Annotated Bibliography for Neuroplastic Symptoms

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Introduction

The Association for the Treatment of Neuroplastic Symptoms (Neuroplastic.org) recommends new evidence-based psychotherapeutic techniques for diagnosis, treatment and relief from persistent pain or illness not caused by organ disease or structural injury. We refer to this form of illness as neuroplastic symptoms (NS) because it is generated by nerves in the brain (neuro) and has a capacity for change (plastic). The symptoms include chronic pain, medically unexplained symptoms, chronic functional syndromes (such as fibromyalgia, irritable bowel syndrome and many others) and somatisation disorders.

However, because a wide range of specialties has addressed these issues, the relevant science has been published in a very large number of journals making it a challenge to comprehensively review. Consequently, few clinicians are aware of the quality and quantity of evidence supporting a psychological approach to neuroplastic symptoms. The bibliography below compiles the most relevant published research. Each paper is annotated with a description of its key findings.

You can search this document using Command-F.

The papers are also divided into the following categories (with a few listed in more than one):

I. Psychological Treatment **Pages 3-11**
Evidence for the benefit of psychological treatment for persistent physical symptoms, particularly for Emotional Awareness & Expression Therapy, Pain Reprocessing Therapy and Intensive Short-Term Dynamic Psychotherapy with much smaller effect sizes from Cognitive Behavioral Therapy, Acceptance & Commitment Therapy and Educational Techniques.

II. ACEs and Trauma **Pages 12-16**
Evidence regarding the link between adverse life experiences (child or adult) and persistent physical symptoms.

III. Pain Perception **Pages 17-20**
Evidence that psychological factors can change pain perception.

IV. Predicting the Clinical Course **Pages 21-26**
Evidence that objective measures of organ disease or structural abnormality (such as imaging studies) are not good predictors of persistent symptoms and/or that psychological factors are better predictors.

V. Ineffective Treatments **Pages 27-31**
Evidence that invasive treatment, non-invasive non-psychological treatment and opioids are ineffective for chronic pain.

VI. Neuroscience **Pages 32-35**
Studies of the neuroscience of chronic pain including the key role of altered nerve pathways in the brain.

VII. Adjunct Treatments **Pages 36-37**
Evidence for the benefits of expressive writing, reappraisal of arousal, and exercise plus a review of smartphone apps for persistent pain.

VIII. Economics **Pages 38-39**
The prevalence and economic impact of neuroplastic symptoms.

The Association for the Treatment of Neuroplastic Symptoms welcomes recommendations for additions to the bibliography which can be sent via email to **info@neuroplastic.org**. The ATNS expects you will find this evidence helpful in accounting for the excellent outcomes we observe in our clinical practice.

Tip: use Ctrl/Command + F to search by keyword

I. Psychological Treatment

Evidence for the clinical and cost benefits of psychological treatment for persistent physical symptoms, particularly for Emotional Awareness & Expression Therapy, Pain Reprocessing Therapy and Intensive Short-Term Dynamic Psychotherapy with lesser effect size from Cognitive Behavioral Therapy, Acceptance & Commitment Therapy and Educational Techniques.

1. **Abbass, A., et al. (2009)** Short-Term psychodynamic psychotherapy for somatic disorders: Systematic review and meta-analysis of clinical trials. *Psychotherapy and Psychosomatics*, 78, 265–274.

   "Reviewed 23 studies (13 RCTs and 10 case series with pre/post assessments) of ISTDP. Of these, 21/23 (91.3%), 11/12 (91.6%), 16/19 (76.2%) and 7/9 (77.8%) reported significant or possible effects on physical symptoms, psychological symptoms, social-occupational function and healthcare utilization respectively. Meta-analysis was possible for 14 studies and revealed significant effects on physical symptoms, psychiatric symptoms and social adjustment which were maintained in long-term follow-up."

2. **Abbass A, Campbell S, Magee K, Tarzwell R (2009).** Intensive short-term dynamic psychotherapy to reduce rates of emergency department return visits for patients with medically unexplained symptoms: preliminary evidence from a pre-post intervention study. *Canadian Journal of Emergency Medicine*, 11(6), 529-34.

   Cost savings of treatment of medically unexplained symptoms in a hospital emergency department using ISTDP, found a 69% reduction in repeat emergency visits, amounting to an average cost saving per patient twice the average cost of treatment provided: these effects were greater than a control condition.

3. **Abbass A, Rasic D, Kisely S, Katzman J. (2013).** Residency training in intensive short-term dynamic psychotherapy: methods and cost-effectiveness. *Psychiatr Ann*. 43(11):501-506.

   Reviews the efficacy and cost-savings data for ISTDP in a study training residents in this model

4. **Abbass A, Bernier D, Kisely S, Town J, Johansson R (2015).** Sustained reduction in health care costs after adjunctive treatment of graded intensive short-term dynamic psychotherapy in patients with psychotic disorders. *Psychiatry Research*, 228(3), 538-43.

   In the largest naturalistic evaluation of ISTDP, the long-term healthcare costs were assessed in 890 consecutively referred cases of which 61% had Somatoform Disorder: ISTDP treated cases had significantly reduced physician and hospital costs at 1-, 2-, and 3-year post treatment follow-up with a mean savings of over $12,000 by 3 year follow-up. A subsample of this population, consisting of 28 patients with psychogenic non-epileptic seizures who received ISTDP, exhibited similar improvements.

5. **Abbass A, Town J, Holmes H et al (2020).** Short-Term Psychodynamic Psychotherapy for Functional Somatic Disorders: A Meta-Analysis of Randomized Controlled Trials. Psychotherapy and Psychosomatics, on-line publication DOI: 10.1159/000507738

   In meta-analyses of 17 RCTs, STPP significantly outperformed minimal treatment, treatment as usual, or waiting list controls on somatic symptom measures at all time frames, with small to large magnitude effect sizes. Descriptive reviews of 5 RCTs suggest that STPP performed at least as

well as other bona fide psychological therapies. Limitations of this meta-analysis include small samples of studies and possible publication bias.

6. **Abbass AA, Town JM, Kisely S. (2022)**. Intensive Short-term Dynamic Psychotherapy for Pain. J Anesthesiol & Pain Therapy. 2022;3(2):4-7

   Intensive short-term dynamic psychotherapy (ISTDP) has been studied for a broad range of somatic symptom presentations including chronic pain. Ten studies, including 6 randomized controlled trials, were examined. ISTDP yielded large and persistent treatment effects for both pain and depression within group. When ISTDP was compared to cognitive behavioral therapy methods (CBT) in randomized controlled trials, it yielded superior effects to CBT on pain and depression measures in both short- and medium-term follow-up. Two studies suggested the method was cost effective by reducing healthcare costs, medication and disability costs. Based on these findings ISTDP should be considered for chronic pain treatment guidelines.

7. **Ashar YK, Gordon A, Schubiner H et al (2021).** Effect of Pain Reprocessing Therapy vs Placebo and Usual Care for Patients with Chronic Back Pain. A Randomized Clinical Trial. *JAMA Psychiatry.* Published online September 29, 2021. doi:10.1001/jamapsychiatry.2021.2669

   In this randomized clinical trial, 33 of 50 participants (66%) randomized to 4 weeks of pain reprocessing therapy were pain-free or nearly pain-free at posttreatment, compared with 10 of 51 participants (20%) randomized to placebo and 5 of 50 participants (10%) randomized to usual care, with gains largely maintained through 1-year follow-up. Treatment effects on pain were mediated by reduced beliefs that pain indicates tissue damage, and longitudinal functional magnetic resonance imaging showed reduced prefrontal responses to evoked back pain and increased resting prefrontal somatosensory connectivity in patients randomized to treatment relative to patients randomized to placebo or usual care. Psychological treatment focused on changing beliefs about the causes and threat value of primary chronic back pain may provide substantial and durable pain relief.

8. **Ashar YK, Low EL, Knight K, et al (2025).** Pain Reprocessing Therapy vs Placebo and Usual Care for Patients With Chronic Back Pain: 5-Year Follow-Up of a Randomized Clinical Trial. JAMA Psychiatry. Published online July 30, 2025. doi:10.1001/jamapsychiatry.2025.1844

   This letter reports five-year follow-up from the Boulder Back Pain study (2021) showing sustained significant improvement in the PRT group compared to the two control groups.

9. **Baikie KA. (2012)** Expressive writing and positive writing for participants with mood disorders: an online randomized controlled trial. *Journal of Affective Disorders* Feb;136(3):310-9.

   "The expressive writing, positive writing and time management control writing groups all reported significantly fewer mental and physical symptoms for at least 4 months post-writing."

10. **Baldoni F, Baldaro B & Trombini G. (1995).** Psychotherapeutic Perspectives in Urethral Syndrome. *Stress Medicine* 11: 79-84.

    RCT of 36 patients with urinary symptoms without organic lesions with follow-up of 4 years. Of the 13 who received intensive short-term dynamic psychotherapy (14 weekly sessions), 10 had complete relief and 3 had significant improvement. Depression, anxiety and hostility also improved. The 23 controls had traditional urologic care and no significant improvement was found.

11. **Bergmans RS, Clauw DJ, et. al. (2024).** Chronic overlapping pain conditions increase the risk of long COVID features, regardless of acute COVID status. *PAIN,* 2024, 165:1112-1120. DOI: 10.1097/j.pain.0000000000003110

Chronic overlapping pain conditions (COPCs) refer to conditions that have similar central nervous system pathophysiologic mechanisms driving widespread pain as well as common comorbid symptoms such as fatigue and problems with sleep, memory, and mood. Having a COPC increased the risk of long COVID features among those with COVID by 47%, by 39% among those with influenza and by 57% in the noninfected cohort. Recognizing this avoids the pitfall of viewing long COVID exclusively in the framework of postinfectious disease.

12. **Burger AJ**. **(2016)** The effects of a novel psychological attribution and emotional awareness and expression therapy for chronic musculoskeletal pain: A preliminary, uncontrolled trial. *Journal of Psychosomatic Research.* Feb;81:1-8.

"This was an initial trial of a newly developed therapy aimed at psychological attribution and emotional awareness and expression. They treated 72 patients and did pre-and post- treatment assessments and a six-month follow-up. Pain was reduced following treatment, and was either maintained or enhanced at the six-month follow-up."

13. **Burton, C. (2003).** Beyond somatisation: A review of the understanding and treatment of medically unexplained physical symptoms (MUPS). The British Journal of General Practice, 53, 231–239.

"Patients with MUPS may best be viewed as having complex adaptive systems in which cognitive and physiological processes interact with each other and with their environment. Cognitive behavioural therapy and antidepressant drugs are both effective treatments, but their effects may be greatest when the patient feels empowered by their doctor to tackle their problem."

14. **Cherkin DC et al. (2016).** Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults with Chronic Low Back Pain. A Randomized Clinical Trial. *JAMA*. 315(12):1240-1249.

MBSR and CBT were provided to groups for up to two hours weekly for eight weeks. Eighteen weeks after the sessions, clinically meaningful improvement in disability was found in 61% of MBSR and 58% of CBT patients but also in 44% of UC patients. Clinically meaningful improvement in how bothersome the pain felt was found in 44% of MBSR, 45% of CBT but only 27% of UC patients. These are modest benefits. Studies of Pain Reprocessing Therapy and Emotional Awareness and Expression Therapy have documented better outcomes.

15. **Clarke, D., Sondag, M., Goldberg M. H., & Gustafson A. (2025).** How Americans Experience and Understand Neuroplastic Symptoms. Association for the Treatment of Neuroplastic Symptoms. Portland, OR, USA. https://doi.org/10.66323/20250928

A nationally representative survey of 1500 U.S. adults showed 25% had no diagnosis for their pain or illness and 23% had been given a diagnosis but were not responding to treatment as their physician expected. This group of nearly half of the population are likely to have neuroplastic pain or illness, had an average of nearly three symptoms simultaneously and were often willing to consider a psychosocial cause.

16. **Clarke, D., Gustafson, A., Goldberg, M. H. (2026).** Why Do Many People Struggle to See Their Own Neuroplastic Symptoms? Association for the Treatment of Neuroplastic Symptoms. Portland, OR, USA. https://doi.org/10.66323/20260318

Often when people hear about neuroplastic symptoms and their treatment they struggle to apply this knowledge to themselves. This is linked to a web of cognitive biases that social psychology researchers have studied for decades and that are described in this paper.

17. **Clarke, DD (2016).** Diagnosis and treatment of medically unexplained symptoms and chronic functional syndromes. *Families, Systems, & Health*, 34(4), 309-316.

    The author cites the data that 25-33% of primary care patients have medically unexplained symptoms. He advocates a systematic approach to interviewing based on his experience with 7,000 MUS patients, leading to better outcomes. In so doing doctors can identify neuroplastic symptoms. He lays out ways of talking to patients who may be sceptical about psychological links to their physical symptoms, and also outlines a treatment approach, and the article is illustrated with numerous case vignettes.

18. **Donnino MW, Howard P, Mehta S et al. (2023).** Psychophysiologic symptom relief therapy for Post-Acute Sequelae of Coronavirus Disease 2019. Mayo Clin Proc: Vol 7 (4), 337-348. https://doi.org/10.1016/j.mayocpiqo.2023.05.002

    Twenty-three adults under the age of 60 years with PASC were enrolled. The median duration of symptoms before joining the study was 267 days. Participants received PSRT during a 13-week (approximately 44-hour) course. Symptom improvement included an 80% decrease in shortness of breath, a 77% decrease in pain interfering with activity, a 67% decrease in brain fog and a 52% decrease in Pain. A majority experienced improvement in the first four weeks of treatment. In addition, before treatment 57% strongly agreed that exercise made their symptoms worse. After 8 weeks only 4% strongly agreed.

19. **Donnino MW, Thompson GS et al. (2021).** Psychophysiologic symptom relief therapy for chronic back pain: a pilot randomized controlled trial. PAIN Reports: September/October 2021 - Volume 6 - Issue 3 - p e959. doi: 10.1097/PR9.0000000000000959

    At 26 weeks, 64% of the Psychophysiologic Symptom Relief Therapy arm reported being pain free (0/10 pain) compared with 25% and 17% in Mindfulness Based Stress Reduction and Usual Care arms, respectively.

20. **Drossman DA, Ringel Y, Vogt BA, Leserman J, Lin W, Smith JK, & Whitehead, W. (2003).** Alterations of brain activity associated with resolution of emotional distress and pain in a case of severe irritable bowel syndrome. *Gastroenterology*,124, 754–761. http://dx.doi.org/10.1053/gast.2003.50103

    During severe illness, the patient had major psychosocial impairment, high life stress, a low visceral pain threshold, and activation of the midcingulate cortex (MCC), prefrontal area 6/44, and the somatosensory cortex, areas associated with pain intensity encoding. When clinically improved, there was resolution in activation of these 3 areas, and this was associated with psychosocial improvement and an increased threshold to rectal distention.

21. **Edwards, T. M., Stern, A., Clarke, D. D., Ivbijaro, G.,& Kasney, L. M. (2010).** The treatment of patients with medically unexplained symptoms in primary care: A review of the literature. *Mental Health and Family Medicine*, 7, 209–221.

    Medically unexplained symptoms (MUS) are among the most common and frustrating in primary care. Our goal was to review published evidence to guide busy general practitioners working with a culturally diverse, challenging patient population coping with MUS. A search of PubMed and PsycINFO from 1985 to the present was conducted using MUS and related terms. The literature was then organised into sub-categories based on its relevance to primary care. We conclude with a description of gaps in the literature based on the literature review and the clinical experience of the authors.

22. **Engel, GL. (1977**). The need for a new medical model: A challenge for biomedicine. *Science*,196, 129 –136. http://dx.doi.org/10.1126/science.847460

The landmark initial description of the biopsychosocial model.

23. **Escobar, JI, Gara, MA, Diaz-Martinez, AM, Interian, A, Warman, M, Allen, LA, . . . Rodgers, D. (2007).** Effectiveness of a time-limited cognitive behavior therapy type intervention among primary care patients with medically unexplained symptoms. *Annals of Family Medicine*, 5, 328–335. http://dx.doi.org/10.1370/afm.702

A significantly greater proportion of patients in the CBT group had physical symptoms rated by clinicians as "very much improved" or "much improved" compared with those in the usual care group (60% vs 26%). The intervention's effect on unexplained physical symptoms was greatest at treatment completion, led to relief of symptoms in more than one-half of the patients, and persisted months after the intervention, although its effectiveness gradually diminished.

24. **Fors EA et al. (2002)** The effect of guided imagery and amitriptyline on daily fibromyalgia pain: a prospective, randomized, controlled trial. *Journal of Psychiatric Research*, 36(3), 179–87

"Pleasant imagery (PI) was an effective intervention in reducing fibromyalgic pain during the 28-day study period. Amitriptyline had no significant advantage over placebo during the study period."

25. **Geenenyz, R. and. Bijlsm J.W.J. (2010**).Editorial: Psychological management of osteoarthritic pain. *Osteoarthritis and Cartilage*,18,pp. 873-875

"No really effective, let alone disease-modifying, therapy exists for osteoarthritis. This editorial suggests that controlled research has continued to provide support for the efficacy of psychosocial interventions in treating pain from osteoarthritis."

26. **Gordon, A. (2010).** Miracles of mindbody medicine. *Healthcare Counseling & Psychotherapy Journal,* 10(1), 13-18.

This is a very good summary article, appropriate for the general public, that includes some review of the research listed in this bibliography. Also publishes some of Dr. Sarno's retrospective studies of his patient's recoveries.

27. **Gormsen L, Rosendal M and Fink P, (2026).** A nationwide healthcare program for functional somatic disorders (FSD) in Denmark, *Journal of Psychosomatic Research,* https://doi.org/10.1016/j.jpsychores.2026.112664

The national strategy for FSD has been successfully integrated into the Danish health care system, achieving high levels of patient and physician satisfaction. The program provides a comprehensive, accessible, and evidence-based framework for managing FSD through a stepped-care approach and may serve as an inspiration for other countries.

