Obituary

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In memoriam: Joel D. Greenspan 1952 to 2021

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"If you wou'd not be forgotten,
As soon as you are dead and rotten,
Either write things worth reading,
Or do things worth the writing."
Benjamin Franklin, Poor Richard's Almanack, 1738.[7]

So read the sign on Joel Greenspan's office door for the past decade. Joel will not be forgotten.

Our dear colleague, mentor, and friend Joel Daniel Greenspan passed away the morning of February 8, 2021, in the comfort of his home beside Debbie, his wife of over 40 years.

Summarizing any life's work is a daunting task, but Joel's odyssey illuminated our understanding of pain physiology and is well worth reflection. His science reflects an amalgamation of old and new, a truly interdisciplinary approach that encompassed psychophysics, electrophysiology, neuroimaging, and neurostimulation. He was always careful to focus on the details of experimental results. His detailed approach allowed specific inferences about the relationship between physical stimulus characteristics and human perception or neurophysiological responses.

Joel grew up in Florida and obtained a bachelor's in behavioral sciences at Rollins College in 1974. Joel earned his PhD in neuroscience at Florida State University with Dan Kenshalo, Sr (**Fig. 1**).

While at Florida State, Joel met Karen Berkley, who became a life-long friend, mentor, and colleague. "Joel was one of the best people encountered in my 78 years," she said on his passing. A sentiment shared by all who knew him.

1. Psychophysics and primary afferent electrophysiology

Joel focused much of his early professional research on investigating the relationship between physical characteristics of mechanical stimuli, perception, and neurophysiological responses in primary afferent fibers. He was a "grounding father of quantitative sensory testing" and reminded trainees there is no such thing as "mechanical pain," but that there are "painful mechanical stimuli." This distinction between physical characteristics of the stimulus and human perception is frequently glossed over, sacrificed at the altar of brevity.

While at Florida State, Joel's dissertation provided insight into the relationship among tactile perceptual intensity, mechanical force applied to the skin, and depth and velocity of skin indentation.[9,11] Previously, the relationship between perceptual intensity and mechanical stimuli was believed to be dependent on tension, pressure, and other derivatives of force. This resulted from failure to rigorously measure the numerous physical properties associated with mechanical stimuli. Joel found tactile threshold was independent of indentation velocity, whereas suprathreshold intensity ratings depended on skin indentation depth and velocity, producing 2 distinct psychophysical slopes. He integrated these psychophysical findings with electrophysiological reports, suggesting tactile threshold depended on rapidly adapting mechanoreceptors, whereas suprathreshold ratings involved rapidly and slowly adapting mechanoreceptors.[11] Comparing effects of force and skin indentation depth on suprathreshold tactile perception, while varying skin indentation velocity, Joel concluded tactile intensity reflected skin indentation depth, not force as previously believed.[9] This attention to detail and intensity of focus would characterize his entire career.

From 1987 to 1995 as an assistant professor at SUNY Health Sciences Center at Syracuse, Joel contributed to our understanding of sharpness and pain perception and neural encoding of nociceptive mechanical stimuli.[8,13,14,18] His studies of painful mechanical stimuli revealed the following: (1)

Figure 1. Joel Greenspan on receiving his PhD with his mentor Dan Kenshalo, Sr. circa 1980.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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mechanical nociception or pain is dependent on probe circumference, not force, (2) mechanical stimulation of nociceptive afferents elicits the distinct percepts of sharpness and pain, (3) A-fiber mechanically insensitive afferents closely reflect suprathreshold mechanical pain perception, and (4) sharpness can be elicited by firing of single nociceptive afferents. Joel's careful studies demonstrated that as mechanical force increased, perception changed from dull pressure to sharp pressure to sharp pain.[13] As supported by subsequent studies, force is not a sufficient descriptor for pain studies because nociceptors respond to the edges of stimuli (eg, perimeter of a cylindric probe).[25] The pain-eliciting pinpricks developed during these studies inspired those used by the German Research Network on Neuropathic Pain and the multicenter OPPERA study (see below).[37]

