Neuromodulatory Approaches for Chronic Pain Management: Research Findings and Clinical Implications

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ABSTRACT. Two lines of evidence provide preliminary support for the role that brain state, measured via electroencephalogram (EEG), may play in chronic pain. First, research has identified a link between brain EEG activity and the experience of pain. Second, there are a number of published studies documenting the beneficial effects of interventions that impact the cortical activity associated with chronic pain. These interventions include neuro-behavioral treatments such as neurofeedback and hypnosis as well as invasive and non-invasive brain stimulation. Preliminary data showing the efficacy of neuromodulator strategies for treating pain provides compelling reason to examine how cortical activity (as measured by EEG) may underlie the experience of pain. Existing data already suggest specific approaches that neurofeedback clinicians might consider when treating patients with chronic pain. Reciprocally, observations by neurofeedback practitioners could provide important ease data that could foster the design of more definitive randomized clinical trials using such strategies for the treatment of chronic pain.

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INTRODUCTION AND OVERVIEW

Chronic pain is now known to produce plastic changes in an extensive neural network that involves...
areas associated with somatosensory and emotional-affective processing. An understanding of the specific neurophysiological changes that are associated with chronic pain could contribute to the development of novel treatments aimed at central nervous system (CNS) modulation. Research from a number of sources suggests a link between electroencephalographic (EEG) activity and the experience of pain. As described in more detail in the section that follows, this research suggests that (a) in most otherwise healthy individuals, the subjective experience of pain is associated with relatively lower amplitudes of alpha activity and relatively higher amplitudes of beta activity and (b) individuals with chronic pain associated with neurological disorders, such as spinal cord injury, evidence higher amplitudes of theta activity and lower amplitudes of alpha activity than individuals who do not have chronic pain.

The purpose of this article is to summarize the extant evidence concerning the associations between EEG-assessed brain activity and pain, and then to discuss the implications of these findings for understanding the mechanisms of treatments that modulate cortical activity such as neurofeedback, hypnosis, and noninvasive brain stimulation. We also include a discussion of neurofeedback treatment approaches that may be used for chronic pain management that are based, in part, on the available evidence concerning the EEG activity most closely associated with pain. The goals of this article are therefore to (a) alert clinicians to recent findings on this field that might contribute to the development of effective chronic pain treatments now and in the future and (b) encourage more research to examine the efficacy of neuromodulator interventions and to understand the mechanisms of their effects.

**INTEGRATION AND PLASTICITY IN THE NEUROPHYSIOLOGY OF PAIN**

Before the middle of the 20th century, pain was viewed primarily as a simple reflexive response to physical damage. In that view, pain information (nociception) was thought to be transmitted directly from nerves in damaged tissue through a single channel directly to a "pain center" in the brain. When seeking to diagnosis or understand pain from this model, the area of primary interest was the periphery, that is, where pain was thought to originate from; the notion was that "real pain" was mostly related to the amount of physical damage or inflammation that occurred in peripheral structures. The brain was viewed as an essentially passive recipient of sensory information.

An initial important turning point in our understanding of pain occurred with the publication of the gate control theory of pain (Melzack & Wall, 1965). This theory provided a model for how nociceptive input is influenced and modulated in the spinal cord before it reaches the cortex and then, ultimately, leads to the experience of pain. In addition, pain associated with neurological lesions such as spinal cord injury and stroke started to be viewed in the context of this new understanding that the brain plays a major role in chronic pain. More recently, a significant increase in the use of advanced neuroimaging methods for understanding the brain mechanisms involved in pain has helped to confirm this notion that chronic pain can result from dysfunction in the central nervous structures. As a result of recent research, pain is now understood as an experience that is influenced by a dynamic series of multiple interlocking neurophysiological mechanisms that modulate nociceptive information at many levels, including supraspinal sites such as the cortex (Apkarian, Bushnell, Treede, & Zubieta, 2005; Craig, 2003a, b; Deleo, 2006; Katz & Rothenberg, 2005; Melzack, Coderre, Katz, & Vaccarino, 2001; Miltner & Weiss, 1998; Tina7zi et al., 2000).
Moreover, we now know that, in addition to the effects caused by input from the periphery (e.g., nociceptive information that is sent along the A-delta, A-beta, and C fibers to the spinal cord and into the CNS) supraspinal structures such as the primary and secondary somatosensory cortex, insular cortex, anterior cingulate cortex, prefrontal cortex, and thalamic nuclei all work together to represent and modulate the experience of pain (see Figure 1). Thus, although activity in the peripheral nervous system and the spinal cord certainly can play an important role in the experience of pain, the key role that multiple conical and subcortical sites play in the perception and emotional response to pain is now more clearly acknowledged and understood.

