

Original Research

Natural Neurostimulation for Chronic Pain Management: A Case Series of 3 Patients with Dysmenorrhea and Menstrual Migraine

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Abstract

Accumulating evidence suggests that chronic pain occurs in various disorders due to correlated processes of spontaneous cortical reorganization and dysregulation of cortical excitability in consciousness-related networks. This case series tracks three patients with chronic pain associated with the menstrual cycle treated by a novel non-invasive brain stimulation technique that applies qualities of the mother-fetus neurocognitive model. Previous research has shown that a low-frequency pulsed electromagnetic field and a complex acoustic wave from the mother's heart contribute to the synchronization of these two nervous systems, thereby developing a balanced nervous system in fetuses. Therefore, we hypothesize that the scaled parameters of these natural forces can be used to treat an injured nervous system in adults. Acoustic photonic intellectual neurostimulation (APIN) emulates the central parameters of this natural brain stimulation during pregnancy. Based on evidence from previous research, we suppose that weak stimulations with these therapeutic agents excite different neuronal networks in specific consciousness-related brain areas; their



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integrated impact modulates mitochondrial functions and causes neuronal tissue oxygenation and adenosine-5'-triphosphate protein release, leading to pain relief and facilitating neuronal plasticity. This sequence of physicochemical interactions produces a change in brain connectivity that supports a change in symptoms such as chronic pain. The case series of three patients shows a therapeutic effect.

Keywords

Brain stimulation; chronic pain; neurostimulation; dysmenorrhea; migraine; menstrual pain; mother-fetus neurocognitive model

1. Introduction

The most common menstrual disorders are dysmenorrhea and headache; the latter is often related to migraine and referred to as menstrual migraine [1]. According to the received view, the pathogenesis of menstrual-related pain conditions is associated with the overproduction of prostaglandins [1].

1.1 Dysmenorrhea

Primary dysmenorrhea (PDM) is defined as painful cramps in the lower abdomen that occur before or at the beginning of menses in the absence of any pelvic pathology [2]. On the contrary, secondary dysmenorrhea is caused by chronic medical problems. According to Liu et al. [2], PDM often co-occurs with many other chronic pain conditions, including chronic headache, low back pain, irritable bowel syndrome, fibromyalgia, and painful bladder syndrome, with the highest prevalence rates after the age of 30 [3]. The worldwide prevalence of PDM ranges from 70% to 93% in adolescents and from 45% to 95% in all females of reproductive age; 2% to 29% experience severe pain [3, 4]. The differences between the rates were explained by the variation in the assessing methodologies and measured samples: the age groups and selected populations with culturally-varied specific pain perception [3].

A recent review [5] observed pharmacologic and non-pharmacologic treatment options. The first-line therapy for PDM is with nonsteroidal anti-inflammatory drugs due to the inhibition of cyclooxygenase enzymes, thereby blocking both prostaglandin formation and hormonal contraception [5]. Other pharmacological treatment options include Paracetamol and Gonadotropin-Releasing Hormone Analogs, typically used to treat endometriosis [5]. It is essential to note that a cautious and individualized approach should be taken when addressing the risks associated with pharmacological treatment [5]. It is advisable to use the lowest effective dose for the shortest possible time and carefully monitor for side effects [5]. A medical evaluation is necessary before beginning any pharmacologic therapy if a patient has pre-existing conditions, such as kidney, cardiovascular, or gastrointestinal disease [5].

Non-pharmacologic treatments with strong evidence include heat therapy and physical exercise [5]. However, these methods are less efficacious than pharmacologic ones. More evidence-based data on other modalities for treating PDM, such as dietary supplements, acupuncture, and

transcutaneous electrical nerve stimulation (TENS), are needed [5]. Analysis suggests using these methods only in conjunction with first-line therapy after discussing risks and benefits [5].

1.2 Menstrual Migraine

The term menstrual migraine (MG) refers to migraine that is associated with menstruation. MG affects about 20–25% of female migraineurs in the general population, and 22–70% of patients presenting to headache clinics [6]. Attacks of menstrual migraine are usually more debilitating, of longer duration, more prone to recurrence, and less responsive to acute treatment than nonmenstrual migraine attacks [6].

