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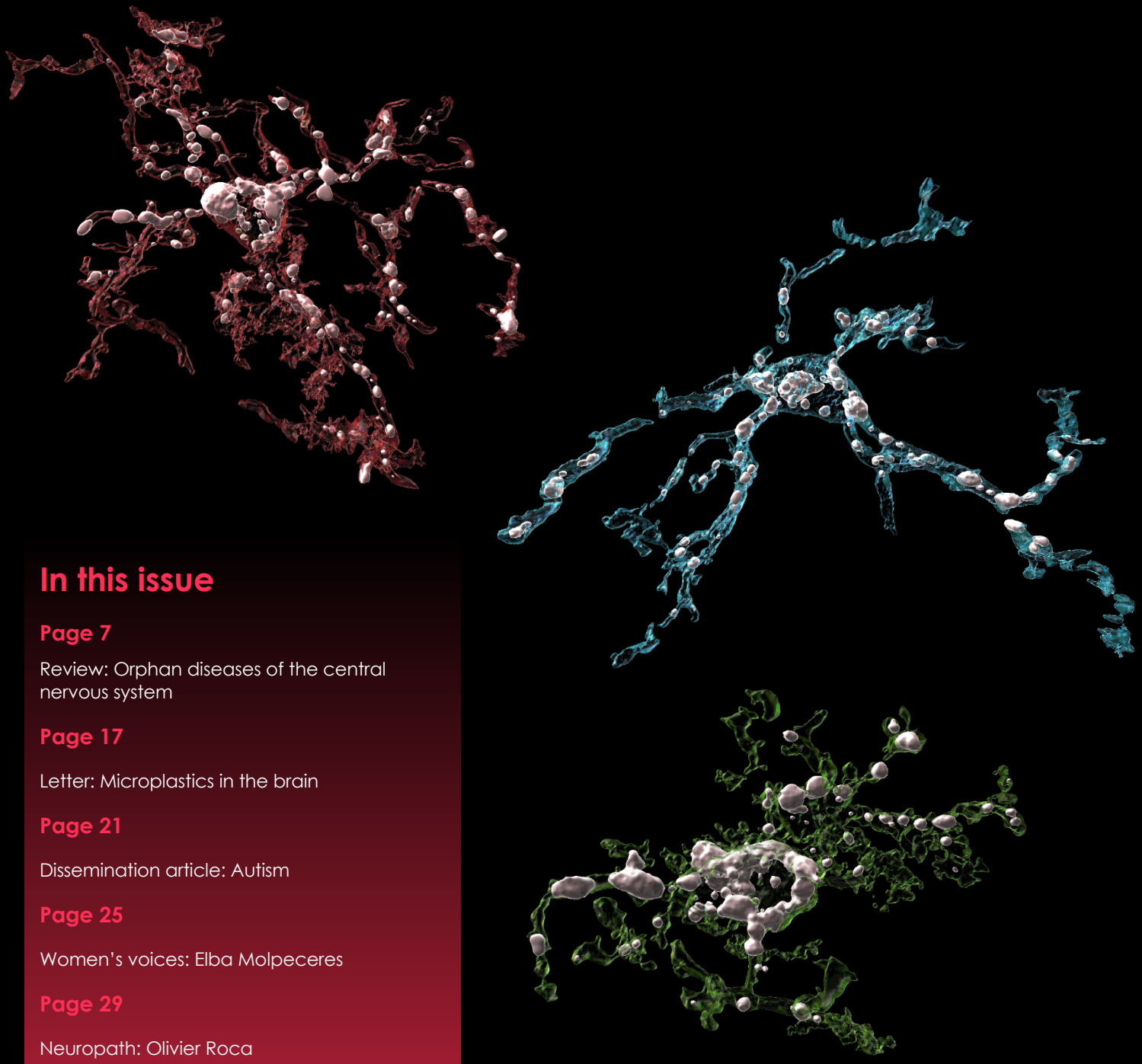

In this issue

Page 7

Review: Orphan diseases of the central nervous system

Page 17

Letter: Microplastics in the brain

Page 21

Dissemination article: Autism

Page 25

Women's voices: Elba Molpeceres

Page 29

Neuropath: Olivier Roca

Page 31

Interview: Richard Hahnloser

Page 34

Neurometeme and Announcements

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TABLE OF CONTENT

REVIEW 07

ORPHAN DISEASES OF THE CNS

Sarah Bou Sader Nehme

LETTER 17

MICROPLASTICS IN THE BRAIN

Maria-Carmen Medrano

DISSEMINATION ARTICLE 21

AUTISM

Daniele Stajano

WOMEN'S VOICES 25

ELBA MOLPECERES

Sara Carracedo

NEUROPATHS 29

OLIVIER ROCA

Sara Carracedo

INTERVIEW 31

RICHARD HAHNLOSER

Juan Garcia-Ruiz

NEUROMEME & ANNOUNCEMENTS 34

Orphan diseases of the central nervous system

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Abstract

Orphan diseases are defined as rare conditions with no or very few treatments. Their etiology is multifactorial as they can be triggered by genetic predisposition or unknown external factors. They can affect multiple organs, including the brain. Rare central nervous system (CNS) diseases are often accompanied by neurodegeneration and are generally chronic. They can become life-threatening, especially due to the lack of effective therapeutic strategies. In this review, I will present some CNS orphan diseases and emerging gene therapy-based treatments.

Keywords

CNS, gene therapy, orphan diseases, rare diseases, therapeutic strategies

Abbreviations

AAV	Adeno-associated viral vectors
ASO	Antisense oligonucleotides
CNS	Central nervous system
CRISPR	Clustered regularly interspaced palindromic repeats
DNA	Deoxyribonucleic acid
mTOR	Mammalian target of rapamycin
RNA	Ribonucleic acid

Introduction

The CNS is one of the most complex and vital systems of the Human body. It is the processing center that manages our feelings, thoughts, and movements. Its good functioning is essential for daily life, autonomic activities (walking, breathing, etc…), and more complex tasks (learning, feeling emotions, memory, thinking, etc…). Therefore, CNS impairments can result in drastic and deleterious consequences in our everyday lives.

The CNS can be the target of harmful pathogens (for example, Streptococcus agalactiae, Escherichia coli, Toxoplasma gondii, Herpes simplex virus) (1). Not only, as genetic predisposition and/or environmental influence can also disrupt its homeostasis leading to the development of mental and neurological disorders (attention-deficit/hyperactivity disorder, autism spectrum disorder, epilepsy, etc…) (2, 3, 4).

Within conditions affecting the CNS are those known as "rare" diseases, so-called due to their very low prevalence. They affect less than 200,000 individuals in the United States according to the U.S. Food and Drug Administration (5) and around 300 million individuals worldwide (6). These disorders mainly possess neurological and genetic etiology (7). Among them are the "orphan" diseases which currently lack efficient treatments. Due to inappropriate management, these conditions decrease the quality of life of the patient. In more severe cases, they can invalidate the patient and become fatal (8).

