19th Annual Meeting of the LARC-Neuroscience network

November 13th 2015
Amiens, IFSI CHU Sud

Contact: grap.er24@u-picardie.fr
PROGRAM

8h30: Registration and Set up Posters – Coffee

9h20: Opening address

9h30: Plenary lecture 1: « The pharmacological link between two neuropeptides, cholecystokinin and enkephalins. Evidences in models of pain and pharmacodependence in rodents » Dr Florence NOBLE (Université Paris Descartes)

10h15 - 11h45: Oral session 1

10h15 - 10h30: speaker 1 Dr Gangarossa G (Post-doc, Collège de France, Paris)
10h30 - 10h45: speaker 2 Mr Anfray Clément (PhD, UMR 6301-ISTCT, Caen)
10h45 - 11h00: speaker 3 Dr Gonzales-Marin C (Post-doc, INSERM ERI 24 GRAP, Amiens)
11h00 - 11h15: speaker 4 Melle Leger C (PhD, INSERM ERI 28 NeoVasc, Rouen)
11h15 - 11h30: speaker 5 Mr Adekimpe A (PhD, INSERM U1105 GRAMFC, Amiens)
11h45 - 12h00: Buffet and Poster session 1

14h00 - 15h30: Oral session 2

14h00 - 14h15: speaker 7 Melle Grimoin E (PhD, UMR ISTCT 6301, Caen)
14h15 - 14h30: speaker 8 Mr Li X (PhD, EA3830, Rouen)
14h30 - 14h45: speaker 9 Mr Segobin S (PhD, INSERM-EPHE 1077, Caen)
14h45 - 15h00: speaker 10 Melle Vanacker C (PhD, INSERM U1172, JPARC, Lille)
15h00 - 15h15: speaker 11 Mr Breton J (PhD, UMR 1073, Rouen)
15h15 - 15h30: speaker 12 Dr Aid S (Post-doc, UMR 938, Paris)

15h30 - 16h30: Coffee Break and poster session 2

16h30 - 17h15: Plenary lecture 2: "Nicotinic modulation of dopaminergic system: role in nicotine addiction" Dr Philippe Faure (CNRS UMR8246, INSERM U1130 - Université Pierre et Marie Curie UM 119)

17h15 - 17h30: Awards ceremony - End of the day
Session 1

10h15 - 10h30: ORAL 1  Dr Gangarossa G (Post-doc, Collège de France, Paris)
10h30 - 10h45: ORAL 2  Mr Anfray Clément (PhD, UMR 6301-ISTCT, Caen)
10h45 - 11h00: ORAL 3  Dr Gonzalez-Marin C (Post-doc, INSERM ERI 24 GRAP, Amiens)

11h00 - 11h15: ORAL 4  Melle Leger C (PhD, INSERM ERI 28 NeoVasc, Rouen)
11h15 - 11h30: ORAL 5  Mr Adebimpe A (PhD, INSERM U1105 GRAMFC, Amiens)

11h15 - 11h30: ORAL 6  Mr Coly P-M (PhD, INSERM U982, DC2N, Rouen)
**Title of the publication**  
Role of the atypical vesicular glutamate transporter VGLUT3 in L-DOPA-induced dyskinesia

**Author(s)**  
Giuseppe Gangarossa(1,2), Salah El Mestikawy (3), Emmanuel Valjent (2)

**Author's affiliation**  
1 Collège de France - Paris  
2 Institut de Génomique Fonctionnelle - Montpellier  
3 Université UPMC - Paris

**Abstract**  
Parkinson’s disease is characterized by the degeneration of dopaminergic neurons. The gold standard therapy relies on dopamine (DA) replacement by the administration of levodopa (L-DOPA). However, with time L-DOPA treatment induces severe motor side effects characterized by abnormal and involuntary movements, or dyskinesia. Earlier studies suggested a role of striatal cholinergic interneurons, or striatal tonically active neurons (TANs), in L-DOPA-induced dyskinesia (LID), even though the underlying mechanisms remain to be characterized. Although the number of TANs was not changed, we found that DA depletion was accompanied by an increased expression of the choline acetyltransferase (ChAT) and of the two transporters expressed by TANs, the vesicular acetylcholine transporters (VACHT) and the atypical vesicular glutamate transporter type 3 (VGLUT3). In dyskinetic mice, while VACHT levels remain high, the expression of VGLUT3 decreases. Interestingly, LID is strongly attenuated in VGLUT3 deficient mice but not in mice bearing a selective inactivation of VACHT in TANs. Finally, the absence of VGLUT3 reduced L-DOPA-induced phosphorylation of ERK1/2, ribosomal subunit (rpS6) and GluA1. Our results reveal that VGLUT3 plays a critical role in the development of LID and should be considered as a potential and promising therapeutic target for LID.

**Keyword(s)**  
Parkinson's Disease, VGLUT3, VACHT, Dyskinesia, Cell Signaling
**Title of the publication**: Hypoxia-inducible inhibition of erythropoietin pathway on glioblastoma.

**Author(s)**: Anfray C, Gérault AN, Pérès EA, Petit E, Bernaudin M, Bordji K and Valable S.

**Author's affiliation**: UMR6301-ISTCT, CERVOxy group, France.

**Abstract**

Introduction: Hypoxia, a hallmark of glioblastoma (GBM), is one of the major event inducing erythropoietin (EPO) and its receptor (EPOR). EPO/EPOR signaling has recently been shown to be involved in glioma growth and its response to conventional treatments (Pérès et al., 2011; 2015) and may represent an attractive therapeutic target. However, due to its hematopoietic properties, a non-targeted inhibition of EPO may be problematic. The vectorization through the use of monocytes/macrophages (Mo/Ma) of a truncated form of EPOR (EPORT), acting as a negative dominant to the native form of EPOR would therefore represent a very attractive strategy. However, despite an elevated tropism to the tumor, and in particular to the most hypoxic area (Leblond et al., 2015), Mo/Ma also have the propensity to migrate into the spleen or the liver (Valable et al., 2011). In this study, we aimed i) to vectorize EPORT through the use of Mo/Ma and ii) to condition the expression of EPORT in these cells toward hypoxia.

Methods: A human macrophage cell line (THP1) was infected by lentiviral vector expressing EPORT. Two human GBM cell lines (U87-MG used as a non-hypoxic model and U251 used as a hypoxic model) were orthotopically implanted in the brain of nude mice. THP1-EPORT vector cells were labeled with BrdU and intravenously injected. Tumor growth was sequentially measured by MRI and finally, mice were euthanized for subsequent immunohistochemistry.

A hypoxia specific plasmid expressing EPORT was developed, by positioning HRE sequences upstream of the promoter (pGL3-HRE-EPORT). Negative control contained no HRE. THP1 cells were transfected with these constructs and co-cultured in hypoxia (1% O2) with U87-MG and U251 cells. EPORT expression was measured at both mRNA and protein levels and proliferation of GBM cells was assessed by WST-1 test.

Results: i) Cellular vectorization of EPORT with Mo/Ma: In vivo, THP1 cells intravenously injected were observed within the tumor and an effective protein overexpression after lentiviral infection was seen. Interestingly, EPORT overexpression in Mo/Ma induced a decrease in the tumor volume in the hypoxic model (U251) in vivo as compared to the U87 model. After having demonstrated that Mo/Ma could be used as vectors of EPORT to reduce tumor growth, we aimed to develop more specific vectors to hypoxia.

ii) Validation of hypoxia specific vectors of EPORT into Mo/Ma: In vitro, we first validated our inducible constructs in U87-MG and U251 cells cultured in hypoxia for which we observed a significant induction of EPORT and a concomitant decrease in cell proliferation specifically in hypoxia as compared to its respective non-inducible pGL3-EPORT construct. Interestingly, the co-culture of THP1 cells expressing inducible EPORT with GBM cells significantly reduced GBM cells proliferation only in hypoxic condition.

Conclusion: We developed hypoxia-inducible constructs for EPORT associated with a functional impact on glioma cells. These results encourage for further work with inducible constructs on vector cells such as Mo/Ma to reduce GBM growth in vivo.

**Keyword(s)**: Glioblastoma, hypoxia, erythropoietin, macrophages.
**Title of the publication**
Efficacy of current medications for alcoholism (baclofen, acamprosate, naltrexone and nalmefene) in a new model of binge drinking in rats

**Author(s)**
María del Carmen GONZÁLEZ-MARÍN*, Sophie LEBOURGEOIS* and Mickaël NAASSILA
*Both authors contributed equally to this work.

**Author's affiliation**
Research Group on Alcohol & Pharmacodependences (GRAP) INSERM ERi 24, Université de Picardie Jules Verne, Centre Universitaire de Recherche en Santé, SFR CAP Santé, Amiens

**Abstract**
Alcohol use disorder is a devastating illness with a profound health impact. New strategies for the treatment of alcohol dependence are a pressing need. Binge drinking pattern may be an important component on the early steps of developing alcohol dependence but there is no relevant animal model available so far. The goal of the present study was two-fold: to set up an animal model of binge drinking and use this model for testing the current pharmacotherapies of alcoholism on the appetitive or motivational properties of alcohol in binge drinker subjects. It is interesting to note that baclofen, acamprosate, naltrexone and nalmefene are used exclusively in alcohol-dependent patients and no data are currently available regarding their potential efficacy in individuals not displaying dependence but only excessive ethanol intake, such as in binge drinker subjects. We set up an original model of binge drinking (dipsomania) in which rats voluntarily self-administer 20% ethanol solution in an operant paradigm in a very short period of time, i.e. 15 min. This short period of time of access to alcohol induces very high levels of responding associated with high levels of ethanol intake (>1g of pure alcohol/kg/15min). Thus, animals display signs of intoxication day after day at the end of the 15 min ethanol self-administration sessions. We found that all the tested compounds were effective in reducing ethanol intake in an animal model of binge drinking. Overall, some compounds appear to be more efficient in decreasing ethanol consumption when compared to vehicle dose: baclofen and naltrexone (-52 and -66%, respectively) appear to be better pharmacotherapy than acamprosate and nalmefene (-28% and -43%, respectively). Our results demonstrate that the different treatments aiming at maintaining abstinence or reducing alcohol intake in alcohol-dependent patients who cannot stop drinking could be also effective in binge drinker subjects that did not develop addiction.

**Keyword(s)**
Binge drinking, EtOH self-administration, baclofen, acamprosate, naltrexone, nalmefene.
Title of the publication | Glutamate increases endothelial t-PA and MMP-9 activities in cortical microvessels from mouse neonates and stimulates migration of immature GABA interneurons

Author(s) | Léger C¹, Aligny C¹, Hauchecorne M¹, Dupre N¹, Roux C¹, Ramdani Y¹, Lebon A⁵, Bénard M², Galas L², Carmeliet P⁸, Vivien D³, Marret S¹, Leroux P¹, Gonzalez BJ¹

Author's affiliation
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2Department of Neonatal Pediatrics and Intensive Care, CHU Rouen.
3 Inserm, U919, SP2U, Cyceron, Caen, France
4 Laboratory of Angiogenesis and Neurovascular link, Department of Oncology, KU Leuven, B-3000 Leuven, Belgium
5 Inserm, PRIMACEN, Cell Imaging Platform of Normandy, Mont-Saint-Aignan, France

Abstract | In the developing brain, the NMDA receptor exerts trophic activities and impacts the differentiation of immature GABA interneurons. The objective of this study was to clarify the action of glutamate on the migration of GABAergic neurons. Indeed, several studies have highlighted the important role of the cerebral vasculature in the cortical migration of GABAergic neurons (Vasudevan and Bhide, 2009). In addition, some works from the laboratory demonstrated the expression of functional NMDA receptors on immature endothelial cells (Lecointre et al., 2014; Legros et al., 2009). We therefore hypothesized that glutamate could impact on the migration of immature GABAergic interneurons. The first experiments have shown the existence, in the developing cortex, of a tangential vascular network in close association with migrating immature neurons. Zymography experiments demonstrated that glutamate could stimulate MMP and t-PA endothelial activities in brain microvessels from the superficial layers II-IV of the neocortex. Time-lapse videomicroscopy has shown an effect of glutamate on neuronal migration, increasing their maximal speed and distance covered. Moreover, the effect of glutamate on MMP activation was abrogated in tPA-/- mice. Taken together, these data suggest that glutamate actively contributes to the migration of GABAergic interneurons in the neocortex via endothelial NMDA receptors and regulation of vascular protease (t-PA and MMP) activities. Funded by Inserm, Rouen University, Région Haute-Normandie, LARC-Neuroscience network, IREB.

