

From: [Brown, Patricia \[OLAW\] \(NIH/OD\) \[E\]](#)
To: [Goldentyer, Betty J - APHIS](#)
Cc: [Morse, Brent \(NIH/OD\) \[E\]](#)
Subject: FW: Animal welfare concerns at an NIH laboratory
Date: Thursday, June 25, 2020 11:09:53 AM
Attachments: [Complaint from PETA re Brain Lesion Experiments on Rhesus Macaques at NIMH, June 25, 2020.pdf](#)
[Brief Review of Neurological Experiments on Rhesus Macaques at the NIH.pdf](#)

Hi, Betty,

The process you propose is in keeping with the MOU. OLAW accepts this referral and the Division of Compliance Oversight will proceed with an investigation of the animal welfare concerns.

Best wishes,

Pat

Patricia Brown, VMD, MS

Director, Office of Laboratory Animal Welfare,

Office of Extramural Research,

Office of the Director, NIH

6700B Rockledge Drive

Bethesda, MD 20892-6910

301-496-7163, fax: 301-480-3394

brownp@mail.nih.gov

Disclaimer: Please note that this message and any of its attachments are intended for the named recipient(s) only and may contain confidential, protected, or privileged information that should not be distributed to unauthorized individuals. If you have received this message in error, please contact the sender.

From: Goldentyer, Betty J - APHIS <betty.j.goldentyer@usda.gov>

Sent: Thursday, June 25, 2020 10:56 AM

To: Brown, Patricia [OLAW] (NIH/OD) [E] <brownp@od.nih.gov>

Subject: FW: Animal welfare concerns at an NIH laboratory

Hi Pat,

Hope all is well with you all.

I think a good process here would be for us to log this in as a complaint and close it with a referral to you.

Sound good? Any other thoughts or anything you need from us, just let me know.

Thanks

Betty

From: (b) (6)
Sent: Thursday, June 25, 2020 9:21 AM
To: Goldentyer, Betty J - APHIS <betty.j.goldentyer@usda.gov>
Subject: Animal welfare concerns at an NIH laboratory

Dear Dr. Goldentyer,

I hope this correspondence finds you well. I am writing on behalf of People for the Ethical Treatment of Animals (PETA) to respectfully request that the U.S. Department of Agriculture

(USDA) Animal and Plant Health Inspection Service (APHIS) investigate possible violations of the Animal Welfare Act (AWA) related to the use and treatment of monkeys in a laboratory at a National Institute of Mental Health (NIMH) Intramural Research Program (IRP) within the National Institutes of Health in Bethesda, Maryland.

Please see the attached letter for more details.

Thank you,



This electronic message contains information generated by the USDA solely for the intended recipients. Any unauthorized interception of this message or the use or disclosure of the information it contains may violate the law and subject the violator to civil or criminal penalties. If you believe you have received this message in error, please notify the sender and delete the email immediately.

Benson, Amy V - APHIS

Sent: Thursday, June 25, 2020 11:30 AM
To: Marks, Andrea K - APHIS
Subject: FW: Animal welfare concerns at an NIH laboratory
Attachments: Complaint from PETA re Brain Lesion Experiments on Rhesus Macaques at NIMH, June 25, 2020.pdf;
Brief Review of Neurological Experiments on Rhesus Macaques at the NIH.pdf

Hi Andrea,

Would you log this as a complaint? And then log it out as having been referred to Dr. Patricia Brown at NIH, OLAW.

From: (b) (6)
Sent: Thursday, June 25, 2020 9:21 AM
To: Goldentyer, Betty J - APHIS <betty.j.goldentyer@usda.gov>
Subject: Animal welfare concerns at an NIH laboratory

Dear Dr. Goldentyer,

I hope this correspondence finds you well. I am writing on behalf of People for the Ethical Treatment of Animals (PETA) to respectfully request that the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) investigate possible violations of the Animal Welfare Act (AWA) related to the use and treatment of monkeys in a laboratory at a National Institute of Mental Health (NIMH) Intramural Research Program (IRP) within the National Institutes of Health in Bethesda, Maryland.

Please see the attached letter for more details.

