Early Life and Later Health: New Evidence from Rhesus Monkeys

Web Appendix

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March 26, 2012

1 Methods

1.1 Permutation

The permutation testing procedure relies on the exchangeability properties of the joint distribution of outcomes and treatment assignments, i.e. the joint distribution is invariant to permutation of its elements. In practice, the permutation testing procedure compares a test statistic computed on the unpermuted data with a distribution of test-statistics computed by re-sampling the data. In cases like ours, however, where randomization has been compromised, conditional inference can also be implemented. In this case, the conditional exchangeability property is applied, and independence between the distribution of outcomes and treatment assignment is tested, conditional on a set of variables (X). Given our sample size, full nonparametric conditioning is not an option, so we assumed a linear relationship between the outcomes and a subset of the variables (X^L, year of birth and total time spent in the primate center), and we restricted the permutation orbits to the remaining subset (X^N, a dichotomous indicator for being firstborn). According to this procedure, residuals computed from a regression of the outcomes on the covariates for which a linear relationship is assumed (X^L) are permuted within orbits defined by the variables which enter nonparametrically (X^N). This method is known as the Freedman-Lane (1983) procedure, and it has been found to be superior to the others in a series of Monte Carlo studies (Anderson and Legendre, 1999).

1.2 Stepdown

To illustrate the stepdown procedure, consider the null hypothesis of no treatment effect for a set of K joint outcomes, where the complement of this set is that there exists at least one hypothesis out of K that we reject. The Romano and Wolf procedure starts by considering a joint test of all null hypotheses for the set of K hypotheses, by comparing the maximum of the set of statistics associated with the hypotheses being jointly tested with the α-quantile of its distribution,[1] to determine whether this first joint hypothesis is rejected or not. If we fail to reject the joint null hypothesis, then the algorithm stops; if we reject it, then we iterate and consider successive joint hypotheses which exclude the outcomes with the highest associated test statistics. So, the procedure "steps-down", and at each successive step it is implemented on a set of $K - 1$ null hypotheses. The process iterates until only one hypothesis remains.

[1] α is the level of FWER we want to control for.

Table A1: Summary Statistics

	Subjects	Percentage (%)
Rearing Status		
Mother Reared	122	52.81
Peer Reared	57	24.68
Surrogate Reared	52	22.51
Sex		
Male	126	54.55
Female	105	45.55
Birth Order		
Primiparious	56	24.24
Multiparious	175	75.76
Year of Birth		
2002	41	17.75
2003	31	13.42
2004	31	13.42
2005	38	16.45
2006	46	19.91
2007	44	19.05
Outcomes	*Prevalence*	*Frequency*
Stereotypy	0.46	0.21
Illness	0.74	0.18
Illness - Main	0.74	0.17
Illness - Main: EENT	0.22	0.02
Illness - Main: Mouth/Head	0.50	0.08
Illness - Main: Abdominal	0.32	0.05
Illness - Main: Chest	0.13	0.02
Illness - Main: Urogenital	0.16	0.03
Illness - Other	0.31	0.05
Illness - Other: Diarrhea	0.14	0.02
Illness - Other: Non-Diarrhea	0.19	0.03
Illness - Other: Non-Diarrhea: Rash	0.10	0.02
Wound	0.48	0.09
Alopecia	0.46	0.14
	Observations	Mean (S.D.)
Weight (grams)	3180	3962 (2213)

Note: All summary statistics refer to the analytical sample of 231 monkeys, observed after their first year of life. The category "illness - main" includes EENT, mouth/head, abdominal, chest and urogenital issues. The category "illness - other" includes both diarrhea- and non-diarrhea-related diseases (rash being the bigger component of the latter).

