A Randomized, Controlled, Double-Blind Pilot Study of the Effects of Cranial Electrical Stimulation on Activity in Brain Pain Processing Regions in Individuals with Fibromyalgia

Ann Gill Taylor, EdD, RN,[1,#] Joel G. Anderson, PhD,[1] Shannon L. Riedel, PhD, RN,[1] Janet E. Lewis, MD,[2] and Cheryl Bourguignon, PhD, RN[1]

Objective: To investigate the effects of microcurrent cranial electrical stimulation (CES) therapy on activity in pain processing brain regions.

Design: A randomized, controlled, three-group, double-blind pilot study.

Participants: Persons with physician-diagnosed fibromyalgia.

Intervention: Active CES device, sham device, and usual care alone.

Results: Those individuals using the active device had a greater decrease in average pain ($P = .023$) than individuals using the sham device or receiving usual care alone over time. Preliminary analyses of the functional magnetic resonance imaging data on a subset of six participants from each of the two device groups show that individuals using an active CES device had a decrease in activation in the pain processing regions of the brain compared to those using a sham device.

Conclusions: The observed decrease in activation in the pain processing regions may indicate a decrease in neural activity in these regions that may be related to decreased pain. This is the first randomized, controlled trial of CES in patients diagnosed with fibromyalgia to report functional magnetic resonance imaging data.

Key words: fibromyalgia, pain, cranial electrical stimulation, brain, fMRI

(Explore 2013; 9:32-40.

INTRODUCTION

Fibromyalgia (FM) is a chronic syndrome characterized by widespread pain, tenderness, and hypersensitivity to pain in specific locations. It often is categorized with other pain syndromes or affective disorders, including irritable bowel syndrome, temporomandibular disorder, headache, and major depressive disorder.[1] Fibromyalgia affects between 2% and 4% of the U.S. population. Women are almost 10 times more likely to have FM compared with men,[2,3] with the prevalence of FM increasing from <1% in women ages 18 to 30 to almost 8% in women ages 55 to 64.[3,4]

The hallmark of FM is pain. Nociceptive pain is transmitted from nociceptive peripheral nerves to the spinal dorsal horn or spinal trigeminal nucleus via the spinothalamic and trigeminothalamic tract to the thalamus, which conveys pain signals to the somatosensory cortices (for review, see Clauw et al[5]). This pathway is believed to support the sensory and discriminatory aspects of pain. In addition to this direct pathway, pain is mediated through other thalamic nuclei and "limbic areas," including the cingulate, insula, and regions of the prefrontal cortex, as well as the amygdala and hypothalamus, regions that coordinate emotion, stress, and autonomic responses and are likely to contribute to the affective dimensions of pain.

Although the etiology of FM is not completely understood, alterations in central pain processing have indeed been identified. The pathophysiology of central pain includes a deficit in descending pain inhibitory systems,[6,7] with evidence that reduced levels of neurotransmitters, such as the catecholamines, contribute to the insufficient inhibition of pain in FM.[8-16] In particular, Wood and colleagues[8] found that presynaptic dopamine metabolism was significantly lower in the cingulate, insula, mesencephalon, medial thalamus, and hippocampus in those with FM compared with healthy control patients.

On the basis of evidence that brain processing of pain is disturbed in patients with FM, treatment with actions targeted toward the brain should be particularly promising. Over the years, several types of electrical stimulation of the brain have been used to reduce pain or depression.[17] However, most electrical stimulation procedures use high strength current (electroconvulsive therapy) or electrical field (repetitive transcranial electromagnetic stimulation), and thus the use of these modalities is limited to specialized facilities with trained healthcare professionals. In contrast, microcurrent cranial electrical stimulation (CES) devices deliver modified square-wave biphasic stimulation at 0.5 Hz and 100 μA, with the electrodes of the device placed on the ear lobes. One such device, Alpha-Stim (Electromedical Products International, Inc, Mineral Wells, TX), is a medical device approved by the Food and Drug Administration

1 Center for the Study of Complementary and Alternative Therapies, University of Virginia, Charlottesville, VA
2 Division of Clinical Rheumatology, Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA

Corresponding author. Address:
Center for the Study of Complementary and Alternative Therapies, University of Virginia, Charlottesville, VA 22908
e-mail: mailto:agt@virginia.edu

ISSN 1550-8307/$36.00

http://dx.doi.org/10.1016/j.explore.2012.10.006

(FDA K903014) for pain relief and is suitable for at-home use, expanding the potential range of therapeutic applications. The safety of low strength CES devices has been demonstrated with very few adverse effects.[18,19]

Whereas the mechanisms of CES are still speculative, it is generally believed that the effects are primarily mediated through a direct action on the brain, likely at the limbic system, hypothalamus, thalamus, and/or the reticular activating system.[20] Studies in rats have shown as much as a threefold increase in endorphin concentration after only one session of CES.[21] In humans, electroencephalogram (EEG) studies have shown that CES can influence alpha activity (increase or decrease) and decrease delta and theta activity. In human participants with pain, sessions of CES reportedly changed EEG patterns to more closely resemble pain-free participants. In preliminary clinical studies in which CES was used participants had increases in plasma serotonin and β-endorphin.[22]

Although a few studies have investigated changes in EEG patterns after CES use, few data exist on the potential neural correlates of mechanisms (eg, functional magnetic resonance imaging [fMRI]) by which CES may affect pain in general, or more specifically, in those with FM. Thus, we sought to examine the effects of CES therapy by using a double-blind, randomized, controlled design to collect fMRI data on activation in pain processing brain regions.