28. **Guthrie, E., Creed, F., Dawson, D., & Tomenson, B. (1993).** A randomised controlled trial of psychotherapy in patients with refractory irritable bowel syndrome. *British Journal of Psychiatry*, 163, 315–321. http://dx.doi.org/10.1192/bjp.163.3.315

For women, psychotherapy was found to be superior to supportive listening. There was a similar trend for men, but this did not reach significance. Following completion of the trial, patients in the control group were offered psychotherapy; 33 accepted and following treatment experienced a marked improvement in their symptoms. At follow-up 1 yr later, those patients who had received psychotherapy remained well, patients who had dropped out of the trial were unwell with severe symptoms.

29. **Gutkin M, McLean L, Brown R, et al. (2021).** Systematic review of psychotherapy for adults with functional neurological disorder. Journal of Neurology, Neurosurgery & Psychiatry 2021;92:36-44.

A reviewe of 12 studies examining cognitive behavioral therapy (CBT) and 7 investigating psychodynamic therapy (PDT). Eleven were pre–post studies and eight were randomised controlled trials. Most studies recruited a single symptom-based subtype rather than all presentations of FND. Effect sizes, where calculable, showed generally medium-sized benefits for physical symptoms, mental health, well-being, function and resource use for both CBT and PDT.

30. **Guzman J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. (2001).** Multidisciplinary rehabilitation for chronic low back pain: systematic review. BMJ 2001;322(7301):1511–6.

Ten trials reported on a total of 12 randomized comparisons of multidisciplinary treatment and a control condition. There was strong evidence that intensive multidisciplinary biopsychosocial rehabilitation with functional restoration improves function when compared with inpatient or outpatient non-multidisciplinary treatments.

31. **Hann KEJ, McCracken LM. (2014**). A systematic review of randomized controlled trials of acceptance and commitment therapy for adults with chronic pain: outcome domains, design quality, and efficacy. *J Contextual Behav Sci* 2014;3:217–27.

ACT is efficacious particularly for enhancing general, mostly physical functioning, and for decreasing distress, in comparison to inactive treatment comparisons but pain severity changed little.

32. **Hilton L, Hempel S et al (2017).** Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. Ann Behav Med 51 (2), 199-213, https://doi.org/10.1007/s12160-016-9844-2

We found low-quality evidence that mindfulness meditation is associated with a small decrease in pain compared with all types of controls in 30 RCTs. Pain reduction was 19% for MM but 8% for controls. Statistically significant effects were also found for depression symptoms and quality of life.

33. **Hsu MC et al. (2010)** Sustained pain reduction through affective self-awareness in fibromyalgia: a randomized controlled trial. *Journal of general internal medicine*. Oct;25(10):1064-70.

"This RCT studied 45 women with fibromyalgia and randomly assigned them to a manualized therapy called Affective Self-Awareness or a waitlist control group. The intervention group had significantly lower pain severity ($p<0.001$), higher self-reported physical function ($p<0.001$), and higher tender-point threshold ($p=0.02$) at 6 months compared to the control group."

34. **Hughes LS, Clark J et al (2017).** Acceptance and Commitment Therapy (ACT) for Chronic Pain. Clin J Pain, Volume 33, Number 6, June 2017, pp. 552-568(17)

Eleven trials were included. Significant, medium to large effect sizes were found for measures of pain acceptance and psychological flexibility. Significant small to medium effect sizes were found for measures of functioning, anxiety, and depression. Measures of pain intensity and quality of life were not significantly different from zero. Generally, effect sizes were smaller at follow-up.

35. **Jones B, Williams AC. (2019)** CBT to reduce healthcare use for medically unexplained symptoms: systematic review and meta-analysis. *British Journal of General Practice* 2019; 69 (681): e262-e269.-**DOI:** https://doi.org/10.3399/bjgp19X701273

A meta-analysis of 22 RCTs showing small reductions in healthcare contacts and medication use with CBT compared with active controls, treatment as usual, and waiting list controls, but not for medical investigations or healthcare costs. Concludes that Cognitive Behavioural Interventions show weak benefits in reducing healthcare use in people with MUS.

36. **Kaufmann D, Sturgeon JA et al (2026).** Emotional awareness and expression therapy for migraine: a preliminary randomized controlled trial. *Pain Medicine*, 2026, 1–4 https://doi.org/10.1093/pm/pnag034

EAET had a significant, large effect on monthly migraine days (MMD), which reduced by 7.0 days (43%) from baseline compared to 1.7 days (11%) among Wait List Controls (*P*=.006). Pooled data from all 24 participants who received EAET (15 in the EAET arm and 9 WLCs), found that EAET had a large effect size on MMD (*P*<.001, *d*=−0.86)

37. **Kroenke K., Swindle R. (2000)** Cognitive-Behavioral Therapy for Somatization and Symptom Syndromes: A Critical Review of Controlled Clinical Trials. *Psychother Psychosom* 69:205-215. https://doi.org/10.1159/000012395

A total of 31 controlled trials (29 randomized and 2 nonrandomized) was identified. Twenty-five studies targeted a specific syndrome (e.g. chronic fatigue, irritable bowel, pain) while 6 focused on more general somatization or hypochondriasis. Primary outcome assessment included physical symptoms, psychological distress and functional status in 28, 26 and 19 studies, respectively. Physical symptoms appeared the most responsive: CBT-treated patients improved more than control subjects in 71% of the studies and showed possibly greater improvement (i.e., a trend) in another 11% of the studies. A definite or possible advantage of CBT for reducing psychological distress was demonstrated in only 38% and 8% of studies respectively, and for improving functional status in 47% and 26%.

38. **Lackner, JM, Jaccard J et al. (2018).** Improvement in Gastrointestinal Symptom After Cognitive Behavior Therapy for Refractory Irritable Bowel Syndrome. *Gastroenterology* 155 (1):47-57.

RCT of 436 subjects comparing standard CBT, workbook CBT with minimal therapist contact and IBS education. 6 months post-treatment 58% of the two CBT groups had moderate to substantial improvement compared to 45% in the IBS education group (p=.05).

39. **Laird KT, Tanner-Smith EE, Russell AC, Hollon SD, Walker L. (2016).** Short- and Long- Term Efficacy of Psychological Therapies for Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. *Clin Gastro Hep* Vol 14(7), p 937-947.e4. https://doi.org/10.1016/j.cgh.2015.11.020

Forty-one trials were included in the meta-analysis, comprising data from 2290 individuals. Psychological therapies had a medium effect on GI symptom severity (effect size = 0.69) immediately after treatment. On average, individuals who received psychotherapy had a greater reduction in GI symptoms after treatment than 75% of individuals assigned to a control condition. After short-term follow-up (1–6 months) and long-term follow-up (6–12 months), this effect remained significant and medium in magnitude (0.76 and 0.73, respectively).

40. **Lilliengren P, Johansson R, Town JM, Maroti D. (2026).** Session-level emotional processing and subsequent somatic symptom change in online ISTDP for treatment-resistant somatic symptom disorder: A lagged within-person secondary analysis. Journal of Psychosomatic Research, Volume 210, 112926,ISSN 0022-3999, https://doi.org/10.1016/j.jpsychores.2026.112926.

Twenty-five participants with moderate to severe Somatic Symptom Disorder and non-response across two prior intervention phases received a mean of 14 sessions of online ISTDP delivered by 17 therapists. After each session, therapists rated rise in complex feelings (0–6). Higher-than-usual

rise in complex feelings was associated with lower somatic symptom severity at the subsequent assessment.

41. **Lumley, M.A. & Schubiner, H., et al (2017).** Emotional awareness and expression therapy, cognitive behavioral therapy, and education for fibromyalgia: a cluster- randomized controlled trial. Pain, 158(12):2354-2363.

"This RCT compared Emotional Awareness and Expression Therapy (EAET) with fibromyalgia education and CBT for symptom management. The 230 patients with fibromyalgia were assessed pre-and post-treatment and the EAET group did better overall than the education group, and had some advantages over CBT in terms of pain relief."

42. **Lumley, M.A. & Schubiner, H. (2019).** Psychological Therapy for Centralized Pain: An Integrative Assessment and Treatment Model. *Psychosomatic Medicine*, V 81, 114-124.

"Greater pain treatment efficacy may be possible if clinicians: (a) distinguish patients with primarily centralized (i.e., somatoform or nociplastic) pain from those with primarily peripheral (nociceptive, inflammatory, or neuropathic) pain; (b) acknowledge the capacity of the brain not only to modulate pain but also generate as well as attenuate or eliminate centralized pain; (c) consider the powerful role that adverse life experiences and psychological conflicts play in centralized pain; and (d) integrate emotional processing and interpersonal changes into treatment. Our integrative treatment involves delivering a progression of interventions, as needed, to achieve pain reduction: tailored pain neuroscience education, cognitive and mindfulness skills to decrease the pain danger alarm mechanism, behavioral engagement in avoided painful and other feared activities, emotional awareness and expression to reverse emotional avoidance and overcome trauma or psychological conflict, and adaptive communication to decrease interpersonal stress." Meticulously documented with over 100 references.

43. **Lumley, M.A. & Schubiner, H. (2019).** Emotional Awareness and Expression Therapy for Chronic Pain: Rationale, Principles and Techniques, Evidence, and Critical Review. *Current Rheumatology Reports* (2019) 21:30. https://doi.org/10.1007/s11926-019-0829-6

This article presents the rationale for EAET, describes its principles and techniques, reviews its development and early testing as well as recent clinical trials, and critically analyzes the evidence base.

44. **Lumley MA, Marshall LM, Kitts TC, Schubiner H, Yarns, BC. (2021**) Emotional awareness and other emotional processes: Implication for the assessment and treatment of chronic pain. Pain Management, 2021, volume 11, no. 3.

Emotional awareness (EA) is a key emotional process that is related to the presence and severity of chronic pain (CP). We describe primary and secondary emotions, discuss the distinction between emotional states and emotional regulation/processing, and summarize theory and research highlighting the significance of EA for CP. We describe ways to assess EA and diagnose centrally-mediated CP, for which emotional processes appear most relevant. We review several psychological interventions designed to enhance EA as well as several broader emotional processing treatments developed to address trauma and psychosocial conflicts underlying many patients' pain. We conclude by offering our perspective on how future integration of emotional processing into pain care could promote recovery from CP.

45. **Lumley MA, Yamin JB, Pester BD, Krohner S, Urbanik CP** (2022). Trauma matters: psychological interventions for comorbid psychosocial trauma and chronic pain. PAIN, 2022, volume 163, 599-603.

Numerous retrospective studies link trauma or posttraumatic stress disorder (PTSD) to Chronic Pain (CP) and prospective studies indicate that earlier trauma is a risk factor for later CP. But current models have rarely informed treatment initiatives, leaving key questions unanswered. How does one define trauma in populations with CP? Is it beneficial to treat comorbid trauma in CP? What interventions effectively do so? This topical review addresses these questions.

46. **Moreley S, Eccleston C, Williams, A. (1999).** Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain* 80: 1-13.

A meta-analysis of 25 trials found that when compared with the waiting list control conditions cognitive-behavioural treatments were associated with median effect size across domains = 0.5. Comparison with alternative active treatments revealed that CBT produced significantly greater changes for pain experience, cognitive coping and appraisal (positive coping measures), and reduced behavioural expression of pain. Differences on the following domains were not significant: mood/affect (depression and other, non-depression, measures), cognitive coping and appraisal (negative, e.g. catastrophization), and social role functioning.

47. **Nahman-Averbuch H, Schneider VJ et al (2020).** Alterations in Brain Function After Cognitive Behavioral Therapy for Migraine in Children and Adolescents. Headache, 60, 1165-1182.

Uncontrolled trial of 8 sessions of CBT in 18 adolescents. Headache frequency decreased from 15 ± 7.4 headaches per month before CBT to 10 ± 7.4 after CBT ($P < .001$). After CBT, greater brain activations in frontal regions involved in cognitive regulation of pain were found as was increased connectivity between the amygdala and frontal regions was observed. Associations between brain activation and amygdalar connectivity with a reduction in headache frequency were also observed.

48. **Peabody, F. (1927).** The Care of the Patient. *JAMA*, 88, 877-882.

"In all your patients whose symptoms are of functional origin, the whole problem of diagnosis and treatment depends on your insight into the patient's character and personal life." Detailed discussion of neuroplastic symptoms as relevant today as it was nearly a century ago.

49. **Powers SW, Kashikar-Zuck SM, Allen JR, LeCates SL, Slater SK, Zafar M, Kabbouche MA, O'Brien HL, Shenk CE, Rausch JR, Hershey AD. (2013).** Cognitive Behavioral Therapy Plus Amitriptyline for Chronic Migraine in Children and Adolescents. A Randomized Clinical Trial. *JAMA 310,* (24), 2622-2630.

At the 20-week end point, days with headache were reduced from the baseline 21 days per month by 11.5 for the CBT plus amitriptyline group vs 6.8 for the headache education plus amitriptyline group ($P = .002$).

50. **Rasmussen, NH, Furst, JW, Swenson-Dravis, DM, Agerter, DC, Smith, AJ, Baird, MA, & Cha, SS. (2006).** Innovative reflecting interview: Effect on high-utilizing patients with medically unexplained symptoms. *Disease Management*, 9, 349-359. http://dx.doi.org/10.1089/dis.2006.9.349

High-utilizing patients with medically unexplained physical symptoms who participated in a reflecting interview had reduced total health care costs, primarily through the reduction of hospitalization or inpatient expenses, despite a modest increase in outpatient primary care clinic visits.

51. **Russell LA, Abbass A A, Allder SJ, Kisely S, Pohlmann-Eden B, Town JM (2016).** A pilot study of reduction in healthcare costs following the application of intensive short-term dynamic psychotherapy for psychogenic nonepileptic seizures. *Epilepsy & Behavior* : E&B , 63, 17-19.

28 patients with psychogenic non-epileptic seizures who received ISTDP, exhibited improvements which resulted in a total combined healthcare cost reduction of over 80% in each of the three years post treatment compared to the year pre-treatment.

52. **Schechter D et al. (2007).** Outcomes of a mind-body treatment program for chronic back pain with no distinct structural pathology-a case series of patients diagnosed and treated as tension myositis syndrome. *Alternative therapies in health and medicine,* Sep-Oct;13(5):26-35.

"51 patients diagnosed with neuroplastic symptoms were treated and evaluated pre- and post-treatment using self-report measures. Mean Visual Analog Scale (VAS) scores with the mind-body treatment program decreased 52% for "average" pain (P=.005). Medication usage decreased (P=.0008). Activity levels increased (P=.03). Participants aged >47 years and in pain for >3 years benefited the most."

53. **Schroder A, Rehfeld E et al (2012).** Cognitive–behavioural group treatment for a range of functional somatic syndromes: randomised trial. *British Journal of Psychiatry* 200, 499–507. doi: 10.1192/bjp.bp.111.098681

45 patients with functional somatic syndromes who received an average of 28 hours of a CBT based group format treatment (over 8 sessions) improved only from a score of 36 to 40 (on a 15 – 65 scale of the Short Form Health Survey) compared to usual care. Maximum effect size of .61 at 16 months follow-up.

54. **Serrat M, Almiral M, Muste M, et al. (2020).** Effectiveness of a Multicomponent Treatment for Fibromyalgia Based on Pain Neuroscience Education, Exercise Therapy, Psychological Support, and Nature Exposure (NAT-FM): A Pragmatic Randomized Controlled Trial. J. Clin. Med. 2020, 9, 3348; doi:10.3390/jcm9103348

An unblinded but controlled trial in 169 fibromyalgia (FM) patients conducted by a single therapist comparing TAU (treatment as usual: FM education, exercise advice) with a group that received 12 weeks of pain neuroscience education (PNE), cognitive behavioral therapy (CBT), mindfulness and exposure to nature while doing yoga, walking, photography and Shinrin Yoku (forest bathing). Subjects averaged 18 years of FM with significant comorbidity including chronic fatigue (71%), migraine (50%), irritable bowel (38%), and multiple chemical sensitivity (27%). With an effect size (d) greater than 0.8 considered large, at 12 weeks the treatment effect size on pain was 5.6, on kinesiophobia (fear of movement) 2.2, pain catastrophizing 2.0, on anxiety 1.6, depression 1.4, on physical function 1.4, and fatigue 0.9. The FM impact score (physical dysfunction, life impact, symptom intensity) improved by at least 20% in 67% of treated subjects.

55. **Smith, RC, Lein, C, Collins, C, Lyles, JS, Given, B, Dwamena, FC, . . . Given, C. W. (2003).** Treating patients with medically unexplained symptoms in primary care. *Journal of General Internal Medicine*, 18, 478–489. http://dx.doi.org/10.1046/j.1525-1497.2003.20815.x

We developed a multidimensional treatment plan by integrating several areas of the literature: collaborative/stepped care, cognitive-behavioral treatment, and the provider-patient relationship. The treatment is designed for primary care personnel (physicians, physician assistants, nurse practitioners) and deployed intensively at the outset; visit intervals are progressively increased as stability and improvement occur.

56. **Speckens, AEM, van Hemert, AM, Spinhoven, P, Hawton, KE, Bolk, JH, & Rooijmans, HGM. (1995).** Cognitive behavioural therapy for medically unexplained physical symptoms: A randomised controlled trial. *British Medical Journal*, 311, 1328–1332. http://dx.doi.org/10.1136/bmj.311.7016.1328

At six months of follow up, the intervention group reported a higher recovery rate (odds ratio 0.40), a lower mean intensity of the physical symptoms, less impairment of sleep (odds ratio 0.38), lower frequency of the symptoms, fewer limitations in social and leisure activities, and

reduced illness behaviour. At 12 months of follow up, the differences between the groups were largely maintained.

57. **Sturgeon J, Trost Z, Ashar YK, Lumley MA, Schubiner H, (2025).** Brief pain reprocessing therapy for fibromyalgia: a feasibility, acceptability, and preliminary efficacy pilot. Reg Anesth Pain Med. 2025 Sep 18:rapm-2025-107076. doi: 10.1136/rapm-2025-107076.

A very brief, mechanism-targeted, telehealth-delivered BPRT protocol for fibromyalgia is feasible, highly acceptable, and shows promising (large effect size of 0.89 for pain reduction at three months) preliminary efficacy for reducing pain, interference, and pain-related fear.

58. **Tankha H, Lumley MH, Gordon A, Schubiner H, Uipi C, et al (2023).** "I don't have back pain anymore": Patient Experiences in Pain Reprocessing Therapy for Chronic Back Pain**.** The Journal of Pain, 2023, ISSN 1526-5900, https://doi.org/10.1016/j.jpain.2023.04.006.

