Foresight Symposium 2024

“Pain”

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“Outreach and interaction activities”

led by Inserm and CNRS

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Welcome

Dr. Ulrike Busshoff, DLR-PT - NEURON coordinator (Germany)

Ulrike Busshoff, as coordinator of ERA-NET NEURON, introduced this Foresight symposium on "Pain" by welcoming all attendants: scientific speakers, researchers, representative of patient organization, members of the NEURON Scientific Advisory Board, representatives of NEURON partner organizations. She highlighted for funding organizations the two main aims of this meeting: (i) to provide an expert overview on "Pain", and (ii) to shape the transnational call for next year. Neuron is a network of funding organizations in the area of translational neuroscience research. Over the years, several projects were funded by the European Commission, but all the research that is being done in the context of the Era-Net arefunded by the national funding organizations. Neuron has representatives from more than 35 institutions, funding organizations and others, from 30 countries, from Europe, Asia, North America and Australia.

What are Neuron projects?

- To support scientists for example, via the excellent paper awards in neurosciences and privileged access to courses, training workshops, poster sessions and much more
- Interactions with society and social engagement on every level of this network, but also educational media, posts, social media, outreach activities, lay lectures.

Neuron is lobbying at the European level for more money into this area but also to set up a European partnership on Brain Health starting in 2026. Neuron collaborates with other organizations in the EBRA project with the European brain council, JPND, the Human Brain Project and EBRAINS, and try to find a common view.

Introduction

Dr. Etienne Hirsch, INSERM (France) & Bernard Poulain, CNRS (France)

The aim here is really to help the funding organizations to shape the call on pain for 2025, and one the most important discussion when organizing this symposium was whether should we talk about pain in general or just neuropathic pain.

Pain is a very subjective sensation, but some somatosensory, cognitive and psychological aspects must be taken into count which will be explained by many of the experts. As the leading cause of medical consultation, pain manifests itself in different forms: nociceptic, neuropathic, neuroplastic… but the problem is that pain is both everywhere and anywhere which is one of the major difficulties in its treatment and management.

What is pain? Clinical description, classification, neurophysiological basis and pathophysiology

Rolf-Detlef Treede (Heidelberg university, Germany)

1) Nociception and Pain

According to Sir Charles Scott Sherrington, nociceptors are sense organs that respond to noxious stimuli (that either threaten or actually produce damage) and transmit pain signals to the central nervous system. Found in various tissues like skin, muscles, and inner organs, these receptors respond to thermal, mechanical, and chemical stimuli. When activated, nociceptors generate signals that travel to the spinal cord and brain, where they are interpreted as pain, an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. This process, known as nociception, alerts the body to potential harm, prompting protective responses. The nociceptive system adapts its sensitivity rapidly to any challenge, mostly in the direction of sensitization both of peripheral nocicetpors and central nociceptive neurons in spinal cord or brain. Altered nociceptive signal processing contributes to many chronic pain conditions.

2) Acute pain as an alarm system

In acute pain, short-lasting nociceptive signals are sent after an actual or potential tissue damage. It alerts patient, family and health care professionals to medical problems and should be alleviated once existence of medical problem is recognized.

3) The difference between chronic neuropathic and chronic nociceptive pain

Chronic nociceptive pain is described as a symptom of continuous or recurrent tissue damage. It activates the peripheral nociceptive nerve terminals and nociceptive signals are processed in spinal cord and in the brain. Pain is perceived in damaged body parts or as referred pain in HEAD zones.

Chronic neuropathic pain is described as a symptom of damage to the somatosensory nervous system. It activates the nociceptive system along the way and ectopically generated nociceptive signals are processed in spinal cord and in the brain. Pain is perceived in innervation area of damaged nervous system parts (projected pain).

4) Chronic primary pain

Chronic primary pain is recognized as a disease characterized by persistent pain, lasting for more than three months and that is not explained by tissue damage nor by somatosensory system damage. It is mostly unknown where nociceptive signals are generated; these signals are also processed in the brain. Pain is often perceived as regional or widespread.
Unlike pain resulting from an injury or illness, chronic primary pain is considered a disorder in itself and requires specific diagnostic evaluation, therapy and rehabilitation.

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For example, fibromyalgia is a widespread pain and hyperalgesia characterized by a deficient descending inhibition with comorbid anxiety and depression.

5) Classification of chronic pain

The classification of chronic pain includes different types based on origin and characteristics. By definition, chronic pain is characterized by persistent pain (more than 3 months).

Chronic primary pain is a persistent pain, a health condition in its own right without an identifiable cause, such as tissue damage or somatosensory system damage. Its management generally requires a multimodal approach.

Chronic secondary pain is identified as a symptom of another disease and is caused by tissue damage or injury to the somatosensory system. In ICD-11, six subgroups are codable: Chronic cancer-related pain, Chronic postsurgical or posttraumatic pain, Chronic secondary musculoskeletal pain, Chronic secondary visceral pain, Chronic neuropathic pain, Chronic secondary headache or orofacial pain. These subgroups have distinct mechanisms and treatments. Treatment of the underlying disease is necessary, but often insufficient.

Conclusion:

In the research on pain, major progress has been made in understanding signal pathways and mechanisms of different subtypes of acute or chronic pain. Several major controversies and gaps still exist as: how to distinguish pathological from physiological nociceptive system plasticity? or What are the reasons for individual differences in the sensitivity of the nociceptive system?

Neuroinflammation in pain

Franziska Denk (King's College, UK)

Introduction

- In chronic pain states, there are abnormalities on all levels of the nervous system: sensory nerves innervating peripheral tissues are abnormal; there are abnormalities in complex spinal cord circuitry; and finally, there are abnormalities in the brain.

