

Randomized controlled trial of the cognitive side-effects of magnetic seizure therapy (MST) and electroconvulsive shock (ECS)

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Abstract

Magnetic seizure therapy (MST) is under development as a means of improving the cognitive side-effect profile of electroconvulsive therapy (ECT) by inducing more spatially delimited seizures that spare cortical regions involved in memory. We tested whether MST had a cognitive side-effect profile distinct from electroconvulsive shock (ECS) in a non-human primate model, using the Columbia University Primate Cognitive Profile, which has been shown to be sensitive to the cognitive effects of ECS. Using a within-subject cross-over design, daily ECS, MST, and sham (anaesthesia-only) interventions were administered in 5-wk blocks. Rhesus macaques ($n=2$) were trained on a long-term memory task, an anterograde learning and memory task, and a combined anterograde and retrograde task where learning and memory were evaluated for new and previously learned 3-item lists. Acutely following each intervention, monkeys were tested on the cognitive battery twice daily, separated by a 3-h retention interval. Overall, monkeys were least accurate following ECS (p 's < 0.05) compared to sham and MST. This effect was most marked for long-term memory of a constant target, short-term memory of a variable target and recall of previously learned 3-item lists. Monkeys were slowest to complete all tasks following ECS (p 's = 0.0001). Time to task completion following MST did not differ from sham. These findings suggest that MST results in a more benign acute cognitive side-effect profile than ECS in this model, consistent with initial observations with human MST.

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Introduction

The risk of cognitive impairment associated with electroconvulsive therapy (ECT) has limited its usage, despite the fact that it is the most effective treatment for major depression. ECT's most severe deficits occur during the immediate postictal period, when disorientation is prominent, and learning and memory are compromised (Sackeim, 1986, 1992). Specifically, ECT impairs retention of newly learned information [anterograde amnesia (AA)] and memory for

information learned prior to treatment [retrograde amnesia (RA)]. While the AA produced by ECT is usually short-lived (Sackeim, 1992; Sackeim et al., 1993, 2000; Squire, 1986; Squire and Miller, 1974), the RA displays a temporal gradient, with events occurring closest in time to the treatment both most vulnerable to initial loss and the slowest to return (McElhiney et al., 1995; Squire et al., 1975). Furthermore, the severity of acute cognitive deficits and the duration of postictal disorientation appear to predict the extent of persistent RA (Sobin et al., 1995).

While the efficacy of ECT is strongly influenced by the anatomical positioning of stimulating electrodes and by the electrical dosage (McCall et al., 2000; Sackeim et al., 1987a, 1993, 2000), these factors can contribute to the magnitude and persistence of

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cognitive side-effects. For example, early findings suggested that bifrontotemporal (bilateral, BL) electrode placement resulted in more severe short- and long-term RA than right unilateral (RUL) electrode placement (McElhiney et al., 1995; Weiner et al., 1986) (see Daniel and Crovitz, 1983; Sackeim, 1992, for reviews). Relative to BL ECT, the advantage of RUL ECT with respect to RA is hypothesized to be due to relative sparing of left medial temporal lobe structures as sites of seizure propagation. As such, techniques that elicit seizures without inducing significant current density or seizure spread in medial temporal lobe structures would be expected to result in reduced RA (Sackeim, 1994). A treatment innovation with better control over the current density patterns could represent an advance with the potential to carry significant clinical benefit for patients needing ECT.

Magnetic seizure therapy (MST) was proposed as a method to realize this goal, and to induce seizures from superficial cortex that do not propagate as robustly to the hippocampus and other regions critical for memory (Lisanby, 2002; Lisanby et al., 2003a; Sackeim, 1994). Since the scalp and skull are transparent to magnetic fields, transcranial magnetic stimulation (TMS) can produce focal brain stimulation, with a resolution that can approach 0.5 cm at the cortical surface (Branston and Tofts, 1990; Tofts and Branston, 1991). In addition to offering greater focality of stimulation, MST provides greater control over intracerebral electrical dosage. The high impedance of the skull shunts the majority of the ECT stimulus away from the brain. Furthermore, individual differences in skull anatomy, particularly the extent and location of fissures, results in current sinks when external electrical stimulation is applied (see Sackeim et al., 1994 for a review). In contrast, the amount and distribution of current induced in the brain by TMS is primarily determined by the intensity of stimulation in the magnetic coil (pulse amplitude), coil geometry and orientation, the distance of the tissue from the coil, and local tissue impedance (i.e. grey vs. white matter) (George et al., 1999; Roth et al., 1991; Rothwell, 1991).

