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May 20, 2019

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Via email: joshua.gordon@nih.gov

RE: NIMH's use of the forced swim, tail suspension, foot shock, and social defeat tests on animals

Dear Dr. Gordon,

I am writing on behalf of People for the Ethical Treatment of Animals (PETA) and our more than 6.5 million members and supporters, and as a fellow neuroscientist, to request that the National Institute of Mental Health (NIMH) stop conducting and funding the cruel and useless forced swim, tail suspension, foot shock, and social defeat tests on animals.

In March 2018, we received copies of videos recorded by NIMH personnel of experiments conducted under two NIMH intramural grants. These videos show vulnerable animals being used in a battery of behavioral tests that cause fear, stress, panic, and a sense of helplessness in the animals.

The Forced Swim Test

In the forced swim test, a mouse or rat is dropped into a container of water with no way to escape nor any place to rest out of the water. One of the videos obtained from NIMH shows four panicked mice frantically swimming in cylinders of water, looking for an exit that does not exist. The mice try desperately to keep their heads above water and are subject to the terror of near-drowning for 11 minutes.

Because the time an animal spends swimming during this test may *sometimes* be extended by giving the animal *some* forms of human antidepressant drugs, earlier scientists (in particular the developer, Porsolt[1]) asserted that less time spent immobile was a sign of the animal being less "depressed" and more time spent immobile meant that the animal was more "depressed," as though they had "given up" and were in "despair." Human depression is characterized, in part, by a generalized feeling of sadness and hopelessness, but these symptoms are not assessed by observing a patient's behavior floating in a pool of water.

As Dutch scientists Molendijk and de Kloet have discussed, immobility in the forced swim test likely reflects an animals' adaptation to their situation and should not be used to determine an animal's mood.[2] Individual animals who are quicker to float also save their energy and are less likely to sink, meaning that animals who more rapidly pick up on this reality, and spend less time struggling, are simply learning this adaptive behavior

[1] Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature*. 1977;266:730-732.
[2] Molendijk ML, de Kloet ER. Immobility in the forced swim test is adaptive and does not reflect depression. *Psychoneuroendocrino*. 2015;62:389-391.

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more readily. Further, the immobility response also occurs after treatment with drugs that do not have antidepressant effects at all, such as antihistamines and other miscellaneous drugs,[3] meaning the forced swim test is prone to false-positives.

Time spent swimming vs. floating is also influenced by an animal's strain and experimental variances, such as water depth and temperature.[4] At best, scientists do not appear to be in agreement about what, if anything, the forced swim test tells us, yet NIMH is subjecting animals to this torment.

A 2017 article—which includes interviews with Steven E. Hyman, director of the Stanley Center for Psychiatric Research at the Broad Institute of the Massachusetts Institute of Technology and Harvard and director of the National Institutes of Mental Health from 1996 to 2001, representatives from Eli Lilly and Novartis, along with other experts—describe how use of the forced swim and other poorly-validated animal behavioral tests are contributing to the high failure rate of therapies developed in an effort to treat human depression.[5]

Emphasizing this reality, pharmaceutical giant AbbVie recently implemented a new animal welfare commitment stating, "AbbVie does not currently use or intend to use or fund animal forced swim tests." STAT News' Pharmalot reported on the development: "AbbVie (ABBV17) became the latest big drug maker to disavow use of a decades-old test for antidepressant research over concerns the testing may traumatize rodents while failing to yield any reliable outcomes for drug development."[6] Johnson & Johnson followed suit in March 2019, pledging to not use the forced swim test in its own laboratories or to support its use in sponsored external research. AbbVie and Johnson & Johnson, companies whose bottom line depends on conducting experiments that hold value for human conditions, understand that the forced swim test is worthless. Just this month, DSM Nutritional Products, a Netherlands-based ingredient manufacturer, also stated it will no longer use the forced swim test.

The Tail Suspension, Foot Shock, and Social Defeat Tests

The tail suspension test is similarly used erroneously to test an animal's level of "despair" based on their movement or immobility during a stressful situation. In one of the videos obtained by PETA from NIMH, we see two mice who have been taped to a horizontal bar to hang, suspended upside down in the air by their sensitive tails. The mice struggle to right themselves, summoning the effort to pull their bodies up and hold on for dear life to the tape affixed to their tails—only to drop back down repeatedly over the course of the six-minute video.

The NIMH videos depicting foot shock show a mouse alone in a compartment with an electrified grid floor. The experimenters deliver unpredictable electric shocks to the animal's feet that cause stress and possibly pain—likely making the mouse anxious and overcome with a sense of helplessness. When the shock comes, we see the mouse jump and scramble around the chamber, colliding into the walls because there is no escape. Some mice freeze, terrified to move a muscle after being shocked, potentially confused as to why this is happening to them.

Social defeat is used in intramural projects at NIMH and the agency also funds the experiment in extramural projects. In this test, social conflict is used to produce psychological stress, depression, and a sense of resignation

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[3] Arai I, Tsuyuki Y, Shiomoto H, Satoh M, Otomo S. Decreased body temperature dependent appearance of behavioral despair in the forced swimming test in mice. *Pharmacol Res*. 2000;42:171-176.

[4] De Pablo JM, Parra A, Segovia S, Guillamon A. Learned immobility explains the behavior of rats in the forced swimming test. *Physiol Behav*. 1989;46:229-237.; Jeffrys D, Funder J. The effect of water temperature on immobility in the forced swimming test in rats. *Eur J Pharmacol*. 1994;253:91-94.; Lucki I, Dalvi A, Mayorga AJ. Sensitivity to the effects of pharmacologically selective antidepressants in different strains of mice. *Psychopharmacology*. 2001;155:315-322.

