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Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: A replication study

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Abstract

Background—In a recent preliminary trial in 20 patients after gastric bypass surgery, 20 minutes of repetitive transcranial magnetic stimulation (TMS) over the left prefrontal cortex was associated with a 40% reduction in postoperative patient-controlled morphine use. As is the case with all novel scientific findings, and especially those that might have an impact on clinical practice, replicability is paramount. This study sought to test this finding for replication and to more accurately estimate the effect size of this brief intervention on postoperative morphine use and postoperative pain and mood ratings.

Methods—Twenty participants who underwent gastric bypass surgery completed this replication and extension study. Beck Depression Inventory and Center for Epidemiological Studies Depression scale scores were collected before surgery and at the time of discharge from the hospital. Immediately after surgery, participants were randomly assigned to receive 20 minutes of real or sham repetitive TMS (rTMS) (10 Hz, 10 seconds-ON, 20 seconds-OFF for a total of 4000 pulses). Patient-controlled morphine pump usage was tracked throughout each participant's postoperative hospital stay. In addition, pain and mood ratings were collected via visual analogue scales twice per day.

Results—Findings from the original postoperative TMS trial were replicated, as cumulative morphine usage curves were significantly steeper among patients receiving sham TMS, and participants receiving real TMS had used 35% less morphine at the time of discharge than participants

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receiving sham TMS. At the time of discharge, subjects who had received real TMS had used 42.50 mg of morphine, whereas subjects receiving sham TMS had used an average of 64.88 mg. When the data from the original preliminary trial were combined with the data from this replication trial, a significant difference in cumulative morphine usage was observed between subjects receiving real and sham TMS. Overall, participants who received real TMS used 36% less morphine and had significantly lower ratings of postoperative pain-on-average, and pain-at-its-worst than participants receiving sham. In addition, participants who received real TMS rated their mood-at-its-worst as significantly better than participants receiving sham. The effect of a single 20-minute session of TMS on postoperative pain and morphine use appears to be large (Cohen's $d = 0.70$) and clinically meaningful. Lastly, cross-lag correlational analyses indicate that improvements in mood follow improvements in pain by approximately 12 hours, supporting the notion that postoperative analgesic TMS effects are not driven by antidepressant effects.

Conclusions—Although more research is needed to verify these observed effects independently, findings from the original postoperative TMS trial were replicated. TMS may have the potential to significantly improve current standards of postoperative care among gastric bypass patients, and further studies may be warranted on other surgical populations. Future investigations should use methodology that permits more definitive conclusions about causal effects of TMS on postoperative pain (for example, double-blinding, sham stimulation that is matched with real TMS with respect to scalp discomfort).

Keywords

transcranial magnetic stimulation; TMS; postoperative; pain

Some emerging brain imaging research suggests that left prefrontal cortex activation is negatively correlated with the affective dimension of pain experience,¹ and there is evidence suggesting that some types of chronic pain are associated with decreased prefrontal gray matter density.² The prefrontal cortex connects with both the nucleus cuneiformis and periaqueductal gray in a functionally characterized top-down pain inhibitory system.³ Although the prefrontal cortex appears to be involved in pain perception, more research is needed on the potential analgesic effects associated with directly manipulating prefrontal activity in humans.

A few studies have demonstrated analgesic effects associated with stimulation of the prefrontal cortex via transcranial magnetic stimulation (TMS). In a published case report, Reid and Pridmore⁴ used fast repetitive TMS (rTMS) (20 Hz) at 100% of resting motor threshold (rMT) over the left prefrontal cortex to significantly reduce reported pain experience in a single patient with chronic facial pain. A recent large-scale, controlled study investigated the effects of rTMS over the right dorsolateral prefrontal cortex on pain tolerance in healthy adults. Slow rTMS (1 Hz) of the right prefrontal cortex was associated with significant antinociceptive effects over and above other cortical targets (for example, left and right motor cortex and vertex).⁵ In addition, Sampson et al⁶ found that slow TMS over the right prefrontal cortex was associated with significant pain relief in patients with fibromyalgia. Very recently, Avery et al⁷ found that 10 Hz TMS over the left prefrontal cortex significantly reduced pain perception in patients with major depression. Further, this effect could not be explained by antidepressant effects of the TMS.

