Parental rejection is associated with intergenerational inheritance of reduced survival, altered behaviours and miRNAs in Owl Monkeys

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Short title: "Intergenerational effects of parental rejection in owl monkeys"

Key words: Rejection, early life adversity, lifespan, stress, miRNAs, Aotus.

Abstract

Introduction. Intergenerational inheritance of stress is the transmission of acquired exposures down to the next generation. Complete parental rejection of newborns in captive primate colonies is considered a severe form of early life stress and widespread across globe. Intergenerational effects associated with parental rejection are uncharacterised but could have significant impact on progeny, affecting their welfare.
Methods. We investigated intergenerational inheritance of rejection in a species where parental rejections occurs spontaneously in captivity (*Aotus nancymaae*), and its effects across 2 generations. We analysed demographic records (n=1389), observed stress and affiliative behaviours (n=65, 10 families, 2 generations), and profiled miRNAs expression in blood (48 from 10 families, 2 generations).
Results. Rejected individuals showed significantly reduced lifespan, and a lower probability of reaching reproductive age and increased rates of clinic visits throughout life. Remarkably, well-reared descendants of rejected animals showed a similar reduction in surviving to reproductive age and lifespan as seen in their parents. Behavioural analysis revealed persistent alterations in stress reactivity and social behaviour, with rejected adults showing significant increase in fear aggression and reduced infant care, and infants showing reduced locomotion and biting, but also positive stress coping. Blood miRNA analysis revealed no significant differences between rejected and controls, but rejected female offspring, showed a significant upregulation of mml-miR-30a-5p an miRNA upregulated in the plasma of humans who after exposure to early life stress, suffer from behavioural disorders.
Discussion. Our findings demonstrate that parental rejection is associated intergenerational effects on stress and affiliative behaviours, reduced survival, and miRNA expression, suggesting intergenerational inheritance of stress. This report contributing to understanding developmental origins of ill health and mortality in captive primates.

Introduction

In recent years, epidemiological research has suggested that stress experienced by parents and associated negative effects on health[1] can be passed on to the next generation[2-4]. Studying parental stress and its intergenerational inheritance in humans is difficult, due to extended lifespans, and social and ethical complexities.
Non-human primates serve as valuable models due to their shared cognition and physiology with humans. Studies in primates exposed to early-life parental adversity (ELA) such as experimental parental separation, rejecting styles, parental loss show these individuals display developmental and lifelong alterations in stress behaviour[5], neurocircuitry[6,7], inflammatory disorders[8], negative health outcomes[9], decreased survival in early life[10], and shorter lifespans[11,12]. Some of these effects appear heritable, with offspring showing altered behaviours[13-16], immune profiles[8] and reduced longevity[17].
Maternal or parental abandonment of newborns is the most severe form of rejection, as dependency of infants from mothers or fathers in early age is greatest, abandonment is usually lethal[18]. Complete rejection (from now on referred to as 'rejection') is a stubborn behavioural problem afflicting captive bred primate colonies across the globe and has been identified in every branch of the Primate order (in prosimians[19]; new world monkeys[20-26]; old world monkeys[13,27,28] great apes[29,30]). In most cases hand or nursery rearing is used by veterinarians to avoid mortality of rejected infants. There is a recognition that rejected primates which are then nursery reared behave abnormally, and can present different physiology[31,32]. However, the effects of rejection on long-term health and life history outside traditional primate models is not well characterised. Furthermore, parental rejection seems to affect progeny's behaviour and physiology, it is likely that descendants of rejected also suffer from the intergenerational effects of stressful experience, impacting their welfare in captivity.
Important candidate mechanisms that explain embodiment of parental stress are alteration of epigenetic marks, which can become modified in response to environmental cues[33]. Patterns of DNA methylation in genes involved in regulation of stress physiology and social sensitivity are associated with parental ELA as demonstrated in primate populations[34,35] and link stressful exposures and epigenetic modifications with health outcomes[36].

Studies of maternal neglect in rats shows poor maternal care is associated with changes in DNA methylation in brain expressed glucocorticoid receptor genes in offspring which persist until adulthood[37]. More recently studies have focused on circulatory small non-coding RNAs, molecules that capable to carry on stress exposure information across generations. In worms, small RNAs can be inherited through multiple generations, and contribute to modify stress tolerance phenotypes in descendants[38]. Altered expression of miRNAs have also been detected in stressed parents and in their offspring in mammals (in mouse sperm[39]; in human blood plasma[40]). The role of miRNAs in the intergenerational inheritance of stress remains poorly explored in non-human primates.

Considering above evidence, we propose that if effects of complete rejection seen in captive primates is 'heritable' i.e. effects of exposure are detectable in next generation, transmission of effects might involve alteration of epigenetic marks such as miRNAs.
To test these hypotheses, we studied parental rejection and its intergenerational effects in a captive population of owl monkeys (*Aotus nancymaae*). This species is a Neotropical primate, is uniquely monogamic, nocturnal, which displays biparental care[41,42]. In the IVITA captive colony, spontaneous rejection has been documented before[43]. Rejection events mostly

occur within first days or weeks after birth, with mothers refusing to feed newborns. In occasions, maternal rejection is also followed by paternal aggression (Nofre Sanchez, personal communication, 1st September 2023). To rescue rejected infants, nursery rearing is practiced in this colony.

