© iStock.com/Goddard_Photography

PETA

Review of Neuropsychology Experiments on Rhesus Macaques at the National Institutes of Health

PREPARED BY

Katherine V. Roe, Ph.D.
Senior Research Associate, Laboratory Investigations Department
People for the Ethical Treatment of Animals

March 2021

‘Mental Illness’ Experiments on Primates at the National Institutes of Health: An Executive Summary

For more than 30 years, National Institutes of Health (NIH) investigator Elisabeth A. Murray has been inflicting permanent, debilitating brain damage on rhesus macaques and conducting painful, frightening, and unnecessary experiments on them. The experiments have cost U.S. taxpayers nearly $49 million since 1998 and have not resulted in any new treatments or cures for human mental illness. NIH needs to stop supporting these archaic experiments and close this laboratory.

These experiments cause extreme harm to sensitive, vulnerable monkeys.

- Young monkeys in this laboratory are subjected to numerous invasive surgical procedures, including the following:
  - Experimenters cut into the animals’ heads, remove a portion of their skulls, and inject toxins into their brains to kill off large areas of brain tissue.
  - They then surgically and permanently affix objects called “head posts” directly into the monkeys’ skulls. These are used to force the animals to hold their heads completely still for hours at a time.
  - Experimenters also cut permanent holes into the primates’ skulls so that they can inject drugs directly into their brains.
- Monkeys in this laboratory are forced to endure fear- and stress-inducing living conditions and experimental procedures, including the following:
  - Experimenters place them alone in small, dark cages and then deliberately terrify them with fake but realistic-looking snakes and spiders, which they innately fear.
  - Experimenters restrain the monkeys for hours at a time, startle them with puffs of air blown directly into their eyes, force them to drink bitter-tasting liquids, and deprive them of food and water to compel them to “cooperate.”
  - Experimenters also deprive these animals of social interactions with their peers, which causes them severe physiological and physical damage, including hair loss, systemic inflammation, and self-injurious behavior.
- After enduring years of captivity, social isolation, painful surgeries, and terrifying experimental procedures, these monkeys are killed and dissected.

These experiments are scientifically meaningless, unnecessary, and inapplicable to humans with mental illness.

- Captivity induces negative effects in primates, causing numerous confounding physiological and psychological health issues that make data from this laboratory worthless.
- Humans with mental illness do not have brain damage similar to what is being caused in this laboratory.
- The behavioral tasks used in this laboratory do not measure the types of complex behavior typically problematic for individuals with mental-health conditions.
- Numerous humane, clinically relevant research methods are available for studying the underlying causes of mental illness in humans.

Review of Neuropsychology Experiments on Rhesus Macaques at the National Institutes of Health

For more than 30 years, Elisabeth Murray, an investigator at a National Institute of Mental Health laboratory in the Intramural Research Program, has been inflicting permanent brain damage on rhesus macaques via aspiration (suctioning out brain tissue) or excitotoxic lesions (cell death caused by the injection of toxins) and then studying their response to threatening or aversive stimuli. The purported aim of these experiments is to clarify the roles of different brain regions in behavioral flexibility, reward processing, and social behavior and to apply the findings to humans with neuropsychiatric illness.

As will be demonstrated below, we believe these experiments are ethically and scientifically unjustifiable given the considerable **harms** inflicted on the monkeys involved, the **limited applicability** of the results to humans and human illness, the **lack of benefits** produced for humans or animals, the **financial costs**, and the numerous **alternative research methods** available.

Harms

Murray inflicts permanent brain damage in monkeys by subjecting them to craniotomies (cutting into and removing part of the skull to expose the brain) and performing intracranial injections of excitotoxins (compounds that may cause injury to nerve cells). These injections can cause tachycardia (rapid heart rate) or respiratory arrest, which may take between 30 minutes and five hours to resolve. Monkeys used in the laboratory's "disconnection" experiments undergo two or three separate invasive surgeries to lesion different parts of the brain in stages. Additional surgeries are sometimes required to repair misplaced or incomplete lesions.