METHODS

Subjects

Potential participants were recruited as part of a larger study[23] from rheumatology practices and the surrounding Central Virginia communities. After persons expressed interest in the study, the study coordinator thoroughly described the study and reviewed the University of Virginia Institutional Review Board for Health Sciences Research approved consent form with them. Those who agreed to participate signed the consent form, a copy of which was given to the study participant. After obtaining informed consent, participants were randomized to one of three groups (active CES device, sham device, and usual care alone) in a ratio of 1:3 by the use of masked allocation as generated by computer.

Inclusion and Exclusion Criteria

The criteria for inclusion in the study were as follows: meeting the diagnostic criteria for FM as established by the American College of Rheumatology[24]; reporting an initial pain level equal to or greater than 3 on a 0-10 numeric rating scale; having stable medication use related to FM for at least 4 weeks; having right-handed dominance because of potential of assignment to undergo fMRI; and the ability to read, write, and understand the English language. Potential participants were excluded if they were pregnant or breastfeeding, had epilepsy or history of seizures, or had a pacemaker and/or other implanted device (eg, insulin pump, opioid pump, defibrillator). In addition, excluded were those who were unable to undergo an fMRI, which would have included anyone with certain types of metal or metallic objects in the body, diaphragm or intrauterine device, dermal patches, ear or eye implants, implanted electrical stimulators, artificial heart valve, implanted catheter or tube, tattoos, claustrophobia, or a weight of more than 275 lbs. Forty-six persons with a confirmed diagnosis of FM (3 men and 43 women) were enrolled and assigned to one of the three study groups: usual care alone (n = 15); active CES device (n = 17), and sham device (n = 14; Figure 1). All participants remained on their usual care regimen during the study, including medications.

CES Intervention

Participants in the two device groups were instructed to use the Alpha-Stim CES device for 60 continuous minutes each day for 8 weeks. Participants in the CES device group received devices that were active and preset at the factory to provide a maximum of 60 minutes of modified square-wave biphasic stimulation at 0.5 Hz and 100 μA, the lowest setting that has been used in previous studies with patients with FM and below the level of perception. Participants in the sham device group received sham devices that appeared to be activated but did not deliver any stimulation. Because the devices were preset at the factory, participants were unable to change the settings. To monitor device usage, participants documented at what time and for how long the device was used each day.

Study Questionnaires

Participants completed questionnaires on demographics and general information related to FM, pain, fatigue, sleep disturbances, perceived stress, functional status, and psychological factors at baseline. All participants recorded their pain ratings each night in the diary using a 0−10 Numeric Rating Scale (NRS) and recorded any unusual symptoms or feelings they experienced that day. NRS is a simple, yet sensitive, measure of pain intensity that has yielded reproducible results in many different patients with various diagnoses, including FM.[25] All participants were instructed to call the study coordinator if they experienced any unusual feelings. One day, each week, all participants completed questionnaires on pain (Short-Form McGill Pain Questionnaire), fatigue (Lee's Fatigue Inventory), sleep disturbances (General Sleep Disturbance Scale), perceived stress (Daily Stress Inventory), and functional status (Fibromyalgia Impact Questionnaire). Symptom data from the larger study have been reported previously.[23] Once a week, the study coordinator called all participants to monitor adverse effects and the use of devices.

fMRI Procedures

A subset of participants (n = 6) in each of the two device groups had an fMRI at baseline and at week 8 to measure brain activation at rest and during a pain stimulation procedure. The fMRI evaluation consisted of a 1-hour session that included an anatomical MRI of the head and 3 functional scans during which participants received painful pressures applied to the left thumbnail bed via the pain stimulation device developed by Gracely et al.[26] The pain stimulation system has a maximum stimulus force of 10 kg that is limited by the capacity of the regulator (100 psi), a limited supply pressure (125 psi), and inline safety release valves. Pressure stimuli were delivered by a 1-cm diameter hard rubber probe to the left thumbnail bed, just above the cuticle.

