ERA-NET NEURON

NEWSLETTER 46

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From the desk of the coordinator | October 2024

Dear Readers,

Welcome to the 46th edition of the NEURON newsletter, where we delve into the latest advancements and challenges in the fascinating field of Pain, as highlighted by leading experts at our recent foresight symposium. This May, we had the pleasure of hosting our annual foresight symposium in Berlin, Germany, focusing on the theme of 'Pain.' Organized by NEURON partners Etienne Hirsch (INSERM) and Bernard Poulain (CNRS), the event featured presentations from distinguished scientists and a discussion panel led by NEURON's coordinator, Ulrike Bußhoff. The panel brought together researchers and patient organization representatives to explore the critical issues in pain research. For more details on the Foresight Symposium, see page 3.

Funded by the European Commission

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In this issue, we are thrilled to present in-depth interviews with two remarkable neuroscientists. We begin with Prof. Asya Rolls, a leading figure in neuroscience, who reflects on her journey from receiving the EPNA2009 award to delivering the NEURON plenary lecture at FENS2024. She discusses the key experiences that have shaped her approach to neuroscience and shares her insights on the future intersection of neuroscience with immunology. Following this, we feature an interview with Dr. Ana Dorrego-Rivas, the EPNA2023 awardee, who is at an early stage of her research career. The ERA-Net NEURON Excellent Paper in Neuroscience Award (EPNA) is designed to support and recognize the achievements of early-career researchers (ECRs), highlighting promising new talents in the field. Through her interview, Dr. Dorrego-Rivas shares her research focus, career milestones, and aspirations, offering advice to young neuroscientists. These interviews provide a unique look into the paths and perspectives of an expert scientific leader and a promising newcomer in the field. Find the full interviews on pages 8 and 11.

We are also excited to announce the launch of the new call for the ERA-Net NEURON Excellent Paper in Neuroscience Award (EPNA) 2024. This prestigious award, aimed at supporting and recognizing early-career researchers, will focus on two fields this year: biomedical research related to cerebrovascular diseases and ethical, legal, and social aspects (ELSA) of neuroscience. We encourage eligible ECRs to apply and showcase their contributions to these critical areas of neuroscience.

With this, we invite you to explore our accomplishments and keep up with our activities on our website, by following us on X and by joining our LinkedIn community.

Sincerely yours

Foresight Symposium on Pain

May 15th, 2024

The Foresight Symposium on 'Pain', organized by NEURON partners Etienne Hirsch (INSERM) and Bernard Poulain (CNRS) in May 2024 in Berlin, brought together seven experts and a patient representative from Pain Alliance Europe, Viorica Cursaru, for a full day of educational lectures and discussions. The symposium facilitated enriching exchanges between the speakers, members of the Scientific Advisory Board (SAB), NEURON partners, and the patient representative, underscoring the importance of collaborative dialogue.

Pain poses a significant global health challenge, with an estimated 20% of the population suffering from chronic pain. Despite its prevalence, chronic pain remains underdiagnosed and undertreated, largely due to the complexity of the mechanisms that cause and maintain it. Chronic pain impacts not only the quality of life of those affected but also contributes to significant healthcare costs and reduced productivity. Understanding the biological, psychological, and social factors that contribute to chronic pain, as highlighted by the experts at the symposium, is vital to developing effective treatments. This need is particularly urgent given the way pain can manifest in diverse forms—such as nociceptive, neuropathic, and neuroplastic pain—each requiring nuanced approaches to diagnosis and management.

The symposium addressed a wide range of critical topics, from the clinical description and classification of pain to neuroinflammation, biomarkers, and both pharmacological and non-pharmacological interventions. Key areas such as sex differences in chronic pain and the link between pain and mental health were also discussed, emphasizing the multifaceted nature of pain and the need for interdisciplinary approaches to research. Following the symposium, NEURON funding organizations recognized the necessity of advancing research on pain mechanisms to develop more effective diagnosis and treatments.

