ARTICLE
Use of the Pyrithiamine-Induced Thiamine Deficient Animal Model of Korskoff's Syndrome for Exploratory Research Activities in Undergraduate Physiological Psychology

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Undergraduate neuroscience laboratory activities frequently focus on exercises that build student's wet/dry laboratory skills, foster critical thinking, and provide opportunities for hands-on experiences. Such activities are, without a doubt, extremely important, but sometimes fall short of modeling actual research and often lack the 'unknown' hypothetical nature accompanying empirical studies. In this article we report a series of research activities using an animal model of Korsakoff's syndrome in a Physiological Psychology course. The activities involve testing hypotheses regarding performance of animals with experimentally-induced Korsakoff's syndrome and the effectiveness of glucose as a memory-enhancer in this model. Students were given a set of 24 articles for use in answering a series of laboratory report questions regarding the activities. At the conclusion of the course, students were asked to complete a questionnaire designed to assess the effectiveness of the laboratory activities. Results of the laboratory exercises indicated that locomotor activity, environmental habituation, and anxiety were unaffected in the Korsakoff condition, and glucose had no effect. Results of performance in the T-maze indicated that Korsakoff animals had significantly fewer spontaneous alternations than controls, but Korsakoff animals given glucose did not reveal this difference. Results of the student assessments indicated that the activities were considered educational, challenging, and more interesting than standard laboratory activities designed to reproduce reliable phenomena.

Key words: laboratory activity, behavioral neuroscience, physiological psychology, Korsakoff's syndrome, animal model, thiamine deficiency, rats, exploratory research, environmental habituation, glucose, locomotor activity, spatial working memory

Laboratory research activities are an integral part of most neuroscience courses. These experiences provide students with many opportunities to acquire new laboratory skills and techniques, observe real neuroscientific phenomena, and reinforce knowledge gained through lectures and readings. Such activities serve a very important role in the training and education of undergraduate students, especially for those who may endeavor to become future neuroscientists. Given that neuroscience is a highly equipment intensive discipline, faculty are often limited by the available equipment or facilities at their respective institutions. As a result, many laboratory activities may involve modest deviations from the faculty's own research or may simply replicate reliable findings in the field. Often these activities fall short of their potential to engage students in valid exploration of scientific hypotheses which may harbor the potential of making contributions to the scientific community. In other words, as neuroscience instructors we should consider the possibility that laboratory activities may be valuable opportunities to conduct small scale studies or pilot research of scientific value. In doing so, this may afford us an opportunity to truly engage students in realistic neuroscience activities for which "expected" or "easily predicted" outcomes are more elusive. In this paper we report the results of a series of novel laboratory exercises using this approach with an animal model of Korsakoff's syndrome in a Physiological Psychology class.

Animal models often make useful and interesting laboratory activities, as students seem to make a stronger connection and show greater interest when the research topic is more familiar or tangible to a human condition. Korsakoff's syndrome is a well-known memory disorder that is associated with long-term alcohol use (Butters, 1985; Victor et al., 1989; Kopelman, 1995). Individuals with Korsakoff's syndrome suffer from retrograde and anterograde amnesia which may extend to both explicit and implicit memory (Carlesimo, 1994; d'Ydewalle & Van Damme, 2007). The disorder is believed to result from a thiamine deficiency, and neuroscience research has led to the development of an animal model involving thiamine-deficient food and injections of pyrithiamine, a thiamine antagonist (pyrithiame-induced thiamine deficiency or PTD). Despite the severity of this disorder, relatively little research has been done examining the animal model, making it an ideal topic for novel laboratory exercises. A quick search of PsychINFO using "Korsakoff" and "animal model" in any field reveals only 16 hits, while MEDLINE reports only five hits.

Glucose-induced memory modulation is a well-established phenomenon in the neuroscience literature (Messier and Gagnon, 1996). A wide variety of studies have demonstrated memory-facilitating effects of glucose when administered immediately after learning (consolidation) or shortly prior to testing (retrieval) (Flint, 2002), and cognitive neuroscience laboratory activities have been previously reported for use with human participants (Flint, 2004). Research on glucose has also revealed common dose-response relationships indicating that moderate doses between 100 and 250 mg/kg of

glucose are optimal for memory enhancement (Flint and Riccio, 1996, 1999). Despite the effectiveness of glucose as a memory modulator, the mechanisms of glucose-induced memory enhancement remain unclear.