Keyword(s) | glutamate, GABAergic interneurons, MMPs, t-PA, microvessels
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<thead>
<tr>
<th>Title of the publication</th>
<th>Neonatal connectome during preterm brain development</th>
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<tr>
<td>Author(s)</td>
<td>Azeez Adebimpe¹, Ardalan Aarabi¹, Laura Routier², Mahdi Mahmoudzadeh², Guy Kongolo², Sabrina Goudjil², Fabrice Wallois¹².</td>
</tr>
</tbody>
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| Author's affiliation     | 1 INSERM U 1105, CURS, CHU Sud, Salouël, Av. Laennec, 80054 Amiens Cedex, France  
2 INSERM U 1105, EFSN Pédiatriques, CHU Sud, Salouël, Av. Laennec, 80054 Amiens Cedex, France |
<p>| Abstract                 | Theta temporal activity in premature neonates has been known to be one of the neurodevelopment biomarkers and its absence suggests brain damage and poor prognosis. In this study we investigated the functional brain organization during theta activity in early preterm infants. EEG recordings were recorded from 12 healthy preterm (31.26 ± 0.18 weeks) infants. The experiment was performed in the neonatal intensive care unit of Amiens University Hospital, Amiens, France. The data were recorded during quiet sleep using high density EEG caps (ANT, Netherlands) with 59 channels positioned according to the international 10-10 standard system. Two EEG experts (LR, FW) selected artifact free segments with theta temporal burst. The phase locking value was computed between all pairs of EEG channels in two frequency bands (delta and theta). Graph theoretical measures including degree, clustering coefficient and local efficiency were computed from the resulting connectivity matrix to characterize the functional connectivity between EEG channels. The results showed significantly increased connectivity within and restricted to frontal and parieto-occipital areas in both frequency bands. Statistical comparison on the functional connectivity between EEG segments with and without theta activity revealed higher functional connectivity within and restricted to each temporal regions in theta band. Graph theoretical analysis also confirmed significantly higher functional connectivity values at the frontal and parieto-occipital regions; and higher degree, clustering coefficient and efficiency at each temporal region. The present observations show that short distance connectivity might be enhanced but that long distance connectivity are still not established between the different areas in early premature. In additions, our results offer guidance for the functional organization of preterm brain networks from the early stage. |
| Keyword(s)               | Neonates, Preterm, functional connectivity, theta temporal, brain development |</p>
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<th><strong>Title of the publication</strong></th>
<th>Chemotactic GPCRs control cell migration by suppressing autophagosome biogenesis: Involvement in glioma cell invasion</th>
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<td><strong>Author(s)</strong></td>
<td>Coly Pierre-Michaël, Perzo Nicolas, Le Joncour Vadim, Lecointre Céline, Schouft Marie-Thérèse, Desrues Laurence, Tonon Marie-Christine, Wurtz Olivier, Gandolfo Pierrick, Castel Hélène, Morin Fabrice</td>
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<tr>
<td><strong>Author's affiliation</strong></td>
<td>Inserm U982, DC2N Laboratory of Neuronal and Neuroendocrine Cell Differentiation and Communication, Institute for Biomedical Research and Innovation, University of Rouen, Normandy, France.</td>
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<td><strong>Abstract</strong></td>
<td>Glioblastoma are the most frequent and aggressive primary brain tumors in adults. They are characterized by intense neoangiogenesis and massive invasion of the healthy brain parenchyma. These two processes are controlled by endogenous factors, including chemotactic cytokines (chemokines), the majority of which bind to cell surface receptors that belong to the G-protein-coupled receptor (GPCR) superfamily. As a prototypical chemokine receptor, CXCR4 has been shown to play a crucial role in the chemotaxis of many cell types, including metastatic glioma cells. Besides “classical” chemokine receptors, GPCR for vasoactive peptides have also been shown to display chemotactic activity. Studies carried out in our team showed a critical role of UT, the GPCR for the vasoactive peptide urotensin II (UII), on glial tumorigenesis. Autophagy is an evolutionarily conserved lysosomal pathway involved in degradation of damaged proteins and cytoplasmic organelles. Despite data demonstrating the autophagic degradation of key proteins involved in cell migration, the functional impact of autophagy on chemotaxis remains elusive. Using both the HEK-293 cell line and the U87 glioblastoma cell line, we found that ligand-induced CXCR4 or UT activation triggered a marked reduction in the rate of formation of mature autophagosomes. Chemotactic GPCRs exert their anti-autophagic effects by preventing the targeting of Atg16L protein to clathrin-coated preautophagic vesicles forming from the plasma membrane. We further demonstrated that CXCR4- or UT-induced inhibition of autophagy favors the formation of adhesion complexes to the extracellular matrix and is required for chemotactic migration. Altogether, our data reveal a new link between GPCR signaling and the autophagy machinery, and may help to envisage therapeutic strategies for highly invasive glioblastomas.</td>
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<td><strong>Keyword(s)</strong></td>
<td>Autophagy, chemotactic migration, CXCR4, urotensin II, glioma</td>
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14h00 - 14h15: ORAL 7  Melle Grimoin E (PhD, UMR ISTCT 6301, Caen)
14h15 - 14h30: ORAL 8  Mr Li X (PhD, EA3830, Rouen)
14h30 - 14h45: ORAL 9  Melle Segobin S (PhD, INSERM-EPHE 1077, Caen)
14h45 - 15h00: ORAL 10  Melle Vanacker C (PhD, INSERM U1172, JPARC, Lille)
15h00 - 15h15: ORAL 11  Mr Breton J (PhD, UMR 1073, Rouen)
15h15 - 15h30: ORAL 12  Dr Aid S (Post-doc, UMR 938, Paris)
**Title of the publication**  
Implication of astrocytes in the neurovascular coupling: studies with two photon laser scanning microscopy in adult rats

**Author(s)**  
Grimoin E., Chazalviel L., Menard B., Bernaudin M., Touzani O.

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UMR 6301-ISTCT, CERVOxy Group, CNRS, CEA, Université Caen-Normandie

**Abstract**  
The neurovascular coupling is classically defined as the increase of local blood flow in response to neuronal activation. Recently, many studies have suggested that astrocytes, strategically positioned by contacting both neurons and blood vessels, are directly involved in the dialogue between neuronal and vascular compartments. However, most of these studies were performed in ex vivo preparations or in very young rodents. Accordingly, it is crucial to investigate the role of astrocytes in the neurovascular coupling in more aged animals since it is known that this coupling is altered in many age-related diseases such as arterial hypertension, dementia and stroke. To investigate this issue in vivo, we developed a protocol of somatosensory stimulations coupled with an astrocytic calcium imaging and vascular diameter measurement. A cranial window for optical access to cerebral cortex was installed on the skull of 20 days post-natal to 3 months old rats. We combined two fluorescent dyes, the first one is sensitive to changes in astrocytic intracellular calcium (Fluo4-AM) and the other one is specific to astrocytes (Sulforhodamine-101, SR-101). Because astrocytic endfeet border blood brain vessels, SR-101 also allows imaging of blood vessels. Under α-chloralose/urethane anesthesia and using two-photon laser scanning microscopy, this protocol allowed us to analyze simultaneously the astrocytic activity and the vasoreactivity at micro scale in the deep of the intact somatosensory cortex. First, we observed an age-depend loading of Fluo4-AM indicator, so that the younger animals are, the better the loading is, limiting the use of animals older than three months. Second, this work shows that following an electrical forepaw stimulation, 60% of cortical arterioles respond with an increase in diameter. This vascular response is preceded by an increase in astrocytic somatic calcium activity which accounts for 13% of astrocytes. Consistent with the literature, these results suggest that in vivo in adult as observe in very young animals, cortical astrocytes participate in the local vasodilation following a somatosensory stimulation and thus in the neurovascular coupling.

**Keyword(s)**  
astrocytes, calcium, in vivo, two photon laser scanning microscopy
### Title of the publication
FoxJ1 is transiently expressed in specific cell populations in a time and space specific manner and regulates spinal cord development

### Author(s)
Xiaofei Li\(^1\)*, Nicolas Guérout\(^{1,2}\)*, Elisa M. Floriddia\(^1\)*, Konstantinos Toskas\(^1\), Troy Ghashghaei\(^3\), Karl Fernandes\(^4\), Fanie Barnabé-Heider\(^1\)#

### Author's affiliation
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4 Department of Pathology and Cell Biology, Faculty of Medicine, Université de Montréal, QC, Canada  
*equal contribution

### Abstract
Forkhead Box protein J1 (FoxJ1) – a transcription factor classically involved in ciliogenesis – has recently risen interest in neural stem cells and regenerative medicine. Indeed, in the postnatal brain, the expression of FoxJ1 is required for the differentiation of radial glia into ependymal cells and astrocytes, suggesting a crucial role for FoxJ1 in stem cell niche formation.

In the spinal cord, despite the fact that many neurons have been fate-mapped, the development of glial cells is still largely unknown. During adulthood, FoxJ1 is only expressed by the ependymal cells with multi-potent potential surrounding the central canal of the spinal cord. However, we observe FoxJ1 is transiently expressed by different cell populations in the developing spinal cord. Therefore, we hypothesize that FoxJ1 also plays a crucial role in spinal cord development and is required for cell fate determination during spinal cord development.

We observed that FoxJ1-YFP inducible and non-inducible mice transiently express this transcription factor during different developmental stages by subtypes of neurons, astrocytes, and ependymal cells clustered in specific areas of the developing and postnatal spinal cord. Floor plate cells and neurons in the ventro-lateral grey matter are the first cell populations expressing FoxJ1 from early developmental stages (E10). Astrocytes in the ventro-lateral white matter and dorsal horn express FoxJ1 from E14.5 and E16.5, respectively. From E16.5, ependymal cells around the central canal start expressing FoxJ1 which is completed by P0. The neuronal and astrocytic populations stop expressing FoxJ1 postnatally, while ependymal cells express it throughout adulthood. More interestingly, all the FoxJ1+ cells are restricted only around the central canal when foxj1 is knocked out.

The time and space specific FoxJ1 expression suggests that this transcription factor can have important roles in maintaining a precursor phenotype, cell fate commitment, migration, or integration. We aim to further identify the FoxJ1+ neuronal and astrocytic subpopulations and to elucidate the functional role of FoxJ1 in the developing and postnatal spinal cord taking advantage of additional transgenic models.