In pain management, there are several methods for acute treatment: triptans, combination therapy, prostaglandin synthesis inhibitors, and ergot alkaloids [7]. For preventive treatment, triptans, combined therapy, oral contraceptives, estrogen, nonsteroidal anti-inflammatory drugs, phytoestrogen, gonadotropin-releasing hormone agonist, dopamine agonist, vitamins, minerals, and nonpharmacological therapy were selected. Among other therapies, triptans have strong evidence for treatment in both acute and short-term prevention of MG [7].

Triptans are serotonin (5-hydroxytryptamine, or 5-HT) agonists with high affinity for 5-HT 1B and 5-HT 1D receptors. The most common adverse effects of triptans, such as paresthesia, flushing, tingling, neck pain, and chest tightness, are collectively referred to as "triptan sensations." Triptans may cause nausea, dizziness, and coronary vasoconstriction [8]. It was reported about ischemic colitis, splenic infarction, spinal cord infarction and cranial nerve paresis induced by triptans [8].

1.3 Neurostimulation for Chronic Pain Management

Noninvasive neurostimulation methods have attracted significant attention from the scientific community because they can be personalized, modulate neuronal plasticity independently of underlying conditions, and are designed to be noninvasive. A growing body of literature presents evidence of the efficiency of noninvasive neurostimulation for the treatment of women with primary dysmenorrhea [9] and chronic migraine [10].

However, a recent review highlighted several limitations of these techniques; the most crucial of them are: (a) the healthy intensity and duration of the interventions are not defined; (b) protocols are different, including different electrode sizes, shapes, and locations [11]. These limitations raise an essential challenge for noninvasive neurostimulation methods: these techniques target a large area of poorly characterized tissue, which, together with an undefined dose, can damage healthy cells during treatment [11].

1.4 Central Features of Feeling Chronic Pain Sensation

Could chronic pain in different conditions have the exact etiology and is it associated with structural brain reorganization of consciousness-related neuronal networks?

1.4.1 Loss of Synaptic Connections Causes Chronic Pain

Following Santiago Ramón y Cajal, we understand that the brain can enhance its function by improving neuronal communication, establishing a paradigm now known as neuroplasticity [12]. Neuroplasticity can be thought of as a continuum of involuntary neuronal activity in a healthy

nervous system, resulting in the organization of relevant neuron structure and adequate excitability regulation to improve brain function through an iterative and cooperative process. In contrast, in the injured nervous system, the continuum of spontaneous neuronal activity may lead to counterproductive processes: a reorganization of neuronal structures in the brain, accompanied by dysregulation of neuronal excitability. Indeed, research on chronic pain conditions has revealed aberrations in long-term potentiation (LTP) [13]. Pathological changes at the synaptic level play a role in several psychiatric and neurodegenerative diseases [14-16].

1.4.2 Chronic Pain is Associated with a Structural Brain Reorganization

Because chronic pain can occur in various disorders due to correlated processes of spontaneous cortical reorganization and dysregulation of cortical excitability, the grounds of chronic pain in different disorders may also arise from comparable processes, even if cortical reorganization and dysregulation proceed in different brain areas. Suppose dysfunction of specific neuronal structures is the cause of chronic pain. It may be assumed that the neurons of these structures cease to function properly throughout the brain, and connections among networks of neurons break down. Loss of synaptic connections leads to brain cortical reorganization [17, 18]. Specifically, neighboring neuronal structures begin to invest in (insert) injured neuronal structures; such an unexpected appearance of new non-evolutionary neuronal networks may cause pain sensation, analogous to the widely accepted theory of phantom pain [17]. In other words, loss of synaptic connections in specific neural structures might be one of the leading causes of chronic pain. A neuroscience review of research on pain-induced neuroplastic changes highlighted evidence of pain-induced changes in large-scale neuronal network connectivity, and that chronic pain is associated with structural brain changes in patients [19].

1.4.3 Chronic Pain is Associated with Brain Reorganization of Consciousness-Related Networks

According to the conventional view of scientists from the International Association for the Study of Pain [20], the experience of pain is always a subjective sensation influenced to varying degrees by biological, psychological, and social factors. Crucially for the current study, this experience cannot be reduced to activity in sensory pathways [20].

