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Laser-Evoked Potentials in Fibromyalgia: The Influence of Greater Occipital Nerve Stimulation on Cerebral Pain Processing

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Objective: Fibromyalgia causes widespread musculo-skeletal pain in the four quadrants of the body. Greater occipital nerve stimulation has recently shown beneficial effects in fibromyalgia patients on pain, fatigue, and mood disorders. Laser-evoked potentials (LEPs) are used for research to understand the pathophysiological mechanisms of pain and to evaluate the effects of pain treatment. In fibromyalgia patients, LEPs tend to have a higher N2 amplitude, a tendency to shorter latencies, and patients have a lower pain threshold. Greater occipital nerve stimulation might exert a modulation of the medial pain pathways processing the affective motivational components of pain (unpleasantness) as well as the descending pain inhibitory pathways (reducing pain), both of which are contributing to the N2P2 peak.

Materials and Methods: To test this hypothesis, the authors performed LEPs in a group of fibromyalgia patients with and without greater occipital nerve stimulation.

Results: Occipital nerve stimulation does not alter the amplitudes of the LEP recordings, although a significant difference in latencies can be seen. More specifically, latencies of the N2P2 increased in the condition after stimulation, and especially at the Pz electrode.

Conclusion: Our results suggest Occipital Nerve Stimulation (ONS) induces a modification of the balance between antinociceptive pain inhibitory pathways and pain-provoking pathways.

Keywords: C2 stimulation, fibromyalgia, greater occipital nerve stimulation, laser-evoked potentials, pain, pain processing

Conflict of Interest: Drs. Plazier and De Ridder have consulted for St. Jude Medical. The remainder of the authors declare no potential conflicts of interest.

INTRODUCTION

Fibromyalgia is a disease with a prevalence as high as 20% in developed countries (1). The economic burden of this disease is high and yearly costs are estimated up to $11,049 per patient per year in the United States and up to €10.087 per patient per year in Europe (2,3). It mainly affects women between 30 and 50 years of age. Fibromyalgia causes widespread musculo-skeletal pain in the four quadrants of the body. It is a chronic disease, associated with sleep disorders, fatigue, bowel symptoms, headaches, and mood disorders. Quality of life is seriously compromised by this disease (4,5). Lacking a specific abnormality on examination, the diagnosis remains a purely clinical diagnosis. However, following clinical guidelines, the diagnosis can be made with adequate precision (4,6).

Treatment options consist of non-steroidal anti-inflammatory drugs, antidepressants, gabapentin, physical exercise, and psychological support. However, the results of these treatments, even in combination, are poor (7–9). Because this pathology is lacking specific abnormal findings in the peripheral tissue because of the associated symptoms, it is thought to be caused by a central nervous system malfunction/abnormality. Scientific evidence supports a central hypervigilant state of arousal in which central pain sensitization plays an important role (10,11). It has been attributed to dysfunctional descending μ-opioid antinociceptive pathways, rather than increased ascending nociceptive inputs. Multiple functional imaging studies support this theory, in which brain areas involved in central pain processing are differently activated in fibromyalgia patients (12).

Greater occipital nerve stimulation is a well-known treatment in occipital neuralgia and primary headache syndromes (13,14). Recent studies describe beneficial effects of greater occipital nerve stimulation in fibromyalgia patients in reduction of pain, fatigue, and mood disorders (15–17).

The greater occipital nerve has extensive connections to the nuclei of the trigeminal nerve and higher cerebral regions through a

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connection at the level of the pons called the trigemino-cervical complex (18,19). Functional imaging studies have shown alteration of neuronal activity in regions involved in pain processing caused by stimulating this nerve (20–22). This might help explain why stimulation of this specific nerve influences widespread pain syndromes like fibromyalgia. However, in order to better understand these possible central effects, further research is needed.

