Acute Migraine Pain Relief via Remote Electrical Nerve Stimulation - a systematic analysis

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Part I: Background

1. Propagation of sensory stimulus along nerve cells

All nerve cells - neurons - are electrically excitable. They maintain voltage gradients across their membranes by means of metabolically driven ion pumps, which, in concert with the ion channels in the membrane, generate opposite intracellular and extracellular concentrations of ions such as sodium, potassium, chloride, and calcium. Changes in the cross-membrane voltage can change the function of the voltage-dependent ion channels.

At "rest" state, i.e., with no external stimulus, the nerve cell membrane maintains a potential of about 70 to 90 mV between the inside and outside of the cell (with the inside being the negative side), by continually moving ions of Na+ from inside the cell to the outside, and balancing this positive charge movement by moving K+ ions from outside the cell to the inside. This is illustrated in 1.

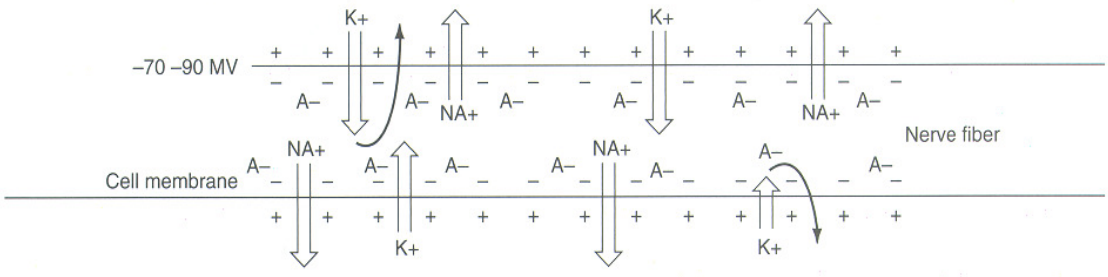

Figure 1: constant electrical potential across the nerve cell membrane

In order to create transmission of an impulse in the nerve, the resting potential of cell membrane must be reduced (depolarized) below a certain threshold level. When this happens, changes in membrane's permeability occur, creating an **action potential** that propagates as an impulse along the nerve in both directions, causing a propagating depolarization of the membrane.

Thus, stimulus to a nerve cell creates an effect of depolarization of the voltage potential.

If the voltage gap across the cell membrane changes by a sufficiently large amount, an electrochemical pulse - the **action potential** - is generated and travels rapidly along the cell's

axon (nerve fiber). As this pulse propagates it may – if it is strong enough - activate synaptic connections with other cells when it arrives, and in this way carry the "message" through the spinal cord, to the brain.

The stimulus must have sufficient intensity and duration such as to exceed the membrane's basic threshold for excitation. The stimulus must alter membrane permeability such that that the number of ions pushed across the membrane exceed the ability of the cell's active transport pumps to maintain the resting potential, thus forcing the membrane to depolarize - resulting in an action potential. This is illustrated in 2.

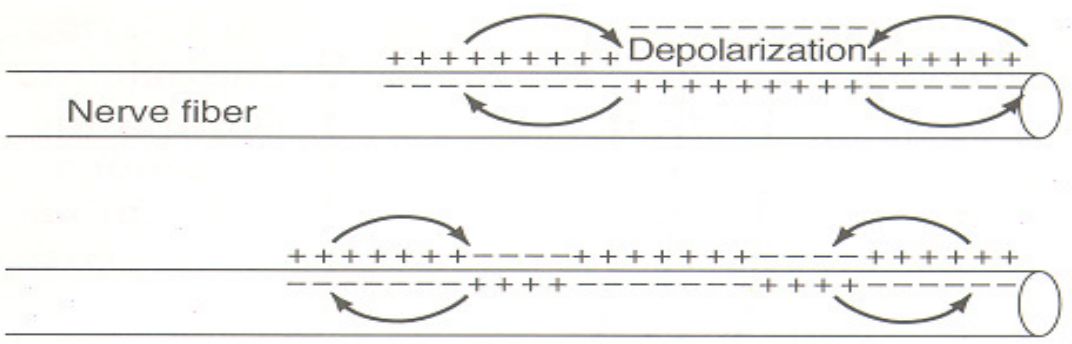

Figure 2: a depolarization impulse exceeding the required action potential (top) propagates along the nerve fiber in both directions (bottom).