A recent comprehensive review highlighted the multidimensional role of pain in several cognitive domains, including attention, memory, processing, executive functioning, decision-making, psychomotor efficiency, and reaction time, and observed growing evidence of a link between pain and these cognitive domains [21]. Evidence showed that attention capture by other stimuli is more difficult in a condition of continued noxious stimuli (i.e., pain) because pain impacts attentional control [22]. Feeling pain sensation leads to decreased task performance [22]. Clinical studies have shown an association of attention deficit in patients with chronic pain [23]. Conversely, pain sensitivity is reduced in patients with engagement in cognitive load [24]. Regarding the relationship between chronic pain and working memory, research has shown that chronic pain adversely affects working memory, recall, and recognition memory [25-27].

A recent scoping review by Calabrò et al. [28] on neurophysiological evaluations of pain perception in individuals with prolonged disorders of consciousness argues that pain perception increases with the level of consciousness. When a patient is aware, they are presumably able to feel pain. Since awareness implies sentience, the absence of awareness precludes any sentience [28].

Insofar as the above data mean that patients mainly feel chronic pain in wakefulness and awareness, in the chronic pain condition, patients experience pain when they are awake and aware. Given the data above, chronic pain is associated with structural brain reorganization of consciousness-related neuronal networks. Chronic pain management should also involve a therapy that stimulates conscious perceptive inputs.

1.5 Hypothesis of Chronic Pain Etiology

Summarizing the abovementioned data, we hypothesize that chronic pain in different conditions has a similar etiology. Here, we provide a brief explanation of the revealed evidence. Being a common symptom of other chronic disorders, chronic pain is positively associated with altered brain activities [13]. Brain reorganization in chronic pain involves multiple brain areas. Different reviews of fMRI clinic studies highlighted inconsistent and dissimilar research outcomes, even in cases of similar pathogenesis [14-16]. A recent comprehensive review highlighted the multidimensional role of pain in several cognitive domains, including attention, memory, processing, executive functioning, decision-making, psychomotor efficiency, and reaction time, and observed growing evidence of a link between pain and cognitive functions [21]. Patients feel chronic pain in wakefulness and awareness [25-27].

Because of the above arguments, although brain mapping in chronic pain is problematic, growing evidence shows that chronic pain occurs in different disorders because of correlative processes of spontaneous cortical reorganization and dysregulation of cortical excitability in consciousness-related networks [25-27]. According to growing data, various neurological disorders can be treated by noninvasive neurostimulation [11]. Chronic pain is a significant component of many neurological disorders. Taken together, the treatment of chronic pain may rely on non-invasive brain stimulation of consciousness-related networks.

1.6 Natural Neurostimulation

A mother-fetus neurocognitive model [11, 29] offers insights into developing a new approach to brain stimulation, grounded in knowledge about natural neurostimulation [11]. According to this model, the proper development of the child's nervous system during gestation is facilitated by physical interactions between the mother and fetus, in which the mother's heart plays a central role [11, 29]. The low-frequency pulsed electromagnetic field of the mother's heart and its complex acoustic wave synchronize two nervous systems [11, 29-31]. During the mother's intentional acts, this natural neurostimulation facilitates proper neuronal plasticity in the child's nervous system, which is relevant to the mother's ecological context [11, 29-31]. Therefore, the coupled neuronal activity in their nervous systems provides adequate biological sentience in the fetus [11, 29-31]. At the same time, as empirical data shows, sound vibrations modulate the mitochondrial functions [11, 32] and low-frequency pulsed electromagnetic fields induce vasodilatation and mitochondrial stress that increases neuronal oxygenation and adenosine-5'-triphosphate (ATP) protein release [11, 33-35] by producing ATP protein, mitochondria impact synaptic activity, altering neurological functions because mitochondria are commonly found in synaptic terminals [11]. These physical interactions of coordinated neuronal activity in both nervous systems yield a template for balanced, yet dynamic, system development and social learning in the child. Because natural neurostimulation contributes to the balanced development of the nervous system in fetuses with adequate biological sentience,

the scaled parameters of these natural forces can potentially treat an injured nervous system in adults [11, 28].

