From:	Wolff, Axel (NIH/OD) [E]
To:	McCoy, Devora (NIH/OD) [E]
Subject:	FW: Use of invasive brain experiments on infant macaques to study brain processes of facial recognition at Harvard Medical School
Date:	Monday, May 22, 2023 7:21:14 AM
Attachments:	image001.png

Please add this to the file we placed the other memo in on Friday. Thanks.

From: Brown, Patricia [OLAW] (NIH/OD) [E] <brownp@od.nih.gov> Sent: Friday, May 19, 2023 10:42 AM

To:

(b) (6)

Cc: Wolff, Axel (NIH/OD) [E] <wolffa@od.nih.gov>; robert.m.gibbens@aphis.usda.gov; Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>

Subject: RE: Use of invasive brain experiments on infant macaques to study brain processes of facial recognition at Harvard Medical School

Deer	(b)	(6)
Dear	(0)	(0)

This is to acknowledge receipt of your letter concerning research conducted at Harvard Medical School. At this time your concerns are under review.

Sincerely yours,

Patricia Brown, VMD, MS, DACLAM (she/her) 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 brownp@mail.nih.gov

From:	(b) (6)
Sent: Wednesday, May 17, 2023 7:00 AM	
To: Brown, Patricia [OLAW] (NIH/OD) [E] <brown< th=""><th>np@od.nih.gov>; robert.m.gibbens@aphis.usda.gov</th></brown<>	np@od.nih.gov>; robert.m.gibbens@aphis.usda.gov

Cc: president@harvard.edu; office_of_the_dean@hms.harvard.edu; (b) (6) (b) (6) brian_corning@hms.harvard.edu; margaret_livingstone@hms.harvard.edu; Wolff, Axel (NIH/OD) [E] <<u>wolffa@od.nih.gov</u>>; <u>iacuc@fas.harvard.edu</u> Subject: [EXTERNAL] Use of invasive brain experiments on infant macaques to study brain processes

Subject: [EXTERNAL] Use of invasive brain experiments on infant macaques to study brain processes of facial recognition at Harvard Medical School

Dear Directors:

Citizens for Alternative to Animal Research & Experimentation (CAARE) submits this

complaint to Animal and Plant Health Inspection Service (APHIS) Animal Care and the National Institutes of Health's Office of Laboratory Animal Welfare (OLAW) to investigate the use of invasive brain experiments on infant macaques at Harvard Medical School to study the neural pathways of facial recognition when nonanimal alternatives are readily available and already in wide use.

Harvard neuroscientist Margaret S. Livingston is conducting invasive visual deprivation experiments on infant monkeys, intended to reveal insights into human vision disorders. In these experiments, newborn macaques are separated from their mothers and subjected to monocular or binocular deprivation experiments. In some cases, newborn monkeys' eyes are sutured closed, and in others, they spend up to a year without the opportunity to see other monkeys' faces or human faces, with caretakers wearing welding masks.

In addition to visual and maternal deprivation, the young monkeys are routinely subjected to invasive surgeries, in which head posts, eye coils, and intracranial electrode arrays are implanted in their skulls. During these experiments, monkeys are fully immobilized with restraint chairs, helmets, and chin straps. All of these events impose considerable suffering and distress for the monkeys.

Harvard Medical School claims these experiments will study the visual pathways involved with facial processing in the brains of infant and very young macaque monkeys. By manipulating factors in early development, they claim the research will explore how these alterations can affect how the brain processes visual information and how that relates to disorders of facial recognition.

These experiments conflict with various sections of the Animal Welfare Act and policies under USDA which stipulate that principal investigators must research appropriate alternatives to procedures that may cause more than momentary pain and distress to animals.

Under the Animal Welfare Act, Harvard Medical School meets the statutory definition of a "research facility" and is therefore required to comply with the statute's regulations and standards. As part of this required compliance, any use of live animals for research, testing, or training must be approved by Harvard Medical School's Institutional Animal Care and Use Committee (IACUC). Harvard Medical School is currently registered with the USDA under certification number 14-R-0019.

The specific regulatory violations are:

1. Harvard Medical School failed to conduct an adequate search of non-animal methods to study visual processing of facial recognition in the brain

Section 2143 of the Animal Welfare Act and CFR Title 9, Section 2.31(d)(1)(i, ii) of the Animal Welfare Act's implementing regulations require that the principal investigator (PI) consider alternatives to procedures that may cause more than momentary or slight pain or distress to any animal used for research or educational purposes.

The PI must provide a written narrative description of the methods and sources used to determine that alternatives were not available. The content of this narrative is detailed in the

APHIS *Animal Care Policy Manual* (2011), which states in Policy 12: "The written narrative should include adequate information for the IACUC to assess that a reasonable and good faith effort was made to determine the availability of alternatives or alternative methods."

A proper alternatives search would have revealed a range of well-established, nonanimal, human-based methods to study the brain's processing of facial recognition, including its manifestation in early development, as well as for studying pathologies that impair facial recognition, like autism spectrum disorder and prosopagnosia. Thus, the PI and Harvard Medical School did not meet this requirement for animal use to study human disorders of impaired facial recognition.

Below we detail numerous examples of such nonanimal research and note that this is far from comprehensive:

- A study currently funded by the National Eye Institute uses human participants and multimodal brain imaging to thoroughly investigate anatomical and functional components of facial recognition from childhood to adulthood. The research combines cross-sectional and longitudinal measurements in children and adults by obtaining measurements of functional magnetic resonance imaging (fMRI), quantitative MRI (qMRI), diffusion weighted imaging (DWI), and behavior in each participant. Both quantitative magnetic resonance imaging (qMRI) and diffusion-weighted imaging (DWI) measure properties of water molecules within tissue to provide information about myelination, iron and cell membranes and molecular function and anatomical microarchitecture in the living brain. Population receptive field (pRF) modeling uses fMRI data to map the visual pathway from the retina to neurons in the brain and can be designed to describe various sensory and cognitive processes. Using this data, this study will provide the first measurements of multiple facets of the anatomy and function of the human ventral temporal cortex and will be valuable for treating developmental disorders involving altered visual and facial processing, such as congenital prosopagnosia, Williams Syndrome, and autism. [1][1] [1][2]
- Researchers used functional near-infrared spectroscopy to measure oxygenation in the brains of newborns to examine regions involved in visual processing in infant development. They studied 100 babies, about half of which were born at full term and half prematurely. Testing occurred at 6 months of age, based on the babies' conception date. Researchers imaged the infants while they were exposed to a sound pattern, followed by an image of a smiley face. After several rounds, the researchers continued the sound but randomly stopped showing the image. They found that in these cases the visual areas of the brain lit up in full-term infants but not in premature infants. This insight may help scientists understand why these babies are at greater risk for later developmental delays. ^{[1][3]}
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• In this final example, researchers were able to discover a new region of the human brain, something that is impossible using animal experiments. The scientists used high spatial resolution neuroimaging data from human patients and post-mortem tissues to investigate the visual sensory thalamus, an area of the brain linked to several vision disorders. In so doing, they discovered two new regions of the visual sensory thalamus, not previously described before. The ability to use this novel imaging method to study these visual pathways in live patients will allow scientists to learn more about the causes

and treatments of dyslexia, glaucoma and other vision disorders. [1][10]

Having failed to provide objective evidence to support animal use in view of numerous recognized alternatives, this requirement of the AWA was not met.

2. The use of live animals to study visual pathways in the brain is not "unavoidable for the conduct of scientifically valuable research."

