Pain Centre Versus Arthritis Annual Report

Co-Directors: Professors David Andrew Walsh and Victoria Chapman

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PAIN CENTRE VERSUS ARTHRITIS at the University of Nottingham

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2 MISSION

Pain Centre Versus Arthritis pursues international excellence in multidisciplinary, translational research, thereby enhancing understanding of chronic pain and improving its treatment.

3 INTRODUCTION FROM THE CO-DIRECTORS

During the eventful 2020-21 period, Pain Centre Versus Arthritis has continued to be at the core of research and capacity building in chronic pain. We have, in collaboration with national and international partners from across academic, commercial and public sectors, developed and tested mechanistic hypotheses and translated our knowledge from mechanistic models into clinical tools in order to improve the wellbeing of people living with chronic pain. The Centre's founding Director (Walsh), has taken up the role of Director of the UKRI/Versus Arthritis Advanced PainDiscovery Platform (APDP), and Chapman and Walsh have now formalised their partnership as co-Directors of the Pain Centre Versus Arthritis. With the planned Biomedical Research Centre rebid, APDP and several other opportunities, we are delighted that opportunities are open to expand the Centre's research portfolio even beyond what thus far has been possible. As Pain Centre Versus Arthritis, we emphasise our partnership with and the substantial contributions to our shared mission from the charity, and our historical focus on and continuing commitment to solve the problems of chronic musculoskeletal pain. Our research furthermore aims to benefit from synergies with research on painful conditions beyond the musculoskeletal system, as indicated by our broader mission to reduce the burdens of `chronic pain' in general.

3.1 Pain Centre strategy

The Pain Centre Versus Arthritis research strategy is to build upon the expertise and resources within the partner institutions, and through national and international academic, commercial and stakeholder collaboration, to identify key areas of unmet need and opportunities, to make step changes in the understanding of chronic pain in order to improve its management. The Centre has built an infrastructure for forward and backward translational research, through which information from preclinical and clinical research are integrated within mechanistic pain models. Assessment tools and interventions are developed which can be applied across preclinical and clinical research, enabling new therapeutic targets and biomarkers to be identified, and new treatments to be tested and developed into clinical practice. We have focused on knee osteoarthritis as a common and burdensome model of arthritis pain, and developed novel insights from that condition to inform on other forms of chronic pain, such as rheumatoid arthritis, low back, post-arthroplasty and neuropathic pain. We combine biological, psychological and societal perspectives to better understand and manage the complexity of chronic pain.

3.2 The story so far

Pain Centre Versus Arthritis has become, since its inception in 2010, an internationally leading, translational research Centre which has the goal of advancing mechanistic understanding of chronic pain and improving its treatment. Our unique and integrated multidisciplinary team has expertise bridging orthopaedics, rheumatology, neurosciences, neuroimaging, psychology, genetics, epidemiology, clinical trials and evidence-based medicine, biobanks, preclinical modelling, as well as education and training. Our translational pipeline ensures that key findings from fundamental research move forwards to real benefit for people with arthritis, from increased understanding of mechanisms and target identification to the development of new interventions, their testing through randomised controlled clinical trials. We drive the implementation of positive findings into clinical practice and changing the context of arthritis pain by influencing stakeholder agendas, including funding bodies, government and the public at large.

The multidisciplinary and translational strategy of Pain Centre Versus Arthritis has continued to sustain a high volume of novel research outputs, with 81 peer reviewed publications and scholarly articles during its first 5 years and 411 to date, 56 during the past year alone. The Centre is currently responsible for research underpinned by a total £17.3M active grants (Funding - Table 5), in addition to Versus Arthritis Centre of Excellence award. Core funding from Versus Arthritis has enabled the Centre to attract additional resources from its partner institutions, and from NIHR, MRC, charities and commercial entities. Successful awards in 2017 from NIHR of Biomedical Research Centre (BRC, £4.5 million allocated to musculoskeletal theme) and Clinical Research Facility (CRF, £2.4 million) continue to support the Pain Centre's programme of translational research, under programme leadership from Walsh (Phenotyping Research Area lead), Chapman (Joint Research Area lead), Valdes (Brain Research Area lead), Abhishek (PI for Complex Interventions) and Auer (Imaging cross-cutting theme lead).

The Pain Centre has also contributed to advances in **translational research beyond arthritis**, including the links between arthritis pain and frailty (led by Walsh and Abhishek with Prof John Gladman, Healthcare for the Elderly, and with Prof Paul Greenhaff, Life Sciences), between arthritis pain and the gut microbiome (Valdes and Stocks with Gastroenterology), between pain and mental health and cognitive deficit (led by Auer, Bast, Ferguson with Gladman, Harwood and Greenhaff), and between pain and fatigue (Valdes, Walsh). The Centre's Knee Pain and related health In the Community (KPIC) cohort has contributed both to understanding chronic pain, and by collating systematic data from pain-free (control) populations to facilitate an understanding of benefits and adverse events from Sports and Exercise. Through NIHR funding we have established a large pain and frailty cohort (the Investigating Musculoskeletal Health and Wellbeing survey, IMH&W) with validated datasets on 8570 participants at baseline, and year 1 and 2 follow up surveys completed.

Ongoing expansion of our **biorepositories** (blood, joint fluids and tissues; https://directory.biobankinguk.org/Profile/Biobank/GBR-1-278) from well phenotyped patients and recently deceased individuals provides a platform for lipidomics, proteomics, gene expression and imaging of in order to develop novel joint-specific biomarkers which contribute to and predict OA knee pain. This valuable biorepository has attracted additional funding from the Kennedy Institute and Versus Arthritis charities (including the STePUP-OA project with Oxford), and from other academic and

commercial partners, so as to accelerate the identification of pain targets in the joint, and their translation into clinically useful biomarkers and treatments.

We have continued to develop and benefit from diverse **recruitment** methods to clinical studies, including to questionnaire, imaging and interventional research. Our KPIC and IMH&W cohorts have provided recruitment sources of phenotyped participants for efficient and stratified recruitment to other clinical research studies. We have demonstrated the appropriateness and efficiency of Facebook-based recruitment into an RCT of web-supported exercises for knee pain (WEB-Ex). Ongoing development of **clinical trial methodologies** is aimed at improving their translatability into real clinical benefit. Two group, placebo controlled randomised controlled trials are essential to demonstrate efficacy of interventions to reduce pain. However, translation into patient benefit is often compromised by contextual factors and lack of generalisability from RCT environments. We are addressing between-trial heterogeneity through systematic review and meta-analysis, including between-treatment comparisons through network meta-analysis.

Integration of preclinical and clinical research objectives and forward and back-translation is achieved by close scientific exchange and the development of preclinical models and assessment tools to best model human disease, and clinical assessments to best measure mechanisms of pain identified as potential therapeutic targets in preclinical models. Building upon our previous work demonstrating the bidirectional link between psychological distress and arthritis pain, we have now demonstrated how specific medicines might influence those mechanistic links. For example, the impact of opioid analgesics on the link between arthritis pain and anxiety has been revealed to be bidirectional, with anxiety and catastrophizing associated with increased opioid use, but with opioids being less effective at relieving pain. This barrier to effective opioid relief of chronic pain has been demonstrated both in humans and animal models of OA.

Understanding pain progression has been a major area of Pain Centre research since 2015. We have moved away from the commonly held perspective that pain progression is inevitably one of increasing pain severity, an idea that might have been based on the incorrect assumption that osteoarthritis is simply a disease of ageing and wear and tear. We have shown that for many (we found a majority of) people, knee pain progresses to a place of acceptance, or even resolution. We have reached similar conclusions from our cohorts of people with rheumatoid arthritis. Nevertheless, for an important group of people arthritis pain persists or deteriorates. For many people, the problem of pain changes its character, with increasing psychological impact over time. We have shown how people are often bewildered by why their pain does or doesn't change, and their understanding frequently does not reflect our evidence-based knowledge and might be in conflict with recommended treatment approaches. Our complex interventions strive to address unhelpful beliefs and lift barriers to treatment uptake and benefit.

Our holistic and multidisciplinary research is built upon the understanding we have gained from close partnership with patients and members of the public. Our **Patient and Public Advisory Group** (PPAG) has provided substantial contributions that led us to formulate research questions that not only are tractable, but moreover address important needs of people with arthritis. We combine individual patient experience and perspective, obtained through PPI and qualitative research, with an understanding of societal need. This broader perspective is, in part, gained through the

epidemiological analysis of data collected by the Centre, including our Knee Pain and related health In the Community (KPIC) and IMH&W cohorts. Our PPAG has contributed to the development of 9 major grant applications during the past year, and PPAG members are involved through steering groups throughout the research process for funded projects. Our PPAG has also continued to help us to communicate our findings to a wider public through lay summaries of scientific publications on our website (https://www.nottingham.ac.uk/paincentre/research-publications/publications.aspx). Members of our PPAG provide valuable contributions to our training initiatives, helping our researchers at all stages of their careers to understand how patient and public involvement can best ensure that our research effectively addresses important problems and leads to real change for people with arthritis pain. We contribute to PPI and PPE at a national level, by supporting numerous funding applications and helping steer pain research across the UK.