Thank you,

(b) (6)





PEOPLE FOR
THE ETHICAL
TREATMENT
OF ANIMALS

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

Prepared by



June 2020

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 or excitotoxic lesions 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 and performing intracranial injections of excitotoxins. 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. 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

Washington, D.C.
1536 16th St. N.W.
Washington, DC 20036
202-483-PETA

Los Angeles
2154 W. Sunset Blvd.
Los Angeles, CA 90026
323-644-PETA

Norfolk
501 Front St.
Norfolk, VA 23510
757-622-PETA

Berkeley
2855 Telegraph Ave.
Ste. 301
Berkeley, CA 94705
510-763-PETA

Info@peta.org
PETA.org

Affiliates:

- PETA Asia
- PETA India
- PETA France
- PETA Australia
- PETA Germany
- PETA Netherlands
- PETA Foundation (U.K.)

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, 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 an fMRI 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

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 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 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} and using transcranial magnetic stimulation to study the effects of temporarily disabling regions of the brain safely⁴² 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 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.

-
- ¹Hannibal, 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.
- ²Novak, 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.
- ³Lutz, 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.
- ⁴Gottlieb, 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.
- ⁵Lutz, 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.
- ⁶Novak, 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.
- ⁷Avitsur, R., Levy, S., Goren, N., & Grinshpach, R. (2015). Early adversity, immunity and infectious disease. *Stress*, 18(3), 289–296.
- ⁸Sharif, 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.
- ⁹Godbout, 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.
- ¹⁰Flynn, 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.
- ¹¹Sparks, 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.
- ¹²Drevets, 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.
- ¹³Cahn, 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-naïve schizophrenia: A study of multiple brain structures. *The British Journal of Psychiatry*, 181(S43), s66–s72.
- ¹⁴Bailey, J. (2014). Monkey-based research on human disease: The implications of genetic differences. *Alternatives to Laboratory Animals*, 42(5), 287–317.
- ¹⁵Kametani, 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.
- ¹⁶Charvet, 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.
- ¹⁷Sakai, 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.
- ¹⁸Fukushima, 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.
- ¹⁹Charvet, 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.

- ²⁰Abbott, 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.
- ²¹Chen, 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.
- ²²Sherwood, 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.
- ²³Sánchez, 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.
- ²⁴Rommeck, 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.
- ²⁵Capitanio, 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.
- ²⁶Chilosì, 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.
- ²⁷Ballantyne, 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.
- ²⁸Szaflarski, 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.
- ²⁹Stiles, 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.
- ³⁰Jacobs, 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.
- ³¹Donders, J., & Warschusky, S. (2007). Neurobehavioral outcomes after early versus late childhood traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, 22(5), 296–302.
- ³²Golkar, 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.
- ³³Fellows, 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.
- ³⁴Tsuchida, 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.
- ³⁵Kringelbach, 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.
- ³⁶Milad, 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.
- ³⁷Howard, 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.
- ³⁸Gottfried, J. A., O'Doherty, J., & Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science*, 301(5636), 1104–1107.
- ³⁹Berlin, 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.
- ⁴⁰Angrilli, 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.

- ⁴¹Noonan, 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.
- ⁴²Howard, 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.
- ⁴³Meyer-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.
- ⁴⁴Meador-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.
- ⁴⁵Passamonti, 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.
- ⁴⁶Morrison, 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.
- ⁴⁷Wright, 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.
- ⁴⁸Edmonson, 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.
- ⁴⁹Martins-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.
- ⁵⁰Spinrad, 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.
- ⁵¹Silk, 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.
- ⁵²Rutland, 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.
- ⁵³Maggioni, 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.
- ⁵⁴Dunn, 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.

Uploaded to Animal Research Laboratory Overview (ARLO) on 01/28/2021

I. Failure to ensure that animals would not be used in more than one major operative survival surgery

Section 2.31(d)(1)(x) of the AWRs stipulates that in its review of “proposed activities related to the care and use of animals,” the Institutional Animal Care and Use Committee (IACUC) must ensure that “no animal will be used in more than one major operative procedure from which [he or she] is allowed to recover.”