We reported that MST-induced seizures in rhesus monkeys differ from ECS-induced seizures in their effects on the hippocampus. Specifically, MST results in less induced current, less robust seizure spread, and less marked anatomical changes in the dentate gyrus than ECS (Lisanby et al., 2003b; Scalia et al., 2004). This relative sparing of the hippocampus is predicted to result in less impact of MST seizures on hippocampal-dependent functions.

The vast majority of preclinical studies of ECS-induced amnesia have been conducted in rodents,

with passive avoidance of an aversive stimulus the most common measure of memory function. That paradigm's generalizability to human ECT and its ecological validity as a model of amnesia are limited by both the relative simplicity of the rodent brain and the task demands. To our knowledge, Moscrip et al. (2004) was the first attempt to model the cognitive side-effects of electrically induced seizures in the non-human primate. In that study, we developed the Columbia University Primate Cognitive Profile (CUPCP), a 3-task cognitive battery that was presented to rhesus macaques (*Macaca mulatta*) on a touch-sensitive computer monitor. Task 1 assessed post-intervention reorientation and long-term memory, likened to asking ECT patients 'What is your name?' Task 2 assessed working memory, immediate learning, and retention over a delay (AA). Task 3 was a serial memory task in which monkeys' learning and memory skills were assessed for 3-item lists. Monkeys learned new 3-item lists each day of the intervention period, and were also tested on their memory of lists learned during the training period, prior to the intervention phase. Performance was dependent on the cognitive processes involved in learning and remembering lists in which a sequence of arbitrary steps is key (e.g. dialling a telephone number). Monkeys were administered the cognitive battery twice a day, with an interval of 2 h before re-test. Poor retention over the delay, of the 3-item list learned that day, would be indicative of AA, while poor performance on lists learned prior to the intervention would indicate RA.

Significant effects of the interventions (sham and ECS) were apparent on the CUPCP. The degree of impairment varied across tasks, and as a function of task difficulty. ECS did not differ from the sham condition in accuracy on the less difficult tasks (tasks 1 and 2), but it did increase the amount of time required to complete the tasks. This effect was cumulative with additional ECS exposure. Additionally, ECS impaired the acquisition and memory of new lists compatible with an anterograde memory deficit, while recall of old lists was relatively spared.

An important limitation of this earlier work was the observation that the sham condition alone resulted in significant impairment relative to pre-intervention baseline. We hypothesized that these impairments were due in part to the use of ketamine, a sedative agent used to remove the animals from the home cage. The use of ketamine may have masked some of the seizure-induced effects by producing persistent sedation and appetite suppression. Ketamine has also been shown to block some of the effects of ECS on

mossy fibre sprouting in the dentate gyrus (Chen et al., 2001), that may have reduced treatment-related cognitive impairments. As such, the effects of ketamine in our prior work are probably complex. While ketamine may have impaired performance in the sham condition resulting in an underestimation of cognitive functioning, ketamine's ability to block glutamatergic response to seizures may have led to an underestimation of the cognitive impairment attributable to the interventions. These two confounds would make it more difficult to detect a difference between sham and active treatment. The fact that we did find significant differences, despite these confounds, supported our hypotheses regarding treatment effects, but the size of the treatment effect may be underestimated due to these confounds.

Other non-human primate cognition studies of ketamine use lend support to our findings. Taffe and colleagues, for example, assessed the cognitive effects of acute, subanaesthetic doses of ketamine in a sample of seven adult male rhesus monkeys that were trained on a neuropsychological battery including tests of memory, reaction time, and attention. They found that ketamine not only slowed reaction times, but it also impaired visual recognition memory and working memory indices in a dose by difficulty-dependent manner (Taffe et al., 2002a,b).

Hypofunction of *N*-methyl-D-aspartate (NMDA) receptors, as occurs with NMDA antagonists like ketamine, may result in similar cognitive effects in humans. Rowland et al. (2005), for example, have found that subanaesthetic doses of ketamine impaired learning of spatial and verbal information. Additionally, a double-blind, placebo-controlled human study performed by Morgan and colleagues found that ketamine produced a dose-dependent impairment in episodic and working memory and a slowing of semantic processing. Ketamine was also responsible for impairing recognition memory and procedural learning (Morgan et al., 2004). As such, removing the confound of ketamine in the current study should increase the sensitivity of the tasks and permit examination of differences closer in time to the intervention than was formerly possible.

