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ABSTRACTS

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Contents

Multi-electrode array analysis of the functional maturation of the spinal dorsal horn over postnatal development

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Background

Neonates display altered responses to noxious stimuli compared to adults. They have lower behavioural thresholds and exaggerated responses to nociceptive stimuli. The dorsal horn (DH) of the spinal cord is the principle integrative centre of somatosensory information in the central nervous system (CNS). Afferent information conveyed via primary afferent sensory neurons (PAFs) innervate distinct regions of the spinal dorsal horn (DH) synapsing with heterogenous populations of DH interneurons. We know substantial changes in the underlying DH circuitry occur during postnatal development that support these age-related differences in nociception. Within the DH wide-dynamic range neurons in DH lamina V have larger cutaneous receptive fields, lower activation thresholds and prolonged firing in response to somatosensory stimuli (Fitzgerald, 2005). Traditional electrophysiological approaches do not account for the heterogenous lamina structure of the spinal DH, failing to recognise how individual lamina respond and interact with each other, and therefore how the networking properties may mature. We have employed multielectrode array (MEA) electrophysiology to investigate the postnatal changes that occur in the spinal DH in response to nocuous and innocuous stimulation.

Methods

All procedures were performed in accordance with the Animals (Scientific Procedures) Act 1986/2012 and were licensed by the UK Home Office under the project licence PB3DA999F. Neonatal (P9-11), juvenile (P14-16), adolescent (P21-23) and young adult (P42-60) mixed sex Sprague-Dawley rats were used. Animals were anaesthetised and prepared for MEA electrophysiology via a laminectomy exposing lumbar spinal cord. A 16-channel linear MEA with 50 µm inter-electrode spacing (NeuroNexus) was used to record neuronal activity across the DH before, during, and after electrical stimulation of the ipsilateral hindpaw (Greenspon et al., 2019).

Results

Age is a significant factor in stimulus intensity encoding in the DH. Although not functionally mature, we detected the presence of A-fibre responses at all ages. Clear age-dependent differences in A-fibre responses occur in the DH following electrical stimulation (Stimulation, $F(1.944, 33.05) = 98.34$, $p<0.0001$; Age, $F(3, 17) = 3.812$, $p=0.0295$). A-fibre mediated activity in the DH increases significantly as the DH matures, especially in the deeper laminae ($F(3, 17) = 5.830$, $p=0.0063$). As the animal ages, the A-fibre responses to electrical stimulation become steeper. C-fibre responses change to high intensity electrical stimulation change through postnatal maturation. Although not significant, there are more threshold crossings in the YA rats compared to the younger age groups. C fibre encoding doesn't appear to be present until after the third postnatal week. Conclusions- Our findings show that contrary to substantial evidence showing enhanced single-cell excitability in the DH in the postnatal period, DH networks are in fact less active. This could suggest an increase in inhibitory activity with postnatal maturation which correlates with increased neuronal activity in populations which we have measured here. Full adult maturation may not occur until ages much older than often referred to in the literature. These findings are important for the appreciation of how nociceptive networks in the DH influence each other and mature at different rates after birth.

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Lay Summary Points

Pain thresholds are lower early in life and reactions to pain are greater. The amount of pain experienced by someone is directly related to how excited specific cells are in an area of the spinal cord, called the dorsal horn.

This project looks at how networks of these cells change as we develop from birth to adulthood, which has never been done before. Previous studies have measured the activity of a single cell as an estimation of the changes occurring in the rest of the dorsal horn. Our approach uses a new technique that produces detailed recordings of electrical activity across the whole dorsal horn, which allows us to investigate how different areas might develop at different rates.

We show that, unexpectedly, these networks are less active in early life and increase their activity as we age.

Acute nerve pathology and neuropathic pain after whiplash injury: preliminary cohort findings

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Background

Whiplash Associated Disorders (WAD) commonly occur after motor vehicle collisions and often include signs and symptoms of pain, psychological distress, and sensory/motor dysfunction. The severity of WAD is graded from zero (no pain and physical signs of injury) to four (neck fracture/dislocation). The most common type is WAD grade 2 (WAD2), which includes neck symptoms and musculoskeletal signs in the absence of a frank nerve injury on routine diagnostic testing. This is an ongoing cohort study aimed to assess peripheral nerve pathology in WAD2 and its role in prognosis. The current objective is to determine the presence of nerve pathology and neuropathic pain in the acute phase of our cohort of people with WAD2.

Methods

This is a prospective longitudinal multicentre cohort study currently recruiting in Brighton and Oxfordshire, UK. Participants aged 18-85 with a clinical diagnosis of acute WAD2 are recruited within 4 weeks of injury. Exclusion criteria for all participants included: pregnancy; history of cervical/arm pain lasting >3 months; diagnosis of a peripheral neuropathy; systemic illness that is known to cause neuropathy or small fibre pathology. Detailed demographic details and questionnaires were collected, including neuropathic pain grading. Upper extremity neurological assessment was performed including cutaneous light touch, pin prick, thermal sensation, myotomal strength and deep tendon reflexes. Quantitative sensory testing (QST) was performed using the German Research Network for Neuropathic Pain protocol. Serum marker of axonal injury Serum protein concentration of neurofilament light chain (NfL) will be analysed using Simoa® SR-X and NF-Light v2 Advantage Kit (Quanterix, Billerica, MA, USA). Statistical Analysis The distribution of clinical phenotypic data was calculated for normally distributed and skewed data as mean/ standard deviation (SD) and median/interquartile range (IQR), respectively. Serum results were analysed using independent t-tests or non-parametric alternatives. Statistical significance was set at $P<0.05$.

Results

Clinical phenotype One hundred patients with WAD2 (53% female) and 55 healthy controls (56.4% female) were recruited. The mean age of patients and healthy controls was 38.9 years (SD 14.1) and 45.8 years (SD 16.7), respectively. Overall symptom intensity for whiplash patients was 35/100 (VAS). Patient reported outcome measures indicated moderate disability and post-traumatic symptoms using the NDI (median 15, IQR 10) and IES (median 27, IQR 29). Neuropathic Pain According to the NeuPSIG grading system 38% of patients were classified as unlikely, 25% as possible, and 37% as probable neuropathic pain. Using the painDETECT, 10% (9/90) were grading as likely having a neuropathic component. Neurologic exam Signs of neurologic dysfunction were identified throughout the upper extremity (C5-T1) in WAD2 patients. The most affected nerve root showing at least one abnormal neurologic examination finding was C6 (39% loss of function (39/100); 11% gain of function (11/100)). QST Sensory detection thresholds were significantly reduced over the index finger in whiplash patients compared to controls, including for cold ($P<0.001$), warm ($P<0.01$), sensory thermal limen ($P<0.001$), and mechanical detection ($P<0.001$). There were no significant differences in cold, heat, pressure pain, windup ratio or mechanical pain thresholds. Serum marker of axonal injury There was a significant increase in NfL concentration in whiplash patients compared to controls ($p<0.01$). CONCLUSIONS Preliminary findings from our current cohort of patients with WAD2 suggest that a subgroup present with signs of acute nerve pathology and neuropathic pain. Our data suggest that a subgroup of WAD2 patients presents with acute signs of nerve pathology and neuropathic pain.

Examination of spontaneous sensory neuron activity in models of rheumatoid- and osteo-arthritis

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Introduction

Under normal conditions, neurons that transmit painful information (nociceptors) are silent and only activated in the presence of stimuli that are actually, or potentially, damaging to tissue. In contrast, in a disease context, e.g. in arthritis, nociceptive neurons can become sensitised by inflammatory mediators and start firing spontaneously. Evidence from microneurography studies in humans suggests this abnormal activity is the neurophysiological correlate of spontaneous pain[1,2]. In order to generate more targeted analgesics to treat spontaneous pain in musculoskeletal conditions, we need to determine which types of sensory neurons develop spontaneous activity. We have recently shown that in vivo calcium imaging can be used for large-scale assessment of spontaneous activity in sensory neurons[3]. Here, we have utilised this technique to examine spontaneous firing in joint afferents in murine models of arthritis.

Methods

Spontaneous sensory neuron activity was examined in joint pain models using in vivo GCaMP6s calcium imaging recordings from murine L4. Fast blue (FB, 2% w/v 2ul) was injected into the knee to back label joint afferents (visualised in the DAPI channel when in vivo imaging). Inflammatory joint pain was modelled by injecting 2.5-5µL mBSA (200µg) into the knee of mice previously immunised with a mBSA/CFA emulsion (antigen-induced arthritis, AIA). A saline injection was used as a control. Osteoarthritis was modelled by performing a partial medial meniscectomy (PMX). Spontaneous activity was detected using a

machine learning algorithm. Lidocaine (2% w/v) was applied to the sciatic nerve at the end of the recording to determine the origin of spontaneous firing. Static weight bearing behaviour was performed on osteoarthritis mice at baseline and at 2-week intervals post-surgery.

Results

The size of injected knee joints in mBSA-injected mice increased (1.30:1 +/-0.06, ipsi vs contra knee size, n=6) compared to controls (1.05:1 +/-0.01, n=8; p=0.0004, t-test). There was an increase in the proportion of neurons with spontaneous activity on day 2 following injection of 2.5-5ul mBSA (All L4 = 28.7% +/-6.1, FB+ knee joint = 36.2% +/-11.8, n=6,), compared to saline injected (All L4 = 13.7.0% +/-2.6, FB+ knee joint 7.7% +/-3.8, n=8; p=0.015 treatment, RM ANOVA) and uninjured mice (All L4 = 10.1% +/-1.1, n=3). In contrast, despite PMX mice developing signs of pain in the affected hind limb (ipsilateral/contralateral weight bearing ratio 0.87+/-0.04. vs 1.05+/-0.02 sham at week-12, n=7/group), there was no difference in the proportion of neurons with spontaneous activity between PMX and sham mice at week-13 post-surgery (PMX All L4 = 7.1% +/-1.5, FB+ knee joint = 3.5% +/-2.3; Sham All L4 = 9.5% +/-2.2, FB+ knee joint = 5.5% +/-5.5; p=0.78 treatment, RM ANOVA). In AIA mice, the majority of spontaneously active neurons were blocked by lidocaine application to the sciatic nerve (77.3% +/-5.7).

Conclusions

We find an increased proportion of spontaneously active joint neurons in a model of rheumatoid arthritis, which is consistent with a previous electrophysiological report4. AIA-induced spontaneous activity was attenuated following lidocaine peripheral nerve block suggesting that it originated within the inflamed knee joint. In contrast, elevated levels of spontaneously activity were not found in the in the PMX model of osteoarthritis at 12-weeks post-surgery. Acknowledgements We thank Jadwiga Zarebska, Victoria Bachelor and Tonia Vincent for PMX surgery and weight bearing behaviour training.

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Lay Summary Points

- Pain in individuals with arthritis is often sensed by nerves within the joints. We know this because replacing the damaged joint or injecting a local anaesthetic into the joint (to numb the nerves) relives pain in most cases.
- Unfortunately, the pain killers we have do not work for many people and often have terrible side effects, like addiction in the case of opioids. We therefore urgently need to increase our understanding of what causes joint pain, to help us develop better treatments.
- Under normal conditions, the pain-signalling nerves in our joints are only activated when an actual or potentially damaging event occurs, for example twisting your ankle. However, in arthritis, the pain nerves in the joint become activated more easily and some are active spontaneously.
- Our lab has recently developed a new approach for studying this abnormal activity in joint nerves, and here we have used it to understand which nerve types become spontaneously active in mouse models of arthritis.
- We are currently in the preliminary phase of our investigation. So far, we find that there is increased spontaneous nerve activity in a model of rheumatoid arthritis but not in a model of osteoarthritis.

Interim overview of the FORECAST Study cohort

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Background

Sciatica is a common and distressing musculoskeletal condition, associated with higher levels of pain and disability and worse quality of life than low back pain alone. While many people with sciatica recover, around a third will not, with pain and other symptoms persisting for one year or longer. Unfortunately, routine clinical tests (clinical MRI, symptom severity, mood) are not consistent prognostic factors for sciatica outcome and so it remains unclear who will recover and who will go on to develop persistent pain. The FORECAST study is a longitudinal prognostic factors study aiming to explore whether alternative measures, including those that may give clues to the differing mechanisms that might underlie different sciatica presentations, can better predict symptom persistence. FORECAST is designed to address the following aims: 1. To explore mechanism-based subgroups in patients with acute/subacute sciatica 2. To investigate whether a mechanism-based approach can identify factors that predict pain persistence in people with sciatica Launched in May 2022, FORECAST is currently mid-recruitment. Here we present a preliminary overview of the FORECAST cohort at this mid-point.

Methods

Within FORECAST, we are collecting the richest multidimensional dataset for sciatica to date. This includes psychosocial factors, detailed symptom characterisation, clinical examination, psychophysical measures (quantitative sensory testing, QST), biological samples (blood and skin samples), and Magnetic Resonance Neurography of the nerve roots. Cohort characteristics Demographics Of n=50, 29 are female (58%), the mean age is 53.4(sd 17, range 25-85), ethnicity: 34 (68%) White British, 6 (12%) White other, 3 (6%) Other. Clinical features Affected side: Left 27 (54%), Right 20 (40%), Both 3 (6%). Sciatica Sum

Score: median 8 (IQR: 7-10). Leg pain severity over previous two weeks (mean(range,sd)): worst 7.4(2-10, 1.93), least: 3.26(0-10, 2.76), average 5.66(0-10,2.28). Low back pain severity over previous two weeks: worst 6.04(0-10,2.72), least 2.84(0-10,2.92), average 4.62(0-10,2.81). Mean disability score (Oswestry Disability Index (ODI)) for leg 33.2(18) and for the back 30.42(19). Mean sciatica bothersomeness index (SBI) score: 14.02(5.02). Quality of life EQ-5D overall health rating (0-100 with 0 worst health you can imagine, and 100 the best health you can imagine) mean(sd): 59.4(20.4).

Discussion

Our cohort is representative of a sciatica population, with a similar gender balance to previous large primary care studies, similar ethnicity distribution to our local populations based on census data (for Oxfordshire County and Oxford City), and participants across a broad range of ages. As expected, leg pain averages are higher than back pain across all three collected measures, and participants report a range of symptom severity and disability. Recruitment continues through 2023, with care and commitment to exploit a broad variety of recruitment routes across Oxfordshire to minimise accessibility barriers and ensure representative recruitment.

Lay Summary Points

Sciatica is very common and is caused by injured or irritated nerves in the lower back. Sciatica causes pain, tingling or weakness in the leg. It can have a devastating effect on everyday life. Sadly, about one in three patients develops persistent sciatica pain.

We currently do not understand why some patients develop persistent pain and why some recover. This is the goal of the FORECAST study.

We are currently halfway through recruitment for the FORECAST study and share some information here about a sample of 50 of the people (all of whom are in the early stages of an episode of sciatica) who have taken part in the study so far:

the average age for our participants is 53 years old, 58% are female, 68% are White British

the average reported leg pain (worst pain over the previous two weeks on a scale of 0-10 where 0 is no pain and 10 is the worst pain you can imagine) was 7.4. The average disability score was 33.2 (ODI). The average Sciatica Bothersome Index score was 14. These scores reflect the symptom impact experienced by FORECAST participants, with average scores reflecting severe pain and moderate disability

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Beyond tokenistic involvement: the recruitment of a public contributor network

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Background and aims

The Consortium to Research Individual, Interpersonal and Social Influences in Pain (CRIISP) is a collaboration of nine UK universities investigating how thoughts and feelings, personal relationships and lifestyle can affect chronic pain. This work was supported by equal investment from UKRI and Versus Arthritis through the Advanced Pain Discovery Platform initiative. Within CRIISP, we have a public involvement (PI) workstream, co-led by people with lived experience, which aims to establish a network of public contributors (PCs) to work in equal partnership with researchers across all workstreams.

Methods

Targeted advertising via pain organisations invited adults with chronic pain, or caring for someone with chronic pain, to apply for PCs roles. An inclusive recruitment strategy promoted diversity including gender, age, ethnicity, and prior experience of PI work. Interested individuals were provided with a role outline and access to a

bespoke website with 'Find Out More' video content. Governance documentation was produced by the PI team to ensure data protection and safeguarding safe practice. The leadership and contribution of the PC's were integral to all processes.

Results

28 PCs were appointed. Induction training sessions were delivered as a recorded video or 'live' via Microsoft Teams.

Conclusions

The PI network has successfully begun working in collaboration with the CRIISP research teams to ensure the voices of people with chronic pain are heard in all aspects of CRIISP. Working in partnership with people with lived experience of pain, will fully embed their contribution across all workstreams. We will evaluate all processes to inform future PI involvement.

Lay Summary Points

A network of public contributors was established to support the work being done by the Consortium to Research Individual, Interpersonal and Social Influences in Pain (CRIISP)

Advertising for this opportunity was aimed at people with experience of chronic pain from a range of backgrounds

Twenty eight public contributors now work closely with the researchers throughout CRIISP, to ensure that the voices of people with chronic pain are heard in all aspects of the work.

Multiplex Spinal Somatosensory-Evoked Potentials as a High Content Biomarker of Analgesic Actions in Rats

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Current treatments for chronic pain often provide only modest symptom relief and are associated with adverse effects. Efforts to develop new treatments are hampered by the lack of reliable translation from preclinical models. One approach to improve the success rate during the development of new treatments is to use translatable biomarkers to demonstrate modulation of the nociceptive system in vivo. Spinal somatosensory-evoked potentials (SEPs) are one such class of biomarkers that may enable target engagement within the spinal cord to be assessed. This study will characterise the basic properties of the rodent SEP across the spinal lamina, as well as their modulation by 3 "standard-of-care" treatments. Ultimately the translatability will be assessed via comparisons with equivalent clinical data from other research groups in the IMI-PainCare consortium. Adult male Wistar rats (n=52, 250-375g) were anaesthetised with isoflurane, a spinal laminectomy (over L3-4) was performed, and a linear multi-electrode array (64 channel) was inserted into the dorsal horn. Electrical stimuli (4Hz x 250s low-intensity electrical stimuli and 3x stimulus ramps) were delivered to the sciatic nerve in each 10min block, with recordings consisting of a 30min baseline period and up to 90min post-dose. Drugs were administered in a blinded manner following a block-randomised design (vehicle, 3, 10 and 30mg/Kg i.p.). Time-course data will be compared using two-way repeated measures ANOVAs (dose x time) for each drug. Detailed methods are prespecified on the Open

Science Framework. Low-intensity SEPs within the spinal dorsal horn have a characteristic depth profile (peak amplitude in lamina III/IV). The 4ms delay to the principle negative peak (N4) is consistent with peripheral conduction via Aβ-fibres. Waveform and multi-unit activity analyses of the ramp stimuli revealed intensity dependent activation of multiple primary afferent fibres classes (A/C-fibres), each exhibiting distinct dorsoventral distribution patterns within the dorsal horn. Baseline N4 SEPs were stable, with an average amplitude of -425±50 μV (n=8). Final analysis of the pharmacological data is in progress and the effects of analgesics on low and high intensity evoked-SEPs will be presented.