Table A2: Primary Outcomes, Surrogate Peer Reared vs. Mother Reared

				Panel A: **Main vs. Other Illness**			
		Effect		*p-Values*			
Outcome	Control Mean	Uncond.	Condit.	Asympt.	Naive Permut.	Condit. Permut.	Con.Per. (Adj.)
Prevalence of Stereotypy	0.215	0.716	0.669	**0.000**	**0.000**	**0.000**	**0.000**
Frequency of Stereotypy	0.046	0.485	0.478	**0.000**	**0.000**	**0.000**	**0.000**
Prevalence of Illness - Main	0.723	0.001	-0.020	0.496	0.602	0.492	0.492
Frequency of Illness - Main	0.150	0.084	0.072	**0.028**	**0.017**	**0.031**	0.178
Prevalence of Illness - Other	0.200	0.352	0.311	**0.001**	**0.000**	**0.001**	**0.006**
Frequency of Illness - Other	0.029	0.072	0.066	**0.006**	**0.002**	**0.002**	**0.038**
Prevalence of Wound	0.385	-0.005	-0.004	0.481	0.386	0.331	0.331
Frequency of Wound	0.052	0.006	0.011	0.399	0.382	0.422	0.719
Prevalence of Alopecia	0.369	0.217	0.156	**0.028**	**0.038**	**0.038**	0.210
Frequency of Alopecia	0.113	0.053	0.041	0.106	**0.088**	**0.066**	0.514
				Panel B: **Diarrhea vs. Non-Diarrhea Illness**			
		Effect		*p-Values*			
Outcome	Control Mean	Uncond.	Condit.	Asympt.	Naive Permut.	Condit. Permut.	Con.Per. (Adj.)
Prevalence of Stereotypy	0.215	0.716	0.669	**0.000**	**0.000**	**0.000**	**0.000**
Frequency of Stereotypy	0.046	0.485	0.478	**0.000**	**0.000**	**0.000**	**0.000**
Prevalence of Illness - Main	0.723	0.001	-0.020	0.496	0.602	0.492	0.492
Frequency of Illness - Main	0.150	0.084	0.072	**0.028**	**0.017**	**0.031**	0.178
Prevalence of Illness - Other: Diarrhea	0.046	0.230	0.216	**0.007**	**0.003**	**0.004**	**0.037**
Frequency of Illness - Other: Diarrhea	0.004	0.025	0.024	**0.015**	**0.001**	**0.003**	**0.059**
Prevalence of Illness - Other: Non-Diarrhea	0.154	0.225	0.196	**0.016**	**0.004**	**0.017**	0.128
Frequency of Illness - Other: Non-Diarrhea	0.025	0.047	0.042	**0.026**	**0.013**	**0.020**	0.172
Prevalence of Wound	0.385	-0.005	-0.007	0.481	0.386	0.331	0.331
Frequency of Wound	0.052	0.006	0.011	0.399	0.382	0.422	0.719
Prevalence of Alopecia	0.369	0.217	0.156	**0.028**	**0.038**	**0.038**	0.210
Frequency of Alopecia	0.113	0.053	0.041	0.106	**0.088**	**0.066**	0.514

Note: n=94 for males, 80 for females. p-values below 0.1 are in bold. Control = MR. Uncond. = unconditional difference in means between the treatment and the control group. The corresponding p-values are computed in the columns "Asympt." and "Naive Permut.". Condit. = conditional treatment effect with linear covariates year of birth and total time spent in the primate center. The corresponding p-value is computed in the column "Condit. Permut.". Asympt. = one-sided p-values for the hypothesis of no treatment effect based on asymptotic inference - estimated effect size in the "Uncond." column. Naive Permut. = one-sided p-values for the hypothesis of no treatment effect based on unconditional permutation inference - estimated effect size in the "Uncond." column. Condit. Permut. = one-sided p-values for the hypothesis of no treatment effect based on the Freedman-Lane procedure, using the linear covariates year of birth and total time spent in the primate center, and restricting permutation orbits within strata formed by being first or later born - estimated effect size in the "Condit." column. Cond. Perm. (Adj.) = p-values from the previous column, adjusted for multiple inference using the stepdown procedure.

