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# Peripheral Nerve Stimulation for Fibromyalgia

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## Abstract

Fibromyalgia is a condition marked by widespread chronic pain, accompanied by a variety of other symptoms, including sleep and fatigue disorders, headaches, disorders of the autonomic nervous system, as well as cognitive and psychiatric symptoms. It occurs predominantly in women and is often associated with other systemic or autoimmune diseases. Despite its serious socioeconomical burden, the treatment options remain poor. In this chapter, the authors discuss the possibilities of using greater occipital nerve stimulation as a treatment for fibromyalgia, based on available clinical studies. Greater occipital nerve stimulation has already been used successfully to treat occipital neuralgia and various primary headache syndromes. Testable hypothetical working mechanisms are proposed to explain the surprising effect of this treatment on widespread bodily pain.

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## Introduction

### *Fibromyalgia*

Fibromyalgia is a disease characterized by widespread musculoskeletal pain. It is lacking a clear pathophysiology and doesn't influence specific laboratory tests nor causes specific abnormalities on physical examination. Hence, the diagnosis of fibromyalgia remains a pure clinical diagnosis. The American College of Rheumatology (ACR) proposed diagnostic criteria in 1990. These criteria include a history of widespread pain, lasting for more than three months, affecting all quadrants of the body. Furthermore, 18 tender points were defined which elicit a painful sensation by applying a force of 4 kg. These points include myofascial structures at the occipital area, the neck area, chest area, back area, the elbows and knees. Eleven of these 18 trigger points should elicit pain in order to consider the diagnosis of fibromyalgia [1].

Besides pain, fibromyalgia is accompanied by a variety of other symptoms which is why it is called a syndrome. The most common of these associated symptoms are headaches, sleeping disorders, fatigue, irritable bowel syndrome and cognitive dysfunction [2, 3]. Other symptoms include nocturnal jaw tightness, morning stiffness, paresthesias of arms and legs, urinary urgency, esophageal dysmotility, dryness of mouth and eyes, allergic complaints, and cold and swollen hands [4–6]. Psychiatric disorders are frequently encountered in fibromyalgia patients as well, such as depression and anxiety disorders [7].

Fibromyalgia not only frequently mimics other diseases but also is often associated with them. These include lupus erythematosus (20%), Sjögren syndrome (20%), rheumatoid arthritis (30%), inflammatory bowel disease (7–49%), hepatitis C (9%), HIV (12%), Lyme (8%), and diabetes mellitus (11%). This complicates its diagnosis.

The prevalence of fibromyalgia is as high as 2.9–4% in a general population and it mainly affects women in a 9:1 ratio. The mean age of onset is between 20 and 55 years [6, 8].

Because of this high prevalence and the multisymptomatic characteristics health care utilization in fibromyalgia patients is extensive, resulting in a high socioeconomic burden. Fibromyalgia has a large financial impact on both direct medical costs consisting of treatment costs and patient care and indirect costs due to work loss. Several estimations of these costs have been published. Berger et al. [9] estimate the mean total healthcare costs in a study sample of 33,176 patients at USD 9,573 per patient over 12 months in the United States. Boonen et al. [10] report an average annual disease-related cost per patient of EUR 7,813 in a Dutch population.

The pathophysiology of fibromyalgia is poorly understood. Several theories have been proposed in order to explain this condition. Amongst them sleep disturbances, a general hyperactivity of the nociceptive system, sympathetic hyperreactivity and hormonal disturbances have been proposed [11–14]. More and more evidence points to an abnormal function of the central nervous system. Patients are characterized by a more pronounced sensation of mechanical and heat pain and this form of hyperalgesia is caused by a supraspinal central nervous system etiology [15, 16]. Furthermore, various functional brain-imaging studies have shown cortical and subcortical augmentation of pain processing and an increased sympathetic and decreased parasympathetic tone [13, 16–19].

The treatment of fibromyalgia is mainly symptomatically and comprises combinations of pharmaceutical, psychological and physical approaches [20, 21]. Besides pain medication, antidepressant medication has been proven to be effective in fibromyalgia as well as medication used in the treatment of neuropathic pain such as gabapentin and pregabalin [22–26]. The US Food and Drug Administration has approved the use of pregabalin for the treatment of fibromyalgia.