In previous studies in this owl monkeys, we reported elevated cortisol and poor health outcomes in 17 months juveniles which were parentally rejected and rescued[44]. More recently, we showed that accelerated blood DNA hypomethylation with age[45], characterised this cohort. Together these studies associate parental rejection history with long-term stress, negative health outcomes and epigenetic modifications.

In the present study we explore the demographic and individual based health records of this colony, to compare health outcomes and lifespan of rejected and progeny against controls. Second, using a family cohort, we determine if stress-reactive and affiliative behaviours, and miRNA expression in blood are altered across in rejected and descendants.

Materials and Methods

Ethics statement. All experimental procedures for nonhuman primate research adhered to the American Society of Primatologists (ASP) Principles for the Ethical Treatment of Non-Human Primates. This study was approved by the Welfare and research Committee of San Marcos University and were in line with ethical standards and approved by the ethics approved by the UNMSM ethics committee and by the Peruvian authority SERFOR to Dr. Paredes (following permit AUT-IFS-2021-040 and SERFOR RDG NO D000334-2021-MIDAGRI-SERFOR-DGGSPFFS).

Location. This study was conducted at the Centre for Reproduction and Conservation of Non-Human Primates (CRCP) of IVITA at the National University of San Marcos (UNMSM), located in the city of Iquitos, Peru.

Sampling. Each analysis varied in number of individuals included, due to availability of records, and biological samples. A table describing distribution of samples for each analysis is included in **Supplementary File 1.**

Survival Analysis of Rejected Individuals: A comprehensive survival analysis was conducted on a study population comprising 1,389 individuals, categorised as "rejected by parents" (indicating that the mother suspended lactation and/or the father attacked the baby, leading to nursery rearing, n = 152) or non-rejected (n = 1,237). As the control population was contemporary, death data were not available, as most were still alive. Consequently, the data collection date was used for age estimation. A comparative analysis was then conducted between individuals categorised as rejected by their parents and controls. For individuals who were still alive at the time of data collection, their age at death was approximated using the same data collection date. Mean ages at "time of death" were calculated for both groups, with standard deviations indicating variability within each group. Using a two-sample Welch's t-test, significant differences in mortality patterns between these groups were evaluated. Figures were generated using R to illustrate the observed differences in age-at-death distribution between rejected and non-rejected individuals.

Reproductive Age Analysis: The impact of infant rejection behaviour on the probability of reaching reproductive age was investigated using a sample of 1,161 individuals. Based on previous research by Dixson[41], individuals were considered to have reached reproductive age in captivity if they were 1.5 years or older. Within this population, 60 individuals were rejected and reached reproductive age due to veterinary intervention, whilst 1,101 remained non-rejected. A Pearson's chi-square test with Yates' continuity correction was used to examine the association between rejection status and the probability of reaching reproductive age.

Effects of Parental Rejection on offspring of rejected: A generalised logistic regression analysis was conducted to explore the relationship between parental rejection and the probability of rejected reaching reproductive age. The sample consisted of 813 individuals, of these, 31 offspring were rejected. Logistic regression coefficients were estimated to determine the impact of parental rejection on rejected infants in reaching reproductive age.

Family Cohort Study-Experimental Animals: We reviewed medical records to identify individuals with a history of parental rejection who survived parental rejection, reached adulthood, and had offspring at the time of the experiment. In total, we found 10 families that included at least one adult rejected by their parents who met these requirements. We identified age-matched individuals with offspring to serve as control families. In total, 65 owl monkeys were assigned to two groups: parental rejection and control. The parentally rejected (P0) included 11 adult monkeys (n=6 females, n=5 males), 8 well-reared adult monkeys who were breeding partners of the rejected ones (n=3 females, n=5 males), and offspring (F1): 14 juvenile offspring (n=9 females, n=5 males). The control group (P0) had 19 well-reared adult monkeys (n=9 females, n=10 males) and 13 juvenile offspring (F1) (n=8 females, n=5 males). Selection criteria for both adult monkey groups was: age, condition and location in breeding cages, and the presence of offspring (similar age and quantity).

Housing. Families were housed in single enclosures (2 m^3, width=1 m, depth=1 m, height=2 m) with access to the natural biological period throughout the year. Owl monkeys are fed once daily with a diet composed of seasonal fruits, home-prepared balanced dry food, and water *ad libitum*.

Blood Collection: Whole blood extraction from a subset of 48 owl monkeys (adult rejected [n = 12, 8 females, 4 males]; offspring of rejected [n = 11, 7 females, 4 males], adult controls [n = 15, 10 females, 5 males], and offspring controls [n = 10, 7 females, 3 males]) was performed when the primate was sedated (ketamine 8 mg/kg). Blood samples were taken by femoral venepuncture with 3 ml syringes and 1"x 23G needles collected in a Vacutainer® with EDTA (ethylenediaminetetraacetic acid). From the sample collected in each tube, 0.5 ml per primate was taken and placed on filter paper.

