tDCS Modulation of Visually Induced Analgesia

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Abstract

■ Multisensory interactions can produce analgesic effects. In particular, viewing one's own body reduces pain levels, perhaps because of changes in connectivity between visual areas specialized for body representation, and sensory areas underlying pain perception. We tested the causal role of the extrastriate visual cortex in triggering visually induced analgesia by modulating the excitability of this region with transcranial direct current stimulation (tDCS). Anodal, cathodal, or sham tDCS (2 mA, 10 min) was administered to 24 healthy participants over the right occipital or over the centro-parietal areas thought to be involved in the sensory processing of pain. Participants were required to rate the intensity of painful electrical stimuli while viewing either their left hand or an object occluding the left hand, both before and immediately after tDCS. We found that the analgesic effect of viewing the body was enhanced selectively by anodal stimulation of the occipital cortex. The effect was specific for the polarity and the site of stimulation. The present results indicate that visually induced analgesia may depend on neural signals from the extrastriate visual cortex. ■

INTRODUCTION

The experienced level of pain strongly depends on the context in which nociceptive stimuli occur. Attention, expectations, and motivation are well-known examples of contextual modulation (Wiech, Ploner, & Tracey, 2008). In addition to modulation of pain by psychological contexts, multisensory perceptual contexts may also modulate pain. For example, simply looking at one's own body can be analgesic. In neurologically unimpaired participants, passive vision of the hand reduces pain ratings and the N2/P2 complex of laser-evoked potentials for the same stimuli (Longo, Betti, Aglioti, & Haggard, 2009). Furthermore, viewing one's own hand increases contact heat pain thresholds by 3.2°C, relative to viewing a neutral object (Mancini, Longo, Kammers, & Haggard, 2011). This "visually induced analgesia" can be considered a form of multisensory modulation in which the visual representation of the body has effects on pain processing.

Interactions between visual and somatosensory areas seem to mediate this modulatory effect of viewing the body. A recent functional MRI experiment demonstrated that changes in the effective connectivity between visual and pain centers in the cerebral cortex underlie visually induced analgesia (Longo, Iannetti, Mancini, Driver, & Haggard, 2012). In particular, that study showed increased functional coupling between visual and parietal areas that are activated by the visual perception of one's own body, including the "extrastriate body area" (EBA) in the lateral occipital cortex (Downing, Jiang, Shuman, & Kanwisher, 2001) and areas activated by painful stimuli. In this study, we tested the causal role of the extrastriate visual cortex in triggering the cross-modal modulation of pain perception. To achieve this aim, we modulated the level of excitability of the extrastriate visual cortex by transcranial direct current stimulation (tDCS) and examined the resulting effect on visually induced analgesia.

tDCS is a noninvasive technique of brain stimulation that can modulate cortical excitability by polarizing brain tissue in a polarity-dependent fashion, with anodal stimulation generally increasing excitability, and cathodal stimulation generally reducing excitability (Brunoni et al., 2012; Paulus, 2011; Nitsche et al., 2003; Nitsche & Paulus, 2001). When delivered to specific cortical areas, tDCS can alter physiological, perceptual, and higher-order cognitive processes (Vallar & Bolognini, 2011; Antal, Nitsche, & Paulus, 2001; Nitsche & Paulus, 2001). tDCS alters activity of cortical areas situated under the electrodes, but also of distant areas, probably through interconnections of the primary stimulated area with these structures (Polania, Nitsche, & Paulus, 2011).

The behavioral task was to rate the intensity of a painful sensation elicited by trains of electrical shocks applied to the left hand in two different visual contexts: participants were required to look at their own left hand ("hand-view" condition) or at an object occluding that hand (a wooden block, "object-view" condition). In two separate experiments, we investigated the effect of anodal (Experiment 1) and cathodal (Experiment 2) tDCS over the occipital cortex (extrastriate visual) and the centro-parietal cortex, which contributes to sensory processing of nociceptive stimuli (Valentini et al., 2012; Liang, Mouraux, & Iannetti, 2011; Tracey, 2011). We expected that tDCS over the occipital

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cortex would not modulate pain generally, but specifically influence the analgesic effect of viewing the body (increasing or decreasing analgesia, depending on the tDCS polarity). Conversely, tDCS over the centro-parietal cortex might induce analgesia independent of the visual context, according to previous reports that demonstrate analgesic effects of both anodal and cathodal stimulation of the motor cortex without any explicit visual task (for reviews, see Vallar & Bolognini, 2011; Lefaucheur et al., 2008).

METHODS

Participants

Twenty-four naive right-handed (Oldfield, 1971) participants (mean age = 23.4 years, *SD* = 4.4 years; 17 women) took part in the two experiments (n = 12 each). All were free of medical disorders, substance abuse or dependence, CNS effective medication, and psychiatric and neurological disorders (Poreisz, Boros, Antal, & Paulus, 2007) and participated on the basis of informed consent. Guidelines of the ethical committees of the University of Milano-Bicocca (Milan, Italy) and the Declaration of Helsinki (BMJ 1991; 302: 1194) were followed.

Stimuli

For stimulation, we used a custom planar concentric electrode, consisting of a central metal cathode (diameter = 0.5 mm), an isolation insert (diameter = 5 mm), and an external anode ring (diameter = 6 mm), and providing a stimulation area of 19.6 mm^2. The electrode was applied along the digital nerve path, approximately on the second metacarpal space of the left hand. In each trial, a 500-msec train of electrical shocks at 10 Hz was generated by a Digitimer DS7A electrical stimulator (www.digitimer.com/) under computer control.

By virtue of its concentric design and small anode–cathode distance, this somatosensory stimulating electrode produces high current density at low current intensities. It can therefore depolarize the superficial layer of the dermis containing nociceptive A-delta fibers (Kaube, Katsarava, Kaufer, Diener, & Ellrich, 2000); however, A-beta fibers also might be concomitantly stimulated (de Tommaso et al., 2011). Pinprick-like painful sensation is generally produced at currents between 0.6 and 1.6 mA. Mean onset latencies of blink reflexes and pain-related evoked potentials for such stimulation were found to be compatible with conduction velocities of A-delta fibers (Katsarava et al., 2006; Katsarava, Ellrich, Diener, & Kaube, 2002).