Laser-evoked potentials (LEPs) are used in order to test the integrity of the nociceptive system. The nociceptive system consists of two ascending pathways (23,24): 1) a medial pathway that encodes the affective/motivational component of pain (unpleasantness), which is processed by the dorsal anterior cingulate cortex and the insula, and 2) a lateral pathway that encodes the discriminatory components of pain (pain intensity), localization and quality, which is processed by the somatosensory cortex and the parietal area (23,24). The medial pain pathway, which has also been called the pain matrix, is actually multimodal salience network (25–27), attributing salience (28) to the pain stimulus. The ascending pathways are kept in balance by the descending pain inhibitory antinociceptive pathway consisting of the pregenual anterior cingulate cortex, (para)hippocampus, hypothalamus, and periaqueductal gray (29,30). Besides this purpose, LEPs are used for research to understand the pathophysiological mechanisms of pain and to evaluate the effects of pain treatment (31). The technique makes use of a painful laser stimulus applied to the skin, which is believed to stimulate the Aδ- and c-fibers and the spinothalamic ascending tracts. Subsequently, the evoked response at the cortical matrix is captured with scalp electrodes. These measurements result in well-identifiable potentials with a positive and negative complex. The amplitude and latency of these complexes permit interpretations about the central pain processing (32). The measured signal represents a measurement for the complete pain matrix, instead of only a representation of the somatosensory cortex (31,33). The evoked potentials are generated by components of both the ascending medial and lateral pain pathways (34,35) (i.e., the anterior cingulate, insula, and somatosensory cortex (26,27)). The P2 is not only generated by the dorsal Anterior Cingulate Cortex (dACC) and insula but also by the pregenual Anterior Cingulate Cortex (ACC) (36), part of the descending antinociceptive system. Therefore, it could reflect the balance between ascending and descending pain processing pathways.

The LEPs can be recorded with a single electrode at the midline or with an electroencephalogram (EEG) cap. Most commonly, the amplitude and latency of the N2 and P2 peak are measured. Amplitude seems to correlate with the subjective sensation of pain and varies with intensity, attention, salience, and novelty to the stimulus (37). In fibromyalgia, several changes in the LEPs are shown compared with healthy subjects whereas fibromyalgia patients tend to have lower pain thresholds, higher N2 amplitudes, and a tendency to shorter latencies (38–40).

Concerning neuromodulation techniques in pain, LEPs seem to be an interesting research tool. In several studies in which both peripheral nerve stimulation (PNS) techniques have been applied (i.e., transcutaneous electrical nerve stimulation [TENS] and central stimulation techniques like transcranial magnetic stimulation), amplitudes and latencies decrease significantly. This might be explained by distracting attention to pain caused by the paresthesia and effects in the central nervous system caused by stimulation (41–44).

The authors hypothesize that greater occipital nerve stimulation might exert a modulation of the descending pain inhibitory pathway. This can be either directly or by modulating the medial pain pathway, as not only pain discrimination is modulated by the greater occipital nerve stimulation, but also the affective component of pain perception (15,16). To test this hypothesis, the authors performed LEPs in a group of fibromyalgia patients with and without greater occipital nerve stimulation. The authors expect that LEPs differ in either the amplitude or latency of the N2P2 complex, as this reflects the balance between the ascending pain-provoking and descending pain inhibitory pathways.

METHODS

Participants

Ten participants diagnosed with fibromyalgia and implanted with a greater occipital nerve stimulator were included in this study. Patients were implanted during two previous trials. After a successful trial period, which comprehended an overall decrease in fibromyalgia-related pain on a visual analog scale and decreased fibromyalgia-related complaints on the Fibromyalgia Impact Questionnaire (FIQ), patients got the chance to get implanted with a permanent stimulation device. Coinciding headaches and the beneficial effect of stimulation on headaches did not influence this decision. Overall, patients were included in accordance with the following inclusion criteria: 1) Participants had to suffer from fibromyalgia and be diagnosed with fibromyalgia in accordance with the criteria proposed by the American Academy of Rheumatology (ACR-90). These criteria imply the presence of widespread chronic pain, lasting for more than three months in all four quadrants of the body. All participants were diagnosed by the Department of Physical Medicine and Rehabilitation at the University Hospital Antwerp, Belgium (45). Mimicking pathologies were ruled out by physical examination, blood samples (sedimentation, inflammation parameter, etc.), and if required, further examinations (radiological examinations, ultrasound). Psychiatric disorders were ruled out by a pain-specialized psychologist. 2) Participants had to be implanted with a subcutaneous occipital nerve stimulation device for at least six months and had to have beneficial effects on their disease during this period. 3) Participants age had to be between 18 and 65 and had to be able to keep their medication unchanged for the time of the study protocol. Exclusion criteria excluded patients with severe medical illness, history of substance abuse, severe psychiatric disorders, and pregnancy. Ten patients were approached to participate in this study and all ten fulfilled the diagnostic criteria and agreed to participate. Mean age of the patients was 51.7 years (standard deviation [*SD*] = ±12.06 years; range 32–72). Nine patients were female and one patient was male. All patients gave written informed consent and the ethical committee of the University Hospital Antwerp, Belgium approved the study.