This symposium served as an important consultation step, providing scientific insights that will shape the upcoming JTC2025 call for proposals. The aim of this call will be to foster multinational, interdisciplinary research projects that address critical translational and clinical questions in pain neuroscience.

Following this introduction, you will find brief abstracts of the lectures presented by the symposium's speakers, offering a taste of the critical topics discussed.

Rolf-Detlef Treede

What is pain?

Prof. Dr. Rolf-Detlef Treede

University of Heidelberg, Germany

Pain is both a protective mechanism and persistent health issue. Nociception, the process by which pain signals are generated and interpreted, serves as an alert to potential harm. While acute pain signals immediate threats, chronic pain is more complex, often persisting without clear tissue or nervous system damage. The distinction between different types of chronic pain, such as nociceptive and neuropathic underscores the need for varied treatment approaches.

Franziska Denk

Neuroinflammation in pain

Prof. Franziska Denk

Kings College London, UK

Chronic pain involves abnormalities in the nervous system and inflammation-related changes. While anti-rheumatoid drugs reduce inflammation and joint deformity, pain relief remains inadequate, as shown in studies like Gullick et al. (2005). Research indicates that non-neuronal cells, such as synovial fibroblasts, play a significant role in pain (Chakrabati et al., 2020). Neuropathic pain studies, like those by Denk's team (Liang et al., 2020), reveal increased immune cells in injured nerves. Translational research faces challenges due to limited human tissue access and differences between animal and human models. Efforts like Sandy-Hindmarch et al. (2024) and the ERA-NET Neuron Networking consortium aim to standardize protocols and improve data sharing, emphasizing the need for interdisciplinary approaches and robust models to understand the inflammation-pain link.

Andre Truini

Clinical assessment of pain

Prof. Andre Truini

Sapienza University of Rome, Italy

Neuropathic pain results from a lesion or disease of the somatosensory system. The International Association for the Study of Pain categorizes pain into nociceptive, neuropathic, and nociplastic types. Diagnosing neuropathic pain requires a comprehensive approach, combining clinical suspicion and diagnostic tests like neurophysiological testing and skin biopsy. Emerging tools, including genetic testing, may enhance the accuracy of neuropathic pain assessment, reflecting its complex interaction between environmental factors and genetic predispositions.

Karen D. Davis

Biomarkers of pain

Prof. Karen D. Davis

University of Toronto, Canada

Chronic pain is recognized as a complex condition often linked to faults in brain processing. Effective management of chronic pain requires a personalized approach that integrates both psychological and pharmacological strategies, though these are not universally effective. Recent research emphasizes the importance of understanding patient heterogeneity, with a focus on individualized pain management through biomarkers and brain imaging techniques. Future advancements aim to refine treatment strategies, minimizing side effects while improving patient outcomes and quality of life. Ensuring data privacy and addressing societal implications remain essential in this evolving field.

Nadine Attal

Pharmacological and non-pharmacological intervention for chronic pain

Prof. Nadine Attal

University Versailles Saint-Quentin, France

Chronic pain, seen as a disease involving multiple brain areas and neural networks, includes nociceptive, neuropathic, and nociplastic pain. Differentiation often requires specific questionnaires due to overlapping conditions. Effective treatment is complex due to links with psychological factors like anxiety and depression. Initial management typically includes neuroscience education, psychotherapy, physical activity, and neuromodulation, combined with pharmacological treatments. Personalized pain management now integrates prediction algorithms and genotyping, emphasizing a multimodal approach that combines pharmacological and non-pharmacological therapies.

Chris Eccleston

Pain & Mental Health

Prof. Chris Eccleston

University of Bath, UK

Pain is often defined by its structural features like intensity and location, but it may be better understood by its functional roles, such as promoting healing and preventing harm. As suggested by Wall in 1979, pain acts as an awareness of a need-state, akin to hunger or thirst, rather than just a sensation. This functional view shifts the focus from modifying pain signals to addressing the adaptive or maladaptive behaviors that pain triggers. Chronic pain, affecting 20% of Europeans, significantly disrupts daily life, with 20% of these cases being high-impact, leading to severe disability and increased healthcare demands. Understanding pain's broader implications is essential for improving treatment and care.