Joel's laboratory examined stimulus–response functions of cutaneous nociceptors and compared A-fiber and C-fiber nociceptor sensitivity.[8] In contrast to most previous animal studies, Joel used stimuli and techniques matched to his human psychophysical studies.[13,14] Cross-species comparisons remain rare in the literature. Joel found human perception of repeated painful mechanical stimuli shows sensitization, but in the rat, nociceptive afferent responses show habituation. This suggests that perceptual temporal summation (TS) in humans depends on short-term central sensitization. Joel demonstrated A-fiber nociceptor responses in the rat more closely parallel human pain thresholds than C-fiber nociceptors, and mechanically sensitive afferents showed response saturation while mechanically insensitive afferents (MIAs) did not. Joel concluded A-fiber MIAs have the capacity to encode painful mechanical stimuli. Joel's novel work suggested primary afferent firing in A-fiber MIAs is the principal mechanism underlying perceived intensity of suprathreshold painful mechanical stimuli in humans.[1,6,22]

In 1996 Joel moved to the University of Maryland, Baltimore, where he continued investigating the neural mechanisms underlying pain perception.[3–5] In a series of primary afferent electrophysiology experiments, Joel and postdoc David Andrew investigated the peripheral consequences of nerve regeneration and inflammation. Investigating neuropathic pain, David and Joel recorded from nociceptors after nerve transection and repair.[4] Nociceptors in healed nerves had similar receptive fields, conduction velocities, and mechanical thresholds to controls. However, regenerated nociceptors were more responsive to suprathreshold mechanical stimuli than controls despite no change in the thermal encoding properties. Finally, regenerated nociceptors were not coupled to other fibers. David and Joel concluded abnormal nerve regrowth did not account for increased mechanical sensitivity of regenerated fibers, providing the first evidence that mechanical hyperalgesia after nerve injury involves peripheral mechanisms.

David and Joel also investigated the peripheral mechanisms of inflammatory pain.[3] At this time, studies had failed to evaluate suprathreshold mechanical sensitivity, leading authors to suggest central sensitization was responsible for inflammatory mechanical hyperalgesia. Mechanical thresholds in inflamed nociceptive fields were not different from controls. However, they observed sensitization in nociceptors to suprathreshold mechanical stimuli. Therefore, mechanical hyperalgesia in peripheral inflammation could be explained by primary afferent sensitization. These findings of the utility of suprathreshold painful mechanical stimuli in pathological states provided the empirical foundation for using pinprick-evoked potentials as a possible diagnostic tool to quantify pathology in patients suffering from chronic pain.[24] Measurement of these potentials at the Erb point and at the cortex may allow differentiation of peripheral and central neuropathologic processes in chronic pain.

2. Sex differences in perception of painful stimuli

On his arrival at the University of Maryland, Baltimore, Joel applied his expertise in psychophysics to important research in the burgeoning field of sex differences in pain. The primary focus of Joel's work was exploring central mechanisms potentially underlying sex differences in pain in humans.

In the early 2000s, Joel and graduate student Eleni Sarlani conducted studies exploring the role of sex in temporal summation. Joel developed a paradigm to evoke temporal summation in which a sharp mechanical probe was used to apply trains of repetitive stimuli to the fingers of participants. Although this paradigm elicited temporal summation in both men and women, the magnitude of temporal summation was greater in women.[39,40] In addition, temporal summation was evoked in women when interstimulus intervals (ISIs) were short (2 seconds) or long (5 seconds) but was evoked in men only when ISIs were short.[39] Women also reported more intense, painful, and unpleasant aftersensations than men. A later study in patients with temporomandibular disorder (TMD) found TS was greater in women with TMD than men with TMD or healthy men.[38] Taken together, these studies suggest in women "…central processing of nociceptive input may be more easily upregulated into pathological hyperexcitability…," (page 121) potentially accounting for the higher prevalence of chronic pain in women vs men.[39] This novel conceptualization inspired many future studies that explored the role of CNS hyperexcitability in both sex differences and chronic pain.