At the beginning of each session, the individual threshold for painful pinprick sensations was identified by two ascending and descending stimulation sequences in 0.1 mA steps. The mean threshold was 0.52 mA (*SD* = 0.26 mA). Two different intensities (+0.20 and +0.70 mA above individual pain thresholds) were then selected and used in the main experiments (low-intensity stimulus: mean = 0.70 mA, *SD* = 0.26 mA; high-intensity stimulus: mean = 1.18 mA, *SD* = 0.32 mA).

Procedure

Participants sat at a table with their hands resting palm down on the desktop, gazing toward their left hand (Figure 1). A black cape hid from sight their arms and right hand, so that participants could see only their left hand. Two visual conditions, "hand-view" and "object-view," were presented in different blocks in an ABBA order (initial condition counterbalanced across participants and sessions). In the "hand-view" condition, participants gazed toward their left hand. In the "object-view" condition, the left hand was occluded by a box, and participants looked at a hand-sized wooden block placed on

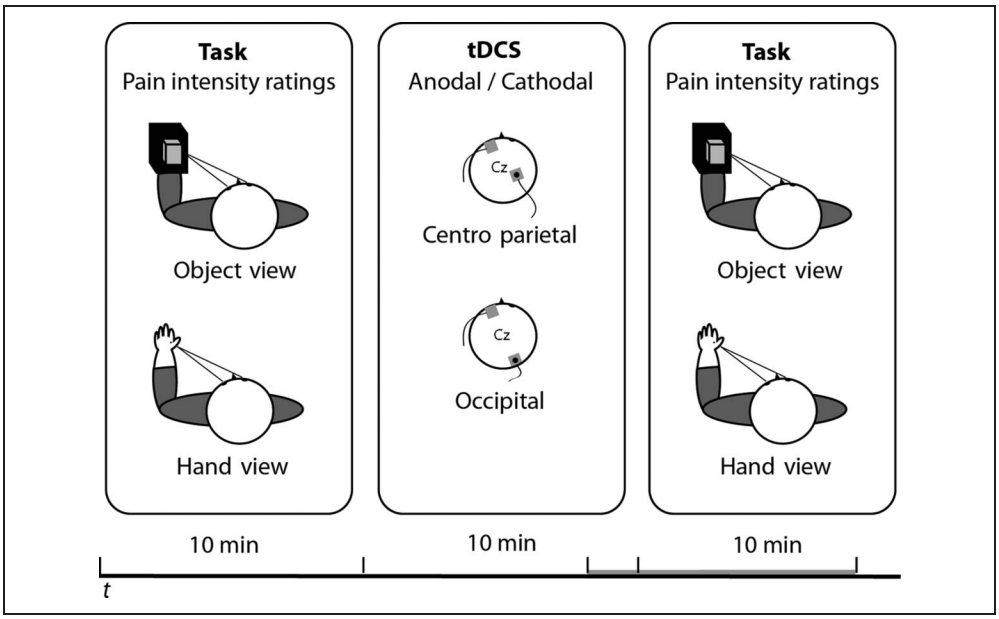

Figure 1. Stimuli and procedure. Two sessions of the same behavioral task were administered before and after 10 min of 2 mA tDCS over either the right occipital or the centro-parietal cortex. During the behavioral task, participants were required to look at their own left hand or at an object in the same spatial location while verbally rating the intensity of electrical shocks delivered on their left hand.

top of it (approximately 3 cm above the hand). Participants were instructed to fixate the hand/object continuously. In each trial, a 500-msec train of five shocks at either low or high intensity was administered. Participants were asked to verbally rate the intensity of the stimulus using a pain scale, from 0 (*just noticeable*) to 100 (*worst pain imaginable*; Ohnhaus & Adler, 1975). The intensity of the stimulus was randomized within each block. Each condition was repeated four times per block, for a total of eight repetitions per behavioral test (32 total trials, taking approximately 10 min). The test was repeated before and after each of the three tDCS sessions (see below).

tDCS

In two different experiments, either anodal (Experiment 1) or cathodal (Experiment 2) stimulation (2 mA/35 cm^2) was administered. The tDCS stimulation was delivered by a battery-driven constant current stimulator (www.eldith.de/products/stimulator), using a pair of surface saline-soaked sponge electrodes. A constant current of 2 mA intensity was applied, complying with current safety guidelines (Poreisz et al., 2007). The stimulating current was ramped up during a 10-sec fade-in phase, then held constant at 2 mA for 10 min, and then ramped down during a 10-sec fade-out phase. The duration of the tDCS stimulation was chosen on the basis of previous literature, with effects on cortical excitability sufficiently enduring to cover the duration of our experimental task (Nitsche & Paulus, 2001). The experimental task was initiated in the last 2 min of tDCS, as shown in Figure 1.

Each participant performed three sessions of tDCS (occipital, centro-parietal, and sham stimulation), presented in counterbalanced order across participants, and separated by at least 90 min to avoid carryover effects and to guarantee a sufficient washout of the effects of the previous run (e.g., Bolognini, Rossetti, Casati, Mancini, & Vallar, 2011; Bolognini, Fregni, Casati, Olgiati, & Vallar, 2010; Bolognini, Olgiati, Rossetti, & Maravita, 2010; Boggio et al., 2009; Sparing et al., 2009; Ragert, Vandermeeren, Camus, & Cohen, 2008). During the 90 min of break, participants were free to leave the laboratory. In different sessions, the active electrode (to which polarity refers) was placed over one of the targeted areas in the right hemisphere, according to the 10–20 system for EEG electrode placement. Importantly, participants were naive to all the stimulation conditions, being not informed as to which they had been assigned to and as to whether the stimulation was real or sham.

For occipital stimulation (O), the active electrode was placed between O2 and PO8 to stimulate the extrastriate visual cortex including visual body-specific regions (Downing et al., 2001).

For centro-parietal stimulation (CP), the active electrode was placed between CP4 and C4, in proximity to the primary somatosensory cortex (Overduin & Servos, 2004; Geyer, Schleicher, & Zilles, 1999). For both areas, the reference electrode was placed over a contralateral supraorbital region (Fp3), as this montage has proven to be effective in previous tDCS experiments (Dasilva, Volz, Bikson, & Fregni, 2011; Vallar & Bolognini, 2011).

