

## Postoperative Left Prefrontal Repetitive Transcranial Magnetic Stimulation Reduces Patient-controlled Analgesia Use

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**Background:** Several recent studies suggest that repetitive transcranial magnetic stimulation can temporarily reduce pain perception in neuropathic pain patients and in healthy adults using laboratory pain models. No studies have investigated the effects of prefrontal cortex stimulation using transcranial magnetic stimulation on postoperative pain.

**Methods:** Twenty gastric bypass surgery patients were randomly assigned to receive 20 min of either active or sham left prefrontal repetitive transcranial magnetic stimulation immediately after surgery. Patient-controlled analgesia pump use was tracked, and patients also rated pain and mood twice per day using visual analog scales.

**Results:** Groups were similar at baseline in terms of body mass index, age, mood ratings, pain ratings, surgery duration, time under anesthesia, and surgical anesthesia methods. Significant effects were observed for surgery type (open *vs.* laparoscopic) and condition (active *vs.* sham transcranial magnetic stimulation) on the cumulative amount of patient-delivered morphine during the 44 h after surgery. Active prefrontal repetitive transcranial magnetic stimulation was associated with a 40% reduction in total morphine use compared with sham during the 44 h after surgery. The effect seemed to be most prominent during the first 24 h after cortical stimulation delivery. No effects were observed for repetitive transcranial magnetic stimulation on mood ratings.

**Conclusions:** A single session of postoperative prefrontal repetitive transcranial magnetic stimulation was associated with a reduction in patient-controlled analgesia pump use in gastric bypass surgery patients. This is important because the risks associated with postoperative morphine use are high, especially among obese patients who frequently have obstructive sleep apnea, right ventricular dysfunction, and pulmonary hypertension. These preliminary findings suggest a potential new noninvasive method for managing postoperative morphine use.

FOR many years, it has been known that chronic motor cortex stimulation (MCS) *via* implanted epidural elec-

trodes controls neuropathic pain.<sup>1-4</sup> The antinociceptive mechanisms of MCS are unclear; however, the magnitude of pain relief is correlated with activation of portions of the anterior cingulate and orbitofrontal cortex.<sup>5,6</sup> Thus, MCS may exert some of its analgesic effect by altering the affective dimension of pain experience.

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technology that can focally stimulate the brain of an awake individual.<sup>7,8</sup> A localized pulsed magnetic field transmitted through a figure-eight coil induces electrical currents in the brain<sup>9</sup> and focally stimulates the cortex by depolarizing superficial neurons.<sup>10,11</sup> TMS at different intensities, frequencies, and coil angles excites several elements (*e.g.*, cell bodies, axons) of various neuronal groups (*e.g.*, interneurons, neurons projecting into other cortical areas).<sup>12-14</sup> When TMS pulses are delivered repeatedly, it is referred to as repetitive transcranial magnetic stimulation (rTMS).

Findings from studies of rTMS for depression and from studies that integrate TMS and functional magnetic resonance imaging suggest that TMS over the prefrontal cortex can cause secondary activation in important pain and mood-regulating regions, such as the cingulate gyrus, orbitofrontal cortex, insula, and hippocampus.<sup>15</sup> Moreover, rTMS affects the perception of laboratory-induced pain in healthy adults as well as chronic neuropathic pain in clinical samples.<sup>16-29</sup> Although most of these investigations have shown short-lived effects of rTMS on pain, a recent study demonstrated that antinociceptive effects can be sustained for at least 15 days after 3 consecutive days of rTMS.<sup>28</sup>

Following the literature from MCS, most studies of rTMS effects on pain perception have targeted the motor cortex. This approach is frequently hypothesized to work by normalizing activity of sensory neurons corresponding with the painful area.<sup>20,24,27</sup> However, as noted previously, much of the variance in clinical response to MCS seems to be explained by limbic activity.<sup>5,6</sup> If one of the mechanisms by which cortical stimulation alleviates pain is by modulating the processing of the affective dimension of pain experience, the prefrontal cortex might be a more efficient cortical target for pain management.<sup>15</sup> Consistent with this notion, a few recent studies have demonstrated acute and transient antinociceptive effects with prefrontal cortex TMS.<sup>23,29,30</sup> In addition, functional imaging research has shown that activation of the left dorsolateral prefrontal