The purpose of this study was to provide a unique means through which students could examine behavioral indices of anxiety, locomotor activity, environmental habituation, and spatial working memory in laboratory rats. The activities involved novel research hypotheses about the effects of PTD on these behavioral measures, and the potential impact of glucose on the performance of PTD animals. The effectiveness of these activities as a laboratory exercise was assessed using an anonymous questionnaire at the conclusion of the course.

MATERIALS AND METHODS

Human Participants. Twenty-one students enrolled in Physiological Psychology at The College of Saint Rose participated in these activities. All but one student returned the questionnaires at the end of the course. This group of students had a mean age of 20.65 years (SE=.35) and was comprised of two males and 19 females, nine of whom were seniors, eight juniors, and three sophomores. The racial/ethnic composition of the class included 18 white/ caucasion, one black/African American, and one Latino/ Hispanic student. Students received information regarding the allergenic risks associated with exposure to rodents and received training on proper care and handling of animals prior to the laboratory activities. Permission from The College of Saint Rose Institutional Review Board for research with human participants was obtained prior to the completion of the research questionnaires.

Rats. Twenty-four male Sprague-Dawley rats were purchased from Hilltop Lab Animals, Inc. (Scottdale, PA). Animals were approximately 90 days old at the onset of the PTD treatment, were housed in groups in large Plexiglas cages, and were maintained on a 12:12 hour reversed light:dark cycle. Behavioral tests were conducted during the light phase between 6:30 and 10:00 PM. The animal colony room was kept at 72°±2° C with an average relative humidity of 68%. Food and water were available *ad libitum* throughout the experiment. However, during the thiamine deficiency protocol, animals assigned to the PTD condition were given thiamine deficient chow. Following the thiamine deficiency protocol, animals were given approximately five weeks to recover. Animals were handled prior to the onset of behavioral tests. Protocols were approved by The College of Saint Rose Institutional Animal Care and Use Committee prior to the onset of the study. Two animals died on the last day of the thiamine deficiency protocol, presumably as a result of the treatment, and one animal died for unknown reasons before the onset of behavioral testing. Mean bodyweight at the onset of the PTD treatment was 415.42 g (SD=24.71).

Thiamine Deficiency Procedure. In order to establish the PTD animal model of Korsakoff's syndrome for the laboratory activities, 18 animals were placed on a thiamine deficient diet (Harlan Teklad diet 85027, Madison, WI) and were given a daily intraperitoneal injection of pyrithiamine (0.25 mg/ml at 1 ml/kg bodyweight; Sigma Chemical, St. Louis, MO) for 14 days. Injections were administered by research assistants at the same time each day. On day 14, animals were monitored every two hours for 24 hours for signs of seizure activity. As soon as signs of seizure activity were evident, or once 24 hours had elapsed, animals were administered a 100 mg/kg intraperitoneal injection of thiamine (100 mg/ml at 1 ml/kg bodyweight; Sigma Chemical, St. Louis, MO) and the thiamine-deficient diet was replaced with standard laboratory rodent chow (Harlan Teklad diet 2014, Madison, WI). Animals in the control condition (n=6) were maintained during the 14-day period on standard chow and received daily intraperitoneal injections of saline (1 ml/kg). Animals were given approximately five weeks to recover following this treatment before beginning the behavioral tests which took place across a three-week period.

Rat Behavioral Testing Materials. Animals were tested in both an open field activity box and in a T-maze. The open field chamber was constructed of black Plexiglas measuring 61 cm by 61 cm with 46 cm high walls. The animal tracking software AnyMaze (Stoelting, Wood Dale, IL) was used to monitor activity. The open field was divided into two zones, a center zone measuring 30.5 cm by 30.5 cm and a surround zone containing the region outside of the center zone. Total distance traveled, overall average speed, number of entries into the center zone, and time spent in the center zone were recorded as dependent measures.