Using a randomized, sham-controlled design, the present study sought to examine the differences between MST and ECS in their cognitive effects without the confound of ketamine. This was accomplished by training monkeys for voluntary venepuncture which obviated the need for an intramuscular (i.m.) sedative. We hypothesized that the magnitude of AA and RA would be reduced with MST as compared to that of ECS.

Method

Subjects

The experiments were performed at the New York State Psychiatric Institute (NYSPI) with Institutional Animal Care and Use Committee approval and in accordance with NIH guidelines. Three male rhesus monkeys were trained for voluntary venepuncture using positive reinforcement procedures (Reinhardt, 1991). The first subject (4 yr old) was used to pilot the ketamine-free anaesthetic protocol that was subsequently used on the remaining two monkeys (hereby referred to as subject 1 and subject 2). Subjects 1 and 2 were experimentally naive and were 2.5 yr old at the start of training. The monkeys were group-housed and maintained on a 12-h light/12-h dark cycle. They had ad-lib access to water and daily feedings of standard monkey chow (LabDiet[®], W.F. Fischer & Son Inc., Somerville, NJ, USA), fruit, treats hidden in enrichment toys, and daily human contact.

Columbia University Primate Cognitive Profile (CUPCP)

Details of the cognitive testing apparatus, stimuli presentation, and training procedures can be found in Moscrip et al. (2004). Briefly, the cognitive battery is composed of three tasks of increasing difficulty: task 1 – an orientation task (long-term or automatic memory); task 2 – a variable target task (anterograde learning and memory); and task 3 – a serial learning and memory task (anterograde and retrograde memory).

Task 1 (Recall of an over-learned stimulus)

Task 1, which required minimal learning, was a retrograde memory task modelling the kind of questions about over-learned information that patients are asked when assessing the return of orientation after ECT (e.g. 'What is your name?', 'What is your birth date?'). Monkeys were required to select a single, constant target that was presented amongst 15 distracters. The target's location was changed randomly from trial to trial, and a new set of 15 distracters was presented on each trial, ensuring that the response was not influenced by the target's position or particular distracters.

Task 2 (Learning new targets by trial and error)

Task 2 provided a measure of immediate learning and AA. A *novel* target was presented at the start of each session, with as many 15 distracters. At the start of each session, the only way to identify the new target was by trial and error. The monkey's accuracy on this

Table 1. Design of intervention schedule

	Weeks						
	1–2	3–7	8–20	21–25	26–31	32–36	37–41
Subject 1	Baseline	MST	Recovery	ECS	Recovery	Sham	Recovery
Subject 2	Baseline	ECS	Recovery	MST	Recovery	Sham	Recovery

MST, Magnetic seizure therapy; ECS, electroconvulsive shock.

task was based upon the effectiveness of their trial-and-error search, and their ability to remember the target-of-the-day on subsequent trials.

Task 3 (Serial memory for temporally graded 3-item lists)

On task 3 the monkeys had to learn, by trial and error, the order in which to respond to three simultaneously presented photographs. Lists were trained using the simultaneous chaining paradigm (Swartz et al., 1991; Terrace et al., 2003). From the start of training on each list, all list items were presented simultaneously. Their physical positions on the touch screen changed randomly on each trial. To learn the correct item order of each new list, the monkey had to remember the consequences of incorrect responses as they attempted to execute the sequence. Errors (e.g. B, C, A→B→A or A→C) were followed by a brief (2 s) time-out during which the screen was dark. Food reward was provided only if the monkey responded to all list items in the correct order (A→B→C). After ~7 wk of training on two new 3-item lists/day, two new lists were introduced during *each* session to provide an inventory of lists that could be used to measure RA during the treatment intervention phase. To be included in that inventory, monkeys had to respond correctly on at least 35% of the trials during a single session.

Testing sequence

To advance from task 1 to task 2, and from task 2 to task 3, monkeys had to respond correctly during the prior task on four out of five consecutive trials. Two list types were presented during task 3 – *new* and *old*. *New* lists were composed of three photographs of arbitrary objects that the monkeys had not seen previously. On these lists, the monkeys had to learn the correct sequence de novo. *Old* lists were trained 4–6 wk prior to the start of the treatment intervention. During testing, the type of list presented on any given trial varied randomly. A total of 205 new lists and 123 old lists were tested across the 41-wk experiment.

