Neuromodulation Techniques and Innovations: A Primer for Healthcare Providers

How Neuromodulation for Pain Works

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Disclosure

The City University of New York: Patents on brain stimulation.
Soterix Medical: Produces tDCS and High-Definition tDCS.
Grants, assigned inventions, and/or serves SAB for SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple.

Slides @MaromBikson

Support

NYS DOH, NIH (NIMH, NINDS) – *BRAIN Initiative*, NSF, Grove Foundation, Harold Shames, CCNY Fund, 21st Century Fund.

What is Neuromodulation Dose?

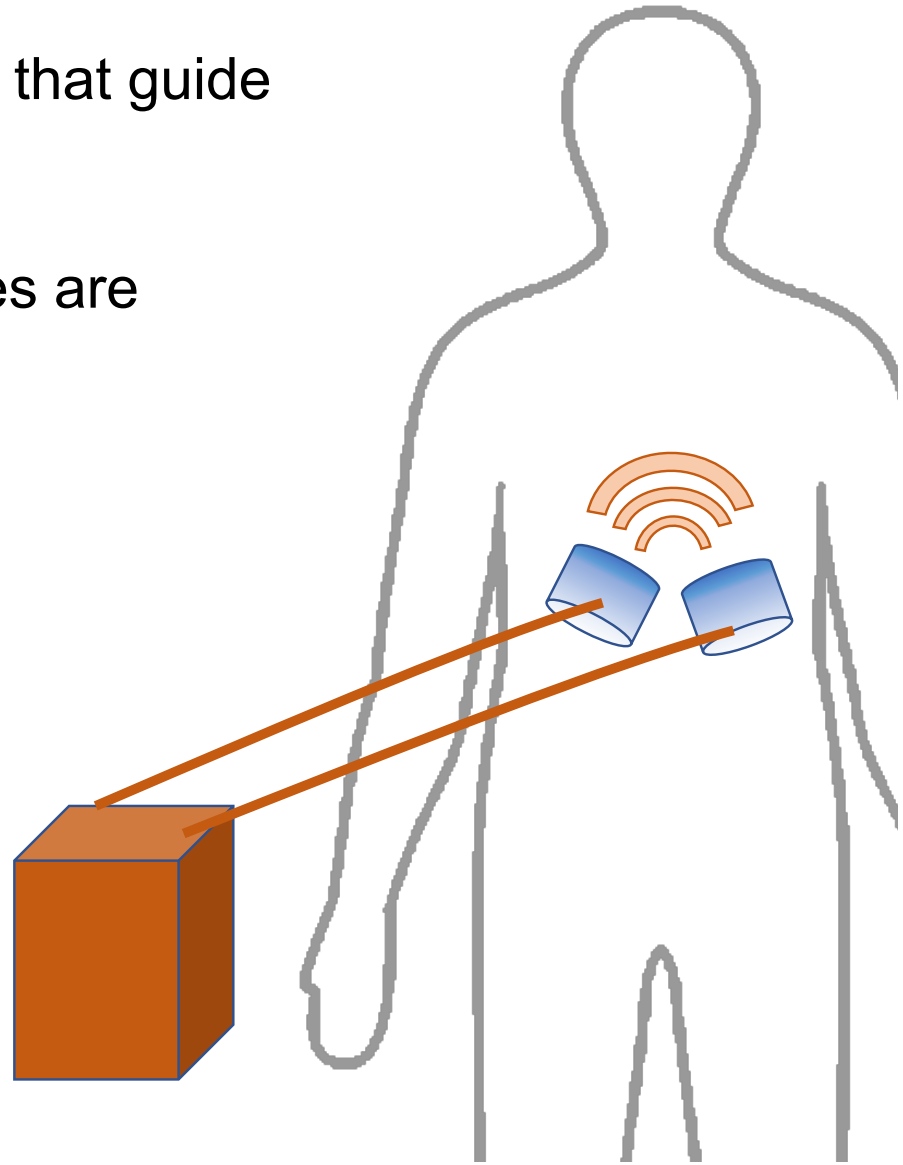
Only those aspects of the neuromodulation device that guide the delivery of energy (electricity) into the body.

1) **The position of the electrodes.** The electrodes are the only part of the device when electricity can enter/exit from the device.

Example: 1 cm^2 electrode placed epidurally over T1

2) **The intensity and timing of pulses applied by the device** through the electrode to the body.

Example: 1 mA amplitude, pulses at 100 Hz



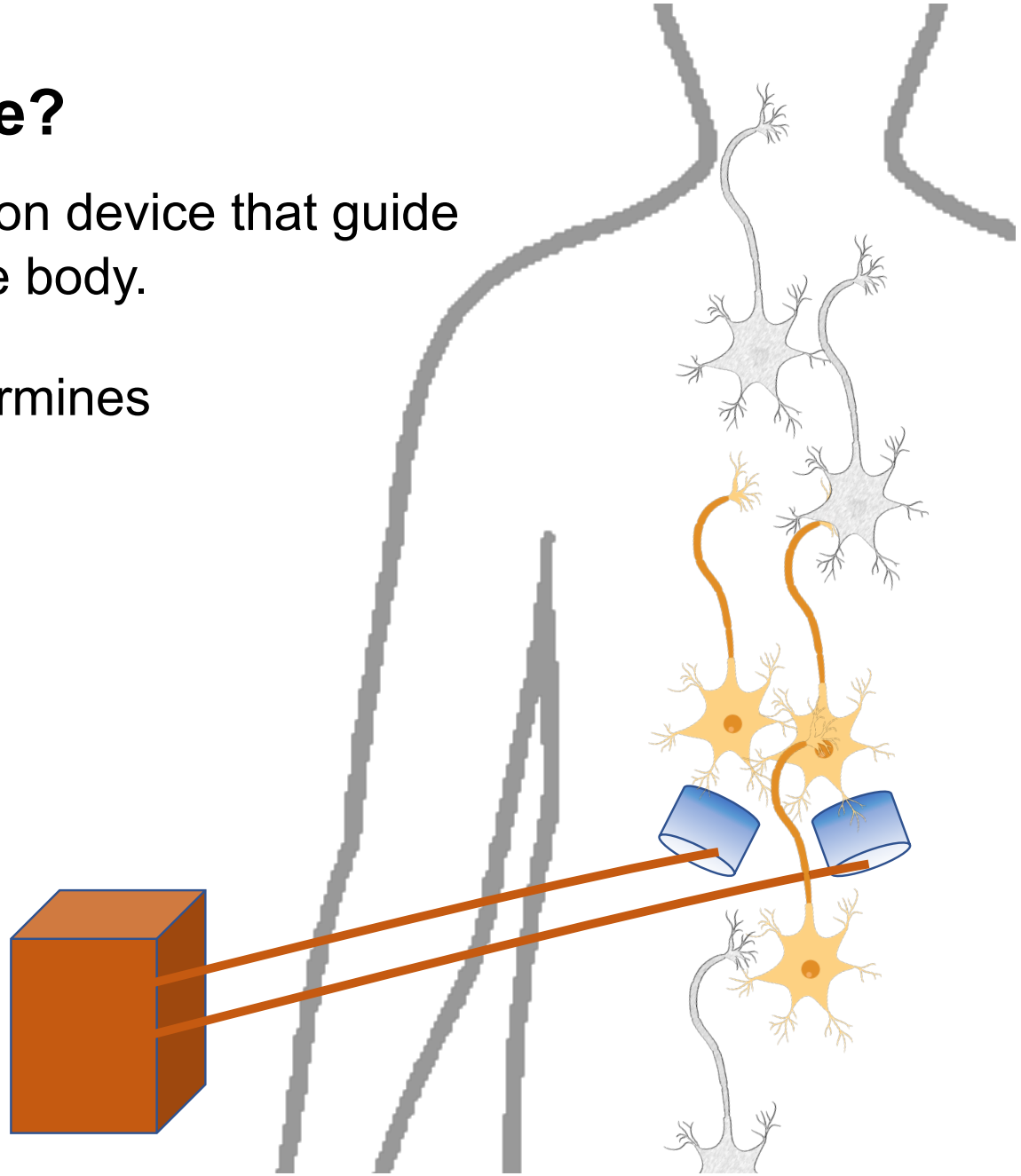
What is Neuromodulation Dose?