- In addition, there are inflammation-related abnormalities, with changes in spinal cord microglia and the peripheral inflammatory environment.

What's holding researchers back?

1) **Neuron-centric narratives:**

a) Example of rheumatoid arthritis

In rheumatoid arthritis, the invention of disease-modifying anti-rheumatoid drugs and biologics like anti-TNF has revolutionized the life of patients. They no longer have swollen and deformed joints as a result of chronic inflammation. However, the same improvements have not been seen when it comes to their pain. As an example, there is the work by Gullick et al in 2005, who enrolled a longitudinal cohort of rheumatoid arthritis patients upon first diagnosis and followed them up for 10 years. Anti-rheumatic drugs were shown to reduce inflammation and the number of swollen joints, but a measure of quality of life (including pain) didn't change over that same period.

A lot of cells are involved in inflammation. Our sensory neurons sit in a very complex resident immune environment with different resident macrophage populations, mast cells, different stromal cell populations and endothelial cells that can all communicate with each other and with neurons. So pain might be generated not only by the nervous system, but by dysfunction in all these cells.

One particular cell type which is likely very important in pain is the synovial fibroblast. In 2020, Dr. Chakrabati *(Chakrabarti et al. 2020, Pain)* showed that if synovial fibroblasts were treated with TNF and their conditioned medium was transfer to sensory neurons, then the neurons would show more activity.

Another study (Bai et al. 2024, Sci Trans Medicine) has shown that the expression of pain-associated-genes are correlated with joint pain in rheumatoid arthritis. The more these genes are expressed, the more intense is the pain. Moreover, pain-associated-genes are over-represented in joint fibroblast.

Besides fibroblasts, there are many other resident non-neuronal cell types that are dysregulated in RA joints; many of these have yet to be investigated in relation to their potential to drive persistent pain.

b) Example of neuropathic pain – neuron-centric view

In neuropathic pain, the nervous system is directly affected by injury or disease. So, what about the inflammation and immune response in neuropathic pain?

Pr. Denk team did an experiment with a mouse model of neuropathic pain (Liang et al. Pain 2020). They extracted immune cells from nerve and sensory ganglia of mice at two different times after the injury (one week after and two and a half months after) and did flow cytometry and sequencing to measure the types of cells in the tissue.

They found that the mouse without injury had few immune cells, but that immune cell numbers were significantly increased both at 1 week and 2 ½ months post injury. This was quantified in batch-controlled fashion to show that the number of live CD45+ immune cells in nerve was identical at both time points.

2) Translational gaps

a) Example of neuropathic pain

There are very few instances in persistent pain states were researchers have access to large quantities of relevant peripheral tissues. Arthritis is an exception, with joints from osteo- and rheumatoid arthritis patients now available in large numbers. This means that the local inflammatory response can be analysed and then effectively back-translated. In neuropathic pain this is different. There are almost no studies involving human nerves, so our animal models are made 'blindly' – we don't know whether the inflammatory responses we observe in rodents actually mirror those found in humans.

Even when they are studies in humans, they aren't always well-aligned with animal work. For example, Pr. Denk's team conducted a systematic review (Choi et al. Pain 2023) where they looked at studies that measured spontaneous sensory neuron activity. A lot of great work has been done on rodents and other animals to study this activity in vivo. Similarly, spontaneous activity has been assessed in humans with the help of microneurography. However, the animal and human work was done on very divergent models – with animal work on traumatic models, while human work is almost exclusively on non-traumatic pain states, like small fibre neuropathies. All these data are therefore not directly comparable.

b) One positive example of translational work in the field.

Translational work is slowly starting in the study of neuropathic pain. The work of Sandy-Hindmarch (*Sandy-Hindmarch, Chang et al., medRxiv 2024*) used peripheral nerves from individuals living with Morton's neuroma, a peripheral entrapment neuropathy.

Immunofluorescent analyses showed a higher presence of CD163+ and MARCO+ macrophage subsets in Morton's neuroma than in control nerves. The number of these cells in nerve was

correlated with the amount of paroxysmal pain reported by patients. Given that the average disease duration at the time of study enrollment was 2 ½ years, this demonstrates that neuro-inflammation can also be very long-lasting in people. This study is therefore a first example of trying to generate data that will allow us to back-translate results.

An ERA-NET Neuron Networking consortium has gotten together to help foster more studies of this kind. It has European and American partners from the field of neuropathic pain. They discussed how to harmonize protocols and data sharing in this area, to facilitate future joint research and the generation of larger scale cohorts of human tissues.

Summary:
Pain – even when neuropathic – is likely to be intimately & causally linked to inflammation. We need to mechanistically dissect local peripheral inflammatory environments by using
• interdisciplinary theoretical frameworks
• human local peripheral tissues from well-phenotyped chronic pain cohorts
• robust translational models, e.g. stem cells or animals

Clinical assessment of pain

Andrea Truini (La Sapienza, university of Rome, Italy)

1) **The different types of pain according to the International Association for the Study of Pain corresponds to**

- Nociceptive pain: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
- Neuropathic pain: Pain caused by a lesion or disease of the somatosensory nervous system
- Nociplastic pain: Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.
  Patient can have a combination of nociceptive and nociplastic pain.

Basically, every clinician identifies the damage of the somatosensory nervous system in patients who complain or suffer from neuropathic pain using a wide complex approach that includes a history examination and the use of different diagnostic tests.

2) **How to definitely diagnose neuropathic pain**

The approach to the diagnosis of neuropathic pain is complex and well represented by the diagnostic grading system issued by experts of the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP).

a) Possible neuropathic pain

Basically, clinicians can establish a possible neuropathic pain when there is a clinical suspicion of a relevant lesion or disease of the somatosensory nervous system and when pain distribution is anatomically consistent with the suspected location of the lesion or disease in the peripheral or central somatosensory nervous system.