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Received from the Departments of Psychiatry, Anesthesiology, and Surgery, Medical University of South Carolina, Charleston, South Carolina. Submitted for publication November 29, 2005. Accepted for publication March 31, 2006. No intramural or extramural grants were used to support this project. The Departments of Psychiatry, Anesthesiology, and Surgery, Medical University of South Carolina, Charleston, South Carolina, supported the personnel for this study. The Brain Stimulation Laboratory, Department of Psychiatry, Medical University of South Carolina, provided the equipment.

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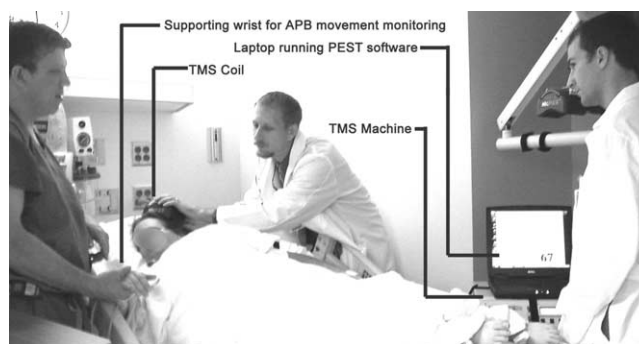
cortex is associated with decreases in pain unpleasantness ratings in healthy adults using laboratory pain induction methods, and it has been proposed that the left prefrontal cortex may inhibit limbic activity associated with painful stimuli.<sup>31</sup>

Although a number of studies have been conducted on the effects of rTMS on chronic neuropathic pain, none to date have investigated the effects of rTMS on acute postoperative pain. This is an important area of study because postsurgical pain is associated with high levels of opioid medication use, and both the immediate and longer-term risks associated with these medications are high, especially among gastric bypass surgery patients who frequently have obstructive sleep apnea, right ventricular dysfunction, and pulmonary hypertension. Therefore, we conducted this study to assess whether one session of prefrontal rTMS could reduce postoperative pain and patient-controlled analgesia (PCA) pump use. In addition, because left prefrontal rTMS has been associated with improvements in mood,<sup>32,33</sup> and mood has been shown to impact pain experience,<sup>34</sup> we examined the effects of TMS on post-TMS mood ratings (visual analog scale).

## Materials and Methods

Despite little published information on the effect size for rTMS on pain perception, the authors arrived at a rough estimate of effect size based on tables and figures from the available rTMS/pain literature (mean Cohen  $d = 1.32$ ). To reach minimum acceptable power (0.80) for pairwise comparisons with an effect size of 1.32, 8 subjects were needed in each group. To minimize the probability of making a type II error for this pilot trial, 10 subjects were recruited for each group, which improved the estimated power to 0.88.

Twenty gastric bypass surgery patients were enrolled (mean age, 43.05 yr; mean body mass index, 50.27 kg/m<sup>2</sup>; 19 female). Gastric bypass was chosen for the surgical procedure in this first test of the postoperative antinociceptive effects of TMS because of the homogeneity of the patient population and because it afforded the opportunity to evaluate open and laparoscopic surgical procedures on a similar patient population. This study was approved by the Institutional Review Board for Human Research at the Medical University of South Carolina (Charleston, South Carolina). Written informed consent to participate was obtained before laparoscopic ( $n = 12$ ) or open gastric bypass surgery ( $n = 8$ ). Open gastric bypass surgery was used in patients with previous abdominal surgery or a body mass index greater than 60 kg/m<sup>2</sup>. Intraoperative management consisted of intravenous premedication with midazolam and induction with propofol, lidocaine, fentanyl, and succinylcholine. Maintenance of anesthesia was accomplished with desflurane, fentanyl (up to 5  $\mu\text{g}/\text{kg}$ ), and cisatracurium. Reversal of neuromuscular blockade was performed with neostigmine and glycopyrrolate. All patients were pretreated for postoperative nausea and vomiting with ondansetron 30 min before emergence from surgery. At the time of arrival in the recovery room, patients were loaded with morphine sulfate up to 0.1 mg/kg ideal body weight based on their clinical level of assessed pain. This individual titration was performed by nursing staff who were blinded to the study protocol and patient randomization scheme.