Lay Summary Points

Background

This work is the result of a collaboration between the EU, academic groups and pharmaceutical companies (via the IMI-PainCare project). We have been investigating translatable techniques (i.e. those that are equally applicable to rodent and human settings) to assess their ability to identify analgesic-induced modulation of pain pathways. Here we present the results of brain-based EEG recordings in rats administered with 3 different drugs (lacosamide, pregabalin and tapentadol).

Hypothesis

Drugs shown to be able to modulate activity in pain-relevant compartments of the nervous system (during preclinical testing and phase 1 studies in humans) will be more likely to ultimately be successful in relieving pain in patients in late-stage trials in humans.

Findings

We demonstrate in rodents that each of the 3 drugs can modulate EEG activity while animals are at rest, and that evoked by thermal stimulation of the paw. Further analysis is continuing to identify which (if any) of the changes are predictive of the analgesic response. Equivalent studies in humans are underway to identify if comparable effects are observed.

Observing touch: in vivo calcium imaging of C-low threshold mechanoreceptors

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C-tactile (CT) fibres, known in animals as C low-threshold mechanoreceptors (C-LTMRs), are unmyelinated sensory neurons which respond to gentle touch. In humans and other animals they relay sensory information related to pleasant touch to the central nervous system. Recent evidence suggests that their role in pain is complex, involving potential inhibitory inputs to painful sensory processing [1,2], while also being implicated in allodynia [3–5].

Despite this likely involvement of CT/C-LTMRs in pain processing it remains difficult to study them functionally. Both microneurography in humans and teased fibre experiments in animals are technically challenging with low throughput. Here we propose to use in vivo calcium imaging, a technique which visualises calcium oscillations as a proxy for neuronal activity, to improve some of these challenges.

Ten mice, expressing GCaMP in TH positive cells (TH is expressed exclusively in C-LTMRs in mouse DRGs) in a tamoxifen dependent manner, were used for in vivo microscopy, in accordance with UK Home Office Regulation. At least 2 weeks after tamoxifen administration mice were anaesthetized and their L4 DRGs exposed and stabilized for single-photon microscopy. In vivo calcium imaging was used to visualize GCaMP in the exposed cell bodies, while mechanical stimuli (brush and Von Frey stimuli) were applied to the ipsilateral hind leg.

We showed that in vivo calcium imaging can be used to reveal stimulus induced activity in TH

positive C-LTMRs in the DRG. TH-positive cells showed the expected decrease in activity when the speed of the brush stimuli increased from 1.5cm/sec to 30cm/sec. This was mirrored by a decrease in the percentage of TH-positive cells activated by the increasing brush speeds. TH cells also showed activation by Von Frey stimulation. C-LTMR neurons also revealed an unexpected directional selectivity: They showed increased activation when brushing against the grain, as compared to with the grain.

We conclude that in vivo calcium imaging is a useful tool for the study of C-LTMR neurons. Using in vivo microscopy, C-LTMR neurons have an expected response to brushing, with increased responsiveness at slower speeds. However, they also reveal an unexpected directional selectivity, responding more to brushing against the grain than with the grain. Further experiments are needed to reveal the reason for this directional selectivity, but this may be related to the wider excursion of the hair when brushed against its natural orientation, the possible differential expression of mechanosensitive channels around hair cells or the variation in tension applied to potential protein tethers synthesized by sensory neurons [6].

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Lay Summary Points

A specific type of sensory nerve cell, known as C-tactile fibre (CT-fibre), is believed to transmit information about pleasant, social touch to the central nervous system. However, studying these cells in intact animals and humans has proven challenging.

By employing in vivo microscopy in mice, we have successfully overcome some of the limitations associated with traditional research methods.

Our findings align with previous studies conducted using established techniques, but we made a striking discovery: CT-fibres exhibit stronger responses to stroking against the grain of the hair compared to with the grain, contrary to the belief that they respond more vigorously to pleasant stimuli. This revelation challenges the prevailing notion that CT-fibre activity solely corresponds to the pleasantness of the stimulus, suggesting a more complex relationship between CT-fibre responses and sensory perception.

An ethnographic understanding of the experience of transition to and from chronic pain in everyday life

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Chronic pain exerts an enormous personal and economic burden on society. Chronic pain affects between one-third and one-half of the UK population, which is just under 28 million adults. Following the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11) we define chronic pain as pain that persists or recurs for longer than three months. We know that people living with chronic pain report negative impact of pain on all domains of functioning including physical, emotional, social, and occupational. We also know that people experience pain in different ways, but that little is known about how social contexts are linked to chronic pain, or why individual variation exists. Our research seeks to address these knowledge gaps by characterising the social context around people's everyday experiences of chronic pain. Using ethnographic approaches drawn from social science, we will spend time over a period of 12 months with people who live with chronic pain. Participants will be identified through the Avon Longitudinal Study of Parents and Children (ALSPAC) and we expect to include 20-30 people with pain, all of whom are around 30 years old. Starting in 2023, we will conduct interviews and periods of shadowing (observations) with participants in their homes and communities. This will enable us to understand the relationship between social context and pain from the viewpoint of people with pain. Our focus on everyday life includes family and social life, environment, leisure and occupation. Data will comprise field notes, audio-recorded interviews and visual materials such as photos. Thematic analysis of data will enable us to describe the different ways in which social and environmental aspects of everyday life influence the onset and transition to and from chronic pain, and the ways in which people can influence these aspects. Together, findings will enable us to understand how and why social forces combine to elevate or reduce the risk of transition to and from chronic pain. This work sits within the wider Consortium to Research Individual, Interpersonal and Social influences in Pain (CRIISP). The author(s) report no conflicts of interest with respect to this research study. Rachael Gooberman-Hill wishes to declare that she is a member of the ALSPAC Board, and that she is Co-Chair of the UK Committee on Research Integrity. The author(s) wish to thank members of our public contributor working development group for their valuable insight and contribution to this study.

The study is funded by joint and equal investment from UKRI [grant number MR/W004151/1] and the charity Versus Arthritis [grant number 22891] through the Advanced Pain Discovery Platform (APDP) initiative. For UKRI, the initiative is led by the Medical Research Council (MRC), with support from the Biotechnology and Biological Sciences Research Council (BBSRC) and the Economic and Social Research Council (ESRC).

Lay Summary Points

- We hope to understand any links between everyday life and people's experiences of pain to understand what makes long-term pain stop, start, get better or worse.
- Starting July 2023, we will spend time and speak with people who have long-term pain. This will be over a period of a year and will take place in people's homes and their communities.
- We expect to include between 20-30 people who have long-term pain. Participants will be around 30 years old and will be people who have been taking part in a large, ongoing study in Bristol since they were born. The study is

called ALSPAC, which is also known as 'Children of the 90s

Recording of Pain within Mental Health Electronic Health Records Text

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Background

Pain and its relationship with mental health are important research topics. Pain has imposed a significant burden on society in terms of medical care costs as well as lost productivity. Pain is multifaceted, affecting physical, psychological, social, and biological variables. Electronic health records for mental health are a significant source of information for studying the intersection between pain and mental health. It also enables researchers to investigate changes in how pain is recorded based on demographic and diagnostic criteria. Such discrepancies in recorded pain from a mental health electronic health records database are presented in this work.

Methods

The Clinical Record Interactive Search (CRIS) database, used in this study, contains an de-identified version of EHR data from The South London and Maudsley NHS Foundation Trust (SLaM), one of Europe's largest mental healthcare organisations. CRIS contains about 30 million free text documents, with an average of 90 documents per patient. A cohort of patients were extracted from the CRIS database. This included patients who were active (i.e., under an accepted referral) and aged 18+ on the index date of July 1, 2018, and whose record contained at least one document (>= 30 characters) within a window of July 1, 2017 to July 1, 2019. A natural language processing based application was run on the sentences from documents of patients within this cohort to identify patients who had relevant pain mentions (physical and affecting the patient).

Results

A total of 18,188 patients and 175,000 documents were retrieved based on the extraction criteria. 57% of the sentences had relevant mentions of pain, and 78% of the patients within the cohort had sentences containing relevant mentions of pain. 54.6% (95% CI 53.7-55.4) of the patients who were identified with mentions of pain were female (cohort: 52.9% female). 26.4% (95% CI 25.6-27.1) of the patients with mentions of pain were of black ethnicity (cohort: 25.2% black). The distribution of index of multiple deprivation (IMD) decile scores was similar between the cohort and the patients who had mentions of pain, with the mean being 3.9 in patients identified with pain (cohort: average of 4.0). The most common diagnosis category was ICD-10 chapter F20-29: Schizophrenia, schizotypical and delusional disorders, which made up for 20.8% (95% CI 20.1-21.4) of the patients identified with mentions of pain (cohort: 19.7%), followed by 14.6% (95% CI 14.0-15.2) with the diagnosis of F30-39: mood [affective] disorders (cohort: 14.0%).

Conclusions

This study utilises the CRIS database to investigate the recorded mentions of pain in patients with mental health conditions. The results reflect current literature findings that pain is a common issue among mental health patients, with 78% of the cohort containing sentences with relevant mentions of pain. The findings of this study have significant implications for the assessment and management of pain in mental health patients, and highlight the importance of utilizing electronic health records for research purposes. As part of future work, this cohort will be compared with GP records, specifically Lambeth DataNet (6), to understand the overlap between primary and secondary care. Further research is needed to better understand the relationship between pain

and mental health, and to develop more effective interventions to manage pain in this population.

Lay Summary Points

The written records in mental health electronic health records are filled with important information that helps researchers understand the relationship between pain and mental health, while also enabling us to examine how pain is documented based on factors such as a person's background (gender, ethnicity, etc.) and the specific mental health diagnosis they have.

In this study, we used special computer techniques called natural language processing that can learn and understand human language to pull out information about pain from the written notes in these mental health electronic records.

Using these methods, in a group of patients selected at a specific time, it was found that 78% of them had documented mentions of pain. These mentions were more common among females, individuals of black ethnicity, and those diagnosed with schizophrenia.

A systematic review of psychosocial factors involved in chronic pain state transitions

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Introduction

People differ in their experience of pain -- some develop chronic pain whilst others do not. Chronic pain can get worse, get better, or stays the same. There is a need to better understand the reason why chronic pain can develop and change over time. The current study sought to conduct a systematic review to isolate the psychosocial factors that have been found to affect how chronic pain changes over time. The focus was on psychosocial factors within the individual (e.g., depression, fear of pain, resilience).

Methods

Three databases were searched up to March 2022 to identify studies that explored the role of individual psychosocial factors in how chronic pain changes over time. Studies were required to have at least two time points for data collection to capture if and how pain changed over time and included at least one psychosocial factor. The titles and abstracts were screened for relevance, and studies that met the requirements were reviewed in full. Studies are assessed for quality, using a psychosocial focused risk of bias measure, and categorised according to sample size. Data extraction is ongoing, and here we report on initial findings from studies with samples >500.

Results

The initial search identified 19,150 papers. 17,970 were excluded at the abstract and title screening phase, and 1180 papers included in the full text review. Of the studies with samples >500, 79 studies met criteria for data extraction. The core factors that have been identified, and most

frequently explored, are depression, anxiety and components of fear avoidance such as fear of pain and catastrophizing. There are initial indications of which psychosocial factors are missing from these large-scale studies – this includes cognitive interference and disruption. There are also inconsistencies in the way pain impact is identified and recorded.

Discussion

This is the first comprehensive systematic review to investigate individual level psychosocial factors that may play a role in how chronic pain develops and changes over time. Whilst psychosocial factors have been explored, these tend to be the usual suspects of anxiety and depression, and do not seem to include measures of cognitive interference; despite these factors being identified as important in smaller studies. The findings will inform our understanding of how chronic pain is explored, and which psychosocial factors influence transitions in pain states. This understanding will hopefully be used in more targeted interventions to support people living with pain. It will also identify factors where there is little evidence, and where there is need to explore these further in large chronic pain studies.

Lay Summary Points

- The review aimed to identify psychosocial factors important to how and why pain changes over time (gets better, worse or stays the same). We focussed on how people think, feel and behave.
- We searched databases to identify previous research papers of psychosocial factors explored in relation to changes in pain.
- The review is ongoing but there is some suggestion some factors (depression, anxiety and fear avoidance) are explored frequently whilst fewer papers explored factors such as attention and memory and how these affect pain changes over time.

Development of a semantic database for building psychosocial models of chronic pain

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Background

Psychosocial factors can contribute to the onset, maintenance and worsening of chronic pain. Modelling the psychosocial contributions to chronic pain, and testing these models against new and existing evidence is key to helping us understand these relationships. To do this we are developing a semantic database that brings together the various pieces of evidence gathered across the CRIISP project; an APDP consortium investigating the psychosocial influences on chronic pain. Examples of evidence include research paper findings, including systematic reviews, as well as actual data (qualitative and quantitative). The advantage of a semantic database (Horrocks, 2008) is that it allows us to connect various concepts/theories with this evidence, and then identify patterns and connections.

Methods

The semantic database project aims to build an interface that allows researchers to create and reason about models. It consists of two parts: a database and a user interface. The semantic database is a Google Firestore Database, a NoSQL document oriented database. It will enable researchers to store and integrate different types of data from different sources. The model building software has been developed with the Godot game engine, using GDScript; this will allow researchers to fit data stored in the database to models. It will also allow researchers to upload data to the database, and to store and edit the models created.

Results

A preliminary version of the software has been created and is in development (Alpha 1.0). It has 2 main functions. First, the database is able to store key information from papers extracted from systematic reviews on psychosocial mechanisms in chronic pain that are being conducted within CRIISP. Second, the model building application connects concepts chosen by users to the information stored in the database. This allows users to view the currently available evidence from a systematic review investigating the psychosocial contributions to chronic pain. Both aspects will be visualised in the poster.

Conclusions

The first version of the database and model building software provides a base for future integration of analysis using tools from computer science and artificial intelligence. This future version of the software will allow researchers to create models of psychosocial contributions to chronic pain, and test them against data available in the semantic database. The semantic database will be used in conjunction with other areas of the CRIISP project, providing complementary analyses to the modelling that will be conducted using directed acyclic graphs (DAGs) in large datasets. This will allow researchers to quickly see where evidence exists for a psychosocial factor of interest, which psychosocial factors have little evidence to support their contribution to chronic pain and which areas have been understudied.

Discosure (acknowledgments)

This work was supported by a joint and equal investment from UKRI [grant number MR/W004151/1] and the charity Versus Arthritis [grant number 22891] through the Advanced Pain Discovery Platform (APDP) initiative. For UKRI, the initiative is led by the Medical Research Council (MRC), with support from the Biotechnology and Biological Sciences Research Council (BBSRC) and the Economic and Social Research Council (ESRC).

Lay Summary Points

- Psychological and social factors can contribute to the onset, maintenance and worsening of chronic pain.
- We are interested in how creating models can help us to understand these relationships better. By models we mean pictures of how we think psychosocial factors influence pain.
- To do this we are creating a database that will store information collected throughout the CRIISP project, as well as accompanying software. This information will include papers and different types of data.
- The software will be a tool for researchers to use, that will allow them to create models and connect these models to data that already exists.
- This will allow researchers to quickly see where evidence exists for a psychosocial factor of interest, which psychosocial factors have little evidence to support their contribution to chronic pain and which areas have been understudied.

Validation of a questionnaire for Central Aspects of joint Pain: the CAP questionnaire

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Background and Aims

Chronic joint pain is associated with dysfunctional pain pathways within the central nervous system. Our previous research has examined these pathways in people with knee pain, and developed a questionnaire called CAP-Knee which measured a `Central Aspects of Pain' factor (CAPf). In this study, we expanded the target population and we developed and validated the Central Aspects of Pain questionnaire (CAP) to measure CAPf in people with all types of joint pain.

Methods

CAP-Knee was modified slightly to derive the CAP questionnaire. CAP used 7 questions (items) asking about depression, anxiety, sleep problems, catastrophising, fatigue and cognition. Participants also marked painful areas on a body pain manikin/diagram. The CAP questionnaire was completed by people in the Investigating Musculoskeletal Health and Wellbeing survey. Data were analysed for all people, plus also 3 subgroups with osteoarthritis, back pain or fibromyalgia. Correlation coefficients were used to examine the classification of the painful areas on the manikin, and to test CAPf against pain scores. Different rules for dealing with 1 or 2 missing CAP items (mean imputation) were examined using Bland-Altman plots to assess whether they biased the outcomes. Confirmatory factor analysis assessed the validity of CAPf for measurement. Repeatability was determined in 200 people who completed the questionnaire on paper forms and electronically, and was analysed using Intraclass Correlation Coefficients (ICC).

Results

Data were used from 3579 people (58% female, median (IQR) age; 71 (66 to 77) years. Diagnoses were OA (n=1158), back pain (n=1292) and fibromyalgia (n=177). Across the 3 diagnostic groups, correlation analyses showed that ≥10/26 painful area on the manikin could be used to score people with widespread pain. High repeatability of CAP was found between paper and electronic administration (ICC= 0.89 (95% CI: 0.84-0.92). Imputation of one missing item closely approximated to the true CAPf and did not appear to bias the CAP score. Questionnaire scores showed fit to a single CAPf factor via CFA. As expected, the CAP scores were associated with worse pain severity.

Conclusions

The CAP questionnaire appears to be a reliable instrument that measures a single underlying factor. The Central Aspects of Pain factor (CAPf) was originally derived for people with knee pain, but these findings show that it can be examined when pain is at other joints (single or multiple). Further research could determine which specific pain mechanisms the CAP questionnaire could be used to measure.

Neuro-immune interactions in rheumatoid arthritis: an in vitro culture model

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Background

In the last thirty years, many new treatments have been developed for rheumatoid arthritis (RA) that target inflammation. Nevertheless, pain remains a persistent problem for many individuals living with RA. A better understanding of how immune and neuronal cells interact in RA may inspire the development of novel analgesic treatments. We set up a human cell culture model to investigate whether immune cells or their mediators, derived from individuals with RA, can sensitise peripheral neurons.