Another study from Joel's laboratory focused on sex differences in the function of CNS endogenous pain modulatory systems. The study explored whether (1) conditioned pain modulation (CPM) differed in men and women, (2) distraction and stress modulated pain differently in men and women, and (3) distraction and stress contributed to CPM. Distraction from painful contact heat reduced pain ratings to a greater degree in men than women.[35] While no sex differences in CPM magnitude were found, regression analysis revealed distraction and stress contributed to CPM, indicating CPM likely results from a combination of distinct central endogenous pain modulatory systems. Interestingly, the contribution of stress to CPM differed between men and women, suggesting sex differences in the neural mechanisms underlying CPM may help explain sex differences in pain.

Joel's interest in central mechanisms underlying sex differences in pain led to important neuroimaging research (below). His work also included examining sex and other demographic factors as predictors of pain sensitivity in the OPPERA study[33] as well as collaborating on studies examining sex effects on pain genetics[29] and the placebo effect.[32]

One of Joel's greatest contributions to the field was leading the IASP "Consensus Conference to Establish Guidelines for Research on Sex Differences in Pain" in 2006. This effort produced a high-impact publication[10] that specified best practices for studying sex differences in pain and identified key unanswered questions. The article continues to guide researchers in the larger field of pain disparities. Commenting on this effort, friend and colleague Rich Traub commented: "Joel spearheaded writing the consensus report, a herculean effort once described as herding cats."

3. Central processing of noxious or painful stimuli: effects of lesions and neuroimaging

As a postdoc, Joel demonstrated the necessity of the anterolateral pathway for the transmission of peripheral nociceptive input to the brain.[19,44] Unilateral anterolateral chordotomy in monkeys reduced the escape response to normally suprathreshold stimuli contralateral to the lesion while also producing a bilateral decrease in flexion reflex amplitude. Concurrently, low-intensity discriminability remained intact. Thus, unilateral anterolateral chordotomy reduced the perceived painfulness of noxious stimuli without affecting perception of low-threshold stimuli. Nociceptive function recovered months postinjury, highlighting spinal cord or brain compensatory mechanisms.

In patients with lesions in the posterior insula and the secondary somatosensory cortex, Joel found deficits in pain and temperature detection.[12,20,41] This pioneering work helped relate neuroimaging and intracranial findings with real-world patient outcomes and has been replicated repeatedly.

Joel started using functional neuroimaging at UMB, working with Rao Gullapalli. Joel's team found that a contact thermode delivering painful heat produced temporally distinct "early" innocuous and "late" noxious fMRI responses.[30] This highlighted primary somatosensory cortex's (S1) capacity to encode pain intensity because the late BOLD signal response demonstrated a graded relationship with painful stimuli separated by only 1°C.

Joel's early work on sex differences found men and women did not differ in spatial extent of the BOLD response across the brain, under conditions of similar stimulus and pain intensity.[31] However, negative BOLD responses were more common in women. He suggested this was due to higher baseline cerebral blood flow in women; with higher baseline flow, increased metabolic demand would not trigger a compensatory flow increase, and the signal decrease in women reflected the departure of oxygen from blood to neural tissues. This was one of the first fMRI studies in the field of pain research to consider sex differences and to highlight negative BOLD responses and their physiological relevance, contributing towards the eventual characterization of resting-state networks.

More recently, Joel examined the role of circulating sex hormones on pain and the brain. His team found pain and unpleasantness evoked by a pressure stimulus did not vary across the menstrual cycle, but pain-related activation in the brain did, specifically in regions related to cognition and motor function.[42] The left inferior parietal lobule showed significant variations in gray matter, cortical thickness, and white matter across menstrual phases.[28] These studies shifted the emphasis of sex differences in pain from sensory-discriminative processing towards brain systems related to cognition and motivation.

