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Differential heart rate response to magnetic seizure therapy (MST) relative to electroconvulsive therapy: A nonhuman primate model

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Abstract

Electroconvulsive therapy (ECT) is an effective treatment for severe depression; however, the induced therapeutic seizure acts on the autonomic nervous system and results in significant cardiac effects. This is an important consideration particularly in the elderly. Magnetic seizure therapy (MST) is in development as a less invasive alternative, but its effects on cardiac function have not been studied. We sought to model those effects in nonhuman primates to inform the development of safer neurostimulation interventions. Twenty four rhesus monkeys were randomly assigned to receive 6 weeks of daily treatment with electroconvulsive stimulation (ECS), magnetic seizure therapy (MST) or anesthesia-alone sham. Digitally acquired ECG and an automated R-wave and inter-R interval (IRI) sampling were used to measure intervention effects on heart rate (HR). Significant differences between experimental conditions were found in the HR as evidenced by changes in the immediate post-stimulus, ictal and postictal epochs. Immediate post-stimulus bradycardia was seen with ECS but not with MST. ECS induced significantly more tachycardia than MST or sham in both the ictal and postictal periods. MST resulted in a small, but statistically significant increase in HR during the postictal period relative to baseline. HR was found to increase by 25% and 8% in the ECS and MST conditions, respectively. MST resulted in significantly less marked sympathetic and parasympathetic response than did ECS. This differential physiological response is consistent with MST having a more superficial cortical site of action with less impact on deeper brain structures implicated in cardiac control relative to ECT. The clinical relevance of the topographical seizure spread of MST and its associated effects on the autonomic nervous system remain to be determined in human clinical trials.

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Columbia University has filed a patent application for novel TMS technology developed in Dr. Lisanby's laboratory, not related to the topic presented here.

Keywords

Magnetic seizure therapy (MST); Electroconvulsive therapy (ECT); Tachycardia; Arrhythmia; Sympathetic outflow

Introduction

Electroconvulsive therapy (ECT), a highly effective treatment for severe major depression and other conditions, is often used when patients do not respond to or cannot tolerate the side effects of medications (Lisanby, 2007). This is especially true for the elderly, who frequently cannot tolerate the cardiac side effects of antidepressant medications (McClintock et al., 2006). However, ECT also exerts powerful effects on cardiac function via its action upon the parasympathetic and sympathetic nervous systems. A greater understanding of the effects of convulsive treatments on cardiac function could aid in the clinical application of ECT, and could inform the development of novel neurostimulation interventions that lack these undesirable effects.

The acute effects of ECT on autonomic function have been well described in the literature. Specifically, ECT initially produces a brief period of increased parasympathetic activity followed by increased sympathetic activity (Gaines and Rees, 1992). The brief parasympathetic autonomic nervous system activation that precedes the sympathetic outflow has been tied to a risk of bradycardia, which at times can be severe and result in an asystole (Burd and Kettl, 1998). This effect is seen most dramatically in the period immediately after the application of the electrical stimulus, i.e. in the first few seconds of the seizure or in the seconds following a subconvulsive stimulation that does not result in seizure. Anticholinergic agents such as atropine are often used to block the bradycardic effect of ECT, especially during seizure threshold titrations involving the application of multiple subconvulsive stimulations (APA, 2001), but these agents also carry their own side effects such as prolonged tachycardia and changes in cognitive function that may be particularly problematic for older patients. Although the low doses of anticholinergic agents used during ECT treatments have not been reported to substantially affect cognition in the long term, cases of ventricular tachycardia have been reported as a possible result of premedication with atropine (Kim et al., 2007).

The increased sympathetic outflow contributes to hypertension and tachycardia acutely during the treatment session. Generally these effects are short-lived and usually resolve without intervention, although on occasion it is necessary to blunt this response through the injection of short-acting antihypertensives like beta-blockers or others. These strategies are usually effective, however increased sympathetic activation may rarely be related to life-threatening arrhythmias. Increased incidents of ventricular tachycardias and significant increase in bigeminy/trigeminy and supraventricular tachycardias have been reported in conjunction with ECT treatment (Huuhka et al., 2003; Larsen et al., 1998). It has also been observed that ECT induced seizures drive HR above the treadmill stress test maximum. This is most likely because the increase in HR during treadmill stress testing is limited by the overall metabolic demand, muscular strength, stamina, and other factors. However, these factors do not play a role during ECT treatment (Swartz and Shen, 2007). This dissociation has led to the speculation that ECT may lead to additional undesirable cardiac risk in the elderly (Zielinski et al., 1993). There is clinical evidence that cardiovascular morbidity associated with ECT occurs more frequently in the elderly. This has also been confirmed by many retrospective studies where the most dangerous cardiovascular events during ECT were ischemic or arrhythmic syndromes affecting the elderly (Alexopoulos et al., 1989).