Methods

Sensory neurons were derived from human-induced pluripotent stem cells (hIPSC) following an established protocol (Chambers 2012). To mimic inflammation, sensory neurons were either incubated for 24 hours with a modified "inflammatory soup" (1μM prostaglandin E2, histamine, serotonin and bradykinin; 100 ng/mL TNFα and 100 ng/mL NGF) or for 3 days with peripheral blood mononuclear cells (PBMC) stimulated with or without αCD3 mAb to promote T cell proliferation in a transwell system. Neuronal excitability was assessed by Ca2+ imaging using the TRPM3 agonist pregnenolone sulphate (PS) or voltage-gated sodium channel opener veratridine. To explore whether inflammatory mediators directly activate neurons, paired serum and synovial fluid derived from individuals with RA were added onto sensory neurons during Ca2+ imaging experiments.

Results

hIPSC-derived sensory neurons expressed neuronal markers, as assessed by immunohistochemistry (βIII-tubulin, BRN3A, NF200) and qPCR (e.g. SCN9A, TAC1). On average, 20% neurons responded to 100μM pregnenolone sulphate and 50% neurons respond to 50μM veratridine in calcium imaging. However, incubation with inflammatory soup did not consistently increase the response percentage to these drugs. Transwell culture of sensory neurons and PBMC was feasible in RPMI media, where neurons remained alive and functional. Initial experiments (n=7 healthy control PBMC) yielded variable results as to whether a transwell system is sufficient to increase neuronal response rate to PS. Testing of paired serum and synovial fluid is currently ongoing.

Discussion

We have set up a human cell culture model of hIPSC-derived sensory neurons. Further optimisation of culture conditions is ongoing to robustly assess neuronal sensitisation by immune cells. Moving on to within-coverslips assays may avoid between-coverslip variations to generate more consistent data.

Microfluidic cell culture system to investigate localised subcellular processes underlying sensory neuron sensitisation by PGE2

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Background

Dorsal root ganglion (DRG) sensory neurons adapt their physiological properties in response to changes in the local environment. During inflammation, mediators secreted from immune cells sensitise DRG neurons by modifying their intrinsic excitability and synaptic connectivity. Peripheral sensitisation is crucial for survival but can lead to the onset of central sensitisation and the establishment of chronic pain.

Prostaglandin E2 (PGE2), a potent inflammatory mediator, is produced by numerous cell types during inflammation and has been shown to potently sensitise neurons. The cognate PGE2 receptor 4 (EP4) and the regulation of its expression plays a significant role in the cellular processes that mediate inflammatory and neuropathic pain states, triggering the cAMP/PKA signalling pathway to sensitise neurons.

DRG neurons possess long pseudo-unipolar axons which emanate from their cell body in the DRG and extend to synapse with interneurons in the spine and innervate peripheral tissues that may be over 1 metre away in humans. Although it has been long recognised that the transport of proteins to the axon terminals of DRG neurons can be relatively slow, in recent times it has been widely recognised that DRG neuronal plasticity mechanisms may be driven by the local translation of mRNAs within the axon terminal itself. Current work by us, and others, attempts to define the molecular and cellular mechanisms regulating this process. Although *in vivo* systems are still heavily relied upon to model acute to chronic pain transitions, they lack molecular detail. Compartmentalised microfluidic chambers can provide a physiologically relevant experimental model to investigate separate microenvironments within DRG neurons (i.e., cell bodies vs axon terminals), and present an accurate *in vitro* system to interrogate molecular and cellular processes driving neuronal sensitisation.

We aimed to demonstrate an *in vitro* model of sensitisation within mouse DRG neurons using PGE2 stimulation and investigate the molecular and cellular mechanisms regulating neuronal plasticity and sensitisation.

Method

Primary mouse embryonic day 16.5 were cultured *in vitro* in compartmentalised microfluidic chambers. The axonal compartment of the chamber was pre-treated with 10µM of PGE2 for 17-hours. Calcium imaging was performed in the cell body of DRG neurons, as a functional assessment of neuronal excitability, using either axonal and/or somal stimulations of capsaicin and potassium chloride (KCl).

Results

Axons displayed significant growth from the somal compartment to the axonal compartment over 6 days. Fluidic and physical compartmentalisation allowed treatment of axons alone with PGE2, mimicking an inflammatory event at axon terminals. Embryonic DRG neurons demonstrated sensitisation following PGE2 treatment, most evident after capsaicin stimulation. PGE2 treatment did not affect the number of cells responding to capsaicin or KCl in embryonic cultures.

Conclusion

These data demonstrate the utility of microfluidic systems for the study of peripheral sensitisation and to elucidate processes at a molecular scale in subcellular compartments which are not possible with *in vivo* systems or with traditional cell culture approaches.

Lay Summary Points

1. Sensory nerves become sensitised after injury and this is partly caused by the release of

inflammatory molecules, such as prostaglandin E2, which interact with the sensory nerves.
2. In order to model this process with cells in the laboratory, we compartmentalised different sections of the neurons using microfluidic culture systems to make our experiments more physiological - the cell body (where the DNA is) was separated from the axon terminal (where the neuron communicates with other neurons/the cell environment).
3. When we added prostaglandin E2 only to the axon terminal using microfluidic chambers, we found that both the neuronal cell bodies and axon terminals became sensitised. This proved that signalling processes in the axon can have an effect on the functional response of the cell body, as shown by the heightened excitability.

Understanding the link between neuropathic pain & neuronal injury after nerve injury

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Microneurography is the only neurophysiological technique that records neuronal activity directly from nerves in awake patients. Recording from nociceptive fibres provides unrivalled insight into peripheral neuronal activity and how it can relate to chronic neuropathic pain. The unmyelinated nociceptive fibres, tested by microneurography, are not assessed by conventional nerve conduction studies and are important for sensing pain. Nociceptive fibres are heterogenous, they show different stimulus-response functions and some are mechanically-insensitive in the naive state. We still have an incomplete understanding of which nociceptive afferent population and which activity is the key driver of neuropathic pain. Microneurography has the potential to answer these fundamental questions. The application of microneurography to the study of neuropathic pain is under-utilised. We believe that these techniques should be adopted more widely by the neuropathic pain field. In my poster I will describe an approach to record from nociceptive fibres and how changes in peripheral nociceptive fibres relate to neuropathic pain.

Opioid prescribing and cognitive function in a large Scottish population sample

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Background

Despite limited evidence of their long-term effectiveness, opioids are widely prescribed to treat patients with chronic pain. Opioid use may affect aspects of cognition, such as memory and processing speed. The relationship between long-term opioid misuse and cognitive impairment is well established; however, it is less clear whether opioid prescribing for treatment of chronic pain is associated with lower cognitive function. Using data from Generation Scotland, a large family health cohort, this study investigated whether being prescribed opioids was associated with lower cognitive function compared with that of people not prescribed opioids.

Methods

Generation Scotland consists of 24,000 adults aged 18-93 years when recruited in 2006-2011. At baseline, participants provided demographic and health data including answering questions about chronic pain and completing a cognitive assessment. Participants also consented to their study data being linked to their electronic health records, including prescribing data, and this was done through secure processes. Multiple linear regression was used to test whether being

prescribed opioids in the year prior to baseline was associated with lower cognitive function at baseline. A sub-sample of 9,379 participants (5,555 female, 3,824 male; mean age = 46.94 years, SD = 15.21) who were recruited from 2010 onwards was used here. Prior to 2009 the prescribing data is less complete, but individuals recruited from 2010 onwards have a full year of complete prescribing data available. Cognitive function was assessed using tests of processing speed, memory, verbal fluency, and vocabulary. A general measure of cognitive function was created from scores on these tests using principal components analysis. All analyses adjusted for age, sex, years of schooling, and deprivation. A second set of models additionally adjusted for pain severity (categorised as: none, mild/moderate, severe).

Results

501 (5.3%) participants received at least one opioid prescription in the year prior to baseline, and 249 (2.7%) received three or more (recurrent prescribing). Those who had been prescribed at least one opioid in the previous year had a cognitive function score that was 0.19 standard deviations lower than in those who were not prescribed opioids (beta = -0.19, $p < .001$). Although with reduced effect size, opioid prescribing remained associated with lower cognitive function when additionally adjusting for chronic pain severity (beta = -0.11, $p = .022$). Effect sizes were stronger when examining recurrent opioid prescribing. Participants who received 3 or more opioid prescriptions had a cognitive function score that was 0.31 standard deviations lower than those who did not (beta = 0.31, $p < .001$). The strength of association reduced slightly after adjusting for chronic pain severity, however, recurrent opioid prescribing remained associated with lower cognitive function (beta = 0.25, $p < .001$).

Conclusions

Participants who received at least one opioid prescription in the previous year had lower cognitive function than those who did not. This relationship was stronger among individuals who were repeatedly prescribed opioids in the previous year and these associations were independent of pain severity. This suggests that opioid prescribing might be associated with a cognitive decrement. Longitudinal studies are needed for confirmation.

Acknowledgements and Disclosures of Interest(s)

None.

Lay Summary Points

Chronic pain is associated with lower cognitive function (e.g., memory and speed of information processing). It is not clear why. One possibility is that individuals with chronic pain are more likely to be prescribed opioids and it is the use of opioids affects cognitive function.

This study investigated whether being prescribed opioids in the last year was associated with lower scores on tests of cognitive function in a sample of Scottish adults.

We found that individuals who were prescribed opioids in the last year had lower cognitive scores than those who were not prescribed opioids. Cognitive scores were lowest for those who were prescribed the largest number of opioids in the last year.

A theory of physiological homeostatic injury state: inference, learning and control

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Background

Chronic pain poses a significant challenge to individuals and society, and understanding the computational mechanisms underlying this condition is crucial for developing effective interventions. Since a significant proportion of chronic pain conditions have clear onset (an injury), we choose to propose a rigorous model of how and why the brain needs to have an injury state representation. Any animal's survival depends on its ability to maintain internal states, such as keeping bodily and interoceptive variables within acceptable ranges, in the face of external hazards. In this theoretical paper, we aim to address the question of how the brain achieves homeostatic regulation in the face of injury and chronic pain. Specifically, we ask: What is the nature of the computational problem that the brain needs to solve to achieve homeostasis? What are its mechanisms of function and dysfunction? And how can this theory be used to design better interventions for people in chronic pain?

Methods

We present a computational framework that models homeostasis as a partially observable Markov process (POMDP) problem and injury state as a possible state of interest in the POMDP. Noting how previous approaches like Homeostatic Reinforcement Learning[1] have failed to address the complete POMDP problem, we then provide possible solutions to it - namely Bayes-Adaptive POMDPs[2] and Active Inference[3]. We identify inherent and deliberate asymmetries in the model that may contribute to chronification. We note that synaptic plasticity can provide an understanding of the transition from injury to the persistent pain despite physiological healing of the injury and be a key in unlearning the injury state. We provide toy simulations to present the idea and then attempt to explain existing datasets or suggest experiments to test our predictions.

Results

Our theory makes three predictions regarding possible inherent asymmetries in the model: (1) information restriction (2) overshadowing of multiple cues during extinction, and (3) automatic increase in sensitivity to punishments post-injury. We define information restriction as when an agent is unable to gather enough evidence to correct its inference about being injured because of maladaptive avoidance. We further provide a normative explanation for increased punishment sensitivity post-injury. Our theory provides multiple routes to deliberate asymmetries, such as sensory habituation, attending to wrong inputs, over-avoidance, etc. We propose experimentally designs to test it in various chronic pain conditions with Bayesian model comparison. Additionally, we present a few additional predictions, such as how agents would seek to spread out their pain and devaluation after injury.

Conclusions

Our theory provides insights into the computational mechanisms underlying chronic pain and presents possible solutions for developing more adaptive interventions beyond graded-exposure therapies.

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Predicting "pain genes": multi-modal data integration using probabilistic classifiers and interaction networks

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Background

High-throughput sequencing techniques have revolutionised the identification of molecular markers for diseases. As we continue to accumulate data, we need effective strategies to integrate these datasets together, while also considering multi-modal data from external sources. Machine learning approaches are well suited to this challenge, and the availability of probabilistic models (that is – models which give the probability something belongs to a specific class) allows us to assign a probability score to each instance. Here, we trained probabilistic classifiers to produce a predictive score that a gene is a pain gene based on an expansive feature space. Features include cross-species transcriptomic datasets as well as proteomic data, network topology, genetic structure (eg. GC content), and pathway assignments. These scores were then curated into an open-access database alongside experimental datasets to facilitate the visualisation of pain-related genes in the context of their network associations, building on previous work by Perkins et al., 2013. The combination of machine learning and protein interaction networks can help inform candidate selection for downstream experimentation.

Methods

Scikit-learn (Sklearn) was used to classify "pain"/"no pain" genes in Python using a variety of algorithms, including: Random Forest, Gradient Boosting, Multi-Layer Perceptron (MLP), Logistic Regression, Naïve Bayes, and Support Vector Classification (SVC). To train each model, genes were initially labelled as "pain genes" due to their presence in the Dolorisk Priority Group (Themistocleous et al., 2023) and/or in the Pain Genes Database (LaCroix-Fralish et al., 2007). The feature space comprised transcriptomic and proteomic datasets, as well as network features from STRING DB, and genetic structure and pathway assignments from Ensembl and Biomart. Model performance was quantified by the area under the receiver operating characteristic curve (AUROC or ROC AUC) and MCC scores. In the absence of a validation gene set, gene set enrichment analyses were also performed against genes in the Human Pain Genetics Database (Meloto et al., 2018). Stacked generalization was used to generate a final ensemble from the highest performing models. Outputs were then integrated with known protein-protein interactions via STRING DB (Szklarczyk et al., 2021) using a customized database framework via R/Shiny to host and visualize high-throughput data.

Results

Network connectivity, transcriptomic fold changes in DRG after injury, and GC content were among the highest predictors of "pain" genes, while many known candidates (eg. SCN10A, SCN11A, BNDF, TNF) had the top predictive pain scores. These were alongside previously understudied candidates, including classes of ion channels, GPCRs, and immune mediators. Ranked prediction scores also show a strong positive enrichment against genes in the Human Pain Genetics Database, lending strength to this approach. Predicted pain scores, as well as their associated networks can then be integrated into an open database as a resource to facilitate candidate selection (livedataoxford.shinyapps.io/drg-directory/).

Conclusions

The use of machine learning for cross-species data integration can provide a "predicted pain score" to guide future work. The accompanying database contributes a resource to the pain community by increasing the visibility and accessibility of data. Together, this allows researchers to more

effectively select targets and will hopefully increase the likelihood of rodent to human translation, ultimately leading to better data utilisation and increased impact of each study.

Lay Summary Points

- **Overview**: Lots of sequencing data related to pain has been collected over the years, from human genetic studies, to the expression of different genes across tissues, to studying how genes are translated into proteins in rodent model systems. Here, we are bringing these different types of data together - along with other known information about each gene - to help predict which lesser known genes may also be important in the context of pain.
- **Approach**: Probabilistic models (that is – machine learning models which give the probability something belongs to a specific class) allows us to classify genes as "pain" or "no pain", and produce a probability that a gene is a "pain" gene.
- **Findings**: We find that how a gene's protein product interacts with other proteins via networks, it's expression and translation in relevant tissues, and if/how it changes in injured states can all help inform relevance to pain. We then curated these results on an online database where users can look up genes and their predictive pain scores in relation to each other.

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Interpersonal mechanisms and their effect on pain over time: two scoping reviews of factors between people with pain, clinicians, and family members

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Background
There are many psychosocial influences on pain which are thought to influence the development, maintenance, and successful management of chronic pain. Interpersonal factors are consistently identified as important both in research and by patients. This study aimed to identify the range of interpersonal factors that effect the onset, maintenance, worsening, or recovery of chronic pain through two scoping reviews: 1) between a person with pain and a clinician, and 2) between a person with pain and family members.

Methods
Two scoping reviews were undertaken. For both reviews the search included key psychosocial interpersonal factors explored in any study with a timeline for any type of pain and the following databases were searched: Embase, MEDLINE, Web of Science Core Collection, and PsycINFO. The patient and clinician search included any type of clinician, and the family search included partners/spouses and parents and children. Two authors completed screening and extraction. PPIE contributed to both the development of the search and interpretation of the findings. The full protocol is available on the Open Science Framework.

Results
Patients and clinicians: The search identified a total of 29709 records to be screened. After title and abstract and full-text screening, 28 studies were eligible for inclusion. For all psychosocial mechanisms, only small numbers of studies were found. Reassurance (three studies, n=2486),

validation (two studies, n=551), empathy (four studies, n=3370) and motivational interviewing (three studies, n=2446) were all associated with small effects on pain and functioning. The quality of this evidence is mixed. Family members: The search identified 14364 records to be screened. After title and abstract and full-text screening, 43 studies were eligible for inclusion. For partners, support type was the most common mechanism (nine studies, n=1657), with autonomous, protective, and emotional support associated with better pain outcomes. For parents and children, parental anxiety (but not depression) was consistently associated with worse child pain outcomes (10 studies, n=4942). Parent catastrophising was also strongly associated with worse pain outcomes for children (seven studies, n=1684).

Conclusions

There is very little research exploring the effect of interpersonal factors on pain over time between partners and people with pain, and clinicians and patients. Although some mechanisms have been identified as having effects on pain, the pathways by which this occurs is unknown. However, there is strong evidence for the effect of parent anxiety and catastrophising on the development of child chronic pain.

Disclosure (acknowledgments)

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Lay Summary Points

- Two scoping reviews explored the effect of interpersonal factors on pain between people with pain and 1) clinicians and 2) family members.
- Clinician review: there were not many studies, but reassurance and validation show small but significant effects in reducing pain.
- Family review: strong evidence that parent anxiety and excessive worry impact on development of child pain; very little research on partners.

