Lyme IACI . . . or another nociplastic syndrome?

Daniel J. Clauw M.D.

dclauw@umich.edu
Professor of Anesthesiology, Medicine (Rheumatology), and Psychiatry
Director, Chronic Pain and Fatigue Research Center
The University of Michigan

Disclosures

- Consulting
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  - Pfizer, Cerephex, Aptinyx
- Litigation – testified against opioid manufacturers in State of Oklahoma, Florida

Chronic Multisymptom Illness Affecting Air Force Veterans of the Gulf War

Keiji Fukuda, MD, MPH; Rosane Nisenbaum, PhD; Geraldine Stewart, MA; William W. Thompson, PhD; Laura Robin, DO, MPH; Rita M. Washko, MD; Donald L. Noah, DVM, MPH; Drue H. Barrett, PhD, MS; Bonnie Randall, MCP; Barbara L. Herwaldt, MD, MPH; Alison C. Mawle, PhD; William C. Reeves, MD, MSPH

Context.—Gulf War (GW) veterans report nonspecific symptoms significantly more often than their nondeployed peers. However, no specific disorder has been identified, and the etiologic basis and clinical significance of their symptoms remain unclear.

Objectives.—To organize symptoms reported by US Air Force GW veterans into a case definition, to characterize clinical features, and to evaluate risk factors.

Design.—Cross-sectional population survey of individual characteristics and symptoms and clinical evaluation (including a structured interview, the Medical Outcomes Study Short Form 36, psychiatric screening, physical examination, clinical laboratory tests, and serologic assays for antibodies against viruses, rickettsia, parasites, and bacteria) conducted in 1995.

Participants and Setting.—The cross-sectional questionnaire survey included 3723 currently active volunteers, irrespective of health status or GW participation, from 4 air force populations.The cross-sectional clinical evaluation included 158 GW veterans from one unit, irrespective of health status.

Main Outcome Measures.—Symptom-based case definition; case prevalence rate for GW veterans and nondeployed personnel; clinical and laboratory findings among veterans who met the case definition.

Results.—We defined a case as having 1 or more chronic symptoms from at least 2 of 3 categories (fatigue, mood-cognition, and musculoskeletal). The prevalence of mild-to-moderate and severe cases was 39% and 6%, respectively, among 1155 GW veterans compared with 14% and 0.7% among 2520 nondeployed personnel. Illness was not associated with time or place of deployment or with duties during the war. Fifty-nine clinically evaluated GW veterans (37%) were noncases, 86 (54%) mild-to-moderate cases, and 13 (8%) severe cases. Although no physical examination, laboratory, or serologic findings identified cases, veterans who met the case definition had significantly diminished functioning and well-being.

Conclusions.—Among currently active members of 4 Air Force populations, a chronic multisymptom condition was significantly associated with deployment to the GW. The condition was not associated with specific GW exposures and also affected nondeployed personnel.

JAMA. 1998;280:981-988

SOON AFTER cessation of Gulf War (GW) hostilities, anecdotal reports of ill- to concerns about a "Gulf War syndrome."[1-3] Subsequent studies have was much lower than expected.[9] No specific illness is evident among the 18 598 GW veterans, according to the Department of Defense Comprehensive Clinical Evaluation Program.[6] Other investigators have found no unusual increases in birth defects,[10] unexplained illness,[11] excess hospitalizations,[12] or excess mortality[13] among GW veterans. However, one study reported excess mortality due to unintentional injuries rather than from disease.[14] Evidence of an Iraqi chemical and biological weapons program has been documented,[15] and although use of such weapons during the GW has not been confirmed,[16] troops may have been exposed to chemical or biological warfare agents during the destruction of storage bunkers. The long-term effects of such chemical exposures are uncertain, although some investigators have suggested that wartime exposures may have contributed to chronic neurotoxic syndromes.[17,18]

For editorial comment see p 1010.

In December 1994, the US Secretary of Defense and the Secretary of Veterans Affairs, and the Commonwealth of Pennsylvania asked the Centers for Disease Control and Prevention (CDC), Atlanta, Ga, to investigate a "mystery illness" reported among GW veterans from an Air National Guard (ANG) unit in Lebanon, Pa.[19] In the first phase of the investigation, we interviewed and exam-

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BMJ

The health consequences of the first Gulf war

The lessons are general (and for many patients) rather than specific to that war

Papers pp 1370, 1373

Two papers in this issue of the *BMJ* describe the long term health of British veterans of the 1990-1 Gulf war. In the article by Hotopf et al the King's Gulf war illnesses research group present another excellent study, this one indicating that 11 years after the conflict the Gulf veterans continue to experience considerably poorer health than control groups (p 1370).[1] The article by Macfarlane et al examines the rate of malignancy in Gulf war veterans and shows that their overall rate of cancer is almost identical

neurological disorder, reported in about 1 in 200 veterans in one population-based study.[7] but not others, and not noted in case-control studies examining neural function.[3 4 8]