The Animal Welfare Act also requires that activities involving animals be designed to "assure that discomfort and pain to animals

will be limited to that which is unavoidable for the conduct of scientifically valuable research." 9 C.F.R. § 2.31(e)(4).

This requirement was not met by Harvard Medical School because of the ready availability of abundant, human-relevant

alternative methods to using live animals, as described above. This demonstrates that such use of monkeys is not

"unavoidable."

3. The Harvard Medical School IACUC failed to properly oversee animal use

Section 2143 of the Animal Welfare Act and Title 9, Section 2.31(d)(1)(i, ii) of the Act require that the IACUC enforce the

requirements described above, thereby assuring that the university's animal research procedures are in accordance with the Animal

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- Further, USDA Policy 12 holds the IACUC additionally responsible for assuring there are no alternatives to replace an animal
- experiment by stating: "The IACUC, in fact, can withhold approval of the study proposal if the Committee is not satisfied with the

procedures the principal investigator plans to use in his study."

These requirements were not met by the Harvard Medical School IACUC because the animal use protocol was approved

despite the violations described in items 1, 2 and 3 above. Thus, CAARE alleges inadequate institutional oversight by the

Harvard Medical School IACUC.

4. The use of live animals to study the visual pathways in the brain violates the principles of Public Health Service Policy and the Guide

The Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals requires that institutions have an

OLAW-approved Animal Welfare Assurance before carrying out any activities involving live vertebrate animals. Harvard Medical

School's OLAW assurance is D16-00270 (A3431-01).

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- consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society."

Principle III provides that "the animals selected for a procedure should be of an appropriate species and quality and the minimum

number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological

systems should be considered."

The problems described above violate the PHS Policy and the Guide for the Care and Use of Laboratory Animals (the Guide).

OLAW must evaluate allegations of noncompliance with the PHS Policy "and, as necessary, restrict or withdraw approval of

[Animal Welfare] Assurances."

CAARE alleges Harvard Medical School has violated the aforementioned laws and regulations. As such, CAARE requests

that APHIS and OLAW investigate this situation to implement corrective action and appropriate penalties.

We believe this issue is of major importance since these laws and regulations exist because the standard of practice requires that

scientists minimize the use of animals. Harvard Medical School has not demonstrated proper adherence to these laws and guiding

principles.

We appreciate your attention to this matter.

Sincerely,

(b) (6)

(b) (б)

cc: Lawrence S. Bacow, President, Harvard University George Q. Daley, M.D., Ph.D. Dean Harvard Medical School

(b) (6)

Brian F. Corning, D.V.M. Director, HCCM IACUC Attending Veterinarian Margaret Livingstone, Department of Neurobiology, Harvard Medical School Dr. Axel Wolff, Deputy Director, OLAW

^{[1][1]} Development of Face Perception: Cross-sectional and Longitudinal Investigations, National Eye Institute, Project Number 5R01EY022318-10 https://reporter.nih.gov/search/i5IrGdWajUy34Ag7TkFdWw/project-details/10376237

^{[1][2]} Differential spatial computations in ventral and lateral face-selective regions are scaffolded by structural connections, Finzi D, Gomez J, Nordt M, Rezai AA, Poltoratski S, Grill-Spector K. Differential spatial computations in ventral and lateral face-selective regions are scaffolded by structural connections. Nat Commun. 2021 Apr 15;12(1):2278. doi: 10.1038/s41467-021-22524-2.

^{[1][3]} Lauren L. Emberson, Alex M. Boldin, Julie E. Riccio, Ronnie Guillet, Richard N. Aslin. Deficits in Top-Down Sensory Prediction in Infants At Risk due to Premature Birth. *Current Biology*, 2017; DOI: <u>10.1016/j.cub.2016.12.028</u>

[1][4] The neuroanatomical basis for face processing deficits in autism spectrum disorder, National Institute of Mental Health, Project Number 5K23MH120510-03 https://reporter.nih.gov/search/i5IrGdWajUy34Ag7TkFdWw/project-details/10400864_

[1][5] Cohen AL. Using causal methods to map symptoms to brain circuits in neurodevelopment disorders: moving from identifying correlates to developing treatments. J Neurodev Disord. 2022 Mar 12;14(1):19. doi: 10.1186/s11689-022-09433-1. PMID: 35279095; PMCID: PMC8918299. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8918299/

^{[1][6]} Joy Hirsch, Xian Zhang, J. Adam Noah, Swethasri Dravida, Adam Naples, Mark Tiede, Julie M. Wolf, James C. McPartland. Neural correlates of eye contact and social function in autism spectrum disorder. *PLOS ONE*, 2022; 17 (11): e0265798 DOI: <u>10.1371/journal.pone.0265798</u>

^{[1][7]} Mark D. Vida, Adrian Nestor, David C. Plaut, and Marlene Behrmann. Spatiotemporal dynamics of similarity-based neural representations of facial identity. *PNAS*, December 27, 2016

DOI: 10.1073/pnas.1614763114

^{[1][8]} Shany Grossman, Guy Gaziv, Erin M. Yeagle, Michal Harel, Pierre Mégevand, David M. Groppe, Simon Khuvis, Jose L. Herrero, Michal Irani, Ashesh D. Mehta, Rafael Malach. Convergent evolution of face spaces across human face-selective neuronal groups and deep convolutional networks. *Nature Communications*, 2019; 10 (1) DOI: <u>10.1038/s41467-019-12623-6</u>

^{[1][9]} Ariane E. Rhone, Kyle Rupp, Jasmine L. Hect, Emily E. Harford, Daniel Tranel, Matthew A. Howard, Taylor J. Abel. Electrocorticography reveals the dynamics of famous voice responses in human fusiform gyrus. *Journal of Neurophysiology*, 2022; DOI: <u>10.1152/jn.00459.2022</u>

^{[1][10]} Christa Müller-Axt, Cornelius Eichner, Henriette Rusch, Louise Kauffmann, Pierre-Louis Bazin, Alfred Anwander, Markus Morawski, Katharina von Kriegstein. Mapping the human lateral geniculate nucleus and its cytoarchitectonic subdivisions using quantitative MRI. *NeuroImage*, 2021; 244: 118559 DOI: <u>10.1016/j.neuroimage.2021.118559</u>

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DEPARTMENT OF HEALTH & HUMAN SERVICES

FOR US POSTAL SERVICE DELIVERY: Office of Laboratory Animal Welfare 6700B Rockledge Drive, Suite 2500, MSC 6910 Bethesda, Maryland 20892-6910 Home Page: http://grants.nih.gov/grants/olaw/olaw.htm PUBLIC HEALTH SERVICE NATIONAL INSTITUTES OF HEALTH

> FOR EXPRESS MAIL: Office of Laboratory Animal Welfare 6700B Rockledge Drive, Suite 2500 Bethesda, Maryland 20817 Telephone: (301) 496-7163 Facsimile: (301) 480-3387

May 17, 2023

Re: Animal Welfare Assurance A3431-01 [OLAW Case 9R]

MEMORANDUM FOR RECORD

The Office of Laboratory Animal Welfare (OLAW) has determined that the May 17, 2023 letter from the Citizens for Alternatives to Animal Research and Experimentation (CAARE) regarding the use of nonhuman primates in research, specifically research conducted by ^{(b) (6)} of Harvard Medical School, contained no allegations of noncompliance with the PHS Policy. OLAW will therefore not investigate further. This case is thereby administratively closed as of this date.

