Appendix A.

The following sections discuss the evidence for comorbid peripheral and central pain contributions.

Peripheral contributions to centralized pain

Conditions now believed to involve high degrees of centralized pain (e.g., FM, IBS) were once thought to be primarily autoimmune or inflammatory in nature. While evidence for peripheral amplification of nociceptive signaling via pro-inflammatory mediators in these conditions is relatively weak, a large body of animal literature suggests that spinal inflammatory mechanisms, especially pro-inflammatory cytokines released by astrocytes and microglia, contribute to amplification and maintenance of chronic pain (Milligan and Watkins 2009). For this reason the role of inflammation in centralized pain may be a matter of "where," rather than "if"; as with other putative mechanisms of centralized pain, spinal inflammatory mediation of pain likely exists on a continuum. Furthermore, the complex system of checks and balances that determine spinal pain transmission involve large numbers of inhibitory factors that can lower the volume control of ascending pain signals. Enkephalins, serotonin, norepinephrine, dopamine and gamma-amino-butyric acid (GABA) are the best characterized neurotransmitters that interact to determine the excitatory/inhibitory balance.

A number of studies also suggest that persistent noxious peripheral signaling may be required to maintain the centralized pain state, even in conditions that do not present with localized sources of inflammation or lesions that are expected to cause pain (Staud et al. 2009). This idea is supported by recent work indicating that peripheral treatment of trigger points in FM patients with injections and hydroelectrophoresis improve pain thresholds at other*, distant* sites, indicating that attenuating peripheral noxious input leads to global improvement of pain sensitivity/augmentation (Affaitati et al. 2011). In TMD, the evidence for enhanced pro-inflammatory cytokine production and activity in peripheral sites (e.g., synovial fluid of the jaw) is fairly strong (Kellesarian et al. 2016), at least in some presentations of the disorder, therefore, whatever degree of centralized pain is present in TMD likely interacts with strong peripheral input in some patients.

Central Contributions to Rheumatic Conditions

Osteoarthritis (OA) is one of the classic examples of a pain condition in which the pain was thought to be proportional to the degree of damage to cartilage and bone. However, population-based studies paint a different picture, one in which 30-50% of individuals with at least moderate to severe OA pathology evident in radiographs are asymptomatic, and about 10% of individuals with moderate to severe knee pain have no radiographic signs of damage (Creamer and Hochberg 1997; Hannan et al. 2000). Only a small part of this variance in perceived pain is due to psychological factors (Creamer and Hochberg 1998; Creamer et al. 1999). The current hypothesis is that for many individuals, knee OA involves not only peripheral nociceptive drive, but also a variety of central factors that can adjust the gain control for pain.

This hypothesis is supported by multiple lines of evidence. OA often appears in patients who also have a variety of conditions (e.g. sleep problems, fatigue) that are also often comorbid with other types of centralized pain (Allen et al. 2008; Zhang and Jordan 2008). In addition, there is evidence of widespread tenderness and impaired CPM in OA (Arendt-Nielsen et al. 2010; Kosek and Ordeberg 2000), implying central pain-processing alterations, but this impairment in CPM seems to partially be due to peripheral maintenance since CPM improves following surgery. Neuroimaging has also provided confirmation of this pain centralization in OA by showing alterations in brain structure and function that are rectified following treatment (Gwilym et al. 2010). It is also important to note that drugs that affect neurotransmitter levels (e.g. serotonin and norepinephrine) in the brain can be helpful in treating OA pain, according to RCTs (Chappell et al. 2009; Fishbain 2000).

Perhaps the best evidence for the importance of central factors for some individuals with OA comes from a series of studies by Brummett and colleagues (Brummett et al. 2013; Brummett et al. 2015). Here, the authors recorded the degree of “fibromyalgianess” (FMness) using the 2011 survey criteria for FM in two large (n>500) cohorts of individuals who were undergoing hip or knee arthroplasty. In one study, they calculated oral morphine equivalents of opioid consumption during the perioperative period, and this was found to positively correlate with the FMness score. Every 1-point

increase in FMness (from 0-31) resulted in a 9mg increase in the amount of oral morphine equivalents in perioperative opioids consumed. Thus, the more centralized the pain, the less effective the opioidergic drugs were. The significance of this result held even when those who used opioids preoperatively were excluded. In a second study, using overlapping patients, Brummett and colleagues showed that high FMness scores were predictive of worse outcomes (relative failure to reduce pain) following arthroplasty. Less pain reduction was also associated (R^2=0.43) with higher amount of opioids taken preoperatively, less preoperative pain, and TKA (vs. THA). These data support the idea that as pain becomes more centralized in OA, decreasing the peripheral nociceptive input with surgery is less effective in reducing pain. The same could be expected for peripheral-pain-targeted treatments (e.g. NSAIDs, arthroscopic lavage) in TMD patients with a high degree of centralized pain.