However, according to ASP # LN-20, the rhesus macaques used in PI Murray’s experiments are subjected to three or more craniotomies, where the skin and muscles of the head are cut into, a portion of the skull is removed, and incisions are made into the dura, or the connective tissue that surrounds the brain beneath the skull. Some monkeys also have head posts surgically affixed to the tops of their skulls; and some monkeys have chambers cut into their skulls. These multiple major operative procedures are described below:

1. Excitotoxic lesion surgeries: The monkeys are subjected to two or more craniotomies and are then given intracranial injections of excitotoxins to cause permanent brain damage to a region of interest. The injection of excitotoxins can cause tachycardia (rapid heart rate) or respiratory arrest which may take 30 minutes to five hours to resolve. These conditions place severe stress on the body’s immune system, internal organs, and normal physiological function. Hippocampal lesions require two craniotomies, and monkeys included in the laboratories “disconnection” experiments undergo two or three separate invasive surgeries to lesion different parts of their brain in stages. Additional surgeries are sometimes required to repair misplaced or incomplete lesions.
2. Head post placement surgeries: Some of the already-lesioned monkeys are subjected to an additional major operative surgery in which head posts are surgically affixed to the tops of their skulls. It takes up to four weeks for the monkeys to heal just from this surgery alone, and some of them end up living with these posts attached to their skulls for years. The dental acrylic used to affix these posts make the monkeys extremely vulnerable to discomfort, infection and inflammation, as well as bone and skin degradation.
3. Chamber placement surgeries: After recovering from head post surgeries, many of these monkeys undergo yet another major operative surgery, in which holes are cut and chambers are placed into their skulls to allow experimenters to inject pharmaceutical compounds directly into their brains. For these procedures, the experimenter uses a number of non-pharmaceutical grade drugs. The doses used in the systemic injections may be toxic and may cause the animals distress. In some instances, if acceptable medical treatments and/or procedures are not effective, the monkeys will be euthanized. During some of these surgeries, experimenters accidentally hit a blood vessel resulting in cerebral hemorrhage, infarctions and raised intracranial pressure. Additional surgeries are sometimes required to remove bone that has grown into the chambers.
4. Tracer studies: Prior to euthanasia, monkeys are subjected to one or more additional craniotomies to allow for tracer injections.

Section 2.31(d)(1)(x) of the AWRs identifies a number of exceptions to the prohibition on multiple major survival surgeries, including justification based on “scientific reasons by the principal investigator.” However, the “justification” provided by Murray in ASP # LN-20 for these experiments is specific to the “disconnection lesion surgeries” and simply states that it is “widely accepted that this is the only way to determine whether a given function, in this case, a specific kind

of sensory memory, is dependent upon the integrity of the anatomical connections between certain specified brain structures.” However, as described in the attached report, this is inaccurate—there are numerous tools available to study the import of individual brain regions and/or their anatomical connections in sensory memory behaviors. Additionally, no scientific justification was provided in ASP # LN-20 for subjecting individual monkeys to excitotoxic lesions, head posts, and chambers.

Using monkeys in more than one major survival surgery, even with “justification,” isn’t only a question of whether Murray and NIMH’s ACUC complied with federal regulation. The cumulative harms inflicted by Murray on individual monkeys, as described in Murray’s own protocol, are so extreme that it’s quite likely that monkeys are experiencing significant morbidity and mortality during the surgical procedures and post-surgically. This would mean that *by design* and with the approval of NIMH’s ACUC, “discomfort, distress, and pain to the animals” was not minimized, as is required by Section 2.31(d)(1)(i) of the AWRs.

II. Failure to report animal use in the appropriate USDA category for pain and distress

Section 2.36 of the AWRs stipulates that research facilities must submit an annual report to the USDA, stating “the common names and the numbers of animals upon which experiments, teaching, research, surgery, or tests were conducted” and classifying the USDA pain and distress category for the procedures in which the animals were used.

The rhesus macaques used in Murray’s protocol were reported in NIH’s Annual Report under Category D, that is, “procedures which would involve more than slight or momentary accompanying pain or distress, and for which appropriate anesthetic, analgesic, or tranquilizing drugs, were used.” However, a veterinary assessment of this protocol suggests that the manipulations to which the macaques are subjected in Murray’s protocol would produce significant unrelieved pain and distress.

The multiple invasive surgeries described in the earlier section cause physical and psychological stress, immune system suppression, and may impair spatial memory and cause cognitive decline. Brain surgery causes high levels of both acute and chronic pain. The skin and muscles of the head and scalp are extensively enervated with pain-transmitting nerves, as is the dura. Tissue injury and nerve entrapment, compression, transection, or other damage in the scalp, cranial muscles, and dura lead to extensive pain following the surgeries. Additionally, the permanent brain damage inflicted in these animals causes myriad negative behavioral outcomes, including impaired emotional responsivity, aberrant social interactions, altered response to fearful and threatening stimuli, and impaired reward processing.