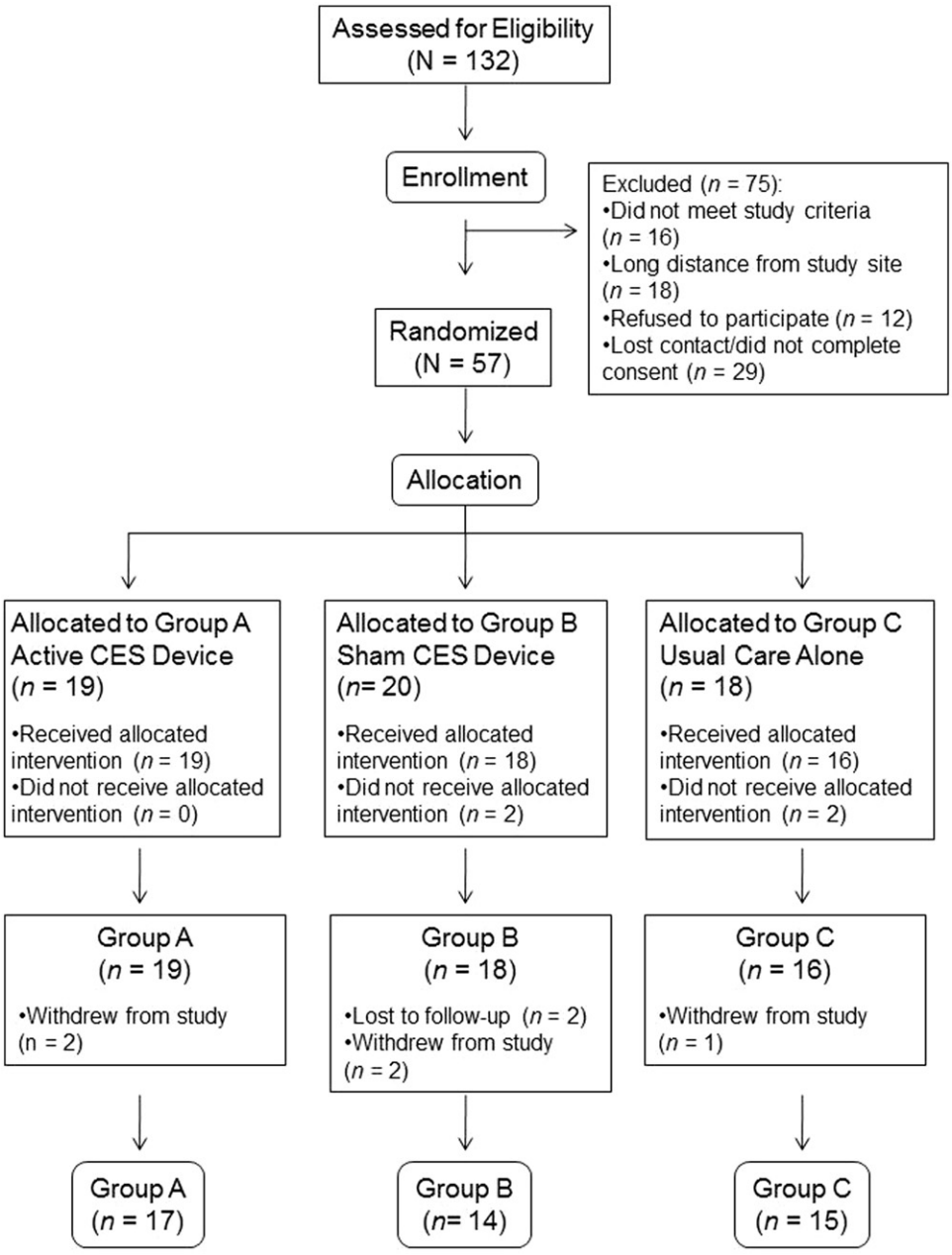

Figure 1. CONSORT flow diagram as reported in Taylor et al.[23] (in press).

Before performing fMRI on each participant, an ascending series of 5-second duration pressure stimuli was delivered at 20-second intervals. The stimulus was begun at 0.5 kg and increased in 0.5 kg increments until a rating of slightly intense pain using the Gracely Box scale (0−20) was achieved. The result of this procedure was used to select individualized stimulus pressures for the functional scans.

Participants were positioned in a 3.0 Tesla Siemens Avanto MRI scanner (NUMARIS/4, versions syngo 2,004V). After localizer images, both T1-weighted (gradient recalled echo, repetition time = 700, echo time = 6.6, flip angle = 90, 192 × 256) and T2-weighted (spin echo, TR = 2,500, TE = 60, 160 × 256) images were acquired to assist in anatomical localization of areas of activation to rule out neurological abnormalities. Preceding the functional scanning, a three-dimensional (3D) structural scan was acquired to provide for more precise anatomical localization (3D gradient recalled echo, repetition time = 25, min echo time, flip angle = 35, field of view = 24, 192 × 256 × 124, slice thickness = 1.4 mm). The functional scans consisted of three scans of 10 minutes each. In the first and third scanning sessions, stimulus pressures were alternated at 30-second intervals between 0 KG (off) and a pressure calibrated for each subject to evoke a slightly painful sensation in intensity on the Gracely Box scale (on). During the intervals when pressure was delivered

to the thumbnail bed, the pressure was released briefly every third second to permit circulation to the nail bed. In the second session, which used the same timing and stimulus parameters, the on condition was varied among three stimulus pressure levels that were presented three times each in a random sequence. Stimulus intensities for the random sequence were those individually determined for each subject in the ascending series to produce sensations corresponding to mild, moderate, and slightly intense pain on the intensity scale (0−20). In all three scans, images were collected at 2.5-second intervals. The sequence started with a 30-second off condition, delivered nine 1-minutes cycles of 30 seconds off and 30 seconds on, and finished with a 30-second off condition.

Preprocessing and Normalization of MRI Data

Motion-corrected functional data (Digital Imaging and Communications in Medicine, ie, DICOM format) for each subject were loaded into BrainVoyager QX (Brain Innovations, Maastricht, Netherlands) for preprocessing and converted to BrainVoyager's internal data format. A standard sequence of preprocessing steps was conducted for each subject following a modified method by Goebel and colleagues.[27] Mean intensity adjustment was carried out for each of the three scans individually for each subject and used as a predictor in the general linear model analysis. Slice scan time correction was performed using sync interpolation based on the order of slice scanning (ascending, interleaved) and information about the repetition time (2500 ms) contained in the file header. Spatial smoothing was accomplished using a Gaussian filter (full weight at half-maximum = 5 mm). In addition to motion correction by the scanner itself, 3D motion correction was performed in BrainVoyager QX to detect and adjust for minute cranial movement through spatial alignment of all volumes of a subject in the first scan to the first volume of that scan by rigid body transformations. Sync motion correction was then used for intrasession alignment of the second and third scans using the motion-corrected data from the first scan.