Clinical trials investigating orphan diseases were predominantly characterized by a low success rate (9). This is mainly caused by the limited evidence of the impact of the drugs, due to the low sample size during trials (10). However, recent advances in gene therapy seem to be encouraging for the treatment of rare conditions. Some promising approaches include the use of antisense oligonucleotides (ASO), adeno-associated viral vectors (AAV), and clustered regularly interspaced palindromic repeats (CRISPR)/Cas9 (11).

ASO are short sequences of single-stranded deoxyribonucleic acid (DNA) that can bind to their reverse complementary sequences through Watson-Crick base pairing (12). Through this

binding, ASO can modify the expression of a specific gene by modulating the expression of its resulting protein (11). AAVs are non-enveloped viruses that can deliver a DNA sequence to specific cells and induce its expression within the targeted cells (11, 13). Finally, the CRISPR/Cas9 technique is a method through which a DNA sequence can be repaired through the action of the endonuclease Cas9, guided by a small ribonucleic acid (RNA) molecule. Cas9 creates a break in the DNA, enabling the inclusion or exclusion of targeted genes (Figure 1) (11).

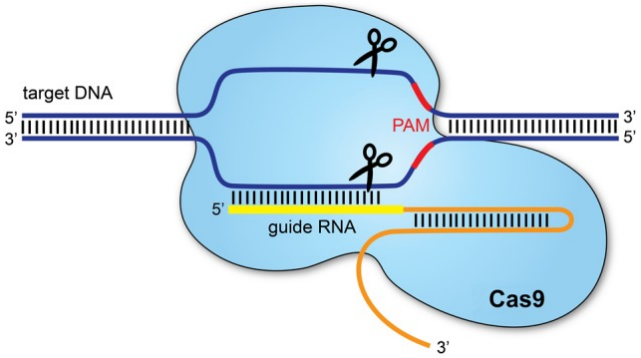

Figure 1: CRISPR/Cas9 technique (14)

In this review, I will present some of the orphan diseases of the CNS and will detail the most promising therapeutic approaches.

Methods

The cited articles were found through PubMed and Google Scholar.

The following terms were used in order to select the most relevant publications: orphan [AND] CNS [AND] diseases, rare [AND] CNS [AND] diseases, rare [AND] neurological [AND] diseases, and orphan [AND] neurological [AND] diseases.

Results and discussion

Examples of CNS orphan diseases

As stated above, most CNS rare diseases result from genetic mutations and neurological impairment. They are mostly characterized by muscular deterioration, neural decline, seizures, cognitive problems, and tumors (11). Summarized in Table 1 are some of them with their type, etiology, and symptoms. These diseases are among the most commonly studied orphan conditions of the CNS.

Current approved treatments

Most of the CNS orphan diseases lack efficient treatments. However, medications were developed for some conditions to enhance the quality of life of the patients and prolong their life expectancy.

Nusinersen is the first approved drug used to treat spinal muscular atrophy. It is marketed under the name Spinraza, since June 2017, in France. It is based on a gene therapy approach and consists of an ASO which helps increase the percentage of exon 7 inclusion in SMN2 messenger RNA transcripts (11, 16). Infants and young children who received Nusinersen have demonstrated improvement in motor functions and prolonged life expectancy (17).

Prednisone is a medication given to patients suffering from Duchenne muscular dystrophy. Even though it does not cure the disease, its daily intake was found to benefit the quality of life of the patients by predominantly enhancing their pulmonary and muscle functions (11, 18).

Other CNS rare diseases still lack specific treatments. For instance, multiple system atrophy patients utilize L-dopa to attenuate the associated Parkinsonian symptoms and undergo physiotherapy to alleviate ataxia (19). Amyotrophic lateral sclerosis is another example. Indeed, even though two medications have been approved for its treatment (riluzole and edaravone), they do not cure or reverse the progression of the disease. However, they display some benefits on patients' survival by limiting the disease-associated cell apoptosis (15). Interestingly, an ASO-based treatment was approved in the United States for amyotrophic lateral sclerosis management. Tofersen was proved to degrade the mRNA encoding the SOD1 protein thereby reducing its expression. Unfortunately, this molecule can't cross the blood-brain barrier and is therefore administered using intrathecal injection, resulting in adverse effects (20). The most common were headache, procedural pain, upper respiratory tract infection, and post–lumbar puncture syndrome (20).

Promising gene therapy approaches

Gene therapy approaches are further being investigated for the treatment of orphan diseases. They mainly rely on the use of ASO, AAV, and the CRISPR/Cas9 system.

Zolgensma is a gene therapy medication developed for the treatment of spinal muscular atrophy. It consists of an AAV loaded with a functional copy of the SMN1 gene. Administeredas an intravenous infusion, it delivers an intact copy of the SMN1 gene to motor neurons (21). Children who received infusions of Zolgensma have displayed an amelioration in their motor skills and a prolonged lifespan (22).

Another AAV-based therapeutic strategy is being developed by Novartis Gene Therapies for the management of amyotrophic lateral sclerosis. This gene therapy consists of a virus loaded with a short RNA that silences the SOD1 protein. During pre-clinical trials, this treatment has shown positive

results not only in mice but also in non-human primates. Indeed, motor neuron degeneration was decreased, the onset of the disease was delayed, and the life expectancy of the animals was improved (23,24).

Treatments with the CRISPR/Cas9 technology have been carried out for the management of Duchenne muscular dystrophy. This disease is characterized by a loss of the dystrophin protein; therefore, the aim of using CRISPR/Cas9 within this context is to upregulate the expression of utrophin, a homolog of dystrophin, and compensate for its absence (11).

Another promising and emerging approach relies on ASO to treat Dravet syndrome. In a mouse model of the disease, ASO were utilized to amplify the expression of the functional SCN1A protein. Not only was this increase successful, but it also decreased seizures' frequency (20).

Unfortunately, some rare CNS diseases do not have yet any gene therapy in clinical trials. This is the case for multiple system atrophy. Furthermore, no cure exists so far for Huntington's disease and the available treatments barely ameliorate the patient's quality of life (15). Brain Neurotherapy Bio, a gene therapy company, is currently planning a randomized, double-blinded, placebo-controlled phase 1 trial for adult patients with multiple system atrophy (25). However, and unlike other promising clinical trials, those regarding the treatment of Huntington's disease mainly failed. Tominersen was a candidate ASO, designed by Roche. Even though this molecule dose-dependently decreased the levels of mutant HTT, results have shown a worsening of the symptoms in patients compared to the placebo group (26).

Discussion

Over the years, orphan diseases of the CNS have gained considerable interest within the research community. Despite this growing concern, most of these conditions still lack proper and effective medications. With current therapeutic strategies hardly alleviating symptoms and targeting the underlying pathological mechanisms, the need for more efficient treatments has become urgent.

Among recently developed therapeutic strategies are gene therapy-based approaches. These comprise the use of ASO, AAV, and the CRISPR/Cas9 system (11). Those treatments are gaining popularity, especially after the promising results demonstrated in clinical trials. Indeed, several pharmaceutical industries are relying on these approaches to design new medications.

However, despite these considerable advances, additional and complementary studies are needed to assess the efficacy and safety of these approaches.