Occipital Nerve Stimulation

All patients were implanted with a subcutaneous occipital nerve stimulator placed on an imaginary line between the two pinnae of the ears just underneath the occipital protuberans. One long (5.2-cm lead span) percutaneous wire electrode (Octrode, St. Jude Medical, Plano, TX, USA) was inserted 2.6 cm laterally from the midline, so that four contacts would cover the contralateral side and four contacts the ipsilateral side using the technique previously described (16,17). Patients were implanted with a rechargeable implanted pulse generator (EON, St. Jude Medical). Stimulation was performed at individually chosen frequencies ranging between 6 and 40 Hz, based on optimal pain suppression. Pulse width was fixed at 300 μsec and electrodes were programmed at individually chosen sets as anodes and cathodes in such a way that stimulation was equally felt at the left and right side of the scalp area. Patients

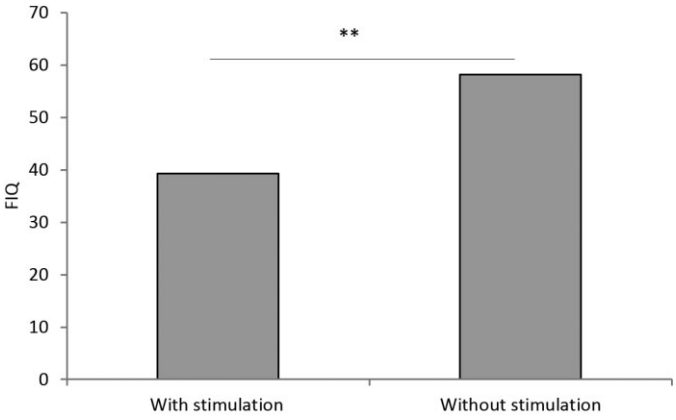

Figure 1. The mean difference on the Fibromyalgia Impact Questionnaire (FIQ) with and without stimulation of the occipital nerve. $^{**}p = 0.008$.

were familiar with this system for at least six months prior to enrollment in this study protocol (Fig. 1).

Study Interventions

Questionnaires

Patients were asked to fill out the FIQ in two conditions: A) *with stimulation*, in which an optimal setting of stimulation parameters was used, representing effective pain suppression, and B) *no stimulation*, in which stimulation was turned off for one week before the data acquisition, representing no pain suppression.

LEP Recordings

LEPs were measured in two conditions. During condition A "with stimulation," patients were at optimal stimulation settings for at least one week prior to the data acquisition. Just before recording the potentials, the stimulator was turned off in order to decrease artifacts caused by the stimulation on the recorded LEP. During condition B "no stimulation," patients had turned off their stimulation device for at least one week prior to the measurements. Laser stimulation was applied at the back of the hand, above pain threshold (3–5 watts). Pain threshold was determined before the actual measurements in both settings. Two sets of 20 stimuli at slightly different areas of the skin of the hand were applied for 15 msec, with a carbon dioxide laser (wavelength 10,6 μM, 8-mm beam diameter) (Neurolas System, DEKA Research and Development Corp, New Hampshire, NY, USA) . Scalp-evoked potentials were recorded at Cz and Pz according to the 19/20 electrode system, with a reference electrode located at the mastoid bone and a ground electrode at the contralateral arm. The late positive and negative peaks were identified (N2 and P2) and amplitude and latency were recorded while mean potentials were subtracted out of the stimuli (Nicolet amplifier AT2, Natus Medical Inc., San Carlos, CA, USA).

Study Design and Objective

This study was a non-randomized open-label trial. Ten participants were included in this study. Participants were not randomized, because the authors wanted to perform a measurement at the maximum effect of stimulation, after a long period of effective stimulation. All patients got stimulated for a period of minimally six months before enrollment in this study. As the patients were on effective stimulation (which gives paresthesia) and on "no stimulation" (without paresthesia), patients were not blinded for the recordings.

The objective of this study was to measure differences in the latency and/or amplitude from the LEPs comparing "stimulation" with "no stimulation."

