A Primate Model of Anterograde and Retrograde Amnesia Produced by Convulsive Treatment

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Summary: A nonhuman primate model of the key cognitive effects of convulsive treatment was developed and tested. Rhesus macaques were trained on 3 tasks: a long-term memory task that required selection of a constant target from a background of distracters, an anterograde task that involved learning a new target each day against a variable number of distracters, and a task that assessed learning and memory for new and previously trained 3-item serial lists. This battery samples a range of cognitive functions, including orientation, working memory, retrograde amnesia for temporally graded stimuli, and anterograde amnesia. Using a within-subject, sham-controlled design, the amnestic effects of electroconvulsive shock (ECS) were evaluated in 2 monkeys. Significant effects of the interventions (sham and ECS) were seen on all tasks. The degree of impairment varied across tasks and as a function of task difficulty. ECS did not impair accuracy on the less difficult tasks (memory for an overlearned item and acquisition of a new item) but did increase the amount of time required to complete the tasks, consistent with a period of disorientation acutely after the intervention. This effect was progressive across the treatments. ECS impaired the acquisition and memory of new lists compatible with an anterograde memory deficit, whereas recall for old lists was relatively spared. This study developed and validated a cognitive battery to assess amnesia in nonhuman primates, providing new experimental paradigms for evaluating the cognitive effects of convulsive treatment.

Key Words: amnesia, electroconvulsive therapy, memory, primate, seizure, electroconvulsive shock

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Electroconvulsive therapy (ECT) is the most effective treatment of major depression. However, patient and clinician acceptance are limited by the ECT's cognitive side effects. Indeed, the American Psychiatric Association Task Force on Electroconvulsive Therapy recently suggested that consent forms be modified to indicate that after ECT some degree of permanent retrograde amnesia is expected.[1]

The cognitive effects of ECT are stereotyped. The most severe deficits occur during the immediate postictal period, when disorientation is prominent and sensorimotor, attention, language processing, learning and memory, and other cognitive functions may be compromised.[2,3] Recovery from the acute effects is typically rapid. In fact, compared with their pre-ECT baseline, patients often have superior performance on tests of most nonmemory-based cognitive functions shortly after the ECT course.[4–7] This improvement reflects normalization of the cognitive impairments associated with the state of major depression. However, after the ECT course, most patients manifest deficits in the retention of newly learned information (anterograde amnesia, [AA]) and in memory for information learned prior to the ECT course (retrograde amnesia, [RA]). The AA produced by ECT is short-lived and, in group data, is rarely apparent more than 10 days after ECT.[3,6,8–10] Similarly, patients' reports of persistent AA are very rare.

Like that often seen with traumatic head injury,[11] the RA produced by ECT displays a temporal gradient, with events occurring closest in time to the treatment both most vulnerable to initial loss and the slowest to return, if ever recovered.[12,13] The extent and persistence of ECT-induced RA appears to be greater for "public" (ie, events in the world) than autobiographical events.[14] Virtually all patients experience some degree of permanent RA. This spottiness in recall or recognition of past events may be limited to a brief interval surrounding the delivery of treatment or it may extend back for considerable periods of time. In rare instances, patients may have prolonged RA that extends back several years.[1,15,16] Of note, the severity of acute cognitive deficits, and especially the duration of postictal disorientation, appear to predict the extent of persistent RA.[17] This is not unexpected because disorientation itself may be a form of rapidly shrinking RA.[18]

Efficacy is strongly influenced by the anatomic positioning of stimulating electrodes, which determines current paths, and by electrical dosage, which determines current density within the current paths.[6,8,19,20] These factors also determine the magnitude and persistence of cognitive side effects. For example, early findings suggested that the bifrontotemporal (bilateral, BL) electrode placement resulted in more severe short- and long-term RA than the right unilateral (RUL) electrode placement.[3,13,21,22] This has now been confirmed in a large sample of patients treated in community settings. Compared with RUL-ECT, BL-ECT resulted in persistent deficits 6 months after completion of ECT (Prudic, Olfson, and Sackeim, personal communication). The electroconvulsive shock (ECS) methods used in this study modeled the clinical administration of high-dosage BL-ECT.

The major aim of this study was to develop in an animal model a battery sensitive to the cognitive effects of ECT. ECS in animals is the most common paradigm used to screen pharmacological compounds for protective effects on memory.[23,24] However, the bulk of this research has been conducted in rodents, with passive avoidance of an aversive stimulus the most frequent measure of preserved cognition.[25–27] This raises questions about the generalizability of these studies to human ECT and about their ecological and construct validity as a model of amnesia. Factors that increase passivity, such as might occur in the postictal state or as a byproduct of the pharmacological agents being studied, can improve task performance independent of effects on memory.[28] This study attempts to assess the cognitive impairment of ECS-induced seizures in a monkey model, rather than the behavioral effects of ECS, as has been previously investigated.[29,30] To our knowledge, there has not been a prior attempt to develop a cognitive battery for nonhuman primates that mirrors the salient forms of cognitive dysfunction seen after ECT.

We developed a 3-task cognitive battery that was presented to rhesus macaques (*Macaca mulatta*) on a touch-sensitive computer monitor. Task 1, an assay of the capacity to retain a single overlearned item, was modeled after the postictal assessment of recovery of orientation in which patients are asked questions like, "What is your name?" Over several months of training, involving 2 sessions, 5 days per week, monkeys learned to select a specific photograph from a background of distracter photographs. The photograph assigned to each monkey remained constant throughout the training and subsequent testing period, just as one's name is invariant and an aspect of long-term memory. Task 2 assayed working memory, immediate learning, and retention over a delay (AA). Monkeys had to determine, by trial and error, which photograph was the new target at the start of each session. As in Task 1, the subject's task was to identify the target imbedded in a background of distracters. In Task 2, however, a new target was used in each twice-daily session. In addition, the distracters were varied from trial to trial as were their number. Task 3 was a serial memory task in which monkeys were trained to respond to 3 simultaneously presented photographs in an arbitrary order (A→B→C), regardless of their position on the monitor. Variation of the position of the photographs from trial to trial prevented the monkeys from learning the required sequence as a series of specific motor responses or by spatial location. Monkeys learned new 3-item lists each day of the test period but were also tested on their memory of lists learned early or late during the training period, prior to the intervention phase. This task assessed the cognitive processes involved in learning and remembering lists in which the sequence of arbitrary steps is key (eg, how to drive to a particular location or dialing a particular telephone number). Monkeys were administered the complete battery twice per day of testing, with an interval of 2 hours before retest. Poor retention over the delay of the 3-item list learned that day would be indicative of AA, whereas poor performance on lists learned prior to ECT (either at the beginning of the daily testing or after the delay) would indicate RA.