Why did this happen? Firstly, no specific environmental exposure, with the possible exception of vaccines given at the time of deployment, has been associated with the development of these symptom complexes. Secondly, since the Gulf war several authors have looked retrospectively at the health con-

CME Article #2

Unexplained Symptoms After Terrorism and War: An Expert Consensus Statement

Daniel J. Clauw, MD
Charles C. Engel, Jr., MD, MPH
Robert Aronowitz, MD
Edgar Jones, DPhil, PhD
Howard M. Kipen, MD, MPH
Kurt Kroenke, MD
Scott Ratzan, MD, MPA, MA
Michael Sharpe, MD
Simon Wessely, MD

Learning Objectives

- Describe the characteristics of unexplained post-exposure symptoms that favor a causal association with a catastrophic event such as war or a terrorist act.
- Suggest possible ways in which pre-event interventions might prevent or minimize post-exposure symptoms.
- What measures might be taken during or after a catastrophic event to lessen or eliminate post-event symptoms?

Abstract

Twelve years of concern regarding a possible "Gulf War syndrome" has now given way to societal concerns of a "World Trade Center syndrome" and efforts to prevent unexplained symptoms following the most recent war in Iraq. These events serve to remind us that unexplained symptoms frequently occur after war and are likely after terrorist attacks. An important social priority is to recognize, define, prevent, and care for individuals with unexplained symptoms after war and related events (eg, terrorism, natural or industrial disasters). An international, multidisciplinary, and multiinstitutional consensus project was completed to summarize current knowledge on unexplained symptoms after terrorism and war.
(J Occup Environ Med. *2003;45:1040–1048*)

From the Department of Medicine, University of Michigan School of Medicine (Dr Clauw); the Department of Psychiatry (Dr Engel), Uniformed Services University of the Health Sciences; History and Sociology of Science (Dr Aronowitz), Family Practice and Community Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; King's College School of Medicine (Dr Jones), London; the Department of Occupational Health (Dr Kipen), Environmental and Occupational Health Sciences Institute (EOHSI), University of Medicine & Dentistry of New Jersey, Robert Wood Johnson Medical School; the Department of Medicine (Dr Kroenke), Regenstrief Institute for Health Care, Indiana University School of Medicine; the University of Edinburgh (Dr Sharpe); and the Department of Epidemiological & Liaison Psychiatry (Dr Wessely), King's College School of Medicine, London.

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The resulting consensus statement finds that divergent yet overlapping constellations of unexplained symptoms occur after war and can also occur after terrorism. These symptoms constitute valid illness, although elucidating pathogenesis is fraught with scientific peril, and sometimes perspective and preconception overwhelms a priori hypothesis formation and testing. At present, there is little scientific basis for future prevention and care of unexplained symptoms after war or terrorism, although evidence suggests that some well-intended strategies are potentially harmful. Research is needed into appropriate responses given the near certainty of unexplained symptoms after future wars and terrorist acts. Consensus statement conclusions are limited to illness in the absence of disease.

Nearly 12 years have elapsed since the end of the Gulf War, and concerns persist of a unique Gulf War syndrome involving a wide range of unexplained symptoms, reminding us that military personnel returning from wars have regularly described disabling symptoms.[1] After September 11, 2001, there have been many reports in the news media about ailments and symptoms among first-responders and people in or around the World Trade Center (WTC).[2] Research suggests respiratory ailments occurred among many who were not directly exposed to dust and other irritants, but experienced psy-

REVIEW

Cancer symptom clusters: current concepts and controversies

Aynur Aktas[a,b]

Purpose of review
Cluster research examines complex interrelationships between multiple concurrent symptoms and their mechanisms. An individual's varying understanding of the cluster concept and variations in assessment tools results in discrepancies. This article will focus on the conceptual and methodological issues associated with definitions, symptom interrelationships, and outcomes of cancer symptom clusters.

Recent findings
An important issue in symptom cluster research is to clarify the definition of a cluster. Some evidence suggests that 'symptom pairs' should be treated as clusters. There is substantial evidence (both qualitative and quantitative) to support a psychoneurological symptom cluster in cancer patients. It has been proposed that consistent clusters are those that have similar 'core' symptoms over time. Research has also shown that a 'sentinel' symptom can predict the presence of other relevant symptoms within a cluster. Identification of patient subgroups with higher symptom severity may be useful in targeting the most needy individuals for intervention. Symptom clusters are predictors of patient outcomes, including decreased functional performance and shorter cancer survival.