Study design

Each monkey underwent seven experimental testing periods in a within-subject multiple cross-over design (Table 1): baseline (2 wk), MST (5 wk), ECS (5 wk), sham (anaesthesia alone, 5 wk), and three post-intervention recovery periods. Allowing each subject to serve as his own control is advantageous considering the significant inter-individual variability in the cognitive effects of ECT, and considering the limited availability of non-human primates for invasive studies. To reduce the risk of carry-over effects, the recovery period following each intervention was continued until performance returned to baseline levels (ranging from 5 to 13 wk). Accuracy and time to completion on each of the CUPCP tasks were the primary outcome measures.

During each intervention condition, monkeys were tested twice daily (5 d/wk). Session I refers to the testing occasion immediately following post-intervention or the first session of the day in the case of baseline or recovery periods. Session II is the second session of the day, starting after a 3-h retention interval following completion of session I.

Ketamine-free anaesthetic protocol

To remove the potential confound of i.m. ketamine, we developed a new anaesthetic protocol that obviated the need for i.m. ketamine sedation through behavioural training of the monkeys to permit intravenous (i.v.) placement in the home cage. Pre-anaesthesia sedation for transport to the treatment suite was achieved with methohexital (4.75 mg/kg i.v.) via voluntary venepuncture in the home cage. Pilot testing determined that this dosage provided a 5-min period of sedation that was adequate for transportation to the procedure room and pre-intervention set up.

Testing in a pilot subject showed that task completion times and accuracy scores were markedly improved using the ketamine-free (i.v. methohexital)

procedure (30–45 min with ketamine pre-treatment vs. 5–7 min without ketamine). On average, the accuracy scores across cognitive tasks were 34% better without ketamine pre-treatment. Furthermore, performance following i.v. methohexital did not differ from baseline (no anaesthesia).

Sham, MST and ECS interventions

As with human ECT, the anaesthetic agents were methohexital (0.5 mg/kg i.v.) and succinylcholine (2.5 mg/kg i.v.). ECG, blood pressure, end tidal CO₂, and pulse oximetry were monitored continuously, and 100% oxygen (positive pressure) was given throughout. The occurrence and duration of seizure activity was monitored with BL frontomastoid EEG channels on a MECTA Spectrum 5000Q (MECTA Corporation, Tualatin, OR, USA) and motor manifestations were monitored using the cuff technique (APA, 2001). Sham involved anaesthesia and monitoring only, with no stimulation or seizure induction.

BL ECS was administered with the MECTA Spectrum 5000Q ECT device, modifying the size of adhesive stimulating electrodes (Somatics Corporation, Lake Bluff, IL, USA) to conform to the monkey cranium. ECS electrodes were placed bilaterally on the right and left temples (just above the ears), mimicking electrode placement for BL ECT in humans, using the same level of precision in placement as is standard in clinical practice. MST was administered via a custom modified MagStim MST device (16 booster) with a pediatric-sized round coil (6.2 cm diameter) placed on the vertex (10–20 EEG system). Seizure thresholds for ECS and for MST were determined using the ascending method of limits titration procedure (Sackeim et al., 1987b). Dosage at subsequent sessions was set at 2.5 times the initial seizure threshold. Initial ECS seizure threshold was 4 mC (subject 1) and 8 mC (subject 2). MST was administered at 50 Hz and 100% maximal intensity, with duration adjusted to achieve 2.5× initial seizure threshold. Initial MST seizure threshold was 240 pulses (subject 1) and 120 pulses (subject 2). These are within the range of MST seizure thresholds that we have previously observed in primates (Dwork et al., 2004; Lisanby et al., 2001).

Immediately following each intervention, monkeys were transported to a test chamber where the cognitive battery was initiated following a response to a start stimulus on the touch screen. Thus, the interval between the treatment session and the start of task 1 was self-paced and provided a measure of how rapidly the subject could respond to stimuli presented on a touch screen.

Statistical analyses

The analyses utilized mixed effects models (MEMs) (Diggle et al., 2002) which evaluated each cognitive outcome separately. Since accuracy data for all tasks were constrained to fall between 0 and 100%, an arcsine transformation was applied prior to statistical analyses. The mean structures of the outcomes were specified as functions of condition (seven levels), day of the condition (as a continuous variable), session per day (two levels), animal (two levels), and all interactions except the four-way.