Signed,

(b) (6)

Axel Wolff, MS, DVM Deputy Director Office of Laboratory Animal Welfare

Wolff, Axel (NIH/OD) [E]

From:	(b) (6)	
Sent:	Wednesday, May 17, 2023 7:00 AM	
То:	Brown, Patricia [OLAW] (NIH/OD) [E]; robert.m.gibbens@aphis.usda.gov	
Cc:	president@harvard.edu; office_of_the_dean@hms.harvard.edu; (b) (6	5)
	(b) (6) brian_corning@hms.harvard.edu;	
	margaret_livingstone@hms.harvard.edu; Wolff, Axel (NIH/OD) [E];	
	iacuc@fas.harvard.edu	
Subject:	[EXTERNAL] Use of invasive brain experiments on infant macaques to study b processes of facial recognition at Harvard Medical School	rain

Dear Directors:

Citizens for Alternative to Animal Research & Experimentation (CAARE) submits this complaint to Animal and Plant Health Inspection Service (APHIS) Animal Care and the National Institutes of Health's Office of Laboratory Animal Welfare (OLAW) to investigate the use of invasive brain experiments on infant macaques at Harvard Medical School to study the neural pathways of facial recognition when nonanimal alternatives are readily available and already in wide use.

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5

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Sincerely,

(b) (6)

cc: Lawrence S. Bacow, President, Harvard University George O. Daley, M.D., Ph.D. Dean Harvard Medical School

(b) (6)

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^{1[3]} Lauren L. Emberson, Alex M. Boldin, Julie E. Riccio, Ronnie Guillet, Richard N. Aslin. Deficits in Top-Down Sensory Prediction in Infants At Risk due to Premature Birth. *Current Biology*, 2017; DOI: <u>10.1016/j.cub.2016.12.028</u>

^{1[4]} The neuroanatomical basis for face processing deficits in autism spectrum disorder, National Institute of Mental Health, Project Number 5K23MH120510-03 <u>https://reporter.nih.gov/search/i5IrGdWajUy34Ag7TkFdWw/project-details/10400864</u>

^{1[5]} Cohen AL. Using causal methods to map symptoms to brain circuits in neurodevelopment disorders: moving from identifying correlates to developing treatments. J Neurodev Disord. 2022 Mar 12;14(1):19. doi: 10.1186/s11689-022-09433-1. PMID: 35279095; PMCID: PMC8918299. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8918299/

^{1[6]} Joy Hirsch, Xian Zhang, J. Adam Noah, Swethasri Dravida, Adam Naples, Mark Tiede, Julie M. Wolf, James C. McPartland. Neural correlates of eye contact and social function in autism spectrum disorder. *PLOS ONE*, 2022; 17 (11): e0265798 DOI: <u>10.1371/journal.pone.0265798</u>

^{1[7]} Mark D. Vida, Adrian Nestor, David C. Plaut, and Marlene Behrmann. Spatiotemporal dynamics of similarity-based neural representations of facial identity. *PNAS*, December 27, 2016 DOI: <u>10.1073/pnas.1614763114</u>

^{1[8]} Shany Grossman, Guy Gaziv, Erin M. Yeagle, Michal Harel, Pierre Mégevand, David M. Groppe, Simon Khuvis, Jose L. Herrero, Michal Irani, Ashesh D. Mehta, Rafael Malach. Convergent evolution of face spaces across human faceselective neuronal groups and deep convolutional networks. *Nature Communications*, 2019; 10 (1) DOI: <u>10.1038/s41467-019-12623-6</u>

^{1[9]} Ariane E. Rhone, Kyle Rupp, Jasmine L. Hect, Emily E. Harford, Daniel Tranel, Matthew A. Howard, Taylor J. Abel. Electrocorticography reveals the dynamics of famous voice responses in human fusiform gyrus. *Journal of Neurophysiology*, 2022; DOI: <u>10.1152/jn.00459.2022</u>

^{1[10]} Christa Müller-Axt, Cornelius Eichner, Henriette Rusch, Louise Kauffmann, Pierre-Louis Bazin, Alfred Anwander, Markus Morawski, Katharina von Kriegstein. Mapping the human lateral geniculate nucleus and its cytoarchitectonic subdivisions using quantitative MRI. *NeuroImage*, 2021; 244: 118559 DOI: <u>10.1016/j.neuroimage.2021.118559</u>

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DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY: Office of Laboratory Animal Welfare 6700B Rockledge Drive, Suite 2500, MSC 6910 Bethesda, Maryland 20892-6910 Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

April 11, 2023

FOR EXPRESS MAIL: Office of Laboratory Animal Welfare 6700B Rockledge Drive, Suite 2500 Bethesda, Maryland 20817 <u>Telephone</u>: (301) 496-7163 <u>Facsimile</u>: (301) 480-3387

Re: Animal Welfare Assurance A3431-01 [OLAW Case 9R]

MEMORANDUM FOR RECORD

The Office of Laboratory Animal Welfare (OLAW) has determined that the February 8, 2023 letter from the Animal Law and Policy Clinic of the Harvard Law School regarding the use of nonhuman primates in research, specifically research conducted by Margaret S. Livingstone of Harvard Medical School, contained no allegations of noncompliance with the PHS Policy. OLAW will therefore not investigate further. This case is thereby administratively closed as of this date.

Signed,

Brent C. Morse - S Morse - S

Digitally signed by Brent C. Morse -S Date: 2023.04.11 16:02:47 -04'00'

Brent C. Morse, DVM Director Division of Compliance Oversight Office of Laboratory Animal Welfare

43431-9R





February 8, 2023

Lawrence A. Tabak Director National Institutes of Health

Michael Lauer Deputy Director for Extramural Research National Institutes of Health

Robert W. Eisinger Acting Director, Division of Program Coordination, Planning, and Strategic Initiatives National Institutes of Health

Re: Request that NIH Take Action to End Macaque Experimentation at Harvard Medical School

Dear Dr. Tabak, Dr. Lauer, and Dr. Eisinger:

This letter is being submitted to the National Institutes of Health (NIH) on behalf of the 381 undersigned scientists, doctors, academics, and lawyers who have serious concerns about NIH's funding of unethical experiments on macaque monkeys and other non-human primates taking place at Harvard Medical School. As the attached more detailed request explains, we urge NIH to review the protocols and justifications for these experiments with an eye toward terminating the funding of these and other ongoing and future experiments on non-human primates that lack ecological validity and involve cruel and unnecessary treatment of laboratory animals.

Please let us know if you have any questions about this submission.

