INTERX THERAPY

INDUSTRY WHITE PAPER – ELECTRICAL NEUROSTIMULATION

Interactive Neurostimulation (InterX)

Optimization of Electrical Stimulation Treatment Parameters

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Introduction

Interactive Neurostimulation (InterX) represents the next generation of electrical stimulation for the treatment of both acute and chronic pain. The design, output and features of InterX are a dynamic advancement in the technology of electrical stimulation which facilitate unique applications, offering the user a highly flexible treatment tool that has been proven to be effective across a broad range of conditions[1,2,3]. InterX is easy to use and completely portable around the clinic, hospital or treatment center yet enables a scientific method of delivering the optimal treatment for each and every patient. The 3-step protocol of scan, target and dynamic integrates easily into current treatment practices and produces consistent results for the treatment of many conditions. There is a growing body of evidence to support the InterX protocol for the effective application of electrical stimulation. There is also increasing awareness that the optimization of treatment parameters is critical for the effectiveness of treatment.[4 5 6,7,20]

Research has shown that the variables of electrode placement[5,6,7], frequency[8,9,11] of stimulation and amplitude[4,5,10] all have an impact on clinical outcomes. Equally, accommodation of nerves to stimulation during single treatments or following long-term use of an electrical modality has been reported[11]. Most therapists are familiar with adjusting amplitude, setting a sweeping frequency, or establishing ramping or random bursts to prevent accommodation during the treatment protocol. But few therapists are able to make evidence-based decisions on which parameter variation should be used to optimize results. Because medical technology has hindered the ability to optimize and combine all of these treatment variables into recommended clinical protocols or preset parameter packages, static localized treatments using relatively low amplitudes (for comfort) with limited frequency options have become the norm. However, it only takes one parameter to be sub-optimal for the efficacy of treatment to be significantly reduced.

It is important for therapists to be able to rely on both the scientific basis of a treatment protocol as well as the technology to be able to deliver it safely and effectively to the patient. The aim of this article is to explain how the technological advancements of Interactive Neurostimulation facilitate an evidence-based protocol that optimizes the treatment variables, reduces physiological accommodation, and delivers a consistent and effective solution for the treatment of a broad range of conditions.

Electrical Stimulation Parameters and Pain Relief

The characteristics of electrical currents that are typically manipulated in order to achieve select stimulation of afferent (A-beta, A-delta, C-fiber) and efferent nerves are waveform, amplitude, frequency, and pulse width. Because there is a wide variety of electrical stimulation available for the treatment of acute and chronic musculoskeletal conditions, it is important for clinicians to have clear parameter guidelines for treatment in order to justify interventions using electrical modalities.

Pulse width and amplitude (strength-duration curve) have often been the most widely adjusted parameters in obtaining select stimulation of nerves although changing waveform shape has not been shown to affect pain relief efficacy[12]. It is widely accepted that lower current amplitudes and shorter pulse widths depolarize large sensory nerves (A-Betas); whereas higher current amplitudes or longer pulse widths are needed to include small diameter sensory nerves (A-deltas and C-fibers). Segmental inhibition (gate control) and the release of endogenous opioids (descending inhibition) are the two main mechanisms that have been used to support the use of electrical stimulation for pain relief following stimulation of these nerves.[8,10]

Segmental inhibition suggests that stimulation of large diameter afferents inhibits nocioceptive fiber evoked responses in dorsal horn neurons of the spinal cord.[10] This mechanism of pain relief is usually achieved with a sensory level of

stimulation; however, it is short-lived and once the stimulation input is removed, the pain relieving effect ceases.

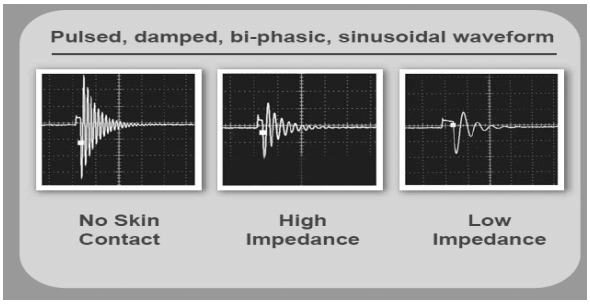
The release of endogenous opiates has also been used to explain the pain relief achieved with electrical neurostimulation and established research supports this effect with both low and high frequency stimulation.[8,10] There are opiate receptors located peripherally, in the spinal cord and areas in the midbrain and brain stem. It is commonly accepted that opiate mediated, descending inhibition produces its effects through activation of the raphe magnus in the rostral ventral medulla and the periaqueductal gray pathway.[10] The stimulation of A-delta or C nerve fibers is necessary for the release of endogenous opiates thus a higher intensity level must be used. The analgesic effects of descending inhibition are expected to last longer and patients may experience pain relief for a number of hours following treatment. However, when using traditional forms of electrical stimulation these higher intensities are often not achievable without significant discomfort to the patient(pain or muscle contraction). Also, steps need to be taken to limit the body's propensity to accommodate to the treatment[11] otherwise any effect gained will be lost after a number of treatments.