Table A3: Auxiliary Outcomes, Blood Tests

	Effect		*p-Values*	
Outcome	Control Mean	Treatment Effect	Permutation	Permutation (Adjusted)
		Panel A: **Males**		
Potassium	3.900	-0.988	**0.000**	**0.001**
Sodium	144.583	-8.083	**0.002**	**0.003**
Hematocrit	37.858	5.873	**0.001**	**0.002**
Glucose	79.333	33.260	**0.007**	**0.007**
Blood Urea Nitrogen	16.250	16.906	**0.000**	**0.001**
Potassium, Abn.	0.000	0.438	**0.000**	**0.002**
Sodium, Abn.	0.083	0.385	**0.002**	**0.003**
Hematocrit, Abn.	0.583	0.104	0.377	0.535
Glucose, Abn.	0.083	0.010	0.265	0.265
Blood Urea Nitrogen, Abn.	0.000	0.313	**0.000**	**0.003**
		Panel B: **Females**		
Potassium	3.613	-0.726	**0.000**	**0.019**
Sodium	141.813	-5.419	**0.013**	**0.026**
Hematocrit	29.531	13.204	**0.000**	**0.000**
Glucose	91.375	5.155	0.365	0.591
Blood Urea Nitrogen	36.625	-2.973	0.334	0.334
Potassium, Abn.	0.000	0.424	**0.000**	**0.000**
Sodium, Abn.	0.313	0.263	**0.017**	0.104
Hematocrit, Abn.	0.500	0.333	**0.008**	**0.082**
Glucose, Abn.	0.188	0.070	0.184	0.424
Blood Urea Nitrogen, Abn.	0.375	0.034	0.302	0.302

Note: For each treatment-control comparison, we present two sets of results: one using the absolute value, and another using binary indicators for the presence of abnormal values (Abn.). Normal range for the various blood tests are as follows: Sodium (Na) = 140-160(mEq/l); Potassium (K) = 2.3-6.7(mEq/l); Blood Urea Nitrogen (BUN) = 8.0-30.0(mg/dL); Glucose = 60-160(g/dL); Hematocrit (Hct) = 30-38(%).
n=44 for males and 82 for females. p-values below 0.1 are in bold. Treatment Effect = unconditional difference in means between the treatment and the control group. Notice here the treatment group is the one affected by diarrhea. The corresponding p-values are computed in the column "Permutation". Permutation = one-sided p-values for the hypothesis of no treatment effect based on unconditional permutation inference - estimated effect size in the "Treatment Effect" column. Permutation Adjusted = p-values from the previous column, adjusted for multiple inference using the stepdown procedure.

