Postnatal Growth, Development and Behavioral/Functional Evaluation in Crl:CD®(SD)IGS BR Rats

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INTRODUCTION:

Within the last decade, new guidelines for assessing developmental neurotoxicity have been issued by the U.S. EPA. A primary purpose of these guidelines is to evaluate the potential of a chemical substance or a mixture (test substance) to induce deleterious functional and/or morphological defects in the developing nervous system of offspring exposed to the substance *in utero* and during lactation through the ingestion of milk. The evaluations performed include observations to detect delays in growth and/or development; gross neurological and behavioral abnormalities; determination of motor activity; response to auditory startle; assessment of learning; neuropathological evaluations and brain weights (1). As these guidelines are fairly recent and relatively few studies have been conducted to date, there is an apparent lack of historical control values for the various parameters measured. The data presented in this document were gathered from six nearly identical developmental neurotoxicity studies performed in the United States. A schematic for a typical developmental neurotoxicity study is presented in Figure 1.

PURPOSE:

The purpose of this compilation is to offer the study director or reviewing toxicologist a range of some reported control values of the various growth, developmental, behavioral and functional parameters measured in standard developmental neurotoxicity studies. In addition, it is our hope that this document will serve as the groundwork for a more detailed and encompassing future document. We encourage any who collect these types of data in their testing facility to contribute to this future document. As always, the strength and usefulness of this type of publication depend on the number of contributors, their comments and their suggestions for improvement. Please contact Mary Giknis at *mlagiknis@att.net* with your helpful suggestions and for instructions on how you can contribute data to a future document.

COMMON STUDY PARAMETERS:

The developmental neurotoxicity studies presented here were conducted between 1997 and 1999. All studies used Crl:CD® (SD)IGS BR rats from four different Charles River Laboratories production sites: Kingston, NY; Raleigh, NC; Portage, MI; or St. Constant, Quebec, Canada as the parental (F0) generation. Female rats were mated at the testing facility.

The rats in these studies were from control groups of dietary or gavage studies. Some groups were untreated while others received 0.5% aqueous methylcellulose, 1% aqueous methylcellulose or deionized water as the vehicle control.

Rats in these studies were housed appropriately as outlined in the *Guide for the Care and Use of Laboratory Animals*; National Academy Press, 1996 (2) and had free access to water. All animals were fed a diet of Purina Mills Lab Chow. The animal rooms were generally maintained at average temperatures of 72 +/- 5 degrees Fahrenheit with an average relative humidity of 30 – 70%. A 12hr/12hr light/dark cycle was employed in all studies. Since these studies were conducted at different times, there was some variation in environmental conditions. However, the overall environmental conditions were not considered by those performing the studies to have had any effect on the quality and integrity of the studies.

DATA PRESENTED:

Postnatal Body weights: Body weight data were obtained from six developmental neurotoxicity studies. The data are presented by sex as mean body weight +/- SD for the specified postnatal day (day of birth = postnatal day 0). On postnatal day 4, litters were culled to 8 pups/litter with an equal number of male and female pups, whenever possible. Pups were randomly selected for culling. These growth data are presented in Table 1 and shown graphically in Figure 2.

Developmental Landmarks: Data on two developmental landmarks, preputial separation for males and vaginal opening for females, are presented in Table 2. These data were derived from six developmental neurotoxicity studies. Male pups were examined for evidence of preputial separation beginning on or about PD 38 and then daily until the criterion was met. To perform the evaluation, the male pup is held in the supine position and gentle pressure is applied to the animal's prepuce. Preputial separation is said to have occurred when the prepuce is observed to completely retract from the head of the penis. Female pups were examined for signs of vaginal opening on or about PD 27 and then daily until the criterion was met. Vaginal opening was defined in these studies as any visible break in the membranous sheath covering the vaginal orifice.

Learning and Memory Evaluations: Tests of associative learning and memory are conducted at the approximate time of weaning and again at around PD 60. The tests included here; Water Maze and Passive Avoidance, are designed to assess an animal's ability to learn (acquisition) across several sessions or learning trials and also to measure both long and short term memory.

Water Maze Data

For the data reported here, one male and one female (whenever possible) from each litter were evaluated for overt coordination, swimming ability, learning and memory in a water filled M-maze. Evaluations were initiated on PD 58-62 in a modified M-maze filled to a depth of approximately nine inches with 21° +/- 1° C water.

On each test trial, the rat was placed at the base of the M-maze stem farthest from the two arms, designated as the starting position, and required to swim to one of the two goals of the M-maze before being removed from the water. On the first trial, the rats were required to enter both arms of the maze before being removed from the water. The initial arm chosen on trial 1 was designated as the incorrect goal during the remaining trials. Any rat failing to choose the correct goal within 60 seconds was guided to the correct goal choice and removed from the water. Each rat was required to successfully complete 5 consecutive trials before the test session was terminated. The trials were separated by a 15 second interval and each session was limited to no more than 15 trials. The amount of time to choose the correct goal (latency) and the number of errors (incorrect turns in the maze) was recorded for each trial. Each rat was tested twice under like conditions. A one week interval separated the test sessions. Water Maze data from six developmental neurotoxicology studies are presented in Table 3.

Passive Avoidance Test

In the Passive Avoidance Test data presented here, learning, short-term memory retention, long-term memory retention and hyperactivity were tested on one male and one female per litter (whenever possible) beginning on PD 22 through 24. The apparatus used in these tests was a two-compartment chamber with hinged Plexiglas® lids and a sliding door separating the compartments. One compartment was equipped with a bright light and Plexiglas® floor while the other compartment was equipped with a grid floor to which a 1 second pulse of mild electric current (1 mA) was delivered. At the beginning of each trial, the rat was placed in the "bright" compartment, the sliding door opened and the light turned on. The rat was allowed to explore the apparatus until it entered the dark compartment. Immediately after the rat entered the dark compartment, the sliding door closed, the light turned off and a brief pulse of current was delivered to the grid floor. The rat was then removed and placed in a holding cage for 30 seconds, and then the trial was repeated. The trials were repeated until the rat remained on in the bright compartment for 60 seconds on two consecutive trials, the criterion for learning, or until 15 trials had been completed. The latency to enter the dark compartment or a maximum time of 60 seconds was recorded for each trial. Each rat was tested twice under like conditions. A one week interval separated the tests. Passive Avoidance data obtained from six developmental neurotoxicology studies are presented for males and females in Table 4.

Auditory Startle Habituation Test: An auditory startle habituation test is typically performed on offspring at the approximate time of weaning and at PD 60. For the studies reported here, one male and one female rat per litter (whenever possible) were evaluated in a sound attenuated chamber on PD 22 and again on PD 60 +/-2 for their reactivity to auditory stimuli and habituation of responses with repeated presentation of the stimuli. The rats were tested in sets of four. Each rat was placed inside a small cage situated above a platform containing a force transducer in its base. A microcomputer sampled the output of the force transducer and controlled the test session. Initially the rats were allowed a five minute adaptation period with ten "blank" trials given during last minute to sample the baseline force in the absence of a stimulus. The rats were then presented with 30 msec, 120 dB bursts of noise at 10 second intervals for 50 trials, followed by ten "blank" trials. The response magnitude was calculated by subtracting the average response of the baseline trials from the peak amplitude of each response. Auditory startle data for males and females from 5 studies is presented in Table 5 and shown graphically in Figure 3.