The Pain Centre has continued to **engage the commercial sector** in the fight against arthritis pain. Commercial engagement has been both through collaborative research (see grants and publication co-authorship), and consultancy. The Pain Centre Versus Arthritis has made major contributions to the international development of nerve growth factor (NGF)-blocking treatments as a novel strategy for addressing OA pain. We have continued to contribute to primary research investigating mechanisms of action and efficacy, both in preclinical models and in clinical trials. We have contributed to the understanding of rare but important joint-related adverse events associated with NGF antibody treatment, helped develop effective mitigation strategies, and contributed to research using real world evidence that will place treatment benefits and risks in the patient's perspective, enabling informed decisions to be made by both patients and physicians about treatment. Recently, we been developing soluble epoxide hydrolase and BDNF/TrkB inhibition as potential novel therapeutic approaches to combat OA pain. We have helped to develop educational packages aiming to move physician understanding of OA from that of a degenerative disease, to its reality as a major cause of pain in which peripheral sensitisation plays a key role.

Our work with **Versus Arthritis** contributed to their development of the Pain Road Map, and has helped catalyse the partnership between Versus Arthritis, UKRI and industry which culminated in the £24m APDP. Walsh was appointed, in open competition, as Director of the APDP, and is bringing together successful consortium and data hub partners, alongside others within the pain research and clinical communities, in order to identify synergies and overlap through which together we can crack the problems of chronic pain. We supported Versus Arthritis to produce its report; `Chronic Pain in England; unseen, unequal, unfair' https://www.versusarthritis.org/about-arthritis/data-and-statistics/chronic-pain-in-england/ . We have hosted the first three annual Versus Arthritis Pain Research in the UK conferences in 2019, 2020 and 2021. The Centre supports Versus Arthritis engagement, training and fundraising activities, and continues to contribute to Versus Arthritis' Advisory and Fellowship Implementation Committees, stakeholder and fellows' meetings, think-tanks and peer review.

The Centre plays a key role in **training and capacity building**. Our Centre for Doctoral Training (CDT) in Musculoskeletal Health and Pain in Ageing and Wellbeing (CDT MHPAW) continues to grow, to the benefit of our clinical and non-clinical scientists. We contributed to postgraduate training at an international level through our partnership in COFUND FRESCO@CNAP and hosting visiting scientists from across the world.. Trainees and graduates from the Centre have progressed to substantive or

higher training positions both within Nottingham, and within the wider research community, further building on their interest and expertise in arthritis pain. Colleagues have gone on to such institutions as Manchester, Newcastle and Bristol Universities. Excellence has been rewarded by numerous prizes to students and staff on their passage through the Centre. Our educational activities aim to support public and other stakeholders, in addition to the pain research community. We are delighted to welcome Dr Sayyed Haybottoallahi to our group of Lead Investigators and Dr Richard James. Richard James is a Research Associate working in Psychology and has since been appointed as Assistant Professor in Psychology. Sayyed was a research associate within the Pain Centre, making important contributions in psychometrics and latent class analysis, and recently appointed Assistant Professor by the University.

The Pain Centre's continuing **outreach activities** engage local and national media, including popular television programmes recently broadcast by Channel 4, and present our research findings and links to other patient and public resources through our website (http://www.nottingham.ac.uk/paincentre). We contribute directly to public and professional educational initiatives, in partnership with international organisations including EULAR, EFIC and OARSI, aiming to increase understanding and so motivate to address the burden and mechanisms of arthritis pain.

Centre members actively shape **national and international healthcare policy**, recently through GDG membership leading to NICE guideline NG193 (Chronic pain in over 16s), and chairing the Technical Committee of the Advisory Council on the Misuse of Drugs (Home Office) and British Pain Society Vice President (Knaggs). We have helped integrate pain research into programmes at other universities where researchers are studying structural, biomechanical, molecular and other clinical aspects of arthritis. Our UK collaborators are based in Oxford University, Kings Colleges and Queen Mary and Westfield in London, Sheffield, Leeds, Leicester, Manchester, Cambridge, Birmingham, Newcastle, Keele, Southampton, and Bristol. International collaborations have spanned the USA, Hong Kong, China and Europe. Engagement with the commercial sector continues to support access to specific and novel drugs for preclinical studies, and funding for collaborative research projects, studies of blood, urine, synovial fluid and tissue biomarkers relevant to OA pain, and randomised-controlled clinical trials.

Headline impacts 2020-21

The joint and the brain are part of the same pain. OA pain almost always has a nociceptive drive, but the OA pain experience is determined by mechanisms within the central nervous system (spinal cord and brain). Our research is shifting the historical perspective that pain is either nociceptive or centrally driven, to better understand that peripheral and central pain mechanisms each provide opportunities for better treatment in every individual with chronic pain. The presence of central pain augmentation does not exclude nociceptive pain, and vice versa. Our questionnaires (CAP-Knee), imaging protocols (joint radiography, ultrasound and MRI, brain MRI) and mechanistic pain assessment tools (e.g. quantitative sensory testing; QST) are enabling both researchers and clinicians to better identify peripheral and central pain mechanisms so as to facilitate personalised and stratified care.

Newly identified molecules in the knee point the way to new treatments: Oxylipins and Brain Derived Neurotrophic Factor are in specific molecular pathways that might be future targets for analgesic development for OA pain.

Osteoarthritis knee pain can get better: We have refuted the commonly expressed public (and professional) perception that OA knee pain is a feature of damage and aging and so will inevitably get worse. Pain progression in OA is not linear and unidirectional. Many people in the community with OA knee pain experience improvement and even resolution with current treatment, and a rush to irreversible interventions such as surgery might for many be avoided. Some people, however, suffer persistent or deteriorating pain. It is difficult to predict who they will be, or for whom treatments might prevent that deterioration and combinations of multiple predictive factors will need to be assessed in order to help individuals with pain to understand their likely outcomes. Similarly, multiple factors predict likely responsiveness to treatment, and predictors of treatment response differ between treatments. We are building on these findings to develop predictive tools in order to help clinicians and patients make informed choices between treatment options.

Anxiety and distress – partners in OA pain: Our research has shifted the research paradigm from seeing biological and psychological aspects of chronic pain as discrete entities that should be studied in isolation, to being integrated into a single pain experience. We have shown that psychological distress has a bigger impact on OA pain than pain has on psychological distress. We have developed techniques and thereby demonstrated alterations in brain functional connectivity that can explain the emotional components of chronic OA pain, as distinct from experimental acute pain, and are conserved between species in humans and rats. The recognition that brain connectivity, rather than structure or local function is the key signature of chronic pain raises opportunities for developing novel interventions for pain, such as transcranial magnetic stimulation, which has already demonstrated benefits in psychiatry by reversing connectivity changes associated with depression. We ensure that both psychological and sensory outcomes are incorporated into studies aiming to improve the burden of pain, by influencing other academic and commercial partners, national and international organisations (e.g. NIHR, UKRI, British Society for Rheumatology, EULAR, American College of Rheumatology and OARSI).

Sometimes the treatment can be the problem: Some impacts of pain can be due to the treatments that people use, as well as to any underlying pathology. We have shown how opioid use is associated with psychological distress in people with arthritis pain, and how anxiety is a barrier to analgesic benefit from opioids, both in humans and in rats. Understanding the molecular mechanisms underlying this observation is leading us to identify novel therapeutic targets that can reduce arthritis pain, and to better advise patients on the likely benefits of specific analgesic agents or adjuvant therapies. We are collaborating with colleagues in Keele University (PROMPPT) to support opioid medicine tapering.

Pain isn't owned by any single diseases: We have demonstrated that arthritis pain phenotypes bridge rheumatological diagnoses, for example with centrally augmented phenotypes associated with knee OA pain, chronic low back pain, and rheumatoid arthritis. We have identified mechanisms of chronic primary pain (e.g. fibromyalgia), neuropathic and bone cancer pain that contribute to the arthritis pain experience. Within diagnoses, some phenotypes might be more dominant than in other diagnoses (for example inflammatory pain in RA), but lessons learned in one disease are informative for the management of pain in other forms of arthritis. We are realising the potential benefit from synergies and overlap between diagnoses, together with the UKRI/Versus Arthritis Advanced Pain Discovery Platform, and the NIHR/NOCRI Musculoskeletal Translational Research Collaboration.

Why me? We have shown that people are often bewildered by changes in their OA knee pain, and often hold beliefs that are contrary to our current understanding of OA pain mechanisms, and might be at odds with empirical evidence on what treatments are likely to be helpful. Patients have quite different perspectives on risks and benefits to those held by clinicians, and different people make different choices when presented with the same information. Helping people to understand and believe the advice that they are given by health professionals, the media and others, requires the development of a therapeutic context that can improve uptake, adherence and benefit from existing treatments. Together with our partners we are developing educational tools for professionals and public, aiming to change understanding of arthritis pain and enable people to benefit from new treatments that work by novel mechanisms.

