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Review of Maternal Deprivation Experiments on Primates at the National Institutes of Health

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This document provides a critical scientific review and assessment of continuing maternal deprivation and psychopathology studies on nonhuman primates conducted within the National Institutes of Health (NIH) Intramural Research Program. A careful analysis of Animal Study Proposals, Board of Scientific Counselors reviews, scientific publications, photographs, and videos related to these projects casts doubt on the worth of these experiments in light of advancements in the field, and offers several examples of human-based studies that successfully address precisely the questions asked by these NIH investigators. Moreover, after consulting numerous experts in the fields of anthropology, primatology. medicine, and mental health, we conclude **that given the harm caused to animals, the experiments' limited relevance to humans, the substantial financial cost, and the existence of superior nonanimal research methods that the continued use of animals in this work is scientifically and ethically unjustifiable.**

Project title: "Biobehavioral Reactivity in Monkeys"
Institute: National Institute Of Child Health And Development (NICHD)
Principal Investigator: Stephen J. Suomi
Intramural Animal Study Proposal: 11-043
Project Number: 1ZIAHD001106
Start/end: 2007–present
Funding: $907,723 in 2013 ($7,786,372 total)

At the foundation of all of the studies in question are maternal deprivation experiments conducted by Stephen J. Suomi and the Laboratory of Cognitive Ethology (LCE) at NICHD. For the past three decades, Suomi's group has utilized a maternal deprivation model of psychopathology, depriving hundreds of infant macaques of maternal contact and resulting in animals with an array of cognitive, social, emotional, and physical deficits that persist throughout their lifetimes. According to the approved Animal Study Proposal (ASP), approximately 45 macaques are selectively bred each year to carry different alleles of the 5H-TTT and MAO-1 genes, known to be risk factors for psychopathology in humans. Half of these captive-born infants are separated

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from their mothers within 24 hours of birth, causing great distress to mother and baby, and are hand-reared by humans in a nursery for one month and then put into a nursery with other like-reared peers, sometimes with a terrycloth-covered water bottle. Starting on their first day of birth, all infants are subject to numerous fear, stress, and pain-inducing tests. Day-old infants are forcibly restrained by experimenters for behavioral tests, such as facial imitation or head-orientation bias trials. Other experiments entail the infants being isolated in small cages, placed in unfamiliar locations, and deliberately startled by threatening human strangers, unfamiliar objects (including realistic-looking snakes, which are innately frightening to monkeys), and unfamiliar conspecifics. In one such procedure designed to measure infants' auditory startle response, newborn infants are restrained inside tiny mesh cages and placed in "startle chambers" where they are presented with unexpected loud noises. During their first few months of life, the infants are repeatedly subjected to blood draws and cerebral spinal fluid taps; hair and saliva samples are also taken. Additionally, in a project funded by the NICHD (Project 5P01HD064653; $877,229 of funding in 2013), Nathan A. Fox from the University of Maryland takes infants as young as one day old from Suomi's colony, shaves their heads, and physically restrains them for electroencephalogram testing.[1,2]

The approved ASP for the breeding and experimentation regimen (11-043) in Suomi's laboratory does not explain the scientific relevance of the single nucleotide polymorphisms that animals are bred to carry, their methods for selective breeding of these animals, the exact conditions they classify as "mother-rearing," the scientific purpose for numerous cognitive and biological tests being conducted, or any risk factors associated with capture, restraint, and biological or behavioral testing that they perform repeatedly on the animals.

The NIH Policy Manual for Animal Care and Use in the Intramural Research Program clearly states that the Principal/Responsible Investigator is accountable for assuring that the "proposed studies are not unnecessarily duplicative" (p. 7).[3] Several of the experiments currently being conducted have already been performed using the same procedures and the results published.[4,5,6,7,8,9,10,11,12] The rearing procedures described have been in place for decades, and behavioral and biological data from these animals have also been collected for decades.[13,14,15,16] Repeating these test batteries and causing suffering to additional infant monkeys is required by law to be justified; however, given the limited information contained in the ASP, it is virtually impossible for a review committee to adequately evaluate the project's design or scientific merit. The LCE's approved ASP emphasizes that the purpose of the study is to model the genetic and environmental contributions to abnormal human behavior and to develop interventions for at-risk individuals. However, a comprehensive review shows that none of the aforementioned studies have resulted in the development or modification of treatments for the human mental illnesses they are purported to model.