Modelling behavioural changes under pain in a free-operant foraging task powered by VR

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We built an interactive virtual reality (VR)-based experimental setup that implements realistic free operant tasks where participants perform natural goal-directed actions. Compared to conventional screen-based tasks, VR-based tasks have at least four advantages. Firstly, a VR-based task inherently involves cognitive-motor interactions, including complex movements and gaits. Also, VR-based tasks generally allow participants to look around freely and produce responses through natural motor actions, which leads to spontaneous and free-operant behaviour. Thirdly, VR gives complex multisensory stimuli, including contextual stimuli. Lastly, VR provides ecological realism. We developed a technology stack that has VR, experimental pain, and real-time physiological data analysis at its core. The system was developed with an emphasis on the following specific abilities: the ability to integrate with other technologies, including invasive recording stimulation, and the highly translational capability concerning rehabilitation and therapeutic technologies. On top of this VR setup, we developed a novel free-operant foraging task with experimental pain. Participants are invited to collect fruits in a complex jungle environment where they get painful shocks when picking up certain types of fruits. We are interested in modelling two questions in participants' behaviour: what choices (painful or non-painful) the participant would make and when they would make the choice. We identified two factors that affect the choices: the distance between the fruit and the participant and the pain intensity of picking up the fruit. We fitted a computational model with the consideration of these two effects to the experimental data and found both distances and pain intensity have negative correlations with the valuation of the choices. The question of when participants perform the action is one of the core questions in the free-operant paradigm. We utilise a reinforcement learning model modified to model this specific free-operant task. In our model, we have two hyper-parameters. One could be interpreted as general fatigue, and the other is an additional pain vigour constant. The model-fitting results suggest a strong correlation between the pain vigour constant and the pain ratings. Overall, our models can capture and quantify both pain intensity and fatigue in a naturalistic task. We can then extend this basic task to answer different pain questions. We applied electric pain stimulation on both fingers and backs with different types of electrodes. The model-fitting results have shown there is a behavioural change when we only look at the differences in the distance coefficients in the choice model. The upcoming step is to introduce tonic pain to our experimental paradigm. With tonic pain stimulation, we can look at the complex interaction between continuous tonic pain and phasic pain in a realistic motor task. This will also help us introduce this technology to help chronic pain patients improve their condition in the future. In conclusion, we have developed a VR pain platform that can be used for developing novel experimental paradigms. The advantages of VR technology enabled us to implement precise quantifications of human behaviour that are close to those in real-world settings, and with these high temporal resolution quantitative models, we can integrate with more personalised closed-loop feedback therapeutics.

Factors predicting the transition from acute to persistent pain in people with 'sciatica': the FORECAST longitudinal prognostic factor cohort study protocol

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Lumbar radicular pain, commonly known as 'sciatica', is a heterogeneous debilitating condition resulting in worse pain, disability, and quality of life than low back pain alone. Sciatica is commonly understood as being caused by nerve compression. While compression forms part of the pathological process, inflammation and neural sensitisation likely play important roles in the development of neuropathic pain, often characterised by burning pain, electric shocks or tingling. Many patients recover well from sciatica however one third of patients develop chronic pain. To date, the nature of the transition from acute to chronic is not fully understood and none of the traditionally considered clinical parameters (e.g., symptom severity, routine MRI) are consistent prognostic factors. The use of a mechanism-based approach will allow better patient stratification by understanding the distinct underlying pathomechanisms at play that may influence treatment outcome and prognosis.

Aim

The FORECAST study (factors predicting the transition from acute to persistent pain in people with 'sciatica') aims to advance our understanding of mechanism-based subgroups of patients with acute/subacute sciatica and identify factors explaining the progression of pain from acute to its chronic stage using a deep-phenotyping approach through assessment of nerve function, nerve structure, inflammation as well as psychosocial factors.

Method

This prospective longitudinal prognostic factor cohort study will recruit 180 individuals aged >18 years experiencing acute/subacute sciatica within

3 months of their symptom onset. Normative data will be provided by n=168 age and gender matched healthy individuals without symptoms of sciatica/lower back pain. A diverse set of potential mechanism-based prognostic factors are measured at baseline. These include self-reported sensory and psychosocial profiles, quantitative sensory testing, blood inflammatory markers and advanced neuroimaging of lumbar nerve roots. Magnetic resonance neurography (MRN) will be performed in a subset of n=100 patients and n=44 healthy controls. The primary outcome for pain persistence will be defined with the sciatica bothersomeness index (SBI) and a Numerical Pain Rating Scale (NPRS) for leg pain severity at 3 and 12 months. To characterise subgroups of patients with sciatica, principal component analysis followed by clustering methods will be carried out. Univariate associations and machine learning methods optimised for high dimensional small data sets will be used to identify the most powerful predictors and model selection/ accuracy.

Results and conclusion

This data set will include the largest deeply phenotyped 'sciatica' cohort to date and the results of FORECAST will provide crucial information about the pathophysiological drivers of sciatica symptoms and may identify prognostic factors of pain persistence.

Neural mechanisms of cued pain anticipation during lateralised tonic pain in healthy volunteers

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Learning to avoid harm is an important facet of survival. Stimuli associated with incoming pain inherently capture attention, triggering preparatory neurobiological pain anticipation and avoidance responses (reviewed in Atlas, 2023). Following injury, incoming threats may pose a greater risk of harm to an individual. Maladaptive pain-learning mechanisms have been implicated in chronic pain development (Vlaeyen & Linton, 2012), but little is known about the neural processes supporting learning after injury.
This study aims to investigate neurophysiological anticipatory responses to cues predicting experimental pain in the presence and absence of tonic pain.

Thirty-five healthy participants with no history of chronic pain will be recruited. Participants will view a dynamic forest scene using a head-mounted display. Animated cues (foxes) are presented, differentiated by colour, followed by an object (a rock) looming towards the left or right body side or the ground. During the acquisition phase, objects looming to the left and right are accompanied by phasic pain on the corresponding site, while objects that hit the ground result in no pain. During the extinction phase, tonic pain is applied to the left or right arm, and phasic pain is not delivered. Physiological, EEG and eye-tracking data are monitored throughout. Analyses will focus on differences in physiological data and EEG power spectra for pain-predictive compared to neutral cues during acquisition, and in the presence and absence of lateralised tonic pain during extinction.

We predict an enhanced anticipatory response to pain-predictive compared to neutral cues during conditioning, indicated by increased amplitude skin-conductance responses and reduced amplitude alpha and beta band power. During the extinction phase, we predict an attenuation of the enhanced anticipatory responses. Critically, we expect changes in neurophysiological measures of extinction for cues associated with lateralised tonic pain.

In conclusion, we have developed a novel, multisensory method for exploring pain learning during tonic pain. Further analysis on completion of data collection will provide a greater understanding of the acquisition and extinction of

pain-related fear following injury. Future work could identify those with maladaptive learning processes, which may contribute to the transition from acute post-injury pain to chronic pain.

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Lay Summary Points

1. We will investigate how the brain anticipates pain in the presence and absence of ongoing (tonic) pain.
2. Healthy participants will view a virtual forest scene and encounter cues associated with short-lasting (acute) pain while their brain activity is monitored.
3. We aim to understand how the brain forms associations between incoming stimuli and pain, and how these associations change during tonic pain.

Pain avoidance learning as arbitration between body-model and world-model pain

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Pain is a crucial cognitive construct to guide flexible decision-making in dangerous environments, requiring evaluation of both the external world and our bodily integrity. The current challenge is understanding how human brains encode such cognitive representations of pain for learning avoidance behaviour. Here we consider a cognitive distinction for pain avoidance learning actions in the objective external world (i.e. world-model) or subjective bodily space (i.e. body-model). That is, whether pain exists cognitively as something 'attached' as primarily a property of external objects or of our body, being 'inferred' from the objective external world or subjective bodily experience. The body-model pain can be learnt with model-free bodily action-oriented outcomes, whilst the world-model pain also requires model-based learning on world state transition. To address this, we design a novel desktop-based virtual reality (VR) navigation task, where pain is associated either with physical actions for body-model pain or with virtual geographical locations for world-model pain. We incorporate this with a neuro-computational reinforcement learning (RL) model that arbitrates between model-free and model-based learning, which outperforms both pure model-based and pure model-free learning across distinct environments. Initial fMRI results show distinct patterns of activation, with greater sensorimotor activity in body-model pain, enhanced hippocampal activity in world-model pain, and separable prefrontal activation. This motivates experimental data to identify model parameters with human behavioural data fitting. In conclusion, our work suggests a single arbitration RL system for cognitive pain representation learning both external threatening environments

and internal bodily integrity. An implication is to interrogate how the model maps onto pain avoidance learning with cognitive functionality differences in persistent pain conditions, and therefore to inform computationally-inspired cognitive and VR therapeutic 'externalisation' strategies to treat chronic pain in humans.

Pain-associated joint cells: A roadmap to understanding and targeting the complexity of patient-reported joint pain in osteoarthritis

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Background

Osteoarthritis (OA) joint pain is a leading cause of disability and shortening of adult-working life in the UK. Despite this, pain-relieving treatments are currently limited and there is a high unmet clinical need to develop a targeted and more effective treatment for OA joint pain. Since patient-reported pain is the primary factor in opting for joint replacement, an effective therapy would reduce the requirement for these patients to undergo significant surgery. In knee OA, inflammation of the joint lining, known as synovitis, strongly correlates with the severity of pain experienced by patients. The joint lining tissue contains specialised cells (synovial fibroblasts) which regulate the degree of joint inflammation. Previously we found that synovial fibroblasts from the different knee joint sites of patient-reported pain exhibit differing biological traits, which may promote inflammation and sensory neurons axonal growth. To follow on from this work, the aim of our current study is to determine the mechanisms by which pain-associated synovial fibroblasts promote inflammation and impact sensory function. For this, we will determine whether selectively modulating the pro-inflammatory traits of fibroblasts can reduce observed effects on axonal growth and sensory neuron responses, which would support their potential as targets to alleviate joint pain and inflammation.

Methods

Patients with knee OA were recruited to the study (n = 61). Patient reported pain was recorded by questionnaire and using an anatomical knee pain map. The location and degree of synovitis was determined by MRI. Joint lining tissue was obtained from 4 sites around the knee joint and classified as either from a painful or non-painful site by referring to the patient-reported knee pain map. The traits of fibroblasts from joint lining tissue were determined by profiling their gene signatures and by analysis of their secreted factors. To experimentally model the anatomical structure of sensory neurons, we used compartmentalised microfluidic chambers that allow the fluidic isolation of axon terminals from their cell bodies, mimicking sensory terminal inputs within the inflammatory joint environment. In this set-up, axon terminals were bathed in fibroblast secreted factors and neuronal sensitisation was quantified by measuring activity dependent Ca2+ transients in the cell body compartment. Synthetic antisense oligos (ASO) were used to silence specific pain-associated genes in fibroblast cells to investigate the contribution of specific targets.

Findings

Synovitis was significantly associated with the pattern of patient-reported pain in knee OA patients. Fibroblasts from sites of patient-reported pain exhibited a different gene signature. Computational analysis predicted that this signature would likely promote inflammation, the growth and increased activity of sensory nerves. Ongoing studies with media collected from patient derived pain-associated fibroblasts have shown that axonal exposure can sensitize sensory axon terminals to stimulation in vitro. ASOs designed against target genes identified to date have selectively silenced identified targets with 87-99% efficiency.

Ongoing work

Following silencing of gene targets of interest, media containing fibroblast secreted factors will be used to treat nerve sensory axons to determine potential effects of specific gene silencing on sensory axonal activity and growth. The most successful ASO will then be tested in a mouse model of OA, which will be observed for pain related behaviours and degree of joint inflammation following administration into the joint.

Hypothesis

We hypothesise that silencing these gene targets will reverse the neuronal sensitisation and reduce pain behaviours and inflammation in an animal model of OA, providing a rationale for the therapeutic targeting of specific populations of fibroblast cells to alleviate joint pain in patients.

Lay Summary Points

The aim of this study is to determine the mechanisms by which pain-associated joint cells promote inflammation and impact sensory function of pain-sensing neurons.

We find factors released by human joint fibroblasts cells promote inflammation, axonal growth, and neuronal sensitization of murine sensory neurons

We hypothesise that silencing pain-associated gene targets in joint fibroblasts will reverse the neuronal sensitisation observed and reduce inflammation and pain behaviours in an animal model of OA, providing a rationale for the therapeutic targeting of specific joint cell populations to alleviate joint pain in patients.

Pressure Pain Thresholds: Anatomical Standardisation and a Novel Device

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Background

Pain is the dominant symptom in many forms of musculoskeletal (MSK) disease, impacting all areas of quality of life (1-3). One mechanism thought to exacerbate pain in MSK is central sensitisation (CS) (4). Indeed, pressure pain thresholds (PPTs) have been shown to be reduced in MSK conditions providing clinical evidence of CS (5,6). For PPT to be a meaningful surrogate measure of CS, a test site distant to clinical pain should be selected (1,7). The German Research Network on Neuropathic Pain (DFNS) has a reference dataset of PPT measures from the thenar eminence (TE) of the non-dominant hand (6). The disadvantage of the TE for MSK conditions is that it often lies near areas of disease. The APDP have therefore recently proposed the brachioradialis as an alternative deep-tissue site that is accessible (e.g. for MRI studies) and infrequently affected by MSK disorders. With this in mind, we have developed a device capable of delivering pressure stimuli to the brachioradialis muscle that is MR compatible and remotely operable. This study thus (A) compares conventional algometry for PPT at the TE and brachioradialis for contribution to APDP-wide standardisation efforts, and (B) evaluates our device's assessment of brachioradialis PPT against conventional algometry.

Methods

Participants were recruited from Cardiff's Psychology student population. PPTs were assessed at the non-dominant TE and brachioradialis using a commercially available algometer (FPX, WagnerTM), and at the brachioradialis using our custom device. Order of

delivery was randomised across participants. For both devices, pressure stimuli were delivered over a 1cm2 area (rubber tip) in each location, at a rate of 50kPa/s. PPTs were calculated as the arithmetic mean of three trials (6,7). Realtime pressure information was displayed and logged (comDebug, Windmill Software; LabChart, ADInstruments). Custom device pressure was calibrated by opposing our device with the algometer, and creating a linear function of the pressure relationship. Pressures were converted to kPa and logged where indicated.

Results

Of the 18 participants, most were female (16/18) and right-handed (14/18), with a mean age of 20 years (s.d. 1.8). Raw PPTs (kPa), mean (sd): brachioradialis device, 150.7 (47.7); brachioradialis algometer, 188.0 (99.7); TE algometer, 275.1 (108.9). All TE algometer PPTs except one lay within DFNS's reference range (215-570; 95% C.I.) (6). Coefficient of variance values for logged data: brachioradialis device, 5.5; brachioradialis algometer, 9.0; TE algometer 7.3. Significant ($p<0.05$) PPT intercorrelations (logged data) were found between algometer brachioradialis and device brachioradialis ($R=0.57$), and between algometer modalities ($R=0.86$). The rate of stimulus delivery for algometry was below the 50kPa/s target (brachioradialis rate, mean=37.4 kPa/s, s.d.=8.4; n=14; thenar rate, mean=40.7 kPa/s, s.d.=5.7, n=14) and because of set-up challenges, lower again for the custom device (mean=20.7 kPa/s, s.d.=14.4, n=18).

Conclusions

(A) Standard algometry-assessed brachioradialis PPTs have strong intercorrelations with equivalent assessment at TE site. Further work, pooling APDP PPT brachioradialis data and including a patient group, is required to assess the power of brachioradialis PPT assessment as a surrogate measure of central sensitisation. (B) Our custom device resulted in a tight clustering of PPTs, with fewer outliers than algometry assessed measures, and with a positive intercorrelation with algometer assessed PPT. Further work (as with A) is required to evaluate its suitability as a surrogate measure of central sensitisation.

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Lay Summary Points

1. People with musculoskeletal conditions sometimes experience pain at greater severity than the direct damage to their joints, bones and muscles would predict. The reason for this is still unclear, but one mechanism that is well supported by human and animal studies is central sensitisation. Central sensitisation is a state in which pain-processing nerve cells in the spinal cord and brain are over-responsive to pain input.

2. Central sensitisation is difficult to directly measures in humans. One way of inferring the degree of central sensitisation, especially suited to musculoskeletal conditions, is to look at pain sensitivity to blunt pressure at a site not directly affected by disease. The pressure at which a person experiences pain is their pressure pain threshold.

3. We have developed a device that can deliver blunt pressure to a muscle of the forearm, the brachioradialis. The brachioradialis is rarely affected by musculoskeletal disease and might therefore be a good option for research and clinical assessment of central sensitisation. We show that our device and conventional tools assessing pressure pain thresholds at the brachioradialis compare well with existing methods used to assess pressure pain on the palm. Our data will be pooled with that of other APDP researchers to help us to decide if brachioradialis pressure pain thresholds are a good substitute measure for central sensitisation.

Embedding Patient and Public Involvement in the Alleviate Pain Data Hub

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Alleviate is the data Hub for the Advanced Pain Discovery Platform (APDP). Alleviate will create an online, safe, Hub to access pain data. This will be a key resource for the national pain research community and for people living with long term pain. Patient and Public Involvement and Engagement (PPIE) has been embedded within the Alleviate Pain Data Hub from inception and has had significant impact on the development of the Hub & the research team. Alleviate aims to tackle pain by creating standardisation of pain research data and making these data more discoverable and re-usable by following FAIR (Findable, Accessible, Interoperable and Re-usable) principles. The Alleviate team have involved people living with pain in different ways, aiming to maximise diversity and inclusion. Involvement in the Alleviate team The Alleviate PPIE strategy was developed by patient partners to be open and inclusive, with different options for people living with pain to be involved and engaged with the Hub. The lead patient partners are co-investigators on Alleviate and have been part of the research team from inception, helping inform its design. The patient advisory group attend all Alleviate team meetings, to provide updates on PPIE and to be involved in the progress and activities within the Hub's development. Involvement community The Alleviate Pain Community was developed to engage with people living with pain across the UK. This is an online community of people living with long term pain who are interested in learning about pain research and the development of the Pain Data Hub. The online community receive Alleviate newsletters, which provide updates on the development of the Hub. Alleviate have hosted open meetings with the Community, to raise awareness of what the Data Hub is and how this can provide public and research benefits. The Community have also been involved in completing surveys to provide feedback and input into the Data Hub and related projects. Involvement training for the research team The lead patient partners on Alleviate developed training for the Alleviate research team and researchers across the APDP. This training session included sharing a personal journey of pain and the impact that living with pain has on daily life, followed by a session on how to support, empower and grow PPIE in pain research. This highlighted the importance of empathy and an understanding of pain, to ensure people with lived experience are valued members of the research team. Video extracts from this talk are now available online and have been shared in a social media campaign to raise awareness of PPIE in pain research. Involvement in communication strategies The PPIE team have been involved in the development of the Alleviate communication strategies. This includes the structure and content of the Alleviate webpages, which have a dedicated PPIE section. This includes a Frequently Asked Questions section on the website as the PPIE team highlighted that an important part of engagement is providing information in an understandable format. Impact The PPIE team give the Alleviate team further motivation to make the Hub successful through the sharing of their lived experiences of dealing with daily chronic pain. These life experiences provide a different perspective to the Hub development team, which continually re-adjusts the way information is communicated round the Hub. This covers writing papers, abstracts, blogs, or updating the website; the suggestions from the PPIE members and their world view help to make the Alleviate team's writing widely accessible and more complete. PPIE in Alleviate ensures that diverse voices of people living with long term pain are heard.