Michelle Roche

Sex Differences in Pain

Dr. Michelle Roche

University of Galway, Ireland

Females, comprising 70% of chronic pain patients, are more sensitive to both experimental and clinical pain and have higher rates of conditions like fibromyalgia and migraines, whereas males more commonly suffer from conditions like spondylitis and chronic lower back pain. Biological factors, including sex hormones and neuroanatomical differences, play significant roles in these differences. Additionally, pain and mood disorders interact differently in males and females, with females experiencing higher rates of depression and pain catastrophizing. Despite progress, pain research often underrepresents females and overlooks sex-based outcomes, emphasizing the need for more comprehensive studies that account for both sex and gender variables. Understanding these differences is crucial for developing effective, personalized pain management strategies.

Interview with Prof. Asya Rolls
ERA-Net NEURON plenary lecture speaker at the FENS2024 & EPNA2009 awardee

Asya Rolls is an Israeli psychoneuroimmunologist and was an International Howard Hughes Medical Institute Investigator. She now leads a research lab at the Tel Aviv University, exploring how mental and emotional processes impact immune function and health. Rolls has made ground-breaking contributions to neuroimmunology, including establishing the link between the brain's reward system and immune function and pioneering the use of advanced technologies to study immune responses, shedding light on phenomena like the placebo effect and tumour immunity.

On June 28th, 2024, Prof. Rolls delivered the ERA-Net NEURON plenary lecture at the FENS2024 Forum titled "Bridging Mind and Body through Neuroimmunology". Introduced by ERA-Net NEURON's coordinator Dr. Ulrike Busshoff, the lecture highlighted Rolls' work on how thoughts and emotions can impact physiological states. ERA-Net NEURON supports these plenary lectures at the FENS Forum as part of its mission to promote cutting-edge neuroscience research, fostering dialogue between pre-clinical and clinical researchers. Rolls, who was among the first winners of the ERA-Net NEURON EPNA in 2009, captivated over 700 attendees by discussing the therapeutic potential and challenges of brain-immune interactions.
Below is an interview we conducted with Asya Rolls following her plenary lecture.

Can you briefly describe the main focus of your research and what motivated you to pursue this area?

I define my research as a physiological approach to the mind-body question. We are trying to understand how thoughts and emotions can influence the body's ability to either combat diseases or potentially generate them. I was motivated to follow this line of research because of my personal experiences. I've always felt a connection to this concept, as my own mental state often seemed to manifest in the way I experienced illnesses. It struck me as strange that this mind-body connection, which many of us intuitively recognize in our personal lives, is largely absent in the way we approach medicine.
This gap likely stems from our lack of understanding of the mechanisms behind

psychosomatic phenomena, which leaves us without the tools to address them. Our approach has been to dissect these networks by exploring how different regions in the brain, particularly those related to emotional circuits, can influence physiology—specifically the immune system. For instance, we study how activating areas in the brain, such as the reward system which is involved in positive expectations and motivation (as seen in the placebo effect), impacts the immune system. We've found in mice that activating this area (e.g. with chemogenetics) can enhance the immune system's ability to combat bacteria, reduce tumour size, and even aid in tissue recovery following heart attacks. Our aim is to map out the pathways through which the brain communicates with the immune system, identifying the various partners involved in this process.

On the other hand, we also explore how the brain encodes the state of the immune system. For example, we discovered that the brain holds a specific representation of the immune system's condition. By reactivating a neuronal ensemble that was previously active during inflammation, we can actually recreate an inflammatory response without any actual inflammatory agent being present—demonstrating that the brain can, in a sense, can induce illness. This opens up an exciting research space to further understand these "mind-body" connections and hopefully, integrate this dimension in medicine.

If you think about your journey from winning the ERA-Net NEURON Excellent Paper in Neuroscience Award in 2009 (EPNA2009) to delivering the ERA-Net NEURON plenary lecture at FENS2024, what key experiences and challenges have shaped your path, and how have they influenced your approach to neuroscience research today?