Motor Activity Assessment: Motor activity is monitored at specific time points by an automated activity recording device capable of detecting both increases and decreases in activity. In the 4 studies presented in this document, motor activity was monitored in one male and one female (whenever possible) per litter using a passive infrared sensor mounted outside a stainless-steel cage (40.6 X 25.4 X 17.8 cm). The tests were performed on PD 13, 17, 21 and 61 +/- 2. During the pre-weaning sessions, each pup was tested on Plexiglas® flooring. Each test session was one hour in duration with the number of movements and time spent in movement tabulated at each ten-minute interval. The data are presented by sex in Tables 6 and 7 and depicted graphically in Figures 4 and 5.

Neuropathological Evaluations: According to U.S. EPA guidelines (OPPTS 870.6300) neuropathological evaluations should be conducted on rats on PD11 and on adult rats at study termination. These evaluations should include a qualitative analysis and semiquantitative analysis as well as simple morphometrics. The data presented here are limited to the qualitative morphological measurements of the PD 11 pup and the adult rat brain. The brains of both PD 11 and adult rats were weighed and gross anterior-posterior lengths of the cerebrum and cerebellum were recorded. Linear microscopic measurements of the frontal cortex, parietal cortex, hippocampal gyrus, corpus callosum and cerebellum were performed and recorded.

Brain Weights and Morphometry of PD 11 and Adult Rat Brains

The F1 pups selected for PD 11 brain evaluation were euthanized by carbon dioxide asphyxiation. The heads were severed between the first two cervical vertebrae, the calvaria removed and the entire head immersed in 10% neutral buffered formalin. Adult rats selected for brain evaluation were administered a combination of heparin and sodium pentobarbital and perfused *in situ* with 10% neutral buffered formalin, the calvaria were then removed and the heads immersed in 10% neutral buffered formalin. After at least 48 hours fixation, both the PD 11 and adult brains were dissected free, leaving the olfactory bulbs intact and attached to the brain. The brains were then weighed and a Vernier caliper was used to obtain two linear measurements from each intact brain, the anterior-posterior length of the cerebrum extending from the anterior pole to the posterior pole, exclusive of olfactory bulbs and anterior-posterior length of the cerebellum, extending from the anterior edge of the cortex to the posterior pole. Additional measurements, seven for PD 11 brains and six for adult brains, were taken on coronal histological sections using a calibrated ocular micrometer and are outlined below and illustrated in Figures 5-7 for PD 11 brains and Figures 8 and 9 for adult brains. The gross anterior-posterior measurements of the cerebrum and cerebellar cortex are expressed in millimeters (mm), whereas the micrometric measurements were multiplied by appropriate factors to yield dimensions in micrometers (*u*m). PD 11 and adult brain morphometric data are shown in Tables 8-11.

Thickness of the frontal cortex: A measurement of the dorsal portion of the cerebral cortex within the coronal section passing through the optic chiasm at a magnification of 40X (Figures 6 and 9). [In this and other sections, the optic chiasm was used as the morphologic landmark at histologic trim. In those sections where the optic nerve and chiasm were lost during processing and sectioning, the correct location was confirmed by the presence of the anterior commissure.]

Thickness of the parietal cortex: A measurement of the dorsolateral portion of the cerebral cortex within the coronal section taken through the optic chiasm at a magnification of 40 X (Figures 6 and 9).

Diagonal width (maximum cross sectional width) of the caudate-putamen: A measurement on the coronal section passing through the optic chiasm at a magnification of 20X (Figures 6 and 9).

Thickness of the corpus callosum: The measurement of the corpus callosum was made bilaterally at the level of Layer 2 within the overlying cingulate cortex (but still within the section passing through the optic chiasm). The average of these bilateral measurements was then recorded at a magnification of 100 X (Figures 6 and 9).

Thickness of the hippocampal gyrus: A measurement on the dorsal to lateral portion of the dentate gyrus within the section taken at the level of the hypothalamus. Measurements were taken from the hippocampus on both sides of the brain section at a magnification of 40 X (Figure 7) and the median value recorded.

Height of the cerebellum: A measurement taken at the level of the deep cerebellar nuclei, including lobes 1-6 and extending from the roof of the fourth ventricle to the dorsal surface (maximum height of the cerebellum), at a magnification of 20X (Figures 8 and 10).

Thickness of the external germinal layer of the cerebellum: This measurement was made for PD 11 brains only. As thickness of this layer varies considerably from region to region, multiple areas were measured over the dorsum of the cerebellum and the mean value recorded. Measurements were made at a magnification of 400X (Figure 8).

CALCULATIONS:

In general, simple descriptive statistics were employed. These included the mean, standard deviation and minimum and maximum value observed. In addition, the coefficient of variation and 95% confidence interval were determined for some parameters.

ABBREVIATIONS:

GD = Gestation Day
PD = Postnatal Day
LD = Lactation Day
GD 0 = Day of Vaginal Plug
F0 Generation = Original Parental Animals also commonly called P1 Generation
F1 Generation = First Generation Offspring of the F0 (P1) Generation
M = Male
F = Female
Min. = Minimum
Max. = Maximum
SD = Standard Deviation
C.V. = Coefficient of Variation
95 % Conf. Int. = 95 % Confidence Interval

ACKNOWLEDGMENTS:

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Figure 1: A Schematic of a Neurotoxicity Test