Summary
Additional efforts should refine the cluster definition and elucidate the cluster stability and sentinel symptom. Both conceptual and empirical contributions should advance symptom cluster research. The qualitative approaches can explore the experience of symptom clusters and provide a conceptual basis for future research.

Keywords
cancer, patient outcomes, symptom clusters, symptoms

The Amplification of Symptoms in the Medically Ill

Arthur J. Barsky, M.D. and David A. Silbersweig, M.D.

Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Road, Boston, MA, USA.

The mechanism of symptom amplification, developed in the study of somatization, may be helpful in caring for patients with symptoms that, while they have a demonstrable medical basis, are nonetheless disproportionately severe and distressing. Amplified medical symptoms are marked by disproportionate physical suffering, unduly negative thoughts and concerns about them, and elevated levels of health-related anxiety. They are accompanied by extensive and sustained illness behaviors, disproportionate difficulty compartmentalizing them and circumscribing their impact, and consequent problems and dissatisfaction with their medical care. A distinction has long been made between "medically explained" and "medically unexplained" symptoms. However, a more comprehensive view of symptom phenomenology undermines this distinction and places *all* symptoms along a smooth continuum regardless of cause: Recent findings in cognitive neuroscience suggest that all symptoms—regardless of origin—are processed through convergent pathways. The complete conscious experience of both medically "explained" and "unexplained" symptoms is an amalgam of a viscerosomatic sensation fused with its ascribed salience and the patient's ideas, expectations, and concerns about the sensation. This emerging empirical evidence furnishes a basis for viewing persistent, disproportionately distressing symptoms of demonstrable disease along a continuum with medically unexplained symptoms. Thus, therapeutic modalities developed for somatization and medically unexplained symptoms can be helpful in the care of seriously ill medical patients with amplified symptoms. These interventions

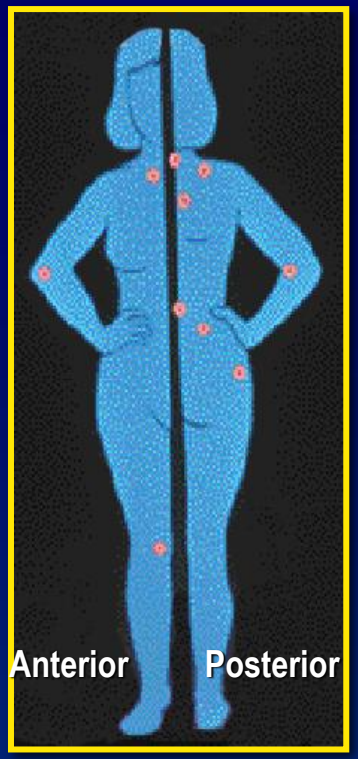
Viscerosomatic amplification is a process whereby patients' thoughts, emotions, and concerns heighten uncomfortable bodily sensations and symptoms, making them more salient, intense, unpleasant, noxious, disturbing, and distressing. The construct emerged from the study of somatization, where empirical support was found for its role in the development of medically unexplained symptoms.[1–4] In this model, somatized symptoms are understood as the product of a self-perpetuating and self-validating cycle of cognition and perception whereby benign bodily sensations become more intrusive and distressing once they are thought to be medically serious and misattributed to disease.[2,3,5] Worrisome ideas about their cause, ominous expectations about their future course, negative assumptions about their significance, and threatening prior illness experiences all amplify the symptom and heighten its noxious, bothersome, and distressing quality. This in turn further substantiates the most worrisome and alarming thoughts, thereby perpetuating a vicious cycle. Somatization may thus be thought of as a diathesis towards symptom amplification due to a top-down tendency to misinterpret and misunderstand bothersome and uncomfortable bodily sensations that are medically unexplained.

Three mechanisms drive this cycle of symptom amplification: more intensive monitoring of one's bodily sensations; increased bodily scrutiny in search of corroborative evidence of disease; and disconfirmatory bias that causes the individual to ignore evidence that contradicts his/her suspicion that something serious is wrong. Misattributing a bothersome but be-

Evolution of Thinking Regarding Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Pathophysiology poorly understood and thought to be psychological in nature



- Chronic
- des d
- ain
- Tenderness in
- ≥ 11 of 18
- ender nts

- Final common pathway (i.e. pain centralization)
- Poster child for nociplastic pain
- Not just pain
- Pathophysiology fairly well understood and is a CNS process that is independent from classic psychological factors