In a recently published randomized controlled trial (Ashar YK, 2021), two-thirds of the patients receiving pain reprocessing therapy (PRT) reported elimination or near-elimination of chronic back pain. A sample of 32 adults with chronic back pain who received PRT completed semi-structured posttreatment interviews about their treatment. 3 major themes reflected participants' understanding of how PRT led to pain relief: 1) reappraisal to reduce fear of pain, which included guiding participants to relate to pain as a helpful indicator, overcoming pain-related fear and avoidance, and reconceptualizing pain as a "sensation;" 2) the link between pain, emotions, and, stress, which included gaining insight into these connections and resolving difficult emotions; and 3) social connections, which included patient-provider alliance, therapist belief in the treatment model, and peer models of recovery from chronic pain.

59. **Thomson, C. J., Pahl, H., & Giles, L. V. (2024).** Randomized controlled trial investigating the effectiveness of a multimodal mobile application for the treatment of chronic pain. Canadian Journal of Pain, 8(1). https://doi.org/10.1080/24740527.2024.2352399

Although the intervention (Curable app) was relatively brief (6 weeks), improvements (of moderate size by Cohen's d) persisted at 12 weeks despite most participants discontinuing app usage. When compared with a 12-week intervention that included optimized analgesic therapy, CBT and self-management strategies supported by physicians and biweekly contact with research nurses, the magnitude of pain severity and interference improvements in our study is comparable. An app-based approach that yields similar results to in-person programs represents a more scalable treatment option.

60. **U.S. Department of Health and Human Services (2019, May).** Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. page 38. Retrieved from U. S. Department of Health and Human Services website: https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html

"**Emotional awareness and expression therapy (EAET)** is an emotion-focused therapy for patients with a history of trauma or psychosocial adversity who suffer from centralized pain conditions. In this approach, patients are taught to understand that their pain is exacerbated or maintained by unresolved emotional experiences that influence neural pathways involved in pain. Patients are taught to become aware of these unresolved experiences, which include suppressed or avoided trauma, adversity, and conflict, and to adaptively express their emotions related to these experiences. Patients learn that control over pain can be achieved through emotional awareness and expression. Enhancing the patient's capacity to approach an experience rather than inhibit or avoid important emotions and interpersonal interactions leads to increased engagement in life activities. Research indicates that EAET has a positive impact on pain intensity, pain interference, and depressive symptoms." (from p 38)

61. **Williams, AC, Fisher E et al (2020).** Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Library https://doi.org/10.1002/14651858.CD007407.pub4
On average, when compared to no treatment or a non-psychological treatment, CBT probably reduces pain and distress by small or very small amounts. (M Lumley PhD: On a 0-10 scale the average patient's pain is 0.4 points better immediately after CBT than after treatment as usual. 6 months later this difference is only 0.2). Compared to a non-psychological treatment, CBT probably reduces disability at the end of the treatment by a very small amount on average. Compared to a non-psychological treatment, CBT may make little to no difference to disability six to 12 months after the treatment.

62. **Yarns BC, Lumley MA, Cassidy JT et al. (2020).** Emotional Awareness and Expression Therapy Achieves Greater Pain Reduction than Cognitive Behavioral Therapy in Older Adults with Chronic Musculoskeletal Pain: A Preliminary Randomized Comparison Trial. *Pain Medicine,* pnaa145, https://doi.org/10.1093/pm/pnaa145
Fifty-three veterans (mean age = 73.5 years, 92.4% male) with chronic musculoskeletal pain. Patients were randomized to EAET or CBT, each delivered as one 90-minute individual session and eight 90-minute group sessions. 42% of EAET patients had >30% pain reduction, one-third had >50%, and 12.5% had >70%. Only one CBT patient achieved at least 30% pain reduction.

63. **Yarns BC, Jackson NJ, Alas A, Melrose RJ, Lumley MA, Sultzer DL (2024).** Emotional Awareness and Expression Therapy vs Cognitive Behavioral Therapy for Chronic Pain in Older Veterans: A Randomized Clinical Trial. *JAMA Netw Open.* 2024;7(6):e2415842. doi:10.1001/jamanetworkopen.2024.15842
In this randomized clinical trial with 126 participants, 63% of EAET participants had clinically significant (at least 30%) posttreatment pain reduction vs only 17% in CBT. In addition, EAET was superior to CBT on 50% pain reduction (35% vs 7%), anxiety, depression, general life satisfaction, and PTSD symptoms. Patients with higher baseline symptoms of depression, anxiety, or PTSD had particularly robust pain reduction following EAET but not CBT.

64. **Ziadni MS, Carty JN, Doherty HK, Porcerelli JH, Rapport LJ, Schubiner H, Lumley MA. (2018).** A life-stress, emotional awareness and expression interview for primary care patients with medically unexplained symptoms: a randomized controlled trial. *Health Psychol* 2018;37:282–90.http://dx.doi.org/10.1037/hea0000566
Compared with treatment as usual, the interview led to significantly lower pain severity, pain interference, sleep problems, and global psychological symptom.

II. ACEs and Trauma

Evidence regarding the link between adverse life experiences (child or adult) and persistent physical symptoms.

65. **Afari N, Ahumada SM, Wright LJ, et al. (2014).** Psychological trauma and functional somatic syndromes: a systematic review and meta-analysis. *Psychosom Med*. Jan;76 (1):2-11

    In a review of 71 studies, individuals who reported exposure to trauma were 2.7 (95% CI = 2.3 – 3.1) times more likely to have a functional somatic syndrome. The magnitude of the association with PTSD was significantly larger than with sexual or physical abuse. Chronic fatigue syndrome had a larger association with reported trauma than either irritable bowel syndrome or fibromyalgia.

66. **Akhtar E, Ballew AT, Orr WN et al (2019).** The prevalence of PTSD Symptoms in Chronic Pain Patients in a tertiary care setting: A Cross-Sectional Study. *Psychosomatics* 60: 3, 255-262.

    The prevalence of PTSD symptoms in their chronic pain population was 28%, four-fold higher than in the general population. Patients with chronic pain and PTSD were younger and reported more severe pain than those without PTSD.

67. **Anderberg UM et al. (2000)**. The impact of life events in female patients with fibromyalgia and in female healthy controls. *European Psychiatry,* Aug;15(5):295-301.

    "Stressful life events in childhood/adolescence and in adulthood seem to be very common in FMS. Furthermore, the life events were experienced as more negative than the life events experienced by healthy controls."

68. **Berntsen D, Johannessen KB et al. (2012).** Peace and War: Trajectories of Posttraumatic Stress Disorder Symptoms Before, During and After Military Deployment in Afghanistan. Psychol Sci 23(12): 1557-1565. doi: 10.1177/0956797612457389

    PTSD symptoms in 746 Danish soldiers were measured on five occasions before, during, and after deployment to Afghanistan identifying six trajectories of change in PTSD symptoms. Two resilient trajectories had low levels across all five times, and a new-onset trajectory started low and showed a marked increase of PTSD symptoms. Three temporary-benefit trajectories showed decreases in PTSD symptoms during (or immediately after) deployment, followed by increases after return from deployment. Predeployment emotional problems and predeployment traumas, especially childhood adversities, were predictors for inclusion in the nonresilient trajectories, showing that factors other than immediately preceding stressors are critical for PTSD development, with childhood adversities being central.

69. **Bertone-Johnson ER, Whitcomb BW et al (2014).** Early Life Emotional, Physical, and Sexual Abuse and the Development of Premenstrual Syndrome: A Longitudinal Study. J Women's Health; 23(9). https://doi.org/10.1089/jwh.2013.4674

    Women reporting the highest level of emotional abuse had 2.6 times the risk of PMS as those reporting no emotional abuse. Women reporting severe childhood physical abuse had an odds ratio of 2.1 compared with those reporting no physical abuse. Sexual abuse was less strongly associated with risk.

70. **Bethell C, Jones J et al (2019).** Positive Childhood Experiences and Adult Mental and Relational Health in a Statewide Sample. Associations Across Adverse Childhood

Experiences Levels. JAMA Pediatr.
doi:10.1001/jamapediatrics.2019.3007 Published online.

The Positive childhood experiences (PCEs) score asked how often or how much as a child they: (1) felt able to talk to their family about feelings; (2) felt their family stood by them during difficult times; (3) enjoyed participating in community traditions; (4) felt a sense of belonging in high school; (5) felt supported by friends; (6) had at least 2 nonparent adults who took genuine interest in them; and (7) felt safe and protected by an adult in their home. Adult Reported Social & Emotional Support (ARSES) is assessed with "How often do you get the social and emotional support you need?" with five choices Always -> Never. PCEs show dose-response decreases in Depression/Poor Mental Health (D/PMH) and increases in ARSES after accounting for exposure to ACEs. The adjusted odds of D/PMH were 72% lower for adults reporting 6 to 7 vs 0 to 2 PCEs. Odds were 50% lower for those reporting 3 to 5 vs 0 to 2 PCEs. Associations were similar in magnitude for adults reporting 1, 2 to 3, or 4 to 8 ACEs. The adjusted odds that adults reported "always" on the ARSES variable were 3.5 times greater for adults with 6 to 7 vs 0 to 2 PCEs. The PCE associations with D/PMH remained stable across each ACEs exposure level when controlling for ARSES. The proactive promotion of PCEs for children may reduce risk for adult D/PMH and promote adult relational health. Joint assessment of PCEs and ACEs may better target needs and interventions and enable a focus on building strengths to promote well-being.

71. **Brennenstuhl S, Fuller-Thomson E (2015).** The Painful Legacy of Childhood Violence: Migraine Headaches Among Adult Survivors of Adverse Childhood Experiences. Headache 55 (7), 973-983. **https://doi.org/10.1111/head.12614**

Study of 23,000 Canadians that found a strong association between self-reported physical abuse, sexual abuse or witnessing domestic violence as children and migraines as adults even after controlling for sociodemographics, comorbid adversities, health behaviors, depression and anxiety. For example, the odds ratio for migraine comparing those with all three adversities vs those with none was 2.8 for women and 3.3 for men.

72. **Brown, TT, Partanen J, Chuong L, et al (2018).** Discrimination hurts: The effect of discrimination on the development of chronic pain. Soc Sci Med 204:1-8. https://doi.org/10.1016/j.socscimed.2018.03.015

We estimate that 4.1 million people in the US in 2016, aged 40 and older, experience chronic pain that is caused by increased psychological distress, where psychological stress has increased due to perceived discrimination.

73. **Burton T, Farley D, and Rhea A. (2009).** Stress-induced somatization in spouses of deployed and nondeployed servicemen. *J Am Ass Nurse Prac*, 21 (6), 332-339.

Spouses of deployed servicemen had significantly higher perceived stress scores than spouses of nondeployed service members (p <.001). Somatization scores were also significantly higher in spouses of deployed versus nondeployed servicemen (p <.001). A significant positive correlation was found between level of perceived stress and level of somatization (r = .878, p <.001).

74. **Bussières, A, Hancock, MJ et al (2023).** Adverse childhood experience is associated with an increased risk of reporting chronic pain in adulthood: a systematic review and meta-analysis. European Journal of Psychotraumatology, 14(2). https://doi.org/10.1080/20008066.2023.2284025

A review of 85 studies of over 800,000 adults. The risk of chronic pain in adulthood significantly increased from one ACE (29% increase), to four or more ACEs (95% increase). Pain-related disability also increased.

75. **Davis DA, Leucken L, Zautra AJ. (2005).** Are reports of childhood abuse related to the experience of chronic pain in adulthood? A meta-analytic review of the literature. *Clinical Journal of Pain* 21(5): 398-405.

Results provide evidence that individuals who report abusive or neglectful childhood experiences are at increased risk of experiencing chronic pain in adulthood relative to individuals not reporting abuse or neglect in childhood.

76. **Douglas A. Drossman, MD; Nicholas J. Talley, MD; Jane Leserman, PhD; Kevin W. Olden, MD; and Marcelo A. Barreiro, MD, MSc (1995)** Sexual and Physical Abuse and Gastrointestinal Illness: Review and Recommendations. *Ann Intern Med.* 123:782-794

Abuse history is associated with gastrointestinal illness and psychological disturbance; appears more often among women, patients with functional gastrointestinal disorders, and patients seen in referral settings; is not usually known by the physician; and is associated with poorer adjustment to illness and adverse health outcome.

77. **Egloff N et al. (2013)** Traumatization and Chronic Pain: A Further Model of Interaction. *Journal of Pain Resolution,* 6, 765-770

"Up to 80% of patients with severe posttraumatic stress disorder are suffering from "unexplained" chronic pain. Introducing the hypermnesia–hyperarousal model, which focuses on two psychoneurobiological aspects of the physiology of learning. Threat-induced hypermnesia is meant to make sure that an individual will, in future, recognize a particular danger again, in order to avoid it. Threat-induced hyperexcitability and sensitization are supposed to detect a potential hazard as early as possible. The intense hypermnesia of trauma-associated pain experiences thus becomes the basis for memory-related pain, whereas the trauma-induced hyperexcitability forms the basis for hyperalgesia (heightened sensitivity to pain – ed.) and allodynia (central pain sensitization – ed)."

78. **Felitti VI, Anda R. (1998)** Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventative Medicine,* May;14(4):245-58

"We found a strong graded relationship between the breadth of exposure to abuse or household dysfunction during childhood and multiple risk factors for several of the leading causes of death in adults." A landmark paper that launched the ACE movement.

79. **Goldberg RT et al. (1999)** Relationship between traumatic events in childhood and chronic pain.. *Disability and Rehabilitation,* Jan;21(1):23-30.

"All pain groups had a history of abuse exceeding 48% and a history of family alcohol dependence exceeding 38%. Child traumatic events are significantly related to chronic pain. Since the problem of child abuse is broader than physical and sexual abuse, health and rehabilitation agencies must shift from individualized treatment to interdisciplinary treatment of the family and patient."

80. **Gupta, M. A. (2013).** Review of somatic symptoms in posttraumatic stress disorder. *International Review of Psychiatry*, 25, 86–99. http://dx.doi.org/10.3109/09540261.2012.736367

Post-traumatic stress disorder (PTSD) is associated with both (1) 'ill-defined' or 'medically unexplained' somatic syndromes, e.g. unexplained dizziness, tinnitus and blurry vision, and syndromes that can be classified as somatoform disorders (DSM-IV-TR); and (2) a range of medical conditions, with a preponderance of cardiovascular, respiratory, musculoskeletal, neurological, and gastrointestinal disorders, diabetes, chronic pain, sleep disorders and other immune-mediated disorders in various studies.

81. **Harrop-Griffiths J, Katon W, Walker E, Holm L, Russo J, Hickok L. (1988).** The Association Between Chronic Pelvic Pain, Psychiatric Diagnoses, and Childhood Sexual Abuse. *Obstet Gynecol, 71*, 589-94.

Compared with controls, the patients with chronic pelvic pain showed significantly greater prevalence of lifetime major depression, current major depression, lifetime substance abuse, adult sexual dysfunction, and somatization. They were also 3-fold (64% vs 23%) more likely than controls to have been a victim of childhood or adult sexual abuse. There were no significant differences in either the degree or type of pelvic disease between patients with pelvic pain and controls (affecting about 1/3 of each group).

82. **Heim, C, Wagner D, et al (2006).** Early Adverse Experience and Risk for Chronic Fatigue Syndrome: Results From a Population-Based Study. *Arch Gen Psychiatry.* 2006;63(11):1258-1266. doi:10.1001/archpsyc.63.11.1258

Among 43 CFS patients, exposure to childhood trauma was associated with a 3- to 8-fold increased risk for CFS across different trauma types compared to 60 non-fatigued controls. There was a graded relationship between the degree of trauma exposure and CFS risk. Childhood trauma was associated with greater CFS symptom severity and with symptoms of depression, anxiety, and posttraumatic stress disorder. The risk for CFS conveyed by childhood trauma increased with the presence of concurrent psychopathology.

83. **Jones GT et al. (2009)** Adverse events in childhood and chronic widespread pain in adult life: Results from the 1958 British Birth Cohort Study. *Pain*, May;143(1-2):92-6.

At age 7 yrs data were collected, by parental report, on physically traumatic events (hospitalisation following a road traffic accident, or for surgery); and factors indicating poor social and psychological environment (periods in local authority care, death of a parent; or parental divorce, alcoholism, or financial hardship). Chronic Widespread Pain was assessed at 45 yrs using self-completion questionnaires. 7571 individuals provided pain data at 45 yrs (71.5%). There was no association between childhood surgery and CWP in adulthood. However, children who had been hospitalised following a road traffic accident experienced a significant increase in the risk of future CWP (relative risk 1.5; 1.05–2.1). Children who had resided in institutional care also experienced an increase in the risk of CWP (1.7; 1.3–2.4) as did those who experienced maternal death (2.0; 1.08–3.7) and familial financial hardship (1.6; 1.3–1.9). Further these associations were not explained by adult psychological distress or social class.

84. **Kapoor E, Okuno M, Miller V, et al. (2021).** Association of Adverse Childhood Experiences with Menopausal Symptoms: Results from the Data Registry on Experiences of Aging, Menopause and Sexuality (DREAMS). Maturitas. 2021 Jan; 143: 209–215.

The association between severe menopausal symptoms and higher childhood adversity (ACE score 1-3 vs 0, OR 1.8, p<.01 and ACE score ≥4 vs. 0, OR 4.5, p<.01) remained significant after adjusting for age, partner status, education, employment, depression, anxiety, and hormone therapy use.

85. **Kessler RC et al (2010)** Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br J Psychiatry*, Nov; 197(5): 378–385.

"To examine joint associations of 12 childhood adversities with first onset of 20 DSM–IV disorders in World Mental Health (WMH) Surveys in 21 countries. Childhood adversities have strong associations with all classes of disorders at all life-course stages in all groups of WMH countries. Long-term associations imply the existence of as-yet undetermined mediators."

86. **Lane, R.D., Anderson, F.S., & Smith, R. (2018).** Biased competition favoring physical over emotional pain: A Possible explanation for the link between early adversity and chronic pain. *Psychosomatic Medicine*, 80(9), 880-890.