### Keyword(s)
Ependymal cells, spinal cord, stem cells, development, spinal cord injury
**Title of the publication** | Specific alterations of thalamic subgroups in alcoholics with and without Korsakoff’s syndrome: a DTI investigation
---|---
**Author(s)** | Shailendra Segobin (1), Ludivine Ritz (1), Coralie Lannuzel (1), Celine Boudehent (1,2), Francois Vabret (1,2), Francis Eustache (1), Helene Beaunieux (1), Anne-Lise Pitel(1).
**Author's affiliation** | (1) Université de Caen Normandie, unité INSERM-EPHE 1077 « Neuropsychologie et neuroanatomie fonctionnelle de la mémoire humaine ». (2) Service d’addictologie, Centre Hospitalier Universitaire de Caen

**Abstract**
Introduction: Two brain networks are particularly affected by the harmful effect of chronic and excessive alcohol consumption: the frontocerebellar circuit (FCC) and the Papez circuit (PC). The thalamus, a relay organ consisting of several nuclei, plays a key role in both circuits. Shrinkage of the thalamus is known to be more severe in alcoholics with Korsakoff’s syndrome (KS) than in those without neurological complications (UA). However, the specificity of shrinkage and disconnection among the different thalamic nuclei has to be determined.
Objectives: Our aim is to examine how thalamic nuclei that are connected to key regions of the FCC and PC are altered in terms of volume and connections in UA and KS.
Materials and methods: Forty-nine subjects (16 healthy controls (HC); 26 UA and 7 KS) underwent a Diffusion Tensor Imaging (DTI) sequence and a T1-weighted MR image. State-of-the-art probabilistic tractography algorithms (Behrens et al, 2003; Behrens et al, 2007) were used to segment the thalamus in terms of brain regions they are connected to (the prefrontal cortex and the cerebellar Crus I and II for the executive loop of the FCC, the precentral gyrus and the cerebellar lobs IV-VI for the motor loop of the FCC, and the hippocampus for the PC).
Results: The segmentation algorithm outputs clusters of thalamic voxels that are the most highly connected to the defined regions; and the number of fibre tracts (connectivity measures) that are contained in each voxel that links to the defined regions. The clusters of voxels were used to evaluate their corresponding gray matter volumes from the T1-weighted image, taking brain sizes into account. ANCOVA on connectivity measures showed significant differences for voxels connected to the hippocampus only (F(2,45)=7.79; p<0.001)). Post-hoc comparisons revealed lower connectivity between HC and UA (p=0.006), as well as between HC and KS (p=0.003). For the volumes of the segmented thalamic sub-nuclei, significant differences were essentially observed for the nuclei connected to the prefrontal cortex (F(2,45)=15.7; p<0.001)) and the hippocampus (F(2,45)=5.22; p=0.009)). Post-hoc comparisons showed lower volumes of the thalamic nuclei connected to the prefrontal in UA compared to HC (p<0.001) and KS versus HC (p<0.001). Volumetric comparisons for the hippocampal nuclei approached significance between the HC and KS group only (p=0.09). For both connectivity and volume measures, there was no significant difference between UA and KS groups.
Discussion: Volumetric and connectivity measures of thalamic nuclei seems to point at two different mechanisms affecting the thalamus. The first mechanism involves atrophy of the nuclei connected to the prefrontal area (anterior nuclei of the thalamus visually) as the leading factor. The second mechanism involves disconnection of the nuclei connected to the hippocampus (medio-dorsal nuclei of the thalamus visually) as the leading factor. Thalamic sub-nuclei are therefore differentially affected based on whether they are inherent to the FCC or the PC.

**Keyword(s)** | alcohol-dependence, Korsakoff's syndrome, thalamus, frontocerebellar circuit, Papez circuit, Diffusion Tensor Imaging
Calcium-dependent exocytosis in GnRH neurons is required for sexual maturation and body weight homeostasis but not hypothalamic targeting in female mice

Charlotte Vanacker\textsuperscript{1,2,3}, Manon Duquenne\textsuperscript{1,2,3}, Andrea Messina\textsuperscript{1,2,3}, Danièle Mazur\textsuperscript{1,2,3}, Erik Hrabovszky\textsuperscript{4}, Frank W Pfrieger\textsuperscript{5}, Paolo Giacobini\textsuperscript{1,2,3}, Vincent Prevot\textsuperscript{1,2,3}

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Puberty is initiated by activation of the hypothalamic-pituitary-gonadal axis. The initial steps involve GnRH release by hypothalamic neurons into the pituitary portal circulation triggering of gonadotropin release by the pituitary. Intriguingly, GnRH signaling has been shown to be dispensable in the proper development and maintenance of GnRH neurons. However, whether calcium-dependent transmitter release plays a role in this process remains unclear. To address this question, we generated mice in which activity-dependent exocytosis is blocked by the Cre recombinase-dependent expression of the Clostridial botulinum neurotoxin serotype B light chain, which cleaves vesicle-associated membrane protein 2. Here we show that toxin expression in GnRH neurons promotes GnRH deficiency leading to hypogonadotropic hypogonadism in a subpopulation of female mice that also develop overweight and hyperleptinemia. This effect depends on the actual proportion of GnRH neurons expressing the transgene, which does not alter the anatomic placement and projections of GnRH neurons in the hypothalamus. These data establish the existence of a threshold effect for congenital GnRH deficiency in which small environmental changes in individuals harboring an identical pool of genes may have major consequences on their reproductive and metabolic status throughout life.

GnRH, Puberty, Vamp2
Title of the publication: Proteins of commensal E. coli activate host anorexigenic pathways after nutrient-induced bacterial growth

Author(s): Jonathan Breton,1,4 Naouel Tennoune,1,4 Nicolas Lucas,1,4 Marie Francois,1,4 Romain Legrand,1,4 Alexis Goichon,1,4 Charlène Guérin,1,4 Johann Peltier,2,4 Martine Pestel-Caron,2,4,5 Philippe Chan,3,4 Jean Claude Do Rego,4,6 David Vaudry,3,4 Ivor S. Ebenezer,7 Tomas Hökfelt,8 Pierre Déchelotte,1,4,5 Sergueï O. Fetissov,1,4

Author's affiliation: 1, Inserm UMR1073, Nutrition, Gut and Brain Laboratory, Rouen, 76183, France. 2, Microbiology Laboratory GRAM, EA2656, Rouen, 76183, France. 3, PISSARO Proteomic Platform, Mont-Saint-Aignan, 76821, France. 4, Institute for Research and Innovation in Biomedicine (IRIB), Rouen University, Normandy University, 76000, France. 5, Rouen University Hospital, CHU Charles Nicole, 76183, Rouen, France. 6, Animal Behavior Platform (SCAC), Rouen, 76183, France. 7, Neuropharmacology Research Group, School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, PO 1 2DT England, UK. 8, Department of Neuroscience, Karolinska Institute, Stockholm, 17176, Sweden.

Abstract: Introduction: Composition of gut microbiota has been associated with host metabolic phenotypes, but it is not known if bacterial proteins may directly influence host control of food intake and if this effect may depend on bacterial nutritional status.

Methods: In this work, gut commensal E. coli K12 bacteria were in vitro supplemented every 12h for 3 and 5 days with nutrient rich medium as a model of two daily meals in humans. Total proteins were extracted from E. coli during two phases of growth and corresponding proteomes were compared by 2-dimensional gel electrophoresis and the mass spectrometry showing differentially expressed proteins. These proteins were tested in their ability to impact: i) the release of gut satietogenic hormones by intestinal infusion, and ii) food intake by acute and chronic intraperitoneal injections.

Results: We found that such feeding schedule, starting after the 5th nutrient provision, induces E.coli immediate exponential growth for 20 min followed by the stationary phase till the next nutrient provision. Intestinal infusion in rats of E.coli proteins in the exponential and stationary phases stimulated plasma GLP-1 and PYY, respectively. Acute and chronic intraperitoneal administrations to free feeding rats and mice of 0.1 mg/kg of E.coli proteins from the stationary but not the exponential phase reduced food intake and increased c-fos expression in anorexigenic proopiomelanocortin neurons of the hypothalamic arcuate nucleus and in the central nucleus of amygdala receiving anorexigenic projections of calcitonin gene-related peptide neurons from the parabrachial nucleus.

Conclusions: Thus, bacterial proteins produced during nutrient-induced growth of E.coli may physiologically influence host appetite via acute stimulation of gut satietogenic hormones and via their long-term systemic changes, activating central anorexigenic pathways.

Keyword(s): E. coli; microbiota; food intake; ClpB; satiety
**Title of the publication**
BLOCKING IGF SIGNALING IN ADULT NEURONS ALLEVIATES ALZHEIMER PATHOLOGY THROUGH Ab CLEARANCE

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**Abstract**
Alzheimer disease (AD) is a frequent and irreversible age-related neurodegeneration without efficient treatment. Experimental AD in mice responds positively to decreased insulin-like growth factor I (IGF-I) signaling, a pathway also implicated in aging. We found compelling evidence in vivo that AD progression is significantly delayed when IGF signaling is blocked in adult neurons. To show that, we built a novel mouse model, combining inducible neuron-specific IGF-I receptor (IGF-1R) knockout with Alzheimer transgenics. Analysis of the experimental Alzheimer phenotype revealed fewer plaques, less abundant Aβ peptides, and diminished neuroinflammation in mutants with inactivated IGF signaling, together with clearly preserved behavioral and memory performances. Surprisingly, adult neurons undergoing IGF-1R knockout reduced their apical soma and developed leaner dendrites, indicative of remarkable structural plasticity entailing condensed forebrain neuroarchitecture in this model. Neurons lacking IGF-1R in AD showed less accumulation of Ab-containing autophagic vacuoles. At the same time, plasma Ab levels were increased. Our data indicate that neuronal IGF-1R ablation protects lifelong from Alzheimer pathology by clearing toxic Ab, via preserved autophagic compartment and enhanced systemic elimination. Our findings indicate in a model highly pertinent to translational research that neuronal IGF resistance may represent a pathophysiologically relevant mechanism of the brain preventing Aβ accumulation.