Chronic Pain 2

Nociplastic pain: towards an understanding of prevalent pain conditions

Mary-Ann Fitzcharles, Steven P Cohen*, Daniel J Clauw, Geoffrey Littlejohn, Chie Usui, Winfried Häuser*

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See Comment page 2029

This is the second in a Series of three papers about chronic pain

*Contributed equally

Department of Rheumatology and Alan Edwards Pain Management Unit, McGill University, Montreal, QC, Canada (M-A Fitzcharles MBChB); Department of Psychiatry and Behavioral Sciences and Department of Anesthesiology and Critical Care Medicine, Neurology and Physical Medicine and Rehabilitation at

Nociplastic pain is the semantic term suggested by the international community of pain researchers to describe a third category of pain that is mechanistically distinct from nociceptive pain, which is caused by ongoing inflammation and damage of tissues, and neuropathic pain, which is caused by nerve damage. The mechanisms that underlie this type of pain are not entirely understood, but it is thought that augmented CNS pain and sensory processing and altered pain modulation play prominent roles. The symptoms observed in nociplastic pain include multifocal pain that is more widespread or intense, or both, than would be expected given the amount of identifiable tissue or nerve damage, as well as other CNS-derived symptoms, such as fatigue, sleep, memory, and mood problems. This type of pain can occur in isolation, as often occurs in conditions such as fibromyalgia or tension-type headache, or as part of a mixed-pain state in combination with ongoing nociceptive or neuropathic pain, as might occur in chronic low back pain. It is important to recognise this type of pain, since it will respond to different therapies than nociceptive pain, with a decreased responsiveness to peripherally directed therapies such as anti-inflammatory drugs and opioids, surgery, or injections.

Introduction

occur in isolation or as a comorbidity in individuals with

Chronic Overlapping Pain Conditions

- Most highly prevalent pain conditions in individuals under age 50
  - Headache
  - Fibromyalgia
  - Irritable bowel
  - TMJ Disorder
  - Interstitial cystitis
  - Low back pain
  - Endometriosis
  - Vulvodynia
  - Chronic fatigue syndrome
- Same central mechanisms play significant roles in all pain conditions, even those with known peripheral contributions

Role of Infections in Triggering FM/CFS like Illnesses

- **Infections can trigger any of these conditions in approximately 10% of exposed individuals**
  - ***The initial location of the infection determines the subsequent pain syndrome***
  - **Common upper respiratory infections are not capable of triggering these conditions**
- **Infections causing diffuse pain and fatigue (e.g., EBV, Lyme disease, brucellosis, Ross River virus, Q Fever) lead to fibromyalgia and/or CFS**
- **Any type of infectious diarrhea will trigger IBS in 10 - 20% of those exposed[1]**
- **Interstitial cystitis, chronic prostatitis, and vulvodynia are all often preceded by infections in those regions of the body[2]**

1. Parry et. al. Am J Gastroenterol. 2003 Sep;98(9):1970-5. 2. Warren et. al. Urology. 2008 Jun;71(6):1085-90

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Research

BMJ

Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study

Ian Hickie, Tracey Davenport, Denis Wakefield, Ute Vollmer-Conna, Barbara Cameron, Suzanne D Vernon, William C Reeves, Andrew Lloyd, for the Dubbo Infection Outcomes Study Group

Abstract

Objective To delineate the risk factors, symptom patterns, and longitudinal course of prolonged illnesses after a variety of acute infections.

Design Prospective cohort study following patients from the time of acute infection with Epstein-Barr virus (glandular fever),

have been linked to a diverse spectrum of infections, including brucellosis (which is caused by an intracellular bacterium),[7] glandular fever (caused by the herpesvirus Epstein-Barr virus),[8] Lyme disease (caused by infection with the tickborne spirochaete *Borrelia burgdorferi*),[9] Q fever (caused by the intracellular, rickettsia-like pathogen *Coxiella burnetii*),[10] Ross River virus (a mosquito-borne arbovirus found in countries around the Pacific

Dubbo study

- **Network of 92 MDs in Dubbo region of Australia performed population-based longitudinal study of serologically confirmed new cases of acute Epstein-Barr virus, Q fever, or Ross River virus**
- **There were dramatically different rates of these infections, and they had differing acute presentations, but 9% of each type (22/250 total) met criteria for persistence fatigue and somatic sx. at 12 months**
- **Four factors of post-infective or chronic fatigue state were very similar despite initial infection, and included fatigue, pain, mood disturbance, and "neurocognitive" factors**
- **The only predictor of the likelihood of developing CFS was the intensity of the original somatic symptoms. Was not associated with:**
  - **Cytokine profile of acute infection**
  - **Clearance of pathogen[2]**
  - **Baseline psychological factors**