"While other studies have shown that early adversity is a risk factor for later chronic pain, no mechanism for this link has been proposed. The authors propose that since survivors of early adversity have difficulty being aware of and expressing distressing emotions, that physical pain can help them to manage these by competing for attention with them. Paying attention to physical pain is reinforced then, as a way to avoid intolerable emotional pain."

87. **McWilliams LA. (2017).** Adult attachment insecurity is positively associated with medically unexplained chronic pain. *Eur J Pain* 21(8) 1378-1383.

In a sample of U.S. adults, the two insecure attachment styles (i.e. anxious and avoidant) were positively associated with MUCP. These associations remained statistically significant after adjusting for demographic variables and depressive and anxiety disorders. When the two insecure attachment styles were considered together, only avoidant attachment remained significantly associated with MUCP. Odds of past-year MUCP increased by 27% for each unit increase (on a 4 point scale) in avoidant attachment. [People with avoidant attachment style see themselves as independent and able to "go it alone." They often maintain strict boundaries, can be emotionally distant, and have a hard time opening up to their partners or making and keeping close friendships.]

88. **Meltzer-Brody S, Leserman J et al (2007).** Trauma and Posttraumatic Stress Disorder in Women With Chronic Pelvic Pain. *Ob & Gyn* 109: 902-908.

Of 713 consecutive women seen in a referral-based pelvic pain clinic, 47% reported having either a sexual or physical abuse history. A total of 31% had a positive screen for PTSD. A trauma history was associated (all at P<.001) with worse daily physical functioning due to poor health, more medical symptoms, more lifetime surgeries, more days spent in bed, and more dysfunction due to pain.

89. **Nelson CA, Bhutta ZA, Burke-Harris N, Danese A, Multhanna S. (2020).** Adversity in childhood is linked to mental and physical health throughout life. life. *BMJ* 2020;371:m3048. doi: https://doi.org/10.1136/bmj.m3048

A review of the literature. Most relevant to this bibliography are the papers showing impacts on physical health during the adult years. Expressed as odds ratios for the group with 4+ ACEs vs the group with 0 ACEs, the relative risk for unexplained somatic symptoms was 2 – 2.7, headaches 2.1, fibromyalgia 1.8, arthritis 1.5, chronic back pain 1.3, and chronic pain 1.2 .

90. **Nicol AL, Sieberg CB, Clauw DJ, Hassett AL, Moser SE, Brummett CM. (2016).** The association between a history of lifetime traumatic events and pain severity, physical function, and affective distress in patients with chronic pain. *J Pain*. 17:1334–48.

A cross-sectional analysis of 3,081 individuals presenting with chronic pain was performed using validated measures and a history of abuse was assessed via patient self-report. Multivariate logistic regression showed that individuals with a history of abuse (n=470; 15.25%) had greater depression, greater anxiety, worse physical functioning, greater pain severity, worse pain interference, higher catastrophizing, and higher scores on the Fibromyalgia Survey criteria (*P*<.001 for all comparisons).

91. **Reuber M. (2008).** Psychogenic non-epileptic seizures: answers and questions. *Review. Epilepsy Behav* 2008; 12: 622–35.

Lists several reports finding that between 32 – 88% of patients with Psychogenic Non-Epileptic Seizures (PNES) had experienced physical or sexual child abuse,

much higher than in epilepsy patients or the general population.

92. **Sachs-Ericsson, N.J., Sheffler, J.L et al (2017**). When emotional pain becomes physical: Adverse childhood experiences, pain, and the role of mood and anxiety disorders. *J Clin Psych*, 73(10), 1403-1428.

"Using data from the 10-year longitudinal Adverse Childhood Experiences (ACE) study, the authors demonstrate the link between child abuse and trauma of various types and the development of physical pain in adult life. People with 4 or more ACEs had twice as many painful conditions as those with no ACEs. They also examine the mediating role that anxiety and depression play in this linkage. The article is a bit difficult to read, but this piece summarizes it well: http://www.stressillness.com/blog/?p=1626."

93. **Schofferman, J., Anderson, D., et al (1992).** Childhood psychological trauma correlates with unsuccessful lumbar spine surgery. *Spine,* 17 (6 suppl), pp. S138-144.

"In a retrospective study of 86 patients who underwent lumbar spine surgery, patients who had three or more of a possible five serious childhood psychological traumas (risk factors) had an 85% likelihood of an unsuccessful surgical outcome. Conversely, in patients with a poor surgical outcome, the incidence of these traumas was 75%. In the group of 19 patients with no risk factors, there was only a 5% incidence of failure."

94. **Schrepf A, Naliboff B et al (2018).** Adverse Childhood Experiences and Symptoms of Urologic Chronic Pelvic Pain Syndrome: A Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network Study. *Annals of Behavioral Medicine,* Volume 52 (10), p 865–877, https://doi.org/10.1093/abm/kax060

ACE severity was elevated in UCPPS (n = 421) participants compared with healthy controls (n = 414; p < .001), and was most strongly associated with factors associated with complex chronic pain, including more diffuse pain, comorbid functional symptoms/syndromes, and worse perceived physical well-being (all p < .001). Finally, worse physical well-being mediated the relationship between ACE severity and less likelihood of painful symptom improvement (OR = .871, p = .007)) and a greater likelihood of painful symptom worsening (OR = 1.249, p = .003) at 1 year.

95. **Schubiner H, Jackson B, Molina KM, et al. (2023).** Racism as a Source of Pain. J Gen Intern Med. DOI: 10.1007/s11606-022-08015-0

Numerous studies indicate that Black Americans have more severe pain, pain-related disability, and other pain-related outcomes (e.g., disturbed sleep) compared to their White counterparts. We propose that racism is an overlooked but preventable source of, or exacerbating factor for, chronic pain and its consequences, and we advance a framework offering innovative pathways for research, treatment, advocacy, and policy.

96. **Sheinberg R, Campbell C, et al (2019).** Childhood Adversity Linked to Heightened Pain Sensitivity in Adults. *Journal of Pain,* 20 (4), S4-S5. DOI https://doi.org/10.1016/j.jpain.2019.01.031

Correlations revealed significant associations between ACEs and psychosocial factors, including traumatic life events, catastrophizing, fear of pain, depression, insomnia and sleep quality, aches and pains (r's=0.2-0.5), as well as pain facilitation (r=0.2).

97. **Shields GS, Spahr CM, Slavich GM (2020).** Psychosocial Interventions and Immune System Function: A Systematic Review and Meta-analysis of Randomized Clinical Trials. JAMA Psychiatry. doi: 10.1001/jamapsychiatry.2020.0431

Estimates suggest that more than 50% of all deaths worldwide are attributable to inflammation-related diseases. (ACEs are also associated with several organ diseases, possibly mediated via inflammation.) Across 56 RCTs and 4060 participants, being randomly assigned to a psychosocial intervention condition vs a control condition was associated with a 15% improvement in beneficial immune system function and an 18% decrease in harmful immune system function over time. These associations persisted for at least 6 months following treatment and were robust across age, sex, and intervention duration.

98. **Spertus IL et al (2003).** Childhood emotional abuse and neglect as predictors of psychological and physical symptoms in women presenting to a primary care practice. Child Abuse & Neglect 27, (11), 1247-1258.

A history of childhood emotional abuse and neglect was associated with increased anxiety, depression, posttraumatic stress and physical symptoms, as well as lifetime trauma exposure. Physical and sexual abuse and lifetime trauma were also significant predictors of physical and psychological symptoms.

99. **Von Houdenhove B et al (2001**). Victimization in chronic fatigue syndrome and fibromyalgia in tertiary care: a controlled study on prevalence and characteristics. *Psychosomatics*, Jan-Feb;42(1):21-8.

95 patients suffering from chronic fatigue syndrome (CFS) or fibromyalgia (FM) compared with a chronic disease group, including rheumatoid arthritis (RA) and multiple sclerosis (MS) patients, and a matched healthy control group. CFS and FM patients showed significantly higher prevalences of emotional neglect and abuse and of physical abuse, with a considerable subgroup experiencing lifelong victimization. The family of origin and the partner were the most frequent perpetrators.

100. **Yang T, Roberts C, Winton-Brown T et al (2022).** Childhood trauma in patients with epileptic vs nonepileptic seizures. Epilepsia 27 October 2022. **https://doi.org/10.1111/epi.17449**

Patients diagnosed with PNES reported greater childhood emotional abuse, emotional neglect, physical abuse, sexual abuse, and physical neglect relative to patients with epilepsy. These differences were replicated in the prospective cohort, except for physical abuse. Reported sexual abuse showed the best screening performance of PNES, although no psychometric scores were adequate as isolated measures.

101. **You, DS & Meagher, MW (2016).** Childhood adversity and pain sensitization. *Psychosomatic Medicine, 78*, 1084-1093.

The high adversity group showed greater temporal summation of second pain sensitization whereas the low-adversity group showed minimal sensitization. The high adversity group also showed blunted cardiac and skin conductance responses. These findings suggest that enhancement of central sensitization may provide a mechanism underlying the pain hypersensitivity and chronicity linked to childhood adversity.

102. **You, DS & Meagher, MW (2018).** Childhood adversity and pain facilitation. *Psychosomatic Medicine,* 80(9), 869-879.

"This study compared pain facilitation between 31 people reporting high levels of childhood adversity with 31 reporting low levels of childhood adversity. They found that the group with

childhood adversity had greater levels of pain, correlated with their PTSD symptoms. The authors suggest that this finding helps explain why people who experience childhood adversity are more likely to experience widespread pain as adults."

III. Pain Perception

Evidence that psychological factors can change pain perception.

103. **Aaron RV, Fisher EA et al** (2019) Alexithymia in individuals with chronic pain and its relation to pain intensity, physical interference, depression, and anxiety: a systematic review and meta-analysis. *Pain,* May;160(5):994-1006

"Meta-analysis findings demonstrated that alexithymia is elevated in individuals with chronic pain and related to greater pain intensity and physical interference, although the latter relationships may be accounted for by negative affect."

104. **Bardin et al (2009)** Chronic restraint stress induces mechanical and cold allodynia, and enhances inflammatory pain in rat: Relevance to human stress-associated painful pathologies. *Behavioural brain research* 205: 360-366

"Whereas acute stress often results in analgesia, chronic stress can trigger hyperalgesia/allodynia. This influence of long-term stress on nociception is relevant to numerous painful pathologies, such as fibromyalgia (FM), characterized by diffuse muscular pain (hyperalgesia) and/or tenderness (allodynia). Hence, there is a need for pre-clinical models integrating a chronic-stress dimension to the study of pain."

105. **Berna et al (2010)** Induction of a depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. *Biological Psychiatry* 67: 1083-1090

"The increase in negative pain-specific cognitions during depressed mood predicted the perceived increase in pain unpleasantness. Following depressed mood induction, brain responses to noxious thermal stimuli were characterized by increased activity in a broad network including prefrontal areas, subgenual anterior cingulate cortex, and hippocampus, as well as significantly less deactivation when compared with pain responses in a neutral mood."

106. **Biesiekierski, JR et al (2025).** Non-coeliac gluten sensitivity. Lancet (online)

Non-coeliac gluten sensitivity (NCGS) refers to individuals who report intestinal and extraintestinal symptoms related to the ingestion of gluten-based or wheat-based foods, in the absence of coeliac disease or wheat allergy. Although approximately 10% of adults worldwide self-report gluten or wheat sensitivity, meta-analyses suggest that, during controlled challenge studies, only 16–30% of these individuals have symptoms specifically triggered by gluten.

107. **Campbell, C.M., Buenaver, L.F., et al. (2015).** Sleep, pain catastrophising, and central sensitization in knee osteoarthritis patients with and without insomnia. *Arthritis Care and Research,* 67 (10), pp.1387–1396.

"Study found that insomnia and catastrophising increase pain in people with knee arthritis."

108. **Carroll, L.J., Cassidy, J.D., & Coté, P. (2004).** Depression as a risk factor for onset of an episode of troublesome neck and low back pain. *Pain,* 107, 134-139.

"The authors set out to assess whether depression is an independent risk factor for severe neck and back pain. They followed 790 randomly selected adults for 12 months, and found that depression was a strong independent predictor for the onset of intense or disabling neck and low back pain."

109. **Carson, J.W, Keefea, F.J., & Lowrya, K.P. (2007).** Conflict about expressing emotions and chronic low back pain: Associations with pain and anger. *J Pain.* 8(5), 405-11.

"This study found that in patients with chronic low back pain, ambivalence about expressing emotions was positively correlated with both pain and anger."

110. **Castro WH et al. (2001)** No stress--no whiplash? Prevalence of "whiplash" symptoms following exposure to a placebo rear-end collision. *International Journal of Legal Medicine.* 114(6):316-22.

"Approximately 20% of subjects exposed to placebo, low-velocity rear-end collisions will thus indicate whiplash, even though no biomechanical potential for injury exists. Certain psychological profiles place an individual at higher risk for this phenomenon."

111. **Chou, E.Y., Parmer, B.L. & Galinsky, A.D. (2016).** Economic insecurity increases physical pain. *Psychological Science,* 27(4), 443-454.

"The authors found a causal connection between economic insecurity and physical pain. They reviewed five studies and found that economic stress caused physical pain and also decreased pain tolerance. Another study found that financial problems predicted the use of pain relief medication. Their analysis includes a meta-analysis of the included studies."

112. **Eisenberger, N.I. (2012).** The neural bases of social pain: Evidence for shared representations with physical pain. *Psychosomatic Medicine*, 74(2), 126-135.

"The author speculates that the human social attachment system may have "co-opted" the pain system. She summarizes the research exploring whether social and physical pain share the same neural systems, that is, "experiences of social pain activate neural regions that are also involved in physical pain processing." The ramifications of this are explored,and found that "individual differences in sensitivity to one kind of pain relate to individual differences in sensitivity to the other and that factors that modulate one type of pain experience affect the other in a similar manner."

113. **Eisenberger, N.I. (2015).** Social pain and the brain: Controversies, questions, and where to go from here. *Annual Review of Psychology*, 66, 601-629.

"The author summarizes and addresses the controversy surrounding the findings in her previous article (above). Her conclusions include this statement: "There is a strong tendency among those who study and treat pain to view pain as a physical phenomenon that is caused by damage to the body. Nonetheless, years of research have shown that there can be tissue damage with no pain (e.g., wounded soldiers in battle) as well as severe pain with no tissue damage (e.g., migraines, fibromyalgia). These dissociations illustrate that, from an experiential perspective, the critical component of painful experience may stem from the mental experience of suffering."

114. **Gracely RH. (2015)** Programmed Symptoms: Disparate Effects United by Purpose. *Current Rheumatology Reviews*, 11, 116-130

"In this new model central sensitization is part of an ensemble that includes also the symptoms of widespread pain, fatigue, unrefreshing sleep and dyscognition. The main feature is an intrinsic program that produces this ensemble to guide behavior to restore normal function in conditions that threaten survival."

115. **Hellman, N., Kuhn, B.L. et al (2018).** Emotional modulation of pain and spinal nociception in sexual assault survivors. *Psychosomatic Medicine,* 80(9),861-868.

"This study compared 33 survivors of sexual assault with 33 matched adults with no sexual assault history. They gave each group identical pain stimuli, but the sexual assault survivors experienced the same stimuli as more painful. They hypothesize reasons for this finding."

116. **Kross E, Berman MG, Mischel W, Smith EE and Wager TD (2011).** Social rejection shares somatosensory representations with physical pain. *PNAS* 108 (15) 6270-6275; https://doi.org/10.1073/pnas.1102693108

When people who recently experienced an unwanted break-up view a photograph of their ex-partner as they think about being rejected - areas that support the sensory components of physical pain (secondary somatosensory cortex; dorsal posterior insula) become active.

117. **Kulkarni, B., Bentley, D.E., Elliott, R., et al. (2007).** Arthritic pain is processed in brain areas concerned with emotions and fear. *Arthritis and Rheumatology*, 56(4), 1345-54.

"Using functional neuroimaging studies, they compared pain from arthritis to experimental pain (acute pain). The acute pain activated the brain structures knows as the "pain matrix." However, the pain from arthritis activated the cingulate cortex, the thalamus, and the amygdala; these areas are involved in the processing of fear, emotions, and in aversive conditioning."

118. **Lumley M, Cohen J et al (2011).** Pain and Emotion: A Biopsychosocial Review of Recent Research. J Clin Psychol. Sep; 67(9): 942–968.

"Neurobiological research documents the neural processes that distinguish affective from sensory pain dimensions, link emotion and pain, and generate central nervous system pain sensitization. Psychological research demonstrates that greater pain is related to emotional stress and limited emotional awareness, expression, and processing. Social research shows the potential importance of emotional communication, empathy, attachment, and rejection."

119. **Mcbeth et al (2005)** Hypothalamic-pituitary-adrenal stress axis function and the relationship with chronic widespread pain and its antecedents. *Arthritis Research Therapy,* 7 (5) R992-R1000

"In clinic studies, altered hypothalamic-pituitary-adrenal (HPA) axis function has been associated with fibromyalgia, a syndrome characterised by chronic widespread body pain. These results may be explained by the associated high rates of psychological distress and somatisation. We address the hypothesis that the latter two, rather than the pain, might explain the HPA results."

120. **Montemayor Z, Elizondo S, et al (2026).** Linking central sensitization to multisystemic manifestations in hypermobile Ehlers-Danlos syndrome. Front. Pain Res. 7:1799439. doi: 10.3389/fpain.2026.1799439

While central sensitization in hEDS/HSD involves a broad multisystemic impact, it is independently associated with a triad of fatigue, pain, and cardiac dysautonomia. These results underscore the need for a clinical shift toward integrated, multi-system phenotyping therapies.

121. **Quartana, P.J., Burns, JW. (2007).** Painful consequences of anger suppression. *Emotion*, 7(2), pp. 400–414.

"The authors experimentally examined the effects of anger suppression on pain perception. Participants who were instructed to suppress experiential or expressive components of emotion during harassment reported the greatest pain levels. "Results suggest that attempts to suppress anger may amplify pain sensitivity..."