SenseCheQ : Developing novel quantitative sensory testing approaches for early detection of neuropathy

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Background

Chemotherapy-induced peripheral neuropathy (CIPN) affects almost 30% of patients. It can cause chronic pain, numbness, poor co-ordination, and autonomic symptoms and is ranked as one of the worst side effects of cancer treatment. There is currently no effective treatment or preventative strategy, and chemotherapy dose-reduction or agent switching are considered when CIPN is detected. Diagnosis often occurs late as the initial symptoms are subtle and peculiar, standard clinical examination has low sensitivity for detection of nerve damage and patients are often focussed on the impacts of cancer. Formal quantitative sensory testing (QST) has shown that there are changes in thermal and vibration detection thresholds in patients that develop neuropathy (Kroigard et al 2020). However, QST is not used in a routine clinical setting because it requires time, skilled practitioners and relatively expensive equipment. The SenseCheQ project aims to establish the feasibility of a novel sensory testing approach allowing patients to test their own nerve function during their treatment in their homes.

Methods

We have developing compact thermal (Peltier-driven, ThermoCheQ,) and mechanical stimulators (Haptic actuator, VibroCheQ) to allow identification of warm/cool and vibration detection thresholds (WDT, CDT and VDT, respectively). These have been compared with standard QST devices (Rydel-Seiffer calibrated tuning fork and Medoc TSA-II Thermal stimulator) in healthy volunteers (aged 18-69). After ethical approval from the University of Bristol, participants were consented for testing. Stimuli were applied to the forefoot, ankle, knee and thumb. To model neuropathy, subjects had blockade of their superficial peroneal nerve (1% lidocaine, 5mls).

Results

VibroCheQ has been tested on 94 healthy participants. We delivered both ascending and descending ramping vibration stimuli (at 64 / 128Hz, 0-30µm amplitude) with subjects being better at detecting ascending ramps. The distal test sites had greater sensitivity for vibration detection. There was a poor correlation between VibroCheQ measures and the tuning fork at the most sensitive areas, because of a floor effect seen with the tuning fork. There was excellent test-retest reliability for VibroCheQ over a period of 1-3 months (Thumb - Pearson's correlation >0.9, $P<0.001$). Following nerve blockade (n=12) both VibroCheQ and pinprick testing showed a loss of sensory function ($P<0.001$) over time that was not detectable with the tuning fork. A comparison of young (age 21.4, n=25) and older subjects (age 58, n=18) showed graded deterioration in VDT in the feet with aging but a preservation in the hands. The hands also showed a lower variance in VDT in both age groups.

Conclusions

VibroCheQ is a simple to operate, cheap, robust and reliable tool to quantitatively assess sensory function in heathy subjects. It shows clear advantages over the calibrated tuning fork and can track acute loss of nerve function.

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Acknowledgements and Disclosures

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Lay Summary Points

Chemotherapy can cause damage to nerves leading to persistent pain and disability which is one of the most feared complications for survivors of cancer treatment.

Current methods for detecting this sensory nerve damage are not practical for normal clinical use and so it is a hidden problem that is often detected too late for prevention

The SenseCheQ project aims to develop simple to use devices to allow patients to test their own nerve function at home and we present (and demonstrate) our initial findings.

Multiplexing human microneurography: A route to improved diagnostics and mechanistic understanding in Chronic Pain

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Background

Microneurography (MNG) is the only method to directly measure nociceptor activity in people. In MNG, an electrode is inserted through the skin into a peripheral nerve enabling extracellular recordings of neural activity to be made. MNG offers unparalleled opportunities to dissect pain mechanisms and should therefore hold a key role in diagnostics and monitoring responses to therapy, both during drug development and treatment.

MNG is, however, encumbered by technical difficulties which have limited its application. These include small signal to noise ratios and the skill set required to locate the nerve. The technique is therefore regarded as a specialist research tool.

To address these issues, we are developing multi-contact electrodes for human microneurography so that established clustering techniques can be used to increase both data yields and richness. Here, we validate this approach in rodents.

Methods

Experiments conformed to UK Animals (Scientific Procedures) Act 1986. Rats were anaesthetized with isoflurane. The saphenous nerve was exposed, and a mineral oil pool created. Electrodes were introduced into the saphenous nerve using a micromanipulator. The receptive fields of cutaneous afferents on the foot dorsum were stimulated electrically & mechanically for classification and then thermally, using a NdYAP laser, or with formalin (2.5%, 30uL).

Recordings were made with multi-contact-silicon electrodes (Neuronexus and Cambridge Neurotech), and our own multi-contact MNG probes. Our novel electrodes were produced by Newcastle university based upon their multi-contact electromyography electrodes, which have already received approval for use in healthy volunteers.

The electrodes are fabricated on silicon wafers using semiconductor processing techniques where the recording surfaces are sandwiched between layers of Parylene-C, a biocompatible polymer. They are then bonded to standard MNG needles using biocompatible adhesive.

Signals were filtered (0.3-6KHz) and acquired using Intan RHD2200 chips and visualized with OpenEphys. Following artifact removal, units are clustered using Kilosort and curated in PHY. Further analysis and data presentation were performed using Matlab.

Results

The commercially available silicon multi-contact electrodes enable single unit responses to be extracted from multi-unit recordings. The utility of this approach is demonstrated in two examples. Firstly, injection of formalin into the receptive field of a C-nociceptor causes ongoing activity after ~20mins, corresponding to the second behavioural phase of the formalin test. Secondly, laser stimulation of the paw elicits energy dependent discharges in C fibre nociceptors, where increasing energy results in increasing recruitment and discharge at C fibre latencies. Importantly, the novel electrodes also resolve clear C fibre potentials over multiple channels, demonstrating their functionality.

Conclusions

We extend our previous work, demonstrating single unit resolution of C-nociceptors recorded using multi-contact electrodes. This activity is elicited using diverse stimuli relevant for translational pain medicine. Importantly, we demonstrate functionality of novel multi-contact electrodes for microneurography. Future work will improve contact geometry to optimise for nociceptor clustering and obtain approvals required for human use.

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Acknowledgements and Disclosures

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Quantifying the Effect of Lidocaine on Mouse C- and Aδ-fibre Nociceptors Using Single-Neuron Electrical Threshold Tracking

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Background

Nociceptors are a class of primary afferent neurons that signal potentially harmful noxious stimuli. An increase in nociceptor excitability occurs in acute and chronic pain conditions. Single-neuron electrical threshold tracking can quantify nociceptor excitability (1,2). Electrical threshold tracking could be used in chronic pain patients to confirm whether a therapeutic agent is reducing the hyperexcitability of nociceptors. Furthermore, changes in electrical threshold could be used as a biomarker of efficacy for novel analgesics targeting nociceptors. We have recently developed a plugin for the Open Ephys platform called APTrack, to allow for single-neuron electrical threshold tracking (1). Our aim is to provide validation for APTrack and electrical threshold tracking when combined with pharmacological interventions.

Methods

C57BL/6J mice of 2-4 months of age, and both sexes, were used for these experiments. Electrophysiological recordings were made from C- and Aδ-fibre nociceptors in the mouse skin-nerve preparation, using the teased fibre method in the saphenous nerve. Data were bandpass filtered (0.3-3kHz), 50/60Hz noise filtered (Hum-Bug), and then acquired at 30kHz using the Open Ephys system. Electric stimulation was provided using a concentric bipolar electrode and a Digitimer DS4 constant current stimulator. Nociceptors were classified by their response to thermal and mechanical stimuli, and their conduction velocity. Localised exposure of lidocaine to the receptive fields of C- and Aδ-fibres was achieved using custom aluminium isolation chambers.

Results

Data collection is ongoing, but initial experiments show localised exposure of 1mM lidocaine to the receptive fields of C- (n = 1) and Aδ-fibre (n = 2) nociceptors causes an increase in their electrical thresholds of greater than 50% in each fibre. The study will target a sample size of 12 fibres, based on power analysis conducted after initial experiments ($d = 0.8$, $\alpha = 0.05$, $\beta = 0.8$, paired t test). Experiments examining the dose-response relationship between lidocaine concentration (vehicle, 0.1mM, 0.3mM, and 1mM) and nociceptor electrical thresholds are underway. Initial results show electrical threshold increases in a dose-dependent manner with lidocaine concentration (n = 1, Aδ-fibre).

Conclusions

Lidocaine increases the electrical threshold of C- and Aδ-fibre nociceptors. Electrical threshold tracking may be a sensitive method for examining the effects of pharmacological intervention on nociceptor excitability. Results showing whether there is a dose-dependent effect of lidocaine on nociceptor electrical threshold will be presented.

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Disclosures of Interest

GWTN is a BBSRC Collaborative Training Partnership Doctoral Studentship with the University of Bristol and Eli Lilly and Company.

Lay Summary Points

Nociceptors are neurons that detect potential harm from painful stimuli - we want to measure

how their excitability changes when they are stimulated or inhibited.

We have developed a tool that tracks the electrical threshold of nociceptors in humans and animals, allowing us to monitor changes in excitability over time. We aim to test its sensitivity for measuring the effects of drugs.

Using lidocaine, a common local anaesthetic, we have shown that electrical threshold tracking can detect dose-dependent changes in neuronal excitability in real-time. This is significant as our tool may help confirm if a treatment reduces the hyperexcitability of pain-sensing neurons in patients.

Engineering a path to SenseCheQ nerve function via home quantitative sensory testing

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Background

Chemotherapy for cancer commonly causes neuropathy which can be both chronic and painful. It is known that the chemotherapy causes loss of function in sensory nerves in a glove and stocking distribution. This loss of function is detectable using formal quantitative sensory testing (QST) and the most sensitive modalities are vibration (reflecting A-beta-fibre function) and cold / warm detection (reflecting smaller A-delta and c-fibre activity). While there is a rationale to use this sensory testing, to identify developing neuropathy and make changes to chemotherapy management, this is not done in clinical practice because of the challenge (in terms of time, cost and expertise) in conducting formal QST.

The SenseCheQ project has a goal of developing a simplified form of QST, that can be deployed by patients to test their nerve function in their home. This would enable repeated testing during their cancer treatment, to make a longitudinal assessment of changes in nerve function, potentially facilitating early and objective diagnosis. A key component of this project is the engineering challenge to develop a cheap, portable, simple, safe, convenient and accurate test that will be acceptable to patients.

Methods and Results

We have embarked on an iterative, collaborative design process, to identify the key characteristics of existing testing approaches for vibration and thermal testing and implementing them in the final integrated SenseCheQ device. This has also involved extensive and ongoing discussions with our PPIE group to determine what form factor, user interface, duration of testing and stimulation sites would be most likely to be effective and compatible with their needs on their cancer treatment pathway.

Having determined our initial design specification and limiting parameters we have implemented a series of solutions using off-the-shelf components and 3D printed housings. This design work-package is most advanced for the vibration component – VibroCheQ. This uses Arduino microcontrollers that are interfaced with peripheral haptic (vibration) device in a custom housing to provide a simple but tightly controllable method for delivering vibration stimuli (ranging from <1µm increasing into the range of 100µm across a wide range of frequencies). The subjects respond to the ascending or descending stimuli via a subject-actuated stop button, to self-report detection thresholds. This has been iterated into a simple test routine that takes less than 3 minutes to conduct per site, can be applied reliably to upper or lower limb and has better resolution and sensitivity at the low end of the detection range than the calibrated tuning fork, with the additional advantage that we can demonstrate that the descending and ascending ramps identify distinct thresholds reflecting different aspects of the psychophysics.

Conclusions

We have demonstrated proof of principle and plan to improve this initial VibroCheQ device with a unique feature set and testing paradigm. We have followed a similar path and set of solutions for the ThermoCheQ device but this time using Peltier devices to deliver precisely controlled thermal stimuli. We will demonstrate both devices at the meeting and will plan to collect a dataset from attendees to inform our future developments as we look to merge the capabilities into a final prototype for testing in proof-of-concept patient studies.

Lay Summary Points

Chemotherapy can cause damage to nerves leading to persistent pain and disability which is one of the most feared complications for survivors of cancer treatment.

Current methods for detecting this sensory nerve damage are not practical for normal clinical use and so it is a hidden problem that is often detected too late for prevention

The SenseCheQ project aims to develop simple to use devices to allow patients to test their own nerve function at home and we present (and demonstrate) our initial findings.

Novel genetic associations for chronic pain by optimised control cohorts using the 450K WES in UK Biobank

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Introduction

Chronic pain is a complex disease with varying aetiology, clinical manifestation, and polygenic architecture. We performed genetic associations within a broad spectrum of pain phenotypes using optimized control groups. The main objective of our research application aims to understand the genetic architecture of chronic pain, and its interaction with other risk factors and protective variants. Given the heterogeneity of chronic pain and co-morbidities, we also explored the stability of genetic associations using optimized control cohorts.

Results & Methods

For this study we used the UK Biobank data showcase category 154 online pain questionnaire data as well as 47 ICD9 and 226 ICD-10 diagnostic codes from 129 pain related data fields with 167,228 participants as well as pain medications like Pregabalin to identify subgroups of individuals with musculoskeletal pain (osteoarthritic pain), neuropathic pain (painful diabetic neuropathy), visceral pain and chronic widespread pain (fibromyalgia). Based on counts in each category we also built 40 groups of aggregated ICD-10 codes in case counts where below 100 (rare polyneuropathies). Further, we defined several 'pain-free' control cohorts by the absence of any chronic condition across all available pain

phenotypes that allowed us to balance the group sizes in cases vs. controls. This includes control groups with no diagnosis, operation/procedure codes, no prescription medication, no chronic pain (150,374 EIDs), no acute pain (94,998) as well as a group with additional no OTC medications (69,617). Genetic associations have been performed using PLINK v2.00a2.3LM, REGENIE v2.2.4 and MAGMA v1.09. Rare variant counts have been calculated to identify homozygous minor allele carriers within a range of 1-500. Further, we annotated respective variants with dbNSFP, dbSNP and SNPeff to predicted functional consequences such as amino acid exchanges or frameshift loss of function mutations.

Conclusions

We found that optimization of the control and pain cohorts lead to the identification of robust novel genome-wide significant loci in osteoarthritis like SDCCAG8 relevant for microtubule organization, TCF4 for neuronal differentiation as well as amplification of signals like WDR46 of formerly not genome wide statistical significance reveal a higher overall confidence in the validation of novel therapeutic targets. Moreover, homogeneous control cohorts improved statistical power and biological specificity of genetic associations.

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Acknowledgements

This research has been conducted under UK biobank application ID 64765, a major biomedical database, please find detailed information under www.ukbiobank.ac.uk.

Lay Summary Points

1. We identified novel rare and protective variants for chronic pain conditions.
2. Carefully defining the ”control” cohort improves the outcome of genetic association studies.
3. Hard threshold for statistical significance hide biologically plausible genetic associations, which are often used in catalogues of genetic associations.

Sensing behaviour change in chronic pain? A scoping review of sensor technology for use in the wild

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Background and aims

Digital technologies for capture of data on physical activity in humans have developed over several decades, with substantial improvements in ease of use, methods of capture, and analysis. This scoping review aimed to provide an up to date description of sensor units employed to capture pain behaviours, physiological responses, and other biodata used to study the experience of chronic pain both in laboratory and naturalistic settings.

Methods

We searched PsychINFO, Web of Science, PubMed, from inception to July 2022. Our primary outcome was to map sensors by type, target, research application, and challenges imposed by each technology. Additionally, the characteristics of the sensors were reported in relation to the purpose of measurement (e.g. detecting pain) and to the complexity of the technological setups. This scoping review adopted the scoping review framework by Joanna Briggs Institute.

Results

60 references were included. There were four major categories of wearable sensors aimed at monitoring "physical activity", "autonomic activity", "muscle activity", and "Multi-dimensional activity". Sensors were used to detect pain, to

recognise and measure pain behaviours, to monitor frequency and intensity of physical activity, sleep quality, and to study the association between biodata and psychosocial outcomes.

Conclusions

In the last decade the number of studies involving these technologies have grown exponentially and yet we felt that the growth of wearable technology has largely outpaced the growth in the demand from chronic pain research. The current availability of technology provides a vast number of potential research and clinical applications and some suggestions are proposed.

Lay Summary Points

- Technology offers possibilities for quantification of behaviours and physiological changes of relevance to chronic pain. Beyond lab studies, what wearable sensors and devices are suitable for the wearer's own environment?
- We conducted a scoping review of wearable and passive sensor technologies that sample data of psychological interest in chronic pain, including in social situations.
- We compiled a list of research suggestions that can promote innovation in future studies

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Integrative multi-omics analysis of human synovium to uncover novel pain mechanisms in knee osteoarthritis

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Knee Osteoarthritis (KOA) is a chronic, painful joint disease which is age-related and characterised by pain, osteophyte growth and progressive loss of articular cartilage. Chronic pain is the most prominent disabling symptom of KOA, and at its most severe can necessitate total joint replacement. Whilst the mechanisms are not completely understood, accumulating evidence points toward synovitis and bone marrow lesions as being key local factors connected with pain in KOA. The overarching aim of this study is to perform deep molecular characterization of human synovium tissue to uncover novel mechanisms underlying KOA pain and to identify new novel targets for analgesic drug development. We used a hypothesis-free approach to generate the genetics, transcriptome, and proteome landscape of 60 synovium samples from patients undergoing total knee replacement (symptomatic KOA) and 60 synovium samples from post-mortem donors (non-symptomatic KOA) from the SFH/UoN Human Joint Tissue Repository. Our analysis identified dysregulated genes/proteins and novel biological process that may be important for driving pain in symptomatic versus non-symptomatic KOA. By integrating significant findings across the 3 omics data layers in synovial samples we discovered 13 candidate targets and 4 key biological pathways of interest for further assessment.

Lay Summary Points

We performed deep molecular characterization of human synovium tissue to uncover novel mechanisms underlying KOA pain and to identify novel targets for analgesic drug development.