Anatomical data (DICOM format) for each subject were loaded into BrainVoyager QX for preprocessing and converted to the internal data format used by BrainVoyager. Data were transformed using iso-voxel scaling and corrected for spatial intensity inhomogeneities using a method by Vaughan and colleagues.[28] The data were then transformed into Talairach standard space to allow for intersession and intersubject comparisons. Functional data were transformed into Talairach spatial coordinates by coregistering with each subject's preprocessed 3D anatomical dataset using the same steps for transforming the anatomical data before generating a normalized, 4D volume time course to use in multisubject statistical analyses within BrainVoyager QX. A mean 4D volume time course for each treatment group (n = 6) was created for each scan, both at baseline and after the intervention, which were used for group analysis.

fMRI Analysis

For each scan, random effects models calculated a beta value for each group while we accounted for serial correlation among measurements taken on the each participant, as well as mean intensity adjustment. Comparisons were made between baseline and postintervention scans in each of the two treatment groups (active and sham). Because of the volume of voxel analyses, correction for multiple comparisons available in BrainVoyager QX software was used. Regions of interest (ie, cingulate, insula, prefrontal and somatosensory cortices, amygdala, and thalamus) were identified using areas of the brain in which the blood oxygen level-dependence (BOLD) changes were significantly different in clusters restricted by number of voxels to reduce error. Talairach coordinates of the cluster centers were used to identify the regions of interest using the freeware application Talairach Client.

Statistical Analysis

Separate multilevel models[29] were used to estimate mean differences among the three groups for each of the pain measures (NRS and Short-Form McGill Pain Questionnaire). Model parameters were estimated by restricted maximum likelihood, and the within-subject variance-covariance matrix modeled in the form determined by Akaike's information criterion.[29]

RESULTS

Sample Characteristics

Sample characteristics of the full sample have been reported previously.[23] The sample consisted primarily of white women who on average had a high school education or slightly greater (Table 1). Participants were asked at the conclusion of the study if they perceived any sensations from the device and whether they believed they were in the active or sham group. Participants were not able to determine group assignment and reported no perception of sensations from the devices.

Pain

As previously reported,[23] the change in the slope for average pain in the usual care and sham device groups both significantly increased over time in comparison to the active CES group, indicating more pain over the course of the study, whereas the active CES group had a decreasing slope, indicating that the report of pain was decreasing over the course of the study (P = .023). The overall mean ratings of pain intensity during the pain stimulation procedure decreased from baseline (15.50 ± 1.56) to week 8 (13.44 ± 3.61) in the active CES group versus the sham group (baseline, 12.17 ± 5.46; week 8, 13.33 ± 1.81), which exhibited a slight increase. Although not statistically significant, this decrease represents a clinically significant change of two points on a 20-point scale.

fMRI Data Analysis

fMRI is used to assess changes in hemodynamics resulting from neural activity. This change is reflected in a BOLD signal. Representative fMRI are shown in Figure 2. A significant decrease in BOLD signal was observed in the posterior cingulate gyrus (P = .034), cingulate gyrus (P < .001), anterior cingulate (P = .0056), and thalamus (P = .031) from baseline to week 8 in the active CES group versus the sham device group. A significant increase in BOLD signal was observed in the insula (P = .044) and the

Table 1. Demographic Data

	Total Sample (n = 46)	Active CES Group (n = 17)	Sham Device Group (n = 14)	Usual Care Alone Group (n = 15)	*P*-Value
Age	50.8 ± 10.4	51.9 ± 10.6	51.5 ± 10.9	48.6 ± 9.8	.61
Sex					.99
Male	3 (6.5%)	1 (5.9%)	1 (7.7%)	1 (6.7%)	
Female	43 (93.5%)	16 (94.1%)	13 (92.3%)	14 (93.3%)	
Race					.97
White	41 (88.9%)	15 (88.9%)	13 (90%)	13 (87.5%)	
Nonwhite	5 (11.1%)	2 (11.1%)	1 (10%)	2 (12.5%)	
Years of education	13.7 ± 2.1	13 ± 1.7	14.1 ± 1.7	14.1 ± 2.7	.18

Modified from Taylor et al.[23]

prefrontal cortex ($P = .0003$) from baseline to week 8 in the sham device group versus the active CES group. No significant differences were observed in the somatosensory cortices or the amygdala (data not shown) between the two groups.

DISCUSSION

Analyses of the study data indicate the potential benefit of CES therapy for symptom management in FM. As previously reported, those individuals using the active device had a greater decrease in average pain, fatigue, and sleep disturbance than individuals using the sham device or in UC alone over time.[23] Preliminary analyses of fMRI data show that individuals using an active CES device had a decrease in activation of the pain processing regions of the brain compared to those using a sham device (Figure 1). This decrease in activation of the pain processing regions may indicate a decrease in neural activity in these regions that may be related to decreased pain given that pain ratings during the pain stimulation procedure decreased from baseline to week 8 and a decrease in pain over time was observed in the larger, overall study in the active CES device group.[23]

In three pilot studies of the Alpha-Stim CES device, researchers have explored the effects of this therapy on pain, sleep, fatigue, depression, and mood specifically in persons with FM during a 3-week intervention period and found that participants reported decreased pain and tenderness after using the Alpha-Stim device.[30-32] Two of the studies reported improvements in subjective sleep quality,[30,31] whereas only one study found a significant reduction in fatigue.[31] All three studies reported improvements in depression or mood. None of these studies specifically measured stress in persons diagnosed with FM. The current study is the first randomized, controlled trial of CES in patients with FM to report fMRI data.

The only study known to the authors to have investigated the mechanisms of action of CES in persons with FM and to use fMRI to document changes in brain activation after using CES is a quasi-experimental feasibility study conducted by two of the current authors, Bourguignon and Taylor (unpublished data). Six participants received active CES devices and served as their own controls. After using active CES for 4 weeks, improvements were observed in pain and functional status. Ratings of both pain intensity and pain affect were significantly decreased over time, after the authors controlled for baseline fatigue levels. In addition, functional status, as measured by the Fibromyalgia Impact Questionnaire, significantly improved after 4 weeks of CES use. These data are in agreement with data from the larger, overall randomized controlled trial from which the current study sample was taken.[23] Although fMRI data were collected during the previous feasibility study, without a control group (sham device) statistical comparisons could not be determined.