At this stage, additional aspects such as the description of pain are also considered. Neuropathic pain presents with a variety of symptoms and signs; the specific combination of these symptoms and signs can assist in diagnosing neuropathic pain.

a.1) Screening questionnaires

Given that certain sensory disturbances may indicate neuropathic pain, screening questionnaires evaluate characteristic symptoms such as burning, tingling, sensitivity to touch, pain from light pressure, electric shock-like pain, pain from cold or heat, and numbness. These questionnaires are designed to distinguish between neuropathic and non-neuropathic pain.

Some questionnaires also contain an optional physician-completed element, usually in the form of a simple sensory examination. Screening questionnaires include the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), the Douleur Neuropathique en 4 Questions (DN4), their self-administered versions and the PainDETECT.
These questionnaires are useful to screen patients for further level diagnostic tests. They do not provide a definite diagnosis, rather they represent a support for a diagnosis of possible neuropathic pain.

b) Probable neuropathic pain

The next step is to reach a diagnosis of probable neuropathic pain.
Based on the grading system, it is evident that medical history and clinical examination are indispensable in the process leading to a definite diagnosis of neuropathic pain. Specifically, a thorough examination of somatosensory systems aims at highlighting signs and symptoms of neuropathic pain, particularly sensory deficits. Demonstrating sensory deficit in one or more modalities and mapping the affected area are essential for determining if a nervous system lesion is causing pain and sensory disturbances. Positive sensory signs (e.g. mechanical dynamic allodynia) generally correspond to the areas of sensory loss.

c) Definite neuropathic pain

To certify neuropathic pain, an objective diagnostic test is required to confirm lesion or disease of the somatosensory nervous system.

c.1) Conventional neurophysiological testing

It gives the possibility to test the function of the peripheral or central nervous system and identify the evidence of the damage of the somatosensory nervous system. This test also provides information on the severity of the lesion, and in some cases, the prognosis. Nevertheless, only non-nociceptive fibers are assessed which is fine because 90% of patients have concomitant damage of nociceptive and non-nociceptive fibers. But in some specific conditions, characterized by a selective damage of the nociceptive system (e.g. small fibre neuropathy, syringomyelia), more specific tests are needed to selectively assess the damage to the nociceptive system. Alternative neurophysiological techniques are available for studying the nociceptive system. Among these, evoked potentials elicited by nociceptive stimuli are commonly used (e.g. laser evoked potentials).

c.2) Skin biopsy

Skin biopsy is the reference diagnostic method for patient suffering from neuropathic pain associated with small-fiber neuropathy. Using immunofluorescence and bright-field immunohistochemistry, this technique allows to measure the density of intraepidermal nerve fibers. Skin biopsy, however, identifies small fibre loss only, and does not provide any information on small fibre function. Also, several non-neuropathic pain conditions are linked to small-fibre loss. For instance, the reduction in small nerve fibres seen in skin biopsies of patients with amyotrophic lateral sclerosis and Parkinson’s disease is not enough to classify their pain as neuropathic. These problems may hamper the accuracy of this technique.

3) Where is the future of neuropathic pain assessment?

Clinical experience suggests that while damage to the somatosensory nervous system is necessary for the development of neuropathic pain, not all patients with such damage will experience it. For instance, people with diabetes may develop peripheral neuropathy, but this condition can be either painful or painless. Increasing evidence now suggests that the risk of developing neuropathic pain is strongly linked to specific genetic profiles associated with sensory neurons. Consequently, in the near future, genetic testing may become increasingly important for determining individual risks for developing neuropathic pain and potentially guiding treatment.

Conclusion:

Neuropathic pain results from a lesion or disease of the somatosensory system. Diagnosing it involves identifying damage to this system in patients suffering from pain. A careful examination is needed to assess sensory deficits and pain ensuring they align with the anatomy of the peripheral or central nervous system. Diagnostic tests offer objective evidence of somatosensory system damage, but their results must be interpreted within the clinical context. Genetic testing is also emerging as a new tool in assessing neuropathic pain.

Biomarkers of pain

Karen Davis (University of Toronto, Editor-in-Chief of Pain, Canada)

Introduction

Chronic pain is due to a kind of fault in the brain. The need for the future is, first of all to understand it, second of all, to figure out how to repair, and even if it's impossible to repair it is important to figure out how to treat it and improve the quality of life.

1) **Treating chronic pain:**

a) How to approach pain management

Both psychological and pharmacological methods can be effective in certain situations. While these can be beneficial for some individuals, it doesn't work well for everybody. Additionally, even for those who do respond, sometimes, the duration of treatment is limited due to side effects, particularly with pharmacological options.

b) The patient homogeneity myth

This is not a new concept. The issue has been present for decades. Recently, there has been a more serious effort to address the problem known as "patient heterogeneity," which acknowledges that not everyone is the same. The challenge is determining how to categorize people into subgroups for pain management, considering factors like sex differences, culture, and combinations of these elements. This is why it is important to collect the data to try to extract issues about individuality and come up with models. So, the aim is not to put everybody into one box but to see how they fit into these models, and hopefully to be able to get an idea of the different approaches possible and their ability to help the individuals.