Difference in electrical potential between the depolarized region and neighboring inactive regions causes the current to flow from the depolarized region intercellular material to the inactive membrane. Current also flows through extracellular materials, back to the depolarized area, and finally into cell again. This makes the depolarization self propagating, as the process is repeated along the fiber in each direction from original depolarization site. As the nerve impulse reaches another nerve cell, the impulse is transferred between the two at the synapse.

2. Delivery of pain messages in the neural system

Sensory messages are carried to the brain by two classes of afferent (sensory) nerves:

> **Nociceptive** nerve fibers carry pain messages invoked by stimuli such as pressure, heat and cold.
> **Non-nociceptive** fibers are nerves which do not transmit pain signals.

There are 3 types (structures) of nerve fibers connecting the periphery of the body to the spinal cord, and the brain. These are the A-beta = "the large fibers", A-delta, and "C = the thin fibers":

Nerve fiber type	A-beta (Aβ)	A-delta (Aδ)	C
Diameter	Large	Medium (2-5 micron)	Small (< 2 micron)
Myelination	High	Thin	No
Signal propagation	Fast (> 40 mS^{-1})	Medium (5-15 mS^{-1})	Slow (< 2mS^{-1})
Activation threshold	Low	High and low	High
Sensation on stimulation	Light touch, **non-noxious**	Rapid, sharp, localized pain (e.g., pinch)	Slow, diffused, dull pain

The fast, medium-size, myelinated "Aδ" fibers carry intense pain messages quickly, and the slow, thin, unmyelinated "C" fibers carry longer-term throbbing and chronic pain messages.
The large-diameter Aβ fibers are non-nociceptive – they do not transmit pain stimuli, but their "firing" inhibits the propagation fired by the "painful" Aδ and C fibers.

The signals carried by nerve fibers have two destinations in the dorsal horn of the spinal cord:

- Transmission cells – carry the pain signal up to the brain
- Inhibitory inter-neurons - impede the transmission cell activity

3. Characteristics of migraine pain

The exact cause of migraine is still unknown (8). For a long time it was believed that constriction and/or dilation of cerebral blood vessels was the reason for migraine attacks. However, advances in functional brain imaging[(1)] suggest that vascular changes are not the primary cause for head pain in migraine. Experimental and clinical data suggest an activation of the trigeminal innervation of the cranial circulation to explain the peripheral pain mechanisms. The periodicity and other clinical features of migraine are explained by a significant dysfunction of the midbrain endogenous anti-nociceptive system and the neural control of Cerebral Blood Flow (CBF).

That is, the latest hypotheses claim that the source is in the trigeminovascular system.
The trigeminal nerve (aka fifth cranial nerve) is a nerve located in the head, responsible for sensation in the face and motor functions such as biting and chewing. The **trigeminovascular system** consists of neurons, in the trigeminal nerve, which innervate cerebral blood vessels.

This location in the brain is involved in the pain process in a indirect," triggering" manner, rather than as a response to first-division nociceptive pain impulses.

Acute migraine attacks occur in the context of the patient's inherent level of vulnerability. The greater the vulnerability or lower the threshold, the more frequent attacks occur. Attacks are

initiated when internal or environmental triggers are of sufficient intensity to activate a series of events which end up with a migraine headache. A typical migraine attack consists of 5 phases [(2)]:

(1) **Prodrome**: the first phase, experienced by many migraineurs is a vague vegetative or affective sensation of symptoms as much as 24 hours (or less) prior to the onset of a migraine attack.

