Published in final edited form as:

Psychosom Med. 2016 ; 78(9): 1066–1071. doi:10.1097/PSY.0000000000000402.

Early Life Experiences and Telomere Length in Adult Rhesus Monkeys: An Exploratory Study

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Abstract

Objective—Child rearing environments have been associated with morbidity in adult rhesus monkeys. We examine whether such links are also seen with leukocyte telomere length.

Methods—To determine telomere length in leukocytes, blood was collected from 11 adult females aged seven to ten years who had been exposed to different rearing environments between birth and seven months. Four had been reared with their mothers in typical social groups comprised of other females, their offspring, and 1–2 adult males. The other seven had been reared in either small groups of peers or in individual cages with extensive peer interaction daily. After seven months, all shared a common environment.

Results—Telomere lengths were longer for those adults who had been reared with their mothers in social groups (median = 16.0 kb, interquartile range = 16.5–15.4) than for those who were reared without their mothers (median = 14.0 kb, interquartile range = 14.3–12.7; 2.2 kb/telomere difference, $p < 0.027$).

Conclusions—This observation adds to emerging knowledge about early adverse child rearing conditions and their potential for influencing later morbidity. As newborns were randomly assigned to the mother or other rearing conditions, the findings are not confounded by other conditions that co-occur with adverse child rearing environments in humans (e.g., prenatal stress, nutrition and health as well as postnatal nutrition and negative life experiences over and above rearing conditions).

Keywords

Rhesus monkeys; early social rearing; adult telomere length

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Conflicts of Interest: None of the authors declare a conflict of interest.

INTRODUCTION

Emerging research is examining links between adverse life experiences and telomere length. Telomere length is being seen as a measure of biological aging, especially when comparing length variations in same-aged individuals who have had more and less adversity in their early lives. During DNA replication, DNA polymerase cannot synthesize DNA *de novo*. Replication begins with the synthesis of a short RNA primer, which the DNA polymerase elongates in a 5' to 3' direction. Because RNA is unstable, this primer is subsequently removed. This means that the end of one strand of the chromosome shortens with each cycle of chromosomal replication and cellular division, resulting in an "end replication problem". To prevent the loss of vital genetic information, chromosome ends are capped by nucleoprotein complexes, termed telomeres. Telomeric DNA consists of long simple double-stranded repeats; in vertebrates this repeat is TTAGGG in the 5'-3' direction toward the chromosome end. In addition to preventing loss of genetic information, telomeres prevent chromosomal fusion and activation of the DNA damage checkpoint (reviewed in (1)).

Several human hereditary diseases are due to mutations in genes involved in telomere maintenance. For example half of individuals with dyskeratosis congenita have mutations in genes encoding the protein (*TERT*) or RNA (*TERC*) telomerase components, a regulator of *TERC* (*DKC1*), or a telomere-binding protein (*TINF2*), respectively (2). Additionally, telomere attrition is associated with aging, coronary artery disease and cancer-associated chronic inflammation (3). Although it is established that telomeres shorten with each cell division, the cause-effect relationship between telomere shortening and disease is not clear.

Numerous studies have reported negative associations between telomere length and environmental and social stress in humans. For example, perceived neighborhood quality (4–6), anxiety (7), exposure to intimate partner violence (8, 9), and being the primary caregiver of a child with a chronic condition (10) are all inversely correlated with telomere length, as typically measured during adulthood. Associations between telomere length and adverse early life experiences have also been observed (11–13). Adults reporting physical or emotional neglect during childhood had shorter telomeres than their counterparts who did not report any childhood maltreatment (14). In contrast, Verhoeven and colleagues found a greater association between short telomeres and recent stressful life events in a cohort of adults participating in the Netherlands Study of Depression and Anxiety (15).