1. Hickie et. al. *BMJ*. 2006 September 16; 333(7568): 575. 2. Cameron et. al. 575 Infect Dis 2006;193: 664-71.

Topical Review

PAIN®

Considering the potential for an increase in chronic pain after the COVID-19 pandemic

AQ:1

Daniel J. Clauw[b], Winfried Häuser[b,c], Steven P. Cohen[d,e], Mary-Ann Fitzcharles[f,g,*]

1. Introduction

The COVID-19 pandemic has impacted the lives and health of persons worldwide, with potential for further effects in the future. The experience of living within this pandemic has disrupted daily life across all sectors, including those living with chronic pain (CP), those infected with the coronavirus Severe Acute Respiratory Syndrome (SARS)-CoV2, healthcare providers and essential workers, as well as those who remained physically healthy. The toll of this pandemic extends beyond physical illness, with important psychosocial stressors that include prolonged periods of limited interpersonal contact, isolation, fear of illness, future uncertainty, and financial strain. Uncertainty is fuelled by the organ-specific biological factors, which may preferentially occur in individuals with a fragile stress response system.[8,10,24,40,47] The COVID-19 pandemic has many characteristics that could potentially increase the prevalence of CP, especially with stressors extending over many months.

The worldwide pain community is invited to consider the possible downstream consequences of COVID-19, not only for patients surviving infection, but also for the wider community that has experienced psychological, social, and economic effects. Although we address these issues from the perspective of physicians practicing in developed countries, many of the consequences discussed will be particularly relevant for people in other countries, with a call for colleagues in Asia, Africa, and

nature reviews neurology

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Review article

Check for updates

Deciphering nociplastic pain: clinical features, risk factors and potential mechanisms

Chelsea M. Kaplan[1], Eoin Kelleher[2], Anushka Irani[3,4], Andrew Schrepf[1], Daniel J. Clauw[1] & Steven E. Harte[1]

Abstract

Nociplastic pain is a mechanistic term used to describe pain that arises or is sustained by altered nociception, despite the absence of tissue damage. Although nociplastic pain has distinct pathophysiology from nociceptive and neuropathic pain, these pain mechanisms often coincide within individuals, which contributes to the intractability of chronic pain. Key symptoms of nociplastic pain include pain in multiple body regions, fatigue, sleep disturbances, cognitive dysfunction, depression and anxiety. Individuals with nociplastic pain are often diffusely tender — indicative of hyperalgesia and/or allodynia — and are often more sensitive than others to non-painful sensory stimuli such as lights, odours and noises. This Review summarizes the risk factors, clinical presentation and treatment of nociplastic pain, and describes how alterations in brain function and structure, immune processing and peripheral factors might contribute to the nociplastic pain phenotype. This article concludes with a discussion of two proposed subtypes of nociplastic pain that reflect distinct neurobiological features and

Sections

Nociplastic states can be triggered by a number of physical, immune, and emotional stressors:

- Deployment to war
- Trauma/maltreatment
- Motor vehicle accidents (“whiplash”)
- Infections
- As a co-morbidity in individuals with other pain mechanisms (secondary pain)
  - autoimmune disorders (approximately 1/3)
  - sickle cell disease
  - Hypermobility syndromes

Is the development of nociplastic pain associated with neural vulnerability?

As most neuroimaging studies are performed in adults who have often had chronic pain for years, studying the role of the central nervous system in pain development or vulnerability is challenging[295]. To our knowledge, only two studies[296,297] to date have examined brain structure and function before the onset of pain, as described below.

In a 2022 study of pain-free children enrolled in the longitudinal Adolescent Brain Cognitive Development Study (ABCD Study), we compared resting-state functional connectivity in children who developed multisite pain 1 year after neuroimaging with children who remained pain-free. At baseline, children who developed multisite pain had increased functional connectivity between regions of the salience network (SLN), sensorimotor network (SMN) and default mode network (DMN)[296]. Subsequently, a study in chemotherapy-naive adults has found similar results: people who developed pain after chemotherapy treatment had increased brain activity in SMN, SLN and DMN regions and reduced activity in a key pain inhibitory region, the periaqueductal grey, in response to a painful stimulus at baseline when they were pain-free, compared with individuals who remained pain-free[297]. Interestingly, neither of these studies found brain structure to be predictive of future pain, suggesting that changes in brain structure result from neuroplasticity as a consequence of pain rather than the cause, as previously thought[298]. These observations are in line with studies in adults with established nociplastic pain features, in which heightened connectivity between the DMN, SLN and SMN is one of the most consistent findings (as discussed in the section 'Brain network enmeshment')[175,182,186,189,190]. Together, the findings suggest that these patterns of brain connectivity are trait-like and indicate an underlying vulnerability in which brain function can predispose an individual to developing pain.