Rising to the challenge of a pandemic: Solving the problems of chronic pain may feel overwhelming, both for researchers and for those who they are trying ultimately to help. However, step changes in understanding that have arisen from the work of Pain Centre Versus Arthritis highlight that opportunities are even more within our reach than are barriers to our success. 2020-21 raised additional threats to the lives of people living with chronic pain, as the covid-19 pandemic focused attention on life and death and health service overload, forced many people to curtail their activity and activities, and reduced access to the help so urgently needed. Some seductively simple ideas prove much more complex when we start our journey to address them. The covid-19 pandemic necessitated suspension of clinical and laboratory research in order to protect participants and staff. The team in the Pain Centre Versus Arthritis have responded brilliantly. Our research leads have been able to reprioritise their activities to take advantage of the protection and focus enabled by home working. We have initiated research through our existing cohorts investigating the impact of lockdown and particular needs of people with arthritis pain. We have adapted paper questionnaires for web-based administration, and rapidly developed web-based communication systems and conferencing skills. Many of the changes that we have implemented will remain a gold standard for future research practice. Effects of the pandemic have further highlighted the importance of psychosocial factors in chronic pain and its management. We must now use this opportunity to refocus attention on life quality and pain. For many, chronic pain can be worse than death, and it's our duty to help people to live well, rather than barely to survive.

4 RESEARCH HIGHLIGHTS

To achieve our mission to better understand chronic pain in order to improve its management, we describe our research falls under 5 major themes. During 2020-21 we have made substantial inroads into understanding biopsychosocial pain mechanisms under themes of (1) Biomarkers and Novel Therapeutic Targets, (2) Nociplasticity, and (3) Neurocognitive and Psychological Function. We have built upon this increased mechanistic understanding to undertake research that will transform (4) Treatment Efficacy and Real-World Evidence, and (5) Phenotyping and Personalised Medicine.

Research under these 5 themes has highlighted a current and urgent need to address the importance of Comorbidities and Multimorbidity, and the Social Context of Pain, two new and emergent themes.

4.1 Theme 1: Biomarkers and Novel Therapeutic Targets

Pain Centre Versus Arthritis is identifying molecular biomarkers of chronic pain through a combination of `-omics' and targeted approaches, at the level of lipid metabolite pathways, and gene and protein expression. Our biomarker development is linked to pain assessment, in order to optimise prediction or modification of mechanisms that drive pain experience. Biomarkers are selected which reflect key pain mechanisms which might be targeted by existing or novel therapeutics with potential to improve pain. We are developing biomarkers as predictors of need for, amenability to or response to specific pain management approaches.

Pain assessment

Pain biomarkers indicate key determinants of pain experience, and require robust validation against measures of that that experience. Pain assessment remains both rewarding and challenging. Pain is a subjective experience, complex and driven by multiple mechanisms, each of which requires robust assessment in order to understand its underlying mechanisms, the pain experience, and to evaluate its burden and outcomes. Pain Centre Versus Arthritis is pursuing pain assessment tools in humans and in rodent models.

We have been working on **harmonisation of pain-related Patient Reported Outcome Measures (PROMs)**. In partnership with the STEpUP OA consortium we have used systematic literature review and individual patient data to compare psychometric properties of available PROMs used for knee pain. We have demonstrated that Patient Acceptable Symptom State (PASS; the level of pain that an individual would be willing to experience for the remainder of their life) depends less on the specific PROM used, than on diagnosis and therapeutic interventions to which individuals are exposed (Georgopoulos et al., oral communication OARSI). In contrast, pain trajectories differed between different PROMs, suggesting that **discrete aspects of pain may change differently over time** (Haybatollahi et al., submitted). We have developed and validated a self-report mechanistic pain measure, the **Central Aspects of Pain in the Knee (CAP-Knee) questionnaire**, which predicts quantitative sensory testing (QST) evidence of central sensitisation, and predicts future pain severity in people with chronic knee pain (Akin-Akinyosi et al., 2021). The questionnaire is currently being adapted and validated in other painful chronic musculoskeletal conditions, such as rheumatoid arthritis, and tested as a tool to determine who will gain most benefit from treatments that target central sensitisation.

Self-report questionnaires are the gold standard for measuring the subjective experience of pain, but have limitations in people with communication difficulties, are not amenable to continuous monitoring, and are not feasible in preclinical research. We have developed a **mobile App** suitable for administering pain questionnaires as frequently as daily (Stocks; EOSCsecretariat.eu (831644)). We use and are further developing additional behavioural indices of pain. We are exploring **automatic chronic pain assessment from facial and bodily expressions** in humans. Through the EmoPain 2020 international data challenge, Valstar's team are using recent advances in Computer Vision technologies to create a uniform platform for the comparison of multi-modal machine learning and multimedia processing methods of chronic pain assessment from human expressive behavior. The EmoPain dataset has been made available to researchers in a competition framework to develop automated systems that can recognize or quantify pain from facial and bodily expressions. Such an approach will enable real-time monitoring and feedback, as well as identification of previously unrecognized pain-related behaviours. Our work progresses from existing systems that are built on pain expressions induced in constrained environments and by non-threatening stimuli, towards a fuller representation of real-world distressing physical activities encountered by people with chronic pain. The EmoPain dataset consists of behavioural and physiological signals collected from people with or without chronic pain performing everyday activities.

Behavioural pain assessment in humans is particularly important in people with verbal communication difficulties, such as children and those with cognitive impairment. Pain relief in children is a moral imperative, and also inadequate pain treatment could negatively impact the infant's neurological development later in life. Valstar et al. are developing a **machine-assisted automatic neonatal pain assessment system** that combines multimodal pain cues—behavioural, autonomic, muscle and brain activity—for pain estimation in neonates. This approach will provide repeatable, real-time pain monitoring via analysis of human expressive pain-related behaviours, and give notifications when excessive pain levels are detected. Joy Egede was also awarded the L'Oreal-UNESCO 2020 UK For Women in Science Rising Talents fellowship award for this work (https://unesco.org.uk/https/unescoorguk/loreal-for-women-in-science-award/joy-egede/).

Biomarkers and novel therapeutic targets

We have used liquid chromatography-high resolution mass spectrometry to characterise **metabolic signatures of OA** in human urine (Abdelrazig et al., 2021), and identified plasma lipids that are associated with pain behaviour in murine OA (Pousinis et al., 2020). We have identified that the balance between epoxy- and dihydroxyeicosatrienoic acids (EETs and DHETs) is associated with more severe pain in human and rodent OA, leading us to successfully target enzymes which modulate lipid balance to reduce pain behaviour in rodent models. These lipid pathways are important in determining the balance between inflammation and its resolution, and correspondingly between the generation and resolution of chronic pain. We have shown that in addition to actions within the periphery, **resolution pathways act within the central nervous system as neuroimmune mediators to modulate spinal neuronal excitability** and, thereby, central sensitisation (Meesawatsom et al., 2020).

We have extended understanding of the potential for neurotrophin inhibitors to alleviate OA pain. We have demonstrated that osteochondral innervation density is associated with OA pain both in humans and rats, and that inhibition of TrkA, the high affinity receptor for nerve growth factor (NGF), reduced OA-associated osteochondral innervation in the meniscal transection OA model in rats, in proportion to reductions in pain behaviour (Aso et al, 2020). NGF pathway inhibition therefore may not only have short term analgesic benefit by reducing peripheral sensitisation, but might also **reduce the long term structural changes (neoinnervation) that are associated with chronic OA pain**. Furthermore, we showed that **brain derived neurotrophic factor (BDNF) also contributes to OA pain mechanisms in the joint** through peripheral expression and effects on sensitisation (Gowler et al., 2020). BDNF was previously thought of as a component only of central nervous system neuromodulatory pathways,

Donaldson and colleagues have identified **splicing factor kinases as exciting novel therapeutic targets for OA pain**. VEGF-A comprises of two splice variant families, VEGF-Axxxa and VEGF-Axxxb resulting from alternative splice site selection in exon 8, controlled by Serine/Arginine Rich Splicing Factor Kinase 1 (SRPK1), which phosphorylates Serine/Arginine Rich Splicing Factor 1 (SRSF1). In most normal tissues, VEGF-Axxxb isoforms predominate, with antinociceptive and anti-angiogenic functions. In contrast, in inflammation SRPK1/SRSF1 activation causes VEGFAxxxa isoforms to predominate, exerting pro-nociceptive actions. Donaldson and colleagues have now used human synovial tissues from age- and sex-matched cases, further matched for structural OA severity, with or without symptoms (n=20 per group). Total VEGF-A, SRPK1 and SRSF1 expression and activation, and ratio of a to b isoforms were higher in symptomatic than in asymptomatic synovia. Successful proof-of-concept experiments have used our novel small molecule splicing kinase inhibitors to reduce pain behaviour in a rodent model of chemotherapy-induced painful peripheral neuropathy.

De Moor and colleagues are developing **polyadenylation as a therapeutic target in chronic pain**. Mechanistic insight in to the synthesis, degradation and function of the poly(A) tails of messenger RNAs is linked to biological actions of the natural product cordycepin. We have generated a large dataset of mRNAs that are localised in axons of primary nociceptive neurons, and, in collaboration with Ted Price (UT Dallas), has obtained an mRNA set of interest for siRNA knockdown and polyadenylation inhibition. We have compared several high throughput datasets for cordycepin to identify shared pathways affected in different cell types, revealing strong association with PI3K signalling as the likely mechanism by which polyadenylation inhibition by cordycepin reduces inflammatory pain. We are further exploring medicinal chemistry and molecular pharmacokinetics of cordycepin in order to develop pharmaceutical products suitable for clinical trials.

Additional molecular targets for OA pain, identified through genetic, expression and proteomic approaches, have become foci for analgesic development, including metalloproteinases, and IL15 (Warner et al, 2020).