2) **Personalized pain management**

Personalizing pain management involves developing biomarkers to gather valuable information. Researchers focus on identifying peripheral and brain abnormalities in terms of structure, function, circuitry, and cellular activity. It is essential to connect these abnormalities to specific behaviors related to pain or disability. Then they can figure out who might have a certain resilience versus a certain vulnerability or who will be able to respond better to treatment to a certain point. The purpose is not looking at predictors of developing pain but work on predictors of treatment outcome. But what is the capacity for things to change, maladaptively or adaptively? For instance, with the treatment there is a capacity to change and to figure out the personalized approach. What has become significant over the last 10-15 years, especially with advancements in brain imaging, is the societal impact, particularly with AI development. Ensuring access and protecting information is crucial. This issue, which some of researchers have championed since the 90s, has gained attention recently with the rise of AI, prompting a more careful consideration.

3) Assessment of pain

When assessing pain, it's crucial to evaluate its impact beyond just intensity scores. Focusing solely on intensity overlooks other important mechanisms and misses what truly matters to the patient. Additionally, pain is inherently a subjective experience. Claims that brain imaging can definitively determine if someone is in pain cannot replace the need for self-reporting.

4) Brain-behavior relationships

In the brain imaging field, it's crucial to consider the nuances of how pain accounts affect data interpretation. When examining brain-behavior relationships, a recurring question is: what type of pain data should we collect and use? It's important to understand the patient's current pain, the average pain over the past month, and other temporal details about the pain. Additionally, we need to assess how much the pain interferes with daily activities. In most countries, the outcome measure of clinical trials is essentially pain intensity, the intensity of change, which is not sufficient and needs to change as it does not assess aspects of the pain experience. Generally, this is the framework needed to understand the mechanisms behind brain-behavior relationships. Researchers must collect comprehensive data, not just on what individuals report at the moment, but also over time, along with inherent attributes or traits.

5) Recording individualities

Therefore, it's crucial to develop quick and straightforward bedside tests that can identify what's not functioning well. These tests should amplify key areas since there are therapeutics, like opioids for CPM or NMDA receptor-dependent mechanisms, that can target these issues. Behavioral measures that tap into these areas on a general level are essential.

a) Sex differences

Women are more sensitive to pain and chronic pain conditions which are more prevalent in women than men. But there are also chronic pain conditions which are more prevalent in men and women. Brain imaging has shown that the connectivity of the ACC receptor in women, particularly within the modulation pathway.

b) When pain interferes with other activities

This issue, you have a task at hand and you've got pain. Where are you putting your focus? Where are you putting your emphasis? How people cope better in a chronic pain situation than others?

In an experiment, researchers had participants perform a task and then exposed them to a painful stimulus. They identified P-type individuals, who focused on the pain and struggled

with the task, and A-type individuals (more than half), who perform better on the task in the presence of a painful stimulus than when there is no concurrent pain. Brain scans of these people revealed that A-type and P-type brains responded differently, even at rest, with distinct networks active in each group. In another series of experiments, participants received painful zaps. Some had high intrinsic attention to pain (high IAP) and others had low IAP, allowing them to tune out the pain. Imaging showed that these two patterns really became part of the story to explain the salience network. Researchers observed that individuals had different relationships between these systems. They called it a "dynamic pain connectome" because the interaction between the default mode network and the pain modulation pathway was variable, dynamic, and flexible in the mind wanders.

c) Chronic pain abnormalities in the dynamic pain connectome

It turns out if you look at people with all sorts of different types of chronic pain, you will see abnormalities in this system. Sometimes there are sex differences. For example, in people who have chronic pain, that anti correlation between the two systems disappears, they both kind of coupled together. So, it will be complicated if you look at sex differences because they are also influenced by factors like age and treatment effects.

6) What Are Alpha Oscillations?

Alpha oscillations are 8-12Hz fluctuations of neural activity. Why are they interesting? Well, these alpha oscillations, outside the world of pain, are something everyone looks at because they relate to general aspects of attention, top-down cognitive processes, working memory, acute pain sensitivity and chronic pain. In the pain research field, it was observed 20 years ago that individuals with chronic pain showed a slowing of the alpha peak. Researchers have been investigating whether alpha peak frequency could be a marker for neuropathic or chronic pain in general. The findings indicate abnormalities in the alpha band, particularly more pronounced in individuals with neuropathic pain compared to those with non-neuropathic pain. There are companies (especially in China) which can measure alpha waves to determine attention levels and see if people are developing feedback systems. However, the commercialization and ethical implications of these products require careful consideration.

7) Individuals therapeutic targets

What to do with all this information in terms of predicting treatment success? The aim is to move toward personalized medicine and try to fit the right therapy to a person. The idea being to measure these things, and if you want to change the brain, for instance, target something that's broken, if it's not broken, don't target it. So this bring us closer to pain management for better pain relief, fewer side effects and treatments, reduce societal costs and to improve the quality of life.

Conclusion:
Researchers need to understand patient's concerns and issues relating of their data, privacy and stigma.

Pharmacological and non-pharmacological intervention in pain

Nadine Attal (Ambroise Paré hospital, Paris, France)

1) What is chronic pain?

While acute pain is a symptom, chronic pain can be considered as a disease, and even as a brain disease, as it involves the activation of multiple cerebral areas and neural networks. Chronic pain includes nociceptive pain (e.g. unspecific low back pain and rheumatoid arthritis), neuropathic pain (due to e.g. trigeminal neuralgia, traumatic nerve lesion, diabetes, herpes zoster, multiple sclerosis, stroke, spinal cord lesion) and nociplastic pain, characterized by pain without clear evidence of tissue damage or lesion of the nervous system (e.g. fibromyalgia). Specific questionnaires such as those developed to detect neuropathic pain (screening questionnaires) may contribute to differentiate these pains from each other, although these conditions often overlap.

