# From Trauma to Treatment

## Addressing the crisis in treating Post-Traumatic Stress Disorder

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## About Citizens for Alternatives to Animal Research

Founded in 2014, Citizens for Alternatives to Animal Research & Experimentation (CAARE) is a national nonprofit organization dedicated to promoting a fundamental shift in the way the U.S. conducts biomedical research, one that involves focusing on human science and medicine with far less reliance on animal models of human diseases.

CAARE's goal is to demonstrate that there are modern, ethical, human-based methods of research for biology and medicine that should be given priority over animal experimentation. We believe that these technologies can replace the use of sentient animals with superior applicability for human medicine.

CAARE is working to change the current paradigm of widespread, repetitive, and unnecessary animal testing by raising awareness of how the abundance of new technologies can successfully replace research using animals.

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Citizens for Alternatives to Animal Research and Experimentation

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# Executive Summary

Post-Traumatic Stress Disorder (PTSD) is widely recognized as one of the major public health crises of our time, one that impacts the mental health, physical well-being, and interpersonal and social relationships of patients. More than 43 million Americans suffer from mental health challenges, including PTSD, but 57% never receive treatment.[1]

More than 43 million Americans suffer from mental health challenges, including PTSD, but 57% never receive treatment.

Additionally, there is an elevated risk of suicide, attempted suicide, and suicidal ideation among those suffering from PTSD, as described in several studies. In 2016, the U.S. Department of Veterans Affairs (VA) disclosed that an average of 20 veterans commit suicide every day.[2]

This is tragic because there are evidence-based therapies that are well-established, rigorously tested, and recommended by many professional health organizations for treating PTSD. These treatments, however, are not reaching those in need.[3]

This disparity has led to a belief that we lack effective treatments for PTSD. Specifically, many believe we lack a basic understanding of the neurobiology behind PTSD and conclude that this calls for basic research involving animal experiments.

This report details how animal experiments fail in this regard. Instead of investing millions of dollars on animal research that doesn't translate to humans, stakeholders must direct funding to overcoming barriers to access so that those currently suffering from PTSD can receive existing, effective treatments.

## Existing, Effective Therapies to Treat PTSD

**Over the past 15 years, researchers have made considerable headway in understanding and treating PTSD, as acknowledged by the VA, the U.S. Department of Defense (DoD), and the American Psychological Association (APA).** These agencies and professional associations recognize the efficacy of targeted psychotherapies, such as cognitive behavioral therapy, exposure therapy (ET), and newer therapies such as

[1] Nguyen *et al*, 2018, p. 5.

[2] Sareen *et al*, 2005. Referenced by Hudenko, Homaifar, and Wortzel in a comprehensive article on PTSD published online by the National Center for PTSD of the U.S. Department of Veterans Affairs.

[3] "VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder," 2017.

accelerated resolution therapy (ART). Yet these effective and evidence-based treatments backed by prestigious and influential organizations have not been well integrated into practice.

Exposure therapy is one of the most studied psychotherapies used for treating PTSD. Under the guidance of a therapist, a patient gradually confronts negative memories or feared situations in a safe setting.

100% of single-trauma victims and 77% of multiple-trauma victims were no longer diagnosable with PTSD after six sessions of EMDR.

Another highly recommended psychotherapy is Eye Movement Desensitization and Reprocessing (EMDR), which is derived from the principles of exposure therapy. During EMDR a patient recalls a traumatic memory while focusing on a therapist-directed external signal such as hand-tapping or while following a finger.[4] The resulting horizontal eye movements have been shown to desensitize the discomfort felt from recalling the traumatic memories.[5]

EMDR has been rigorously tested and confirmed to be effective for treating trauma and PTSD, with multiple studies demonstrating remarkable outcomes.[6,7]

One study funded by the HMO Kaiser Permanente determined that 100% of single-trauma victims and 77% of multiple-trauma victims were no longer diagnosable with PTSD after only six 50-minute sessions of EMDR. In another study, 77% of combat veterans were free of PTSD in 12 sessions.[8]

ART is quickly gaining recognition based on its rapid successful results. Most patients saw relief from PTSD symptoms after fewer than four ART sessions.

A newer therapy boasting a shorter treatment time is accelerated resolution therapy (ART), which uses the same mechanisms as EMDR and adds to it imaginal exposure and re-scripting, which help the patient to reframe the trauma. A positive connotation of the memory then replaces the initial trauma.

ART is quickly gaining recognition as a first-line treatment for PTSD based on its rapid successful results. In one randomized controlled study, most patients saw relief from PTSD symptoms after fewer than four ART sessions.[9]

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[4] Shapiro, 1989.

[5] Novo Navarro *et al*, 2018.

[6] Foa *et al*, 2009.

[7] Galea *et al*, 2012.

[8] EMDR Institute, Inc.

[9] Kip *et al*, 2013.

Existing psychotherapies are low-cost, drug-free, and highly effective, yet are vastly underutilized.

These therapies are low-cost, drug-free, and highly effective at treating PTSD, yet are vastly underutilized. Barriers to access include stigma of engaging in psychotherapy, lack of awareness, and lack of clinician training.

Given the abundance of professional endorsements for these therapies and the pressing need among large populations of PTSD patients, there is dubious justification for funding animal-based studies of basic neurology. Rather, funds should go toward bridging the gaps in access to existing, evidence-based treatments for PTSD.

### Human-Based Research into PTSD Causes and Treatments

Not only have researchers developed effective therapies, they have devised sophisticated and advanced methods of studying the neurobiology of the disorder in humans. Using these methods, it is possible—and preferable—for PTSD to be studied ethically and non-invasively in humans. These technologies are far more effective and cost-efficient than animal research and provide a direct way of looking at the human brain to study PTSD.

Non-invasive neuroimaging techniques are currently being used to map the internal components of the brain in PTSD patients.

Non-invasive neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) scans, and electroencephalograms (EEGs), are currently being used to map the internal components of the brain, detect PTSD pathways in the brain, and study brainwave patterns in PTSD patients. All of these technologies offer valuable, direct insight into the human brain and are so safe that they can be used on infants.

Other emerging models, such as graph theory (or graph analysis), utilize fMRI data combined with computer modeling and statistics to study how brain networks connect and interact. One graph theory study demonstrated that PTSD symptoms are a result of weakened connections between the part of the brain that processes memories and the part that provides contextual information.[10]Additionally, graph theory has enabled scientists to confirm the differences between the neural pathways of PTSD patients and normal controls.[11]Graph theory has enormous potential for furthering information and treatment options for PTSD and would benefit greatly from increased funding.

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[10] Spielberg *et al*, 2015.

[11] Koizumi *et al*, 2017.

There is already a massive amount of data collected about PTSD patients, and modern high-speed computers and software are now available to efficiently and thoroughly analyze that data. Computers are being used to predict drug toxicity and to match patients to the most appropriate drug for treatment.

"Organs-on-chips," or mini organs grown from adult human stem cells, are being used to study biochemical reactions in the human body, such as testing chemicals and drug reactions for PTSD research. While still in an early stage, these mini organs that function identically to human organs are proving to be a much more accurate way of studying biochemical reactions in humans than animal tests.

Biomarkers, such as cortisol levels, are detectable substances in the human body that correlate to a specific condition, in this case stress. Currently, researchers have identified biomarkers associated with PTSD and would benefit greatly from increased funding for further research. Genetic sequencing studies also identify potential PTSD biomarkers; they have already determined several predictors of PTSD and several DNA mechanisms implicated in PTSD.[12]

Donated brain tissue from deceased patients has been analyzed to provide information about PTSD's impact on the brain.

Finally, postmortem tissue analysis is revealing much more about PTSD than could possibly be gained from animal studies. Several brain banks have opened in the last two decades in response to the need for greater access to human brain tissue. These donated human brains from deceased patients can be genetically and histologically analyzed for clues into the disorder. A recent analysis found astroglial (brain cell) scarring in those with traumatic brain injury and PTSD.[13] Other studies have linked anatomical brain changes to increased production of certain cellular proteins and have revealed the epigenetic effects of PTSD, correlating postmortem tissue to actual behaviors in real patients.[14]

As more funds are directed toward these emerging human-based tools, our knowledge of PTSD and potential treatments will increase.

## Invalidity of Animal Research to Study PTSD

Scientists are increasingly noting the fundamental flaws of animal research and how results obtained from animals do not translate to

[12] Sheerin *et al*, 2017.

[13] Shively *et al,* 2016. The study involved looking at the brains of individuals with acute and chronic blast exposure, most of whom were clinically diagnosed with PTSD while alive.

[14] Young *et al*, 2015.

Tests on mice have been shown to correctly predict human toxicity with only 43% accuracy.

humans. Tests on mice have been shown to correctly predict human toxicity with only 43% accuracy in one large study comparing human and animal drug toxicities.[15] This is less predictive than tossing a coin. Such inaccuracy has resulted in dangerous drugs advancing to human clinical trials, and some have entered the market with serious consequences, including death.

Although mice and humans share 98% of protein-coding genes, the small differences are significant enough that this results in massive incompatibility. Animal experiments do not produce results that are predictive or relevant to humans due to these vital differences. This lack of translation is evident not just in PTSD studies, but also in decades of disease research on animals. Using the examples of diabetes and Alzheimer's disease, this report details how extensive animal research into these disorders has failed to produce any viable treatments.

PTSD research using animals is especially problematic because a diagnosis of PTSD depends on a verbal description of symptoms, nightmares, and flashbacks, and there is no way to confirm that animals suffer from such a condition. Some researchers note the similarity in hormones released after a traumatic event, but that is not enough to make a PTSD diagnosis, and the cause could be stress alone.

Drug safety is another area in which the differences between species hamper extrapolation of data. **Only 8% of investigational new drugs that test safe or effective in animals ultimately achieve approval by the U.S. Food and Drug Administration. The other 92% pass animal trials but prove to be unsafe when they reach human clinical trials**.[16,17] Even the 8% of drugs that are approved often turn out to be unsafe for humans, as millions of Americans are hospitalized yearly due to adverse drug reactions and some drugs are recalled or relabeled.

It is virtually impossible to establish an appropriate animal model for PTSD.

Many PTSD researchers acknowledge the extreme difficulty of modeling PTSD in animals. They point out that PTSD is a complex and debilitating neuropathology with frequent overlap of symptoms and comorbidity with other disorders, including depression, anxiety disorders, drug abuse, and suicidal ideation. For these reasons, it is virtually impossible to establish an appropriate animal model that reproduces the myriad behavioral and biochemical abnormalities

[15] Uhl and Warner. 2015, p. 220.

[16] Akhtar, 2015.

[17] Marshall *et al*, 2018.

observed in PTSD patients. They note that to date, there is no single suitable pharmaceutical preparation to treat PTSD, despite years of research, millions of dollars spent, and untold numbers of animals made to suffer.

## Causing Trauma to Animals to Study PTSD

There is no evidence that animals experience anything like PTSD, and, in fact, evidence points to the contrary.

In order to study PTSD and its potential treatments in animals, researchers first attempt to induce psychological trauma in animals. The stress, pain, and violence the animals endure is intended to provide an understanding of the neurophysiological mechanisms that cause PTSD, but there is no evidence that animals experience anything like PTSD, and, in fact, evidence points to the contrary.

**The use of painful electric shocks is perhaps the most common method for inducing trauma, often in conjunction with other modes.** Physical restraint is also common, wherein researchers force rats and mice into thin tubes for several hours at a time. These tubes impose total immobilization and the animal cannot make any movements at all. Another common technique involves hanging rats or mice by their tails for several minutes. When the animals stop struggling, the behavior is labeled "immobility," and scientists consider this to be a viable indicator for PTSD.

**PTSD researchers have devised a method referred to as "underwater trauma," which simulates drowning. Animals are forced to swim for a time in a circular pool, then held underwater with a metal net for 30 seconds. Investigators posit that this method works well to induce PTSD because the animals believe they are truly drowning**.[18]

Experimenters also tamper with an animal's normal social and environment in order to induce trauma. Nests are destroyed, newborn babies are taken from their mothers, and small mice are pitted against large mice within a small cage in order to create extreme feelings of stress and fear.

Some studies involve chronically stressing animals for much of their lives with electric shocks, temperature extremes, and food deprivation.

Other experiments involve chronically stressing animals for much of their existence. Animals are exposed to excessive noise. Next, experimenters randomly expose them to electric shocks, force them to swim in freezing cold water, transfer them to an intense heat chamber, shake them in a tube, reverse their day and night cycle, and even deprive them of food and water for days at a time. The rationale for this

[18] Schöner *et al*, 2017.

approach is purportedly to simulate the stress of military personnel in combat.[19]

Significantly, PTSD research on animals is not only harmful, but that harm is inherent in the pursuit of a traumatic psychological state. Yet despite these methods, little to no gain has been achieved in deriving treatments for PTSD, nor are advances probable through these means given that animals' brains cannot be reliably considered to reproduce a state of human PTSD.

## Financial Burden of Treating PTSD

**Current PTSD treatments incur great costs for individual patients, healthcare organizations, and government agencies, with some estimates suggesting that up to $2 billion a year has been spent on veterans of the Afghanistan and Iraq wars with PTSD**.[20]

Animal research is also extremely costly, with billions of dollars spent each year on studies that largely amount to nothing. The majority are not published, cited, or useful in finding treatment to diseases. This translates to billions of dollars and countless resources wasted annually.

**Currently, it costs $1 billion and 10 years to develop a drug,[21] with the vast majority failing in human trials.** Drug companies and the healthcare system are also overburdened with a massive amount of post-approval failures, ensuing lawsuits, and loss in value. These costs do not include the incalculable suffering of those inflicted with diseases and conditions, or that of their families.

Researchers and companies are realizing that animal research is an ill-advised financial venture, not just for PTSD, but for all diseases. Consequently, many are decreasing funding for animal experiments, as is evidenced by a 25% reduction in animal studies in Europe between 2005 and 2009.[22]

**Developing drugs for mental health disorders has proven to be expensive and high risk, with the vast majority of promising drugs failing after years of costly clinical trials. As a result, pharmaceutical companies worldwide are scaling back or outrightly abandoning**

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[19] Goswami *et al*, p. 5.

[20] Reisman, 2016.

[21] Marshall *et al*, 2018

[22] Pound *et al*, 2014, p. 2 of Abstract.

**drug-discovery programs in neuroscience due excessive failures with mental health drugs**. This includes Pfizer and Merck in U.S., GlaxoSmithKline and AstraZeneca in the UK, and Novartis and Sanofi in Europe.[23]

The most cost-effective solution to the PTSD crisis is to increase access to existing treatments.

The most cost-effective solution to the PTSD crisis is to increase access to existing treatments that are proven to be safe, effective, and low-cost. One study showed that by implementing effective, existing therapies in VA facilities, the government and taxpayers would save upwards of $2,000 per veteran per year.[24]

## Conclusion

The evidence is overwhelming: If humans are to benefit from medical and clinical advancements into PTSD, existing, effective therapies must be adequately disseminated to patients, and animals must be factored out of the research equation. Funding organizations, including government, should take into account the striking invalidity of animal research and cease funding such projects, instead investing in ethical, effective, reliable, human-based methodology. It is up to lawmakers and funders to ensure that science remains bound to the ideal of promoting human outcomes. Eliminating animal research in PTSD and other mental illnesses is essential to accomplishing this goal.

### Recommendations

- Funders of PTSD research should make efforts to direct their dollars toward projects and programs that promote evidence-based treatment options.
- For basic research, investments should be made into ethical, non-invasive neurobiological research that is human relevant.
- Financial support should be directed to resolving barriers and gaps within society that currently prevent access to and delivery of care to those who desperately need help.
- Legislators should work to pass laws that fund and disseminate evidence-based treatments to PTSD patients, which would ensure that taxpayer dollars intended for the treatment of PTSD are being spent in the most logical and efficient way possible.

[23] Abbott, 2011.

[24] Meyers *et al*, p. 97.

# I. Introduction

In recent decades, America, and indeed the world, has endured a number of catastrophic events. From the World Trade Center and other terrorist attacks to school shootings, cataclysmic hurricanes, floods and fires, and multiple wars in the Middle East, the last several decades have been inundated with traumatic events. From that trauma comes declining mental health, most notably seen as increases in the prevalence of Post-Traumatic Stress Disorder (PTSD).

The lifetime prevalence of PTSD among U.S. adults is over 6%, with members of certain subpopulations suffering from much higher rates.

Those with PTSD experience symptoms that include flashbacks and uncontrollable thoughts about the traumatic event. Over time, these negative thoughts can lead to additional symptoms such as depression, anxiety, impaired sleep, trouble concentrating, emotional extremes, and violent outbursts. The lifetime prevalence of PTSD among adults in the United States is over 6%. Members of other subpopulations, such as active duty service members and childhood trauma survivors, suffer much higher rates of PTSD.[25]

Additionally, there is an elevated risk of suicide, attempted suicide, and suicidal ideation among those suffering from PTSD, as described in several studies. One 2005 study analyzing data from the National Comorbidity Survey showed that PTSD alone out of six anxiety diagnoses was significantly associated with suicidal ideation or attempts, indicating a strong relationship between PTSD and suicide. This study controlled for comorbid disorders such as anxiety and other diagnosed mental health disorders.[26]

While most studies into the connection between PTSD and suicide have involved veterans (in whom the link is particularly high), other population studies have been carried out in firefighters and Emergency Medical Services personnel,[27] refugees,[28] and the general population.[29] All revealed a significant connection between PTSD and suicide. In 2016, the U.S. Department of Veterans Affairs (VA) disclosed that an average

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[25] "VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder," 2017.

[26] Sareen *et al*, 2005. Referenced by Hudenko, Homaifar, and Wortzel in a comprehensive article on PTSD published online by the National Center for PTSD of the U.S. Department of Veterans Affairs.

[27] Martin *et al*, 2017. PTSD symptom severity was significantly associated with suicide attempts.

[28] Ferrada-Noli, *et al*, 1998, Parts 1 and 2.

[29] Giacomoni, 2018.

of 20 veterans commit suicide every day.[30] This clearly demonstrates the robust relationship between PTSD and suicide.

Current treatments incur great costs for individual patients, healthcare organizations, and government agencies, with some estimates suggesting that the healthcare and social costs for veterans returning from wars in Afghanistan and Iraq, were, for a two-year period, approximately $925 million.[31]

Effective, evidence-based treatments backed by prestigious and influential organizations have not been well integrated into practice.

Over the past 15 years, researchers have made considerable headway in understanding and treating PTSD, as acknowledged by the VA, the U.S. Department of Defense, and the American Psychological Association. These agencies and professional associations recognize the efficacy of targeted psychotherapies, such as cognitive behavioral therapy, exposure therapy, and newer therapies such as Accelerated Resolution Therapy. Yet these effective and evidence-based treatments backed by prestigious and influential organizations have not been well integrated into practice.

Because a multitude of patients do not receive effective treatments and are still suffering, there is a substantial push by both patients and supporting organizations for further research. While some of this research shows clearly that effective treatments need to be more widely disseminated, many scientists and healthcare professionals conclude that we must instead continue the search for pharmacological treatments for PTSD. These scientists either ignore or are unaware of mounting evidence supporting the use of existing therapies designed to treat PTSD.

The majority of these drug development studies waste millions of dollars on basic and translational science that produces little to no viable human outcomes. Further, in pursuing these kinds of experiments, animals are forced to undergo physical and mental suffering in ways that are clearly unethical. As such, this report calls on those who oversee funding and implementation for PTSD resources to reject animal-based research on PTSD and other mental illnesses. By laying out a compelling case for how these experiments harm animals without helping human patients, this report promotes the redirection of resources into truly effective therapies that can relieve suffering in PTSD patients.

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[30] Office of Suicide Prevention, 2016.

[31] Foa *et al*, 2013.

# II. Evidence-Based Treatments and Therapies for PTSD

PTSD is increasingly recognized as one of the most important public health crises of our time due to its impact on mental health, physical well-being, and associated interpersonal and social problems.[1] Despite the seriousness of this burgeoning concern, the majority of people afflicted do not receive treatment.

According to the major international health organizations cited throughout this section, the best treatments for trauma-initiated mental health conditions include psychotherapies that help alter patients' perceptions of their traumatic memories. These therapies include exposure therapy, Eye Movement Desensitization and Reprocessing (EMDR), accelerated resolution therapy (ART), and other cognitive psychotherapies.

Over 43 million Americans suffer from mental health challenges including PTSD, yet about 57% of adults have not received treatment.

As stated in the 2018 report produced by Mental Health America, a nonprofit organization that tracks mental illness in the U.S., over 43 million Americans suffer from mental health challenges, including PTSD, yet about 57% of adults have not received treatment. Further, "over 76% of youth with severe depression—1.7 million kids—did *not* receive the treatment they needed."[2]

These staggering numbers elucidate a critical issue: The problem is not a lack of existing effective treatments but rather that these treatments are not reaching those who are in desperate need of relief. Thus, bridging this gap must be the first priority in dealing with the PTSD crisis, ahead of more research into developing new therapies.