(2) **Aura**: the aura phase, apparent with about 15% of the migraineurs, consists of focal neurological symptoms that persist up to one hour. Symptoms may include visual, or language disturbance as well as symptoms localizing to the brainstem. Not all migraineurs go through the aura phase.

(3) **Headache**: within an hour of resolution of the aura symptoms, the migraine headache usually appears, typically with unilateral throbbing pain and possibly associated nausea, vomiting, photophobia, or phonophobia. Typically, **the level of pain increases gradually, with a steep slope of growth within the first half hour to hour**, and builds up to a high climax. Without treatment, the headache may persist long hours, for up to 72 hours in some cases, before ending in a…

(4) **Resolution** phase, often characterized by deep sleep.

(5) **Hangover**: for up to twenty-four hours after the spontaneous throbbing pain has resolved, many patients may experience malaise, fatigue, and transient return of the head pain in a similar location for a few seconds or minutes following coughing, sudden head movement, or valsalva movements. This phase is sometimes called the migraine hangover.

Part II: Pain inhibition

Several different mechanisms of pain inhibition have been found out and investigated. This part reviews them shortly.

1. The gate control theory

The gate control theory [3] asserts that activation of nerves which do not transmit pain signals, i.e., the non-nociceptive fibers, interferes with signals from pain fibers, thereby inhibiting pain.

More specifically, the gate theory describes a paradigm of “competition” between the non-nociceptive A-beta fibers and the pain C fibers:

- A-beta fiber activity excites transmission cells and excites inhibitory cells.
- C fiber activity excites transmission cells, but impedes inhibitory cells.

Thus, if a stimulus is applied such that the “large fiber” activity is larger than the “thin fiber” activity, the pain sensation is reduced.

The pain stimuli are regulated in certain centers of the peripheral nervous system. For example, some areas in the dorsal horn of the spinal cord (called laminae) that receive pain stimuli from Aδ and C fibers, also receive input from Aβ fibers. The non-nociceptive Aβ fibers indirectly inhibit the effects of the Aδ and mainly C pain fibers, by 'closing a gate' to the forward transmission of the stimuli.
In other parts of the laminae, pain fibers also inhibit the effects of non-nociceptive fibers, trying to ”open the gate”.

The principle of this mechanism is illustrated in *Figure 1*.