Specific protocol recommendations for the waveform, amplitude, frequency (pulse or cycle repetition), or pulse width of stimulation, are often not available from manufacturers. This may be due to the lack of clarity in early research to support specific parameters or because the relevant data with sufficient clarity are only more recently published.[3,4,5,6,7,8] The choice of treatment sites can vary significantly and proper recommendations of ideal sites are limited. Many therapists only treat directly where symptoms present, despite research showing other sites possibly offering superior efficacy[7,15,20.]

What's different about InterX?

Technically, there are differences and advancements in the circuitry of the InterX that mean the stimulation is interactive. Hence, the name Interactive Neurostimulation. This interactivity means that the stimulation responds to changes in the electrical property of the skin and tissue (fig.1). The waveform automatically adjusts as the impedance of the treatment area varies from one point to another as the device is moved or varies as a result of response to the stimulation. This technical advancement facilitates a number of differences in the application of the device which are aimed at optimizing the clinical outcome. Those include, the identification of optimal treatment points and the delivery of a very high amplitude and high density stimulation. The InterX is characterized by an interactive biphasic high amplitude waveform,

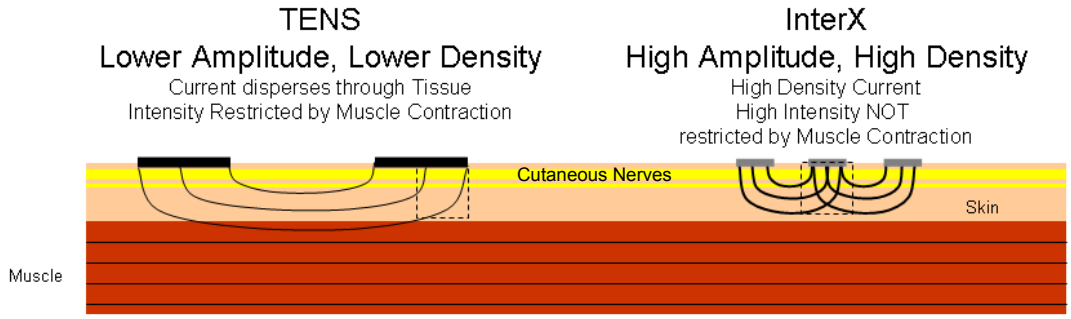
Figure 1: The Interactive Waveform



several different frequency ranges (15-480Hz), and the fixed/focal electrodes with a variety of designs.

The interactive waveform allows for the use of a range of different size and shape of electrodes which provide easy applications virtually anywhere on the body. The Small Classic and Circular electrodes can be used on boney prominences for instance, around the fingers and hands, as well as the face. The Soft Tissue electrode facilitates the delivery of manual soft tissue manipulation at the same time as Interactive Neurostimulation, and the Flexible Array electrodes can be used during therapeutic exercise to help facilitate greater pain free range of motion. The Comb electrode is designed for use in areas where body hair may affect contact with the skin, offering the ability to treat up to the occipital area for patients with neck and pain and over the scalp for patients with facial pain syndromes. All of these electrodes are applied directly to the skin without the need for a conductive medium.

Figure 2. Current Amplitude and Density: TENS compared to InterX



When using a traditional TENS device that does not have that interactivity, there is no feedback loop to the device so the user needs to apply some form of conductive medium and apply the electrodes to a static site to protect the patient from uncomfortable variations in current that are caused as the tissue responds to the stimulation. This application inhibits the way in which TENS can be used, both in terms of identifying optimal treatment points and also delivering sufficient stimulation to have a meaningful effect. Interactive Neurostimulation is a technological progression that dispenses with the need for a conductive medium and subsequently enters into a new realm of treatment applications that serve to optimize clinical efficacy.