For sham stimulation, the electrodes were placed over one of the target areas, the same parameters of stimulation were employed, but the stimulator was turned off after 30 sec. This ensured that participants could feel the initial itching sensation at the beginning of tDCS but was assumed not to produce any effective modulation of cortical excitability by tDCS (Gandiga, Hummel, & Cohen, 2006). In-house software switched the tDCS on and off without intervention from the participant or experimenter, allowing for a successful blinding of both of them. For each experiment, six participants received sham stimulation at the occipital site and six at the centro-parietal site.

Multiple testing sessions were used to allow tDCS effects to wash out. A corollary of this design, however, is the session-to-session variability in pain ratings (Rosier, Iadarola, & Coghill, 2002; Yarnitsky & Sprecher, 1994). Nevertheless, because we were interested in the modulation of context and time within sessions, rather than main effects of session, changes in overall pain levels between sessions were not problematic.

Analyses

Statistical analyses were performed separately for each experiment. First, planned comparisons were conducted to assess visually induced analgesia; we averaged the raw pain ratings across all three pre-tDCS conditions and compared the view-hand and view-object conditions with a paired t test.

Second, we explored the effect of tDCS submitting raw pain ratings into repeated-measures ANOVAs with the main within-subject factors of Stimulation Session (active tDCS over occipital cortex, active tDCS over centro-parietal cortex, sham tDCS), Time (pre- and post-tDCS), and Visual Context (hand-view, object-view). Bonferroni correction was used to adjust p values of post hoc tests.

RESULTS

Experiment 1: Anodal/Excitatory tDCS

The results are shown in Figure 2. In the pre-tDCS sessions, pain ratings were reduced in the hand-view condition in comparison with the object-view condition, $t(11) = 2.88$, $p < .015$, confirming visually induced analgesia for electrical nociceptive stimulation.

Omnibus ANOVA on raw pain ratings showed a significant main effect of Visual Context, $F(1, 11) = 19.18$, $p < .001$, $\eta_p^2 = 0.64$: pain ratings were reduced in the hand-view condition, in comparison with the object-view condition, replicating the finding that viewing one's own body is analgesic (Mancini, Longo, et al., 2011; Longo et al., 2009). The main effects of Session, $F(2, 22) = 2.89$, $p = .08$,

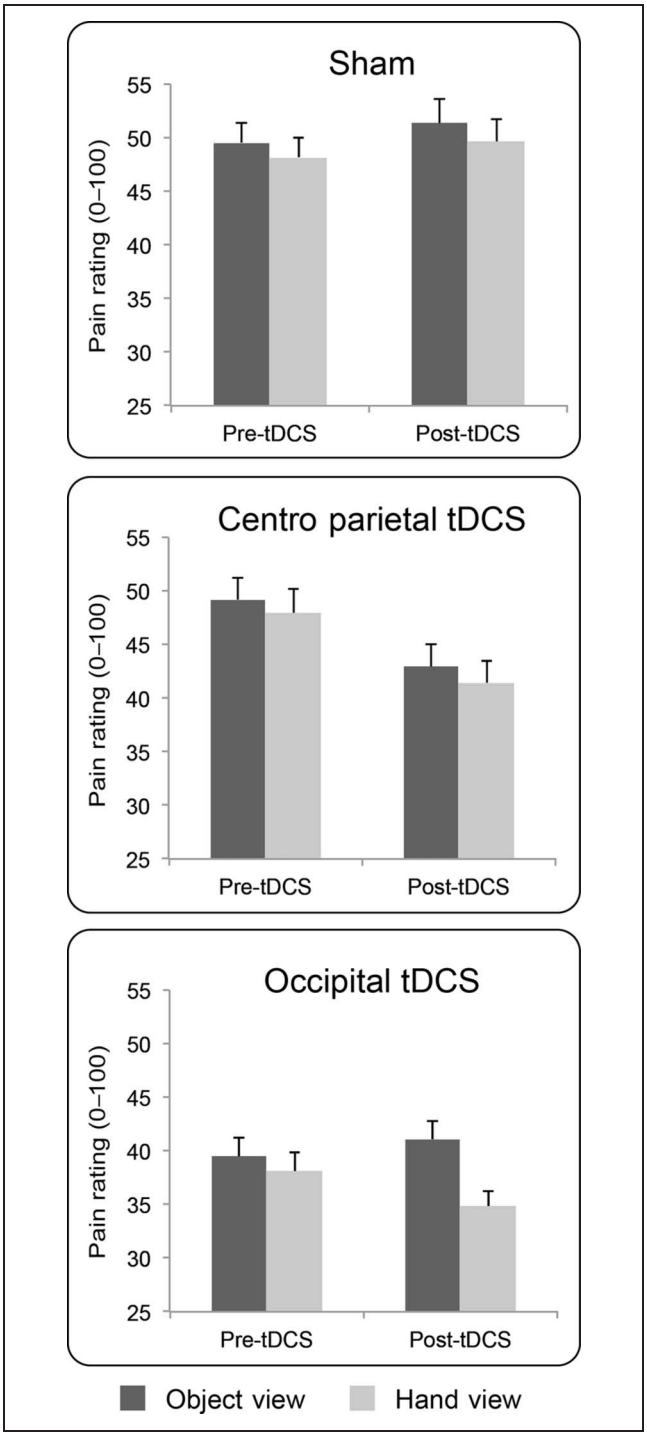

Figure 2. Experiment 1. Anodal stimulation: Group results. Mean (± *SEM*) pain intensity ratings (0–100) by stimulation session, visual context, and time.

$\eta_p^2 = 0.21$, and of Time ($F < 1$) were not significant, nor was their interaction, $F(2, 22) = 2.26$, $p = .13$, $\eta_p^2 = 0.17$, indicating that anodal tDCS over either the contralateral occipital or centro-parietal cortex did not modulate overall pain levels. Importantly, the interactions of session by context, $F(2, 22) = 3.62$, $p < .04$, $\eta_p^2 = 0.25$, time by context, $F(1, 11) = 6.01$, $p < .03$, $\eta_p^2 = 0.35$, and session by time by context, $F(2, 22) = 4.68$, $p < .02$, $\eta_p^2 = 0.30$, were all significant, suggesting that tDCS modulations were specific for the visual context and the session (Figure 2).