Only those aspects of the neuromodulation device that guide the delivery of energy (electricity) into the body.

1) **The position of the electrodes** determines what parts (neurons) are stimulated.

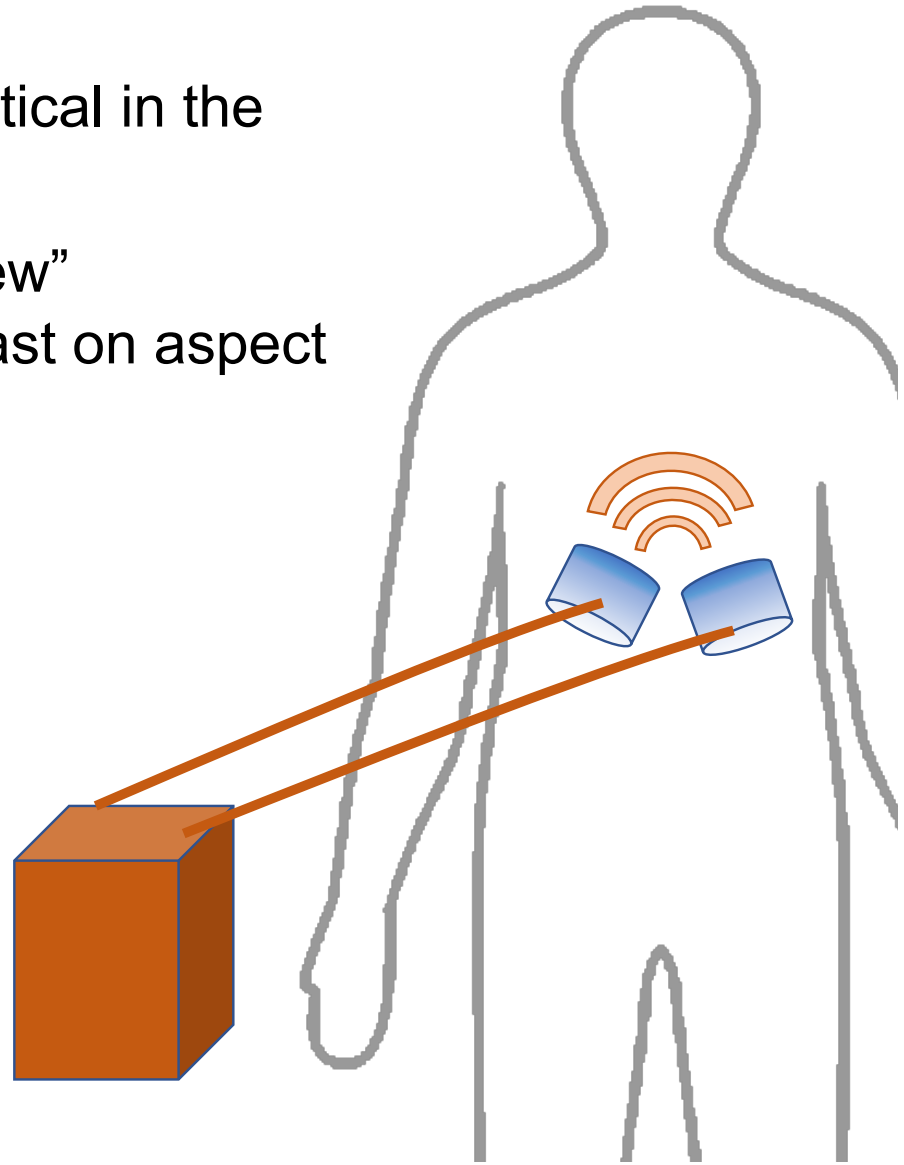
2) **The intensity and timing of pulses applied by the device** determines how neurons respond.

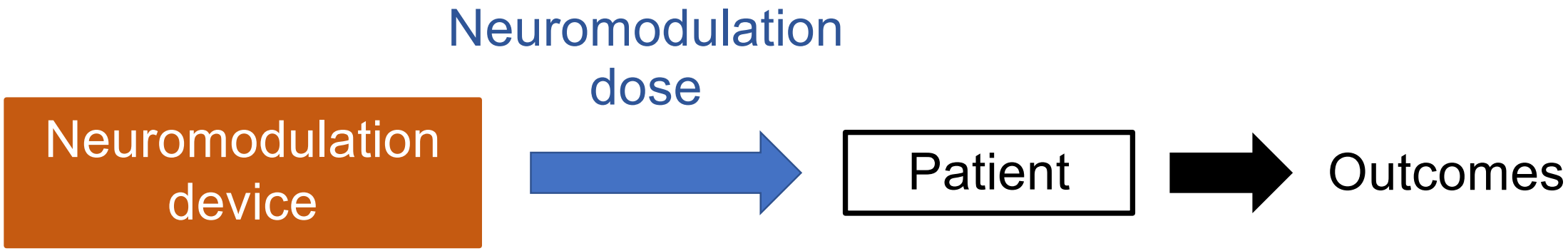
Neurons are exposed to the same waveform (eg. 100 Hz) as generated by the device. And respond more to higher intensity.



What is Neuromodulation Dose?

- Two devices that apply the same dose are identical in the effects they produce on the body
- Conversely, regarding effects on the body a “new” neuromodulation deice should change on at least on aspect of dose.
- Device features of than those governing dose matter (e.g., battery life, MRI conditional…) but for different reasons
- Each device can provide many different doses. And each device need to adjusted to a person / over time. **Dose instructions** are required guidance on how to adjust dose.