Ethological Characterisation: A Stress Sensitivity Test (modified human intruder's test[31]) was conducted, and spontaneous behaviours were collected in an ethogram (n=65). This test was carried out one month before blood sampling, but after having undergone collection for sanitary measures. The behaviour test schedule was from 7 to 8 pm when the monkeys are most active due to their nocturnal habits[46]. The monkeys were exposed to low-intensity stressors: a light stimulus (camera light), a physical stimulus (presence of a human observer not previously seen by the monkey, 'the intruder') and a mechanical stimulus (opening of the enclosure door). The owl monkeys' behaviours were video recorded. Three one-minute sessions per video were conducted with five-minute intervals where the monkey was not exposed to any stimulus. Frequency quantification of each behaviour was performed by classifying potential behaviours in previous studies conducted in the same species and prepared ethograms (Supplementary File 2). The behavioural events of the reactivity test were observed with behavioural observation interactive research software (BORIS). The total duration of the behaviours presented, and the number of episodes shown per individual were quantified. The behaviours were evaluated by two independent observers to avoid biased observations and have a reliability percentage greater than or equal to 95 per cent. A summary of the unadjusted percentages by sex in parents and offspring is shown in Supplementary File 3.

Statistical Analysis of Behaviour: Behaviour frequency or percentage differences were estimated using logistic regression adjusted for family/cage, sex effects and age category with Bayesian estimation and non-informative backgrounds. In the model, we used parental rejection as the main predictor and the outcome was whether an individual monkey showed

or not a specific behaviour during the observation periods as binary (0/1), where 0 was a monkey without a specific behaviour and 1 was a monkey with at least one event of a specific behaviour. The predicted or adjusted frequencies or percentages were compared using an exact Wilcoxon rank sum test to report p-values for these comparisons. The average treatment effect was estimated using formula G, assigning all individuals to each treatment and estimating the difference between the 2 predicted posterior distributions. The ethogram data generated and used in this study are found in Supplementary File 4. The statistical models and previous values used are described in Supplementary File 5. We considered results with $p<0.05$ significant.

MicroRNA Expression Analysis through Next-Generation Sequencing. Extraction for microRNA Sequencing: Whole blood extracted from a subset of owl monkeys (n=48, rejected P0, females n=4, males n=4, F1 females n= 7, males n=5; Non rejected: P0 females n=10; males n=8; F1 females n=7, males n=2) belonging to 10 families described above was stored on filter paper to form dried blood spots and then left to dry at room temperature. The extraction of dried blood spots and preparation methods for next-generation microRNA sequencing was described previously[47,48]. Total RNA was extracted from 3 6-mm punches of dried blood spot per owl monkey using the mirVana microRNA isolation kit (Thermo Fisher Scientific, Cat No: AM1560) according to manufacturer's instructions. Briefly, the spots were suspended in a cell disruption buffer, then a denaturing solution was added. After adding and shaking an acid phenol: chloroform mixture, the solution was centrifuged at 4°C. The upper aqueous layer was collected and mixed with 100% ethanol, then the total RNA was transferred to a filter cartridge. After several washes, pre-heated elution buffer was added, and total RNA was eluted into a new RNase-free tube. Total RNA in each sample was concentrated using the RNeasy MinElute Cleanup kit (Qiagen, Cat No: 74204) according to manufacturer's instructions. Briefly, lysis buffer containing guanidine thiocyanate was added to the total RNA sample, followed by ethanol. The mixture was added to the RNeasy MinElute spin column, and, after several washes, high-quality concentrated RNA was eluted in a 12 µl volume of RNase-free water and stored at -80°C until further processing. Libraries were prepared using Qiagen's QIAseq miRNA Library kit, according to manufacturer's instructions. Library quality was controlled using the Nanodrop 8000 (Thermo) and TapeStation 4200 (Agilent) before being sequenced on a next-generation sequencing machine (NextSeq 2000, Illumina Inc.). **Bioinformatic Preprocessing:** Raw sequencing reads were trimmed using Trimgalore v0.6.6 to remove adapters and low-quality bases. Trimmed reads were then aligned to the owl monkey genome (*Aotus nancymaae*, Anan_2.0) using STAR v2.7.3a. Gene-level counts were summarised using HTseq. Raw counts were then loaded into Partek Flow for further analysis. Counts were normalised (CPM), filtered to remove unexpressed genes, and a PCA was performed to evaluate sample variability and detect outliers. Based on this, we removed one sample (T-1499, P0 female control) whose expression was far from all others (Supplementary File 6). After filtering, we obtained around ~3000 matches against the owl monkey genome. **Data Manipulation in PartekFlow:** The RNA hits were mapped against the sequenced genome reference of *Aotus nancymaae*. As this genome is not fully annotated, we mapped the owl monkey small non-coding RNA hits against the rhesus macaque *Macaca mulatta* genome. (Mmul_10 (GCA_003339765.3) to identify miRNAs. Normalised counts (ratio) were loaded into the Partek Flow suite to perform expression analysis (https://www.partek.com/partek-flow/) and to account for multiple comparisons, we applied the Benjamini-Hochberg procedure to control the false discovery rate (FDR) is set to $p<0.05$ and a fold change greater than (+/-) 1.5 as significant (Partek Flow). All reported p-values are FDR-adjusted unless otherwise stated. The LIMMA TREND method was used to detect differential miRNA expression in parentally rejected adults and controls, and between offspring of rejected and controls, within each sex category.

The dysregulated miRNAs identified according to these parameters are reported in Supplementary File 7. For heatmaps, miRNA expression data were log2-transformed and z-scores were calculated by subtracting the mean expression of each miRNA across all samples and dividing by the standard deviation, allowing for comparison of expression differences for multiple miRNAs.