We explored this significant three-way interaction by submitting raw pain ratings to three 2 × 2 ANOVAs, one for each session, with main factors of Context and Time.

Ratings in the sham session were not modulated by time ($F < 1$). There was a near-significance main effect of Context, $F(1, 11) = 4.13$, $p = .067$, $\eta_p^2 = 0.27$, and no significant Time × Context interaction ($F < 1$).

For centro-parietal tDCS, the ANOVA revealed a significant main effect of Time, $F(1, 11) = 9.91$, $p = .009$, $\eta_p^2 = 0.47$, because pain ratings decreased after anodal centro-parietal tDCS (Figure 2). The main effect of Context, $F(1, 11) = 3.23$, $p = .10$, $\eta_p^2 = 0.23$, and the Time × Context interaction ($F < 1$) were not significant.

For occipital tDCS, the main effect of Time was not significant ($F < 1$), but there was a significant main effect of Context, $F(1, 11) = 22.27$, $p = .001$, $\eta_p^2 = 0.67$, and a significant Time × Context interaction, $F(1, 11) = 10.78$, $p = .007$, $\eta_p^2 = 0.49$. This occurred because the difference in ratings between view-object and view-hand contexts was bigger (mean difference = 6.28, *SEM* = 1.5, $p = .002$) after occipital tDCS, as compared with before stimulation (mean difference = 1.35, *SEM* = 0.5; $p = .046$). In other words, occipital tDCS enhanced the analgesic pain modulation caused by viewing the hand (Figure 2).

Experiment 2: Cathodal/Inhibitory tDCS

The results are shown in Figure 3. Visually induced analgesia for electrical stimuli was again replicated in the pre-tDCS sessions of Experiment 2, because pain ratings were reduced during vision of the hand in comparison with the object, $t(11) = 2.22$, $p < .048$.

Omnibus ANOVA on raw pain ratings showed a significant main effect of Context, $F(1, 11) = 8.15$, $p < .02$, $\eta_p^2 = 0.43$, indicating a visually induced analgesia. The main effect of Session, $F(2, 22) = 1.12$, $p = .34$, $\eta_p^2 = 0.09$, was not significant, but a significant effect of Time was found, $F(1, 11) = 5.19$, $p < .04$, $\eta_p^2 = 0.32$. The interactions were not significant (Context × Session: $F(2, 22) = 1.43$, $p = .26$, $\eta_p^2 = 0.11$; Time × Context: $F < 1$; Session × Time: $F < 1$; Session × Time × Context: $F(2, 22) = 2.04$, $p = .15$, $\eta_p^2 = 0.16$). Therefore, cathodal stimulation of the occipital and centro-parietal cortices did not modulate pain levels differently from sham. There was a significant pain reduction in the poststimulation session in comparison with the prestimulation session, independently of the tDCS session, possibly because of nociceptor habituation (Milne, Kay, & Irwin, 1991).

DISCUSSION

Viewing one's own body reduces the level of acute pain caused by an electrocutaneous stimulus, relative to viewing

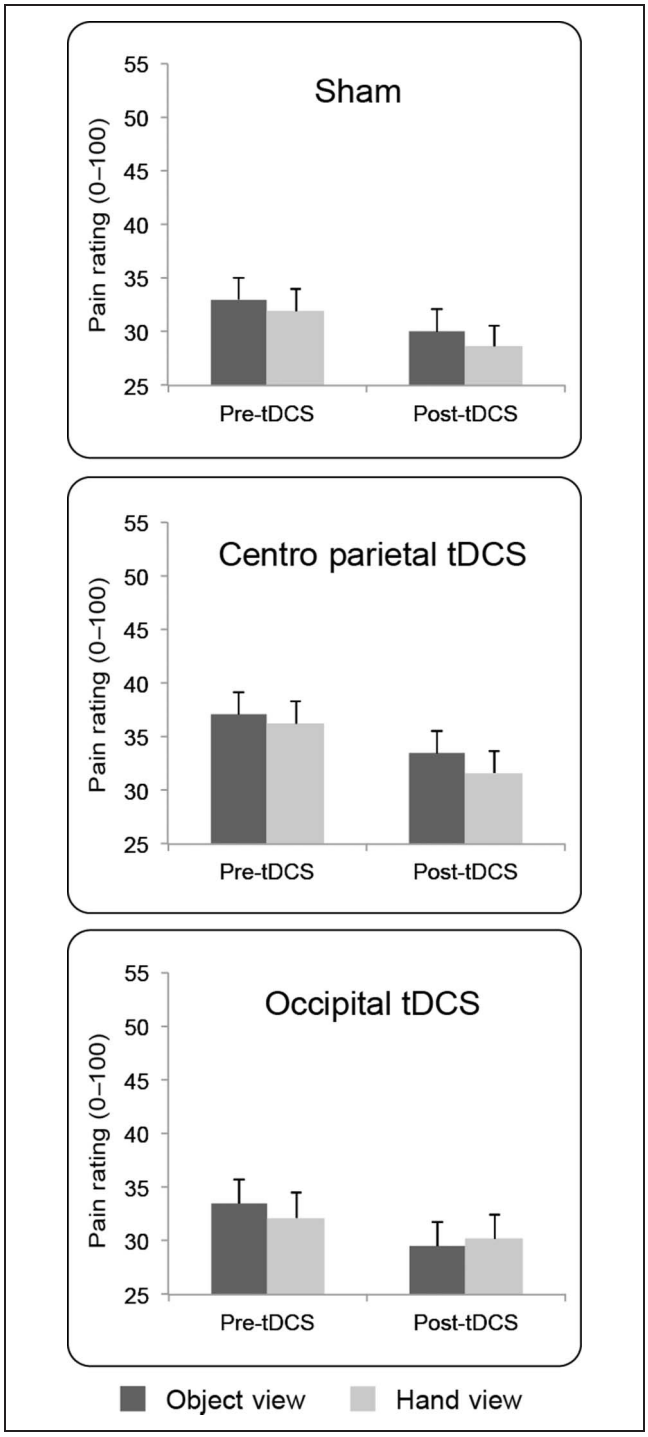

Figure 3. Experiment 2. Cathodal stimulation: Group results. Mean (± *SEM*) pain intensity ratings (0–100) by stimulation session, visual context, and time.