In addition to the study designed to create and quantify mental illness in infant macaques, the LCE has also received $6,289,327 since 2007 to assess whether the laboratory-reared, mentally ill animals they created can adapt to a nonlaboratory environment (Project 1ZIAHD001107). According to the approved ASP associated with this project (11-105), the purpose of the study is to understand "how humans of all ages and backgrounds adapt to new physical and social settings, as well as what aspects of their immediate environment might be affecting their psychological well-being." However, in their 2013 annual NIH Intramural Database report, the experimenters describe several findings related to infant-mother

communication, facial processing in infants, the effect of oxytocin on monkey-human interactions, and cortisol levels in nursing mothers' milk. The discrepancy between the procedures and purposes outlined in the ASP and the reported findings from those procedures makes it difficult to evaluate the value of this study in understanding human health and behavior.

Though the ASPs for these projects claim the protocols are designed to elucidate genetic and environmental influences on pathological behavior unattainable with human participants, many resultant publications from these projects merely address whether macaques exhibit visual preferences, facial asymmetries, facial preferences, imitative behaviors, or similar hand- and head-orientation biases as those already well documented in human infants.[17,18,19,20,21] Given the wealth of knowledge about human behaviors of this sort—and the non-invasive research with humans available to further explore these same issues—these studies are gratuitous.

Project title: "Assessment of Neural and Behavioral Alterations Associated with Chronic Fluoxetine Administration in Adolescence"
Institute: National Institute of Mental Health (NIMH)
Principal Investigator: Bruno Averbeck
Intramural Animal Study Proposal: IPC-01-09
Project Number: MH002902
Start/end: 2007–present
Funding: $9,034,371 total

At NIMH, the Non-Human Primate Core purchases many of the maternally deprived, at-risk for illness animals created in Suomi's laboratory for its own battery of experiments. Some of these studies expose the animals to additional acute startle and isolation[22] in hopes of eliciting a pathological response to stress as a function of their early-adverse rearing conditions. For example, infants and juveniles are restrained inside tiny mesh cages or in restraint chairs and placed into startle chambers where they are deliberately startled by the presence of a human, loud auditory stimuli, or powerful bursts of air. To acclimate them to the chair restraint, the older animals spend up to an hour a day, every day, strapped to a chair for weeks *prior* to testing. In other experiments, the infant monkeys are caged with their mothers—who are chemically sedated so as to be unresponsive—and placed in a car seat.[23] Videos of these experiments indicate that infants are terrified and confused while they try to revive their mothers.

In addition to various oral, subcutaneous, and intramuscular administrations of drugs, some animals are surgically implanted with devices that allow intracranial administration of pharmaceuticals, requiring multiple surgeries, weeks of recovery and pain management, and constant monitoring for infection. According to the ASP, the purpose of this pharmaceutical treatment is to "define specific neural pathways important to the expression of emotional, social, or cognitive deficits associated with differential rearing histories." However, the exact drugs administered intracranially are not specified but described as "substances of interest [that] are likely to include NM concentrations of the neuropeptides oxytocin, vasopressin, CRH, MEK inhibitor PD98592, or GABA agonists such as muscimo and bicuculine, as well

as genes attached to viral vectors (AAV-P11)." Without including this critical information in the ASP, there is no way for reviewers to evaluate the merits of the proposed experiments.

Some animals are injected with Interferon-alpha, which creates depressive-like symptoms in the monkeys and causes heightened sensitivity to pain, ahedonia, and anorexia. This procedure is classified as causing unrelieved pain and/or distress to those animals to whom it is administered. An unspecified number of animals in this project will be killed following pharmaceutical administration.

In their approved ASP to conduct these experiments (IPC-01-09), the experimenters argue that "these experiments could provide important insights about the pathoetiology as well as potential, novel treatments for human syndromes with social detachment." In their 2010 annual NIH Intramural Database report, they write, "A major public health concern has emerged regarding the treatment of children with psychotherapeutic drugs. This study seeks to inform this important concern." However, these statements seem to contradict other claims from this same project in a subsequent publication in *The American Journal of Psychiatry* in which the authors themselves conclude the following:

"…[M]any findings from behavioral and biochemical studies in monkeys and other animals are not replicated in humans. Accordingly, this study cannot directly address the safety and efficacy of SSRIs in children and adolescents with psychiatric disorders. … [T]his animal model of maternal separation has never been validated as a measure of drug efficacy in humans[.] … The only way to know definitively whether SSRIs persistently upregulate SERT in humans would be to study our species"(p. 7-8).[24]

In addition to the projects and procedures described above, many animals from Suomi's LCE have been used for additional testing with the NIAAA. One project (Project Number: 1ZIAAA000214), which received $4 million dollars between 2007 and 2010, studied juvenile monkeys' response to acute social separation,[25] spontaneous alcohol consumption,[26] and even acute ethanol exposure,[27] which requires the animals to be restrained while high concentrations of ethanol are administered intravenously. These alcohol exposure studies often result in alcohol addiction, increased aggression, and increased susceptibility to depression in macaques.[28,29,30,31] Other animals are transported to Wake Forest University to be used in Project 5U01AA014106 where they undergo additional alcohol exposure testing before being killed and dissected.[32,33,34] The Wake Forest study received $3,931,858 in funding from 2003 and 2011.