**Fig. 1.** Photo of transcranial magnetic stimulation (TMS) motor threshold assessment in the postanesthesia care unit. Dr. Weinstein (*left*) supports the patient's right wrist to allow free movement of thumb and fingers, which are moved *via* TMS stimulation of the corresponding area of the patient's motor cortex. Dr. Borckardt (*middle*) positions the coil over the motor cortex and locates the area corresponding with abductor pollicis brevis (APB). Neil Shelly (*right*) runs the Parameter Estimation by Sequential Testing (PEST) algorithm software and adjusts the TMS machine output to the specified levels until the amount of TMS output is determined that is necessary to cause visible thumb movement 50% of the time. The subject's face has been blurred to protect confidentiality.

After surgery, in the postanesthesia care unit, each subject underwent a motor threshold assessment. The TMS device was set to 80% of machine output and fired single pulses at the rate of 1 per 2 s (0.5 Hz). The coil was systematically moved around the left scalp, and the stimulus intensity was adjusted until the area of the motor cortex involved in movement of the right abductor pollicis brevis was located. The interstimulus interval was then decreased to 4 s (0.25 Hz), and a custom-designed software program was used to run an adaptive Parameter Estimation by Sequential Testing (PEST) algorithm.<sup>31</sup> The researchers, with the aid of the program, determined the amount of TMS machine output necessary to produce visibly detectable movement of the thumb 50% of the time (resting motor threshold).<sup>35,36</sup> Subjects' prefrontal cortices were then located by moving the coil 5 cm anterior from the area of the motor cortex associated with thumb movement along the parasagittal line. Figure 1 shows the TMS setup in the postanesthesia care unit during a resting motor threshold assessment.

After the motor threshold assessment, subjects were started on a morphine PCA pump. The PCA pump was

set at a 1-mg bolus with a 6-min lockout interval. If the patient was allergic to or could not tolerate morphine sulfate, hydromorphone was used instead ( $n = 2$ ; 1 in the sham group, 1 in the active group). For statistical analyses of PCA pump use, morphine equivalent analgesic dose was calculated ( $0.2 \text{ mg hydromorphone} = 1.0 \text{ mg morphine}$ ).

Subjects were randomly assigned to receive real rTMS ( $n = 10$ ) or sham rTMS ( $n = 10$ ). Randomization was accomplished with the aid of a custom-developed visual BASIC application that was designed to randomize the TMS condition (real *vs.* sham) within the constraints of the predetermined group sizes (a total of 12 laparoscopic and 8 open surgery cases) and to ensure equal numbers of patients in the groups (10 active and 10 sham). Thus, there were 6 laparoscopic and 4 open surgery cases in each group. The randomization scheme was stored in a spreadsheet file that was available only to the researcher (J.J.B.) who was responsible for delivering rTMS. Contact between this researcher and the subject was limited to the motor threshold assessment and TMS delivery session. The researcher was not involved in the data collection process.

The active TMS coil is a figure-eight design with a solid core interior (Neopulse Neotonus devices, Malvern, PA). The sham coil is externally identical to the active TMS coil except that it does not actually stimulate, because an aluminum insert on the surface next to the scalp blocks passage of the magnetic field. Subjects received 20 min of 10-Hz rTMS at 100% of resting motor threshold (10-s stimulation trains with 20-s interstimulus intervals) for a total of 4,000 pulses. This dose is within the published safety guidelines,<sup>37</sup> although it is higher than most used in previously published studies on the effects of rTMS on pain perception. However, most other TMS/pain studies have examined the effects of motor cortex stimulation on pain perception. The motor cortex is more excitable than prefrontal cortex.<sup>37,38</sup> Therefore, a higher dose may be necessary to achieve desired effects when targeting the prefrontal cortex. In addition, the investigators were interested in maximizing the potential effects of rTMS on pain perception and did not want to err on the side of underdosing and risk a type II error during this pilot trial. This dosing decision was, of course, balanced against potential risks to the patients, which were determined to be minimal given that (1) the dose conformed to the published safety guidelines, (2) the cortical target (prefrontal cortex) is less excitable and is associated with a lower risk for seizures than the motor cortex, and (3) in the postanesthesia care unit, there is immediate availability of highly skilled physicians and nursing staff as well as the availability of critical care equipment if a seizure were to occur.