2) Therapeutic interventions

Chronic pain is difficult to treat due to its bi-directional links with psychological factors such as anxiety, depression, sleep disorders, and cognitive symptoms. Neuroscience education, psychotherapy, physical activity and various techniques of neuromodulation are therefore often mandatory and generally represent a first step in therapeutic management. These approaches are generally combined with pharmacological therapy to effectively address individual needs.

A- Pharmacological treatments

a) Conventional analgesics

Most people are familiar with conventional analgesics (eg salicylates, NSAIDS, paracetamol…), commonly used for pain relief. They are mainly recommended for acute and chronic nociceptive pain, although not all patients with chronic nociceptive pain (e.g. ostearthritis) respond to NSAIDs. These analgesics are generally considered ineffective for nociplastic and neuropathic pain, but there are very few studies confirming their inefficacy.

b) Opioids

Opioids are effective for acute cancer pain and some nociceptive pains, and they are also recommended as last choice for neuropathic pain, but are generally ineffective and should not be proposed for nociplastic pain. The distinction between weak opioids such as tramadol or codeine and strong opioids such as morphine or oxycodone is now debatable because they may have the same risk of dependency.

c) Psychotropic drugs

Psychotropic medications are primary used in psychiatric conditions, but also recommended for chronic pain. The latter include some antidepressants (duloxetine, tricyclic antidepressants) and antiepileptics such as pregabalin and gabapentin. They are effective in various types of chronic pain, including nociplastic , neuropathic, and to some extent chronic nociceptive pains. Conversely, cannabinoids are less effective than anticipated based on recent large scale randomized controlled trials.

d) Topical analgesics

Topical analgesics such as topical NSAIDs are commonly used for arthritis or tendinitis while EMLA is used for procedural pain. Other topical analgesics are effective for peripheral neuropathic pain, such as capsaicin. For decades, it has been used in low-concentration creams without full elucidation of its mechanisms of action. In 1997, David Julius's group cloned the TRPV1 receptor for capsaicin, a discovery that allowed them to receive the Nobel Prize in 2021. Modern capsaicin is now available in the form of high concentration patches used every three months, maintaining the same concept of nerve targeting. Ongoing studies suggest that capsaicin high concentration may also have a disease-modifying effect. Botulinum toxin A, known for its effectiveness in treating conditions such as dystonia and spasticity, is also generally assimilated to a topical agent and has been found effective after subcutaneous injections for peripheral neuropathic pain.

<u>B- Noninvasive neurostimulation techniques</u>

These techniques are generally safe with few side effects and are relatively easy to use. The most commonly used is TENS (Transcutaneous Electrical Nerve Stimulation). Newer noninvasive techniques involve brain neurostimulation such as repetitive transcranial magnetic stimulation (rTMS), which uses electromagnetic induction to activate neuronal circuits and induce synaptic changes. Initially used by psychiatrists for major depression, it has more recently shown promise for various chronic pain conditions. Another related technique is transcranial direct current stimulation (tDCS). While potentially less effective than rTMS, tDCS also targets central modulation pathways and is being explored for its broad applicability across chronic pain types. Overall, these neurostimulation techniques are expanding due to their ability to modulate central mechanisms.

3) Towards personalized pain management

Over the past decade, there has been a shift from empirical to “personalized” management of pain, although this corresponds more to a stratified therapeutic approach. Researchers are now developing prediction algorithms, leveraging artificial intelligence, and integrating genotyping into clinical trials.

In conclusion, because of its complexity, the modern management of chronic pain should as best multimodal and encompass pharmacological and nonpharmacological therapy.

Sex differences in (chronic) pain

Michelle Roche (University of Galway, Ireland)

Intro: difference between sex and gender

In order to understand the impact of sex on pain, it is important to first distinguish between sex and gender. Sex refers to biological factors and differences (genes, chromosomes, brain structures), and is assigned at birth as male, female, or intersex. Gender, a social construct, includes self-identity and beliefs, is non-binary, and may not align with biological sex. Misuse of these terms has caused confusion in research, highlighting the need to identify and analyze sex and gender in studies.

Recent until now primarily has focused more on sex differences in pain rather than effects of gender differences. Therefore, for today's discussion will discuss sex differences between males and females in pain prevalence, perception, experience and treatment.

1) **Who is the more sensitive to pain?**

A common question in pain research is: who is more sensitive to pain, males or females? While individual experiences vary, data shows that females make up about 70% of chronic pain patients and 50% of chronic pain conditions are more prevalent in females. Conditions like fibromyalgia, migraines, irritable bowel syndrome, and neuropathic pain are more common in females, whereas conditions like spondylitis and chronic lower back pain are more prevalent in males. Regarding sensitivity to pain, females in general are more sensitive to both experimental and clinical pain. There are also notable sex differences in responses to pharmacological and psychological therapies for pain and placebo effects, though these differences can vary based on the pain condition, age, and other factors.

2) **Pain and mood disorders**

There is a well recognized bidirectional interaction between pain and mood disorders. Between 50 to 80% of chronic pain patients experience a mood condition, depending on the type of pain. Notable sex differences exist: males primarily report more anxiety-like symptoms, while females report more depressive-like symptoms. Females also exhibit higher pain catastrophizing and greater negative appraisal of pain. Behaviorally, women are more likely to seek health information and attend clinics, while men use distraction and avoidance techniques. Women tend to use more social support. These differences arise from various factors.

3) **Biopsychosocial factors involved in sex differences in pain**

The factors driving sex differences in pain can be categorized into biological, psychological, and social factors. These factors are not exclusive and interact significantly. For example, a biological factor can lead to different responses in different social contexts. This overlap underscores the need for more research, as a biological pathway might show no effect in one context but profound effects in another. More work is needed to explore these interactions comprehensively. While there is not time today to explore all of the various factors involved Dr. Roche highlight a few that have received interest recently.

a) Sex bias in pain research

As mentioned, females represent about 70% of chronic pain patients. Despite increasing inclusion of both males and females in clinical research over the past 20 years, a recent analysis of the published research revealed that less than 20% of studies analyze sex differences in their research outcomes. This gap makes it very difficult to understand the existence of sex-based effects, and prevents detailed interrogation of the data.