Inapplicability to human mental illness

The experimenters that are discussed above seek to justify the use of animals by positing that maternally deprived macaques model the effect of early-life stress on the development of mood and anxiety disorders in humans. In addition to fundamental differences in gene expression,[35,36,37,38] brain anatomy and physiology,[39,40,41,42] and development[43,44] among humans and other primates, these adverse environments *do not* adequately represent the type of early social and physical stressors that precipitate mental illness in human children and adults. In reality, sexual abuse, physical abuse, prenatal stress, parental drug abuse, parental mental illness and/or criminal behavior, and economic stress are more common early life traumas affiliated with later mental illness and often co-occur in affected individuals.[45,46,47] However, details regarding infants' *in utero* environment are not described in these studies,

nor are details regarding the mothers' genetic makeup, rearing history, or mental health status—all of which are far likely more important contributors to the development of mental illness than the postnatal manipulations imposed by these researchers. Additionally, while macaque social structure may be as complex as human social structure, it is decidedly different from that of most modern human societies. For example, it is typical for infant macaques to stay in *constant* physical contact with their mothers for their first month of life,[48]making even the briefest separation stressful for infants as well as chronic separation more detrimental than can be expected in humans in most cultures. Therefore, any applicability of this nonhuman primate model is likely to vary dramatically across different human cultures with different social structures and traditional rearing practices. Even the "typical" mother-reared infants who are used as a control group in most of these experiments spend much of their time in barren, metal cages, and are subject to constant experimental testing, requiring multiple separations from their mother, and involving stress and/or fear-inducing tests.[22,49] These living conditions and frequent maternal separations likely impact the natural infant-mother behavior that would occur in the wild, and as reviewed below, increase the stress levels and mental health of all animals included in the study. The mother-reared infants cannot provide an accurate example of "typical" or "healthy" development for any species, and the additional stress of laboratory conditions confound the experimental stressors introduced in maternally deprived animals. Therefore, these studies using a "well controlled" nonhuman primate model fail to properly model the complex relationship between genes, early life experience, and mental illness in the human population. The evidence of this fact is that, collectively, the project has not resulted in any new treatments for human mental illness.

Existing clinical research and nonanimal methodologies readily available

The principal investigators on the aforementioned projects contend that controlled studies of gene-environment interactions in humans are ethically and practically untenable. However, this contention is inaccurate. Numerous large-scale epidemiological studies in humans have documented the effects of early life stress,[50,51,52] genetic risk,[53,54,55] and gene-environment interactions,[56,57,58,59,60,61] on abnormal social, emotional, and behavioral development. These studies include investigating the contribution of both genes and the environment in the development of mood disorders,[57,58] addiction,[62] depression,[63] and altered brain structure and function[64,65,66] in humans.

Recent human studies have also begun to unlock the complex biological and molecular mechanisms that underlie these gene and environmental interactions.[62,67,68,69] For example, McGowan et al.[62] and Klengel et al.[69] studied the interaction between early childhood trauma and genetic variation on gene transcription in the brains of humans. Similarly, in a large-scale study of nearly 200 individuals, Buchman et al.[68] tested the interaction between early-life psychosocial adversity, genetic make-up, and plasma levels of brain-derived neurotrophic factor, critical for brain development and plasticity. DNA methylation, studied in the brain tissue of monkeys killed in the NIH studies, can be non-invasively measured in monocytes and T-cells and correlated with neurotransmitter synthesis using positron emission tomography *in vivo* in humans, a technique recently used to determine the relationship between childhood aggression, DNA methylation, and serotonergic function in humans.[67] Postmortem studies using brain tissue from humans at different stages of development[70] as well as those from individuals suffering from or carrying genes associated with autism,[71,72] depression,[73] and schizophrenia[74,75] have identified critical differences in gene expression

across age, species, and clinical populations. These groundbreaking studies have already begun detailing genetic *and* epigenetic effects on human brain structure, function, and development in humans suffering from mental illness—details not attainable from animal models.