The majority of studies on the effects of rTMS on pain perception suggest short-lived pain-modulation effects. Thus, it has been suggested that currently, clinical rTMS applications may be limited to repeated use for controlling neuropathic pain syndromes for a short period, perhaps while a patient is waiting for surgical implantation of motor cortex stimulation (MCS) systems.^{8,9} However, there has been little attention paid to the potential impact of rTMS on acute postoperative pain. This is an important area of research to consider. If an appropriately timed, brief, relatively noninvasive intervention can significantly reduce acute postsurgical

pain and consequent opioid use, standard interventions for postsurgical pain management could be significantly enhanced.

Recently, Borckardt et al.¹⁰ found that 20 minutes of fast rTMS over the left prefrontal cortex was associated with a reduction in postoperative patient-controlled analgesia (PCA) use in 20 gastric bypass surgery patients. These findings are especially significant given the negative respiratory side effects of opioid treatment and the high proportion of obese patients with apnea and other respiratory problems. Given the relatively small sample size of the original trial, and the potential clinical significance of the findings, more research on the use of cortical stimulation techniques in perioperative samples is warranted to determine replicability, accurate effect-size estimates, and potential for future clinical applications. The current study is an attempt to replicate and extend the previous study of Borckardt et al.¹⁰ In addition, we sought to calculate a better effect-size estimate and provide more power to detect possible randomization differences (confounds) between groups, assess response predictors, and test whether the analgesic effects were different from transient mood effects.

Materials and methods

Twenty-two gastric bypass surgery patients were enrolled (mean age = 42.30, mean body mass index [BMI] = 51.36; 20 women). This study was approved by the Institutional Review Board for the Protection of Human Subjects at the Medical University of South Carolina. Written informed consent to participate in this study was obtained before surgery.

One participant withdrew from the study while in the postanesthesia care unit (PACU) because of discomfort with the rTMS. One participant was excluded because the motor threshold was higher than the maximum intensity of the TMS machine. Sixteen patients received laparoscopic gastric bypass surgery and 4 received open surgery. Open gastric bypass surgery was the procedure of choice in patients with previous abdominal surgery or a BMI > 60.

After surgery, in the PACU, each participant underwent a motor threshold assessment. The TMS device was set to 40% of machine output and single pulses were delivered at a rate of 1 every 2 seconds. The investigator moved the coil systematically around the scalp and adjusted the stimulus intensity until they located the area of the motor cortex involved in moving the right abductor pollicis brevis muscle (APB). The interstimulus interval was then decreased to 4 seconds and parameter estimation by sequential testing (PEST)¹¹ was used to estimate the amount of TMS machine output necessary to produce visibly detectable movement of the thumb 50% of the time (rMT). Participants' prefrontal cortices were then located according to convention by moving the coil 5 cm anterior from the area of the motor cortex associated with thumb movement along the parasagittal line. Although more sophisticated image-guided systems are available for locating specific cortical areas, we chose this approach for several reasons: (1) we did not have an image-guided system available in the PACU, (2) the image-guided systems that we do have are not especially portable, (3) TMS image-guided systems require structural magnetic resonance imaging (MRI) scans that are costly to acquire, and (4) we wanted to evaluate the effects of TMS using methods that are easy for others to replicate.

Participants were then randomly assigned to receive real TMS (n = 12) or sham TMS (n = 8). Of the 4 participants who received open surgery, 2 were assigned to each TMS group (real and sham). The active TMS coil is a figure eight design with a solid core interior (Neuronetics Inc, Malvern, PA). The sham coil is externally identical to the active TMS coil, except that no cortical stimulation occurs as a hidden aluminum insert on the surface next to the scalp blocks passage of the magnetic field. Participants received 20 minutes of 10 Hz rTMS at 100% of rMT (10-second stimulation trains with 20-second interstimulus intervals) for a total of 4000 pulses.