Studies involving neuroimaging have provided findings to suggest that FM may be linked to hyperalgesia,[26,33] disturbances in resting-state functional brain connectivity,[34] alterations in the morphology in pain processing regions of the brain,[35-37] and dysfunction of neurotransmission.[38-40] However, the majority of these studies have been cross-sectional.[41] Thus, the findings do not address clearly whether the aforementioned changes are causal or consequential in relation to pain in FM, or if these factors more related to chronic pain generally.

Increased pain sensitivity usually is present in FM[42]; however, when imaging is done at rest without pain stimulation, the results from brain imaging studies are variable. For instance, no significant differences in brain activation between those with FM and healthy controls were found using positron-emission tomography,[43] although the authors of another study who used single-photon emission computed tomography imaging did find significant differences in the somatosensory cortices, cingulate, frontal, parietal, temporal, and cerebellar regions.[44] However, when pain stimulation testing is used to reveal correlates of enhanced pain sensitivity during imaging, significant differences in brain activation between those with FM and healthy controls are revealed consistently. In pain stimulation testing during fMRI, Gracely et al[26] reported that although the pressure stimulation was low (nonpainful stimulus), those with FM had significantly greater, often twice as much, brain activation in the somatosensory cortices, insula and cingulate (both in the limbic cortex), temporal gyrus, and motor regions in the cerebellum, compared to healthy controls. The same absolute pressure was used for the pain stimulus in both those with FM and controls. Other studies demonstrated similar results,[32,45,46] illustrating observable augmentation of pain processing in the brains of persons with FM.[26] Taken together, these findings provide evidence that FM may involve increased pain transmission in the brain.

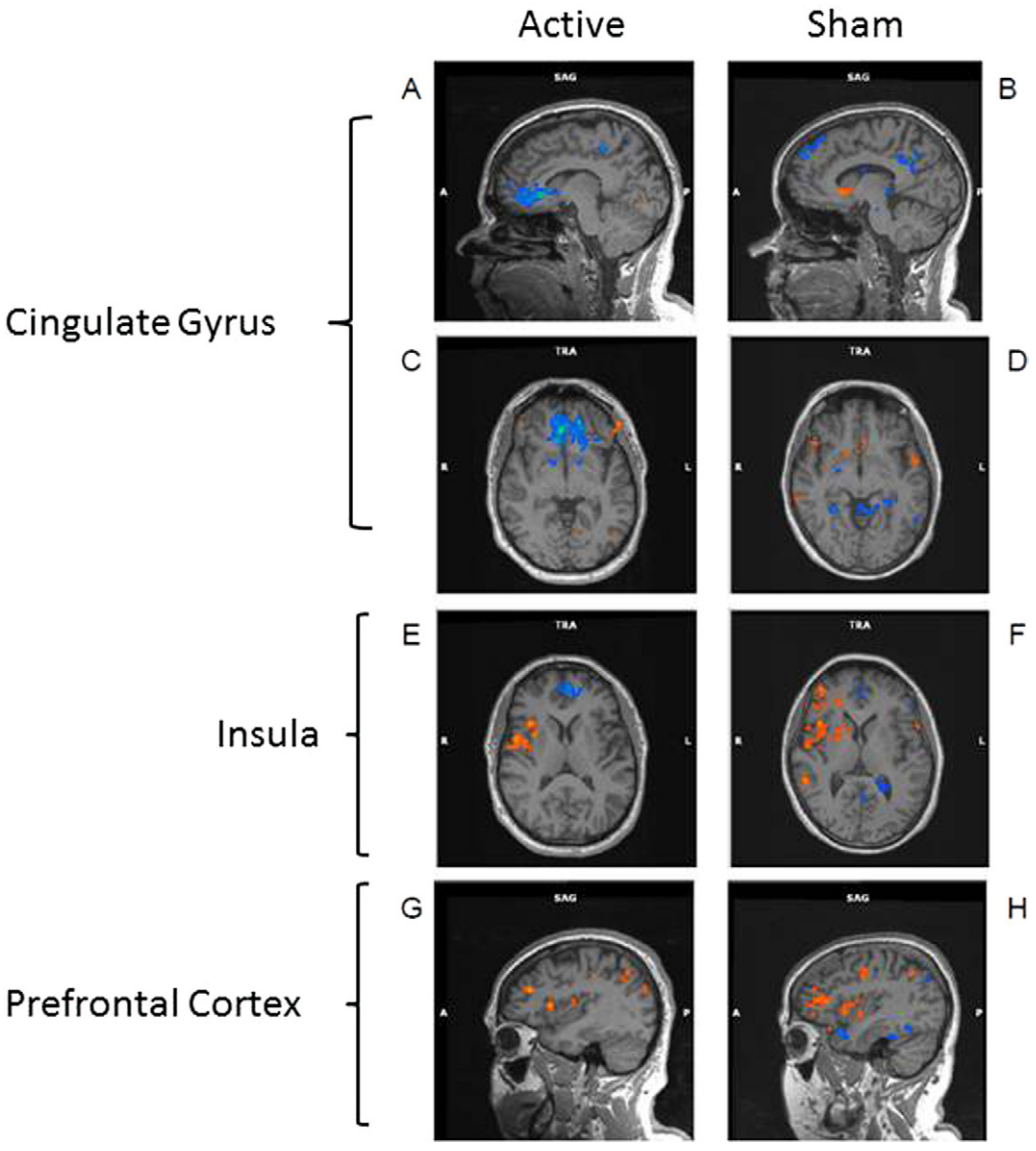

Figure 2. fMRI data analysis. Mean representative images of changes in BOLD activation between the active device group versus the sham device group from baseline (preintervention) to week 8 (postintervention), showing increases in activity (orange) and decreases in activity (blue) in the (A–D) cingulate gyrus, (E and F) insula, and (G and H) prefrontal cortex. (Figure is available in color online).