Monkeys in this laboratory are subjected to multiple painful intramuscular (IM) injections that can cause bruising, swelling, and impaired movement. Some monkeys will receive painful IM injections of neurotransmitter receptor agonists and antagonists, which can cause dyskinesia (uncontrolled muscle twitching), sedation, and agitation.

For training and behavioral testing, the monkeys in this laboratory are fitted with a metal or hard plastic collar and strapped into a restraint chair that keeps their head, arms, and/or legs immobilized. In some behavioral experiments, monkeys’ autonomic responses (pupil responses, heart rate, blood pressure) are recorded. This requires the monkeys’ arms to be tied behind their backs and their heads completely immobilized via the implanted head post. Monkeys are subjected to this type of restraint for hours at a time, as many as five days a week.

For structural neuroimaging, monkeys in this laboratory are sedated several times a month, requiring repeated fasting and prolonged restraint, and resulting in post-anesthetic malaise. For functional neuroimaging experiments they are also required to lie awake, with their bodies and heads completely immobilized, inside a magnetic resonance imaging (MRI) scanner, in some cases for up to five hours at a time. Some monkeys receive injections of a substance containing iron for fMRI studies. In order to prevent toxicity due to high levels of iron, these monkeys also receive IM injections of iron chelators. Side effects include pain and swelling at injection site, itching, redness, hearing impairment, and blurred vision. They may receive these injections three to four times per week while undergoing fMRI studies.

To improve the monkeys' willingness to repeatedly perform behavioral tests, experimenters often restrict their food and water intake. In one behavioral paradigm, to get the monkeys to cooperate, the experimenters withhold food and water until they perform the required task, then provide them with the entire daily food ration at one time. The biscuits are presented in "mash" form to both increase the ease of consumption and to restrict access to water. This so-called "lunch box" procedure forces the monkeys to "earn" their entire daily allotment of fluid and food while "working" in the apparatus. This requires that the monkeys consume their full day's nourishment within a 15-minute window of time. In addition to the acute gastrointestinal dilation that would likely occur with this quick devouring of a large quantity of food, causing pain and discomfort in the monkeys, this practice would also cause psychological distress in the monkeys since they would access to food for only 15 minutes during a 24-hour period.

Given the extensive catalogue of invasive, painful, and distressing procedures carried out on the macaques in Murray's laboratory, the suggestion that the complete universe of pain and distress suffered by the monkeys—which is frankly, overwhelming and unimaginable—is preposterous. The rhesus macaques used in PI Murray's experiments should be reported as Category E experiments, reflecting their unrelieved pain and distress.

III. Failure to consider alternatives to painful procedures

Section 2.31(d)(1)(ii) of the AWRs stipulates that in its review of "proposed activities related to the care and use of animals," the IACUC must ensure that the principal investigator has "considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals."

However, the animal study proposal for these experiments indicates that the experimenters failed to conduct an adequate search for alternative procedures. When searching on the PubMed database, the investigators used the term "primate" in each individual search, eliminating the possibility of discovering human-based research methodologies. In other searches, the investigators employed databases dedicated to primate experimentation. As described in the attached report, there are numerous non-animal alternatives available for these experimenters to investigate their research questions. Had the experimenters chosen proper search terms and databases these alternatives would have revealed themselves, and hundreds of monkeys could have been spared extensive suffering.

Also, it is unclear from Murray's protocol whether any consideration was given to alternatives to dental acrylic/cement to facilitate attachment of the head post. As noted earlier, these materials are more likely to fail and are known to cause irritation and infection for the monkeys. European neuroscientists and some experimenters at the University of Pennsylvania have done away with such materials for these reasons. Instead they are refining their techniques using 3D scans of the skulls to

fabricate precisely fitted attachments. These refinements also mean that the monkeys are less likely to undergo ‘repair’ surgeries. It is unclear whether Murray conducted a search for alternatives to the use of dental acrylic/cement to affix head posts in the monkeys, and it is unclear whether the NIMH ACUC requested that such a search be carried out. It is amply clear that by continuing to use an antiquated method of implanting head posts, Murray failed to minimize discomfort, distress, and pain to the animals—and the ACUC failed to ensure that her protocol complied with federal animal welfare regulations in this regard.