Sincerely,

(b) (6)

On behalf of the undersigned

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(b) (6)

REQUEST THAT NIH TAKE ACTION TO END MACAQUE EXPERIMENTATIONAT HARVARD MEDICAL SCHOOL

We have grave concerns about experimentation on macaque monkeys taking place at a Harvard Medical School laboratory and funded by the National Institutes of Health (NIH). As scientists and lawyers dedicated to ensuring humane treatment of primates used in research, we urge NIH to review the protocols and justifications for these experiments with an eye toward terminating the funding of ongoing and future experiments on non-human primates that lack ecological validity and involve cruel and unnecessary treatment of laboratory animals. The Harvard Law School Animal Law & Policy Clinic has already attempted to address these concerns by contacting the relevant Institutional Animal Care and Use Committee—to no avail. Accordingly, we now request that NIH take immediate action to deal with this matter.¹

In an article published in the Proceedings of the National Academy of Sciences (PNAS) last September, Dr. Margaret S. Livingstone reported her observations that distressed mother monkeys will clutch a soft toy—which she calls an "inanimate surrogate infant"—when their babies are taken from them soon after birth.² These observations are incidental to the routine maternal separation that occurs in this Harvard Medical School laboratory, which uses baby monkeys as its primary test subjects. According to the publication, this work was supported by NIH grants EY16187, EY 025670, EY012196, and NS123778, and, so far, has cost taxpayers many millions of dollars. Prominent media coverage of the publication has led to scientific and public outcry regarding the ethics of such research.³

This line of research has not and, we suggest, cannot add any meaningful contribution to our knowledge of either non-human or human primate behavior. Contrary to the Harvard Medical School's statement⁴ that these experiments have implications for understanding maternal bonding in humans, the relevant publication itself concedes that "*there is no way of knowing the extent to which these observations bear on human maternal bonding, or on other kinds of*

¹ See Letter from Katherine Meyer, Rachel Mathews, & Rebecca Garverman, Harvard Animal Law & Policy Clinic to Arlene Santos-Diaz, Harvard Medical School Office of the IACUC (Oct. 26, 2022),

https://animal.law harvard.edu/wp-content/uploads/ALPC-Letter-to-HMS-IACUC.pdf. To date, we have received no substantive response to this communication.

² Margaret S. Livingstone, Triggers for Mother Love, 119 PROC. NAT'L ACAD. SCI. 1 (2022).

³ See Letter from Catherine Hobaiter et al., Wild Minds Lab, to Proceedings of the National Academy of Sciences Editors (Oct. 11, 2022), <u>https://doi.org/10.5281/zenodo.7347808</u>; Barbara J. King, *Addressing the Harms of Animal Research: What Role Might Journals Play?* MEDIUM (Nov. 3, 2022),

https://medium.com/@barbarajking/addressing-the-harms-of-animal-research-what-role-might-journals-play-3f5425ce341; Harvard Study on Monkeys Reignites Ethical Debate Over Animal Testing, CBS NEWS (Nov. 3, 2022), https://www.cbsnews.com/news/monkey-study-harvard-reignites-debate-animal-testing/; David Grimm, Harvard Studies on Infant Monkeys Draw Fire, Split Scientists, SCIENCE (Oct. 19, 2022),

https://www.science.org/content/article/harvard-studies-infant-monkeys-draw-fire-split-scientists; Paul Bedard, PETA Urges End of Harvard Monkey Tests, Sewing Eyes Closed, WASHINGTON EXAMINER (Oct. 14, 2022), https://www.washingtonexaminer.com/news/washington-secrets/peta-urges-end-of-harvard-monkey-tests-sewingeyes-closed.

⁴ Statement in Response to Concerns About Research at HMS, HARVARD MEDICAL SCHOOL (Oct. 14, 2022), https://hms.harvard.edu/news/statement-response-concerns-about-research-hms.

bonding."⁵ As Dr. Barbara J. King and several colleagues explained in a letter to PNAS protesting the publication of these experiments:

Laboratory research using stressed animals suffers from limited applicability to humans; the impact of stress thoroughly alters an individual's physiology, severely reducing cross-species translatability. In the [Livingstone] study, monkey mothers faced social separation right at the point when their pregnancy was detected. Might their stress affect the validity of results regarding their response to soft toys?⁶

Science already has a deep understanding of the mother-infant primate bond from decades of work.⁷ The infamous original maternal deprivation tests conducted by Dr. Harry Harlow in the 1960s described the effects on infant primates of months of isolation as "devastating and debilitating."⁸ Subsequent moves towards pairing separated infants with age-mates shows that they endure significant long-term negative consequences,⁹ so much so that mother-deprived infant primates continue to be used as models for depression and anxiety.¹⁰ We see the same patterns of behavioral and physiological impact in observations of wild primates. Maternally deprived primates show marked differences in their stress profiles. In the wild, amongst a natural system of social support they are sometimes able to (partially) recover,¹¹ but in captivity these effects can be life-long.¹² Wild primates similarly show behavior we would describe as anxiety or depression in humans when their maternal and/or social needs are not met.¹³ Today, we have an entire field of primate thanatology which explores, through natural observation, the psychological impacts on primates of the permanent loss of key social partners,¹⁴ including the impact on mothers of the loss of their infants.¹⁵ The undersigned scientists together represent collective centuries of expertise, and include both early career researchers and some of the

⁵ See Livingstone, supra note 2 at 4 (emphasis added).

⁶ King, *supra* note 3.

⁷ See, e.g., SARAH HRDY, MOTHER NATURE: A HISTORY OF MOTHERS, INFANTS, AND NATURAL SELECTION (1999); K. D. Broad, et al., *Mother-Infant Bonding and the Evolution of Mammalian Social Relationships*. 361 Phil. TRANSACTIONS ROYAL SOC'Y 2199 (2006).

⁸ Harry F. Harlow et al., Total Social Isolation in Monkeys, 54 PSYCH. 90, 94 (1965).

⁹ Amanda M. Dettmer & Stephen J. Suomi, Nonhuman Primate Models of Neuropsychiatric Disorders: Influences of Early Rearing, Genetics, and Epigenetics, 55 ILAR J. 361, 362 (2014).

¹⁰ Id. See also Stephen J. Suomi, Mother-Infant Attachment, Peer Relationships, and the Development of Social Networks in Rhesus Monkeys, 48 HUM. DEV. 6 (2005).

¹¹ See generally Cédric Girard-Buttoz et al., Early Maternal Loss Leads to Short- But Not Long-Term Effects On Diurnal Cortisol Slopes In Wild Chimpanzees, ELIFE 1 (2021).

¹² See generally Xiaoli Feng et al., Maternal Separation Produces Lasting Changes in Cortisol and Behavior in Rhesus Monkeys, 108 PROC. NAT'L ACAD. SCI. 14312 (2011).

¹³ See generally Maria Botero et al., Anxiety-Related Behavior of Orphan Chimpanzees (Pan Troglodytes Schweinfurthii) At Gombe National Park, Tanzania, 54 PRIMATES 21 (2013); Catherine Hobaiter et al., 'Adoption' by Maternal Siblings in Wild Chimpanzees, 9 PLOS ONE 1 (2014); Rachna B. Reddy & John C. Mitani, Social Relationships and Caregiving Behavior Between Recently Orphaned Chimpanzee Siblings, 60 PRIMATES 389 (2019).

¹⁴ See generally James R. Anderson, et al., Evolutionary Thanatology, 373 PHIL. TRANSACTIONS ROYAL SOC'Y 1 (2018); André Gonçalves & Susana Carvalho, Death Among Primates: A Critical Review of Non-Human Primate Interactions Towards Their Dead and Dying, 94 BIOLOGICAL REVS. 1502 (2019).

¹⁵ See generally Adrian Soldati et al., Dead-Infant Carrying by Chimpanzee Mothers in the Budongo Forest, 63 PRIMATES 497 (2022).

leading international names in primate behavior and welfare, as well as researchers working on observational study in the wild, and those working with primates in captivity. All agree that *experiments like this do not add any meaningful contribution to our knowledge of primate or human behavior* and that maternal-separation methods fail to meet modern scientific and ethical standards.