**Keyword(s)**
Insulin-like growth factor, Alzheimer disease, neuron, amyloid-beta, conditional mutagenesis, mouse model.
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<td><strong>Title of the publication</strong></td>
<td>SHORT TERM AND LONG TERM PROTECTIVE EFFECTS OF MgSO4 PRE-TREATMENT ON HISTOLOGICAL, BEHAVIOURAL AND NEUROCHEMICAL ALTERATIONS IN A MOUSE MODEL OF PERINATAL BRAIN LESION</td>
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<td><strong>Author(s)</strong></td>
<td>Ismaël Daher¹, Nathalie Dourmap¹, Stéphane Marret¹, Philippe Leroux¹, Vincent Roy², Bruno Gonzalez¹, Carine Cleren¹ and Isabelle Leroux-Nicollet¹</td>
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<td><strong>Author's affiliation</strong></td>
<td>1: NeoVASC, ERI-28 - Endothélium Microvasculaire et Lésions Cérébrales Néonatales, Institute for Research and Innovation in Biomedicine (IRIB), UFR de Médecine-Pharmacie, Université de Rouen, France ; 2: PSY-NCA, EA 4700 - Laboratoire de Psychologie et Neurosciences de la Cognition et de l’Affectivité, Université de Rouen, France</td>
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<td><strong>Abstract</strong></td>
<td>Preterm birth is the leading cause of cerebral palsy (CP), a long term non progressive acquired motor disability, often associated with cognitive deficits. There is a critical need for therapies reducing the incidence and severity of brain injury in premature infants. The clinical use of magnesium sulfate (MgSO4) appears to reduce CP occurrence by 30%, but the mechanisms and long-term effects are poorly documented. As excitotoxicity underlies the neurological alterations, a validated mouse model consists in injecting ibotenic acid intracortically at postnatal day 5 (P5). The aim of our study was to analyse MgSO4 effects on the behavioural development of NMRI lesioned mice, and to investigate its neuroprotective potency in the short term (P6-P10) and in the long term (from P35). For this purpose, MgSO4 was administered i.p. at a 600 mg/kg dose prior to the lesion. The excitotoxic lesion led to an impairment of the sensorimotor development in P6 and P7 mice, reduced by MgSO4. In parallel, cresyl-violet staining at P10 highlighted a decreased cortical thickness in the ipsilateral hemisphere of lesioned mice, as well as a disorganized cellular pattern, which were prevented by MgSO4. HPLC assay performed at P10 in lesioned mice revealed an increase in glutamate levels in the prefrontal cortex of females, while GABA levels were increased in males. These increases were prevented by MgSO4 in absence of any proper effect. Once adults, neonatally lesioned mice displayed walking coordination, fine motor skills and memory impairments, which were also prevented by MgSO4 administration, which did not induce any long term behavioural proper effect. In conclusion, at short and long terms, MgSO4 prevented histological, neurochemical and behavioural alterations observed in this lesion model, without showing any deleterious effects. Neurochemical studies in adult mice are in progress to further characterize the mechanisms underlying the MgSO4 effects.</td>
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<td><strong>Keyword(s)</strong></td>
<td>neonatal lesion, sex, neuroprotection, behaviour, sensorimotor development, motor skills, memory</td>
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<td><strong>Title of the publication</strong></td>
<td>Freezing behavior as a response to sexual visual stimuli as demonstrated by posturography</td>
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<td><strong>Author(s)</strong></td>
<td>Harold Mouras 1 5, Thierry Lelard 4 5, Said Ahmaidi 4 5, Olivier Godefroy 1 4, Pierre Krystkowiak 2 3 5</td>
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<td><strong>Author's affiliation</strong></td>
<td>1 EA 7273, Centre de Recherche en Psychologie: Cognition, Psychisme et Organisations, UFR de Sciences Humaines Sciences Sociales et Philosophie, Département de Psychologie, Université de Picardie Jules Verne, F-80000 Amiens, France. 2 EA 4559, Laboratoire de Neurosciences Fonctionnelles et Pathologies, UFR de Médecine, Université de Picardie Jules Verne, 3 rue des Louvels, F-80000 Amiens, France. 3 Service de Neurologie, CHU Amiens, Place Victor Pauchet, F-80054 Amiens Cedex 1, France. 4 EA 3300, Adaptations Physiologiques à l'Exercice et Réadaptation a l'Effort, UFR des Sciences du Sport, Université de Picardie Jules Verne, F-80025 Amiens, France. 5 Structure Fédérative de Recherche en Santé CAP-Santé, Université de Picardie Jules Verne, F-80000 Amiens, France, and Université de Reims-Champagne-Ardenne, F-51097 Reims, France. Corresponding author: Harold Mouras ; EA 7273, Centre de Recherche en Psychologie: Cognition, Psychisme et Organisations, UFR de Sciences Humaines Sciences Sociales et Philosophie, Département de Psychologie, Université de Picardie Jules Verne, F-80000 Amiens, France ; email: <a href="mailto:hmouras@gmail.com">hmouras@gmail.com</a>; phone: + 33 6 51 52 04 29</td>
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<td><strong>Abstract</strong></td>
<td>Posturographic changes in motivational conditions remain largely unexplored in the context of embodied cognition. Over the last decade, sexual motivation has been used as a good canonical working model to study motivated social interactions. The objective of this study was to explore posturographic variations in response to visual sexual videos as compared to neutral videos. Our results support demonstration of a freezing-type response in response to sexually explicit stimuli compared to other conditions, as demonstrated by significantly decreased standard deviations for (i) the center of pressure displacement along the mediolateral and anteroposterior axes and (ii) center of pressure's displacement surface. These results support the complexity of the motor correlates of sexual motivation considered to be a canonical functional context to study the motor correlates of motivated social interactions.</td>
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<td><strong>Keyword(s)</strong></td>
<td>Social neuroscience; Affective neuroscience; Embodiment</td>
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**Title of the publication**  
Ventilatory response to hypoxia during sleep in premature neonates: preliminary results

**Author(s)**  
Christelle KOUAKAM, Erwan STEPHAN-BLANCHARD, André LÉKÉ, Stéphane DELANAUD, Karen CHARDON

**Author's affiliation**  
LABORATOIRE PERITOX - CURS  
CHU Amiens Picardie

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<th>Abstract</th>
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<td>Introduction: The hypoxic test allows to assess peripheral chemoreceptors (PC) sensitivity and to estimate their capacity to adapt the ventilation to diverse stimulations (apnea, fall of PaO2...). PC play an important role in the regulation of ventilation. However, only few studies have investigated the impact of sleep state on their activity. In addition, until now PC sensitivity was evaluated by quantifying the variation of minute ventilation between a normoxic and a hypoxic phase. The hypoxic ventilatory response (HVR) being biphasic with an initial hyperventilation followed by a progressive decrease of ventilation, this analysis could underestimate the real involvement of the PC in the HVR. The aim of the present study was to assess the impact of sleep state on the HVR in preterm infants by using a reproducible method that evaluates with more precision the response following hypoxia onset.</td>
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<td>Materials and methods: The hypoxic test was performed on 12 premature neonates (gestational age: 36.7 ± 1.0 weeks) during active (AS) and quiet sleep (QS) determined according to neurophysiological criteria. PC sensitivity was analyzed by the increase of minute ventilation (VE) in response to the hypoxic test (15% O2) and the response time (RT).</td>
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<td>Results: VE during the control period was significantly higher in AS (488.3 ± 95.1 mL.min⁻¹.kg⁻¹) as compared to QS (414.4 ± 85.7 mL.min⁻¹.kg⁻¹) (p=0.01). The increase of VE following the hypoxic test was greater in AS than QS (22.9 % and 16.1 % respectively; p=0.04) at the same RT in both states.</td>
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<td>Conclusion: The present study support the effect of sleep state on resting ventilation. For the first time, it also suggests an impact on the HVR, as PC sensitivity was lower in QS, which emphasis the fragility of preterm infants during this state. This founding remains to be confirmed by the analysis of a greater number of subjects.</td>
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**Keyword(s)**  
Hypoxia, premature infants, ventilation, sleep states
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<th><strong>Title of the publication</strong></th>
<th>Structural and functional analysis of tunneling nanotubes (TnTs) in PC12 cells</th>
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<td><strong>Author(s)</strong></td>
<td>Magalie Bénard $^{1,2}$, Damien Schapman $^{1,2}$, Alexis Lebon $^{1,2}$, Baptiste Monterroso $^{1,2}$, Marine Bellenger $^{1,2}$, Frank Le Foll $^3$, Jennifer Pasquier $^{3,4}$, Hubert Vaudry $^{1,2}$, David Vaudry $^{1,2}$ and Ludovic Galas $^{1,2}$</td>
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<td><strong>Author's affiliation</strong></td>
<td>1 Cell imaging platform of Normandy (PRIMACEN), Infrastructure en Biologie, Santé et Agronomie (IBiSA), Institut National de la Santé et de la Recherche Médicale (Inserm), Mont-Saint-Aignan, France. 2 Normandie University, Institute for Research and Innovation in Biomedicine (IRIB), Rouen, France. 3 UMR-I 02 INERIS-URCA-ULH SEBIO / Unité Stress Environnementaux et BIOsurveillance des milieux aquatiques, Université du Havre, France. 4 Department of Genetic Medicine, Weill Cornell Medical College, New York, USA; Stem Cell and Microenvironment Laboratory, Weill Cornell Medical College in Qatar, Doha, Qatar.</td>
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<td><strong>Abstract</strong></td>
<td>Tunneling nano Tubes (TnTs) are thin plasma membrane bridges mediating transfers of materials and signals between cells. Due to large disparity of TnT-like structures in neuronal, immune, cancer or epithelial cells, high and super resolution approaches are necessary for full characterization of these yet poorly understood routes of cell-to-cell communication. We propose here imaging strategies designed to dissect structural and dynamic aspects of TnT formation and function in fixed or living PC12 cells. Through time-gated Continuous Wave STimulated Emission Depletion (gCW STED) nanoscopy associated to deconvolution, we provided nanoscale details of membrane and cytoskeleton organizations in two subtypes of tunneling nanotubes, namely TnT1 and TnT2. In fixed PC12 cells, TnT1 (length, several tens of µm; diameter, 100-650 nm) exhibited a large trumpet-shaped origin, a clear cytosolic tunnel and different bud-shaped connections from closed-ended to open-ended tips. TnT1 contained both actin and tubulin. TnT2 (length, max 20 µm, diameter, 70-200 nm) only contained actin without clear cytosolic tunnel. In living PC12 cells, we observed through gCW STED additional details, unrevealed so far, including a filament spindle emerging from an organizing center at the origin of TnT1 and branched or bulbous attachments of TnT2. We were also able to monitor dynamics of bud-shaped tips and intercellular transfer of WGA-labeled cellular elements through time-gated confocal microscopy. Our work identified new structural characteristics of two subtypes of TnTs in PC12 cells as well as dynamics of formation and transfer through complementary imaging methods combined with image processing. Therefore, we could achieve maximum lateral resolution and sample preservation during acquisitions to reveal new insights in TnT studies.</td>
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<td><strong>Keyword(s)</strong></td>
<td>Cell-to-cell communication, Tunneling nano Tubes, STED nanoscopy, deconvolution, PC12 cells</td>
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<td><strong>Title of the publication</strong></td>
<td>Tonic and phasic GABAergic signalings differently control corticostriatal spike timing-dependent plasticity along development</td>
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<td><strong>Author(s)</strong></td>
<td>GANGAROSSA Giuseppe, PAILLE Vincent, VALTCHEVA Silvana, FINO Elodie, VENANCE Laurent</td>
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<td><strong>Author's affiliation</strong></td>
<td>CIRB, Collège de France</td>
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<td><strong>Abstract</strong></td>
<td>Synaptic plasticity is a main neuronal substrate for learning and memory. The synaptic strength between neurons can be modified by their activity and the timing of their neuronal firing on either side of the synapse. Spike-timing dependent plasticity (STDP), a synaptic Hebbian learning rule, depends on the relative timing of pre- and postsynaptic spikes. GABAergic circuits control the input-output gain function of principal neurons by modulating efficiently their spike timing. We have previously shown that GABA controls the polarity of STDP at corticostriatal synapses and thus operates as a Hebbian/anti-Hebbian switch (Paillé et al., 2013). Indeed, blockade of ionotropic GABAA receptors reversed the temporal order of STDP. Depending on the synaptic location of GABAA-Rs we can distinguish two ionotropic GABAergic signalings: the tonic and the phasic components which rely on extrasynaptic and synaptic GABAA-Rs, respectively. Here, we show in corticostriatal rat brain slices that both tonic and phasic GABAergic signalings are differently implicated in controlling STDP. In conclusion our results strongly suggest that maturation of GABAergic signaling drives STDP-timing rule.</td>
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<td><strong>Keyword(s)</strong></td>
<td>GABA, Striatum, Plasticity</td>
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### Title of the publication
Distal vasomotor control and heart rate variability in preterm neonates.

### Author(s)
Boissière AM1; Barcat L1,2; Bodin E1,2; Decima P1; Delanaud S1; Libert JP1; Stephan-Blanchard E1; Leke A1,3; Tourneux P1,2; Bach V1.

### Author's affiliation
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### Abstract
Heart rate variability (HRV) describes the variations of the time interval between two consecutive heart beats. HRV can be investigated by calculating simple statistical indices in the time domain and by spectral analysis in the frequency domain. HRV reflects the activity of the autonomic nervous system, especially in the frequency domain. In particular very low frequencies VLF (0.003-0.04 Hz) would result from long term regulation mechanisms, probably related to thermoregulation and vasomotor activity. We questioned whether the characteristics describing VRC in the frequency domain (especially those in the very low frequencies) are correlated with thermoregulation, and in particular with vasomotion, in preterm neonates.

13 preterm neonates (gestational age: 29.7 ± 1.3 weeks of amenorrhea, birth weight: 1315 ± 354 g, weight: 1283 ± 297 g) were studied at thermoneutrality at night 9 of life (8 p.m. – 8 a.m.). Polysomnography, skin temperatures and HRV analyses were performed. Skin temperatures were measured by infrared thermography on 2 sites: abdominal and right foot. The index of vasomotor proposed by Lyon et al. (1997) was calculated from the temperature difference Td = Tinternal - Tperipheral. This difference was calculated here as: Td = Tabdo - Tfoot right since Tabdo is a good estimator of internal temperature because of the absence of the abdominal region anastomoses. Tfoot was chosen as distal temperature because this area with many arteriovenous anastomoses is the first one to vasoconstrict when neonates are exposed to non thermoneutral environment. Multiple regressions were calculated between HRV characteristics (dependent variable) and air temperature in the incubator and (Tabdo – Tfoot right) (independent variables).