Many monkeys undergo an additional surgery in which head posts are affixed to the top of their skulls with screws and cement. It takes up to four weeks for them to heal from this surgery, and some of them end up living with these posts attached to their skulls for years. After recovering from head-post surgeries, many monkeys undergo yet another major surgery, in which holes are cut for chambers to be placed in their skulls so that experimenters can inject pharmaceutical compounds directly into their brains. In some instances, experimenters accidentally hit a blood vessel, resulting in brain hemorrhaging. Additional surgeries are sometimes required in order to scrape away bone that has grown into the chambers.

The behavioral deficits caused by many of the lesions that Murray inflicts impair the monkeys' ability to engage normally with conspecifics (other monkeys), so many of the animals in this laboratory are forced to live in isolation. Social isolation causes primates severe physiological and psychological harm and frequently leads to the development of abnormal and self-injurious behavior patterns, including hair-plucking, hair-pulling, biting, digit-sucking, eye-poking, self-clasping, and other forms of self-mutilation that can lead to significant injury and morbidity.[1]

In some experiments, monkeys are deliberately terrified with realistic-looking rubber snakes and spiders as well as the fear-inducing "Human Intruder Test," in which an unfamiliar, apparently threatening human approaches and stares at the monkeys. In other experiments, Murray and her laboratory staff blow puffs of air into the monkeys' eyes or deprive them of water to make them thirsty enough to drink bitter-tasting liquids like citric acid and quinine so that experimenters can see how they react to aversive stimuli. For many experiments, the monkeys are forced to wear a metal or hard-plastic collar and are strapped into a restraint chair that keeps their heads, arms, and legs immobilized. Monkeys in this laboratory are also required to lie awake with their bodies and heads restrained in a magnetic resonance imaging (MRI) scanner for up to five hours at a time.

Rhesus macaques, like all primates, are highly intelligent, complex, social animals who endure extreme physiological and psychological harm when held captive in laboratories. Pacing, rocking, head-twisting, biting their own flesh, and pulling out their own hair are just some examples of the stress-related behavior exhibited by primates in laboratories.[2,3,4,5] They also suffer from various immune system abnormalities, including increased stress hormone levels, dysregulation of the hypothalamic-pituitary-adrenal axis, and immune system depression.[6] This stress-induced immune dysfunction often leads to increased vulnerability to infection,[7] chronic autoimmune disease,[8] delayed wound healing, delayed recovery from surgeries,[9] and accelerated aging.[10]

Rhesus macaques, like all primates, are highly intelligent, complex, social animals who endure extreme physiological and psychological harm when held captive in laboratories.

Scientific Limitations

The experimenters justify the extremely harmful procedures described above with the argument that they will provide a better understanding of the neural underpinnings of neuropsychiatric illness. However, there are numerous limitations to these experiments that make the likelihood of these data being meaningfully applicable to humans extremely low.

Decades of research with patients have taught us that the brain abnormalities associated with most neuropsychiatric illnesses are not comparable to the type of brain damage inflicted on monkeys in this laboratory. Neuropsychiatric patients have very subtle anatomical

abnormalities not usually detectable by standard imaging methods.[11,12,13] Moreover, there are fundamental species differences in gene expression and protein function,[14] immune system functioning,[15] neurodevelopment,[16,17] neuroanatomy,[18,19] age-related changes in hormone production,[20] and age-related neurodegeneration.[21,22]

The rearing history of these monkeys (whether they were raised by their mothers or in a nursery and whether they were born in a laboratory or in nature) is also variable, despite the wealth of data indicating that rearing conditions have a profound impact on primates' brain development as well as their social, cognitive, and physical well-being.[23,24,25] Additionally, the monkeys in this laboratory are of a variety of ages at the time the lesions are inflicted, even though the age at lesion onset is known to have an impact on the type and degree of behavioral impairments experienced by humans.[26,27,28,29,30,31] Many of the monkeys are obtained from the National Institutes of Health nonhuman primate "recycling" program, indicating that they have previously undergone experimental procedures, which may have been harmful and could certainly introduce confounding variables.

Non-Animal Alternatives

There are several alternative research methods available for studying the neural correlates of behavior (brain activity that corresponds with and is necessary to produce a particular experience) in healthy and clinical human populations. Researchers have been studying the roles of specific brain regions for emotional regulation,[32,33] behavioral flexibility,[34,35,36] and reward processing[37,38] in humans for decades.