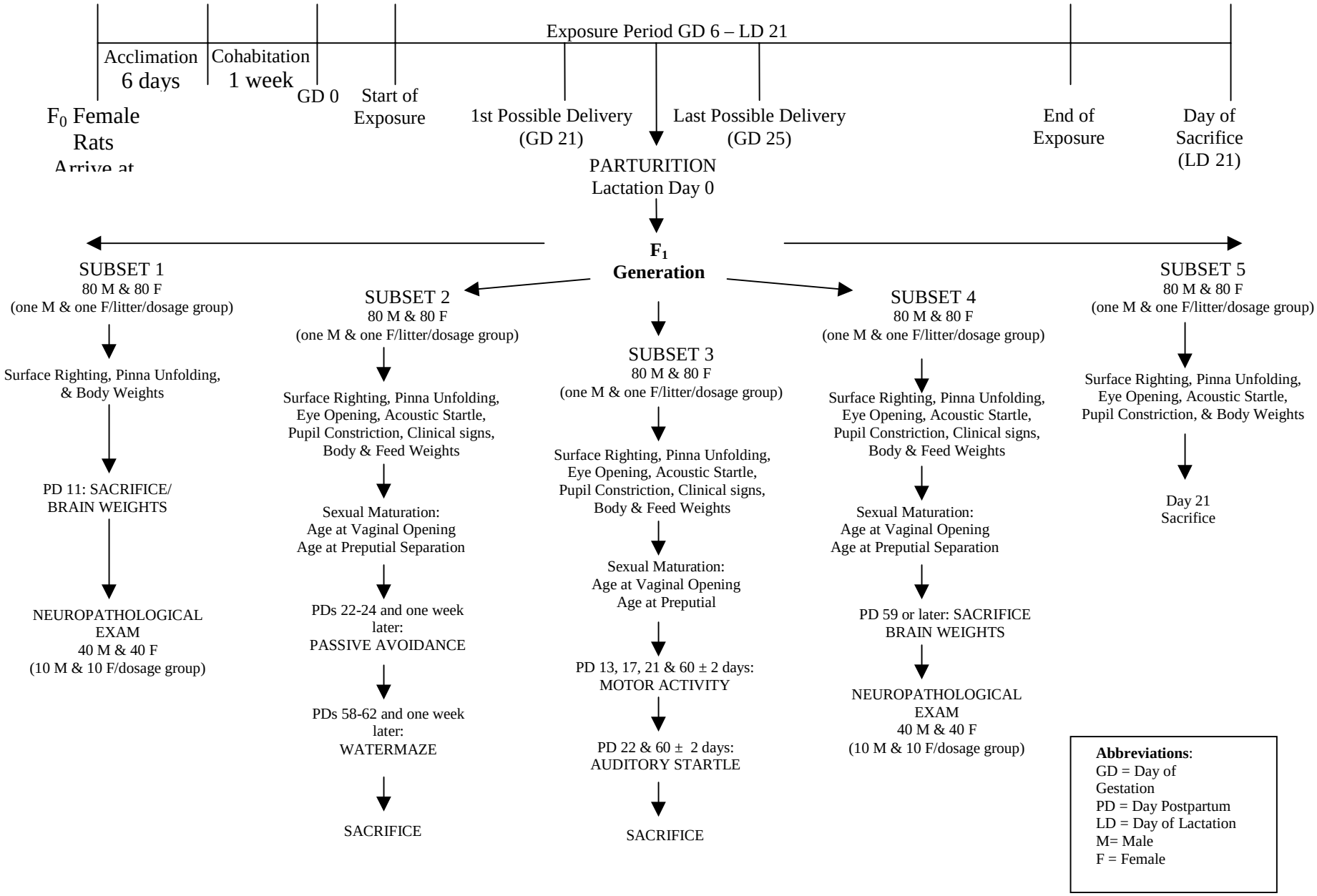


Table 1: Mean Pup Body Weight Data

Males								
Day of Study	**0**	**4 (Precull)**	**4 (Postcull)**	**7**	**11**	**13**	**17**	**21**
Body Weight (g) ± SD	6.7 ± 0.3	9.9 ± 0.7	10.0 ± 0.7	15.6 ± 1.6	23.6 ± 3.1	29.0 ± 4.0	38.1 ± 5.5	51.1 ± 7.2
Females								
Day of Study	**0**	**4 (Precull)**	**4 (Postcull)**	**7**	**11**	**13**	**17**	**21**
Body Weight (g) ± SD	6.3 ± 0.3	9.5 ± 0.7	9.7 ± 0.7	15.0 ± 1.6	22.7 ± 3.0	28.1 ± 3.8	37.0 ± 4.9	49.3 ± 6.3

Figure 2: Male and Female Growth Curves

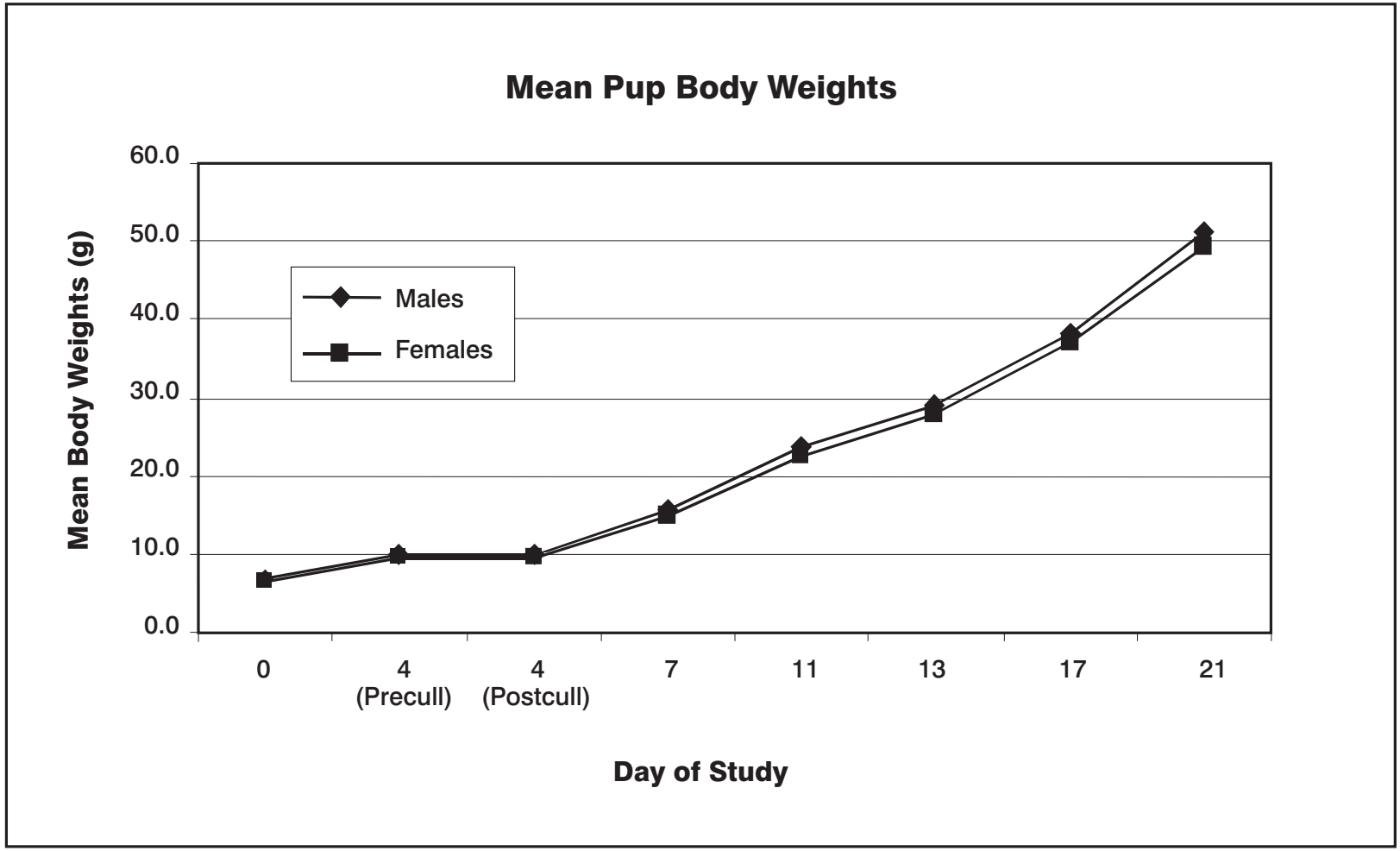


Table 2: Pup Sexual Maturation Data

		Males				Females		
		Mean Day of Preputial Separation				**Mean Day of Vaginal Opening**		
Number of Rats			375				370	
Mean± SD			46.39+ 3.20				32.43+ 1.98	
C.V.			6.9				6.11	
Min., Max.			40.0, 76.0				28.0, 37.0	
95% Conf. Int.			46.07, 46.71				32.23, 32.63	