The experiments occurring in Dr. Livingstone's laboratory also raise significant animal welfare concerns. Scientific studies have long shown that—just as would be the case with removing *human* infants from their mothers—separating non-human primate infants from their mothers increases stress and abnormal behavior patterns in the infants (such as pacing, finger sucking, and self-grasping),¹⁶ causes depression,¹⁷ increases distress, and has a negative impact on social behaviors (such as play and proximity to other non-human primates).¹⁸

The specific protocols involved in Dr. Livingstone's laboratory also raise many *ethical* concerns. For example, the PNAS article describes forcibly separating a mother macaque from her infant, and then returning the infant to her just six hours later, at which point, not surprisingly, the traumatized mother rejected the infant.¹⁹ Practices like this raise profound ethical concerns for both mother and infant and are clearly not in the best interest of either. "Many researchers who are serious about understanding and facilitating human bonding rightly focus on ethical, meaningful research with children and their caregivers. In any case, no speculative benefit to humans ethically justifies maternal separation of nonhuman primates."²⁰

The primary line of research at the Livingstone laboratory involves subjecting baby monkeys to "abnormal visual experiences of faces."²¹ This was achieved by having laboratory staff wear "welders' masks that prevented the monkey from seeing the staff member's face," or raising monkeys "under conditions of binocular-visual-form deprivation via eye lid suturing for the first year." In other words, the researchers sewed shut the eyes of the infant monkeys so that they could not see in order to ascertain whether this would have a negative impact on their visual and brain development. According to the 2020 publication on these studies, this work was supported by NIH grants RO1 EY 16187, R01 EY 25670, and P30 EY 12196—again, at great taxpayer expense.

The laboratory has defended these experiments,²² asserting that "eyelid closure was and remains *routine* protocol across research labs that study vision disorders," and that the "technique, in fact, paved the way for the modern non-invasive methods we use now." However,

¹⁶ See Feng et al., supra note 12 at 14315.

¹⁷ See generally L. Drago & B. Thierry, Effects of Six-day Maternal Separation on Tonkean Macaque Infants, 41 PRIMATES 137 (2000).

¹⁸ See generally Mark L. Laudenslager et al., Total Cortisol, Free Cortisol, and Growth Hormone Associated With Brief Social Separation Experiences in Young Macaques, 28 DEVELOPMENTAL PSYCHOBIOLOGY 199 (1995).
¹⁹ See Livingstone, supra note 2.

²⁰ Ving summa note 2

²⁰ King, *supra* note 3.

²¹ Michael J. Arcaro et al., Anatomical Correlates of Face Patches in Macaque Inferotemporal Cortex, 117 PROC. NAT'L ACAD. SCI. 32667, 32667 (2020).

²² Professor Livingstone's Personal Statement About Recent Concerns Over Animal Research, HARVARD MEDICAL SCHOOL (Oct. 24, 2022), <u>https://hms harvard.edu/news/professor-livingstones-personal-statement-about-recentconcerns-over-animal-research.</u>

in actuality, these "modern" methods are *face masks and goggles*.²³ In our opinion, there is absolutely no need to fund researchers to sew infant monkeys' eyes shut simply to conclude the obvious—i.e., that non-invasive goggles and face masks, which have been available for centuries,²⁴ could be used instead for ocular deprivation.

The assertion that the "work points to possible interventions for children with autism who might choose not to look at other people or their faces"²⁵ is similarly lacking in scientific justification. The macaques used in this research are already physically, psychologically, and environmentally compromised. They are in laboratory settings that deprive them of anything resembling a natural socio-ecological environment. The absence of basic environmental, as well as social, enrichment has a well-established negative impact on both brain development and behavior.²⁶

Thus, in addition to being deprived of the ability to see, these macaques experience general overall sensory and social deprivation that makes their world experience, and thus their brain development, very different from that of a child who avoids looking directly at an individual's face. In sharp contrast, autistic children and children with face blindness are *not* deprived of many typical human life experiences and continue to live with their families. Any scientific argument for these studies is compromised as it is impossible to disentangle any possible effects arising from the deprivation of human faces from the significant widespread impacts of maternal deprivation and abnormal social environment on these primates. As a result, it is extremely difficult to understand the applicability of these experiments to human children, whether autistic or not.

The experiments occurring at Harvard Medical School are just one example of ongoing animal experimentation throughout the country with highly concerning ethical implications. We are deeply troubled by these experiments and ask NIH to internally review not only these particular studies at the Harvard Medical School, but also all other ongoing non-human primate experiments of a similar nature, and to permanently end funding for current or future projects that lack ecological validity²⁷ and involve cruel and inhumane treatment of animals used in experimentation. As demonstrated by the recent outcry about this research, the public has a strong interest in bringing these practices to an end.²⁸

Instead of spending tens of millions of taxpayer funds each year on such experiments, NIH should direct its grant money to research investigating alternatives to animal testing. Such alternatives will both alleviate the need to subject non-human primates and other animals to

²⁴ Patricia Bauer, Goggles, BRITANNICA, <u>https://www.britannica.com/technology/goggles</u> (last visited Feb. 6, 2023).
 ²⁵ Personal Statement, supra note 22.

²³ Id. ("My lab now uses entirely non-invasive techniques to study early visual experiences. These include caregivers wearing facial masks and having the animals wear goggles [which are] the modern non-invasive methods we use now.").

²⁶ See generally Mark J. Prescott & Katie Lidster, Improving Quality of Science Through Better Animal Welfare: The NC3Rs Strategy, 26 LAB ANIMAL 152 (2017).

²⁷ Ecological validity examines whether study findings can be generalized to real-life settings. *See, e.g.*, Chittaranjan Andrade, *Internal, External, and Ecological Validity in Research Design, Conduct, and Evaluation,* 40 INDIAN J. PSYCH. MED. 498 (2018). Studies such as those described in this letter lack ecological validity and are applicable only to the specific laboratory setting in which they were conducted. Consequentially, they fail to contribute to our knowledge of primate and human health and behavior.

²⁸ See supra, note 3 (collecting evidence of public and scientific outcry).

laboratory conditions and experimentation and be more likely to produce results that may actually benefit human health. Indeed, for both reasons, President Biden recently signed bipartisan legislation that would end the Food and Drug Administration (FDA) mandate requiring experimental drugs to be tested on animals before they can be used in human clinical trials.²⁹ The FDA itself has also committed to exploring alternative methods to animal testing to produce findings that are more relevant to humans.³⁰ Approximately 90% of drugs fail clinical trials, despite the use of animal testing in preclinical tests, suggesting that successful animal trials are a poor indicator of the efficacy of drugs in humans.³¹ On the other hand, recent studies³² have discovered an effective, economical method for creating cells similar to human brain neurons for use in scientific research. Such novel cell culture systems could increase the human relevance of research into neurodiversity, including autism, and neurological disorders such as Alzheimer's disease. We urge NIH to consider channeling its funds to further research efforts such as these to encourage the discovery and adoption of ethical and efficacious alternatives to animal experimentation.

Furthermore, *behavioral* research, which maternal deprivation experiments purport to be, should be carried out in such a way as to do no harm. The study of the biological relevance of behavioral mechanisms, such as attachment and social bonding in primates, can be effectively conducted through the observational study of free-living animals in the natural habitats to which they are adapted, particularly now that modern methods allow for the non-invasive analysis of physiological measures, such as hormone reactivity, in tandem with these observations. There is also substantial scope for the use of experimental enrichment in studies that contribute to enhancing the lives of already captive individuals, but it is fundamental that all actions—including those that are potentially enriching—be subject to ethical review. Where research must be conducted using captive animals, good welfare has proven essential to ensure robust and reliable research outcomes.³³

As many of the undersigned scientists explained in the recent letter to PNAS concerning this matter:

We cannot ask monkeys for consent, but we can stop using, publishing, and in this case actively promoting cruel methods that knowingly cause extreme distress. "Doing science to promote welfare becomes a moral obligation. It is what we owe the animals who live with us, given our autonomy violations in the past."³⁴

https://www.nature.com/articles/d41586-022-03569-9.