We generated one of the largest genetics, transcriptome, and proteome landscape of synovium samples from 60 patients undergoing total knee replacement (TKR, symptomatic KOA) and synovium samples from 60 post-mortem donors (PM, non-symptomatic KOA).

Multi-Omics integrative analysis of 3 data layers identified 13 putative pain targets and 4 pathways of interest for further evaluation.

Cancer-related pain: a review of patient education to challenge a dominant biomedical view

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Background

Cancer-related pain is a significant and growing problem for those living with and surviving cancer, requiring biopsychosocial (BPS) management independent to treatment of underlying disease. Best practice pain management has been established in the field of chronic non-cancer pain (CNCP), starting with education that is grounded in pain science. Consideration of this approach for cancer-related pain management is scarce, yet there is strong rationale for its use. The aim of this study was to explore the use of pain science in explaining cancer-related pain to patients through education, facilitating communication of a BPS phenomenon.

Methods

An exploratory narrative review was used to unveil a practice in its inception and deepen understanding of the field, capturing all available literature defined by inclusion of target concepts of pain education. A descriptive synthesis of the findings was interpreted and critiqued in the discussion. Methodological quality was included to assess the impact on findings, not as criteria for exclusion.

Results

Pain science education is poorly established in the cancer pain management literature. 8 studies met the inclusion criteria and were difficult to locate,

akin to finding a needle in a haystack. Conclusive findings from a small evidence base of variable design and quality were limited, but positive individual outcomes provide rich detail for clinical application and a plausible basis for further research. Impending results promise a firmer foundation from which to raise awareness, encourage research and establish structure.

Conclusions

To the author's knowledge, this is the first review to explore the use of pain science in explaining cancer-related pain to patients through education. It provides a basis to illuminate this field and focus and develop the evidence-base for clinical practice. A biomedical model continues to dominate the management of cancer-related pain when an evidence-base exists for reconceptualising and communicating a BPS phenomenon through high quality education. The evidence base is in its inception, but the future potential is significant.

Acknowledgements and Disclosures of Interest(s)

The authors report no competing interests to declare, nor funding associated with this work.

Lay Summary Points

This study explored the way that clinicians use education to explain cancer-related pain to service users. A review of the existing literature focussed on whether the most up to date science of pain was used and whether this helped to communicate the complexity of the experience.

A biomedical approach continues to dominate the management of cancer-related pain when an evidence base exists for expanding its management using high quality education.

This review revealed a field in its inception, but it provides a starting point to focus and develop the evidence base, in communicating a more complex and multidimensional pain experience for service users.

The effects of healthy ageing upon spinal somatosensory networks in rats

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Pain Centre Versus Arthritis, School of Life Sciences, University of Nottingham, Nottingham, UK

Background

Pain perception changes across the life-course in humans, with reduced sensitivity to touch in old age, but increased incidence and severity of pain. However, most preclinical pain research only studies young adult animals, meaning the effects of healthy ageing on sensory processing remain largely unknown. Given the massive clinical burden of pain and the growing size of the ageing population, this represents a significant knowledge gap. The spinal cord dorsal horn (DH) is a key area in pain processing, combining ascending input from the body with descending control from the brain to set the intensity of pain. The DH is a layered structure, and each layer plays a different role in pain processing. However, traditional methods to record spinal pain signals rely on the activity of single cells in the deep DH as a proxy measure of the activity of the whole spinal sensory network, missing much of the complexity. We have recently developed in vivo multi-electrode array (MEA) recordings in rats, enabling simultaneous detection of neuronal activity across the whole DH. To determine the effects of healthy ageing on spinal somatosensory signalling, we assessed basal pain thresholds in aged and young adult rats, then utilised in vivo MEA recordings to compare DH sensory network activity in response to mechanical and electrical stimulation of the hindpaw.

Methods

50% paw withdrawal thresholds (PWT) were determined via application of von Frey filaments (vFH; 2-26g) in aged adult (AA; 18-20 months) and young adult (YA; 2 months) male Sprague Dawley rats. In vivo spinal recordings of neuronal activity

across the whole DH were obtained via 16-electrode MEAs (NeuroNexus) under anaesthesia. The L4/5 lumbar spinal cord was exposed via laminectomy, and whole DH responses to a range of mechanical (2-26g) and electrical (0.01-5mA) stimulations of the hindpaw were recorded. Threshold crossings (spiking events) at each electrode were sorted by response latency (Aβ=3-11ms, Aδ=11-90ms, C=90-300ms), and region (superficial, intermediate, & deep DH), then compared between age groups.

Results

Aged rats were far more sensitive to touch than young adult animals (Median 50% PWT; AA = 7.3g; YA = 14.5g, $p<0.0001$). However, whole DH neuronal activity in response to painful touch was actually significantly lower in aged rats, with notably less sustained activity during stimulation. In young adult rats, greater activity was detected in response to more forceful touch stimulation, whereas in aged adult rats responses were similar for all stimuli. Fast responses (3-11ms) to low intensity electrical stimuli (0.5mA) were significantly smaller across the whole DH in aged rats (-41%, $p<0.05$), most prominently in the intermediate region where the Aβ fibres that carry fast messages about light touch terminate (-51%, $p<0.001$). Painful electrical stimuli (5mA) evoked significantly less slow whole DH activity (90-300ms, -52%, $p=0.05$) in aged rats, most markedly in the intermediate (-70%, $p<0.01$) and deep (-61%, $p<0.01$) regions.

Conclusion

We observed smaller responses to painful and non-painful mechanical and electrical stimuli in aged rat spinal sensory networks. Some of these differences may be due to changes in pain fibre myelination and conduction velocity in aged rats, as has previously been reported in both animals and humans. These smaller responses with ageing likely contribute to age-related changes in somatosensation, and could potentially reflect reduced intrinsic spinal inhibition, leading to greater behavioural pain sensitivity. Ongoing studies investigating the underlying anatomical changes will shed further light on how healthy ageing alters sensory processing in the spinal cord dorsal horn.

Acknowledgements & Disclosures of Interest(s)

The authors thank Eli Lilly for supplying aged rats. This work was supported by Versus Arthritis (grants 18769, 20777). All authors have no conflicts of interest to declare.

Lay Summary Points

1. In humans, we know that how we feel pain changes as we age. Older people tend to have greater sensitivity to pain. Despite this, most basic studies in pain research only use young adult animals. This means we don't know why this change happens. We tested older rats and found that, as in humans, healthy ageing leads to higher pain sensitivity.
2. The spinal cord dorsal horn is a key site in pain processing, mixing signals from the body and brain to set the strength of pain. Our new method allows more detailed recording of electrical activity in the spinal cord dorsal horn. This means we can now measure how this vital network of nerve cells responds to touch and electrical stimulation of the hind paw in anaesthetised rats.
3. We used a wide range of touch (mechanical) and electrical stimulation of the hind paw and compared responses in aged and young adult rats. Surprisingly, we found much lower activity in the older rats. This could mean less inhibitory activity, which leads to more pain. We are now using other methods to find out where and why this happens.

Measuring the effect of immersive virtual reality (VR) in people with persistent low back pain–what can quantitative sensory testing tell us?

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Background

Persistent pain is considered as a complicated multisensory and multidimensional neurophysiological phenomenon that is accompanied with psychosocial manifestations. In addition, Persistent musculoskeletal pain and particularly persistent low back pain is considered a nociplastic pain that develops as a result of distorted nociception without a clear indication of actual or susceptible tissue damage. Immersive VR including embodiment and distraction-based immersive VR are currently being used as a potential tool for treating different types of persistent pain, including persistent low back pain. Patients can actively interact with an artificial environment through Immersive VR in a manner expected to decrease their persistent pain. In order to evaluate its impact, normally patient reported outcome measures are utilised. However, we propose that quantitative sensory testing (QST) is appropriate alongside these measures. QST allows evaluation of the sensory processing within small and large afferent nerve fibres or different afferent and efferent pathways. Also, it can provide data about the central processing of sensory inputs and can reveal both the strength and inhibition of neural transmission, which are essential aspects of pain hypersensitivity and persistence of pain. Aim: To evaluate the impact of distraction- and embodiment-based Immersive VR approaches utilising QST.

Method

A quasi-experimental, repeated measures, two-arm randomised pre-test-post-test design will be conducted.

Discussion

Immersive VR may stimulate subconscious motor adaptation, which may affect patients' physiological and motor behaviours, consequently decreasing pain. Also, immersive VR might change how patients might feel towards their bodies, assumably due to improving spatial processing in the central nervous system, since spatial processing is affected in individuals with persistent low back. The immersive VR may provide a significant positive effect on pain perception. Both embodiment and distraction-based approaches are shown to provide analgesic effects and are thus commonly used with persistent pain patients, including persistent low back pain patients. However, the mechanism of effect is still unknown. QST has been used to quantify the processing of nociceptive information through the endogenous descending pain modulatory system and the spinal wind-up of pain as a part of the endogenous ascending pain modulatory system. This will be done using two different elements of QST: the conditioned pain modulation (CPM) paradigm and the temporal summation (TS) paradigm. Both CPM and TS paradigms are valid and reliable QST measurements for endogenous pain modulatory systems. Endogenous descending modulatory system (top-down pain processing) will be evaluated using CPM. Two different types of nociceptive stimulus are delivered, a cold-water bath as conditioning stimulus and a heat pain as a test stimulus. The spinal wind-up of pain is a phenomenon that occurs in the endogenous pain modulatory system and its pathway at the spinal level (also known as the bottom-up pain processing). It will be evaluated using TS, which refers to an increase in the perception of pain resulting from repeated exposure to noxious stimuli. It can be argued that an analysis of top-down pain processing as well as bottom-up pain processing will aid us in understanding how immersive VR has an effect on pain.

Lay Summary Points

Both immersive virtual reality (VR) approaches that involve being fully engaged in the virtual environment, and that distract the mind away from

pain successfully provide pain relief to people with long-lasting lower back pain. However, we don't fully understand how exactly these approaches work.

Immersive VR is often a combination of distraction (looking at a relaxing scene) and embodiment (being fully engaged in the virtual environment). That's why it's quite difficult to distinguish their impact separately. There isn't enough evidence comparing these two approaches. However, both methods have been shown to decrease the severity of pain and improve the overall quality of life for people with long-lasting lower back pain.

When studying the effects of immersive VR on pain, researchers often rely on what patients report about their experiences. These patient-reported outcome measures (PROMs) are helpful in understanding changes in different aspects of pain-related behaviours. However, PROMs do not explain the physiological processes happening in the body when using immersive VR. To better understand these processes, we suggest using a method called quantitative sensory testing (QST) in addition to PROMs. QST provides valuable information about how the central pain processing systems in our body are affected and how the two different VR approaches impact them. QST also helps us understand how participant characteristics such as anxiety, fear avoidance, catastrophizing thoughts, and pain duration play a role in response to immersive VR. By combining PROMs with QST, we can gain a more comprehensive understanding of how immersive VR affects pain and the factors that influence its effectiveness. So we can figure out how to improve the interventions and the way they are provided in the most effective and suitable way possible.

Is Central Aspects of Pain a state or trait in people with chronic knee pain?

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ACADEMIC ABSTRACT

Background

Discrete pain mechanisms contribute to various extents at different times to an individual's pain experience. The Central Aspects of Pain (CAP) questionnaire measures a unitary factor associated with fatigue, cognitive difficulty, catastrophising, anxiety, sleep disturbance, depression, neuropathic-like and widespread pain. Pain severity fluctuates over time. The central nervous system modulates pain, but it is unclear how central aspects of pain fluctuate. Modifiable central aspects of pain are potential treatment targets.

Aim

To determine if CAP scores change (state) or are stable (trait) over time in individuals with knee pain.

Methods

Individuals with knee pain from the Investigating Musculoskeletal Health and Wellbeing cohort with 3 annual follow ups were included. Chronic pain was assessed in 2155 participants by questionnaire including CAP, NRS pain intensity, and McGill Pain questionnaire.

Results

At a group level median pain scores did not change over time. However, all pain variables showed a statistically significant minimally clinical important change over time on an individual basis (P≤0.01). Median (IQR) CAP scores also differed little between time points (all medians 8 or 9). However significant heterogeneity was found within individuals over time (Friedman test; χ^2=210.131, 3 df, p<0.001). Up to 50% of participants displayed increases or decreases in CAP scores each year that were greater than the Minimal Important Difference of 2.

Conclusions

On a population level CAPbehaves as a stable trait over. However, CAP, along with NRS and McGill demonstrated clinical important changes over time on an individual basis, and therefore might represent a modifiable state. Further investigation of the mechanistic underpinning of CAP's unitary factor may reveal novel therapeutic targets, and CAP is a sensitive measure by which to evaluate interventions that address those targets.

Acknowledgements

This work was supported by Versus Arthritis (Centre initiative grant number = 20777) and NIHR Nottingham Biomedical Research Centre, and the University of Nottingham as sponsor and host university.

PPI ABSTRACT

Background

Pain is an unpleasant sensory and emotional experience which fluctuates over time. The central nervous system (brain and spinal cord) plays a role in controlling pain. However, it is unclear if these central aspects of pain are stable or change over time. This study looked to determine if central aspects of pain are stable or change over time.

Main Body

A total of 2155 individuals with knee pain from the Investigating Musculoskeletal Health and Wellbeing study of individuals from the East Midlands. Individuals completed questionnaires annually over 3 years. Questionnaires included pain severity and central aspects of pain.

When all participants were grouped together there was no change in pain over time. When pain was looked at on an individual participant by participant basis pain severity and central aspects of pain either increased or decreased over time.

Conclusion

On a population basis central aspect of pain appears stable over time. However, on an individual basis central aspects of pain demonstrated clinically important changes over time, alongside changes in pain severity.

Acknowledgment

This work was supported by Versus Arthritis (Centre initiative grant number = 20777) and NIHR Nottingham Biomedical Research Centre, and the University of Nottingham as sponsor and host university.

Modulation of laser evoked potentials (LEPs) by lacosamide, pregabalin & tapentadol in awake rats

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Introduction

Current treatments for pain often provide incomplete symptom relief and can also be accompanied by adverse effects and the potential for addiction, yet efforts to develop new treatments are adversely impacted by the lack of reliable translation from preclinical models. One approach to improve the success rate is to utilise biomarkers to confirm target-engagement and demonstrate relevant modulation of the nociceptive system in vivo. Laser-Evoked Potentials (LEPs) are one such measure that could fulfil these requirements. Here we profile the effects of 3 standard-of-care compounds on LEPs in awake, behaving rodents in advance of comparable clinical data being made available from the IMI-PainCare consortium.

Methods

12 male, Wistar rats were implanted with multiple EEG electrodes to record resting-state and evoked activity (LEPs/auditory-evoked potentials [AEPs]). For each compound, dosing was performed according to a balanced, cross-over design with a minimum of 5 days between treatments. On each recording day, a baseline session was performed, followed by 3 post-dosing time points (1, 2 & 4hr). At each time point, rats were stimulated with 12 laser pulses delivered to the plantar surface of their hind paws and 60 auditory stimuli.

Statistical analysis

Stimulus response curves were analysed using one-way repeated measures ANOVAs. The time course of pharmacological effects was compared to vehicle using two-way repeated measures ANOVAs. Post-hoc analyses were performed using the Bonferroni adjustment.

Results and conclusions

In response to a 1.5J stimulus, all compounds (30mg/Kg ip) caused a reduction in LEP amplitude relative to the vehicle group. This was typically associated with a concomitant reduction in nocifensive behaviours and AEP amplitude. Notably, the LEP & behavioural changes elicited by tapentadol were evident at both 1 & 2 hour timepoints, while the AEP effects were restricted to the 1 hour session. This suggests that the relative effect of compounds on LEPs Vs AEPs may be able to dissociate between specific effects on the nociceptive system versus more global changes in nervous system function.

Analgesic Prescribing in Patients with Inflammatory Arthritis in England: Observational Studies in the Clinical Practice Research Datalink (CPRD) Aurum

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ACADEMIC ABSTRACT

Background

Despite little evidence that analgesics are effective in inflammatory arthritis (IA), studies report substantial opioid prescribing. The extent this applies to other analgesics is uncertain. We undertook an evaluation of analgesic prescribing in patients with IA in a national primary care electronic health record database (CPRD Aurum).

Methods

From 2004-2020, cross-sectional analyses evaluated annual prevalence of analgesic prescriptions in patients with diagnosed rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA), stratified by age, sex, ethnicity, deprivation, and geography. Cohort studies determined prognostic factors at diagnosis for chronic analgesic prescriptions using Cox proportional hazards models.

Results

Prevalence of analgesic prescribing declined over time from 84.2/100 person-years (PY) (95% CI 83.9, 84.5) in 2004 to 64.5/100PY (64.2, 64.8) in 2020, but remained common. In 2004, NSAIDs were the most commonly prescribed analgesic (56.1/100PY; 55.8, 56.5), falling over time. Opioids were most prescribed in 2020 (39.0/100PY; 38.7, 39.2). Gabapentinoid prescribing increased: 2004 prevalence 1.1/100PY (1.0, 1.2); 2020 prevalence 9.9/100PY (9.7, 10.0). Most opioid prescriptions were chronic (2020 prevalence 23.4/100PY [23.2, 23.6]). Non-NSAID analgesic prescribing was commoner in older people, females, deprived areas, and North England. Conversely, NSAID prescribing was commoner in males, varying little by deprivation/geography. Prognostic factors for chronic opioid/gabapentinoid and NSAID prescriptions differed, with NSAIDs having no consistent association with deprivation (unlike opioids/gabapentinoids).

Conclusions

IA analgesic prescribing of all classes is widespread. This is neither evidence-based nor in-line with guidelines. Interventions are needed to reduce IA analgesic prescribing.

Acknowledgements and Disclosures of Interest

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PPI ABSTRACT

Title

How are Pain Medicines Being Prescribed in People with Inflammatory Arthritis Living in England?

Introduction

Inflammatory arthritis includes conditions causing inflamed joints. The commonest types are rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. Many people with inflammatory arthritis suffer daily pain. This has great impact on their lives.

Whilst it is commonly believed that pain medicines reduce arthritis pain, research has shown they help little, if at all, but have many side-effects. Despite this, people with inflammatory arthritis often receive strong "opioid" pain medicines. It is uncertain how often they receive other pain medicines.

We used information from anonymised GP health records of patients from across England to examine how pain medicines are being prescribed in people with inflammatory arthritis fro12m 2004 to 2020.