The magnitude of the cardiovascular response to ECT varies across individuals. Interestingly, the individual patient's HR increase during the ECT treatment has been proposed as a measure of clinical response. Swartz et al. reported that patients who maintained a robust HR increase across their ECT course required fewer ECTs to receive therapeutic benefit (Swartz, 2000). It was proposed that a substantial decrease in peak HR during the ECT may be a sign of an inadequate seizure and therefore may indicate a need to increase the stimulus dose (Swartz, 2000; Swartz and Manly, 2000).

Further work would be useful to test that proposal, and determine if it applies equally to other forms of ECT, such as unilateral and ultra-brief pulse width. Indeed, alterations in ECT technique have been associated with differential effects on HR. For example, alterations in pulse width have been reported to exert an effect on cardiovascular response. Under identical charge delivered, shorter pulse widths of 0.5 ms were found to produce a higher peak heart rate than 1 ms pulse width stimuli, consistent with the finding that briefer pulses are more efficient in eliciting seizures (Swartz and Manly, 2000). There is also a good body of evidence that electrode placement has significant effects on cardiovascular response. In a relatively large study, postictal cardiac response, as measured by the product of HR and systolic blood pressure, was significantly lower after unilateral ECT than bilateral ECT (Mayur et al., 1998). These results confirmed findings from a smaller study of 11 melancholic patients. In this study, Lane et al. examined cardiovascular response in patients receiving bilateral versus unilateral ECT and reported that mean and minimum postictal HRs were greater after bilateral ECT (Lane et al., 1989), presumably due to greater catecholamine response. However, some literature is at variance with those findings (Prudic et al., 1987). Within unilateral stimulation, hemispheric laterality seems to be important. A study examining right versus left unilateral stimulation found laterality differences, consistent with the view that cortical cardiac control affecting HR is predominantly located in the right hemisphere (Swartz et al., 1994).

The well-documented cardiovascular effects of ECT motivate the development of modifications that could minimize the risk of cardiovascular side effects. Magnetic seizure therapy (MST) is a novel convulsive treatment under development as a less invasive form of convulsive therapy that uses the focality of magnetic fields to better control the site of seizure initiation and limit its spread (Lisanby et al., 2003a). The development of MST has been predicated on the hypothesis that the ability to control the initiation and spread of the therapeutic seizure will result in a better side effect profile, while maintaining efficacy. Most of the previous work on MST has focused on cognitive side effects, and has reported less amnesia with MST than ECT in nonhuman primates (Moscrip et al., 2006; Spellman et al., 2008), and humans (Lisanby et al., 2003a). However, ECT carries a risk of other side effects where increased control over seizure expression might be of benefit, such as its effects on cardiac function (Fu et al., 1997; Swartz and Shen, 2007). Because the electrical currents induced by MST are more superficial and limited to the lateral regions of the cortex (Lisanby et al., 2003b), we would predict that there would be less impact of MST on deeper cortical regions implicated in cardiovascular control, such as the insular cortex. To date, the effects of MST on cardiac regulation have not been systematically studied.

The ability to elicit the seizures from superficial cortex via MST represents a means of evaluating whether the subcortical spread seen with ECT but not MST contributes to the cardiovascular response to ECT. Recent studies suggest that sympathetic control of the cardiovascular system in the rat, monkey, and human is not only modulated by the brainstem, but also receives significant input from the cortex, specifically the right insula (Manitius-Robeck et al., 1998). Experimental models have indicated that the insular lesions may generate arrhythmias and there is some evidence that similar stroke lesions in humans affect cardiac rate and rhythm control (Manitius-Robeck et al., 1998; Oppenheimer, 2006).