IV. Failure to establish and maintain a program of adequate veterinary care

Section 2.33(a) of the AWRs stipulates that “[e]ach research facility shall have an attending veterinarian who shall provide adequate veterinary care to its animals.” Policy 3 of the USDA’s *Animal Care Policies* expounds on this directive as it relates to the use of pharmaceutical-grade compounds in research. In particular, the policy states:

Investigators are expected to use pharmaceutical-grade medications whenever they are available, even in acute procedures. Non-pharmaceutical-grade chemical compounds should only be used in regulated animals after specific review and approval by the IACUC, for reasons such as scientific necessity or non-availability of an acceptable veterinary or human pharmaceutical-grade product. Cost savings is not a justification for using non-pharmaceutical-grade compounds in regulated animals.

However, Murray reports the use of non-pharmaceutical-grade drugs on her study, including GDR 12909 and nomifensine. Murray admits that the doses used in the systemic injections of these non-pharmaceutical-grade compounds may be toxic. It is unclear from the protocol whether the ACUC considered key issues in allowing Murray to use non-pharmaceutical-grade drugs in her study, including the level of pain and distress suffered by the monkeys injected with the compounds; whether purity differences between pharmaceutical-grade and non-pharmaceutical-grade compounds would result in toxic and adverse effects, and possibly, an increase in pain and distress.

V. Failure to ensure that the attending veterinarian has appropriate authority

Section 2.33(a)(2) of the AWRs stipulates that the research facility must ensure “that the attending veterinarian has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.”

However, the animal study proposal for these experiments specifies that the veterinarian must consult “with the investigator” before “an animal [who] is experiencing distress that cannot be relieved by applying acceptable medical treatments and procedures” can be euthanized. This deference to the investigator undermines the authority of the veterinarian and opens the door to the possibility that the investigator’s desire for experimental data will trump the imperative to prioritize the animal’s welfare.

VI. Failure to promote psychological well-being of nonhuman primates

Section 3.81 of the AWRs stipulates that “research facilities must develop, document, and follow an appropriate plan for environment enhancement adequate to promote the psychological well-being of nonhuman primates.” Section 3.81(a) of the AWRs addresses the issue of social grouping, stating:

“The environment enhancement plan must include specific provisions to address the social needs of nonhuman primates of species known to exist in social groups in nature.”

Rhesus macaques in the wild live in multi-male, multi-female groups within a profoundly social environment. However, the brain lesions inflicted in the monkeys as part of Murray’s protocol cause behavioral deficits that impair their ability to engage normally with conspecifics. These induced deficits are, and have been, used to justify the confinement of many monkeys in this laboratory in isolation.

To be clear, Murray has been inflicting brain lesions in rhesus macaques—and caging monkeys in isolation—for more than 30 years. While the importance of housing primates in social groupings was understood 30 years ago and certainly in 1989 when the USDA promulgated regulations aimed at promoting the psychological well-being of nonhuman primates, today the scientific literature is replete with overwhelming and irrefutable evidence that social isolation causes primates severe psychological and physiological harm. Caging monkeys alone frequently leads to the development of abnormal and self-injurious behaviors including hair plucking and pulling, biting, digit sucking, eye poking, and self-clasping, and other forms of self-mutilation that can lead to significant injury and morbidity. These very behaviors can be seen in the video footage produced by experimenters working in Murray’s laboratory and obtained by PETA via a FOIA request; a small sampling of this footage may be viewed [here](#).

Conclusion

For 30 years, Murray’s protocols have necessitated caging monkeys in isolation; for 30 years, this egregious privation has caused extreme psychological suffering for rhesus macaques in Murray’s laboratory; for 30 years, Murray has requested exemptions from social grouping requirements; and for 30 years, the NIMH ACUC has approved the exemptions. The ACUC has also approved the use of monkeys in multiple invasive survival surgeries and other harmful procedures that resulted in acute and chronic pain and distress for the animals. Murray’s use of cruel and archaic experimental methods and the ACUC’s rubberstamping of her protocols have violated the spirit and letter of the Animal Welfare Act and its implementing regulations. As a result, hundreds of rhesus macaques have been condemned to suffer lives marked by loneliness, depression, anxiety, and depression.

We urge you to investigate the concerns summarized in this letter and, if the claims are substantiated, to take swift and decisive action against NIMH. If you have any questions about these concerns, please contact me at (b) (6). Thank you for your time and consideration.

Sincerely,

(b) (6)

Encl.: Brief Review of Neurological Experiments on Rhesus Macaques at the NIH