This section describes several existing PTSD therapies that are evidence-based, drug-free, and low-cost. They are the most rigorously tested, well-established, and advanced cognitive therapies available. Most of these therapies fall under the umbrella of cognitive behavioral therapy (CBT), which strives to change the thought patterns that are disturbing the patient's life.

These treatments are not only effective; they are recognized by international professional health organizations, such as the World

[1] Foa *et al*, 2013.

[2] Nguyen *et al*, 2018, p. 5.

Health Organization and the Centers for Disease Control and Prevention. The methods are fully endorsed by the U.S. Department of Veteran Affairs (VA) and the U.S. Department of Defense (DoD). In their 2017 PTSD treatment guidelines, the VA and DoD both recommend individualized trauma-focused psychotherapies while recommending drug-based therapies only for patients who choose not to engage in trauma-focused psychotherapy.[3]

A systematic review and meta-analysis found that as a first-line treatment, psychotherapy is generally more effective than pharmacotherapy.

Concerning pharmacological treatments for PTSD, a systematic review and meta-analysis was carried out by Daniel Lee, MD, and a large group of colleagues in a multi-center study. They sought to evaluate the effectiveness of psychotherapy versus pharmacotherapy for patients diagnosed with PTSD. The findings indicated that as a first-line treatment, psychotherapy is generally more effective than drugs.[4]

## Proven Evidence-Based Treatments

### *Exposure Therapy*

One of the oldest treatments for anxiety and PTSD, exposure therapy has been around since the 1950s. It typically consists of a trained therapist guiding a patient as he or she confronts negative, fearful memories in a safe setting.[5,6] The National Academy of Sciences recommends several types of exposure therapy as safe and effective, especially prolonged exposure (PE) therapy, which is strongly recommended by the American Psychological Association.[7] Exposure therapy has been shown to have a high efficacy, to be more cost-effective than drug-based interventions,[8,9] and to be more acceptable to patients than pharmacotherapy.[10]

Exposure therapy, along with the other cognitive therapies detailed in this section, is readily adaptable to different cultures and individual patients, and can be adapted to different formats.[11] For instance,

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[3] "VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder," 2017.

[4] Lee *et al*, 2016.

[5] Galea *et al*, 2012.

[6] Foa *et al*, 2013.

[7] Courtois *et al*, 2017.

[8] Le *et al*, 2014.

[9] Lee *et al*, 2016.

[10] Foa *et al*, 2013.

[11] *Ibid*.

exposure therapy can be enhanced with simulated virtual reality (VR) environments so that patients can more vividly experience aspects of their trauma to resurface the memories. It creates fictitious, safe, and controllable situations that can enhance emotional engagement and acceptance.[12,13] A combined Virtual Reality with Exposure (VRE) therapy is catching on and has been the focus of several studies. Specifically, VRE has been shown to greatly augment exposure therapy by "maximizing the fit between the exposure and the patient's feared stimuli."[14]

Not only has virtual reality (VR) added invaluable knowledge to the mental health field, it also presents an entirely new way to study and understand PTSD. Researchers have used VR during treatments to study the brainwaves and pathology of patients with PTSD.[15] This allows for refinement and study of the treatment protocols without using animals as a poor and unreliable substitute. Considered a "technological revolution in mental health care,"[16] VR allows for the repeated presentation of potentially distressing scenarios that are objectively safe. As such, VR allows patients to learn new thought patterns in a safe environment, which is one of the key aspects to successful exposure therapy.[17]

However, even without advanced technologies, all of the meta-studies and care guidelines reviewed here, including the meta-analytical reports created by the National Academy of Sciences[18] and the VA/DoD,[19] identified PE therapy not only as an effective and useful tool for treating PTSD, but also as the highest-ranking therapy in strength of evidence supporting its use.[20]

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[12] Botella *et al*, 2015.

[13] Difede *et al,* 2007.

[14] Maples-Keller *et al*, p. 555.

[15] Freeman *et al,* 2017.

[16] *Ibid*, p. 2393.

[17] Norrholm, *et al*, 2016. Researchers in this study also measured cortisol as a biomarker to indicate efficacy of the treatment regimen. Cortisol levels decreased from baseline to the post-VR session.

[18] Galea *et al,* 2012.

[19] "VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder," 2017.

[20] Cusack *et al*, 2016. This large multi-center study investigated, by a meta-analysis, psychological treatments for PTSD. The strongest support was for exposure therapy.

### *Eye Movement Desensitization and Reprocessing (EMDR)*

EMDR was first introduced by North American psychologist Francine Shapiro in the late 1980s as a type of psychotherapy that helps people heal from the symptoms and emotional distress that are the result of disturbing life experiences, including PTSD.

Shapiro described the procedural details, hypotheses for its effectiveness, and a case study in her initial publication.[21] EMDR consists of elements that are compatible with other psychological approaches, and after continued refinement, its standardized protocol now involves eight distinct phases.[22]

**During EMDR sessions, the client recalls traumatic experiences while simultaneously focusing on a therapist-directed external stimulus such as following a finger, hand-tapping, or audio that demands their attention.**[23] It has been found that the patient's horizontal eye movements during the rhythmic task can desensitize the discomfort felt during the recall of traumatic memories. In doing this, the therapy aims to reprocess the memories and include them within the patient's set of normalized memories.[24] **Rapid eye movements remove the psychological barriers involved in processing the images and feelings from a past trauma, and the step-by-step protocol is easy for any trained therapist to follow.**

The eye movements have been studied in detail, and there are several theories that explain the success of EMDR therapy. Results from various studies have shown that the eye movements themselves alter the processing of emotional memories, specifically by aiding in the process of converting these negative memories into neutral or positive ones.[25] This theory is supported by evidence that a fundamental symptom of

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[21] Shapiro, 1989. The editor's note on page 211 states: "The results that are claimed in post-traumatic stress disorder are of great magnitude and rapidly achieved." The paper gives a comprehensive account of EMDR.

[22] Novo Navarro *et al*, 2018. A study carried out and authored by a number of researchers in Spain, Australia, and Italy. The Spanish title translates as: "25 years of Eye Movement Desensitization and Reprocessing (EMDR): The EMDR therapy protocol, hypotheses of its mechanism of action and a systematic review of its efficacy in the treatment of post-traumatic stress disorder." The eight-step protocol involves (1) patient history, (2) patient preparation, (3) evaluation of the primary aspects of the memory, (4) desensitization of the memory, (5) installation of the positive cognition, (6) body scan, (7) debriefing, and (8) reevaluation.

[23] Shapiro, 1989.

[24] Novo Navarro *et al*, 2018.

[25] Lee and Cuijpers, 2013. This large meta-analysis of 849 participants concluded that eye movements change the processing of emotional memories.

PTSD is a disconnection between areas of the brain responsible for memory recall and processing, as shown by studies on human PTSD patients using functional magnetic resonance imaging and other brain mapping techniques.[26] Rapid eye movements, or any rhythmic attention-keeper, can enhance the connection between the regions of the brain that are necessary to transform traumatic memories into normalized memories, effectively relieving the symptoms of PTSD.

Since its inception more than three decades ago, EMDR has been further developed and rigorously tested in randomized trials and multiple systematic meta-analytical reviews.[27,28] In addition, multiple randomized controlled and non-randomized trauma studies have consistently confirmed evidence for EMDR treatment of children and adults, including combat veterans, as the treatment of choice to achieve relief from affective distress, negative beliefs, and physiological arousal. According to the website of the EMDR Institute, Inc., of which Francine Shapiro was the founder:

> More than thirty positive controlled outcome studies have been conducted on EMDR therapy. **Some of the studies show that 84%-90% of single-trauma victims no longer have post-traumatic stress disorder after only three 90-minute sessions.** Another study, funded by the HMO Kaiser Permanente, found that 100% of the single-trauma victims and 77% of multiple trauma victims no longer were diagnosed with PTSD after only six 50-minute sessions. In another study, 77% of combat veterans were free of PTSD in 12 sessions.[29]

More than 30 positive controlled outcome studies have been conducted on EMDR, which is now a top-ranked treatment for PTSD by most respected organizations.

EMDR is now a top-ranked treatment for trauma and PTSD by organizations such as the American Psychiatric Association, the World Health Organization, the DoD, the VA, the American Psychological Association, the National Institute for Health and Care Excellence of the United Kingdom, the National Health and Medical Research Council of Australia, and the International Society for Traumatic Stress Studies.[30]

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[26] Sadeh *et al*, 2014.

[27] Foa *et al*, 2009.

[28] Galea *et al*, 2012

[29] EMDR Institute, Inc.

[30] Beauvais *et al*.

### *Accelerated Resolution Therapy (ART)*

Developed in 2008, ART is a newer treatment that combines evidence-based psychotherapies with eye movements to accomplish emotional healing from trauma or other mental health problems. As such, it employs a two-phase approach during which, in phase one, the therapist guides the patient in recalling a traumatic event and reducing the psychological sensations associated with this memory. In phase two, the patient "replaces" the distressing images and sensations with positive ones. This is accomplished through talk therapy while a clinician guides the patient through bilateral side-to-side eye movements. Through this process, known as "Voluntary Memory/Image Replacement," patients are able to lessen or release the pain associated with the disturbing memories through imaginal exposure and re-scripting of reactions to the memory.

In one study using ART, most patients saw relief from PTSD symptoms after fewer than four sessions.

ART is characterized by interventions that do not inhibit but rather serve to accelerate the natural resolution of the problem. This results in fewer sessions necessary, often only between one and five sessions depending on the issues addressed. For example, in one randomized controlled study most patients saw relief from PTSD symptoms after fewer than four ART sessions (3.7 ± 1.1).[31]

Using ART, most patients experience a "substantial reduction in symptoms".[32] This has been shown in several randomized, controlled experiments.[33] These trials have been conducted on patients suffering from PTSD stemming from combat, domestic and child abuse, violent crimes, loss of loved ones, illness, and divorce.[34]

**The majority of patients receiving ART also experience a significant reduction in symptoms from other related disorders, such as depression and anxiety.** In one study, large, clinically significant reductions in symptoms of PTSD were consistently reported after treatment completion and at a two-month follow-up.[35] Most patients who completed an average of five sessions showed a significant reduction in symptoms.

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[31] Kip *et al*, 2013.

[32] Kip *et al*, 2012, p. 127.

[33] Kip *et al*, 2012, 2013, and 2014.

[34] Kip, *et al*, 2012.

[35] *Ibid*.

ART's approach builds on techniques of imaginal exposure and re-scripting, active processes whereby the therapist helps the patient reframe the experience. Like Eye Movement Desensitization and Reprocessing (EMDR), ART is an eye movement therapy. However, there are some major differences between the two: (1) EMDR uses a variable number of eye movements, while ART uses a fixed number; (2) EMDR uses free association, while ART therapists are directive; (3) EMDR pays attention to content, whereas ART therapists focus on visual imagery and emotional sensations; and (4) EMDR is content-oriented, while ART has a procedural orientation.[36] As a result of ART treatment, researchers maintain, patients can no longer bring up the negative images and thoughts triggered by certain events or memories.

After ART treatment patients felt a reduction in PTSD symptoms along with relief from the pain associated with injuries received during trauma.

Using these methods, researchers discovered that they could even reduce pain related to the trauma that caused the patient's PTSD. The study analyzed neuropathic pain before and after ART interventions and showed that patients not only felt a reduction in their PTSD symptoms, but also found relief from the pain associated with injuries they received during the trauma.[37]

While ART is newer than other therapies, it is receiving increasing attention and is supported by several controlled studies. Further, it has a low cost, high completion rate, short process, and no drug-induced side effects.

Tragically, many patients with PTSD suffer for years because of ineffective and costly treatments. More human-based research into ART and similar treatments could effectively reduce treatment time to a few hour-long sessions for the majority of patients. This could provide significant relief to patients with PTSD, as well as being a boon for the overburdened VA. The social cost of rehabilitating those suffering from PTSD as well as the economic loss from people not being able to work is highlighted in a later section. It follows that if effective treatments are available, they ought to be used without delay.

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[36] Hoge, 2015. While Hoge is a senior scientist of the Walter Reed Army Institute of Research, the Walter Reed National Military Medical Center, and the Office of the Army Surgeon General, this publication reflects the author's personal notes and is not an official position paper.

[37] Kip *et al*, 2014.

### *Animal Assisted Therapy (AAT)*

Animals have been intricately linked with human existence for millennia. The first evidence of domestication of animals was around 10,000 to 13,000 years ago, mainly for agricultural and transportation purposes.[38] Companion animal domestication came later. As animals became part of our homes, the animal–human bond developed. Nowadays, there is a general understanding that the animal–human bond is a reciprocal one, with animals showing loyalty, companionship, unconditional acceptance, and empathy toward their humans.

In AAT, the patient connects with one or more animals who provide comfort and support to facilitate healing and recovery from physical or mental disorders. As early as 1792, animals were part of therapy at the Quaker Society of Friends York Retreat in England. Indeed, Florence Nightingale recognized the benefits of companion animals in treatment of individuals with illness.[39] For treating PTSD, the presence of an animal assistant encourages socialization and comforts the patient, disrupting the emotional numbing, hyperarousal, and avoidance that are common symptoms of PTSD.[40]

Dr. Eric L. Altschuler described in 2018 several cases from media reports where traumatized victims suffering from PTSD made remarkable progress toward recovery with the assistance of animals. The animals were mostly dogs and horses. However, one individual, a combat veteran with PTSD, worked with parrots at a bird sanctuary. Coincidentally, the parrots themselves had been rescued after trauma. Altschuler concluded that symptoms of PTSD were significantly alleviated after working with animals and that AAT had its place in the recovery of those with this debilitating condition. He suggested that this form of therapy would even prevent suicide.

An earlier systematic review revealed that AAT showed great promise in PTSD and suggested that it should be used as a complementary treatment to other first-line therapies.[41] The animals in this review were dogs, horses, and some farm animals. The individuals concerned ranged from war veterans to children. In all cases there was a marked reduction of PTSD symptoms. In particular, sleep was greatly improved.

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[38] Lear, 2012.

[39] Velde *et al*, 2005.

[40] Galea *et al*, 2012.

[41] O'Haire *et al*, 2015.

In one study of Animal-Assisted Therapy, feelings of pain, depression, and loneliness were reduced by 82%.

Debra Mims and Rhondda Waddell suggested in 2019 that "the goals of Animal-Assisted Therapy (AAT) is to provide long term group or individual therapy for survivors of trauma that incorporate AAT in conjunction with exposure therapy, cognitive behavior therapy, or empowerment therapy."[42] They give a comprehensive account of the history of AAT through modern times and mention that even rabbits and farm animals were part of the York Retreat. Even simply caressing an animal releases endorphins, the "feel-good" chemical in the body. Feelings of pain, depression, and loneliness were markedly reduced through AAT, with one study using dogs demonstrating an 82% reduction in patients' symptoms.[43]

A complete review of AAT is not within the scope of this work. Notwithstanding, it is clear that the unconditional and enduring support of animals confers healing on PTSD patients and can play a vital role in the recovery of PTSD victims.

### *Other Evidence-Based Treatments*

There are a variety of other evidence-based treatments not discussed here. Most of these are cognitive treatments similar to prolonged exposure or EMDR therapies. They aim to help patients re-experience the initial trauma, normalize the memory, and cope with it. One of the hallmarks of the human mind is its ability to dramatically visualize and imagine scenarios and respond adaptively to them. All of the highly-supported therapies for PTSD tap into this capacity to activate the process of visualization, while using the exposure to negative trauma memories as an opportunity to reprocess and normalize those memories.

The key to successful application of cognitive therapies is adapting them to the patient's needs; patient participation and compliance are the first steps to a positive treatment outcome. Additionally, cognitive therapies can be expanded or adapted to include patients who prefer different types of procedures and therapy styles.

Other well-established treatments include cognitive writing therapy, which has the same focus and general procedure, but is conducted via exchanges of writing.[44] Even patients who prefer not to engage in talk

[42] Mims and Waddell, 2019, p. 14.

[43] Mims and Waddell, 2019.

[44] Foa *et al*, 2013.

therapy can engage in cognitive writing therapy. Email is discouraged because of privacy concerns; however, patients write essays that they share with their therapist over a secure online website. The therapists give feedback via the same method.[45] Writing in itself is therapeutic, and patients are encouraged to write essays and poetry and to be creative as they go along, even illustrating their work with drawings and photographs.

Finally, researchers have established protocols for group-based cognitive therapies, which some patients prefer over individual sessions.[46] This may lead to higher patient participation and improved patient outcomes, demonstrating yet another way that effective cognitive treatments for PTSD can be adapted to patient preferences.

### Lack of Dissemination of Existing, Evidence-Based Therapies

Despite the high success rate of cognitive psychotherapies, they remain underutilized. One-fifth of adults and two-thirds of children with mental health issues do not receive treatment.

Evidence-based, effective treatments for people suffering from PTSD have suffered from lack of adequate implementation. Despite the fact that EDMR, ART, and other cognitive psychotherapies have a high success rate and are recognized by a growing number of international and professional health organizations, they remain largely underutilized. Mental Health America state in their 2019 report that one-fifth of adults do not receive any kind of mental health support at all, while about two-thirds of children and young people with mental health issues do not receive treatment.[47]

Research has identified numerous causes for the severe underutilization of the aforementioned therapies. Barriers such as access to and delivery of care exist at the patient, provider, and institutional levels. For the individual, these may be concerns about mental health stigma, lost wages or unemployment, a lack of awareness of existing resources, financial concerns, or geographical barriers. Provider barriers may be a lack of training and time commitments as well as institutional culture and rigid, internal organizational paradigms.[48] There may even be a lack of awareness and a resistance to these effective therapy approaches due to commitment to current practice.[49]

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[45] Ruwaard and Lange, 2016.

[46] Galea *et al*, 2012.

[47] Nguyen *et al*, 2018.

[48] Galea *et al*, 2012.

[49] Foa *et al*, 2013.

Nevertheless, clinicians and their professional associations are increasingly pointing toward the urgent need for concerted action among public health stakeholders to overcome societal barriers so that evidence-based therapies can be integrated into clinical settings.[50] Recommendations for better dissemination of these therapies include the use of novel technologies such as telehealth (or telemedicine) and other internet-based technologies, which not only are expedient and low-cost but have already proven to be successful in delivering high-quality care that is as effective as person-to-person therapy for patients with anxiety and depression.[51]

**If declared a research priority,[52] greater funding for access to and support for these therapies would clearly address this deficiency.** Given the abundance of professional endorsements for these therapies and the pressing need among large populations of PTSD patients, there is dubious justification for funding animal-based studies of basic neurology. Such a shift in funding priorities promises to significantly reduce the suffering of thousands of patients while reducing the burden of PTSD on the healthcare system. Indeed, studies have even shown that *simply educating patients about PTSD* can dramatically improve the outcomes of therapy.[53]

## Conclusion

Cognitive therapy approaches are evidence-based, drug-free, low-cost, and have few to no side effects. They have been in existence for several decades, have been rigorously tested, and are supported by an extensive body of scientific evidence that affirms their effectiveness.

Subjecting animals to invasive and painful testing cannot provide the sort of vital human-relevant information built on knowledge of human psychology and neurobiology.

These therapies could not have been developed or studied using animal experiments. Whereas animal researchers seek to understand the pathology of PTSD by probing the brain of a different species, tested therapies such as those mentioned above build on knowledge acquired through an understanding of human psychology and neurobiology and supported by rigorous clinical trials on humans. Subjecting animals to invasive and painful testing cannot provide this sort of vital human-relevant information.

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[50] *Ibid.*

[51] *Ibid.*

[52] *Ibid.*

[53] Yanos *et al*, 2016.

Evidence-based psychotherapies are exceedingly under-utilized. Investments need to be made in dismantling barriers to reach more PTSD patients with known effective treatments.

Tragically, evidence-based psychotherapies are exceedingly underutilized due to a severe lack of access and gaps in the delivery of care to those who urgently need help. Neither the government nor private funders are sufficiently addressing this deficiency. Rather than calling for more research using animals as test subjects, investments need to be made in dismantling these barriers to reach more PTSD patients with treatments already known to be effective.

# III. Available Methods for Studying PTSD in Humans

As discussed in the previous section, there are a number of highly effective treatments currently available for PTSD. Despite these reliable therapies, many scientists argue that animals are still necessary for fundamental research into PTSD treatments. Although there are many excellent reasons to avoid using animals for researching psychiatric disorders, perhaps the most notable is the existence of successful methods available for studying humans. In this section, we will outline these technologies and the ways in which PTSD can be studied ethically and non-invasively in human subjects.