Research has also shown that nociceptive input, via neural adaptation, may modify neural networks’ responses to repeated stimuli (Flor, 2003; Katz & Melzack, 1990). For example, sensitivity to noxious stimulation increases as a result of ongoing nociceptive input (Bromm & Lorenz, 1998); in other words, the experience of pain itself makes the
CNS more sensitive to pain—this phenomenon is called nervous system sensitization. This hypersensitivity may have an evolutionary advantage as increased pain can promote healing by inducing behavioral changes, compelling a person to take special care of injured anatomy. However, this mechanism can at the same time extend discomfort and suffering beyond the time it takes for healing to occur, and potentially contribute to the development of a chronic condition. Some studies have identified the CNS changes that occur with chronic pain as a potential target of treatment to produce pain relief; interventions that reprogram or interrupt central sensitization, at the cortical level, could also possibly provide significant relief for some individuals with chronic pain (Flor, Braun, F. lbert, & Birbaumer, 1997; Maihofner, Handwerker, Neundorfer, & Birklein, 2003; Pleger et al., 2004; Tinazzi et al., 2000).

Another important issue related to focusing on supraspinal systems as a target for chronic pain interventions is that the brain should be viewed as a two-way system, in which the processing of information results in changes in efferent systems through top down mechanisms such as regulation of endocrine and immune systems. It is therefore also possible that modulation of pain by altering CNS activity directly may promote health by stimulating salutogenic mechanisms (Fregni, Pascual-Ivone, & Freedman, 2007).

MEASURING THE NEUROPHYSIOLOGICAL CORRELATES OF PAIN

Researchers have used a number of tools for studying and identifying the neurophysiological correlates of pain. Functional magnetic resonance imaging (fMRI) has been used to measure localized changes in blood flow in the brain (and therefore neuronal activity) associated with pain. Positron emission tomography (PET) has been used to assess localized brain metabolic changes induced by aversive stimuli. EEGs have also been used to infer changes in brain electrical field activity after experience of pain. Finally, transcranial magnetic stimulation (TMS) has been used in two different manners to assess chronic pain: (a) via single and paired pulse TMS to assess cortical excitability changes associated with chronic pain (e.g., Lefaucher. Drouot. Menard-Lefaucheur. Keravel, & Nguyen. 2006) and (b) via repetitive TMS (rTMS) to functionally and transiently disrupt activity in the anatomical sites of pain experience (inducing "virtual lesions" that can link brain anatomy and its functional behavior) or by facilitating activity. Each approach has its advantages and limitations.

A primary strength of fMRI and PET is that these imaging strategies can localize activity throughout the brain. For fMRI, localization can occur at a relatively high degree of spatial resolution. However, as measures of the correlates of experience, the ability of these imaging methods to establish cause-effect relationships is limited. Also, with these methods of neuroimaging, temporal resolution is relatively poor. Measurement of cortical excitability via single and paired pulse TMS has the advantage of providing reliable functional measurements. However, this approach is limited to motor (and to a less extent, visual) cortex. rTMS, on the other hand, has the advantage of having a good temporal resolution, and it can also allow for inferences about causal relationships. Because pain is a complex experience associated with activation in an extensive neural network, some of the temporal resolution of rTMS may be lost. In addition, this method assesses function by instituting changes; it does not itself directly measure activity (Pascual-Leone et al., 1998) except when using single and paired pulse TMS.

EEG measures, although less commonly employed than fMRI and PET studies, can provide information complementary to fMRI. PET, and TMS/rTMS. Specifically, EEG can assess cortical rhythms in specific frequency bands, which are associated with different brain states. Significant support for the potential of EEG measures for contributing to our understanding of pain processing comes from evidence that the power of different EEG band widths has been shown to be associated with pain severity. Data from acute (induced) pain models to study the
effects of pain on HEG measures have shown a consistent pattern. Specifically, these data have shown that with more intense painful stimulation, all EEG frequencies increase in power, but beta frequencies increase relatively more than other bandwidths, and the relative power of alpha activity tends to decrease (Bromm, Ganzel, Herrmann, Neier, & Scharein, 1986; Bromm, Meier, & Scharein, 1986; Chang, Arendt-Nielsen, Graven-Nielsen, Svenson, & Chen, 2001; Chen, Dworkin, & Drangsholt, 1983; Huber, Bartling, Pachur, Woikowsky-Biedau, & Lautenbacher, 2006: see also reviews by Bromm & Lorenz, 1998; Chen, 1993, 2001): in summary, more acute pain appears to lead to more relative beta and less relative alpha activity. At the same time, this research indicates that acute pain relief is associated with decreases in the relative power of beta activity and increases in the relative power of alpha wave activity (see also Kakigi et al., 2005; Pelletier & Peper, 1977).

There is much less research examining the effects of chronic pain on EEG measures. The findings from the few studies that have examined EEG activity in patients with chronic pain are generally consistent with those from acute (induced) pain studies, with one interesting exception: A significant increase in relative very slow (theta) activity is found in individuals with chronic pain. At the same time, this research indicates that acute pain relief is associated with decreases in the relative power of beta activity and increases in the relative power of alpha wave activity (see also Kakigi et al., 2005; Pelletier & Peper, 1977).