These insights underlie the new noninvasive brain stimulation technique—acoustic photonic intellectual neurostimulation (APIN). The APIN technique emulates the central parameters of natural brain stimulation during gestation [11, 30, 31]. During the APIN therapy, weak stimulation of three therapeutic agents (electromagnetic field, complex acoustic wave, and cognitive load) excites different neuronal networks in specific consciousness-related brain areas. They stimulate perceptive inputs of various modalities that intersect in consciousness-related brain areas. In the case of lost synaptic connections, a weak stimulation does not induce long-term potentiation (LTP). As noted in section 1.4.1, chronic pain conditions are associated with aberrations in LTP. However, even weak stimulations, if they are cooperatively delivered to intersecting neurons of neural networks of different sensory inputs, provide the effect of synaptic cooperativity, causing LTP (as is already known, weaker stimulations applied simultaneously cause LTP) [36]. This multi-stimuli impact may rehabilitate the loss of synaptic connections and reduce chronic pain. The integrated effect of pulsed electromagnetic field, complex acoustic wave, and cognitive load modulates the mitochondrial functions and causes neuronal tissue oxygenation and adenosine-5'-triphosphate protein release [11, 32-35], leading to pain relief and facilitating neuronal plasticity in consciousness-related networks. Recent case studies observed successful APIN treatment of patients living with chronic pain in different conditions, such as neurodegenerative disease [37], chronic headache [38], and dysmenorrhea [39].

2. Materials and Methods

The case series observes three patients with primary of various disorders: dysmenorrhea (PDM) and menstrual migraine (MG). They reported living with chronic pain related to the menstrual cycle. We measure patients' pain sensation and the pain reduction effect using the subjective pain scale that rates pain on a maximum scale of ten points. Sampling is based on a specific outcome and the presence of a particular exposure: noninvasive APIN treatment.

Because during pregnancy, a low-frequency pulsed electromagnetic field and a complex acoustic wave of the mother's heart contribute to the synchronization of these two nervous systems, developing the balanced jumpy system in fetuses [11, 29-31], we suppose that the scaled parameters of these natural forces can treat an injured nervous system in adults. APIN emulates the central parameters of this natural brain stimulation during pregnancy. To induce "natural neurostimulation", the APIN technique emits three neurostimulation stimuli (electromagnetic fields, complex acoustic waves, and flashing lights) along with cognitive therapy, which together stimulate different neuronal networks in specific consciousness-related brain areas. The weak stimulations (but simultaneously through several sensorial inputs) provide an effect of synaptic cooperativity, causing Long Term Potentiation [36]. The integrated impact of these therapeutic agents modulates the mitochondrial functions and causes neuronal tissue oxygenation and adenosine-5'-triphosphate protein release [11, 32-35], leading to pain relief and facilitating neuronal plasticity [11]. Therefore, this sequence of physicochemical interactions produces a change in brain connectivity that supports a change in a symptom such as chronic pain [11].

The APIN technique operates through both visual and auditory sensory inputs. As shown in the Introduction section, chronic pain is associated with various disorders due to correlated processes

of spontaneous cortical reorganization and dysregulation of cortical excitability in consciousness-related networks [25-27]. Most environmental dynamics are processed in consciousness-related networks that receive visual and auditory sensory inputs. According to recent research, light can directly modulate synaptic activity in the brain through the image-forming vision pathways and the photoreceptive ganglion cell pathways by stimulating ATP production in the mitochondria of the retina [11]. Specifically, research has shown that electromagnetic oscillations (e.g., light) increase the density of adenosine A(2A) receptors in cortical cell membranes [11, 35]. Adenosine A(2A) receptor stimulation enhances mitochondrial metabolism [11, 33]. Because electromagnetic oscillations improve mitochondrial bioenergetics [11, 34], mitochondrial energy metabolism increases ATP release [11, 34]. Color lights of different wavelengths stimulate neuronal activity of various frequency bands across multiple networks [11, 40-42]. The color red elicits higher brain activity in the frontal and parietal areas [11, 40]. In contrast, violet only evokes a response in the prefrontal cortex [11, 42]. Therefore, flashing alternately red and violet lights of low frequency, approximately 1 Hz, can increase ATP release, thereby enhancing brain activity in the frontal, parietal, and prefrontal cortex areas. Sound oscillations also modulate mitochondrial functions [11, 32].