122. **Raspe H, Hueppe A, Neuhauser H. (2008)**. Back pain, a communicable disease? International Journal of Epidemiology, Volume 37, Issue 1, February 2008, Pages 69–74, https://doi.org/10.1093/ije/dym220

Analyzing five German health surveys from 1991–2003, the authors observed a 10–16% higher BP prevalence in West Germany compared to East Germany shortly after reunification (1990), which narrowed to near-zero by 2003. This occurred alongside increased exposure to West German media emphasizing BP as inevitable, medically complex, and disabling.

123. Rhudy & Meagher (2000) Fear and anxiety: divergent effects on human pain thresholds. *Pain*, 84 65-75.

"Animal studies suggest that fear inhibits pain whereas anxiety enhances it; however it is unclear whether these effects generalize to humans. Both subjective and physiological indicators (skin conductance level, heart rate) confirmed that the treatment conditions produced the targeted emotional states. These results support the view that emotional states modulate human pain reactivity."

124. Rivat et al (2010) Chronic stress induces transient spinal neuroinflammation, triggering sensory hypersensitivity and long-lasting anxiety-induced hyperalgesia. *Pain*, 150 (2), 358-368.

Chronic stress affects spinal plasticity through a mechanism involving local neuroinflammation. The functional consequences of such neuroinflammation are associated with a transient decrease in the mechanical nociceptive threshold, ie increased pain sensitivity.

125. Shibata M, Ninomiya, T et al (2014) Alexithymia Is Associated with Greater Risk of Chronic Pain and Negative Affect and with Lower Life Satisfaction in a General Population: The Hisayama Study. *PLoS One.* 9(3): e90984.

With N=927, the odds ratio (OR) for having chronic pain was significantly higher in the high-normal (OR: 1.5) and alexithymic groups (OR: 2.6) compared to the low normal alexithymic group. Approximately 40% of the participants belonged to the two high-risk groups. Of the 439 participants with chronic pain, the levels of pain intensity, disability, depression, and anxiety were significantly increased and the degree of life satisfaction was decreased with elevating alexithymia categories.

126. Suarez-Roca et al (2008) Reduced GABA neurotransmission underlies hyperalgesia induced by repeated forced swimming stress. *Behavioural Brain Research*, 189 (1): 159-169.

"We determined if cutaneous hyperalgesia and pain-induced c-Fos overexpression in the spinal cord produced by repeated forced swimming (FS) stress in the rat were related to changes in GABA neurotransmission by studying spinal release of GABA and the effect of positive modulation of GABA-A receptors with diazepam. In conclusion, stress-induced reduction in GABA-A receptor activation is involved in the development of FS stress-induced hyperalgesia."

127. Trucharte A, Leon L et al (2020) Emotional regulation processes: influence on pain and disability in fibromyalgia patients. *Clin Exp Rheumatol,* 38 (Suppl. 123): S40-S46.

Although FM patients do not differ in terms of the attention paid to their emotional states, FM patients had greater difficulties in the emotional regulation process. In addition, emotional rejection (not accepting emotional reactions that make them feel uncomfortable) and interference (difficulty concentrating or performing tasks when experiencing negative emotions) are two variables that influence the pain severity and disability.

128. Wager, TD, Rilling, J.K., Smith, E.E, et al. (2004). Placebo-induced changes in fMRI in the anticipation and experience of Pain. *Science,* 303, pp. 1162-1167.

"The investigators showed that placebo can change fMRI images of the brain, demonstrating

that pain perception is not dependent on physical or structural issues" at the site of pain."

129. **Wiech, K et al. (2009)** The influence of negative emotions on pain: behavioural effects and neural mechanisms. *NeuroImage*, 47(3): 987-994

"There is evidence for the reverse causal relationship in which negative mood and emotion can lead to pain or exacerbate it. Here, we review findings from studies on the modulation of pain by experimentally induced mood changes and clinical mood disorders."

130. **Wise, BL, Niu, J, et al (2010).** Psychological factors and their relation to osteoarthritis pain. *Osteoarthritis and Cartilage,* 18, pp. 883-887.

"The authors demonstrate an association between worsened measures of mental health and osteoarthritis pain and risk of pain flares. They recommend that mental health treatment is a way to prevent pain flares."

131. **Yang H, Haldeman S (2020).** Chronic Spinal Pain and Financial Worries in the US Adult Population. *Spine,* 45 (8), p528-533. doi: 10.1097/BRS.0000000000003319

Different types of financial worries were significantly (Odds Ratios 2.2 – 2.5) associated with chronic spinal pain, controlling for demographic characteristics and socioeconomic status. These worries included paying monthly bills, maintaining standard of living, credit card payments, paying rent/mortgage/housing costs, medical costs for healthcare, money for retirement, medical costs of illness/accident, and paying for children's college (OR 1.4). Sample size was 33,672.

IV. Predicting the Clinical Course

Evidence that objective measures of organ disease or structural abnormality (such as imaging studies) are not good predictors of persistent symptoms and/or that psychological factors are better predictors.

132. **Bedson, J. and Croft,P.R. (2008).** The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskeletal Disorders,* 9, pp. 116-127.

"Knee osteoarthritis shown on x-ray is an imprecise guide to the likelihood that knee pain or disability will be present. The results of knee x rays should not be used in isolation when assessing individual patients with knee pain."

133. **Bigos, S.J. et al (1992).** A Longitudinal, prospective study of industrial back injury reporting. *Clinical Orthopeadics and Related Research*, 279(June), 21-34.

Authors prospectively assessed 3,020 volunteer employees at a Boeing plant for risk factors of filing back injury claims. They followed the subjects for four years, and found that the 279 people who reported back problems had only one physical predictor: previous medical treatment. The most predictive individual factors were (1) job task dissatisfaction and (2) distress as reported on Scale 3 of the MMPI. "This data perhaps explains why the focus on purely physical and injury-related factors has met with little success in dealing with what has become the most expensive orthopedic problem.

134. **Boos, N., Rieder, R., Schade, V., et al. (1995).** The Diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disc herniations. *Spine*, 20, 2613-25. DOI: 10.1097/00007632-199512150-00002

In an age-, sex-, and risk factor matched group of asymptomatic individuals, disc herniation had a substantially higher prevalence (76%) than previously reported in an unmatched group. Individuals with minor disc herniations (i.e., protrusion, contained discs) are at a very high risk that their magnetic resonance images are not a causal explanation of pain because a high rate of asymptomatic subjects (63%) had comparable morphologic findings. The only highly significant difference between the pain/sciatica group and asymptomatic control group regarding morphologic findings was the criteria of a nerve root compromise. Work perception and psychosocial factors were helpful in discriminating between symptomatic and asymptomatic disc herniations.

135. **Borenstein D.G., O'Mara, J.W., Boden, S.D., et al. (2001).** Lumbar Spine MRI to Predict Low-Back Pain in Asymptomatic Subjects. *Jnl Bone Joint Surg,* 83-A(9), 1306-11.

"A prospective study of 67 asymptomatic individuals had MRIs in 1989. 31% had an identifiable abnormality in the spine. Seven years later the investigators looked at these subjects to see how they were doing. The findings on magnetic resonance scans were not predictive of the development or duration of low-back pain. Individuals with the longest duration of low-back pain did not have the greatest degree of anatomical abnormality on the original, 1989 scans."

136. **Brinjikji W et al. (2015).** Systematic Literature Review of Imaging Features of Spinal Degeneration in Asymptomatic Populations. *American Journal of Neuroradiology* 36:811–16.

Thirty-three articles reporting imaging findings for 3110 **asymptomatic** individuals met our study inclusion criteria. The prevalence of disk degeneration in asymptomatic individuals increased from 37% of 20-year-old individuals to 96% of 80-year-old individuals. Disk bulge prevalence increased from 30% of those 20 years of age to 84% of those 80 years of age. Disk protrusion prevalence increased from 29% of those 20 years of age to 43% of those 80 years of age.

137. **Brown TT, Lee W (2020).** The FuturePain study: Validating a questionnaire to predict the probability of having chronic pain 7-10 years into the future. PLOS ONE. https://doi.org/10.1371/journal.pone.0237508

The FUTUREPAIN study developed a questionnaire, based on the biopsychosocial model, to predict the probability of developing or maintaining moderate-to-severe chronic pain 7–10 years into the future. From an initial set of 82 variables, a machine learning algorithm derived an 18-variable model tested on a new cohort with sensitivity of .88 and specificity of .76 for future pain. The five items on the questionnaire with the largest coefficients (listed from largest to smallest) were Psychological Distress (Kessler K6), Fair Health, Lost Home, Parental Abuse and Current Chronic Pain.

138. **Burns JW, Janssen I, Lillis T et al (2020).** The transition from acute to persistent pain: the identification of distinct trajectories among women presenting to an emergency department. PAIN: November 2020 - Volume 161 - Issue 11 - p 2511-2519 doi: 10.1097/j.pain.0000000000001960

Women (N = 375) who presented to an inner-city emergency department (ED) with complaints of acute pain were followed up for 3 months. One group (early recovery; n = 93) had recovered to virtually no pain by the initial visit, whereas a second group (delayed recovery; n = 120) recovered to no pain only after 1 month. A third group (no recovery; n = 162) still reported elevated pain at 3 months after the ED visit. The

no recovery group reported significantly greater PTSD symptoms, anger, sleep disturbance, and lower social support at the initial visit than both the early recovery and delayed recovery groups.

139. Carragee E, Alamin T, et al (2006). Are first-time episodes of serious LBP associated with new MRI findings? *Spine,* 6(6), 624-635.

"The authors point to the practice of doing MRIs on first time episodes of lower back pain (LBP), and interpreting the abnormal results as causing the pain. They did a prospective study of 200 subjects over five years. MRIs were done at the beginning on people with no LBP. They then compared these baselines with MRIs taken during episodes of LBP and find no significant differences. Most new changes represent progressive age changes not associated with acute events."

140. Carragee, E.J., Lincoln, T., et al (2006). A Gold standard evaluation of the "discogenic pain" diagnosis as determined by provocative discography. *Spine*, 31(18), 2115-2123.

A sophisticated x-ray exam was done to carefully select patients who were most likely to have pain relief from spinal fusion surgery. Even under those strict conditions, in only 27% was the outcome considered highly effective and in 57% it was not even minimally acceptable. In the same study, in a comparison group having spine fusion for a non-pain condition (spondylolisthesis), the corresponding figures were 72% and 9%.

141. Carroll LJ, Holm LW, Ferrari R, Ozegovic D and Cassidy JD (2009). Recovery in Whiplash-Associated Disorders: Do You Get What You Expect? Journal of Rheumatology May, 36 (5) 1063-1070; DOI: https://doi.org/10.3899/jrheum.080680

A cohort of 6,015 adults with traffic-related whiplash injuries was assessed. After adjusting for the effect of sociodemographic characteristics, post-crash symptoms and pain, prior health status and collision-related factors, those who expected to get better soon recovered over 3 times as quickly (hazard rate ratio = 3.62, 95% confidence interval 2.55–5.13) as those who expected that they would never get better. Patients' early expectations for recovery are an important prognostic factor in recovery after whiplash injury and are potentially modifiable by clinicians.

142. Chiodo A, Haig AJ et al (2007). Needle EMG has a lower false positive rate than MRI in asymptomatic older adults being evaluated for lumbar spinal stenosis. Clinical Neurophysiology,Vol 118, Issue 4, p. 751-756

In 35 *asymptomatic* older adults, 16% had disk herniations and 56% had spinal stenosis on MRI. 37% had an abnormal EMG (those with herniations all had normal EMG). On re-examination 18 months later the EMGs were normal, and no one developed symptoms.

143. Christensen JO et al. (2012) Work and back pain: a prospective study of psychological, social and mechanical predictors of back pain severity. *European Journal of Pain.* Jul;16(6):921-33. 21.

"The most consistent predictors of back pain were protective factors including decision control, empowering leadership and fair leadership. Some of the most important predictors included in this study were factors that have previously received little attention in back pain research."

144. Connor PM et al. (2003) Magnetic resonance imaging of the asymptomatic shoulder of overhead athletes: a 5-year follow-up study. *American Journal of Sports Medicine* Sep-Oct;31(5):724-7

"Eight of 20 (40%) dominant shoulders had findings consistent with partial- or full-thickness tears of the rotator cuff as compared with none (0%) of the nondominant shoulders. Five of 20 (25%)

dominant shoulders had magnetic resonance imaging evidence of Bennett's lesions compared with none (0%) of the nondominant shoulders. None of the athletes interviewed 5 years later had any subjective symptoms or had required any evaluation or treatment for shoulder-related problems during the study period."

145. **Culvenor et al (2018).** Prevalence of Knee Osteoarthritis Features on Magnetic Resonance Imaging in Asymptomatic Uninjured Adults: A Systematic Review and Meta-Analysis. Br J Sports Med. Oct; 53(20):1268-1278.

We included 63 studies (5397 knees of 4751 adults) of asymptomatic, uninjured adults. The overall pooled prevalence of cartilage defects was 24% and meniscal tears was 10%, with significantly higher prevalence with age.

146. **Elliott J et al (2010)** Asymptomatic Spondylolisthesis and Pregnancy *Journal of Orthopaedic & Sports Physical Therapy,* Volume:40 Issue:5 Pages:324–324

"The patient was a 32-year-old woman diagnosed with grade III spondylolisthesis at the age of 18. While the patient had not experienced back pain in recent years, she anticipated a recurrence of symptoms during her final trimester of pregnancy. Lumbar magnetic resonance imaging was used to confirm the presence of grade IV spondylolisthesis"

147. **Englund, M., Guermazi, A., Gale, D., et al. (2008)** Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *NEJM*, 359(11), 1108-15.

Knee MRIs from 991 subjects, ages 50-90 years old. The findings indicated that meniscal tears are common in the general population and increases with age. However, 61% of the subjects who had meniscal tears in their knees had not had any pain, aching, or stiffness during the previous month."

148. **Feyer AM et al. (2000)** The role of physical and psychological factors in occupational low back pain: a prospective cohort study. *Occupational and Environmental Medicine*, Feb;57(2):116-20

"Other than a history of LBP, pre-existing psychological distress was the only factor found to have a pre-existing influence on new episodes of LBP."

149. **Frank JD, Harris JM et al (2015).** Prevalence of Femoroacetabular Impingement Imaging Findings in Asymptomatic Volunteers: A systematic Review. Arthroscopy 31(6): 1199-1204.

26 studies for inclusion, comprising 2,114 asymptomatic hips. The prevalence of an asymptomatic cam deformity was 37%, pincer deformity was 67% and labral injury, which was found on MRI without intra-articular contrast was present in 68% of hips.

150. **Girish G et al (2011).** Ultrasound of the Shoulder: Asymptomatic Findings in Men. Am J Roentgenol 197 (4): W713-W719.

Asymptomatic shoulder abnormalities were found in 96% of the 51 subjects (age 40-70). Subacromial-subdeltoid bursal thickening was present in 78%, acromioclavicular joint osteoarthritis in 65%, supraspinatus tendinosis in 39%, subscapularis tendinosis in 25%, partial-thickness tear of the bursal side of the supraspinatus tendon in 22%, and posterior glenoid labral abnormality in 14%.

151. **Ibounig T, Järvinen TLN, Raatikainen S, et al. (2026)** Incidental Rotator Cuff Abnormalities on Magnetic Resonance Imaging. *JAMA Intern Med.* Published online February 16, 2026. doi:10.1001/jamainternmed.2025.7903

RC abnormalities were present in 96% of asymptomatic shoulders (1039 of 1076) and 98% of symptomatic shoulders (126 of 128). Only Full Thickness Tears were more prevalent in

symptomatic shoulders (14.6%) than in asymptomatic shoulders (6.5%), but this difference diminished after adjustment.

152. **Jensen, M.C., Brant-Zawadzki, et al. (1994).** Magnetic resonance imaging of the lumbar spine in people without back pain. *NEJM*, 331(2), 69-73.

"A classic study in which MRIs were performed on 98 people with no back pain. They found that only 36% of these people had normal spines, the other 64% had various evidence of disc degeneration. "Given the high prevalence of these findings and of back pain, the discovery by MRI of bulges or protrusions in people with low back pain may frequently be coincidental."

153. **Kaplan LD et al. (2005)** Magnetic resonance imaging of the knee in asymptomatic professional basketball players. *Arthroscopy*, May;21(5):557-61.

"The results of our study show an equal to or higher prevalence of meniscal lesions in male professional basketball players than previously reported in the literature. We found a large number of patella-femoral articular cartilage lesions in our study population of male professional basketball players. These athletes perform at the highest demand level, which indicates that the presence of these lesions did not cause any symptoms.

154. **Karppinen J. (2001)** Severity of symptoms and signs in relation to magnetic resonance imaging findings among sciatic patients. *Spine* (Philadelphia Pa 1976), Apr 1;26(7):E149-54.

"The degree of disc displacement in magnetic resonance imaging did not correlate with any subjective symptoms, nor did nerve root enhancement or nerve compression."

155. **Kendall SA, Elert J et al (2002)**. Are perceived muscle tension, electromyographic hyperactivity and personality traits correlated in the Fibromyalgia Syndrome? J Rehabil Med 34: 73-79.

Thirty-six women with fibromyalgia performed forward flexion of the shoulder with EMG measurement. Perceived muscle tension did not correlate with EMG hyperactivity but did correlate with anxiety proneness on a personality inventory. EMG hyperactivity did correlate with pain, particularly pain at rest and with a number of personality traits including high impulsiveness, monotony avoidance and inversely with psychasthenia, verbal aggression and irritability.

156. **Kim SJ et al. (2013)** Prevalence of disc degeneration in asymptomatic Korean subjects. Part 1: lumbar spine. *Journal of Korean Neurosurgical Society*, Jan;53(1):31- 8.

"All lumbar disc degenerations are not pathologic, especially in children and adolescents."

157. **Kivimäki M et al. (2004)** Work stress and incidence of newly diagnosed fibromyalgia: prospective cohort study. *Journal of Psychosomatic Research*, Nov;57(5):417-22.

"The odds ratio of incident diagnosed fibromyalgia for workplace bullying was 4.1 (95% CI 2.0–9.6). The corresponding odds ratios for high workload and low decision latitude were 2.1 (1.2–3.9) and 2.1 (1.1–4.0), respectively. Stress seems to be a contributing factor in the development of fibromyalgia, but further research is needed to examine whether stress perceptions are affected by undiagnosed fibromyalgia. "Central sensitivity syndromes" denotes an emerging nomenclature that could be embraced by researchers investigating each of these disorders. Moreover, a shared paradigm would be useful in promoting cross-fertilization between researchers. Scientists and clinicians could most effectively forward the understanding and treatment of fibromyalgia and other common chronic pain disorders through an appreciation of their shared pathophysiology.