However, other investigators have reported contrasting results. Previous studies had used the same absolute pressure for the pain stimulus for both patients with FM and controls.[26] In a study by Jensen et al,[47] as in the current study, the pressure for the pain stimulus was calibrated to subjective pain levels so that both patients with FM and controls reported the exact same levels of pain. Activity in regions pertaining to the affective-motivational domain and sensory-discriminatory components of brain processing did not differ between persons with FM and controls.[47] These findings do not support the hypothesis of augmented affective modulation of pain as a potential pathophysiological mechanism in individuals with FM.[47] Two other studies in different study populations report similar results, demonstrating no increase in the affective modulation of pain in individuals with other pain syndromes[48] or controls.[49] Moreover, until recently the majority of fMRI studies in which researchers investigated pain focused on activation rather than deactivation. However, exploring deactivation in response to pain may yield a better understanding of the mechanisms involved in central pain processing, particularly as it relates to chronic pain.[50] Negative BOLD responses have been shown to correlate with decreased neuronal activity.[51,52] Alternatively, assessment of resting intrinsic brain connectivity using fMRI, rather than acute experimental pain, has been proposed to be a better measure of the chronic pain experience in FM,[41] with altered intrinsic connectivity in pain processing regions observed in patients with FM[34] and other chronic pain conditions.[53]

In the current study, a significant decrease in activation was observed in the posterior cingulate gyrus, cingulate gyrus, anterior cingulate, and thalamus in the active CES group versus the sham device group. Activation of the posterior cingulate is associated with increased affective pain,[54] whereas the anterior cingulate is known for its role in modulating executive pain processing.[55] In most studies of functional pain imaging, activation of the cingulate is detected during pain stimulation,[56] and increased activation in the cingulate after pain stimulation has been reported in patients with FM.[26,33,45,46] Thus, the decreased activity observed in the current study may indicate a decrease in pain sensitization in the active CES group over the course of the study versus the sham group. The areas of the brain associated with the cingulo-frontal cortex play an important role in the modulation of pain perception and changes in these areas have been postulated as a mechanism behind the transition from acute to chronic pain, as experience in FM.[35]

There is increasing evidence for altered thalamic function in pain patients with chronic pain, including neuropathic pain[57,58] and FM.[26,59,60] It is generally thought that chronic pain is a consequence or cause of alterations in thalamocortical connections, leading to the dysregulation of thalamic feedback. This would result in dysfunction in FM within the descending pain inhibitory networks, which play a crucial role in pain modulation. The differences in thalamic activation observed in the current study, as well as the results of others,[47,61] further support a hypothesis of impaired descending pain inhibition as a pathophysiological mechanism in FM.[6,7,62,63]

A significant increase in activation was observed in the insula and the prefrontal cortex in the sham device group versus the active CES group, indirectly indicating a potential decrease or moderation of activity in these regions in those using an active CES device. The insula is one of the most commonly activated regions in neuroimaging studies of acute experimental pain.[64] In a study of the use of transcranial magnetic stimulation for central pain management after a stroke, investigators reported decreased activity in the insula in treatment responders post-treatment after having observed an increase in activity in the same region pretreatment.[65] As stated earlier, regions of the cingulofrontal cortex function in the modulation of pain perception and difference in activity in this have been observed in patients with FM versus healthy controls,[35,66] supporting the idea of impaired connectivity between crucial nodes of the pain inhibitory network in FM.[61]

Limitations of the current study include a lack of statistical power with regard to the fMRI data. In the current pilot study, fMRI was used only in a subset of participants because of budgetary constraints. The current study did not involve a comparison group of individuals with FM who did not use an active CES device or with healthy controls using a device. Given that no other studies to date have used fMRI to examine the effects and potential mechanisms of CES, these two additional studies are needed to delineate and fully interpret differences in brain regional activation. In addition, the multiple comparisons inherent in the analysis of fMRI data can potentially increase the likelihood of finding statistically significant results. To account for this possibility, functional data within each group were normalized to each other, essentially providing a "mean image" with which comparisons were made between baseline and postintervention, and between treatment groups. This method allowed for the determination of changes in BOLD from baseline to postintervention within and between groups. The same intensity threshold was used for each analysis to diminish background noise and interference. Those regions of the brain found to be statistically significantly different were based on both *a priori* regions of interest and *a posteriori* regions identified by the BrainVoyager QX software. Although there were consistent effects by group over time, not all of these were statistically significant in this small pilot study because of sample size. No significant differences in neural activity were observed in the somatosensory cortices or the amygdala between the two groups, which were regions of interest chosen *a priori* given that these brain regions are involved in pain networks. This may have been because of the setting threshold of the analysis, scanning parameters needed to adequately assess the amygdala, or a lack of comparison with a no treatment group.

Despite these weaknesses, the robust design of the current study was developed to address the methodological issues from previous studies of the Alpha-Stim CES device. Strengths of the current study include the use of a randomized, double-blind, placebo-controlled experimental design and an 8-week study period, as well as the novel aspect of collecting fMRI data to examine the effects of CES on pain processing regions of the brain. Additional analyses of the study data will be conducted to correlate symptom assessments and psychological factors with fMRI data of neural activity in pain processing regions. Specifically, differences in neural activity will be examined in other regions of the brain associated with movement, such as the basal ganglia, and memory, including the hippocampus, a region in which increased activation has been reported in response to the anxiety-induced exacerbation of pain.[67] As increasing evidence points toward dysregulation of the brain pain networks in the etiology of FM, the use of noninvasive neuroimaging as biomarker may enhance the characterization of this disease state and track changes in pain and other symptoms over time in this patient population,[41] as well as provide data to support the use of nonpharmacological interventions such as CES.