A more recent study compared EEG-assessed cortical activity in three groups: (a) patients with spinal cord injury and chronic pain (n = 8), (b) patients with spinal cord injury without pain (n = 8), and (c) healthy controls (n = 16; Boord et al., 2008). Consistent with the finding from both Stern et al. (2006) and Sarnthein et al. (2006), these investigators found that the peak activity in the chronic pain sample was in the theta range, on average, whereas peak activity in the nonpain samples was in the alpha range. Similar to the findings of Sarnthein et al., Boord et al. reported that the use of centrally
acting medications among the patients with pain was associated with some differences in EEG activity, relative to those who were not taking medications, such that EEG activity in those taking medications was shifted a little in the direction of activity that was a little more like those without pain. However, this effect occurred at only 3 (P3, P7, and Pz) of 14 assessment sites. Also, overall, the differences observed between those with and without pain were found over many sites, suggesting a diffuse effect of pain and raising the question of whether some cortical areas may contribute more or less to the differences found than others.

NEUROFEEDBACK TRAINING AND PAIN RELIEF

Based on the evidence showing that EEG activity is linked to the experience of pain, it is possible that neurofeedback training could be used to teach patients to increase or decrease relative power of different EEG band widths as a way to treat chronic pain, specifically to alter brain activity in such a way that it reflects the EEG activity that has been shown to be associated with less pain (Batty, Bonnington, Tang, Hawken, & Gruzelier, 2006; Egner, Strawson, & Gruzelier, 2002; Vernon et al., 2003). Preliminary evidence is consistent with this hypothesis (see Table 1).

One case study, one laboratory study, and a case series were published in the 1970s that address this hypothesis. In the first of these, Gannon and Sternbach (1971) developed a procedure for training alpha activity (measured from the occipital region) in a patient with 3-year history of severe headaches following multiple head traumas. After a little more than 32 hr of training (sixty-seven 29-min sessions), and during no-headache periods, the patient was able to increase his alpha activity from 20% to 92% of the time with eyes closed. He was also able to increase alpha activity to 50% of the time with eyes open, supporting the efficacy of EEG biofeedback training for making changes in bandwidth activity. However, when he began training during a headache period, he was unable to concentrate enough to increase alpha activity the headache appeared to interfere with his ability to generate alpha. On the other hand, the intensity and duration of headaches did decrease gradually over the course of treatment for this patient. The patient also reported that after the first 20 sessions, he had a larger attention span and was able to read for 30 min without getting a headache (whereas prior to treatment, reading for 15 min induced a headache). Also, following 50 treatment sessions, other activities that prior to treatment induced a headache (swimming, attending concerts) no longer did so.

Andreychuk and Skriver (1975) treated 33 individuals with migraine headaches with 10 sessions of one of three treatments: hand-warming biofeedback, autogenic relaxation instructions, and alpha enhancement feedback. EEG activity for the alpha (8-13 Hz) enhancement feedback was assessed via bipolar measurement from electrodes placed over the right and left occipital areas, using the right ear as a common ground. Thirty min of training, provided in two 15-min blocks, were provided at each session. Participants in all three treatment conditions, including those in the alpha enhancement group, reported significant reductions in headache rates, and there were no significant differences in improvement between the treatment conditions.