The insula is a relatively deep cortical structure that lies at the base of the Sylvian Fissure, covered by the opercula folds where the frontal, temporal and parietal lobes meet. Because of the deep location of the insular cortex, the spread of the exogenous current and the subsequent seizure propagation from distinct therapeutic neurostimulation modalities may have differential effect on this region. Studies in nonhuman primates that compared the distribution of current density evoked by electroconvulsive stimulation (ECS), as well as the measurements of subsequent seizure generalization throughout the brain, show near uniform and complete penetration of the current throughout all of the brain anatomical structures (Sekino and Ueno, 2002). In contrast to ECS, the peak density of the electrical field induced by MST is prominent only in the immediately targeted superficial cortical areas and shows considerable drop-off in magnitude in the deeper brain structures (Lisanby et al., 2003b).

An important rationale for studying the differential effects of ECT versus MST on the HR is to enhance our understanding of how HR is regulated and to improve the safety profile of antidepressant convulsive treatments. Sparing brain centers responsible for HR control from unnecessary stimulation may result in decreased risk of tachyarrhythmia, ischemia and myocardial infarction as well as bradycardia and asystole. This is particularly important for elderly depressed patients, who are the most frequently referred group for convulsive treatment and yet are also most likely to have known or unknown cardiac risk factors (Huuhka et al., 2003). In this study, we tested the hypothesis that MST would have less effect on deep cortical regions that modulate parasympathetic and sympathetic response by contrasting HR measures during MST and ECS in non-human primates.

Materials and methods

Subjects

The subjects included 24 pathogen-free (12 male and 12 female) rhesus *Macaca mulatta* monkeys obtained from the same National Institutes of Health (NIH) breeding colony. The mean age of the monkeys was 2.79+/−0.45 years and the mean weight was 3.65+/−0.59 kg at their first treatment. Monkeys were separately housed in a colony where they were maintained on a 12-hour light–dark cycle, had ad-lib access to water, and received daily food consisting of standard monkey chow (LabDiet©, W.F. Fischer & Sons, Inc., Somerville, NJ, USA) and fruit. The 24 subjects were randomly assigned to one of the following three groups: ECS, MST or anesthesia-only (sham control).

Subject preparation

In preparation for daily treatments, subjects were sedated in their homecage with intramuscular injections of methohexital, ketamine (5 mg/kg) and xylazine (0.35 mg/kg). Subjects were administered atropine (0.4 mg/kg) on titration days to protect them from the bradycardic effects of subconvulsive stimulation. Following transportation into the treatment room, hair on the subject's head, chest, and leg was shaved to facilitate physiological recordings and an IV line was placed in the leg. Physiological monitoring at each treatment session included 1-channel bipolar surface ECG, 2-channel bilateral scalp EEG, pulse oximetry which measured HR and PO2, end-tidal PCO_2, and noninvasive blood pressure.

Treatment and sham interventions

Prior to treatment, subjects received anesthesia consisting of methohexital (1 mg/kg IV) and succinylcholine (3 mg/kg IV). A tourniquet was placed on the left upper limb before succinylcholine administration to prevent distribution and allow for visual recognition of motor contractions (in sham sessions, the tourniquet was removed after 1 min). Adequacy of muscle paralysis was determined by noting fasciculations and by the use of a peripheral nerve stimulator on the right arm. A bite block was inserted in the mouth to protect against

dental fractures and tongue lacerations. Subjects were oxygenated (100% O_2, positive pressure) until the return of spontaneous respiration. Seizure expression was monitored via scalp EEG and motor manifestations in the nonparalyzed limb.

ECS was administered bilaterally with a human ECT device (MECTA Spectrum 5000Q, MECTA Corporation, Tualatin, OR) at 2.5×the seizure threshold, which was calculated as the minimum amount of electrical stimulation (mC) required to elicit a tonic–clonic seizure. For MST, treatments were administered with a custom modified device with 16 power booster modules that generated 50 Hz for 8 s at maximal stimulator output (The Magstim Co Ltd., Wales, U.K.) with a pediatric-sized round coil (6.2 cm diameter) on the vertex. MST seizure threshold was defined as the minimum number of pulses required to induce a tonic–clonic seizure. At the first session, seizure threshold was identified in the ECS and MST groups, using the ascending method-of-limits procedure in which only the duration of the stimulus was increased in a standardized, stepwise fashion until seizure was elicited. After titration, stimulus intensity at subsequent sessions was fixed at 250% above the initial threshold by increasing the duration of stimulation to reach the appropriate charge (mC) calculated as 2.5×the charge at threshold for electrical stimulation and the total number of pulses calculated as 2.5×the number of pulses at threshold for magnetic stimulation.