[5] Katsnelson A. What the rats brain tells us about yours. *Nautilus*. http://nautil.us/issue/47/consciousness/what-the-rat-brain-tells-us-about-yours. Published April 13, 2017. Accessed March 7, 2019.

[6] Silverman E. Pharmalittle: China is first to approve a big pharma drug; J&J plans $5 billion stock buyback to blunt criticism. *STAT News*. https://www.statnews.com/pharmalot/2018/12/18/china-approvals-buybacks-fda/. Published December 18, 2018. Accessed March 7, 2019.

in animals. Repeated social defeat can have a devastating effect on the animal's immune function, cardiac and circadian rhythms, and metabolism. While the social defeat paradigm may give us insights into the biological mechanisms at play in mice when they are bullied, this information does not readily translate to humans.

Animal Experiments Are Not Improving Human Mental Health

These and other animal behavioral tests are aimed at modeling human neuropsychiatric disorders; however, they lack critical aspects of model validity: construct validity, since the mechanistic underpinnings creating the observed symptoms in animals are different than those that lead to the disorder in humans, and face validity, since animals lack the ability to "recapitulate important anatomical, biochemical, neuropathological, or behavioural features of a human disease."[7] No animal model is able to replicate all aspects of a particular condition and features of human behavior representing hallmarks of these disorders cannot be produced or properly assessed in animals.

Animal experiments, such as the ones using the tests depicted in the NIMH videos obtained by PETA, have been cited as the primary source of attrition in neurobehavioral clinical trials.[8] Significant differences in physiology between humans and other animals likely accounts for a large percentage of failed translation. Thus, the use of these problematic behavioral tests does not advance NIMH towards its vision of "a world in which mental illness are prevented and cured" and does not meet its mission of "transform[ing] the understanding and treatment of mental illnesses…paving the way for prevention, recovery, and cure."[9]

PETA's Request

Due to the inherent cruelty of these tests and their irrelevancy to the prevention and treatment of human neuropsychiatric disorders, NIMH's limited public funds should be allocated away from the forced swim, tail suspension, foot shock, and social defeat tests and towards more relevant, human-based experimental models. These may include computational modeling using already well-defined biomarkers[10] and the use of patient-specific stem cells for personalized medicine, which "affords the ability to general neuronal cell-based models that recapitulate key aspects of human disease"[11] and can be used in drug discovery.

Your own publication record indicates extensive experience with animal behavioral experiments including foot shock,[12] food and water deprivation,[13] and social defeat. In the latter experiment, which you published in 2017 shortly before being appointed NIMH Director, three to four-month-old female mice had their tails and vaginas rubbed with male mouse urine and were placed into cages with larger, aggressive male mice. For 10 days, these female mice were placed directly into the aggressive mouse's cage for 5-10 minutes so that they would be

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[7] Nestler EJ, Hyman SE. Animal models of neuropsychiatric disease. *Nat Neurosci*. 2010;13(10):1161-1169.
[8] Garner JP. The significance of meaning: Why do over 90% of behavioral neuroscience results fail to translate to humans, and what can we do to fix it? *ILAR J*. 2014;55(3):438-456.
[9] National Institute of Mental Health. About NIMH. https://www.nimh.nih.gov/about/index.shtml. Accessed March 7, 2019.
[10] Siekmeier PJ. Computational modeling of psychiatric illnesses via well-defined neurophysiological and neurocognitive biomarkers. *Neurosci Biobehav Rev*. 2015;57:365-380.
[11] Haggarty SJ, Silva MC, Cross A, Brandon NJ, Perlis RH. Advancing drug discovery for neuropsychiatric disorders using patient-specific stem cell models. *Mol Cell Neurosci*. 2016;73:104-115.
[12] Klemenhagen KC, Gordon JA, David DJ, Hen R, Gross CT. Increased fear response to contextual cues in mice lacking the 5-HT1A receptor. *Neuropsychopharmacol*. 2006;31(1):101-111.; Stujenske JM, Likhtik E, Topiwala MA, Gordon JA. Fear and safety engage competing patterns of theta-gamma coupling in the basolateral amygdala. *Neuron*. 2014;83(4):919-933.
[13] Klemenhagen; Stujenske; Parnaudeau S, O'Neill PK, Bolkan S, *et al*. Inhibition of medio-dorsal thalamus disrupts thalamo-frontal connectivity and cognition. *Neuron*. 2013;77(6):1151-1162.

assaulted by the male mice. They were cohoused with their aggressor—separated only by a divider—for the remaining 24 hours of that day. They encountered a new aggressor every day of the 10 days.[14]

The terror and distress experienced by mice and rats used in experiments conducted and funded by NIMH is particularly concerning in light of our evolving understanding that mice and rats are highly social, sensitive animals who excel at learning, enjoy playing, and express empathy and altruism. They feel pain, experience a wide plethora of emotions, and value their lives just as we do.

We therefore call on NIMH to cease conducting and funding the forced swim, tail suspension, foot shock, and social defeat tests. When are you available to discuss this important matter?

Sincerely,

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[14] Harris AZ, Astak P, Bretton ZH, *et al*. A novel method for chronic social defeat in female mice. *Neuropsychopharmacol*. 2017;43:1276-1283.