Melzack and Perry (1975) recruited 24 patients with a number of different chronic pain conditions (including back pain [/i = 10], peripheral nerve injury pain [/i > = 4], and pain from cancer [/i = 3], among other chronic pain conditions) and provided them with both self-hypnosis and alpha enhancement training (12 participants), hypnosis training alone (6 participants), or alpha enhancement training alone (6 participants). Alpha bandwidth activity and subjective measures of pain were assessed before and after each treatment session. They found larger pre- to post possession decreases in pain (as measured by the McGill Pain Questionnaire, which assesses different pain qualities and scores them into Sensory and Affective subscales) during training for those participants who received both hypnosis and neurofeedback
<table>
<thead>
<tr>
<th>Author (Date); Type of Pain</th>
<th>Type of Study</th>
<th>N; No. of Sessions</th>
<th>Electrode Placement</th>
<th>Bandwidth(s) Reinforced</th>
<th>Bandwidth(s) Inhibited</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gannon &amp; Sternbach (1971); Headache following multiple head injuries.</td>
<td>Case report</td>
<td>N= 1 ; 67 29&quot; sessions</td>
<td>Occipital region, right side</td>
<td>Alpha (9-11 Hz)</td>
<td>None</td>
<td>Treatment resulted in increases in eyes open alpha, although the patient was un-able to generate alpha during a headache. Intensity and duration of headaches decreased from pre- to post-treatment. - After 20 sessions, the patient reported an increase in attention span, and after 50 sessions, that he was able to attend a rock concert and swim without developing a headache.</td>
</tr>
<tr>
<td>Andreychuk &amp; Skriver (1975); Migraine headache</td>
<td>Treatment comparison (alpha enhancement [*=11], hand-warming biofeedback [n=11], autogenic training [/n= 11])</td>
<td>N= 33; 10 sessions (that included 2 15&quot; training sessions each)</td>
<td>Occipital region, right and left sides</td>
<td>Alpha (8-13 Hz)</td>
<td>None</td>
<td>Participants receiving alpha enhancement training reported significant reductions in headache rates, as did participants in the other two treatment conditions.</td>
</tr>
<tr>
<td>Melzack &amp; Perry (1975); Mixed chronic pain conditions</td>
<td>Treatment comparison (alpha enhancement alone /n=6], hypnosis alone [n = 6], both treatments [/n=12]).</td>
<td>N = 24; 8 20&quot; sessions</td>
<td>Occipital</td>
<td>Alpha (specific frequencies not specified)</td>
<td>None</td>
<td>Participants receiving both neurofeedback and hypnosis reported larger pre- to post-sessions decreases in pain than those that received only one treatment.</td>
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<tr>
<td>Study</td>
<td>Condition</td>
<td>Treatment Comparison</td>
<td>Sample Size</td>
<td>Additional Details</td>
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<tr>
<td>Cohen et al. (1980); Migraine headache</td>
<td></td>
<td>Treatment comparison (forehead cooling/hand warming biofeedback (n=11), frontalis EMG biofeedback (n=11), temporal artery vasoconstriction biofeedback (n=10), alpha enhancement neurofeedback (n=10)).</td>
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<td>02 and P4</td>
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<tr>
<td>Caro &amp; Winter (2001); Fibromyalgia</td>
<td></td>
<td>Case series (N=42); 24 20&quot; sessions</td>
<td></td>
<td>CZ</td>
<td></td>
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<tr>
<td>Sime (2004); Trigeminal neuralgia</td>
<td></td>
<td>Case study</td>
<td></td>
<td>1 29 sessions</td>
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<td></td>
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<td>neurofeedback preceded &amp; followed by EMG/respiration</td>
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| | | biofeedback | | Multiple sites used, including T4-A2, C3-A1, }
C4-A2.
C3-C4.
&
T3-T4.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency Range</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha (8-13 Hz)</td>
<td>None</td>
<td>- All participants reported reductions in the number of headaches per week; no between-group differences found.</td>
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<tr>
<td></td>
<td></td>
<td>- No changes in headache intensity or duration found.</td>
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<td>- No changes in alpha activity observed in the neurofeedback group.</td>
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<tr>
<td>SMR (4-7 Hz and 22-30 Hz)</td>
<td>4-7 Hz and 22-30 Hz</td>
<td>- Participants demonstrated significant improvements in attention.</td>
</tr>
<tr>
<td>(12-15 Hz)</td>
<td>22-30 Hz</td>
<td>- There was a strong association between improvement in attention and a decrease (improvement) in the mean tender pain assessment score, and a moderate association between improvement in attention and decrease (improvement) in fatigue.</td>
</tr>
<tr>
<td>Variable, including 7.5-10.5 Hz, 12-15 Hz, 7-10 Hz, 11-14 Hz, 8.5-11.5 Hz.</td>
<td>2-7 Hz and 22-30 Hz</td>
<td>- Training using T3-T4 sites (7.5-10.5 Hz reword. 2-7 and 22-30 Hz inhibit) resulted in the greatest pre- to postsession pain reductions.</td>
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<td></td>
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<td>- The participant reported reductions in pain and improvement in sleep quality</td>
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<td>- Benefits were maintained at 13-month follow-up.</td>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Jensen et al. (2007); Complex regional pain syndrome - Type 1</td>
<td>Case series</td>
<td>A/-18; analyses focused on pre- to postsession changes.</td>
<td>Multiple sites used, including P3-P4, FP1-FP2, T3-T4, FP02-A2, CZ-FZ, F7-F8.</td>
<td>Variable, ranging from 0-3 Hz to 14-17 Hz.</td>
<td>Not specified</td>
<td>- Significant pre- to postsession improvements were found on patient ratings of pain intensity (at the primary, secondary, and tertiary pain sites), muscle spasm, muscle tension, and global well-being.</td>
</tr>
<tr>
<td>Kayran et al. (2007); Fibromyalgia</td>
<td>Case series</td>
<td>N 3; 10 30” sessions</td>
<td>C4</td>
<td>SMR (12-15 Hz)</td>
<td>Theta</td>
<td>- All three participants reported significant pre-to posttreatment decreases in pain intensity. Fatigue, depression, and anxiety. - The participants showed variability in changes in EEG activity; one showed minimal changes and two showed substantial decreases in theta activity.</td>
</tr>
</tbody>
</table>
training than in participants who received only one type of training. Moreover, although participants in both of the neurofeedback conditions showed an increase in alpha output, those who received both hypnosis and neurofeedback demonstrated the most increase in alpha output over the course of treatment, whereas those who received neurofeedback training only demonstrated the most increase in pre- to postsession alpha output.

Cohen, McArthur, and Rickles (1980) assigned 42 patients presenting with migraine headache to 24 sessions (over the course of 8-10 weeks) of one of four biofeedback conditions: (a) forehead cooling/hand warming, (b) frontalis EMG reduction, (c) temporal artery vasoconstriction, and (d) alpha enhancement. Alpha EEG activity (8—13 Hz) was measured from O2 and P4, with feedback provided as tone-off (alpha above threshold with the threshold adjusted according to performance) or tone-on (alpha below threshold). All of the participants reported a significant reduction in the number of headaches per week, although there were no changes in the intensity or duration of headaches that did occur, nor were there any significant changes in alpha activity from pre- to posttreatment in participants in the neurofeedback group.