an object. This replicates previous findings obtained using different nociceptive stimuli (radiant heat in Longo et al., 2009; contact heat in Mancini, Longo, et al., 2011). The present novel finding is that visually induced analgesia can be modulated by the level of excitability in the contralateral extrastriate occipital cortex. Specifically, experimentally increasing excitability of this area by means of anodal tDCS enhanced the analgesic effect of viewing the body. This effect is specific for stimulation site, because it was not found for anodal stimulation of the centro-parietal cortex. Anodal centro-parietal stimulation produced an overall reduction in pain levels, but no interaction with visual context. The occipital tDCS effect is also specific for the polarity of stimulation, because cathodal tDCS on either occipital or centro-parietal cortex did not differ from sham.

Extrastriate Visual Cortex

The finding that viewing the body reduces acute pain may seem counterintuitive, given that acute pain is often associated with the sight of stimuli threatening the body and given that attention to threatening stimuli increases pain, rather than reducing it (e.g., Hofle, Hauck, Engel, & Senkowski, 2012; Van Damme, Legrain, Vogt, & Crombez, 2010; Legrain, Guerit, Bruyer, & Plaghki, 2002). Importantly, however, in our study, participants viewed their body but did not see any visual event corresponding to the painful stimulus. The painful electrode shocks in our experiment were entirely invisible. The mechanisms underlying inhibitory pain modulation from viewing the body may differ from those involved in facilitatory pain modulation from viewing nociceptive or potentially nociceptive stimulation events, such as threatening objects approaching the body. In particular, the latter process involves expectation of pain, which can be triggered either by viewing a threatening stimulus (Hofle et al., 2012) or by almost any other stimulus that has previously been associated with pain (Atlas, Bolger, Lindquist, & Wager, 2010; Koyama, McHaffie, Laurienti, & Coghill, 2005).

Our results suggest that pain reduction induced by viewing the body may involve an inhibitory interaction between visual areas and pain networks. Interestingly, Longo et al. (2012) have recently shown that visual analgesia for laser pain is associated with increased effective connectivity between areas activated when viewing the body and areas activated by noxious stimuli. Our result is consistent with theirs and further shows that this visual-nociceptive coupling plays a causal role in visual analgesia. Other examples of visual-somatosensory links have been suggested from behavioral experiments. For example, viewing the body enhances tactile spatial acuity (Kennett, Taylor-Clarke, & Haggard, 2001) and vibrotactile amplitude discrimination but reduces vibrotactile detection (Harris, Arabzadeh, Moore, & Clifford, 2007).

Moreover, the effect is specifically triggered by viewing the body, because occipital tDCS does not modulate overall pain levels, but only the analgesic effect of viewing the body. We suggest that visual areas specific for representing the body are likely to mediate these effects. The spatial resolution of tDCS is relatively poor, and we did not assess the precise location of body-specific visual areas in our participants. Therefore, this conclusion remains tentative. However, extensive neuroimaging evidence shows that occipital-temporal areas, including EBA (Downing

et al., 2001) and the fusiform body area (Peelen & Downing, 2005), are preferentially activated by the view of bodies and body parts (Orlov, Makin, & Zohary, 2010). Anodal tDCS may boost neural responses to viewing the hand in these body-specific visual areas, producing a neural drive that inhibits processing in pain networks. This connection is unlikely to be direct. Rather, visual information about the body may reach the multisensory areas of the posterior parietal cortex (Vallar & Maravita, 2009). These areas may then modulate the somatosensory regions of the pain matrix, including the somatosensory and insular cortices (Longo et al., 2012).

Interestingly, the analgesic effect of viewing the body may require recognition of personal identity. A previous study found no modulation of pain ratings and laser-evoked potentials when viewing the hand of another person (Longo et al., 2009). It is still controversial whether activity in EBA varies with the identity of the body that is viewed and whether this region might contribute to discriminating the self from the other (Hodzic, Muckli, Singer, & Stirn, 2009; Myers & Sowden, 2008; Saxe, Jamal, & Powell, 2006). Lamm and Decety (2008) did not find evidence for EBA involvement in empathy for pain in others. Recognition of identity seems also to involve other multisensory associative regions in the posterior parietal cortex, including the inferior parietal lobule and the inferior parietal sulcus (Hodzic, Kaas, Muckli, Stirn, & Singer, 2009). These regions are connected with visual body areas and are also associated with visually induced analgesia (Longo et al., 2012).

It is worth noting that EBA itself may be a multisensory area, because it is activated by haptic and visual body perception (Kitada, Johnsrude, Kochiyama, & Lederman, 2009) and by motor commands (Astafiev, Stanley, Shulman, & Corbetta, 2004). This suggests that the body representations formed in EBA might be partly multisensory, as indeed are representations of nonbody objects in other visual areas (Mancini, Bolognini, Bricolo, & Vallar, 2011; Lacey, Tal, Amedi, & Sathian, 2009).

Cathodal stimulation of the occipital cortex did not modulate visual analgesia. The analgesic effect induced by the view of the body was resistant to excitability-reducing cathodal tDCS. Sensorimotor effects of tDCS are frequently limited to one polarity of stimulation (for a recent review, see Vallar & Bolognini, 2011). This may be because of additional factors such as orientation of the electric field (e.g., Nitsche & Paulus, 2000) and the background level of activity in the system when tDCS is applied. As a result, some features of task-related activation may interact with the physiological state of the cortex and polarity of tDCS stimulation (Vallar & Bolognini, 2011; Antal & Paulus, 2008; Antal et al., 2004). Further experiments are required to address the potential role of these additional factors with respect to the absence of effects of cathodal stimulation.

Finally, it is worth mentioning that tDCS may even alter the activity of the areas below the reference electrode, in this case, the supraorbital region. This area has many connections with the other brain structures that are involved in pain modulation (Mendonca et al., 2011; Boggio, Zaghi, Lopes, & Fregni, 2008). The fact that in this study the two sites of anodal tDCS (occipital and centro-parietal) had different effects on perception, despite the same cathodal position, argues against a significant effect of the frontopolar return current. Instead, our results suggest that the critical factor for influencing neural activity with tDCS is anodal stimulation, in this case, over occipital areas.