Human-centric methods are more accurate and revealing than animal testing could ever be, offering researchers a direct way to look at the brain and symptoms of PTSD.

The methods presented below provide a human-centric view of the disorder that is more accurate and revealing than any animal testing could ever be. These methods offer researchers a *direct* way to look at the human brain and the symptoms of PTSD. Not only can researchers gain an unprecedented view of the human brain using advanced neuroimaging techniques, but they can also amplify these techniques through computers and computational analyses to produce striking results. Using information obtained from neuroimaging and brain mapping studies, researchers have identified areas in the brain related to PTSD and the common neural networks shared by patients with the condition.[1]

Below we discuss research methods and techniques that have significant applications for studying PTSD. Not only can these tools give us an incredibly accurate picture of the disorder, they can also be used to study every aspect, from behavioral changes to the nightmares it causes. While scientists claim to observe some aspects of PTSD using animal "models," there is no way animals can provide the level of insight gained from visualizing the actual activity in the human brain.

## Non-Invasive Neuroimaging Techniques

There are many methods currently in use in medical centers and clinical research centers that have the ability to explore the human body in meticulous detail. These methods are already being used in PTSD research without discomfort or adverse effects for patients. In studying

[1] Boccia *et al,* 2016.

These technologies are safe enough for use on teenagers, children, and infants.

PTSD using neuroimaging methods, researchers have identified many aspects of the disorder in the human brain. These technologies are so safe that they are commonly used on teenagers, children, and even infants to study brain disorders and trauma.[2,3,4]

### *Functional Magnetic Resonance Imaging (fMRI)*

One of the most valuable methods used to study PTSD is fMRI. Magnetic resonance imaging uses computers and magnetic fields to map the internal components of the human body. In fMRI, the computer traces neural activity in specific brain regions by tracking the flow of blood in those areas over time. By analyzing blood flow in the brain, scientists can identify which parts of the brain require the most oxygen and, therefore, are the most active. By following the sequence of blood flow, researchers can then detect which parts of the brain are actively working together. Brain maps can be constructed showing which parts of the brain are communicating in those with PTSD versus healthy patients. Utilizing fMRI methodology in research has revealed many insights about the effects of PTSD on the brain's physiology.

Using fMRI data, scientists have been able to track the changes that occur in the brain in real time during recall of trauma-related memories.[5] It has also been used to detect the changes in brain structure, particularly cortical thinning, that occur in PTSD patients.[6] A feature of fMRI is that it can be used to demonstrate clear changes in the brain before symptoms of PTSD arise. In a 2015 study, people who had been traumatized showed changes in the brain that were not evident in control groups; the authors concluded that such changes could preempt the transition to PTSD.[7] Brain blood flow patterns in patients with anxiety and PTSD show significant deviation from certain neural circuits observed in patients who have not experienced trauma.[8]

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[2] Cservenka *et al,* 2015. A study investigating emotional conflicts in adolescents ages 10 to 15.

[3] Carrión *et al,* 2010. A study on 27 adolescents ages 10 to 17 with symptoms of PTSD. Reduced hippocampal activity was demonstrated

[4] Hart *et al*, 2018. A study on 70 young people ages 12 to 20 with a history of severe childhood trauma. The study was biased towards right-handedness.

[5] Sadeh *et al*, 2014.

[6] Sadeh *et al*, 2015.

[7] Stark *et al*, 2015.

[8] Oathes, *et al*, 2015. A study that compared patients who had depression and/or anxiety with those who had no evidence of either of these.

fMRI can be used to study the effects of psychotherapies on brain function in PTSD.

More importantly, fMRI can be used to study the effects of various psychotherapies on brain function. Some studies have even revealed how psychotherapies influence the connectivity of various brain regions.[9] This provides clear evidence that therapy alone can directly impact the brain and relieve the symptoms of PTSD. Additionally, fMRI has been used to study the effects different chemical substances, such as oxytocin, have on the brain,[10,11] demonstrating how neuroimaging can be effective for evaluating drug therapies for PTSD.

### *Positron Emission Tomography (PET) Scans*

While fMRI has been used widely for PTSD and anxiety research, it is only one of several neuroimaging tools. Also widely used to study the human brain are PET scans and electroencephalography (EEG). PET scans rely on the detection of radionuclides in the brain, which clinicians inject to trace different pathways. Using PET scans, a single study was able to shed light on pathways of PTSD. Animal studies had failed to elucidate this for several decades. By imaging the brains of dozens of patients, some diagnosed with PTSD and others considered healthy controls, researchers were able to identify altered glutamate pathways in the brain.[12] Glutamate is an important neurotransmitter that plays a role in synaptic plasticity and the formation of memories, and as such has been implicated in the pathogenesis of PTSD.

### *Electroencephalography*

EEG use is similarly increasing in research and has been used to study various brainwave patterns in PTSD patients. EEGs can be used to identify different wave patterns in the brain, which can be related to various conditions. Researchers have shown that PTSD patients have decreased activity in a specific type of brainwave called an alpha wave.[13] Further research in this area could find a way to increase alpha wave activity and reverse PTSD. EEG studies have also shown

[9] Fonzo *et al*, 2017.

[10] Frijling *et al*, 2014.

[11] Frijling, 2017.

[12] Holmes *et al*, 2017. In this study, molecular gene expression analyses using Quantitative RT-PCR were carried out on post-mortem tissue of brains of 19 individuals with PTSD and 19 individuals without PTSD. The results demonstrate that molecular analyses are a useful tool in the assessment of PTSD.

[13] Taghva *et al,* 2015. In this study, the power of the Alpha band increased and there was a trend toward EEG normalization after stimulation of the brain with magnetic resonance therapy and simultaneous clinical improvement.

Studies have shown that EEG results can provide a significant biomarker for PTSD.

abnormal sleep patterns in PTSD patients.[14] EEGs can give direct insight into the electrical activity within the brain. They could be used effectively to study different treatments for PTSD without the use of animals or harm to human patients. Studies have shown that EEG results can provide a significant biomarker for PTSD.[15]

In several of these studies, the investigation was carried out before and after the administration of drugs or hormones. Similarly, other investigations were carried out before and after therapies such as those mentioned in the previous section. Some studies used a combination of investigative procedures—for instance, EEG together with fMRI. All studies were conclusive in demonstrating either the presence of PTSD or the relief of clinical symptoms after therapy, with concomitant changes in the brain.

## Biomarkers in PTSD

Biomarkers are detectable substances or symptoms exhibited by the body that correlate to a specific condition. Some common examples include elevated blood sugar levels as an indicator of diabetes, and a fever may indicate the presence of an infection. Currently, there are several prominent biomarkers for diagnosing and measuring PTSD, such as cortisol levels and EEG patterns. The National Academy of Sciences and others have called for more research to expand our knowledge in this area.[16,17]

PTSD biomarkers are related to other anxiety-based conditions and can be predictive of patient outcomes. For instance, cortisol is a stress hormone that tends to be highly elevated in PTSD patients. While researchers have known about the relationship between elevated cortisol levels and stress for some time, they are now studying how initial assessments of hormone levels after trauma can inform and direct treatment. One study showed that patient outcomes were negatively affected by initially high cortisol levels, providing support for the use of

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[14] Neylan *et al,* 2006. The researchers investigated Delta sleep in relation to Corticotrophin Releasing Factor.

[15] Lobo *et al,* 2015. A large systematic review that yielded promising results. EEG is indeed a useful indicator of the severity of PTSD.

[16] Galea *et al*, 2012.

[17] Zhang *et al,* 2009. The authors posit that "a simple blood test or a biomarker that could detect PTSD in its earliest and potentially most treatable stages would be beneficial for physicians and patients" (p. 404). They also remark that animal models have been insufficient and recommend that further research be human-based.

certain drugs to treat patients in an effort to mitigate the increased stress response.[18] Going forward, doctors may be able to use a reliable biomarker like cortisol to estimate a patient's treatment needs.

Cortisol is just one of many biomarkers for PTSD. Other potential biomarkers can be discerned from alterations in brain structure. MRI studies have revealed that the size of certain brain regions is reduced in PTSD patients and that this could serve as a potential biomarker for the disorder.[19] Aside from these still images, fMRI has provided many insights into the structures and underlying networks of the brain.[20] Neural network imaging using fMRI and graph theory shows huge potential to become an important tool for studying as well as diagnosing PTSD.

Several important DNA mechanisms have been implicated in PTSD through large-scale genetic research.

Gene sequencing studies are likely to identify genetic biomarkers for PTSD. Using only a saliva sample, genetic studies have shown several predictors of PTSD that could be used to recognize those who are more likely to experience the disorder after trauma.[21] Through large-scale genetic research, several important DNA mechanisms have also been implicated in PTSD.[22] Combining neuroimaging with genetic analysis can also provide insights into how DNA changes the structure and function of the brain.[23] While biomarkers need further investigation, they can be potent tools for identifying and treating PTSD in patients, especially before symptoms become severe, enhancing the effectiveness of first-line therapies and decreasing dependence on pharmaceuticals.

## Emerging Technologies in Non-Animal Methods

### *Graph Theory or Graph Analysis*

In addition to conventional medical imaging techniques, there are a variety of other neuroimaging tools available that can expand our

[18] Norrholm *et al*, 2016.

[19] Hu *et al*, 2018. The authors measured cortical thickness, area, and volume in motor vehicle accident subjects. Thinning of the cortex indicated a susceptibility to PTSD and was suggested as a potential biomarker. This concurs with the Sadeh *et al*, 2015, study.

[20] Oathes, *et al*, 2015.

[21] Sheerin *et al*, 2017.

[22] Frijling *et al*, 2014; McNerney, *et al*, 2018. Both studies looked at epigenetics, measuring the methylation of DNA. This was said to be a reliable indicator that PTSD would eventually manifest itself in the classical symptoms. Such predictors would allow for better management of the disorder.

[23] Miller *et al*, 2015. The 13 authors looked at the cortical structure together with certain gene loci that are said to be biomarkers of oxidative stress.

understanding of the impact of PTSD on the brain and body. Of these, graph theory (also referred to as graph analysis) is one of the most potent and innovative ways to study the human brain. It uses fMRI data, computer modeling, and statistics to develop an understanding of how various brain networks connect and interact. In PTSD research, scientists compare the findings between individuals diagnosed with PTSD and healthy patients to evaluate whether significant differences exist. In one study of 208 veterans, graph theory showed that two major brain networks are implicated in PTSD symptoms. The study demonstrated that PTSD symptoms are a result of weakened connections between the region of the brain that processes memories and the region that provides contextual information.[24]

Other studies using graph theory have confirmed the differences in neural patterns of PTSD patients, and have even been used to study treatments that work by reconditioning those networks using positive reinforcement.[25] Combining graph theory and fMRI data, scientists have identified neural circuits pertaining to memory functions that are impaired in PTSD and general anxiety disorder.[26] Graph theory is so effective that it can even detect the underlying neurons involved in identifying facial cues.[27] With more funding and research, graph theory could potentially identify all of the neural networks and processes involved in PTSD. Further, it could be an excellent tool for analyzing the effectiveness of various therapies.

### *Computerized Studies and Machine Learning*

In other technological advancements, computer sciences continue to expand machine learning and artificial intelligence capabilities. This could have significant applications for the study of PTSD and should be seriously considered as a viable method for future research. In a 2017 publication evaluating the use of machine learning for predicting childhood PTSD, Dr. Glenn Saxe of the New York University School of Medicine concluded that:

> These analyses, consistent with the theory of modern statistical machine learning, vividly demonstrate that traditional analysis methods, used for years in the field, cannot cope with high-

[24] Spielberg *et al*, 2015.

[25] Koizumi *et al*, 2017.

[26] Mueller *et al*, 2015.

[27] Chen and Etkin, 2013.

dimensional large datasets commonly found in present-day research, and that modern methods can provide valuable enhancements.[28]

Artificial intelligence has been used to identify predictive features of children who developed PTSD after physical trauma.

Using these methods, investigators have studied over 20,000 PTSD cases, along with other trauma-exposed individuals, or those who experienced trauma but did not develop PTSD. This massive amount of information is already available for a vast population of human patients and includes everything from fMRI data to DNA testing. Computers can be programmed to process and analyze data much faster than traditional analytical methods and reveal a far more comprehensive understanding of the complications and intricacies of the disorder. In fact, by studying certain DNA loci (single-nucleotide polymorphisms, or SNPs) of vast numbers of the population, predictions can be made that will indicate who is likely to experience PTSD and who, after treatment, is likely to relapse.[29,30] Artificial intelligence and machine learning have also been used to predict the onset of PTSD. In one study, machine learning was used to identify predictive features of children who developed PTSD after severe physical trauma.[31]

### *Methods for Drug Development*

Computers can also be used to accurately predict the toxicity of various chemicals or identify potential drug candidates. Computer-aided drug design (CADD) is a suite of software that can be used to predict the binding affinity and chemical properties of various drug candidates. This technology can also be used to identify potential carcinogens and other toxins based on a massive library of information collected from studied chemicals and their impact on human biology. Structure-activity relationship (SAR) programs can help design drugs based on the shape and chemical affinity of the biological receptors the drugs will affect. Predictions made from these systems have been shown to be just as effective, faster, and much cheaper than using animals to identify drug candidates.[32] However, computers are not the only advanced technology ready to replace animals in research.

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[28] Saxe *et al*, 2017, p 229.

[29] Logue *et al*, 2015. A large-scale meta-analysis study with a combined number of over 74,000 subjects from across the United States, the Netherlands, Denmark, and South Africa.

[30] Sheerin *et al*, 2017.

[31] Saxe *et al*, 2017.

[32] Doke and Dhawale, 2015.

Scientists are developing a multitude of methods to study the individual biochemical reactions in the human body. One of these cutting-edge methods is "organs-on-chips," or organ chips. The process involves growing human cells on silicon chips, which can then simulate the functions of an organ, such as blood flow and electrical impulses.[33] Using these technologies, researchers and pharmaceutical companies are working to develop an entire system of organ chips consisting of a network of all the organ systems within the human body.

Researchers at MIT have developed a full set of organ chips that can accurately test a multitude of chemicals and conditions on a wide variety of human tissues simultaneously.[34] A full system of these organ chips is currently being pursued by scientists to interconnect and model the human body, and many biotech companies are actively working to develop these more advanced methods. Several companies are already producing chip kits, complete with software, that researchers can purchase and utilize in their own research. Despite this innovative technology that offers a viable alternative to animal research, most of the current PTSD drug research is conducted using animals.

Using organ chips—which will be faster, cheaper, and much more predictive than animal models—could effectively cut research time in half.

An entire kidney glomerular filtration system-on-a-chip can be grown in only 26 days.[35] When mass-produced, these organ chips will be faster, cheaper, and much more predictive than using animals. For instance, it takes over 40 days for mice to become sexually mature, and longer for them to fully mature into adults. Using organ chip technology, researchers could effectively cut their research time in half, in addition to achieving more human-relevant results.

Organ chip technology is successfully being used not only in drug development testing, but also in many different fields of disease research.[36,37] By using cells from patients with a specific disease, cell lines can be generated to produce disease symptoms. There is even potential to grow entire organs for study using these methods.[38] Thus far, these methods have been focused largely on drug discovery.

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[33] Meyers, 2006.

[34] Edington *et al*, 2018.

[35] Musah *et al*, 2018.

[36] Barrile *et al,* 2018. The authors worked on a suitable model for human thromboses.

[37] Wang *et al*, 2018. The authors investigated a suitable human model that would allow for development of drugs intended for use in Alzheimer's disease.

[38] Marshall *et al*, 2018.

However, more advanced systems may lead to the study of genetic and cellular influences on neurological diseases.

### *Postmortem Tissue Analysis*

The Biorepository Brain Bank includes tissue specifically from PTSD patients. By analyzing brain tissue, investigators have been able to identify scarring associated with traumatic brain injury and PTSD.

In the early 2000s, many prominent PTSD researchers started calling for increased access to postmortem brain tissue through the establishment of a brain bank for PTSD.[39] While previously there was a lack of access to postmortem brain tissue, a number of brain banks have opened since the early 2000s. This includes the VA's Biorepository Brain Bank, which opened in 2006. In 2015, the brain bank expanded its collection to include tissue specifically from PTSD patients.[40] The National Institutes of Health has its own brain bank, the NIH NeuroBioBank, which can also be accessed by researchers. These resources provide access to a variety of real human tissues, which may be genetically and histologically analyzed for clues into the disorder.

Many studies have been conducted utilizing the tissue from brain banks and have revealed much more than imaging studies alone. By analyzing the morphology of the brain, investigators were able to directly identify astroglial scarring associated with traumatic brain injury and PTSD.[41] Postmortem tissue has the potential to yield many more research insights.

By genotyping PTSD brain tissues, then analyzing them histologically, researchers can directly see the anatomical changes caused by various gene alterations. These studies have shown that changes in the microanatomy of brain structures present in PTSD patients are also associated with increased production of specific cellular proteins.[42] Other researchers studying postmortem tissue found significant markers in the PTSD tissues and then correlated these results with those in living patients through the use of PET scans.[43] Another study revealed the epigenetic effects of PTSD and correlated results found in

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[39] Friedman and Harris, 2004.

[40] VA Biorepository Brain Bank News: A Year in Review, 2015. This newsletter provides the latest information and news regarding donations of brain tissue and what is done with it, specifically the studies that have resulted from brain donations of deceased individuals with PTSD.

[41] Shively *et al,* 2016. The study involved looking at the brains of individuals with acute and chronic blast exposure, most of whom were clinically diagnosed with PTSD while alive.

[42] Young *et al*, 2015.

[43] Holmes *et al*, 2017.

postmortem tissue to actual behavioral tasks in real patients. The study also revealed a genetic risk toward PTSD.[44]

Human postmortem studies promise the best information to unravel the complex molecular underpinnings of PTSD.

These results reveal much more about PTSD than could possibly be gained through animal studies. A research review published in *Biological Psychiatry* examined the relationship between protein production and PTSD in which the authors concluded that "human postmortem transcriptome studies of brain tissue promise the best source of information to unravel the complex brain molecular underpinnings of PTSD."[45] Other studies from around the world have corroborated this need for more research using postmortem brain tissue.[46] Government and funding organizations need to come together to support the use of brain banks and encourage the donation of much-needed tissues.

## Conclusion

There is an abundance of available data that can be obtained ethically and non-invasively from volunteer human patients.

In biomedical research, there is a strong push toward human-based research and development. Animal research, as we will see in the next section, does not predict human outcomes as well as human-based research.[47] With millions of Americans suffering from PTSD, there is an abundance of available data that can be obtained ethically and non-invasively from volunteer patients.

With the tools described above and many others, scientists can build a comprehensive and valid understanding of PTSD in humans. These tools can be used to study the disorder, study treatments for the disorder, and even predict which people are most at risk for PTSD. Most of these tools are already used in clinical applications, and the data they produce can easily be incorporated into large-scale, human-centric studies.

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[44] Bharadwaj *et al,* 2018.

[45] Girgenti and Duman, 2017, p 844.

[46] De Lange, 2017.

[47] Marshall *et al*, 2018.

# IV. The Flaws and Invalidity of Animal Research

In the last two decades, a bold and pervasive movement has uncovered the fundamental flaws of using animals in translational research for human diseases and disorders. This section shows how animal research is often highly invalid when translated to humans and how PTSD is an especially problematic area for translational studies.

Researchers are increasingly critical of the translational animal model.

Increasingly, researchers have been highly critical of the so-called "translational animal model," in which data gathered from animals is extrapolated to humans. One researcher points out that "the unreliability of animal experimentation across a wide range of areas undermines scientific arguments in favor of the practice."[1]

And yet, scientists continue to defend the use of animals in research, despite how animal use has been shown to have deeply inherent flaws. Typically, scientists' faith in translational animal studies is based on longstanding false assumptions and anecdotal evidence. Scientific scrutiny of the rationales for using animals as surrogates for humans has revealed devastating evidence against these claims.

The main reason animal research fails to translate to humans is the complexity of nature itself. While humans do share a large percentage of our genes with some animals, this is far from a guarantee that data from other species will produce comparable human outcomes. Evolution is based on common descent, not necessarily common function. Thus, while we may share the same or similar genes, they have evolved over millions of years to be expressed and utilized in very different ways in each species. The human body contains billions of biological pathways, each of which has evolved specifically to the human condition.

In addition, diagnosing PTSD in animals is an exercise in imagination. PTSD in humans is diagnosed using a number of mental symptoms that must be verbalized to a healthcare practitioner. Most of them deal with things that patients can only describe with language, such as nightmares and the inability to suppress negative thoughts. While researchers claim that an animal's behavior is a valid determinant for

[1] Akhtar, 2015, p. 407.

diagnosing PTSD in animals, diagnosing PTSD in animals is a logical fallacy. Most PTSD research in animals is subjective: The researcher expects certain outcomes and interprets the experimental data accordingly. Not only is this irresponsible, it also represents bias.