Research Paper

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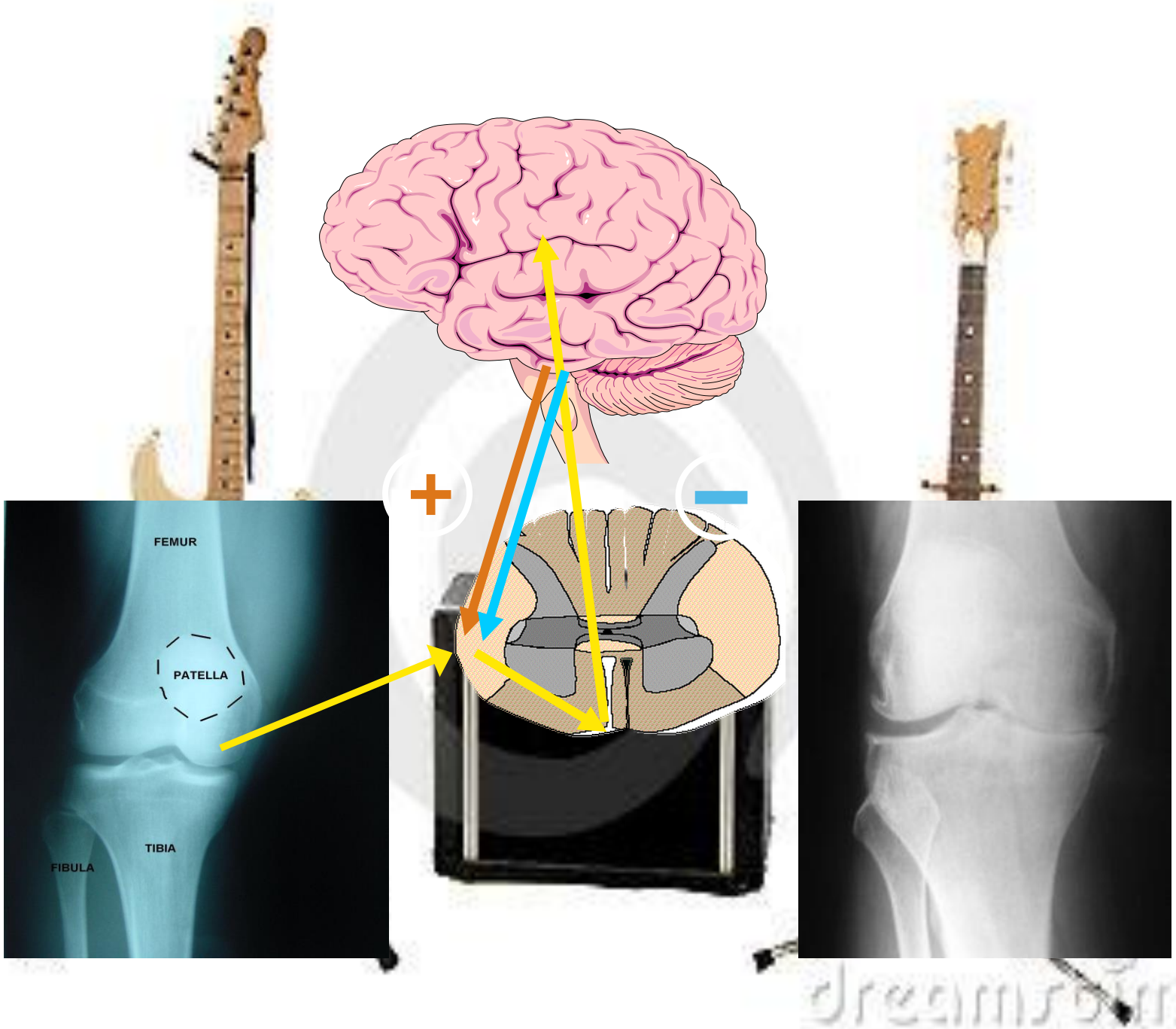
Neurobiological antecedents of multisite pain in children

Chelsea M. Kaplan[a,*], Andrew Schrepf[a], Ishtiaq Mawla[b], Eric Ichesco[a], Kevin F. Boehnke[a], Adriene Beltz[c], Emily Foxen-Craft[d], Michael P. Puglia II[a], Alexandre Tsodikov[e], David A. Williams[a,b,f,g], Afton L. Hassett[a], Daniel J. Clauw[a,f,g], Steven E. Harte[a,b,g], Richard E. Harris[a,b,g]