Centro-parietal Cortex

Our study also demonstrates that the tDCS effects on visual modulation of pain are specific for anodal stimulation of the occipital cortex. Anodal stimulation of the centro-parietal cortex reduced pain levels independently of the visual condition, whereas cathodal stimulation over any site failed to modulate pain levels. Previous evidence suggests that centro-parietal stimulation might influence activity in relevant areas of the pain matrix, including somatosensory cortex (Valentini et al., 2012; Liang et al., 2011).

The current literature does not provide a clear view of the modulation of pain by centro-parietal stimulation. A previous report shows that cathodal, but not anodal, stimulation of contralateral primary somatosensory cortex (SI) can reduce both pain ratings and the N2 component of nociceptive laser evoked potentials (Antal et al., 2008). On the other hand, Grundmann et al. (2011) report that neither anodal nor cathodal tDCS over contralateral SI modulate pain thresholds, whereas cathodal tDCS over the same region increases cold and warm detection thresholds. Finally, there is also evidence of analgesic effects of cathodal (Csifcsak et al., 2009; Terney et al., 2008) and anodal (Boggio et al., 2008) stimulation of the contralateral primary motor cortex in healthy participants (for reviews, see Vallar & Bolognini, 2011; Lefaucheur et al., 2008). Reduced pain perception is mostly associated with anodal stimulation of the primary motor cortex, whereas the effects of tDCS stimulation of SI remain unclear both in healthy participants (Grundmann et al., 2011; Antal et al., 2008) and in patients (Tracey, 2011; Zaghi, Thiele, Pimentel, Pimentel, & Fregni, 2011; Zaghi, Heine, & Fregni, 2009; Lima & Fregni, 2008).

Our finding of analgesia after anodal centro-parietal tDCS is in line with previous evidence, but several caveats need to be kept in mind. In the experiment with cathodal tDCS, conducted on a different group of participants, pain levels were reduced after every tDCS session, including sham (but independently of the visual context). The simplest explanation is pain habituation (Milne et al., 1991); however, it is also possible that weak inhibitory effects of cathodal tDCS have been masked by pain habituation mechanisms. Likewise, also the analgesia induced by anodal tDCS over the centro-parietal cortex may include an element of pain habituation independent of specific brain stimulation and needs to be confirmed in future studies.

Several methodological and anatomical factors should also be considered in interpreting our centro-parietal results. First, our current intensity and tDCS duration were different from those of some previous studies (e.g., 1 mA for 15 min: Antal et al., 2008; 2 mA for min in our study). Electrode placement may also be important (e.g., Mendonca et al., 2011), because tDCS effects on pain may be not based on modulations of focal activity, but on connectivity changes (Dieckhofer et al., 2006; Matsunaga, Nitsche, Tsuji, & Rothwell, 2004). Furthermore, no single primary nociceptive- or pain-specific cortex has been found so far, and the specific role of centro-parietal areas in coding pain levels is not fully clear (Oertel et al., 2011; Iannetti & Mouraux, 2010). Finally, different types of nociceptive stimulation and different pain measures (e.g., thresholds vs. ratings) have been used in previous studies, complicating comparisons between different tDCS results.

Conclusion

To conclude, we show that multisensory interactions can be facilitated by anodal occipital tDCS. In particular, cortical excitability shifts induced by tDCS can modulate visual–nociceptive interactions, enhancing visual analgesia. tDCS is becoming popular clinically in the treatment of neuropathic and chronic pain (Brunoni et al., 2012; Zaghi et al., 2009; Lefaucheur et al., 2008; Fregni, Freedman, & Pascual-Leone, 2007). Mounting evidence suggests that other sensory modalities including touch (Drew & MacDermott, 2009; Inui, Tsuji, & Kakigi, 2006) and vision (Mancini, Longo, et al., 2011) can significantly modulate pain. The present findings might motivate research on tDCS pain therapies beyond the range of nociceptive brain regions currently targeted by tDCS.

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REFERENCES

Antal, A., Brepohl, N., Poreisz, C., Boros, K., Csifcsak, G., & Paulus, W. (2008). Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clinical Journal of Pain, 24,* 56–63.

Antal, A., Nitsche, M. A., Kruse, W., Kincses, T. Z., Hoffmann, K. P., & Paulus, W. (2004). Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. *Journal of Cognitive Neuroscience, 16,* 521–527.

Antal, A., Nitsche, M. A., & Paulus, W. (2001). External modulation of visual perception in humans. *NeuroReport, 12,* 3553–3555.

Antal, A., & Paulus, W. (2008). Transcranial direct current stimulation and visual perception. *Perception, 37,* 367–374.

Astafiev, S. V., Stanley, C. M., Shulman, G. L., & Corbetta, M. (2004). Extrastriate body area in human occipital cortex responds to the performance of motor actions. *Nature Neuroscience, 7,* 542–548.

Atlas, L. Y., Bolger, N., Lindquist, M. A., & Wager, T. D. (2010). Brain mediators of predictive cue effects on perceived pain. *Journal of Neuroscience, 30,* 12964–12977.

Boggio, P. S., Fregni, F., Valasek, C., Ellwood, S., Chi, R., Gallate, J., et al. (2009). Temporal lobe cortical electrical stimulation during the encoding and retrieval phase reduces false memories. *PLoS One, 4,* e4959.

Boggio, P. S., Zaghi, S., Lopes, M., & Fregni, F. (2008). Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *European Journal of Neurology, 15,* 1124–1130.

Bolognini, N., Fregni, F., Casati, C., Olgiati, E., & Vallar, G. (2010). Brain polarization of parietal cortex augments training-induced improvement of visual exploratory and attentional skills. *Brain Research, 1349,* 76–89.

Bolognini, N., Olgiati, E., Rossetti, A., & Maravita, A. (2010). Enhancing multisensory spatial orienting by brain polarization of the parietal cortex. *European Journal of Neuroscience, 31,* 1800–1806.