In parallel to our studies of molecular biomarkers and novel therapeutic targets, we have been using brain magnetic resonance imaging (MRI) to characterise nociplasticity in chronic pain, as a biomarker of chronic pain and of beneficial and adverse effects of analgesic interventions, and as a tool to target novel neurostimulation interventions aiming to relieve pain by modifying brain connectivity (see below). Auer and colleagues are using data from UK Biobank to identify, as potential novel targets for treatment, imaging-derived pain phenotypes linked to genotypic data. Dajas-Bailador and colleagues are further exploring DRG micro-arrays and axoplasm sequencing in microfluid chambers, enabling targeting to axon terminals. In parallel we are developing intra-articular siRNA delivery to modulate peripheral nocicicceptive activity.

4.2 Theme 2: Nociplasticity

Nociceptive mechanisms are not hard-wired, but rather change across the life course, and with time from disease onset. This nociplasticity (Walsh, 2021) may manifest clinically as sensitisation or endogenous analgesia, and is underpinned by changes in both peripheral and central nervous systems.

We have demonstrated how various **joint insults lead to similar structural changes of osteoarthritis in mice and rats, but very different pain phenotypes**, indicative of different adaptive responses in nociceptive pathways (Gowler et al., 2020). One mechanism by which peripheral nociceptive nerves adapt is referred to as hyperalgesic priming, whereby repeated stimuli generate enhanced neuronal activation. Another is by changing dorsal horn innervation. We show that, **in contrast to adults, neonatal rodents display reduced nociplastic responses to peripheral inflammation** (Cooper et al., 2020).

Using arterial spin labelling MRI (Iwabuchi et al., 2020) and BOLD fMRI, we showed that **brain connectivity changes with pain chronification in knee osteoarthritis**. The antidepressant duloxetine, a combined serotonin and noradrenalin reuptake inhibitor, has mild-moderate analgesic effects in musculoskeletal pain. We undertook a randomized placebo-controlled double-blinded mechanistic imaging trial to investigate the neural mechanisms of duloxetine analgesia in knee OA, and to assess baseline imaging predictors of its analgesic response. Fifty six participants with chronic painful knee OA completed the trial, receiving 6 weeks of duloxetine or placebo (2:1 allocation). We showed that **subgenual functional connectivity at baseline may have value in predicting analgesic response to duloxetine**. Lower baseline functional connectivity of the right anterior insula (rAI) with the right posterior insula and striatum ($Z>2.3$, FWE and FDR corrected, $p<0.05$) predicted analgesic response to duloxetine, whereas high baseline subgenual anterior cingulate cortex (sgACC) connectivity with the cerebellum and occipital cortex predicted non-response ($P=0.05$, $Z>2.3$, FWE and FDR corrected). Our data suggest that **rAI-left M1 functional connectivity decreases may be a key neural mechanism driving pain relief after duloxetine treatment**. Specific (placebo-controlled) functional connectivity

changes with duloxetine comprised decreased connectivity between the rAI and parieto-occipital and left pericentral cortices, and increased connectivity between the anterior mid-cingulate and medio-dorsal thalamus/habenula, and between the left amygdala and parieto-occipital cortices. Other pharmacological actions of duloxetine on functional connectivity did not overlap with analgesic effects, but may rather mediate other specific effects of duloxetine on affective brain circuits.

Functional connectivity changes in human OA underpin co-morbid psychological distress linked to chronic pain. Over the last year we have developed new fMRI experimental protocols to study functional connectivity in rodent models of OA pain. In normal anxiety rats, **functional connectivity differences were observed in rats after OA induction by intra-articular monoiodoacetate injection**, when compared to saline injected controls. Our data support the hypothesis that **changes in brain functional connectivity explain co-morbidity between chronic pain and anxiety**. We found differences in the relationship between pain behaviour and functional connectivity in rats with normal versus high anxiety phenotypes. In Wistar Kyoto rats, which display anxiety-like behaviour, different functional connectivity changes occurred after OA induction, between regions related to pain processing, including the ventromedial prefrontal cortex (vmPFC) and the periaqueductal grey (PAG). These differences suggest enhanced coupling of pain with emotional processing and descending modulatory systems. Correlations between vmPFC functional connectivity and weight borne on the affected joint support these changes being related to the pain phenotype in the model, consistent with observations in people with OA. These studies pave the way for future research studies investigating the longitudinal changes in functional connectivity during the initiation and progression of OA pain, in order to understand early versus late brain mechanisms contributing to the chronification of pain.

fMRI biomarkers of chronic pain directly inform novel interventions to modulate brain connectivity through transcranial magnetic stimulation (TMS)(Hodkinson et al., 2021). Ongoing experimental work is developing accelerated imaging-guided TMS in people with chronic OA pain, to inform design of an efficacy randomised controlled trial.

Opioids are often used by people with chronic musculoskeletal pain, and opioid pathways underlie some endogenous analgesic mechanisms. However, long-term opioid use is often associated with diminished pain relief, hyperalgesia, and addiction, and inefficient endogenous analgesia may contribute to chronic pain. We and others have shown high opioid use despite poor response to opioids are associated with psychological phenotype in people with chronic pain. We have now demonstrated **opioid-related brain network alterations in people with chronic knee pain in the right amygdala and left mediodorsal thalamic nuclei**, brain regions that play key roles in affective pain processing and are particularly rich in mu opioid receptors. Our findings indicate key brain networks which may underpin opioid response, non-response and adverse events in people with chronic pain, and may be targets for interventions aiming to facilitate endogenous and pharmacological analgesia.

4.3 Theme 3: Neurocognitive and Psychological Function

We have elucidated key roles of psychological processes in pain progression. We have demonstrated a dynamic relationship between arthritic pain, cognition and anxiety (James and Ferguson, 2020). **Cognitive ability is initially protective against adverse pain experience following a diagnosis of arthritis, but over increasing time with pain the beneficial effects of cognitive ability reduce**. Cognitive decline with aging may both contribute to the escalation of pain, and be driven by chronic pain or its treatment. Our analysis of data from the Survey of Health, Ageing and Retirement in Europe (SHARE) database (n =1,240) indicates that cognitive ability may in part explain links between social deprivation, low educational attainment and chronic pain (Kouraki et al., submitted). Therefore, improving cognitive function may dampen the impact of social deprivation and low educational attainment on poor health and chronic pain, and may help to promote independence in patients with osteoarthritis. Cognitive impairment is not only a problem for ageing populations, and we are also exploring associations with joint damage, pain and cognitive decline in former professional footballers (Zhang and colleagues).

Bast and colleagues have begun studies using classical and newly developed **translational behavioural assays of distinct neuro-cognitive functions** (prefrontal cortex-dependent attentional and executive functions, hippocampal-dependent memory functions). These will be used alongside measurements of pain and other psychological functions in people with knee OA in order to investigate the impact of chronic pain on specific neuro-cognitive functions (REC approval obtained, Kouraki et al., submitted). In collaboration with colleagues at Hong Kong Polytechnic University (Ben Yee, Frank Lai), Bast plans to apply our new translational assay of hippocampus-dependent rapid place learning to examine hippocampus-dependent memory in people living with rheumatoid arthritis or osteoarthritis in the Hong Kong community. In parallel studies in rats, we have now also developed approaches to measure clinically relevant cognitive functions following induction of the monoiodoacetate-induced model of knee OA pain.

We have shown that **pain progression varies dependent on personality traits**, providing a novel perspective on the limitations of conclusions based on average rather than individual participant data, and the need for personalized approaches to pain management (James et al., 2021). Our longitudinal analysis over 14 years, used data from a subsample of 443 arthritic respondents from the English Longitudinal Study of Ageing (ELSA) study. Modelling heterogeneity led to the identification of specific stratified effects for personality (neuroticism, agreeableness, and extraversion) that were not observed when these data are treated as homogenous. Higher agreeableness was associated with worse pain for those in a sub-group reporting the greatest pain, and higher extraversion was protective against pain among those whose pain improved.

4.4 Theme 4: Treatment Efficacy and Real-World Evidence

Better understanding the nature, mechanisms and consequences of existing treatments is key to reducing the burden of chronic pain, before new and more effective treatments become available. Pain Centre Versus Arthritis therefore combines experimental medicine studies of existing therapies (for example studies using duloxetine, above), with systematic literature review, observational and cohort studies, and randomised controlled trials of new therapies. Findings in clinical practice may not always replicate those from the highly controlled context of clinical trials, due both to the highly selective nature of participant recruitment and outcome assessment. Pain management, and its consequences in the real world are determined by more than specific analgesic mechanisms. We use methods from Evidence Based Medicine and real-world evidence to better understand the burden of chronic pain, to produce guidance to people with chronic pain, clinicians and other stakeholders, and to accelerate the translation of experimental findings towards clinical benefit.

We have used systematic review, traditional, network and individual patient data (IPD) meta-analysis to estimate efficacy of current interventions for musculoskeletal pain. We have quantified the **limited specific analgesic benefit gained from glucocorticoids**, either administered by intra-articular injection in osteoarthritis (Ayub et al., 2021), or systemically in rheumatoid arthritis (McWilliams et al., 2021). Analgesic benefit from the use of glucocorticoids is substantially enhanced by contextual (placebo) effects. We have synthesised evidence that **various interventions improve pain in people with fibromyalgia** (Kundakci et al, ACR Convergence Meeting Abstract 2020).