Caro and Winter (2001) provided 15 patients with fibromyalgia 40 or more sessions of sensorimotor rhythm (SMR) training (reinforcing 12-15 Hz and inhibiting 4-7 Hz and 22-30 Hz). The study participants evidenced significant improvement in a visual test of attention (TOVA scores), and there was a strong association between improvements in attention and improvements (decreases) in physician-assessed tender point scores (e.g., r = - .64, -.85, and -.69 for the associations between the TOVA ADHD, Commission Errors, and D Prime scores and the tender point score, respectively). Weak to moderate correlations (r = -.29, -.46, and .16, respectively) were also found between the TOVA scores and patient ratings of fatigue.

Sime (2004) presented a case report of a patient with trigeminal neuralgia treated with both neurofeedback (29 sessions) and peripheral biofeedback (10 sessions). The electrode placement and bandwidths reinforced varied as treatment progressed and included training at T4-A2, C3-A1, C4-A2, C3-C4, and T3-T4. The bandwidths reinforced also varied, although 2-7 Hz and 22-30 Hz were consistently inhibited in each session. Sime reported that rewarding low alpha (e.g., 7.5-10.5 Hz) measured from T3-T4 was associated with the most immediate improvements in pain. Following treatment, the patient chose to avoid a planned surgery (severing the trigeminal nerve) for pain treatment and discontinued the use of an opioid/acetaminophen combination analgesic. Moreover, the benefits of treatment were maintained in this patient at a 13-month follow-up assessment.

We recently reported our experience in a retrospective analysis of 18 patients with CRPS-1 who had been given neurofeedback training as part of a multidisciplinary pain treatment program (Jensen. Gricrson. Tracy-Smith, Bacigalupi, & Othmer, 2007). In the study, participants were administered 0 to 10 numerical rating scale measures of pain intensity at their primary pain site, as well as pain at other sites and other symptoms (e.g., muscle tension), before and after a 30-min neurofeedback training session. The specific neurofeedback training used varied from patient to patient and from session to session, depending on the needs of the patient and goals of each treatment session. Self-reported changes in symptoms were statistically compared using a series of r tests. Across the different treatment protocols, a substantial and statistically significant pre- to postsession decrease in pain intensity at the primary pain site (from an average intensity of 5.2 to 3.2 on a 0-10 scale) was reported, with half of the study participants reporting changes in pain intensity that were clinically meaningful (30% or greater). Five of seven secondary outcome measures also showed statistically significant improvements following neurofeedback treatment. These included pain at secondary and tertiary sites, muscle spasm, muscle tension, and global well-being.

Finally, Kayran and colleagues (Kayran. Dursun, Ermutlu. Dursun. & Karamursel. 2007) described a case series of 3 individuals
with fibromyalgia who were given ten 30-min sessions of SMR (12-15 Hz activity) training. During training, EEG was assessed from C4, and SMR activity was reinforced and theta activity was inhibited. Each participant reported decreases in pain (absolute pre- to posttreatment intensity rating decreases were 4.0, 1.5, and 3.0 on a 0-10 numerical scale), fatigue, depression, anxiety. However, the 3 participants also showed variability in pre- to posttreatment changes in EEG activity. One participant showed minimal changes in SMR activity, theta activity, or the theta/SMR ratio. The other 2 participants show no or minimal changes in SMR activity but substantial decreases in theta activity (and therefore associated decreases in the theta/SMR ratio).

As a group, the case and case series reports suggest that neurofeedback training may be associated with decreases in pain and improvement in other symptoms (such as depression and anxiety). Although controlled trials comparing neurofeedback to no treatment (standard care) or placebo treatment have not yet been performed, at least three studies have compared neurofeedback to other established treatments (e.g., hand-warming biofeedback, EMG biofeedback, hypnotic analgesia; Andrcychuk & Skriver, 1975; Cohen et al., 1980; Melzaek & Perry, 1975). In each of these studies, the neurofeedback intervention was shown to be at least as effective as the comparison treatments. When specified, the goal of the neurofeedback training in the published studies has most often been to increase relative alpha activity, although treatment protocols were also sometimes developed to decrease theta and increase in SMR (12-15 Hz) activity. Beta activity was rarely directly targeted, and when it was, the goal was to decrease this activity.

**OTHER TREATMENTS THAT ALTER EEG ACTIVITY ALSO PRODUCE CHANGES IN CHRONIC PAIN**

**Cortical Stimulation**

If cortical activity is related to the experience of pain, then any intervention that alters cortical activity has the potential to impact the experience of pain. Recent data studying the effects of cortical stimulation for this purpose are promising. There are several techniques to stimulate cortical areas such as invasive ( epidural cortical stimulation) and noninvasive approaches using TMS or transcranial direct current stimulation (tDCS). It is also possible to implant electrodes in deep areas such as periventricular/ peraqueductal gray matter, internal capsule, and sensory thalamus, and stimulation of these areas has shown promising results for chronic pain management (Green et al., 2005; Wallace, Ashkan, & Benabid, 2004).