Researchers studying patients with naturally occurring focal lesions[39,40,41] (injury to limited areas of brain tissue) and using transcranial magnetic stimulation to study the effects of temporarily disabling regions of the brain safely[42] have successfully determined the role of different brain regions in the behavior types being studied in Murray's laboratory. These tools have been used to study brain structure and function in neuropsychiatric patient groups that exhibit difficulties with the types of behavior that she is trying to measure in monkeys.[43,44,45]

Additionally, postmortem analysis of brain tissue from patients[46,47,48,49] and large-scale epidemiological studies[50,51] are also helping researchers understand the neurobiological underpinnings[52,53] and the complex genetic and environmental factors that contribute to neuropsychiatric illness.[54]

Conclusion

These experiments, which inflict considerable harms upon primates, have extremely limited potential to elucidate the complex etiology (the cause or origin of a disease) of human mental illnesses and have not yet improved our treatment of these conditions or otherwise advanced human health in any measureable way. Continuing these projects represents an enormous financial burden on taxpayers and is particularly wasteful given that there are readily accessible, humane research methodologies available for obtaining data that are applicable to human mental illness and its treatment. Murray's experiments on monkeys are not scientifically or ethically justifiable.

Endnotes

[1] Hannibal, D. L., Bliss-Moreau, E., Vandeleest, J., McCowan, B., & Capitanio, J. (2017). Laboratory rhesus macaque social housing and social changes: Implications for research. *American Journal of Primatology*, *79*(1), 1–14.
[2] Novak, M. A. (2003). Self-injurious behavior in rhesus monkeys: New insights into its etiology, physiology, and treatment. *American Journal of Primatology*, *59*(1), 3–19.
[3] Lutz, C., Well, A., & Novak, M. (2003). Stereotypic and self-injurious behavior in rhesus macaques: A survey and retrospective analysis of environment and early experience. *American Journal of Primatology*, *60*(1), 1–15.
[4] Gottlieb, D. H., Capitanio, J. P., & McCowan, B. (2013). Risk factors for stereotypic behavior and self-biting in rhesus macaques (*Macaca mulatta*): Animal's history, current environment, and personality. *American Journal of Primatology*, *75*(10), 995–1008.
[5] Lutz, C. K., Coleman, K., Worlein, J., & Novak, M. A. (2013). Hair loss and hair-pulling in rhesus macaques (*Macaca mulatta*). *Journal of the American Association for Laboratory Animal Science*, *52*(4), 454–457.
[6] Novak, M. A., Hamel, A. F., Kelly, B. J., Dettmer, A. M., & Meyer, J. S. (2013). Stress, the HPA axis, and nonhuman primate well-being: A review. *Applied Animal Behaviour Science*, *143*(2–4), 135–149.
[7] Avitsur, R., Levy, S., Goren, N., & Grinshpahet, R. (2015). Early adversity, immunity and infectious disease. *Stress*, *18*(3), 289–296.
[8] Sharif, K., Watad, A., Krosser, A., Coplan, L., Amital, H., Afek, A., & Shoenfeld, Y. (2019). Psychological stress and the kaleidoscope of autoimmune diseases. In C. Perricone & Y. Shoenfeld (Eds.), *Mosaic of autoimmunity: The novel factors of autoimmune diseases* (pp. 323–331). Academic Press.
[9] Godbout, J. P., & Glaser, R. (2006). Stress-induced immune dysregulation: Implications for wound healing, infectious disease and cancer. *Journal of Neuroimmune Pharmacology*, *1*(4), 421–427.
[10] Flynn, M. G., Markofski, M. M., & Carrillo, A. E. (2019). Elevated inflammatory status and increased risk of chronic disease in chronological aging: Inflamm-aging or *inflamm-inactivity*? *Aging and Disease*, *10*(1), 147–156.
[11] Sparks, B. F., Friedman, S. D., Shaw, D. W., Aylward, E. H., Echelard, D., Artru, A. A., Maravilla, K. R., Giedd, J. N., Munson, J., Dawson, G., & Dager, S. R. (2002). Brain structural abnormalities in young children with autism spectrum disorder. *Neurology*, *59*(2), 184–192.