First, the covariance structure for each outcome was modelled taking into account the stronger correlation between the repeated assessments on the same day (two sessions), with the correlation gradually decreasing with increasing time-lag between repeated assessments of the same animal on different days, and potential heterogeneity of the outcome at different conditions and sessions. The models evaluated for the covariance structure included compound unstructured, compound symmetry, autoregressive(1), other spatial models and their heterogeneous variants, as well as random animal × day-of-condition effects.

For each outcome the best-fitting covariance model was selected based on Akaike's Information Criterion (AIC) and Schwartz's Bayesian Information Criterion (BIC) (Burnham and Anderson, 2002). After identifying the appropriate covariance structure, simplification of the mean structure was sought by one-term-at-a-time backward elimination, preserving the hierarchical principle, i.e. if a higher order interaction is retained in the model, all lower order terms included in that interaction are preserved regardless of their statistical significance. The inferences are based on the final model for each outcome, in which non-significant terms were maintained only if a statistically significant higher order term included them. Statistical significance everywhere was judged based on $\alpha=0.05$. The parameters were estimated with the iterative maximum-likelihood method. The analyses were conducted using the PROC MIXED procedure of SAS[®] (Littell et al., 1996).

The amount of time to reach the criterion level of accuracy on each task was coded in minutes. The modelling of the time variables followed the strategy outlined above for the accuracy data. The mean structures of the time outcomes were specified as functions of condition (three levels), day of the condition (as a continuous variable centred at zero, including linear and quadratic term), animal (two levels), and all two- and three-way interactions. Using this model for the mean structure, the covariance structure was

Table 2. Results summary

	Did the intervention induce significant* impairment?		
	MST vs. sham	ECS vs. sham	ECS vs. MST
Accuracy†			
Task 1	No	Yes	Yes
Task 2	No	Yes	Yes
Task 3: New	Yes	Yes	No
Task 3: Old	No	Yes	Yes
Time to criterion			
Task 1	No	Yes	Yes
Task 2	No	Yes	Yes
Complete battery	No	Yes	Yes

MST, Magnetic seizure therapy; ECS, electroconvulsive shock.

* Statistically significant difference between the conditions, $p \leq 0.05$.

† Session II accuracy was better than session I accuracy for all tasks.

modelled allowing for correlation between the repeated measures on the animals. We examined compound symmetry, AR(1), Toeplitz with three and five parameters, and their homogeneous and heterogeneous variants (SAS Institute, 1985). The models for the covariances were selected based on AIC and BIC criteria and the selection of the final model for the mean structure followed the strategy described above for making inferences about the accuracy data.

Results

Cognitive performance following MST and ECS – summary

Table 2 summarizes the results for MST, ECS and sham interventions for each task of the CUPCP across the two monkeys. The average performance of each monkey for each of the three tasks is presented in Figures 1 and 2. Compared to sham, ECS reduced accuracies and markedly increased completion times for all tasks of the cognitive battery. Additionally, ECS resulted in greater impairment of accuracies and completion times compared to MST. This effect was most marked for task 1, task 2 and old list accuracies. In general, session II performance was better than that of session I. Except for impairment in learning new lists, MST did not differ from sham. In general, accuracy during the recovery periods following sham, MST

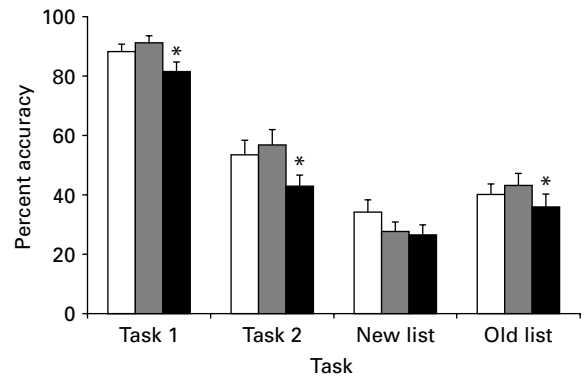


Figure 1. Average accuracy across testing sessions. Electroconvulsive shock (ECS) resulted in marked reduction of average accuracy compared to magnetic seizure therapy (MST) across both testing sessions. This is apparent for tasks 1 and 2 and old list performance (* $p < 0.054$). □, Sham; ■, MST; ■, ECS.