The interactive nature of the biphasic waveform allows for the use of different waveforms and amplitudes based on the feedback of skin impedance at the treatment site (fig.1). This along with the fixed/focal electrodes (size < 1 in^2) allow for a customized approach to electrode placement. The therapist can scan a treatment area to identify optimal treatment locations before the stimulation is delivered specifically.

The relatively small and focal electrodes also allow for the delivery of high amplitude and high-density stimulation, which may effectively activate the body's endogenous pain relieving mechanisms without eliciting discomfort. The concomitant use of a broad range of frequencies ensures better pain relief and less propensity for the body to accommodate to treatment[8,11,] thus extending the period for which the treatment can be effective.

InterX Parameters

Electrode Size, Current Intensity/Density

One of the biggest single factors that influence the success of an electrical stimulation treatment is that the intensity of stimulation needs to be high enough to affect the most meaningful response in the targeted nerve[4,5,10]. Many TENS applications will range in amplitude from 10mA to 40mA peak amplitude. Because TENS application requires larger electrodes and inter-electrode distance, the current can and does penetrate deeper and muscle tissue and motor nerves may be depolarized. Muscle contraction can begin at as little as 12mA; therefore, the ability to increase the amplitude further without discomfort is inhibited. Bjordal et al classified high amplitude TENS as anything over 15mA or a strong sensory sensation[4]. Even though the InterX usually stimulates at peak amplitude between 45mA and 60mA on the skin, the small inter-electrode distance and shallow current depth significantly reduce the likelihood of muscle contraction (Fig. 2). When using InterX, muscle contraction may not occur until amplitudes are as high as 70mA.

Because the effect of peak amplitude is related to the current density and area of stimulation[13], a machine that provides a high current density with comfortable amplitudes is important. The ratio of intensity/density used with the InterX is significantly higher than traditional electrical stimulation because of the small focal electrodes. If the stimulation is spread over too large an area the current per square inch is significantly reduced and this may affect the ability to stimulate nerves[13,14]. For instance, if 20mA of stimulation is delivered through a TENS electrode measuring 2 inches by 2 inches, the effective

current density is 5mA/in^2. Calculations based upon use of the small classic electrode of the InterX (for which the inner electrode is 0.22 in^2) indicate that the effective current density at amplitude of 20mA would be 91mA/in^2. In reality, when InterX is used at the correct intensity of a strong but comfortable tingling sensation, the current density would be 205mA/in^2. Therefore, the InterX provides a higher current density as well as increased amplitude. The biphasic and interactive nature (damping) of the waveform of InterX ensures that these current densities feel comfortable to the patient and create no adverse reaction on the skin. Using these current densities with a TENS device that is not interactive would most probably create skin reactions and/or discomfort to the patient. Indeed, manufacturers of TENS often recommend a minimum electrode size to reduce the risk of this.

Frequency

The InterX has a broad range of pulse repetitions available to the user from 15 pulses per second (pps) to 480 pps. There are also three variable pulse repetition presets that sweep the frequency range from a low pps to high pps. During the scan and target parts of the protocol a continuous or burst pattern of either low or high pps is used. For the treatment of points of pain during the dynamic function protocol a variable pps is used. The InterX application ensures that all of the frequency ranges are covered with either a low or high pps combined with a sweeping range from low to high pps in every treatment. Research evidence shows that using different and varying pulse repetitions is more effective for pain relief than restricting the treatment parameters to either low of high pps.[4,7,8,9,11]

The rationale for using varied frequencies is also supported with mechanism studies. Using low pps stimulation has been shown to release endomorphins, beta-endorphins and enkephalins, while high pps stimulation causes the release of dynorphins[8]. With different opiate release being triggered through various pulse repetitions and ranges of frequencies there have been reports of synergistic effects, greater pain relief[9,] and better overall responses[7.] This variability in frequencies can also extend the period of time it takes for physiological accommodation to occur by over 100%[11].