Bolognini, N., Rossetti, A., Casati, C., Mancini, F., & Vallar, G. (2011). Neuromodulation of multisensory perception: A tDCS study of the sound-induced flash illusion. *Neuropsychologia, 49,* 231–237.

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., & Merabet, L. (2012). Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimulation, 5,* 175–195.

Csifcsak, G., Antal, A., Hillers, F., Levold, M., Bachmann, C. G., Happe, S., et al. (2009). Modulatory effects of transcranial direct current stimulation on laser-evoked potentials. *Pain Medicine, 10,* 122–132.

Dasilva, A. F., Volz, M. S., Bikson, M., & Fregni, F. (2011). Electrode positioning and montage in transcranial direct current stimulation. *Journal of Visualized Experiments, 23,* 2744.

de Tommaso, M., Santostasi, R., Devitofrancesco, V., Franco, G., Vecchio, E., Delussi, M., et al. (2011). A comparative study of cortical responses evoked by transcutaneous electrical vs CO(2) laser stimulation. *Clinical Neurophysiology, 122,* 2482–2487.

Dieckhofer, A., Waberski, T. D., Nitsche, M., Paulus, W., Buchner, H., & Gobbele, R. (2006). Transcranial direct current stimulation applied over the somatosensory cortex—Differential effect on low and high frequency SEPs. *Clinical Neurophysiology, 117,* 2221–2227.

Downing, P. E., Jiang, Y., Shuman, M., & Kanwisher, N. (2001). A cortical area selective for visual processing of the human body. *Science, 293,* 2470–2473.

Drew, L. J., & MacDermott, A. B. (2009). Neuroscience: Unbearable lightness of touch. *Nature, 462,* 580–581.

Fregni, F., Freedman, S., & Pascual-Leone, A. (2007). Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *Lancet Neurology, 6,* 188–191.

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology, 117,* 845–850.

Geyer, S., Schleicher, A., & Zilles, K. (1999). Areas 3a, 3b, and 1 of human primary somatosensory cortex. *Neuroimage, 10,* 63–83.

Grundmann, L., Rolke, R., Nitsche, M. A., Pavlakovic, G., Happe, S., Treede, R. D., et al. (2011). Effects of transcranial direct current stimulation of the primary sensory cortex on somatosensory perception. *Brain Stimulation, 4,* 253–260.
Harris, J. A., Arabzadeh, E., Moore, C. A., & Clifford, C. W. (2007). Noninformative vision causes adaptive changes in tactile sensitivity. *Journal of Neuroscience, 27,* 7136–7140.
Hodzic, A., Kaas, A., Muckli, L., Stirn, A., & Singer, W. (2009). Distinct cortical networks for the detection and identification of human body. *Neuroimage, 45,* 1264–1271.
Hodzic, A., Muckli, L., Singer, W., & Stirn, A. (2009). Cortical responses to self and others. *Human Brain Mapping, 30,* 951–962.
Hofle, M., Hauck, M., Engel, A. K., & Senkowski, D. (2012). Viewing a needle pricking a hand that you perceive as yours enhances unpleasantness of pain. *Pain, 153,* 1074–1081.
Iannetti, G. D., & Mouraux, A. (2010). From the neuromatrix to the pain matrix (and back). *Experimental Brain Research, 205,* 1–12.
Inui, K., Tsuji, T., & Kakigi, R. (2006). Temporal analysis of cortical mechanisms for pain relief by tactile stimuli in humans. *Cerebral Cortex, 16,* 355–365.
Katsarava, Z., Ayzenberg, I., Sack, F., Limmroth, V., Diener, H. C., & Kaube, H. (2006). A novel method of eliciting pain-related potentials by transcutaneous electrical stimulation. *Headache, 46,* 1511–1517.
Katsarava, Z., Ellrich, J., Diener, H. C., & Kaube, H. (2002). Optimized stimulation and recording parameters of human "nociception specific" blink reflex recordings. *Clinical Neurophysiology, 113,* 1932–1936.
Kaube, H., Katsarava, Z., Kaufer, T., Diener, H., & Ellrich, J. (2000). A new method to increase nociception specificity of the human blink reflex. *Clinical Neurophysiology, 111,* 413–416.
Kennett, S., Taylor-Clarke, M., & Haggard, P. (2001). Noninformative vision improves the spatial resolution of touch in humans. *Current Biology, 11,* 1188–1191.
Kitada, R., Johnsrude, I. S., Kochiyama, T., & Lederman, S. J. (2009). Functional specialization and convergence in the occipito-temporal cortex supporting haptic and visual identification of human faces and body parts: An fMRI study. *Journal of Cognitive Neuroscience, 21,* 2027–2045.
Koyama, T., McHaffie, J. G., Laurienti, P. J., & Coghill, R. C. (2005). The subjective experience of pain: Where expectations become reality. *Proceedings of the National Academy of Sciences, U.S.A., 102,* 12950–12955.
Lacey, S., Tal, N., Amedi, A., & Sathian, K. (2009). A putative model of multisensory object representation. *Brain Topography, 21,* 269–274.
Lamm, C., & Decety, J. (2008). Is the extrastriate body area (EBA) sensitive to the perception of pain in others? *Cerebral Cortex, 18,* 2369–2373.
Lefaucheur, J. P., Antal, A., Ahdab, R., Ciampi de Andrade, D., Fregni, F., Khedr, E. M., et al. (2008). The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. *Brain Stimulation, 1,* 337–344.
Legrain, V., Guerit, J. M., Bruyer, R., & Plaghki, L. (2002). Attentional modulation of the nociceptive processing into the human brain: Selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. *Pain, 99,* 21–39.
Liang, M., Mouraux, A., & Iannetti, G. D. (2011). Parallel processing of nociceptive and non-nociceptive somatosensory information in the human primary and secondary somatosensory cortices: Evidence from dynamic causal modeling of functional magnetic resonance imaging data. *Journal of Neuroscience, 31,* 8976–8985.
Lima, M. C., & Fregni, F. (2008). Motor cortex stimulation for chronic pain: Systematic review and meta-analysis of the literature. *Neurology, 70,* 2329–2337.
Longo, M. R., Betti, V., Aglioti, S. M., & Haggard, P. (2009). Visually induced analgesia: Seeing the body reduces pain. *Journal of Neuroscience, 29,* 12125–12130.
Longo, M. R., Iannetti, G. D., Mancini, F., Driver, J., & Haggard, P. (2012). Linking pain and the body: Neural correlates of visually induced analgesia. *Journal of Neuroscience, 32,* 2601–2607.
Mancini, F., Bolognini, N., Bricolo, E., & Vallar, G. (2011). Cross-modal processing in the occipito-temporal cortex: A TMS study of the Muller-Lyer illusion. *Journal of Cognitive Neuroscience, 23,* 1987–1997.
Mancini, F., Longo, M. R., Kammers, M. P., & Haggard, P. (2011). Visual distortion of body size modulates pain perception. *Psychological Science, 22,* 325–330.
Matsunaga, K., Nitsche, M. A., Tsuji, S., & Rothwell, J. C. (2004). Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. *Clinical Neurophysiology, 115,* 456–460.
Mendonca, M. E., Santana, M. B., Baptista, A. F., Datta, A., Bikson, M., Fregni, F., et al. (2011). Transcranial DC stimulation in fibromyalgia: Optimized cortical target supported by high-resolution computational models. *Journal of Pain, 12,* 610–617.
Milne, R. J., Kay, N. E., & Irwin, R. J. (1991). Habituation to repeated painful and non-painful cutaneous stimuli: A quantitative psychophysical study. *Experimental Brain Research, 87,* 438–444.
Myers, A., & Sowden, P. T. (2008). Your hand or mine? The extrastriate body area. *Neuroimage, 42,* 1669–1677.
Nitsche, M. A., Liebetanz, D., Antal, A., Lang, N., Tergau, F., & Paulus, W. (2003). Modulation of cortical excitability by weak direct current stimulation-technical, safety and functional aspects. *Supplements to Clinical Neurophysiology, 56,* 255–276.
Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology, 527,* 633–639.
Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57,* 1899–1901.
Oertel, B. G., Preibisch, C., Martin, T., Walter, C., Gamer, M., Deichmann, R., et al. (2011). Separating brain processing of pain from that of stimulus intensity. *Human Brain Mapping, 33,* 883–894.
Ohnhaus, E. E., & Adler, R. (1975). Methodological problems in the measurement of pain: A comparison between the verbal rating scale and the visual analogue scale. *Pain, 1,* 379–384.
Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9,* 97–113.
Orlov, T., Makin, T. R., & Zohary, E. (2010). Topographic representation of the human body in the occipitotemporal cortex. *Neuron, 68,* 586–600.
Overduin, S. A., & Servos, P. (2004). Distributed digit somatotopy in primary somatosensory cortex. *Neuroimage, 23,* 462–472.
Paulus, W. (2011). Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. *Neuropsychological Rehabilitation, 21,* 602–617.
Peelen, M. V., & Downing, P. E. (2005). Selectivity for the human body in the fusiform gyrus. *Journal of Neurophysiology, 93,* 603–608.
Polania, R., Nitsche, M. A., & Paulus, W. (2011). Modulating functional connectivity patterns and topological functional