Participants completed the Beck Depression Inventory (BDI) and the Center for Epidemiological Studies 10-item Depression scale (CES-D) at admission and discharge from the hospital. Participants also provided visual analog scale (VAS) ratings of pain (on average, at its worst, and at its least) and mood (on average, at its worst, and at its best) twice per day. PCA pump usage was collected and recorded from the medical record after the patients had been discharged from the hospital. Participants, medical staff providing clinical care to participants, and personnel collecting ratings were blind to whether participants had received real or sham TMS. The only person who knew the randomization was the TMS administrator (J.B.), who was not aware of the surgical history and medication loading. The administrator followed a careful script with patients, physicians, and nurses, and had no contact with any of the patients after the TMS session (ie, during the period when participants were using their PCA pumps and providing ratings of pain and mood).

Results

No baseline differences were found between the active and sham TMS groups in terms of age, BMI, midazolam, fentanyl, pre-TMS morphine bolus, ketorolac, lidocaine, presurgery pain ratings, presurgery mood ratings, pre-TMS pain ratings, pre-TMS mood ratings, BDI scores, or CES-D scores. Table 1 shows the means and SDs for each of these variables for both the active and sham groups from the current study ($n = 20$).

Hierarchical linear modeling (HLM) was used to assess the effects of surgery type (laparoscopy vs open) and TMS condition (real vs sham) on cumulative PCA pump usage curves over time.¹² All participants' PCA orders in this study were discontinued (clinical determination) after 54 hours independent of the study protocol. Cumulative PCA usage curves more than 54 hours postsurgery were square root transformed to correct for nonlinearity, and average post-TMS mood ratings were included in the model as participant-level covariates. Significant effects were observed for both surgery-type ($P < .01$) and TMS condition ($P < .01$) on cumulative PCA pump usage curves. At the time of discharge, participants who had received real TMS had used 42.50 mg of morphine, whereas participants receiving sham TMS had used an average of 64.88 mg. Participants who received active TMS used 35% less morphine than participants who received sham. TMS was not associated with any significant change in BDI or CES-D scores from presurgery to discharge [$F(1,18) = 0.003$, ns; $F(1,17) = 0.127$, ns].

Next, the data from the original study¹⁰ were combined with the data from the present replication to calculate a better effect-size estimate and provide more power to detect possible randomization differences between groups, and assess response predictors. Even with the expanded sample, no differences were found between the active and sham TMS groups in terms of age, BMI, midazolam, fentanyl, pre-TMS morphine bolus, ketorolac, lidocaine, presurgery pain ratings, presurgery mood ratings, pre-TMS pain ratings, or pre-TMS mood ratings. Table 2 shows the means and SDs for each of these variables for both the active group and the sham group after the data from both studies are combined ($n = 40$).

Figure 1 shows the mean cumulative morphine usage for participants ($n = 40$) in each group. A 2×2 (surgery type; open vs laparoscopic by TMS condition; real vs sham) analysis of covariance (ANCOVA) model was used, controlling for pre-TMS pain and mood ratings on total PCA morphine used at the time of discharge. A significant main effect was found for surgery type [$F(1,33) = 2.07$, $P < .05$] and TMS condition [$F(1,33) = 5.35$, $P < .05$]. No interactions were present; however, pre-TMS pain ratings were significantly related to PCA morphine use [$F(1,33) = 5.48$, $P < .05$]. Participants receiving open surgery used more morphine than did participants receiving laparoscopic (68.00 mg, SD = 37.26 and 41.99 mg, SD = 27.08, respectively). Participants who received real TMS used an average of 39.59 mg (SD = 19.33) of morphine and participants who received sham TMS used 62.27 mg (SD = 40.44). Real TMS

was associated with a 36% decrease in total morphine usage at the time of discharge (Cohen's $d = 0.70$) in 40 participants.

Next, mean pain and mood VAS ratings were examined. Ratings were averaged across time and a multivariate analysis of variance (MANOVA) was conducted to evaluate differences in ratings between groups. There was a significant effect for TMS condition [sham vs real; $F(6,31) = 3.06, P < .05$]. Participants who received real TMS reported lower ratings of pain-on-average, pain-at-its-worst, and reported better mood-at-its-worst than did participants receiving sham TMS (Figure 2).