In the preclinical field, studies on sex differences are limited but increasing. A 2020 metanalysis by Prof Jeff Mogil found female rodents were generally more sensitive to pain than males, mirroring clinical findings. However, most preclinical research uses male subjects and while the inclusion of both sexes is increasing over 50% of preclinical research is still conducted in male rodents only. Furthermore, over 50% of human studies and over 90% of rodent studies do not justify single-sex use, indicating a need for better justification and inclusion practices in research.

Sex bias in pain research has significant implications for the development of pharmaceuticals and pain management strategies, which may be based on factors specific to one sex. For example, CGRP plays a key role in migraines, and research shows that adding CGRP to the brain's meninges induces migraine-like symptoms in female animals only. Consequently, CGRP agonists and antibodies have been developed and marketed effectively, However, there is no analysis to say whether they worked as well in males compared to females. Despite this, these treatments are prescribed to both sexes. This issue highlights the need to include both sexes in pain research.

4) Biological factors that may account for sex differences in pain

a. Sex hormones and pain

It is well recognized that sex hormones significantly impact pain and as such this is often cited as reasons for excluding females from preclinical research. For example, estrogen has a bidirectional effect: it is analgesic at high levels and enhances pain at low levels. Progesterone generally increases pain perception, while testosterone is typically analgesic in both males and females. Since these hormones fluctuate in both males and females, their pain-amplifying and pain-suppressive effects are believed to balance each other out most of the time.

A common misconception is that females, due to hormonal cycles, are more variable in pain perception. However, research findings are mixed and several metanalysis suggest hormone cycles may have minimal effects. As such, this variability should not be an excuse to exclude females from research. In clinical research, menstrual cycle stages should be considered into analyses.

b. Changes in neuroanatomical regions between the sexes

While hormones play a role, they're other players as well. Significant research has revealed sex-specific differences in key brain regions that regulate pain perception and affective responding. One particular region that has received considerable attention is the anterior cingulate cortex (ACC). The ACC is a key hub for processing the sensory, emotional and cognitive aspects of pain and several clinical studies have demonstrated sex-specific changes

in this region in chronic pain patients. In rodent experiments, the circuitry between the ACC and other brain areas influences pain-related aversion and allodynia. However, most preclinical studies are conducted in males, resulting in a reliance on male circuitry analysis. So the question is this circuitry the same in male and female rodents. As such we asked the question as to what the effect of switching on or off glutamatergic neurons within the ACC, would have on pain behavior in male and female rodents?

With the use of an optogenetic approach, Michelle Roche and David Finn teams at Galway (*Jarrin, Roche, Finn et al. (2020) Front Behav Neurosci*) showed that in the absence of ACC activation the behavioral pain response was similar between males and females. However, if glutamatergic neurons were switched on in the ACC this increased pain responding in females but reduced it in males. Furthermore, the activating these neurons inhibited pain-related aversion in females but had no effect in males. These data demonstrate that while pain responding may appear similar between males and females, different neuronal circuits may underlie profound sex differences in pain processing.

c. Sex differences in pain a tale of two immune cells

The immune system is crucial both peripherally, in the spinal cord and in the brain for establishing chronic pain behavior. Research over the past 10 years have demonstrated key sex-specific effects of that immune cells and circuits in the spinal cord in the initiation and maintance of neuropathic pain. For example, in males, microglia in the spinal cord play key roles in chronic neuropathic pain behavior, while in females, this mechanism is driven by T cells and is regulated by testosterone. However, not all immune cells or mechanisms in the spinal cord exhibit a sex specific effects on chronic pain e.g. astrocytes.

d. Neuroinflammation linking Mood and Pain

Michelle Roche's team suggests that the neuro-immune system is crucial in linking pain and mood disorders, particularly in depression. She suggests that mood disorders such as depression can result in the priming of microglia, astrocytes, and other immune cells, leading to exaggerated responses to subsequent injuries. Accordingly, her research and other have demonstrated key roles for microglia and neuroimmune signaling pathways in stress-depression-chronic pain interactions. Interesting she presented data demonstrating sex specific effects on early life stress on nociceptive pathway development and is a risk factor for chronic pain. Maternal deprivation, an early life stressor, affects pain response differently in males and females with only females subjected to maternal deprivation show enhanced neuropathic pain responses. These behavioural changes were associated with sex-specific increases in neuroimmune mediators in key brain regions such as the hippocampus, suggesting that this signaling pathway might make females more susceptible to chronic pain exacerbation.

In addition to immune factors and hormones, neurotransmitters also play a key role in pain perception. One particular system the Roche group are interested in is the role of the endocannabinoid system.

e. Sex differences in the endocannabinoid system

The consensus on the efficacy of cannabinoids for pain relief is still debated. Several recent special interest groups have been convened to examine this and while there is good preclinical support for the efficacy of cannabinoids in various pain model it is widely acknowledged that more research clinical research is required. However, it is also notable that there is a lack of sex comparison data. The endocannabinoid system, is widespread throughout the body, particularly along pain pathways. There is significant evidence of sexual dimorphism in the endocannabinoid system. Research from the Roche and Finn groups in Galway and others have suggested that alterations in the endocannabinoid system may underlie sex-specific pain effects and that the endocannabinoid system may represent a sex-specific biomarker for chronic pain. Further research is ongoing.