Recent studies also demonstrate an association between telomere length and the quality of parent interaction. Early indications came from the Bucharest Early Intervention Project, a longitudinal, randomized trial, which compared foster care with institutional care in Romania. A negative correlation was observed between the duration of exposure to institutional care before the age of 54 months and telomere length measured when the children were between six and ten years old (16). Similarly, telomere length in children between 3.9 to 6.5 years old at high risk for maltreatment was shorter than the control group (17). Measurement of telomere length in early adulthood of individuals exposed to non-supportive parenting during adolescence also indicated an inverse association (18, 19). This was at least partly mediated by increased smoking and drinking in young adulthood (18). Adolescents exposed to non-supportive parenting who participated in a family intervention

program designed to foster resilience to stress (Adults in the Making (AIM) program) had longer telomeres than those who did not (19). An extension of this work compared the interaction between non-supportive parenting at age 17, telomere length at age 22 and genotype of rs53576, located within intron 3 of the *OXTR* gene, with and without intervention (20). This study demonstrated that nonsupportive parenting was associated with shorter telomeres in individuals having a homozygous GG genotype (20). Telomere length in individuals exposed to intervention or having at least one A allele at rs53576 did not show a significant association with nonsupportive parenting (20). A longitudinal study of 236 children from the Environmental-Risk Longitudinal Twin Study found that children exposed to violence had greater telomere attrition between the ages of five and ten years old than the control group, even after omitting more than 10 percent of the children from the analyses because they had longer telomeres at age 10 than at age five (9). Analysis of telomere length in a small sample of nine-year-old children exposed to harsh or nurturing social environments illustrated that the association between telomere length and social environment is moderated by polymorphisms in the dopaminergic and serotonergic pathways (21).

Despite these findings, the underlying processes and the biological significance are not well understood. Stress is known to influence certain physiological responses, such as hypothalamic-pituitary-adrenal (HPA) axis activation and inflammation which increase the cellular oxidative burden. This oxidative burden may damage the telomere, increasing rate of attrition (reduced length). It is also possible that this effect is mediated through components of the telomere maintenance machinery, such as telomerase. However, data directly linking oxidative stress to telomere length are limited (10, 22).

The study of stress in nonhuman primates has been very informative in understanding the effects on humans, not only because of their phylogenetic relationship, but also because of their social organization and cognitive abilities (reviewed in (23)). One form of early life adversity studied in considerable detail to date in rhesus monkeys and other macaque species has been nursery rearing from birth onward, followed by extensive socialization with same-age conspecific peers. Previous studies have demonstrated that, compared with infants reared by their biological mothers from birth and also given opportunities for socialization with peers (mother-reared), nursery-reared infants cling more, play less, tend to be more impulsive and aggressive, and exhibit significantly more behavioral and biological disruption, including higher levels of HPA activity following short-term social stressors, through 6–7 months of age. During their juvenile years, in the absence of any social intervention, nursery-reared youngsters show deficits in serotonergic function, have lower levels of serotonin transporter (5-HTT) binding throughout multiple brain regions, differ in patterns of brain lateralization and other aspects of brain structure and function, and are generally lower in social dominance rankings and in some measures of health status. Significant genome-wide differences in epigenetic patterns of gene expression in late infancy and in genome-wide patterns of methylation in both lymphocytes and prefrontal cortex in adulthood are found between nursery-reared and mother-reared subjects matched for age and sex (see (24–28) for recent comprehensive reviews of this extensive literature). The current study explored the effects of nursery-rearing during infancy on telomere length in adult female rhesus macaques.