Exploratory cross-lag correlation analyses were conducted on serial VAS pain and mood ratings to determine whether changes in mood preceded changes in pain or vice versa. In the group that received active TMS, decreases in "pain at its worst" preceded improvements in "mood at its worst" [$r(99) = -0.24, P < .05$], preceded improvements in "mood on average" [$r(99) = -0.30, P < .05$], and preceded improvements in "mood at its best" [$r(99) = -0.24, P < .05$] by 1 rating period (~12 hours). No other significant cross-lag correlations were observed for other VAS measures in the active group, and no significant cross-lags were observed for any VAS measures in the sham group. Participants who received active TMS experienced improvements in mood approximately 12 hours after decreases in pain.

Efforts were made to identify TMS responders, based on a full array of demographic variables as well as BDI and CES-D scores, BMI, and pre-TMS pain ratings. No significant predictors were found.

Side effects

In this replication trial, 1 participant who received active TMS (8%) reported having a headache at some point during the postoperative hospital stay and no participants in the sham group reported headaches. Three participants in the active group (25%) evidenced fever during or after their hospital stay as did 2 participants (25%) in the sham group. Two participants in the active group (17%) compared with 1 participant (13%) in the sham group reported nausea during or after their hospital stay. These data do not suggest significantly increased postoperative risk for fever or nausea associated with TMS.

Taken together with findings from the first study, of all the participants who have received prefrontal TMS postoperatively to date, 4 participants receiving active TMS (18%) reported nausea, as did 3 from the sham group (17%). However, 27% ($n = 6$) of the participants in the active TMS groups reported having a headache at some point during their hospital stay after TMS, whereas only 11% ($n = 2$) participants in the sham group reported headaches. Although these rates are not statistically significantly different ($\chi^2 [df = 1] = 1.62, P = .193$), we believe that there is a trend here consistent with previous reports of safety and tolerability of rTMS that TMS is associated with increased risk of headache. None of the headaches in either study were rated as severe and none required additional medical intervention (over and above PCA pump usage) to manage.

Discussion

This study replicates and extends the findings from the previous study by Borckardt et al.¹⁰ that a single 20-minute postoperative prefrontal rTMS session in gastric bypass surgery patients may significantly reduce patient-administered morphine usage. The combination of data from both studies suggests that real TMS was associated with an overall 36% reduction in PCA usage (Cohen's $d = 0.70$). In addition, participants who received real TMS rated their postoperative pain-on-average and pain-at-its-worst significantly lower than participants who received sham TMS, despite having less morphine in their systems. Participants receiving real

TMS rated their mood-at-its worst as better than participants receiving sham. Lastly, cross-lag correlational analyses indicate that improvements in mood followed improvements in pain by approximately 12 hours, supporting the notion that postoperative analgesic TMS effects are not driven by antidepressant effects.

The mechanisms by which prefrontal rTMS may modulate pain experience are unclear. However, previous research suggests that prefrontal rTMS may lead to inhibition of limbic activity associated with both pain and depressed mood¹³ and there is evidence to support the concept that left prefrontal activation is negatively correlated with pain unpleasantness.¹⁴ In addition, prefrontal activation has also been linked with pain catastrophizing¹⁵ and this idea was supported with our findings that participants receiving real TMS had significantly lower pain-at-its-worst and significantly better mood-at-its-worst ratings than participants receiving sham TMS. Interestingly, the clinical effectiveness of MCS has been found to be associated with activation of the reciprocally connected perigenual anterior cingulate cortex (pACC) and the periaqueductal grey (PAG) area. Prefrontal TMS may engage similar circuits as MCS thus attenuating pain experience by possibly blunting the affective dimension of pain (pACC) while engaging descending pain inhibitory control circuits that involve the prefrontal cortex, orbitofrontal cortex, pACC, basal ganglia, thalamus, and PAG.¹⁶

It is not clear whether the prefrontal cortex is the only (or even the best) cortical target for modulating postoperative pain. The current study does not allow for any conclusions to be drawn about optimal cortical targets for pain management. In addition, the current study does not provide information about optimal device parameters (TMS intensity, frequency, and number of pulses) for managing pain.