Subjects provided visual analog scale ratings of mood twice per day (0 = extremely sad or depressed and 100 = extremely happy or great mood), and PCA pump use data were collected from each subject's medical record

once per day (morphine use data were available in 2-h intervals). Subjects, medical staff providing clinical care to subjects, and personnel collecting ratings were blind to whether subjects had received real or sham rTMS. The only person who knew the randomization was the rTMS administrator (J.J.B.), who was not aware of the surgical history and medication loading and who followed a careful script with patients, physicians, and nurses.

#### Statistical Analysis

Independent sample *t* tests were used to compare the active and sham TMS groups across a number of baseline variables that might have influenced postoperative PCA pump use. Hierarchical linear modeling was used to assess the effects of surgery type (laparoscopic *vs.* open) and rTMS condition (real *vs.* sham) on cumulative PCA pump use curves over time. Hierarchical linear modeling has been shown to appropriately handle nested models with serially dependent data points,<sup>39,40</sup> and it allows for modeling of variables at the individual subject level (*e.g.*, each subject's cumulative PCA pump use over time) and at the broader organizational level to which each individual belongs or is assigned (*e.g.*, surgery type and TMS condition). All subjects' PCA orders in this study were discontinued after 44 h. This time frame was clinically determined and was independent of the study protocol. Cumulative PCA use curves over 44 h after surgery were square-root transformed to correct for nonlinearity and nonnormality. The estimation method of the model was restricted maximum likelihood, and the covariance structure was "unstructured." Means are reported with accompanying SE values. An independent sample *t* test was used to compare postoperative mood ratings between groups, and hierarchical linear modeling was used to assess for differences between groups in change in mood over time.

## Results

No significant differences were found between the active and sham TMS groups in terms of pre-TMS pain ratings, pre-TMS mood ratings, surgery duration, anesthesia duration, morphine loading, or fentanyl, hydromorphone, ketorolac, or lidocaine use. A significant difference was found between groups for midazolam use ( $P = 0.04$ ). However, the active TMS group was given less midazolam (1.75 mg) than the sham group (3.0 mg), which, if anything, would be expected to reduce PCA pump use in the sham group. Table 1 shows the means and SEs (as well as *P* values from the independent *t* tests) for each of these variables for both the active and sham TMS groups.

Significant effects were observed for both rTMS condition ( $t(436) = 5.72, P < 0.0001$ ) and surgery type ( $t(436) = 7.69, P < 0.0001$ ) on PCA pump use over time. Model estimates suggest that subjects receiving active

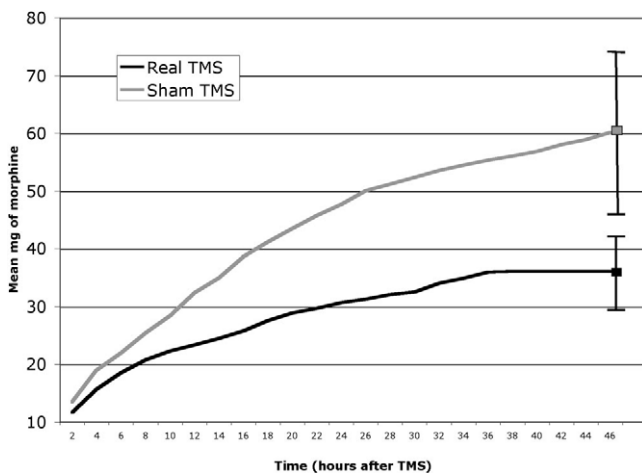
**Table 1. Means and SEs for Subject Characteristics and Key Variables before (or Immediately after) TMS for Each Group (Active or Sham)**