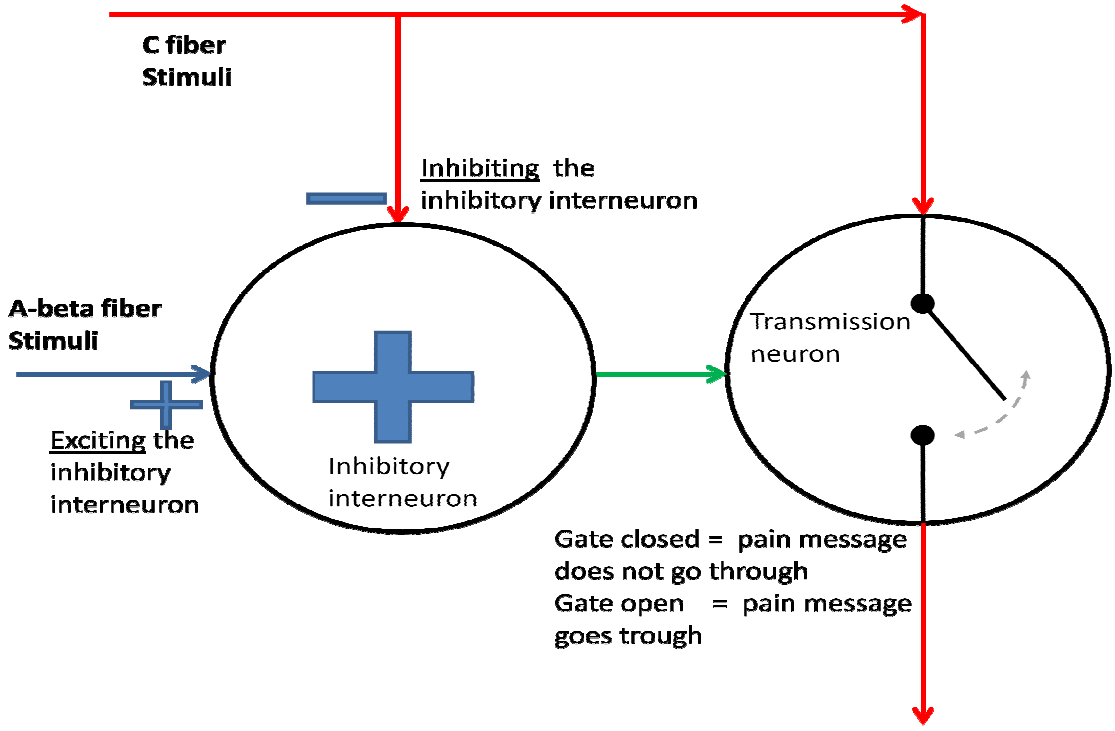

Figure 1: principle of the pain gate theory

The conclusion is that, what can reduce the pain sensation is stimulation of the large fibers, which does not also increase the stimulation of the thin fibers.

2. Conditioned Pain Modulation (CPM)

CPM is an endogenous analgesic mechanism originated in the brainstem. It is mediated by descending serotonergic pathways (i.e., neurons of the Raphe nuclei in the brainstem which deploy serotonin (5-hydroxytryptamine or 5-HT) as the neurotransmitter).

One of the characteristics of this mechanism, also known as “pain inhibits pain” is that, once there is a noxious stimulus at a certain body location, it may be inhibited by a second painful stimulus, delivered at a different body location (4). The inhibition process invoked by the noxious stimulus was found to be “global” in nature, i.e., has impact over the pain sensations anywhere in the body. Furthermore, it was found (7) that while its effectiveness depends on the intensity of the noxious stimulus, it does not depend on the perceived pain sensation caused but the noxious stimulus. This implies that, if the secondary noxious stimulus is engineered such as its intensity as a stimulus is high, but the pain **perception** it invokes is very mild (or none) - this can work as **pain relief therapy**.

3. External electrical sensory stimulation as a means of analgesia

Different sensory nerves are sensitive to different types of stimuli: heat, cold, pressure, movement, etc. However, a direct electrical current can create the resulting depolarization without the "natural source" for which the nerve cell is built. Hence, ALL nerve cells are in fact sensitive to electrical current. This is the principle of the operation of Electrical Nerve Stimulation.

Electrical stimulation may be delivered directly to the nerves, invasively, or applied through the patient's skin (non-invasively).

In the case of TENS (Transcutaneous Electrical Nerve Stimulation), the stimulation reaches nerve cells located just below the skin, and, if the stimulus is strong and/or long enough, it penetrates and reaches nerve cells located in deeper tissues.

The TENS pulse has to be strong enough and/or long enough (in time) in order to exceed a certain threshold and generate the required action potential and create a propagating impulse. This is illustrated in *Figure 2*.