Another option being currently explored for the treatment of rare CNS diseases is the inhibitors of the mammalian target of rapamycin (mTOR). mTOR is a kinase whose alteration was previously involved in the pathophysiology of neurodegenerative disorders and the development of tumors. Blocking its signaling cascade could therefore potentially inhibit the occurrence of its associated diseases (11).

Conclusions

In conclusion, gene therapy-based approaches have become promising strategies for the management of CNS orphan diseases. As most of the currently available treatments merely improve the diseases' symptoms, gene therapy offers hope for the patients. Further studies are certainly warranted as the results of the clinical trials can sometimes be enigmatic. However, the outcomes highlight the potential of these approaches in treating rare diseases.

Disease	Type	Causes	Manifestations
Spinal muscular atrophy	Neuromuscular disease	• Caused by deletions/mutations in SMN1 gene • Particularly characterized by the absence of exon 7 (chromosome 5)	• Progressive and irreversible degeneration of anterior horn cells in the spinal cord • Muscle weakness and atrophy • Can result in respiratory failure
Duchenne muscular dystrophy	Neuromuscular disease	• X-linked inherited disorder • Caused by mutations in the dystrophin gene (chromosome Xp21)	• Severe and gradual muscle wasting and weakness • Difficulty in moving • Can result in the need for assisted ventilation or wheelchair use • Premature death (in the twenties) caused by respiratory failure or cardiomyopathy • Affects males more than females
Dravet syndrome	Epileptic syndrome	• Caused by mutations in the SCN1A gene (chromosome 2q24)	• Seizures • Neurodevelopmental delay • Motor and cognitive problems
Ohtahara syndrome (Early Infantile Developmental and Epileptic Encephalopathy syndrome)	Epileptic/seizure syndrome	• Mutations affecting several genes: PRRT2, SCN1A, KCNQ2, and SLC2A1	• Frequent spasms in neonates and infants • Cognitive and physical impairments • Premature death
Friedreich ataxia	Neurodegenerative disorder	• Mutations in the FXN gene (chromosome 9q13) • Mainly due to increased frequency of guanine–adenine–adenine trinucleotide repeats in intron 1	• Degenerative atrophy of the posterior spinal cord columns • Abnormal axonal thinning of the dorsal spinal roots • Degeneration of peripheral sensory neurons • Dysfunctions in the heart (left ventricular hypertrophy), endocrine organs (mainly the pancreas), peripheral nervous system, and CNS • Ataxia, muscle weakness, peripheral sensory loss

Multiple System Atrophy	Neurodegenerative disorder	• Etiology largely unknown • Some potential genes involved: SNCA, COQ2, MAPT, GBA1, LRRK2, and C9ORF72	• Glial cytoplasmic inclusions accompanied by insoluble proteinaceous filaments are found in the oligodendrocytes • Parkinsonism • Cerebellar ataxia • Autonomic failure
Amyotrophic lateral sclerosis	Neurodegenerative disorder	• Familial or sporadic forms • Mainly caused by mutations in the SOD1 gene • Other mutated genes: C90RF72, TDP-43, FUS, OPTN, TBK, GRN, NEK1, and C21ORF2	• Motor neuron degeneration • Muscle weakness, respiratory failure, speech problems
Huntington's disease	Neurodegenerative disorder	• Increased frequency of CAG trinucleotide sequence on the HTT gene	• Progressive cognitive, motor, and psychiatric problems
Rett Syndrome	Neuro-developmental disorder	• Mutations in the MECP2 gene	• Affects girls only • Premature death • Impairments in learning, language, coordination • Autism symptomatology • Epilepsy
Prader-Willi syndrome	Inhibited cognitive development	• Alterations in the 15q11-q13 region (paternal contribution)	• Hyperphagia (insatiable hunger) • Hypogonadism (production of little or no hormones) • Short stature (height below typical) • Mild mental retardation
Neurofibromatosis-1 (Von Recklinghausen disease)	Tumors	• Mutations in the NF-1 gene (tumor suppressor gene, chromosome 17)	• Bone abnormalities • Vascular problems • Cognitive impairment

Table 1: Some CNS orphan diseases (11,15)

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Microplastics in the brain: a trigger for neurodevelopmental disorders?

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Maria Carmen is a Doctor in Pharmacy currently working as a senior postdoctoral researcher at INCIA and IMN (Bordeaux Neurocampus). Her research has primarily focused on addiction and neuropathic pain, exploring their reciprocal relationship and impact on cognitive functions like attention deficits. Her work has advanced the understanding of neural networks including the spinal cord, locus coeruleus and ventral tegmental area.

Plastics have become an integral part of our environment, but their improper disposal leads to persistent pollution. Over time, plastics break down into micro- and nanoplastics (smaller than 5 and 0.1 µm, respectively; for the sake of simplicity, from now on I will refer to both as microplastics). Microplastics contain chemicals like phenols and phthalates, which are used as plasticizers—substances intentionally added to certain plastics to enhance their flexibility and durability. These tiny particles and chemicals infiltrate ecosystems and pose a significant environmental threat. Microplastic pollution was initially seen as a problem only for the oceans. However, research into microplastics has grown quickly over the past decade, revealing that these particles are now found in every part of the environment. They are ingested by many species, including humans, and are causing harmful effects on health and ecosystems (1). This form of pollution is not a distant issue. The Mediterranean, despite representing only 1% of the world's marine waters, contains 7% of all microplastics, with concentrations four times higher than those found in the infamous 'plastic island' of the North Pacific (2). These microplastics are not just in the sea water; they are part of our local ecosystem, affecting the marine life, food chain, and environment we depend on (3).

Much has been said about the alarming claim that we consume the equivalent of a credit card's worth of plastic each week or several plastic bags annually. While detailed research on the exact amount of microplastic particles in the human body are still lacking, some estimation studies suggest that our ingestion could range from 0.1 to 5 grams per week (4). Over the past decade, research on the impact of plastics and plastic-associated chemicals on human health has significantly advanced our understanding and raised awareness of their inescapable presence and potential nocebo effects (5). However, the primary conclusion remains that further research is needed. Given the growing evidence of microplastics' potential health effects from the embryonic stage, understanding their role in neurodevelopmental disorders is a genuine concern. Research in this area is crucial to uncovering how microplastics may interfere with brain development, potentially contributing to cognitive and behavioral disorders. Highlighting the efforts of basic research in developing accurate models is

essential, as these models enable the rapid and effective testing of hypotheses, paving the way for a deeper understanding of the neurological risks associated with microplastic exposure.

Recent studies in mice suggest that acute (three weeks) exposure to water containing microplastics (0.0025- 0.125 mg/ml) resulted in accumulation of these particles not only in peripheral organs but also in the brain (6). Microplastics have also been found in the human brain in studies post-mortem (7,8), raising significant concerns about their potential role in the onset and progression of neurological disorders. Development is a critical period for the brain, as neural connections are highly malleable and responsive to environmental influences. Thus, exposure to plastics during neurodevelopment—pregnancy and infancy—may act as a putative origin for neurodevelopmental disorders (9). Indeed, recent studies have demonstrated that microplastics can cross the placenta, potentially exposing the developing fetus to environmental contaminants (10,11). This raises the question of whether the increasing consumption of microplastics, coupled with their ability to cross the placenta, could be linked to the rising prevalence of certain neurodevelopmental disorders.

Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are two of the most common neurodevelopmental conditions, with estimated prevalence rates of approximately 1–2% for ASD and 7–8% for ADHD (12). Evidence indicates that the occurrence of these conditions has been increasing over time (13). These are clinically and metabolically distinct conditions, characterized by differing behavioral phenotypes and underlying biochemical pathways, despite occasional symptom overlap. However, both ASD and ADHD are characterized by a male predominance (13) and it has been suggested that they might share a similar etiology (14), which is still unknown. While heightened awareness, improved diagnostic criteria, and greater access to healthcare services partially explain this rise in ASD and ADHD diagnoses, other contributing factors must be considered. These include genetic predispositions, epigenetic mechanisms, and the impact of environmental exposures during critical periods of early development. These factors highlight how complex it is to understand the impact of external influences, such as exposure to small particles, on long-term brain development.

Given these challenges, researchers are working to identify specific links between environmental contaminants and neurodevelopmental disorders. In this context, a team led by Professor Anne-Louise Ponsonby (The Florey, Australia; who was recently a visiting researcher for three months in Professor Marc Landry's laboratory at the IMN) analyzed two significant birth cohorts to investigate the link between prenatal exposure to plastic-related chemicals, such as bisphenol A (BPA, a chemical used to make water bottles and food containers, for example), and autism (15). Previous studies had suggested a connection between maternal exposure to BPA during pregnancy and an increased risk of autism in children. Their study went further since it specifically focused on boys with low levels of the enzyme aromatase, which converts testosterone into neuroestrogen in the brain. Postmortem analysis of male ASD adults had already shown markedly reduced aromatase activity compared to age-matched controls (16). Professor Ponsonby and her colleagues' findings revealed that boys with lower aromatase levels were 3.5 times more likely to exhibit autism symptoms by age 2, and 6 times more likely to have a confirmed autism diagnosis by age 11. Importantly, both cohorts showed that higher maternal BPA exposure was linked to the suppression of the aromatase enzyme via epigenetic mechanisms (gene regulation). In this study they also included very insightful results obtained from mice exposed to BPA. They observed that prenatal BPA exposure (50 µg/kg/day, subcutaneous injection, during a mid-gestation window of E10.5 to E14.5) suppressed aromatase in the male offspring, resulting in anatomical, neurological, and behavioral phenotypes resembling autism spectrum disorder. This study is groundbreaking as it not only corroborates the link between maternal exposure to BPA and autism but also identifies a biological pathway—aromatase suppression—through which this pollutant disrupts hormone-regulated male brain development during pregnancy.

Regarding ADHD, research on the link between this neurodevelopmental disorder and microplastics remains still limited, with most studies providing indirect evidence of an association. Nevertheless it is worth mentioning that epidemiological data have revealed a positive correlation between urinary BPA levels in children and ADHD (17), as well as a threefold higher likelihood of ADHD diagnoses in children born to mothers with higher phthalate exposure during pregnancy (18). One significant barrier to establishing direct evidence is the scarcity of animal models investigating the effects of microplastics on ADHD phenotype and comorbidities—a gap that Professor Marc Landry's laboratory (IMN) is actively working to address. Notably, the European Union has recently endorsed the study of microplastic pollution and its plasticizing additives, such as phthalates, on the nervous system and brain function. This initiative, named *PsyCoMed*, is an international initiative involving 10 Euro-Mediterranean countries, aiming to identify Mediterranean pollutants as risk factors for neuropsychiatric disorders and comorbidities. Bordeaux Neurocampus is also represented in the *PsyCoMed* project through the expertise of Professor Landry's team. The specific objective of the pre-clinical subproject in which I actively participate, led by Prof. Landry, is to investigate whether pollutant exposure during pregnancy can lead to ADHD phenotypes and comorbidities, such as pain, in the offspring of mice. Additionally, the project aims to identify the biological pathways involved in these outcomes.

It is clear that addressing the risks of microplastics requires both scientific advancements and policy changes. While raising awareness and informing the public about the dangers of microplastics is crucial, it is equally important to intensify research efforts to fully understand their impact on human health—particularly among vulnerable populations such as pregnant women and children—and to develop strategies to mitigate their effects. Consequently, governments must be called upon to prioritize funding for this critical research, proposing legislative actions aimed at addressing and reducing this escalating environmental threat. Together, such steps can pave the way toward protecting both public health and the planet's future.

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Investigating the developing brain: how research is progressing to the understanding of Autism

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This section has been created in collaboration with the Maison du Cerveau, an association that brings together all those involved with diseases from the nervous system. Our goal is to increase visibility and to provide information about these pathologies, treatments, and research advancements for the general public.

The human brain is an astonishing organ, controlling thought, memory, emotion, touch, motor skills, vision, breathing, temperature, hunger and every cognitive function and process that regulates our body. The brain contains billions of computational units, the neurons. They exchange each other's information through special communication nodes called synapses, forming an immense web of connections. These synaptic connections are similar to a vast and intricate city with roads, bridges, and highways that enable communication. During early childhood, an overproduction of these connections occurs, ensuring that all the connections needed for the brain's functions are formed. However, there is then the necessity of removing excessive connections that do not fall under the domain of the coherent brain network. Therefore, the "synaptic pruning" process occurs, where unnecessary connections are eliminated. Imagine a gardener cutting away excess branches to obtain a detailed tree structure, functional and coherent to optimize the vital process of the plant—synaptic pruning promotes the refinement and optimization of the brain networks, granting that only useful connections are preserved [1].

However, when synaptic connections are not correctly pruned or become disrupted, the communication of information becomes affected and non-functional. This is what happens in neurodevelopmental disorders like Autism Spectrum Disorder (ASD), where brain connections are impaired in providing a coherent and functional flow of information in the neural network [2]. Researchers worldwide are working hard to reveal the biological processes that impact the development of brain connections, aiming to improve prediction and prevention interventions in the treatment of neurodevelopmental disorders.

Understanding Autism Spectrum Disorder: A Growing Concern

Autism spectrum disorder (ASD) is a neurodevelopmental pathology leading to impairment in social interaction and repetitive movements. In Europe, ASD prevalence is increasing, with currently around

1 in 100 children receiving a diagnosis. This rising prevalence has significant societal and financial impacts, with the annual economic burden in the European Union estimated at €258 billion. European health programs, along with initiatives such as ERA-NET and EURAS, are placing great emphasis on the treatment of ASD.

The precise causes of ASD are still unclear, but both genetic and environmental factors, such as parental age at conception, maternal nutrition, infection during pregnancy, and prematurity, have been shown to contribute [3]. Notably, recent studies propose that ASD is not only a brain disorder but also involves impairments of immune system function and metabolic alterations [4, 5].