Table A4: Auxiliary Outcomes

	Effect			*p-Values*		
Outcome	Control Mean	Uncond.	Condit.	Naive Permut.	Condit. Permut.	Con.Per. (Adj.)
Panel A: **Surrogate Peer Reared vs. Mother Reared, Males**						
Cortisol (μg/dl), mean	50.926	7.889	10.296	**0.047**	**0.019**	**0.022**
ACTH (pg/ml), mean	221.677	-56.356	-43.647	**0.023**	**0.023**	**0.023**
5-HIAA (pmol/ml), mean	716.824	-112.011	-93.850	**0.002**	**0.065**	**0.069**
Cortisol (μg/dl), day 90	50.671	10.797	11.932	**0.028**	**0.016**	**0.027**
ACTH (pg/ml), day 90	212.143	-45.191	-43.512	**0.092**	**0.040**	**0.040**
5-HIAA (pmol/ml), day 90	675.786	-79.632	-71.269	**0.018**	**0.061**	**0.067**
Panel B: **Surrogate Peer Reared vs. Mother Reared, Females**						
Cortisol (μg/dl), mean	56.440	-1.595	-1.847	0.308	0.275	0.725
ACTH (pg/ml), mean	269.795	-72.477	-70.491	0.107	**0.092**	0.252
5-HIAA (pmol/ml), mean	706.200	-54.109	-29.648	0.303	0.346	0.611
Cortisol (μg/dl), day 90	55.622	-1.667	-1.801	0.352	0.344	0.656
ACTH (pg/ml), day 90	263.489	-85.289	-88.818	**0.075**	**0.070**	0.187
5-HIAA (pmol/ml), day 90	608.667	0.444	15.489	0.492	0.354	0.931
Panel C: **Peer Reared vs. Mother Reared, Males**						
Cortisol (μg/dl), mean	50.926	2.004	3.960	0.316	0.211	0.326
ACTH (pg/ml), mean	221.677	11.134	-12.352	0.406	0.638	0.362
5-HIAA (pmol/ml), mean	716.824	-135.824	-71.565	**0.035**	0.147	0.270
Cortisol (μg/dl), day 90	50.671	3.329	4.654	0.285	0.279	0.388
ACTH (pg/ml), day 90	212.143	-2.493	-30.038	0.500	0.253	0.253
5-HIAA (pmol/ml), day 90	675.786	-138.036	-59.694	0.046	0.122	0.296
Panel D: **Peer Reared vs. Mother Reared, Females**						
Cortisol (μg/dl), mean	56.440	7.197	6.639	0.247	0.259	0.432
ACTH (pg/ml), mean	269.795	-44.032	-59.587	0.282	0.509	0.575
5-HIAA (pmol/ml), mean	706.200	-70.450	-21.428	0.367	0.395	0.395
Cortisol (μg/dl), day 90	55.622	16.078	13.371	0.298	0.404	0.737
ACTH (pg/ml), day 90	263.489	-29.339	-23.894	0.416	0.805	0.805
5-HIAA (pmol/ml), day 90	608.667	-123.167	-42.167	**0.070**	0.341	0.804

Note: For each treatment-control comparison, we present two sets of results: one using the mean value (in case there is more than one valid observation for each measurement), and another using the day 90 measurements (the day in which the sample size is maximized). We exclude the day 60 cortisol and ACTH measurements as the month-2 sample was taken during a "non-stressed" session, while the other samples were collected after 30-minute separation and isolation period in a single 64×61×76cm cage in an empty room.
n=33 (mean) and 27 (day 90) in Panel A, 21 and 18 in Panel B, 22 and 18 in Panel C, 14 and 11 in Panel D. p-values below 0.1 are in bold. Uncond. = unconditional difference in means between the treatment and the control group. The corresponding p-values are computed in the column "Naive Permut.". Condit. = conditional treatment effect with linear covariates year of birth and total time spent in the primate center. The corresponding p-value is computed in the column "Condit. Permut.". Naive Permut. = one-sided p-values for the hypothesis of no treatment effect based on unconditional permutation inference - estimated effect size in the "Uncond." column. Condit. Permut. = one-sided p-values for the hypothesis of no treatment effect based on the Freedman-Lane procedure, using the linear covariates year of birth and total time spent in the primate center, and restricting permutation orbits within strata formed by being first or later born - estimated effect size in the "Condit." column. Cond. Perm. (Adj.) = p-values from the previous column, adjusted for multiple inference using the stepdown procedure.

Table A5: Aggression and Self-Grooming, Females

Peer Reared	0.038***	0.074
	(0.013)	(0.049)
Surrogate Peer Reared	-0.002	0.366***
	(0.005)	(0.062)
Observations	1912	1911

Note: Included above are coefficients from linear regressions. Aggression and self-grooming are binary variables for the existence of such behaviors in a 5 minute observation period. Included in parentheses are robust standard errors, clustered at the individual level. Peer Reared and Surrogate Peer Reared are binary indicators of the respective rearing statuses. Also included in each specification are controls for year of birth and primiparous birth. * p<0.10, ** p<0.05, *** p<0.01.