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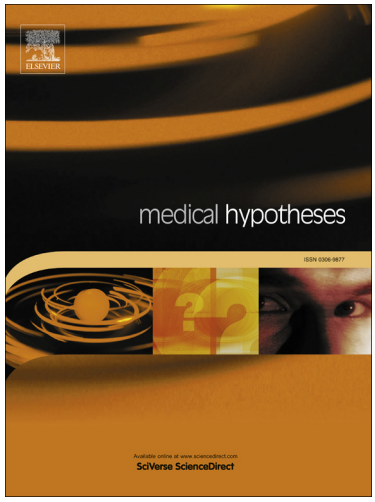

On the Origin of Pain – The 'Pain Channel' Hypothesis

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ABSTRACT

Theories of pain have traditionally attributed the sensory experience of pain to the brain. We present here a new hypothesis on the origin of pain which is based on a novel approach to the management of persistent pain. We call it the 'pain channel' hypothesis of the origin of pain. There are key components to the development of our hypothesis: (1) Our clinical outcome of a persistently pain-free state, representing a maintained pain score of 0/10 has been achieved in a growing cohort of various presentations of persistent pain now exceeding 130 patients over the course of the last five years. With complete control of pain, the patients rapidly return to their premorbid state and level of function. This result requires careful consideration and explanation. (2) Regional anaesthesia has been used as a diagnostic tool to confirm the clinically suspected source of the persistent pain. The pharmacodynamics of local anaesthetics identify the sodium channel of the primary nociceptive sensory neuron as the critical subcellular structure generating pain. (3) Sodium channel function has been recognised as a bioelectromagnetic phenomenon. (4) Neuromodulation has been used to provide our long-term pain relief result. We understand the neuromodulation unit as producing an electromagnetic field within the super low wavelength range of the electromagnetic spectrum and we have devised a strategy which we believe delivers maximal electromagnetic field effect to the intended sodium channels to create a long-term conduction block.

We believe that our clinical outcome challenges the current understanding of the role of the brain in pain. We hypothesise that pain is a peripheral phenomenon rather than being a construct of the brain, as our strategy is peripherally based and completely reverses the presenting clinical profile of persistent pain. More specifically we hypothesise that the sensory phenomenon of pain is a function of specific sodium channels which are coded for pain and which are part of the subcellular structure of peripheral nociceptive sensory nerves.

We believe that these hypotheses can lead to a change in focus in the diagnosis and management of pain and drive improvement in current technology and medications to facilitate effective treatment of persistent pain.

INTRODUCTION

Theories of pain date back to ancient times and share an understanding that pain is a phenomenon of the brain (1-3). In more recent times the contributions of psychological and emotional factors to the pain experience have been emphasised (2,3), becoming key factors in the development of the biopsychosocial approach for managing persistent pain (3).

This paper presents a new hypothesis on the origin of pain based on a novel approach to the management of persistent pain and which achieves its effect in the peripheral nervous system. We have been using and refining this approach over the last 5 years with a growing cohort of persistent pain patients now in excess of 130. The cohort includes patients with a wide variety of presentations, including low back pain, whiplash syndrome, cervicogenic headache, chronic post-surgical pain, facial pain, radicular pain, neuroma pain, vertebral crush fracture, thoracic back pain, phantom limb pain, pelvic pain, visceral pain and cancer survivor pain (table 1). They range in age from 14–100 years and in weight from 45–150 kg (table 2). The key outcome and defining feature of our approach is that the pain with which the patient presented is now completely controlled with a pain score = 0/10. As a direct consequence of being pain-free, they no longer require analgesic medications and have been able to re-engage in their lives. We believe this result is unique and requires explanation.

Our approach originated with the successful treatment of a patient suffering from phantom limb pain (4,5). Central to that treatment strategy was the observation that peripheral nerve block completely controlled phantom limb pain for the duration of the block. This observation was important as phantom limb pain had been regarded as a phenomenon of the brain (6) and therefore not amenable to peripherally based strategies. Our question at the time was how to make the analgesic effect of the nerve block last indefinitely and one which we answered using neuromodulation. In association with that therapeutic result we observed a complete reversal of the patient's psychosocial profile and pondered whether the pain had driven the profile.

Our approach draws from a standard medical paradigm (history, physical examination, diagnostic investigation, treatment), supported by a nursing model (patient education; assessment of compliance issues for prescribed care; wound care; neuromodulation programme design; follow-up), and grounded in neuroscience, pharmacology, applied anatomy, physics and mathematics. This model of care differs from the standard pain medicine multidisciplinary approach to the management of persistent pain, derived in large part from Loeser's model (3), which promotes the management of psychosocial factors to improve functional abilities with an acceptance that pain relief is not routinely and consistently achievable and is therefore not the goal.

Our initial goal with patients has been to 'source the pain'. This has evolved from our observation that whilst patients struggle to describe the quality of their pain, they are usually able to indicate the location of their pain. During the taking of the patient's history and physical examination we seek to answer the following questions. Where is the pain? Where does it originate? Where does it radiate? Is there a recognisable pattern? What is the innervation of that structure or region of the body? Which nerve/s is/are involved? The answers to these questions generate an hypothesis of source of pain, e.g., sacroiliac joint dysfunction, cervical facet joint dysfunction, iliohypogastric nerve neurapraxia.