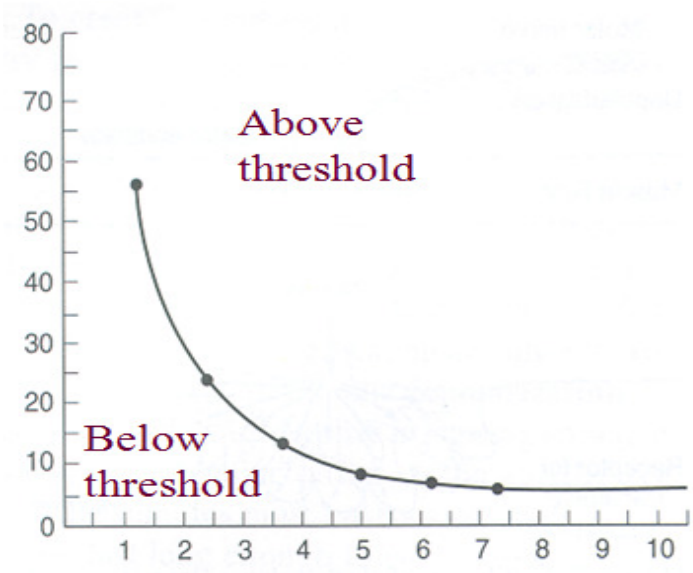

Figure 2: stimulation threshold is the curve which relates the intensity of electrical stimulus (current, Y axis, in miliampers) and its length in time (duration, X axis, in 1/10's of second) necessary to cause depolarization

Recall that, according to the gate theory of pain, in order to reduce pain, we would attempt to excite the A-beta sensory nerves, preferably without exciting the A-delta and C nerves. In

addition, when targeting pain relief we would try not to excite motor nerves in order to avoid involuntary movement and discomfort. Referring to *Figure 3*, we would program the stimulation device to a point on the current-duration curve such as to only excite the A-beta nerves. Luckily, this is possible, as can be seen in *Figure 3*. For example, the value of current of around 50mA, with a pulse duration of about 100 to 200 mircoseconds - seems just the sweet spot.

In reality, the current-duration thresholds differ from one tissue to another, and of course from one person to another. Thus, the best approach is in fact to let the patient adjust the current and duration (or more practically, just the current) such that the stimulation does not result with a local pain, but rather a comfortable sensation of “rubbing” or “running ants”, and at the same time does not result with local muscle contractions (or only mild contractions).

We would also target to recruit more A-beta fibers to the pain inhibition job. Increasing the pulse current will excite smaller fibers and fibers farther away from the stimulation location. Increasing the pulse duration will have a similar impact. However, increasing any of those parameters too much will start exciting motor, A-delta, and finally C fibers – which will not support the pain inhibition. Thus, a better way to recruit more A-beta fibers without exciting the other nerves would simply be to increase the **area** of the electrodes, i.e., enlarging the localization of the stimulus and thus “hitting” more nerve cells – but maintaining a low enough current and duration, such as to only excite the A-beta nerves.

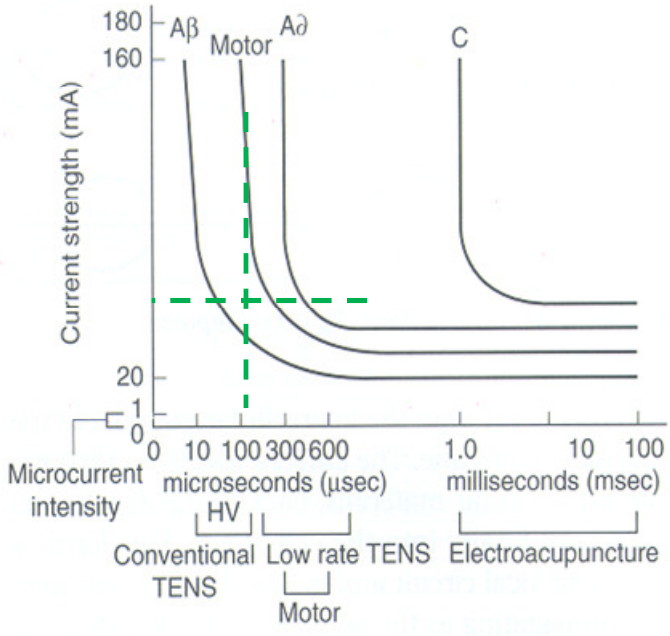

Figure 3: Intensity-duration threshold curves of different nerve types.
The point at the crossing of the two perpendicular dashed lines indicates a suitable “working point” for pain inhibition, or pain relief.