Lastly, this section will examine the invalidity of animal research specifically as it relates to PTSD research. There is a severe lack of experimental control employed in animal studies that results in unscientific, irreproducible, and even injurious outcomes. These experiments waste time and money and endanger the patients meant to benefit from the research.

## Faith in the Animal Model

Scientific research places great faith in animal data to predict human outcomes, even though much research counters this reliance.

For example:

> Rodent models, including the mouse, have correctly predicted human toxicity in only 43% of the cases in one large study comparing human and animal drug toxicities. Because of the low predictive value of rodents, the US Food and Drug Administration (FDA) requires drug testing to be done in at least two species, one of which is a non-rodent (i.e., one with a closer phylogenetic relationship to humans). Even with two species, the ability to use animal-derived data to predict human toxicity is only accurate in 71% of cases. Thus, drugs with substantial human toxicity have advanced into clinical trials and even entered the marketplace with serious consequences to patients, including death.[2]

Rodent models correctly predicted human toxicity in only 43% of cases, leading to the advancement of drugs with serious human consequences into clinical trials and even the marketplace.

Shanks *et al* point out that in general, scientists use animals because they *feel* that animals are predictive. Yet, as their evidence showed, very little about animal research is truly predictive for human studies. In fact, they note that most researchers are just assuming the biological mechanisms are the same in humans and animals.[3] Other authors have shown that the majority of scientific studies on animals fail to recognize this simple bias. Rather than recognizing the bias as an inherent weakness, they blindly put their confidence in the data they receive

[2] Uhl and Warner, 2015, p. 220.

[3] Shanks *et al*, 2009.

from animals, instead of basing their research protocols or findings on evidence of scientific rigor.[4]

## Complexity of Modeling the Human System

Many DNA variations and gene expression patterns are dissimilar between mice and humans, limiting the mouse's use as a disease model.

Though mice have been used for decades as stand-ins for human research subjects, recent findings increasingly demonstrate that the genetic disparities between humans and mice are considerable and cast doubt on the widespread dependency of using mice. In 2014, NIH released the results of a several large studies published in *Nature* that provided a comprehensive review of the mouse genome. The studies showed that while certain genes are similar to both species, many DNA variations and gene expression patterns are not, "potentially limiting the mouse's use as a disease model. Mice and humans share approximately 70 percent of the same protein-coding gene sequences, which is just 1.5 percent of these genomes."[5]

**Evidence has shown that mice have too many biochemical disparities to be useful in translational research; the regulatory mechanisms in humans and mice are vastly different,[6] and studies have noted that there are significant structural differences between mouse, macaque, and human brains, particularly in the cerebellum, beginning in the embryo**.[7]

The microanatomy and cytoarchitecture of rodent brains are markedly different from those of humans. In addition, the macrostructural differences between rodent and human brains are stark; rodent brain cortical surfaces are smooth, whereas those of a human are deeply convoluted to increase the surface area.

Deficiencies with the mouse as an accurate model have led many scientists to conclude that primates, who share more genetic sequences with humans, should produce more predictive results; however, actual scientific evidence does not support this hypothesis.

An extensive meta-review of cancer in chimpanzees revealed that chimpanzee research has contributed little, if anything, to human outcomes in cancer research.[8] Further research on the genetic

[4] Vogt *et al*, 2016.

[5] National Institutes of Health: News Releases, 2014.

[6] Yue *et al*, 2014.

[7] Haldipur *et al*, 2019.

[8] Bailey, 2009.

differences between chimpanzees and humans revealed that there are key differences in the expression of certain genes in both species that completely undermine their genetic similarities. The author notes that "the collective effects of these differences are striking, extensive and widespread, and they show that the superficial similarity between human and chimpanzee genetic sequences is of little consequence for biomedical research."[9]

The seemingly small difference in protein-coding genes and their interaction with the environment is what drives this massive incompatibility. In terms of molecular biology, the difference is enormous.

Shanks *et al* have explored in detail the failings of animal experiments to be *predictive* for human biological outcomes, with results from animal data being about as accurate as a coin toss. They analyze in depth the difference between simply generating data and generating data that is germane for human medicine:

> When one empirically analyzes animal models using scientific tools they fall far short of being able to predict human responses. This is not surprising considering what we have learned from fields such evolutionary and developmental biology, gene regulation and expression, epigenetics, complexity theory, and comparative genomics.[10]

"When one empirically analyzes animal models using scientific tools they fall far short of being able to predict human responses."

They point out that lacking predictivity, results from animal studies fail to be truly scientific, because it cannot be determined in advance which results will apply to the human condition. They write:

> If a modality such as animal testing or using animals to predict pathophysiology in human disease is said to be a predictive modality, then any data generated from said modality should have a very high probability of being true in humans. Animal models of disease and drug response fail this criterion.[11]

A large body of evidence shows that the human system, like other species-specific systems, is unique. One study showed that rats and primates have completely different neurological circuits in response to

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[9] Bailey, 2011, p. 527.

[10] Shanks *et al,* 2009, p. 1 of PDF.

[11] *Ibid,* p. 18 of PDF.

an identical stimulus—the acoustic startle response—although their outward behavior was identical.[12] If rats and primates are controlled by dissimilar neural circuits, there is little evidence to support that these species can be predictive of human outcomes.

Moreover, the human brain is the most complex organ in the human body, being incredibly receptive and adaptable to circumstances. As a result, even individuals react to the same stimuli in slightly different ways. PTSD originates in the brain and has such diverse effects that it is extremely difficult to recreate these aspects in any model.[13]

For example, one study using fMRI in human patients demonstrated that age and gender alone create significant differences in response to conflict stimuli.[14] Other authors have also reported similar differences in neurology based on age and gender.[15] Researchers have even identified different subtypes of PTSD within human subjects.[16]

Other PTSD-specific studies have shown the resiliency of the human brain by revealing that simply the patient's *belief of being safe* can lead to a reduction in PTSD symptoms.[17] Researchers have also shown that the placebo effect may be responsible for increased outcomes in PTSD treatments.[18] Some authors have even gone so far as to conclude that "at a conceptual level, it is presumed that individual differences in structural brain plasticity and central neuroadaptations in specific circuits contribute to susceptibility to and/or resilience from PTSD following exposure to a traumatic stressor."[19]

Animals have also failed to contribute to many other significant areas of human disease research. In diabetes research, for example, publications based on animal research averaged over 50 publications per month for three decades. Yet, from all that experimentation, little progress has resulted. Instead, the studies revealed that there are significant

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[12] Aguilar *et al*, 2018.

[13] Borghans and Homberg, 2015.

[14] Cservenka *et al*, 2015.

[15] Klabunde *et al*, 2017.

[16] Wolf *et al,* 2016. The authors identified a dissociative subtype of PTSD.

[17] Hoffman *et al*, 2016.

[18] Ori, *et al,* 2015.

[19] Whitaker *et al*, p. 9 of Abstract.

differences at every level of glucose regulation between animals and humans.[20] One publication notes:

> While decades of T2DM [Diabetes Type 2] research efforts have elucidated the details of rodent glucose regulation, the critical knowledge base that is lacking is a detailed understanding of the mechanisms underlying human glucose homeostasis, obesity, insulin resistance, and β-cell dysfunction as well as their sequelae and responses to interventions in human T2DM.[21]

In summary, the results show that rodents have failed to have any translational value for diabetes, despite 30 years of well-funded research. The authors conclude by saying that even other researchers are questioning the validity of using animals in glucose metabolism studies.

A total of 413 drugs that showed promise in treating Alzheimer's resulted in a 99.6% failure rate when tried in human patients.

Similar abject failures in translating animal results onto humans are seen in Alzheimer's disease research. In the area of Alzheimer's drug development, a 2014 study published in *Alzheimer's Research & Therapy* reported a 99.6% failure rate of new Alzheimer's treatments from 2002 to 2012. This was based on 413 drugs that had passed preclinical animal trials.[22]

Of the research being done at the time, 65% was aimed at understanding the amyloid-beta (Aβ) protein in rodents, which was regarded as highly concordant with human Alzheimer's. However, later research uncovered that the Aβ protein is not as involved in human Alzheimer's as was previously thought.[23] The authors introduce the paper by saying that there is a pressing need to study Alzheimer's in human model systems and suggested the use of human neurons. They conclude:

> This observation highlights the phenotypic differences between mouse and human cellular models of AD [Alzheimer's disease]. Those differences must be recognized to understand why so many AD drugs in development failed in human clinical trials, even though they worked very well in mouse models of AD,

[20] Chandrasekera *et al*, 2014.

[21] *Ibid*, p. 168.

[22] Cummings *et al*, 2014.

[23] Wang *et al*, 2018.

> and to develop drugs that are more likely to be effective in patients with AD.[24]

**Massive amounts of money and time were wasted chasing a promising cellular pathway observed in animal experiments, only to find out that essential species differences render these pathways inapplicable to the human disorder.**

Beyond diabetes and Alzheimer's disease, there have been multiple meta-reviews of the utility of animal experiments in a variety of research areas. These have shown an overall lack of benefit for humans across broad range of areas.[25]

Most translational animal studies never continue into human trials.

Unfortunately, most translational animal studies never continue into human trials. Dr. Andrew Knight from the Oxford Centre for Animal Ethics carried out a review in 2011 of cited literature. In one example, he describes a German study of 17 animal experiments at three universities between 1991 and 1993. These experiments' citations were analyzed over a period of 12 years, and none of the experiments resulted in any new therapies or any clinical benefit.[26] Knight goes on to say:

> The poor human clinical or toxicological utility of many animal experiments is unlikely to result solely from methodological flaws. Several intrinsic characteristics of animal models also markedly limit their human predictivity. … Such obstacles could be technically and theoretically insurmountable.[27]

### *Sweeping Drug Failures Based on the Invalidity of Animal Tests*

These massive failures of translational animal research do not end here. The complexity of the human system and its uniqueness from other species results in the inability of animal experiments to ensure safe drugs. Adverse drug reactions and deaths are one devastating result.

At least 90% of drugs approved for use based on animal tests fail in human clinical trials.

Scientists, health clinicians, and the public alike are increasingly aware that the greatest setback in the drug development process is animal testing. The cause is a staggering statistic: In 2004, the U.S. Food and

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[24] *Ibid*, p. 654.

[25] Pound *et al*, 2014.

[26] Knight, 2011.

[27] *Ibid*, p. 291.

Drug Administration estimated that 92% of drugs developed using required animal tests that had passed preclinical trials failed to make it to the market. Subsequent studies indicate that this number has not improved, with the general consensus being that at least 90% of drugs that are approved for use based on animal tests fail when reaching human clinical trials.[28,29]

One study estimated that over 2.2 million people are hospitalized and over 106,000 die annually from adverse drug reactions.[30] Many drugs are tested on multiple animal species, only to be withdrawn from the market after serious and often fatal side effects are found in humans.

A 2018 study in Brazil revealed that "For each medication introduced during hospitalization, there was a 10% increase in the rate of adverse drug reaction" and that overall the frequency of adverse drug reactions and potentially serious events was high, particularly for patients with other medical problems.[31]

## Inability to Diagnose PTSD in Animals

Even though the human system is incredibly complex and unique from any other species, researchers are still trying to create a model for PTSD in animals. In this context, researchers rely on behavioral observations of the animals after they have been subjected to trauma. However, a doctor cannot diagnose PTSD in humans in a similar manner.

PTSD symptoms are impossible to identify in animals, who lack the ability to communicate their thoughts.

PTSD is considered a psychological disorder. Key symptoms of the disease include nightmares and disturbing flashbacks.[32] These symptoms are impossible to identify in animals, who lack the ability to communicate their thoughts. A key symptom in human PTSD is thought to be situational avoidance, in which the patient actively avoids thoughts or situations that will stimulate flashbacks, nightmares, or memories of the trauma.[33] Without the ability to measure these mental avoidance symptoms in animals, researchers turn to other methods.

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[28] Akhtar, 2015.

[29] Marshall *et al*, 2018.

[30] Lazarou *et al*, 1998.

[31] Ribeiro *et al*, 2018, p. 2 of Abstract. A large meta-analysis carried out and compared with 472 patients from a teaching hospital in Brazil.

[32] Foa *et al*, 2013.

[33] *Ibid*.

The only observable change in traumatized animals is behavior. Some animals do not respond much to trauma, while some display behaviors like freezing (immobility) and decreased sociability. With this as their only measure, researchers claim without evidence that these behaviors are the manifestation of PTSD in rodents and other species. However, there are inherent issues with using animals, and especially rodents, as models for PTSD. Steimer at the University of Geneva offers salient reasons based on his research with rats:

> **A first and important issue is whether various animal species can really be used as "models" of human pathologies, given the highly subjective nature of anxiety. Do animals experience something like human anxiety, and how can we measure it, since we cannot "think like a rat."**[34]

He also suggests that "some important aspects of human pathology will probably never be accessible in animal models (e.g., sadness or suicidal ideation in depression)."[35]

Steimer's review was based on anxiety, which is only one symptom of PTSD; it is not PTSD itself. Authors have noted that acute stress disorder is experienced by many, but PTSD often takes months to develop and is diagnosed mainly through verbal descriptions of a patient's state of mind.

Further, all eight criteria as described by the DSM-5 diagnostic manual must be met to diagnose PTSD. It is impossible to diagnose these criteria, which are mainly subjective, in animals. Because of these limitations, PTSD researchers consider any animal subjected to the "trauma" protocols as being "affected," simply due to the complexity of diagnosing PTSD in animals. At the same time, researchers caution that one must not take results from animal models too literally.[36] While these animals were subjected to experimental trauma, they are not all representative of humans with PTSD.

By way of a human analogy, this is the same as trying to study PTSD in humans by classifying everyone who has undergone trauma as having PTSD. Clearly, while many people experience trauma, not all trauma

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[34] Steimer, 2011, p. 495.

[35] *Ibid*, p. 502.

[36] Cohen *et al*, 2004.

survivors develop PTSD.[37] This underlying, irrational assumption of PTSD research has resulted in misleading conclusions.

## Inability to Model PTSD in Animals

Many animal experimenters realize the significant inadequacies of trying to recreate PTSD in animals. As Aspesi and Pinna compellingly write:

> **PTSD is complex and debilitating neuropathology with a frequent overlap of symptoms and comorbidity with other disorders, including depression, anxiety disorders, drug abuse, and suicidal ideation. Taking into account its heterogeneity, the hypothesis that single alterations might be found that are responsible for the multifaceted aspects of the disorder is not conceivable. For this reason, it is also challenging to establish an appropriate animal model that recapitulates the several behavioral and biochemical abnormalities observed in PTSD patients.**[38]

Indeed, no one readily acknowledges the tremendous challenges and severe shortcomings of using animals to study human PTSD as much as the researchers using animals.

Borghans and Homberg state that "choosing a model to experiment with can be challenging. … The difference between models indicates that their suitability depends on the situation; each model has shown different amounts of success in replicating individual criteria or aspects of PTSD."[39]

According to Cohen *et al*, "Extrapolation from such models to the human conditions must be carried out with care, always keeping in mind that models are no more than partial approximations, and that there is an inherent risk of overhumanizing animal behaviors."[40]

"It is unlikely that a single animal model will reproduce the complexity of the human disorder."

Goswami *et al* agree: "It is unlikely that a single animal model will reproduce the complexity of the human disorder."[41]

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[37] Foa *et al*, 2013.

[38] Aspesi and Pinna, 2019, p. 144.

[39] Borghans and Homberg, 2015, p. 387.

[40] Cohen *et al*, 2004, p. 1962.

[41] Goswami *et al*, 2013, p. 9.

Finally, Shekhar *et al*, who were part of a workshop at the National Institute of Mental Health discussing animal models for anxiety disorders, state that "there exists a wide range of animal models and measures designed to assess anxiety or fearfulness. However, the relationship between these models and clinical anxiety symptoms and syndromes is unclear."[42]

Yet, instead of rejecting translational animal studies and their logical shortcomings, Shekhar *et al* still conclude:

> Ample opportunity remains to better define and extend existing models and behavioral measures related to specific processes that may be disrupted in anxiety disorders and to develop new models that consider the impact of combined factors in determining anxious behaviors.[43]

In other words, despite the fact that animal models have a low probability of success, researchers are going to keep trying anyway. **This inability to accept the wholesale failure of animal models is typical among animal researchers, who, in the face of successive research failures, are continually in search of "better" animal models.**

Other scientists have explained why producing "improved" animal models is scientifically untenable:

> We conclude that preclinical animal models can never be fully valid due to the uncertainties introduced by species differences. We suggest that even if the next several decades were spent improving the internal and external validity of animal models, the clinical relevance of those models would, in the end, only improve *to some extent*. This is because species differences would continue to make extrapolation from animals to humans unreliable. … Research should focus instead on human-relevant research methods and technologies.[44]

Yale University Emeritus Professor of Epidemiology Michael Bracken agrees:

> Even if excellent research methodology is achieved, prediction to humans fails because the disease model, often in rodents, is

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[42] Shekhar *et al*, 2001, p. 327.

[43] *Ibid*, p. 336.

[44] Pound and Ritskes-Hoitinga, 2018.

> wrong: biological pathways are different, drug doses are not comparable, and the assessed recovery measures do not translate from mouse to human.[45]

## Lack of Scientific Control in Animal Research on PTSD

In recent years, there has also been a heightened awareness of the lack of rigor in scientific reporting, focusing particularly on animal studies. Post-publication investigations of animal studies have shown that some of the most highly cited translational publications contain misleading information or experiments that are not reproducible.[46] One analysis showed that out of nearly 500 published animal experiments, only one published the full protocol necessary for replication.[47] Another examination of the literature revealed that animal studies often fail to address or publish any biases.[48]

Modeling, in general, is a bias. It is a form of estimation. This simple but powerful bias is rarely reported in animal studies. In addition, many animal studies never report their findings at all, or they greatly overestimate the translational value.[49]

Over 90% of behavioral neuroscience results obtained from animals fail.

A number of scientists have openly called out the shortcomings of using animals in anxiety and PTSD research. Investigators have shown that animal studies have fundamentally ignored the individuality of response in human PTSD.[50] One review paper showed that over 90% of behavioral neuroscience results obtained from animals fail. The author, Joseph Garner, concludes:

> At the end of the day, the real challenge is to persuade researchers to adopt new methodologies on the basis of a leap of faith that doing so will improve human outcomes over a decade in the future. Unsurprisingly, few researchers have been willing to take such a risk.[51]

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[45] Chakraverty, 2020.

[46] Landis *et al*, 2012.

[47] Iqbal *et al*, 2016. The authors investigated 441 biomedical journal articles published over 14 years between 2000 and 2014.

[48] Macleod *et al*, 2015. These authors investigated a random sample of 2,000 publications indexed on PubMed.

[49] Holman *et al*, 2016.

[50] Cohen *et al*, 2004.

[51] Garner, 2014, p. 453.

Others have pointed out how animal models fail many of the standard tests required for experiments to be rigorous and scientific. They write:

> For the first time, the scale of the reproducibility and translatability crisis is widely understood beyond the small cadre of researchers who have been studying it and the pharmaceutical and biotech companies who have been living it. Here we argue that an emerging literature, including the papers in this focus issue, has begun to congeal around a set of recurring themes, which themselves represent a paradigm shift. This paradigm shift can be characterized at the micro level as a shift from asking, "what have we controlled for in this [animal] model?" to asking "what have we chosen to ignore in this model, and at what cost?"[52]

These authors state that the success rates in human trials are progressively worsening: **Only one in nine drugs that enter human clinical trials will succeed.** They recognize that most drugs fail in human clinical trials and that the failure of translation from animal to human has led to a growing suspicion that reflects the animal work itself. They also note that pharmaceutical companies are divesting from animal research and development and that there is a growing trend to focus on human and not animal work for basic drug discovery.

With specific reference to PTSD, a number of authors concur that the pharmaceutical industries are becoming increasingly dissatisfied with animal research because the knowledge gained has not led to better management of the condition.

Developing drugs to treat mental health has proven to be high risk, with the vast majority of promising drugs failing after years of costly clinical trials.

Developing drugs for mental health disorders has proven to be expensive and high risk, with the vast majority of promising drugs failing after years of costly clinical trials. "Standard approaches to developing drugs for mental health have not reaped significant benefit in the past two decades," according to Ken Kaitin, director of the Tufts Center for the Study of Drug Development in Boston, Massachusetts. As a result, pharmaceutical companies worldwide are scaling back research and discovery in this area.[53]

Significantly, these companies are abandoning psychiatric drug-discovery programs due to lack of confidence in animal models of fear

[52] Garner *et al*, 2017, p. 103.