MATERIALS AND METHODS

Subjects

Two male rhesus monkeys (*Macaca mulatta*) served as subjects. One monkey, named Coltrane, was 4 years old at the start of training and was experimentally naive. The other monkey, named Puck, was 8 years old and had previously served in experiments on other cognitive tasks.[31] These monkeys had multicontact intracerebral electrodes implanted that were used in earlier experiments to map the electric field induced by magnetic seizure therapy (MST) and ECS.[32] The experiments were performed at the New York State Psychiatric Institute with Institutional Animal Care and Use Committee approval and in accordance with NIH guidelines. The monkeys were housed individually and maintained on a light cycle of 12 hours light/12 hours dark. They had access to water ad libitum and daily feedings of standard monkey chow (LabDiet®), fruit, and treats hidden in enrichment toys.

Cognitive Tasks: Columbia University Primate Cognitive Profile (CUPCP)

Test Chamber and Stimulus Presentation

Monkeys were transferred from their home cages to the test chamber prior to each testing session. Training and testing took place in a custom chamber (23″ × 27″ × 28.5″) that contained a 15″ touch-sensitive video monitor and a reinforcement hopper. The test chamber was housed in a sound-attenuating booth equipped with a white-noise generator.

Color photographs were used as the stimuli to be learned and/or remembered for each task. Photographs were chosen because they are easier to discriminate than colors or geometric forms and because they are essentially unlimited in supply and content. Each photograph, which measured 1.5″ × 1.5″,

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could be displayed in any of the 16 positions defined by a 4 × 4 matrix. The photographs were selected from a library of approximately 2500 digital images of natural and human-made objects (eg, animals, people, scenery, flowers, automobiles, bridges). No assumptions were made as to what was perceived in the photographs.[33,34] A transparent Lexan template was placed between the front wall of the experimental chamber and the touch screen to minimize the likelihood that the monkeys would swipe the screen as they moved from 1 stimulus to another. The template contained sixteen 1.5″ × 2″ cutouts (in a 4 × 4 matrix) that corresponded to the 16 positions on the video monitor at which a stimulus could appear. A Macintosh G3 computer (Apple Computer, Cupertino, CA), using programs written in RealBasic©, controlled all experimental events.

Preliminary Training

The purpose of preliminary training was to familiarize the monkeys with the 3 component cognitive tasks and to stabilize performance. To maximize the reliability of reaction time (RT) data, the monkeys had to initiate each trial by responding to a "start" stimulus. They were rewarded at the end of each correctly completed trial by the delivery of a 190 mg pellet (Noyes®) in a small hopper below the touch-sensitive monitor.

Task 1 (Recall of an Overlearned Stimulus)

Task 1, which required minimal learning, was a retrograde memory task modeling the kind of questions about overlearned information that patients are asked while recovering from ECT (eg, What is your name? What is your birth date?). At the start of training, a fixed target (an arbitrarily selected photograph) was presented on the monitor. Once the monkey responded to the target reliably, other photographs were introduced as distracters and their number was increased gradually until the 15 remaining monitor positions were filled. The target's location was changed randomly from trial to trial, and a new set of distracters was presented on each trial, ensuring that the response was not influenced by the target's position or by particular distracters. Training on Task 1 continued until each monkey responded correctly on at least 80% of the trials in a single session. An example of the displays used in Task 1 is shown in Figure 1A.

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, initially with 1 distracter and, subsequently, with as many 15 distracters. At the start of each session, the only way to identify a new target was by trial and error. To make the task more difficult, new distracters were displayed on each trial and their number varied randomly from 2 to 15. Training continued on Task 2 until each monkey had responded correctly on at least 55% of the trials presented in a single session. An example of the displays used in Task 2 is shown in Figure 1B.

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 3 simultaneously presented photographs. Lists were trained using the simultaneous chaining paradigm.[31,35] 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 on each new list, the monkey had to remember the consequences of incorrect responses as they attempted to execute the sequence. All errors (eg, B, C, A→B→A or A→C) were followed by a brief (2 seconds) time-out during which the screen was dark. Correct responses to items A and B were followed by secondary reinforcement (a brief—0.5 seconds—presentation of a 1000 Hz tone and a black border surrounding the correctly selected item). Food reward was provided only if the monkey responded to all list items in the correct order (A→B→C). Monkeys were trained until they satisfied an accuracy criterion of 65% correctly completed trials during a single session. The probability of responding correctly by chance to all of the items on a new 3-item list was 17%. An example of the displays used in Task 3 is shown in Figure 1C.

Training the Cognitive Battery

Tasks were trained individually in the order of increasing complexity. Training sessions took place 5 days per week, 2 sessions per day. After completion of training on the individual tasks, the monkeys were trained to execute all 3 tasks during the same session (in the order of increasing difficulty: Task 1→Task 2→Task 3), again with 2 sessions/d. During training, the monkeys had to produce a total of 10 correct responses (regardless of the number of trials) on Task 1 before proceeding to Task 2. They also had to respond correctly 10 times on Task 2 before proceeding to Task 3. For Task 3, 2 new lists were introduced at the start of each session. At the start of the second session of the day, a new target was presented on Task 2 and 2 new lists were introduced in Task 3. Task 3 was presented for 30 trials, half of which were devoted to each new list.