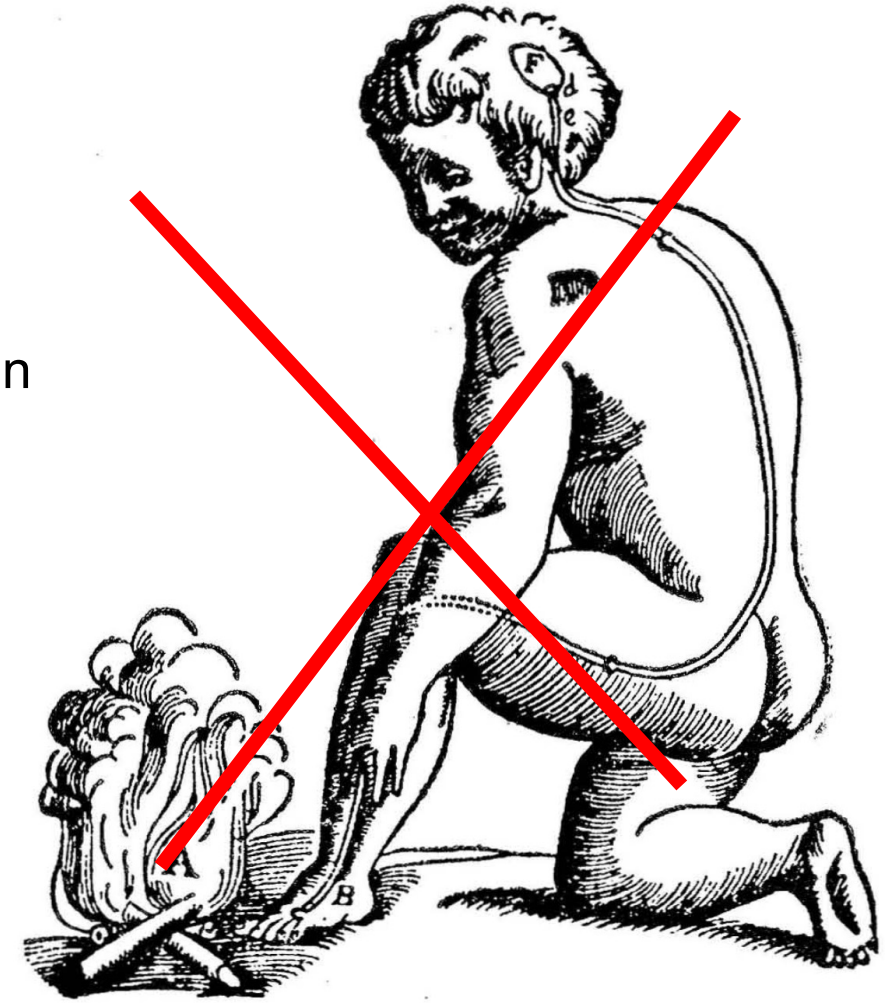


Dose instructions indicate how to adjust dose for each indication / patient

Gate control theory of pain (Melzack and Wall 1965)

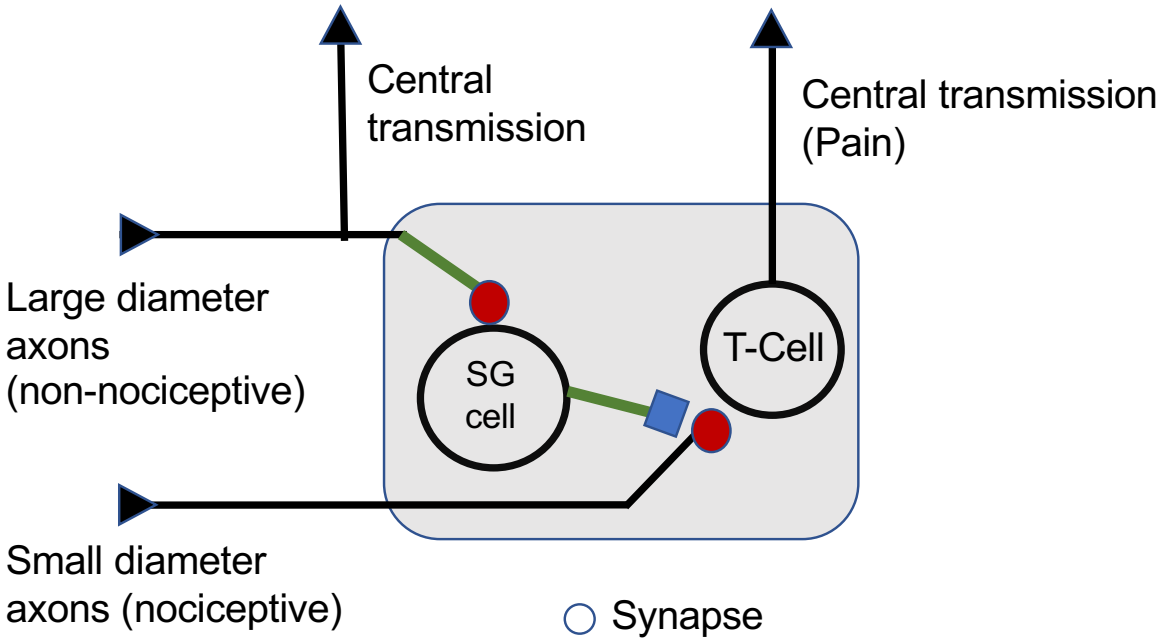
Descartes, 1664

A direct line from pain receptor to brain.



Gate control theory of pain (Melzack and Wall 1965)

Two types of sensory: non-noxious (large fibers) or noxious (small fibers) input. Both are excitatory signal into the spinal cord. Inside the spinal cord, the non-noxious input activate secondly inhibitory signal that blocks transmission of noxious signals to the brain.



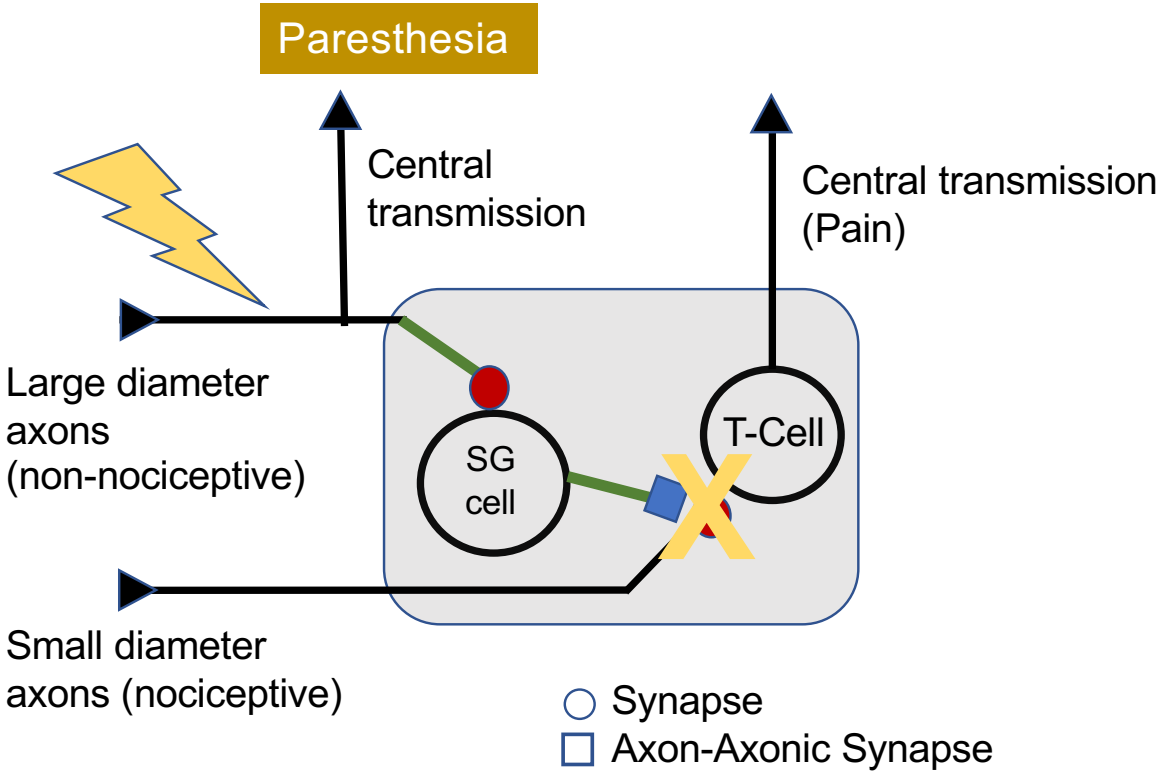
Ex = substantia gelatinosa excitatory interneuron
In = substantia gelatinosa inhibitory interneuron
PN = projection neuron

○ Synapse
□ Axon-Axonic Synapse

● Excitatory synapse ● Inhibitory synapse ╲ Pathways for negative synaptic feedback of noncoercive input

Gate control theory of pain (Melzack and Wall 1965)

Recommendation for pain control: Apply electrical stimulation to activate non-noxious fibers in dermatome associated with pain.



