



Citizens for Alternatives to Animals Research & Experimentation

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Via email to brownp@od.nih.gov; robert.m.gibbens@aphis.usda.gov

Re: 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, non-animal, 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 micro-architecture 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 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.³
- In this study, scientists are investigating the neuropathology of face processing seen in autism spectrum disorder (ASD) by utilizing "lesion network mapping" to correlate with data obtained from stroke patients experiencing facial recognition abnormalities. Adolescents with and without ASD are evaluated for face processing ability using behavioral assessments and resting state functional MRI. That information is analyzed and compared to brain imaging of patients who develop face recognition abnormalities following a stroke, a condition known as acquired prosopagnosia. Comparing the involvement of brain regions and connectivity differences in these two forms of prosopagnosia will inform the development of biomarkers and treatment targets for prosopagnosia.^{4 5}
- This research study used functional near-infrared spectroscopy to image two human subjects simultaneously to investigate why some individuals with autism spectrum disorder (ASD) avoid eye contact. During the study, pairs of participants, one with ASD

and one without, underwent imaging while interacting socially. The results showed that while making eye contact, participants with ASD had significantly less brain activity in the dorsal parietal cortex than those without ASD. Additionally, social symptomatology measurements correlated with the degree of activity in this region. ⁶

- Researchers used magnetoencephalography (MEG) and computational methods in human participants to measure the real-time brain processes that convert the appearance of a face into the recognition of an individual. MEG measured ongoing brain activity while participants viewed images of different individuals with varying facial expressions. The MEG scans allowed the researchers to map which parts of the brain encode appearance-based vs. identity-based information. The results were validated by comparing the neural data to an artificial neural network that was trained to recognize individuals from face images. These findings will help locate the exact point in the brain at which the visual perception system breaks down in disorders with impaired facial recognition. ⁷
- This project investigated how the human brain processes facial recognition by studying 33 epilepsy patients who were undergoing surgical treatment for seizures. The patients volunteered to have electrodes implanted into their brain regions involved with facial perception. The electrodes monitored neuronal activation while they were shown a series of faces. The researchers then compared the way faces are encoded in the brain using their findings from the electrode data with that of an artificial intelligence system known as deep neural networks. The scientists found a striking similarity between the human and artificial systems, especially with regards to the pictorial appearance of faces rather than the abstract identification of the faces. ⁸
- Another study worked with epilepsy patients who had temporary electrodes implanted for seizure treatment to explore the brain's processing of facial recognition. The study revealed that the same brain region is used when people identify either a voice or a face. Participants were presented with either photographs or voice recordings of three U.S. presidents and tasked with identifying them. Researchers found that when participants heard the recordings, the part of the brain responsible for processing visual cues exhibited electrical activity, although it was lower in magnitude and slightly delayed when compared with visual identification. ⁹
- 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. 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 Welfare Act and CFR Title 9, Section 2.31(d).

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).

The PHS Policy’s Principle II of the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training states that “procedures involving animals should be designed and performed with due 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,



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