Table 3: Water Maze Data

		MALES		
	Trials to Criterion	**Errors**	**Latency Trial 1a**	**Latency Trial 2b**
Session 1 (119 rats)				
Mean ± SD	9.18 ± 2.83	0.41 ± 0.21	NA	14.85 ± 9.44
C.V.	30.79	51.16	NA	63.54
Min., Max.	6.0, 15.0	0.17, 1.27	NA	5.0, 60.0
95% Conf. Int.	8.68. 9.69	0.38. 0.45	NA	13.15, 16.54
Session 2 (115 rats)				
Mean ± SD	6.19 ± 2.07	0.10 ± 0.14	10.44 ± 8.53	NA
C.V.	33.41	152.61	81.72	NA
Min., Max.	5.0, 15.0	0.00, 0.50	3.0, 54.0	NA
95% Conf. Int.	5.81, 6.57	0.07, 0.12	8.88, 12.00	NA
		FEMALES		
Session 1 (119 rats)				
Mean ± SD	8.65 ± 2.64	0.40 ± 0.20	NA	14.52 ± 10.10
C.V.	30.54	50.7	NA	69.59
Min., Max.	6.0, 15.0	0.17, 1.46	NA	4.0, 60.0
95% Conf. Int.				
Session 2 (113 rats)				
Mean ± SD	6.83 ± 2.50	0.14 ± 0.17	11.42 ± 8.77	NA
C.V.	36.54	127.91	76.79	NA
Min., Max.	5.0, 15.0	0.00, 0.78	3.0, 52.0	NA
95% Conf. Int.	6.37, 7.29	0.10, 0.17	9.80, 13.03	NA
a. Calculated in Session 2 Only				
b. Calculated in Session 1 Only				

Table 4: Passive Avoidance Data

			MALES	
		Trials to Criterion	**Latency Trial 1**	**Latency Trial 2a**
Session 1 (119 rats)				
	Mean ± SD	4.97 ± 2.32	7.32 ± 5.74	27.23 ± 21.21
	C.V.	46.74	78.36	77.89
	Min.,Max.	3.0, 15.0	1.0, 30.0	2.0, 60.0
	95% Conf. Int.	4.55, 5.38	6.29, 8.35	23.42, 31.04
Session 2 (117 rats)				
	Mean ± SD	3.09 ± 2.02	34.44 ± 22.57	N/A
	C.V.	65.19	65.55	N/A
	Min.,Max.	2.0, 15.0	2.0, 60.0	N/A
	95% Conf. Int.	2.73, 3.46	30.35, 38.53	N/A
			FEMALES	
Session 1 (119 rats)				
	Mean ± SD	4.74 ± 1.65	8.37 ± 7.01	25.07 ± 19.17
	C.V.	34.9	83.7	76.49
	Min.,Max.	3.0, 13.0	1.0, 45.0	1.0, 60.0
	95% Conf. Int.	4.44, 5.04	7.11, 9.63	21.62, 28.51
Session 2 (119 rats)				
	Mean ± SD	3.09 ± 1.78	30.61 ± 23.33	N/A
	C.V.	57.41	76.2	N/A
	Min.,Max.	2.0, 15.0	2.0, 60.0	N/A
	95% Conf. Int.			
a. Calculated in Session 1 Only				

Table 5: Auditory Startle Data

	Block 1	Block 2	Block 3	Block 4	Block 5
		MALES			
Day 22 (97 rats)					
Mean ± SD	17.55 ± 9.83	12.46 ± 9.56	12.57 ± 10.02	12.03 ± 9.05	12.54 ± 9.14
C.V.	56.04	76.66	79.72	75.27	72.87
Min., Max.	2.00, 61.70	0.90, 53.80	(-)5.60, 48.00	(-)5.90, 37.10	(-)4.50, 40.00
95% Conf. Int.	15.59, 19.50	10.56, 14.36	10.58, 14.57	10.23, 13.83	10.72, 14.36
Day 60 ± 2 (98 rats)					
Mean ± SD	80.34 ± 60.60	48.70 ± 47.61	38.36 ± 28.72	33.54 ± 25.11	31.63 ± 22.39
C.V.	75.43	97.75	74.87	74.86	70.79
Min., Max.	8.70, 312.60	(-)6.80, 224.80	(-)5.90, 136.60	(-)13.80, 152.50	(-)5.60, 105.10
95% Conf. Int.	68.34, 92.34	39.28, 58.13	32.68, 44.05	28.57, 38.51	27.19, 36.06
		FEMALES			
Day 22 (97 rats)					
Mean ± SD	18.91 ± 11.41	13.87 ± 9.46	12.75 ± 10.26	12.93 ± 10.95	13.05 ± 11.78
C.V.	60.34	68.17	80.45	84.71	90.3
Min., Max.	2.40, 84.10	(-)0.70, 47.90	0.00. 52.40	(-)3.00, 55.70	(-)0.80, 54.90
95% Conf. Int.	16.640, 21.18	11.99, 15.75	10.71, 14.80	10.75, 15.11	10.70, 15.39
Day 60 ± 2 (98 rats)					
Mean ± SD	46.38 ± 35.38	26.59 ± 24.13	21.17 ± 18.84	15.83 ± 13.28	16.42 ± 16.18
C.V.	76.28	90.74	88.97	83.92	98.58
Min., Max.	2.80, 202.10	(-)4.90, 142.10	(-)4.30, 78.20	(-)6.40, 63.20	(-)9.60. 100.00
95% Conf. Int.	39.38, 53.39	21.81, 31.37	17.44, 24.90	13.20, 18.46	13.21, 19.62