Using InterX

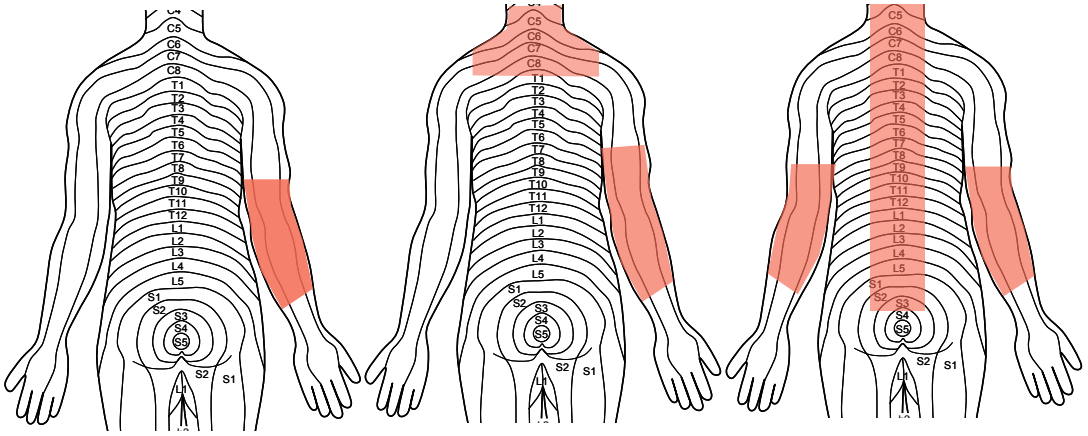
Scanning for Optimal Treat Points with InterX

Interactive Neurostimulation technology allows the therapist to scan an area of skin to identify optimal treatment points, without the need for conductive gel. The InterX waveform is impedance sensitive and is used to identify points or areas of low impedance[1,2] which are optimal points to apply electrical stimulation.[15] The low impedance of the skin is caused by an increase in the galvanic skin response or sympathetic skin response[16,18] and research shows that these points correlate to myofascial trigger points[16], acupuncture points[17] and localized sympathetic changes[18]. Melzack et al[19] compared the spatial distribution and associated pain patterns of trigger points and traditional acupuncture points using body maps compiled by several authors and concluded that there was a high degree of correlation (71%) for both criteria. In essence, these are treatment points which will respond best to electrical stimulation; their locations vary and are unique to each patient. Much like manual therapists scan muscles with their hands before deciding where best to apply pressure based upon finding trigger points and adhesions, an InterX therapist identifies the most responsive cutaneous nerves based upon relative skin impedance differences.

This scanning methodology ensures patient specific, multiple and varied treatment locations to elicit the most effective pain relief. Melzack[20] showed that treating major nerve branches, trigger points, and secondary areas on the dermatome, in addition to the area of pain, with high amplitude stimulation provided the most effective and sustained pain relief as opposed to lower amplitude treatment delivered only to the point of pain. Scanning for and then targeting areas of low impedance with InterX stimulation as well as points of pain ensures all of these aspects are included in an InterX protocol. This follows a scientific basis for the selection of optimal treatment points.

There are two ways in which the InterX can be used to scan the treatment area. a)Optimal treatment points can be identified by sliding the electrodes over the skin until a dragging sensation or increased friction is felt. The increased sympathetic skin response at these

Figure 3. Recommended InterX scanning sites for elbow pain, depending on etiology



Acute Chronic Complex Chronic/ Neuropathic

localized points increases the moisture and hydration of the skin[16,18]. This causes the electrode to drag more over the skin due to the increased friction co-efficient[21]. b) A numerical feedback on the screen of the device also gives objective feedback to the user of the effect that skin impedance has had on the waveform[1]. Lower impedance alters the waveform (widens pulse width and damps amplitude) and this generates higher numbers on the screen. To use the numerical feedback the operator places the device at adjoining locations on the skin and is able to measure where skin impedance is lower relative to surrounding areas. This scanning process applies to all the InterX handheld electrode applications.

When using the Flexible Array electrodes which cover a larger area of the skin and are fixed to the body using straps, the stimulation is automatically delivered to areas of lower impedance under the electrode. As the interactive stimulation does not need any conductive gel to safely deliver the stimulation and the arrays have both positive and negative electrodes in series, the stimulation follows Ohms Law and is delivered to areas or points of lower resistance or impedance as previously described. Thus, even with a static electrode position with the flexible array, the stimulation remains dynamic and interactive, continually adjusting to alterations in the sympathetic skin response to both pain and the stimulation itself.