Although there have been some promising results using deep brain stimulation, the more common approach is the stimulation of motor cortex. The rationale here is that stimulation of the motor cortex can inhibit pain relays in the thalamus (perhaps by impacting thalamocortical dysrythmia). In fact, investigators have studied the efficacy of electrical stimulation applied directly to the motor strip of the cortex via surgically implanted electrodes and have demonstrated 28% to 47% reductions in pain intensity in patients with chronic pain who have received this procedure (Nguyen et al., 1999; Nuti et al., 2005).

However, in addition to the elevated costs, surgical implantation and maintenance of electrodes inside the brain carry substantial risks. Noninvasive brain stimulation techniques can be used instead of invasive ones to address these risks. One such procedure, already mentioned, is rTMS. with which pulses of electromagnetic currents are used to induce electric currents inside the skull. Depending on the stimulation frequency and amplitude, rTMS can stimulate or inhibit activity a focal cortical area. A number of studies have found at least temporary decreases in pain experience in chronic pain sufferers following rTMS applied using inhibitory frequencies to the motor cortex (Lefaucheur, Drouot, Keravel, & Nguyen, 2001; Pleger et al., 2004). Unfortunately. rTMS equipment is expensive and lacks portability, making it less practical than other approaches. In addition, depending on the intensity of stimulation, rTMS can
be uncomfortable and the procedure is difficult to administer in a blinded fashion. Finally, rTMS induces a strong electric current in the brain that results in action potentials. It is still unclear whether supra-threshold stimulation is the best approach to modulate cortical activity.

Another noninvasive technique studied is tDCS. In tDCS, very weak electrical currents (1 to 2 mA) are applied directly onto the scalp via one of two electrodes. Most often, the active electrode is placed over a site of interest, and the other electrode is placed on the contralateral side of the forehead or at an extracephalic area. There is evidence that cortical activity under the scalp where a positive electrode (anode) is placed increases, and activity under a negative electrode (cathode) decreases (Antal, Nitsche, & Paulus, 2001; Nitsche & Paulus, 2001). Additional modeling studies suggest functionally significant amount of electric current may reach the cortex from appropriately large electrodes suitably placed (Miranda, Lomarev, & Ittali, 2006; Wagner et al., 2007). tDCS has promise over the other available stimulation techniques in that (a) it does not require implantation of invasive hardware; (b) it is easy to apply; (c) the tDCS equipment is inexpensive and easy to maintain; (d) given the very low currents involved, active tDCS is very difficult to detect by patients (making a sham-stimulation condition in clinical trials possible); and (e) some evidence suggests that the modulatory effects of tDCS may be stronger than rTMS (Nitsche & Paulus, 2001). Finally tDCS has an interesting advantage as it modulates spontaneous neuronal firing via modulation of resting membrane potential; therefore, this technique may be suitable to enhance learning effects associated with behavioral tasks. In the context of pain treatment, it is possible to envision the use of tDCS coupled with cognitive restructuring therapy or self-hypnosis training, which might work synergistically to enhance overall treatment effects.

Evidence suggests that tDCS holds promise for treating chronic refractory spinal cord injury pain. Fregni and colleagues randomized 17 patients with spinal cord injury and chronic pain to receive sham or active motor cortex tDCS (2 mA, 20 min each. 5 consecutive days; Fregni, Boggio, et al., 2006). They found (a) a significant reduction in pain intensity ratings after active anodal (positive electrode) stimulation of the primary motor cortex in the active, but not the sham, condition; (b) the reductions in pain intensity following each session lasted at least 24 hr until the next treatment session; and (c) there was a cumulative analgesia effect with multiple treatments, such that each treatment produced further reductions in pain from one day to the next. After 5 days of tDCS, average pain scores decreased more than 50% from baseline (6.2/10 to 2.9/10) in the active group, whereas they actually increased slightly, on average, in the sham group.

In another study of 32 patients with fibromyalgia randomly assigned to receive active or sham stimulation over the motor cortex or dorsolateral prefrontal cortex, significant benefits were found only for active tDCS over the motor cortex (Fregni, Gimenes, et al., 2006). This second study supports not only the specificity of tDCS over placebo effects but also the specificity of site placement for the effects of tDCS. However, the extent to which effective tDCS treatment is associated with changes in EEG has not yet been examined.

Hypnosis

Controlled trials, published over the past decade, have demonstrated that hypnosis training can result in reductions in the severity of both acute and chronic pain (Montgomery, DuHamel, & Redd, 2000; Patterson & Jensen, 2003). Moreover, self-hypnosis training in persons with chronic pain appears to have two primary effects: a short-term reduction in chronic pain that occurs during the treatment session or hypnosis practice that lasts for several hours in about 70% of persons with chronic pain, and a longer term permanent reduction in baseline daily pain, experienced by a smaller subset (about 25%) of patients (Jensen, Barber, et al., 2008).

PET and fMRI studies show that the effects of hypnotic analgesia are "real."
the sense that hypnosis with suggestions for analgesia produces reliable reductions in activity in the sensory cortex and other areas of the brain that are associated with the experience of pain and are known to process nociceptive information (Hofbauer, Rainville, Duncan, & Bushnell, 2001; Rainville, Duncan, Price, Carrier, & Bushnell, 1997). However, imaging research has not identified a mechanism for the effects of hypnotic analgesia, as it is possible that the observed changes in cortical activity could be due to a number of factors (e.g., increase control over subsystems that process nociception, distraction).