After approximately 7 weeks of training on 2 new 3-item lists per day, 2 new lists were introduced during *each* session. The purpose of training 2 new lists during each session was 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.

Performance at Baseline and During Treatment and Recovery

ECS and the sham intervention were compared during 3 testing periods: baseline, treatment intervention, and recovery. During each period, the monkeys were tested twice daily

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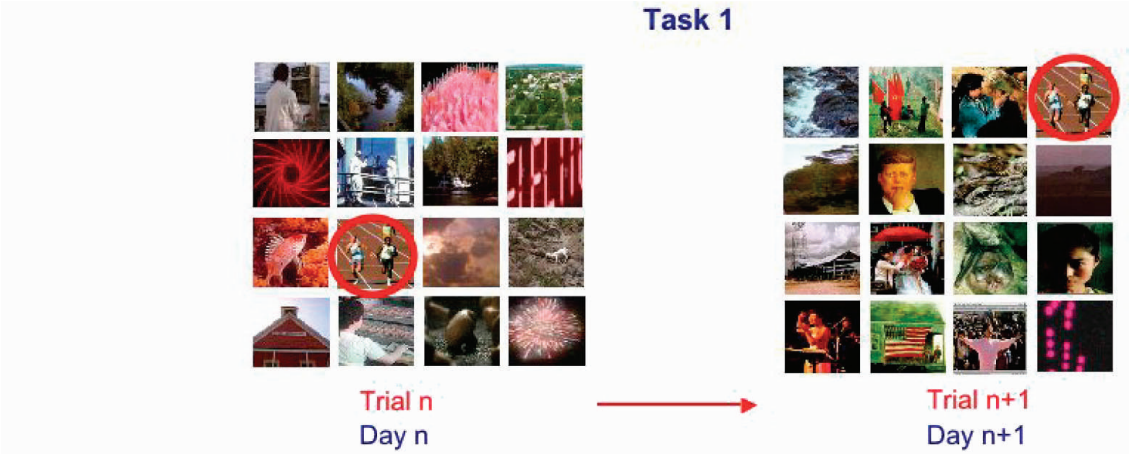

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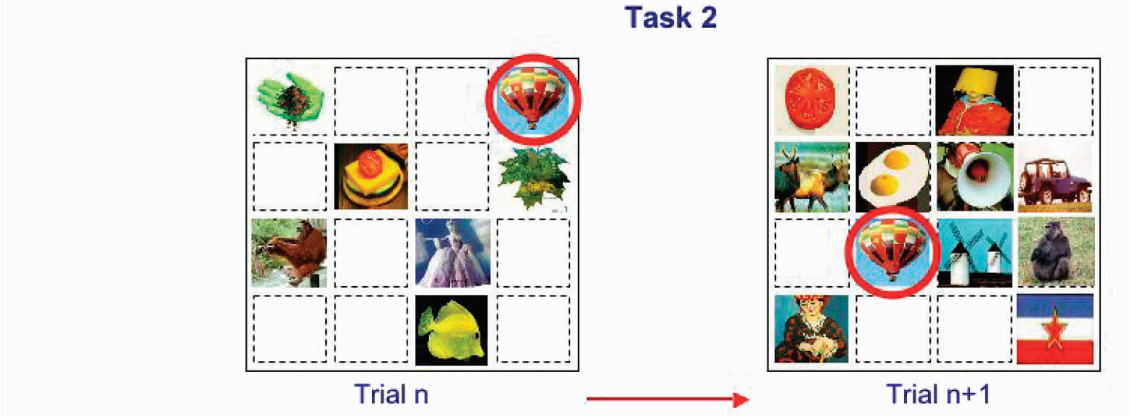

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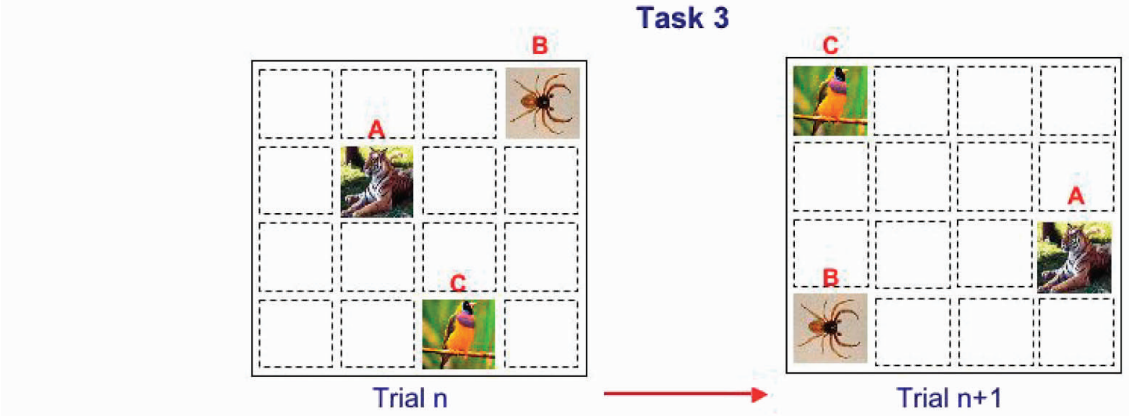

1C.

FIGURE 1. Columbia University Primate Cognitive Profile (CUPCP). The CUPCP is a 3-task cognitive battery for assessing intervention effects in rhesus monkeys. A, The same target photograph (circled in red above) is displayed on each trial throughout the experiment, along with 15 distracters. The position of the target is varied randomly from trial to trial and a new set of distracters is presented on each trial. B, The target photograph used on Task 2 was changed daily. A new set of distracters was presented on each trial. The number of distracters varied randomly between 2 and 15. C, Simultaneous chaining paradigm for training 3-item lists. Each list is composed of 3 photographs that had to be touched in a prescribed order (A→B→C). The configuration of the list items is changed randomly on each trial. Errors result in a time out and a repositioning of stimuli. Correct responses to items A and B were followed by secondary reinforcement. Primary reinforcement was provided only after the subject completes the sequence correctly.