 ²⁹ Consolidated Appropriations Act, 2023, Subtitle B, Ch. 1, § 3209 Animal Testing Alternatives (2023).
 ³⁰ Rachel Nuwer, US Agency Seeks to Phase Out Animal Testing, NATURE (Nov. 4, 2022),

³¹ See generally Danilo A. Tagle, The NIH Microphysiological Systems Program: Developing In Vitro Tools For Safety And Efficacy In Drug Development, 48 CURRENT OP. PHARMACOLOGY 146 (2019).

³² See, e.g., Emily-Rose Martin et al., A Novel Method For Generating Glutamatergic SH-SY5Y Neuron-Like Cells Utilizing B-27 Supplement, FRONTIERS PHARMACOLOGY, 01 (2022).

³³ See generally T. Poole, Happy Animals Make Good Science, 31 LAB'Y ANIMALS 1 (1997); Prescott & Lidster, supra note 26.

³⁴ Kristin Andrews, *Ethical Implications of Animal Personhood and the Role for Science*, 22 ETICA & POLITICA/ETHICS & POL. 13, 32 (2020).

NIH is required by law to ensure that the millions of dollars of taxpayer funds provided via grants to research institutions are not used for inhumane or other improper purposes, and to terminate and/or cease the funding for any research that does not meet these requirements.³⁵ Therefore, it is imperative that the agency investigate the funding of the experiments occurring at Harvard Medical School, and similar experiments occurring elsewhere in this country, and ensure that taxpayer money is not being used to continue to support unethical and cruel practices that simultaneously fail to advance scientific knowledge in any meaningful way.

³⁵ See Health Research Extension Act, 42 U.S.C § 289d(d) (1985); PHS Policy on Humane Care and Use of Laboratory Animals, NATIONAL INSTITUTES OF HEALTH (2015), <u>https://olaw.nih.gov/policies-laws/phs-policy.htm#Introduction</u>.

SIGNATORIES TO REQUEST THAT NIH TAKE ACTION TO END MACAQUE EXPERIMENTATION AT HARVARD MEDICAL SCHOOL

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Morse, Brent (NIH/OD) [E]

From:	Brown, Patricia [OLAW] (NIH/OD) [E]
Sent:	Sunday, February 19, 2023 3:34 PM
То:	Morse, Brent (NIH/OD) [E]
Subject:	FW: [EXTERNAL] Request Regarding Experimentation on Macaques at Harvard Medical School
Attachments:	2023-02-08_Letter to NIH_Experiments on Monkeys at Harvard_Final.pdf
Follow Up Flag:	Follow up
Flag Status:	Flagged

Dear Brent,

I am forwarding this letter sent to Drs. Tabak, Lauer and Eisinger for review of the allegations concerning Harvard Medical School.

Sincerely,

Pat

Patricia Brown, VMD, MS, DACLAM (she/her) Director, Office of Laboratory Animal Welfare, Office of Extramural Research, Office of the Director, NIH 301-451-4209, <u>brownp@mail.nih.gov</u>

From: Lauer, Michael (NIH/OD) [E] <michael.lauer@nih.gov>
Sent: Sunday, February 19, 2023 5:58 AM
To: Brown, Patricia [OLAW] (NIH/OD) [E] <brownp@od.nih.gov>; Laboratory Animal Welfare, Office of (NIH/OD)
<OLAW@OD.NIH.GOV>
Cc: Lauer, Michael (NIH/OD) [E] <michael.lauer@nih.gov>
Subject: FW: [EXTERNAL] Request Regarding Experimentation on Macaques at Harvard Medical School

Hi Pat – as we discussed the other day, I am forwarding this to you / OLAW.

Many thanks, Mike

From:

(b) (6)

Date: Wednesday, February 8, 2023 at 7:21 AM

To: "Tabak, Lawrence (NIH/OD) [E]" <<u>lawrence.tabak@nih.gov</u>>, "Lauer, Michael (NIH/OD) [E]"

<michael.lauer@nih.gov>, "Eisinger, Robert (NIH/OD) [E]" <robert.eisinger@nih.gov>

Cc: "senator murray@murray.senate.gov" <senator murray@murray.senate.gov>,

"Mindi Linguist@murray.senate.gov" < Mindi Linguist@murray.senate.gov >,

"<u>Robert.aderholt@mail.house.gov</u>" <<u>Robert.aderholt@mail.house.gov</u>>, "<u>kerry.knott@mail.house.gov</u>" <kerry.knott@mail.house.gov>

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Subject: [EXTERNAL] Request Regarding Experimentation on Macaques at Harvard Medical School

Dear Dr. Tabak, Dr. Lauer, and Dr. Eisinger:

Please find the attached letter submitted on behalf of 381 scientists, doctors, academics, and lawyers who have serious concerns about the NIH's funding of unethical experiments on macaque monkeys and other non-human primates, including those taking place at Harvard Medical School. As the letter explains, we urge your agency to review the protocols and justifications for these experiments with an eye toward terminating the funding of these experiments.

Sincerely,

· ... ·

(b) (6)

3431-9R



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health Bethesda, Maryland 20892

February 19, 2023

President Lawrence Bacow President, Harvard University president@harvard.edu

Dean John Manning Dean, Harvard Law School <u>deansoffice@law.harvard.edu</u> jmanning@law.harvard.edu

Dean George Daley Dean, Harvard Medical School george_daley@hms.harvard.edu

Re: Letter of February 8, 2023, from Harvard Law School Animal Law and Policy Clinic to National Institutes of Health (NIH) leadership regarding "Request that NIH Take Action to End Macaque Experimentation at Harvard Medical School"

Dear President Bacow, Dean Manning, and Dean Daley:

I wanted to bring to your attention a letter from Harvard Law School that was sent to my colleagues, Dr. Lawrence Tabak and Dr. Robert Eisinger, and to me (attached). It appears that there is an internal dispute within Harvard University regarding certain experiments taking place at Harvard Medical School.

While NIH will follow its standard procedures and follow-up on allegations of compliance concerns, NIH generally does not get involved in internal institutional disputes, such as a dispute between one entity at Harvard University and another entity at Harvard University. NIH thinks it would be helpful for the three of you to work with each other.

Sincerely yours,

Michael S. Lauer -S Date: 2023.02.19 07:24:15 -05'00'

Michael S Lauer, MD NIH Deputy Director for Extramural Research Director, NIH Office of Extramural Research <u>Michael.Lauer@nih.gov</u>

Morse, Brent (NIH/OD) [E]

From: Sent: To: Subject:	Brown, Patricia [OLAW] (NIH/OD) [E] Sunday, February 19, 2023 3:38 PM Morse, Brent (NIH/OD) [E] FW: [EXTERNAL] Re: From National Institutes of Health (NIH) Deputy Director for Extramural Research regarding internal Harvard University dispute being brought to our attention
Attachments:	From National Institutes of Health (NIH) Deputy Director for Extramural Research regarding internal Harvard University dispute being brought to our attention
Follow Up Flag: Flag Status:	Follow up Flagged

Dear Brent,

Below and attached is more information on the allegations concerning Harvard Medical School.