The ability to identify exactly where best to apply the stimulation is crucial to ensure that the physiological response to the treatment is optimized.[7,20,22]. Melzack demonstrated a statistical significance in the pain relief achieved on positive (responsive) treatment points compared to negative (non-responsive) treatment points in patients with chronic pain. The areas scanned during an InterX treatment may vary depending on patient response but may include the direct area of injury or pain, the related dermatome, the whole spine, nerve branches on the face and even over the scalp using the comb electrode. Treating at various locations has been demonstrated to be the most effective for the treatment of neuropathic pain in humans[7]. These locations may include areas ipsilateral or contralateral to the area as pain as well as the corresponding spine root. InterX protocols recommend that for treatment of acute conditions the direct and surrounding tissue area should be scanned. For treatment of chronic conditions the direct area and spine root should be scanned. For complex chronic conditions the areas to be scanned should include the direct area, the corresponding contralateral area and dermatome, the whole spine and even the face (fig. 3). These areas may vary depending on how a patient responds but these guidelines are a good starting point in most cases. The various electrodes allow the user to easily access all of these areas if the treatment protocol requires.

Targeting Stimulation with InterX

After optimal treatment points have been identified, these points are stimulated with a specific, interactive, high amplitude and high density current. InterX electrodes are small and closely spaced so the current is only delivered to the cutaneous nerves. The InterX should not cause muscle contractions which could be painful to the patient and restrict the amplitude that can be used. High amplitude and high density current effectively recruits the nerve endings and the interactive, constantly changing waveform ensures nerves receive a continually changing stimulation. A-beta, A-delta and possibly small diameter C fibers can be stimulated by the InterX in this way, which evidence suggests would efficiently and consistently activate a number of pain relieving mechanisms[10]. Treating at higher intensities has been shown to cause greater

inhibition[23] and therefore pain relief and using various frequencies has been shown to release different endogenous opiates[8] which also enhances the effect of the treatment.[9]

When the electrodes are in contact with the skin, the InterX automatically adjusts the waveform in response to changes in skin impedance. This both protects the skin of the patient and offers feedback to the user. The stimulation is targeted for between six and sixty seconds and this timing is determined by how quickly the impedance of the skin responds to the stimulation. Generally, the quicker changes occur, the shorter the duration of a point treatment (point-stim). The InterX notifies the therapist by way of numeric and audible feedback when the point-stim is complete.

Dynamic Function with InterX

Acute and chronic pain present as common problems in the clinical setting and inhibits the ability of patients to restore function and performance. Pain is often a guide as to when to stop using a motion. However, if motions are ceased then permanent deficits in motion and strength may result (e.g., frozen shoulder). Electrical modalities are therapeutic interventions and can be core elements in a rehabilitation plan; however, the best plans use both an electrical modality and active exercise to stimulate healing.

Exercises are usually difficult during electrical stimulation treatments unless a portable TENS unit is being used. However, even with a portable TENS unit the preset electrical stimulation treatment may become ineffective as the skin's impedance changes due to muscle activity and sweating. If the impedance increases, the electrical stimulation may not penetrate and if the impedance decreases, the electrical stimulation may become uncomfortable. Researchers have demonstrated that skin impedance does change in response to joint strain during exercises[24]; therefore, to optimize treatment of pain during exercises the electrical stimulation should be interactive. Because the InterX alters its waveform and amplitude in response to the changes in skin impedance, a patient may experience better pain relief and be able to perform exercises with greater ease and quality without the risks of discomfort.

The InterX allows for active engagement during electrical stimulation via dynamic techniques. Therapists are encouraged to apply passive or active techniques including stretches, muscle contractions, and resistive exercises while using the InterX to treat points of pain, tightness or restriction. The electrode placement during the dynamic technique should be based on patient feedback. The goal is to use the InterX to help facilitate greater pain free range of motion so targeting the stimulation wherever the patient is felling tightness, restriction or pain is preferred. Therapists can determine which motions are needed to improve function and which of these motions elicit pain. Then they can target a treatment area for 30 seconds at a time while the patient repeats the painful motion. This dynamic part of the protocol should last 5-10 minutes in total but can be longer if required by the functional rehabilitation program. The therapist can determine any advances in exercise and different positions for electrical stimulation. Clinical judgment should always be used to determine if an exercise program is appropriate.