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(5 days per week), with a 2-hour interval between each testing session.

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 4 of 5 consecutive trials. Three list types were presented during Task 3: new, recent, and old. New lists were composed of 3 photographs of arbitrary objects that monkeys had not seen previously. On these lists, the monkeys had to learn the correct sequence de novo. Recent lists were trained 3–5 days prior to the start of the treatment intervention; old lists, 4–5 weeks prior to that point. During testing, the type of list presented on any given trial varied randomly. Forty lists of each type were used (old, recent and new).

The main design features of the experiment are presented in Table 1. For each monkey there were 5 experimental testing periods: baseline (1 week), ECS (2 weeks), post-ECS recovery (2 weeks), sham ECS (anesthesia alone) (2 weeks), and post-sham recovery (2 weeks). One monkey (Puck) received the sham intervention (and its recovery) prior to ECS. This order was reversed for the other monkey (Coltrane).

Sham and ECS Interventions

To prepare the monkeys for transport to the treatment suite, preanesthesia sedation was achieved by administering ketamine (2.5 mg/kg IM), xylazine (0.25 mg/kg IM), and atropine (0.04 mg/kg IM) in the home cage. The anesthetic methods used for the interventions were modeled after ECT in patients. The agents were methohexital (0.5 mg/kg, IV) and succinylcholine (2.5 mg/kg, IV). EKG, blood pressure, end-tidal CO_2, and pulse oximetry were monitored continuously, and 100% oxygen (positive pressure) was given. The occurrence and duration of seizure activity was monitored with 2 EEG channels on a MECTA Spectrum 5000Q (MECTA Corporation, Tualatin, OR) and motor manifestations were monitored using the cuff technique.[1]

Seizure threshold was determined on the first ECS day using the ascending method of limits, titration procedure.[36] ECS was administered with the MECTA Spectrum 5000Q ECT device, modifying the size of adhesive stimulating electrodes (Somatics Corporation, Lake Bluff, IL) to conform to the monkey cranium. The traditional bifrontotemporal electrode placement was used. In the 2 monkeys, initial seizure threshold was 40 mC (Puck) and 16 mC (Coltrane). Electrical dosage at the 9 subsequent ECS sessions (5 per week) was set at a charge 2.5 times (or 150% above) each monkey's seizure threshold. The sham intervention involved the procedures noted above for transport and anesthesia induction, except that the muscle relaxant was not given and there was no electrical stimulation or seizure induction. All other procedures, including oxygenation and physiological monitoring, were identical to those used with ECS.

After each intervention, the 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 (approximately 30 minutes). The 3 tasks were presented in the same order as during the training period.

Statistical Analyses

The major goal of this study was to contrast the 5 experimental conditions (baseline, sham, sham-recovery, ECS, and ECS-recovery) in cognitive performance across and within the 2 monkeys (see Appendix for details of analysis). For Tasks 1 and 2, accuracy and time to task completion were analyzed separately (time to criterion was not determined for the subcomponents of Task 3). Since accuracy data for all tasks were constrained to fall between 0 and 100%, an arc sine transformation was applied prior to statistical analyses. Time to reach criterion was coded in minutes. To achieve normal distributions, these values were subjected to a logarithmic (base 10) transformation.

These analyses relied on repeated measures, longitudinal mixed models (LMM), which used animal (Coltrane versus Puck), session type (first versus second of the day), and experimental condition (5 levels: baseline, sham, sham-recovery, ECS, and ECS-recovery) as fully factorial fixed effects. Day of testing (coded 1–10) was a covariate and other than the term for animal, all interactions of the fixed effects with day of testing were tested. The subject (random) effect for the repeated measures factor of experimental condition was the day of testing (within animal). When significant interactions were obtained involving animal, the same LMM analysis was conducted separately for each monkey. In the text and figures, the reported least-square means and standard errors (SEs) are derived from the LMMs.

RESULTS

The average performance of each monkey for each of the 3 tasks is presented in Figures 2 to 4. The recovery conditions were not included in these figures to simplify the presen-

TABLE 1. Design of Intervention Schedule

Week	1	2	3	4	5	6	7	8	9
Coltrane	Baseline	ECS I	ECS II	Recovery I	Recovery II	Sham I	Sham II	Recovery III	Recovery IV
Puck	Baseline	Sham I	Sham II	Recovery I	Recovery II	ECS I	ECS II	Recovery III	Recovery IV

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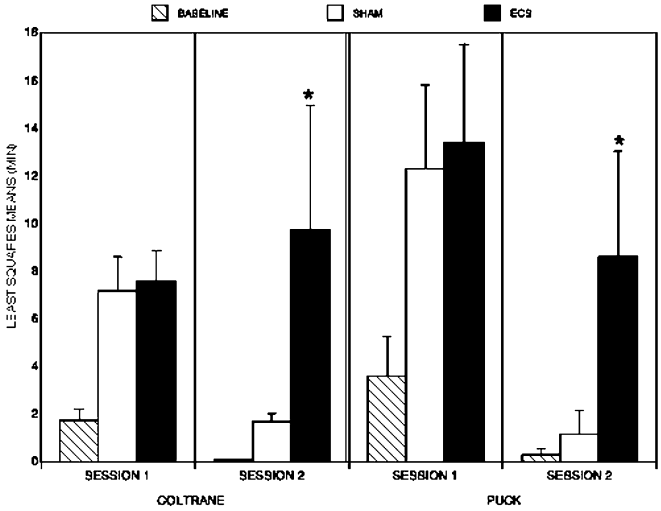

FIGURE 2. Time to reach criterion on Task 2 of the CUPCP. The number of minutes post intervention required to achieve the accuracy criterion for Task 2 (the learning of a new variable item among a background of distracters) is shown for both subjects (Coltrane and Puck). ECS (black bars) resulted in slower performance than sham (white bars) in both animals. Although both ECS and sham slowed performance immediately after intervention (Session 1), the effects of ECS persisted during Session 2 whereas the effects of anesthesia-alone sham were no longer apparent (*$P \leq 0.06$).