Combining pharmaceutical treatment with psychological therapy, such as cognitive behavioral therapy, and physical treatment, such as aerobic exercise, seems to be the most effective. The American Pain Society published guidelines for the

management of fibromyalgia patients in 2005 [27]. The European League Against Rheumatism (EULAR) formulated recommendations and evidence-based guidelines for its treatment as well [28]. Still, the search for new and more effective treatment possibilities continues. One of these new treatment possibilities consists of peripheral nerve stimulation of the greater occipital nerve by implantation of an occipital nerve stimulator [29; (Plazier, unpubl. data)].

#### *Greater Occipital Nerve Stimulation*

The greater occipital nerve is a branch of the dorsal ramus of the 2nd cervical nerve. This particular nerve provides sensory innervation to the occipital scalp, together with the lesser occipital nerve. Anastomoses between the first, second, third and fourth cervical nerves form the upper cervical plexus.

Stimulation of this nerve has been shown to be effective in the treatment of occipital neuralgia and primary headache syndromes. Picaza et al. [30] performed the first surgical stimulation of this nerve for the treatment of occipital neuralgia in 1977. A variety of primary headache syndromes tend to respond to occipital nerve stimulation [31, 32] as well, raising the question how this form of peripheral nerve stimulation exerts its effects.

The greater occipital nerve has connections with the trigeminal nerve at the level of the cervico-trigeminal complex located at the dorsal horn of the cervical spinal cord. Le Doaré et al. [33] revealed this connection in a rat model by measuring the FOS expression at the dorsal horn and the nucleus caudalis after infiltrating the cervical musculature with a nociceptive agent. This connection has been shown in cats and humans as well [34, 35].

Results in headache treatment are promising with success rates between 70 and 100% [36] (table 1).

However, none of these studies have been performed in a placebo-controlled way due to the fact that paresthesias are felt at higher stimulation amplitudes. In a study published by Thimineur and De Ridder [29], in which greater occipital nerve stimulation was applied in fibromyalgia patients suffering from migraine, the results revealed not only an improvement in headache-associated pain, but in widespread bodily pain as well.

#### *Greater Occipital Nerve Stimulation in Fibromyalgia*

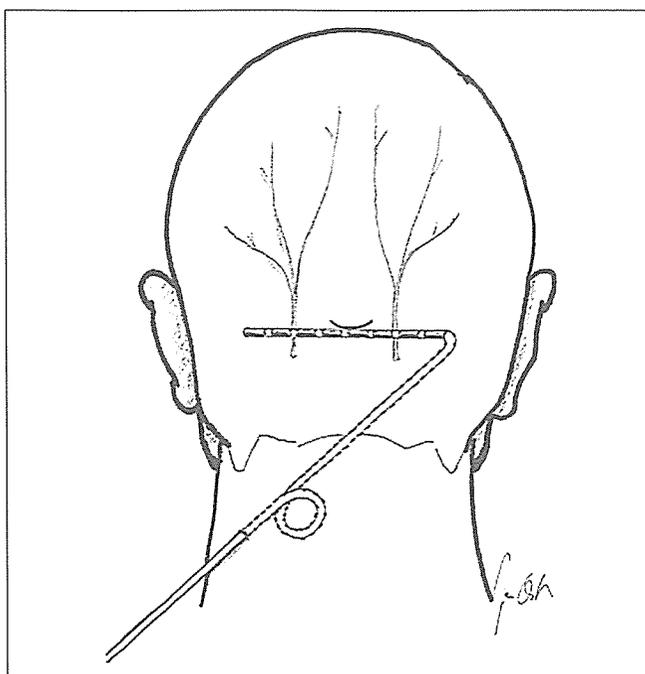
Thimineur and De Ridder [29] implanted 12 patients with an occipital nerve stimulator for chronic daily headache, all of whom also fulfilled the criteria for fibromyalgia. Two Quatrode® (St. Jude Medical Neuromodulation, Plano, Tex., USA) leads were placed bilaterally, subcutaneously at the occipital scalp, approximately 2 cm above the inion at an imaginary line drawn between the top of the ears. In this group of patients the severity of headache-associated pain, diffuse bodily pain and associated symptoms such as sleep disturbance, fatigue and depression were monitored. The patients were stimulated with a rechargeable internal pulse generator (IPG) at