Variable	Active, Mean (SEM)	Sham, Mean (SEM)	P Value
Age, yr	45.60 (3.28)	40.50 (2.86)	0.56
Pre-TMS pain, VAS	61.00 (10.26)	64.50 (7.98)	0.79
Post-TMS pain, VAS	58.90 (6.30)	57.60 (5.35)	0.88
Pre-TMS mood, VAS	55.67 (7.75)	58.33 (4.55)	0.76
Post-TMS mood, VAS	50.80 (6.92)	61.60 (3.82)	0.19
Body mass index, kg/m <sup>2</sup>	49.01 (2.16)	51.54 (4.17)	0.60
Surgery duration, min	117.42 (3.04)	126.12 (7.24)	0.28
Anesthesia duration, min	189.54 (7.21)	190.02 (8.88)	0.97
Midazolam, mg	1.75 (.37)	3.00 (.42)	0.04
Fentanyl, $\mu$ g	277.50 (34.65)	317.50 (39.62)	0.46
Pre-PCA morphine, mg	8.80 (1.61)	9.20 (1.98)	0.88
Hydromorphone, mg	0.20 (.20)	0.33 (.33)	0.84
Ketorolac, mg	12.00 (4.90)	20.00 (4.47)	0.24
Lidocaine, mg	84.44 (8.01)	90.00 (6.15)	0.56

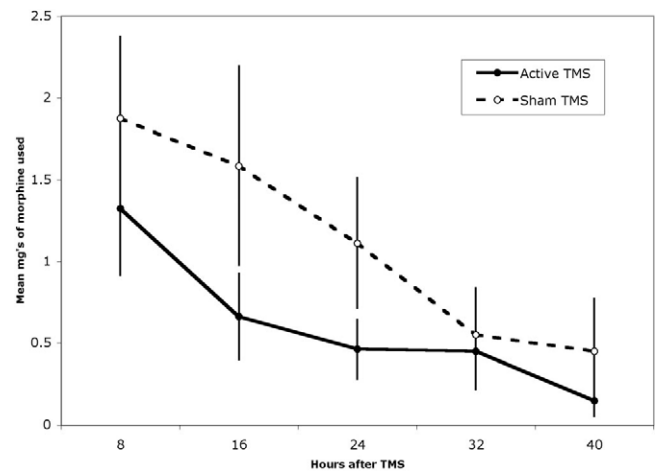
No significant differences were found except for midazolam use; however, subjects in the sham transcranial magnetic stimulation (TMS) group were given more midazolam than subjects in the active TMS group.

PCA = patient-controlled analgesia; VAS = visual analog scale score.

rTMS used 1.21 (0.21) cumulative milligrams of morphine less than subjects in the sham condition per 2 h. Figure 2 shows the mean cumulative morphine use for subjects in each group. At the time of discharge, subjects who had received real rTMS had used an average of 40% less morphine than subjects who had received sham rTMS. Subjects in the active rTMS group used 36.10 (6.27) mg on average, and subjects receiving sham rTMS used 60.18 (14.70) mg. Figure 3 displays mean absolute morphine use in 8-h blocks after surgery for subjects in each group. The largest absolute difference between active and sham TMS seems to occur within the first 24 h after stimulation (determined by visual inspection of the figure). Model scores suggest that subjects receiving laparoscopic surgery used 1.48 (0.19) mg morphine less than subjects receiving open surgery per 2 h during the



**Fig. 2. Mean cumulative patient-controlled analgesia pump use in milligrams of morphine for patients randomly assigned to 20 min (4,000 pulses) of either active or sham left prefrontal transcranial magnetic stimulation (TMS) after gastric bypass surgery.**



**Fig. 3. Mean (and SE) absolute morphine used per 8 h by patients receiving either active or sham transcranial magnetic stimulation (TMS) after gastric bypass surgery.**

44 h after surgery. At the time of discharge, subjects who received laparoscopic surgery had used an average of 34.90 (7.25) mg morphine, and subjects receiving open surgery used 68.00 (15.61) mg.