Conclusions:

- It is clear that there are quantitative and mechanistic sex differences in nociceptive and affective pain responding. However, many questions remain unanswered because as this is still a very early field with much research still being conducted in one sex or not disaggregarded by sex.
- Also, much research is still required to uncover the mechanisms that underlie these sex differences, examine changes across the lifespan and how these different factors interact.
- Research into the effects of gender on pain is in its infancy and required further in-depth examination.

- Overall, studying sex and gender as variables in pain research matters. We have some indications that sex and gender play key roles in pain, but much more research is needed in this area in particular regarding sex and gender across different ages.

Pain and mental health

Chris Eccleston (University of Bath, UK)

1) Introduction

Pain is typically characterised by its structural characteristics: intensity, duration, quality, location, severity, but pain is often better characterised by its functional characteristics: it what context it emerges, what it achieves, what happens next.

This functional view of pain is not new, but is an idea that keeps being forgotten. For example, in the first editorial of the first edition of the journal PAIN, its first editor – Patrick Wall - said: "*Pain is better classified as an awareness of a need-state than as a sensation. It serves more to promote healing than to avoid injury. It has more in common with the phenomena of hunger and thirst than it has with seeing or hearing*." (Wall, 1979).

The overall function of pain is to protect one from harm, whether immediate, perceived or predicted. Largely pain achieves that defensive function by capturing the organism and motivating it toward a singular goal of protection in withdrawal from a noxious input, avoidance of stimuli associated with pain, or escape from threat. Further, pain has a repair function by promoting withdrawal for healing after trauma. And finally, pain has a social function to warm others of danger.

All of our embodied physical senses have these singular functions of protection: apnea promotes breathing, itch promotes scratch, fatigue promotes switching out of unrewarding behaviour, appetite promotes consumption, etc. (Eccleston 2016). Pain is similarly uni-functional: pain urges the avoidance of harm.

2) Pain as embodied defence.

Adopting this view shifts our scientific perspective from attempting to alter the characteristics of the signal (intensity, duration, location) to focussing on the adaptive or maladaptive behaviour the organism adopts in response to threat.

When the threat is chronic, it **interrupts** frequently, **interferes** with everyday life, and alters one's **identity**. The lifeworld of the chronic pain patient is one of constant repetitive inescapable threat to self. (Eccleston, 2018). This focus on the experience of pain brings the promise of treatment strategies.

First, it is important to identify which behaviour is most important. Chronic pain is a common problem. Consider that a conservative estimate of the prevalence of pain is 20%. 20% of the 750 Million people in Europe have chronic pain, which means that 150 million in Europe (or the population of France and Germany combined) are living with chronic pain. (Eccleston et al, 2018).

Hidden in this figure is a different reality. Most of the 20% have what we call low-impact chronic pain, in that it does not affect engagement in valued life activities. But 20% of the 20%, or 5% of the overall population have **high impact pain** (or 30 million people). These people have extensive disability and distress, have shortened lives, and have a high demand on health services (Eccleston et al, 2018). These 30 Million people have complicated extensive disability, are typically out of the workforce, have a high risk of co-morbidity, and ultimately have shorted lives, as their all-cause mortality is higher than the norm.

This is the population who we need to better understand why pain comes to function not to promote healing or protection, but functions to disable and maintain that distressing disability.

3) Opportunities (mechanism)

There are opportunities in pain science that could be supported by this call. First in terms of mechanisms of the function of pain: (1) One can focus on the salience mechanism of the pain interruption. If nociception does not interrupt current attentional engagement, emerging or interrupting as pain then it is does not interfere. Rather than a focus on the felt experience of the sensation when it has already interrupted and interfered, we could and should be focussing on what predicts its interruption? Work on the how pain becomes salient is arguably more important than altering its quality when attended to. (2) Taking this idea further, we can measure the interruptive effect of pain on a primary task, giving an objective measure not only of the impact of pain, but also using that as an analgesic assay. If an analgesic agent reduces the frequency, duration, quality, and impact of the interruption, this is arguably better than the industry standard of 50% reduction in the severity of the experience attended to. (3) What are the higher order processing (executive function, memory updating, task switching) that can alter a pain experience? We are focussing currently on the cognitive and affective factors that make pain and pain behaviour 'sticky' in other words, why it is difficult to replace pain from focal attention, why does it successfully demand to be a processing priority. The answers are partly about the threat-value of the signal and partly about how one processes that threat. (4) Finally, we propose a shift in clinical focus away from curing pain (transitioning from chronic pain to no pain) and focus instead on how to shift people from high impact chronic pain to low impact chronic pain. What is the evidence and innovation in treatments that focus on impact not sensation? Eccleston et al (2023).

4) Opportunities (treatment)

There are also opportunities in pain science to focus on novel treatments. The evidence for psychological treatments for the rehabilitation of chronic pain is excellent (Williams et al 2020). These are the treatments that aim to shift people from high to low impact pain. There are remaining questions: (1) The evidence base is general. It is not clear for whom these treatments are most effective. Further, evidence is emerging that the general formulation of the biopsychosocial model with an emphasis on fear-avoidance works well for musculoskeletal pain but may be insufficient or partial for other pain conditions, such as endometriosis, painful diabetic neuropathy, and chemotherapy induced neuropathy. We need more specific evidence to focus on these areas. (2) Further, the evidence has to date focussed on chronic pain as if it were a singular problem, when in reality it is often co-morbid to other long-term conditions, including obesity, dizziness, itch, fatigue, and dypsnea. Chronic pain is a risk factor for cardiovascular disease, largely due to disability, and reduced participation. (3) the need for supported self-management far outstrips the workforce, and floods acute services ill-designed to manage chronic pain. There is a interest in digital therapeutics (Eccleston et al, in press), which have the potential to radically increase the scope and uptake of these evidence-based interventions? We have also worked on automating these treatments, for example we have developed a novel Virtual Reality

treatment with an automated Semi Autonomous Mentoring Intelligence (Bartlett, 2022). These digital treatments also give one the opportunity to collect digital biomarkers to help with prediction and the personalisation and precision of interventions (Liikkanen et al 2022).