Dose instructions: Place electrodes on axon pathways associated with painful region. Apply sufficient electrical stimulation to activate non-noxious fibers (producing paresthesia).

Gate control theory of pain (Melzack and Wall 1965)

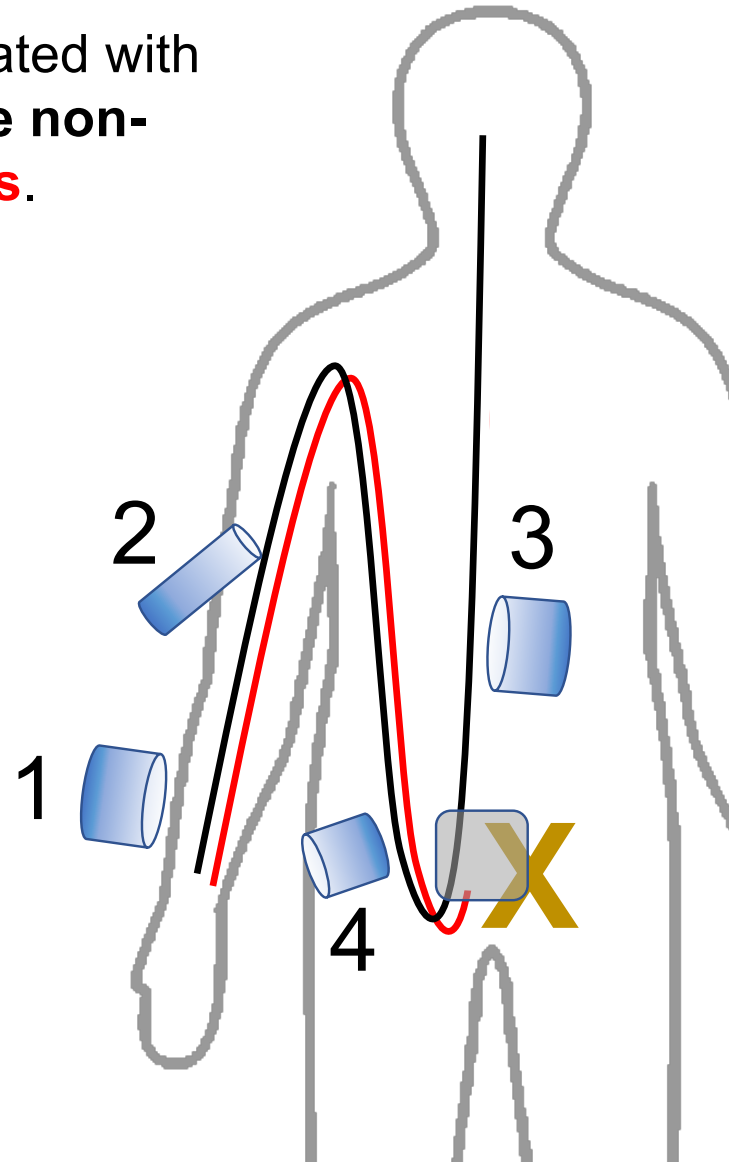
Dose instructions: Place electrodes on axon pathways associated with painful region. Apply sufficient electrical stimulation to **activate non-noxious fibers** (producing paresthesia). Block **noxious fibers**.

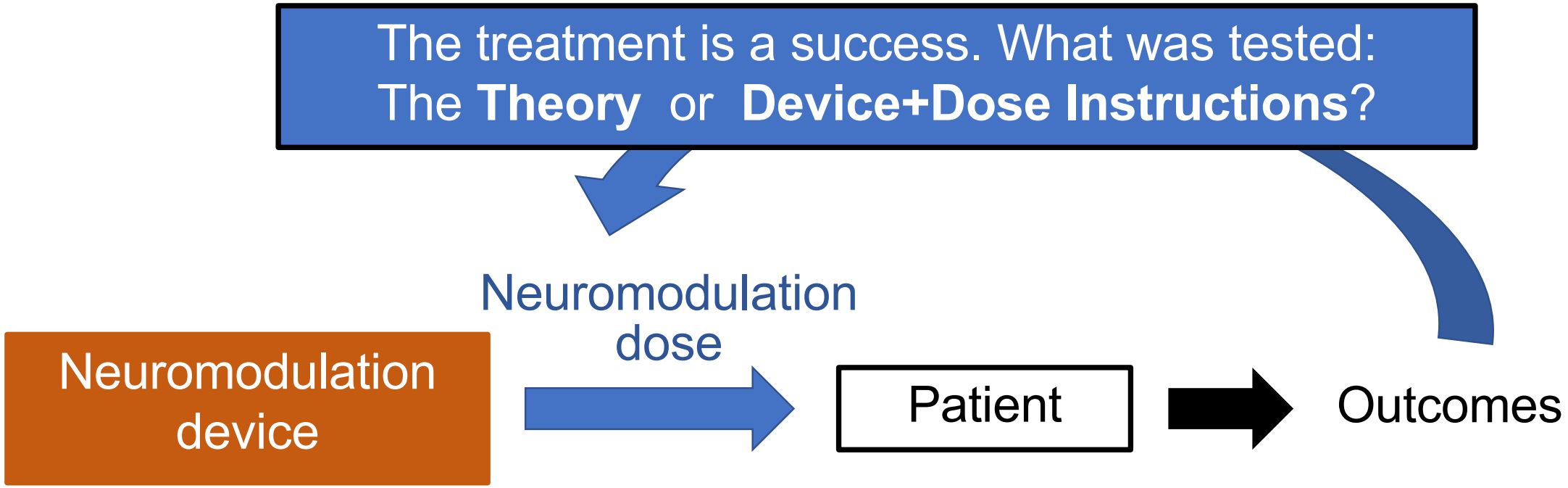
1: Electrode on the skin. Transcutaneous Electrical Nerve Stimulation (TENS)

2: Electrode near nerves. Percutaneous Nerve Stimulation (PNS). Wall and Sweet 1967

3: Electrode near dorsal columns. Spinal Cord Stimulation (SCS). Shealy, Mortimer, Reswick 1967

4: Electrode near dorsal root ganglion. (DRGs).