Each subject received a total of 24 treatments over a period of 6 weeks. This included 3 seizure threshold titrations administered at the baseline, middle and last treatment. The threshold was used to adjust parameters for stimulation, and data from the titration days were not included in the overall analysis. For the sham group, all 24 sessions involved only the administration of anesthesia.

ECG monitoring and acquisition

ECG data were recorded from the time the subject was brought into the procedure room until at least 1 min following seizure end. Inter-R interval (IRI) on ECG was used to compute HR. The data was visually inspected and artifacts were marked and excluded from further analysis.

Data analysis

The IRI was automatically calculated via a computer algorithm and was based on measurement of time in seconds between R-waves on ECG. The ECG data were divided into 6 epochs as follows: 1st epoch —20 s prior to methohexital injection (baseline); 2nd epoch — 20 s prior to succinylcholine injection; 3rd epoch — 20 s prior to stimulation; 4th epoch — throughout seizure duration (ictal period); 5th epoch — 15 s immediately following seizure end (1st silent period); 6th epoch —15 s following the 1st silent period (2nd silent period). All epochs were of fixed duration across subjects and conditions except for the ictal period, which varied depending on seizure duration. For sham subjects, the duration of ictal period was set to 24 s that represents the mean seizure duration of subjects in the convulsive conditions. To represent tachycardia, we used the minimum IRI computed for each of the 6 epochs.

ECG data were collected during each of the 24 sessions for each subject. However, due to technical difficulties and electrical noise, complete analyzable data during all epochs were not available for all subjects in all conditions and sessions. Since there was no evidence that IRI changed across treatment session, we averaged each epoch data of 3 consecutive sessions. This resulted in a complete set of 6 treatment sessions that were subject to further analyses.

Repeated measure analysis of variance (ANOVA) were performed using SPSS V. 15 for Windows where between group factors included the experimental conditions (three levels:

ECS, MST, sham), and within group factors included epoch (three levels) and treatment (6 levels). Where appropriate, significant main effects and interactions were followed with post hoc analyses. Statistical significance was based on two-tailed tests with alpha set at 0.05.

Results

Fig. 1 presents the averages of HR for the ECS, MST and sham during baseline, ictal and postictal periods. In the first analysis we tested whether HR differed between conditions during the baseline periods. Repeated measure ANOVA with 3 Conditions (ECS, MST, sham) as a between subject factor and Epoch (1st, 2nd, and 3rd) and Treatment day (6 weeks) as within subject factors revealed no main effect of Condition or any interaction with Condition ($P>0.01$). Thus, this analysis demonstrates that at baseline HR was similar for all conditions.

In the second analysis we tested whether the HR differed between the conditions during the ictal and the postictal periods. Repeated measure ANOVA with 3 Condition (ECS, MST, sham) as a between subject factor and Epoch (4th, 5th, and 6th) and Treatment days (6 weeks) as within subject factors revealed a significant main effect of Condition ($F_{2,21}=11.63$, $P < 0.001$), and the interaction of Condition and Epoch approached significance ($F_{4,42}=2.56$, $P < 0.053$). Post hoc tests demonstrated that HR after ECS was significantly faster than after MST or sham ($P<0.05$), and that HR after MST was significantly faster than after sham ($P<0.05$). Although the interaction of Condition and Epoch only approached significance ($P<0.053$), based on our a priori hypothesis, post hoc analyses were performed and revealed that during the ictal period HR was significantly different between ECS and sham ($P<0.05$) but not from MST ($P>0.05$), and sham and MST did not differ ($P>0.05$). However, during both postictal periods, post hoc tests showed significant differences between ECS and both MST and sham, and between MST and sham (Ps<0.05). These differences in HR during ictal and postictal periods are presented in Fig. 2.

We next investigated the issue of immediate post-stimulus bradycardia, which occurs in the first few seconds of the ictal period and in the immediate seconds following a subconvulsive stimulation. This analysis included the subset of subjects in which the first R-wave following the termination of the electrical stimulus could be resolved with artifact-free recording. The immediate post-stimulation heart rate was compared during a subconvulsive electrical stimulation on the seizure threshold titration day, and during the final stimulus in the titration which led to a seizure. ANOVA on percent change in heart rate immediately before and after subconvulsive and convulsive stimulations with MST and ECS revealed a main effect of intervention condition ($F(1,10)=22.6$, $P<0.0008$), and a condition by dosage interaction ($F(1,10)=5.3$, $P<0.04$). As can be seen in Fig. 3, heart rate was slowed by ECS (to a greater degree with convulsive than subconvulsive stimulation, $t(5)=-3.84$, $P<0.01$), while immediate post-stimulation heart rate was increased by MST (to a greater degree with convulsive than subconvulsive stimulation, $t(5)=3.4$, $P<0.02$).