[53] Abbott, 2011.

and trauma exposure to produce a reliable outcome when translated to humans. As Richter-Levin *et al* note:

> The stalled progress in providing better understanding and improved treatments has been a major factor contributing to the withdrawal of leading pharmaceutical companies from psychiatry drug development, but in addition, it raised serious doubts regarding the possibility of animal models to contribute to PTSD-related research and to related drug development.[54]

## Conclusion

Many researchers have now come out strongly against translational animal research in anxiety and PTSD. A cohort of animal researchers recently came forward to say that the future of PTSD and anxiety research is in psychotherapy methods, such as those described in section II of this report, aimed at using the plasticity of the human brain to heal itself.[55]

Authors such as Aspesi and Pinna emphasize that PTSD is a complex and debilitating neuropathology with frequent overlap of symptoms and comorbidity with other disorders. For this reason, it is virtually impossible to establish an appropriate animal model that reproduces the myriad behavioral and biochemical abnormalities observed in PTSD patients.[56] They make a point of saying that to date, there is no single suitable pharmaceutical preparation to treat PTSD.

It is incumbent upon funders of PTSD research and lawmakers to recognize the invalidity of animal experiments by withdrawing support for animal research. Many scientists are highlighting these failures and have developed recommendations for moving toward human-centric disease research.[57]

Only by moving toward human-based research will scientists be able to understand the neurobiology of PTSD in humans.

Only by recognizing the limitations of reductionistic, animal-based research and moving toward superior human-based research will scientists be able to fully understand the neurobiology of PTSD in humans.

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[54] Richter-Levin *et al*, 2019, p. 1141.

[55] Yehuda *et al*, 2016.

[56] Aspesi and Pinna, 2019.

[57] Marshall *et al*, 2018.

# V. Inducing Trauma in Animals for PTSD Research

Sections II and III of this report gave a clear overview of (1) the evidence-based therapies available for PTSD patients and (2) the human-based methods available for investigating and researching PTSD. Section IV showed the scientific flaws of using animal research with the intent to understand the mechanisms of PTSD and investigate potential therapies to the disorder.

This section will give an account of the methodologies of some of that research being done on animals, with a focus on the harm and suffering animals experience in the course of these experiments. Much of this research involves stressing, tormenting, and, in some cases, inflicting violent actions toward animals in the name of PTSD research.

The rationale behind such research is to give scientists and clinicians a better understanding of the neurophysiological mechanisms that cause PTSD so that biomarkers may be developed and potential targets for novel pharmacotherapies can be investigated. Animal research is also used to screen drugs for their potential use as PTSD treatments in humans.[1,2] However, as we have seen, adequate and reliable methods exist to study these areas in a more human-relevant way, and virtually none of this animal research has ever led to any conclusive understanding or effective treatment of human PTSD.

## Learned Helplessness and PTSD Research

Learned helplessness is an area of research typically used to model depression but that has additionally transitioned to a model for PTSD.[3] Inducing learned helplessness is one of the classic experiments performed in animal studies of fear and anxiety. It occurs when an animal is repeatedly subjected to an adverse stimulus, usually an electrical shock, from which there is no escape. Eventually, the animal will stop trying to avoid the stimulus and behave as if they are utterly helpless to change the situation. Even when opportunities to escape are presented, this learned helplessness will prevent any action. While the concept is strongly tied to animal experimentation, it can also apply to

[1] Daskalakis *et al*, 2013.

[2] Flandreau and Toth, 2017.

[3] Conoscenti and Fanselow, 2019.

situations involving human beings. For instance, people who have been subjected to ongoing trauma often simply give up and accept their fate.[4]

The term "learned helplessness" was first proposed by Maier and Seligman in their 1976 paper. In this paper, the authors reviewed various situations in which animals and humans had been exposed to adverse stimuli that caused them to display hopeless and helpless behavior. Experiments reviewed went as far back as 1965 and included dogs, rats, cats, mice, birds, primates, fish, and humans. Most of the experiments carried out on the animals involved electric shocks. Those carried out on humans involved mental tasks (unsolvable problems) and loud sounds.

In the learned helplessness experiments, animals were given three kinds of electric shocks: inescapable shocks, escapable shocks, or no shocks. When the animals in the inescapable shock group were transferred to an area where escape from the painful electroshock was possible, they demonstrated learned helplessness by failing to make any attempts to avoid the shocks. The animals in the second and third groups were able to escape the shocks. This model, first intended to condition animals to endure rather than escape moderate amounts of pain, has been adapted to include more extreme procedures to induce anxiety for PTSD research.

## PTSD Research on Mice and Rats

A comprehensive review of the literature reveals that the vast majority of PTSD research is conducted on rats and mice.[5] In this field of study rats and mice are typically referred to as "preclinical models," and the objective of using them in such research is to attempt to mimic the symptoms associated with PTSD.[6] However, Whitaker *et al* admit that:

> **[Animals do not] replicate the human condition in its entirety. … Few adequately capture the complex nature of the disorder and the observed individual variability in susceptibility of humans to develop PTSD. … Animal models lack the ability to examine certain symptoms that manifest in individuals with PTSD, such as intrusive thoughts or nightmares.**[7]

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[4] Cherry, 2020.

[5] Steimer, 2011.

[6] Whitaker, *et al*, 2014.

[7] *Ibid*, pp. 1 and 13 of Abstract.

Procedures carried out encompass a wide variety of stress-inducing and physically violent situations that have been developed simply to induce fear or create severe distress.[8,9] The literature abounds with descriptions of such stressors. Beyond the moral implications of inflicting great stress and often pain on animals, these stressors are poor replicas of the life-threatening situations humans experience that can result in PTSD.

### *The Electroshock Approach*

Rats and mice are often exposed to inescapable and unpredictable electrical shocks to their sensitive paws.

Rats and mice are often exposed to inescapable and unpredictable electrical shocks to their sensitive paws, a procedure referred to as footshock. This is designed to induce learned helplessness as described above. This state, now termed "immobility" in more recent PTSD literature, is a key step in traumatizing animals for PTSD research.

Although PTSD and learned helplessness are very different concepts, researchers have widely accepted that these methods produce models for PTSD. Scientists commonly place rats and mice into "shock boxes" designed to electrocute them randomly and induce a state in which animals exhibit the classic signs of learned helplessness: immobility and disinclination toward escape.[10,11,12]

Researchers have found that when previously shocked rodents are placed back into the metal-floored cage, they become frightened. The researchers use this frightened state to justify the animal as a subject for PTSD and call the procedure a "situational reminder" (SR). As described by the authors of a large review of PTSD research on animals:

> It has been shown that animals exposed to SR exhibit a distinct behavioral response (e.g., crouching near the back wall of the box, increase in respiratory rate, etc.) despite the absence of the stressor itself. The incorporation of SR in rodent models provides an interesting new research perspective as it recalls human PTSD symptoms such as re-experiencing and intrusions.[13]

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[8] *Ibid.*

[9] Cohen *et al*, 2004.

[10] Cohen *et al,* 2004.

[11] Schöner *et al*, 2017.

[12] Whitaker *et al*, 2014.

[13] Schöner *et al*, 2017, p. 2250.

This state differs from PTSD because here the animal is justifiably terrified, being in the same place where they received inescapable shocks. However, as section IV showed, scientists conveniently but falsely interpret this state to be equivalent to the symptoms of re-experiencing and intrusions that characterize PTSD. Re-experiencing and intrusions are when a patient has flashbacks or nightmares or avoids objectively safe locations because the place somehow triggers traumatic memories. The metal cage is clearly not objectively safe. The animals should expect to get shocked there. This is not the same as a PTSD patient having a flashback at home or work, or in any other reasonably safe location.

But unfortunately, physical harm and existential threats have been taken even farther in other PTSD experiments

### *Simulated Drowning*

The Morris water maze is a device designed to study learning and spatial memory in mice and rats. This maze normally consists of a basin of deep water with small, hidden platforms providing rest at various points throughout the body of water. Many neurobiologists and behaviorists use the maze to study how injury and drugs affect the animals' ability to find the hidden platforms.[14] Rats and mice are naturally proficient swimmers, but to swim under forced or hampered circumstances is very stressful to them.

After the animal victims swim helplessly in a basin for a full minute, they are held underwater with a metal net for another 30 seconds.

PTSD researchers have modified the Morris water maze into a much more stressful experience. Typically, they remove all the platforms so there is no possibility of rest or relief. After leaving the victim to swim hopelessly for a full minute, they hold the animal underwater with a metal net for another 30 seconds.[15] This is, in effect, simulated drowning. The inventors of this method call it "underwater trauma" and argue that it works well as a model for PTSD because the animals believe they are truly drowning. They claim that "this kind of stressor is more ethologically relevant than electric shocks since the threat of drowning is quite real in the life of a rat living in the wild."[16]

Subjecting animals to a drowning experience is an extreme level of torment akin to torture. The dubious defense for inflicting this heinous

[14] Hooge and De Deyn, 2001.

[15] Schöner *et al*, 2017.

[16] *Ibid*, p. 2250.

suffering on animals appears to be that it is more "natural" than electric shocks, an admission that procedures that induce fear in animals through the use of painful electric shocks would never occur in their natural lives.

### *Restraint, Immobilization, and Other Physical Abuse*

Restraint-based methods are often used to inflict stress, again purportedly to model human PTSD. Some of these methods use devices such as thin tubes, which rats and mice are forced into for several hours at a time. These tubes impose total immobilization and the animal cannot make any movements at all. Alternatively, rodents may be securely fixed to a metal platform by all four paws. Other methods include hanging rats or mice by their tails for several minutes. When the animals stop struggling and begin freezing, the behavior is labeled "immobility" and scientists consider this to be a viable indicator for PTSD research.

Researchers have also developed the technique of direct predator attack, letting cats attack the animals in a confined area,[17,18,19] as another "natural" stimulus of a fearful state. Of note is that rodents are prey species. It has been hardwired into their brains through millennia of evolution to avoid predation at all costs.

In one standard protocol, rats are restrained for two hours followed by a forced 20-minute swim test and then exposure to diethyl ether until they lose consciousness.

While all of the above demonstrate extreme cruelty, there is an even more severe method, known as "single prolonged stress" (SPS). Despite the name, SPS is actually a continual series of violent and aggressive acts that are committed against the animal subject. Authors of a literature review describe the process in rats: "In the standard SPS protocol, the animal is restrained for two hours followed by a 20-min forced swim test and then exposure to diethyl ether until loss of consciousness."[20]

Following this, the rats are left undisturbed for seven days. This is supposed to represent an incubation period, which is thought to be essential for the development of PTSD-like symptoms.

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[17] Cohen *et al,* 2014.

[18] Schöner *et al*, 2017.

[19] Whitaker *et al*, 2014.

[20] *Ibid*, p. 5 of Abstract.

In a more intense iteration of this procedure called "chronic variable stress," mice or rats are subjected to one of the above abusive treatments for six days a week and for several weeks in a row. Researchers recognize how inhumane these experiments are, but justify them with more analogy: "Admittedly, this class of models is extreme, yet it probably comes closest to simulate the chronic stress conditions experienced by military personnel in front-line positions."[21]

### *Social Stress*

The next category of stressors involves disrupting the animals' housing and social lives. Like all mammals, rats and mice have strong social bonds and require stability in their housing conditions to stay healthy and unharmed.

One common form of social stress is to destroy the nests of animals, often disrupting the care of their young. This impacts their ability to feel safe and to maintain body heat and overall well-being. In these situations, mothers can become so stressed that they fail to properly care for their young, and babies can die from neglect.

Removing baby mice from their mothers permanently alters brain development, and many of these babies fail to develop or simply die.

Another form of abusive social stress is the act of removing babies from their mothers (maternal deprivation), which is such a traumatizing process that it permanently alters normal brain development.[22] Without the touch, care, and stimulation provided by parental care, many of these baby mice and rats fail to develop and, in many instances, simply die.

Researchers have found that removing babies from their parents for short periods of time makes them more fearful as adults. Mice that have been removed from their mothers are often more susceptible to subsequent stressors, such as the simulated drowning test. Both rats and mice demonstrate increased anxiety behaviors in adulthood.[23,24] Researchers claim that this creates a better model for PTSD, despite the much more obvious connection to separation anxiety and despite the lack of translation to human PTSD biochemical pathways.

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[21] Goswami *et al*, p. 5.

[22] Janetsian-Fritz *et al*, 2018.

[23] Schöner *et al*, 2017.

[24] Whitaker *et al*, 2014.

Other methods of causing social stress involve forcing animals to be unnaturally aggressive or the subject of aggressive attacks that they would normally avoid. Small male mice are pitted against larger males in a situation known as "social defeat." While some protocols protect the smaller male from physical damage by placing a cage within a cage, other researchers let the animals physically interact and fight. The submissive one often loses weight and exhibits stress when outside of the fight situation, such as being startled more easily and tending to freeze in place.[25,26] In many instances, the aggressive mouse has been selectively bred (genetically engineered) to show overt dominance, larger size, and aggression.

Researchers will often isolate mice for weeks at a time to make them fearful and vulnerable.

Social stress can also be accomplished by socially isolating animals from their family or peers to induce stress and anxiety.[27] In addition, socially isolated animals demonstrate states of anxiety, aggression, and increased locomotion.[28] The last is known as stereotypical behavior and indicates that the animal has been severely stressed such that they are withdrawing into a reclusive world of their own. PTSD researchers will often isolate mice for weeks at a time to induce them into a fearful and vulnerable state.

It should be noted that the lifespan of a mouse or rat is much shorter than a human's. What may be only weeks to a human is likely be perceived as a much longer span to a mouse or rat. This applies also to the hours during which an animal is confined in a restraint tube, as described above. There is no evidence that animal researchers ever take this into account.

### *Environmental Stress*

Yet another category of trauma-inducing methods in PTSD research with small mammals is focused on environmental stressors. These can include reversing the day-night cycle with artificial lighting, playing extremely loud and distressing noises, or infiltrating the environment with the scent of a predator. These activities put the animal in a state of constant stress.

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[25] *Ibid.*

[26] Schöner *et al*, 2017.

[27] Goswami *et al*, 2013.

[28] Schöner *et al*, 2017.

If these stressors are not enough on their own, one final method of inducing PTSD-like symptoms includes chronically stressing animals for much of their existence. This method combines all stressors into the daily life of a mouse or rat. For instance, the day might start with white noise at 95 decibels, which is roughly the same level as music played in a nightclub. Then, researchers randomly shock the animals, force them to swim in freezing cold water, transfer them to an intense heat chamber, shake them in a tube, reverse their day and night cycle, and even deprive them of food and water for days at a time.[29]

## PTSD Research with Other Animals

While mice and rats are the most common animals used for PTSD experiments, other species are also subjected to the torment of PTSD research. Rabbits, for example, have been subject to painful experiments that attempt to study how fear is processed in the brain.

In one experiment, young rabbits were placed in restraint boxes and had a nylon loop sutured into their inner eyelids. Metal clips delivered electric shocks to either side of the eye.

In one experiment, 43 young rabbits were placed in restraint boxes and a nylon loop was sutured into the nictitating membrane (inner eyelid) of each eye, connected to a lever to measure its movement. Next, stainless steel clips that delivered electric shocks together with an audible tone were attached to either side of the eyeball. This induced a fear response, as measured by the movement of the nictitating membrane.

Researchers then gave the animals experimental doses of a drug, propranolol, to assess whether it would mitigate the fear response. They then stopped the electric shocks, but continued playing the tone, to evaluate how quickly the rabbits would cease to exhibit the fear response. Results showed that the drug conferred only a transient effect on dampening the fear response. The authors acknowledged that pharmacological intervention is unlikely to confer a lasting effect, stating in the introduction to their paper: "In addition, there is a learning, or more specifically, a dysfunctional fear conditioning component underlying PTSD that cannot easily be resolved by pharmacological treatment alone."[30]

Studies have also been carried out on macaque monkeys. To restrain the macaques, researchers place them in a primate chair,[31] a specially

[29] *Ibid.*

[30] Burhans *et al*, 2018, p. 386.

[31] Aguilar *et al*, 2018.

designed apparatus to confine the entire body, allowing only the head to extend outside of the box. Once restrained, the researchers can either stimulate electrodes that have been implanted into the brain or inject the monkey's brain with test substances, usually through a surgically implanted infusion platform.

Many studies infuse various drugs into key regions of the brain that are said to be associated with PTSD, including the amygdala and the hypothalamus, among others. The rationale behind such experiments is to interfere with the specific brain region and assess the subsequent social behavior, which can be highly abnormal.[32] Additional research has been carried out by exposing the monkeys to loud noises and investigating the response.[33]

Scientists found the results from more than 60 years of brain experimentation in primates to be contradictory.

The authors graphically describe the aberrant behavior of the monkeys after cerebral infusion with a drug. Behaviors such as cowering, escape-like behaviors, crying out, attacking objects, and howling were all observed.[34] Wellman, *et al*, described similar experimental procedures on monkeys.[35] These authors (Aguilar, *et al*; Forcelli, *et al*; DesJardin, *et al;* and Wellman, *et al*) were all part of the same research facility. Their experiments were carried out repetitively over many years and yielded no conclusive results that could be applied to humans. In fact, the authors outrightly state that after more than 60 years of this line of experimentation in primate models, the scientists found the results to be contradictory and key questions remained unaddressed.[36]

## Conclusion

Arguably, a state of anxiety can only be achieved with methods that cause pain or stress. If the situation were not painful or stressful, the animals would not elicit a reaction of avoidance. Without acute pain or distress, the animal would not need to escape or become immobile. **Thus, not only is PTSD animal research *harmful*, but the harm is inseparable from research methods.**

The methods of inducing physical and emotional trauma in animals discussed in this section are by no means comprehensive; experiments

[32] Forcelli *et al*, 2016 and 2017.

[33] Aguilar *et al*, 2018.

[34] DesJardin *et al*, 2013.

[35] Wellman *et al*, 2016.

[36] *Ibid,* p. 8746.

have been carried out, and continue to be carried out, utilizing a myriad of methods.

While meaningful results produced by these methods are extremely scant if they exist at all, researchers claim that traumatizing these animals has provided many insights into PTSD. The lack of outcomes refutes that theory.

It is critical that funders and stakeholders of PTSD research acknowledge the abject failure of animal experiments. In these experiments, animals are continually subjected to procedures such as the ones described in this section, with vague objectives and little outcome. The experiments consume millions of dollars in funding that could be directed to research and treatments that would directly benefit PTSD patients.

It should also be noted that PTSD experiments using animals are part of a much larger category of animal experimentation into emotional states like fear, anxiety, and stress. These experiments similarly fail in many ways, including in reproducing the human state; producing treatment outcomes, pharmacologic or otherwise, for human patients; and consuming vast amounts of funding that could be directed toward better access to mental health treatments known to be effective.

The next section of this report provides an overview of the costliness of using animals in research into treatments for PTSD.

# VI. The Cost of PTSD Research on Animals

In light of the invalidity, inapplicability, and harm of animal-based research on PTSD, it is important to evaluate the financial cost that PTSD research imposes on patients, governments, taxpayers, and other stakeholders.

The social costs of PTSD for American veterans of wars in Afghanistan and Iraq are up to $2 billion per year.

**The burden of caring for PTSD sufferers is enormously costly to society. One study focused on veterans of Afghanistan and Iraq showed that the projected social costs of PTSD within those two groups alone would be around $923 million over a two-year period.[1] Other studies have analyzed the cost to be even higher, around $2 billion a year for American veterans of the Afghanistan and Iraq wars.[2]**

CAARE conducted a review of the National Institutes of Health (NIH) database that revealed that in 2016 there were 615 active projects focusing on PTSD and anxiety, with total funding of over $170 million. Of the 615 PTSD projects, 119 used animals; this represents about 19% of the research. These animal-based studies consumed $33 million worth of funding, which represents about 18% of the total funding. Funding was provided by the NIH and its subdivision, the National Institute of Mental Health. In 2019, the total NIH funding for PTSD was $138 million.[3] This does not include funding from the VA and is simply the expenditure in the United States. The global cost is higher still.

The NIH database reveals that the monkey experiments (Forcelli, *et al*; Aguilar, *et al*; DesJardin, *et al* and Wellman, *et al*) described in section V of this report cost around half a million dollars every year from 2013 through 2018, for a total of $2.3 million.[4] This federal grant funding ultimately yielded nothing of benefit to treatment for PTSD. After five years, the project was ended. With such enormous costs required to address the crisis in treating PTSD, it is imperative that we reexamine funding these and other similar experiments on animals.

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[1] Kilmer *et al*, 2011. A microsimulation model study. Such a study pulls together data from several data sources to simulate outcomes and risks.

[2] Reisman, 2016.

[3] National Institutes of Health: Research Portfolio Online Reporting Tools [RePORT]; Funding.

[4] National Institutes of Health: Research Portfolio Online Reporting Tools [RePORT]; Project Information.