Dose instructions indicate how to adjust dose for each indication / patient

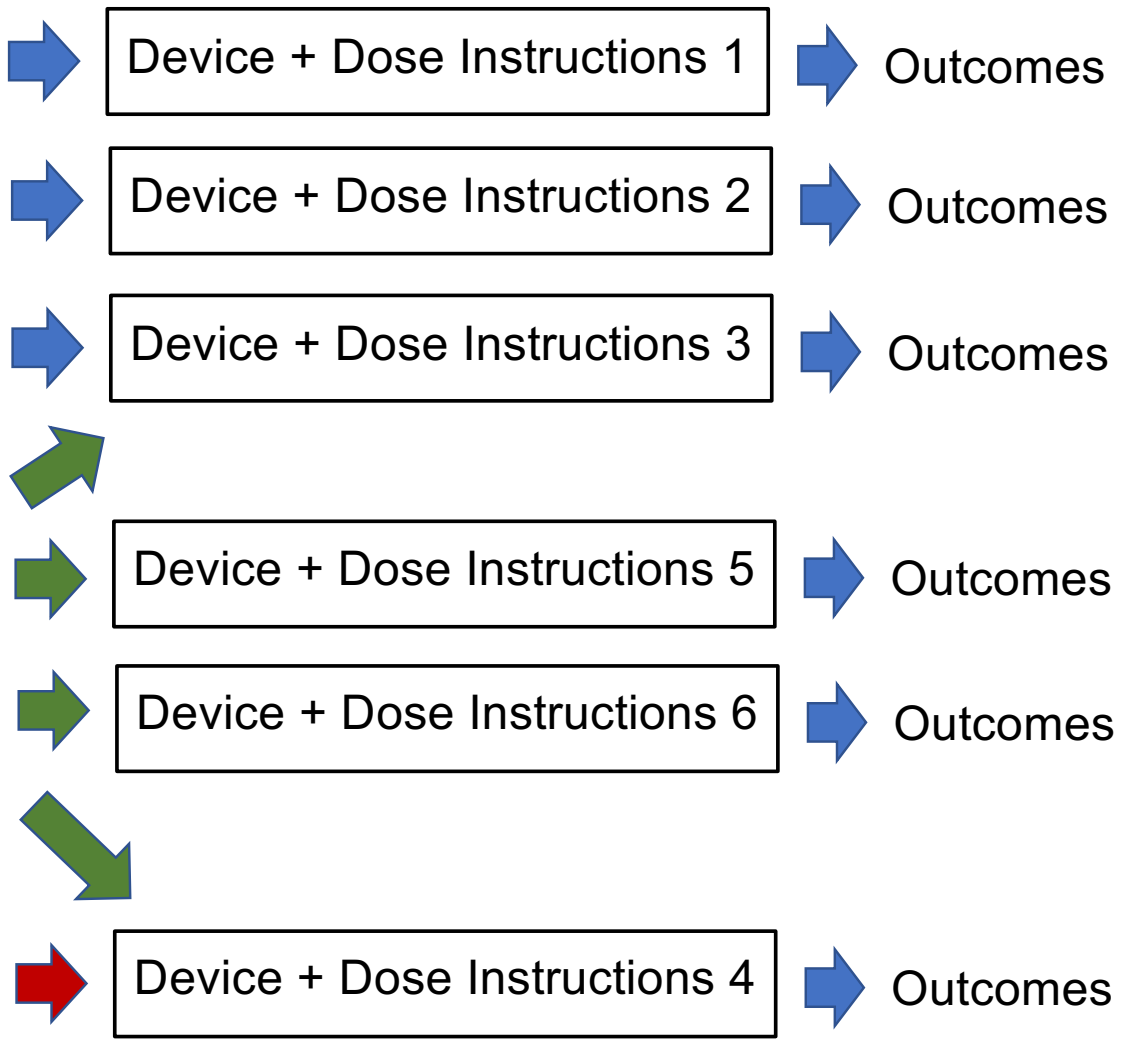
Theory (how neuromodulation works for pain) inspires the device and dose instructions

From mechanisms theory to device design

Gate Control Theory
(Paresthesia expected)

Scrambling Theory
Electricity stimulation adds noise, so the brain dose not perceive pain.
(Paresthesia optional)

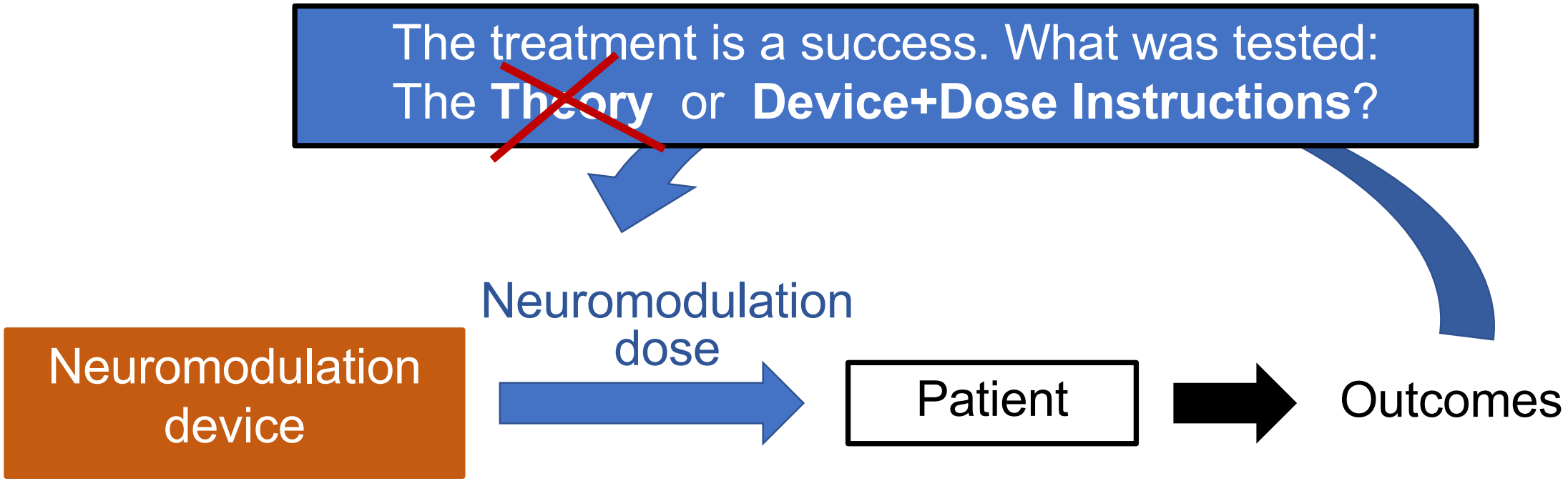
Blocking Theory
Enough electricity to suppress transmission.
(No paresthesia.)



One theory can inspire **distinct** devices / dose instructions

Different theories can inspire the **same** devices / dose instructions

New theory can inspire **new** devices / dose instructions



Dose instructions indicate how to adjust dose for each indication / patient

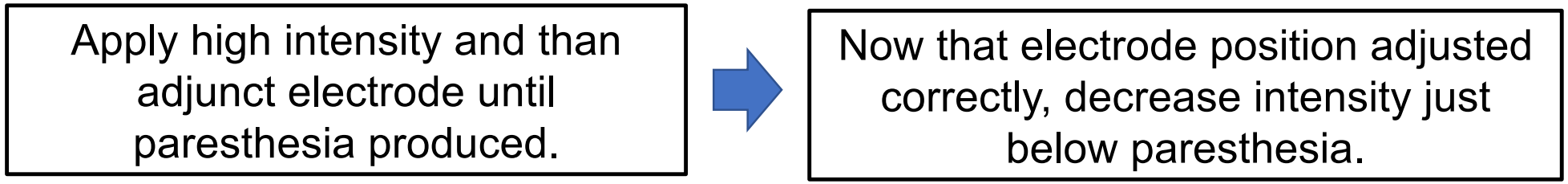
Theory (how neuromodulation works for pain) inspires the device and dose instructions

Is paresthesia required in paresthesia-based neuromodulation for pain?

Dose instructions based on Gate Theory (Version 1): Place electrodes on axon pathways associated with painful region. Apply sufficient electrical stimulation to activate non-noxious fibers (producing paresthesia).

Dose instructions based on Gate Theory (Version 2 generic): Place electrodes on axon pathways associated with painful region. Apply sufficient electrical stimulation to activate non-noxious fibers. Paresthesia can result depending on the waveform.