Our results in the temporal domain showed that the lower the air temperature, the higher the level and the variability of heart rate. Regarding the frequency domain, our results pointed out that when the air temperature in the incubator decreased and, simultaneously when the difference Tabdo – Tfoot right increased (featuring distal vasoconstriction), the power of VLF and of LF (0.04-0.24 Hz) increased, the HF (0.24-heart rate max/2 Hz) power decreased and, consistently, the ratio LF/HF increased.

Our results point demonstrate that HRV is related to body temperatures and distal vasomotoricity in preterm neonates explored at 9th day of life. In particular, VLF power increases as a result of simultaneous decreased air temperature and vasoconstriction (increased Tabdo – Tfoot). Effects are also observed on LF and HF, arguing in favor of increased sympathetic tone and/or decreased parasympathetic tone.

LARC neurosciences, Amiens, 13 nov 2015

### Keyword(s)
sleep, ANS, HRV, thermoregulation, neonate
### Title of the publication
Contrasting effects of peripherally administered urotensin II and arginine vasotocin on the QT interval of the electrocardiogram in trout

### Author(s)
Gilmer Vanegas\(^1\), Frédéric Lancien\(^1\), Jérôme Leprince\(^2\), Hubert Vaudry\(^2\), Jean-Claude Le Mével\(^1\)

### Author's affiliation
\(^1\)INSERM UMR1101, Laboratoire de Neurophysiologie, SFR ScInBioS, Université de Brest, France  
\(^2\)INSERM U982, UA CNRS, Différenciation et Communication Neuronale et Neuroendocrine, Université de Rouen, Mont-Saint-Aignan, France

### Abstract
Urotensin II (UII) and arginine vasotocin (AVT) are two potent vasoconstrictor neuropeptides that elevate blood pressure and provoke vagally-mediated bradycardia. However, their potential effects on the QT interval of the electrocardiogram, a measure of the duration of the ventricular depolarization and repolarization, have never been described. Consequently, the goal of the present study was to compare the effects of UII and AVT on the QT interval in our established in vivo trout model. To this end, the effects of UII and AVT on dorsal aortic blood pressure (PDA), RR interval, a measure of the cardiac cycle length, QT interval and corrected QT (QTc) for RR interval, were investigated after intra-arterial (IA) injection of an equimolar dose of 50 pmol. IA injection of vehicle had no effect on the various parameters. At the 50- pmol dose, UII evoked an increase in PDA with a peak value observed 15 min after the injection (+22% from baseline, \(P<0.001\)). A concomitant increase in the RR interval (+18%, \(P<0.001\)), i.e. a bradycardia, appeared during this hypertension. The QT interval did not change during the bradycardic action of UII but the QTc interval significantly decreased. IA administration of 50 pmol AVT provoked quite similar increase in PDA, and elevation of the RR interval to those evoked by IA injection of UII but, in contrast to UII, AVT injection induced a highly significant and sustained prolongation of the QT interval compared to baseline (+7%, \(P<0.001\)) without change in QTc. These results indicate that the the usual tendency of RR interval lengthening to prolong QT was only observed following IA injection of AVT but not after IA injection of UII. The potential for UII to prevent detrimental prolongation of cardiac ventricular repolarization deserves further studies.

### Keyword(s)
urotensin II, arginine vasotocin, electrocardiogram, RR interval, QT interval, fish
**Title of the publication**
Ethnobotanical survey of plant species used in folk medicine against CNS/neurodegenerative disorders in Togo

**Author(s)**
Yendube T. Kantati
Magloire K. Kodjo
David Vaudry
Mesanvi Gbeassor

**Author's affiliation**

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| Ethnopharmacological relevance: Neurological, neuropsychiatric and neurodegenerative diseases are rising all around the world. In Togo a developing country, although plant-based medicines are the only means, still very little is known about the medicinal plants use to manage central nervous system (CNS) affections and their outcomes by the indigenous people.

Aim of the study: In this paper, the ethnobotanical survey aimed to report plant species used in traditional medicine (TM) for the management of CNS/neurodegenerative disorders in Togo.

Materials and Methods: 52 Traditional actors (TA) including 33 traditional healers (TH) and 19 medicinal plant sellers (MPS) were interviewed, using a questionnaire mentioning informants’ general data and uses of medicinal plants.

Results: 44 medicinal plants species distributed in 26 families are presented mentioning scientific and common local names, traditional medicinal use, plants organs used, preparation and administration as a first report of this study.

Conclusion: Consistent knowledge on medicinal plants used in the treatment of CNS/neurodegenerative disorders exists in Togo. The local flora abounds of potentially neuroactive and neuroprotective plants that could be useful for further neuropharmacological studies, neuroprotective and CNS drugs discovery.

**Keyword(s)**
Ethnobotanical survey, Togo, traditional medicine, CNS/neurodegenerative disorders.
**Title of the publication**
Remifentanil is neuroprotective against neonatal excitotoxic brain damage

**Author(s)**
Lecointre M (1,4), Tourrel F (1,2), Chollat C (1,3), Ramdani Y (1), Dureuil B (2), Marret S (1,3), Gonzalez BJ (1) and Jégou S (1).

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4 Rouen University Hospital, France

**Abstract**
Neuroprotection of premature newborns is a public health issue. The goal is, ultimately, to limit motor and cognitive impairments in the neonatal period. We have already shown that the morphinic remifentanil (Rf), used during caesarian delivery and in neonatal intensive care could be an interesting molecule to this end. Using an ex vivo model of brain slices from postnatal day 2 mice (P2), we previously showed that Rf exerts an anti-apoptotic activity (Tourrel et al., Anesth Anal 2014). Considering these initial results, a model of neonatal brain injury by intracortical (ic) ibotenate injection was used to evaluate in vivo the effects of Rf treatment. 3 groups of P2 mice were used: the Rf and NaCl groups received 3 intraperitoneal (ip) injections of Rf (500 ng/g over a 10-min period) or saline, respectively. Just after the last injection, ic injection of ibotenate (Ibo, 10 µg) was performed. A third group was composed of untreated mice. In situ labeling of cortical caspase activity was determined 5 hours after Ibo injection. The lesion size was assessed 5 days after the injection of Ibo. Finally, behavioral tests were done later between 3 and 12 days of life: righting and grasping reflex, negative geotaxis. Cortical caspase substrate consumption was significantly lower in Rf group (n = 11) vs NaCl group (n = 7) (p<0.05). The size of the Ibo-induced lesion was significantly reduced in the Rf group (n = 32) vs NaCl group (n = 32) (up to 67%, p<0.001). Behavioral results showed that in the negative geotaxis test, the Rf-treated mice more rapidly rotated as compared to NaCl-treated mice (p <0.0001 for males and p = 0.011 for females). Performance of grasping reflex was better in the Rf group, only in males (p=0.0027). In both tests, Rf-treated mice exhibited similar performance to untreated mice. No difference was found between Rf and NaCl groups for the negative righting reflex, treated pups turning less rapidly to a prone position than untreated mice. The anti-apoptotic effect of Rf on the immature mouse brain previously shown using a model of organotypic cortical slices was found in a neonatal mice lesional model. This effect is associated with a neuroprotective action and preservation of some behavioral functions in the first 12 days of life. Further experiments are required to better understand the mechanisms involved in this neuroprotective effect. Supported by the Normandy University, INSERM, IRIB, CHU Rouen, Région Haute-Normandie and the LARC Neuroscience network.