Discussion

These findings support our initial hypothesis that MST would result in a less marked effect on parasympathetic and sympathetic outflow as indexed by HR changes than ECT in a rhesus model. Specifically, we demonstrated that MST resulted in less immediate stimulation bradycardia and less tachycardia in the ictal and postictal periods than ECS. Moreover, while both MST and ECS showed a significant difference in comparison with sham in the postictal periods, during the ictal period MST and sham did not differ. As shown in Fig. 2, the sham and MST difference in the postictal period stemmed in part due to a decreased HR for sham during the time period. This finding of less marked decreases and

increases in heart rate with MST supports the notion that MST carries a lower risk of cardiovascular complications, which could be especially relevant in the treatment of the elderly and those with cardiovascular disease.

The significantly reduced autonomic response following MST treatment compared to ECS treatment is consistent with MST having a more superficial cortical site of action than ECT, with less impact on deeper cortical structures implicated in cardiac control, such as the insula. Due to its more localized nature MST offers better control over site of seizure initiation and the pattern of activation, factors that are hard to control in ECT. Specifically, MST-induced electrical currents are confined to superficial cortex and offer more precise control over intracerebral current paths, while ECT induces radial currents that penetrate more deeply (Lisanby et al., 2003b). Therefore, with MST it may be possible to induce seizures that originate in superficial cortex, sparing deeper brain structures that might be related to side effects. Indeed the superficial stimulation of MST has been shown to spare cognitive side effects when compared with ECS (Cycowicz et al., 2009; Moscrip et al., 2006; Spellman et al., 2008).

As predicted based upon its involvement of superficial cortex, MST did not show the immediate post-stimulus bradycardia seen with ECS (Fig. 3), suggesting that MST does not activate substantial parasympathetic outflow which can be a concern regarding risk of cardiac complications, including asystole. It is notable that we found a difference in immediate post-stimulation bradycardia, since those analyses were performed on the seizure threshold titration day during which atropine was used which might have obscured the difference between the conditions. The lack of immediate post-stimulation bradycardia with MST could represent an advantage in terms of cardiovascular complications of ECT.

There is only one previous study that reported the hemodynamic response with MST versus ECT (White et al., 2006). White et al. found that both MST and ECT were associated with an acute hyperdynamic response immediately following the treatment in a group of 20 adults with depression. In fact, in contrast to our results, they reported the magnitude of this response to be greater after MST as measured by mean arterial blood pressure. There were no significant HR differences observed between the two groups. However, it should be noted that the investigators gave significantly higher doses of Nicardapine (in conjunction with Labetolol, neither of which were used in our study) to the ECT group as compared to the dosage of these given to the MST group, in order to reduce the presumed higher hemodynamic response of ECT. In our study, medications were held constant between MST and ECS so that we could more directly examine the HR differences between those conditions in the absence of the medication confounds. Of note, this paper does not discuss the potential differential efficacy of MST versus ECT, as early human studies in several centers are still in progress. Furthermore, little data has been published on the efficacy of MST alone, although initial reports are starting to appear in peer-reviewed publications (Kayser et al., 2009). We cited earlier a hypothesis that the degree of heart rate response is an indicator of clinical effectiveness (Swartz, 2000) and thus it may be tempting to postulate that while MST has more benign effects on heart rate, it may also be less effective for the treatment of depression. However, we have attempted to argue here, that the diminished response of the HR is a direct benefit of the more precise targeting of this treatment and the sparing effect on the deeper brain centers responsible for HR control. Indeed, one of the main hypothesized benefits of MST is the ability to control the stimulation that will enable improved targeting of the therapy to maximize efficacy and minimize side effects. Another aspect of the relationship between depression and cardiovascular disease is that emergence of either one is a risk for the occurrence of the other (Roose et al., 2001; Carney et al., 2009; Goodwin et al., 2009). Though ECT (and presumably any new convulsive treatment) may be a risk for arrhythmias, these do not necessarily cause mortality, whereas depression

substantially increases the risk of cardiovascular mortality. Therefore, patients considering a convulsive antidepressant treatment should be advised by their clinician to consider this in the overall risk to benefit ratio. For example, some evidence suggests that treating depression may reduce mortality from cardiac causes (Glassman, 2008; Licht et al., 2009).