Results

Adult owl monkeys that were rejected have shorter lives, are less likely to reach reproductive age, and suffer poorer health. Upon examining death dates among the study population (n = 958, females n= 431, males n = 494), our aim was to understand whether rejection was associated with shorter lives and poorer health compared to non-rejected individuals (Figure 1a). Linear regression was conducted to investigate the impact of rejection behaviour on owl monkeys' health and life expectancy. The results indicated that those rejected by their parents tend to experience earlier mortality, with significantly lower mean age at death compared to controls (3.41 years (SD = 4.58) versus 7.03 years (SD = 6.02), and this difference was significant ($p < 0.001$). A subsequent sex analysis showed no significant difference in life expectancy between parentally rejected males or females once they had reached reproductive age (males 9.05 years (SD = 5.55) versus females (8.24 years (SD = 5.37)).

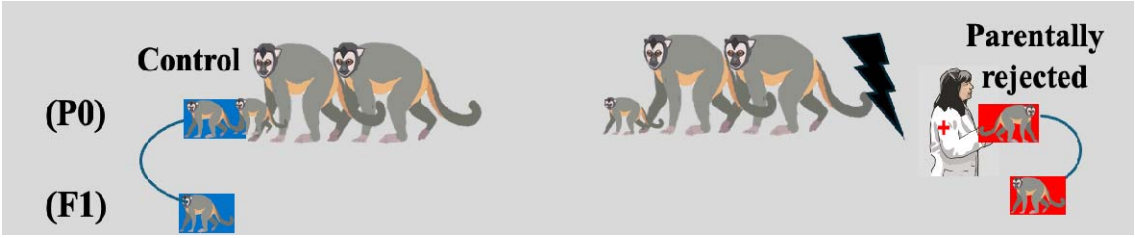
A chi-square test was performed to determine whether there was a significant difference in parentally rejected individuals reaching reproductive age (Figure 1.b). A significant association was observed between having been rejected and reaching reproductive age ($p < 0.01$), with odds being approximately 0.581 times lower for rejected compared to non-rejected. Therefore, based on this model, being rejected decreases the odds of reaching reproductive age by approximately 41.9%.

Based on our previous findings[44], and significant reduction in survival we used a linear regression model to understand whether parental rejection was associated with worsened health (Figure 1.c). We used clinic visits as a marker of health and constructed a model to predict the likelihood of clinic visits when controlling for age to assess the independent influence of rejection. The results revealed that rejected individuals visited clinics 1.13 more times throughout life when age and sex was controlled for ($p = 0.05$).

Parental rejection in P0 reduces the chances of rejected F1 reaching reproductive age. We studied the probability of reaching reproductive age for offspring (F1) of rejected individuals (Figure 1.d) using a generalised logistic regression analysis. The probability decreased significantly when having a father or mother who were rejected (a generalised linear regression was performed and the results were significant $p < 0.001$, n = 958, P0 = 194, parent rejected = 31, not rejected = 927). The estimate was -0.545, meaning that the odds of reaching reproductive age are approximately 0.553 times lower for offspring of rejected parents compared to offspring of control parents. Therefore, based on this model, having a rejected parent decreases the odds of offspring reaching reproductive age by approximately 44.7%. These results show that the effects on fitness of parental rejection are transmitted inter-generationally and are detrimental to offspring. There were no significant differences in parent sex ($p = 0.246$) or offspring sex ($p = 0.571$).

Parental rejection in P0 significantly reduces the lifespan of rejected F1 individuals. We studied the lifespan of F1 using a Welch two-sample t-test. The results indicated a significant reduction in lifespan for rejected F1 individuals compared to controls ($t=2.94$, $p=0.018$, n=736, Control = 727, F1 = 9). The mean lifespan of rejected F1 individuals was 3.89 years (SD= 4.68), while the mean lifespan of control individuals was 8.50 years (SD= 4.37). The difference in means was 4.61 years, with a 95% confidence interval of 1.01 to 8.21 years.

These results demonstrate that rejection at the P0 level has significant negative effects on the lifespan of F1 offspring, highlighting the intergenerational transmission of the fitness consequences of parental rejection.