The average mood rating for subjects who received active rTMS was 78.24 (4.97), and the mean for subjects receiving sham was 72.33 (4.78). These mean ratings were not significantly different ( $t(18) = 0.86$ ). In addition, there were no effects observed for TMS condition on change in mood ratings over time (using hierarchical linear modeling;  $t(66) = 1.32$ ). At the time of discontinuation of the PCA pumps, the mean mood ratings of subjects who received active TMS was 73.11 (6.36), and the mean for subjects who received sham TMS was 74.33 (6.76). Therefore, in our sample, a single 20-min prefrontal TMS session did not seem to produce changes in mood ratings relative to sham TMS.

Throughout the study, two subjects in the active rTMS group (20%) reported nausea, as did two from the sham group (20%). No subjects in the study vomited during the hospital stay. However, 50% ( $n = 5$ ) of the subjects in the active rTMS group reported headache at some point during their hospital stay after rTMS, whereas only 20% ( $n = 2$ ) of the subjects in the sham group reported headache. Group assignment (real or sham) was not a significant predictor of headache status (Cox and Snell  $R^2 = 0.10$ ; Wald = 1.8; odds ratio = 0.25,  $P = 0.17$ ). In all cases, the headaches were not severe and were easily managed using standard clinical pain protocols. No unusual measures were necessary for managing discomfort or complications in subjects who received active rTMS relative to those receiving sham.

## Discussion

This trial suggests that a single 20-min postoperative prefrontal rTMS session in gastric bypass surgery patients may significantly reduce patient-administered mor-

phine use over time. This effect seems to be most prominent during the first 24 h after rTMS delivery.

The mechanisms by which rTMS modulates pain experience are unclear. However, previous research suggests that rTMS may lead to inhibition of limbic activity associated with both pain and depressed mood. The findings from this study, although in no way definitive, suggest that rTMS may be used to modulate pain experience during critical time periods to alter the course of acute pain and the consequent trajectory of opioid use. However, the inference that a single session of left prefrontal rTMS affected pain experience should be made tentatively because previous research on TMS and pain experience suggests that multiple TMS sessions are needed to cause detectable changes in pain perception. However, it should be noted that the TMS dose used in this study was much higher than what previous studies have used.

The effect of being on the real rTMS trajectory translated into an average decrease of 24.08 mg morphine at discharge (40%). This degree of morphine reduction is clinically significant in this group of patients who frequently have obstructive sleep apnea, right ventricular dysfunction, and pulmonary hypertension. Although thoracic epidurals may be used to reduce morphine use in many surgical patients, unfortunately they may be difficult to place in these morbidly obese patients.

There is no evidence to date that TMS is associated with respiratory depression. Although not specifically studied, it is possible that patients would experience a decrease in pulmonary complications in those who received rTMS. This possibility should be evaluated in future trials.

It is important to note that all patients were given morphine sulfate postoperatively by nursing staff before sham or active rTMS administration and initiation of the PCA pump. Although there was no significant difference between the two groups in terms of pre-TMS morphine administration, the active group was given slightly less than the sham group. This minimizes the likelihood that the observed difference in PCA pump use between groups could be a carryover effect from a higher baseline morphine loading. Consistent with previous research on the effects of rTMS on pain perception,<sup>28-30</sup> the observed effect may have been somewhat short-lived (< 24 h). This relatively acute and rapid effect, if validated, suggests that additional benefit and reduction of narcotic use may be observed if rTMS is repeated within the first 24 h after surgery.