The base of the T-maze was constructed of 1.3 cm wood sealed with multiple coats of black paint. Sides of the T-maze were constructed of clear Plexiglas measuring 30.5 cm high. Arms of the T-maze measured 14 cm wide and 38.7 cm long. The common-space where the three alleys joined measured 14 cm by 14 cm and was marked with white tape. A black/white security camera was mounted above the T-maze and connected to a video projection system allowing students to observe each animal's behavior. Standard laboratory timers were used to record the duration of the tests. Dependent measures for the T-maze included the number of arm entries and the order of arm entries. From these measures, the number of alternations and percent spontaneous alternation could be determined as described in the results.

Open Field Activity Procedure. Locomotor activity was assessed on two separate days, seven days apart. Using this test, students examined locomotor activity, environmental habituation as indicated by decreases in behavioral indices from day one to day two, and anxiety measured by entries and time in the center zone (Hinojosa et al., 2006). Animals were placed into the apparatus and allowed to freely explore the environment for five minutes. The apparatus was cleaned with disinfectant and dried after each animal was tested. Twenty-five (±2) minutes prior to the test on day two, animals were administered a subcutaneous injection of glucose (or saline as a control) in the nape of the neck in an attempt to modulate memory

retrieval (Flint and Riccio, 1997; Harrod et al., 2001; Flint et al., 2007). Students were shown how to administer injections which were given by volunteers from the class and the instructor. Animals in the non-PTD control group (n=6) were given an injection of saline (1 ml/kg) and animals in the PTD group were divided into two conditions so that one group received an injection of saline (n=7) while the other received an injection of 100 mg/kg of glucose (n=8; Sigma).

T-Maze Procedure. Spatial working memory was tested using the T-maze. Twenty-five (±2) minutes prior to testing, animals received a subcutaneous injection of either saline or 100 mg/kg of glucose. Non-PTD control animals (n=6) were given saline. For the PTD animals, those that received glucose during the open field test were now administered saline (n=8) and those who had been given saline before now received 100 mg/kg of glucose (n=7). Injections were administered by the instructor so that students could remain blind to each animal's treatment/condition as they coded the behavior. Animals were placed into the maze facing the end of one alley and were given five minutes to freely explore their environment. Student researchers viewed each animal's behavior and independently recorded the order of arm entries during the test. The apparatus was cleaned with disinfectant and dried between testing of each animal.

Korsakoff's Syndrome Laboratory Report. Students were required to complete a laboratory report project on Korsakoff's syndrome. A set of 24 readings (see Appendix) were made available to help them with this assignment. The project consisted of the following five questions for which students were to compose two-page responses.

1. Describe the neuroantomical similarities and differences between humans with Korsakoff's Syndrome and non-human animal research on Korsakoff's Syndrome.
2. Describe the similarities and differences in memory impairments between human and non-human animals with Korsakoff's Syndrome.
3. From both a behavioral (i.e., different types of memory tests) and a neuroscientific (i.e., neurotransmitter and neuroanatomy) perspective, what evidence suggests that glucose might attenuate the memory loss associated with Korsakoff's syndrome?
4. Describe the results of our laboratory exercises on locomotor activity and habituation. Is there evidence that Korsakoff animals are different from control animals? Is there evidence that glucose had an effect? How do these results compare/contrast to the results in the supplemental readings? Are there any alternative interpretations that you can provide for the results that we obtained?
5. Describe the results of our laboratory exercise on working memory using the T-maze. Is there evidence that Korsakoff animals are different from control animals? Is there evidence that glucose had an effect? How do these results compare/contrast to the results in the supplemental readings? Are there any alternative interpretations that you can provide for the results that we obtained?

Human Participant Assessment. Year in school, age, sex, major, and race/ethnicity were obtained with a demographic questionnaire. A Korsakoff's Laboratory Assessment Questionnaire asked students to rate statements (see Table 1) using a five-point Likert scale ranging from 1=Disagree Strongly to 5=Agree Strongly. Two open response questions were provided; "What recommendations, if any, do you have regarding the laboratory exercises with rats?" and "What recommendations, if any, do you have regarding the Korsakoff's Syndrome laboratory report project?" Students were instructed to place the completed questionnaires into the appropriately labeled box. Consent to participate was inferred by the return of the completed questionnaires. One student failed to return the questionnaires. All questionnaires were completed anonymously.

RESULTS

Data for each of the laboratory activities was entered into SPSS. Data analysis was conducted in class, even though some students had not yet completed the department's research methods sequence of courses. The data analysis activities were viewed as an opportunity to discuss research design, statistical testing, and interpretation of statistical analyses from the SPSS output files.