Evidence on Pain Relief Mechanisms Relating to InterX

There are a complex set of mechanisms that may be activated by the InterX depending on how and where it is applied and more research is warranted to understand how these mechanisms interact and how best to elicit them. However, it is clear that there are both immediate and cumulative benefits to using InterX Therapy for patients with both chronic and acute pain.

There is no doubt that InterX activates the segmental inhibition (gate control) mechanism, as it provides a sensory input to the patient[10]. However, the often sustained and cumulative reductions in pain reported by patients receiving InterX indicate that this is not the primary mechanism of pain relief.[1,2,3]

More recently, studies have looked at some of the centrally mediated mechanisms relating to strong stimulation of specific points along neural pathways. These points are described as nerve points, trigger points, motor points, acupuncture points and homeostatic points in various literatures. Acupuncture points and trigger points have been described in the literature as having a low impedance characteristic[16,17]. The InterX is

used to identify areas of low impedance before delivering the stimulation with a high level of specificity. It is suggested that the specificity of InterX protocols takes into account these points described in the literature and the mechanisms related to the stimulation of them.

Han[8] found that stimulating specific points at high amplitude and low frequency was required for the most meaningful patient response. Using functional MRI (fMRI) studies, the stimulation described by Han has been shown to affect the hypothalamic-pituitary-adrenal axis and limbic areas[25]. Stimulation of the hypothalamus regulates hormonal control while activation of autonomic nervous system maintains homeostatic balance. This is a growing area of research and fMRI studies offer a much better insight into the centrally mediated mechanisms than has previously been available to both researchers and clinicians alike. A greater understanding of these mechanisms and the applications that most effectively activate them will undoubtedly expand the indications for InterX Therapy while also optimizing patient outcomes for current indications.

More recently, the metabolic response of white blood cells to activation following InterX treatment has been investigated. White blood cells metabolize at a higher rate in injury or disease processes[26], so increasing their ability to respond would be favorable. Following InterX treatment, lymphocytes responded to activation with an oxidative metabolism 476% higher than the pre-treatment control cells[27]. Genomic assays also showed up-regulation of proteins such as Adenonisine Tri-phosphate (ATP) and Lysyl Oxidase-like-4 (LOXL-4), both of which relate to the body's pro-inflammatory healing mechanisms. Conversely, down regulation of proteins which promote cell adhesion may indicate an anti-inflammatory effect. A clinical trial using InterX for the treatment of pain following ankle surgery demonstrated reduced edema when compared to placebo treatment ($p<0.001$) which suggests that while both pro and anti-inflammatory physiological mechanisms may be activated, the net effect is reduced edema in patients.[3]

Conclusion

The application of InterX and the protocols of InterX Therapy are very much driven by the technological advances that the device offers. The internal circuitry, the fixed electrodes and the high amplitude/density, interactive waveform all combine to allow the user to safely and effectively stimulate multiple, customized and patient specific points with a high amplitude stimulus that automatically adjusts in response to the reactions of the nerves and skin.

Experience with other techniques such as manual therapy and therapeutic exercise demonstrate the value to the therapist for a patient specific protocol to optimize outcomes and this approach is very evident in the InterX Therapy methodologies of Scan, Target and Dynamic. Any therapist using the InterX needs to ensure that device is applied efficiently for every patient. This approach is the best way to begin a treatment program but decisions can be made thereafter depending on how a patient responds. If a patient is slow to respond to the treatment then evidence-based choices may include changing the treatment area[7,20,22], ensuring the intensity is high enough[10,20,21], using a greater variety of frequencies[7,9,11]or a combination of all of the above. Every patient is unique and as such a customized approach is strongly encouraged.

If the individual variables of neurostimulation treatment can be optimized, the pain relief achieved can be more consistent across a broader patient population. With a scientific, evidence-based approach to electrode placement, amplitude selection and stimulation frequency the InterX plays an important role in consolidating many of the applications that have been shown to be most effective for the treatment of pain. In the modern era of physical therapy with advanced manual therapy techniques and new technologies the InterX offers a treatment protocol that can help facilitate a rehabilitation program without the inhibition of pain.

Further research should be explored to fully understand the complexities of Interactive Neurostimulation and how various protocols may elicit specific mechanisms. However, the current recommended InterX protocols of scan, target and dynamic can be confidently delivered as a safe, effective and evidence-based methodology that optimizes treatment parameters to deliver pain relief in humans for a broad range of conditions.

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