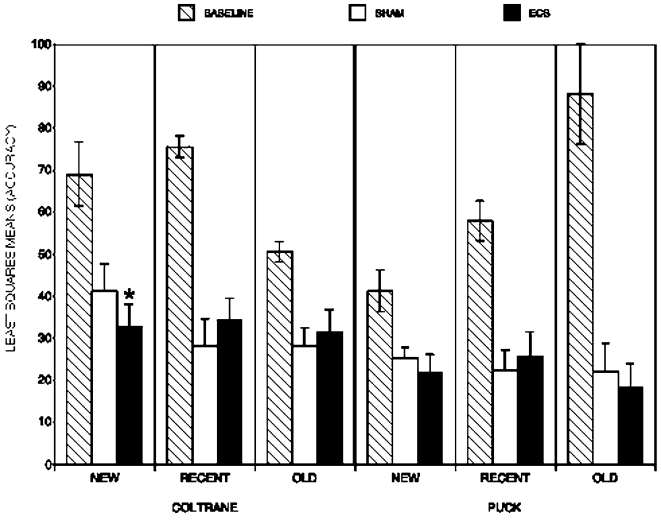

FIGURE 3. Three-item list accuracy immediately after Intervention (Session 1). The accuracy of 3-item list performance during Session 1 (initiated immediately upon recovery from anesthesia) is shown for both subjects. Results for newly acquired lists, recently learned lists, and old lists are presented separately. Both ECS and sham impaired performance on 3-item lists to a comparable degree. With the exception of Coltrane's new list performance (*$P < 0.05$), differences between ECS and sham were minimal at this time point, possibly due to the confound of lingering effects of intramuscular sedative agents.

tation and to highlight the significant findings of most interest. Session One refers to the testing occasion immediately following the sham or ECS intervention or first session of the day in the case of baseline or recovery periods. Session Two is the second session of the day, starting 2 hours after completion of Session One.

Task 1

Accuracy

The mixed model applied to the accuracy scores of the 2 animals yielded main effects of animal ($F_{1,34}$ = 12.18 $P = 0.001$) and session type ($F_{1,34} = 28.41$, $P < 0.0001$). There were also significant interactions between animal and experimental condition ($F_{4,108}$ = 3.60, $P < 0.009$), and a marginal interaction between animal and session type ($F_{1,34}$ = 3.98, $P = 0.05$). There was a trend for the main effect of the covariate, day of testing, ($F_{1,34}$ = 3.94, $P < 0.06$) and a significant interaction between this covariate and experimental condition ($F_{4,108}$= 3.43, P = 0.01). Examination of beta estimates and least-square means indicated that, across all conditions, Coltrane (mean ± SE: 75.9% ± 3.0) had inferior performance compared with Puck (84.8% ± 3.1). There was a large improvement in accuracy in Session Two (93.6% ± 3.8) relative to Session One (67.1% ± 3.8). The interactions involving animal indicated that the effects of the experimental conditions differed for the 2 monkeys, and subsequent analyses were conducted separately for each animal.

The LMM analysis restricted to the Task 1 data for Coltrane yielded 4 effects: main effects of session type ($F_{1,16}$ =

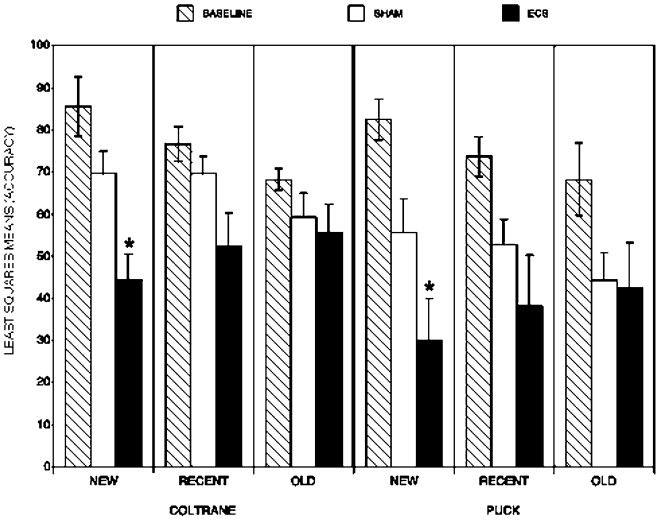

FIGURE 4. Three-item list accuracy 2 hours after intervention (Session 2). The accuracy of 3-item list performance during Session 2 (initiated 2 hours after session 1) is shown. ECS impaired accuracy for newly learned lists relative to sham for both subjects (*$P < 0.05$).

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4.75, $P < 0.05$), condition ($F_{4,52} = 2.91$, $P < 0.04$), and the covariate (day of testing), ($F_{1,16} = 9.74$, $P < 0.007$), and an interaction between experimental condition and the covariate ($F_{4,52} = 5.00$, $P < 0.002$). Coltrane performed significantly more accurately in Session Two (92.8% ± 5.3) than Session One (67.29% ± 5.3). Post-hoc comparisons of least squares adjusted means indicated that the main effect of experimental condition was due to better performance at baseline than in each of the remaining 4 conditions (all P values ≤ 0.05). In particular, accuracy on the days of ECS did not differ from that on sham days ($P = 0.30$). The interaction between the covariate and experimental condition was due to deterioration in performance with additional days of testing in all conditions other than baseline.

The LMM analysis restricted to the Task 1 data for Puck yielded 2 effects: a main effect of session type ($F_{1,16} = 35.28$, $P < 0.0001$) and an interaction between the covariate and experimental condition ($F_{4,48} = 2.91$, $P = 0.03$). There was also a trend for an interaction between session type and experimental condition ($F_{4,48} = 2.12$, $P = 0.09$). This monkey also had markedly superior performance in Session Two (95.1% ± 4.5) relative to Session One (68.5% ± 4.5). Compared with each of the 4 other experimental conditions, performance was significantly more impaired following ECS (all P values ≤ 0.01). The interaction between session and type and condition was due to a greater increase in accuracy from Session 1 to Session 2 on days of ECS compared with all other conditions. The interaction between experimental condition and day of testing was also attributable to the ECS intervention. With increasing exposure to ECS, accuracy on Task 1 decreased (beta = −5.17, SE = 7.24), an effect not seen with any of the other conditions.