Implications

Often an individual patient's pain will be derived from multiple underlying pain mechanisms. This means that treatment can be targeted to a patient's signs and symptoms that most closely resemble one of the categories, but that a single treatment regimen might not be enough for someone with mechanistically mixed chronic pain. None of this changes the standing recommendation of employing conservative, reversible treatment options for TMD; however, clinicians now have the ability to address mechanisms of TMD pain that lie beyond the TMJ and associated peripheral structures, and can attempt to guide treatment based on a more comprehensive assessment of each individual's underlying mechanism(s) of pain.

References

Affaitati G, Costantini R, Fabrizio A, Lapenna D, Tafuri E, Giamberardino MA. 2011. Effects of treatment of peripheral pain generators in fibromyalgia patients. European journal of pain (London, England). 15(1):61-69.

Allen KD, Renner JB, DeVellis B, Helmick CG, Jordan JM. 2008. Osteoarthritis and sleep: The johnston county osteoarthritis project. The Journal of rheumatology. 35(6):1102-1107.

Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. 2010. Sensitization in patients with painful knee osteoarthritis. Pain. 149(3):573-581.

Brummett CM, Janda AM, Schueller CM, Tsodikov A, Morris M, Williams DA, Clauw DJ. 2013. Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: A prospective, observational cohort study. Anesthesiology. 119(6):1434-1443.

Brummett CM, Urquhart AG, Hassett AL, Tsodikov A, Hallstrom BR, Wood NI, Williams DA, Clauw DJ. 2015. Characteristics of fibromyalgia independently predict poorer long-term analgesic outcomes following total knee and hip arthroplasty. Arthritis Rheumatol. 67(5):1386-1394.

Chappell AS, Ossanna MJ, Liu-Seifert H, Iyengar S, Skljarevski V, Li LC, Bennett RM, Collins H. 2009. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: A 13-week, randomized, placebo-controlled trial. Pain. 146(3):253-260.

Creamer P, Hochberg MC. 1997. Why does osteoarthritis of the knee hurt--sometimes? BrJRheumatol. 36(7):726-728.

Creamer P, Hochberg MC. 1998. The relationship between psychosocial variables and pain reporting in osteoarthritis of the knee. Arthrit Care Res. 11(1):60-65.

Creamer P, Lethbridge-Cejku M, Costa P, Tobin JD, Herbst JH, Hochberg MC. 1999. The relationship of anxiety and depression with self-reported knee pain in the community: Data from the baltimore longitudinal study of aging. Arthritis Care Res. 12(1):3-7.

Fishbain D. 2000. Evidence-based data on pain relief with antidepressants. AnnMed. 32(5):305-316.

Gwilym SE, Filippini N, Douaud G, Carr AJ, Tracey I. 2010. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: A longitudinal voxel-based morphometric study. Arthritis and rheumatism. 62(10):2930-2940.

Hannan MT, Felson DT, Pincus T. 2000. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol. 27(6):1513-1517.

Kellesarian SV, Al-Kheraif AA, Vohra F, Ghanem A, Malmstrom H, Romanos GE, Javed F. 2016. Cytokine profile in the synovial fluid of patients with temporomandibular joint disorders: A systematic review. Cytokine. 77:98-106.

Kosek E, Ordeberg G. 2000. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain. 88(1):69-78.

Milligan ED, Watkins LR. 2009. Pathological and protective roles of glia in chronic pain. Nature reviews Neuroscience. 10(1):23-36.
Staud R, Nagel S, Robinson ME, Price DD. 2009. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: A randomized, double-blind, placebo-controlled study. Pain. 145(1-2):96-104.
Zhang Y, Jordan JM. 2008. Epidemiology of osteoarthritis. RheumDisClin North Am. 34(3):515-529.