**Keyword(s)**
remifentanil, neonatal lesion, neuroprotection, behavior
<table>
<thead>
<tr>
<th>Title of the publication</th>
<th>Effect of chlorpyrifos exposure during development on respiration in juvenile and adult rats</th>
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<tr>
<td>Author(s)</td>
<td>Walaa Darwiche(1.2), Stéphane Delanaud(1), Véronique Bach(1), Jérôme Gay-Quéheillard(1), Wissam Joumaa(2), Wiam Ramadan(3)</td>
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<tr>
<td>Author's affiliation</td>
<td>1 PériTox, Périnatalité &amp; Risques Toxiques, UMR-I 01 Unité mixte INERIS, Amiens, France 2 UL, Environnemental Physio-Toxicity (PhyToxE), EDST, ER 017, Lebanon 3 LIU, School of Arts and Sciences, Department of Biological and Chemical Sciences, Lebanon</td>
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<tr>
<td>Abstract</td>
<td>Chlorpyrifos (CPF) is an organophosphorous pesticide widely used in the world. CPF acts by inhibiting the acetylcholinesterase (AChE) resulting in overstimulation at cholinergic synapses. Its residues are detected in food and drinking water and exposure to this compound is harmful during in utero and postnatal period. This study was aimed at determining the effects of prenatal and postnatal exposure to CPF on respiratory parameters during sleep, occurrence of sleep apnea and diaphragm contractility in juvenile and adult rats. Pregnant rats were exposed by gavage to CPF (1mg/kg/day or 5mg/kg/day) vs. vehicle until post-natal day 21 (PND21). Respiration and diaphragm contractility of half of rat pups were examined at this age and the others were then individually gavaged with the same dose of CPF until PND60. Measurements of ventilation during sleep and apnea index were made by whole-body plethysmography at PND21 (juvenile) and PND60 (adult). Diaphragm strips were dissected for the assessment of in vitro contractile function and acetylcholinesterase activity in the diaphragm was measured. CPF5 exposure was associated with a decrease in the body weight of rat pups at birth, at weaning and adult age. However, rats exposed to CPF1 showed a decrease in body weight only at adult age. Exposure to CPF5 at adult age induces an increase in expiratory time and tidal volume and a decrease in respiratory frequency. In addition, sleep apnea index was increased in CPF1 and CPF5-exposed groups at both ages. Twitch tension and fatigability index of the diaphragm were increased in CPF5 groups at both ages and it is associated with a decrease in AChE activity. In conclusion, we observed that prenatal and postnatal exposure to CPF, by inhibiting the AChE, alters the contractility of the diaphragm and impairs the ventilatory function in juvenile and adult rats at the dose of 5mg/kg/d.</td>
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<td>Keyword(s)</td>
<td>Pesticides, Chlorpyrifos, respiration, diaphragm</td>
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<tr>
<td>Title of the publication</td>
<td>Plasminogen activators (tPA and uPA) exhibit different involvement in mice neonatal brain edema after excitotoxic or hypoxo-ischemic insults.</td>
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<td>Author(s)</td>
<td>Nicolas Dupré¹; Bruno Gonzalez¹; Stephane Marret¹,²; Philippe Leroux¹</td>
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</table>
| Author's affiliation     | 1 ERI28 “NeoVasc” IRIB, University of Rouen, Rouen.  
2 Department of Neonatal Pediatrics and Intensive Care, CHU Rouen |
<p>| Abstract                 | Hypoxia-ischemia (HI) and excitotoxicity are validated causes of neonatal brain injuries. Brain lesions are mainly accompanied by cytotoxic edema (water retention within cells) and/or vascular edema (water retention within extra-cellular compartment). Brain edema appears to be an important complication, possibly leading to cell death. Plasminogen activators (tPA and uPA) are known to participate in injury processes through proteolytic and receptor-mediated pathways. tPA is also involved in matrix metalloproteinase (MMP) expression-induction and activation. These proteases are widely described as effectors of blood-brain barrier leakage in adult models of stroke, however their involvement in neonatal models of brain lesions deserve to be better understood. We have studied brain edema and the involvement of several proteases in neonatal brain lesions at two different ages (P5 and P10) in mice: we used an excitotoxic model based on intra-cerebral injection of a NMDA receptor agonist (ibotenic acid; 10µg) and a HI model based on common left carotid ligation followed by 40 min hypoxia (8% O2). Excitotoxic model shows bilateral water accumulation at both, P5 and P10. Water retention lasted 5 days after injury. In tPA knockout (KO) mice there is water retention only 24 hours after the injury at P5, meaning that after P5, water retention is tPA dependant. HI model shows ipsi-lateral water accumulation after P5 and P10 lesion, but does not last 5 days after injury. There is no significant difference in edema pattern in tPA KO mice, meaning that in HI model, edema is tPA independent. In HI model, MMP-9 and uPA activities are increased whereas there is no MMP-9 increased-activity in tPA KO mice. Altogether, these results demonstrate differential tPA impact on brain edema. Indeed, catalytic tPA activity appears to be largely involved in excitotoxic-induced edema whereas the absence of tPA and MMP-9 activities did not reduce HI-induced edema. |
| Keyword(s)               | excitotoxicity; hypoxia-ischemia; brain; neonate; mice; edema |</p>
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<tr>
<th>Title of the publication</th>
<th>DELAYED MEMORY IMPAIRMENT IN YOUNG RAT AFTER ONLY TWO BINGES OF ETHANOL INVOLVED GLUN2B-DEPENDENT METAPLASTICITY IN THE HIPPOCAMPUS</th>
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<td>Author(s)</td>
<td>K. Rabiant, B. Silvestre de Ferron, K-E. Bennouar, M. Kervern, S. Alaux-Cantin, A. Robert, J. Antol, M. Naassila, O. Pierrefiche</td>
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<tr>
<td>Author's affiliation</td>
<td>INSERM ERI-24, GRAP, Groupe de Recherche sur l’Alcool et les Pharmacodépendances, Université Picardie Jules Verne, Bât. CURS, CHU-Sud, Amiens, France.</td>
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<tr>
<td>Abstract</td>
<td>Binge drinking is common in adolescents but the impact of only few binges on learning and memory and cellular mechanisms remain unknown. We studied the effects of one (3 g/kg, i.p, 197.5±19 mg/dl blood ethanol content) or two ethanol intoxications (given 9 h apart) on adolescent rat’s learning capacity and synaptic plasticity in hippocampus slice at 24 h, 48 h or 8 days delay. Animals treated with two ethanol intoxications 48 h before training phase in the novel object recognition task failed during test phase. Ketamine had the same effect than ethanol whereas D-serine co-applied with ethanol, prevented learning deficit. In hippocampus slice, NMDA-dependent LTD was abolished 48 h but not 8 days after ethanol while NMDA-dependent LTP remains unaffected. Similarly to behavioural experiments, i.p. ketamine treatment had the same effect on LTD than ethanol whereas ethanol + D-serine (i.p.) prevented ethanol-induced LTD abolition. In contrast, i.p. treatment with MK-801 had no effect as well as with THIP or muscimol to test for the GABAergic component of ethanol’s effects. Input/output curve for NMDA-fEPSPs was shifted to the left 48 h after 2 binges and a stronger effect of Ro25-6981, an antagonist of GluN2B subunit was found. These results lead to a leftward shift of the relationship between synaptic signal and stimulation frequency. Interestingly, there was no cellular effects after only one ethanol injection. We conclude that two “binges” in adolescent rat are sufficient to reversibly abolish LTD and to evoke cognitive deficits via a short-lasting, repeated blockade of NMDA receptors inducing a change in the NMDA receptor subunit composition. Furthermore, ethanol effects developed over a 48 h period of abstinence indicating an important role for the intermittent periods during a repeated long-duration binge behaviour1.</td>
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<td>Keyword(s)</td>
<td>Ethanol, adolescence, binge, NMDA, GluN2B</td>
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1- Silvestre de Ferron B et al. Int J Neuropsychopharmacol. 2015 [Epub ahead of print]
**Title of the publication**: CHLORIDE HOMEOSTASIS IN RAT IS DISTURBS AFTER ETHANOL EXPOSURE DURING BRAIN DEVELOPMENT LEADING TO CHANGES IN HIPPOCAMPUS SYNAPTIC PLASTICITY

**Author(s)**: B. Silvestre de Ferron, C. Vilpoux, M. Kervern, A. Robert, J. Antol, M. Naassila, O. Pierrefiche

**Author’s affiliation**: INSERM ERI-24, GRAP, Groupe de Recherche sur l’Alcool et les Pharmacodépendances, Université Picardie Jules Verne, Bât. CURS, CHU-Sud, Amiens, France.

**Abstract**: In utero ethanol exposure in human induces irreversible learning and memory deficits in the newborn. At preclinical level, we previously showed that ethanol exposure in rat during the equivalent of the three trimester of human pregnancy reduced Long Term Potentiation (LTP) and increased Long Term Depression (LTD) in hippocampus slice. These effects were accompanied by 1) a reorganization of glutamatergic synapses and 2) a reversed modulatory role of GABAA inhibitions. We hypothesized that the new role of GABAA inhibitions was due to disturbance of the ionic co-transporters NKCC1 and KCC2 which control the electrochemical gradient of chloride ions in neurons. We thus performed immunohistochemistry and western blot for the two co-transporters in CA1 area of the hippocampus in control (CTRL) and perinatally ethanol exposed (EtOH) rats and tested both in vitro and in vivo the diuretic bumetanide, known to block these co-transporters, on synaptic plasticity. Immunolabeling and western-blot revealed an overexpression of KCC2 in EtOH group whereas expression of NKCC1 was unaffected. In vitro dose-response curve for bumetanide (10-100 μM) revealed a progressive correction of the abnormal LTD in EtOH group but also and interestingly, a correction of the lower LTP magnitude. In vivo treatment with bumetanide showed a partial correction of aberrant LTD recorded in vitro. These results demonstrate for the first time that the chloride gradient in hippocampal neurons is disrupted after in utero ethanol exposure in rat due to an upregulation of the KCC2 co-transporter. Furthermore, bumetanide is to our knowledge, the first substance described as compensating both deficits in LTP and LTD, suggesting a potential therapeutic value.

2-Silvestre de Ferron et al., In revision in Addiction Biology

**Keyword(s)**: KCC2, Ethanol, in utero, hippocampus, LTD
<table>
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<th><strong>Title of the publication</strong></th>
<th>Quantification of Octa Deca Neuropeptide in complex biological matrices</th>
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<td><strong>Author(s)</strong></td>
<td>Marie-Laure Walet-Balieu,¹,² Philippe Chan,¹ Rhita Lamtahri,² Julien Chuquet², Jerôme Leprince,² &amp; David Vaudry,¹,²</td>
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<tr>
<td><strong>Author's affiliation</strong></td>
<td>¹ PISSARO Platform, IRIB, University of Rouen, France ; ² INSERM U982, University of Rouen, France</td>
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<td><strong>Abstract</strong></td>
<td>Octa Deca Neuropeptide (ODN) is a peptide with potent in vitro neuroprotective properties. Its quantification at very low levels in biological tissues was needed to study its effects in vivo. Nevertheless, identification and quantification of peptides in complex matrices such as CerebroSpinal Fluid (CSF) is still challenging and requires development. For ODN, the heavy peptide was added to samples then they were purified by extraction on C18 ziptips and the peptide was eluted with a mixture of H2O/AcN 40/60 v/v. Then samples were analysed on an Agilent 6490 Triple Quadrupole using the MRM (Multiple Reaction Monitoring)-based detection system. The Optimizer software was used to determine MRM parameters of the compounds, especially transitions (couple precursor ion – product ion) and combined collision energies. The MRM acquisition allowed to achieve quantification ranges of 1 fmol/µL to 500 fmol/µL in the presence of BSA (Bovin Serum Albumin) and of 5 fmol/µL to 500 fmol/µL in the presence of CSF. Despite the complexity of the matrix, the limit of quantification was very low through the Agilent 6490 LC-QQQ system due to its ion funnel technology. The quantification of other peptides such as PACAP and small organic compounds in different complex matrices (CSF, plasma, biological tissues) is now being implemented.</td>
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<td><strong>Keyword(s)</strong></td>
<td>Quantification, ODN, complex matrices, MRM</td>
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Developments supported by FEDER (Fonds Européen de Développement Régional)
**Title of the publication**

Effects of anti-alpha-MSH autoantibodies on melanocortin 4 receptor dependant satiety signaling in patients with eating disorders and obesity.

**Author(s)**

Nicolas Lucas $^{1,2}$, Romain Legrand $^{1,2}$, Kirsti Akkermann $^3$, Jaanus Harro $^3$, Christine Bôle-Feysot $^{1,2}$, Jonathan Breton $^{1,2}$, Pierre Déchelotte $^{1,2,4}$, Sergueï O. Fetissov $^{1,2}$

**Author's affiliation**

1 Inserm UMR1073, Nutrition, Gut and Brain Laboratory, Rouen, France; 2 Institute for Research and Innovation in Biomedicine (IRIB), Rouen University, Normandy University, France; 3 Department of Psychology, Centre of Behavioural and Health Sciences, University of Tartu, Tartu, Estonia; 4 Rouen University Hospital, CHU Charles Nicolle, Rouen, France.

**Abstract**

Activation of the hypothalamic melanocortin 4 receptor (MC4R) by alpha-melanocyte-stimulating hormone (alpha-MSH) is critical in inducing satiety. It has been described that MC4R knockout leads to obese phenotype in rodents, supporting that altered MC4R signaling may be an important mechanism underlying obesity (OB) and eating disorders (ED). As we have previously shown, humans naturally display alpha-MSH-reactive autoantibodies which plasma levels correlate with psychopathological traits in patients with anorexia nervosa (AN) and bulimia (BN). It suggests that anti-alpha-MSH autoantibodies may modify MC4R-mediated satiety depending on their properties. In this study, we used surface plasmon resonance to characterize affinity kinetics of plasma extracted IgG binding to alpha-MSH in patients with OB, restrictive AN, BN and binge-eating disorder (BED) as compared to healthy controls (Ctrl). We found that values of association and dissociation constants of OB IgG were significantly lower compared to both Ctrl and ED groups. Furthermore, we discovered that the affinity of alpha-MSH/anti-alpha-MSH IgG immunocomplexes (IC) on MC4R+ HEK293 cells was considerably decreased when incubated with OB IgG. Then, we studied by confocal microscopy cell membrane binding and internalization of labeled IC on MC4R+ HEK293 cells. After 30 min of incubation, ratios of cytosolic/membrane IgG localizations on cultured cells were lower in OB and higher in AN as compared to BED and Ctrl groups. To understand if this range of IC kinetic interaction results in difference in MC4R activation, we measured alpha-MSH-induced cAMP release by MC4R+ cells in presence of IgG. We found that adding human IgG from either Ctrl or patients groups resulted in an increased affinity of alpha-MSH binding to MC4R via a left shift of the cAMP activation curve. Moreover, adding IgG from AN or BED patients resulted in a significantly lower maximal cAMP production as compared to OB and Ctrl IgG. Finally, when stereotaxically injected in rat hypothalamus, ED and Ctrl IgG didn’t affect alpha-MSH-induced food intake decrease contrary to OB IgG that reversed the neuropeptide dependant satiety. To conclude, the modulation of alpha-MSH-induced cAMP production suggests a constitutive allosteric role of anti-alpha-MSH autoantibodies in activation of MC4R, IgG from ED patients seems to promote compensatory effects on altered satiety that are not observed with OB IgG.

