Obituary

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# Interoception and AD (Bud) Craig's paradigm-shifting legacy

Irina A. Strigo[a,b,*], David Andrew[c], Alan N. Simmons[d,e], Henry C. Evrard[f,g,h,i], Anders Blomqvist[j], Jonathan O. Dostrovsky[k]

**Keywords:** Insula, Interoception, Pain, Thalamus, C fibers, Lamina I, and Thermoreceptive



In the intricate landscape of neuroscience, few names resonate as profoundly as AD (Bud) Craig's. A luminary in his field, Bud Craig's remarkable contributions to the realms of pain and emotion have redefined our understanding of these fundamental human experiences. His passing in July 2023 marked the end of an era, but his legacy continues to shine brightly, offering a guiding light for future generations of neuroscientists.

Arthur D. (Bud) Craig was born on August 31, 1951, in Lansing, Michigan (**Fig. 1**). Bud attended Michigan State University from which he earned the Bachelor of Science degree in Mathematics in June 1973. He completed his doctorate degree at Cornell University, Ithaca, NY, in neurophysiology, neuroanatomy, and electrical engineering and received his Ph.D. in January 1978. Bud received Doctor of Medicine honoris causa from University of Linköping, Sweden, in May, 2001. Bud's work was recognized through the Kenneth Craik Award in Experimental Psychology from the University of Cambridge in 2002, Frederic W. L. Kerr Award from the American Pain Society in 2011, and his election to be a foreign member of Royal Society of Sciences and Letters in Gothenburg.

Bud Craig importantly shed light on the understanding of the interplay between pain and emotion. Pain, we believed, was a purely physiological phenomenon, while emotion was considered a complex interplay of psychological factors. Yet the work conducted by Bud Craig challenged this orthodoxy, propelling the field towards a different understanding that spanned both these fields.[3,4] He postulated that pain was far from an isolated sensory experience but a fundamental emotion unto itself. Emotion, in turn, wielded the power to amplify or substantiate physical sensations. These understandings were founded in an exceptionally detailed mapping of the neuroanatomical pathways of supraspinal projections originating in nociceptive and thermoreceptive peripheral C fibers that terminated in the superficial dorsal horn of the spinal cord and through thalamic relay projected to the cortex.

Central to Bud Craig's groundbreaking insights was the concept of interoception, a term he redefined with meticulous precision.[2] In the conventional view, the well-discriminated feelings of temperature, itch, and pain were associated with an "exteroceptive" somatosensory system, whereas the less distinct visceral feelings of vasomotor activity, hunger, thirst, and internal sensations were associated with a separate "interoceptive" system. Bud Craig redefined interoception by providing neuroanatomical evidence that interception is the physiological sense of the condition of the entire body, not just the viscera and categorized pain and temperature as part of the redefined interoceptive system. Interoception, in his vision, became the bridge connecting the physical and emotional realms. It represented the body's ability to sense and interpret its internal states, paving the way for the subjective experience of emotions. Through painstaking research and encyclopedic scientific knowledge, Bud Craig's work challenged long-standing dogmas, fostering a profound transformation in our understanding of consciousness itself.

One of the keystones of Bud Craig's research was the exploration of central somatosensory neural mechanisms of pain and temperature and uncovering the intricate pathways that underlie our perception of pain and emotion. Virtually, all this pivotal research was performed at the Barrow Neurological Institute in Phoenix AZ where Bud was the holder of the James R Atkinson Pain Research Endowed Chair, a post that he held from 1986 until his retirement 30 years later. Bud would introduce himself to visitors to his laboratory as a "functional neuroanatomist," a term he used to encapsulate his belief that anatomy and physiology of the nervous system were inextricably linked. When one of us (DA) asked him why he used this term rather than "anatomist," "physiologist," or "neuroscientist," his reply was "when you are going somewhere new, the first thing you need is a map." Bud spent many years making detailed maps of the ascending pathways from the spinal cord and medullary dorsal horn, with

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

[a] *Emotion and Pain Laboratory, San Francisco Veterans Affairs Health Care Center, San Francisco, CA,* [b] *Department of Psychiatry, University of California San Francisco, San Francisco, CA,* [c] *School of Clinical Dentistry, University of Sheffield, United Kingdom,* [d] *San Diego Veterans Affairs Health Care Center, San Diego, CA,* [e] *Department of Psychiatry, University of California San Diego, San Diego, CA,* [f] *International Center for Primate Brain Research, Center for Excellence in Brain Science and Intelligence, Institute of Neuroscience, Chinese Academy of Sciences, Shanghai, China,* [g] *Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, United States,* [h] *Werner Reichardt Center for Integrative Neuroscience, Karl Eberhard University of Tübingen, Tübingen, Germany,* [i] *Max Planck Institute for Biological Cybernetics, Tübingen, Germany,* [j] *Division of Neurobiology, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden,* [k] *Department of Physiology, University of Toronto, Toronto, ON, Canada*

**Corresponding author. Address: Emotion and Pain Laboratory, San Francisco Veterans Affairs Health Care Center, 4150 Clement Street, San Francisco, CA 94121. Tel.: 415-221-4810. E-mail address: Irina.Strigo@ucsf.edu (I.A. Strigo).*

