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LETTER TO THE EDITOR

A Brief History of Slow Spinal Potentials, Gate Theory of Pain, and Spinal Cord Stimulation

To the Editor:

The gate theory of pain was proposed by neurophysiologist Ronald Melzack and psychologist Patrick Wall in 1965.[1] They conjectured that in the substantia gelatinosa of the spinal cord dorsal horn, activity of large nerve fibers carrying nonnociceptive sensory input (eg, tingling) inhibits the transmission of nociceptive sensory input carried by small nerves fibers (Fig. 1a). In 1967, Wall and physician William Sweet put this theory to the test through the electrical stimulation of peripheral axons, which heralded the development of peripheral nerve stimulation and supported modern transcutaneous electrical nerve stimulation. In the same year, physician Norman Shealy, along with engineers Thomas Mortimer and James Reswick, tested the theory by stimulating the axons in the spinal dorsal columns, pioneering the development of spinal cord stimulation (SCS). Subsequent decades of neuroscience have shown ever-increasing complexity and nuance in spinal cord physiology and neurochemistry (Fig. 1b[2]). Yet—60 years on—gate theory remains the touchstone model of pain processing and SCS treatment.

How did Melzack and Wall conjecture such prescient, impactful, and durable theory, given the limited spinal cord neuroscience in 1965? Our emphasis on the previously mentioned career designations was deliberate. We will explain that Wall's study of evoked slow potentials in the spinal cord led to the conjecture of gate theory. We will conclude how the measurements of slow potentials have new-found relevance in closed-loop SCS.

The science of spinal cord physiology and the neuroscience of pain processing circa 1965 were based on available experimental techniques, namely, lesions, tissue/cell staining, and electrophysiology—much of it was recording units or field potentials. Stimulation of nerves and recording of evoked slow field potentials in the spinal column underpinned the analyses of spinal cord circuitry/processing, including studies by Wall.[3] Distinct slow potentials were understood to reflect specific synaptic processes in the spinal dorsal horn and roots. Melzack and Wall's gate theory followed from two related observations of evoked slow spinal potentials: 1) Repeated volleys from small nerve fibers (nociceptive input) are amplified ("wound up") suggesting positive feedback, whereas 2) repeated volleys from large nerve fibers (nonnociceptive input) attenuate ongoing volleys from *both* large and small fibers. Specifically, Wall believed the negative feedback was through axon-axonic synapses in the dorsal horn substantia gelatinosa, producing a slow potential reflecting "primary afferent depolarization" (PAD).

Melzack and Wall conjectured the small and large fiber systems compete in parallel, respectively opening (synaptic amplification) and closing (synaptic attenuation) a "gate" in the dorsal horn substantia gelatinosa. Their profound corollary was that procedures that increase activity specifically of large fibers (eg, rubbing a hurt limb, targeted electrical stimulation) can inhibit transmission of nociceptive signals. Melzack and Wall further linked descending input from the cortex to the dorsal horn substantia gelatinosa as a mechanism for "psychologic" control of pain perception. Gate theory provides a mechanistic explanation for neuropathic pain and its varied manifestations, attributing them to maladaptations of the balance between gate opening/closing processes.

The tone of Melzack and Wall[1] was conjectural. They were careful to cite ideas that overlap with gate theory (such as the interaction between large and small fiber activity). We believe the impact of gate theory derives from Melzack and Wall suggesting 1) a specific network, namely the synaptic negative feedback in the dorsal horn substantia gelatinosa, in relation to experimental observations of pain processing; and 2) empirically testable implications for pain control. Ongoing debate around the adequacy of gate theory has centered on the Melzack and Wall's network schematic (Fig. 1a), but this schematic was intentionally a simplification, and limited by existing neuroscience. We suggest, notwithstanding advances (and revisions) in pain processing neuroscience and therapies, gate theory remains the touchstone model because synaptic negative feedback in the dorsal horn substantia gelatinosa (Fig. 1b) remains central.[2] The genesis of this synaptic negative-feedback circuit mechanism was in fact Wall's study of PAD slow spinal potentials.