**Table 1.** Occipital nerve stimulation for headache syndromes

Study	Indication	Responders	Effect
Melvin et al. (2007)	occipital headache (n = 11)	11/11	67%
Popeney et al. (2003)	migraine (n = 25)	20/25	88.7% improvement MIDAS
Oh et al. (2004)	occipital neuralgia (n = 20)	18/20	90%
Weiner et al. (1999)	occipital neuralgia (n = 13)	13/13	100% good to perfect
Matharu et al. (2004)	migraine (n = 8)	8/8	100% good to perfect
Kapural et al. (2005)	cervicogenic headache (n = 6)	6/6	70%
Rodrigo-Royo et al. (2005)	occipital neuralgia (n = 4)	4/4	100%
Slavin et al. (2006)	occipital neuralgia (n = 10)	10/10	> 50%
Magis et al. (2007)	cluster headache (n = 8)	7/8	50%
Schwedt et al. (2007)	cluster headache (n = 3), hemicrania (n = 6), migraine (n = 8), post-trauma (n = 2)	15/19	52%
Burns et al. (2007)	cluster headache (n = 8)	6/8	64%
Picaza et al. (1977)	occipital neuralgia (n = 6)	3/6	100% good to perfect
Schwedt et al. (2006)	hemicrania continua (n = 2)	1/2	70%
Ghaemi et al. (2008)	postcervical fusion pain (n = 1)	1/1	90%
Amin et al. (2008)	supraorbital neuralgia (n = 10)	10/10	77%
Burns et al. (2009)	cluster headache (n = 14)	10/14	52%

6, 12, 18, 24 and 30 Hz, with a pulse width of 50  $\mu$ s and amplitudes between 5 and 25.5 mA.

Apart from a significant improvement in headache-associated pain, the scores for bodily pain (VAS), depression (BDI), fatigue (FIS) and quality-of-life (SF-36) also improved in a significant way. A reduction of fibromyalgia-related widespread bodily pain of approximately 60% was obtained. Although these results are exciting,



**Fig. 1.** Schematic drawing of an implanted occipital nerve trial lead. The lead is placed just below the inion at the origins of the branches of the greater occipital nerve. Notice the sharp angle of the lead to prevent migration.

one must keep in mind that this study lacked placebo control. The placebo response encountered in most available pain treatments may get as high as 35% [37]. Except for the lack of placebo control, one might suggest that the improvement in headache-related pain might have influenced the other scores as well.

These results motivated the authors to perform a second study in which the effects of greater occipital nerve stimulation on fibromyalgia related symptoms were evaluated in a placebo controlled way [Plazier et al., unpubl. data].

Eleven patients were included in the study protocol, all suffering from fibromyalgia and diagnosed in accordance with the ACR-90 criteria [1]. The patients were implanted with an Octrode® (St. Jude Medical Neuromodulation) lead, which was inserted transversely crossing the midline of the occipital scalp, just below the inion (fig. 1).

Implantation was followed by a trial period, consisting of 10 weeks, and subsequently by an open-labeled follow-up period of 6 months after permanent implantation.

During the trial and the follow-up period after permanent implantation, various scales for pain (VAS, Pain Catastrophizing Scale, Pain Vigilance and Awareness Questionnaire), mood (Beck Depression Inventory II), fatigue (modified Fatigue Impact Scale) as well as the fibromyalgia impact scale and the amount of positive trigger points were monitored.

The patients were stimulated at individually selected frequencies (6, 10, 12, 18 and 40 Hz), based on optimal pain suppression. Stimulation was performed with a pulse

width of 300  $\mu$ s at alternating positive and negative poles by a rechargeable internal pulse generator.

For 10 weeks, the 11 implanted patients were stimulated in a placebo-controlled cross-over design. This design existed of two arms: (1) sham stimulation (stimulation at the absolute minimal amplitude of the stimulation device, which is considered as noneffective stimulation, and so as sham stimulation), and (2) stimulation at subsensory threshold levels, which prevented the sensation of paresthesias at the occipital scalp area. Both arms of this study were using parameters below the sensory threshold. This resulted in a placebo-controlled study, whereas the effective (2) and noneffective (1) arms were intractable for the patients. Afterwards, all 11 patients got the opportunity to get implanted with a permanent IPG. Two patients were not satisfied with their response to stimulation and so eventually 9 patients were implanted with an IPG.