Pain Centre Versus Arthritis has **established bespoke cohort studies**, to complement other national and international databases (e.g. ELSA, CPRD, SHARE, see other sections of this report). Our **Knee Pain and related health In the Community (KPIC)** cohort of people recruited from the community aged >40y with or without early or established knee pain, underwent a 4th wave of data collection in 2020, 6 years after baseline, with approximately 70% response rate. The main objective of this 4th wave data collection, led by Zhang, is to examine whether musculoskeletal pain becomes more prevalent, widespread or severe during during the COVID-19 pandemic, for example due to changing levels of stress and anxiety during lockdown. Our **Investigating Musculoskeletal Health and Wellbeing (IMH&W)** survey of people with or at risk of musculoskeletal pain or frailty (Millar et al., 2020) has undergone its 3rd wave of data collection, led by Walsh. IMH&W has also been linked to a bespoke Covid-19 survey, including additional self-report psychosocial outcome measures (Valdes and colleagues). For both cohorts, electronic data collection has been developed, and the surprisingly low impact of electronic data collection on response, bias and repeatability has been evaluated. Additional analysis of national databases has enable us to improve estimates of the **incidence and prevalence of osteoarthritis in the UK** (Zeng et al., 2021), and the **increased risk of fracture in people taking opioids** (Peach et al., 2021), as well as highlighting **disparities between initial analgesic prescriptions for osteoarthritis and evidence-based guidelines** in the UK during the period to 2016 (Zeng et al., 2021). The Nottingham cohorts will be integrated with other national datasets through the recently awarded UKRI/Versus Arthritis Advanced Pain Discovery Platform Data Hub.

We have extended findings from these large scale, data-driven studies with more detailed evaluation of factors which drive preferences in people seeking analgesic medications for osteoarthritis or low back pain (Turk et al, 2020, Walsh et al., submitted). We demonstrated **heterogeneity between individuals in patterns of analgesic preference, driven by their different perspectives of treatment efficacy, adverse event risk or cost**. Remarkable similarity was demonstrated between UK and USA populations. Opioid-related tolerance and addiction emerged as of particular concern, although many participants were generally willing to accept substantial risk of adverse events in return for analgesic benefit. Opioid-related constipation was characterised as a major limitation of strong opioids in a separate study (Morgan et al., 2021). Personalised approaches are needed to enable people to balance benefits against risks when selecting analgesic interventions, according to their own values.

We continued our contributions to **development of Nerve Growth Factor (NGF) blocking antibodies towards clinical practice** through design and interpretation of a Phase 3, international, randomised controlled trial in people with lower limb osteoarthritis who were eligible for, but had inadequate analgesic benefit from oral NSAIDs (Hochberg et al., 2021). We demonstrated significant and sustained analgesic efficacy of tanezumab in people with lower limb osteoarthritis, together with precise estimates of incident rapidly progressive osteoarthritis (RPOA). Recognising the complexity and multimodal nature of evidence-based treatment, we have designed and evaluated feasibility of a **multiple randomised controlled trial cohort study to test health-professional led delivery of a complex package of pharmacological and non-pharmacological osteoarthritis care** based on current NICE guidelines (Hall et al., 2020). This study benefits from embedding within the IMH&W cohort, with a design that permits concealment of the study intervention from cohort controls, thereby avoiding some limitations of `usual care' trial designs evaluating complex interventions. We have demonstrated intervention fidelity (Nomiokos et al., 2021), and patient and professional acceptability (Nomiokos et al., submitted).

We demonstrated through individual patient data (IPD) analysis the currently weak predictability of specific analgesic response to topical non-steroidal anti-inflammatory drugs (Persson et al., 2020). We then demonstrated the feasibility of using a **multiple n of 1 trial to demonstrate potential predictive factors of analgesic responses to topical treatments for knee OA pain** (Persson et al., 2021). Ultrasound evidence of synovitis and quantitative sensory testing evidence of central sensitisation emerged as potential predictors of response to topical NSAIDs or capsaicin respectively. Further IPD analyses in collaboration with the OA Trial Bank (https://www.oatrialbank.com/) are exploring predictors of analgesic response to placebos, oral NSAIDs, Vitamin D and exercise therapy.

We use contribute to guideline development in order to translate research on treatment efficacy and real world evidence into patient benefit, through contribution to guidelines and consensus statements (Levy et al., 2021), and professional and public educational materials.

4.5 Theme 5: Phenotyping and Personalised Medicine

Our research findings converge with those of others to highlight heterogeneity in pain mechanisms, outcomes and perspectives between different people with musculoskeletal pain, while recognising shared patterns between diagnostic groups. Balance between peripheral nociceptive drive and central pain modulation explains some heterogeneity in pain experience between individuals with osteoarthritis, rheumatoid arthritis or low back pain. Various genetic backgrounds, comorbidities, personality, affect and cognitive function and style, treatment history and social context contribute to the diversity of pain experience and aspirations. We have modelled specific aspects of this heterogeneity in our preclinical studies, through different species and strains, modes of OA induction, and stages of disease progression. We have used our increased understanding of pain heterogeneity to predict prognosis and treatment outcomes. Our ideal would be to offer individual patients an informed choice, based on their personal probabilities of treatment success or failure, enabling them to embark on treatments that meet their own particular needs. Such a personalised approach contrasts with the `try it and see' or `one size fits all' approaches prevalent in current clinical practice, which too often leads to protracted and repeated treatment failure and disengagement from healthcare before treatment can be optimised.

Our cohort studies have identified participant subgroups with discrete pain prognosis, and indicate potential early predictors of subgroup allocation. Personalised care is at the centre of our multiple randomised controlled trial cohort study of health professional led pharmacological and non-pharmacological intervention for OA knee pain (Hall et al., 2020). Our n of 1 feasibilty trial of topical NSAID and capsaicin treatment for OA knee pain demonstrated clinically important and frequent individual differences in treatment response to either agent, despite similar overall mean efficacy for the study group as a whole (Persson et al., 2021). Our patient preference studies have demonstrated heterogeneity in personal values, that will lead different patients to choose different treatments when provided with the same information (Turk et al., 2020, Walsh et al., submitted).

We have developed and validated a simple self-report questionnaire (Central Aspects of Pain in the Knee; CAP-Knee) as a marker of central pain mechanisms (Central Mechanisms Trait; CMT). CAP-Knee is derived from 8 characteristics which we have demonstrated to be associated with QST evidence of central sensitisation; anxiety, depression, catastrophizing, cognitive impact, sleep disturbance, fatigue, neuropathic pain qualities and widespread pain distribution. CMT predicted poor pain prognosis in people with knee pain from the KPIC cohort (Akin-Akinyosoye, 2020), and the validated CAP-Knee questionnaire was validated and also demonstrated prognostic utility in IMH&W participants (Akin-Akinyosoye, 2021). Our ongoing work is investigating the potential for CMT to predict specific analgesic response to duloxetine, its specific associations with muscle function and activity, and prognosis and outcomes in other musculoskeletal conditions such as rheumatoid arthritis.

4.6 Emergent themes

Our findings within our 5 key research themes has repeatedly directed our attention towards 2 additional emergent themes; comorbidity and comorbidity, and the social context of chronic pain.

Comorbidity/Multimorbidity

Most forms of arthritis, and particularly osteoarthritis, increase in prevalence with increasing age, such that **people with arthritis pain commonly have additional morbidities** which influence disease, its treatment and outcomes (Swain et al., 2020). Higher numbers of comorbidities are associated with greater pain severity and impact, whether comorbidities precede or follow arthritis onset (Swain et al., 2021). Comorbidities affect both disease and treatment choice or response, either directly or through interventions used to treat the comorbidity itself (Sarmanova et al., 2020). Use of NSAIDs and polypharmacy are particularly influenced by multimorbidity. We are now exploring how associations of comorbidities associations with central pain mechanisms and BMI may explain variations between individuals. Zhang is leading the "Comorbidities in Osteoarthritis (OA)" initiative, supported by the European Foundation of Research in Rheumatology (FOREUM) (https://www.foreum.org/comorbidities_oa.cfm), with collaborators from UK, Netherlands, Sweden and Spain. Through it we will identify the temporal relationship between OA and comorbidities, clusters, trajectories and associated risk factors, and explore causality between painful OA and comorbidities. We anticipate that strategies that we are developing to facilitate de-prescribing of analgesics will reduce multimorbidity in people with OA.

Social Context of Pain

Pain experience, outcome, impact and burden display substantial inequalities across ethnic and social groups, both within communities, and across the world. Zhang is leading the Comorbidities in Osteoarthritis (OA) study to characterise and explain variations across Europe, and, by doing so to inform strategies to improve outcomes in currently disadvantaged communities. Using the SHARE database, we have shown that social deprivation before osteoarthritis diagnosis predicts higher pain levels and functional impairment after diagnosis. Functional impairment prediction by premorbid social deprivation was partly mediated by impaired cognitive function (see above). We also showed for the first time that education may improve cognitive function and reduce anxiety before diagnosis, and was protective against impairments in daily living after diagnosis. These findings suggest that improving cognitive function and managing anxiety may dampen the impact of social deprivation and low educational attainment on poor health and chronic pain, and may help to promote independence in patients with osteoarthritis (Kourakis et al., submitted). Effects of social context are insidious, and may be concealed by introducing biases into pain research. Ferguson and colleagues are exploring temporal trends and diversity, particularly effects of ethnicity, on research participation. Pain mechanisms may differ between people from different cultural backgrounds, through differences in biological, psychological and social factors. We are undertaking a systematic review and meta-analysis

on ethnicity and pain and created an integrated data set from the Health Survey of England (HSE) over 14 years (1977-2010) to examine associations between ethnicity, pain, Socio-Economic-Status (SES), arthritis diagnosis and pain [Prospero CRD42020210045]. Latent class growth models are helping us to further investigate reciprocal effects of social domains (e.g. social isolation, effects on communities, deprivation) on pain phenotypes and medication use.