*PAIN 00 (2024) 1–3*



*http://dx.doi.org/10.1097/j.pain.0000000000003208*

**Figure 1.** AD (Bud) Craig, summer 2005 hiking the Nebelhorn ("Fog Horn") mountain in the Allgäu Alps in southernmost Germany, bordering Austria, near the tiny town of Oberstdorf. Courtesy of Lora Sanders.



a focus on pain but with his mind open to other somatosensory modalities, particularly not only temperature but also itch and even muscular effort. During the "pain, itch, and temperature" era of Bud's research, one of the most important aspects of his experiments was the use of nonhuman primates. This turned out to be a prescient point due to the highly significant differences in the anatomy of the ascending nociceptive pathways and their cortical terminations compared with species commonly used by others, which were limited primarily to rats and mice.

The thalamus, which is the final relay nucleus in the pain and temperature pathways, receives its major nociceptive inputs from the spinothalamic and trigeminothalamic tracts (TTTs; for inputs from orofacial region). These tracts terminate in several regions of the medial thalamus and lateral thalamus.[15] Using tiny iontophoretic injections of neuroanatomical tracers into functionally defined laminae of the spinal cord/medullary dorsal horn, Bud identified that the nociceptive-specific neurons in lamina I of the spinal and medullary dorsal horn terminate in the posterior ventromedial nucleus (VMpo), ventroposterior inferior nucleus (VPI), and the ventrocaudal medial dorsal nucleus (MDvc), whereas the nociceptive, but modality ambiguous neurons in the deeper layers of cord terminate in the ventroposterior nucleus (VP) as well as in VPI and in the ventral lateral (VL) and central lateral (CL) nuclei.[15] The main cortical targets of the thalamic regions receiving lamina I neuron projections are the insular cortex through the VMpo and the anterior cingulate cortex through the MDvc, whereas the VP that receives nociceptive inputs primarily from the deep dorsal horn projects to primary somatosensory cortex. Nociceptive-specific neurons with small contralateral receptive fields are located in VMpo and are topographically arranged. VP, which contains primarily neurons responding to innocuous tactile stimuli, also contains nociceptive-responsive neurons in register with the somatotopic pattern of the low-threshold neurons. Stimulation in the human VPI and VMpo region can produce pain, but stimulation in VP is rarely painful (except in poststroke pain patient).[13,14] Damage to the lateral thalamus, usually because of a stroke, can lead to chronic central pain. These[15] observations suggest that the thalamus plays a prominent role in the pathophysiology of central neuropathic pain (pain caused by damage to the CNS rather than its normal origin from damage to nonbrain tissues, which activates nociceptors).

When Bud and his coauthors published their work on VMpo in 1994,[10] it provoked a contentious response from Pat Wall, one of the then Editors-in-Chief of PAIN, which was published in this journal in 1995.[17] Bud's subsequent rebuttal letter[1] poignantly upended the dogmas in the field whilst at the same time acknowledging the contrast between basic neurobiological properties of neurons in anaesthetized animals and the symptoms experienced by patients with chronic pain due to damage/disease. It was the thalamocortical projections of the spinal lamina I pathway that led Bud to focus his research on insular cortex, with his studies of the thermal grill illusion of pain[9,12] and the central representation of cool sensation[11] providing a springboard for his change in direction.

Bud's meticulous investigation of the insular cortex illuminated a previously uncharted territory, revealing its pivotal role in interoception.[7] The insula, Bud Craig argued, held the key to our ability to sense and integrate our physiological condition, laying the foundation for the emergence of subjective feelings. His work unveiled the insular cortex as the primary sensory cortex for interoception, where the material representation of the self resides, allowing us to understand our physiological condition on an intimate level. Bud Craig's research extended to the perception of time, shedding light on how our subjective awareness interacts with temporal experiences, reinforcing the intricate connection between the physical and emotional dimensions of our existence.[5]

Bud's research elucidated the effective organization and regulation of ambivalent emotions, sentiments, and sympathovagal equilibrium within the 2 hemispheres of the forebrain[6,16] and how these components of lateralized (left-right) emotional processing are arranged asymmetrically as positive/negative, approach/avoidance, and parasympathetic/sympathetic. His

work on the neuroanatomical structure of interoception provides profound insights into the functional arrangement of all human emotional feelings and behaviors.[8]

As we reflect on Bud Craig's legacy, we must acknowledge the profound impact of his work on our understanding of pain, emotion, mental health, and consciousness. His research has left an indelible mark on neuroscience, inspiring a wealth of new studies that continue to explore and refine his proposals. AD (Bud) Craig's outstanding achievements are not only remarkable in themselves but are also a testament to the power of unwavering dedication to scientific inquiry. His legacy invites us to build upon his foundation, unraveling the mysteries of pain, emotion, and consciousness and their interactions that continue to captivate the human mind. We, who have had the privilege to work with Bud, remember him with deep affection, and the scientific community will forever be indebted to his pioneering spirit.

## Conflict of interest statement

The authors have no conflict of interest to declare.

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