It is important to understand that, while applying non-invasive electrical nerve stimulation at the right frequency, pulse duration, current intensity, and at sufficiently large area – does result in pain inhibition, the reduction in pain sensation is usually temporary, and does not last too long after stopping the stimulation. This is so because, normally, if there exists a "structural", physiological source for the pain, such as a fracture, torn muscle or ligament, "burn", inflammation, etc., which generates a long lasting nociceptive stimulation, that stimulation will continue to cause pain sensation, and, once the inhibition caused by the electrical nerve stimulation, as explained by the gate theory – is stopped, the original pain would become dominant again.

Another characteristic is that the pain inhibition, which is invoked in this way and expresses the gate control theory – is local in its nature. This means that, if we were to utilize this in the case of migraine pain (or any other type of headache), the stimulation would have had to be applied on the head – which has a number of negative impacts.

Thus, the gate control theory of pain is not sufficient to reduce migraine pain.

However, CPM may work for migraine. If the threshold of the applied stimuli is designed to be lower than the local pain threshold, i.e., lower than the threshold required for the stimuli to create an overall pain message, this applied stimuli would arouse the descending inhibition mechanism, possibly resulting in a relief of the pain caused by the primary (non-voluntary) stimulus.

Part III: Putting it all together

1. Utilizing the characteristics of migraine pain.

The nature of migraine headache is complex. Clearly it is not stimulated by a" tangible" source, such as external pressure, external heat or cold, incision, or any other known structural or mechanical damage.

It is partially a visceral pain in the sense that it is stimulated by chemical alterations - in the brain itself, in this case. These alterations may be invoked by a number of individual triggers such as certain emotions and mood, mental pressure, certain types of food, etc. However, the migraine headache is episodic in nature, i.e., once it is invoked it quickly escalates, unless it is inhibited in some way, gets to a peak, and then decays. Once it is inhibited though, since there is no "external" source which maintains the pain stimulation, it usually does not continue – until the next triggering event, and the next episode. In this case, we refer to the migraine attack being "aborted".

This is why this particular pain has the potential of positively respond to a CPM stimulation. This hypothesis was verified in a clinical study (5). Moreover, the study results show (6) that the sooner the CPM stimulation is applied after the onset of the migraine pain, the higher

probability it has to reverse the typical escalation curve, and bring the pain sensation to a quick termination.

2. Principle of operation of the Nerivio Migra

The electrodes of the Nerivio Migra are applied on the mid upper arm, on the outer side. This location is easy to handle independently by the patient without help; it is discrete such as to maintain intimacy and privacy, and the stimulated location is very safe, not over-sensitive, and fairly scarce is hair. The area of the electrodes is relatively large, in order to recruit a large number of fibers. The pulse frequency and duration are designed such that a large number of A-beta fibers are locally stimulated; and less motor nerves, C fiber sensory nerves and A-delta fiber sensory nerves are stimulated beyond their thresholds. (Refer to *Figure 3*.) This is intended to keep the local sensation below pain threshold, utilizing the gate theory mechanism, while still passing sufficient messages to the central nerve system such as to invoke the global CPM inhibition. Furthermore, in order to continue the CPM process going on for the entire duration of the device operation, the pulse frequency is gradually changed by the device, such as to avoid the known habituation phenomenon. The patient is guided to apply stimulation intensity as high as possible but just below the perceived local pain level. This approach utilizes the findings of Youssef et al ("pain inhibits pain", (4)), and Yarnitsky et al (7), namely that higher intensity of the secondary noxious stimulus is more effective in enabling the CPM analgesic mechanism.

3. Initial study results

As reported in (5) and (6), the results of a first clinical study indicate significant positive response to the device, with pain reduction similar to those of Triptans, and suggest that the Nerivio Migra can be an effective, drug-free treatment for episodes of migraine.

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