Inflammation and Its Impact on Neurodevelopment

Emerging research highlights a strong link between inflammation and ASD. Neuroinflammation, characterized by the overactivation of immune cells in the brain, has been observed in both animal models and human patients with autism [6]. Studies have shown increased levels of pro-inflammatory cytokines, such as Tumor Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6), in the cerebrospinal fluid and blood of individuals with ASD [7, 8].

Inflammation during critical stages of brain development can disrupt normal neurodevelopmental processes, including synaptic pruning. Picture a construction site where too many workers are demolishing useful structures instead of clearing only unnecessary debris—this chaotic environment can lead to inefficient or excessive pruning. For instance, maternal immune activation (MIA) during pregnancy has been associated with an increased risk of ASD in offspring. In animal models, maternal infections or inflammatory responses have been shown to alter neural circuitry and lead to ASD-like behaviors [9, 10].

Moreover, the gut-brain axis, a bidirectional communication system between the gastrointestinal tract and the brain, has been implicated in ASD. Many individuals with autism experience gastrointestinal issues, which may be linked to imbalances in gut microbiota and immune dysfunction [11, 12]. Imagine a phone line between two cities—if the connection is faulty, important messages may not be transmitted correctly. Similarly, disruptions in gut health can impact brain function, suggesting that targeting inflammation and gut health could be potential strategies for managing ASD symptoms.

The Interplay Between Neurodevelopment and the Immune System

New evidence suggests that immune system dysfunction may play a larger role in ASD than previously thought. The brain's immune cells, known as microglia, are responsible for maintaining neural homeostasis and clearing out unnecessary synapses. However, in individuals with ASD, microglia appear to be overactive, leading to excessive synaptic pruning or neuroinflammatory damage [13].

In addition, prenatal immune challenges, such as maternal viral infections, have been linked to an increased risk of ASD. Studies show that maternal infections can trigger immune responses that alter fetal brain development, potentially leading to long-term neurodevelopmental consequences [14]. This research suggests that prenatal health and maternal immune regulation play critical roles in shaping neurodevelopmental outcomes.

Towards Future Therapies

By investigating the interplay between synaptic pruning, inflammation, and ASD, researchers may develop new therapeutic strategies for treating neurodevelopmental diseases affecting synaptic connectivity. One promising approach is the application of immunomodulatory treatments to reduce neuroinflammation. Initial studies have shown that the administration of immunoglobulin therapy decreasing inflammation can ameliorate behavioral and cognitive symptoms in some ASD patients [15].

Another interesting approach involves genetic studies to identify the molecular pathways involved in ASD. By focusing on specific mutations correlating with ASD, researchers may develop personalized treatments, aiming to address the causes of ASD rather than just its symptoms [16].

Interestingly, new studies also bring hope with therapies involving modulation of the gut microbiome. Probiotics, dietary changes, and microbiota transplants have been suggested to ameliorate ASD symptoms by regulating the gut-brain axis [17].

While these therapeutic strategies are still in the development stage, they demonstrate the relevance of systemic factors in neurodevelopmental disorders.

The Importance of Continued Research

Understanding how the brain matures is not just about science; it has practical consequences for millions of people. ASD diagnoses present strong challenges for affected individuals, their families, and society as a whole. The estimated annual cost of autism's economic burden in the European Union is reaching €258 billion [20]. Understanding the key biological mechanisms linked to ASD pathophysiology is therefore a crucial challenge of our time to develop therapies that can improve lives

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Women's Voices: inspiring the neuroscientist community

Elba Molpeceres

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Women's Voices is an interview section created in partnership with the Neurocampus Parity and Inclusion Committee (NeuroPIC) a local group committed to promoting equality and organizing actions to close the gap between women and men in academia. The goal of this section is to increase the visibility of early career female researchers at the Bordeaux Neurocampus of the University of Bordeaux. We interview researchers about their scientific contributions, insights and opinions about equity, diversity, and gender bias in academia. Through these interviews, we aim not only to highlight their achievements but also to serve as inspiration for our scientific community and other female scientists.

Together, we will bridge the gap!

This month in Women's Voices, we interview **Elba Molpeceres**, a Spanish PhD student at the IMN. Elba began her academic path in Madrid, where she studied biochemistry, and later she spezialized in Neuroscience at the University of Bordeaux. After completing her Master's internship at the University of Oxford, she returned to Bordeaux for pursing her PhD, where she works on Parkinson's Disease. In this interview, she shares her academic journey and opinions about some challenges women face in science. Do you want to know more? The floor is yours, Elba.

Sara Carracedo: Could you start by sharing a bit about yourself and your academic journey?

Elba Molpeceres: My name is Elba, I am 25 years old and I am from Madrid. My journey in science started during my Bachelor's degree in biochemistry at the "Universidad Autónoma de Madrid". During this degree, I completed several summer research internships in different fields of science, in order to discover what I enjoyed more. I found myself increasingly drawn to Neuroscience, that is why I decided to do my Master in Neuroscience at the University of Bordeaux. I decided to complete my masters abroad to satisfy a need for overseas experience and because I believe it is really positive to immerse yourself in different scientific environments. Following this idea, I left Bordeaux to do my Master thesis internship at the University of Oxford, where I continued to explore different ways of approaching science, in an incredibly rich place in terms of culture and ways of thinking. At this point, my focus in Neuroscience was to contribute to the search for therapies for neurodegenerative diseases in order to make a meaningful impact on the lives of those affected by

these debilitating conditions. That is why I decided to return to Bordeaux and pursue my PhD at the IMN to focus on Parkinson's Disease.

Sara Carracedo: What area of research are you currently focused on, and what impact do you hope your work will have?

Elba Molpeceres: My PhD project is focused on the subthalamocortical pathway and its contribution to the pathophysiology of Parkinson's Disease. More specifically, the project is focused on studying the involvement of this pathway on parkinsonian motor and nociceptive symptoms. Motor symptoms have been more studied and addressed in terms of therapies; however, pain is a predominant symptom in this disease, being present in up to 85% of the patients, but this symptom still lacks efficient treatments. We are therefore investigating the potential beneficial effect for the treatment of these symptoms by modulating activity in the subthalamocortical pathway. With this project we hope to contribute to the understanding of the alterations of the circuitry that occur during Parkinson's Disease, and to potentially open the window to new therapeutic avenues.

Sara Carracedo: You've been awarded several prestigious grants along the way. Could you highlight some of them and what they've meant for your career?

Elba Molpeceres: The first recognition I received was a grant to cover the costs of my first year of bachelor studies, awarded for academic excellence during the two final years of high school. Later, my first pursuit of international experience during a summer internship in Stockholm was supported by an Erasmus+ mobility grant. I am also a FENS (Federation of European Neuroscience Societies) awardee, since they granted me with their FENS Exchange Grant (now FENS/IBRO-PERC Exchange Fellowships Programme) to enable me to conduct my research in Oxford. At the end of my master's program, I was honored as Major, top student of the Master in Neuroscience class 2022. More recently, I have been awarded a prize for the best oral presentation at the IMN Scientific Day 2024, where I presented my PhD results to the institute. These recognitions and grants have been a source of motivation and satisfaction for the acknowledgement of all the hard work.

Sara Carracedo: As a member of the NeuroPIC, which initiatives do you find most impactful or significant?

