta-amyloid peptide
Dormal Giulia. Behavioural and neurophysiological correlates of sight restoration after longstanding visual deprivation

14h30 – 15h15  Second posters session

15h15 – 15h30  Coffee Break

15h30 – 16h30  Fourth session of oral presentations
Stancu Ilie-Cosmin. Aggravated Tau-pathology in a mouse model with combined amyloid and Tau-pathology is preceded by deregulated GSK3β signaling
Riquelme Immaculada. Use of prism adaptation in children with cerebral palsy: is it feasible?
Pierrat Nathalie. Alteration of neuronal metabolism of cholesterol by human APP

16h30 – 17h00  Conclusion – Speed dating

17h00  Awards & Drink

PhD STUDENT DAY

2013 held the IoNS PhD Student Day which is organized by PhD Students as well as Postdoctoral Fellows. This meeting is an excellent opportunity to join together all the young scientists from the three orientations of the Institute (Clinical, System & Cognition, Cellular & Molecular) as well as coming from Mont-Godinne, Louvain-La-Neuve or Brussels. It also aims at welcoming new PhD students within IoNS as well as presenting the research projects or results of the three IoNS divisions.

During this day, PhD students and Postdoctoral Fellows have the possibility to present in the form of a poster or oral presentation their research tasks or projects.