158. **Kopp B, Furlough K et al (2021).** Factors associated with pain intensity and magnitude of limitations among people with hip and knee arthritis. J Orthop May 21;25:295-300.doi: 10.1016/j.jor.2021.05.026.

The magnitude of limitations was independently associated with years of education, work status, time spent exercising, catastrophic thinking (PCS-4), and symptoms of depression. They accounted for 50% of variability in physical function, with the major contributor being catastrophic thinking. The model for pain intensity included time spent exercising and fear of painful movement. Anatomic site and radiographic severity of arthritis were not associated with either physical function or pain in our patient sample. This study confirms that limitations and pain from osteoarthritis of the hip and knee are more closely related to personal and psychological factors.

159. **Lederman E. (2011)** The fall of the postural-structural-biomechanical model in manual and physical therapies: exemplified by lower back pain. *Journal of bodywork and movement therapies*, Apr;15(2):131-8.

"Can a person's physical shape/posture/structure/biomechanics be the cause of their lower back pain?"

160. **Masselin-Dubois, A., Attal, N.,et al (2013).** Are psychological predictors of chronic postsurgical pain dependent on the surgical model? A Comparison of total knee arthroplasty and breast surgery for cancer. *Journal of Pain,* 14(8), pp. 854-864.

"This prospective study looked at two groups of patients who had surgery: a group of men and women undergoing total knee replacements who had pain pre-surgery, and a group of women with no pre-surgical pain who would have breast surgery for cancer. The predictive value of measures of anxiety, depression and catastrophising were assessed, and it was found that anxiety, level of pain immediately post-surgery, and catastrophising predicted pain at 3 months post-surgery, regardless of which surgery was done."

161. **Matsumoto M et al. (2013)** Tandem age-related lumbar and cervical intervertebral disc changes in asymptomatic subjects. *European Spine Journal*, Apr;22(4):708-13.

"MRI indicated degenerative changes in the lumbar spine in 79 subjects (84 %), with decreased disc signal intensity in 74.5 %, posterior disc protrusion in 78.7 %, Degenerative findings in both the lumbar and cervical spine, suggesting tandem disc degeneration, was common in asymptomatic subjects. These results provide normative data for evaluating patients with degenerative lumbar and cervical disc diseases."

162. **Milde C, Glombiewski J et al (2023).** Psychological factors predict higher odds and impairment of post-COVID symptoms: A prospective study. *Psychosomatic Medicine* ():10.1097/PSY.0000000000001214, May 5, 2023. | *DOI:* 10.1097/PSY.0000000000001214

After controlling for medical (BMI, disease score) and demographic factors (gender, age), psychosomatic symptom burden (measured by the SSD-12) predicted higher odds and magnitude of COVID-related symptom impairment in the post-COVID phases (subacute and chronic). We found that other psychological factors were associated with an overall increase (i.e., chronic stress and depression) or decrease (i.e., trait positive affect) in the odds and magnitude of COVID-related symptom impairment.

163. **Nakashima H, Yukawa Y et al (2015).** Abnormal Findings on Magnetic Resonance Images of the Cervical Spines in 1211 Asymptomatic Subjects. Spine 40, (6), 392-398.

Most subjects had cervical disc bulging (88%), which significantly increased with age in terms of frequency, severity, and number of levels. Even in their 20s, 75% had bulging discs. In contrast, few asymptomatic subjects were diagnosed with Spinal Cord Compression (5.3%) or increased

signal intensity (2.3%).

164. **O'Neil JT et al (2016).** Peroneal Tendon Abnormalities on Routine Magnetic Resonance Imaging of the Foot and Ankle. Foot Ankle Int. Jul;37(7): 743-7

The most commonly occurring primary pathology in 294 MRIs of asymptomatic subjects was Achilles tendinosis/tears (29%), followed by posterior tibial tendon dysfunction (15%) with 35% of the peroneal tendons demonstrating some pathology.

165. **Rajasekaran S et al (2021).** The catastrophization effects of an MRI report on the patient and surgeon and the benefits of 'clinical reporting': results from an RCT and blinded trials. Eur Spine J. https://doi.org/10.1007/s00586-021-06809-0

Patients with low back pain who were given a full factual explanation of their MRI reports, (compared to a control group who were told their reports reflected age-related changes), failed to get better and were also keen for an intervention to avoid possible deteriorations and future complications. Our study clearly proves that a misinterpretation of the patient's spinal condition's status through the MRI report leads to a negative impression of their spine. In a second phase, the authors generated both 'routine' and 'clinical' reporting for MRIs of 20 chronic LBP patients. Terminologies causing anxiety and fear in Routine Reporting, such as degeneration, tears, fissures, nerve compression, etc., were replaced by alternate terminologies in Clinical Reporting. The effect of Clinical Reporting was significant in orthopaedic surgeons, orthopaedic residents, and physiotherapists as for the same MRI, they perceived lesser severity of the disease, prescribed conservative treatment in more patients, and also assessed lower probability of surgery.

166. **Symeonidis PD et al (2012).** Prevalence of Interdigital Nerve Enlargements in an Asymptomatic Population.

Ultrasound, even in highly skilled hands, has a high rate (54%) of incidental finding of an asymptomatic interdigital nerve enlargement, which can lead to a false diagnosis of a Morton's neuroma.

167. **Simotas AC, Shen T (2005)** Neck pain in demolition derby drivers. *Arch Phys Med Rehabil*, Apr;86(4):693-6.

"40 drivers participated in a mean of 30 career events and had an average of 52 car collisions per event at a mean of 26 mph. Only 2 drivers reported their worst neck pain lasted more than 3 months. 37 drivers reported no chronic neck pain. These data suggest that demolition derby drivers sustain less chronic neck pain after multiple car collision events than might otherwise be expected. Further study of this unique population of car drivers may contribute to understanding whiplash disorder."

168. **Silvis ML et al. (2011)** High prevalence of pelvic and hip magnetic resonance imaging findings in asymptomatic collegiate and professional hockey players. *The Am J Sports Medicine.* Apr; 39(4):715-21.

"The study included 21 professional and 18 collegiate hockey players. Self-reported symptoms were measured using a modified Oswestry Disability Questionnaire. Participants underwent 3-T MRI evaluation of the pelvis and hips. Given the high prevalence of MRI findings in asymptomatic hockey players, it is necessary to cautiously interpret the significance of these findings in association with clinical presentation."

169. **Udby PM, Ohrt-Nissen S, et al. (2020).** The Association of MRI Findings and Long-Term Disability in Patients with Chronic Low Back Pain. Global Spine Journal. https://doi.org/10.1177/2192568220921391

In this study of 170 patients with LBP with severe Disc or Facet Joint degeneration, no association was found between baseline MRI findings and 13-year disability. This highlights the limited

prognostic value of a single baseline MRI scan on long-term disability. None of the MRI changes suggesting degeneration were associated with a worse outcome at 13-year follow-up.

170. Widhe T et al. (2001) Spine: posture, mobility and pain. A longitudinal study from childhood to adolescence". *Eur Spine J*. (PMID: 11345632) Apr;10(2):118-23

"A longitudinal study was undertaken to analyse the development of posture and spinal mobility during growth and its relationship to low back pain and sports activities. Occasional low back pain was reported by 38% of the children at the age of 15-16 years, but back pain was not related to posture, spinal mobility or physical activity."

171. Wise, B.L., Niu, J, et al (2010). Psychological factors and their relation to osteoarthritis pain. *Osteoarthritis and Cartilage,* 18, pp. 883-887.

"The authors demonstrate an association between worsened measures of mental health and osteoarthritis pain and risk of pain flares. They recommend that mental health treatment is a way to prevent pain flares."

172. Young, A.K., Young, B.K, et al. (2014). Assessment of pre-surgical psychological screening in patients undergoing spine surgery: Use and clinical impact. *J Spinal Disord Tech*, 27:76–79.

"A prospective survey found that only 37% of spinal surgeons used pre-surgical psychological screening (PPS), despite the North American Spine Society guidelines regarding the use of PPS. Depression is associated with longer recuperations, delayed returns to work, more postsurgical complications and failures to comply with medication schedules after patients leave the hospital."

173. Young, Casey C et al. (2008) Transition from acute to chronic pain and disability: a model including cognitive, affective, and trauma factors. *Pain*. Jan;134(1-2):69-79.

"Early detection of elevated depressive symptoms and high trauma exposure may identify individuals at greater risk for developing chronic pain syndromes who may benefit from early multidisciplinary intervention."

V. Ineffective Treatments

Evidence that invasive treatment, non-invasive non-psychological treatment and opioids are *ineffective* for chronic pain.

174. **Anheyer, D, Haller H, Barth J et al (2017).** Mindfulness-Based Stress Reduction for Treating Low Back Pain. *Ann Intern Med.* 166:799-807.

In seven RCTs involving 864 patients with low back pain, MBSR compared to usual care led to short term improvements in pain intensity and physical functioning that were not sustained in the long term. Disability, mental health, pain acceptance and mindfulness also were not significantly different in the short or long term.

175. **Berthelot JM. (2015)** Strong opioids for noncancer pain due to musculoskeletal diseases: Not more effective than acetaminophen or NSAIDs. *Joint Bone Spine.* Dec;82(6):397-401.

"In patients with chronic noncancer low back pain, morphine and other strong opioids in dosages of up to 100mg/day were only slightly more effective than their placebos, no more effective than acetaminophen, and somewhat less effective than nonsteroidal anti-inflammatory drugs (NSAIDs)."

176. **Buchbinder R, Osborne RH, Kallmes D. (2009)** Vertebroplasty appears no better than placebo for painful osteoporotic spinal fractures, and has potential to cause harm. *Med J Aust.* Nov 2;191(9):476-7.

"Two randomised placebo-controlled trials show Vertebroplasty appears no better than placebo for painful osteoporotic spinal fractures, and has potential to cause harm. Shows the importance of establishing the efficacy of procedures before adopting them into clinical practice."

177. **Carragee, E.J., Lincoln, T., et al (2006).** A Gold standard evaluation of the "discogenic pain" diagnosis as determined by provocative discography. *Spine*, 31(18), 2115-2123.

A sophisticated x-ray exam was done to carefully select patients who were most likely to have pain relief from spinal fusion surgery. Even under those strict conditions, in only 27% was the outcome considered highly effective and in 57% it was not even minimally acceptable. In the same study, in a comparison group having spine fusion for a non-pain condition (spondylolisthesis), the corresponding figures were 72% and 9%.

178. **Carreon, L.Y., Glassman, S.D., et al (2010).** Clinical outcomes after posterolateral lumbar fusion in workers' compensation patients. *Spine* 35(19), 1812–1817.

"Compared outcomes post-surgery between people on workers compensation and matched subject not on workers compensation. Only 16-19% of workers compensation patients showed improvement, while 36-40% of patients not on workers compensation showed improvement."

179. **Chaparro LE. (2014)** Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. Spine Apr 1;39(7):556- 63.

"The effectiveness and safety of long-term opioid therapy for treatment of CLBP remains unproven."

180. Chou R, Baisden, J, et al. (2009). Surgery for low back pain: a review of the evidence for an American Pain Society Clinical Practice Guideline. Spine, 34(10), 1094-109.

"Reviewed online databases of RCTs and systematic reviews. Surgery for radiculopathy with herniated lumbar disc and symptomatic spinal stenosis is associated with short-term benefits compared to nonsurgical therapy, though benefits diminish with long-term follow-up in some trials. For non-radicular back pain with common degenerative changes, fusion is no more effective than intensive rehabilitation, but associated with small to moderate benefits compared to standard nonsurgical therapy."

181. Chou R. (2015) Epidural Corticosteroid Injections for Radiculopathy and Spinal Stenosis: A Systematic Review and Meta-analysis. *Ann Intern Med.* Sep 1;163(5):373- 81.

"Epidural corticosteroid injections for radiculopathy were associated with immediate reductions in pain and function. However, benefits were small and not sustained, and there was no effect on long-term surgery risk. Limited evidence suggested no effectiveness for spinal stenosis."

182. Deyo RA, Mirza SK, Turner JA, Martin BI. (2009). Overtreating chronic back pain: time to back off? J Am Board Fam Med. 22:62–8.

Recent studies document a 629% increase in Medicare expenditures for epidural steroid injections; a 423% increase in expenditures for opioids for back pain; a 307% increase in the number of lumbar magnetic resonance images among Medicare beneficiaries; and a 220% increase in spinal fusion surgery rates. The limited studies available suggest that these increases have not been accompanied by population-level improvements in patient outcomes or disability rates.

183. Dhruva SS, Murillo J et al (2023). Long-term Outcomes in Use of Opioids, Nonpharmacologic Pain Interventions, and Total Costs of Spinal Cord Stimulators Compared With Conventional Medical Therapy for Chronic Pain. JAMA Neurol. 2023 Jan 1;80(1):18-29. doi: 10.1001/jamaneurol.2022.4166.

Over two years, the 1,260 patients using spinal cord stimulators (SCS) didn't have lower use of opioids, or most other pain treatments, than did those pursuing conventional medical management (CMM) without implantation. 18% treated with SCS experienced SCS-related complications within 2 years, and 279 of 1260 patients (22.1%) had device revisions and/or removals, which were not always for complications. Total costs of care in the first year were $39,000 higher with SCS than CMM.

184. Franklin GM, Haug, et al (1994). Outcome of lumbar fusion in Washington State workers' compensation. *Spine,* 19(17):1897-1903.

"This study looked at patients from the workers compensation program who had had lumbar surgery to look for predictive factors for disability and reoperation. Most patients reported that back pain (67.7%) was **worse** and overall quality of life (55.8%) was no better or worse than before surgery."

185. Fritzell, P., Hagg, O. et al (2001) Lumbar fusion versus nonsurgical treatment for chronic low back pain. *Spine,* 26, (23), 2521–2534.

"This is a RCT multi-site study with 2-year follow-up with independent observer comparing pain and disability outcomes between surgery and non-surgery for lower back pain. The non-surgical group had physical therapy, and the surgical group had fusion surgery. Surgical group's pain was reduced by 33% and the non-surgical group by 7%. Pain improved most in the first six months, and then gradually got worse."

186. **Geiss A. (2005)** Predicting the failure of disc surgery by a hypofunctional HPA axis: evidence from a prospective study on patients undergoing disc surgery. *Pain*, Mar;114(1-2):104-17.

"Patients with postoperative ongoing sciatic pain have been shown to exhibit reduced cortisol levels along with enhanced IL-6 levels. The aim of the present study was to clarify the relationship between a reduced cortisol secretion and enhanced cytokine levels by performing a prospective study on patients with disc herniation. These findings suggest that chronically stressed patients are at a higher risk for a poor surgical outcome as their reduced cortisol secretion promotes the postoperative ongoing synthesis of proinflammatory cytokines."

187. **Grossman, P., Ackland, G. L., Allen, et al. (2026).** Why the polyvagal theory is untenable. An international expert evaluation of the polyvagal theory and commentary upon Porges, S.W. (2025). Polyvagal theory: current status, clinical applications, and future directions. Clin. Neuropsychiatry, 22(3), 169-184. Clinical Neuropsychiatry, 23(1), 100-112.

39 co-authors agree that major tenets of the PVT are not supported by past or current knowledge and, in several instances, are inconsistent with the broader evidence base. Since the topics addressed constitute fundamental premises of the PVT, they concluded that the PVT is untenable, because it is not defensible based on existing neurophysiological and evolutionary evidence. The psychological elements composing the superstructure of the PVT are primarily derived from earlier psychological literature and are neither clarified nor strengthened by PVT constructs that lack evidence.

188. **Hadler, N.M. (2003).** MRI for regional back pain: Need for less imaging, better understanding. *JAMA*, 289(21), 2863-2865.

This is an editorial commenting on a study in the same issue that showed that substituting rapid MRI neither saved money nor led to improved clinical outcomes. Rather, the data suggested that substituting rapid MRI increases cost in part because it predisposes patients to undergo surgical intervention. The author makes the point that there has yet to be any evidence that a structural issue causes back pain. Therefore, "Imaging only serves to bolster the notion that back pain is nothing more than the symptom of an underlying disease. This is a social construct that nurtures an enormous treating enterprise far more than it helps the patient."

189. **Hara S, Andresen H, Solheim O. (2022).** Effect of Spinal Cord Burst Stimulation vs Placebo Stimulation on Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery: A Randomized Clinical Trial. JAMA. 2022;328(15):1506-1514. doi:10.1001/jama.2022.18231

There was no difference in disability between periods of spinal cord stimulation and placebo stimulation. 18% of patients suffered adverse events necessitating removal of the SCS in 8%.

190. **Jonas WB, Crawford C et al (2019).** Are Invasive Procedures Effective for Chronic Pain? A Systematic Review. *Pain Medicine*, 20(7), 2019, 1281–1293 doi: 10.1093/pm/pny154

Twenty-five trials (2,000 participants) were included in the review assessing the effect of invasive procedures over sham. Conditions included low back pain (N.7 trials), arthritis (4), angina (4), abdominal pain (3), endometriosis (3), biliary colic (2), and migraine (2). The risk of any adverse event was significantly higher for invasive procedures (12%) than sham procedures (4%). In the two meta-analysis subsets, the standardized mean difference for reduction of low back pain in seven studies (N.445) was 0.18, and for knee pain in three studies (N.496) it was 0.04. The relative contribution of within-group improvement in sham treatments accounted for 87% of the effect compared with active treatment across all conditions. Conclusions: There is little evidence for the specific efficacy beyond sham for invasive procedures in chronic pain. A moderate amount of

evidence does not support the use of invasive procedures as compared with sham procedures for patients with chronic back or knee pain. Given their high cost and safety concerns, more rigorous studies are required before invasive procedures are routinely used for patients with chronic pain.