We then use regional anaesthesia to confirm the hypothesised source of pain by blocking its sensory supply, the principle being to accurately and specifically identify the involved peripheral nociceptive pathway. This may involve specific nerve blocks, e.g., the medial branches of the dorsal rami to investigate facet joint dysfunction, or the lateral sacral branches of the sacral nerve roots to investigate sacroiliac joint dysfunction, or nerve root/s to investigate radicular pain. It may also involve blocking nerves more peripherally to identify/confirm the involved area, e.g., rectus sheath block to identify an entrapment neuropathy of the abdominal wall, followed by more specific blocks to identify the actual nerve roots involved (table 3).

Achievement of complete control of pain with a pain score of 0/10, usually for a time period of 24 hours, is accepted as confirmation of source of pain.

This short-term diagnostic result is then converted to long-term complete control of pain with the electronic technology of neuromodulation (table 4, figure 1). Our model for understanding and using this technology is explained in detail later.

The absence of presenting symptoms post-treatment in our persistent pain cohort, combined with the peripheral site of diagnosis and therapy, have led us to conclude that pain must be a peripheral phenomenon. Given the known site of action of local anaesthetic medication and our model for the site of action of neuromodulation, we have concluded that this common site identifies the source of pain and hence generates our hypothesis.

We hypothesise that the sensory phenomenon of pain is a function of the specific sodium channels which are coded for pain and which are part of the subcellular structure of peripheral nociceptive sensory nerves. Furthermore, we hypothesise that pain is a peripheral phenomenon rather than being a construct of the brain.

We aim first to comprehensively review the scientific basis of neural conduction since this forms the foundation stone of our hypothesis. We then briefly discuss the phenomenon of sodium channelopathy, i.e. dysfunction of the sodium channel, and its potential relationship to persistent pain. We review the pharmacodynamics of local anaesthetic drugs as they relate to the sodium channel in peripheral nociceptive nerves.

We then revisit the scientific basis of neuromodulation, describe our understanding of its mechanism of action and our mode of application of this technology.

We then describe how we link neural conduction, regional anaesthesia and neuromodulation to achieve our clinical outcome.

Finally, we discuss how we intend to investigate our hypothesis using electrophysiological techniques, functional magnetic resonance imaging and a randomised controlled trial of

implanted patients. We also pose a number of questions related to the role of the brain in pain which arise from our unique perspective of observing patients who now have complete control over their persistent pain.

DISCUSSION

The Scientific Basis of Neural Conduction

Conduction occurs along an axon by voltage-dependent alterations in membrane conductance of sodium channels. The channels are closed and inactive at rest but undergo structural changes in response to depolarisation, leading to cycling of the channels through activated, inactivated and repriming states (7). These processes apply to all axons, including those which conduct noxious stimuli such as pain, and without which there is no sensory experience of pain (8).

The genetics, structure and function of the sodium channel have previously been described in great detail (9-13). The sodium channel is composed of alpha and beta subunits, embedded as heterodimeric and heterotrimeric complexes of either 1x alpha and 1x beta, or 1x alpha and 2x beta units in the lipid membrane of the neuronal cell wall (9). There are 9 isoforms of the alpha subunits in humans, designated $Na_v1.1$ - $Na_v1.9$ (10). They are encoded by the genes SCN1A-SCN5A and SCN8A-SCN11A (11), with those for Nav1.1, Nav1.2, Nav1.3 and Nav1.7 at chromosomal locations 2q24, 2q23-24, and 2q24 respectively, for Nav1.6 at chromosomal location 12q3, and those for Nav1.5, Nav1.8 and Nav1.9 at chromosomal locations 3p21, 3p22-24 and 3p21-24 respectively (9). The sodium channel isoforms encoded from the same chromosome share similarities in sequence, biophysical characteristics, and expression in neurons. $Na_v1.7$, 1.8 and 1.9 are preferentially expressed in the peripheral nervous system (11). These different channels play multiple roles in electrogenesis in both the central and peripheral nervous systems (12), somatic (13) and visceral (14) structures, and throughout the primary nociceptive neuron up to and including the intra-epidermal nerve terminals (15,16). $Na_v1.7$

exhibits slow closed-state inactivation and activation in response to small slow depolarisations close to resting potential so as to produce its own depolarisation, thereby having the capability of amplifying inputs such as generator potentials and setting the gain on nociceptors (12). $Na_v1.8$ is relatively resistant to inactivation by depolarisation and recovers rapidly from inactivation, and thus produces repetitive firing in depolarised neurons (12). $Na_v1.9$ is characterised by very slow activation and inactivation with a large overlap centred near resting potential and contributes a sodium conductance at rest that modulates the excitability of neurons (12). Under non-pathological conditions the firing properties of nociceptors, like those of most neurons, are maintained within a circumscribed range (12), at least in part a function of homeostatic regulation of ion channel expression, post-translational modification, and interactions with binding partners or modulators. Observations of neuronal activity lead to the conclusion that there is molecular and functional remodelling of neurons, whereby these cells selectively activate specific ion channel genes and deploy functional channels to maintain homeostatic tuning of the sodium channels (12).