Elba Molpeceres: I consider all of the initiatives to be of essential importance to reach our objectives within the Neurocampus. However, I think a particularly successful idea was the Extended PhD seminar in the context of the International Day of Women and Girls in Science, together with the Marian Diamond Prize. The idea of this prize is to recognize the outstanding achievements in Neuroscience of early career female researchers, who often do not receive the recognition or professional opportunities that they deserve. The fact that this prize was announced during the PhD seminar centered around the International Day of Women and Girls in Science, helped to increase its visibility and significance, as reflected by the high numbers of attendees at the event. During the event there were also two very inspiring talks by Violetta Zujovic and Tara Spires-Jones who provided their vision on how to reach gender equity in science and about their journeys in Neuroscience as women. These events and talks are really necessary for raising awareness, and in the case of this specific occasion I hope for it to have had the desired effect on our colleagues and teammates.

Sara Carracedo: Shifting from the academic path towards a social perspective, does the lack of female principal investigators in your department influence your motivation or sense of belonging?

Elba Molpeceres: On one hand and inevitably, yes. The lack of female role models in science can significantly influence decisions of young girls to pursue scientific careers from the beginning, because it can make it difficult to visualize yourself in such roles. Similarly, the lack of representation of women can be demotivating during your scientific career. More specifically, the sometimes complete absence of female figures in positions of power and influence within institutes or departments can create the impression that these roles are still not achievable for women, perhaps favoring other professional decisions and perpetuating the gender gap in science.

However, I would not say it affects my sense of belonging to the scientific community. The barriers women face are not a reflection of our potential, and it is not our capacities or abilities as women that prevent us from being more represented or from reaching those leadership positions; but rather a systemic issue that requires change. Women have as much to offer in science as male scientists do, but they have to be given the opportunities to be there, to prove themselves and to advance in their careers. I think this is the most important message, that women do belong in science.

Sara Carracedo: Have you ever noticed women underrepresentation during conferences or scientific networking events?

Elba Molpeceres: As of today, I haven't noticed significant differences in how men and women researchers are treated in this type of event. I think lately there are increasing efforts being made by institutions and organizers to decrease the underrepresentation of women for example as keynote speakers or awardees in conferences. I believe the scenario is improving in this sense.

Sara Carracedo: Do you have any advice you would like to give to other early career women who wish to pursue a PhD?

Elba Molpeceres: My main advice would be to focus and work hard towards their objectives, always keeping in mind what I mentioned before: as women, we belong in science. Nothing is granted of course, and success requires dedication and perseverance, and you also need to be prepared to fight for your opportunities and learn to advocate for yourself. But you can also always look for additional help in mentorship and I consider it essential to have a supportive network. Additionally, learning to raise your voice against clearly discriminatory situations is vital. When you speak out you are not only defending your own position, but you also contribute to achieving this equality for future generations of women in science.

NeuroPath: exploring careers beyond academia

Olivier Roca, scientific communicator

Sara Carracedo[1]
[1]IMN, University of Bordeaux

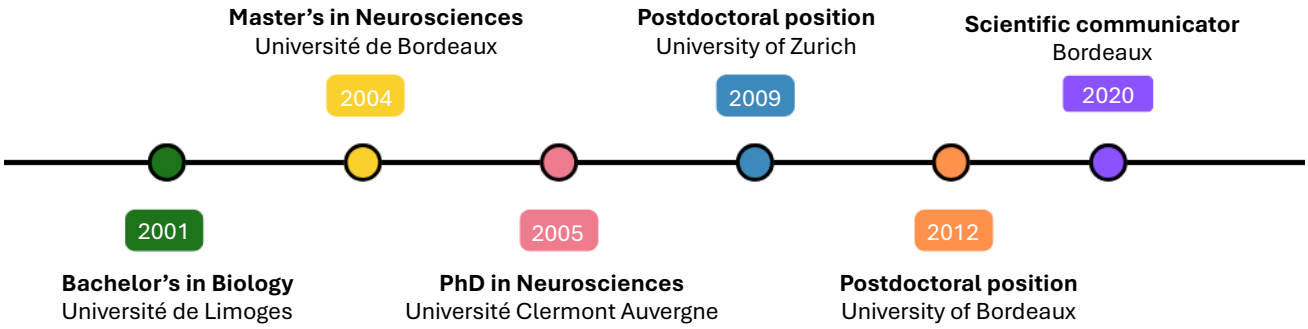
The world of science offers many exciting paths, and academia is just one of them. Each year, both the public and private sectors actively seek PhD graduates to fill diverse roles. However, many of them may seem unfamiliar to most of us. At Brainstorm, we want to help you explore career options that align with your interests, and aspirations.

That's why we created NeuroPath: a section dedicated to highlight scientific related careers outside academia. We reached out to professionals, who like us, have earned a PhD in neurosciences, most of them from the Neurocampus, but chose to apply their expertise in different fields. Through their stories, they share insights into their career journeys and practical information regarding their current positions.

Science is a lifelong pursuit, but the path you take is yours to choose.

Follow the one that excited you the most!

This month in Neuropath, we interview **Olivier Roca**, a ex postdoctoral student at the IINS. Nowadays, Olivier is a freelance working as a **scientific communicator**, spreading sciences through his youtube channel named **La science en schémas**. Through schemes and videos, Olivier focused on integrative physiology to disseminate different sciences related topics, including neurosciences, cancer and cardiology. He also works as film-maker, creating visual content for scientific institutions and pharmaceutical companies.



Are you interested in knowing more about the scientific communicator job as a career path? Then this section is for you!

Scientific communicator

Olivier Roca

"I create videos and films dedicated to science, for commercial, educational, or scientific popularization projects. "

Why did you choose this professional path?

I have always enjoyed going to congresses, communicating science as well to creating scientific illustrations. After the second postdoc I decided to start my career as scientific communicator as I didn't want to regret not have tried it in 10 years.

What's a matching profile?

You need to be patient, to like scientific communication and sharing knowledge, graphism, illustration and collaboration.

Do you have some advice for PhDs interested in this path?

If you like this path, do it! You will always be good at the things you like to do.

Main tasks

- Study of new scientific topics to develop the content of each video.
- Creation of scientific illustrations and videos for companies.
- Prospection of clients in pharmaceutical and biotech congresses.
- Promotion of the content through social media.

Requirements

Adobe Illustrator, Photoshop, After Effects, DaVinci Resolve

E-learning: technical formations in audiovisual and photography

Professional perspectives

I would like to grow professionally towards a film-maker, for documentaries.

Working conditions

Work environment: mainly home office-based job except for meetings, shootings and prospection of clients.

Pressure level: middle.

Work-life balance: I can adapt my working hours to my personal life.

Salary: variable but increasing through years. Close to a postdoc salary.

Do you have further questions?

Contact Olivier at contact@olivierroca.com

The beautiful melody of life

Interview with Richard Hahnloser

Juan Garcia-Ruiz[1]
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What's neuronhub? It is an outreach website hosting interviews with researchers from all corners of the planet about their work in the field of neuroscience. The idea is that you get something from people who have a long career in science, that you learn something new and cool, and above all that you don't lose track of the latest discoveries in neuroscience that are being made in other parts of the world.