Joel also explored the neuromodulatory effects of noninvasive transcranial electrical stimulation on motor processing and pain in volunteers. While stimulating the primary motor cortex (M1) during fMRI, M1's resting-state network connectivity decreased.[2] Furthermore, M1 stimulation normalized perceptual and cortical correlates of central sensitization in a capsaicin-heat pain model, acting through descending modulation.[27] Others have replicated these findings,[21,23] giving further credence to Joel's suggestion that M1 stimulation could be a target to treat chronic pain involving central sensitization.

Joel also addressed other fundamental questions regarding the brain and pain, including (1) the reproducibility of pain-related fMRI signals,[34] (2) aging and decreased nociceptive processing in S1 and anterior insula,[36] (3) how cold stimuli produce evoked potentials near the Sylvian fissure, using electrophysiological measurements from the surface of the brain,[15] and (4) qualitatively different heat pain sensations evoked by laser produce differential brain activation.[43] These studies exemplify Joel's interdisciplinary approach, reflecting his eagerness to collaborate and evolve study design with rigor across new technologies as they became available.

4. Orofacial Pain Prospective Evaluation and Risk Assessment study

Joel applied his experience in psychophysics and quantitative sensory testing (QST) to the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) Study, managing the Baltimore site and leading QST development.[26] Joel's specific contributions to the project included adapting his QST protocols for perception measurement of painful mechanical stimuli using pinprick probes and interpreting and writing the articles on pain sensitivity as an associated or predictive factor in chronic pain development. Joel described the presence of greater experimental pain sensitivity at extracranial body sites in patients with chronic TMD.[16] Joel et al. found the strongest predictors of case status included suprathreshold heat pain ratings to 48 and 50°C stimuli, cranial pressure pain thresholds, and suprathreshold mechanical pain ratings. The most recent phase of the OPPERA study included patients with chronic pain with chronic overlapping pain conditions (COPCs) including TMD, headache, irritable bowel syndrome, low back pain, and fibromyalgia.[17] Presence of one syndrome was associated with greater sensitivity to mechanical

Figure 2. Joel Greenspan as chair of the Department of Neural and Pain Sciences at the University of Maryland, Baltimore, 2018.

and pressure pain. Mechanical and pressure pain sensitivity was progressively greater with each additional COPC. In addition to his contributions to the project in the form of QST protocol development, co-investigators on the OPPERA project agreed: "Joel was routinely the calming voice of reason in our discussions, which was an incredibly important role for our work together."

Joel was cofounder and codirector of the University of Maryland Center to Advance Chronic Pain Research from 2014 to 2021. Joel chaired the Department of Neural and Pain Sciences from 2008 to 2021 (**Fig. 2**). He mentored PhD recipients Eleni Sarlani, Eric Moulton, Raimi Quiton, and Timothy Meeker and postdoctoral fellows David Andrew, Elizabeth Roy Felix, D. S. Veldhuijzen, Anne-Christine Schmid, and Yiming Liu. Over his career, Joel contributed to over 125 research articles with an H-index of 44 and several book chapters, including *Gender Differences in Pain and Its Relief* in Melzack and Wall's Textbook of Pain.

Joel was a cerebral and inquisitive scientist, patient and supportive mentor, calming voice of reason, good-humored and generous friend, and a kind and gentle soul. When it came to research, Joel focused on science foremost, rather than the endless chase toward academic career advancement. He preferred keeping his laboratory a small, closely knit team. Without hyperbole, he gave new depths to the phrase "full and undivided attention" when it came to his trainees. Speaking with Joel, one could sense the intensity of his concentration and intellect. Slow, steady, and methodical, he would carefully consider all facets of data without overinterpretation. He could not imagine a more fulfilling career than that of a researcher. He epitomized the considerate scientist, yet to identify him as such would limit who he was as a person. He was fully vested in his wife and family and to his role as a mentor and colleague. He will be sorely missed.

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