4.7 Public and Patient Involvement and Engagement

Patient and Public Involvement, Engagement and Participation (PPI/E/P)

Pain Centre Versus Arthritis - PPIE Strategy

Our strategy is to support people with chronic pain through a process of open and two way communication to allow a better understanding of patient needs and priorities for research and quality of life. We will achieve this by facilitating public and patient engagement and involvement throughout all research activities and ensuring their opinions are embedded within all pain research at the University of Nottingham with involvement and collaboration across the School of Medicine and NUH harmonising patient involvement of each and every pain research team, and across each and every disease. We will take a proactive approach to make our work as relevant, and our approach to research as transparent, to the public and patients as it is to all other stakeholders in chronic pain research.

Strategic priorities:

- Create a supportive culture with opportunities for two-way communication.
- Encourage partnerships between researchers and PPAG members.
- Provide guidance and clarity to all stakeholders in the PPI/E process and instil the UK standards for good public involvement in research in all PPI activity (https://sites.google.com/nihr.ac.uk/pi-standards/home).
- Create a framework of training and support to inspire participation in the PPI/E process.
- Drive forward PPI/E impact in research by creating measurable research goals.
- Align our PPI/E activities with our partners (esp. School of Medicine, but also NUH, Versus Arthritis, etc) to grow a network of support and collaboration.

Aims:

Our aim will be to support research leaders in the co-design of research by offering opportunities for training in the principles and practice of PPI/E whilst also continuing to grow and diversify our network of lay members to ensure sustainability. Our membership of Sharebank will encourage shared learning and resources to support our advisory group members perform effectively and with confidence. We will work towards a model of co-production, co-creation of research design and inclusivity of all stakeholders including lay partners, scientists, and practitioners to ensure greater depth of understanding and to capture all opinion to drive innovation in pain research from bench to bedside.

PPIE Research Activity

CASE REPORT:

An example of our continued efforts to increase diversity in PPI involvement are demonstrated in our ongoing activities for diversifying our patient advisory group. Initial activity focussed on the IMHW cohort to approach registered IMHW participants. Bonnie Miller and Team, disseminated our invitation to join the Patient Advisory Group (PAG) to approximately 600 cohort participants who identified with two groups under-represented in the PAG. The invitations were sent out in small batches via email and to date we have recruited 3 additional members. However, this activity highlighted the low level of diversity within both the PAG and the IMHW cohort and has now informed a proposal for funding to investigate this disparity further. Current activity includes the creation of a Research team and funding application as follows.

Title: **Bias in Pain Research: Barriers to recruitment and retention of culturally diverse patient groups for PPI and research** (working title)

Summary (max 250 words): Increasing ethnic diversity in the UK patient population requires a step change in the relationship between patient, research and healthcare provider. Findings from a review in 2008 (1) examining cultural influences on pain perception, found disparities in pain treatment based on ethnic background. Culture is mistakenly thought to drive health-seeking behaviour. However more likely an acceptance of their own pain and any treatment required may be shaped by a person's ethnicity, lived experience and social culture which in turn will drive belief of their own healthcare needs.

Patient and public involvement (PPI) in research is designed as an activity that can explore the patients perspective of health and treatments and identify any barriers to health-seeking behaviour. To achieve a successful programme of PPI activity, and support research that fully represents the UK standards for public involvement in research, the PPI community needs to be representative and fully inclusive. However current and ongoing practice based pain research has identified significant gaps in recruitment to both PPI groups and patient research cohorts from ethnically diverse patient populations (unpubl).

Multidisciplinary pragmatic research is needed to examine different models of pain. Urgent research is needed to understand own health perceptions and treatment seeking behaviour in different cultural groups to better understand how pain is perceived, including beliefs and expectations about the need for treatment, in these groups and to allow pain researchers and healthcare providers to offer practical, relevant and effective evidence-based pain management.

PPI/E ACTIVITY:

This year we have supported the following activities.

Table 1. PPI Involvement Activities

Event	Month/Year	Researcher	Facilitator
Multimorbidity Co-Applicant request	Jan-20	Prof Weiya Zhang	Julie Jones-Diette
COVID 19 PPI task force	Apr-20	Kate Frost	Julie Jones-Diette
CAP-Knee questionnaire	Jun-20	Steph Smith	Julie Jones-Diette
CAP-Knee questionnaire	Aug-20	Steph Smith	Julie Jones-Diette
Microbiota questionnaire	Aug-20	Prof Ana Valdes	Julie Jones-Diette
APDP consortium email	Aug-20	Prof David Walsh	Julie Jones-Diette
NICE Guideline development for VA	Sep-20	Laura Boothman	Julie Jones-Diette
Cap knee Co-app recruitment for cap knee study.	Nov-20	Steph Smith	Julie Jones-Diette
Request for lay summary protocol review.	Nov-20	Steph Smith	Julie Jones-Diette
Lay summary review for publication x 3 27th Nov 2020 only sent to 6 x PPI lay summary volunteers	Nov-20	Julie Jones-Diette	Julie Jones-Diette
Lianne Woods RfPB grant questionnaire	Dec-20	Lianne Woods	Julie Jones-Diette
Fibromyalgia data review- personal invitation to patient reps to attend discussion group on 1st Feb 2021	Jan-21	Prof Abhishek Abhishek	Julie Jones-Diette
Request for feedback on summary of protocol for knee pain and OA. Pain relief foundation. Sent to subset of PAG	Jan-21	Steph Smith	Julie Jones-Diette

Event	Month/Year	Researcher	Facilitator
IMHW cohort diversity recruitment	Feb-21	Julie Jones-Diette	Julie Jones-Diette
Request RA grant application discussion	Mar-21	Prof Abhishek Abhishek	Julie Jones-Diette
Podcast EULAR involvement invitation email sent	Mar-21	Prof David Walsh and Steph Smith	Julie Jones-Diette
Lay summary review for publication x 1 only sent to 2 x PPI lay summary volunteers	Mar-21	Julie Jones-Diette	Julie Jones-Diette
Co-applicant approach for Covid study	Apr-21	Prof Abhishek Abhishek	Julie Jones-Diette

Table 2 - PPI Engagement activities

Event	Month/Year	Researcher	Facilitator
COVID 19 message of support	Apr-20	Prof David Walsh	Bismillah Kosser
PPIE summary email	Jun-20	Julie Jones-Diette	Bismillah Kosser
Email flyer 'How to beat pain' Channel 4 TV program	Aug-20	Joanne Stocks	Bismillah Kosser
Emailed 'hello from the PPI lead'	Nov-20	Julie Jones-Diette	Julie Jones-Diette
Christmas card sent to all PAG	Dec-20	Pain centre	Bismillah Kosser
SoM blog email- 50 at 50 celebrations	Mar-21	Julie Jones-Diette	Rose Farrands-Bentley
Midlands PPI/E training email flyer	Mar-21	Julie Jones-Diette	Julie Jones-Diette
PPI event- PPIE Oxford BRC statistics webinar email flyer	Mar-21	Julie Jones-Diette	Julie Jones-Diette
Virtual research lounge event flyer sent	Apr-21	Julie Jones-Diette	Julie Jones-Diette
Spring seminar event -SoM PPIE working group flyer	Apr-21	Julie Jones-Diette	Julie Jones-Diette
Spring seminar event 2- SoM PPIE working group flyer	Apr-21	Julie Jones-Diette	Julie Jones-Diette

Event	Month/Year	Researcher	Facilitator
Oxford PPI webinar flyer	Apr-21	Julie Jones-Diette	Julie Jones-Diette
Spring seminar event 3- SoM PPIE working group flyer	May-21	Julie Jones-Diette	Julie Jones-Diette

4.8 Impact Case/Added Value Example

Identification and translation of novel treatments and biomarkers for chronic pain

BRC clinical and academic activity has enabled us to access expertise and infrastructure and attracted funding from industry. This synergy has led the MSK theme to achieve early translational success within the Pain Centre Versus Arthritis at Nottingham. Commercial support attracted to Nottingham for pain-related research within the MSK theme includes £800k in active grants within the past year, supporting human validation for novel targets associated with OA pain identified through –omics approaches in human tissues (Eli Lilly and Co), development of a stratification tool for targeted pain management in rheumatoid arthritis (Pfizer Ltd), and identification and validation of circulating biomarkers of central pain sensitisation in knee osteoarthritis (Pfizer Ltd/ Eli Lilly). Commercial partnerships have given the NIHR Nottingham BRC access to expertise and infrastructure within the pharmaceutical sector, including proteomics, gene expression, pathway analysis, genomic analysis, biomarker probe synthesis and SiRNA technologies to support its early translational pain research. Partnership with industry (Pfizer Ltd, AbbVie) has enabled the NIHR Nottingham BRC to elucidate real world evidence using CPRD and HES datasets on the management of osteoarthritis and low back pain, patient perspectives on balancing risks and benefits of pain management in a UK population compared with USA, and to develop educational materials alerting the clinical community to the unmet needs of patients and health systems due to the great burden of musculoskeletal pain, how current guidelines may best be implemented, and to approach the future of MSK pain management with optimism. Pharmaceutical support (Lilly, UCB Pharma) combined with BRC and charitable funding has enabled us to develop a sustainable cost-recovery model for collecting and curating human data and biosamples underpinning the study of pain in MSK disease