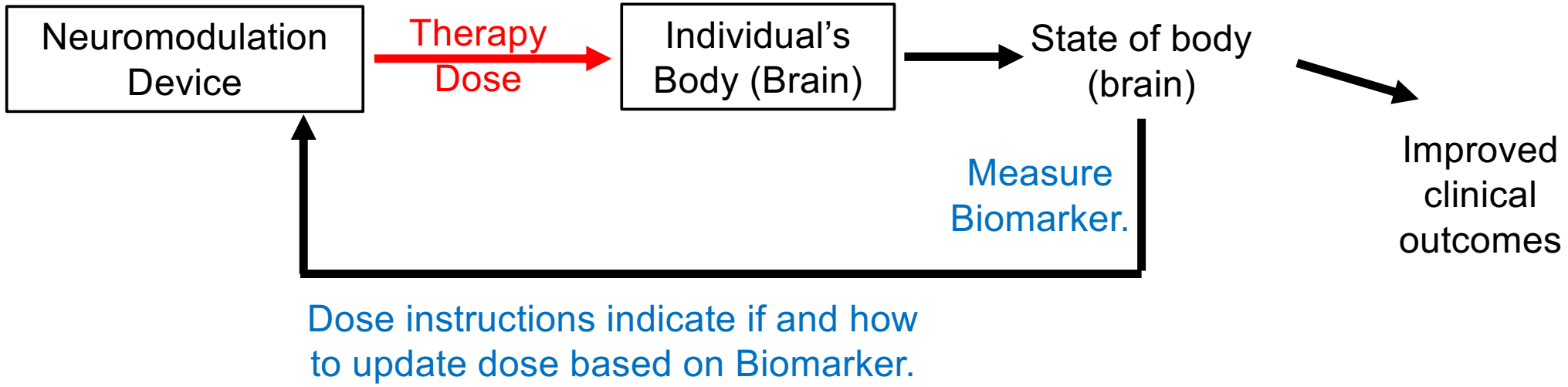
Dose instructions based on Gate Theory (Version 2 specific):.



Clinical success (still) does not establish mechanism is true. It does show that using paresthesia a **biomarker** in dose instructions is useful.

When neuromodulation therapy dose is adjusted based based on an objective or subject measure from the patient, that measure is a biomarker.

Neuromodulation biomarker: Any measurement used in neuromodulation dose instructions.



- A biomarker is not necessarily a mechanism, and clinical success does not establish (or even suggest) it is.
- Closed loop: When dose instructions (using a biomarker) are by a computer

Two general classes of neuromodulation biomarkers. They are precisely distinguished by how they are used.

1) Responsive Biomarker: Changes with effective therapy dose, in a manner anticipating clinical changes. Necessary for clinical changes. May or may not be mechanism.

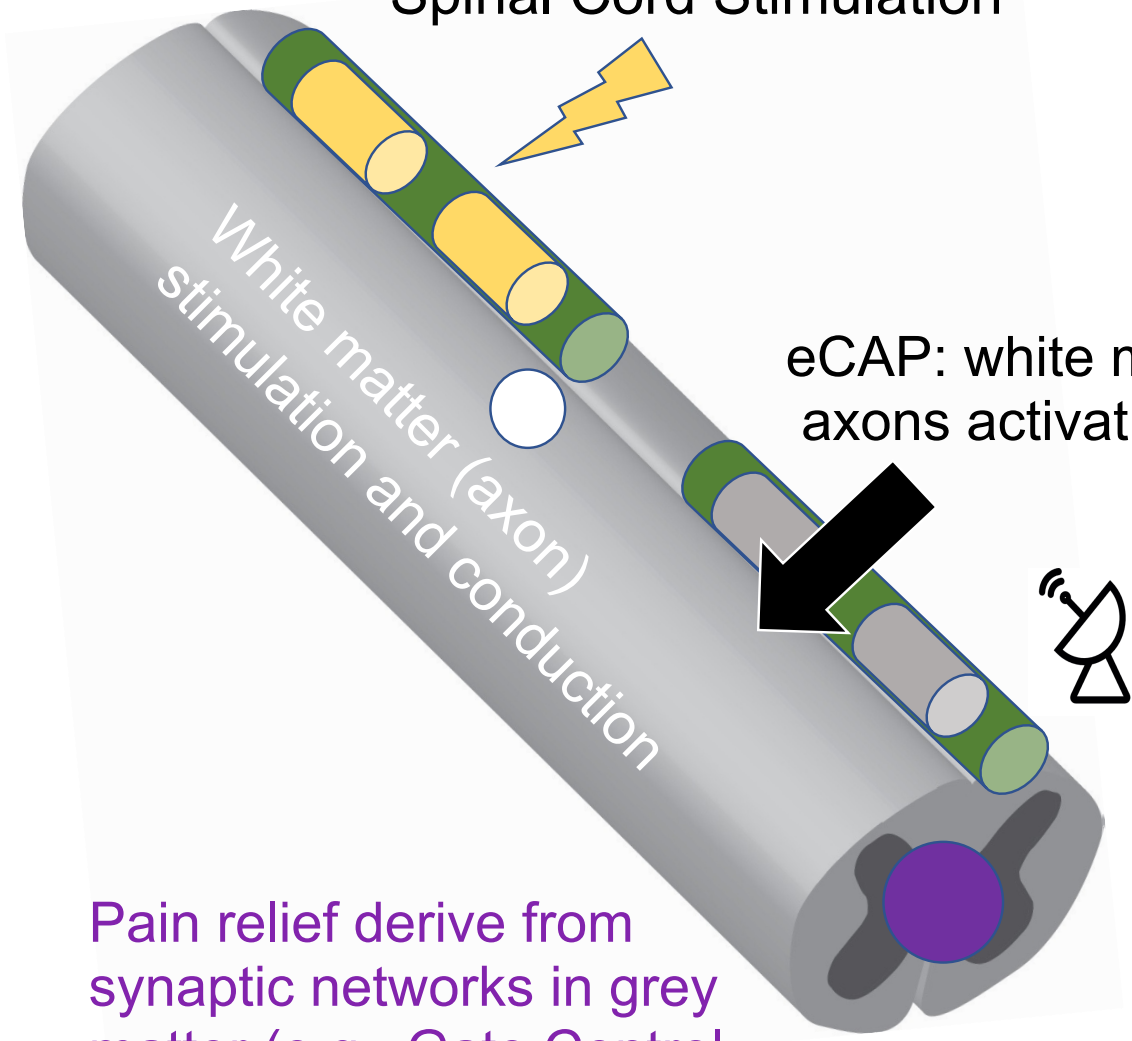
e.g. A brain imaging marker of pain. Paresthesia if assumed necessary.

2) Predictive Biomarker: Objective of subject measure used to adjust therapy dose irrespective of if (how) they change with dose. Not a mechanism.

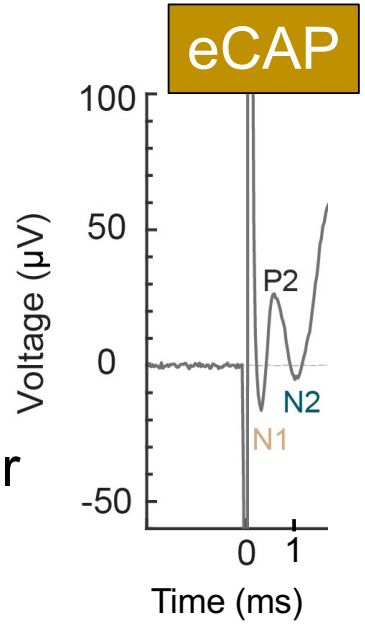
e.g. Image guided placement. Patient stratification.