Time to Criterion

The mixed model applied to the time to criterion measure for the 2 animals yielded robust main effects of session type ($F_{1,34} = 40.33$, $P < 0.0001$) and condition ($F_{4,108} = 3.48$, $P = 0.01$). There were also significant 2-way interactions between animal and experimental condition ($F_{4,108} = 19.93$, $P < 0.0001$), session type, and condition ($F_{4,108} = 3.54$, $P < 0.01$) and between condition and the covariate ($F_{4,108} = 3.55$, $P < 0.01$). Additionally, a 3-way interaction was significant among animal, session type, and condition ($F_{4,108} = 8.01$, $P < 0.0001$).

Across the animals, there was a large reduction in the time to complete Task 1 in Session Two (0.97 minutes ± 1.3) relative to Session One (5.1 minutes ± 1.3). The main effect of condition resulted from ECS producing the longest Task 1 completion times as compared with the other 4 conditions (10.0 minutes ± 1.06). An interaction between session type and condition was due to a significant decrease in the time to complete Task 1 from Session One (15.5 minutes ± 1.5) to Session Two (4.6 minutes ± 1.5) that only occurred in the ECS condition. The interaction between experimental condition and day of testing was also attributable to the ECS intervention. With increasing exposure to this condition, time to complete Task 1 increased (beta = 1.19, SE = 2.05).

The interactions involving animal indicated that the effects of the experimental conditions differed for the 2 monkeys. The mixed model analysis restricted to the Task 1 data for Coltrane only yielded one effect: a main effect of session type ($F_{1,16} = 24.31$, $P = 0.0002$). Task completion was faster during Session Two (0.15 minutes ± 0.67) compared with Session One (2.8 minutes ± 0.67).

The analysis of the Task 1 time data for Puck yielded 4 effects: main effects of session type ($F_{1,16} = 21.67$, $P = 0.0003$), experimental condition ($F_{4,48} = 4.13$, $P = 0.006$), and interactions between session type and condition ($F_{4,48} = 5.46$, $P = 0.001$), and the covariate and the condition ($F_{4,48} = 4.6$, $P = 0.0032$). This monkey performed markedly faster in Session Two (1.77 minutes ± 2.36) relative to Session One (7.52 minutes ± 2.36). Additionally, Puck performed significantly slower in the ECS condition as compared with each of the other 4 conditions (all P values < 0.05). An interaction between session type and condition was due to a significant decrease in the time to complete Task 1 from Session One (29.57 minutes ± 2.92) to Session Two (8.91 minutes ± 2.93) that only existed in the ECS condition. The interaction between experimental condition and day of testing was also attributable to the ECS intervention. With increased exposure to this condition, the time required to complete Task 1 increased (beta = 2.55, SE = 3.81).

Summary

Both monkeys had markedly higher levels of accuracy and faster completion times during Session Two than Session One. Coltrane (the younger monkey) performed less accurately on Task 1 than Puck. Coltrane's accuracy was highest during baseline training and the decrements in accuracy resulting from the ECS and sham interventions treatments were nearly equivalent. By contrast, Puck showed an expected pattern of results. For both accuracy and time to completion, ECS was associated with greater deficits than with any of the 4 remaining conditions. This differentiation was most marked for Session One, close in time to the administration of the ECS or sham interventions, and the improvement in performance from Session One to Session Two was greatest for the ECS condition. Consistent with this pattern, both Puck's accuracy and time to task completion showed increasing deficits over the course of ECS administration, an effect not seen in the other conditions.

Task 2

Accuracy

The LMM applied to the accuracy scores of the 2 animals yielded main effects of animal ($F_{1,34} = 11.01$ $P = 0.002$)

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and session type ($F_{1,34}$ = 7.40, P = 0.01). There was also a significant interaction between animal and session type ($F_{1,34}$ = 8.06, P = 0.008). Across all conditions, Coltrane (51.0% ± 3.7) had inferior performance compared with Puck (59.1% ± 3.7). There was a large improvement in accuracy in Session Two (62.8% ± 4.6) relative to Session One (47.3% ± 4.6). The interactions indicated that the effects of the experimental conditions differed for the 2 monkeys.

The LMM on the Task 2 accuracy data for Coltrane yielded 2 effects: a main effect of session type ($F_{1,16}$ = 4.67, $P < 0.05$). The main effect of session was due to better performance in Session One (55.6% ± 5.9) than Session Two (51.9% ± 5.9).

The analysis of the Task 2 accuracy data for Puck yielded one marginal effect: a trend toward a main effect of session type ($F_{1,16}$ = 3.64, P = 0.07). This monkey had superior performance in Session Two (75.4% ± 6.7) relative to Session One (41.8% ± 6.6).

Time to Criterion

The LMM applied to the time to criterion data for the 2 animals yielded a main effect of session type ($F_{1,34}$ = 4.27, $P < 0.05$). There was also a trend for a main effect of experimental condition ($F_{4,108}$= 4.27, P = 0.056). The time needed to complete the Task 2 in Session Two (2.9 minutes ± 1.4) was shorter than in Session One (6.1 minutes ± 1.4). The marginal main effect of condition resulted from ECS producing the longest Task 2 completion times (9.8 minutes ± 1.12) as compared with the other 4 conditions (all P values ≤ 0.005). There was no main effect or interactions involving animal. Both animals had longer times for task completion during ECS than the other 4 intervention periods (Coltrane: all P's ≤ 0.06; Puck: all P's ≤ 0.02).