Limitations of this study include the use of bilateral ECT as our comparator condition, since RUL treatments have been reported to have a less robust impact on HR. In addition, in this study we delivered MST at 2.5×seizure threshold, which matched the dosage of ECS; however, higher dosages above seizure threshold of MST have been used in more recent work in humans (Kirov et al., 2008) and monkeys (Spellman et al., 2008). Future studies are needed to examine whether the cardiovascular response to MST is dose-dependent.

Another limitation concerns our data collection and analytic methods, which permitted us to examine average heart rate, but not ectopic (i.e., beat to beat) variability. Thus, since ectopy represents another cardiovascular treatment consideration, we were unable to describe it with our current methods and will pursue this in future investigations. Finally, while animal models are an important step in the evaluation of novel treatments, the cardiovascular response to the interventions may well be different between monkeys and humans that may prevent generalization of the findings across species. Another aspect of this is that the monkeys used in this experiment were healthy animals of reproductive age, much younger than a geriatric population of depressed patients for whose potential benefit this paper was mainly considered. Also, the cardiovascular effects of a convulsive treatment might differ as a function of the depressed versus non-depressed state, although the full consideration of this goes beyond the scope of this paper.

In conclusion, our findings suggest that MST results in less marked effects on parasympathetic and sympathetic outflow. Future research is warranted to replicate these findings in humans, which could address some of the limitations presented by using the animal model. To that end, we are currently collecting HR data in our clinical trial that compares and contrasts the safety and efficacy of MST and ECT in humans with severe major depression.

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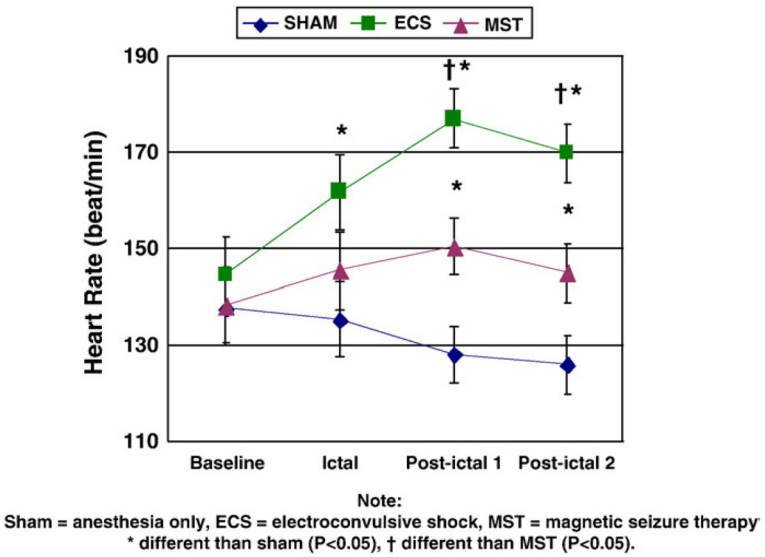

Fig. 1.

Average heart rate (beats/min) for each of the 4 recording epochs (baseline, ictal, postictal-1, and postictal-2) and for each of the 3 groups (ECS, MST, and sham). Points indicate mean heart rate within each recording epoch. Bars indicate standard error of the mean.

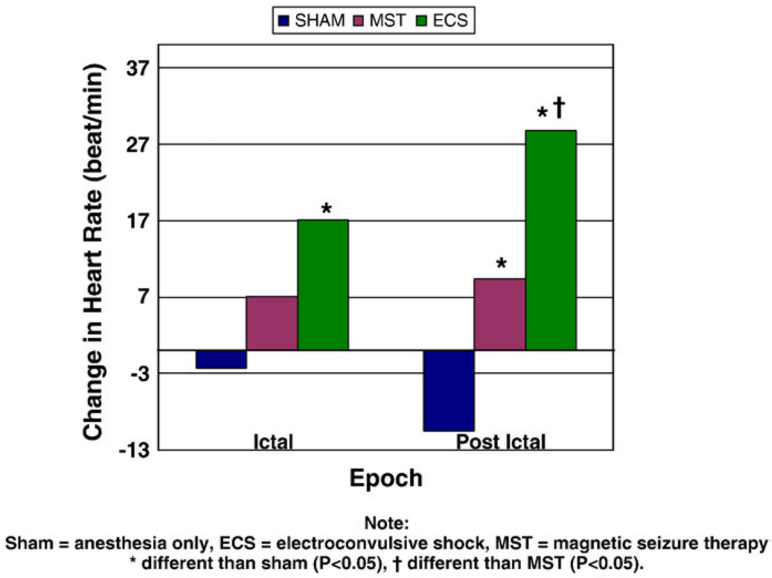

Fig. 2.