Previous studies on the effects of rTMS on pain perception have focused on neuropathic pain in clinical samples,<sup>16,18,20,25,26,28</sup> or on laboratory pain induced in healthy adults.<sup>21,22,24,29,30</sup> Most of these studies have examined how motor cortex stimulation affects pain perception. There are only two published reports to date examining the effects of prefrontal rTMS on pain perception. One is a case report of a single subject with chronic pain,<sup>23</sup> and the other is a laboratory study using

healthy adults with slow right prefrontal TMS.<sup>29</sup> Both studies reported significant antinociceptive effects of TMS. The majority of published studies investigating the effects of rTMS on pain perception (clinical or laboratory) report promising, although short-lived results. The current study is the first to demonstrate the potential impact of appropriately timing a brief TMS intervention in a predictable acute pain scenario.

There are several limitations that should be kept in mind when evaluating these preliminary results. The small sample size ( $n = 20$ ) in a specific surgical population (gastric bypass) may limit generalizability to other surgical patients. Although the subjects, nurses, medical staff, and researchers collecting pain ratings from patients were blind to the rTMS condition, this study is still technically single-blind because the rTMS administrator was aware of subjects' conditions. Even though the non-blinded researcher had no contact with subjects after the rTMS delivery, this may weaken causal inferences that can be made. Despite our efforts to identify systematic differences between the two groups that may have influenced PCA pump use (*e.g.*, surgery duration, anesthesia procedures, body mass index, age, baseline mood, pain ratings), no statistically significant or clinically meaningful differences were observed other than for midazolam administration (and the sham TMS group received more than the active group). However, our groups may have systematically differed on variables that were not measured, or power may have been too low to detect systematic group differences (other than TMS condition and surgery type) that may have influenced ratings. In addition, clinical depression was not formally assessed at the time of enrollment in the study or at the time of surgery, but was likely similar between subjects given the homogeneity of the gastric bypass surgery population. Given the considerable overlap in the neurobiology of pain and depression,<sup>41</sup> and given the high likelihood of depression in this clinical group,<sup>32</sup> this may be an important area of consideration in future studies. It is possible that rTMS improved mood or depression in our sample, which led to observable changes in PCA pump use. However, the average response time of depressed patients to rTMS for depression is longer than was observed in this study, and response often requires numerous rTMS sessions.<sup>37,38</sup> In addition, no differences were found between active and sham groups in terms of post-TMS mood ratings, nor was group membership predictive of post-TMS changes in mood ratings over time.

This study demonstrates the feasibility and safety of conducting rTMS research in postoperative care settings. All subjects were attached to standard monitoring units (heart rate, pulse oximetry, blood pressure, and respiratory rate). There was minimal interference of the rTMS machine with these monitors and no observed heating of electrodes. Two subjects in the active rTMS group (20%) reported nausea, as did two from the sham group (20%).

No subjects in the study vomited during the hospital stay. However, 50% ( $n = 5$ ) of the subjects in the active rTMS group reported headache at some point during their hospital stay after rTMS, whereas only 20% ( $n = 2$ ) of the subjects in the sham group reported headache. Group assignment (real *vs.* sham) was not a statistically significant predictor of headache status in our small sample, but there is some evidence that rTMS can cause headaches for some patients.<sup>37</sup> This risk is routinely presented to potential rTMS subjects during the informed consent process. In this study, none of the reported headaches were rated as severe by the subjects, and all were easily managed using standard clinical pain protocols. No unusual measures were necessary for managing discomfort or complications in subjects who received active rTMS relative to those receiving sham.

This trial is the first to demonstrate that a single 20-min prefrontal rTMS session in a postoperative setting can significantly reduce PCA morphine use. Although these preliminary results are promising, replication using more rigorous methodology in larger samples is needed.

The authors thank Saxby Pridmore, M.D., F.R.A.N.Z.C.P. (Professor, Department of Psychological Medicine, Royal Hobart Hospital, Tasmania, Australia), for helpful conversations regarding using transcranial magnetic stimulation to understand and treat pain. The authors also thank Marian Cook, R.N., B.S., Neal Shelly, B.A., and Audrey Barry, B.S. (Anesthesiology Research Assistants, Department of Anesthesiology, Medical University of South Carolina, Charleston, South Carolina), and Minnie Dobbins, M.S.W. (Program Coordinator, Brain Stimulation Laboratory, Department of Psychiatry, Medical University of South Carolina), for administrative and technical support.

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