The alpha subunit is a protein with approximately 2000 amino acids in its peptide chain (9,10). The alpha subunit chain folds into 4 domains (I-IV), with each domain consisting of 6 transmembrane segments (S1-S6), each coil length approximately the width of the membrane (9,13) (figure 2). The nonpolar sidechains of each coil length face outward where they readily interact with the lipids of the membrane, and the polar peptide bonds of each coil length face inward. A central pore is created at the extracellular end by the re-entrant loop between the S5 and S6 segments of each of the 4 domains (9,10,13). This re-entrant loop is embedded into the transmembrane region of the channel to form the narrow, *ion-selective filter* (9,10,13). One residue in this re-entrant loop (Asp/Glu/Lys/Ala: the DEKA residue) determines ion selectivity (10). The surfaces above the selective filter contain multiple negatively charged residues on the S5 and S6 loops which act as a shield to exclude anions (10,13). S6 segments of each of

the 4 domains, arranged as a tetrahelix, form the inner lining of the pore as well as the wider intracellular end of the *central pore* (9,13). The S1 to S4 segments form a *voltage-sensing domain* (9,13). The S4 transmembrane segments contain 4-8 repeated motifs of a positively charged amino acid residue, proposed to carry the gating charges in the sliding helix model of voltage sensing (9,13). The four voltage-sensing domains have different numbers of gating-charge residues and are symmetrically associated with the outer rim of the pore module, although each is most closely associated with the pore-forming module of its neighbour, an arrangement believed to facilitate coordinated functioning of all pores (9,13). The short intracellular loop connecting domains III and IV of the alpha subunit contains the key hydrophobic sequence (Ile-Phe-Met: the IFM motif) (9,13) which, in combination with polar residues in 3 other areas - the carboxyl-terminal domain, the voltage-sensing domain, and adjacent transmembrane segments of the channel (10) - form the *inactivation mechanism*.

The alpha subunit is believed to function as follows; with voltage sensing and subsequent activation in the S4 segments there is an outward movement of the S4 segment (9,13). Sodium conductance then increases with ionic movement through the selective filter, facilitated by a conformational rearrangement by the S6 tetrahelical bundle (9,13). Inactivation of the channel occurs when the short intracellular loop connecting domains III and IV of the alpha subunit bends at a key pair of glycine residues and folds into the pore and blocks it (9,13). Inactivation is coupled to activation (17).

The previous paragraph describes a predominantly mechanical model of alpha subunit functioning. In the final paper of their 1952 series (18), Hodgkin and Huxley suggested that ionic permeability changes due to alterations in membrane potential arose ‘from the effect of the electric field on the distribution or orientation of molecules with a charge or dipole moment’ within the membrane. This was a prescient observation. Molecules with those properties within the structure of the alpha subunit include amino acids with polar properties (19), charged

amino acid residues in key functional positions (9) and strings of connected dipoles (19) lining the central channel. The observation by Hodgkin and Huxley is therefore a forerunner to ultimately understanding alpha subunit activation and deactivation as bioelectromagnetic events (20), functioning according to the principles of Maxwell's equations (21).

The beta subunits have a single transmembrane segment, and their role seems to be in localisation and immobilization of sodium channels in specific locations (9-13,22).

Sodium Channel Dysfunction

Sodium channel dysfunction is a well-recognised phenomenon, and there is a growing body of evidence showing that sodium channelopathies play at least some role in the development of persistent pain states (11,22-29), especially related to the $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ channels. Inherited erythromelalgia was the first human pain disorder known to be produced by sodium channels, specifically a gain-of-function mutation of the $Na_v1.7$ isoform (23). $Na_v1.3$ is up-regulated within primary sensory neurons following peripheral nerve injury and displays three properties which can contribute to primary sensory neuron hyperexcitability: small ramp-like inputs, rapid recovery from inactivation, and production of a significant persistent current. $Na_v1.7$ and $Na_v1.8$ can interact to produce subthreshold membrane potential oscillations that can trigger ectopic repetitive firing in nociceptors. $Na_v1.3$, $Na_v1.7$ and $Na_v1.8$ channels have been shown to accumulate in neuromas, and $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ contribute to inflammation-induced pain (22). In the neuroma model, voltage-sensitive sodium channels have been demonstrated to be the fundamental entity responsible for the abnormal electrical activity (29). $Na_v1.6$ gain-of-function mutations have been reported in trigeminal neuralgia (11).

The Pharmacodynamics of Local Anaesthetic Drugs.

Local anaesthetic drugs produce their neural conduction block by inactivating the sodium channel. This involves several mechanisms. They stabilise the S4 in domain III in an outward, depolarised position and partially stabilise the S4 in domain IV which increases the binding affinity of local anaesthetic in the sodium channel and thereby impede the activation mechanism (30). They also bind to amino acid residues lining the inner surface of the S6 segments in domains I, III and IV, and impede ion penetration. These residues can be accessed in both the activated state of the channel through the central pore (31), and also in the inactivated state via side-fenestrations in the channel (9,23). Finally, they act as allosteric effectors of sodium channel inactivation, i.e., when they bind to residues on the inner pore of the channel, they facilitate inactivation (32).

In the context of our work, we term the actions of local anaesthetic drugs on the sodium channel short-term chemical conduction block.