Acknowledgments

We thank Jewel, Holmberg and Rochelle Jobes for their editorial assistance in the preparation of the manuscript. The project described was supported by an intramural award from the University of Virginia School of Nursing Center for Nursing Research and support from the Center for the Study of Complementary and Alternative Therapies. Research-related fMRIs were provided by the University of Virginia Medical Center Department of Radiology Research Laboratory. The Alpha-Stim devices were loaned to the investigators by Electromedical Products International, Inc, (Mineral Wells, TX).

REFERENCES

1. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med*. 2000;160:221-227.

2. Wolfe F, Ross K, Anderson J, Russell IJ. Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. *J Rheumatol*. 1995;22:151-156.
3. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum*. 1995;38:19-28.
4. White KP, Speechley M, Harth M, Ostbye T. Co-existence of chronic fatigue syndrome with fibromyalgia syndrome in the general population. A controlled study. *Scand J Rheumatol*. 2000;29:44-51.
5. Clauw DJ, Arnold LM, McCarberg BH, FibroCollaborative. The science of fibromyalgia. *Mayo Clin Proc*. 2011;86:907-911.
6. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain*. 2005;114:295-302.
7. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. *Clin J Pain*. 1997;13:189-196.
8. Wood PB, Patterson JC, 2nd, Sunderland JJ, Tainter KH, Glabus MF, Lilien DL. Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: A pilot study. *J Pain*. 2007;8:51-58.
9. Wood PB, Schweinhardt P, Jaeger E, et al. Fibromyalgia patients show an abnormal dopamine response to pain. *Eur J Neurosci*. 2007; 25:3576-3582.
10. Wood PB. A reconsideration of the relevance of systemic low-dose ketamine to the pathophysiology of fibromyalgia [see comment]. *J Pain*. 2006;7:611-614.
11. Wood PB. Mesolimbic dopaminergic mechanisms and pain control. *Pain*. 2006;120:230-234.
12. Wood PB. Stress and dopamine: implications for the pathophysiology of chronic widespread pain. *Med Hypotheses*. 2004;62:420-424.
13. Russell IJ. Advances in fibromyalgia: possible role for central neurochemicals. *Am J Med Sci*. 1998;315:377-384.
14. Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Javors MA, Bowden CA. Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome. *J Rheumatol*. 1992;19:104-109.
15. Russell IJ, Vaeroy H, Javors M, Nyberg F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis Rheum*. 1992;35:550-556.
16. Legangneux E, Mora JJ, Spreux-Varoquaux O, et al. Cerebrospinal fluid biogenic amine metabolites, plasma-rich platelet serotonin and [3H]imipramine reuptake in the primary fibromyalgia syndrome. *Rheumatology (Oxford)*. 2001;40:290-296.
17. Allan CL, Ebmeier KP. The use of ECT and MST in treating depression. *Int Rev Psychiatry*. 2011;23:400-412.
18. Rose KM, Taylor AG, Bourguignon C. Effects of cranial electrical stimulation on sleep disturbances, depressive symptoms, and caregiving appraisal in spousal caregivers of persons with Alzheimer's disease. *Appl Nurs Res*. 2009;22:119-125.
19. Rose KM, Taylor AG, Bourguignon C, Utz SW, Goehler LE. Cranial electrical stimulation: potential use in reducing sleep and mood disturbances in persons with dementia and their family caregivers. *Fam Community Health*. 2008;31:240-246.
20. Ferdjallah M, Bostick FX, Jr, Barr RE. Potential and current density distributions of cranial electrotherapy stimulation (CES) in a four-concentric-spheres model. *IEEE Trans Biomed Eng*. 1996;43:939-943.
21. Krupitsky EM, Burakov AM, Karandashova GF, et al. The administration of transcranial electric treatment for affective disturbances therapy in alcoholic patients. *Drug Alcohol Depend*. 1991;27:1-6.
22. Liss S, Liss B. Physiological and therapeutic effects of high frequency electrical pulses. *Integr Physiol Behav Sci*. 1996;31:88-95.
23. Taylor AG, Anderson JG, Riedel SL, Lewis JE, Kinser PA, Bourguignon C. Cranial electrical stimulation improves symptoms and functional status in individuals with fibromyalgia. *Pain Manag Nurs*. in press. (http://dx.doi.org/10.1016/j.pmn.2011.07.002)
24. Wolfe F, Smythe HA, Yunus MB, et al. The American College of rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum*. 1990; 33:160-172.
25. Harris RE, Clauw DJ. Newer treatments for fibromyalgia syndrome. *Ther Clin Risk Manag*. 2008;4:1331-1342.
26. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum*. 2002;46:1333-1343.
27. Goebel R, Esposito F, Formisano E. Analysis of functional image analysis contest (FIAC) data with BrainVoyager QX: from single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. *Hum Brain Mapp*. 2006;27:392-401.
28. Vaughan JT, Garwood M, Collins CM, et al. 7T vs. 4T: RF power, homogeneity, and signal-to-noise comparison in head images. *Magn Reson Med*. 2001;46:24-30.
29. Littell RC, Milliken GA, Stroup WW, Wolfinger RD, Schabenberger O. *SAS for Mixed Models*. 2nd ed. *Cary*, NC: SAS Institute, Inc; 2006.
30. Lichtbroun AS, Raicer MM, Smith RB. The treatment of fibromyalgia with cranial electrotherapy stimulation. *J Clin Rheumatol*. 2001; 7:72-78.
31. Tyers S, Smith R. A comparison of cranial electrotherapy stimulation alone or with chiropractic therapies in the treatment of fibromyalgia. *Am Chiropractor*. 2001;23:39-41.
32. Cork R, Wood P, Ming N, Shepherd C, Eddy J, Price L. The effect of cranial electrotherapy stimulation (CES) on pain associated with fibromyalgia. *Internet J Anesthesiol*. 2004;8. Volume 8 Number 2. (http://dx.doi.10.5580/25a1)
33. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. *J Rheumatol*. 2004;31:364-378.
34. Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis Rheum*. 2010;62:2545-2555.
35. Burgmer M, Gaubitz M, Konrad C, et al. Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia. *Psychosom Med*. 2009;71:566-573.
36. Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *J Neurosci*. 2007;27:4004-4007.
37. Schmidt-Wilcke T, Luerding R, Weigand T, et al. Striatal grey matter increase in patients suffering from fibromyalgia–a voxel-based morphometry study. *Pain*. 2007;132(suppl 1):S109-S116.
38. Harris RE, Sundgren PC, Craig AD, et al. Elevated insular glutamate in fibromyalgia is associated with experimental pain. *Arthritis Rheum*. 2009;60:3146-3152.
39. Harrison MJ, Davies LM, Bansback NJ, Ingram M, Anis AH, Symmons DP. The validity and responsiveness of generic utility measures in rheumatoid arthritis: a review. *J Rheumatol*. 2008;35:592-602.
40. Foerster BR, Petrou M, Edden RA, et al. Reduced insular γ-aminobutyric acid in fibromyalgia. *Arthritis Rheum*. 2012;64:579-583.
41. Napadow V, Kim J, Clauw DJ, Harris RE. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. *Arthritis Rheum*. 2012;64:2398-2403.

42. Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.
43. Yunus MB, Young CS, Saeed SA, Mountz JM, Aldag JC. Positron emission tomography in patients with fibromyalgia syndrome and healthy controls. *Arthritis Rheum*. 2004;51:513-518.
44. Guedj E, Cammilleri S, Colavolpe C, de Laforte C, Niboyet J, Mundler O. Follow-up of pain processing recovery after ketamine in hyperalgesic fibromyalgia patients using brain perfusion ECD-SPECT. *Eur J Nucl Med Mol Imaging*. 2007;34:2115-2119.
45. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum*. 2004;50:613-623.
46. Wik G, Fischer H, Bragée B, Kristianson M, Fredrikson M. Retrosplenial cortical activation in the fibromyalgia syndrome. *Neuroreport*. 2003;14:619-621.
47. Jensen KB, Kosek E, Petzke F, et al. Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. *Pain*. 2009;144:95-100.
48. Arnold LM. Management of fibromyalgia and comorbid psychiatric disorders. *J Clin Psychiatry*. 2008;69(suppl 2):14-19.
49. Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely RH. Differences in unpleasantness induced by experimental pressure pain between patients with fibromyalgia and healthy controls. *Eur J Pain*. 2005;9:325-335.
50. Kong J, Loggia ML, Zyloney C, Tu P, Laviolette P, Gollub RL. Exploring the brain in pain: activations, deactivations and their relation. *Pain*. 2010;148:257-267.
51. Shmuel A, Augath M, Oeltermann A, Logothetis NK. Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nat Neurosci*. 2006;9:569-577.
52. Pasley BN, Inglis BA, Freeman RD. Analysis of oxygen metabolism implies a neural origin for the negative BOLD response in human visual cortex. *Neuroimage*. 2007;36:269-276.
53. Malinen S, Vartiainen N, Hlushchuk Y, et al. Aberrant temporal and spatial brain activity during rest in patients with chronic pain. *Proc Natl Acad Sci U S A*. 2010;107:6493-6497.
54. Schnitzler A, Ploner M. Neurophysiology and functional neuroanatomy of pain perception. *J Clin Neurophysiol*. 2000;17:592-603.
55. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron*. 2007;55:377-391.
56. Iadarola MJ, Berman KF, Zeffiro TA, et al. Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. *Brain*. 1998;121 (Pt 5):931-947.
57. Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. *Pain*. 1995;63:225-236.
58. Iadarola MJ, Max MB, Berman KF, et al. Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. *Pain*. 1995;63:55-64.
59. Kwiatek R, Barnden L, Tedman R, et al. Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. *Arthritis Rheum*. 2000;43:2823-2833.
60. Mountz JM, Bradley LA, Modell JG, et al. Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. *Arthritis Rheum*. 1995;38:926-938.
61. Jensen KB, Loitoile R, Kosek E, et al. Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. *Mol Pain*. 2012;8:32.
62. Vierck CJ, Jr, Staud R, Price DD, Cannon RL, Mauderli AP, Martin AD. The effect of maximal exercise on temporal summation of second pain (windup) in patients with fibromyalgia syndrome. *J Pain*. 2001;2:334-344.
63. Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. *Pain*. 1997;70:41-51.
64. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain*. 2005;9:463-484.
65. Diers M, Yilmaz P, Rance M, et al. Treatment-related changes in brain activation in patients with fibromyalgia syndrome. *Exp Brain Res*. 2012;218:619-628.
66. Guedj E, Cammilleri S, Niboyet J, et al. Clinical correlate of brain SPECT perfusion abnormalities in fibromyalgia. *J Nucl Med*. 2008; 49:1798-1803.
67. Ploghaus A, Narain C, Beckmann CF, et al. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci*. 2001;21:9896-9903.