Participants were enrolled after fulfilling the inclusion criteria and providing consent. After enrollment, participants were having occipital nerve stimulation in optimal conditions. This means providing an optimal decrease in their fibromyalgia-related symptoms. After this week of stimulation, they filled out the FIQ and underwent LEP recordings for condition A "with stimulation." After this moment of data acquisition, stimulation devices were turned off for one week by the investigators. Participants returned after one week to fill out the FIQ and to undergo the LEP recordings for condition B "no stimulation." All ten patients completed this study protocol.

Outcome Parameters

FIQ

The FIQ makes an inventory of the overall impact of fibromyalgia-related symptoms on daily life. It has proven to be a well-designed questionnaire to measure the impact of fibromyalgia on the overall quality of life of the patients. The maximum score is 100 and a higher score indicates a greater impact of the syndrome on the patient (46). The FIQ was taken for both conditions (i.e., condition A with stimulation and condition B without stimulation).

Pain Threshold

In both conditions, the pain threshold was determined by stepwise method, increasing the wattage of the laser stimulus until pain was experienced. The results were measured in watts.

N2 Latency on Cz and Pz

In each condition, the latency of the N2 peak was measured two times at the level of the Cz and Pz electrode according to the 19/20 electrode system. Measurements were performed in milliseconds.

Latency P2 on Cz and Pz

In each condition, the latency of the P2 peak was measured two times at the level of the Cz and Pz electrode according to the 19/20 electrode system. Measurements were performed in milliseconds.

Amplitude N2P2 on Cz and Pz

In each condition, the amplitude of the N2P2 complex was determined and measured in microvolts at the Cz and Pz electrode according to the 19/20 electrode system.

Statistics

To analyze the results, the SPSS 20.0 software package (SPSS, Inc., Chicago, IL, USA) was used. We averaged the obtained LEP results of the two sets of stimuli for the stimulation and the no stimulation conditions to have a more vigorous measurement. As only ten patients were included, we conducted non-parametrical statistics to compare the conditions with and without occipital nerve stimulation using a Wilcoxon test. To obtain correlations, Pearson correlations were calculated.

RESULTS

Behavioral Measure

A comparison of the overall impact of fibromyalgia-related symptoms on daily life during stimulation and after one week of no

stimulation revealed a significant effect ($Z = -2.65$, $p = 0.008$; see Fig. 1) demonstrating that the impact of fibromyalgia is higher after one week of no stimulation (mean [*M*] = 58.19, *SD* = 23.32) in comparison with stimulation (*M* = 39.32, *SD* = 21.05).

Pain Threshold

No significant effect was obtained when comparing the pain threshold between the condition "with stimulation" (*M* = 4.20, *SD* = 1.03) and the condition "no stimulation" (*M* = 3.80, *SD* = 1.03) ($Z = -1.41$, $p = 0.16$; see Fig. 2a).

Latency

No significant effect for both N2 ($Z = -0.46$, $p = 0.65$) and P2 ($Z = -0.46$, $p = 0.65$) on the Cz site was obtained when comparing the condition "with stimulation" (N2: *M* = 237.45, *SD* = 44.75; P2: *M* = 348.85, *SD* = 69.10) with the condition "no stimulation" (N2: *M* = 231.04, *SD* = 33.30; P2: *M* = 361.62, *SD* = 16.00). See Figure 2b for on overview.

No significant effect was demonstrated for N2 ($Z = -0.46$, $p = 0.64$) on the P site. During stimulation (*M* = 236.82, *SD* = 46.49), the latency was similar to the condition of "no stimulation" (*M* = 273.39, *SD* = 41.80). For P2, comparing the condition during stimulation (*M* = 346.15, *SD* = 74.94) with the "no stimulation" (*M* = 320.06, *SD* = 33.45) demonstrated no difference ($Z = -0.15$, $p = 0.88$). See Figure 2b for an overview.

In addition, the latency difference between N2 and P2 was significantly larger in condition "with stimulation" (*M* = 109.32, *SD* = 53.71) in comparison with "no stimulation" (*M* = 17.14, *SD* = 51.15) on the Pz site ($Z = -2.67$, $p = 0.008$). No significant difference was obtained between "with stimulation" (*M* = 111.41, *SD* = 52.28) and "no stimulation" (*M* = 130.57, *SD* = 25.66) on the Cz site ($Z = -0.26$, $p = 0.80$). See Figure 2c for an overview.