Neuromodulation – Physics & Mechanism of Action

A neuromodulation unit consists of a battery and connected wires which are sheathed by a protective covering to form a lead, with each wire attached to its own electrode in an array at the end of the lead. The predominant use of neuromodulation for analgesia, known as dorsal column stimulation (33), has the electrode array placed in the epidural space and was pioneered by the neurosurgeon Dr Norman Shealy and his colleagues in the 1960's (34-37). More recently the electrode array has been placed in the subcutaneous tissues 'within the area of pain', a technique known as peripheral nerve field stimulation (38). The mechanism of action for both of these techniques is more often explained by reference to the 'gate control' theory of Melzack and Wall (2). In this scenario electric current from the neuromodulation unit stimulates large non-nociceptive sensory fibres, which subsequently inhibit small nociceptive fibres through

interconnections within the substantia gelatinosa of the dorsal horn of the spinal cord and thereby modulate the afferent nociceptive signal to the brain. However, there are two reasons why this mechanism of action is unlikely to be correct – firstly, experimental evidence for such an effect between these sensory fibre types was lacking (39); secondly, the electrical output of the neuromodulation unit is not in the form of an electric current.

A neuromodulation unit produces a digital pulsatile waveform with a square wave configuration (figure 3). Effectually this means that there is an intermittent voltage difference applied across the electrode array rather than an electric current. A time-varying voltage difference across the electrode array is a source of time-varying electric and magnetic fields, the inter-relationship between these being described by electromagnetic theory (figure 4; 40) and expressed mathematically by Maxwell's equations (figure 5). In theoretical terms, an electromagnetic field transmits at the speed of light, affects the behaviour of charged objects in the vicinity of the field and extends indefinitely throughout space in a vacuum (40). Within the human body, an electromagnetic field transmits by volume conduction (41).

The application of electromagnetic theory already has an established place in medical practice, albeit as a diagnostic rather than a therapeutic tool, e.g. it forms the theoretical basis of electrocardiography (42-46). At a frequency of 50 Hz, the neuromodulation unit transmits within the super low wavelength range of the electromagnetic spectrum (figure 6). This can be seen on an oscilloscope (figure 3) or observed as interference on a concurrently run electrocardiogram.

Various investigators have utilised intermittent voltage differences applied across an electrode array in neurophysiological models. Eccles et al. (47) demonstrated depressed excitatory action in presynaptic afferents, while da Costa et al (48) and Bhadra and Kilgore (49) demonstrated deactivation of sodium channels in an axonal model. Kent et al (50) demonstrated suppression of afferent neuronal activity in a dorsal root ganglion model. With the exception of Da Costa

et al (48), the concept of intermittent voltage differences producing an electromagnetic field was not considered.

We suggest therefore that neuromodulation produces analgesic effects by deactivating sodium channels in nociceptive sensory axons through the effect of an applied electromagnetic field. In the context of our work we call this effect long-term electronic conduction block.

Mathematical Modelling of Neuromodulation for Analgesic Effect

In our cohort a pain-free state has been achieved by applying the following mathematical model to the use of neuromodulation. In producing an electromagnetic field, the electrode array of the neuromodulation unit is a transmitting antenna. In antenna theory, a Cartesian co-ordinate system is used to describe array position (51) and radiation pattern (52). For our use, this is adapted to anatomic correlates which are referenced to the neural target: 'x' – medial/lateral positioning of the electrode array relative to the neural target, 'y' – cephalad/caudad positioning of the electrode array relative to the neural target, and 'z' – the depth of the electrode array from the skin surface. The imaging modalities of fluoroscopy and ultrasound facilitate this process, with standard antero-posterior fluoroscopic imaging providing 'x' and 'y' co-ordinates and ultrasound imaging providing the 'z' co-ordinate.

The 'x' and 'y' coordinates are used to position the array such that 'x' = 'y' = 0 (prone position; array overlying neural target). This places the array at the centre of a radiating electromagnetic field with the neural target at radius 'r' to deliver maximal field effect to the target (figure 7:1-3). Electromagnetic energy is then titrated until a pain-free state is attained (figure 7:4).

The ‘z’ Coordinate & Achievement of Tolerance to Electrical Energy

We have found a critical depth for positioning the electrode array corresponding to the junction between the hypodermis and the dermis. At this depth the energy required to achieve maximal analgesic effect is minimised which enables greater tolerance of the neuromodulation unit’s electrical energy output (53-55). This critical depth forms the ‘z’ co-ordinate. This positioning is also as close as possible to the stratum corneum (56-58) without causing unpleasant sensations such as occur with intradermal placement of the array (38). The skin layers are associated with electromagnetic scatter, in particular backward scatter at the stratum corneum (59). Scatter occurs when the emitted field is forced to deviate from its straight trajectory by the medium through which it is passing (60,61) and occurs throughout the electromagnetic spectrum. We believe that the stratum corneum, due to its unique electrical and electromagnetic properties (56-59) may act rather like a paraboloid reflector and hence increase directivity of the radiating electromagnetic field (51). This positioning also ensures the neural target lies within the far field or Fraunhofer region of the antenna (52), the area of the electromagnetic field associated with a stable field pattern and which we believe is likely important to stability of field effect on the sodium channel.