During the trial period, a significant decrease in fibromyalgia-related pain (approximately 40%) and pain catastrophizing scores were noted. However, mood and fatigue scores were not influenced in a significant way by applying occipital nerve stimulation.

After the trial period the results remained stable for a period of 6 months with a decrease in pain of approximately 45% as well as a significant decrease in the amount of positive trigger points and the overall score on the fibromyalgia Impact Questionnaire.

These results confirm the previously obtained results by Thimineur and De Ridder [29] in a placebo-controlled manner, and suggest that occipital nerve stimulation could become part of the treatment modality for fibromyalgia-related pain. However, how this kind of stimulation works is entirely unknown.

It is proposed that the central nervous system plays a critical role in the pathophysiology of fibromyalgia. Neuroendocrine, autonomic nervous system and neuroimmunological factors might also be involved in the widespread bodily pain [13, 17, 18, 38]. Thus, it is expected that stimulation of the greater occipital nerves modulates these systems in one or another way.

The greater occipital nerve afferents enter the C2 segment of the spinal cord at the level of the nucleus caudalis of the trigeminal nerve forming the trigeminocervical complex. The nucleus caudalis projects to the thalamus, which relays sensory input to the cortex [33, 34, 39, 40]. Furthermore, animal studies have shown connections between neurons of the C2 spinal cord and the hypothalamus [41], the thalamus [42, 43], the periaqueductal grey (PAG) [42], the caudate nuclei [44], the amygdala and orbitofrontal cortex [43] as well as the cerebellum [45]. Thus, the C2 spinal cord is connected to many other brain structures directly.

#### *Greater Occipital Nerve Stimulation and the Brain*

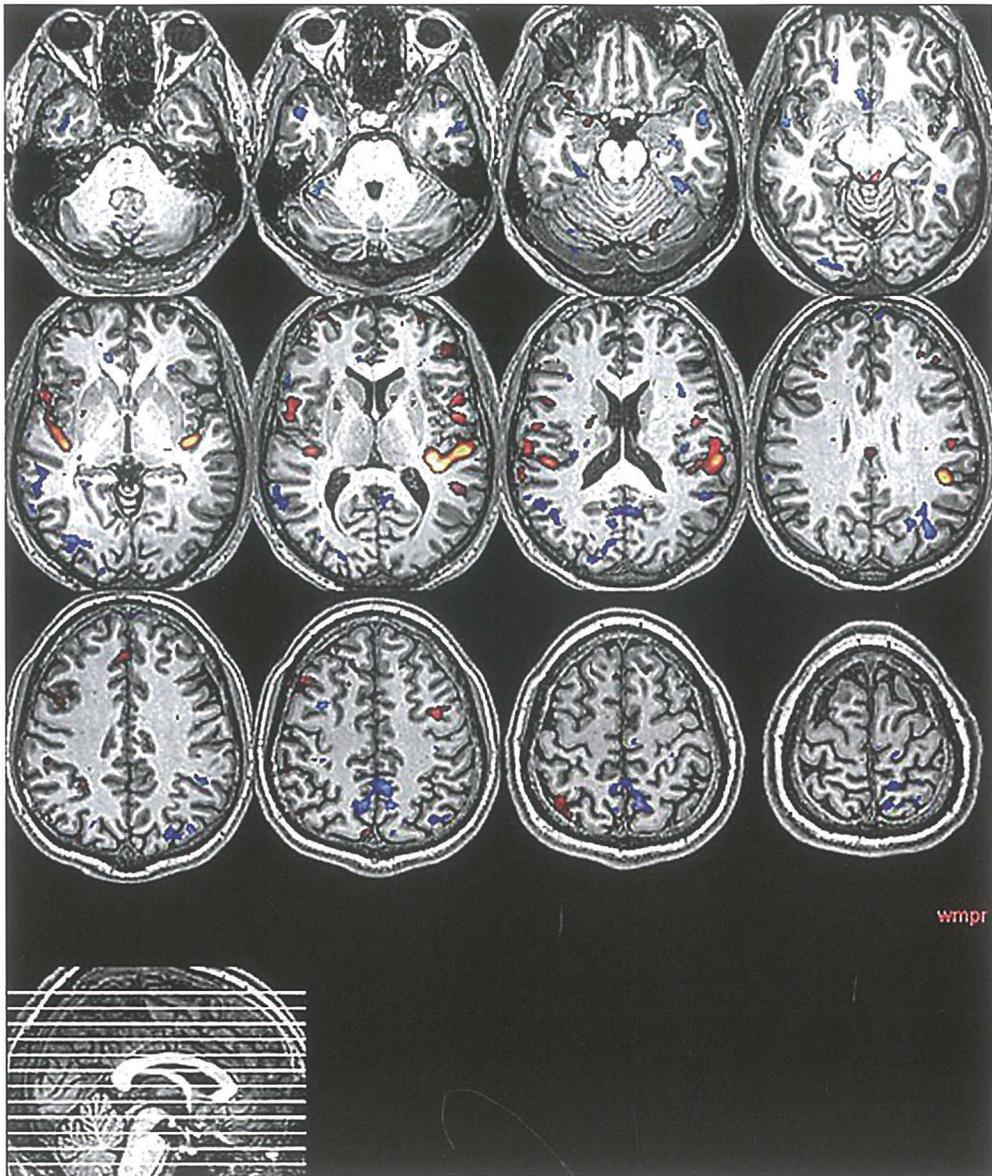
A few studies have been performed analyzing the influence of greater occipital nerve stimulation on the brain function. Matharu's group performed PET scans in 8 patients implanted with a greater occipital nerve stimulator for chronic migraine.