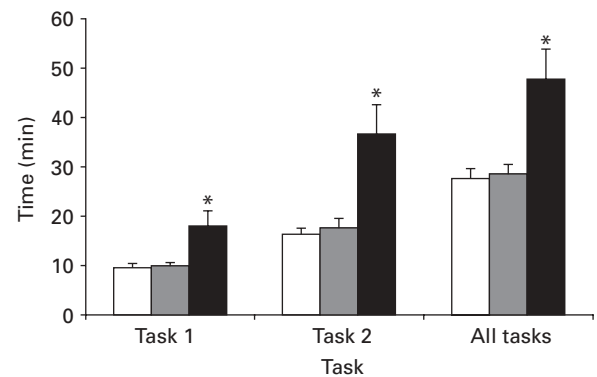


Figure 2. Time to task completion. Electroconvulsive shock (ECS) resulted in significantly longer completion times for all tasks as compared to both magnetic seizure therapy (MST) and sham (* $p = 0.0001$). □, Sham; ■, MST; ■, ECS.

and ECS did not differ from baseline measures for tasks 1 and 3 (old lists). For tasks 2 and 3 (new lists), recovery periods following MST and ECS resulted in impaired performance relative to baseline measures of accuracy, but did not differ from one another. Detailed results for post-intervention accuracy and completion times are presented for each task below.

Task 1

Accuracy

Accuracy scores showed significant main effects of condition and session ($F_{6,733} = 6.86$, $p = 0.0001$ and $F_{1,733} = 26.11$, $p = 0.0001$ respectively), as well as significant animal \times condition and condition \times session two-way interactions ($F_{6,733} = 5.11$, $p = 0.0001$ and

$F_{6,733}=6.72$, $p=0.0001$ respectively). As shown in Figure 1, accuracy was poorer following ECS than MST or sham (p 's <0.0001 and 0.006 respectively). MST and sham did not differ. Accuracy was poorer in session I compared to session II for all three interventions (p 's <0.0001), consistent with some recovery of function with more time post-anesthesia; this effect was not seen during baseline or recovery. In general, the performance of subject 2 was better than that of subject 1, except at baseline and MST, where they did not differ.

Time to criterion

Time to criterion yielded a main effect of condition ($F_{2,140}=15.41$, $p=0.0001$). As shown in Figure 2, ECS resulted in longer completion times compared to MST and sham ($t_{140}=4.23$, $p=0.0001$ and $t_{140}=5.28$, $p=0.0001$ respectively). MST did not differ from sham.

Task 2

Accuracy

There were significant main effects of condition and session ($F_{6,744}=10.08$, $p=0.0001$ and $F_{1,744}=209.35$, $p=0.0001$ respectively), and a significant animal \times session interaction ($F_{1,744}=4.44$, $p=0.04$). As shown in Figure 1, ECS resulted in impaired accuracy compared to both MST and sham ($t_{744}=3.64$, $p=0.0003$ and $t_{744}=2.74$, $p=0.006$ respectively). MST did not differ from sham. As with task 1, accuracy was significantly better in session II compared to session I ($t_{744}=14.47$, $p=0.0001$). Across conditions, subject 1 significantly outperformed subject 2 in session II ($t_{744}=2.46$, $p=0.014$).

Time to criterion

There were significant main effects of condition and animal ($F_{2,133}=30.48$, $p=0.0001$ and $F_{1,133}=8.47$, $p=0.0042$ respectively), an animal \times condition interaction ($F_{2,133}=3.74$, $p=0.03$), and day of testing \times animal \times condition interaction ($F_{2,133}=6.56$, $p=0.002$). As shown in Figure 2, ECS prolonged completion times significantly more than MST or sham ($t_{133}=6.53$, $p=0.0001$ and $t_{133}=7.02$, $p=0.0001$ respectively). MST did not differ from sham. Subject 2 was faster than subject 1 during the ECS condition. The three-way interaction was a result of ECS having a cumulative effect on increasing task 1 completion times with each additional treatment session, and this effect was most marked for subject 1 ($t_{133}=3.80$, $p=0.0002$).

Task 3

New list accuracy

Analyses yielded main effects of condition ($F_{6,738}=6.98$, $p=0.0001$) and session ($F_{1,738}=76.38$, $p=0.0001$), as well as interaction effects of animal \times session ($F_{1,738}=5.62$, $p=0.018$) and condition \times session ($F_{6,738}=2.48$, $p=0.0221$). As shown in Figure 1, both ECS and MST differed from sham ($t_{738}=2.84$, $p=0.005$ and $t_{738}=2.23$, $p=0.03$ respectively), but ECS and MST did not differ from one another. Although both monkeys performed significantly better in session II compared to session I ($t_{738}=8.74$, $p=0.0001$), subject 2 showed greater improvement in session II than subject 1. Compared to all other conditions, the baseline condition resulted in the greatest improvement from session I to session II.