Sincerely, Pat

From: Lauer, Michael (NIH/OD) [E] <michael.lauer@nih.gov> Sent: Sunday, February 19, 2023 11:17 AM To: Brown, Patricia [OLAW] (NIH/OD) [E] <brownp@od.nih.gov> Cc: Lauer, Michael (NIH/OD) [E] <michael.lauer@nih.gov> Subject: FW: [EXTERNAL] Re: From National Institutes of Health (NIH) Deputy Director for Extramural Research regarding internal Harvard University dispute being brought to our attention

Hi Pat

More on Livingstone.

Thanks, Mike

From: "Daley, George Q." <<u>George Daley@hms.harvard.edu</u>> Date: Sunday, February 19, 2023 at 10:25 AM To: "Lauer, Michael (NIH/OD) [E]" <<u>michael.lauer@nih.gov</u>> Cc:

(b) (6) "Lawrence S. Bacow" <<u>president@harvard.edu</u>>, "Bacow, Lawrence S." <<u>lawrence_bacow@harvard.edu</u>>, HLS-Dean's Office <<u>deansoffice@law.harvard.edu</u>>, "Manning, John" <jmanning@law.harvard.edu>, (b) (6)

Subject: [EXTERNAL] Re: From National Institutes of Health (NIH) Deputy Director for Extramural Research regarding internal Harvard University dispute being brought to our attention

Dear Dr. Lauer,

Thank you for your email correspondence encouraging us to address the issues raised by our colleagues at the Harvard Law School Animal Law and Policy clinic. Harvard

(b) (6)

Medical School and Dr. Livingstone have both previously addressed the specific matters raised in the letter sent to you at the NIH. Here are the links to those statements for reference:

- https://hms.harvard.edu/news/statement-response-concerns-about-research-hms
- https://hms.harvard.edu/news/professor-livingstones-personal-statement-aboutrecent-concerns-over-animal-research

Animal research conducted at Harvard Medical School, including Dr. Livingstone's work, follows applicable federal, state, and institutional policies and regulations that aim at humane and safe care of and use of animals. Additionally, HMS scientists continuously strive to refine the use and care of animals, reduce the number of animals used in research, and replace animals with nonanimal models whenever possible.

Harvard Medical School believes the regulated use of animal models in biomedical research remains indispensable for understanding the biological processes that give rise to disease, for designing new therapies and interventions to improve physical and mental health, and for ensuring such treatments are safe and effective.

HMS acknowledges and respects the academic freedom of our investigators, which is fundamental to the role of research institutions. We believe that the work referenced, as rigorously peer reviewed in compliance with regulatory, institutional, sponsor and publication requirements, is for the academic community to consider as part of scientific discourse.

Sincerely,

George Q. Daley, MD, PhD Dean, Harvard Medical School Caroline Shields Walker Professor of Medicine Professor of Biological Chemistry and Molecular Pharmacology

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From: "Lauer, Michael (NIH/OD) [E]" <michael.lauer@nih.gov> Date: Sunday, February 19, 2023 at 7:36 AM To: "Lawrence S. Bacow" <president@harvard.edu>, Larry Bacow <lawrence bacow@harvard.edu>, HLS-

Dean's Office <<u>deansoffice@law.harvard.edu</u>>, John Manning <<u>imanning@law.harvard.edu</u>>, Public HMS Email <<u>George_Daley@hms.harvard.edu</u>>

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(b) (6)"Lauer, Michael (NIH/OD) [E]" <michael.lauer@nih.gov>

Subject: From National Institutes of Health (NIH) Deputy Director for Extramural Research regarding internal Harvard University dispute being brought to our attention

Dear President Bacow, Dean Manning, and Dean Daley:

Please see attached.

Many thanks, Mike

Michael S Lauer, MD NIH Deputy Director for Extramural Research Director, NIH Office of Extramural Research 1 Center Drive, Room 144, Bethesda MD 20892 <u>Michael Lauer@nih.gov</u>

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News & Research

Statement in Response to Concerns About Research at HMS

October 14, 2022 | Research

Harvard Medical School is deeply concerned about the personal attacks directed at scientists who conduct critically important research for the benefit of humanity.

The content presented on the PETA website is misleading and contains factual inaccuracies. The video, certain photos, and some of the behaviors described on the website are not from Dr. Margaret Livingstone's lab, and descriptions related to her methods contain inaccuracies and exaggerations. A3431-9R

Research led by Dr. Livingstone continues to provide critical knowledge about vision, visual disorders, brain development and neurological disorders. Insights from Dr. Livingstone's research in macaques have been instrumental in developing a clinical treatment for tremor, as well as for therapies for <u>Alzheimer's disease</u> in and a <u>lethal brain cancer</u> <u>called glioblastoma</u> in that are now under clinical investigation.

Dr. Livingstone's <u>research on facial recognition</u> has illuminated how deficits in certain brain regions may lead to disorders such as face blindness and certain social problems seen in autism spectrum disorders. Dr. Livingstone <u>observations on maternal attachment</u> can help scientists understand maternal bonding in humans and can inform comforting interventions to help women cope with loss in the immediate aftermath of suffering a miscarriage or experiencing a still birth.

The humane and regulated use of animal models in biomedical research remains indispensable for understanding the biological processes that give rise to disease, for designing new therapies and interventions to improve health, and for ensuring such treatments are safe and effective. Such knowledge has yielded numerous life-altering and life-saving treatments in human and veterinary medicine, including therapies for diabetes, polio, tuberculosis, organ transplantation, hypertension, cancer, and more. The treatment and eventual eradication of many diseases will be enabled by knowledge generated from research in animal models.

As they work to achieve that goal, Harvard Medical School scientists continuously strive to refine the use and care of animals, reduce the number of animals used in research, and replace animals with nonanimal models whenever possible. As with all animal research conducted at Harvard Medical School, Dr. Livingstone rigorously follows applicable federal, state, and institutional policies and regulations that ensure the humane and safe care of and use of animals, including the <u>Animal Welfare Act</u> in accordance with USDA regulations and the <u>Public Health Service</u> <u>Policy on Humane Care and Use of Animals</u>. In addition, Harvard Medical School is accredited by <u>AAALAC International</u>, a voluntary peer-review accreditation program, in which research programs must demonstrate they meet the standards required by law, and are going the extra step to achieve excellence in animal care and use.

See Prof. Livingstone's <u>personal statement</u> on this matter.

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JANUARY 12, 2023

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News & Research

Professor Livingstone's personal statement about recent concerns over animal research

October 24, 2022 | Research

I have been a neuroscientist for nearly 50 years. I have dedicated my life's work to unraveling the mysteries of the human brain, the ultimate frontier in science.

Research into the function of the brain can not only help us understand how it works, but can inform our understanding of what goes awry in brain disease and how we can treat it.

The joys and rewards of this labor are many. Our research has become the basis for a new <u>clinical treatment for tremor</u>. Our work has informed the design of experimental therapies for neurodegenerative diseases such as Alzheimer's, as well as for the deadly brain cancer glioblastoma, the disease that killed my mother. A3431-9R

Knowing that my research may help treat people with conditions that kill them swiftly (such as glioblastoma) or diseases that slowly rob them of memory, personality, joy, and, eventually, life is what propels me to go into my lab every day.

Despite the many joys of my work, it has at times, been misunderstood. Over the last several days, I have joined the ranks of scientists targeted and demonized by opponents of animal research, who seek to abolish lifesaving research in all animals. In doing so they threaten to thwart medical progress for the benefit of all people and, indirectly, for other animals.