Linking Blocks - The Applied Anatomy of the Nociceptive Primary Sensory Neuron

In this section, we discuss linking short-term chemical conduction block for diagnostic purposes with long-term electronic block for therapeutic purposes. The sodium channel as the targeted subcellular element is a component of the nociceptive primary sensory neuron (62) which extends from the dorsal horn of the spinal cord through the dorsal rootlets, dorsal root ganglion, nerve root, dorsal and ventral rami, plexus, peripheral nerve trunk, sensory branches, to the peripheral nerve ending. In theory this provides multiple sites and opportunities for effecting the required conduction blocks. However, the point targeted for conduction block

along this neural pathway must comply with certain criteria - specificity within neuroanatomic organisational principles, accessibility for application of both short-term chemical and long-term electronic conduction blocks, and stability of site for implantation of the electrode array. As an example of this process, the specificity of segmental organisation is utilised for pain of somatic origin, the nerve root being the fundamental identifier at single sensory level of an involved nociceptive primary sensory neuron. Sensory nerves such as the medial branches of the dorsal rami of the spinal nerves or the lateral sacral branches provide specificity, selectivity and simplicity, and are targeted for the diagnosis of facet joint dysfunction or sacroiliac joint dysfunction respectively. For other sources of pain of musculoskeletal or nerve origin, identifying the involved ventral root/s is the ultimate goal, as the segmental organisation at this point of the neural pathway provides specificity and simplicity. It may however be necessary to initially block more distally to clarify a source of pain, e.g., rectus sheath block in the setting of abdominal pain, which can distinguish between an abdominal wall and intra-abdominal source of pain. It is then necessary to identify the specific spinal nerves involved in the pathway. Accessibility to the nerve root is achievable posteriorly at the point of its emergence from the intervertebral foramen, where there is no interference by bone for either passage of a needle or transmission of the electromagnetic field (63). The subcutaneous tissues of the back provide stability of site to minimise movement of the array during the healing phase and hence prevent lead migration. Using this approach neural targets from C2-S4 have been identified using short-term chemical block, and then long-term electronic block has been applied to the same site for long-term therapeutic effect.

Behavioural Science.

Programming of the electrode array has dual aspects. On one hand there is the technical aspect including determination of cathodic or anodic pattern specific to the individual, variation in

duration of pulse, frequency of pulse delivery, and amount of energy delivered per pulse. On the other hand, there is the unit-patient interface. This is of particular importance in maximising efficacy and minimising intolerance of the electromagnetic field source. It requires physical and cognitive ability, cooperation, understanding and a willingness of the patient to manipulate the programs and to interact with the equipment, as opposed to a 'set and forget' approach as is employed with a cardiac pacemaker for example. Engagement of the patient and their carers for self-management is a key factor in success of this therapy, as is recognised in other positive treatment outcomes (64,65).

Complete control of persistent pain in a sustained fashion provides a unique opportunity to observe the individual without pain. The desire to re-engage with life is universally present, as is the desire to discontinue analgesic and anti-neuropathic medications. Mental health improves simultaneously with relief from pain and with regeneration of hope, a phenomenon which has been noted previously (67). Indeed, the recovery of emotional stability with relief of pain is so marked that we have concluded that pain is not an emotional experience per se but rather that it provokes an emotional response. In brief, stopping the pain stops the response.

Summary

The primary aim in this paper has been to propose the hypothesis that the sensory phenomenon of pain comes from the specific sodium channels which are coded for pain and which are part of the subcellular structure of the nociceptive primary sensory neuron. This hypothesis derives from our work in persistent pain and we refer to it as the 'pain channel' hypothesis of the origin of pain. Our large and growing cohort of persistently pain-free patients from a wide spectrum of presentations represents a unique and important outcome and requires explanation. Regional anaesthesia has been used to confirm the source of the persistent pain which has been deduced from the history and physical examination. The pharmacodynamics of local anaesthetics

identify the sodium channel of the primary nociceptive sensory neuron as the critical subcellular structure generating pain. Sodium channel function has been recognised as a bioelectromagnetic phenomenon and susceptible to the influence of an applied electromagnetic field. The mechanism of action of neuromodulation has been explained by reference to electromagnetic theory. To our knowledge this has not previously been considered. Principles of applied anatomy underlie determination of the site for coordinating the short and long-term conduction blocks. Mathematical modelling lends precision to the process of placing the electrode array. The linking of short-term chemical and long-term electronic conduction blocks takes advantage of their commonality of site of action to reproduce the initial short-term pain relief on a long-term basis. In this context neuromodulation can be viewed as electronic local anaesthetic. The above process differs from that employed in peripheral nerve field stimulation (38), a difference we believe is reflected in our clinical outcome.

Others have identified the sodium channel of the nociceptive primary sensory neuron as a potential target in the management of persistent pain using pharmacological and gene-based strategies (11,22,66), but no one else to date has achieved complete and sustained relief of pain across such varied presentations. This would infer that the applied electromagnetic field has been effective in spite of differences in isoform or phenotype. Variations in programming of the electrode configuration may however reflect those differences.

Our hypothesis contrasts with the traditionally held view that pain is a phenomenon of the brain, a view which has been supported by studies demonstrating apparent changes in central nervous system morphology in chronic pain states (6,68,69). A peripherally based strategy such as ours should therefore be ineffective but this has proven not to be the case and indeed, the rapid return to normal function with relief of pain in our patients suggests that no permanent central nervous system changes have occurred at all.

Our hypothesis also suggests a different organisation of pain mechanisms, which we believe may be supported by two classic neuroanatomic studies. The studies by Rexed (70) and Szentagothai (71) suggested at least some degree of separation between the peripheries and the brain at spinal cord level, a separation which probably formed the anatomic basis for spinal cord-mediated reflex functions such as withdrawal from a painful stimulus. We suggest that this points towards two levels of neurological function – spinal and supraspinal, the former with a largely reactionary/reflexive function and the latter coordinating multiple physiological, sensory and emotional responses to the painful stimulus.