These scans were performed in three different states: (1) stimulator at optimal settings (pain-free, experiencing paresthesia), (2) stimulator off (experiencing pain), and (3) stimulator partially activated (intermediate pain and paresthesia). This study revealed significant changes in the regional cerebral blood flow in the dorsal rostral pons, anterior cingulate cortex (ACC) and the cuneus, correlated to pain scores. Changes in the ACC and the left pulvinar correlated to paresthesia scores [46]. As these structures are well known to be involved in the brain pain matrix [47], these data might suggest that stimulation of the greater occipital nerve results in a modulation of brain activity in pain related cortical and subcortical structures. This might be a direct or indirect effect; however, these changes in cerebral blood flow might be solely related to the changes in pain sensation and paresthesias and not the direct product of the stimulation. In order to provide an answer to these questions, the effects of greater occipital nerve stimulation in healthy subjects might be useful.

The authors performed a functional MRI on a healthy subject, one of the co-authors (D.D.R.), implanted with an occipital nerve stimulator. Analysis of the data revealed significant increases in BOLD signal in the thalami, hypothalami, orbitofrontal cortex, premotor cortex, peri-aqueductal gray matter, inferior parietal cortex and cerebellum. During stimulation, deactivation could be found in primary areas like the primary motor (M1), visual (V1) and somatosensory areas (S1) as well as in the secondary somatosensory area (S2) and the amygdala [Kovacs et al., in press]. The results of Matharu's study showed a correlation between paresthesias and changes in blood flow in the ACC and left pulvinar. This might suggest that the sensation of paresthesias might be, at least partially, responsible for the changes in brain activity. However, in the fMRI study we performed stimulation at both supra-sensory threshold levels (inducing paresthesias at the occipital scalp) and at the sub-sensory threshold level. Both conditions resulted in altered BOLD signals, which might suggest that occipital nerve stimulation alters brain activity as a direct result of the stimulation. Hence, this study suggests that greater occipital nerve stimulation exerts its effect at the level of the central nervous system (fig. 2).

Results from an EEG source localization study (LORETA) [48] support these findings in fibromyalgia patients implanted with an occipital nerve stimulator [Plazier et al., unpubl. data]. EEG data were acquired in 9 patients in two conditions: (1) during stimulation (pain suppression), and (2) without stimulation (no pain suppression). Making use of the LORETA-Key software package [48], which permits solving the inverse problem and to localizing EEG activity to cortical structures, statistical analysis revealed differences in brain activity in several pain-matrix-related structures, amongst them the cingulate cortex (fig. 3).