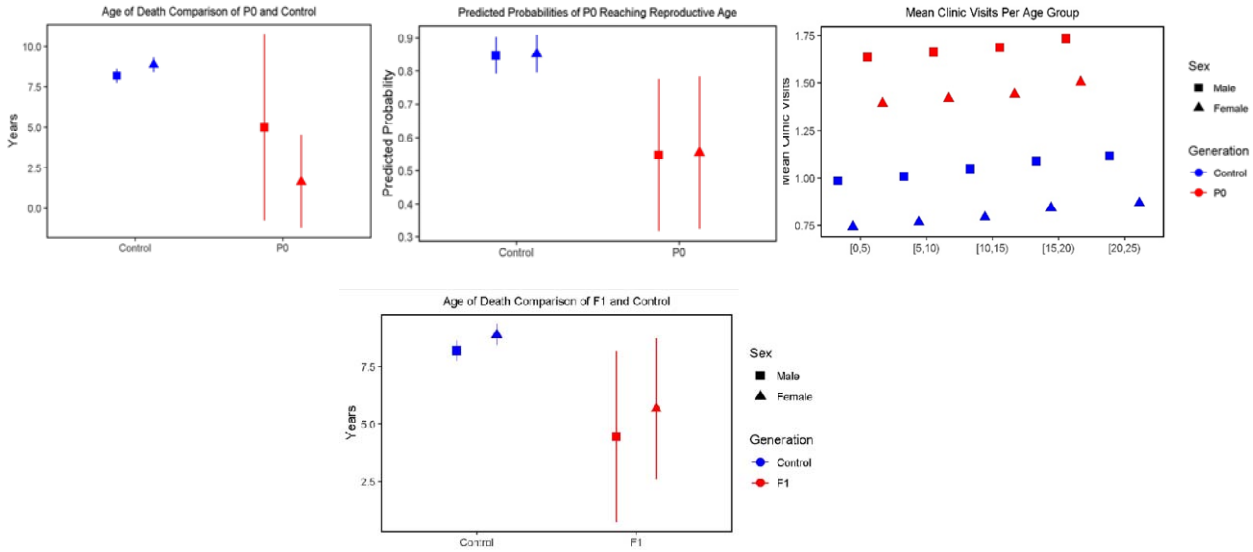


Figure 1. Reduced life expectancy and health in rejected owl monkeys and descendants. 1.a. Age of death was lower for rejected vs. control monkeys (P0). 1.b. Probability of rejected owl monkeys reaching reproductive age was significantly lower than controls (P0). 1.c. Clinic visits controlling for age. Rejected individuals in average visit the clinic more frequently than controls (P0). Males and females shown separately, with no significant sex-related differences. 1.d. Parental rejection status negatively affects offspring (F1) achieving reproductive age. Males and females shown separately, with no significant sex-related differences.

Adult monkeys who experienced parental rejection are more fearful, bold and more aggressive. The results of adjusted logistic regression with Bayesian estimation showed that behaviours such as fear (+5%, p=0.03), hugging (+2%, p=0.01), approach (+20%, p=0.01) and hitting others (+10%, p=0.01) increased in parents that were rejected in early life (n=11), whilst hiding on the perch (-44%, p<0.01), carrying their offspring (-7%, p=0.04) and jumping locomotion (-5%, p<0.01) decreased compared to control parents (n=27) (Supplementary File 8). When comparing behavioural differences adjusted for parent sex, some behaviours were more evident in females. Mothers with a history of parental rejection showed greater fear (+4%, p=0.01), hugging (+2%, p<0.01), approach (+19%, p=0.07) and agonistic social behaviours such as hitting other monkeys (+11%, p=0.07) and biting (+13%, p=0.30), whilst freezing (-10%, p=0.01), jumping locomotion (-5%, p=0.01) and furtive glancing (-1%, p<0.01) decreased compared to controls. Similarly, fathers with parental

deprivation showed increased fear (+5%, p=0.70), approach (+28%, p=0.05) and hitting others (+8%, p=0.07), whilst time spent hiding on the perch (-39%, p=0.01) and hiding behind (-11%, p<0.01) decreased. They also showed decreased baby carrying (-8%, p=0.03) and jumping locomotion (-5%, p<0.01) compared to controls (Figure 2). Only one adult male monkey displayed stereotyped behaviour (head twirl).

Offspring of rejected parents showed more fearfulness and less locomotion like their parents. Using the same statistical analysis, we show offspring of rejected parents (n=14) also display behaviours such as fear (+18%, p=0.14) and hiding in the nest and hiding behind another monkey (+12%, p=0.13; +9%, p=0.8 respectively) increased. However, significant results were only detected amongst behaviours which were decreased for offspring of rejected parents (n=13): hiding on the perch (-15%, p=0.05), jumping locomotion (-14%, p<0.01) and biting (-12%, p=0.01) (Supplementary File 9). When considering offspring independently, the same pattern emerges. Female offspring of parents with parental deprivation showed more fear (+18%, p=0.2), hiding in the nest (+12%, p=0.3) and furtive glancing (+7%, p=0.06) but decreased jumping locomotion (-14%, p<0.01) and biting (-11%, p=0.01) compared to female control offspring. Additionally, male offspring showed increased fear (+10%, p=0.4) and decreased jumping locomotion (-14%, p=0.2) and biting (-12%, p=0.3) compared to male control offspring (Figure 2 and Supplementary File 9). Although some differences in behaviours are not statistically significant, numerically they show larger average treatment effects across all groups.