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One of my most joyful moments is waking up early on summer mornings to the chirping and singing of my best neighbors: songbirds. As an amateur piano player, I often feel frustrated that I cannot carry my instrument with me wherever I go. This only deepens my fascination with these winged musical machines, which carry their instruments within their bodies and make up half of the total bird population. Of course, it is far less romantic to realize that their songs are not the analog of an artistic solo in the shower or a soprano recital at Carnegie Hall; instead, they are simply a way of marking territory or a scheme to flirt.

How wonderful would it be if men on the streets of Paris adopted the seduction strategies of songbirds, rather than their usual whistling or out-of-context dirty talk? But unfortunately, we are far from singing like them (sorry, Anna Netrebko). Unlike us, songbirds possess a specialized vocal organ called the syrinx, which can produce multiple tones simultaneously thanks to its two sound sources. Songbirds control this syrinx

through the coordination of respiratory muscles, syringeal muscles, and airflow. They also have a dedicated brain circuitry that involves motor areas, and something called the anterior forebrain pathway, which enables them to learn songs and adjust them.

But songbirds are not superior to us in every way. In fact, we share with them surprising similarities, particularly in language acquisition through imitation. In our first year of life, humans are natural producers of drool and snot, and we are crying and babbling professionals. Little by little, we start imitating the sounds in our surroundings like birds do, and after that we start uttering our first words. There is nothing banal about this imitation during language acquisition. In fact, even mammals very close in evolution to humans such as chimpanzees, gorillas, and orangutans, are unable to do this. In turn, other mammals like cetaceans (killer whales, bottlenose dolphins, sperm whales…) can reproduce sounds. But for some reason, researchers have decided to study this ability with songbirds instead of killer whales, as if birds were not dangerous predators.

Anyway, songbirds are an excellent animal model for studying and understanding how humans develop the ability to speak, and they are very cool. However, I can't tell you much more about it. I'll leave that to the real expert on the subject: Richard Hahnloser. He's a full professor at the ETH Zurich, at the Department of Electrical Engineering and Information Technology. He studied theoretical physics and did a PhD in Computational Neurosciences. Then he realized that experiments were still dominating the field of neurosciences, so he got started on that. He was interested in working with songbirds to study their song system to better understand the neural mechanisms underlying song production, the neural codes of a given song, or how a song is learned.

Juan Garcia-Ruiz: What can we learn from songbirds as humans?

Richard Hahnloser: They have fantastic vocal skills. Even though they have a larynx like we do, they don't sing with it but instead they use a specialized singing organ called the syrinx, and maybe that's why they are so fantastically good at imitating sounds. Maybe we cannot learn from them how they produce the sound because we don't have the same vocal organ they have. But what we can learn from them is what is the evolutionary algorithm that has allowed them to imitate each other, how does this vocal imitation work, and how do they learn by listening to adult singers. Some of these things can be hard to study in humans, because we cannot really experiment with infants. Ethically it is not justifiable to use babies. Some of the answers about what is going on in the first years of life of an infant can be found in birds.

JGR: Is learning a song for a songbird always a matter of imitation? Could a bird start singing if it is completely isolated from other members of the colony?

RH: They just want to sing something, and they just need a kind of model. They want to be taught. Without the template, they will still sing something, but it will sound strange, not stereotyped, and not clean.

JGR: Could you briefly describe the song system of songbirds in a way a child would understand?

RH: The sound system is a set of brain regions with the sole purpose of producing a song. If a bird has an accident and these song areas are damaged, then the bird would be able to do everything a normal bird can do except produce the songs it has learned as a young bird. It's a very specific system dedicated to singing and nothing else.

JGR: Humans possess both language and the ability to sing, while birds' productions are limited to singing but, this is commonly associated with bird language. My question is: are bird songs analogous to human language or is it something very different in nature?

RH: People typically compare more birdsong with speech, but there's way less combinatorial complexity in their songs than there is in language. The syllables they sing do not have so much meaning, so I wouldn't say it's comparable to human language. They mostly sing to attract females or to defend territory. But you can find some analogies between human language and birdsongs. In fact, what these birds produce until they are adult is the same as a baby does until it's one year old. First a baby will cry, then it starts bubbling, and later it starts to combine different syllables until they produce the first words after they are one year old. This process of crying and bubbling until the first words arrive is very similar to the birds' process of learning.

JGR: What is the natural language processing and how is it related to your research?

RH: Natural language processing is about how a computer process text. We study how birds learn songs, right? The idea is that we teach them two songs. We first give them one song until they can sing it and then we give them the second song that we reproduce through a loudspeaker. Then the question was: when a bird can already sing one song, how will it change this song to go towards the second song? And we figured out this mathematical way that they use to achieve that, and we put it in a simple algorithm. After that we found out that computational linguists, people who work with text, use the same formula that birds use. Birds came up with this millions of years ago while computational linguists did it only a few years ago, and that's why I got interested in the analogy between biology and text processing.

JGR: What are the main discoveries made in your team?

RH: People in neuroscience use rewards or punishment. A bird learns a song without being externally rewarded for that, it's like a little baby. We were the first group to study the way birds reward themselves, or what we call intrinsic reward. We have found that in the end what the bird wants is to sing a song, which is a sequence, but what rewards them is the vocabulary. For instance, take the sentence "hi, how are you?". What I want to say is the sequence: "hi, how are you?" but the bird will care about the sounds, about the "hi", the "are", the "you", and the "how". It does not matter how the words come, what matters for them is getting the vocabulary right and then the order of it is a separate problem.

JGR: What are the frontiers of this field?

RH: There are three types of vocal song learning. I only talked to you about one of them, the template-based learning. The second one is the reinforcement learning, when you get instantaneous punishment or reward during the production of sounds. And the third one is the feedback-driven learning, that explains how birds learn their songs by comparing their vocalizations to an auditory feedback that you can manipulate, for instance by switching the pitch up to see how they adjust their productions. I would love to come up with a theory that can explain all three at the same time.

JGR: Do you have a message to share with the readers?

RH: Sometimes the biggest discoveries come from what we would call a stupid question, so do not be afraid of asking them.

🌍🔬 Women and Girls in Science Day 🔬🌍

The 11th February we celebrated the achievements of women in science and recognized the challenges they still face—underrepresentation in leadership, pay gaps, and shorter careers. Structural changes are needed, but we also have a role as individuals.

Unconscious bias still shapes how we acknowledge women's contributions, judge their leadership, and set higher bars for them to stand out. We are the generation of tomorrow—future researchers, editors, and policymakers. Let's commit to building a more inclusive scientific community, one that truly values talent over gender.