Concluding Remarks.

Our hypothesis provides fertile ground for ongoing research and investigation. We intend to conduct neurophysiological measurements in the affected nociceptive sensory afferents, investigate implanted patients using functional magnetic resonance imaging of the brain, and investigate the role of placebo. Notwithstanding these further research activities, our clinical outcomes point to a successful strategy for many patients with persistent pain.

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REFERENCES

1. Moayedi M, Davis KD. Theories of pain: from specificity to gate control. *J Neurophysiol.* 2013;109:5-12.
2. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971-978.
3. Loeser JD. Concepts of pain. In: *Chronic Low Back Pain*, Edited by Stanton-Hicks M. Boaz R: Raven, 1982, p. 146.
4. Cornish P, Wall C. Successful peripheral neuromodulation for phantom limb pain. *Pain Med.* 2015;16:761-764.
5. Cornish PB. Successful peripheral neuromodulation for phantom limb pain: an update. *Pain Med.* 2016;17:991.
6. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 1995;375:482-4.
7. Hille B. *Ion channels of excitable membranes*, 3rd edition. Sunderland: Sinauer, 2001.
8. Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, Karbani G, Jafri H, Mannan J, Raashid Y, Al-Gazali L, Hamamy H, Valente EM, Gorman S, Williams R, McHale DP, Wood JN, Gribble FM, Woods CG. An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 2006;444:894-898.
9. Catterall WA. Voltage-gated sodium channels at 60: structure, function and pathophysiology. *J. Physiol.* 2012;109:2577-2589.
10. Shen H, Zhou Q, Pan X, Li Z, Wu J, Yan N. Structure of a eukaryotic voltage-gated sodium channel at near-atomic resolution. *Science* 2017;355:6328.
11. Dib-Hajj SD, Geha P, Waxman SG. Sodium channels in pain disorders: pathophysiology and prospects for treatment. *Pain* 2017;158(suppl. 1):97-107.

12. Waxman SG. Sodium channels, the electrogenisome and the electrogenistat: lessons and questions from the clinic. *J. Physiol.* 2012;590:2601-2612.

13. Yu FH, Catterall WA. Overview of the voltage-gated sodium channel family. *Genome Biol.* 2003;4:207.

14. Erickson A, Deiteren A, Harrington AM, Garcia-Caraballo S, Castro J, Caldwell A, Grundy L, Brierley SM. Voltage-gated sodium channels: (Na_v)igating the field to determine their contribution to visceral nociception. *J. Physiol.* 2018;596:785-807.

15. Persson A-K, Black JA, Gasser A, Cheng X, Fischer TZ, Waxman SG. Sodium-calcium exchanger and multiple sodium channel isoforms in intra-epidermal nerve terminals. *Mol. Pain* 2010;6:84.

16. Black JA, Frezel N, Dib-Hajj SD, Waxman SG. Expression of Nav1.7 in DRG neurons extends from peripheral terminals in the skin to central preterminal branches and terminals in the dorsal horn. *Mol. Pain* 2012;8:82.

17. O'Leary M, Chen L, Kallen R, Horn R. A molecular link between activation and inactivation of sodium channels. *J. Gen. Physiol.* 1995;106:641-658.

18. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerves. *J. Physiol.* 1952*d*;117:500-544.

19. Pethig R. Dielectric properties of biological materials: biophysical and medical applications. *IEEE Trans. Electr. Insul.* 1984;5:453-474.

20. Malmivuo J, Plonsey R. Anatomical and physiological basis of bioelectromagnetism. In: *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields.* New York, Oxford, 1995, p. 33-124.

21. Malmivuo J, Plonsey R. Appendix B: Application of Maxwell's Equations in Bioelectromagnetism. In: *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields.* New York, Oxford, 1995, p. 455-461.

22. Dib-Hajj SD, Black JA, Waxman SG. Voltage-gated sodium channels: therapeutic targets for pain. *Pain Med.* 2009;10:1260-1269.

23. Ahern CA, Payandeh J, Bosmans F, Chanda B. The hitchhiker's guide to the voltage-gated sodium channel galaxy. *J. Gen. Physiol.* 2015;147:1-24.

24. Devor M. Sodium channels and mechanisms of neuropathic pain. *J. Pain* 2006;7(suppl. 1):3-12.

25. Devor M, Govrin-Lippmann R, Angelides K. Sodium channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. *J. Neurosci.* 1993;13:1976-1992.

26. Waxman SG. Acquired channelopathies in nerve injury and MS. *Neurology* 2001;56:1621-1627.

27. Waxman SG. Channelopathic pain: a growing but still small list of model disorders. *Neuron* 2010;66:622-624.

28. Kullmann DM, Waxman SG. Neurological channelopathies: new insights into disease mechanisms and ion channel function. *J. Physiol.* 2010;588 (Pt 11):1823-1827.

29. Matzner O, Devor M. Hyperexcitability at sites of nerve injury depends on voltage-sensitive Na+ channels. *J. Neurophysiol.* 1994;72:349-359.

30. Sheets MF, Hanck DA. Outward stabilisation of the S4 segments in domains III and IV enhances lidocaine block of sodium channels. *J. Physiol.* 2007;582:317-334.