[12] Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure and Function*, *213*(1–2), 93–118.
[13] Cahn, W., Hulshoff Pol, H. E., Bongers, M., Schnack, H. G., Mandl, R. C. W., Van Haren, N. E. M., Durston, S., Koning, H., Van Der Linden, J. A., & Kahn, R. S. (2002). Brain morphology in antipsychotic-naive schizophrenia: A study of multiple brain structures. *The British Journal of Psychiatry*, *181*(S43), s66–s72.
[14] Bailey, J. (2014). Monkey-based research on human disease: The implications of genetic differences. *Alternatives to Laboratory Animals*, *42*(5), 287–317.
[15] Kametani, Y., Shiina, T., Suzuki, R., Sasaki, E., & Habu, S. (2018). Comparative immunity of antigen recognition, differentiation, and other functional molecules: Similarities and differences among common marmosets, humans, and mice. *Experimental Animals*, *67*(3), 301–312.
[16] Charvet, C. J., & Finlay, B. L. (2018). Comparing adult hippocampal neurogenesis across species: Translating time to predict the tempo in humans. *Frontiers in Neuroscience*, *12*, 706.
[17] Sakai, T., Komaki, Y., Hata, J., Okahara, J., Okahara, N., Inoue, T., Mikami, A. Matsui, M., Oishi, K., Sasaki, E., & Okano, H. (2017). Elucidation of developmental patterns of marmoset corpus callosum through a comparative MRI in marmosets, chimpanzees, and humans. *Neuroscience Research*, *122*, 25–34.
[18] Fukushima, M., Ichinohe, N., & Okano, H. (2019). Neuroanatomy of the marmoset. In R. P. Marini, L. M. Wachtman, S. D. Tardif, K. Mansfield, & J. G. Fox (Eds.) *The common marmoset in captivity and biomedical research* (pp. 43–62). Academic Press.
[19] Charvet, C. J., Palani, A., Kabaria, P., & Takahashi, E. (2019). Evolution of brain connections: Integrating diffusion MR tractography with gene expression highlights increased corticocortical projections in primates. *Cerebral Cortex*, *29*(12), 5150–5165.
[20] Abbott, D. H., Barnett, D. K., Colman, R. J., Yamamoto, M. E., & Schultz-Darken, N. J. (2003). Aspects of common marmoset basic biology and life history important for biomedical research. *Comparative Medicine*, *53*(4), 339–350.
[21] Chen, X., Errangi, B., Li, L., Glasser, M. F., Westlye, L. T., Fjell, A. M., Walhovd, K. B., Hu, X., Herndon, J. G., Preuss, T. M., & Rilling, J. K. (2013). Brain aging in humans, chimpanzees (*Pan troglodytes*), and rhesus macaques (*Macaca mulatta*): Magnetic resonance imaging studies of macro- and microstructural changes. *Neurobiology of Aging*, *34*(10), 2248–2260.
[22] Sherwood, C. C., Gordon, A. D., Allen, J. S., Phillips, K. A., Erwin, J. M., Hof, P. R., & Hopkins, W. D. (2011). Aging of the cerebral cortex differs between humans and chimpanzees. *Proceedings of the National Academy of Sciences*, *108*(32), 13029–13034.
[23] Sánchez, M. M., Hearn, E. F., Do, D., Rilling, J. K., & Herndon, J. G. (1998). Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. *Brain Research*, *812*(1–2), 38–49.
[24] Rommeck, I., Gottlieb, D. H., Strand, S. C., & McCowan, B. (2009). The effects of four nursery rearing strategies on infant behavioral development in rhesus macaques (*Macaca mulatta*). *Journal of the American Association for Laboratory Animal Science*, *48*(4), 395–401.
[25] Capitanio, J. P., Mendoza, S. P., Mason, W. A., & Maninger, N. (2005). Rearing environment and hypothalamic–pituitary–adrenal regulation in young rhesus monkeys (*Macaca mulatta*). *Developmental Psychobiology*, *46*(4), 318–330.
[26] Chilosi, A. M., Cipriani, P., Pecini, C., Brizzolara, D., Biagi, L., Montanaro, D., Tosetti, M., & Cioni, G. (2008). Acquired focal brain lesions in childhood: Effects on development and reorganization of language. *Brain and Language*, *106*(3), 211–225.
[27] Ballantyne, A. O., Spilkin, A. M., Hesselink, J., & Trauner, D. A. (2008). Plasticity in the developing brain: Intellectual,