Figure 3: Male and Female Auditory Startle Data

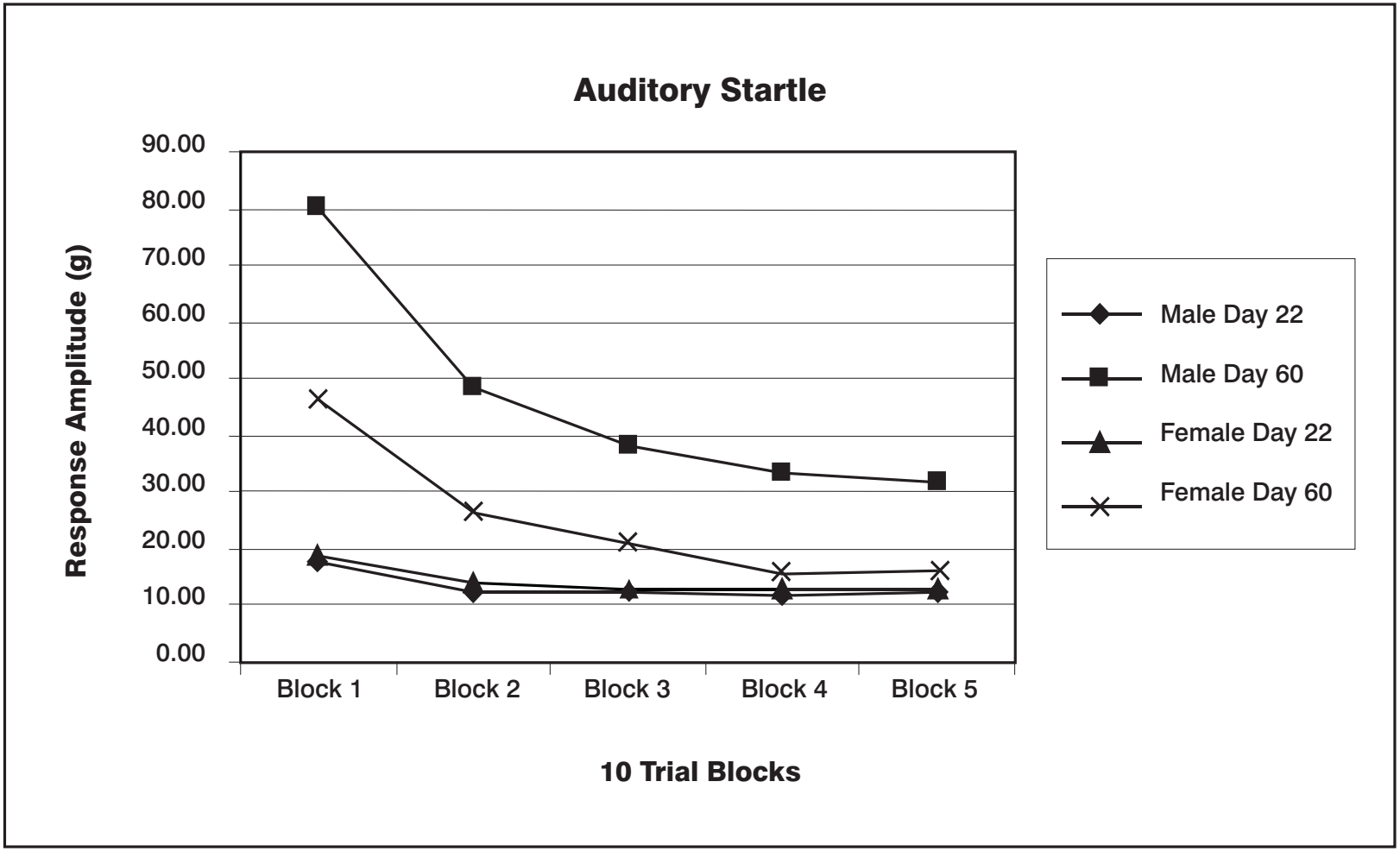


Table 6: Male Motor Activity Data

Day 13 (99 rats)	**Block 1**	**Block 2**	**Block 3**	**Block 4**	**Block 5**	**Block 6**
Mean ± SD	26.54 ± 30.96	32.94 ± 38.56	34.31 ± 38.64	25.97 ± 33.74	20.67 ± 34.68	18.80 ± 29.82
C.V.	116.68	117.07	112.6	129.92	167.79	158.63
Min., Max.	0.0, 154.0	0.0, 157.0	0.0, 158.0	0.0, 165.0	0.0, 148.0	0.0, 135.0
95% Conf. Int.	20.44, 32.63	25.34, 40.54	26.70, 41.92	19.32, 32.62	13.84, 27.50	12.92, 24.67
Day 17 (99 rats)						
Mean ± SD	65.80 ± 45.04	71.79 ± 46.53	65.67 ± 51.65	54.80 ± 51.15	45.96 ± 50.45	39.25 ± 49.10
C.V.	68.45	64.81	78.66	93.34	109.78	125.1
Min., Max.	0.0, 167.0	0.0, 184.0	0.0, 182.0	0.0, 162.0	0.0, 164.0	0.0, 161.0
95% Conf. Int.	59.93, 74.67	62.62, 80.95	55.49, 75.84	44.72, 64.87	36.02, 55.90	29.58, 48.93
Day 21 (99 rats)						
Mean ± SD	91.18 ± 36.82	59.58 ± 44.66	47.64 ± 43.21	45.42 ± 47.22	35.39 ± 45.40	32.54 ± 41.30
C.V.	40.38	74.97	90.72	103.96	128.29	126.93
Min., Max.	1.0, 164.0	0.0, 156.0	0.0, 152.0	0.0, 158.0	0.0, 162.0	0.0, 141.0
95% Conf. Int.	83.93, 98.44	50.78, 68.37	39.12, 56.15	36.12, 54.73	26.45, 44.34	24.40, 40.67
Day 60 ± 2 (98 rats)						
Mean ± SD	134.53 ± 14.34	133.54 ± 17.58	124.54 ± 30.25	113.49 ± 38.78	105.73 ± 46.71	92.05 ± 52.61
C.V.	10.66	13.17	24.29	34.17	44.18	57.15
Min., Max.	96.0, 176.0	47.0, 168.0	7.0, 177.0	0.0, 172.0	0.0, 174.0	0.0, 172.0
95% Conf. Int.	131.69, 137.37	130.06, 137.02	118.55, 130.53	105.81, 121.17	96.49, 114.98	81.64, 102.47

Table 7: Female Motor Activity Data

Day 13 (100 rats)	**Block 1**	**Block 2**	**Block 3**	**Block 4**	**Block 5**	**Block 6**
Mean ± SD	41.80 ± 36.36	43.41 ± 39.08	41.76 ± 41.49	32.14 ± 36.51	28.10 ± 34.10	21.97 ± 32.70
C.V.	86.98	90.04	99.34	113.6	121.34	148.83
Min., Max.	0.0, 172.0	0.0, 158.0	0.0, 130.0	0.0, 155.0	0.0, 133.0	0.0, 174.0
95 % Conf. Int.	34.67, 48.93	35.75, 51.07	33.63, 49.89	24.98, 39.30	21.42, 34.78	15.56, 28.38
Day 17 (100 rats)						
Mean ± SD	77.48 ± 45.77	78.30 ± 50.41	73.64 ± 52.85	63.75 ± 55.08	52.49 ± 56.25	47.01 ± 57.45
C.V.	59.08	64.39	71.76	86.4	107.16	122.2
Min., Max.	0.0, 155.0	0.0, 195.0	0.0, 198.0	0.0, 192.0	0.0, 169.0	0.0, 194.0
95 % Conf. Int.	68.51, 86.45	68.42, 88.18	63.28, 84.00	52.95, 74.55	41.47, 63.51	35.75, 58.27
Day 21 (100 rats)						
Mean ± SD	100.79 ± 34.45	64.03 ± 45.55	47.53 ± 47.97	47.55 ± 45.12	40.30 ± 45.01	36.91 ± 44.74
C.V.	34.18	71.14	100.94	94.88	111.69	121.23
Min., Max.	8.0, 171.0	0.0, 164.0	0.0, 156.0	0.0, 148.0	0.0, 147.0	0.0, 145.0
95 % Conf. Int.	94.04, 107.54	55.10, 72.96	38.13, 56.93	38.71, 56.39	31.48, 49.12	28.14, 45.68
Day 60 ± 2 (100 rats)						
Mean ± SD	133.92 ± 15.52	139.76 ± 17.34	136.89 ± 23.54	124.92 ± 38.00	106.60 ± 54.88	88.30 ± 53.56
C.V.	11.59	12.41	17.2	30.42	51.48	60.66
Min., Max.	97.0, 173.0	64.0, 168.0	41.0, 178.0	3.0, 178.0	0.0, 179.0	0.0, 179.0
95 % Conf. Int.	130.88, 136.96	136.36, 143.16	132.28, 141.50	117.47, 132.37	95.84, 117.36	77.80, 98.80