Evoked slow potentials recorded from the dorsal surface of the spinal cord, known as "cord dorsum potentials" (Fig. 1c, bottom right), have been characterized over decades, showing reliability across vertebrate animal models and human studies.[4] These include a fast (~1 millisecond) "triphasic spike" potential that reflects axon conduction, followed by slow (3–80 milliseconds) negative or positive potentials. An initial slow (~5–8 milliseconds) negative wave is attributed to synaptic excitation of interneurons in the dorsal horn substantia gelatinosa. This is followed by a slower (tens of milliseconds) positive wave attributed to inhibitory synaptic feedback—the PAD. Following Melzack and Wall, several studies attribute the PAD as a mechanism of pain relief.[4] Incidentally, Wall's own studies of the PAD were not cord dorsum potentials but rather "dorsal root potentials" (DRPs). DRPs measure a field potential difference between the nerve terminus and trunk to reflect changes in terminal polarization (Fig. 1c, left). DRPs were

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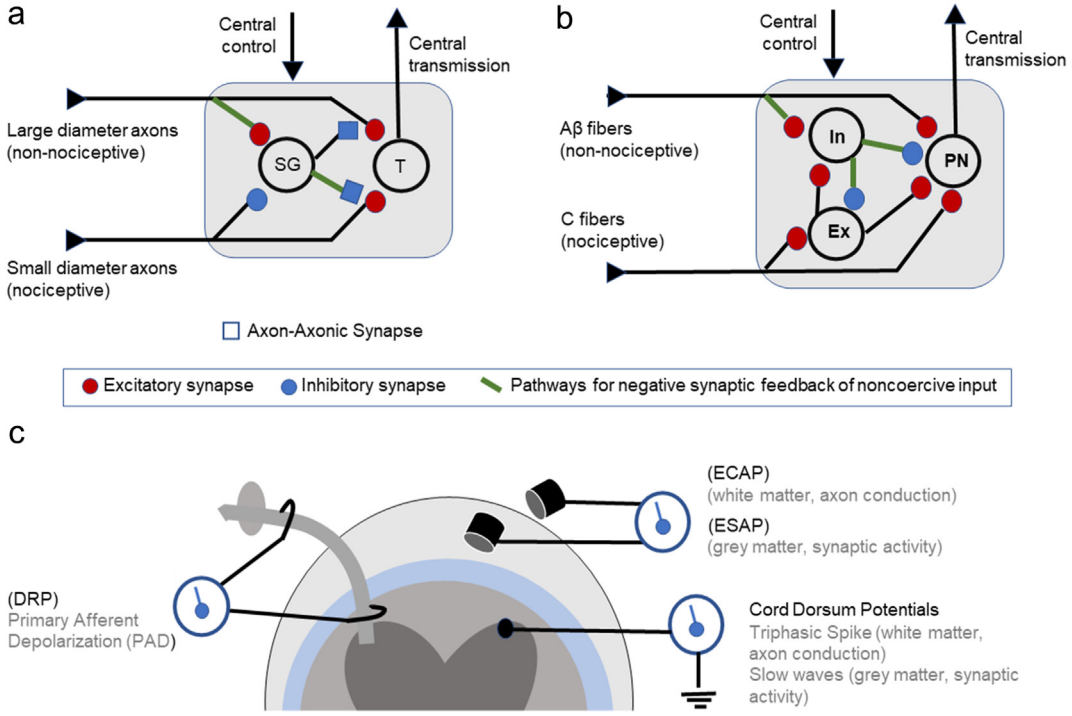