Their tactics have miscast my work, twisted facts, and spread inaccurate and false information wrapped in emotionally charged, inflammatory language. This rhetoric has spurred aggressive and threatening messages, and I have become increasingly fearful for my safety and for the safety of my family.

I will attempt to dispel some of the pernicious myths about my research and set the record straight. I owe this explanation to the general public, to medical science, to my colleagues who are treating patients at their bedside, to my peers who study basic mechanisms of disease at the lab bench, and, most of all, I owe it to all the people and other animals who stand to benefit — in the near or distant future — from research conducted in animals.

Though I have been a neurobiologist for more than four decades and worked with rhesus monkeys throughout the years, I only started working with young macaques in 2014. While non-human primates make <u>up a tiny portion of animals</u> used in biomedical research, they are invaluable in studies that require animals with a visual system, brain, immune system, and certain disease susceptibility similar to those of humans. In 2016, we performed two reversible eyelid-closure procedures in macaques using dissolvable sutures, as described in the peer-reviewed literature. This procedure is also performed in human children and infants with certain eye tumors or to treat invasive eye infections. Pediatric surgeons give these children anesthesia and pain-relief medications. We did the same with our infant macaques to ensure they do not experience pain.

The two cases we performed in 2016 built on studies performed in the 1960s by HMS <u>Nobel Prize winners Hubel and Wiesel</u> who mapped the organization of the human visual system — research that has <u>been</u> <u>described as a quantum leap</u> in our understanding of how the brain "sees." Hubel and Wiesel's work changed the treatment of <u>congenital</u> <u>cataracts</u>, <u>strabismus</u> (misaligned eyes) and lazy eye, or <u>amblyopia</u> and, over the years, <u>have helped save millions of children from vision loss</u>

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Building on Hubel and Wiesel's early transformative work, we wanted to probe further how the brain works. To do so, we used non-invasive brain MRI—a technique that was not available at the time of the original studies. Using brain MRI allowed us to go beyond these original observations and see in full detail the effects of temporary vision deprivation on the entire brain rather than just on parts of it, with a level of precision that Hubel and Wiesel could not foresee.

We have **not** performed eyelid closures since the two isolated cases in 2016 and have **no** plans to do so again. However, the two 2016 cases have been studied and reported in subsequent papers because they yielded many insights. My lab now uses entirely non-invasive techniques to study early visual experiences. These include caregivers wearing facial masks and having the animals wear goggles. Notably, eyelid closure was and remains <u>routine</u> protocol across research labs that study vision disorders. This technique, in fact, paved the way for the modern non-invasive methods we use now.

Although we do **not** pursue maternal attachment as a line of research, our lab made observations on <u>maternal bonding and attachment</u> in the course of other research. It started when one of our macaques delivered a stillborn. In an attempt to comfort the distressed mother, we gave her a stuffed toy. She relaxed and adopted the toy as her baby. We subsequently provided other macaque moms with Beanie Babies and soft-cloth toys. We now use this comforting measure for newborn macaques abandoned by their mothers and on the occasions when they are separated from them. These newborns were calm and held on to their soft toys. In fact, they are behaviorally indistinguishable from infants reared by their mothers. Other researchers working with monkeys, as well as primatologists, should benefit from this knowledge and use this as a calming measure in their own work.

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But people might ask how this work helps humans. Beyond showing that maternal attachment could be triggered by soft touch, these observations can inform the development of comforting interventions to help women cope with loss in the immediate aftermath of a miscarriage or still birth.

Our <u>research on face recognition</u> has illuminated how deficits in some brain regions can lead to face blindness and to certain social difficulties in children with autism spectrum disorders. Our work demonstrates that our brains get wired up according to what we experience in early childhood during critical windows. This insight is important for how we deal with children who have experienced deprivation early in life. This can also help inform education measures for such children. Finally, our work points to possible interventions for children with autism who might choose not to look at other people or their faces. Our work with adult macaques focuses on how the brain processes visual information at a higher level. We use standard techniques common across nonhuman primate labs that involve the implantation of electrodes similar to those used in patients with epilepsy or for deepbrain stimulation in people with Parkinson's disease. Indeed, these brain-machine interfaces that now benefit so many with neurologic disorders were developed through research in nonhuman primates. We use this same approach to see how adult macaques process visual information they see on-screen.

Our other research in adult macaques involves the <u>blood-brain barrier</u>, a complex network of blood vessels that protects the brain from toxins and pathogens. Yet, this protective barrier also hinders the delivery of medicines into the brain, posing a daunting therapeutic challenge. To circumvent this hurdle, we use focused ultrasound waves to nonsurgically inactivate, or ablate, certain brain regions and to temporarily "open" the blood-brain barrier. This temporary permeability of the barrier can allow the delivery of targeted therapies into the brain and transform the treatment of brain cancer and neurodegenerative diseases.

Some of this work has already led to clinical treatments. Our technique is now being investigated in clinical trials as a way to deliver chemotherapy directly into the brain for the treatment of glioblastoma and for breast cancer that has spread to the brain. The approach has also shown enough promise to be used in clinical trials to treat Alzheimer's disease. None of this would have been possible without our studies in macaques. The implications of our work for human health are important, but so are the contributions to our broader understanding of the brain's most sophisticated and highly evolved aspects of visual processing, especially those related to object recognition, such as faces, bodies, and scenes. This knowledge forms the foundation for future generations of neurobiologists and is already a part of neurology and psychology textbooks.

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All of the research procedures we use are done in a manner that aims to provide comfort, minimize distress, and reduce or completely eliminate pain.

All of my research is subject to extensive federal, state, and institutional policies, regulations, and oversight groups charged with ensuring the proper care and treatment of research animals and ensuring that the use of animals is justified and cannot be achieved through alternative means. Beyond our natural instinct to care for our animals, the humane treatment of animals is also critical to our ability to conduct our research in the first place: Animals that experience distress, pain, or discomfort cannot be studied and our results would not be valid.

All of my work is reviewed by peer scientists and funded by the federal government. For more than three decades, this work has garnered sustained support from the National Institutes of Health, which underscores the value and promise of this research for our understanding of the human brain in health and disease.

Our work has direct and indirect implications for human health, whether it leads to therapies for vision disorders, treatments for neurologic diseases and cancer, or helps alleviate the sense of loss experienced by women who suffer miscarriage. Do I wish we lived in a world where generating this important knowledge were possible without the use of lab animals? Of course! Alas, we are not there yet. We continue to work toward this future through our ongoing efforts to refine, reduce, and replace animal models — the three Rs of animal research.

I realize that working with animals is a privilege that requires vigilance and responsibility. To honor that, we take great care of our animals beyond what's mandated by even the most stringent federal regulations. We provide a nurturing environment, and I am proud to be an integral part of the animal care team. For example, as a morning person, I do all the early-morning bottle feedings of our baby macaques.

If you or a loved one has ever had a vaccine, taken a pill for high blood pressure, or been treated for diabetes, cancer, infection, or heart disease, you have benefited from animal research.

Whether you support animal research or not, you have benefited from therapies derived from work done in animals. And so have your pets. Veterinary medicine also relies on studies in animals. Pets that receive antibiotics, pain killers, cancer treatments, or vaccines or have surgery are the beneficiaries of research done in animals.

I love the animals I work with, and I am forever grateful for their vast contributions to medicine and science. We all should be.

Marge Livingstone is the Takeda Professor of Neurobiology at Harvard Medical School.

See Harvard Medical School's institutional statement on this matter

<u>here</u>.

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