#WomenInScience #GirlsInSTEM #WomenInSTEM #ScienceForAll #BreakTheBias

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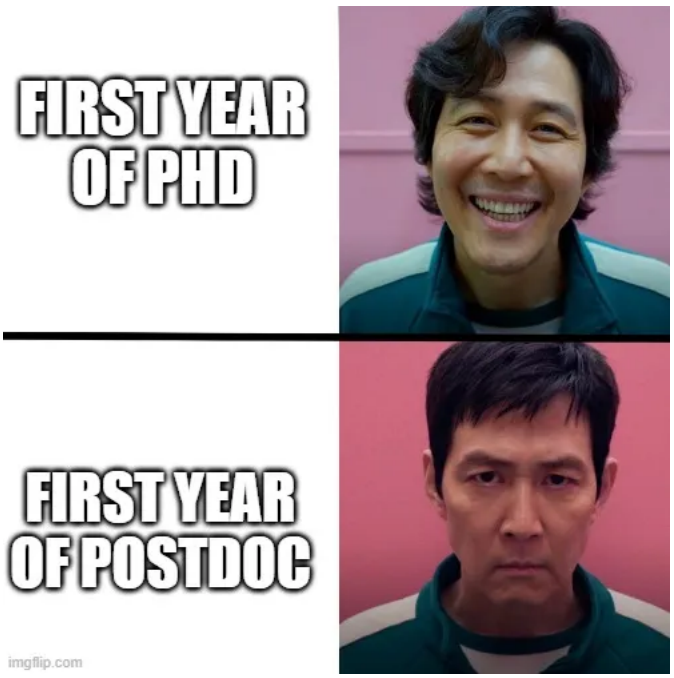

Juan Garcia-Ruiz, 3rd year PhD student at Magendie

Formations

Introduction to Experimental Neurosciences

The Workshop "Introduction to Experimental Neuroscience" will run its 5 th edition this Summer (July 21st – August 2nd). David Perrais, organizer of this workshop, tell us more about its objectives and organization.

The workshop "Introduction to Experimental Neuroscience" was born a bit more than five years ago. Its first edition was scheduled in July 2020 but could not take place because of the lock-down. Its official start was thus in July 2021. The purpose of this workshop is to use the Bordeaux School of Neuroscience, famous for organizing the Cajal Courses, to offer a hands-on workshop to students who are interested by experimental neuroscience. We thrive to welcome students from various backgrounds: neuroscience, but also physics (e.g. optics), engineering, data computing, immunology, cancer research, economy, etc. We try to cover many aspects of neuroscience, from molecular to behaviour, neuro-computation and human data. Typically, the workshop brings together 20 students with 16 to 20 instructors, about half from Bordeaux and half from elsewhere in France, Europe and the world. Groups of 2-3 students work on a one week-long mini-project supervised by an instructor. In the mornings, there are short lectures by scientists from Bordeaux Neurocampus, and in some evenings a round-table discussion on various topics like open science, gender bias in neuroscience, outreach, which lead to animated discussions. Each week ends with

a dinner in downtown Bordeaux. What makes the workshop special is that instructors are young researchers, PhD students or post-doctoral fellows, who teach students their favourite technique and tell them about their research project. It is a very good learning experience for both students and instructors. The call for instructors in now open until March 7th.

The website for registration with an introductory video is available here:

https://bss-neurosciences.u-bordeaux.fr/en/

The call for students will be from March 10th to April 24th.

Finally, I want to thank the Bordeaux Neuroscience Graduate Program for generous funding, Bordeaux Summer Schools for help with the communication and registration, and all the instructors for their involvement and enthusiasm.

PhD seminars 24-25: part 2

Registration deadline: 23/02/25

Remember to register on ADUM for the PhD seminars from March to June 2025. Keep an eye on upcoming PhD seminars with the Neurocampus Newsletter.

Mental health and well-being webinar - Academic burnout

Date: 27/03/25 - 12h00 to 13h30

In the high-pressure environment of academia, burnout has become an increasingly common challenge. This webinar delves into academic burnout, distinguishing it from mere stress or temporary exhaustion. We will explore the underlying causes and key triggers, such as excessive workload, lack of control, and insufficient support. Participants will gain insights into recognizing the signs of burnout and learn effective strategies to manage and recover from it. We will offer proactive measures to prevent burnout, emphasizing the importance of self-care, balanced workloads, and establishing robust support systems.

Editorial board

Simon Lecomte

Simon is originally from Lyon, France. He did his Bachelor's of Psychology from Strasbourg, after which he did the NeroBIM master's degree from the University of Bordeaux. He is a PhD student in the IINS where he is studying how the Fragile X Syndrome impacts the presynaptic mechanisms at the DG-CA3 synapses.

Aude Verboven

Aude, directly coming from Bordeaux, is a PhD student at the IMN. She previously graduated from the MultiPublic track of Bordeaux Neurosciences Master. She is currently studying the dopaminergic afferences to pain modulating nuclei in the context of Parkinson's disease.

Sara Carracedo

Born in Spain, Sara is a PhD student at the IMN. She holds a Veterinary Medicine Bachelor's degree from the University of Santiago de Compostela and the NeuroBIM Master's degree from the University of Bordeaux. Her PhD is focused on understanding the microglial and neuronal role of P2X4 receptor in ALS.

Toshiko Sekijima

Toshiko, originally from New Zealand, is currently PhD student at the Nutrition et Neurobiologie Intégrative (Nutrineuro). She holds a bachelor's in Biology from the University of Hawaii and a master's in agro-biomedical Science from the University of Tsukuba, Japan. She is also passionate by scientific illustration!

Juan Garcia-Ruiz

With two Bachelor's degree, in Psychology and Biochemistry, and the NeuroBIM Master's degree from the University of Bordeaux, Juan is pursuing a PhD focused on the role of lactate in basal synaptic transmission. Although he speaks near-perfect French, Juan comes from Huelva, Spain. He is also the co-founder of neuronhub (www.neuronhub.org).

Daniele Stajano

Daniele Stajano was born in Naples (Italy). He has a Bachelor's degree in Biology and a Master's degree in Neurobiology. After his Ph.D. in neurosciences at the ZMNH of Hamburg (Germany), he joined the IINS as post-doc at the "Dynamic organization and function of synapses" group. He is currently interested in molecular mechanisms orchestrating brain maturation in neurodevelopmental disorders such as the autistic spectrum disorder.

Ludovica Congiu

Hailing from Sardinia (Italy), Ludovica obtained a master's degree in Neuropsychobiology at the University of Cagliari and pursued a Ph.D. in neuroscience at the Universitätsklinikum Hamburg-Eppendorf (UKE) in Hamburg. Currently, she is a PostDoc at the IMN, where she is investigating the role of P2X4 receptors in ALS and anxiety disorders.

BRAINSTORM

A Journal for the students, by the students

Are you a MSc, PhD or a PostDoc student in neuroscience?

Then you are more than welcome to participate in our journal.

JOIN  US!

You can write either a short-review on a topic of your choice, a one-page letter (a reflection, a project or an insight you would like to share) or a neurojoke.

Don't start to worry, you won't be alone! You will work hand-by-hand with our editors, and we will send you guidelines and a template to make your life easier. Perhaps you would like to know that the best review will get a special prize by June 2025.

If writing is not your thing and you prefer to express yourself through art, we have a place for you too! For each issue we recruit an artist to design the cover page illustration. Remember that microscopic images are also a form of art!

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