4.9 Training and capacity building in chronic pain

The Centre plays pivotal roles in training and capacity building. We provide an ideal environment in which both trainees and established researchers thrive. Our Centre for Doctoral Training (CDT) in Musculoskeletal Health and Pain in Ageing and Wellbeing (CDT MHPAW), launched in October 2015, has continued to grow, and with the current implementation of Versus Arthritis' new strategy for its Centres of Excellence, the management of the CDT is moving increasingly to the NIHR Nottingham BRC, with continuing input from the Pain Centre Versus Arthritis, and continuing to benefit to our students. A recently awarded Nottingham-Adelaide PhD scholarship will explore pain mechanisms relevant to physiotherapeutic assessment and intervention (Hall). The CDT provides PhD training for clinical and non-clinical scientists. We contributed in 2021 as partners in COFUND FRESCO@CNAP (led from Aalborg, Denmark, funded through the Marie Sklodowska-Curie framework) to CNAPs highly successful virtual workshop, open to all international PhD students. The Pain Centre has also provided research training to undergraduate and Masters students,

Clinical Fellows, ST2 trainees and clinical psychology doctorate. Visiting scientists have originated from Birmingham, Japan and China, building their own expertise and consolidating productive international collaboration. Trainees and graduates from the Centre have progressed to substantive or higher training positions both within Nottingham, and within the wider research community, further building on their interest and expertise in arthritis pain. Colleagues have gone on to such institutions as Manchester, Newcastle and Bristol Universities.

The Pain Centre's continuing outreach activities engage local and national media, and present our research findings and links to other patient and public resources through our website (http://www.nottingham.ac.uk/paincentre). Dr Jo Stocks and Walsh have helped develop and film popular Channel 4 programmes aiming to help people with self-management for chronic pain (2020), and on exercise and chronic pain (`Steph's Packed Lunch', spring 2021). We work closely with trainees and staff to help them to develop skills communicating beyond the scientific community. Our research is leading us to contribute directly to public and professional educational initiatives, in partnership with EULAR, EFIC and OARSI, aiming to increase understanding of the burden and mechanisms of arthritis pain, of what can best be done to relieve chronic pain, and of the cutting-edge research being undertaken both within the Centre and internationally that should change the fate of people with arthritis in the near future. The Centre has contributed workshops or plenary sessions to national and international conferences, including the Pharmacology, EULAR, OARSI, EFIC, SOPATE, and the International Cartilage Repair Society.

5 PUBLICATIONS 2020-21

5.1 Pain Centre Publications

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5.3 Pain Centre Collaborations

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6 ORGANISATIONAL STRUCTURE

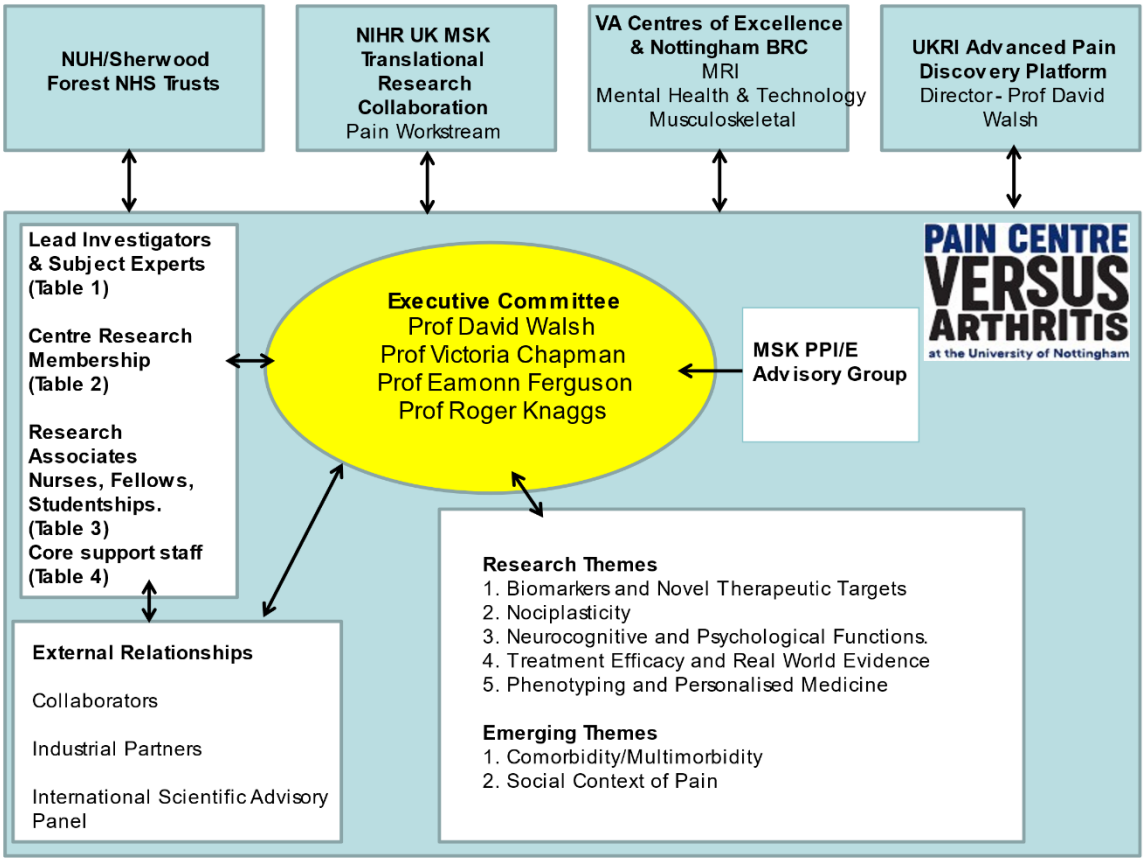

Fig 1. Organisational chart for Pain Centre Versus Arthritis

PAIN CENTRE VERSUS ARTHRITIS
at the University of Nottingham

6.1 Centre Members and Roles

Table 3. Co-Directors

Title	Name	School	Faculty	Position	Area of expertise
Prof	Chapman, Victoria Pain Centre Executive Committee member	Life Sciences	Faculty of Medicine & Health Sciences	Co-Director, Pain Centre Versus Arthritis. Professor of Neuropharmacology	In vivo studies, pharmacological intervention, pain biomarkers, CNS function, forward and back translation.
Prof	Walsh, David Pain Centre Executive Committee member	Medicine	Faculty of Medicine & Health Sciences	Co-Director, Pain Centre Versus Arthritis. Professor of Rheumatology and Consultant Rheumatologist at Sherwood Forest Hospitals NHS Foundation Trust.	Pain phenotyping in arthritis, mechanistic pain modelling and assessment across preclinical and clinical studies, pharmacological and non-pharmacological therapeutic intervention, biorepositories.

Table 4. Lead Investigators – University of Nottingham

Title	Name	School	Faculty	Position	Area of expertise
Prof	Abhishek, Abhishek	Medicine	Faculty of Medicine and Health Science	Professor of Rheumatology Honorary Consultant Rheumatologist, Nottingham University Hospitals NHS Foundation Trust	Autoimmune Rheumatic Disease Epidemiology, Gout, CPPD, OA clinical research, Clinical Trials - CTIMPs, Pragmatic trials, Ultrasound imaging
Prof	Auer, Dorothee	Medicine	Faculty of Medicine & Health Sciences	Professor of Neuroimaging	Clinical neurosciences using advanced MRI techniques.
Prof	Barrett, David	Pharmacy	Faculty of Science	Emeritus Professor of Analytical Bioscience	Founder of the Centre for Analytical Bioscience.
Dr	Bast, Tobias	Psychology	Faculty of Science	Associate Professor	Brain mechanisms of cognition and behaviour, neuroscience and biological psychology