191. **Kallmes DF et al (2009**) A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med*, Aug 6;361(6):569- 79

"We randomly assigned 131 patients who had one to three painful osteoporotic vertebral compression fractures to undergo either vertebroplasty or a simulated procedure without cement (control group). Improvements in pain and pain-related disability associated with osteoporotic compression fractures in patients treated with vertebroplasty were similar to the improvements in the simulated procedure (control) group."

192. **Kalske R et al (2026).** Arthroscopic Partial Meniscectomy for Degenerative Tear — 10-Year Outcomes. *N Engl J Med* 2026;394:1757-1759. DOI: 10.1056/NEJMc2516079

In this trial of arthroscopic partial meniscectomy for degenerative medial meniscal tear in adults, participant-reported and radiologic outcomes over 10 years of follow-up suggested no benefit and possible harm from the procedure.

193. **Keller A et al. (2007)** Effect sizes of non-surgical treatments of non-specific low-back pain. *European Spine Journal*, Nov;16(11):1776-88.

"As a conclusion, the effect of non-surgical treatments for LBP is only small to moderate. Therefore, there is a dire need for developing more effective interventions."

194. **Khan, M., Evaniew, N., et al (2014).** Arthroscopic surgery for degenerative tears of the meniscus: a systematic review and meta-analysis. *CMAJ*, 186(14), pp. 1057-1064.

"Included seven RCTs in this review and found moderate evidence to suggest that there is no benefit to arthroscopic surgery in comparison with non-operative or sham treatments in middle-aged patients with mild or no concomitant osteoarthritis. The authors recommend a trial of non-operative management as the first-line treatment for such patients."

195. **Kirkley A, Birmingham TB, Litchfield RB, et al. (2008).** A Randomized trial of arthroscopic surgery for osteoarthritis of the knee. *NEJM*, 359(11), 1097-1107.

"RCT comparing 86 patients who had surgery for osteoarthritis of the knee with 86 who underwent physical and medical therapy. There was no difference in outcome between the two groups."

196. **Lian, J., Mohamadi, A et al (2018).** Comparative efficacy and safety of nonsurgical treatment options for enthesopathy of the extensor carpi radialis brevis: A Systematic review and meta-analysis of randomized placebo-controlled trials. *American Journal of Sports Medicine*, published online October 31.

"This meta-analysis of tennis elbow found that in 36 RCTs with placebo controls, most patients experienced pain resolution after receiving placebo within 4 weeks of follow-up. At best, all treatments provided only small pain relief while increasing the odds of adverse events."

197. **Mirza, S.K. and Deyo, R.A. (2007).** Systematic review of randomized trials comparing lumbar fusion surgery to nonoperative care for treatment of chronic back pain. *Spine,*32:816-23.

"Examined five RCT studies comparing surgery to non-surgical approaches to chronic back pain. Found methodological problems in all five studies. However, concluded that surgery is better than unstructured nonsurgical care, but structured therapy was better than surgery."

198. **Nguyen TH. (2011)** Long-term outcomes of lumbar fusion among workers' compensation subjects: a historical cohort study. *Spine*, Feb 15;36(4):320-31.

"Compared return-to-work (RTW) data, permanent disability, postsurgical complications, opiate utilization, and reoperation status for chronic low back pain subjects who had lumbar fusion surgery with nonsurgical controls. They concluded that lumbar fusion surgery for the diagnoses of disc degeneration, disc herniation, and/or radiculopathy in a Workers Compensation setting is associated with significant increase in disability, opiate use, prolonged work loss, and poor Return-To-Work status. In addition, in the surgical group, 36% had complications, 27% needed reoperation."

199. **Pape E, Hagen KB et al (2012).** Early multidisciplinary evaluation and advice was ineffective for whiplash-associated disorders. *European Journal of Pain.* Volume 13, Issue 10, November 2009, Pages 1068-1075.

Assessed the effect of early multidisciplinary evaluation and advice on the frequency of chronic neck pain three years post-injury in persons with minor or moderate traffic injuries. The advice actually increased the risk of having chronic neck pain three years later. Literally, the intervention may therefore have done more harm than good.

200. **Staal JB. (2009)** Injection therapy for subacute and chronic low back pain: an updated Cochrane review. *Spine*, Jan 1;34(1):49-59.

"The effectiveness of injection therapy for low back pain is still debatable. Heterogeneity of target tissue, pharmacological agent, and dosage, generally found in RCTs, point to the need for clinically valid comparisons in a literature synthesis."

201. **Thordarson, D., Ebramzadeh, E. et al (2005).** Correlation of Hallux Valgus Surgical Outcome With AOFAS Forefoot Score and Radiological Parameters. *Foot and Ankle International*, 26 (2), pp, 122-127.

"This prospective study looked at people who had undergone three different surgical procedures for bunions. The authors note their surprise that neither the degree of deformity pre-surgery, nor the degree of residual deformity post-surgery significantly affected the improvement that patients experienced, including pain scores. This suggests that the degree of deformity is not a good predictor of pain nor of success of surgery."

202. **Traeger AC, Lee H, Hubscher M, Skinner IW, Moseley GL et al. (2019).** Effect of Intensive Patient Education vs Placebo Patient Education on Outcomes in Patients With Acute Low Back Pain. A Randomized Clinical Trial. *JAMA Neurol.* 2019;76(2):161-169. doi:10.1001/jamaneurol.2018.3376

In this randomized clinical trial of 202 adults with acute low back pain from Sydney, Australia, adding intensive patient education to first-line care of patients was no better at improving pain outcomes than a placebo intervention.

203. **Truong K, Meier K, Ahrens LC, et al (2024).** Cryoneurolysis versus radiofrequency ablation outcome on pain experience in chronic low back pain (COPE): a single-blinded randomised controlled trial. RMD Open 2024;10:e004196. doi: 10.1136/rmdopen-2024-004196 https://rmdopen.bmj.com/content/10/2/e004196

120 people who had at least 50% pain relief an hour after a block of the medial branch nerve with local anesthetic were divided into three groups of 40 patients and given either cryoneurolysis, Radio Frequency Ablation (RF), or a placebo.

Four weeks later they were assessed with the Patient Global Impression of Change. They also were assessed for pain intensity, quality of life, disability, depression, and catastrophizing at 4 weeks, 3, 6 and 12 months. There were no differences between the three groups on these measures. Neither the cryoneurolysis nor the RF were better than placebo for back pain.

204. **Verbeek JH. (2012)** Proper manual handling techniques to prevent low back pain, a Cochrane systematic review. *Work: a journal of prevention, assessment, and rehabilitation;* 41 Suppl 1:2299-301.

"Training and provision of assistive devices are considered major interventions to prevent and treat low back pain (LBP) among workers exposed to manual material handling (MMH). None of the included RCTs and CCTs provided evidence that training and provision of assistive devices prevented LBP when compared to no intervention or another intervention."

205. **Wang X, Martin G. (2025).** Common interventional procedures for chronic non-cancer spine pain: a systematic review and network meta-analysis of randomised trials. BMJ 2025;388:e079971. http://dx.doi.org/10.1136/bmj-2024-079971

For chronic axial spine pain, compared with sham procedures, several common invasive treatments provided little or no benefit. For example, epidural injection of local anaesthetic with or without steroids, and joint-targeted steroid injection probably result in little to no difference in pain relief (moderate certainty evidence); intramuscular injection of local anaesthetic, epidural steroid injection, and joint-targeted injection of local anaesthetic with or without steroids may provide little to no difference in pain relief (low certainty evidence); and intramuscular injection of local anaesthetic with steroids may increase pain (low certainty evidence). Available evidence for joint radiofrequency ablation proved of very low certainty.

VI. Neuroscience

Studies of the neuroscience of chronic pain including the key role of altered nerve pathways in the brain.

203. Apkarian AV, Baliki MN and Farmer MA (2013). Predicting transition to chronic pain. Curr Opin Neurol Aug; 26(4): 360-367. doi: 10.1097/WCO.0b013e32836336ad

In a longitudinal brain-imaging study, individuals who developed an intense back pain episode were followed over a 1-year period, during which pain and brain parameters were collected repeatedly. A smaller number of healthy individuals and chronic back pain patients were also studied concomitantly, as controls. At the time of entry into the study, strength of synchrony between the medial prefrontal cortex and nucleus accumbens (i.e. functional connectivity) was predictive (>80% accuracy) of individuals who subsequently transition to chronic pain 1 year later. Properties of the brain's emotional learning circuitry predict the transition from acute to chronic pain.

204. Aybek S et al. (2014) Neural correlates of recall of life events in conversion disorder. *JAMA Psychiatry*. Jan;71(1):52-60.

"This study offers support for the notion that the way adverse events are processed cognitively can be associated with physical symptoms in Conversion Disorder."

205.Berry MP, Lutz J, et al (2020). Brief Self-Compassion Training Alters Neural Responses to Evoked Pain for Chronic Low Back Pain: A Pilot Study. Pain Medicine, 0(0), 1–14 doi: 10.1093/pm/pnaa178

Investigated the effects of brief (eight contact hours, two weeks of home practice) self-compassion training on pain-related brain processing in chronic low back pain (cLBP). Observed reduced clinical pain intensity and disability ($P < 0.01$) and increased trait self-compassion and interoceptive awareness (all $P < 0.05$) following training. Evoked pressure pain response in the right temporo-parietal junction (TPJ) was reduced following training, and decreases were associated with reduced clinical pain intensity. Further, increased fMRI responses to pain anticipation were observed in the right dorsolateral prefrontal cortex (dlPFC) and ventral posterior cingulate cortex (vPCC), and these increases were associated with mean post-training changes in Self-Compassion Scale scores and scores from the body listening subscale of the Multidimensional Assessment of Interoceptive Awareness. These findings, though exploratory and lacking comparison with a control condition, suggest that self-compassion training supports regulation of pain through the involvement of self-referential (vPCC), salience-processing (TPJ), and emotion regulatory (dlPFC) brain areas.

206.Brown CA et al. (2014) When the brain expects pain: common neural responses to pain anticipation are related to clinical pain and distress in fibromyalgia and osteoarthritis. *European Journal of Neuroscience* 39(4): 663-672.

"This experiment applied laser-induced pain to the skin of three groups, people with fibromyalgia, people with osteoarthritis, and a group of healthy controls. Though there was no difference between the three groups in the degree of pain experienced, both the fibromyalgia and osteoarthritis groups had abnormal anticipatory responses to pain, suggesting that these may represent common brain mechanisms for both chronic regional and widespread pain."

207. Delvecchio G, Rossetti MG, Caletti E et al (2019). The Neuroanatomy of Somatoform Disorders: A Magnetic Resonance Imaging Study. *Psychosomatics* 60: 3. 279 – 288.

Compared to healthy controls, Somatoform Disorder (SD) patients showed reduced gray matter in the hypothalamus, left fusiform gyrus, right cuneus, left inferior frontal gyrus, left posterior cingulate and right amygdala. Greater clinical symptomatology correlated with greater reductions in gray matter in frontal-limbic and parietal regions. Results suggest selective impairments in specific cortico-limbic regions associated with two overlapping circuits, the neuromatrix of pain and the emotion regulation system.

208. Derbyshire SW et al. (2004) Cerebral activation during hypnotically induced and imagined pain. *Neuro Image*. Sep;23(1):392-401.

"The authors used hypnotic suggestion of pain to generate the experience of pain with no injury. The fMRI of the brains of these subjects indicated activation of the same brain areas activated in physical pain."

209. Drossman DA, Ringel Y, Vogt BA, Leserman J, Lin W, Smith J K, & Whitehead W. (2003). Alterations of brain activity associated with resolution of emotional distress and pain in a case of severe irritable bowel syndrome. *Gastroenterology*,124, 754–761. http://dx.doi.org/10.1053/gast.2003.50103

During severe illness, the patient had major psychosocial impairment, high life stress, a low visceral pain threshold, and activation of the midcingulate cortex (MCC), prefrontal area 6/44, and the somatosensory cortex, areas associated with pain intensity encoding. When clinically improved, there was resolution in activation of these 3 areas, and this was associated with psychosocial improvement and an increased threshold to rectal distention.

210. Eisenberger NI et al. (2003) Does rejection hurt? An FMRI study of social exclusion. *Science.* Oct 10;302(5643):290-2.

"A neuroimaging study examined the neural correlates of social exclusion and tested the hypothesis that the brain bases of social pain are similar to those of physical pain. Participants were scanned while playing a virtual ball-tossing game in which they were ultimately excluded. Paralleling results from physical pain studies, the anterior cingulate cortex (ACC) was more active during exclusion than during inclusion and correlated positively with self-reported distress. Right ventral prefrontal cortex (RVPFC) was active during exclusion and correlated negatively with self-reported distress. ACC changes mediated the RVPFC-distress correlation, suggesting that RVPFC regulates the distress of social exclusion by disrupting ACC activity.

211. Eisenberger, N.I. (2012). The neural bases of social pain: Evidence for shared representations with physical pain. *Psychosomatic Medicine*, 74(2), 126-135.

"The author speculates that the human social attachment system may have "co-opted" the pain system. She summarizes the research exploring whether social and physical pain share the same neural systems, that is, "experiences of social pain activate neural regions that are also involved in physical pain processing." The ramifications of this are explored and found that "individual differences in sensitivity to one kind of pain relate to individual differences in sensitivity to the other and that factors that modulate one type of pain experience affect the other in a similar manner."

212. Eisenberger, N.I. (2015). Social pain and the brain: Controversies, questions, and where to go from here. *Annual Review of Psychology*, 66, 601-629.

"The author summarizes and addresses the controversy surrounding the findings in her previous article (above). Her conclusions include this statement: "There is a strong tendency among those who study and treat pain to view pain as a physical phenomenon that is caused by damage to the body. Nonetheless, years of research have shown that there can be tissue damage with no pain (e.g., wounded soldiers in battle) as well as severe pain with no tissue damage (e.g., migraines, fibromyalgia). These dissociations illustrate that, from an experiential perspective, the critical component of painful experience may stem from the mental experience of suffering."

213. Fisher JP, Hassan DT, O'Connor N (1995). Minerva Column case report of severe pain from a nail passing through a boot without tissue trauma. BMJ. Jan 7;310(70).

214. Gracely RH, Geisser ME et al (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain, Apr;127(Pt 4):835-43. doi: 10.1093/brain/awh098. Epub 2004 Feb 11.

These findings suggest that pain catastrophizing, independent of the influence of depression, is significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala) and motor control. These results support the hypothesis that catastrophizing influences pain perception through altering attention and anticipation, and heightening emotional responses to pain.

215. Gündel, H., Valet, M., Sorg, C., Huber, D., Zimmer, C., Sprenger, T., & Tölle, T. R. (2008). Altered cerebral response to noxious heat stimulation in patients with somatoform pain disorder. *Pain*, 137,413–421. http://dx.doi.org/10.1016/j.pain.2007.10.003

Comparing somatoform pain disorder patients with controls, a pain related hypoactive state of the ventromedial prefrontal/orbitofrontal cortex (BA 10/11) and a hyperactive state of the parahippocampal gyrus, amygdala and anterior insula were found in the patient group. Our findings of an altered cerebral processing of experimentally induced pain in patients with somatoform pain disorder support the hypothesis of dysfunctional pain processing, especially in affect regulating regions.

216. Harper, M. (2012). Taming the amygdala: An EEG analysis of exposure therapy for the traumatized. *Traumatology*, *18*(2), 61-74.

Animal and human studies have shown that the emotional aspects of fear memories mediated in the lateral nucleus of the amygdala can be extinguished by application of low-frequency tetanic stimulation or by repetitive sensory stimulation, such as tapping the cheek. Sensory input creates a remarkable increase in the power of the low-frequency portion of the electroencephalogram (EEG) spectrum. Glutamate receptors on synapses that mediate a fear memory in attention during exposure therapy are depotentiated by these powerful waves of neuronal firings, resulting in disruption of the memory network. In this study nearly all sensory inputs applied to the upper body result in wave power sufficiently large to quench fear–memory networks regardless of input location and type and whether the sensory input is applied unilaterally or bilaterally.

217. Hashmi JA, et al, Apkarian AV (2013) Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain*. Sep; 136(9): 2751– 2768.

This study looked at how activation in the brain shifts when pain evolves from acute to chronic. We observed that brain activity for back pain in the early, acute/subacute back pain group is limited to regions involved in acute pain, whereas in the chronic back pain group, activity is confined to emotion-related circuitry.

218. Hong JY, Labus JS,et al (2014). Regional neuroplastic brain changes in patients with chronic inflammatory and non-inflammatory visceral pain. PLoS One. 2014 Jan 8;9(1):e84564. doi: 10.1371/journal.pone.0084564.

Chronic inflammatory and non-inflammatory visceral pain syndromes are associated with distinct regional cortical thickness changes, implying different dominant mechanisms of brain remodeling: inflammation-driven peripheral input in UC versus primarily central processes in IBS, even though both present clinically with chronic visceral pain.

219. **Kim J, Loggia ML, Cahalan CM, Harris RE, Beissner F, Garcia RG, Kim H, Barbieri R, Wasan AD, Edwards RR, Napadow V. (2015).** The somatosensory link in fibromyalgia: functional connectivity of the primary somatosensory cortex is altered by sustained pain and is associated with clinical/autonomic dysfunction. *Arthritis Rheumatol*, 67, 1395-1405.

Our study demonstrates that both somatic and non-somatic dysfunction in Fibromyalgia, including clinical pain, pain catastrophizing, autonomic dysfunction, and amplified temporal summation, are closely linked with the degree to which evoked deep tissue pain alters S1 connectivity to salience/affective pain-processing regions. Additionally, diminished connectivity between S1 subregions during the rest phase in FM may result from ongoing widespread clinical pain.

220. **Kim SM, Hong JS, Min KJ et al. (2019).** Brain Functional Connectivity in Patients with Somatic Symptom Disorder. *Psychosomatic Medicine,* 81, 313-318.

Patients with Somatic Symptom Disorder (SSD) had greater functional connectivity on fMRI study within the sensorimotor network (SMN), default mode network (DMN) and salience network than healthy controls. Patients with SSD also had increased functional connectivity between the SMN and DMN, the SMN and salience network, SMN and dorsal attention network (DAN) and salience network and DAN. This suggests that SSD may be associated with alterations of sensory-discriminative processing of pain and other somatic symptoms, which is influenced by affective processing.