If the above arguments are correct, chronic pain management can rely on non-invasive brain stimulation of consciousness-related networks through visual and auditory sensory inputs. It can be applied to pain relief in PDM and MG, specifically based on the evidence of the efficiency of neurostimulation in treating primary dysmenorrhea [9] and chronic migraine [10].

2.1 Case Study with the Patient PDM01

The patient, 16 years old, has been living with pain in the lower abdomen sensation during the menstruation cycle since the beginning of the first menstruation period. The patient estimated this pain as 8-point on a scale from 0 (no pain) to 10 (unbearable). She reported that the most efficient therapy in previous cycles was using superficial heat via heat packs (pain decreased to 5 scores after treatment).

2.2 Case Study with the Patient MG01

The patient, 40 years old, has been living with headaches during the menstruation period for 9 years. The patient estimated this pain as 8-point on the scale from 10. She reported the most efficient therapy was using non-steroidal anti-inflammatory drugs (4 after taking the medicine).

2.3 Case Study with the Patient MG02

The patient, 41 years old, has been living with headaches during the menstruation period for the last 5 years. The patient estimated this pain as 7 scores out of 10. She reported the most efficient therapy was using non-steroidal anti-inflammatory drugs (4 after taking the medicine).

2.4 Therapeutic Intervention

The APIN treatment exerts its function through the LED display emitting an electromagnetic field with a frequency of 50-60 Hz and a magnetic flux density of 0.13-0.3 μT at a distance of 0.2-0.4 m, with an illumination of 450 lux. Due to the specific software, the display emits impulses of

alternately flashing color lights with wavelengths of 400 nm and 700 nm (corresponding to violet and red, respectively) at a frequency of 1.3 Hz, alternating between the two colors. The acoustic transducer emits a complex acoustic wave via headphones (with a magnetic field flux density of 0.08 T near the left and right temporal lobes) at an operating frequency of 1.3 Hz, formed by the first sinusoid S1, the second sinusoid S2, and the third sinusoid S3, which correspond to heart sinusoids. The first sine wave has an amplitude of 70 dB, and the second and third sine waves have an amplitude of 21 dB. The cognitive load consists of 40 mathematical problems that must be solved mentally in a limited time. All stimuli used in APIN were produced by standard electronic devices approved for public use in the EU, including standard tablets and headphones.

During treatment, patients were seated with headphones at a distance of 25-40 cm in front of the displays. They were asked to focus only on the displays and tackle the math problems presented on them. The session duration for each patient was 22 minutes once a day for 3 days at the beginning of two menstrual cycles.

2.5 Ethics Statement

The patients were informed about the treatment procedure, their rights, and their privacy. The method is based on the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, revised in 2000 and 2008. The research was approved by the RTU Liepaja Academy (Latvia), with approval number No. 0L000-4.2/13, dated September 4, 2024. The informed consent process ensured our participants understood the study and willingly agreed to participate, protecting their rights and promoting ethical conduct. It involved disclosing necessary information, facilitating understanding, and ensuring the decision to participate was voluntary. Written informed consent to publish the results has been obtained from the patients. We used the CARE checklist for case studies when writing our report [43].

3. Results

We tracked three patients for two consecutive menstrual cycles. They received APIN therapy the day before each cycle and for three days thereafter. Patient PDM experienced relief of lower abdominal pain after treatment. Patients MG01 and MG02 reported successful complete relief of headaches. The results of each treatment are described in Table 1 based on patients' estimates. We observed the three patients with chronic pain associated with the menstrual cycle during the following three months. During this period, patients MG01 and MG02 reported no complaints of pain related to their menstrual cycles. Because of the repetitive pain sensation during these three months, the patient PDM01 asked to continue treatment. The ongoing procedures in PD01 demonstrated the same dynamics in pain relief, reducing pain by half on the day before and the first day of the cycle, and eliminating pain on the second day.

Table 1 Three case studies results.