**Keyword(s)**

neuropeptide, autoimmunity, obesity, eating disorder
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<th><strong>Title of the publication</strong></th>
<th>Q-PCR on PRIMACEN platform</th>
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<td><strong>Author(s)</strong></td>
<td>DI GIOVANNI MARINE</td>
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<tr>
<td><strong>Author's affiliation</strong></td>
<td>VAUDRY DAVID, BENARD MAGALIE</td>
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<tr>
<td><strong>Abstract</strong></td>
<td>PRIMACEN (<a href="http://www.primacen.fr">http://www.primacen.fr</a>) is a research infrastructure for life sciences that encompasses 5 facilities covering the field of cellular imaging from the synthesis of biomarkers to the localization and the determination of biological activity of molecules of interest. The PRIMACEN facility ‘microdissection and Q-PCR’ offers equipment for small animal surgery, histology, laser microdissection and quantification of gene expression. Two 96-wells real-time instruments are available on PRIMACEN (a 7500 Fast Real-Time PCR system and a QuantStudio 12K Flex Real-Time PCR system; Life technologies). The final PCR reaction has been optimized to 13 µl and the run is performed in less than 1h. A high-throughput quantitative PCR device, the LightCycler 1536 qPCR system (Roche), allows analysis of 1536 samples in a final reaction volume of only 2 µl in less than 50min. An automated liquid handling platform (Agilent Technologies) dispenses reagents and samples to 1536-well plates. In complement to those equipments, PCR panels (cell cycle, oxidative stress, ischemia, PACAP regulated genes…) were also developed for mouse and rat species. Primers design was realized with the Primer Express software (Life technologies) and each set of primers has been experimentally validated for specificity and efficiency. Data analysis is conducted on the FastR software (PRIMACEN, <a href="http://www.fastr.fr">http://www.fastr.fr</a>). Finally, a new generation of PCR, the Digital PCR, is also available on PRIMACEN with the QuantStudio 3D (Life technologies). Digital PCR provides greater precision and sensitivity relative to real-time PCR. Samples are partitioned across thousands of reactions. Digital PCR is ideal for rare events detection and enables direct absolute quantification of gene expression in a sample.</td>
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<td><strong>Keyword(s)</strong></td>
<td>q-PCR</td>
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The effects of N-Acetylcysteine on alcohol seeking and relapse in a rat model of binge drinking

LEBOURGEOIS Sophie, VILPOUX Catherine, JEANBLANC Jérôme, NAASSILA Mickaël

Groupe de Recherche sur l’Alcool et les Pharmacodépendances (GRAP INSERM ERi 24), University of Picardie Jules Verne, Centre Universitaire de Recherche en Santé, CHU Sud, Amiens

The Alcohol Use Disorder is a chronic and highly relapsing disorder, characterized by a loss of control over alcohol consumption and binge drinking episodes which facilitates escalation of alcohol consumption and alcohol craving (uncontrollable desire to consume). A large body of evidence suggests a key role of glutamate in this disease. In recent years, the modulation of cystine/glutamate exchange, via the Xc-system has emerged as a new therapeutic alternative for reducing the excitatory glutamatergic transmission observed in addiction. On the normal state, the balance between intrasynaptic and extrasynaptic glutamate levels is under the control of extrasynaptic glutamate. By binding to the perisynaptic receptors mGluR2/3, the extrasynaptic glutamate exerts a negative feedback which limits the glutamate release. The objective of this study was to determine whether the reduction of the levels of extracellular glutamate via the N-acetylcysteine (NAC), a precursor of the cysteine, could reduce alcohol consumption, alcohol-seeking behavior (i.e., the persistence of drug search behavior in the absence of the drug, a model of craving) and relapse in a preclinical model of “binge drinking”. In order to test if NAC is able to modulate alcohol related behaviors, male Long Evans rats were trained to self-administer 20% EtOH in operant cages. Once the consumption was high (rats displaying clear signs of intoxication as expected with the binge drinking behaviour) and stable (1.0 ± SEM g of alcohol/kg/15min), the effect of an i.p. NAC injection (0, 25, 50 or 100 mg/kg) one hour before the beginning of each test, was evaluated on different aspects of the operant self-administration behavior. Our study showed that only the acute NAC injection of 100 mg/kg was effective in reducing alcohol consumption (-35%). Interestingly, the efficacy of NAC was greater on alcohol-seeking behavior (-80%). However, after one week of extinction sessions, NAC had no effect on the prevention of EtOH relapse. Overall, our results suggest that NAC is able to limit animal’s seeking behavior, making it a potential new treatment for the maintenance of abstinence (anti-craving effect).

SL is the recipient of a grant from the Ministry of Research.

Binge drinking, Ethanol self-administration, Glutamate, Cystine-glutamate exchange, N-acetylcysteine (NAC)
Title of the publication | The rs1806201 polymorphism of the Grin2B gene as a marker of alcohol withdrawal severity
---|---
Author(s) | Charles-Antoine Papillon, Philippe Batel, Philip Gorwood, Mickael Naassila, Hakim Houchi
Author's affiliation | GRAP INSERM-ERi24, Groupe de Recherche sur l’Alcool et les Pharmacodépendances, Université de Picardie Jules Verne, Amiens
Abstract | In patients suffering from alcohol-dependence, one of the most severe clinical sign during withdrawal, which engage the prognosis and is present in one-tenth of the population, is the generalized convulsive seizures (GCS). The complexity of care management of CGS isn’t due to the treatment course but the identification of patients at risk. Indeed, only an historic of GCS during previous episodes of withdrawals can indicate a risk, without it, it is currently impossible to determine whether or not a patient will suffer from it. A possible target that could play an important role in the GCS susceptibility would be N-methyl-D-aspartate receptor of glutamate. Indeed, chronic ethanol exposure induces numerous neuroadaptations, notably in the subunit composition of the NMDA receptor tetramer, in particular an isotype switch between the GluN2A and the GluN2B subunits. This over-expression of the GRIN2B gene, encoding the GluN2B subunit, produces more receptors that are overstimulated, especially in the extra-synaptic part where they mediate excitotoxicity phenomenon. Using a candidate gene strategy, we studied the rs1806201 single nucleotide polymorphism of the GRIN2B gene, and its association with alcohol-dependence and the GCS. We have recruited 159 alcohol-dependant patients from two alcohol treatment-centers (one in Amiens, the second in Paris) and 128 paired controls (the controls from Amiens came from the general population, those from Paris came from a nursing home and hadn’t any history of addiction). Genotyping has been realised by RT-QPCR (TaqMan® Technology) from swab sample. Our results demonstrated that there is no association between alcohol-addiction and rs1806201. However, by a stratification of our population in function of the presence or lack of GCS, we found a significant association between GCS and rs1806201 (p=0.005; OR=3.9). In conclusion, the SNP rs1806201 isn’t a biomarker of alcohol-addiction, but is a marker of GCS during a withdrawal episode in alcohol-dependent patients. The genotyping of this polymorphism could be useful in clinics for a better intervention towards patients at-risk of severe withdrawal episodes. CAP is the recipient of a grant from the Ministry of Research.
Keyword(s) | NMDA, GluN2B, GRIN2B, Ethanol withdrawal, Generalized Convulsive Seizures
**Title of the publication**  
Involvement of the urotensin II peptide system on vasospasm and neurosensitivomotor deficits in sub-arachnoid hemorrhage

**Author(s)**  
M. El-Amki¹, M. Dubois¹, A. Mutel¹, T. Clavier¹, L. Desrues¹, S. Curey⁴, G. Gastaldi⁵, A. Mellot³, F. Morin¹, P. Gandolfo¹, V. Compère¹,², F. Proust¹,³ and H. Castel¹

**Author's affiliation**  
1 Inserm U982, Equipe Astrocyte et Niche Vasculaire, Laboratoire de Différenciation Neuronale et Neuroendocrine, IRIB, Université de Rouen, Mont-Saint-Aignan, France,  
2 Département D’Anesthésie-Réanimation, CHU de Rouen, France ; 3Département de Neurochirurgie, CHU de Rouen, France

**Abstract**  
Sub-arachnoid hemorrhage (SAH) refers to extravasation of blood into the compartment between the brain and the tissue that covers the brain. This is often due to a ruptured aneurysm and accounts for up to 5% of all new stroke cases. Survivors of SAH commonly experience sequels that affect their day-to-day lives and which could persist years after; these include fatigue, memory deficits, executive function, language, depression and sleep disorders. The cerebral arterial vasospasm (CV) is a complication of the SAH, and may by associated with neurological deficits, microthrombosis and cerebral ischemia. The CV may be due to vasoactive peptides which are released locally and which, under normal conditions, control the blood/brain exchange. One of the most potent vasoactive peptides is urotensin II (UII). Urotensin II (UII) and its paralog URP activate a G protein coupled receptor (GPCR) named UT. UII exerts a wide range of physiological effects and regulate the endocrine, cardiovascular, kidney and immune functions.  
We led a single-center prospective study over a period of 24 months, including all patients with SAH of aneurysmal origin with external ventricular bypass and aneurysm exclusion, classified stage 1 or 2 in the WFNS scale. Blood and CSF samples were collected from D0 to D8. The ROC curve showed that the plasma concentration of UII is a discriminating factor for the occurrence of CV (AUC 0.824, P = 0.02, patent FR1356995, 2013). A mouse model of SAH was also developed via a double injection of arterial blood into the magna cisterna during two consecutive days. Occurrence of CV of the cerebral middle, basilar and anterior arteries and a number deposition of fibrin (microthrombis) were observed from the 2nd to the 14th day post-SAH, as well as increase in the activity of caspase-3 from Day 3 to 14 in brain cortex, hippocampus, endothelium and choroid plexus. Impaired sensorimotor functions (beam walking test) were detected from D7 to D10. Then, we investigated the impact of the UII system in this SAH model my means of wild-type (UT+/+) and KO-UT (UT−/−) mice. UT−/− mice do not exhibit any remarkable phenotype. The β-galactosidase activity (reporter of the UT transcription) was very faint in the brain cortex, endothelium, and choroid plexus in Sham UT−/− mice and strong in brain cortex, hippocampus, choroid plexus and microvessels 10 days post-SAH. Consistent with these observations, we demonstrated the expression of UII peptide in the brain cortex, the hippocampus and in some large and small arteries only in SAH mice. Interestingly, the UT ligand urantide, listed so far as "antagonist", but now definitively characterized as a biased ligand, completely prevented CV, microthrombosis and consecutive neurosensitivomotor deficits in SAH mice, suggesting that UT ligands may constitute interesting therapeutic tools.  
We should in the future, explore the effect of other UT biased ligands which may cross the blood brain barrier and bind UT, mainly expressed during the course of the SAH pathology. These compounds with minimal side effects can be extremely innovative in the treatment of SAH, but also in other cardiovascular pathologies.  
Supported by University of Rouen, Rouen CHU Hospital, Inserm and Seinari.

**Keyword(s)**  
sub-arachnoid hemorrhage, urotensin II, vasospasm, diagnostic marker
Pre-clinical animal models and targeted therapies on cognition: Direct Impact of the PI3K inhibitor buparlisib

Dubois M.\(^1\), Tonon M.-C.\(^1\), Perzo N.\(^1\), Gandolfo P.\(^1\); Hilber P.\(^2\), Joly F.\(^3,4\) and Castel H.\(^1\)

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Background: Cancer treatments such as chemotherapy can induce cognitive troubles (memory deficits, psychomotor slowing) referred to as “Chemofog”. Recently, targeted therapies have been introduced in cancer treatment and preliminary investigations suggest direct actions on the central nervous system. In current clinical practice, some targeted therapy-treated patients report important fatigue, lethargy and selective cognitive disorders. Our group previously explored the direct impact of targeted therapies on cognition and brain functioning and demonstrated that drugs targeting the mTOR pathway did not induce cognitive deficits but altered cytochrome oxidase activity in selected brain regions related to the sleep/wake cycle, feeding and motivation, and that anti-angiogenics targeting VEGFA, reduced learning processes. The recent promising effects of phosphatidylinositol-3-kinase (PI3K) inhibitors in cancer therapy, and the crucial role of PI3K in cell proliferation, synaptic plasticity and transmission, led us to question whether PIK3 inhibitors, in particular buparlisib (Novartis Pharmaceutical), may alter cognitive functions and emotional reactivity during cancer treatments.