The data suggests that animal-based research, on a per-project basis, is similar to other research methods for studying PTSD. However, given that human-based methods study PTSD directly in patients, with the benefit of large-scale databases that review evidence within the human system, the costs cannot truly be compared.

Overall trends in assessing healthcare outcomes indicate decreasing confidence in the current methods for deriving successful therapies. As reported by Bowen and Casadevall (2015) in their analysis of spending on drug treatments, "increasing resource investments have led to an explosion in scientific knowledge, but the resulting gains in new therapies and improved human health have been proportionally smaller.[5]

Their research presents evidence that our increased investments in science and healthcare are not efficient and have cost taxpayers billions of dollars in the process. In fact, they describe their results as a "cautionary tale," which they hope will motivate new efforts to influence the efficiency of science in creating practical applications.

Of 500 compounds that reduce the effects of stroke in animals, only two helped human stroke patients recover.

One 2010 study published in *PLOS Medicine* documented that of 500 compounds shown to be effective at reducing the effects of stroke in animals, only two have shown any signs of helping human stroke patients recover.[6] A more updated review on this same topic from 2014 reported that "in stroke medicine, despite decades of immense human, animal, and financial investment, animal models have failed to yield a single neuroprotective treatment for humans."[7]

Over $28 billion is spent yearly on preclinical animal research.

And yet, regardless of the voluminous and compelling information on the invalidity of animal research, vast sums are still sustaining it. A 2015 study reported that over $28 billion is spent on preclinical research every year, the vast majority of which is conducted using animals.[8] Much of the animal research conducted with these funds is never cited after publication, or worse, never makes it to publication.

**Of basic animal research projects that are published, only a small percentage are ever cited in human medical journals. In fact, an author at the Oxford Centre for Animal Ethics, found that only 97**

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[5] Bowen and Casadevall, 2015, p. 11337.

[6] van der Worp *et al*, 2010.

[7] Pound *et al*, 2014.

[8] Freedman *et al*, 2015.

**(8.2%) of the 1,183 animal studies followed over a 12-year period were cited in a clinical study.** Of these citations, only four were used to find a statistically relevant correlation between the animal experiments and human outcomes. This is a mere 0.3%. Worse still, as the author writes, "even in these four cases, however, the hypotheses that had been verified successfully in animal experiments failed when applied to humans."[9]

This pattern of wasted animal experiments defines the current crisis in drug and treatment development, not only for PTSD but for all illnesses. Currently, it costs roughly over $1 billion and 10 years to develop a drug. Further, the rate at which new drugs are approved has plummeted from 40 years ago. Of the drugs developed that pass animal trials, over 90% fail in subsequent human trials.[10] But the exorbitant costs in research and development are not the only expense created by animal experimentation.

Between 1999 and 2009, more than 270 million prescriptions were written for drugs that were ultimately withdrawn or relabeled with black-box lethal side effects.

Drug companies and the healthcare system are also overburdened with a massive amount of post-approval failures, ensuing lawsuits, and loss in value. For instance, one study found that the average loss in company value is around $114 million for every withdrawn or failed product.[11] Between 1999 and 2009, more than 30 million prescriptions were written for each of nine drugs (a total of more than 270 million prescriptions) that were ultimately withdrawn from the market or relabeled with black-box lethal side effects.[12] And these were drugs that had been previously approved by the FDA. These figures do not include the massive untold costs experienced by the suffering patients and their families.

These widespread and sweeping failures have led to a decline in support for animal research. An analysis conducted by prominent epidemiologists at the Yale University Schools of Public Health and Medicine in 2014 reported significant cuts to basic research, which includes exploratory animal research:

> Public funding bodies are becoming aware of the lack of return on investment, and public and charitable spending on basic research has decreased in the UK from 68.3% in 2004-5 to 59.4%

[9] Knight, 2011, p. 290.

[10] Marshall *et al*, 2018.

[11] Ahmed *et al*, 2002.

[12] Frank *et al*, 2014.

in 2009-10. This seems wise since retrospective analysis of the payback from research is beginning to suggest that it is clinical rather than basic research that has most effect on patient care.[13]

Because each translational failure represents a significant loss of invested capital, more companies and researchers are turning to non-animal methods and human-based research strategies. In Europe, drug companies have already cut animal testing by more than 25% from 2005 to 2009 and are decreasing reliance on animal experiments because each translational failure represents enormous losses in capital.[14]

Pharmaceutical companies are scaling back drug programs in neuroscience due to excessive failures with mental health drugs.

Worldwide, pharmaceutical companies are scaling back or outrightly abandoning drug-discovery programs in neuroscience due to excessive failures with mental health drugs following years of expensive clinical trials. This includes Pfizer and Merck in the U.S., GlaxoSmithKline and AstraZeneca in the UK, and Novartis and Sanofi in Europe.[15]

Today all drug companies are feeling the fallout from lack of translation from animal data to successful human medical outcomes. Medical research and development companies have recognized the problem and are calling for new guidelines to retool the ailing industry with more effective methodologies. A report issued by a conglomeration of drug discovery companies in the UK concluded in 2018–2019 that every effort must be made to develop key technologies that humanize drug discovery. The report advocates the use of complex human cell models in place of animal experiments as a blueprint for success in pharmaceutical research.[16]

The most cost-effective and ethical use of funding for PTSD lies in providing proven therapies to all patients and giving therapists and counselors the tools they need to reach the widest number of patients possible. Research funding should be awarded to those scientists who are exploring the modalities discussed in section III to develop a human understanding of the disease pathology.

A cost analysis of 70 veterans who received prolonged exposure (PE) therapy or cognitive processing therapy (CPT) demonstrated

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[13] Pound *et al*, 2014, p. 2 of Abstract.

[14] *Ibid*.

[15] Abbott, 2011.

[16] The BioIndustry Association and the Medicines Discovery Catapult, 2018 and 2019.

substantial reductions in mental health service use and costs. The authors report:

> This statistically significant reduction in service consumption resulted in a 39.4% reduction in direct costs from an average of $5173.20 in the year before treatment to $3133.10 in the year following treatment per veteran. … These preliminary findings are the first to demonstrate that within veteran samples, the successful completion of PE and CPT for PTSD significantly reduces mental health service utilization and outweighs the investment cost of providing these services.[17]

**This massive savings of upwards of $2,000 per veteran per year would mean significant savings to U.S. taxpayers**.

## Conclusion

Disseminating evidence-based treatments for PTSD could save $138 million a year.

Animal research for PTSD is an ill-advised financial endeavor. As seen in previous sections of this report, there are already effective treatments for PTSD and the so-called "animal model" of PTSD is deeply flawed and invalid. Disseminating evidence-based treatments for PTSD could save nearly $138 million a year, according to one analysis. **Researchers have shown that when cognitive therapies were implemented for the treatment of PTSD, cost-effectiveness was increased by 150% over other methods, but only 10% of PTSD patients currently receive cognitive therapy**.[18]

Thorough cost analysis demonstrates that funding for animal research on PTSD is a misguided, broken, and unethical venture. It is already declining as scientists and funders recognize its serious weaknesses and overall unreliability. To continue to fund animal-based projects in light of the powerful evidence against it is a grave disservice to veterans, all PTSD victims, victims' families, and untold numbers of animals forced to endure useless and futile suffering.

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[17] Meyers *et al*, p. 97.

[18] Foa *et al*, 2013.

# VII. Conclusions

This report has given a comprehensive overview of the current trends in PTSD research and treatment. It has provided insight into the various cost-effective and viable treatments that are available to manage this debilitating condition, thereby giving hope to those who suffer from PTSD. Some of these methods have an exceptionally efficacious therapeutic effect, gaining results over a remarkably short period of time.

The report has also provided evidence of the available human-specific methodology to research the pathophysiology of PTSD, as well as human-relevant research into effective drugs that can alleviate symptoms of the disorder. Such methodology is humane, non-invasive, and relevant to the species for which such research is directed: humans.

The immense trauma imposed on animals has been reviewed. Having detailed the extent of animal work being done, the report went on to discuss the high financial as well as moral costs of such experimentation. **Additionally, the report offered much evidence that such research is invalid and has little to no bearing on the human condition. It is becoming increasingly evident that animal research is dangerous, unethical, and unreliable, particularly when applied to complex neuropsychiatric disorders such as PTSD.**

Many scientists agree: More questions need to be asked regarding the ethics and validity of using animals in research.

A recent review in the Netherlands and Germany concluded that the translational value of animal studies may be difficult to prove and that more questions need to be asked regarding the ethics and validity of using animals in research.[1] These authors also remarked that it is impossible to assess several symptoms of neuropsychiatric disorders objectively if animals are used as models of the disorder.

Seifirad and Haghpanah give several examples where drug development using animals has failed. They denounce the use of animals in the majority of research and list a broad array of human pathological conditions for which animal research has proven useless and indefensible. They offer suggestions on how to remedy the situation that include a focus on human-centered research.[2] These

[1] Meijboom *et al*, 2020.

[2] Seifirad and Haghpanah, 2019.

authors specifically mention the failures of animal models in neuropathology.

The evidence is overwhelming: If humans are to benefit from medical and clinical advancements, existing, effective therapies must be adequately disseminated to patients, and animals *must* be factored out of the research equation. Funding organizations must take into account the invalidity of animal research and cease funding such projects, instead investing in ethical, effective, reliable, human-based methodology. It is up to lawmakers and funders to ensure that science remains bound to the ideal of promoting human outcomes. Eliminating animal research in PTSD and other mental illnesses is essential to accomplishing this goal.

# References

Abbott, Allison; 2011 (December); Novartis to shut brain research facility; *Nature*; 480(7376); 161–162; https://doi.org/10.1038/480161a; Accessed April 30, 2020

Aguilar, Brittany L., Patrick A. Forcelli, and Ludise Malkova; 2018 (December); Inhibition of the Substantia Nigra Pars Reticulata Produces Divergent Effects on Sensorimotor Gating in Rats and Monkeys; *Scientific Reports*; 8(1): 9369; https://doi.org/10.1038/s41598-018-27577-w; Accessed April 21, 2020

Ahmed, Parvez, John Gardella, and Sudhir Nanda; 2002 (Autumn); Wealth Effect of Drug Withdrawals on Firms and Their Competitors; *Financial Management*; 31(3): 21-41; doi: 10.2307/3666313; https://www.jstor.org/stable/3666313; Accessed May 05, 2020

Akhtar, Aysha; 2015 (October); The Flaws and Human Harms of Animal Experimentation; *Cambridge Quarterly of Healthcare Ethics*; 24(04): 407–419; https://doi.org/10.1017/S0963180115000079; Accessed April 23, 2020

Altschuler, Eric L; 2018; Animal-Assisted Therapy for Post-traumatic Stress Disorder: Lessons from "Case Reports" in Media Stories; *Military Medicine*; 183(1/2): 11-13; https://doi.org/10.1093/milmed/usx073; Accessed March 26, 2020

Aspesi, Dario and Graziano Pinna; 2019 (February); Animal models of post-traumatic stress disorder and novel treatment targets; *Behavioural Pharmacology*; 30(2): 130-150; https://doi.org/10.1097/FBP.0000000000000467; Accessed April 27, 2020

Bailey, Jarrod; 2009 (September); An Examination of Chimpanzee Use in Human Cancer Research; *ATLA – Alternatives to Laboratory Animals*; 37(4): 399-416; https://doi.org/10.1177/026119290903700410; Accessed April 28, 2020

Bailey, Jarrod; 2011; Lessons from Chimpanzee-Based Research on Human Disease: The Implications of Genetic Differences; *ATLA – Alternatives to Laboratory Animals*; 39(6): 527-540; https://animalstudiesrepository.org/acwp_lab/28/; Accessed April 28, 2020

Barrile, Riccardo, Andries D. van der Meer, Hyoungshin Park, Jacob P. Fraser, Damir Simic, Fang Teng, David Conegliano, *et al*; 2018 (April); Organ-on-Chip Recapitulates Thrombosis Induced by an Anti-CD154 Monoclonal Antibody: Translational Potential of Advanced Microengineered Systems; *Clinical Pharmacology & Therapeutics*; 104(6): 1240-1248; https://doi.org/10.1002/cpt.1054; Accessed April 01, 2020

Beauvais, Danielle, Elissa McCarthy, Sonya Norman, and Jessica L. Hambien; Eye Movement Desensitization and Reprocessing (EMDR) for PTSD; PTSD: National Center for PTSD; U.S. Department of Veterans Affairs; https://www.ptsd.va.gov/professional/treat/txessentials/emdr_pro.asp; Accessed July 18, 2020.

Bharadwaj, Rahul A., Andrew E. Jaffe, Qiang Chen, Amy Deep-Soboslay, Aaron L. Goldman, Michelle I. Mighdoll, John A. Cotoia, Anna C. Brandtjen, JooHeon Shin, Thomas M. Hyde, Venkata S. Mattay, Daniel R. Weinberger and Joel E. Kleinman; 2018 (January); Genetic risk mechanisms of posttraumatic stress disorder in the human brain; *Journal of Neuroscience Research*; 96(1): 21–30; https://doi.org/10.1002/jnr.23957; Accessed April 01, 2020

Borghans, Bart and Judith R. Homberg; 2015 (December); Animal Models for Posttraumatic Stress Disorder: An Overview of What Is Used in Research; *World Journal of Psychiatry*; 5(4): 387–396; https://doi.org/10.5498/wjp.v5.i4.387; Accessed April 22, 2020

Boccia, Maddalena, Simonetta D'Amico, Filippo Bianchini, Assunta Marano, Anna Maria Giannini and Laura Piccardi; 2016 (March); Different neural modifications underpin PTSD after different traumatic events: an fMRI meta-analytic study; *Brain Imaging and Behavior*; 10(1): 226–237; https://doi.org/10.1007/s11682-015-9387-3; Accessed March 27, 2020

Botella, Cristina, Seranno, Berenice, Baños, Rosa M. and Garcia-Palacios, Azucena; 2015; Virtual reality exposure-based therapy for the treatment of post-traumatic stress disorder: a review of its efficacy, the adequacy of the treatment protocol, and its acceptability; *Neuropsychiatric Disease and Treatment*; 11: 2533–2545; https://doi.org/10.2147/NDT.S89542; Accessed March 15, 2020

Bowen, Anthony, and Arturo Casadevall; 2015 (September); Increasing Disparities between Resource Inputs and Outcomes, as Measured by Certain Health Deliverables, in Biomedical Research; *Proceedings of the*

*National Academy of Sciences*; 112(36): 11335–11340; https://doi.org/10.1073/pnas.1504955112; Accessed May 04, 2020

Burhans, Lauren B., Carrie A. Smith-Bell and Bernard G. Schreurs; 2018 (March); Propranolol produces short-term facilitation of extinction in a rabbit model of post-traumatic stress disorder; *Neuropharmacology*; 135: 386-398; https://doi.org/10.1016/j.neuropharm.2018.03.029; Accessed April 21, 2020

Carrión, Victor G, Brian W. Haas, Amy Garrett, Suzan Song, and Allan L. Reiss; 2010 (June); Reduced Hippocampal Activity in Youth with Posttraumatic Stress Symptoms: An fMRI Study; *Journal of Pediatric Psychology*; 35(5): 559–569; https://doi.org/10.1093/jpepsy/jsp112; Accessed March 30, 2020

Chakraverty, Anita; 2020 (May); *Phase III Failure Sinks Drug for Rare Neurological Disorder*; Labiotech.eu; https://www.labiotech.eu/brain/newron-rett-syndrome-fail/; Accessed June 16, 2020.

Chandrasekera, P. Charukeshi and John J. Pippin; 2014; Of Rodents and Men: Species-Specific Glucose Regulation and Type 2 Diabetes Research; *ALTEX – Alternatives to Animal Experimentation*; 31(2): 157-176; https://doi.org/10.14573/altex.1309231; Accessed April 29, 2020

Chen, Ashley C, and Amit Etkin; 2013 (September); Hippocampal Network Connectivity and Activation Differentiates Post-Traumatic Stress Disorder From Generalized Anxiety Disorder; *Neuropsychopharmacology*; 38(10): 1889–1898; https://doi.org/10.1038/npp.2013.122; Accessed March 31, 2020

Cherry, Kendra; Updated on January 08, 2020; What Is Learned Helplessness and Why Does it Happen?; *verywellmind*; Medically reviewed by Steven Gans MD; https://www.verywellmind.com/what-is-learned-helplessness-2795326; Accessed April 16, 2020

Courtois, Christine A. (Chair) *et al*; 2017; Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults; American Psychological Association; https://www.apa.org/ptsd-guideline/ptsd.pdf; Accessed March 15, 2020

Cohen, Hagit, Joseph Zohar, Michael A Matar, Kaplan Zeev, Uri Loewenthal, and Gal Richter-Levin; 2004 (November); Setting Apart the

Affected: The Use of Behavioral Criteria in Animal Models of Post Traumatic Stress Disorder; *Neuropsychopharmacology*; 29(11): 1962–1970; https://doi.org/10.1038/sj.npp.1300523; Accessed April 20, 2020

Conoscenti, Michael A and Michael S. Fanselow; 2019 (May); Dissociation in Effective Treatment and Behavioral Phenotype Between Stress-Enhanced Fear Learning and Learned Helplessness; *Frontiers in Behavioral Neuroscience*; 13: 104; https://doi.org/10.3389/fnbeh.2019.00104; Accessed April 16, 2020

Cservenka, Anita, Madison L. Stroup, Amit Etkin, and Bonnie J. Nagel; 2015 (October); The Effects of Age, Sex, and Hormones on Emotional Conflict-Related Brain Response during Adolescence; *Brain and Cognition*; 99: 135–150; https://doi.org/10.1016/j.bandc.2015.06.002; Accessed March 30, 2020

Cummings, Jeffrey L, Travis Morstorf, and Kate Zhong; 2014; Alzheimer's Disease Drug-Development Pipeline: Few Candidates, Frequent Failures; *Alzheimer's Research & Therapy*; 6(4): 37; https://doi.org/10.1186/alzrt269; Accessed April 29, 2020

Cusack, Karen, Daniel E. Jonas, Catherine A. Forneris, Candi Wines, Jeffrey Sonis, Jennifer Cook Middleton, Cynthia Feltner, *et al*; 2016 (February); Psychological Treatments for Adults with Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis; *Clinical Psychology Review*; 43: 128–41; https://doi.org/10.1016/j.cpr.2015.10.003; Accessed March 15, 2020

Daskalakis, Nikolaos P., Rachel Yehuda and David M. Diamond; 2013 (September); Animal models in translational studies of PTSD; *Psychoneuroendocrinology*; 38(9): 1895-1911; https://doi.org/10.1016/j.psyneuen.2013.06.006; Accessed April 15, 2020

De Lange, Geertje M.; 2017 (June); Understanding the cellular and molecular alterations in PTSD brains: The necessity of post-mortem brain tissue; *European Journal of Psychotraumatology*; 8(1): 1341824; https://doi.org/10.1080/20008198.2017.1341824; Accessed April 01, 2020

DesJardin Jacqueline T., Angela L. Holmes, Patrick A. Forcelli, Clair E. Cole, John T. Gale, Laurie L. Wellman and Ludise Malkova; 2013 (January); Defense-like behaviors evoked by pharmacological disinhibition of the superior colliculus in the primate; *The Journal of*

*Neuroscience: The Official Journal of the Society for Neuroscience*; 33(1): 150–155; https://doi.org/10.1523/JNEUROSCI.2924-12.2013; Accessed April 27, 2020

Difede, JoAnn, Judith Cukor, Nimali Jayasinghe, Ivy Patt, Sharon Jedel, Lisa Spielman, Cezar Giosan, and Hunter G. Hoffman; 2007; Virtual Reality Exposure Therapy for the Treatment of Posttraumatic Stress Disorder Following September 11, 2001; *Journal of Clinical Psychiatry*; 68(11): 1639–1647; https://www.ncbi.nlm.nih.gov/pubmed/18052556; Accessed March 15, 2020

Doke, Sonali K., and Shashikant C. Dhawale; 2015 (July); Alternatives to Animal Testing: A Review; *Saudi Pharmaceutical Journal*; 23(3): 223–229; https://doi.org/10.1016/j.jsps.2013.11.002; Accessed April 01, 2020

Edington, Colin D. Wen Li Kelly Chen, Emily Geishecker, Timothy Kassis, Luis R. Soenksen, Brij M. Bhushan, Duncan Freake, Jared Kirschner, Christian Maass, Nikolaos Tsamandouras, Jorge Valdez, Christi D. Cook, *et al*; 2018 (March); Interconnected Microphysiological Systems for Quantitative Biology and Pharmacology Studies; *Scientific Reports*; 8: 4530; https://doi.org/10.1038/s41598-018-22749-0; Accessed April 01, 2020

EMDR Institute, Inc.; Frequently Asked Questions; http://www.emdr.com/frequent-questions/; Accessed March 18, 2020