31. Hille B. Local anesthetics: hydrophilic and hydrophobic pathways for the drug-receptor reaction. *J. Gen. Physiol.* 1977;69:497-515.

32. Balser J, Nuss H, Orias D, Johns D, Marban E, Tomaselli G, Lawrence J. Local anesthetics as effectors of allosteric gating. Lidocaine effects on inactivation-deficient rat skeletal muscle sodium channels. *J. Clin. Invest.* 1996b;98:2874-2886.

33. Linderoth B, Foreman RD. Conventional and novel spinal stimulation algorithms: hypothetical mechanisms of action and comments on outcomes. *Neuromodulation* 2017;20:525-533.

34. Shealy CN. The physiological substrate of pain. *Headache* 1966;6:101-7.

35. Shealy CN, Taslitz N, Mortimer JT, Becker DP. Electrical inhibition of pain: experimental evaluation. *Anesth. Analg.* 1967;46:299-305.

36. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns. *Anesth. Analg.* 1967;46:489-491.

37. Shealy CN, Mortimer JT, Hagfors NR. Dorsal column electroanalgesia. *J. Neurosurg.* 1970;32:560-4.

38. Verrills P, Russo M. Peripheral nerve stimulation for back pain. *Prog. Neurol. Surg.* 2015;29:127-138.

39. Mendell LM, Wall PD. Presynaptic hyperpolarisation: a role for fine afferent fibres. *J. Physiol.* 1964;172:274-294.

40. Maxwell JE. A dynamical theory of the electromagnetic field. *Philos. Trans. R. Soc. A.* 1865;155:459-512.

41. Malmivuo J, Plonsey R. Volume source and volume conductor. In: *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields*. New York, Oxford, 1995, p. 133-147.

42. Barnard ACL, Duck IM, Lynn MS. The application of electromagnetic theory to electrocardiology. I. Derivation of the integral equations. *Biophys J* 1967;7:443-462.

43. Barnard ACL, Duck IM, Lynn MS, Timlake WP. The application of electromagnetic theory to electrocardiology. II. Numerical solution of the integral equations. *Biophys J* 1967;7:463-491.

44. Frank E. Spread of current in volume conductors of finite extent. *Ann. N. Y. Acad. Sci.* 1957;65:980-1002.

45. Geselowitz DB. On bioelectric potentials in an inhomogeneous volume conductor. *Biophys. J.* 1967;7:1-11.

46. Malmivuo J, Plonsey R. Forward and Inverse Problems. In: *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields*. New York, Oxford, 1995, p. 143-146.

47. Eccles JC, Kostyuk PG, Schmidt RF. The effect of electric polarisation of the spinal cord on central afferent fibres and on their excitatory synaptic action. *J. Physiol.* 1962;162:138-150.

48. da Costa JG, de Moura MA, Consoni L, Nogueira RA. Can electromagnetic radiations induce changes in the kinetics of voltage-dependent ion channels? *Cell Mol Biol.* 2002;48:577-83.

49. Bhadra N, Kilgore KL. Direct current electrical conduction block of peripheral nerve. *IEEE Trans. Neural Syst. Rehabil. Eng.* 2004;12:313-324.

50. Kent AR, Min X, Hogan QH, Kramer JM. Mechanisms of dorsal root ganglion stimulation in pain suppression: a computational modelling analysis. *Neuromodulation* 2018;21:234-246.

51. Bevalacqua PJ. "Antenna Arrays: Performance Limits and Geometry Optimization", thesis, Arizona State University, Phoenix, AZ (2008)

52. Balanis CA. Radiation Pattern. In: *Antenna Theory: Analysis and Design*. New Jersey: Wiley, 2016, p. 25-34.

53. Fish RM, Geddes LA. Conduction of electrical current to and through the human body: a review. *Eplasty* 2009;9:e44.

54. Ehrenwerth J. Lasers and electrical safety in the operating room – electrical shock hazards. In: *Anesthesia Equipment: Principles and Applications*, edited by Ehrenwerth J. Eisenkraft JB:Mosby, 1993, p. 447-449.

55. Dalziel CF, Mansfield TH. Perception of electric current. *Electr. Eng.* 1950;69:794-800.

56. Huclova S, Erni D, Frohlich J. Modelling and validation of dielectric properties of human skin in the MHz region focusing on skin layer morphology and material composition. *J. Phys. D: Appl. Phys.* 2012;45:1-17.

57. Poon C-S, Choy TTC. Frequency dispersions of human skin dielectrics. *Biophys. J.* 1981;34:135-147.

58. Yamamoto T, Yamamoto Y. Electrical properties of epidermal stratum corneum. *Med. Biol. Eng.* 1976a;14:151-158.

59. Igarashi T, Nishino K, Nayar SK. "Cutaneous optics in the appearance of human skin" (Tech. Rep. CUCS-024-05, Columbia Univ., 2005)

60. Bragg WH, Bragg WL. The reflection of X-rays by crystals. *Proc. R. Soc. Lond. A.* 1913;88:428-438.

61. Rutherford E. The scattering of alpha and beta rays by matter and the structure of the atom. *Philos. Mag. Lett.* 1911;6:21.

62. Hogan QH. Labat Lecture: the primary sensory neuron: where it is, what it does, and why it matters. *Reg. Anesth. Pain Med.* 2010;35:306-311.

63. Malmivuo J, Plonsey R. Tissue Resistivities. In: *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields.* New York, Oxford, 1995, p. 140.

