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EDITORIAL

A Different Type of Procedure for a Different Type of Pain

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In a randomized, placebo-controlled trial described in this issue of *Arthritis & Rheumatism*, Fregni and colleagues studied the effect of transcranial direct current stimulation (tDCS) on pain and quality of life in patients with fibromyalgia (1). These investigators observed that this noninvasive approach was safe and effective for the short-term treatment of fibromyalgia-associated pain. The study also highlights the rapid movement toward neuromodulatory treatment of chronic pain, which requires a paradigm shift in how we think of chronic pain and its management.

The use of various procedures to treat pain is certainly nothing new. For centuries, many procedures have been performed to ameliorate the "source" of pain and typically have been aimed at eliminating peripheral inflammation or repairing peripheral tissue. Some of these procedures work well (e.g., hip replacement surgery), while others have widespread use even though they have not been shown to be efficacious when formally tested in randomized controlled trials. For example, recent systematic reviews revealed only limited evidence, if any, for the long-term therapeutic benefits (compared with placebo) of facet joint injections, extracorporeal shock wave therapy for lateral elbow pain, or corticosteroid injections for shoulder capsulitis, rotator cuff tendonitis, and lateral epicondylitis (2–5). Moreover, procedures aimed at stabilizing or fusing vertebrae or joints have shown limited success in treating pain, and only in highly selected patients (6,7).

The failure of peripherally directed procedures to treat many types of pain is consonant with our current understanding that not all chronic pain is attributable to peripheral damage or inflammation, as measured, for instance, radiographically. In patients with osteoarthritis, there is little relationship between the degree of joint space narrowing and the degree of pain (8). In the setting of low back pain, structural abnormalities on magnetic resonance imaging and discography have only a weak association with back pain episodes and no association with disability or future medical care (9). In fact, in nearly any disease there is a poor relationship between an individual patient's level of pain and the extent or degree of peripheral damage or inflammation that can be documented on objective testing.

We are beginning to understand why such discrepancies may occur. In addition to peripheral or nociceptive pain due to damage or inflammation, there are (at least) 2 other mechanistically distinct types of chronic pain, and these may coexist with peripheral pain (10).

Neuropathic pain is a non-nociceptive chronic pain that has been recognized and understood for some time. Although neuropathic pain is usually attributed to damage and subsequent irritability of peripheral nerves, central changes in pain processing constitute a second type of chronic pain in patients with this condition (11).

A third type of chronic pain is caused by disturbances in the central processing of pain, alone rather than in association with identifiable peripheral input or nerve damage. Such conditions have sometimes been included in the category of neuropathic pain, but they have fundamental differences from neuropathic pain and are often termed "central" pain syndromes. Such syndromes include fibromyalgia, irritable bowel syndrome, temporomandibular joint disorder, and idiopathic low back pain (12). The hallmark of these conditions is the evidence of pain amplification occurring in

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the central nervous system, manifest as allodynia (pain in response to normally nonpainful stimuli) and/or hyperalgesia (increased pain in response to normally painful stimuli) on physical examination, that can be corroborated and "objectified" using sensory testing and functional neuroimaging. This pain amplification may be accompanied by psychological factors but can clearly occur independently and is neurobiologically distinct from depression and/or anxiety (13).

We are also beginning to understand the mechanisms behind this "increased gain" in pain and sensory processing systems. For rheumatologists, it is simplest to think of pain and sensory processing systems as being analogous to the immune system. Autoimmune or inflammatory disorders occur because of a regional or systemic imbalance of proinflammatory versus antiinflammatory influences. Similarly, many inhibitory and facilitatory influences on pain processing can act either regionally (at the level of the peripheral nerve or spinal cord) or systemically (at the level of the spinal cord or brain). For example, pain in patients with fibromyalgia might be attributable, in part, to a lack of normal antinociceptive mechanisms, such as a defect in the function of descending inhibitory (analgesic) pathways, and also a possible increase in spinal excitatory activity such as that which occurs in wind-up or central sensitization (14,15). The ultimate proof that these defective central control mechanisms are playing a role in central pain states comes from randomized clinical trials demonstrating that neuroactive compounds that either increase inhibitory activity (e.g., serotonin–norepinephrine reuptake inhibitors) or decrease facilitatory activity (e.g., antiepileptics) can be efficacious in the treatment of fibromyalgia as well as neuropathic pain (16,17).

The report by Fregni and colleagues raises the possibility that we may also be able to reduce pain in patients with these central pain states by transcutaneously electrically stimulating the brain regions that directly or indirectly influence pain processing. In this study, 32 female patients with fibromyalgia were randomized into 3 groups: tDCS of the primary motor cortex (M1), tDCS of the dorsolateral prefrontal cortex (DLPFC), and sham stimulation. Patients in the 2 active-treatment arms received a constant 2-mA current, 20 minutes daily for 5 consecutive days, while patients in the sham group received only 30 seconds of stimulation of M1 each day. Fregni et al observed a significant decrease in pain (as measured by visual analog scale, clinician's global assessment, and patient's global assessment) in the M1 group compared with the sham group. In contrast, patients in the DLPFC group, who received the same magnitude of electrical stimulation but in a different brain region, had no clinical improvement, making it much less likely that the observed effect in the M1 group was a placebo effect. Pain reduction in the M1 group continued through the 21-day followup period, and no significant side effects were associated with tDCS compared with sham treatment.

In a separate study, these investigators also observed that tDCS had analgesic properties for the central pain of spinal cord injury (18). A similar treatment, transcranial magnetic stimulation (TMS), has been more widely studied and used to stimulate neural regions noninvasively and has analgesic properties in both healthy individuals and patients with chronic pain (19). The mechanisms by which these treatments work are not yet precisely understood, but presumably these treatments are either stimulating inhibitory pathways, such as known endogenous analgesic pathways, or reducing facilitatory activity.

The results of this study, if confirmed by other investigators, suggest an alternative mode of therapy for patients with fibromyalgia or other central pain syndromes. Other neurostimulatory therapies, such as deep brain stimulation (20), spinal cord stimulation (21), and vagus nerve stimulation (22), have also shown promising efficacy in decreasing pain and improving quality of life in selected groups of patients with chronic pain. Although implantable neurostimulatory devices are associated with the inherent risk of complications such as (implant-site) infection and hardware failure, tDCS and TMS have the advantage of being both noninvasive and easily transferable between sites and may obviate the need for invasive neuromodulatory procedures. At a minimum, these techniques will help in the selection of appropriate candidates and appropriate sites for implantation of neurostimulatory devices.

It will take some time before we determine the precise role for these types of therapy in patients with fibromyalgia. In the meantime, the study by Fregni et al provides further evidence that fibromyalgia is associated with abnormal neural activity, and that therapy directed toward these underlying mechanisms can have a specific and clinically meaningful effect on symptoms.

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