Bodyweight. Analysis of the animal's bodyweight during the 14-day PTD protocol revealed a significant main effect of day [Huynh-Feldt Correction $F(4.43,97.47)=34.89$, $p<.001$] and a significant group by day interaction [Huynh-Feldt Correction $F(4.43,97.47)=43.94$, $p<.001$]. Figure 1 shows that the bodyweight of the PTD animals began to decline by day 8, while the bodyweight of the saline animals remained relatively stable throughout the treatment.

Open Field Activity. The dependent measures from the open field activity tests were used to assess locomotor activity, environmental habituation, and anxiety. A series of 3 (group) by 2 (day) mixed analysis of variance tests (ANOVAs) were conducted for each of the dependent measures (see Table 2). Results did not reveal any significant effects for group or any group by day interactions. There was a significant effect of day for each of the dependent measures, where performance decreased from day 1 to day 2 of testing. These results provide evidence of environmental habituation. Findings that there were no group differences for the center zone measures suggest that PTD did not have an impact on this measure of anxiety. Center zone measures in the open field have been used as indicators of anxiety because animals with higher levels of anxiety will tend to venture into the center zone less frequently than animals with lower levels of anxiety.

T-Maze.

Data were examined for the number of arm entries, the

Korsakoff's Laboratory Assessment Questionnaire	Mean	SE	t	p
Q1. I believe that non-human animal research is important in the field of Physiological Psychology.	4.30	.13	10.18	.000
Q2. My attitude toward non-human animal research has improved as a result of the Korsakoff laboratory activities.	4.00	.18	5.63	.000
Q3. The Korsakoff laboratory report was challenging.	4.60	.11	14.24	.000
Q4. The Korsakoff laboratory report required me to think critically about Korsakoff's syndrome.	4.60	.13	11.96	.000
Q5. The Korsakoff laboratory report was an educational assignment.	4.35	.13	10.28	.000
Q6. Hands-on laboratory activities with rats helped me learn the material more effectively than just reading about it.	4.20	.20	6.00	.000
Q7. Conducting laboratory activities for which the outcome was unknown was more interesting than if the results had been easily predicted.	4.20	.14	8.72	.000
Q8. As a result of these activities, I have increased confidence in my ability to understand biopsychological research using rats.	3.65	.20	3.32	.004
Q9. The readings on Korsakoff's syndrome improved my understanding of this disorder.	4.25	.20	6.14	.000
Q10. The readings on glucose and memory improved my understanding of these topics.	4.20	.19	6.44	.000
Q11. Overall I think the Korsakoff laboratory activities were educational.	4.30	.11	12.37	.000
Q12. Overall I think the Korsakoff laboratory activities were enjoyable.	3.79	.14	5.46	.000
Q13. Realistic laboratory activities for which the outcomes are unknown should be used in future sections of this course.	4.21	.16	7.40	.000

Table 1. Korsakoff Laboratory Activity Assessment Questionnaire statements with mean responses, standard error of the mean, *t* value from one-sample *t*-tests, and *p* values. Responses were given on a 5-pt Likert scale where 5=strongly agree. Comparison test value for one-sample *t*-tests was set at 3 (neutral score on the Likert scale).

	Day 1		Day 2	
	Mean	SD	Mean	SD
Total Distance Traveled (m)				
Control/Saline	9.29	(2.42)	9.30	(3.91)
PTD/Saline	9.58	(4.01)	5.39	(2.29)
PTD/Glucose	11.26	(2.89)	8.62	(4.77)
Overall Average Speed (m/s)				
Control/Saline	.031	(.008)	.031	(.013)
PTD/Saline	.032	(.013)	.018	(.008)
PTD/Glucose	.034	(.009)	.028	(.016)
Time in Center Zone (s)				
Control/Saline	2.83	(2.71)	0.00	(0.00)
PTD/Saline	5.57	(6.81)	0.17	(0.45)
PTD/Glucose	2.21	(2.52)	0.00	(0.00)
Entries into Center Zone				
Control/Saline	1.00	(0.63)	0.00	(0.00)
PTD/Saline	1.43	(1.51)	0.29	(0.76)
PTD/Glucose	0.88	(0.84)	0.00	(0.00)

Table 2. Mean and standard deviation for each of the three groups for the four dependent measures on days 1 and 2 in the open field.