Additionally, the mood-altering effects of the type of drugs being tested by the NIMH Non-Human Primate Core, including fluoxetine,[76] oxytocin,[77] diazepam,[78] and dopamanergic and serotonergic drugs such as raclopride and buspirone,[79,80] are already well documented in humans suffering from mental illness. These studies have been conducted with healthy volunteers,[81,82,83] children,[75,84,85] and patients with mental illness.[86,87] The impact that these drugs have on brain structure and function have also been evaluated in human volunteers,[78,88,89] and their neural mechanisms in healthy and ill children and adults are already well delineated.[90,91,92,93]

Impact on animal welfare

The physical and psychological harms of confining primates and other animals in laboratories and subjecting them to routine and experimental procedures are well established.[94,95] Primates experience increased stress from common laboratory procedures such as cage cleaning,[96] physical examination,[97] blood draws,[98] and restraint.[99] The mere physical presence of human experimenters and technicians increases stress in primates.[100,101] Numerous studies have demonstrated that even minor changes in primates' captive environment, including temporary changes in cage size or location, increase stress levels.[102,103] It is not surprising that decreased immune system functioning[104] and increased self-injurious behavior are common in primates in laboratories.[105,106]

Specific to the experiments in question, the intention of these projects is to create, psychological illness in primates. Maternal deprivation, repeated restraint and social isolation, repeated exposure to startling sounds and frightening situations, and repeated blood draws, spinal taps, drug injections, and brain imaging procedures take an enormous toll on the psychological well being of these animals.

The numerous long-term negative outcomes of these motherless rearing conditions on monkeys have been well established for decades: mother-deprived infants exhibit excessive fearfulness and/or aggression,[48] produce excess stress hormones,[107] and frequently rank at the bottom of the social dominance hierarchy.[48] They exhibit motor stereotypies indicative of frustration and stress,[108] abnormal sleep patterns,[109] increased susceptibility to alcohol abuse,[110] and increased startle and stress responses to threatening stimuli.[111] Maternal deprivation affects serotonin pathway function[112,113] and cerebral blood flow[114] and alters levels of brain-derived neurotrophic factor and nerve growth factor critical for normal brain function[115] and has long-term effects on brain morphology.[116] Both spontaneous and selectively bred genetic variations in the macaques interact with adverse rearing conditions, often exacerbating the already profoundly negative effects of adverse rearing.[117,118,119]

Additional independent review

To extend the depth of our analysis of these experiments, we have consulted with independent subject matter experts in the fields of mental health, medicine, anthropology, and primatology (they were not compensated in any way by PETA). Concerns of several of these specialists, which they have provided to PETA in writing, are as follows:

- *"Given the current status and progress of the research (as assessed via the published literature), I can no longer see a potential benefit from such experimentation as is ongoing currently. I cannot consider the depicted experiments, designed to create and study psychopathology in monkeys, to be a valuable undertaking that will likely contribute to the health and well being of humans……From the methodologies described in the proposals and articles and the written and visual documentation provided by PETA of actual laboratory procedures and activities, it is my assessment that the monkeys used in these experiments experience substantial psychological (and likely physiological) harm and that there is no current evidence that there will be any results from the studies that move our understanding of human psychopathology forward."*

  Agustìn Fuentes, PhD
  Chair of Anthropology
  University of Notre Dame

- *"The cause of mental illness in humans is unknown, but it is clearly complex and multifactorial. Some genetic studies are promising. Abusing monkeys, however, won't get us any closer to that understanding."*

  Jaymie Shanker, MD
  Board-certified psychiatrist

- *"Taken as a group and without exception, these experiments are cruel, plunging infant monkeys into hellish conditions that they can neither control nor escape from. Ethically and morally, they have no place in science today. The cost to these animals is far too high. As we have seen, it is not as if the experiments lead to an earth-shattering breakthrough that could, in some moral calculus (though not PETA's and not mine), give us reason to think the cost was remotely worth it. This lack of justification is particularly true given the myriad of human-based research methodologies available to study the environmental, genetic, and social causes of mental illness as well as the fact that these experiments on monkeys often seek to replicate knowledge already ascertained in humans."*

  Barbara J. King, PhD
  Chancellor Professor of
  Anthropology
  College of William and Mary