Ferrada-Noli, Marcello, Marie Asberg, Kari Ormstadi, Tom Lundin and Elisabet Sundbom; 1998 (January); Suicidal behavior after severe trauma: Part 1: PTSD diagnoses, psychiatric comorbidity, and assessments of suicidal behavior; *Journal of Traumatic Stress*; 11(1): 103–112; https://doi.org/10.1023/A:1024461216994; Accessed March 08, 2020

Ferrada-Noli, Marcello, Marie Asberg and Kari Ormstad; 1998 (January); Suicidal behavior after severe trauma. Part 2: The association between methods of torture and of suicidal ideation in posttraumatic stress disorder; *Journal of Traumatic Stress*; 11(1): 113–124; https://doi.org/10.1023/A:1024413301064; Accessed March 08, 2020

Flandreau, Elizabeth I. and Mate Toth; 2017; Animal Models of PTSD: A Critical Review; In: Vermetten E., Baker D., Risbrough V. (Eds); *Behavioral Neurobiology of PTSD: Current Topics in Behavioral Neurosciences*; 38: 47–68; Springer; Cham; https://doi.org/10.1007/978-3-319-94824-9; Accessed April 15, 2020

Foa, Edna B., Gillihan, Seth J and Bryant, Richard A.; 2013 (May); Challenges and Successes in Dissemination of Evidence-Based Treatments for Posttraumatic Stress: Lessons Learned From Prolonged Exposure Therapy for PTSD; *Psychological Science in the Public Interest*; 14(2): 65–111; https://doi.org/10.1177/1529100612468841; Accessed March 02, 2020

Foa, Edna B., Terence M. Keane, Matthew J. Friedman and Judith A. Cohen (Eds); 2009; *Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies*; Second Edition; pp 573-576; The Guildford Press; New York; https://www.istss.org/ISTSS_Main/media/Documents/ISTSS_g81.pdf; Accessed March 18, 2020

Fonzo, Gregory A., Madeleine S. Goodkind, Desmond J. Oathes, Yevgeniya V. Zaiko, Meredith Harvey, Kathy K. Peng, M. Elizabeth Weiss, *et al*; 2017 (December); Selective Effects of Psychotherapy on Frontopolar Cortical Function in PTSD; *American Journal of Psychiatry* 174(12): 1175–84; https://doi.org/10.1176/appi.ajp.2017.16091073; Accessed March 30, 2020

Forcelli, Patrick A., Jacqueline T. DesJardin, Elizabeth A. West, Angela L. Holmes, Catherine Elorette, Laurie L. Wellman, and Ludise Malkova; 2016 (August); Amygdala Selectively Modulates Defensive Responses Evoked from the Superior Colliculus in Non-Human Primates; *Social Cognitive and Affective Neuroscience*; 11(12): 2009–2019; https://doi.org/10.1093/scan/nsw111; Accessed April 22, 2020

Forcelli, Patrick A., Laurie L. Wellman, and Ludise Malkova; 2017; Blockade of Glutamatergic Transmission in the Primate Basolateral Amygdala Suppresses Active Behavior without Altering Social Interaction; *Behavioral Neuroscience*; 131(2): 192–200; https://doi.org/10.1037/bne0000187; Accessed April 22, 2020

Frank, Cassie, David U. Himmelstein, Steffie Woolhandler, David H. Bor, Sidney M. Wolfe, Orlaith Heymann, Leah Zallman, and Karen E. Lasser; 2014; Era Of Faster FDA Drug Approval Has Also Seen Increased Black-Box Warnings And Market Withdrawals; *Health Affairs*; 33(8): 1453–1459; https://doi.org/10.1377/hlthaff.2014.0122; Accessed May 05, 2020

Freedman, Leonard P., Iain M. Cockburn, and Timothy S. Simcoe; 2015 (June); The Economics of Reproducibility in Preclinical Research; *PLOS*

*Biology*; 13(6): e1002165; https://doi.org/10.1371/journal.pbio.1002165; Accessed May 05, 2020

Freeman, D., S. Reeve, A. Robinson, A. Ehlers, D. Clark, B. Spanlang, and M. Slater; 2017; Virtual Reality in the Assessment, Understanding, and Treatment of Mental Health Disorders; *Psychological Medicine*; 47: 2393–2400; https://doi.org/10.1017/S003329171700040X; Accessed March 15, 2020

Friedman, Matthew, J. and William W. Harris; 2004; Toward a National PTSD Brain Bank; *Psychiatry*; 67(4): 384–390; https://doi.org/10.1521/psyc.67.4.384.56564; Accessed April 01, 2020

Frijling, Jessie L, Mirjam van Zuiden, Saskia BJ Koch, Laura Nawijn, J Carel Goslings, Jan S Luitse, Tessa H Biesheuvel, *et al*; 2014 (December); Efficacy of Oxytocin Administration Early after Psychotrauma in Preventing the Development of PTSD: Study Protocol of a Randomized Controlled Trial; *BMC Psychiatry*; 14: 92; https://doi.org/10.1186/1471-244X-14-92; Accessed March 30,2020

Frijling, Jessie, L; 2017; Preventing PTSD with oxytocin: effects of oxytocin administration on fear neurocircuitry and PTSD symptom development in recently trauma-exposed individuals; *European Journal Of Psychotraumatology*; 8(1): 1302652; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5400019/pdf/zept-8-1302652.pdf; Accessed March 30, 2020

Galea, Sandro (Chair), *et al*; 2012; Committee on the Assessment of Ongoing Efforts in the Treatment of Posttraumatic Stress Disorder; Board on the Health of Select Populations; Institute of Medicine; *Treatment for Posttraumatic Stress Disorder in Military and Veteran Populations: Initial Assessment*; The National Academies Press; Washington DC; pdf; http://nap.edu/13364; Accessed March 11, 2020

Garner, Joseph P.; 2014 (December); 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 Journal*; 55(3): 438–56; https://doi.org/10.1093/ilar/ilu047; Accessed May 01, 2020

Garner, Joseph P, Brianna N Gaskill, Elin M Weber, Jamie Ahloy-Dallaire, and Kathleen R Pritchett-Corning; 2017 (April); Introducing Therioepistemology: The Study of How Knowledge Is Gained from Animal Research; *Lab Animal*; 46(4): 103–113; https://doi.org/10.1038/laban.1224; Accessed April 30, 2020

Giacomoni, Carlo A.; 2018; Posttraumatic Stress Disorder and Suicide Risk; *Forensic Scholars Today*; 4(1); https://1q5krviw73e3rlh854lufacx-wpengine.netdna-ssl.com/wp-content/uploads/2018/08/FST-4.1-Posttraumatic-Stress-Disorder-Suicide-Risk.pdf; Accessed March 08, 2020

Girgenti, Matthew, J. and Ronald S. Duman; 2017 (May); Transcriptome Alterations in Posttraumatic Stress Disorder; *Biological Psychiatry*; 83(10): 840–848; https://doi.org/10.1016/j.biopsych.2017.09.023; Accessed April 01, 2020

Goswami, Sonal, Olga Rodríguez-Sierra, Michele Cascardi, and Denis Paré; 2013; Animal models of post-traumatic stress disorder: face validity; *Frontiers in Neuroscience*; 7(89); https://doi.org/10.3389/fnins.2013.00089; Accessed April 20, 2020

Haldipur, Parthiv, Kimberly A. Aldinger, Silvia Bernardo, Mei Deng, Andrew E. Timms; Lynne M. Overman, *et al*; 2019 (October); Spatiotemporal expansion of primary progenitor zones in the developing human cerebellum; *Science*; 366(6464): 454–460; doi: 10.1126/science.aax7526; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6897295/; Accessed April 29, 2020

Hart H., L. Lim, M.A. Mehta, A. Simmons A, K.A.H. Mirza and K Rubia; 2018; Altered fear processing in adolescents with a history of severe childhood maltreatment: an fMRI study; *Psychological Medicine*; 48: 1092–1101; https://doi.org/10.1017/S0033291716003585; Accessed March 30, 2020

Hoge, Charles W.; 2015; Accelerated resolution therapy (ART): Clinical considerations, cautions, and informed consent for military mental health clinicians; *Walter Reed Army Institute of Research*; http://acceleratedresolutiontherapy.com/wp-content/uploads/2016/08/ART-vs-EMDR_by-Hoge.pdf; Accessed March 18, 2020

Hoffman, Yaakov, Sara Cohen-Fridel, Ehud Bodner, Ephraim Grossman, and Amit Shrira; 2016 (March); Confidence in the 'Iron Dome' Missile Defense System Combined with a Sense of Resilience Reduced the Effect of Exposure on Posttraumatic Stress Disorder Symptoms after Missile Attacks; *The Journal of Clinical Psychiatry*; 77(3): 407–408; https://doi.org/10.4088/JCP.15l10024; Accessed April 29, 2020

Holman, Constance, Sophie K. Piper, Ulrike Grittner, Andreas Antonios Diamantaras, Jonathan Kimmelman, Bob Siegerink, and Ulrich Dirnagl; 2016 (January); Where Have All the Rodents Gone? The Effects of Attrition in Experimental Research on Cancer and Stroke; *PLOS Biology*; 14(1): e1002331; https://doi.org/10.1371/journal.pbio.1002331; Accessed May 01, 2020

Holmes, Sophie E., Matthew J. Girgenti, Margaret T. Davis, Robert H. Pietrzak, Nicole DellaGioia, Nabeel Nabulsi, David Matuskey, *et al*; 2017 (August); Altered Metabotropic Glutamate Receptor 5 Markers in PTSD: In Vivo and Postmortem Evidence; *Proceedings of the National Academy of Sciences*; 114(31): 8390–8395; https://doi.org/10.1073/pnas.1701749114; Accessed March 30, 2020

Hooge, Rudi D. and Peter P. De Deyn; 2001; Applications of the Morris water maze in the study of learning and memory; *Brain Research Reviews*; 36(1): 60–90; https://www.sciencedirect.com/science/article/abs/pii/S0165017301000674; Accessed April 20, 2020

Hu, Hao, Yawen Sun, Shanshan Su, Yao Wang, Yongming Qiu, Xi Yang, Yan Zhou, Zeping Xiao, and Zhen Wang; 2018 (January); Cortical Surface Area Reduction in Identification of Subjects at High Risk for Post-Traumatic Stress Disorder: A Pilot Study; *The Australian & New Zealand Journal of Psychiatry*; 52(11): 1084–1091; https://doi.org/10.1177/0004867417750757; Accessed March 31, 2020

Hudenko, William, Homaifar, Beeta and Wortzel, Hal; 2018 (January); The Relationship Between PTSD and Suicide; PTSD: National Center for PTSD; U.S. Department of Veterans Affairs; https://www.ptsd.va.gov/professional/treat/cooccurring/suicide_ptsd.asp#five; Accessed March 08, 2020

Iqbal, Shareen A., Joshua D. Wallach, Muin J. Khoury, Sheri D. Schully, and John P. A. Ioannidis; 2016 (January); Reproducible Research Practices and Transparency across the Biomedical Literature; *PLOS Biology*; 14(1): e1002333; https://doi.org/10.1371/journal.pbio.1002333; Accessed May 01, 2020

Janetsian-Fritz, Sarine S., Nicholas M. Timme, Maureen M. Timm, Aqilah M. McCane, Anthony J. Baucum II, Brian F. O'Donnell, and Christopher C. Lapish; 2018; Maternal deprivation induces alterations in cognitive and cortical function in adulthood; *Translational Psychiatry*;

8(1): 71. https://doi.org/10.1038/s41398-018-0119-5; Accessed June 16, 2020.

Kilmer, Beau, Christine Eibner, Jeanne S. Ringel, and Rosalie Liccardo Pacula; 2011 (May); Invisible Wounds, Visible Savings? Using Microsimulation to Estimate the Costs and Savings Associated With Providing Evidence-Based Treatment for PTSD and Depression to Veterans of Operation Enduring Freedom and Operation Iraqi Freedom; *Psychological Trauma: Theory, Research, Practice, and Policy*; 3(2): 201–211. https://doi.org/10.1037/a0020592; Accessed May 04, 2020

Kip, Kevin E., Carrie A. Elk, Kelly L. Sullivan, Rajendra Kadel, Cecile A. Lengacher, Christopher J. Long, Laney Rosenzweig, *et al*; 2012 (June); Brief Treatment of Symptoms of Post-Traumatic Stress Disorder (PTSD) by Use of Accelerated Resolution Therapy (ART®); *Behavioral Sciences*; 2(2): 115–34; https://doi.org/10.3390/bs2020115; Accessed March 18, 2020

Kip, Kevin E., Laney Rosenzweig, Diego F. Hernandez, Amy Shuman, Kelly L. Sullivan, Christopher J. Long, James Taylor, *et al*; 2013 (December); Randomized Controlled Trial of Accelerated Resolution Therapy (ART) for Symptoms of Combat-Related Post-Traumatic Stress Disorder (PTSD); *Military Medicine*; 178(12): 1298–1309; https://doi.org/10.7205/MILMED-D-13-00298; Accessed March 18, 2020

Kip, Kevin E., Laney Rosenzweig, Diego F. Hernandez, Amy Shuman, David M. Diamond, Sue Ann Girling, Kelly L. Sullivan, *et al*; 2014 (May); Accelerated Resolution Therapy for Treatment of Pain Secondary to Symptoms of Combat-Related Posttraumatic Stress Disorder; *European Journal of Psychotraumatology*; 5(1): 24066; https://doi.org/10.3402/ejpt.v5.24066; Accessed March 18, 2020

Klabunde, Megan, Carl F. Weems, Mira Raman, and Victor G. Carrion; 2017 (January); The Moderating Effects of Sex on Insula Subdivision Structure in Youth with Posttraumatic Stress Symptoms; *Depression and Anxiety*; 34(1): 51–58; https://doi.org/10.1002/da.22577; Accessed April 29, 2020

Knight, Andrew; 2011; Weighing the Costs and Benefits of Animal Experiments; *Eighth World Congress on Alternatives and Animal Use in the Life Sciences, Alternatives to Animal Experimentation, Proceedings*; 1(12): 289–294; http://www.altex.ch/resources/289294_Knight131.pdf; Accessed May 04, 2020

Koizumi, Ai, Kaoru Amano, Aurelio Cortese, Kazuhisa Shibata, Wako Yoshida, Ben Seymour, Mitsuo Kawato, and Hakwan Lau; 2017; Fear Reduction without Fear through Reinforcement of Neural Activity That Bypasses Conscious Exposure; *Nature Human Behaviour*; 1(1): 0006; https://doi.org/10.1038/s41562-016-0006; Accessed March 31, 2020

Landis, Story C., Susan G. Amara, Khusru Asadullah, Chris P. Austin, Robi Blumenstein, Eileen W. Bradley, Ronald G. Crystal, *et al*; 2012 (October); A Call for Transparent Reporting to Optimize the Predictive Value of Preclinical Research; *Nature*; 490(7419): 187–191; https://doi.org/10.1038/nature11556; Accessed May 01, 2020

Lazarou, Jason, Bruce H. Pomeranz and Paul N. Corey; 1998; Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies; *JAMA*; 279(15): 1200–1205; https://doi.org/10.1001/jama.279.15.1200; Accessed April 29, 2020

Le, Quang A. Doctor, Jason N., Zoellner, Lori A. and Feeny, Norah C.; 2014; Cost-effectiveness of prolonged exposure therapy versus pharmacotherapy and treatment choice in posttraumatic stress disorder (the optimizing PTSD treatment trial): A doubly randomized preference trial; *The Journal of Clinical Psychiatry*; 75(3); 222–230. https://doi.org/10.4088/JCP.13m08719; Accessed March 15, 2020

Lear, Jessica; 2012; Our Furry Friends: The History of Animal Domestication; *The Journal of Young Investigators;* https://www.jyi.org/2012-february/2017/9/17/our-furry-friends-the-history-of-animal-domestication; Accessed July 18, 2020

Lee, Christopher William, and Pim Cuijpers; 2013 (June); A Meta-Analysis of the Contribution of Eye Movements in Processing Emotional Memories; *Journal of Behavior Therapy and Experimental Psychiatry*; 44(2): 231–39; https://doi.org/10.1016/j.jbtep.2012.11.001; Accessed March 18, 2020

Lee, Daniel J., Schnitzlein, Carla W., Wolf, Jonathan P., Vythilingam, Meena, Rasmusson, Ann M. and Hoge, Charles W.; 2016 (April); Psychotherapy versus pharmacotherapy for Posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments; *Depression and Anxiety*; 33(9): 792–806; https://doi.org/10.1002/da.22511; Accessed March 10, 2020

Lisieski, Michael J., Andrew L. Eagle, Alana C. Conti, Israel Liberzon, and Shane A. Perrine; 2018 (May); Single-Prolonged Stress: A Review of

Two Decades of Progress in a Rodent Model of Post-Traumatic Stress Disorder; *Frontiers in Psychiatry*; 9(196): 1–22; https://doi.org/10.3389/fpsyt.2018.00196; Accessed April 23, 2020

Lobo, Isabela, Liana Cataarina Portugal, Ivan Figueira, Eliane Volchan, Isabel David, Mirtes Garcia Pereira and Letitia de Oliveira; 2015 (September); EEG correlates of the severity of posttraumatic stress symptoms: A systematic review of the dimensional PTSD literature; *Journal of Affective Disorders*; 183(1): 210–220; https://doi.org/10.1016/j.jad.2015.05.015; Accessed March 20, 2020

Logue, Mark W, Ananda B Amstadter, Dewleen G Baker, Laramie Duncan, Karestan C Koenen, Israel Liberzon, Mark W Miller, *et al*; 2015 (September); The Psychiatric Genomics Consortium Posttraumatic Stress Disorder Workgroup: Posttraumatic Stress Disorder Enters the Age of Large-Scale Genomic Collaboration; N*europsychopharmacology*; 40(10): 2287–2297; https://doi.org/10.1038/npp.2015.118; Accessed April 01, 2020

Macleod, Malcolm R., Aaron Lawson McLean, Aikaterini Kyriakopoulou, Stylianos Serghiou, Arno de Wilde, Nicki Sherratt, Theo Hirst, *et al*; 2015 (October); Risk of Bias in Reports of In Vivo Research: A Focus for Improvement; *PLOS Biology*; 13(10): e1002273; https://doi.org/10.1371/journal.pbio.1002273; Accessed May 01, 2020

Maier, Steven F and Martin E. P. Seligman; 1976; Learned Helplessness: Theory and Evidence; *Journal of Experimental Psychology: General*; 105(1): 3–46; https://doi.org/10.1037/0096-3445.105.1.3; Accessed April 17, 2020

Maples-Keller, Jessica L., Carly Yasinski, Nicole Manjin, and Barbara Olasov Rothbaum; 2017 (May); Virtual Reality-Enhanced Extinction of Phobias and Post-Traumatic Stress; *Neurotherapeutics*; 14: 554–563; https://doi.org/10.1007/s13311-017-0534-y; Accessed March 15, 2020

Marshall, Lindsay J., Christopher P. Austin, Warren Casey, Suzanne C. Fitzpatrick, and Catherine Willett; 2018 (November); Recommendations toward a Human Pathway-Based Approach to Disease Research; *Drug Discovery Today*; 23(11): 1824–1832; https://doi.org/10.1016/j.drudis.2018.05.038; Accessed April 01, 2020

Martin, Colleen E., Tran, Jana K. and Buser, Sam J.; 2017 (January); Correlates of suicidality in firefighter/EMS personnel; *Journal of*

*Affective Disorders*; 208: 177–183; https://doi.org/10.1016/j.jad.2016.08.078; Accessed March 08, 2020

McNerney, M. Windy, Tong Sheng, Jordan M. Nechvatal, Alex G. Lee, David M. Lyons, Salil Soman, Chun-Ping Liao, *et al*; 2018 (February); Integration of Neural and Epigenetic Contributions to Posttraumatic Stress Symptoms: The Role of Hippocampal Volume and Glucocorticoid Receptor Gene Methylation; *PLOS ONE*; 13(2): e0192222. https://doi.org/10.1371/journal.pone.0192222; Accessed March 31, 2020

Meijboom, Franck L. B., Elzbieta Kostrzewa and Cathalijn H. C. Leenaars; 2020 (January); Joining forces: the need to combine science and ethics to address problems of validity and translation in neuropsychiatry research using animal models; *Philosophy, Ethics, and Humanities in Medicine*; 15: 1; https://doi.org/10.1186/s13010-019-0085-4; Accessed May 13, 2020

Meyers, Andrew S; 2006 (August); *In Silico* Toxicology: Integration into Current FDA Policies and Procedures; *Biotechnology Law Report*; 25(4): 371–383; https://doi.org/10.1089/blr.2006.25.371; Accessed April 01, 2020