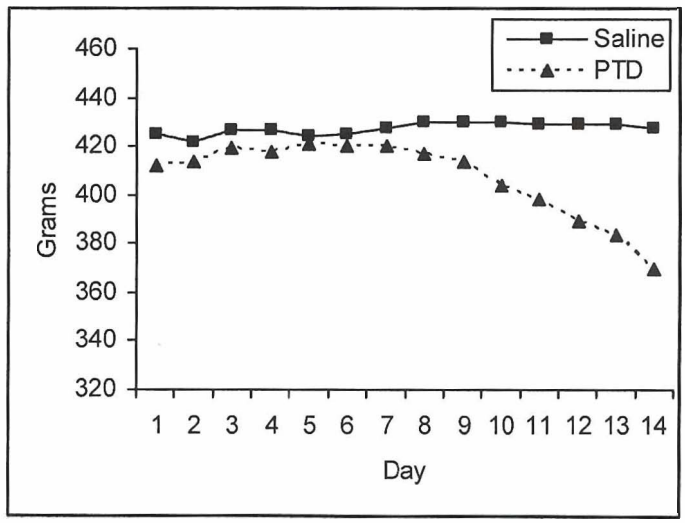

Figure 1. Mean bodyweight for animals in the saline and PTD groups for each of the 14 injection days of the PTD protocol.

number of alternations (entry into three different alleys in three consecutive entries), and the percent spontaneous alternation {[alternations/(# of arm entries – 2)]}. Animals with fewer than five arm entries were excluded from the percent spontaneous alternation calculation. A one-way ANOVA was performed on each of these dependent measures and revealed a statistically significant effect for the number of alternations [$F(2,15)=5.46$, $p<.05$; see Figure 2], but not for number of arm entries [$F(2,20)=2.09$, $p>.05$] or the percent spontaneous alternation [$F(2,14)=0.32$, $p>.05$]. Post-hoc pairwise comparisons of the number of alternations were performed using Tukey's

HSD. Results indicated that the saline control animals had significantly more alternations than the PTD/saline group indicating an impairment in the PTD group. However, the PTD/glucose group did not differ from either the saline control or the PTD/saline groups. The lack of difference between the PTD/glucose and saline control group suggests that glucose may have attenuated some of the alternation deficits, but the lack of difference between the PTD/glucose and PTD/saline implies that this effect was not sufficient to attenuate the impairment completely.

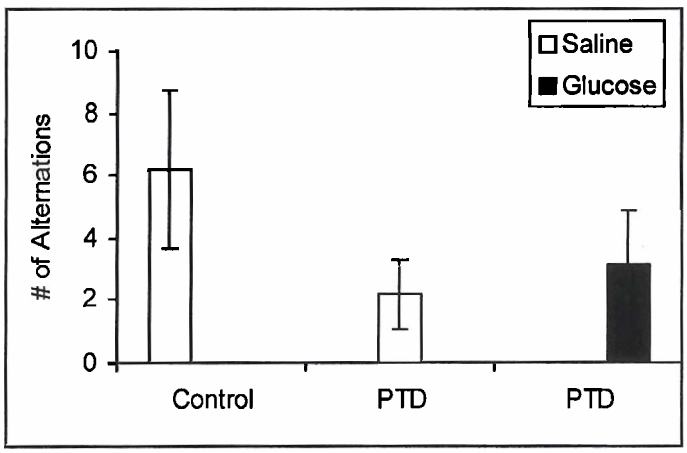

Figure 2. Mean number of alternations in the T-maze for the control and PTD groups. Error bars represent the standard error of the mean.

Student Assessments.

Twenty students completed and returned the demographic and Korsakoff Laboratory Assessment Questionnaires. One student did not complete the last page of the Korsakoff Laboratory Assessment Questionnaire containing statements 12, 13, and the free/open response questions. One-sample *t*-tests were conducted for each statement with the comparison test value for the analyses set at 3, the neutral value on the 5-point Likert scale. Results showed that each question was rated significantly above the neutral test value, indicating that students found the laboratory exercises enjoyable, effective, and educational. Question 8 received the lowest mean rating among the questions, which may suggest that added instruction or discussion on the use of animal models would enhance the student's confidence with respect to understanding biopsychological research with rats. Twelve students responded to one or both open response questions. Comments varied considerably, but recommendations regarding the lab exercises with rats included greater student involvement and more time reviewing the statistical analyses. Recommendations regarding the laboratory report project included increasing the structure of the assignment, dedicating class time for discussion, and review of the assigned articles.