Method: BKM120 or buparlisib was tested on anxious-like (elevated plus maze) and depressive-like behaviours (tail suspension test, TST; forced swimming task, FST) in C57Bl/6J Rj mice. Spontaneous activity, object recognition memory, motor impulsive behaviours in the dark emergence test and compulsive-like behaviours in the marble burying tests were also evaluated.

Results: Buparlisib did not affect memory performances but delayed helplessness in the TST and FST, reduced anxiety/increased impulsivity in the emergence test, and decreased exploratory behaviours and compulsive stereotypy.

Conclusion: Our original observations indicate that inhibition of PI3K is responsible for anti-depressive like behaviour, impulsivity and/or reduced anxiety. It could be associated with a dysfunction of interactions between prefrontal cortex, raphe nucleus and hippocampus sustained by abnormal cross talk between serotonergic and GABA-ergic neurotransmission. This study suggests the beneficial opportunity of co-administration of psychiatric preventive therapeutics or selection of PI3K inhibitors unable to cross the brain blood barrier.

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Keyword(s): Chemofog, PI3k, impulsivity, cancer targeted therapy
<table>
<thead>
<tr>
<th><strong>Title of the publication</strong></th>
<th>Hemodynamic changes preceding interictal spike development in GABA disinhibition model of epilepsy in adult rat: electrocorticography and near-infrared spectroscopy study.</th>
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<tr>
<td><strong>Author(s)</strong></td>
<td>V. Osharina(^1)*, A. Aarabi(^1), M. Manoochehri(^1), L. Araf(^1), M. Mahmoudzadeh(^2), F. Wallois (^1,2)</td>
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<tr>
<td><strong>Abstract</strong></td>
<td>Last decades neurovascular coupling have been largely studied by brain imaging techniques but still has many unclear spots, particularly, the fact that hemodynamic changes precede the electrical one needs to be investigated and is actually highly debated because of its unclassical view on the relationship between neurons and supporting vascular system. The goal of this study was to study the hemodynamic pattern surrounding acutely evoked interictal spike activity in rat’s cortex. Interictal epileptiform activity was evoked in adult Sprague-Dawley rats by local application of penicillin G or bicuculline methiodide on the opened somatosensory cortex. Using combined electrocorticography (ECoG) and near-infrared spectroscopy (NIRS) techniques, we found a triphasic hemodynamic response which started well before the ECoG spike and ended after the ECoG spike in both models. With a similar pattern across all rats, the hemodynamic response was divided into three periods: pre-spike (before the spike), swing (period of vasomotor switch) and post-spike periods (after the spike). Both models support the idea that the hemodynamic changes precede, underlie and sustain the electrical activity in region. Complexity of biological processes in epileptic region and techniques we used make it difficult to surely explain the basis of hemodynamic changes around the spikes in our models. Future studies are required to improve our understanding of neurovascular coupling in epileptic region.</td>
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<td><strong>Keyword(s)</strong></td>
<td>Electrocorticography, near-infrared spectroscopy, epilepsy, interictal spike, neurovascular coupling, GABA disinhibition, animal model</td>
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<tr>
<td>Title of the publication</td>
<td>Neuroprotective mechanisms of endogenous PACAP against alcohol toxicity in the adolescent and adult mice brain</td>
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<td>Author(s)</td>
<td>Hélène Lacaille,¹,² Donovan Liot,¹,²,³ Colas Calbrix,¹,²,³ Hubert Vaudry,¹,²,³ Dominique Duterte-Boucher,¹,² and David Vaudry¹,²,³</td>
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<p>| Abstract                 | Binge drinking is reported in 20% of American high school students and 10% of them experienced extreme binge drinking. One major concern is that such drinking behavior happens during adolescence, a period of age during which brain still exhibits intense reorganization making it vulnerable to alcohol toxicity. The protective effects of PACAP, a 38 amino acid neuropeptide, against alcohol toxicity have already been demonstrated in vitro and in vivo. To explore the potential of endogenous PACAP to struggle against alcohol toxicity, PACAP-deficient mice were injected with alcohol in a Binge drinking-like manner. Biochemical analysis revealed that the activity of caspase-3 and the production of reactive oxygen species were increased in PACAP KO mice after alcohol administrations. Concomitantly, a whole-genome microarray experiment was performed to compare gene regulations induced by alcohol between adolescent wild-type and deficient mice. Data analysis revealed that pathways involved in cell cycle and DNA repair were significantly down-regulated. These results imply specific alterations in proliferating cells. To address this issue, neurogenesis in the dentate gyrus of the hippocampus was investigated. In accordance with the transcriptomic data, the evaluation of neurogenesis by immunohistochemistry in adolescent and adult animals revealed a decrease of cell proliferation in PACAP-deficient mice treated with alcohol and a possible alteration of their survival. These data obtained with knockout animals, highlight that endogenous PACAP has a protective role against alcohol toxicity. |
| Keyword(s)               | This work is supported by Ireb, Inserm, the ANR, the AlcoBinge Project and the Region Haute-Normandie. |</p>
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<th><strong>Title of the publication</strong></th>
<th>Physiologic and Behavioral Assessment of Sciatic Nerve Injury in Wistar Rat Model Treated With Freund's Incomplete Adjuvant</th>
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<tr>
<td><strong>Author(s)</strong></td>
<td>Aziez CHETTOUM(^2), Asma FRAIA(^2), Hacène FRIH(^2), Kamilia Guedri(^3)</td>
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</code></pre>
<p>| <strong>Abstract</strong>               | Major depression disorders are commonly seen in many medical diseases that share chronic inflammatory pain as a common denominator. Pains whether inflammatory or neuropathic, those caused by damage to the central or peripheral nervous system are the most difficult to treat due to their resistance to conventional analgesic treatments. In our study, we chose a model of neuropathic pain (sciatic nerve ligation) associated with intradermal injection of 0.02 ml of AIF in order to achieve an activation of the innate immune system in male Wistar rats subsequently being tested of forced swimming (FST). Our study was completed by an endocrinological study highlighting the importance of sex steroids on the fluctuations of depression by hormonal assays (testosterone and estradiol). Our results showed that the ligation causes a highly significant increase in the depression 10 days postoperative. This is revealed by increased immobility time in the FST. This depression reported among ligated tends to be mitigated over time there has been a significant decrease in twenty days following ligation. Treatment with AIF is in 2 phases: 1st where we see a depressive-like behavior due to the activation of the immune system that causes inflammation and a 2nd phase where there is a less depression antidepressant-like and the inflammation disappears after 20 days. This is also associated with hormonal changes or there is a significant increase in the level of testosterone in subjects ligated and treated (AIF) and a significant decrease of estradiol. These results then takes us to highlight the existence of neuro-immune-endocrine link that acts to benefit the body and restore homeostasis. In case of disruption these systems associated will cause depressive disorders also a major depression. |
| <strong>Keyword(s)</strong>             | AIF, Neuropathic Pain, Inflammation, testosterone, estradiol, depression |</p>
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<th><strong>Title of the publication</strong></th>
<th>SUPPRESSION OF NEURONAL IGF SIGNALING DURING AGING PROTECTS MICE FROM (\beta)-AMYLOID PROTEOTOXICITY</th>
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<td><strong>Author(s)</strong></td>
<td>George C, Holzenberger M and Aïd S</td>
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<tr>
<td><strong>Abstract</strong></td>
<td>Alzheimer's disease (AD) is a neurodegenerative disorder marked by gradual and irreversible decline in cognitive function. AD is characterized by (\beta)-amyloid (A(\beta)) peptide aggregation into oligomers (A(\beta)O), considered the most synaptotoxic species as they strongly correlate with brain dysfunction in AD patients. We recently showed that ablation of insulin-like growth factor receptor (IGF-1R) from adult neurons alleviates amyloid pathology and cognitive deficits in AD mice. Here, we started to identify the mechanistic links between IGF signaling and neuronal protection against A(\beta)O toxicity. We used Cre-mediated tamoxifen-inducible IGF-1R knockout from neurons (inIGF1RKO) to inactivate the receptor gene in 16-month-old mice. At 25 months, inIGF1RKO mice received an ICV injection of 400 pmol of A(\beta)O. Efficient oligomerization of injected A(\beta) peptide was demonstrated by transmission electron microscopy. Administration of A(\beta)O induced a significant neuroinflammation in inIGF1RKO and control brains. Importantly, we found that astrocyte density was markedly decreased in inIGF1RKO mice compared to controls (-23%; (p &lt; 0.01)). Suppression of neuronal IGF-1R also induced a significant reduction of microglial infiltration in inIGF1RKO mice compared to control mice (-16%; (p &lt; 0.01)). Using the Barnes maze test, we demonstrated that inIGF1RKO mice were protected from deleterious effects of AbO on long-term spatial memory. Moreover, the open-field test revealed that neuronal IGF-1R inactivation alleviates A(\beta)O-induced anxiety behavior. Importantly, we found a conspicuous decrease of neuronal soma size in inIGF1RKO compared to controls. To identify which pathways are involved in previously observed neuroprotection, we performed a genome-wide microarray analysis of microdissected hippocampal inIGF1RKO neurons. IPA revealed pathways involved in the regulation of growth, survival and protein synthesis to be associated with neuroprotective effects of IGF-1R inactivation. These findings indicate that blocking neuronal IGF-1R signaling during aging counteracts A(\beta)O-induced neurotoxicity possibly by regulating cell size-controlling pathways.</td>
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<td><strong>Keyword(s)</strong></td>
<td>Insulin-like growth factor, Alzheimer’s disease, (\beta)-amyloid oligomers, neuroprotection, conditional mutagenesis, cell size-controlling pathways.</td>
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Title of the publication | Does empathy is the only framework to explain the corticospinal modulation during pain observation?
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Author(s) | BUCCHIONI Giulia\textsuperscript{1}, FOSSATARO Carlotta\textsuperscript{2}, CAVALLO Andrea\textsuperscript{2}, KRYSTKOWIAK Pierre\textsuperscript{1}, GODEFROY Olivier\textsuperscript{1}, MOURAS Harold\textsuperscript{3} and GARBARINI Francesca\textsuperscript{2}
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Abstract | Objective
Recent studies showed that motor responses similar to those present in one’s own pain (freezing-effect) occur as a result of pain observation in others. This finding has been interpreted as the physiological basis of empathy. Alternatively, it can represent the physiological counterpart of an embodiment phenomenon, related to the sense of body-ownership. We know that simply looking at a fake hand, whenever positioned in a body-congruent egocentric perspective, can lead the subjects to experience it as part of their own body. In the present study, we compared the empathy and the ownership hypothesis, by manipulating, during observation-conditions, the perspective of the view of a hand model receiving pain. Similar results in both the egocentric and the allocentric perspective would confirm the empathy hypothesis; a different result in the egocentric perspective (where the embodiment occurs) would confirm the body-ownership hypothesis.

Participants and methods
We used transcranial magnetic stimulation to record changes in corticospinal motor representations of the hand, while subjects (n=17) observed videos showing a) a needle penetrating or b) a q-tip touching a hand model, presented either in egocentric or in allocentric perspective. Motor evoked potentials (MEPs) were recorded from the right first dorsal interosseus.

Results
Compared to the allocentric perspective, a significantly greater reduction of the mean MEPs amplitude (freezing-effect) was found when the hand model receiving pain (needle-penetration) was presented in an egocentric perspective.

Conclusions
This finding suggests that the freezing effect during pain observation can be better explained by the body-ownership than by the empathy hypothesis.
Keyword(s) | Empathy, Body-ownership, Transcranial Magnetic Stimulation, Motor-Evoked Potentials