- *"The scientific objections to continuing this research are immediately obvious. If the goal is to model neuropathologic/neurophysiologic substrates of human psychiatric diseases, then these efforts are hopelessly crude and antiquated, having long been superseded by in vivo neuroimaging studies of human patients with the psychiatric diseases of interest. Simply conduct a search in PubMed on any psychiatric diagnosis, such as psychopathic personality disorder, depression, schizophrenia, and a host of others, and you will find dozens of current, sophisticated, state-of-the-art neuroimaging studies comparing brain structure and function in patients and controls, clearly delineating structural and functional abnormalities in human patients. These patients, along with their early life experiences, genetic make-up, and medical histories, can be followed longitudinally to*

evaluate illness etiology and treatment efficacy. Modern research methodology has also allowed investigators to measure the separate and interacting contribution of genes and early environmental stress in the development and neural substrates of mental illnesses in humans. Postmortem studies of human brain tissue from individuals with mental illnesses or individuals carrying risk-alleles associated with psychiatric diseases are far better methods for clarifying the molecular etiologies of these complex ailments. , , If the goal of the infant monkey psychological trauma experiments is not to eventually improve our understanding of human psychiatric diseases—as the above cited imaging, genetic, and epidemiological studies are already doing—then in the zero sum game of research funding, the National Institutes of Health (presumably referring to human health) should have nothing to do with them."

Lawrence A. Hansen, MD
Professor of Neuroscience
and Pathology
University of California-San
Diego School of Medicine

- *"It is not surprising that monkeys reared under such adverse conditions at the NIH are physically, mentally, and emotionally unwell. However, despite the outcome being known, it is surprising that experiments in which these animals are deliberately subjected to extreme stress are allowed to continue. Moreover, monkeys are not humans, so any experimental findings that are true of monkeys would not necessarily be true of humans. If the researchers who are performing these experiments wish to argue that the monkeys are similar enough to humans in terms of emotional development that studies done on them can be applied to human development, then they must acknowledge that they are performing studies that cause intense pain and terror to their subjects, much as any human would experience intense pain and terror were these experiments performed on humans……. The American Psychological Association should not permit these experiments, which I believe are in violation of several sections of the APA Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research. Specifically, Guideline I (2) states that "[T]he scientific purpose of the research should be of sufficient potential significance to justify the use of nonhuman animals" and notes that "psychologists should act on the assumption that procedures that are likely to produce pain in humans may also do so in other animals." Yet, in a 2014 paper published in The American Journal of Psychiatry, the experimenters acknowledge that their anti-depressant experiments on monkeys cannot be applied to humans, that maternal deprivation studies on monkeys have never been confirmed as an effective way to test the efficacy of drug treatments for human mental illness, and that the only way to test treatments for human psychological disorders is in humans."*

Michael Radkowsky, PsyD
Clinical psychologist

- *"If these experiments are meant to parallel or predict the psychopathy and mental illness of human infants in the care of negligent, absent, and/or abusive mothers, they fail profoundly. Contrived maternal deprivation, chronic exposure to stressful experimental paradigms, confinement, and social isolation in laboratory settings do not parallel the*

types of early stressors experienced by most human mental illness sufferers. These laboratory versions of early-life adversity are too routinized and methodical to be representative of any real-world experiences faced by humans. The circumstances surrounding physical, social, emotional, and cognitive development in human beings is multifaceted and more complicated than those that can be imposed on infant monkeys reared in a laboratory. Good, creative research either cleverly sets up situations that allow behavioral and biological responses of interest to occur naturally, or it takes the form of field studies to observe real-world dynamics in a natural setting. The NIH experiments depicted on video include constraining infants in small cages and startling them with loud noises, trapping infants and then threatening them with human experimenters, or caging them with a drugged, unresponsive mother. These procedures do not accurately or creatively replicate the stressful situations believed to precipitate mental illness in humans."

Nora J. Johnson, PsyD
Clinical psychologist
University of Pennsylvania
Health System

- *"I do not consider the depicted experiments, designed to create and study psychopathology in monkeys, to be a valuable undertaking that will likely contribute to the health and well-being of humans. Rather, the causes and manifestations of mental illness in humans are most effectively researched without the use of animals."*

Tara West, PhD
Adjunct Associate Professor
of Psychology
CUNY School of
Professional Studies

Conclusion

In a recent paper discussing the inadequacy of regulations governing experimentation on animals, bioethicist Dr. David Wendler of the NIH's Clinical Center called for greater restrictions on the use of primates in experiments, noting that existing regulations "do not mandate that the risks to which nonhuman primates are exposed must be justified by the value of the study in question."[120]

For decades the NIH has continued to review, approve, fund, and conduct the aforementioned studies that deliberately and repeatedly inflict severe and chronic harm to monkeys, are often not at all designed to help humans, or have extremely limited potential to elucidate the complex etiology of human mental illness and have not improved our treatments of these illnesses or human health in general.

These experiments represent an enormous financial burden to taxpayers, particularly as there are a myriad of accessible, humane research methodologies that are more directly applicable to mental illness and its treatment. Continuing to fund this suite of projects appears to be both scientifically and ethically unjustifiable.

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