Amplitude

A comparison of the amplitude (peak to peak) difference between N2 and P2 during stimulation (Cz: *M* = 18.19, *SD* = 8.98; Pz: *M* = 16.75, *SD* = 8.81) in comparison with no stimulation (Cz: *M* = 19.74, *SD* = 6.89; Pz: *M* = 14.33, *SD* = 5.55) yielded no significant effect for both Cz ($Z = -0.97$, $p = 0.33$) and Pz ($Z = -0.87$, $p = 0.39$). See Figure 2d for an overview.

Correlations

Pearson correlations between the FIQ difference during "with stimulation" and "no stimulation" in association with Cz site revealed a significant effect for N2 ($R^2 = 0.36$, $p = 0.04$) and P2 ($R^2 = 0.33$, $p = 0.04$) (see Fig. 3a,b). These findings revealed that the better the suppression effect was on fibromyalgia, the later the N2 and P2 latency was during "with stimulation" as opposed to during "no stimulation." No significant effects were obtained for N2 ($R^2 = 0.00$, $p = 0.24$) and P2 ($R^2 = 0.08$, $p = 0.21$) on the Pz site.

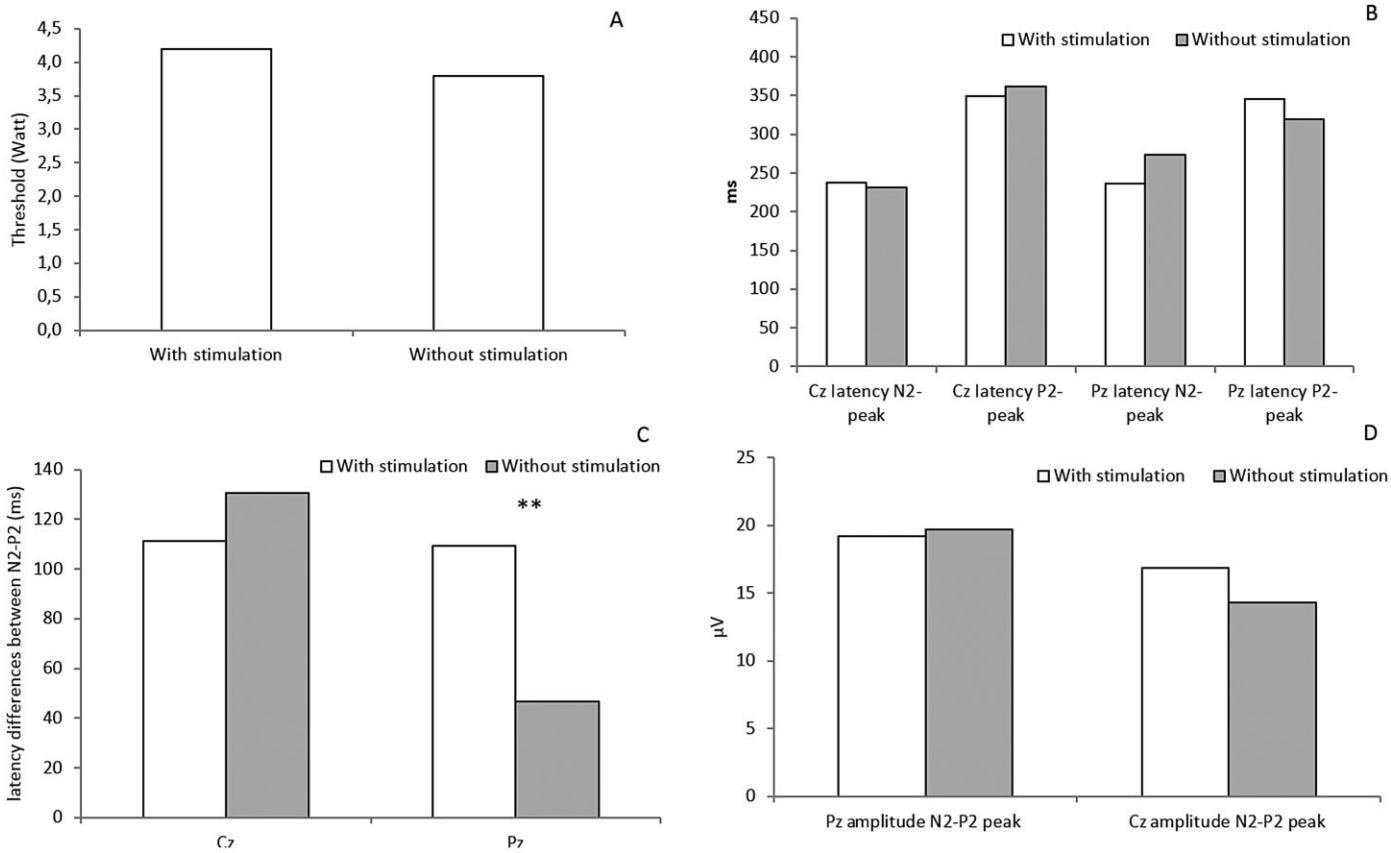

Figure 2. a. A comparison between the thresholds with and without stimulation of the occipital nerve. b. A comparison of the latency for the Cz and Pz electrode on peak N2 and P2 with and without stimulation of the occipital nerve. c. A comparison of the latency differences (N2-P2) for the Cz and Pz electrode with and without stimulation of the occipital nerve. d. Comparisons of the amplitude between N2 and P2 for the Cz and Pz electrode with and without stimulation of the occipital nerve. $^{**}p = 0.008$.

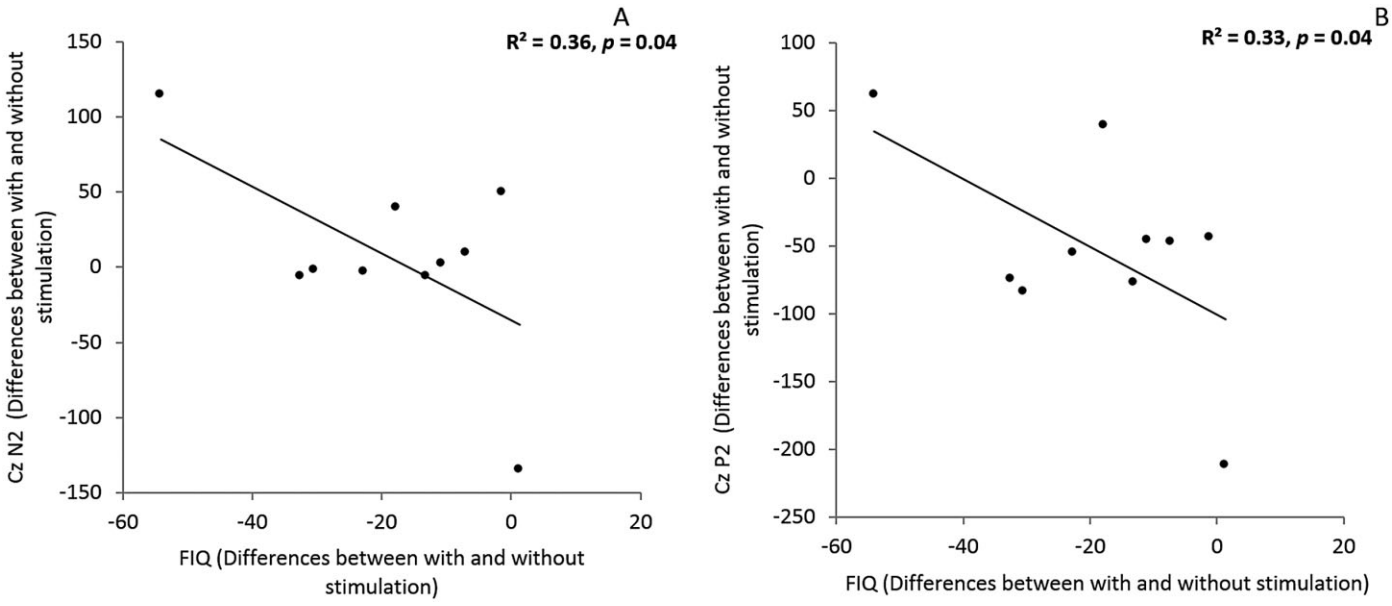

Figure 3. Correlation analysis between the Fibromyalgia Impact Questionnaire (FIQ) scores with and without stimulation of the occipital nerve and for the Cz electrode on peak N2 and P2 with and without stimulation of the occipital nerve.