5) Other gaps

Finally, there are other critical gaps in the psychology-chronic pain interface that could be useful to address. First, the translation pipeline from pre-clinical to clinical studies is acknowledged to be broke. In part this is due to the poor correspondence of animal models of pain to human pain. There is a rich array of human studies with a focus on the effect pain has on cognition including attention, memory, decision making, etc that can be back translated into animal models of pain behaviour to better guide mechanistic studies of salience. Further, developing a model of pain 'stickiness' at multiple levels of levels of explanation is needed, from the molecular to the social. If we stop asking why people develop pain, and instead ask why pain fails to subside will we get different answers? Finally, If we accept that getting 50% pain relief in 1 in 8 patients is currently the best possible outcome from pharmacotherapy in chronic pain (Birkenshaw et al 2023)., can we focus on the treatment resistant 7/8 and ask how we can shift them from high to low impact pain? (Eccleston et al, 2023).

Panel discussion with representative of European patient's organizations

Viorica Cursaru (Board Member of EFNA, European Federation Neurological Associations)

The Foresight *symposium* on the *Chronic Pain* was quite an experience from all perspectives but, first and foremost, the high professional profile of the speakers and participants.

As a patients' advocate and founder of the most important patients' organization for chronic pain patients, Pain Alliance Europe, I was pleasantly surprised, to see how much work and dedication is allocated to the research in the field of chronic pain. On the other hand, I believe that the individual patients and/or the chronic pain patients' organization should be more involved in the projects, from the incipient time, because the chronic pain patients, in my opinion, represent raw materials for the proper development of studies.

When and if involvement in person is not possible, for various reasons, I believe that ERA NET NEURON or any other entity involved in the research on chronic pain should use the survey as a means for collection of the clinical data provided by the patients. The usefulness of the output provided by the chronic patients in the surveys depends a lot of the professional significance of the questions raised in the survey, which afterwards can be used as clinical information during the studies. Unfortunately, neither my national nor European organization have received such requests from the research community.

Another issue of concern is related to communication of the research results in a lay language through training activities delivered by the individual members of the research community and/or by Health Care Professionals.

Last, but not least important, for better communication, and enhanced awareness it would be advisable if, during such professional high-level events as Berlin Symposium, patients' organizations would be also invited to make their presentations as speakers.

Annex

List of Participants

Speakers

Rolfe-Detlef Treed	Heidelberg university, Germany
Franziska Denk	King's College, London, UK
Andrea Truini	La Sapienza, university of Rome, Italy
Karen Davis	University of Toronto, Editor-in-Chief of *Pain*, Canada
Nadine Attal	Ambroise Paré hospital, Paris, France
Michelle Roche	University of Galway, Ireland
Chris Eccleston	University of Bath, UK

NSC meeting NEURON

Maxime Beaudoin	Canada	Fonds de recherche du Québec - Santé (FQRS)
Uldis Berkis	Latvia	LZP
Katarina Bibova	Slovakia	Slovak Academy of Sciences (SAS)
Simona Bifolchi	Italy	IT MoH
Mateo Ante Bosnić	Croatia	Ministry of Science and Education of the Republic of Croatia
Nawel Boulmane	France	INSERM
Philippe Bouvet	France	ANR
Ulrike Busshoff	Germany	DLR-PT
Recep Emrah Çevik	Türkiye	TÜBITAK
Esther Chacón	España	AEI
Marcin Chmielewski	Poland	NCBR
Chiara Ciccarelli	Italy	IT MoH
Estrella Garcia-Fernandez	Spain	AEI
Amanda Daly	Ireland	HRB
Gaëlle Dutour Provenzano	France	ANR
Liron Even-Faitelson	Israel	CSO-MOH
Estrella Fernández García	Spain	AEI
Mauricio Garcia-Franco	España	ISCIII
Anna Gossen	Germany	DRL-PT
Bożena Grzybowska	Poland	NCBR
Etienne Hirsch	France	INSERM
Klára Horváth	Hungary	NKFIH
Katja Hüttner	Germany	DLR-PT
Sandra Jurado	Spain	Institute of Neuroscience (CSIC-UMH)/AEI

Päivi Kolu	Finland	Suomen Akatemia
Clémence Le Cornec	Switzerland	SNSF
Anke Ley	Germany	DFG - German Research Foundation
Hella Lichtenberg	Germany	DLR-PT
Silvia Lorrio	Spain	AEI
Catherine Marquer	France	ANR
Alexandre Maurício	Portugal	Fundação para a Ciência e a Tecnologia
Manole Mihaela	Romania	UEFISCDI
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Cristina Maria Nieto	Spain	ISCIII
Dumitrache Nicoleta	Romania	UEFISCDI
Kristien Peeters	Belgium	Research Foundation - Flanders (FWO)
Bernard Poulain	France	CNRS
Florence Quist	Belgium	F.R.S.-FNRS
Živilė Ruželė	Lithuania	Research Council of Lithuania
Aki Salo	Finland	Research Council of Finland (AKA)
Sophia Schach	Germany	DLR-PT
Heidi Schulte	Germany	DLR-PT
Argo Soon	Estonia	ETAG
Ching-Mei Tang	Taiwan	National Science and Technology Council (NSTC)