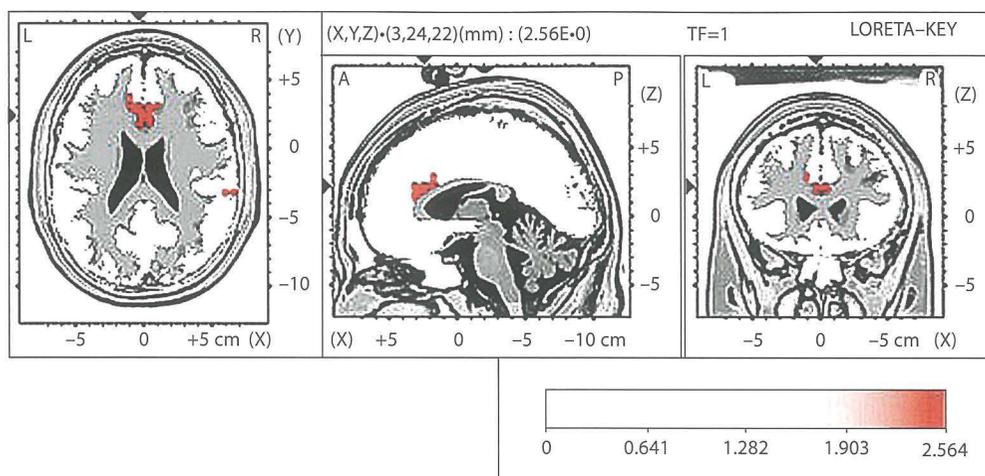
Both fMRI and EEG data suggest that one of the mechanisms involved in fibromyalgia-related bodily pain suppression is based on changes of activity in the central nervous system. Four different hypothetical pathophysiological mechanisms can be proposed on how occipital nerve stimulation might exert its effect in fibromyalgia.



**Fig. 2.** Global BOLD activation and deactivation for occipital nerve stimulation for all stimulation frequencies combined (image by Silvia Kovacs and Stefan Sunaert, KU Leuven, Belgium).

*Hypotheses Concerning the Working Mechanism of Occipital Nerve Stimulation in Fibromyalgia*

Just as the general pathophysiology of fibromyalgia remains unknown, the mechanism by which greater occipital nerve stimulation exerts its effect is still unclear, one can only state possible hypotheses about why greater occipital nerve stimulation is



**Fig. 3.** LORETA source localization of high-frequency EEG activity (24–28 Hz) at the cingulate cortex during occipital nerve stimulation compared to no stimulation. All voxels presented are significant at the  $p < 0.05$  interval.

beneficial in the treatment of fibromyalgia. Several possible explanations can be proposed based on the data presented here.

- 1 Direct modulation of spinothalamic pathways at the level of C2 in the spinal cord can suppress bodily pain.
- 2 C2 stimulation can modulate autonomic nervous system involvement in fibromyalgia.
- 3 C2 modulation acts indirectly via the mesolimbic dopaminergic system as suggested by the first fMRI study performed during C2 stimulation.
- 4 A combination of the three above-mentioned mechanisms.

#### (1) Direct Modulation of Spinothalamic Pathways at the Level of C2 in the Spinal Cord Can Suppress Bodily Pain [29]

The stimulation may exert influence on the lateral spinothalamic pathways, as the largest population of cells of origin of the spinothalamic pathways (35%) are found at the level of C2-C3 (in the Old World monkey) [49]. Interrupting the C1-C2 anterolateral spinothalamic tract of the spinal cord is a well-known neurosurgical technique, causing contralateral loss of pain sensation below the level of the lesion [50, 51]. Evidence, using spinal cord and thalamic stimulation, has been presented that C1-C2 spinal neurons (in the primate) mediate an inhibitory effect of viscerosomatic input on spinothalamic neurons [52]. This suggests not only lesioning but also electrical stimulation might exert a suppressing effect on the spinothalamic input below the level of electrical input. The generalized pain suppressive effect of the C2 stimulation might mediate its effect via modulation of the lateral spinothalamic cell bodies and nerve fibers of C2.