Figure 1. Schematic of synaptic circuits in the spinal cord dorsal horn and methods for measuring spinal potentials. a. Spinal synaptic circuits explaining gate theory schematic as proposed by Melzack and Wall in 1965. b. Schematic of spinal circuits with updated detail. In both the 1965 schematic and increasingly complex modern models of spinal cord processing, a negative feedback synaptic pathway for dampening nociceptive input is featured (green path), including inhibitory cells in the stratum gelatinosa of the dorsal horn. c. Extracellular (field) electrophysiologic methods for recording spinal potentials. DRPs measure voltage between the nerve afferent terminal and trunk, including a slow PAD (left). Cord dorsum potentials measure voltage from the dorsal surface of the spinal cord (relative to a distant refence) (bottom right). These include fast (~1 millisecond) "triphasic potentials" and slow (~3–80 milliseconds) negative or positive potentials, such as the PAD signal (top right). Fast (~1 millisecond) ECAPs and slow (~6–40 milliseconds) ESAPs recorded using epidural electrodes, which are suitable for long-term applications such as SCS. Fast potentials are attributed to conduction along axon of the dorsal column whereas slow potentials are attributed to synaptic potentials in the dorsal horn. Slow spinal potentials, detectable across modalities, were attributed by Melzack and Wall as synaptic negative feedback to nociceptive input, which in turn underpinned gate theory. DRP, dorsal root potentials; ECAP, evoked compound action potential; ESAP, evoked synaptic activity potential; Ex, substantia gelatinosa excitatory interneuron; In, substantia gelatinosa inhibitory interneuron; PAD, primary afferent depolarization; PN, projection neuron; SG, substantia gelatinosa; T, first central transmission cell. [Color figure can be viewed at www.neuromodulationjournal.org]

further used by Wall[3] and others more recently, to show the intersegmental (diffuse) inhibition/PAD.

With advancement of electrophysiology and neurochemical neuroscience techniques, field potentials no longer play an outsized role in the study of spinal circuits. However, the recent validation of closed-loop SCS has galvanized interest in leveraging evoked spinal potentials.

Existing closed-loop SCS systems measure fast (~1 millisecond) "evoked compound action potentials (ECAPs)," which are analogous to triphasic-spikes but are evoked and recorded with epidural electrode leads suitable for chronic therapy (Fig. 1c, top right). In a rodent model, we identified distinct slow (~10–30 milliseconds) potentials elicited and recoded with epidural electrode leads,[5] termed "evoked synaptic activity potentials" (ESAPs). We identified at least two ESAPs, an approximately 6-millisecond S1 wave and an approximately 40-millisecond S2 wave. ESAPs reflect synaptic activity within the dorsal horn (and can be distinguished from stimulation artifacts or myogenic responses). This finding indicates the rich science of evoked spinal slow potentials (which played an instrumental role in the development of gate theory and, as a result, SCS) may be mined through ESAPs for novel closed-loop SCS signals.

Neuropathic pain can reflect maladaptive synaptic plasticity in the dorsal horn substantia gelatinosa—including changes in presynaptic inhibition linked to gate theory. SCS modulates spinal cord synaptic processes, including those linked to feedback inhibition. Following gate theory heuristics, distinct ESAPs may be biomarkers of 1) dorsal horn processing (attenuation by the gate) of nociceptive synaptic input and 2) synaptic drive to the close the 'gate' or the state of the 'gate'.

It is precisely the interpretation by Melzack and Wall of the PAD slow spinal potential as a 'gate' signal that led to the gate theory of pain generation and pain control and consequently the development of SCS.

Authorship Statements

Marom Bikson and Mahima Sharma prepared the manuscript draft and revised it. Both authors approved the final manuscript.

Conflict of Interest

The City University of New York holds patents on brain stimulation with Marom Bikson as inventor. Marom Bikson has equity in Soterix Medical Inc; consults, received grants, assigned inventions, and/or served on the scientific advisory board of SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple, Ybrain, Ceragem, and Remz; and is supported by grants from Harold Shames and the National Institutes of Health (NIH): NIH-

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