A relatively large number of studies have examined the EEG correlates of hypnosis. Two of the consistent findings from this literature are (a) more highly hypnotizable individuals tend to show greater slow wave (theta and alpha) activity than less hypnotizable individuals, both at baseline (i.e., before hypnotic inductions) and during hypnosis, and (b) hypnotizable, and especially high hypnotizable, persons show an increase in slow wave (theta and alpha) activity following hypnotic inductions (Crawford, 1990; Williams & Gruzelier, 2001). These findings are consistent with the possibility that the presence of slow wave EEG activity patterns is correlated with the effects of hypnosis on pain. Also, in one study, neurofeedback training to increase both theta (4-7.5 Hz) and alpha (8-12 Hz) activity, as well as the theta/alpha ratio, was shown to increase responsivity to hypnotic suggestions, providing further support for a possible impact of hypnosis on EEG-assessed bandwidth activity (Batty et al., 2006). These findings, when considered in light of the fact that the majority (about 70%) of persons who receive hypnosis report decreases in pain, are consistent with the possibility (not yet adequately tested, however) that hypnosis's effects on pain might be directly associated with EEG-assessed cortical rhythms; specifically because of the relative increases in the slow wave activity that accompanies hypnosis (Williams & Gruzelier, 2001). Of course, even if consistent associations between specific cortical rhythms (e.g., less beta and/or theta and more alpha) and pain relief are found, this could not be used as evidence proving that changes in cortical rhythms mediate the impact of some treatments on pain experience. Such evidence must come from experimental studies in which cortical rhythms are systematically altered (perhaps through the use of targeted neurofeedback protocols) in some patients and not others, to determine if changes in certain specific rhythms lead to changes in pain experience. Another important point that needs to be considered is that pain may inhibit an individual's ability to be hypnotized, as it is possible that in some patients, the cortical activity associated with chronic pain could inhibit some of the necessary conditions for hypnosis.

**SUMMARY AND IMPLICATIONS OF RESEARCH ON THE ASSOCIATIONS BETWEEN PAIN AND NEUROPHYSIOLOGY**

Research performed over the past decades has confirmed that the brain is not a passive recipient of nociceptive information, but modulates and is itself influenced by nociceptive input. The central sensitization that can occur in the CMS with ongoing nociception, and that can contribute to ongoing pain, could also potentially be reversed or interrupted with interventions that alter pain- related cortical functioning. This possibility provides a rationale for the use of interventions that target pain modulation at the level of the cortex, including nonpharmacological novel interventions that could potentially benefit patients with chronic refractory pain and with the additional advantage of being a more specific and focal treatment. Indeed, there has been a dramatic increase in interest in such treatments in recent years.

Recent, albeit preliminary, research suggests that the cortical modulation of chronic pain may be reflected in EEG bandwidth activity, such that chronic pain relief is associated with a relative increase in alpha activity and a relative decrease in beta. Research also suggests that increased theta activity may be associated with some chronic neuropathic pain conditions. However, further research
is still necessary to confirm the specific EEG signature(s) of chronic pain.

Our understanding of the associations between EEG activity and pain is just beginning; much more research is needed to determine which EEG activity patterns, if any, are consistently associated with the experience of chronic pain. However, if future research supports the relationships that preliminary research suggests exist, this research could provide an empirical basis for designing interventions that target brain activity for pain management (such as a neurofeedback) or be used to guide parameters of stimulation when using tDCS.

NEUROFEEDBACK TREATMENT APPROACHES FOR CHRONIC PAIN MANAGEMENT

This section provides some suggestions regarding how one might utilize neurofeedback in the treatment of chronic pain, based in large part on the literature review just presented. However, it is also important for the clinician to keep in mind that, because of the lack of controlled studies, no single protocol or neurofeedback approach has proven efficacy for pain management at this point in time.

In general, an increase in relative magnitude alpha frequency band (generally defined as 8-12 Hz) is thought to reflect decreases cortical "activation" or directed active engagement. For example, the alpha band has been shown to be associated with an alert yet idle state, or more simply stated, cortical receptivity (Sherlin, 2008). Conversely an increase in relative magnitude beta frequency (generally described as 13-32 Hz) is thought to reflect increased active (directed) cortical engagement. We can therefore hypothesize that if the cortical areas associated with the processing of pain can be conditioned to produce decreases in cortical arousal and increases passive receptivity (through decreasing beta and/or increasing alpha relative magnitude), then the experience of pain may decrease.

The setup required for protocols that would increase relative magnitude alpha and decrease relative magnitude beta is easy using most software and hardware systems currently available for neurofeedback application!. However, questions may be raised concerning the ideal or most practical electrode placement. Two placement protocols that have been described are (a) a T3-T4 sequential montage (i.e., bipolar montage; Sime, 2004) and (2) a C4 placement (Kayran et al., 2007). Although Sime reported an immediate beneficial effect of training using the T3-T4 montage placement, there is the possibility that this protocol could reduce the alpha magnitude and increase the relative beta magnitude at the referential site to achieve the training objective (e.g., T3 active minus T4 reference activity).