Figure 4: Male Motor Activity

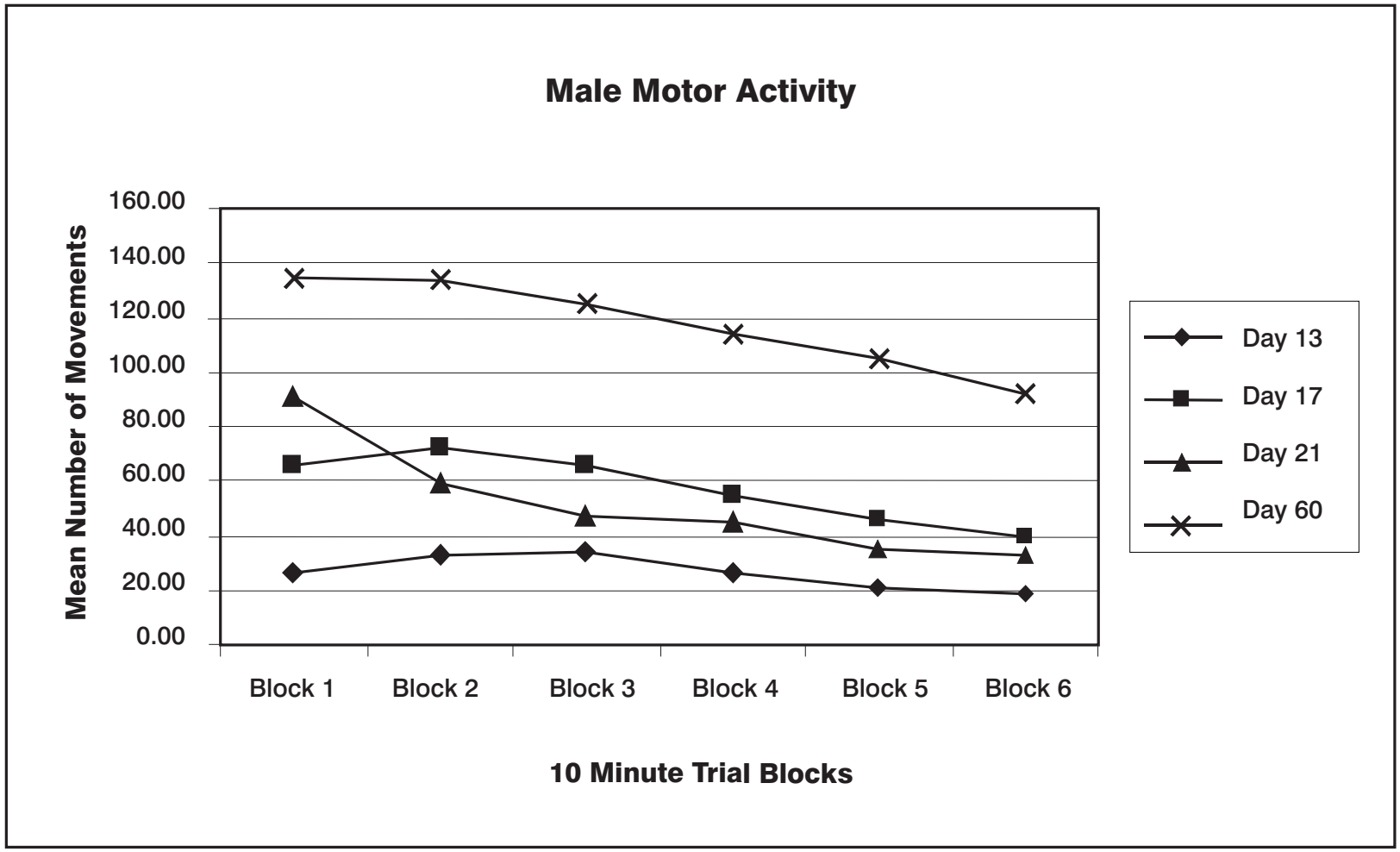


Figure 5: Female Motor Activity

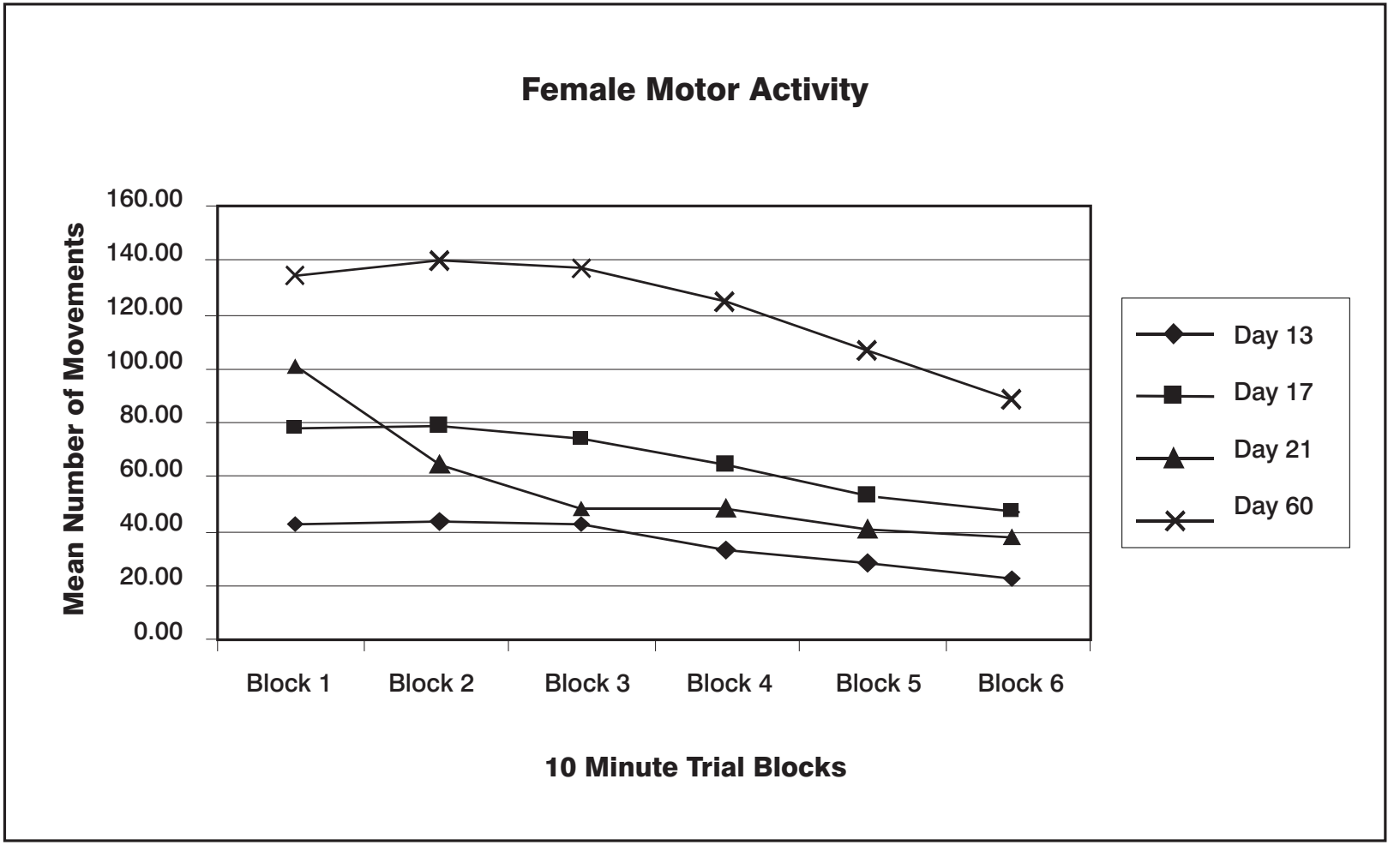


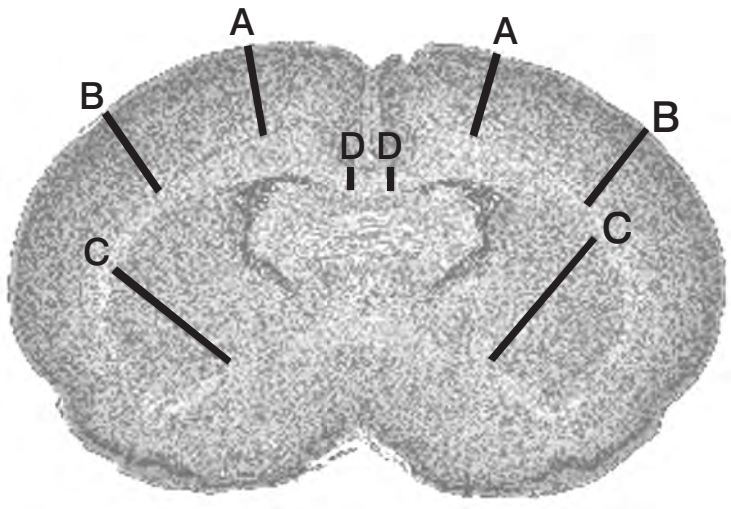
Table 8: Postnatal Day 11 – Male Brain Morphometry Data

	Number Of Studies	Mean	Minimum	Maximum
Brain Weight (grams)	6	1.236	1.132	1.32
Ant/Post Cerebrum (mm)	6	12.2	10.5	12.88
Ant/Post Cerebellum (mm)	6	5.3	3.2	6
Frontal Cortex (*u*m)	6	1428	1264	1551
Parietal Cortex (*u*m)	6	1504	1409	1629
Caudate-Putamen (*u*m)	6	2349	2052	2488
Corpus Callosum (*u*m)	6	292.1	272	312
Hippocampal Gyrus (*u*m)	6	1042	948	1136
Cerebellum (*u*m)	6	3350	3005	3606
Ext. Germinal Layer (*u*m)	6	36.7	30.3	40.6

Table 9: Postnatal Day 11 – Female Brain Morphometry Data