There is emerging evidence that rTMS is a mildly to moderately painful procedure for some patients.¹⁷ This limits the types of inferences that can be drawn from many sham-controlled TMS trials, especially when pain perception is a key dependent variable, because it is possible that the painfulness of the TMS procedure itself may engage endogenous pain regulatory systems in research participants. Although this study does experience this limitation, the observed effects appear to be more robust than one could reasonably argue to be caused by mere exposure to a 20-minute mildly to moderately painful procedure. In addition, the participants in this study were already experiencing moderate-to-severe postsurgical abdominal pain during the TMS procedure and were loaded with a morphine bolus in the PACU before TMS administration. Although 1 participant experienced the TMS stimulation as too uncomfortable to continue with the trial, anecdotal reports from research assistants indicate that more than half of the participants did not even remember receiving TMS, nor did they remember most of the interactions or activities in the PACU.

The findings from this study, confirm previous findings that TMS may be used to modulate pain experience during critical periods, to alter the course of acute pain and the consequent trajectory of opioid usage. In addition, postoperative TMS appears to be a safe intervention, and more research on the use of TMS to help manage postoperative pain and morphine usage is warranted. TMS may have the potential to significantly improve current standards of postoperative care among gastric bypass patients, and further studies may be warranted on other surgical populations. Future investigations should use methodology that permits more definitive conclusions about causal effects of TMS on postoperative pain (for example, double-blinding, sham stimulation that is matched with real TMS with respect to scalp discomfort) and other surgical populations should be studied to determine generalizability of the results.

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References

1. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 2003;126:1079–1091. [PubMed: 12690048]
2. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 2004;24(46):10410–10415. [PubMed: 15548656]
3. Hadjipavlou G, Dunckley P, Behrens TE, Tracey I. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: a diffusion tensor imaging study in healthy controls. *Pain* 2006;123(1–2):169–178. [PubMed: 16616418]
4. Reid P, Pridmore S. Improvement in chronic pain with transcranial magnetic stimulation. *Aust N Z J Psychiatry* 2001;35(2):252. [PubMed: 11284914]
5. Graff-Guerrero A, Gonzalez-Olvera J, Fresan A, Gomez-Martin D, Mendez-Nunez JC, Pellicer F. Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain. *Brain Res Cogn Brain Res* 2005;25(1):153–160. [PubMed: 15935625]
6. Sampson SM, Rome JD, Rummans TA. Slow-frequency rTMS reduces fibromyalgia pain. *Pain Med* 2005;7(2):115–118. [PubMed: 16634724]
7. Avery DH, Holtzheimer PE, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. Transcranial magnetic stimulation reduces pain in patients with major depression: a sham-controlled study. *J Nerv Ment Dis* 2007;195(5):378–381. [PubMed: 17502802]
8. Lefaucheur JP. New insights into the therapeutic potential of non-invasive transcranial cortical stimulation in chronic neuropathic pain. *Pain* 2006;122:11–13. [PubMed: 16564623]
9. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Nguyen JP. Neuropathic pain controlled for more than a year by monthly sessions of repetitive transcranial magnetic cortical stimulation. *Neurophysiol Clin* 2004;34:91–95. [PubMed: 15130555]
10. Borckardt JJ, Weinstein M, Reeves ST, Kozel FA, Nahas Z, Smith AR, et al. Post-operative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. *Anesthesiology* 2006;105(3):1–6. [PubMed: 16809983]
11. Borckardt JJ, Nahas Z, Koola J, George MS. Estimating resting motor thresholds in tms research and practice: a computer simulation evaluation of best methods. *J ECT* 2006;22(3):169–175. [PubMed: 16957531]
12. Singer JD. Using SAS PROC MIXED to fit multilevel models, hierarchical models and individual growth curves. *J Educ Behav Stat* 1998;24(4):323–355.
13. Li X, Nahas Z, Kozel FA, Anderson B, Bohning DE, George MS. Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. *Biol Psychiatry* 2004;55(9):882–890. [PubMed: 15110731]
14. Zubieta JK, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA, et al. Placebo effects mediated by endogenous opioid activity on μ -opioid receptors. *J Neurosci* 2005;25(34):7754–7762. [PubMed: 16120776]
15. Gracely RH, Geisser ME, Giesecke T, Grant MAB, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain* 2004;127:835–843. [PubMed: 14960499]
16. Garcia-Larrea L, Peyron R. Motor cortex stimulation for neuropathic pain: from phenomenology to mechanisms. *Neuroimage* 2007;37:S71–S79. [PubMed: 17644413]
17. Borckardt JJ, Smith AR, Hutcheson K, Johnson K, Nahas Z, Anderson B, Schneider MB, Reeves ST, George MS. Reducing pain and unpleasantness during repetitive transcranial magnetic stimulation. *J ECT* 2006c;22(4):259–264.