METHODS

Subjects and Early Rearing History

This research was approved by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Animal Care and Use Committee and complied with all relevant provisions of the Animal Welfare Act. The subjects were 11 adult female rhesus monkeys (*Macaca mulatta*), ranging in age from 7 to 10 years at time of sampling. Males were not included as they leave their natal group shortly before puberty and thus would likely have had different environmental exposures which might influence telomere length. All had been born in the Laboratory of Comparative Ethology's primate facility at the National Institutes of Health Animal Center, located near Poolesville, MD, and randomly assigned to one of 3 standardized early rearing environments: four of the subjects were raised by their biological mothers in large indoor-outdoor pens, each containing 8–10 other adult females, 1–2 adult males and 3–4 infants born into the group the same year (mother-reared). They remained in these pens with their mothers and peers for their first 7 months of life. The other seven subjects (nursery-reared) were moved to the lab's neonatal nursery within 24 hours of birth and hand-reared by nursery staff for their first 37 days, during which time they received extensive handling from human caregivers as well as continuous exposure to a variety of enrichment items, including a mobile surrogate "mother." At 37 days, three of the seven nursery-reared infants were moved into group cages containing 3–4 like-reared, same-age peers, with whom they remained in continuous contact for the next 6 months (peer-reared). The other four nursery-reared infants were housed in individual cages containing an inanimate surrogate mother, toys, and other enrichment objects and, in addition to receiving extensive contact with nursery personnel, were given two hours of daily interaction with 3–4 similarly reared peers in a "play pen" filled with a changing variety of toys and enrichment devices (reared alone). At 8 months of age, all of the mother-reared and nursery-reared (both those reared with peers and alone) monkeys were moved into one large pen, where they lived together with other male and female same-age peers until puberty. Thus, the differential social rearing occurred only for the first 7 months; thereafter all mother-reared and nursery-reared females shared the same physical and social environment. All subjects were subsequently moved into the afore-described indoor-outdoor pens at least 4 years prior to sampling (more complete descriptions of these standardized rearing procedures can be found in (29, 30). Within each pen, no basic differences in the distribution of relative dominance status as a function of early rearing history were seen, i.e., there were both high-ranking and low-ranking mother-reared females and also both high-ranking and low-ranking nursery-reared females. No differences in the distribution of the rearing conditions of the monkeys' own mothers (some had themselves been mother-reared, peer-reared or reared alone) appeared. No group differences were found in frequency of treatment for gastrointestinal disorders (e.g. shigella/diarrhea), either prior to weaning or after weaning up to the time of sample collection. The three rearing groups had roughly equal numbers of total veterinary treatments, with a slight bias for more treatments for monkeys raised alone (difference not significant). Most treatments were for bite wounds, initiated almost immediately following detection during twice-daily general health checks by caretaking staff, with regular follow up exams continuing as determined by veterinary staff. The number of veterinary treatments was more closely related to the relative social dominance

status of each individual within each of the pens rather than rearing background of the individual herself. No group differences in weight were found at weaning, 65 months after weaning or at time of sampling. None of the subjects were either caring for an infant or pregnant on the day of sampling, although nine of the eleven females had produced infants in previous years (see Table 1).

Blood Sampling Procedure

Blood draws for the present study were taken when the monkeys were sedated for one of their routine quarter-annual standardized veterinary examinations. Sampling of all eleven monkeys took place on the same day (7/8/14). A detailed description of the actual sampling procedure can be found in (30). After completion of the procedure, the blood samples were stored at 4 °C for transfer and prior to DNA isolation.

DNA Isolation

DNA was isolated from whole blood within 24 hours of sampling using the NucleoSpin® Blood purification kit (Macherey-Nagel) according to the manufacturer's protocol.

Telomere Length Measurement

Telomere length was measured using an absolute quantitative real time PCR (qPCR) assay that uses double-stranded oligonucleotide standards to permit measurement of telomeres in kilobases per telomere as previously described (21, 31). Relative telomere length was determined by calculating the ratio of telomere repeats to a single-copy reference gene (*36B4*, which encodes acidic ribosomal phosphoprotein P0). An 84-mer containing TTAGGG repeats and a 79-mer containing 36B4 sequence were used to construct standard curves to determine absolute telomere length and number of diploid genomes, respectively. Telomere length and 36B4 qPCR was performed on separate plates for each sample in triplicate and the results averaged. Individual telomere length was calculated by dividing the telomere length per genome by 92, the number of telomeres per diploid genome. All samples were run on one plate which also included reference DNA from a telomerase⁻ cell line and the same line after stable integration of *TERT* (the gene encoding the protein component of telomerase) to control for inter-plate variation. Human genomic DNA was also included to calculate the coefficient of variation as previously described (32). The experiment was repeated once (such that each sample was measured a total of six times on two plates) and the coefficient of variation was 3.6 percent. Values presented are the average of the two experiments ($r = 0.74$, $p < 0.01$).