Primarily, I've been fortunate to have remarkable mentors. My doctoral research, for which I received the ERA-Net NEURON Excellent Paper in Neuroscience Award in 2009, was conducted under the guidance of Prof. Michal Schwartz, a neuroimmunologist, and Prof. Ofer Lider (who sadly passed away during my PhD), an immunologist. They taught me to always seek the evolutionary basis for the questions I am tackling.

The transition after my PhD to a postdoctoral position at Stanford with Prof. Luis de Lecea, in collaboration with Craig Heller, provided me with a deeper understanding of the brain—its networks and their significance. This experience also connected me to the fields of psychiatry and sleep research, highlighting the physiological role of sleep, which was critical in shaping my thinking and bridging these different domains.

Additionally, the development of methods for neuronal manipulation, such as optogenetics and chemogenetics, and the appreciation I gained at Stanford for the immense potential of these technological tools have been pivotal in advancing my approach to this research direction that essentially connects the dots of this journey.

Your plenary lecture at FENS2024 was highly anticipated. What key messages did you hope to convey to the audience?

The key message I wanted to convey is that the mind-body connection is a question we can scientifically explore. The brain's interaction with physiological processes is evident in epidemiology, such as the link between stress and mortality, or in the pharmaceutical industry with the placebo effect, which is currently seen as a challenge to pharmacology. However, it actually holds immense potential for healing if we can learn how to harness it. By understanding the underlying mechanisms, we can transform this concept from being on the fringes of alternative medicine into something we can integrate into medical practice, allowing for a deeper understanding of our physiology and how we can influence it effectively.

How do you see the intersection of neuroscience and other disciplines (e.g. immunology) evolving in the next few years?

I have no doubt that this is one of the most intriguing avenues for neuroscience. We are witnessing increasing evidence for the connection between the nervous system and other physiological systems, expanding the scope of questions we dare to ask.

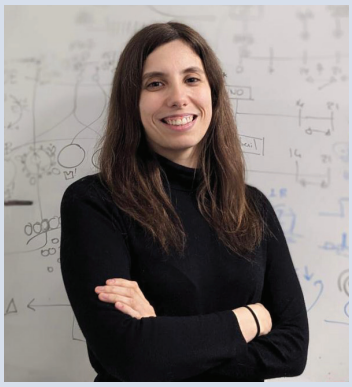
The nervous system innervates all body systems, and once we began exploring the interactions between them, it opened an infinite space of questions. We see this across multiple contexts: immunology, metabolism, vasculature, the microbiome, adipose tissue—essentially every aspect of the body. We are also re-evaluating a vast amount of epidemiological data that links drugs affecting the nervous system with a much wider range of phenomena that we previously didn't understand. For example, we are discovering that people who take beta-blockers for heart conditions are less likely to develop certain cancers. At the same time, new tools are emerging that enable us to examine physiology at the whole-body level, along with computational tools that allow us to explore more complex systems of variables. I believe this trend will only accelerate in the coming years, as evidenced by the growing number of new research and educational programs in this area, research centres dedicated to these questions, large-scale grants, and, most importantly, numerous discoveries that challenge what we thought we knew.

What advice would you give to young neuroscientists who aspire to make significant contributions to the field?

Expect the unexpected!

2023 EPNA AWARDEE
Dr. Ana Dorrego-Rivas
Personal Interview

The Excellent Paper in Neuroscience Award (EPNA) initiative was first introduced by NEURON in 2009, in order to support and encourage young neuroscientists at the early stage of their career. The winners of the award receive a cash prize, as well as an invitation to present their work as special Young Investigators speakers in an international conference. This year the presentation and award took place in the FENS Forum 2024 in June 2024 in Vienna.



The 2023 EPNA awardee is Ana Dorrego-Rivas (@adorrego_r). The award was given to Dr. Dorrego-Rivas for her publication: 'The core PCP protein Prickle2 regulates axon number and AIS maturation by binding to AnkG and modulating microtubule bundling', Science Advances, 2022, Vol 8, issue 36, resulting from her PhD research in the University of Bordeaux, INSERM Neurocentre Magendie, France.