Abstract

Altered brain structure and function is evident in adults with multisite chronic pain. Although many such adults trace their pain back to childhood, it has been difficult to disentangle whether central nervous system alterations precede or are consequences of chronic pain. If the former is true, aberrant brain activity may identify children vulnerable to developing chronic pain later in life. We examined structural and functional brain magnetic resonance imaging metrics in a subset of children from the first 2 assessments of the Adolescent Brain and Cognitive Development Study. Children (aged 9-10) who were pain free at baseline and then developed multisite pain 1 year later (n = 115) were matched to control children who were pain free at both timepoints (n = 230). We analyzed brain structure (cortical thickness and gray matter volume) and function (spontaneous neural activity and functional connectivity). Results were deemed significant at the cluster level $P < 0.05$ false discovery rate corrected for multiple comparisons. At baseline, children who subsequently developed multisite pain had increased neural activity in superior parietal /primary somatosensory and motor cortices and decreased activity in the medial prefrontal cortex. They also exhibited stronger functional connectivity between the salience network, somatosensory, and default mode network regions. No significant differences in the brain structure were observed. Increased neural activity and functional connectivity between brain regions, consistent to that seen in adults with chronic pain, exist in children before developing multisite pain. These findings may represent a neural vulnerability to developing future chronic pain.

Keywords: Multisite pain, Children, fMRI, Functional connectivity, Risk factors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BJA

British Journal of Anaesthesia, 130 (1): 83–93 (2023)

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Advance Access Publication Date: 14 November 2022
Pain

PAIN

Neuroimaging reveals a potential brain-based pre-existing mechanism that confers vulnerability to development of chronic painful chemotherapy-induced peripheral neuropathy

Marta Seretny[1,2,*], Liana Romaniuk[3], Heather Whalley[3], Kim Sladdin[2], Stephen Lawrie[3], Catherine Elizabeth Warnaby[4], Neil Roberts[5], Lesley Colvin[6], Irene Tracey[4,†] and Marie Fallon[3,†]

[1]Department of Anaesthesiology University of Auckland, Auckland, New Zealand, [2]Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, UK, [3]Division of Psychiatry, University of Edinburgh, Edinburgh, UK, [4]Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK, [5]Clinical Research and Imaging Centre (CRIC), University of Edinburgh, Edinburgh, UK and [6]Division of Population Health and Genomics, University of Dundee, Dundee, UK

*Corresponding author. E-mail: m.seretny@auckland.ac.nz
[†]These authors are joint senior authors.

Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating condition impacting 30% of cancer survivors. This study is the first to explore whether a brain-based vulnerability to chronic sensory CIPN exists.
Methods: This prospective, multicentre cohort study recruited from three sites across Scotland. Brain functional MRI (fMRI) scans (3 Tesla) were carried out on chemotherapy naïve patients at a single fMRI centre in Edinburgh, Scotland. Nociceptive stimuli (with a 256 mN monofilament) were administered during the fMRI. Development of chronic sensory/painful CIPN (CIPN+) was determined based upon European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20 changes conducted 9 months after chemotherapy, and imaging data analysed using standard software.
Results: Of 30 patients recruited (two lung, nine gynaecological, and 19 colorectal malignancies), data from 20 patients at 9 months after chemotherapy was available for analysis. Twelve were classified as CIPN+ (mean age, 63.2[9.6] yr, 9.6; six female), eight as CIPN− (mean age 62.9 [SD 5.5] yr, four female). In response to punctate stimulation, group contrast analysis showed that CIPN+ compared with CIPN− had robust activity in sensory, motor, attentional, and affective brain regions. An *a priori* chosen region-of-interest analysis focusing on the periaqueductal grey, an area hypothesised as relevant for developing CIPN+, showed significantly increased responses in CIPN− compared with CIPN+ patients. No difference in subcortical volumes between CIPN+ and CIPN− patients was detected.
Conclusions: Before administration of any chemotherapy or appearance of CIPN symptoms, we observed altered patterns of brain activity in response to nociceptive stimulation in patients who later developed chronic sensory CIPN. This suggests the possibility of a pre-existing vulnerability to developing CIPN centred on brainstem regions of the descending pain modulatory system.