Figure 1.

Mean cumulative PCA pump usage in milligrams of morphine for 40 patients randomly assigned to 20 minutes (4000 pulses) of either active ($n = 20$) or sham ($n = 20$) left pre-frontal TMS after gastric bypass surgery.

Figure 2.

Mean (and 95% confidence intervals) VAS pain and mood ratings of 40 subjects receiving real ($n = 20$) or sham ($n = 20$) TMS after bariatric surgery (* $P < .05$; ** $P < .01$). Higher ratings indicate better mood.

Table 1

Variable	Active TMS	Sham TMS	<i>p</i> -value
Versed	2.58 (1.44)	2.75 (1.98)	.83
Fentanyl	333.33 (221.91)	321.88 (93.96)	.89
Morphine	7.83 (3.43)	10.00 (7.09)	.37
Toradol	20.00 (14.77)	21.25 (13.56)	.85
Lidocaine	63.33 (64.29)	100.00 (54.51)	.20
Age	41.58 (8.17)	43.38 (11.98)	.69
Pre-surgery pain	5.00 (9.07)	5.83 (7.55)	.85
Pre-surgery mood	70.75 (22.28)	84.83 (23.96)	.24
Pre-TMS pain	56.67 (28.39)	74.83 (13.95)	.16
Pre-TMS mood	57.92 (23.98)	52.67 (33.89)	.71
Body mass index	52.43 (12.41)	49.77 (7.85)	.60
Pre-surgery BDI	7.17 (8.00)	6.25 (3.58)	.77
Pre-surgery CES-D	3.42 (3.18)	6.25 (3.85)	.09

Means and standard deviations for subject characteristics and pre-TMS variables in the present replication study ($N=20$) for each TMS group [active ($N=12$) or sham ($N=8$)]. No significant differences were found (all p -values greater than Bonferroni corrected alpha of .004).

Table 2

Variable	Active TMS	Sham TMS	<i>p</i> -value
Versed	2.20 (1.37)	2.89 (1.60)	.15
Fentanyl	307.95 (178.18)	319.44 (109.32)	.81
Morphine	8.27 (4.19)	9.56 (6.46)	.45
Toradol	16.36 (15.29)	20.56 (13.49)	.37
Lidocaine	72.38 (51.18)	94.44 (38.07)	.14
Age	43.41 (9.24)	41.78 (10.22)	.60
Pre-surgery pain	3.26 (7.47)	4.46 (6.32)	.64
Pre-surgery mood	74.26 (20.34)	76.15 (22.87)	.81
Pre-TMS pain	58.52 (28.76)	69.38 (19.77)	.21
Pre-TMS mood	57.17 (21.89)	57.07 (24.02)	.99
Body mass index	50.87 (10.18)	50.75 (10.88)	.97

Means and standard deviations for subject characteristics and pre-TMS variables in from both studies ($N=40$) for each TMS group [active ($N=22$) or sham ($N=18$)]. No significant differences were found (all p -values greater than Bonferroni corrected alpha of .004).