Meyers, Laura L., Thad Q. Strom, Jennie Leskela, Paul Thuras, Shannon M. Kehle-Forbes and Kyle T. Curry; 2013 (January); Service Utilization Following Participation in Cognitive Processing Therapy or Prolonged Exposure Therapy for Post-Traumatic Stress Disorder; Military Medicine; 178(1): 95–99; https://doi.org/10.7205/milmed-d-12-00302; Accessed May 05, 2020

Miller, Mark W., Erika J. Wolf, Naomi Sadeh, Mark Logue, Jeffrey M. Spielberg, Jasmeet P. Hayes, Emily Sperbeck, *et al*; 2015 (December); A Novel Locus in the Oxidative Stress-Related Gene ALOX12 Moderates the Association between PTSD and Thickness of the Prefrontal Cortex; *Psychoneuroendocrinology*; 62: 359–365; https://doi.org/10.1016/j.psyneuen.2015.09.003; Accessed March 31, 2020

Mims, Debra and Rhondda Waddell; 2019 (March); Animal Assisted Therapy and Trauma Survivors; *Acta Scientific Neurology*; 2(3): 14–18; https://actascientific.com/ASNE/pdf/ASNE-02-0026.pdf; Accessed March 26, 2020

Mueller, SG, Ng P, Neylan T, Mackin S, Wolkowitz O, Mellon S, Yan X, Flory J, Yehuda R, Marmar CR, Weiner MW; 2015; Evidence for disrupted gray matter structural connectivity in posttraumatic stress disorder*; Psychiatry Research*; 234(2): 194–201; https://doi.org/10.1016/j.pscychresns.2015.09.006, Accessed June 17, 2020

Musah, Samira, Nikolaos Dimitrakakis, Diogo M. Camacho, George M. Church, and Donald E. Ingber; 2018 (July); Directed Differentiation of Human Induced Pluripotent Stem Cells into Mature Kidney Podocytes and Establishment of a Glomerulus Chip; *Nature Protocols*; 13(7): 1662–1685; https://doi.org/10.1038/s41596-018-0007-8; Accessed April 01, 2020

National Institutes of Health: News Releases; Wednesday, November 19, 2014; *New comprehensive view of the mouse genome finds many similarities and striking differences with human genome*; https://www.nih.gov/news-events/news-releases/new-comprehensive-view-mouse-genome-finds-many-similarities-striking-differences-human-genome; Accessed April 28, 2020

National Institutes of Health: Research Portfolio Online Reporting Tools (RePORT); Funding; https://report.nih.gov/categorical_spending.aspx; Accessed April 23, 2020

National Institutes of Health: Research Portfolio Online Reporting Tools (RePORT); Project Information: Limbic-basal ganglia circuitry in PTSD, Grant Number 5R01MH099505-05; https://projectreporter.nih.gov/project_info_history.cfm?aid=9247846; Accessed June 16, 2020

National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals; 2011; *Guide for the Care and Use of Laboratory Animals. 8th edition*; Washington (DC): National Academies Press (US); doi: 10.17226/12910; https://www.ncbi.nlm.nih.gov/books/NBK54050/; Accessed April 21, 2020

Neylan, Thomas C., Christian Otte, Rachel Yehuda and Charles R. Marmar; 2006 (July); Neuroendocrine Regulation of Sleep Disturbances in PTSD; *Annals of the New York Academy of Sciences*; 1071(1): 203–215; https://doi.org/10.1196/annals.1364.015; Accessed March 30, 2020

Nguyen, Theresa, Michelle Hellebuyck, Madeline Halpern, and Danielle Fritze; 2018; *The State of Mental Health in America 2019*; Mental Health America; pdf: https://www.mhanational.org/sites/default/files/2018%20The%20State%20of%20MH%20in%20America%20-%20FINAL.pdf; Accessed March 02, 2020

Norrholm, Seth Davin, Tanja Jovanovic, Maryrose Gerardi, Kathryn G. Breazeale, Matthew Price, Michael Davis, Erica Duncan, *et al*; 2016 (July); Baseline Psychophysiological and Cortisol Reactivity as a Predictor of PTSD Treatment Outcome in Virtual Reality Exposure Therapy; *Behaviour Research and Therapy*; 82: 28–37. https://doi.org/10.1016/j.brat.2016.05.002; Accessed March 15, 2020

Novo Navarro, Patricia, Ramón Landin-Romero, Rocio Guardiola-Wanden-Berghe, Ana Moreno-Alcázar, Alicia Valiente-Gómez, Walter Lupo, Francisca García, Isabel Fernández, Víctor Pérez, and Benedikt L. Amann; 2018 (April); 25 años de Eye Movement Desensitization and Reprocessing: protocolo de aplicación, hipótesis de funcionamiento y revisión sistemática de su eficacia en el trastorno por estrés postraumático; *Revista de Psiquiatríay Salud Mental*; 11(2): 101–14. https://doi.org/10.1016/j.rpsm.2015.12.002; Accessed March 16, 2020

Oathes, Desmond J., Brian Patenaude, Alan F. Schatzberg, and Amit Etkin; 2015 (February); Neurobiological Signatures of Anxiety and Depression in Resting-State Functional Magnetic Resonance Imaging; *Biological Psychiatry*; 77(4): 385–393. https://doi.org/10.1016/j.biopsych.2014.08.006; Accessed March 30, 2020

Office of Suicide Prevention; 2016 (August); *Suicide Among Veterans and Other Americans 2001–2014*; U.S. Department of Veteran Affairs; https://www.mentalhealth.va.gov/docs/2016suicidedatareport.pdf; Accessed March 08, 2020

O'Haire, Marguerite, Noémie A.Guérin and Alison C. Kirkham; 2015 (August); Animal-Assisted Intervention for trauma: a systematic literature review; Frontiers in Psychology; 6: 1121–1134; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4528099/; Accessed March 26, 2020

Olson, Harry, Graham Betton, Denise Robinson, Karluss Thomas, Alastair Monro, Gerald Kolaja, Patrick Lilly, *et al*; 2000 (August); Concordance of the Toxicity of Pharmaceuticals in Humans and in

Animals; *Regulatory Toxicology and Pharmacology*; 32(1): 56–67; https://doi.org/10.1006/rtph.2000.1399; Accessed April 23, 2020

Ori, Rasmita, Taryn Amos, Hanna Bergman, Karla Soares-Weiser, Jonathan C Ipser, and Dan J Stein; 2015 (May); Augmentation of Cognitive and Behavioural Therapies (CBT) with d-Cycloserine for Anxiety and Related Disorders; *Cochrane Database of Systematic Reviews*; Issue 5; Article Number: CD007803; 113 pp; https://doi.org/10.1002/14651858.CD007803.pub2; Accessed April 29, 2020

Penn State; Animal Resource Program; Use of Electric Shock in Research Animals; https://www.research.psu.edu/arp/experimental-guidelines/rodent-behavioral-tests-1/use-of-electric-shock-in-research-animals.html; Accessed April 22, 2020

Pound, Pandora, Michael B. Bracken and Susan Dwight Bliss; 2014 (May); Is Animal Research Sufficiently Evidence Based to Be a Cornerstone of Biomedical Research?; *BMJ*; 348: g3387; https://doi.org/10.1136/bmj.g3387; Accessed May 05, 2020

Pound, Pandora, and Merel Ritskes-Hoitinga; 2018; Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail; *Journal of translational medicine*; 16(1):304; https://doi.org/10.1186/s12967-018-1678-1; Accessed July 25, 2020

Reichlin, Thomas S., Lucile Vogt, and Hanno Würbel; 2016 (December); The Researchers' View of Scientific Rigor—Survey on the Conduct and Reporting of *In Vivo* Research; *PLoS ONE;* 11(12): e0165999; https://doi.org/10.1371/journal.pone.0165999; Accessed April 09, 2020

Reisman, Miriam; 2016 (October); PTSD Treatment for Veterans: What's Working, What's New, and What's Next; *P&T: a peer-reviewed journal for formulary management*; 41(10): 623–634; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5047000/; Accessed May 04, 2020

Ribeiro, Marisa Rosimeire, Antonio Abílio MottaI, Luiz Augusto Marcondes-FonsecaI and Jorge Kalil-Filho; 2018 (February); Increase of 10% in the Rate of Adverse Drug Reactions for Each Drug Administered in Hospitalized Patients; *Clinics*; 73: e185; https://doi.org/10.6061/clinics/2018/e185; Accessed April 29, 2020

Richter-Levin, Gal, Oliver Stork and Mathias V. Schmidt; 2019 (August); Animal models of PTSD: a challenge to be met; *Molecular Psychiatry*; 24: 1135–1156; https://doi.org/10.1038/s41380-018-0272-5; Accessed April 30, 2020

Rodenburg, Roos, Anja Benjamin, Carlijn de Roos, Ann Marie Meijer, and Geert Jan Stams; 2009 (November); Efficacy of EMDR in Children: A Meta-Analysis; *Clinical Psychology Review*; 29(7): 599–606; https://doi.org/10.1016/j.cpr.2009.06.008; Accessed May 14, 2020

Ruward, Jeroen and Alfred Lange; Online Structured Writing Therapy for Post-traumatic Stress Disorder and Complicated Grief; In: Lindefors Nils and Gerhard Andersson (Eds.); 2016; *Guided Internet-Based Treatments in Psychiatry*; Springer International Publishing Switzerland; Chapter 7; pp 121–141; https://www.researchgate.net/publication/299506204_Online_Structured_Writing_Therapy_for_Post-traumatic_Stress_Disorder_and_Complicated_Grief; Accessed March 24, 2020

Sadeh, Naomi, Jeffrey M. Spielberg, Stacie L. Warren, Gregory A. Miller, and Wendy Heller; 2014 (November); Aberrant Neural Connectivity During Emotional Processing Associated With Posttraumatic Stress; *Clinical Psychological Science*; 2(6): 748–755. https://doi.org/10.1177/2167702614530113; Accessed March 18, 2020

Sadeh, Naomi, Jeffrey M. Spielberg, Mark W. Miller, William P. Milberg, David H. Salat, Melissa M. Amick, Catherine B. Fortier, and Regina E. McGlinchey; 2015 (August); Neurobiological Indicators of Disinhibition in Posttraumatic Stress Disorder: PTSD, Disinhibition, and Neurobiological; *Human Brain Mapping*; 36(8): 3076–3086; https://doi.org/10.1002/hbm.22829; Accessed March 30, 2020

Sareen, Jitender, Tanya Houlahan, Brian J. Cox and Gordon J. G. Asmundson; 2005 (July); Anxiety disorders associated with suicidal ideation and suicide attempts in the National Comorbidity Survey; *Journal of Nervous and Mental Disease*; 193(7): 450–454; https://doi.org/10.1097/01.nmd.0000168263.89652.6b; Accessed March 08, 2020

Saxe, Glenn N., Sisi Ma, Jiwen Ren, and Constantin Aliferis; 2017 (December); Machine Learning Methods to Predict Child Posttraumatic Stress: A Proof of Concept Study; *BMC Psychiatry*; 17(1): 223–235; https://doi.org/10.1186/s12888-017-1384-1; Accessed March 31, 2020

Schöner, Johanna, Andreas Heinz, Matthias Endres, Karen Gertz and Golo Kronenberg; 2017; Post-traumatic stress disorder and beyond: an overview of rodent stress models; *Journal of Cellular and Molecular Medicine*; 21(10): 2248–2256; https://onlinelibrary.wiley.com/doi/epdf/10.1111/jcmm.13161; Accessed April 20, 2020

Seifirad, Soroush and Vahid Haghpanah; 2019 (July); Inappropriate modeling of chronic and complex disorders: How to reconsider the approach in the context of predictive, preventive and personalized medicine, and translational medicine; *EPMA Journal*; 10: 195–209; https://doi.org/10.1007/s13167-019-00176-z; Accessed May 13, 2020

Shanks, Niall, Ray Greek, and Jean Greek; 2009; Are Animal Models Predictive for Humans?; *Philosophy, Ethics, and Humanities in Medicine*; 4(2): 1–20; https://doi.org/10.1186/1747-5341-4-2; Accessed April 23, 2020

Shapiro, Francine; 1989 (September); Eye Movement Desensitization: A New Treatment for Post-Traumatic Stress Disorder; *Journal of Behavior Therapy and Experimental Psychiatry*; 20(3): 211–17; https://www.sciencedirect.com/science/article/abs/pii/0005791689900256; Accessed March 16, 2020

Sheerin, Christina M, Mackenzie J Lind, Kaitlin E Bountress, Nicole R Nugent, and Ananda B Amstadter; 2017 (April); The Genetics and Epigenetics of PTSD: Overview, Recent Advances, and Future Directions; *Current Opinion in Psychology*; 14: 5–11. https://doi.org/10.1016/j.copsyc.2016.09.003; Accessed March 31, 2020

Shekhar, A., McCann U., Meaney M., Blanchard D., Davis M., Frey K., Liberzon I., *et al*; 2001; "Summary of a National Institute of Mental Health Workshop: Developing Animal Models of Anxiety Disorders; *Psychopharmacology*; 157(4): 327–339; https://doi.org/10.1007/s002130100859; Accessed April 22, 2020

Shively, Sharon Baughman, Iren Horkayne-Szakaly, Robert V Jones, James P Kelly, Regina C Armstrong and Daniel P Perl; 2016 (August); Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series; *Lancet Neurology*; 15(9): 944–953; https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(16)30057-6/fulltext; Accessed April 01, 2020

Spielberg, Jeffrey M., Regina E. McGlinchey, William P. Milberg, and David H. Salat; 2015 (August); Brain Network Disturbance Related to Posttraumatic Stress and Traumatic Brain Injury in Veterans; *Biological Psychiatry*; 78(3): 210–216; https://doi.org/10.1016/j.biopsych.2015.02.013; Accessed March 31, 2020

Stark, E.A., C.E. Parsons, T.J. Van Hartevelt, M. Charquero-Ballester, H. McManners, A. Ehlers, A. Stein, and M.L. Kringelbach; 2015 (September); Post-Traumatic Stress Influences the Brain Even in the Absence of Symptoms: A Systematic, Quantitative Meta-Analysis of Neuroimaging Studies; *Neuroscience & Biobehavioral Reviews*; 56: 207–221; https://doi.org/10.1016/j.neubiorev.2015.07.007; Accessed March 30, 2020

The BioIndustry Association and the Medicines Discovery Catapult; 2018 (January); State of the Discovery Nation 2018 and the Role of the Medicines Discovery Catapult; https://md.catapult.org.uk/resources/report-state-of-the-discovery-nation-2018/; Accessed May 05, 2020

The BioIndustry Association and the Medicines Discovery Catapult; 2019 (January); State of the Discovery Nation 2019; https://md.catapult.org.uk/resources/state-of-the-discovery-nation-2019/; Accessed May 05, 2020

Steimer, Thierry; 2011; Animal Models of Anxiety Disorders in Rats and Mice: Some Conceptual Issues; *Dialogues in Clinical Neuroscience*; 13(4): 495–506; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3263396/; Accessed April 30, 2020

Taghva, Alexander, Robert Silvetz, Alex Ring, Keun-young A. Kim, Kevin T. Murphy, Charles Y. Liu, and Yi Jin; 2015 (November); Magnetic Resonance Therapy Improves Clinical Phenotype and EEG Alpha Power in Posttraumatic Stress Disorder; *Trauma Monthly*; 20(4): e27360; doi: 10.5812/traumamon.27360; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4727473/; Accessed March 30, 2020

Uhl, E. W., and Warner, N. J.; (2015); Mouse Models as Predictors of Human Responses: Evolutionary Medicine; *Current pathobiology reports*; 3(3): 219–223. https://doi.org/10.1007/s40139-015-0086-y; Accessed June 18, 2020

U.S. Department of Health and Human Services: Food and Drug Administration; 2004 (March); Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products; https://www.who.int/intellectualproperty/documents/en/FDAproposals.pdf; Accessed April 23, 2020

VA Biorepository Brain Bank News: A Year in Review; Summer 2015; Issue 3; https://www.research.va.gov/programs/tissue_banking/VABBBNewsletter-3.pdf; Accessed April 01, 2020.

VA Biorepository Brain Bank News: A Year in Review; Spring 2019; Issue 6; https://www.research.va.gov/programs/tissue_banking/VABBBNewsletter-6.pdf; Accessed April 01, 2020

"VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder"; 2017; Department of Veterans Affairs, Department of Defense; https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal012418.pdf; Accessed March 15, 2020

van der Worp, H. Bart, Howells, David W. Howells, Emily S. Sena, Michelle J. Porritt, Sarah Rewell, Victoria O'Collins, and Malcom R. Mcleod; 2010 (March); Can animal models of disease reliably inform human studies?; *PLoS Medicine*; 7(3): e1000245; https://doi.org/10.1371/journal.pmed.1000245; Accessed July 16, 2020.

Velde, Beth P., Joseph Cipriani and Grace Fisher; 2005 (March); Resident and therapist views of animal-assisted therapy: Implications for occupational therapy practice; Australian Occupational Therapy Journal; 52(1): 43–50; https://doi.org/10.1111/j.1440-1630.2004.00442.x; Accessed March 26, 2020

Vogt, Lucile, Thomas S. Reichlin, Christina Nathues, and Hanno Würbel; 2016 (December); Authorization of Animal Experiments Is Based on Confidence Rather than Evidence of Scientific Rigor; *PLOS Biology*; 14(12): e2000598; 1–24 (pdf); https://doi.org/10.1371/journal.pbio.2000598; Accessed April 23, 2020

Wang, Chengzhong, Ramsey Najm, Qin Xu, Dah-eun Jeong, David Walker, Maureen E. Balestra, Seo Yeon Yoon, *et al*; 2018 (May); Gain of Toxic Apolipoprotein E4 Effects in Human iPSC-Derived Neurons Is Ameliorated by a Small-Molecule Structure Corrector; *Nature Medicine*;

24: 647–657; https://doi.org/10.1038/s41591-018-0004-z; Accessed April 01, 2020

Wellman, Laurie L., Patrick A. Forcelli, Brittany L. Aguilar, and Ludise Malkova; 2016 (August); Bidirectional Control of Social Behavior by Activity within Basolateral and Central Amygdala of Primates; *The Journal of Neuroscience*; 36(33): 8746–8756; https://doi.org/10.1523/JNEUROSCI.0333-16.2016; Accessed April 30, 2020

Whitaker, Annie M., Nicholas W. Gilpin, and Scott Edwards; 2014 (September); Animal Models of Post-Traumatic Stress Disorder and Recent Neurobiological Insights; *Behavioural Pharmacology*; 25(5–6): 398–409; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4163927/; Accessed April 20, 2020

Wolf, Erika J., Carole A. Lunney, and Paula P. Schnurr; 2016 (January); The Influence of the Dissociative Subtype of Posttraumatic Stress Disorder on Treatment Efficacy in Female Veterans and Active Duty Service Members; *Journal of Consulting and Clinical Psychology*; 84(1): 95–100; https://doi.org/10.1037/ccp0000036; Accessed April 29, 2020

Yanos, Philip T., Beth Vayshenker, Pavel Pleskach, and Kim T. Mueser; 2016 (July); Insight among People with Severe Mental Illness, Co-Occurring PTSD and Elevated Psychotic Symptoms: Correlates and Relationship to Treatment Participation; *Comprehensive Psychiatry*; 68: 172–177; https://doi.org/10.1016/j.comppsych.2016.04.016; Accessed March 25, 2020

Yehuda, Rachel, David Spiegel, Steven Southwick, Lori L. Davis, Thomas C. Neylan, and John H. Krystal; 2016 (December); What I Have Changed My Mind about and Why; *European Journal of Psychotraumatology*; 7(1): 33768; https://doi.org/10.3402/ejpt.v7.33768; Accessed May 04, 2020

Young, Keith A., Peter M. Thompson, Dianne A. Cruz, Douglas E. Williamson, and Lynn D. Selemon; 2015 (September); BA11 FKBP5 expression levels correlate with dendritic spine density in postmortem PTSD and controls; *Neurobiology of Stress*; 2: 67–72; https://doi.org/10.1016/j.ynstr.2015.07.002; Accessed April 01, 2020

Yue, Feng, Yong Cheng, Alessandra Breschi, Jeff Vierstra, Weisheng Wu, Tyrone Ryba, Richard Sandstrom *et al.*; 2014 (November); A comparative encyclopedia of DNA elements in the mouse genome;

*Nature*; 515(7527): 355–364; https://www.nature.com/articles/nature13992; Accessed June 24, 2020

Zhang, Lei, He Li, David Benedek, Xiaoxia Li and Robert Ursano; 2009; A strategy for the development of biomarker tests for PTSD; *Medical Hypotheses*; 73(3): 404–409; https://doi.org/10.1016/j.mehy.2009.02.038; Accessed March 31, 2020