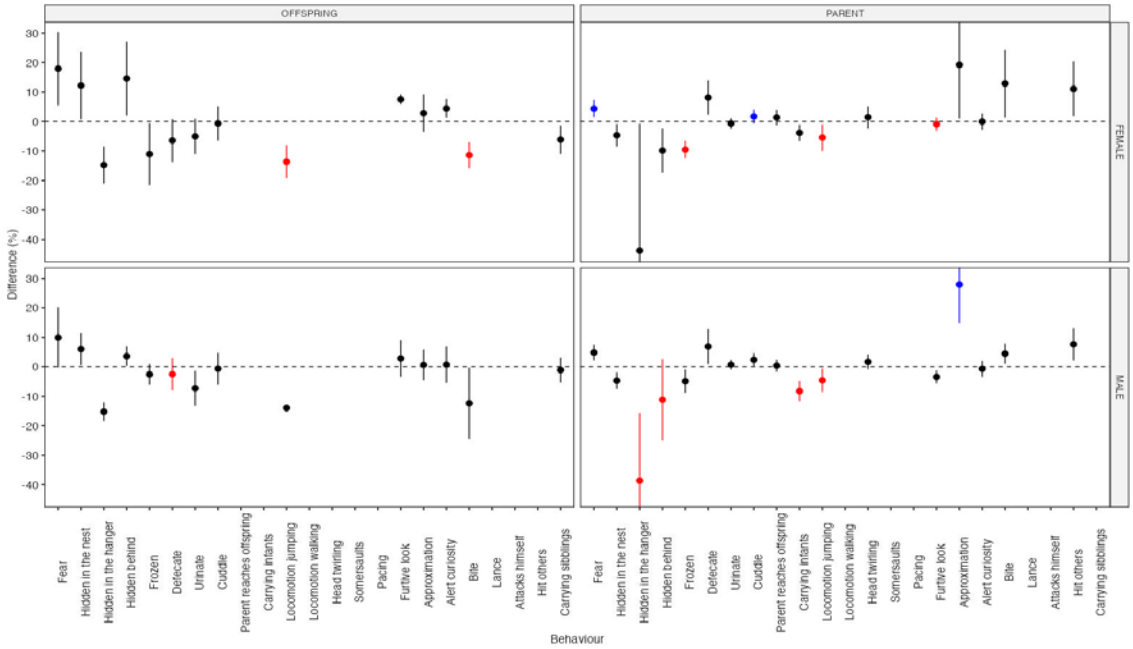


Figure 2. Behavioural differences in percentages between rejected parents and offspring and controls. Fathers n=20, mothers n=18, sons n=10 and daughters n=17. Black: p-value > 0.05, blue: higher presence of behaviour in parent-rejected owl monkeys (p-value < 0.05), and red: higher presence of behaviour in control owl monkeys (p-value < 0.05).

Parental rejection is associated with dysregulation of miRNA expression in blood. We conducted a differential expression analysis of whole blood miRNAs in animals with a history of rejection, their offspring, and controls (n=47). This analysis was performed to identify microRNAs whose expression significantly covaried with parental rejection history.

Whilst this section focused on commenting on significantly dysregulated miRNAs, we provide a complete list of all analysed miRNAs, including those that showed no significant changes (Supplementary File 7). To identify significantly altered miRNAs across these multiple comparisons, we used LIMMA TREND (Partek flow), which provides stringent false discovery rate control.

Our initial analysis demonstrated that, despite the association between adults with a history of rejection and the dysregulation of many miRNAs in blood, none passed the minimum FDR threshold in either rejected males (Figure 3.a) or rejected females (Figure 3.b). However, we did observe a down-regulated miRNA in males and females (mml-miR-182) which p-value was marginal (0.1<FDR-p>0.05). Subsequently, we compared miRNA in well-reared infants (F1) daughters and sons of parents who experienced rejection (n = 11) with offspring of controls (n = 9). This comparison revealed several differentially regulated miRNAs. Again, a miRNA shows common upregulation in female and male offspring (mml-miR320a) but effect did not reach significance (0.1<FDR-p>0.05). However, we did detect an interaction between parental rejection history and the expression of one miRNA: mml-miR-30a-5p, which was significantly overexpressed (FDR p=9.91e-3, FC = 2.09) in naïve daughters. This finding demonstrates the significant intergenerational effect of parental rejection history on well-reared offspring miRNA expression.