Study Findings

In each year many patients with inflammatory arthritis received a pain medicine. This fell over time from 84% of people in 2004 to 65% in 2020.

The types of pain medicines prescribed changed over time. In 2004, "non-steroidal anti-inflammatory drugs" were most prescribed (in 56% of people). This fell over time. In 2020 "opioids" were most prescribed (in 39% of people). The prescribing of "gabapentinoids" rose from 1% of people in 2004 to 10% in 2020.

Concerningly, one-in-four people received a long-term opioid prescription in each year.

Conclusion

Pain medicines are widely prescribed to people with inflammatory arthritis, despite studies showing they often help pain very little, and can cause harms. Further research is needed to understand why this is happening, and how pain medicine prescribing can be improved.

Lay Summary Points

Whilst it is commonly believed that pain medicines reduce arthritis pain, research has shown they help little, if at all, but have many side-effects. We used information from anonymised GP health records of patients from across England to examine how pain medicines are being prescribed in people with inflammatory arthritis.

In each year many patients with inflammatory arthritis received a pain medicine. This fell over time from 84% of people in 2004 to 65% in 2020. Concerningly, one-in-four people received a long-term opioid prescription in each year.

Further research is needed to understand why pain medicines are widely prescribed in patients with inflammatory arthritis and how this can be improved.

The Health Data Research Innovation Gateway: a tool for data discovery, access, and transparency in the use of health data for research in the UK

***Clara Fennessy HDR** , UK Technology Team*

Health Data Research UK

The Heath Data Research Innovation Gateway was established in 2020 to provide a common entry point for researchers to search, discover and request access to health datasets in the UK. It is an integral part of HDR UK's mission to bring together the UK's health data to enable discoveries that save people's lives. Development of the Gateway was initially funded through UKRI's Industrial Strategy Challenge Fund and is now resourced as part of HDR UK's core 2023-2028 funding. It is delivered in partnership with the UK Health Data Research Alliance – an independent network of leading healthcare and research organisations united to establish best practice for the ethical use of UK health data for research at scale. The Gateway does not hold or store any datasets or patient or health data but rather acts as a portal for discovery by listing associated information about each dataset (the dataset's metadata) which can help researchers decide whether a particular dataset could be useful for their work. To date, over 800 datasets descriptions from 70+ data custodians have been made available on the Gateway, including priority COVID-19 datasets as part of the Data and Connectivity programme. However, the Gateway is not limited to being a metadata register – the platform also offers a number of other services. Other health data resources, such as papers and tools for research, can be uploaded to the Gateway and these can be brought together along with the associated metadata to provide a curated Collection around a particular theme or topic. The Gateway data use register aims to improve transparency in the use of health data for research and enables data custodians to publicly show how their data assets are being used, who is using them and for what purpose. Nearly 1000 data uses have already been uploaded to the Gateway. The Gateway offers a simplified approach to the data access request process for both custodians and researchers by provided an end-to-end management system build around the Five Safes Framework to ensure safe and secure research access to health data. Cohort Discovery is a Gateway search function that can be used to find cohorts in pseudonymised datasets based on characteristics such as disease, age, location. Approved researchers can use the tool to determine whether particular datasets contain a cohort (or group) of interest relevant to their project and if yes, submit data access request(s) to the appropriate data custodian(s). This is currently available for a limited number of datasets, with more being added regularly. Our vision for future is that the Gateway becomes the go-to platform for discovering health data assets and other sharable resources, co-created by the wider community to accelerate the trustworthy use of health data for research.

Lay Summary Points

The Heath Data Research Innovation Gateway was established in 2020 to provide a common entry point for researchers to search, discover and request access to health datasets in the UK.

The Gateway does not hold or store any datasets or patient or health data, but rather acts as a portal for discovery by listing associated information about each dataset (the dataset's metadata) which can help researchers decide whether a particular dataset could be useful for their work. It is then possible to request access to the datasets listed in the Gateway via an end-to-end management system build around the Five Safes Framework to ensure safe and secure research access to health data.

To date, over 800 datasets descriptions from 70+ data custodians have been made available on the Gateway, alongside over 4,000 other health data resources including publications, data uses, tools and educational courses.

Dysregulation of osteocyte Sema3A by mechanical load and inflammation may drive neuroplasticity and pain in osteoarthritis

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Objective

Subchondral bone changes in osteoarthritis (OA) are one of few disease characteristics to correlate with pain. Although profound neuroplasticity and nociceptor sprouting occurs in osteoarthritic subchondral bone and is associated with pain and pathology, the mechanisms underlying these changes are unknown. The axon guidance signal, Sema3A, essential for normal innervation of healthy bone, is expressed by osteocytes and downregulated in OA bone1. Sema3a is also differentially expressed in multiple joint components in human OA patients2. We have used human osteocyte and sensory nerve models to investigate whether inflammatory and mechanical stimuli of osteocytes alters their communication with nerves.

Hypothesis

Pathological mechanical load and inflammation of bone causes dysregulation of Sema3A signalling leading to perturbed sensory nerve plasticity and pain.

Methods

Human KOLF2-C1 iPSC derived nociceptors were generated by TALEN-mediated insertion of transcription factors NGN2 and Brn3A and a modified Chambers differentiation protocol3,4 to produce nociceptor-like cells. Nociceptor phenotype was confirmed by immunocytochemistry. Human Y201 MSC cells, embedded in 3D type I collagen gels (0.05 x 106 cell/250µLgel) in 48 well plates or silicone plates, were differentiated to osteocytes for 7 days before stimulation with IL-6 (5ng/ml) with soluble IL-6 receptor (sIL-6r (40ng/ml)), IL6/sIL6r and mechanical load mimetic Yoda1 (5µM) or unstimulated (n=5/group) (48-well plates) or were mechanically loaded in silicone plates (5000 µstrain, 10Hz, 3000 cycles) or not loaded (n=5/group). Nociceptor responses to osteocyte conditioned media transfer was assessed by 24-hour brightfield phase contrast confocal microscopy. 24 hours after stimulation osteocyte RNA (RT-qPCR- IL6/sIL-6r and Yoda1; RNAseq and DEseq2 analysis- Load) and Sema3A protein release (ELISA) was quantified. Normally distributed data with homogenous variances was analysed by two-tailed t test.

Results

IPSC-derived nociceptors display elongated (>5mm) dendritic projections and nociceptive markers such as TUJ1, PrPH and Neun and TrkA. Sema3A signalling ligands were expressed in 100% of osteocyte cultures. Mechanical loading of osteocytes regulated Sema3 pathway; Sema3A (0.4-fold, $p<0.001$), Sema3B (13-fold, $p<0.001$), Sema3C (0.4-fold, $p<0.001$). Inflammatory stimulation of osteocytes by IL6 and sIL6r, regulated expression of SEMA3A (7-fold, $p=0.01$) and its receptor Plexin1 (3-fold, $p=0.03$). IL6/sIL6r + Yoda1 treatment of osteocytes downregulated Sema3A protein release (2-fold, $p=0.02$). 24-hour brightfield phase contrast confocal microscopy revealed that sensory nerve cultures exposed to media from osteocytes stimulated with Yoda 1 and IL-6/sIL-6R displayed significantly more invading dendritic projections ($p=0.0175$, 12-fold±SEM 3.5) across 3 fields of view within a single stimulated neural culture and significantly fewer retracting dendritic projections ($p=0.0075$, 2-fold±SEM 0.33) when compared to control media stimulated cultures.

Conclusions

Mechanical and inflammatory stimuli that mimic osteoarthritic pathology cause osteocytes to regulate Sema3A signalling and induce the branching and invasion of cultured nociceptor-like cells as displayed in OA subchondral bone.

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Lay Summary Points

Bone degeneration is one of the only major disease characteristics to correlate with pain In osteoarthritis.

We have made a stem cell derived model of the nerve bone interface in pathology

Under pathological mechanical loading bone cells down regulate neural signalling this is associated with changes in nerve activity physiology as seen in osteoarthritis

Chemogenetic activation of astrogliosis induces spinal cord microvasculature disturbance – a potential mediator of diabetic neuropathic pain

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Background

Pain perception is modulated by the somatosensory nervous system that relies heavily upon not only sensory neurons, but also the interplay of a heterogenous cell population (endothelial cells, astrocytes). This heterogenic cell population encapsulates the somatosensory nervous system with a protective vascular barrier – blood spinal cord barrier. We have identified in diabetic neuropathic pain that this blood spinal cord barrier is damaged. A pathological hallmark of chronic pain is astrogliosis, a hub that acts as a potent source of inflammatory response, impacting upon vessel integrity and sensory neuronal activity. Here we elucidate using chemogenetic activation, the role of astrogliosis in the modulation of the blood spinal cord barrier and nociception.

Methods

Male C57 bl6 mice were intrathecally administered either GFAP hMD3gq mCherry (GFAP-hMD3gq) or GFAP-mCherry. Baseline nociceptive behaviours were acquired prior to delivery of either vehicle or clozapine n oxide (CNO 0.3mg/kg ip). Alternatively, mice were fed either standard chow or a high fat diet (HFD; 60% kcal fat), with nociceptive behaviours, body weight and blood glucose monitored. Lumbar spinal cords were extracted and either frozen for angiogenesis proteome evaluation, or cardiac perfused with 4% paraformaldehyde and cryosectioned for confocal microscopy or nanostring GeoMX digital spatial profiling performed.

Results

In SC tissues from HFD, markers of astrogliosis were elevated in the dorsal horn when compared

to standard diet tissue. Following AAV administration, GFAP positive astrocytes were mCherry positive in the lumbar dorsal horn. CNO induced nociceptive behavioural hypersensitivity in GFAP-hMD3gq mice, which was accompanied by increased astrocyte number and GFAP fluorescence in the dorsal horn. Furthermore, microvessel volume in the dorsal horn of GFAP-hMD3gq mice was reduced versus controls. In addition, following chemogenetic astrocyte activation angiogenic signalling in the lumbar spinal cord was diminished.

Conclusions

This demonstrates the involvement of astrocytes in modulating nociception through manipulating vascular integrity and function, potentially underlying the development of diabetic neuropathic pain. Acknowledgements and Disclosures of Interest(s) We thank European Foundation for the Study of Diabetes for supporting this work. A PPI abstract: Abstract title Astrocyte activations cause diabetic neuropathic pain Author Name(s) Lydia Hardowar, Richard P Hulse Background/Introduction Blood vessels are damaged due to diabetes causing many diabetic complications. We have found that spinal cord blood vessels are important in controlling pain, and when these vessels are damaged there is a change in how mice feel pain. We think this is because one of the cell types found in the vessel wall, called 'astrocytes' behave differently during diabetes and we want to know how causes painful sensations seen in people with diabetes. Main body We use a mouse model of Type 2 diabetic pain where mice are provided with a diet similar to our modern diet that leads to obesity and diabetes. These mice develop similar pain sensations to those described by human diabetic pain patients. In our experiments we have identified astrocytes are activated. In our next experiments we controlled astrocyte actions to determine that astrocytes cause pain by damaging blood vessels. These experiments show us that astrocytes cause blood vessel and diabetic neuropathic pain.

Lay Summary Points

To understand the effects of how the spinal capillary bed may impact pain development during drug-induced astrocyte activation.

We hypothesise that the activation of spinal astrocytes is a key mechanism during vasculature change associated with pain development.

In animals with drug-induced astrocyte activation, behavioral tests showed painful responses to mechanical and thermal stimulation. In addition to their painful responses, spinal cord tissue showed astrocytes interacting with more capillary vessels compared to the control animal group.

Type 2 diabetic neuropathic pain is dependent upon Hypoxia Inducible Factor 1 alpha mediated activation of dorsal horn neurons

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Background

Our research has demonstrated that diabetic neuropathic pain manifests due to a reduced spinal cord blood perfusion. Loss of vascular support results in dorsal horn neurons becoming hypoxic. In this study, we aimed to explore the hypoxia-inducible factor 1 alpha (HIF1α) dependent molecular mechanisms underlying type 2 diabetes induced neuropathic pain states. Our findings reveal a novel link between HIF1α and diabetic neuropathic pain.

Methods

C57bl6 HIF1alpha floxed (007561 Jax) mice were intravenously injected via tail vein with AAV PHP.eb syn cre eGFP. Mice were given either experimental diet (high fat (60% cal fat)) or intrathecal injection of hypoxia mimetic, dimethyloaxallyl glycine (DMOG). Animals body weight, blood glucose and nociceptive behavioural withdrawals were tested. Paraformaldehyde fixed lumbar spinal cords were extracted and processed (40μM thick sections) for confocal microscopy. In

addition, proteomic evaluation of hypoxia responsive spinal cord neurons was performed.

Results

Intrathecal DMOG treatment and high fat diet led to an induction of neuropathic pain behavioural phenotypes when compared to normal chow fed or vehicle treated mice. Lumbar spinal cord cryosections demonstrated increased abundance of neuronal HIF1a in DMOG and high fat fed mice when compared to lean or vehicle controls. In HIF1aKO mice, DMOG and high fat diet induced pain hypersensitivity was prevented. Western blotting and proteomic evaluation of isolated spinal cord neurons demonstrating a reduction in HIF1a expression as well as cessation of HIFa dependent hypoxia signalling in HIF1aKO mouse spinal cord neurons.

Conclusions

These findings shed light on the molecular mechanisms underlying diabetic neuropathic pain.

Acknowledgements and Disclosures of Interest(s)

We thank Diabetes Wellness and Research Foundation for supporting this work.

Lay Summary

Abstract title

Diabetic neuropathic pain is dependent upon Hypoxia Inducible Factor 1 alpha mediated activation of dorsal horn neurons

Main Idea

Pain is detected by nerve cells (neurons), that work to protect the body against damage. In diabetes these nerve cells stop working properly. This leads to uncomfortable pain sensations in the hands and feet. Existing painkillers don't work, with only a few people getting pain relief.

Hypothesis

We have shown that in diabetes, if the spinal cord sensory neurons fail to receive blood, they become damaged and long-lasting pain develops. We think that pain develops in diabetes as reduced blood flow prevents oxygen getting to the spinal cord. Pain signals are generated in our hands and feet, travel along sensory nerves until they reach the spinal cord, where pain information is filtered. Spinal cord neurons normally turn this signal down or off. In diabetes these neurons lose their ability to turn pain signals off, resulting in people with diabetes feeling pain.

Findings of Abstract

We have used a mouse model of Type 2 diabetes to show that by stopping neurons producing HIF1α we can prevent diabetic neuropathic pain from developing. We have identified a new pathway that causes diabetic pain, allowing us to design drugs to prevent this condition.

Grey matter density in brains of fibromyalgia patients relates to peripheral markers of small fiber pathology

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Background

Fibromyalgia syndrome (FMS) has frequently been investigated using neuroimaging methods to demonstrate structural brain changes in patients relative to healthy people. However, findings across studies are extremely heterogeneous. In recent years, a new focus on peripheral nervous system structure and function points to a potentially important role for small fibre pathology (SFP) in FMS. Despite this, little research has considered brain structure in tandem with peripheral markers of SFP.

Method

28 patients with FMS underwent a deep central and peripheral phenotyping regime including structural MRI scans to consider brain anatomy, skin biopsy and confocal corneal microscopy (CCM). Automated processing of retinal images quantified peripheral markers of SFP including nerve overall density, major nerve length and branching density. Regional grey matter density and cortical thickness were evaluated using the Computational Anatomical Toolbox in SPM12.

Results

Initial findings indicate a relationship between CCM nerve fiber density measurements and grey matter density in several brain regions including bilateral caudate nuclei.

Discussion

Our findings indicate a relationship between structural integrity of the peripheral nervous system with relevant pain processing brain regions identified for importance in previous research of FMS. As a cross sectional study, causality cannot be inferred, but we hypothesise that brain structural changes could potentially occur as a result of SFP in FMS and this is something that warrants further investigation. A more holistic approach considering central and peripheral nervous system structure and function in tandem could improve understanding of FMS pathophysiology.

Experience of recruiting patients with rheumatoid arthritis versus fibromyalgia into longitudinal observational studies: a real world observation

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Background

Rheumatoid arthritis (RA) and fibromyalgia (FM) are both common and debilitating conditions associated with chronic pain alongside other shared features including sleep disturbance, fatigue, mood disturbance and reduced quality of life. Research to advance our understanding of the underlying mechanisms and optimal therapeutic strategies is critical for both conditions and, in an ideal world, studies would recruit a representative subset of patients to produce generalisable results. However this is difficult to achieve, especially in a population with numerous co-morbidities and potential barriers to participating in research. In this opportunistic study, we were able to compare our experience of recruiting patients with RA receiving secondary care treatment, to a very similar study of people living with FM.

Methods

Patients with newly diagnosed RA or FM were recruited from secondary care clinics and followed up for their first year of receiving standard treatments. After screening by the clinical care team, the patients were provided verbal and written information about study procedures. All patients were given time to reflect on their

decision whether or not to participate, and if happy to proceed, signed a study consent form. Included within various study procedures, participants complete a battery of subjective outcome measure questionnaires using the secure, online platform REDCap. A comparison was then drawn between the process of recruiting these two different cohorts and their participation in the study.

Results

383 patients were recruited from September 2020 to December 2022, 173 with newly diagnosed RA (average age 61 years) and 210 newly diagnosed with FM (average age 46 years). 21/173 (12%) patients with RA and 20/210 (10%) patients with FM subsequently withdrew, the most common reason being "too much". 40/100 (40%) patients with RA completed all the research surveys whereas 20/100 (20%) with FM completed all the research surveys. RA patients needed an average of 27 reminders per patient for the 17 questionnaires, with FM patients requiring 29 reminders per patient. All of the RA patients were followed up by their clinician either by telephone or face-to-face to evaluate the effects of their newly prescribed disease-modifying antirheumatic drug (DMARD); 172/173 (99%) continued to take their DMARD at 3 months follow up. All of the FM patients were referred to multidisciplinary pain management in secondary care. Of the first 100 patients with FM, only 40/100 (40%) completed treatment.

Conclusions

These data highlight the barriers to undertaking observational research in patients living with FM compared to those with RA. The first difference is that current infrastructure for care delivery within secondary care is more likely to facilitate patient engagement for patients with RA compared to those with FM. This in turn makes observational clinical research more challenging in patients with FM. Secondly, whilst patients with either condition were equally as likely to withdraw from the research study, those with FM had a greater "response decay" over time than those with RA. Taken together, the consequence of these factors is that observational studies are less likely to produce generalisable findings. These observations should therefore be considered when designing future studies, planning recruitment strategies, conducting sample size calculations and considering timeframes for data collection.