Keywords: chemotherapy induced peripheral neuropathy; descending pain modulatory system; fMRI; pain; multicentre cohort study

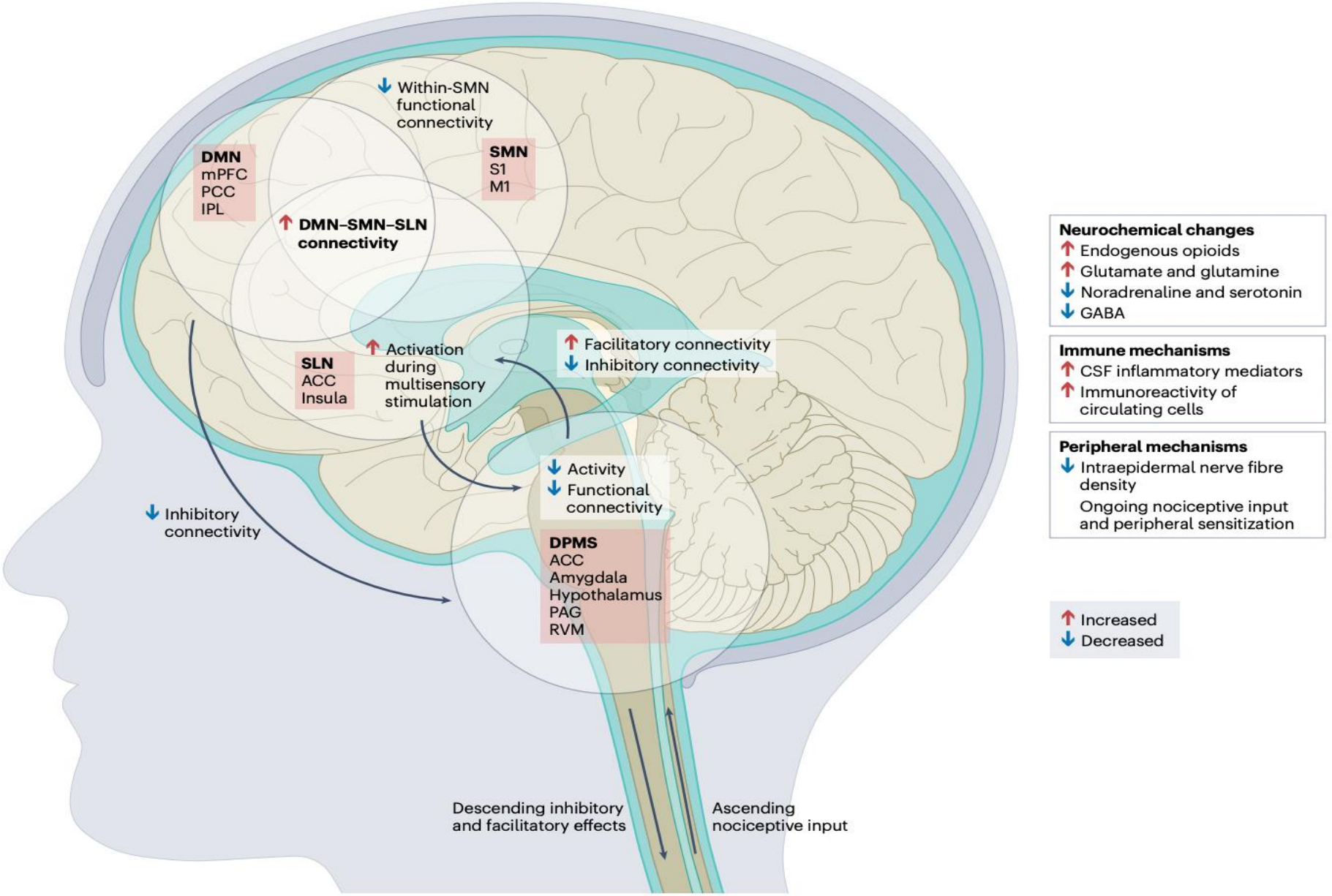

Fig. 3 | The pathophysiology of nociplastic pain. Neuroimaging studies have shown abnormal brain connectivity in people with nociplastic pain. The spatial distribution of pain across the body is associated with increased functional connectivity between regions of the default mode network (DMN), salience network (SLN) and sensorimotor network (SMN) in pain conditions with presumed nociplastic mechanisms. In addition, people with nociplastic pain have altered activity within the descending pain modulatory system (DPMS), which influences on pain perception. Alterations in the immune system and peripheral nervous system are also observed in people with nociplastic pain. Future work is needed to understand how these systems interact in nociplastic pain states. ACC, anterior cingulate cortex; CSF, cerebrospinal fluid; GABA, γ-aminobutyric acid; IPL, inferior parietal cortex; M1, primary motor cortex; mPFC, medial prefrontal cortex; PAG, periaqueductal grey; PCC, posterior cingulate cortex; RVM, rostral ventromedial medulla; S1, primary somatosensory cortex.