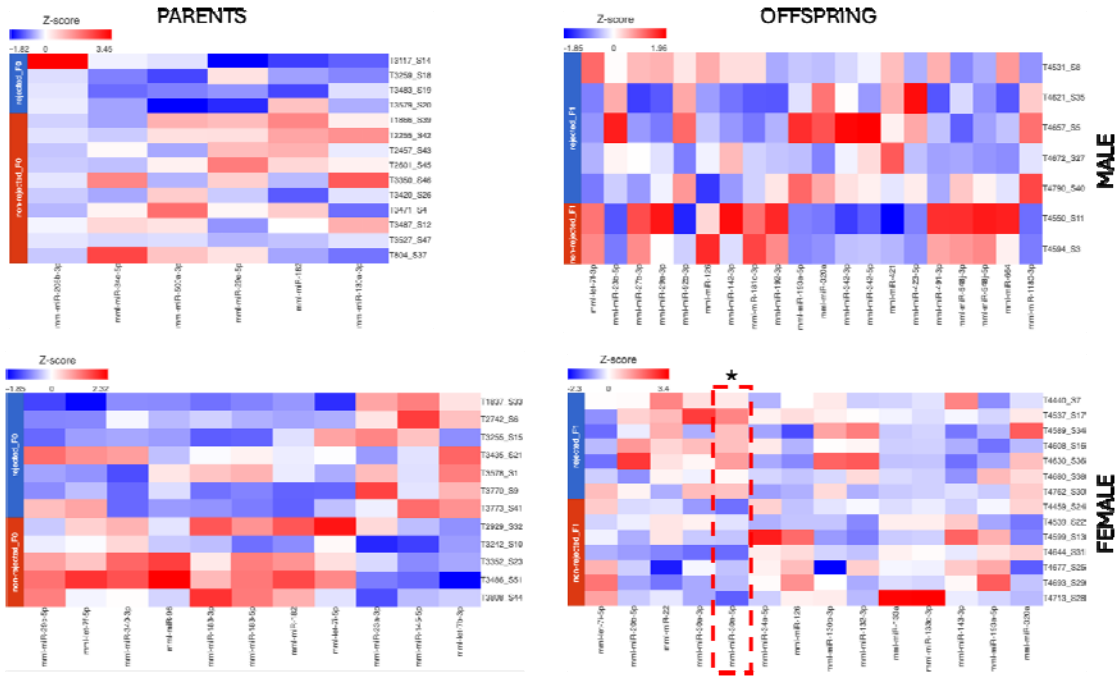


Figure 3. Effects of rejection on miRNA expression in whole blood across two generations of owl monkeys. Z-scores expression heatmaps showing standardise differences in miRNA expression. In heatmaps, blue tiles indicate downregulation, and red tiles indicate upregulation, darker tone indicates stronger dysregulation, and lighter tone denotes little or no change in expression. LIMMA TREND package (Partek Genomics Suite) was used for statistical analyses. Asterisk indicates significantly upregulated expression (FC ≥+1.5, FDR-p<0.05).

Discussion

Our findings suggest that complete rejection of newborns is a predictor of reduced lifespan, altered behaviours across two generations. Furthermore, the signature of rejection on miRNAs is detectable in well-reared daughters, suggesting involvement of epigenetic marks in transmission of stress.

First, our study demonstrated an association between being rejected and reduced probability of reaching reproductive age and a reduction in lifespan of 50%, even though these individuals were hand reared and cared for, and after weaning they lived in exact same conditions as controls. Our study reflects findings from previous studies linking early life adversity (ELA) and earlier mortality in wild baboons, rhesus macaques, and gorillas[,11,12,32]. The exact origin of frailty in the rejected owl monkeys remains unknown, but poorer health could in part explain the observed reduced lifespan in this population. We previously showed a higher frequency of clinic visits in rejected at 17 months[44]. Here, we demonstrate that, rejection remains a predictor of poor health outcomes through their lifespan (Figure 1c). Analysis of medical records of rejected show that rejected individuals were taken to clinics 1.13 times more often. The main reason was to be treated with broad spectrum antibiotics, suggesting greater susceptibility to infections. As pneumonia and enteritis due to infection are leading causes of mortality in this colony[24,43] increased risk for infections might account for observed higher morbidity, as seen in rhesus macaques[9]. Information available was patchy, and did not allow identification of specific pathogens or conditions. Nephropathies, cardiomyopathies, have also been observed in this colony and are associated to recent stressful exposure (e.g. transport) and sudden death in owl monkeys[43,49,50,51]. It remains untested that higher prevalence of these chronic conditions characterised the rejected.

We asked if survival of offspring of rejected owl monkeys might also be compromised, even when offspring of rejected and of controls were well-reared, considering intergenerational and transgenerational effects of stress on lifespan previously observed[17,30,52,53]. Altogether our demographic analysis supports the hypothesis that in captive owl monkeys' rejection history in parents is a contributor to reduction in lifespan in descendants. We found lower survival in F1, with significant reduced odds of survival to reproductive age, and a median lifespan which was half as short as controls. This is observed despite that, all sources of life history variation associated with intergenerational effects in previous studies do not exist in captivity. The only sources of energetic expenditure such as reaching developmental milestones, reproductive effort was also experienced by controls. Redirection of energetic resources to support other siblings could also be a source of ELA[17], however, reproductive rates between rejected and controls were not different (Supplementary File 10) therefore an unlikely cause of effects detected in this study. Retrospective study of health outcomes in F1 to explain earlier morbidity was not possible as medical records in this colony were created only when individuals visited the clinic and were lacking for most of our F1 sample. This in turn might indicate that negative health outcomes were not significant to merit medical attention and went undetected. Similarly, physiological or molecular profiling was not possible for most naïve offspring as they died before sampling for our study was conducted. However, we did characterise behaviour responses to stressor and miRNAs as possible contributors to transmission.

The ethological analysis conducted provided convincing evidence of intergenerational effects of parental rejection on behaviour in owl monkeys, particularly on emotional, locomotor and rejecting behaviours. Most pronounced changes in the rejected centred on fear responses and

boldness. Parentally rejected adults, showed notably greater boldness, frequently displaying reduced hiding behaviour when encountering new stressors. This effect parallels findings in mice subjected to experimental maternal separation[54,55]. Increased emotionality was also detected in rhesus macaques whose fathers were subject to separation from mothers in early life[15]. In our study offspring of rejected also showed increases in boldness and fear behaviours however these were below statistical significance.

Particularly significant were our findings on altered paternal care behaviour. Owl monkeys are renowned for their uniquely caring fathers, who assume primary responsibility for offspring[56]. Our research revealed that fathers who experienced parental rejection showed significantly reduced offspring transport behaviour suggesting a surprising plasticity of a behavioural trait considered an evolutionary constraint. The origin of this deficiency is unknown but could be due to poor development of social and attachment bonds during their early development[57].