Title	Name	School	Faculty	Position	Area of expertise
Dr	Bennett, Andrew	Life Sciences	Faculty of Medicine and Health Science	Associate Professor and Director of the FRAME Alternatives Laboratory	Molecular Biology /Biochemistry, models of inflammation in disease states, neuro-inflammation and metabolic dysfunction
Dr	Blake, Holly	Health Sciences	Faculty of Medicine and Health Science	Associate Professor of Behavioural Science	Health psychology and behavioural science
Prof	Canals Buj, Meritxell	Medicine	Faculty of Medicine and Health Science	Professor of Cellular Pharmacology	Cellular Pharmacology, peptide receptors involved in pain transmission (opioid, neurokinin and calcitonin gene-related peptide receptors) and immune response (chemokine receptors).
Dr	Dajas-Bailador, Federico	Life Sciences	Faculty of Medicine & Health Sciences	Assistant Professor	Physiology Pharmacology and Neuroscience, regulation of axonal protein expression by selective degradation
Prof	das Nair, Roshan	Medicine	Faculty of Medicine & Health Sciences	Professor of Clinical Psychology and Neuropsychology	Clinical Psychology, Health and Care Professions Council Registered Practitioner Psychologist. The evaluation and implementation of complex interventions
Dr	de Moor, Cornelia	Pharmacy	Faculty of Science	Associate Professor in RNA Biology	Post-transcriptional mechanisms of gene expression in arthritis
Prof	Doherty, Michael	Medicine	Faculty of Medicine & Health Sciences	Emeritus Professor Clinical & Epidemiological Research	Clinical and epidemiological research, community-based clinical trials, systematic reviews and meta-analyses.
Prof	Donaldson, Lucy	Life Science	Faculty of Medicine & Health Sciences	Professor of Sensory Physiology	Neurophysiology of acute and chronic pain, particularly in arthritis.
Dr	Dong-Hyun, Kim	Pharmacy	Faculty of Science	Associate Professor	Analytical Bioscience
Prof	Drummond, Avril	Health Sciences	Faculty of Medicine & Health Sciences	Professor of Healthcare Research	Healthcare research and occupational therapy, stroke rehabilitation and rehabilitation research
Prof	Ferguson Eamonn Pain Centre Executive Committee member	Psychology	Faculty of Science	Professor of Health Psychology	Health psychology, cohort studies, statistical modelling, psychosocial impact

Title	Name	School	Faculty	Position	Area of expertise
Dr	Gershkovich, Pavel	Pharmacy	Faculty of Science	Associate Professor of Biopharmaceutics	Biopharmaceutics, Pharmacokinetics, Pharmacodynamics, Bioanalytical Techniques, Oral Drug Delivery, Effects of Disease States on Pharmacokinetics and Pharmacodynamics
Prof	Gowland, Penny	Medicine	Faculty of Medicine & Health Sciences	Professor of Physics	Developing quantitative MRI for biomedical applications
Prof	Greenhaff, Paul	Life Sciences	Faculty of Medicine & Health Sciences	Professor of Muscle Metabolism	Physiology, Pharmacology and Neuroscience
Dr	Hall, Michelle	Health Sciences	Faculty of Medicine & Health Sciences	Assistant Professor Physiotherapy and osteoarthritis.	Musculoskeletal rehabilitation and rheumatology
Dr	Hathway, Gareth	Life Sciences	Faculty of Medicine & Health Sciences	Associate Professor, Director of Neuroscience Degrees	Science of pain and nociception, pain processing and chronic pain states
Dr	Haybottoallahi, Sayyed	Psychology	Faculty of Sciences	Associate Professor	Identifying pain progression trajectories and their associations with physical and mental health
Dr	Hendrick, Paul	Health Sciences	Faculty of Medicine & Health Sciences	Lecturer Physiotherapy and Rehabilitation Sciences	Low back pain research, Pain Research, Clinical outcomes research
Prof	James, Marilyn	Medicine	Faculty of Medicine & Health Sciences	Professor of Health Economics	Applied economic and clinical evaluation
Prof	Kai, Joe	Medicine	Faculty of Medicine & Health Sciences	Clinical Professor and Head of Primary Care,	Expertise in clinical and applied health research, teaching and service development
Dr	Kluzek, Stefan	Medicine	Faculty of Medicine & Health Sciences	Clinical Associate Professor	Sports and Exercise Medicine

Title	Name	School	Faculty	Position	Area of expertise
Dr	Knaggs, Roger Pain Centre Executive Committee member	Pharmacy	Faculty of Science	Associate Professor in Clinical Pharmacy	The appropriate use of analgesic medicines, and associated clinical outcomes and healthcare utilisation
Dr	Lane, Rob	Life Sciences	Faculty of Medicine & Health Sciences	Associate Professor of Molecular Pharmacology,	G protein-coupled receptors (GPCRs) with a particular emphasis on novel approaches towards the development of improved therapeutics for CNS disorders.
Prof	Mahajan, Ravi	Medicine	Faculty of Medicine & Health Sciences	Head of Division Anaesthesia & Intensive Care	Vascular reactivity. Development of models for assessment. Muscle dysfunction in critical care
Dr	Pavlovskaya, Galina	Medicine	Faculty of Medicine & Health Sciences	Associate Professor, Translational Imaging,	Translational and Molecular Imaging
Dr	Pearson, Richard	Medicine	Faculty of Medicine & Health Sciences	Assistant Professor, Orthopaedics and Trauma Group	Quantified changes in bone associated with several disease pathologies
Dr	Picciinini, Anna	Pharmacy	Faculty of Science	Assistant Professor of Inflammation Biology	Inflammation Biology
Dr	Richard James	Psychology	Faculty of Science	Assistant Professor	Psychology
Dr	Ryder, Steven	Medicine	Faculty of Medicine & Health Sciences	Consultant Physician	Hepatology and Gastroenterology
Prof	Scammell, Brigitte	Medicine	Faculty of Medicine & Health Sciences	Dean and Head of School of Medicine	Orthopaedic surgery, biology of fracture healing, osteoarthritis and biomaterials
Dr	Stocks, Joanne	Medicine	Faculty of Medicine & Health Sciences	Assistant Professor in Sport And Exercise Medicine	Healthy aging, focusing on the role of nutrition in frailty, osteoarthritis and pain .

Title	Name	School	Faculty	Position	Area of expertise
Dr	Stocks, Michael	Pharmacy	Faculty of Science	Professor of Medicinal Chemistry and Drug Discovery. Associate Professor, Centre for Biomolecular Sciences	Drug Discovery, Design, Medicinal and Synthetic Chemistry.
Prof	Valdes, Ana	Medicine	Faculty of Medicine and Health Sciences	Professor of Molecular and Genetic Epidemiology	Genetic epidemiology and musculoskeletal genetics
Dr	Valstar, Michal	Computer Science	Faculty of Science	Associate Professor	Automatic Visual Understanding of Human Behaviour
Prof	Vedhara, Kavita	Medicine	Faculty of Medicine & Health Sciences	Professor of Health Psychology	https://www.nottingham.ac.uk/medicine/people/kavita.vedhara
Prof	Zhang, Weiya	Medicine	Faculty of Medicine & Health Sciences	Professor of Epidemiology	Epidemiology, evidence-based medicine, osteoarthritis, Gout research.

Table 5. Researcher Associates

Title	Name	School	Faculty	Position
Dr	Cottam, William	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Fuller, Amy	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Georgopoulos, Vasileios	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Goncalves, Sara	Life Sciences	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Gowler, Peter	Life Sciences	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Hodkinson, Duncan	Medicine	Faculty of Medicine & Health Sciences	Senior Research Fellow
Dr	Lillywhite, Amanda	Life Sciences	Faculty of Medicine & Health Sciences	Research Fellow
Dr	McWilliams, Daniel	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Nakerero, Georgina	Medicine	Faculty of Medicine & Health Sciences	Research Fellow
Dr	Smith, Stephanie	Medicine	Faculty of Medicine & Health Sciences	Research Fellow

Title	Name	School	Faculty	Position
Dr	Woodhams, Stephen	Life Sciences	Faculty of Medicine & Health Sciences	Research fellow
Dr	Wyatt, Laura	Medicine	Faculty of Medicine & Health Sciences	Research Fellow

Table 6. Research Support

Title	Name	School	Faculty	Position
Mrs.	Farrands-Bentley, Rose	Medicine	Faculty of Medicine & Health Sciences	Administrative co-ordinator
Mr.	Gormley, Eoin	Medicine	Faculty of Medicine & Health Sciences	Musculoskeletal Research Administrator
Dr	Jones-Diette, Julie Executive Committee member	Medicine	Faculty of Medicine & Health Sciences	Translational Research Facilitator
Dr	Kelly, Anthony	Medicine	Faculty of Medicine & Health Sciences	Research Nurse
Miss.	Kosser, Bismillah	Medicine	Faculty of Medicine & Health Sciences	Administrative Co-ordinator
Mr.	Lott, Thomas	Medicine	Faculty of Medicine & Health Sciences	Musculoskeletal Data Administrator
Mr.	McLoughlin, Sean	Medicine	Faculty of Medicine & Health Sciences	Musculoskeletal Research Administrator
Dr	Millar, Bonnie	Medicine	Faculty of Medicine & Health Sciences	Musculoskeletal Project Manager
Mrs.	Naushahi, Fozia	Medicine	NUH	Research Nurse, Faculty of Medicine & Health Sciences
Mr.	Millns, Paul	Medicine	Faculty of Medicine & Health Sciences	Laboratory Technician
Dr	Shahtaheri, Seyed	Medicine	Faculty of Medicine & Health Sciences	Laboratory Technician
Ms	Taylor, Jennifer	Clinical Science		Research Administrator
Mrs.	Ward, Marie	Medicine	Faculty of Medicine & Health Sciences	Research Nurse
Ms	Widdowson, Kirsty	Research and Innovation, Nottingham University Hospitals NHS Trust	NUH	Patient and Public Involvement and Engagement Facilitator
Miss	Wilson, Deborah	Kings Mill Hospital	NUH	Research Nurse