Continue reading to learn more about Ana and her scientific journey.

Please tell us briefly about your research interests.

I am deeply fascinated by the mechanisms through which neurons acquire their structural and functional polarity, as well as the dynamic interactions between axons and dendrites during development. My curiosity extends to 'unconventional' neurons, such as those lacking axons entirely, and I am particularly intrigued by their physiology and overall function in the brain compared to more 'classic' neurons with axons and dendrites. In essence, I am passionate about exploring the intricate structure-function relationships in neurons.

Please tell us about your scientific journey to-date. Are there any key moments or milestones that have defined your scientific journey so far?

I explored various fields before finding my path in neuroscience. My research journey began with an undergraduate internship under Dr. Esther Barreiro at the Hospital del Mar Medical Research Institute in Barcelona, Spain, where I investigated the differential expression of type 1 and type 2 macrophages in lung tumors from patients with chronic respiratory disease. Following this, I completed my master's research project with Dr. Susana de la Luna

at the Centre for Genomic Regulation in Barcelona, where I identified new protein partners of DYRK1A, a kinase overexpressed in Down syndrome due to its gene being located on chromosome 21.

I then moved to Bordeaux, France, to pursue my PhD in the lab of Drs. Mireille Montcouquiol and Nathalie Sans at Neurocentre Magendie. My research there focused on characterizing a novel role for planar cell polarity (PCP) proteins in neuronal polarity establishment and axonal development and function.

Currently, I am a postdoctoral researcher in Professor Matthew Grubb's lab at the Centre for Developmental Neurobiology, King's College London, where I investigate neurotransmitter release strategies in dopaminergic neurons within the olfactory bulb. One of the highlights of my career has been publishing the main findings of my PhD, which has not only opened doors to a vibrant research community but also led to invitations for talks and the honor of receiving the EPNA Award in 2023.

What made you choose a career in your field?

I found my way into neuroscience somewhat by chance and only truly immersed myself in the field during my PhD. What ignited my passion was the fascinating ways by which our brains function, along with all the knowledge that still remains unexplored. The opportunity to work with individual neurons, observe their distinct parts, and witness them firing action potentials in real-time is truly fascinating.

Where do you see your field of research in a few years? What are going to be the major breakthroughs?

As we advance our understanding of the brain's functioning in the most physiological way possible, I believe that research on neuronal development at the cellular level will increasingly shift from in vitro and ex vivo approaches—which are still extremely valuable—to in vivo models. One of the most significant breakthroughs would be the ability to study the function of individual neurons in real time, across various contexts, from the molecule to circuit and behaviour.

What were the main challenges you had overcome in your career path and how did you overcome them?

During my PhD, I faced significant challenges due to illness and other external circumstances, including the covid lockdown. What kept me going through these difficult times was the support of my mentor Mireille and the lab, my passion for the science, and a strong focus on my career objectives: completing my thesis and publishing papers.

What are your goals for the future and where would you like to see yourself 5 years from now?

My ultimate goal is to become a principal investigator and establish my own research lab, where I aim to unravel how axons and dendrites influence each other's development, both under normal physiological conditions and in pathological states. I do certainly hope to achieve this dream of mine in 5 years from now.

What advice would you give your younger self or young scientists beginning their research career?

To all young neuroscientists, I would say that success comes through hard work and perseverance, but it's equally important to maintain a healthy work-life balance. Taking time off is crucial for your well-being, creativity, and clear thinking—some of my best ideas come when I step away from the lab! My second piece of advice is to keep an open mind. Research demands flexibility and adaptability, as experiments often don't go as planned. The ability to pause, reflect, reassess priorities, and choose alternative approaches to address your research questions is essential.

How did it feel to present your research at FENS2024 as part of the EPNA Award, and what was the experience like speaking at such a conference?

Giving a talk at such a major conference was an incredible opportunity, and it was gratifying to see people attend the session and show interest in my research. This was my first presentation at FENS, and it undoubtedly marks a significant achievement in my career as a young researcher.