Our study also reports decrease mobility responses to stress as an intergenerational effect associated with parental rejection. Reduced locomotion has also been observed in parentally deprived rhesus macaques[58] and marmosets[59]. In the context of stress, it is thought to reflect 'freezing' or tonic immobility, indicating neurobiological inhibition of fronto-amygdala connections that leads to inhibition of motor systems, as a possible mechanism of stress coping[60]. Decrease mobility in this context might stem from overactivity of HPA axis[61] co-occurring in rejected and offspring owl monkeys.

An interesting exception in behavioural similarities between generations was biting of others, which in female offspring of rejected parents was statistically less expressed than controls and showed an opposite direction of change from rejected parents, who significantly bit other animals more often than controls. In the context of our study, biting might reflect aggression or rejectfulness. Biting was previously reported in captive owl monkeys, as part of the maternal behavioural repertoire when rejecting infants during normal weaning[62]. The fact that we see it elevated in rejected parents would support the view that experiencing rejection might contribute to perpetuate cycles of rejecting behaviours[63-65] and will be studied in the future. However, the decrease of this response in female offspring of rejected suggests a suppression of a rejectful or aggressive behaviour in response to a stressful stimulus, even when higher emotionality was detected. This again suggests positive stress coping in the well-reared offspring of rejected.

Altered parental behaviours in rejected cannot just be explained as result of insufficient learning opportunities, as parents can reject their offspring even when they themselves were well-reared and manage to effectively care for some offspring. The altered behaviours in offspring of rejected can not be explained only as learnt, as behaviours opposed the found in parents (e.g. biting). Altogether, our findings indicate intergenerational inheritance of behavioural plasticity associated with spontaneous rejection in captivity in owl monkeys. This is an ecologically relevant finding, since all owl monkey mothers reject their babies soon after birth, and fathers provide care in captivity and in the wild[41,42,56].

We explored miRNA expression in rejected and progeny, as a possible mechanism of transmission of intergenerational effects, as small RNAs have been implicated on transmission of effects across taxa[38,39,40,66]. In brief, examination of microRNA expression patterns in blood shows that the rejection experience is associated with miRNA differential expression in female descendants in this colony but was not detectable in rejected individuals. It is not known if the dysregulated miRNA significantly identified (mml-miR-30a-5p) is functional in owl monkeys. If it were, the intergenerational effect on its expression, specific to female offspring of rejected parents, could contribute to explain the patterns of rejection in this colony and altered stress behaviours in descendants. This is proposed as miR-30a-5p

belongs to a miRNA family proposed as important mediator of social stress and its effects on behavioural disorders in mammals[67]. This miRNA was identified as a blood biomarker of depression in humans with history of early-life adversity, additionally, these authors revealed intergenerational epigenetic regulation of the gene that codes for this miRNA in rats[68].The overexpression of mml-miR30a-p we identified in offspring of rejected may have been whether inherited through altered miRNA in germline as seen in rodents[39] or the result of altered DNA methylation patterns[68] or be modified by exposure to altered behaviours in rejected parents. Since the miR-30a-5p was specifically upregulated in daughters, higher expression might increase the risk for stress disorders and rejections in future mothers in this population.

One remaining question was that rejected infants had some underlying health or genetic condition which could motivate their parents to cease reproductive investment. Abandonment and filicide of infants with apparent deformities and differences have been reported in humans and non-human primates[69,70]. However, veterinary records would suggest no obvious malformations or traits in rejected infants, as also observed in wild tamarins, where newborns rejected dis no show signs of underlying pathology in necropsy[71]. Significant genetic conditions incompatible with life are unlikely, as rejecting parents successfully reared other infants, and some of the rejected went to live for as long as controls. Genomic analysis also showed that apart from one miRNA, gene expression was similar across all animals, arguing against major genetic aberrations. Perhaps inheritance of other epigenetic marks associated with accelerated organismal senescence[72,73] or their expression in other tissues may contribute to explain effects of rejection on offspring. Indeed, we previously identified accelerated DNA hypomethylation with age in rejected owl monkeys, and that the effect of ageing exposures on DNA methylation like parenting were more pronounced in brain tissue[45]. Future studies will test the role of inherit altered DNA methylation patterns as carriers of intergenerational effects of rejection. Finally, our study highlights importance of additional care of descendants of rejected in captive breeding programmes of owl monkeys and other non-human primate species, where rejection of newborns has been observed[19-32,49,51,58,63]. This is important for preserving both the welfare of primates in captivity, but also to maintain quality of individuals produced for biomedical experimentation, for which non-human primates are commonly bred.

Conclusion

We identified clear associations between parental rejection and multiple intergenerational effects; first on survival rates and reduced probability of reaching reproductive age; second, both generations exhibited distinct behavioural patterns, particularly heightened fearfulness, increased rejectfulness to offspring and decreased locomotion; and third, we observed associated epigenetic differences, specifically the dysregulation of mml-miR-30a-5p in female descendants. Overall, intergenerational effects on rejection stress were largely detrimental, and reduced Darwinian fitness, although positive stress coping might also occur in descendants. Whether these have a role in adaptation whilst in captivity or just byproducts of altered physiology will be studied in the future.

Caveats

We were unable to collect data on foetal development and early life conditions that might influence both parental rejection behaviour and offspring outcomes or underlying contributing factors. The observed associations could be influenced by unmeasured factors, including maternal condition during pregnancy and parental experience. The functional significance of altered miRNAs in owl monkeys is untested.

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