organization of the human brain with transcranial direct current stimulation. *Human Brain Mapping, 32,* 1236–1249.
Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin, 72,* 208–214.
Ragert, P., Vandermeeren, Y., Camus, M., & Cohen, L. G. (2008). Improvement of spatial tactile acuity by transcranial direct current stimulation. *Clinical Neurophysiology, 119,* 805–811.
Rosier, E. M., Iadarola, M. J., & Coghill, R. C. (2002). Reproducibility of pain measurement and pain perception. *Pain, 98,* 205–216.
Saxe, R., Jamal, N., & Powell, L. (2006). My body or yours? The effect of visual perspective on cortical body representations. *Cerebral Cortex, 16,* 178–182.
Sparing, R., Thimm, M., Hesse, M. D., Kust, J., Karbe, H., & Fink, G. R. (2009). Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. *Brain, 132,* 3011–3020.
Terney, D., Bergmann, I., Poreisz, C., Chaieb, L., Boros, K., Nitsche, M. A., et al. (2008). Pergolide increases the efficacy of cathodal direct current stimulation to reduce the amplitude of laser-evoked potentials in humans. *Journal of Pain and Symptom Management, 36,* 79–91.
Tracey, I. (2011). Can neuroimaging studies identify pain endophenotypes in humans? *Nature Reviews Neurology, 7,* 173–181.
Valentini, E., Hu, L., Chakrabarti, B., Hu, Y., Aglioti, S. M., & Iannetti, G. D. (2012). The primary somatosensory cortex largely contributes to the early part of the cortical response elicited by nociceptive stimuli. *Neuroimage, 59,* 1571–1581.
Vallar, G., & Bolognini, N. (2011). Behavioural facilitation following brain stimulation: Implications for neurorehabilitation. *Neuropsychological Rehabilitation, 21,* 618–649.
Vallar, G., & Maravita, A. (2009). Personal and extra-personal spatial perception. In G. G. Berntson & J. T. Cacioppo (Eds.), *Handbook of neuroscience for the behavioral sciences*. (Vol. 1, pp. 322–336). New York: Wiley.
Van Damme, S., Legrain, V., Vogt, J., & Crombez, G. (2010). Keeping pain in mind: A motivational account of attention to pain. *Neuroscience and Biobehavioral Reviews, 34,* 204–213.
Wiech, K., Ploner, M., & Tracey, I. (2008). Neurocognitive aspects of pain perception. *Trends in Cognitive Sciences, 12,* 306–313.
Yarnitsky, D., & Sprecher, E. (1994). Thermal testing: Normative data and repeatability for various test algorithms. *Journal of Neurological Sciences, 125,* 39–45.
Zaghi, S., Heine, N., & Fregni, F. (2009). Brain stimulation for the treatment of pain: A review of costs, clinical effects, and mechanisms of treatment for three different central neuromodulatory approaches. *Journal of Pain Management, 2,* 339–352.
Zaghi, S., Thiele, B., Pimentel, D., Pimentel, T., & Fregni, F. (2011). Assessment and treatment of pain with non-invasive cortical stimulation. *Restorative Neurology and Neuroscience, 29,* 439–451.