Old list accuracy

There were main effects of condition ($F_{6,738}=4.56$, $p=0.0001$) and session type ($F_{1,738}=50.27$, $p=0.0001$), and significant animal \times session and animal \times condition interactions ($F_{1,738}=7.58$, $p=0.006$ and $F_{6,738}=2.26$, $p=0.036$ respectively). Across both monkeys, ECS produced greater impairment than MST ($t_{738}=1.93$, $p=0.05$), but neither ECS nor MST differed from sham. For subject 2, but not for subject 1, ECS resulted in impaired accuracy compared to either MST or sham ($t_{738}=1.98$, $p=0.049$ and $t_{738}=2.45$, $p=0.015$ respectively), while MST did not differ from sham. As before, accuracy was significantly better in session II compared to session I ($t_{738}=7.09$, $p=0.0001$), but subject 2 showed greater improvement from session I to session II than subject 1. Subject 2 significantly outperformed subject 1 during all conditions except baseline and the recovery periods following ECS and sham (p 's <0.04).

Time to cognitive battery completion

There were significant main effects of condition ($F_{2,127}=24.53$, $p=0.0001$), animal ($F_{1,127}=10.68$, $p=0.0014$), and day of session ($F_{1,129}=5.56$, $p<0.02$). As seen in Figure 2, ECS produced the longest completion times compared to either MST or sham ($t_{127}=5.90$, $p=0.0001$ and $t_{127}=6.28$, $p=0.0001$ respectively) and time-to-battery-completion increased with successive ECS administrations. MST did not differ from sham. Subject 2 completed the CUPCP faster than subject 1.

Discussion

Using a neuropsychological test designed to be sensitive to the cognitive side-effects of ECS in non-human

primates (Moscrip et al., 2004), we found that key higher order cognitive functions are less impaired following MST than ECS. Specifically, MST had advantages relative to ECS in its impact on speed and accuracy in performing tasks of 'orientation', learning, and AA and RA.

Previously we reported that the CUPCP is sensitive to the effects of ECS, but that a prior report carried the confound of ketamine pre-treatment (Moscrip et al., 2004). Non-human and human studies of ketamine's effect on cognition have found similar impairments. Specifically, ketamine has been found to impair working memory, recognition memory and procedural learning, suggesting that NMDA mechanisms are required for the formation and/or strengthening of internal representations (Rowland et al., 2005).

As such, here we present a ketamine-free procedure for assessing the cognitive effects of seizures in the non-human primate model. Removing the confound of i.m. ketamine [which could exert complex effects on cognition via prolonged sedation, reduced seizure expression (Borowicz and Czuczwar, 2003; Fujikawa, 1995) and blunted mossy fibre sprouting (Chen et al., 2001)] should give a clearer picture of intervention-induced effects. Using the ketamine-free anaesthetic protocol, we found that ECS produced greater impairment than anaesthesia-alone (sham) on all aspects of the cognitive battery. These effects were more consistent and of greater magnitude than those seen in our prior report that utilized ketamine sedation (Moscrip et al., 2004). Specifically, in the prior report the ketamine + methohexital sham condition resulted in impairments that approached or matched those seen with ECS on tasks 1 and 2 accuracies and on memory for previously learned 3-item lists. Differences between ECS and sham on new-list learning and time to reach criterion on task 2 were only seen during the session II post-intervention delay period, whereas in the present study differences between ECS and sham were marked in these measures immediately after the intervention. In the current study, the use of voluntary i.v. administration of anaesthesia in the home cage allowed us to use the short-acting anaesthetic, methohexital for both transport and sedation during the interventions, which resulted in reduced disorientation/cognitive impairment in the sham condition relative to our previous observations.

While prior human work had reported that MST resulted in a more benign acute cognitive side-effect profile than ECT, that work only examined individual treatment sessions and not the effects of an entire course of treatment (Lisanby et al., 2003a). Moreover, in that work the MST and ECT electrical dosage was

not matched in the degree to which they exceeded seizure threshold. The current study administered both MST and ECS at 2.5 times the seizure threshold, and examined the effects of 5 treatments/wk across a total of 5 wk. Consistent with our hypothesis, the 5-wk block of treatment with ECS resulted in more impairment than 5 wk of MST on all accuracy and speed measures, with the exception of new-list learning. Differences between MST and ECS were detectable even when examining performance in session I, immediately after recovery from the seizure. Accuracy following MST did not differ from sham, except during new-list learning.