An additional important knowledge gap in the field that should be recognized is also related to the issue of electrode placement. Alpha frequency activity can be enhanced globally or regionally. Moreover, global and regional changes in bandwidth activity can influence each other and are probably (somehow) related. For example, T3/T4 alpha is likely driven by occipital alpha, which may have something to do with alert relaxation. C3/C4 for frontal alpha, on the other hand, is probably an enhanced Mu rhythm, which can also be achieved by relaxing hand muscles. One can make similar arguments about regional and global influences on beta or gamma bands. More research is needed to determine how comorbidities in the pain patient influence global brain patterns. In the meantime, and until our knowledge concerning these potential mutual influences is increased, or research demonstrates the superiority of one placement over another, it might make sense for clinicians to compare different options (e.g., T3-T4 vs. C4 vs. other possible sites) in the same patient, and then use the placement that results in the most benefit for that individual patient.

Some recent studies have also identified the dorsal anterior cingulate cortex (dACC: Brodmann Area 24) as critical in the affective experience of pain (e.g., Rainville et al., 1997). Recent advanced neuro-/fMRI-feedback techniques have targeted this location. One study, for example, used fMRI feedback to
demonstrate how the ongoing experience of pain may be modulated by training participants to modify dACC activation accessed via real-time fMRI (DeCharms et al., 2005). In another study, an advanced cortically targeted neurofeedback technique called Standardized Low Resolution Electromagnetic Tomography (or sLOR ETA) targeted this same region with similar results (Ozier, Whelton, Mueller, Lampman, & Sherlin, 2008). Although such advanced feedback techniques are not available to most practitioners, one may postulate targeting the same areas using conventional neurofeedback with a single channel at approximately FZ or just anterior to FZ, or alternatively with two channel referential montage of electrode sites F1 and F2 as active sites. The training goal would be to increase the relative magnitude alpha while decreasing/inhibiting relative magnitude beta in the ACC. The clinician should closely monitor client progress of the training, and particularly focus the client on being able to identify and replicate any state of comfort achieved during training at home, when pain levels are perceived as particularly high.

Although the goal of these protocols is to teach the client to identify and utilize a state of increased alpha and decreased beta for the control of pain, there is also a potential risk that if the client increases the overall (baseline) alpha and decreased beta relative magnitude, he or she could potentially suffer cognitive deficits (Chabot & Serfontein, 2006). However, we have yet to notice this possible side effect in the individuals we have treated using this approach for pain management. Nevertheless, this possibility should be carefully monitored in participants in any neurofeedback training protocol.

As previously noted, in individuals with spinal cord injury and chronic pain, there is evidence for decreased alpha and increased theta frequency band relative magnitude peak, relative to individuals with spinal cord injury who do not have chronic pain. For these patients, a potential goal of treatment would be to shift the peak frequency from the theta frequency band range to the alpha frequency band range to determine if this is associated with improvements in pain. However, the neurofeedback protocol to achieve this goal would be quite similar to that used for increasing alpha and decreasing beta band activity, as both involve increasing alpha. A shift in peak frequency band can be achieved, and has been demonstrated in a variety of populations in our clinical experience, although in our work it has primarily been applied to increase cognitive processing speed and thalamic processing of incoming cortical and sensory information.

The application of this model for neurofeedback training would be very similar to that used in the previously cited study addressing the occipital region (Gannon & Sternbach, 1971). That is, the peak frequency is first identified in both baseline conditions of eyes closed and eyes open in the occipital region. This allows the clinician a very easily detectable and testable hypothesis in determining if this protocol might be potentially useful. In our clinical experience the best electrode placement for this purpose is along the midline in the parietal and occipital region. Typically we choose the active electrode site of POZ referenced to the ear (or other neutral site such as nose) for the eyes open condition; if training in the eyes closed condition we either use site OZ or a two-channel referential montage using sites O1 and O2. The protocol goal here again is to increase the alpha frequency relative magnitude, with the difference that with this protocol, we now inhibit both the beta frequency relative magnitude and the theta frequency relative magnitude.

CONCLUSION

Chronic pain is a significant health problem for many individuals that is not being adequately addressed with the treatments that are currently available (Turk, 2002). Moreover, the available pharmacologic treatments that tend to be used for chronic pain are often associated with significant adverse effects (e.g., opioids can lead to tolerance, constipation, and altered mental states). The understanding that pain experience is modulated at many levels of the CNS, including the cortex, opens the door to interventions that might affect pain at the cortical level, and that may not have as many negative side
effects produced by analgesics. Clinicians knowledgeable in neurofeedback approaches might consider opening their practices to patients with chronic pain and then reporting to the community the outcomes of their clinical work in the form of published case studies and case series. This sharing of clinical experience provides an important foundation for hypothesis generation, which would then contribute to the design and implementation of more definitive clinical trials. Ultimately, the results of such work would help us to understand the extent to which neurofeedback benefits individuals with chronic pain, and if it does, the specific interventions, protocols, and approaches that are most effective.

REFERENCES