Summary

As with Task 1, Coltrane's accuracy on Task 2 was lower than Puck's. Curiously, the effects of session type were opposite for the 2 monkeys. Coltrane was slightly, but significantly, more accurate during Session One; Puck was considerably more accurate during Session Two. Time to satisfy the Task 2 performance criterion was more sensitive in distinguishing the experimental conditions than accuracy, and the effects were seen in both animals. Across all conditions, time to task completion was faster in Session Two than Session One. For both monkeys, the time needed to satisfy the Task 2 criterion was longest following ECS compared with the 4 other conditions.

Task 3

New List Accuracy

The LMM applied to the accuracy scores of the 2 animals yielded main effects of animal ($F_{1,34}$ = 8.74, P = 0.006), session type ($F_{1,34}$ = 5.4, $P < 0.03$) and experimental condition ($F_{4,109}$= 2.62, P = 0.04). Coltrane (57.1% ± 3.1) had superior performance on new lists compared with Puck (46.8% ± 3.1). There was a large improvement in accuracy in Session Two (61.4% ± 3.8) relative to Session One (42.5% ± 3.8). The main effect of condition was largely attributable to the ECS (32.27% ± 2.99), which resulted in significantly lower accuracy as compared with the 4 other conditions (all P values < 0.05).

Recent List Accuracy

The LMM applied to the accuracy scores of the 2 animals yielded main effects of animal ($F_{1,34}$ = 6.49, $P < 0.02$) and session type ($F_{1,34}$ = 11.08, P = 0.002). Coltrane (56.2% ± 3.2) had superior performance on recent lists compared with Puck (47.0% ± 3.2). As with new lists, accuracy was superior in Session Two (59.9% ± 3.9) relative to Session One (43.3% ± 3.9). There were no effects involving experimental condition.

Old List Accuracy

One observation for Session One performance for Puck during the baseline condition was deleted due to doubtful validity. The LMM applied to the remaining accuracy scores of the 2 animals yielded main effects of session type ($F_{1,34}$ = 7.55, $P < 0.01$) and experimental condition ($F_{1,34}$ = 3.28, P = 0.01). There were also a significant interaction between animal and experimental condition ($F_{4,108}$ = 3.67, $P < 0.008$). There was a substantial improvement in accuracy in Session Two (56.1% ± 3.9) compared with Session One (44.7% ± 4.7). Comparisons of least-square adjusted means indicated that the ECS and sham intervention both resulted in greater impairments than the remaining 3 conditions (all P values < 0.05), but did not differ from each other. The interaction involving animal was due to the fact that this pattern of greater impairment with ECS and sham was seen with both animals, but was more accentuated with Puck. The LLM analyses conducted within each animal supported this interpretation.

Summary

A differential effect of ECS relative to the 4 other conditions was only observed in the accuracy scores for new lists. A differential deficit on this task is compatible with a great anterograde memory deficit following ECS. By contrast, the recent and old list tasks were intended to assay RA and its temporal gradient. There was no effect of experimental condition for recent list performance and there were equivalent deficits for ECS and sham with old lists. In contrast to Tasks 1 and 2, Coltrane had superior performance to Puck on new and recent lists, with no difference on old lists. As was the case for Task 1 and 2, performance on all 3 list types in the second session of the day was markedly superior to that in the first session.

DISCUSSION

This study represents the first attempt to develop a cognitive battery for monkeys to model explicitly ECT's cognitive

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effects, including its impact on orientation, learning, and anterograde and retrograde amnesia. The findings of this study, although preliminary, demonstrate that key higher order cognitive effects of ECT can be modeled in non-human primates. Such a model allows for evaluating variation in treatment parameters with respect to cognitive outcome, and provides a means for determining the neurobiological bases of these effects using experimental techniques that could not be applied to patients. While considerable work is needed to increase the sensitivity of the cognitive battery, especially regarding anesthetic regimen and task design, the findings obtained from the 2 subjects in this pilot experiment demonstrate feasibility.

The bulk of the literature regarding the effects of ECS on cognition has used rodent models.[35] Almost all of these studies have examined memory for aversive conditioning and related types of learning. For example, the most common paradigm has been passive avoidance (measured as the latency to enter a region where the subject previously received a foot-shock). The generalizability of these studies to clinical ECT has been criticized due to potential effects of ECT on aspects of the task that are not related to memory (eg, motor activity and analgesia).[23] In contrast, it is established in the human that ECT has no or little effect on non-declarative memory, as would be the case with any type of classic conditioning.[9,10,12] Rather, the amnestic effects of ECT are most pronounced for material that is consciously recalled, eg, verbal list learning, memory for autobiographical events. Although we make no claims that the learning and memory in the battery used here in monkeys involves conscious recollection, it is notable that learning was shaped by appetitive reinforcement, required multiple presentations to enhance and stabilize performance, and involved "recollection" of complex stimuli, such as the order of arbitrary visual stimuli. In these respects, we believe that the model is the closest attempt to date to emulate the essential elements of human declarative learning and memory.

The cognitive battery composed 3 tasks of increasing difficulty: an orientation task (long-term or automatic memory), a variable target task (anterograde learning and memory), and a serial learning and memory task (anterograde and retrograde memory). Accuracy and time-to-completion on each of these tasks was assessed under 5 experimental conditions: baseline, sham and ECS interventions, and the recovery phase following sham and ECS. The greatest relative deficits with ECS were seen with the most difficult task, recalling a newly learned 3-item list. This deficit represents anterograde amnesia for information acquired soon after ECS. As predicted, newly learned material was more affected than older material. For simpler tasks (recalling a newly learned single item and recalling an over-learned single item), speed of completion was more sensitive to differences among the experimental conditions than accuracy. In the case of Task 1, time to reach accuracy criterion increased with successive ECS sessions.