Change in heart rate (beats/min), from baseline to the ictal and combined postictal epochs, for ECS, MST and sham based.

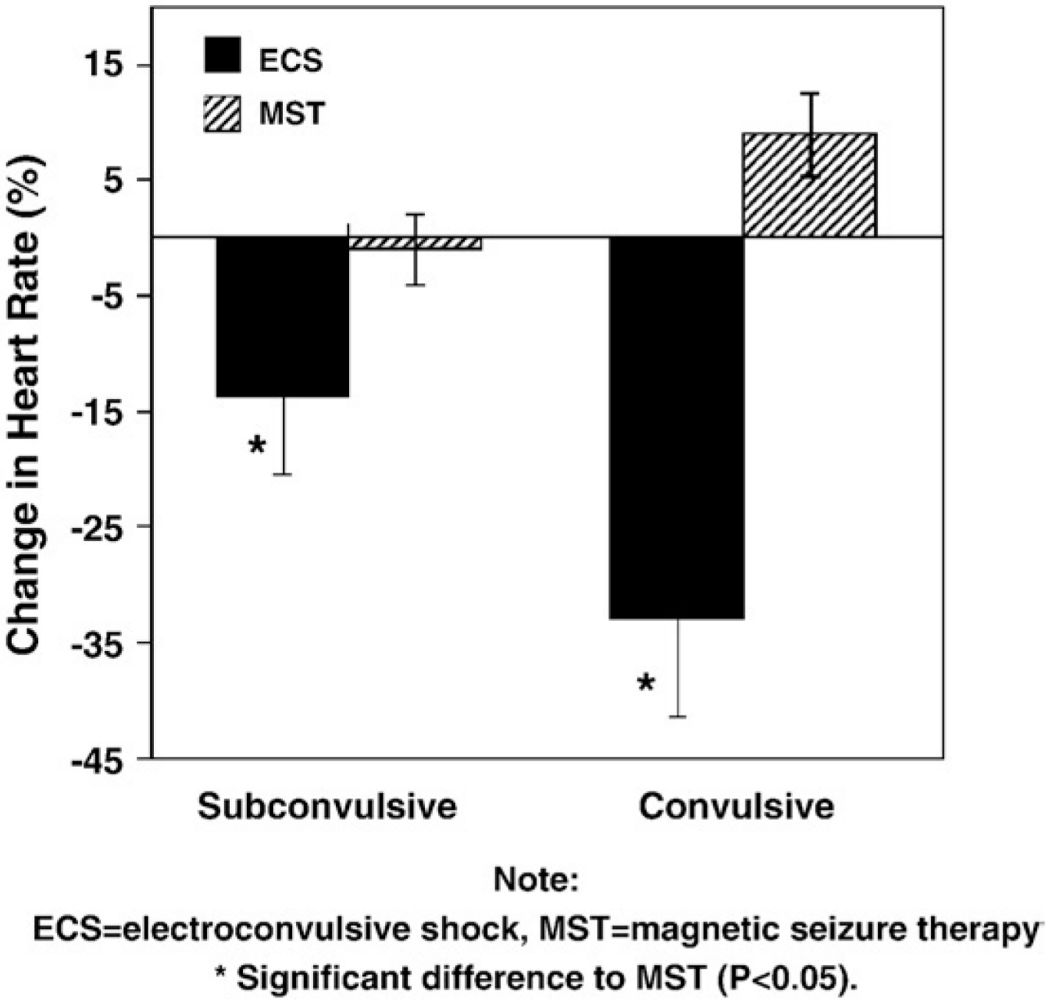

Fig. 3.

Percent change in heart rate from baseline to immediate post-stimulation period monkey for ECS and MST groups. Stimulations that led to seizure are designated “convulsive”, while those that did not lead to seizure are designated “subconvulsive.”