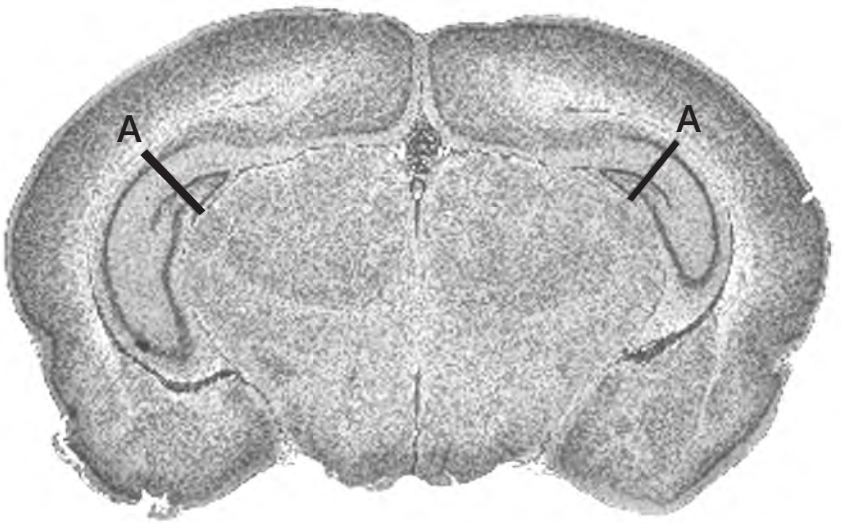
	Number Of Studies	Mean	Minimum	Maximum
Brain Weight (grams)	6	1.214	1.084	1.343
Ant/Post Cerebrum (mm)	6	12.24	10.8	12.98
Ant/Post Cerebellum (mm)	6	5.2	3.1	6
Frontal Cortex (*u*m)	6	1472	1273	1616
Parietal Cortex (*u*m)	6	1515	1410	1626
Caudate-Putamen (*u*m)	6	2311	1938	2530
Corpus Callosum (*u*m)	6	284.3	251	331.2
Hippocampal Gyrus (*u*m)	6	1005	919	1060
Cerebellum (*u*m)	6	3344	2856	3756
Ext. Germinal Layer (*u*m)	6	38.9	35.9	44.8

Figure 6: Coronal Section through the Optic Chiasm (Day 11)



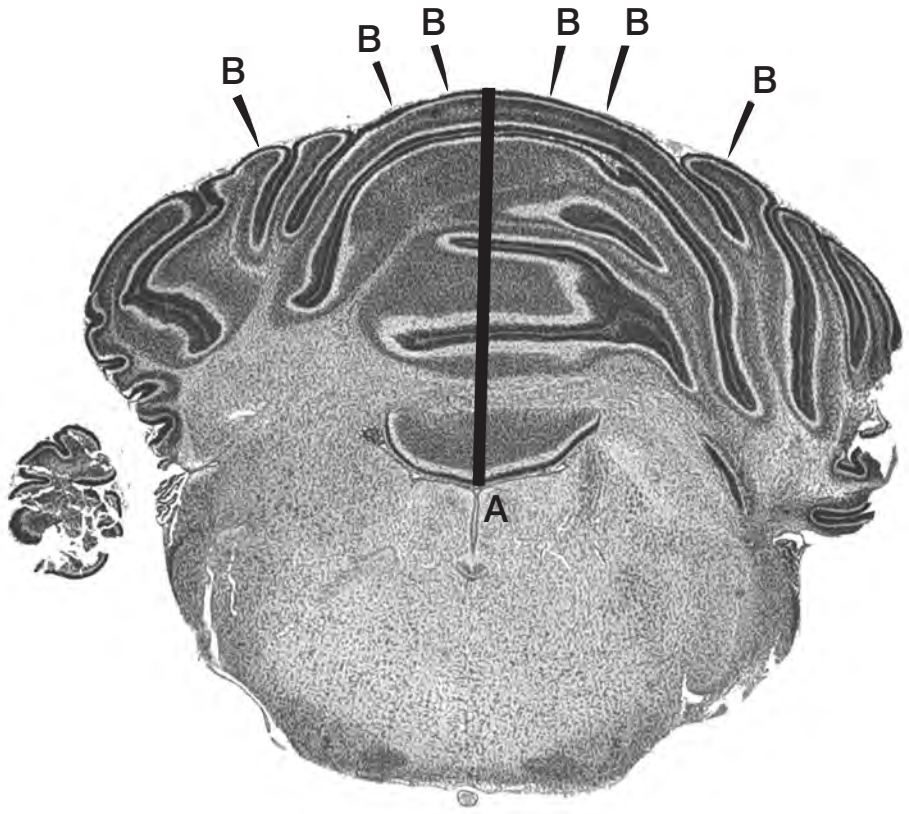
A. Thickness of the Frontal Cortex
B. Thickness of the Parietal Cortex
C. Width (Maximum) of the Caudate-Putamen
D. Thickness of the Corpus Callosum