In neuromodulation, it is common to have a Predictive Biomarker that is itself evoked by a *test* stimulation.
e.g., Paresthesia base adjustment with test dose when therapy dose is sub-paresthesia.

Spinal Cord Stimulation



eCAP: white matter
axons activation

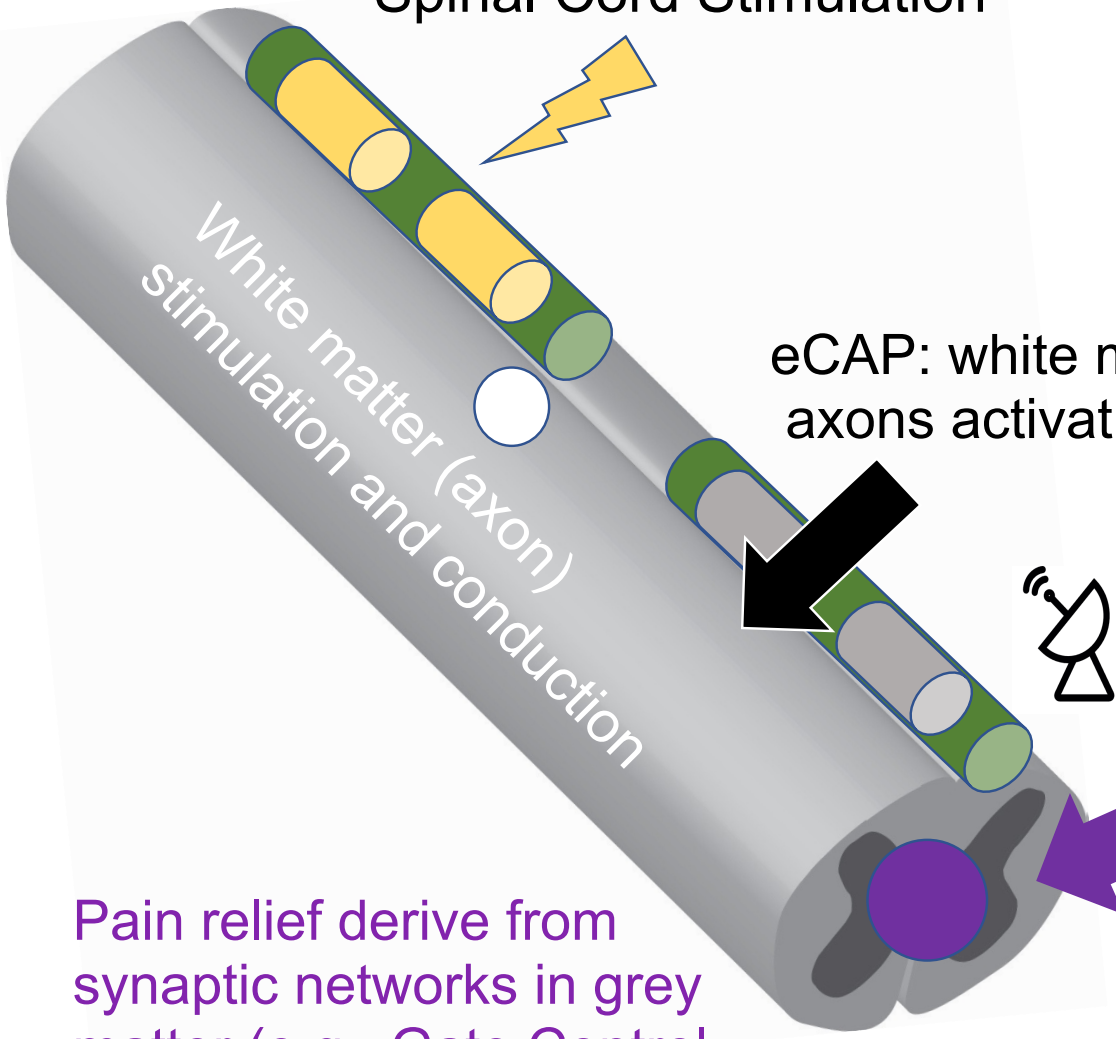


Epidural recorded evoked
electrical response

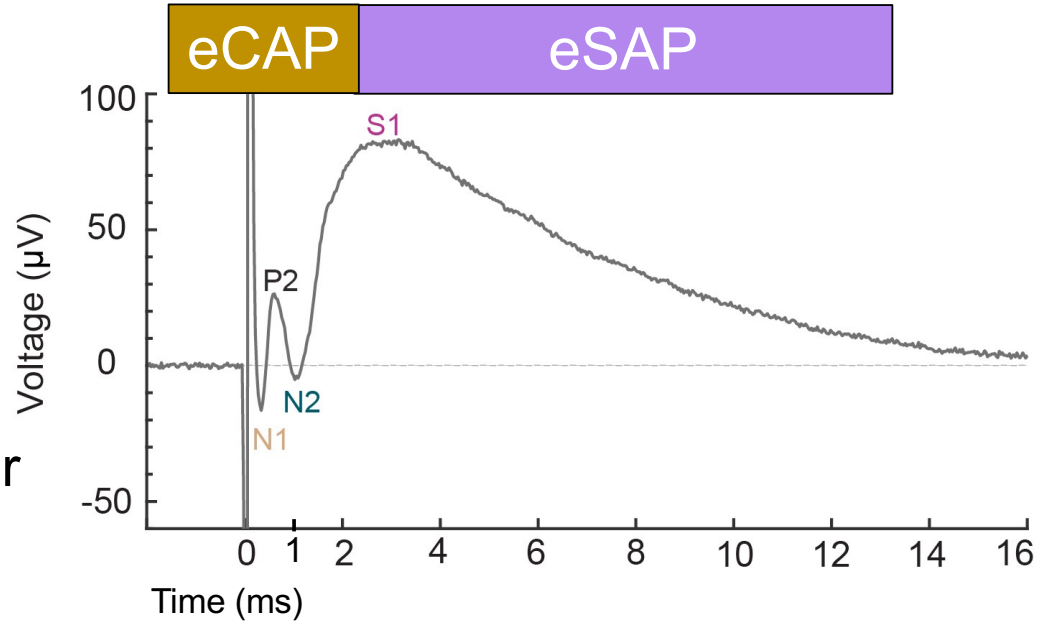
Pain relief derive from synaptic networks in grey matter (e.g., Gate Control theory of pain control)

So long as dose instructions use eCAPS as essential during effective therapy dose, eCAPS are Responsive Biomarkers.