Statistical Analysis

Data were analyzed using R (33) and plotted using the ggplot2 R package (34). Telomere length between groups (nursery-reared versus mother-reared, peer-reared versus surrogate peer-reared) was compared using Student *t*-tests (function *t.test*). Pearson's correlations were calculated using the *cor.test* function.

RESULTS

Genomic DNA was isolated from blood samples of the eleven adult female monkeys. The average telomere length was 14.4 kb/telomere for the eleven monkeys. This length is as expected since non-human primate telomeres are longer than human (35). No significant differences in telomere length were found as a function of parity. No telomere length difference was found between the two groups of nursery-reared monkeys (mean=13.64 $\pm$ 1.1 kb/telomere for the reared alone group and mean=13.59 $\pm$ 1.1 kb/telomere for the peer-reared group; by a two-way *t*-test; (*p*-value = 0.95)). These groups were combined. The average telomere length of the mother-reared group (15.8 $\pm$ 1.3 kb/telomere) was 2.2 kb/telomere longer than that of the nursery-reared group (13.6 $\pm$ 1.0 kb/ telomere; Figure 1). This difference was statistically significant by a two-tailed *t*-test (*p*-value = 0.027). The correlation between chronological age (in years) and telomere length was -0.15 (*p*-value=.66).

DISCUSSION

Early rearing conditions are linked to telomere length in adult female rhesus monkeys. Those adults who were reared with their mothers in species-normative social groups had longer telomere lengths than those who were raised without their mothers but with peer interaction. Even with a small number of monkeys, significant differences were found. No significant differences in telomere length were observed between peer-reared and surrogate peer-reared monkeys. The similarities between the groups in terms of veterinary care and weight at time of sampling are consistent with a shared environment for the the individuals' lives after early childhood.

Although the mechanisms through which stress affects telomere length on an organismal level are unknown, it has been postulated that oxidative DNA damage due to stress pathway activation results in increased telomere attrition (e.g. (8, 10, 36)). Our findings are in line with those reporting inflammatory and immune function differences between mother and peer-reared adult rhesus monkeys also from the Laboratory of Comparative Ethology (19, 26). As such, telomere length may be seen as another indicator of potential disease or at the very least of biological aging.

Fascinating questions remain to be addressed. First, we do not know how early such telomere length differences appear. Our monkeys were seven to ten years of age, well into adulthood. Differences could possibly appear prior to puberty or, in contrast, might not appear until early adulthood. In addition, differences could widen or narrow over age. More developmental research would address these questions.

Second, while the experimental study of child rearing conditions demonstrates negative consequences of being reared without a mother, whether these consequences can be reversed is an open question. For example, interventions such as introducing "foster grandparents" to newly constituted peers groups of monkeys at 8 months of age (19) suggest that at least some reversibility might be possible, at least in behavior and perhaps in reactivity. Other studies have shown that relative complexity of play with peers (37), HPA activity (29), and

maternal competence (38) can be enhanced in nursery-reared individuals by stable social environments. Patterns of genome-wide methylation in lymphocytes (25) may also be reversible, in contrast to the present findings regarding adult telomere length. On the other hand, studies focusing on other outcome measures, e.g., certain long-term health outcomes (39), and adult methylation patterns in prefrontal cortex (40), have found persisting effects that seemingly parallel those seen in telomere length. Given these apparent disparities in long-term consequences of early adverse experiences such as nursery rearing, it would seem useful to know (a) how early do differences in telomere length appear, (b) are those differences stable throughout the whole of development or do they fluctuate, e.g., become reduced during puberty but then re-appear in adulthood and/or become greater with increasing age, and (c) how does change in telomere length relate to documented developmental changes in other aspects of behavioral and biological functioning? Whether telomere length differences would disappear or be attenuated in the face of social or other forms of intervention is unknown at this point.