In Kovacs study [unpubl. data], the primary sensory cortices, inclusive of the somatosensory cortex are deactivated during C2 stimulation, suggesting that pain perception might be decreased, as the primary somatosensory cortex shows a general increase of activity in neural pain syndromes [53, 54].

## (2) C2 Stimulation Can Modulate Autonomic Nervous System Involvement in Fibromyalgia

A considerable amount of publications demonstrate involvement of the autonomic nervous system in the pathophysiology of fibromyalgia [5, 18, 55], many based on Heart Rate Variability measurements. A general increase in sympathetic tone [5, 13, 56–58] and potential decrease in parasympathetic tone [57–59] have been proposed. The structures of the brain which regulate the autonomic nervous system consist of structures such as the autonomic centers at the brainstem (sympathetic locus coeruleus, and parasympathetic nucleus tractus solitarius), the subgenual and dorsal part of the anterior cingulate, the insulae, amygdala and hypothalamus. Most of these structures are connected monosynaptically to the neurons at the C2 spinal cord [41]. Furthermore, some neurons in the C2 spinal cord respond to sympathetic [60] or parasympathetic [61] stimulation or to both sympathetic and parasympathetic stimulation [60, 62]. And many of these structures are involved in the sensation of pain as well [63, 64]. According to the imaging studies described above, the activity in these structures can be altered by greater occipital nerve stimulation, which provides a theoretical basis to hypothesize that greater occipital nerve stimulation might influence the sympathetic and parasympathetic tone. A simple way to prove or disprove this hypothesis is to perform HRV studies in implanted patients.

## (3) C2 Modulation Acts Indirectly Via the Mesolimbic Dopaminergic System

Because dopamine is implicated in both pain modulation and affective processing, it can be hypothesized that fibromyalgia may involve a disturbance of dopaminergic neurotransmission [65]. It has been shown that healthy subjects release dopamine in basal ganglia during painful stimulation, whereas fibromyalgia patients do not. In healthy subjects, the amount of dopamine release correlates with the amount of perceived pain, but in fibromyalgia patients it does not [65]. This has been confirmed by a PET study demonstrating that fibromyalgia might be characterized by a disruption of dopaminergic neurotransmission [66]. Voxel-based morphometry has shown that dopamine metabolism changes might contribute to the associated changes in gray matter density. Fibromyalgia is characterized by gray matter changes bilaterally in the parahippocampal gyri, in the right posterior cingulate cortex, and left anterior cingulate cortex [67]. As our EEG study shows changes in the anterior cingulate, it is possible that occipital nerve stimulation interferes with dopaminergic modulation of this area, which is implicated in the pathophysiology of fibromyalgia. The reward system uses both dopamine and opioid receptors, with dopamine related more to motivational aspects and opioids more to pleasure related aspects [68–70]. In fibromyalgia

both systems seem to dysfunction, as altered endogenous opioid analgesic activity has been demonstrated in the nucleus accumbens, the dorsal ACC and the amygdala [71]. This could explain why opioids often are less beneficial in fibromyalgia patients than in controls. Hypothetically occipital nerve stimulation can interfere with the opioid system via the direct connections between the C2 spinal cord and the amygdala or the indirect modulation of the ACC.

#### (4) A Combination of the Three Above-Mentioned Mechanisms

Future studies will have to elucidate whether 1, 2 or all 3 of the proposed mechanisms are involved in the improvement of fibromyalgia using occipital nerve stimulation.

### Conclusion

Fibromyalgia has a serious impact on society because of its high prevalence and the high direct and indirect medical costs. Since there is no generally accepted pathophysiology of this condition, treatment options remain limited.

Peripheral nerve stimulation, by means of greater occipital nerve stimulation, seems to be a promising addition in the treatment of fibromyalgia and besides the therapeutic value, it is an interesting tool to provide information about the pathophysiology of fibromyalgia.

The mechanism of action of greater occipital nerve stimulation is not completely clear and its effectiveness in syndromes as fibromyalgia might suggest that it has direct and indirect effects on cerebral structures via neurons at the level of the C2 spinal cord. This raises some hypotheses about the possible working mechanism of occipital nerve stimulation in fibromyalgia. It is clear that further research is needed and that it should focus on differences in brain activity, which can be demonstrated by functional imaging studies.

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