64. Battersby M, Von Korff M, Schaefer J, Davis C, Ludman E, Greene SM, Wagner EH. Twelve evidence-based principles for implementing self-management support in

primary care. *Joint Commission Journal on Quality and Patient Safety* 2010;36:561–570.

65. Saunders C, Carter D, Brown J. Primary care experience of older Australians with chronic illness. *Australian Journal of Primary Health*. 2019;25:13-18.
66. Samad OA, Tan AM, Cheng X, Foster E, Dib-Hajj SD, Waxman SG. Virus-mediated shRNA knockdown of $Na_v1.3$ in rat dorsal root ganglion attenuates nerve injury-induced neuropathic pain. *Mol. Ther.* 2013;21:49-56
67. Wallis BJ, Lord SM, Bogduk N. Resolution of psychological distress of whiplash patients following treatment by radiofrequency neurotomy: a randomised, double-blind, placebo-controlled trial. *Pain* 1997;73:15-22.
68. Latremoliere A, Woolf CJ. Central sensitisation: a generator of pain hypersensitivity by central neural plasticity. *J Pain.* 2009;10:895-926.
69. Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. *J Neuroimmune Pharmacol*. 2013;8:518-34
70. Rexed B. The cytoarchitectonic organization of the spinal cord in the cat. *J. Comp. Neurol.* 1952;96:414-495.
71. Szentagothai J. Neuronal and synaptic arrangement in the substantia gelatinosa rolandi. *J. Comp. Neurol.* 1964;122:219-239.

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Figure 1: Representative placements of neuromodulation leads: A: Left cervical facet joint dysfunction B: Right thoracic radiculopathy C: Bilateral sacroiliac joint dysfunction
Figure 2: The Sodium Channel A:Model of the alpha subunit of the sodium channel, viewed from the perspective of looking down through the central pore from outside the cell membrane. B: The sodium channel in figurative format – on the left, viewed from the same perspective as A. above, showing the S6 transmembrane segments forming the central pore, and the 6 transmembrane segments of each of the 4 domains. Colour coding matches to the image shown below, which shows the same structure through the width of the membrane and arranged longitudinally. The image below shows organisation of the alpha subunit into domains and transmembrane segments. Functional components include the voltage sensing area in segment IV, the ion selective filter in the extracellular loop between segments V and VI, and the inactivation mechanism's loop between domains III and IV.
Figure 3: Neuromodulation Unit's Electronic Output Oscilloscopic display of voltage and current pulses from neuromodulation unit, demonstrating time-varying patterns.
Figure 4: Electromagnetic Wave Progression E = time-varying electric field B = time-varying magnetic field c = speed of light A time-varying electric field generates a time-varying magnetic field which generates a time-varying electric field, and so the cycle continues. The ensuing electromagnetic field travels through space at the speed of light.

Table 1: Sites of Presenting Pain

Presenting Pain	n
Neck pain ± headache	18
Facial pain	1
Arm pain	2
Thoracic spinal pain	12
Chest wall pain	9
Upper abdominal pain	1
Lower abdominal pain post-laparotomy	2
Genitourinary tract pain	1
Groin pain post-hernia repair	1
Low back pain	73
Pelvic/perineal pain	3
Leg pain	1
Foot pain	1
Lower extremity phantom limb pain	5

Table 2: Demographic Data

Male : Female (n)	41 : 89
Age range (yrs)	14 – 100
Weight range (kg)	45 – 150

Table 3: Examples of Diagnostic Nerve Blocks with Resultant Diagnoses

Diagnostic Nerve Block/s	Diagnosis
Greater occipital nerve block	Occipital neuralgia
Cervical medial branch blocks	Cervical facet joint dysfunction
Superficial cervical plexus block	Superficial cervical plexus neurapraxia
Cervical epidural block	Cervical radiculopathy
Thoracic nerve root block	Thoracic radiculopathy
Thoracic medial branch blocks	Thoracic facet joint dysfunction
Rectus sheath block	Entrapment neuropathy of abdominal wall
Thoracic nerve root block/s	Entrapment neuropathy of specific abdominal wall nerve/s
Combined lateral sacral branch blocks & sacroiliac joint injection	Sacroiliac joint dysfunction
Lumbar epidural injection	Spinal stenosis
Sciatic nerve block	Lower extremity phantom limb pain
Posterior tibial nerve block	Posterior tibial nerve neurapraxia
S1 nerve root block	Neurapraxia of medial plantar branch of posterior tibial nerve

Table 4: Implantation of Neuromodulation Related to Diagnosis of Source of Pain

Diagnosis of Source of Pain	n
Occipital neuralgia	1

Cervical facet joint dysfunction	17
Maxillary nerve neurapraxia	1
Cervical radiculopathy	1
T2 lateral cutaneous branch neurapraxia	1
Thoracic facet joint dysfunction	19
Thoracic radiculopathy	2
Intercostal neuropraxia post-thoracotomy	2
Pain secondary to medullary sponge kidney disease	1
Rectus sheath entrapment neuropathy	2
Ilioinguinal nerve neurapraxia	1
Pelvic endometriosis	1
Pudendal neuralgia	2
Sacroiliac joint dysfunction	66
Lumbar spinal stenosis	5
Lumbar radiculopathy	2
Phantom limb pain	5
Posterior tibial nerve neurapraxia	1