We correlated the amplitude and the frequency of the stimulation with latency and amplitude findings on LEP for N2 and P2 and the peak-to-peak difference (between N2 and P2). No significant effects were obtained (R^2 between 0.03 and 0.15, *p*-values between 0.64 and 0.13), indicating that the stimulation parameters have no influence on the obtained LEP results. In addition, we calculated the stimulation duration before we started the study with the outcome on LEP of N2/P2 and the peak-to-peak difference (between N2 and P2). No significant results were demonstrated (R^2 between 0.11 and 0.16, *p*-values between 0.17 and 0.13).

Adverse Events

Redness and local skin irritation occurred in some patients at the field of laser stimulation. No medical treatment was needed; total spontaneous recovery occurred in all patients within a few weeks after stimulation.

DISCUSSION

FIQ scores differed significantly between conditions: A lower score on the FIQ could be seen during stimulation. This implies there is a significant difference in the severity and impact of fibromyalgia-related symptoms between the experimental conditions, not only for the pain intensity but also the affective/motivational components of the pain.

The stimulation threshold, which elicited painful sensations, did not significantly differ between both conditions. Occipital nerve stimulation did not alter the nociceptive pain threshold directly in this study, even though thresholds for laser-evoked nociceptive stimuli have shown to be lower in fibromyalgia patients compared with healthy subjects (38–40).

This finding suggests that the lateral pain system (the pathways projecting to the primary and secondary somatosensory cortices) is not modulated by stimulation, but this does not exclude modulation of the medial pain system, as suggested by previous studies (47). Modulation of the pain inhibitory pathway is possible as well, as has been convincingly shown before (48). This pain modulation can be explained by the fact that lowered nociceptive pain thresholds are just one part in the mechanism that is believed to cause chronic pain in the fibromyalgia syndrome. In fibromyalgia patients, pain perception is changed by a general hypervigilance for pain (49), which also involves central summation of painful stimuli (50,51).

In our study, we saw an overall difference in pain experience as pointed out by the FIQ scores. This still suggests a difference in pain processing during stimulation compared with no stimulation.

Hypervigilance to pain is hypothesized to be one of the key mechanisms in the pathophysiology of fibromyalgia. Hypervigilance to pain is a multidimensional process that involves attentional, emotional, and behavioral aspects (24). As a result, patients suffering from fibromyalgia have a raised attention to pain (52). Besides the lower pain threshold, hypervigilance is characterized by a shorter response time to painful stimuli (40). Our study analysis did not yield a significant difference for the amplitudes of N2 or P2 at the Pz and Cz recordings. Amplitudes are described to vary because of multiple contributing factors. It is known that the amplitudes of nociceptive-evoked potentials correlate with the subjective perception of the intensity of pain (53). However, novelty and repetition of a stimulus in a non-random order influence the amplitude of the potential. This results in a disrupted correlation between amplitude and subjective pain intensity (26). Because the interstimulus interval in this study was constant and stimulus intensity was adapted to the subjective pain threshold at each condition, no significant changes in amplitude occurred.

Concerning the latency, a significant difference for the N2P2 latency could be found during stimulation. Latency became longer during stimulation, which implies a prolonged processing time as the conditions at the peripheral nociceptors did not change within the individuals. This is an interesting finding because it might suggest that occipital nerve stimulation alters the central processing of the painful stimulus at a central level. Remember, we hypothesize the balance between the ascending pain-provoking medial

pain pathway and the descending pain inhibitory antinociceptive pathway, as both the dorsal anterior cingulate cortex and insula (i.e., medial pathway) and the pregenual ACC (i.e., pain inhibition) are generators of the N2P2 complex (36). The changes were significant at the Pz electrode measurements. This decrease can be caused by PNS, which can be seen in studies with TENS. By applying TENS at high frequencies, which suppresses pain by aβ-fiber stimulation, several similar changes in LEP have been described in healthy subjects. Krabbenbos et al. found a decrease in the N2P2 amplitude after TENS as well as a decrease of the N2P2 amplitude in a test–retest situation. Ristic et al. described a decrease in N2P2 amplitude after radial nerve stimulation. They described a delay in latency for both N2 and P2 with decreasing pain intensity levels of stimuli and with radial nerve stimulation (54). Ellrich and Lamp described findings in 15 healthy volunteers, which underwent electrical stimulation of the radial nerve making use of superficial electrodes at high frequency, causing a decrease in reported pain. LEP N2P2 amplitudes decreased significantly during PNS compared with no stimulation. Latencies of the N2 and the P2 peak increased. Ellrich and Lamp described a significant reduction of nociceptive processing caused by PNS based on the decrease and delay of the LEP components. An interesting finding in this study is the prolonged effect after stimulation (42). Other studies support this concept as well (55,56).