Case	Cycle	Day before: Pain before /after APIN	1st day: Pain before /after APIN	2nd day: Pain before /after APIN	3rd day: Pain before /after APIN
PDM01	1 st month	-/-	8/3	4/0	0/0
	2 nd month	6/4	9/6	5/3	0/0
MG01	1 st month	0/0	0/0	0/0	0/0
	2 nd month	2/0	0/0	0/0	0/0
MG02	1 st month	5/0	0/0	0/0	0/0
	2 nd month	3/0	0/0	0/0	0/0

4. Discussion

The current research conducted a series of three case studies of 3 patients with dysmenorrhea and menstrual migraine. Statistically, the number needs to be more significant to prove and support the method's effectiveness. There are misconceptions that case study research can only provide exploratory or descriptive evidence [44]. Although the obtained data are still insufficient for a valid outcome, the case study provides evidence regarding context and transferability [44]. It helps strengthen causal inferences when pathways between the intervention and effects are likely to be non-linear [44]. It also suits checking the feasibility of the research design.

Another challenge is an inappropriate control intervention owing to the case study type of research. The study with only one subject cannot control all other aspects related to the treatment, e.g., whether the result is due to the chosen combination of three stimuli or only one or two of them are responsible for the actual result, or perhaps something else. The quantitative research should isolate the active component(s) thought to be responsible for the treatment effect and administer it to the treatment group, ensuring that all other aspects related to the treatment are given to both the APIN treatment and control groups with different methods [45].

Further research would enhance the scientific validity of the APIN method if the research design considered placebo effects, long-term outcomes, and statistical analysis to strengthen the credibility of the outcomes.

For further research, we suggest a research design based on a randomized controlled trial (RCT) that examines the effect of an intervention as a difference between two groups (with and without intervention). The effect size cannot be determined to calculate an appropriate sample size. In such a case, Cohen recommends using small, medium, and large effect sizes rather than specific values (i.e., standardized or unit-free effect sizes) [46, 47]. Since the mean difference between the two groups is of interest, and if an independent sample t-test were used, the standardized effect size would be calculated as the ratio of the difference between the two means and the standard deviation [47]. The sample size would be based on a range of standardized effect sizes and powers: $d = 0.2$ (small), 0.5 (medium), or 0.8 (large) [46, 47]. Since, in our case, the effect size obtained in the first step (the current pilot study) is estimated to be medium, then according to Cohen, the total sample size required to reach a power of 80% is 128 participants in two groups: 50% with and 50% without intervention [46, 47].

Interestingly, all stimuli used in APIN are produced by standard electronic devices approved for public use in the EU, including standard tablets and headphones. The system of generating synchronized impulses and their characteristics in APIN is what distinguishes the impact on the nervous system of this neurostimulation system (based on standard devices) from the effects that these same devices have on a person in daily routine usually and that we all receive every day using them. This knowledge enabled us to treat the PDM01 patient online during a three-month post-research follow-up period. We provided this teleneurotherapy in online sessions using a standard home computer and headphones. We did not find any significant changes in the effects on the pain management of the offline and online procedures; both showed significant pain relief.

The APIN technique operates through three therapeutic agents derived from knowledge gained by studying natural neurostimulation during pregnancy. The APIN method has already demonstrated therapeutic effects in various conditions, including neurodegenerative disease [37], chronic headache [38], and dysmenorrhea [39]. The authors believe that these therapeutic effects in different conditions were achieved because of the similar etiology of various neurological diseases (arising from spontaneous cortical reorganization and dysregulation of cortical excitability in consciousness-related networks) that APIN technique treated through modulation of neuronal plasticity for fine-tuning the injured nervous system.

5. Conclusions

Acoustic photonic intellectual neurostimulation (APIN) treatment of 3 patients showed a therapeutic effect. Patient PDM01 experienced relief of lower abdominal pain after treatment. Patients MG01 and MG02 reported successful complete relief of headaches. This knowledge may have a significant impact on future research in the field of neuromodulation. Further research could enhance the scientific validity of the APIN method if the research design considers placebo effects, long-term outcomes, and statistical analysis to strengthen outcome credibility.

Author Contributions

Igor Val Danilov conceived and designed the experiments. Sandra Mihailova and Dace Medne reviewed the research design and gave valuable remarks. Igor Val Danilov formulated the hypothesis and wrote the first draft of the manuscript. Igor Val Danilov, Sandra Mihailova and Dace Medne improved the text over several iterations.

Competing Interests

The authors have declared that no competing interests exist.

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