DISCUSSION

The goal of this project was to create a laboratory exercise in Physiological Psychology that would provide unique and realistic opportunities for scientific discovery, in addition to facilitating critical thinking skills and providing hands-on laboratory experience in behavioral neuroscience. The results of the student assessments of these activities suggest that we achieved our goals. Students had high ratings for statements reporting that the laboratory activities facilitated critical thinking (Q4), were useful/ educational (Q5, Q6, Q9, Q10, & Q11), and that the unique nature of exploring unknown hypotheses was preferred over other activities (Q7 & Q13). The authors recognize that it would likely be very difficult, and is probably unrealistic, to expect faculty to incorporate activities such as these into every aspect of a laboratory course. However, these results suggest that efforts to develop laboratory exercises that allow students to ask and explore truly unique hypotheses with real scientific merit would be worthwhile on occasion. Exercises such as these might also provide opportunities for faculty to conduct small scale studies or pilot research which may serve as the foundation for more thorough studies at a later point in time. These activities may also serve as a catalyst for students with potential interests in the neurosciences, and may lead to an increase in student involvement in the faculty member's programmatic research.

The results of our laboratory activities indicated that PTD animals did not have any statistically reliable differences from controls on measures of anxiety, locomotor activity, or environmental habituation as measured in the open field apparatus. All animals, regardless of their treatment condition, showed evidence of environmental habituation from day 1 to day 2. However, performance in the T-maze indicated that animals in the PTD group that received saline shortly prior to the test were impaired in comparison to non-PTD controls, and that glucose administration shortly prior to testing may have attenuated some of this deficit in PTD animals. These novel findings provide some preliminary evidence that glucose may modulate memory deficits in animals with PTD, as it does for other disorders such as Alzheimer's disease (Craft, Zallen, & Baker, 1992; Craft et al., 1993), Down syndrome (Manning et al., 1998), and schizophrenia (Newcomer et al., 1999) in humans.

The activities that were selected for the present exercises were based, in part, on the availability of equipment, scheduled class times, and laboratory funds. A number of other potential activities with this model remain. For example, had the Physiological Psychology course been scheduled for two or three meetings per week as opposed to one meeting per week, we might have effectively utilized the Morris Water Maze, completed operant conditioning, or examined extinction. There are also opportunities for teaching basic histology by removing the brains and having students section, stain, and examine the neural tissue for lesions in the thalamic and hypothalamic nuclei.

Research activities such as these are not without their drawbacks. In the case of the activities reported here, the cost of purchasing and maintaining the animals, thiamine-deficient food, pyrithiamne, and thiamine came close to exhausting the laboratory fees for the course ($50/student),

and thus might be prohibitive at some institutions. However, by creating an animal model we were able to repeatedly study the same animals, increasing the number of laboratory activities and decreasing the financial impact of establishing the model. Realistic neuroscience laboratory activities utilizing existing supplies and equipment would likely have a smaller financial impact. Another potential drawback is associated with the protocol necessary to develop the animal model. The PTD model required 14 consecutive days of injections, with 24-hr monitoring on the last day. This required a substantial amount of planning, organization, and time, which might necessitate the involvement of research assistants or work/ study students. Finally, as with all empirical research, there is always the possibility of finding little of interest, or at least the failure to find statistically significant results. While there are certainly opportunities for education under such circumstances, this potential outcome should always be anticipated if activities such as these are developed.

In conclusion, we have provided what we believe is a nice example of a novel research activity used effectively in a Physiological Psychology course. Given the availability of funds and equipment, these activities could easily be replicated at other undergraduate institutions; however, we would encourage the use of this conceptual approach to developing activities as much as the use of these actual activities. Faculty should consider the flexibility provided through the use of animal models, and be encouraged to develop realistic neuroscience activities with the potential of making novel discoveries of potential scientific value.

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APPENDIX

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