Lay Summary Points

1. Researchers need to be aware of the barriers to conducting observational research studies in patients with fibromyalgia
2. The current structure of care available for patients with fibromyalgia needs to be taken into account when designing clinical research studies
3. Researchers should consider allowing additional time for the recruitment phase of an observational clinical research study of patients with fibromyalgia

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Evidence of a genetic background predisposing to Complex Regional Pain Syndrome type 1

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Background

Complex regional pain syndrome type I (CRPS-1) is a rare condition that is initiated by injury to the extremities. The acute phase of CRPS-1 is characterised by severe pain, hyperalgesia, allodynia and inflammation. In about 70-80% of patients, the acute stage evolves into a chronic form where inflammation appears resolved but pain persists. The pathogenesis of CRPS-1 remains largely unknown, and it is unclear why only some people will develop the disorder after injury. We hypothesised that CRPS-1 may result from a combination of both genotype and environmental effects such that CRPS-1 is hereditary, but in order for it to manifest, a person must have the "risk" genotype as well as encounter an environmental trigger (injury). We reasoned that causative SNPs would be enriched in CRPS-1 patient populations compared to unaffected populations.

Methods

We recruited a discovery cohort of chronic CRPS-1 patients (N=34) and determined genome-wide, non-synonymous SNP allele frequencies by analysing individuals' exomes. We then genotyped a CRPS-1 replication cohort (N=50) and a chronic pain cohort to further assess the discovery cohort results. Gene expression of ANO10, P2RX7, PRKAG1 and SLC12A9 were quantified in human macrophages. We determined how the CRPS-1 P2RX7 SNP allele regulates the priming and activation of the NLRP3 inflammasome in different macrophage activation states by assessing IL-1β secretion, IL-18 secretion, ASC speck formation. Pyroptotic cell death was determined via propidium iodide uptake and lactate dehydrogenase (LDH) release.

Results

We found that the allele frequencies of four non-synonymous SNPs were statistically increased in CRPS-1 individuals but not in a contemporaneously collected chronic pain cohort. These SNPs were in the genes ANO10, P2RX7, PRKAG1 and SCL12A9. Males were more likely than females to have one of the four rare SNP alleles, 8/14 versus 17/70, Fischer's p=0.023. ANO10, P2RX7, PRKAG1 and SLC12A9 were expressed in macrophages. We generated knock-in mutations for the P2RX7 SNP into the human monocytic THP-1 cell line and found that after priming and stimulating the NLRP3 inflammasome, the rare allele of P2RX7 resulted in higher levels of IL-1β secretion and ASC speck formation. IL-18 secretion and LDH release were unaffected.

Conclusions

A single SNP in each of the genes ANO10, P2RX7, PRKAG1 and SLC12A9 was associated with developing CRPS-1. Our genetic results suggest CRPS-1 pathogenesis may be different between the sexes. As all four genes are expressed in macrophages, and the P2RX7 SNP rare allele affects the function of NLRP3, we hypothesise that a person's risk of developing CRPS-1 can be caused by altered macrophage activity.

Lay Summary Points

Complex regional pain syndrome (CRPS) is a chronic pain condition that occurs after an injury and results in localised pain and swelling (inflammation). CRPS spontaneously resolves within a year in 20-30% of cases, but after this time, it becomes chronic and rarely improves. Treatment options for CRPS patients are very limited, untargeted and often have very serious side effects. It is therefore important to understand why CRPS develops, and the underlying mechanisms involved in order to try and develop more effective drugs targeting pain and inflammation and improve the lives of those with CRPS.

We can often gain insight into why a disease develops by looking at the changes in genes, called mutations, which can in turn help design new drugs. This is exactly what we have done in this research.

We recruited a cohort of people with CRPS, people with other chronic pain conditions and analysed their genes to identity any genetic changes or mutations. We found that CRPS patients were more likely to have four mutations each in four different genes than people without CRPS, suggesting that these mutations may be responsible for people developing CRPS.

We confirmed that these four genes were present in monocytes and macrophages which are cells that play a key role in immunity and inflammation via a protein called the inflammasome.

We then focussed on one genetic mutation and introduced the mutation into human monocytes and cultured them in the lab. We then tested these cells to see how the mutation affects inflammation. Our results showed that firstly, cells with the mutation had more inflammasomes than cells without the mutation and secondly, cells with the mutation had more inflammatory molecules and hence inflammation than cells without the mutation.

In conclusion, we found four genetic changes that are associated with CRPS. Our results on one mutation suggest that it affects the function of the inflammasome, which in turn contributes to a person's risk of developing CRPS.

Implicit body perception at the pelvic girdle with the two-point estimation task: a reliability study

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Background & aims

Implicit body perception disturbance has been evidenced in low back pain (LBP) using the two-point estimation (2PE) measure. Previous research has only investigated unilateral LBP, not included a pain-free control group, or examined the measure at the pelvic girdle. Aims: 1) design a testing protocol suitable for assessing pain crossing the midline (central) 2) investigate regional 2PE reliability 3) compare left and right sides and lumbar and pelvic regions.

Methods

A central 2PE measure was designed and protocolised. Non-pregnant, pain-free adult women > 18 years old were recruited from a university setting. Participants were assessed with repeated 2PE measures (estimating distance between two points (120mm apart) on a digital calliper). 2PE data was collected via two online and two in-person sessions. In-person intra and inter-rater reliability of the 2PE was assessed using intra-class correlation coefficients (ICC). Differences between lateral (Left versus right) and central (pelvic girdle versus lumbar spine) were assessed using paired t-tests.

Results

22 women (mean age 40.5 +/-13.3) participated. 2PE demonstrated good intra-rater reliability with two repeated measures (lateral ICC=0.71 95%CI [0.49-0.87] / central ICC=0.80 95%CI [0.59-0.91]. Inter-rater reliability ranged from poor to good (lateral ICC=0.48 95%CI 0.58-0.75 / central ICC=0.65 95%CI [0.33-0.84]. There were no differences between the left and right lateral measures (p=.198) but the 2PE was greater for the lumbar compared to the pelvic region (p<0.005).

Conclusion

The 2PE task demonstrates good intra-rater reliability of a central and lateral measure. Differences in 2PE between regions may reflect somatosensory representation differences and may have implications for pain perception.

Lay Summary Points

A method for the assessment of body perception was developed and tested, suitable for the assessment of people with pain crossing the midline of the body.

Two repeated tests stabilised the reliability of the measure, showing good reliability within and between examiners.

Perception of size at the lower back and pelvic area was significantly different.

Associations between serum oxylipin levels with clinical measures of pain and radiographic osteoarthritis in people with knee pain

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Background

Osteoarthritis (OA) is the fastest growing cause of chronic pain worldwide, and the leading cause of disability in the middle-aged and older population. Currently there are no approved treatments that halt or reverse the progression of joint pathology in OA, and current analgesics, which treat the associated pain, are not suitable for long-term use and can have adverse side effects. Identifying molecules that can predict the course of OA pain and / or pathology may aid both the development of new treatments and the appropriate early management of pain progression. The oxylipins are bioactive lipid mediators derived from omega-6 and omega-3 polyunsaturated fatty acids (PUFAs). The oxylipins exert both pro- and anti-inflammatory effects, which support tissue repair and regulate pain signalling. Due to the biological role of the oxylipins, their potential as biomarkers and / or therapeutic targets for OA and chronic pain is worth exploring further.

Aim

In this study, it was investigated whether circulating levels of pro- or anti-inflammatory oxylipins were associated with current measures of pain and radiographic OA, and whether baseline levels of oxylipins were able to predict the progression of knee pain over a 3 year time period.

Methods

Serum samples were collected from participants (n=154) recruited to the Knee Pain in the Community Cohort (KPIC) who were clinically assessed at baseline and 3 years follow-up for pain phenotype. Radiographic knee OA scores (Kellgren-Lawrence (KL) score); self-reported pain scores (numerical rating scale (NRS), and pain detect questionnaire (PDQ)); and pain pressure thresholds (PPT)) were collected on the same visit as the serum samples. Follow-up NRS, PDQ, and PPT scores were also collected 3 years later. Serum levels of oxylipins were quantified using a targeted LC-MS/MS method. Analyses were performed to identify relationships between serum levels of oxylipins with current knee pain and radiographic OA scores, and with pain scores at 3 years follow-up. For some analyses, participants were stratified based on pain and KL scores into two groups: No OA-lower pain (n=56; KL ≤1 & VAS ≤5); and OA-higher pain (n=45; KL≥2 & VAS ≥6).

Results

Linear regression analyses revealed that higher levels of 9-, and 15-HETE, 8,9-EET:DHET ratio and 14-HDHA were significantly associated with more advanced radiographic knee OA. Higher levels of 8,9- and 14,15-DHET, 12-HpETE, and AEA were associated with higher NRS pain scores. AEA was also associated with higher PDQ scores. To study potential differences in the levels of oxylipins in participants at the extreme ends of the clinical phenotype of OA, participants were stratified based on pain and KL scores into two groups: No OA-lower pain, and OA-higher pain. Comparison of these groups found that levels of HETEs, EETs, EET:DHET ratios, and 14- & 17-HDHA were significantly higher in the OA-higher pain group compared to the early OA group. Analyses investigating whether baseline levels could predict

future pain revealed that levels of 8,9-EET and 5-HETE were associated with higher self-reported pain scores, and 5,6-DHET levels were associated with pain pressure thresholds collected at 3 years follow-up. Combining the levels of 8,9-EET and 5-HETE strengthened their association to items on the NRS scale.

Conclusions

This study has highlighted the potential involvement of omega-3 and -6 PUFA derived oxylipins in both OA joint pathology and the associated pain phenotype. The EET/DHET associations with OA and pain are consistent with previous studies and other chronic pain states – adding further evidence to support targeting this pathway to treat pain. The ability to predict future pain using a small subset of oxylipins could have significant benefit to people at high risk of OA, who could be identified at an earlier stage of disease and receive appropriate intervention.

Making Pain data FAIR (Findable, Accessible, Interoperable and Reusable) through Data Standardisation

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Led by the University of Dundee, University of Nottingham, King's College London, Imperial College London, University of Oxford, University of Bath, and Cambridge Institute for Medical Research. Delivered in partnership through UKRI, Versus Arthritis and Eli Lilly. For UKRI, the APDP initiative is led by the Medical Research Council, with support from the Biotechnology and Biological Sciences Research Council and Economic and Social Research Council.

Background

According to National Institute for Health and Care Excellence at least one third of the UK population is affected by chronic pain. It has a detrimental impact on an individual's overall health, quality of life, ability to function and work, family life and even wider society. Pain research helps acquire new knowledge on the mechanisms, pathogenesis, diagnosis, and treatment of pain. To support research pain related data is collected and reused across the UK. Data Standardisation in Pain Data Finding and accessing pain related data is challenging because it is collected from various sources (electronic health records, surveys, assessments, clinical trials etc), each governed

according to varying practices. This data is collected in different formats (free text, vocabularies etc), granularity and measurements (pain scales: NRS, VAS, ANVPS etc), pain parameter units (intensity, quality, duration, aggravating and relieving factors, time course), other biometric measurements, medical conditions and procedures, demographics, and prescribed pain relief medications. and is held in diverse schemas and data storage. This has resulted in limited ability to compare and link data between the various research pain cohorts. There has been no national approach to co-ordinating and managing this data until now with the Alleviate Pain Data Hub.

Methods

Alleviate Pain Data Hub is aimed at making data Findable, Accessible, Interoperable and Reusable. Data standardisation in Alleviate calls for federated data transformation and reformatting using OMOP CDM v5.4 approach before it is made available on HDR Cohort Discovery Portal (a gateway to run queries on federated data safely without accessing the data source). Semi-automated data standardisation methodology is adopted using the Alleviate open-source tools. a) Pre-Processing, data manipulation to resolve inconsistencies, standardise dates, units and numeric values, remove duplicates, interpolate missing information (where possible) and pseudonymise personal information. b) CaRROT Mapper, a webapp that uses the metadata (produced by WhiteRabbit tool) of dataset to produce term and structural mappings from selection of standard vocabularies used in OMOP CDM. c) CaRROT CDM, a python tool to perform ETL on the pain data using the mappings generated from CaRROT Mapper.

Results

Alleviate Pain Data Hub is designed to standardise the structure and content of observational health data. 4 (and counting) pain specific cohorts are live on the HDR Cohort Discovery Portal so that consistent reuse of data for discovery, research, comparison, and collaboration can take place.

Conclusion

Data standardisation improves data quality & data validation, increases data interoperability, facilitates data sharing, data reuse, and data linkage. Common data model makes it easier and faster to perform federated data analysis for evidence-based research and decision making thus improving research collaboration.

Lay Summary Points

Making Pain data FAIR (Findable, Accessible, Interoperable and Reusable) through Data Standadisation

Chronic Pain is one of the largest health problems. It has a detrimental impact on an individual's overall health and quality of life. Pain research is significant in acquiring new knowledge on the mechanisms, pathogenesis, diagnosis, and treatment of pain. Clinical1 and non-clinical2 data is being collected by the researchers across the UK. However, it is difficult to find and access these datasets and reuse them for research because of

- Lack of data standardisation, various data sources present data in their own terminologies and format, making it difficult to understand and compare datasets.
- Data silos, most pain datasets are in an isolated environment. Thus, undiscoverable and/or inaccessible for researchers that could reuse the data for their research, instead of duplicating efforts to collect similar data again.

This has resulted in lack of data visibility, flexibility to explore the dataset to assess how relevant it is for intended research and limited ability to compare and link data between the various research pain cohorts. There has been no national approach to co-ordinating and managing this data until now with the Alleviate Pain Data Hub.

Alleviate Pain Data Hub is an online, safe, platform that hosts pain datasets. All pain data (text, genetic, imaging) is transformed and reformatted to a standard format (OMOP Common Data Model v5.4). OMOP is a common data model that transforms dataset to a common format (data structure) and a common terminology (data content). The platform enables federated3

querying of pain data hosted on this platform thus allowing researchers to see datasets that fit their research question criteria. This hub will improve data visibility and ultimately increase consistent reuse of data for discovery, research, comparison, and collaboration.

A semi-automated approach is adopted for data standardisation process. Combination of hands-on data pre-processing and use of various tools (CaRROT Mapper, CaRROT CDM) developed to automate, validate, and speed up the data standardisation process.

Definitions
1. Clinical data is a fundamental resource for most health and medical research. It is collected during ongoing patient care or as part of a formal clinical trial program. Any data becomes clinical once it has a relation to a disease process.
2. Non-clinical data does not provide information on diagnosis, treatment or care information of patient but may support clinical data. That's why many non-clinical factors are already linked to the healthcare data. For example, an individual's social health determinants such as their living and working conditions and demographic attributes.
3. Data federation is an approach that virtually unifies data from different sources and makes it accessible. The underlying data storage in data federation continue to operate autonomously. Researchers or data consumers can run data query on various data sources through a virtual interface as though all the data was physically stored in a single dedicated database.

Impairment of pro-resolving lipid mediator synthesis in macrophages exacerbates persistent inflammatory pain

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Background

Pain is a persistent symptom of rheumatoid arthritis, even when joint inflammation is controlled by anti-rheumatic drug treatment. Thus, elucidation of mechanisms that underlie pain persisting when overt joint inflammation has subsided will offer innovative therapeutic targets. We utilise the K/BxN serum transfer-induced arthritis model of inflammatory arthritis in which mice display ankle joint swelling and allodynia that peak at day-5 after serum transfer, however, whilst joint swelling resolves by day-25, allodynia persists. We have observed accumulation of M1-like proinflammatory macrophages (MHCII+CD206-) in dorsal root ganglia (DRG) and decreased expression of the pro-resolving lipid mediator Maresin 1 (MaR1) in concomitance to persistent allodynia. Since administration of MaR1 attenuates persistent allodynia, we suggest that an imbalance of pro-resolving mechanisms within the DRG contributes to neuronal sensitization and persistent nociceptive signalling in inflammatory arthritis. To test this hypothesis, we disabled lipid mediator synthesis in macrophages by silencing ALOX12/25 expression and therefore generating CX3CR1Cre:12/15-LOXflox/flox mice and assessed the development of K/BxN serum transfer-induced allodynia and DRG macrophage phenotypes and function.

Methods

Following K/BxN or Control serum transfer (ST), hind paw arthritic scores and mechanical thresholds (von Frey test) were assessed in CX3CR1Cre:12/15-LOX wild type (WT) and CX3CR1Cre:12/15-LOXflox/flox (KO) for up to 25 days. Lumbar DRGs were harvested to isolate macrophages (CD45+CD11b+F4/80+ cells) which

were quantified and phenotyped by flow cytometry. Levels of MaR1 in DRGs were measured by ELISA. Bone marrow derived macrophages (BMDM) were isolated from WT and KO mice and incubated with MaR1 (100 nM) prior to determine phenotypes and efferocytosis properties by flow cytometry. Data are mean ± SE of 6-8 mice per group and statistically analysed using ANOVA+Bonferroni.

Results

K/BxN serum transfer-induced allodynia was exacerbated in KO compared to WT at day 25 post-immunization ($P<0.01$). At this time point, compared to WT DRG, KO displayed higher numbers of MHCII+ (M1) macrophages but less numerous MHCII+MertK+ macrophages. Since the presence of MerTK is associated with pro-resolving mechanisms such as efferocytosis in macrophages, this indicates impairment of pro-resolving mechanisms in KO. Consistently with this suggestion, MaR1 levels were lower in KO compared to WT K/BxN ST DRG. Then, in a series of in vitro experiments, we observed that i) efferocytosis of neutrophils was impaired in KO-derived BMDMs, which expressed lower level of MertK (MFI units) than WT and ii) incubation of MaR1 (100 nM) increased MertK levels in KO derived-BMDMs and restored efferocytic function to WT levels.

Conclusion

Our data suggest that impairment of pro-resolving lipid mediator synthesis in monocyte/macrophages results in macrophage polarization towards a pro-inflammatory phenotype that facilitates nociceptive signalling in DRG under inflammatory pain conditions.

Lay Summary Points

1. Pain is a persistent symptom of rheumatoid arthritis with no current specific treatment
2. We are studying the pro-resolving mechanisms in immune cells for chronic pain
3. Lack of pro-resolving lipid mediators in macrophages increase chronic pain in an animal model of inflammatory arthritis