Third, these findings have relevance for the rapidly emerging research on telomere length in humans as influenced by adverse life conditions. Several different lines of research have found links between adverse life experiences in the early years of life and adult telomere length (11–13). These studies are difficult to interpret given that adversities tend to co-occur. It is virtually impossible without birth cohort studies to isolate the effects of adult adversities from childhood adversities vis-a-vis independent effects of either on telomere length or other biological indicators. Birth cohort studies can overcome some of these difficulties, as can experimental studies such as this one.

Human infants reared in adverse situations, the most severe of which would be abandonment (resulting in being raised in an orphanage or by foster parents)), or persistent severe abuse or neglect, also are likely to have experienced perinatal stress, health or nutrition issues which in and of themselves have biological consequences including altered telomere length. Additionally, postnatal adversities are likely to exist, including but not limited to, nutrition inadequacy, financial hardship, frequent moves, inadequate housing and chaotic home environments. All of these conditions might influence telomere length, again limiting our ability to identify which adverse conditions are responsible for biological aging. Alternatively, telomere length may be compromised not by a specific condition but by the accumulation of adversities. Associations with telomere length might be due to perinatal or postnatal adversities rather than being reared without the mother specifically. The experimental data presented here are able to focus on rearing while excluding many other potential explanations.

Fourth, it is not known whether the telomere lengths of the offspring will be influenced by their mother's rearing conditions. Research on inter-generational effects on methylation using various rodent models suggest that biological cross-generational transmission is possible (41–44).

Of course, answers to such questions cannot be provided by the present study, which only looked at a single point in time and did not examine possible associations between telomere length and other measures of behavioral and biological functioning. In addition, the sample

is small, so that these results might be seen as exploratory. To our knowledge, however, these analyses are the first to examine telomere length as a function of rearing conditions in adult monkeys. Future longitudinal studies examining the relationship between telomere length attrition and rearing conditions will provide additional information to better understand the timing and perhaps the nature of the non-human primate response to maternal separation. Does accelerated telomere shortening occur consistently into adulthood or is it only observed during childhood? Furthermore, incorporation of additional physiological measures of the stress response and long term physiological well being may contribute to our understanding of the significance of telomere length with respect to health and mortality.

Acknowledgments

The authors would like to thank Michelle Miller, and Kristen L. Byers for overseeing the collection and transport of blood samples, Elizabeth Conroy and Iulia Kotenko for aid in measuring telomere length and Sarah Lazzeroni for assistance with the preparation of this manuscript,. Funding for this study was provided by the Division of Intramural Research (S.J.S.) and extramural grant #5R91HD076592 (D.A.N.) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Abbreviations

DNA	deoxyribonucleic acid
HPA	hypothalamic-pituitary-adrenal
C	celsius
PCR	polymerase chain reaction
qPCR	quantitative polymerase chain reaction
kb	kilobase
NR	nursery-reared
SPR	surrogate-peer-reared
PR	peer-reared
MR	mother-reared

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Figure 1. Scatterplot of telomere lengths of subjects that were raised by their biological mothers (MR) or nursery-reared (NR) during the first seven to eight months of their lives. Lines represent group means.

Table 1

Age, parity, rearing, origin and telomere length of subjects in the study.

Sample ID	Age (Years)	Parity	Rear* Rear	Infant Present on 7/8/14	Telomere Length (kb/telomere)
<u>Nursery-Reared</u>					
ZC05	10	3	SPR	No	12.6
ZC09	10	3	SPR	No	15
ZE10	8	2	SPR	No	14.2
ZE25	8	1	SPR	No	12.8
ZE38	8	2	PR	No	12.3
ZE52	8	2	PR	No	14.4
ZF69	7	0	PR	No	14.0
<u>Mother-Reared</u>					
ZE53	8	2	MR	No	14.1
ZE70	8	3	MR	No	15.8
ZE84	8	2	MR	No	16.3
ZE85	8	0	MR	No	17.1

* SPR – Surrogate-peer-reared, PR – Peer-reared, MR – Mother-reared.