The difference in the cognitive effects of MST and ECS may be due to the more spatially delimited nature of MST and its ability to produce more focal seizure induction than ECS (Lisanby, 2002; Sackeim, 1994). Additionally, the magnetic field induced by MST decays exponentially with distance from the coil; thus, even non-focal stimulation with a round coil as used in this study should not directly induce current in medial temporal structures. We previously reported that MST results in less current spread and less seizure propagation to deeper brain structures, including the hippocampus, than ECS (Lisanby et al., 2003b). We have also found that MST in the primate model does not increase mossy fibre sprouting, as occurs with ECS (Dwork et al., 2004). This lack of impact on hippocampal anatomy might relate to the superior cognitive profile of MST. Current studies in our laboratory aim to assess the impact of MST and ECS on aspects of learning and memory that are believed to be subserved by distinct frontal and hippocampal cognitive systems in order to better define the significance of limiting the regionality of seizure propagation (Moscrip et al., 2002).

The absence of differences between MST and ECS in effects on new-list learning may indicate that these conditions produce similar degrees of AA, consistent with preliminary work comparing ECT with MST in humans (Lisanby et al., 2003a). As such, the comparable decrement on new-list performance resulting from MST and ECS may be a function of the equivalent impacts of these interventions on frontally mediated function. The prefrontal cortex, for example, has been shown to be activated during the learning of new sequence information, while it does not appear to be as important during the recall of learned sequences (Jueptner, 1997). While ECS and MST may result in similar cognitive impairment on tasks requiring frontally mediated learning and memory, tasks that impose greater demands upon subcortical brain regions are likely to be most affected by ECS. This is

due to the diffuse stimulation characteristic of ECS and its subsequent impact upon other brain regions involved in memory, particularly the hippocampus. Yet another alternative hypothesis, however, is that new-list learning may have been an artifact of floor effects. Both monkeys performed near chance levels (17% accuracy) on this task at baseline, thus, further impairments resulting from the intervention could not be readily detected.

As in our prior report (Moscrip et al., 2004), we again found significant individual differences in the impact of the interventions across the monkeys. Possible contributors to this individual variability may include age, weight, anaesthetic dosing and previous cognitive training. It is also possible, however, that monkeys differ in their susceptibility to cognitive impairment following seizures, as has been observed with human ECT (Prudic et al., 2000). A non-human primate model in which individual differences in cognitive effects are expressed may provide a means for studying their neurobiological bases. To minimize the confound of individual differences in the present study, which was focused on contrasting MST and ECS, the within-subject design provided the sensitivity needed to consistently distinguish intervention effects despite individual differences in peak performance levels. While the within-subject design has the potential limitation of carry-over effects, the recovery period between interventions was continued until performance returned to baseline levels to reduce this risk. Although the post-intervention recovery period reduces the risk of carry-over effects resulting from the cross-over design on the measured cognitive performance, we cannot completely rule out other lasting physiological effects of the treatment that may have influenced response to the subsequent interventions.

While this study had a small sample size, cognitive studies of this complexity in non-human primate studies necessitate small samples. For example, the twice-daily training sessions over a period of months would not be feasible on a large scale, especially considering that it can take 1.5 yr for monkeys to achieve expertise on these tasks and to accumulate a sufficient number of 'old' lists prior to post-intervention cognitive testing. Despite the small sample, the findings demonstrated statistically reliable differences within and across each animal in the effects of the interventions and the power of the random regression analyses was enhanced by the large number of repeated observations for each intervention condition. Nonetheless, the findings pertain only to the performance of two monkeys and should be

followed up in subsequent studies prior to making generalizations.

Since the cognitive effects of ECT are a significant factor limiting its use, there is considerable clinical interest in developing alternative means of seizure induction that result in less severe and persistent cognitive deficits. However, quite independent of the potential clinical impact of MST, such work can shed light on the neurobiological underpinnings of the cognitive consequences of ECT. For example, our results suggest that deeper spread of current and seizure are necessary to result in the RA seen with ECS, and that cortically initiated seizures are inadequate to produce those effects. This model of the cognitive side-effects of seizures in non-human primates could likewise be used to test other device-based or pharmacological strategies to reduce the cognitive impact of ECT.

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Statement of Interest

None.

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