221. **Kindler LL. (2011)** Central sensitivity syndromes: mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. *Pain Manag Nurs,* Mar;12(1):15-24.

A literature search was performed through PubMed and Ovid using the terms fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, irritable bladder/interstitial cystitis, headache, chronic low back pain, chronic neck pain, functional syndromes, and somatization. The extant literature presents considerable overlap in the pathophysiology of these diagnoses.

222. **Kulkarni, B., Bentley, D.E., Elliott, R., et al. (2007).** Arthritic pain is processed in brain areas concerned with emotions and fear. *Arthritis and Rheumatology,* 56(4), 1345-54.

"Using functional neuroimaging studies, they compared pain from arthritis to experimental pain (acute pain). The acute pain activated the brain structures known as the "pain matrix." However, the pain from arthritis activated the cingulate cortex, the thalamus, and the amygdala; these areas are involved in the processing of fear, emotions, and in aversive conditioning."

223. **Lamm C et al. (2011)** Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *NeuroImage*, 54(3):. 2492-2502

"A growing body of evidence suggests that empathy for pain is underpinned by neural structures that are also involved in the direct experience of pain. Meta-analysis of 41 studies that had investigated empathy for pain using fMRI was conducted. The results indicate that a core network consisting of bilateral anterior insular cortex and medial/anterior cingulate cortex is associated with empathy for pain. Activation in these areas overlaps with activation during directly experienced pain, and we link their involvement to representing global feeling states and the guidance of adaptive behavior for both self- and other-related experiences."

224. Lorenz J. (2003) Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain: a journal of neurology*, 126(5): 1079-1091

"Activities in the right and left DLPFC loaded on a separate Principal Component and correlated negatively with perceived intensity and unpleasantness. The inter-regional correlation of midbrain and medial thalamic activity was significantly reduced during high **left** DLPFC activity, suggesting that its negative correlation with pain affect may result from dampening of the effective connectivity of the midbrain-medial thalamic pathway. In contrast, **right** DLPFC activity was associated with a weakened relationship of the anterior insula with both pain intensity and affect. We propose that the DLPFC (dorsolateral prefrontal cortex) exerts active control on pain perception by modulating corticosubcortical and corticocortical pathways."

225. McEwen BS & Kalia M. (2010) The role of corticosteroids and stress in chronic pain conditions. *Metabolism,* Oct;59 Suppl 1:S9-15.

"We will discuss the new findings demonstrating the fact that steroids and related mediators produce paradoxical effects on pain such as analgesia, hyperalgesia, and even placebo analgesia. In addition, we will examine the physiologic effect of stress, high allostatic load, and idiopathic disease states such as chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome and burnout. The recently observed positive relationship between glutaminergic activity in the insula and clinical pain will be examined in the context of understanding the central role of steroids in chronic pain."

226. Wager, T.D., Rilling, J.K., Smith, E.E, et al. (2004). Placebo-induced changes in fMRI in the anticipation and experience of Pain. *Science,* 303, pp. 1162-1167.

"The investigators showed that placebo can change fMRI images of the brain, demonstrating that pain perception is not dependent on physical or structural issues" at the site of pain.

227. You, DS & Meagher, MW (2016). Childhood adversity and pain sensitization. *Psychosomatic Medicine, 78*, 1084-1093.

The high childhood adversity group showed greater temporal summation of second pain sensitization whereas the low-adversity group showed minimal sensitization. The high adversity group also showed blunted cardiac and skin conductance responses. These findings suggest that enhancement of central sensitization may provide a mechanism underlying the pain hypersensitivity and chronicity linked to childhood adversity.

VII. Adjunct Treatments

Evidence for the benefits of expressive writing, reappraisal of arousal and exercise, and a study of smartphone apps for pain that were available in 2019.

228. Gortner EM et al. (2006) Benefits of expressive writing in lowering rumination and depressive symptoms. *Behavior Therapy*, Sep;37(3):292-303. Epub 2006 May 30.

"Depression-vulnerable college students (with both elevated prior depressive symptoms and low current depressive symptoms) wrote on 3 consecutive days in either an expressive writing or a control condition. As predicted, participants scoring above the median on the suppression scale of the Emotion Regulation Questionnaire (Gross & John, 2003) showed significantly lower depression symptoms at the 6-month assessment when they wrote in the expressive writing versus the control condition."

229. Graham JE, Lobel M, Glass P, Lokshina I. (2008). Effects of written anger expression in chronic pain patients: making meaning from pain. *J Behav Med*. 31:201–12.

Over a 9 week period, participants in the anger-expression group (n=51) experienced greater improvement in control over pain and depressed mood, and marginally greater improvement in pain severity than the control group (n=51). Degree of expressed anger uniquely accounted for intervention effects and meaning-making mediated effects on depressed mood.

230.Hemakumar D, Farmery D et al (2019). Evaluation of Self-Management Support Functions in Apps for People with Persistent Pain: Systematic Review. JMIR Mhealth Uhealth 2019;7(2):e13080 DOI: 10.2196/13080

Evaluation of 19 smartphone apps intended for people with persistent pain via a 14-item checklist for self-management support and a 23-item list for general app quality. The three apps with the largest number of self-management items were Curable, PainScale Diary & Coach, and SuperBetter. Curable was the only app to provide comprehensive neuroscience education and guided relaxation. The three apps with the highest general quality scores were Curable, Headspace and PainScale. No apps have been validated in people with persistent pain.

231. Jamieson JP et al. (2012) Mind over Matter: Reappraising Arousal Improves Cardiovascular and Cognitive Responses to Stress. *J Exp Psychol Gen,* Aug; 141(3): 417–422.

"We examined whether reappraising stress-induced arousal could improve cardiovascular outcomes and decrease attentional bias for emotionally-negative information. Reappraising arousal shows physiological and cognitive benefits. Implications for health and potential clinical applications are discussed."

232. Jamieson JP et al. (2013) Improving Acute Stress Responses: The Power of Reappraisal. *Current Directions in Psychological Science*, February 22: 51-56

"Arousal reappraisal instructs individuals to think of stress arousal as a tool that helps maximize performance. By reframing the meaning of the physiological signals that accompany stress, arousal reappraisal breaks the link between negative affective experiences and malignant physiological responses. We demonstrate how this approach can benefit physiological reactivity, attention, and performance and explore its potential applications."

233. Lumley MA, Sklar ER & Carty JN. (2012). Emotional disclosure interventions for chronic pain: from the laboratory to the clinic. *Translational Behavioral Medicine*, 2, 73-81.

Life stress and the avoidance of negative emotions may contribute to chronic pain. The technique of written or spoken emotional disclosure can reverse emotional avoidance and improve health, and 18 randomized studies have tested it among people with chronic pain. The benefits of emotional disclosure for chronic pain are quite modest overall. Studies in rheumatoid arthritis show very limited effects, but two studies in fibromyalgia suggest that disclosure may be beneficial.

234. Smyth JM et al. (1999) Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis: a randomized trial. *JAMA* Apr 14;281(14):1304-9.

"Patients with mild to moderately severe asthma or rheumatoid arthritis who wrote about stressful life experiences had clinically relevant changes in health status at 4 months compared with those in the control group."

235. Streeter et al (2010) Effects of Yoga Versus Walking on Mood, Anxiety, and Brain GABA Levels: A Randomized Controlled MRS Study. *Journal of Alternative and Complementary Medicine* Nov; 16(11): 1145–1152.

"The 12-week yoga intervention was associated with greater improvements in mood and anxiety than a metabolically matched walking exercise. This is the first study to demonstrate that increased thalamic GABA levels are associated with improved mood and decreased anxiety."

VIII. Economics

The prevalence and economic impact of neuroplastic symptoms.

236. Barsky, A. J., Orav, E. J., & Bates, D. W. (2005). Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. *Archives of General Psychiatry*, 62, 903–910. http://dx.doi.org/10.1001/archpsyc.62.8.903

Annual U.S. cost of NEUROPLASTIC SYMPTOMS estimated at $256 billion in 2005.

237. Blount A, Schoenbaum M, Kathol R, Rollman B, Thomas M, O'Donohue W & Peek CJ. (2007). The economics of behavioral health services in medical settings: A summary of the evidence. *Professional Psychology: Research and Practice*, 38, 290-297.

"Somatizers rarely accept a referral for mental health treatment, because they do not experience their pain as psychological in origin. Consultation by psychiatrists or other behavioral health practitioners to the primary care doctor and targeted programs for somatizers that are part of a primary care practice have been shown to pay for themselves and reduce overall medical costs." "Behavioral health services targeted to chronic pain patients reach enough people and make enough difference in reduced utilization of medical services to more than pay for the cost of the behavioral health services." "Integrated care describes care that has medical and behavioral health components. The patient perceives care as one treatment plan targeted to his or her needs. Because a PCP is directing the plan, most patients experience it as medical. This is necessary for the very high percentage of patients in primary care who have severe behavioral health needs but would not accept care defined as mental health or psychiatric care."

238. Buttgereit T, Gu S, Carneiro-Leão L, Gutsche A, et al (2022). Idiopathic mast cell activation syndrome is more often suspected than diagnosed-A prospective real-life study. Allergy. 2022 Sep;77(9):2794-2802. doi: 10.1111/all.15304. Epub 2022 Apr 7. PMID: 35364617.

In 53% of our patients (80% females), suspicion of MCAS was based on self-evaluation. In total, patients reported 87 different symptoms, mostly fatigue (n = 57), musculoskeletal pain/weakness (n = 49), and abdominal pain (n = 43), with overall high disease activity and impact. Two of 79 patients had increased tryptase (by >20% +2 ng/ml) following an episode. Only 5%, with any of the patient-reported outcome measures used, showed complete response to MC-targeted treatment. Depression and anxiety disorders were frequent comorbidities (n = 23 each), and 65 patients had pathological Hospital Anxiety and Depression Scale values, which were linked to high disease impact and poor symptom control.

239.Deyo RA, Mirza SK, Turner JA, Martin BI. (2009). Overtreating chronic back pain: time to back off? *J Am Board Fam Med*. 22:62–8.

Recent studies document an increase in Medicare expenditures of:

- 629% for epidural steroid injections;
- 423% for opioids for back pain;
- 307% for lumbar MRI
- 220% for spinal fusion surgery.

The limited studies available suggest that these increases have not been accompanied by population-level improvements in patient outcomes or disability rates.

240. Gaskin DJ, Richard P. (2012). The economic costs of pain in the United States. *The Journal of Pain*. Volume 13, Issue 8, Pages 715-724. https://doi.org/10.1016/j.jpain.2012.03.009

In 2008, according to the Medical Expenditure Panel Survey (MEPS), about 100 million adults in the United States were affected by chronic pain, including joint pain or arthritis. Using the 2008 MEPS, we estimated 1) the portion of total U.S. health care costs attributable to pain; and 2) the annual costs of pain associated with lower worker productivity. We found that the total costs ranged from $560 to $635 billion in 2010 dollars.

241. Haller H, Cramer H, Lauche R, Dobos G (2015). Somatoform disorders and medically unexplained symptoms in primary care. Dtsch Arztebl Int. 2015 Apr 17;112(16):279-87. doi: 10.3238/arztebl.2015.0279. PMID: 25939319; PMCID: PMC4442550.

32 studies from 24 countries involving 70,085 primary care patients (age 15–95) found at least one type of somatoform disorder in 26-35%. Patients complaining of at least one medically unexplained symptom ranged from 40-49%.

242.Henderson M. (2005) Long term sickness absence. *British Medical Journal*, Apr 9;330 (7495):802-3.

"Sickness absence is a major public health and economic problem. In 2003, 176 million working days were lost; up 10 million on the previous year. Each week 1 million people report sick, 3000 of whom will still be away from work at six months. Until recently the most common causes were musculoskeletal disorders, in particular low back pain. In 1994-5, 194 000 new awards of social security benefits were made for back related incapacities, accounting for more than one in seven such awards. However, since then awards for back conditions have dropped by 42%.
Over the same decade the contribution of psychiatric disorders to sickness absence has increased markedly, and surveys have shown a doubling in the numbers of people reporting stress that was caused or made worse by their work. Mental and behavioural disorders now account for more incapacity benefit claims than musculoskeletal disorders."

243. Kroenke K, Mangelsdorff AD (1989). Common symptoms in ambulatory care: Incidence, evaluation, therapy, and outcome. The American Journal of Medicine, 86(3), 262-266. https://doi.org/10.1016/0002-9343(89)90293-3

A total of 567 new complaints of chest pain, fatigue, dizziness, headache, edema, back pain, dyspnea, insomnia, abdominal pain, numbness, impotence, weight loss, cough, and constipation were noted, with 38 percent of the patients reporting at least one symptom. Although diagnostic testing was performed in more than two thirds of the cases, an organic etiology was demonstrated in only 16 percent. The cost of discovering an organic diagnosis was high, particularly for certain symptoms, such as headache ($7,778) and back pain ($7,263). Treatment was provided for only 55 percent of the symptoms and was often ineffective. Where outcome was documented, 164 (53 percent) of 307 symptoms improved. Three favorable prognostic factors were an organic etiology ($p = 0.006$), a symptom duration of less than four months ($p = 0.009$), and a history of two or fewer symptoms ($p = 0.001$).

244. Landa A, Peterson BS & Fallon, BA. (2012). Somatoform pain: A developmental theory and translational research review. *Psychosomatic Medicine*, 74, 717–727. http://dx.doi.org/10.1097/PSY.0b013e3182688e8b

25-33% of primary care patients suffer from Neuroplastic symptoms.

245. Nahin RL, Feinberg T et al (2023). Estimated Rates of Incident and Persistent Chronic Pain Among US Adults, 2019-2020. JAMA Netw Open. 2023;6(5):e2313563. doi:10.1001/jamanetworkopen.2023.13563

At baseline in 2019, 40% of participants reported no pain, 39% reported nonchronic pain, and 21% reported chronic pain. Most participants reported the same pain status at both their 2019 baseline report and their 2020 follow-up; for example, 62% of those pain free at baseline remained pain free at follow-up, 54% of those with nonchronic pain in 2019 continued to report nonchronic pain in

2020, and 61% of those with chronic pain at baseline also reported chronic pain at follow-up. Among those pain free in 2019, the 1-year cumulative incidence for chronic pain in 2020 was 6.3%, while the 1-year cumulative incidence for HICP was 1.4%. We also observed evidence for both pain progression and pain recovery. Of those reporting nonchronic pain in 2019, 15% had progressed to chronic pain at follow-up; of those reporting chronic pain in 2019, 10% were pain free in 2020.

246. Nimnuan C. (2001) Medically unexplained symptoms: an epidemiological study in seven specialities. *Journal of Psychosomatic Research,* Jul;51(1):361-7.

"This study aimed to estimate the prevalence and risk factors for medically unexplained symptoms across a variety of specialities. Medically unexplained symptoms are common across general/internal medicine and represent the most common diagnosis in some specialities. Medical behavior, training, and management need to take this into account."

247. Sajid IM, Parkunan A, Frost K (2021). Unintended consequences: quantifying the benefits, iatrogenic harms and downstream cascade costs of musculoskeletal MRI in UK primary care. BMJ Open Quality 2021;10:e001287. doi:10.1136/bmjoq-2020-001287

Of 306 musculo-skeletal (MSK) MRIs requested by 107 clinicians across 29 practices, only 5% appeared clearly indicated and only 16% received appropriate prior therapy. Most had chronic symptoms and half had psychosocial flags. Mental health was addressed in only 12% of chronic sufferers with psychiatric illness, suggesting a solely pathoanatomical approach to MSK care. Only 8% of all patients were appropriately managed without additional referral. 1.3% of scans revealed diagnoses leading to change in treatment. Most imaged patients received pathoanatomical explanations of their symptoms. Only 17% of results appeared correctly interpreted by GPs, with spurious over-perception of surgical targets in 65% who suffered 'low-value' (ineffective, harmful or wasteful) post-MRI referral cascades due to misdiagnosis and overdiagnosis. Unfettered musculoskeletal MRI use by General Practitioners has reached unacceptable indication creep and disutility. Only 1–2 patients need to be scanned for one to suffer mismanagement. GP-MSK-MRI fuels unnecessary healthcare utilisation, generating nocebic patient beliefs and expectations, whilst appropriate care is delayed and a high burden of psychosocial barriers to recovery appear neglected.

248. Schubiner H, Lowry WJ, Heule M, et al (2023). Application of a Clinical Approach to Diagnosing Primary Pain: Prevalence and Correlates of Primary Back and Neck Pain in a Community Physiatry Clinic. Journal of Pain, Online version. https://doi.org/10.1016/j.jpain.2023.09.019

Although almost all the 222 patients (97.7%) had at least 1 spinal anomaly on imaging, the diagnostic approach estimated that 88% of patients had primary (neuroplastic) pain, 5.0% had secondary pain, and 6.8% had mixed pain. Patients with primary pain were more likely than the other 2 groups of patients (combined as "non-primary pain") to report certain functional conditions, central sensitization, and features such as sensitivity to light touch, spreading pain, and pain worsening with stress; however, no difference was detected in depression, anxiety, and catastrophizing between those with primary and nonprimary pain.

249. Tomenson B, McBeth J, Chew-Graham CA, MacFarlane G, Davies I, Jackson J, Littlewood A, Creed FH. (2012). Somatization and health anxiety as predictors of health care use. Psychosom Med, 74(6), 656-664.

These data raise the possibility that both increased health anxiety and number of bothersome somatic symptoms predict frequent medical consultations. A more complex model of predicting future health care is needed than has been studied previously.

250. Zajacova A, Grol-Prokopczyk H, Nahin, R. (2025). Pain among US adults before, during, and after the COVID-19 pandemic: a study using the 2019 to 2023 National Health Interview Survey. PAIN ():10.1097/j.pain.0000000000003764, August 5, 2025.

90,769 community-dwelling adults aged 18 years and older. Chronic pain prevalence increased from 20.5% in 2019 to 24.3% in 2023, representing an 18% increase over the study period. High-

impact chronic pain prevalence, which was 7.5% in 2019, rose to 8.5% in 2023, a 13% overall increase. The 2023 pain increases occurred for all examined body sites except tooth/jaw pain and all population subgroups. Long COVID accounted for approximately 13% of the observed 2019 to 2023 increase in both CP and HICP.