Spinal Cord Stimulation



eCAP: white matter axons activation



Epidural recorded evoked electrical response

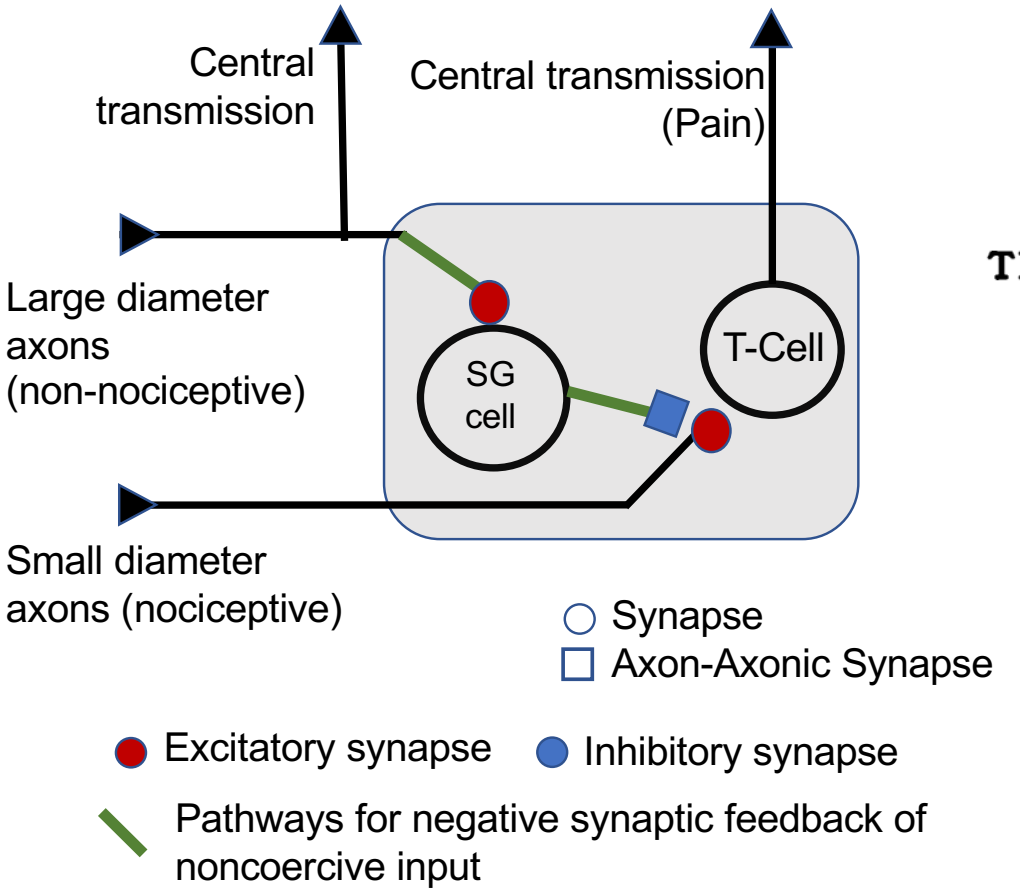
Can we record epidural evoked potentials that reflect gray matter activity?

Yes. Provided some modifications (e.g., record for longer).

Pain relief derive from synaptic networks in grey matter (e.g., Gate Control theory of pain control)

Gate control theory of pain (Melzack and Wall in 1965)

Non-noxious (large fibers) and noxious (small fibers) input; both are excitatory into the spinal cord. Inside the spinal cord, the non-noxious input activates secondary **inhibitory synaptic signal** that blocks transmission of noxious signals to the brain.

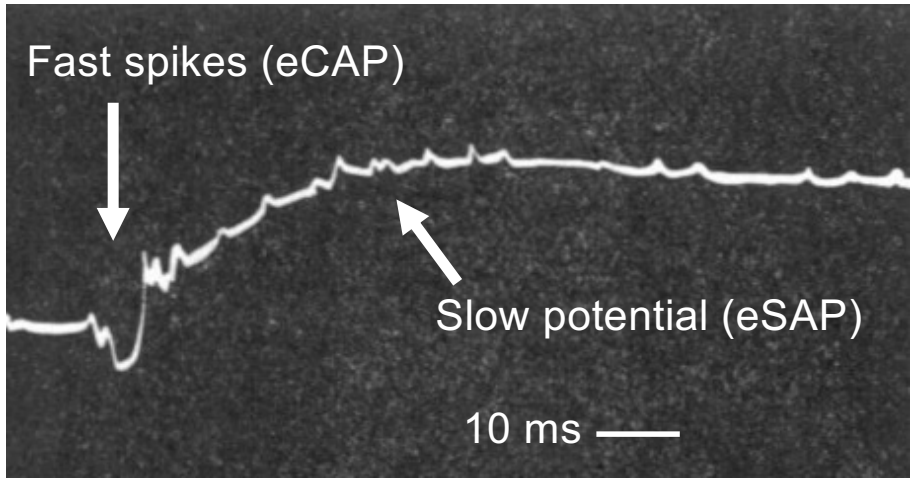


The gate is a inhibitory synaptic signal in the spinal cord, measured as a slow potential.

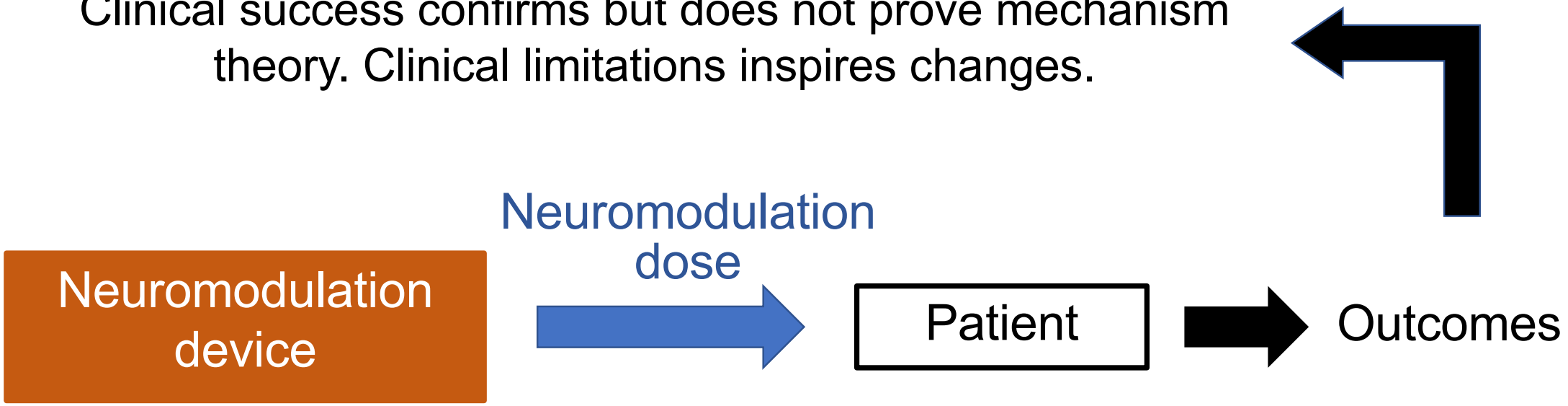
J. Physiol. (1962), **164**, *pp.* 508–526

THE ORIGIN OF A SPINAL-CORD SLOW POTENTIAL

By P. D. WALL



Clinical success confirms but does not prove mechanism theory. Clinical limitations inspires changes.



Dose instructions indicate how to adjust dose for each indication / patient. Essential. Biomarker based.

Theory of how neuromodulation / pain inspires device and dose instructions.

Diverse sources: Clinical observation, basic science, philosophy…

How Neuromodulation for Pain Works

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1. Peterchev, AV, Wagner, TA, Miranda, PC, Nitsche, MA, Paulus, W, Lisanby, SH, Pascual-Leone, A, Bikson, M (2012). Fundamentals of transcranial electric and magnetic stimulation dose: Definition, selection, and reporting practices. *Brain Stim*, 5(4), 435-453
2. Melzack, R, Wall, PD (1965) Pain mechanisms: a new theory. *Science*;150(3699):971-9.
3. Sharma, M, Bhaskar, V, Yang, L, FallahRad, M, Gebodh, N, Zhang, T, Esteller, R, Martin, J, Bikson, M. (2023). Novel Evoked Synaptic Activity Potentials (ESAPs) Elicited by Spinal Cord Stimulation. *eNeuro*, 10(5)

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