Figure 7: Coronal Section at the level of the Hypothalamus (Day 11)



A. Thickness of the hippocampal gyrus

Figure 8: Coronal Section at the level of the Deep Cerebellar Nuclei (Day 11)



A. Height of the Cerebellum

B. Thickness of the External Granular Layer of the Cerebellum

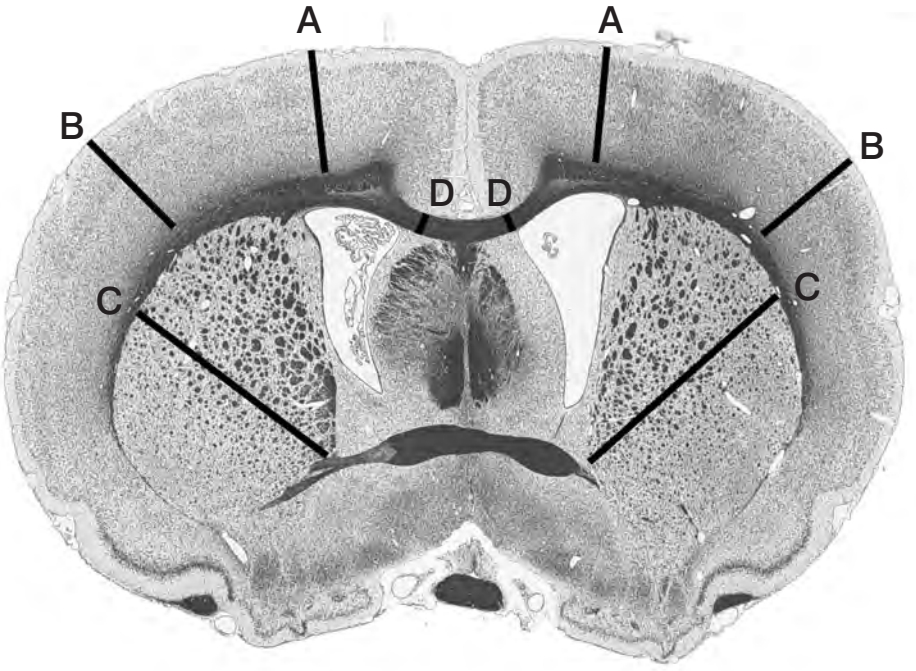
Table 10: Adult Male Brain Morphometry Data

	Number Of Studies	Mean	Minimum	Maximum
Brain Weight (grams)	6	2.282	2.127	2.413
Ant/Post Cerebrum (mm)	6	15.83	14.08	16.73
Ant/Post Cerebellum (mm)	6	7.2	6.3	7.6
Frontal Cortex (*u*m)	6	1792	1660	1838
Parietal Cortex (*u*m)	6	1871	1776	1956
Caudate-Putamen (*u*m)	6	3244	2920	3624
Corpus Callosum (*u*m)	6	272.3	243.2	290.4
Hippocampal Gyrus (*u*m)	6	1654	1552	1819
Cerebellum (*u*m)	6	5116	4648	5419

Table 11: Adult Female Brain Morphometry Data

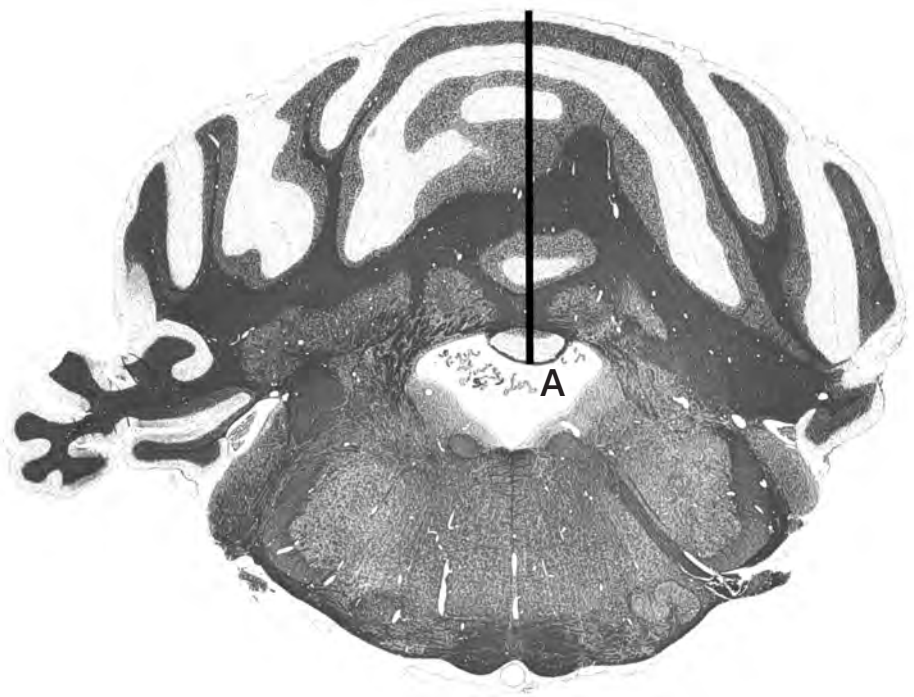
	Number Of Studies	Mean	Minimum	Maximum
Brain Weight (grams)	6	2.071	1.933	2.151
Ant/Post Cerebrum (mm)	6	15.32	13.83	15.88
Ant/Post Cerebellum (mm)	6	7	5.8	7.7
Frontal Cortex (*u*m)	6	1709	1628	1818
Parietal Cortex (*u*m)	6	1764	1656	1905
Caudate-Putamen (*u*m)	6	3080	2834	3379
Corpus Callosum (*u*m)	6	269.1	246.3	291.6
Hippocampal Gyrus (*u*m)	6	1538	1420	1602
Cerebellum (*u*m)	6	4878	4592	5028

Figure 9: Coronal Section through the Optic Chiasm (Adult)



A. Thickness of the Frontal Cortex
B. Thickness of the Parietal Cortex
C. Width (Maximum) of the Caudate-Putamen
D. Thickness of the Corpus Callosum

Figure 10: Coronal Section at the level of the Deep Cerebellar Nuclei (Adult)



A. Height of the Cerebellum