language and academic functions in children with ischaemic perinatal stroke. *Brain*, *131*(11), 2975–2985.
[28] Szaflarski, J. P., Allendorfer, J. B., Byars, A. W., Vannest, J., Dietz, A., Hernando, K. A., & Holland, S. K. (2014). Age at stroke determines post-stroke language lateralization. *Restorative Neurology and Neuroscience*, *32*(6), 733–742.
[29] Stiles, J., Reilly, J., Paul, B., & Moses, P. (2005). Cognitive development following early brain injury: Evidence for neural adaptation. *Trends in Cognitive Sciences*, *9*(3), 136–143.
[30] Jacobs, R., Harvey, A. S., & Anderson, V. (2007). Executive function following focal frontal lobe lesions: Impact of timing of lesion on outcome. *Cortex*, *43*(6), 792–805.
[31] Donders, J., & Warschausky, S. (2007). Neurobehavioral outcomes after early versus late childhood traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *22*(5), 296–302.
[32] Golkar, A., Lonsdorf, T. B., Olsson, A., Lindstrom, K. M., Berrebi, J., Fransson, P., Schalling, M., Igvar, M., & Öhman, A. (2012). Distinct contributions of the dorsolateral prefrontal and orbitofrontal cortex during emotion regulation. *PLoS One*, *7*(11), e48107.
[33] Fellows, L. K., & Farah, M. J. (2003). Ventromedial frontal cortex mediates affective shifting in humans: Evidence from a reversal learning paradigm. *Brain*, *126*(8), 1830–1837.
[34] Tsuchida, A., Doll, B. B., & Fellows, L. K. (2010). Beyond reversal: A critical role for human orbitofrontal cortex in flexible learning from probabilistic feedback. *Journal of Neuroscience*, *30*(50), 16868–16875.
[35] Kringelbach, M. L., & Rolls, E. T. (2003). Neural correlates of rapid reversal learning in a simple model of human social interaction. *Neuroimage*, *20*(2), 1371–1383.
[36] Milad, M. R., Quinn, B. T., Pitman, R. K., Orr, S. P., Fischl, B., & Rauch, S. L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proceedings of the National Academy of Sciences*, *102*(30), 10706–10711.
[37] Howard, J. D., & Kahnt, T. (2018). Identity prediction errors in the human midbrain update reward-identity expectations in the orbitofrontal cortex. *Nature Communications*, *9*(1), 1611.
[38] Gottfried, J. A., O'Doherty, J., & Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science*, *301*(5636), 1104–1107.
[39] Berlin, H. A., Rolls, E. T., & Kischka, U. (2004). Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. *Brain*, *127*(5), 1108–1126.
[40] Angrilli, A., Bianchin, M., Radaelli, S., Bertagnoni, G., & Pertile, M. (2008). Reduced startle reflex and aversive noise perception in patients with orbitofrontal cortex lesions. *Neuropsychologia*, *46*(4), 1179–1184.
[41] Noonan, M. P., Chau, B. K. H., Rushworth, M. F. S., & Fellows, L. K. (2017). Contrasting effects of medial and lateral orbitofrontal cortex lesions on credit assignment and decision-making in humans. *Journal of Neuroscience*, *37*(29), 7023–7035.
[42] Howard, J. D., Reynolds, R., Smith, D. E., Voss, J. L., Schoenbaum, G., & Kahnt, T. (2020). Targeted stimulation of human orbitofrontal networks disrupts outcome-guided behavior. *Current Biology*, *30*(3), 490–498.e4.
[43] Meyer-Lindenberg, A., Hariri, A. R., Munoz, K. E., Mervis, C. B., Mattay, V. S., Morris, C. A., & Berman, K. F. (2005). Neural correlates of genetically abnormal social cognition in Williams syndrome. *Nature Neuroscience*, *8*(8), 991–993.