The effect of stimulation at the level of the occipital nerve might change the central pain processing in a similar way as mentioned above. Even after switching of the occipital nerve stimulation device, a prolonged effect can be expected (42,57). In our data, ONS causes a delay in the latency of N2P2 resulting in a decreased pain experience, which is in accordance with the preexisting literature (42,54–57). This might be the signature of central modulation of pain perception for LEP.

A closer look at the LEP signals in pathological states reveals a specific pattern concerning the differences in latencies.

LEP N2 and P2 latencies are disturbed in pathological states. In patients suffering from complex regional pain syndrome, a delay in the N2 and P2 peak can be found in the affected limb, compared with the non-affected limb. This might be explained by a higher attention to pain, which shortens the latency in the non-affected limb (58). In cluster headache, the latency is decreased at the headache side (higher attention) compared with the non-affected side for C2 and P2 (59). So in general, in pathological pain states, attention to pain is attenuated, which results in decreased latency times for the LEP components. This might be explained by less processing of the painful stimulus, hence a quicker sensory awareness of the stimulus. This can also be seen in fibromyalgia (40).

Study Limitations

This study is a non-randomized prospective study. Patients and investigators were not blinded for the conditions. The authors performed this study in this specific design for the following reasons:

1. Occipital nerve stimulation is known to be effective or more effective after longer periods of stimulation (up to months) (13). By not randomizing the patients and make them all start in condition A "with stimulation," the authors were assured of a maximal effect of stimulation on the symptoms.
2. Supra-sensory threshold stimulation, which implies the sensation of paresthesia at the occipital area, is more effective compared with sub-sensory threshold stimulation (20,60). Hence, the authors choose for a design with supra-sensory threshold stimulation during the period preceding condition A. This implied the impossibility of blinding or a placebo-controlled condition.
3. This study discusses the results in a group of patients suffering from fibromyalgia who respond to greater occipital nerve stimulation. There is no control group, because of the lack of a sufficient group of patients who did not respond to treatment after permanent implantation.

CONCLUSION

Occipital nerve stimulation does not alter the amplitudes of the LEP recordings; however, a significant difference in latencies can be seen. More specifically, latencies of the N2P2 increased in the condition after stimulation, especially at the Pz electrode. This suggests ONS induces a change in balance between the ascending medial pain pathway and the descending pain inhibitory pathway.

In pathological states, the latencies are decreased, which is the case in fibromyalgia as well, acting as the result of the hypervigilant state. This might be explained by attributing too much salience to a painful stimulus, caused by a decreased inhibition of pain inhibitory mechanisms. The decreased action of inhibitory pain mechanisms have been hypothesized as one of the important underlying mechanisms in fibromyalgia (48).

These findings suggest that occipital nerve stimulation alters the pathological shortened latencies, improving hypervigilance and the overall pain experience of the patient.

These data might be of interest to explain the beneficial effects of occipital nerve stimulation in (chronic) pain conditions and might help to understand the central working mechanism. Further research is needed to confirm the above-mentioned conclusion. This could be performed by using multichannel EEG, so that source localization can be performed on the LEPs. The involvement of the medial pain system can be derived from demonstrating changes in the amygdala, insula, and dorsal anterior cingulate, whereas the involvement of the descending system could be assumed by demonstrating changes in the pregenual and rostral anterior cingulate cortex.

Authorship Statements

Mr. Ost, Mr. Vancamp, and Drs. Plazier, Snijders, and Gilbers were responsible for collecting the data. Drs. Vanneste and De Ridder analyzed the data and wrote the manuscript.

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COMMENTS

The paper may provide insight into the effect of occipital nerve stimulation on cerebral pain processing, in particular with laser-evoked potentials in patients with fibromyalgia. However, the pain process in the brain is complicated, and further investigations are necessary to understand the mechanism related to neurostimulation and pain.

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This paper explores an interesting effect of Occipital Nerve Stimulation on the outcome measures of fibromyalgia and laser evoked potentials. The finding of this study would certainly support further investigation.

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This is a well written interesting approach to answering unsolved questions regarding pain processing in peripheral neuromodulation in general and specifically in ONS. Larger studies should elucidate the value of this technique for objectifying pain reduction.

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Comments not included in the Early View version of this paper.