In several cases, the monkeys differed in the impact of the interventions. This may be a function of the ages and/or the cognitive histories of each animal. For example, Coltrane, who was 4 years younger than Puck and experimentally naive, performed significantly less well than Puck on Tasks 1 and 2. Coltrane, however, performed markedly better on new and recent lists as compared with Puck. Furthermore, Puck, who was the older and larger animal, was particularly impaired during the ECS and sham interventions. This effect was most apparent during the 3-item list learning: the most complex task of the Cognitive Battery. This may be a consequence of the fact that older monkeys retain anesthetic agents for longer durations than younger monkeys because of their greater body mass. It is likewise possible that older animals are more susceptible to the adverse cognitive effects of anesthesia and/or seizures.

Nonhuman primate studies necessitate small samples. In addition, the twice-daily training sessions over a period of months would not be feasible on a large scale. Therefore, these individual differences present a challenge for any research focusing on higher cognitive function. Another methodological concern is that although there were only 2 monkeys, the dataset involves many repeated observations over multiple conditions but with some missing observations. A traditional statistical approach could not be applied to data of this nature. The use of the random effects model was a powerful statistical strategy to maximize use of all of the information collected on these subjects, and to support inferential comparison. Restricting claims to findings that were especially robust, and particularly to those that were manifested by both monkeys, guards against results being driven by the behavior of only 1 animal. It should also be noted that there is considerable individual variability in cognitive effects of ECT. It is noteworthy that there have been few attempts to determine what features of patients predict greater or lesser amnestic effects after ECT.[17] A non-human primate model in which individual differences in cognitive effects are expressed may provide a means for determining their neurobiological basis.

Our analysis of subjects' performances also revealed the influence of 2 unanticipated confounding variables: motivation and the after effects of anesthesia. Session 2 performance was almost invariably better than during Session 1. Ordinarily, for sham and ECS, better performance during Session 2 would be interpreted as recovery of function given increasing time since the intervention. However, this same effect was obtained on days with no intervention (baseline, sham recovery, and ECS recovery). An important difference between Sessions 1 and 2 across all conditions was the time since the monkeys were last fed. The monkeys are fed once a day, after they complete all of the testing sessions for that day. The longer interval between last feeding in Session 2 relative to Session 1 may have led to stronger motivation to perform to obtain food. Given this, persistent effects of ECS on performance during Session 2 are all the more impressive.

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The monkeys received the same anesthetic regimen as patients receiving ECT with 1 exception: the use of preanesthesia sedation. An IM injection of ketamine and xylazine was used to sedate monkeys for transport from their home cage to the procedure room. In other work, we have examined the cognitive effects of different anesthetic regimens, and noted that cognitive performance was considerably better without IM sedation (data not shown). Thus, it appears that the IM agents resulted in prolonged sedative effects that may have obscured differences between the ECS and sham conditions, especially during Session 1.

The cognitive effects of ECT are the major factor limiting its use. It is noteworthy that in preclinical research, largely with rodents, numerous compounds have been identified that reduce or block the cognitive effects of ECS.[23] With few exceptions, when these agents have been brought to the human, they have been tested in dementia models with few attempts to examine the more appropriate analog to the context in which they were originally identified–ECS in primates or human ECT. Furthermore, it is noted that the paradigms used to develop promemory drugs have been enfeebled and constrained by the use of rodent models. The development of a battery to assess higher order cognitive functions in nonhuman primates sensitive to the effects of ECS should allow both for investigation of new methods to reduce the cognitive side effects of ECT and to determine their neurobiological bases.

APPENDIX

Nonhuman primate cognitive research necessarily involves intensive training and testing of a small number of animals, each of which may contribute multiple repeated observations. Furthermore, as in clinical contexts, missing data can occur due to intercurrent illness, equipment malfunction, or lack of engagement in the task. Accordingly, a large set of repeated observations obtained from a small number of subjects, with missing data, negate the use of traditional statistical approaches based on general linear models (GLM), eg, a repeated measures analyses of variance or covariance, where independence of observations is required and missing data result in subject loss. Indeed, GLMs assume that observations are uncorrelated and have constant variance. In contrast, the values for any subject within any condition are usually substantially correlated and variance can change systematically with increasing exposure to an intervention or practice on a task.

Given these limitations, a novel statistical strategy was applied in the analyses of each of the 3 tasks. These analyses relied on repeated measures, longitudinal mixed models (LMM), sometimes also referred to as random regression models.[37,38] LMM had the advantage of using all the data from all subjects in every condition. GLMs rely on method of moments (least squares) to contrast between- and within-subject factors, and must drop subjects with missing data. LMM, using likelihood-based estimation methods, use all available data, and produces more accurate estimates of error variance and, therefore, more accurate tests of differences between least square means.[38] Most critically, LMM does not assume or require that error or variance components are independently and identically distributed. Rather, use of LMM is predicated on establishing adequate fit to the covariance structures in the data and LMM incorporate the structures and relationships among the errors and variance components into the model. Especially when the repeated observations on a subject are treated as a random effect, multiple observations on the same individuals can serve as dependent measures. One example of the utility of LMM is that the baseline condition in this experiment involved only 5 days of testing (1 week), while each of the remaining 4 conditions took 10 days of testing (2 weeks). LMM allowed for comparison across the 5 conditions using all the available data, and further, for the determination of whether cognitive performance changed linearly as a function of day of testing across and within experimental conditions.

The analyses were conducted using the PROC MIXED procedure of SAS®.[39] Parameters were estimated with the iterative maximum likelihood method. The same model, including specification of covariance structure and fixed and random effects, was applied to the data for each of the 3 tasks so that comparison of the findings across tasks would be not be complicated by use of different models. Due to the constraints of the PROC MIXED procedure in SAS, there was only 1 blocking factor for repeated measures, experimental condition. Session type (first versus second) was treated as a between-subjects factor. This constraint should have reduced power in detecting effects attributable to this factor.

Compound symmetry (CS) was the covariance structure modeled throughout. After establishing convergence, the fit of this structure was evaluated in every analysis by examining the value of Akaike's Information Criterion[40] and Schwartz's Bayesian Criterion.[41] When applied to the accuracy data for Task 1, CS produced a better fit and required fewer parameters than an unstructured covariance (UN) model. Applying a first order autoregressive covariance structure [AR(1)] did not improve the fit over CS.

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