[44] Meador-Woodruff, J. H., Haroutunian, V., Powchik, P., Davidson, M., Davis, K. L., & Watson, S. J. (1997). Dopamine receptor transcript expression in striatum and prefrontal and occipital cortex: Focal abnormalities in orbitofrontal cortex in schizophrenia. *Archives of General Psychiatry*, *54*(12), 1089–1095.
[45] Passamonti, L., Fairchild, G., Fornito, A., Goodyer, I. M., Nimmo-Smith, I., Hagan, C. C., & Calder, A. J. (2012). Abnormal anatomical connectivity between the amygdala and orbitofrontal cortex in conduct disorder. *PLoS One*, *7*(11), e48789.
[46] Morrison, F. G., Miller, M. W., Wolf, E. J., Logue, M. W., Maniates, H., Kwasnik, D., Cherry, J. D., Svirsky, S., Restaino, A., Hildebrandt, A., Aytan, N., Stein, T. D., Alvarez, V. E., McKee, A. C., Traumatic Stress Brain Study Group, & Huber, B.R. (2019). Reduced interleukin 1A gene expression in the dorsolateral prefrontal cortex of individuals with PTSD and depression. *Neuroscience Letters*, *692*, 204–209.
[47] Wright, C., Shin, J. H., Rajpurohit, A., Williams, C., Jaffe, A., Brandon, N., Hyde, T., Kleinman, J., Cross, A., & Weinberger, D. (2019). Characterization of miRNA isoform expression in schizophrenia using postmortem human brain tissue. *European Neuropsychopharmacology*, *29*(Suppl. 3), S720.
[48] Edmonson, C., Ziats, M. N., & Rennert, O. M. (2014). Altered glial marker expression in autistic post-mortem prefrontal cortex and cerebellum. *Molecular Autism*, *5*(1), 3.
[49] Martins-de-Souza, D., Guest, P. C., Harris, L. W., Vanattou-Saifoudine, N., Webster, M. J., Rahmoune, H., & Bahn, S. (2012). Identification of proteomic signatures associated with depression and psychotic depression in post-mortem brains from major depression patients. *Translational Psychiatry*, *2*(3), e87.
[50] Spinrad, T. L., Eisenberg, N., Cumberland, A., Fabes, R. A., Valiente, C., Shepard, S. A., Reiser, M., Losoya, S. H., & Guthrie, I. K. (2006). Relation of emotion-related regulation to children's social competence: A longitudinal study. *Emotion*, *6*(3), 498–510.
[51] Silk, J. S., Price, R. B., Rosen, D., Ryan, N. D., Forbes, E. E., Siegle, G. J., Dahl, R. E., McMakin, D. L., Kendall, P. C., & Ladouceur, C. D. (2019). A longitudinal follow-up study examining adolescent depressive symptoms as a function of prior anxiety treatment. *Journal of the American Academy of Child & Adolescent Psychiatry*, *58*(3), 359–367.
[52] Rutland, J. W., Brown, S., Verma, G., Feldman, R. E., Sharma, H., Markowitz, M., Schneider, M., Delman, B. N., Murrough, J., & Balchandani, P. (2019). Hippocampal subfield-specific connectivity findings in major depressive disorder: A 7 Tesla diffusion MRI study. *Journal of Psychiatric Research*, *111*, 186–192.
[53] Maggioni, E., Delvecchio, G., Grottaroli, M., Garzitto, M., Piccin, S., Bonivento, C., Maieron, M., D'Agostini, S., Perna, G., Balestrieri, M., & Brambilla, P. (2019). Common and different neural markers in major depression and anxiety disorders: A pilot structural magnetic resonance imaging study. *Psychiatry Research: Neuroimaging*, *290*, 42–50.
[54] Dunn, A. R., O'Connell, K. M. S., & Kaczorowski, C. C. (2019). Gene-by-environment interactions in Alzheimer's disease and Parkinson's disease. *Neuroscience & Biobehavioral Reviews*, *103*, 73–80.

PETA

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS