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Animal models built for women's brain health: progress and potential

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Abstract

Women and men have different levels of risk for a variety of brain disorders. Despite this well-known epidemiological finding, preclinical work utilizing animal models has historically only included male animals. The policies of funders to require consideration of sex as a biological variable has shifted the momentum to include female animals in preclinical neuroscience and to report findings by sex. However, there are many biological questions related to brain health that go beyond sex differences and are indeed specific to women. Here, the focus is on why animal models should be utilized in the pursuit of understanding women's brain health, a brief overview of what they have provided thus far, and why they still hold tremendous promise. This review concludes with a set of suggestions for how to begin to pursue translational animal models in a way that facilitates rapid success and harnesses the most powerful aspects of animal models.

Background

Throughout the lifespan, women are at higher risk for diagnosis of or worse outcomes related to a variety of brain disorders and conditions, including mood disorders, traumatic brain injury, stroke, Alzheimer's disease, multiple sclerosis, and brain tumors (Broshek et al., 2005; Carter et al., 2012; Clayton, 2016; Kessler et al., 2005). Research to date has identified several factors that are linked to increased risk in women (Figure 1), including societal: increased trauma, caregiving responsibilities; periods of dynamic hormonal change: puberty, menstruation, pregnancy, postpartum, menopause/aging; and genetic: sex chromosome and epigenetic (T. Green et al., 2019; Hodes et al., 2017; Li and Graham, 2017; Miller and Cafasso, 1992; Yee and Schulz, 2000). Recent work has also shown that while some brain health issues such as substance abuse disorders are more common in men than in women, the gender gap is closing. For example, women appear to have an accelerated progression from the initiation of substance use to the onset of dependence, and they are likely to enter substance abuse treatment with more severe symptoms than men (Greenfield et al., 2010; Hernandez-Avila et al., 2004). In other disorders, such as autism spectrum disorder, there is increasing acknowledgment that women may be underdiagnosed due to differing phenotypes or the ability to enact behavioral coping to mask symptoms (R. M.

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Green et al., 2019; McFayden et al., 2020). This demonstrates that even brain health issues that have been classically thought of as more specific to men often have differing etiology, progression, and consequences for women.

While these data seem to speak for an obvious need of the inclusion of women in clinical studies and female animals in preclinical studies, it has taken policy measures to push scientists to consider such inclusion at large. Beginning in 2016, there was a formalized policy in place for the United States National Institute of Health (NIH) and the Canadian Institutes of Health Research (CIHR) that preclinical submissions were required to address sex as a biological variable (SABV). A recent five-year report on the success of SABV policy at NIH pointed out that there is still much work to be done in the uptake of the SABV policy despite many efforts on the part of funding agencies (Arnegard et al., 2020). While there were no numbers reported on overall effectiveness of the SABV policy at this juncture, a recent survey of study section members showed that only slightly more than half of members agreed that 1) SABV would improve rigor and reproducibility and 2) SABV was consistently factored into the reviewers' scoring (Woitowich and Woodruff, 2019). A recent analysis of sex bias and omission in neuroscience research showed that 52% of articles published in the last three years at top neuroscience journals reported using both males and females (Mamlouk et al., 2020).

Many of the myths of the 'peril' of including female subjects in preclinical research are expertly covered and debunked elsewhere (Shansky, 2019). Interestingly, two coexisting yet opposing ideas have often been used as justification for why females are not necessary or not useful. The first is that males are broadly representative of their species and that anything found in males would obviously also be true in females. Many studies in humans and non-human animals have shown that males and females differ in a variety of ways, including responses to drugs, the mechanisms underlying pain processing, and function of the immune system (Fish, 2008; Mogil, 2020; Soldin and Mattison, 2009). Another argument that has been made is that females are too complicated to study due to the presence of hormonal cycles. Systematic evaluation of this claim has shown that for a wide variety of behavioral, physiological, and molecular endpoints in mice and rats, there was no greater variability in outcomes in females compared to males (Becker et al., 2016; Prendergast et al., 2014).

The policy of the NIH and other funding agencies is immensely important, as the NIH mandated enrollment of women in human clinical trials in 1993 and other relevant policies have led to women accounting for roughly half of all participants in NIH-supported clinical research (Office of Research on Women's Health, 2019). While including women in clinical trials is important to understanding the impact of sex on brain disorders, it is also not the same as addressing questions that are specifically relevant to the experiences that are unique to women. For example, the impact of pregnancy and lactation on women's brain health is a specific area that requires more attention. It was only in late 2016 that the first human imaging study was published to show that the experience of pregnancy had effects on gray matter that lasted for at least 2 years post-pregnancy (Hoekzema et al., 2017). So, it may not be completely surprising that the study of female-specific research questions lags dramatically in preclinical and clinical neuroscience. An analysis of the last three years of publications in top neuroscience journals showed that only a small percentage of articles

report the sole use of female animals or humans (1.5% in humans, 3.7% in mice, and 6.5% in rats) (Mamlouk et al., 2020).

There are many useful commentaries and reviews on the way forward in clinical work (Carter et al., 2012; Scheyer et al., 2018; Taylor et al., 2019; Tuchman, 2010). Here, the focus is on why animal models should be utilized in the pursuit of understanding women's brain health, a brief overview of what they have provided thus far, and why they still hold tremendous promise. This review concludes with a set of suggestions for how to begin to pursue translational animal models in a way that facilitates rapid success and harnesses the most powerful aspects of animal models. Importantly, terminology usage is one of the difficulties that clinical and preclinical researchers face in communicating across the translational gap. Many specialized fields of research rely on shorthand terminology that can cause confusion when trying to compare to other fields. For the sake of simplicity and readability, the following defined words or phrases will be used throughout the remainder of this review. The term 'animals' will be used to refer to all non-human animals, with the acknowledgment that humans are also animals. Furthermore, the term 'women' assumes gender, which is different from sex in that refers to the socially constructed identity of an individual. Few clinical studies either collect or report on both the sex and gender or participants. Therefore, unless gender was specifically reported in a clinical study, human women will be referred to as females.

Why animal models?

Animal models have much to offer in the pursuit of understanding women's brain health. Work in non-human animals, whether with monkeys, dogs, rodents, flies, zebrafish, or the many other species used as model organisms, has produced a wide variety of benefits for all areas of brain health. There are many practical and biological reasons for using animal models. An important and inherent limitation of research on human subjects is the inability to perform experimental manipulations and collection of brain tissue. These ethical constraints are good and help preserve the dignity of human subjects who elect to participate. Here, though, animal models provide an opportunity to perform otherwise impossible experiments and gain access to many types of biological samples. Even ethical measurements, such as functional and anatomic brain scans, are both cost and time prohibitive. Animal models can help to point the way towards the potentially fruitful avenues of investigation in human studies.

Another limitation of clinical work is the general noise that enters all measures due to the inherent randomness of what humans experience on micro and macro scales. For example, when conducting an assessment of the stress axis by collecting salivary cortisol, there are innumerable factors that can alter both the starting point of the assay and how an individual responds to a stress challenge – was there a stressful commute there? Did someone yell at them on their way to the clinic? Are they experiencing some kind of chronic stress? In as much as these things can attempt to be captured and controlled for in such an experiment, nothing provides the level of controllability as animal models. The counterargument here may be that animal models do not come close to approximating the complexity of the human

experience. However, relevant complexity can easily be built into preclinical research, an idea that is expanded upon in later sections.

Animals also have a shorter life cycle than humans. In terms of lifespan approaches to research, which are certainly important to understanding women's brain health, animal models provide the opportunity to study individuals throughout their entire lifespan and potentially across several generations. This approach gives powerful data across many developmental stages, including the opportunity to collect biosamples at regularly timed intervals from the same individual. Additionally, the compounding of multiple life experiences throughout the lifespan can be observed and understood.

Animal models are also useful for biological reasons. There is deep homology in many body systems between humans and non-human animals. An important aspect of the increased use of animal models has been the conserved mechanisms of gene regulation across species. Whether a researcher has an interest in transcriptional machinery, chromosome regulation, or the regulatory impact of hormones on genetics, animal models provide important and relevant findings regarding the genetic and epigenetic regulation of the brain (Koster et al., 2015; Tschopp and Tabin, 2017). Humans and other animals also share very similar neural circuitry. As circuits, or the connections between certain brain regions that drive specific behavioral responses, are easily manipulated in animals via pharmacological, chemogenetic, and optogenetic methods, animals provide a way to gain mechanistic insight into hypotheses generated from human behavioral and imaging data (Ressler, 2020; Werner et al., 2019). While laboratory mice and rats are the most commonly used species for animal models in neuroscience, these biological similarities extend to nontraditional species as well (Keifer and Summers, 2016). Similar findings across many species greatly strengthens the inferences that can be drawn towards understanding humans, and the use of 'nontraditional' animal models should be embraced.

Progress in animal modeling for women's brain health

Though a small and relatively nascent field of neuroscience, progress has been made in the use of animal models for understanding the female brain beyond the concept of SABV. There are four developmental periods where the biological events or the timing of events in women is either vastly different from that of men or is specific to women: early brain development, puberty, pregnancy and postpartum, and aging. These are easily identified as periods during which there are drastic hormonal differences. While it is true that hormones play a large part in the impact of these life experiences on the female brain, other contributing factors are increasingly recognized as important in driving the long-term consequences of what happens during these developmental periods. This includes the female immune system, genetic state of the brain, and microbiome (Jašarević et al., 2016; Morrison et al., 2020b; Rainville et al., 2018). Below is a brief overview of some of the progress that has been made in these areas.

A developmental period that has been well investigated for sex differences is that of early brain development, which in commonly used laboratory rats and mice encompasses prenatal and early postnatal window. This is a critical period where exposure to gonadal hormones in

male fetuses masculinizes the male brain to respond differently to the later surge of hormones at puberty. Since the organizational-activational hypothesis was developed in 1959, much work has been done to determine the molecular signaling involved in early brain organization (McCarthy et al., 2017; Phoenix et al., 1959). These sex differences are relevant to women's brain health because they have been determined to be associated with the level of risk women may have for neurodevelopmental disorders (McCarthy, 2016). In addition to differences in exposure to hormones from the fetal gonads, male and female fetuses differ in the genetic makeup (XY vs XX) and function of the placenta (Nugent and Bale, 2015). Recent work has shown that sex differences in the genetic makeup of the placenta lead to different levels of key epigenetic regulators, which result in female fetuses demonstrating resilience to prenatal stress (Nugent et al., 2018).

Puberty was classically conceptualized as a developmental period when increased gonadal hormones serve to 'activate' pre-organized brain differences. In recent years, evidence has shown that puberty is a time of important brain organization as well (Schulz et al., 2009). Juvenile male hamsters fail to respond to the behavioral effects of exogenous hormone exposures, suggesting that the important organizational effects of puberty are required to make them responsive to adult levels of hormones (Romeo et al., 2001). Further, absence of testicular hormones during puberty in male hamsters rendered them unresponsive to adult levels of hormones, suggesting there was a critical window during puberty for hormone exposure to organize brain circuitry related to reproductive behaviors (Schulz et al., 2004). Beyond reproductive behavior, it has been demonstrated in both female humans and rats that there is significant cortical reorganization during puberty (Giedd et al., 2006; Juraska and Willing, 2017). In rats, the pubertal transition is marked by sex-specific changes to the structure of the prefrontal cortex, including neuronal loss and dendritic remodeling (Koss et al., 2014; Willing and Juraska, 2015). As Juraska and Willing point out in a recent review, the lack of studies that examine puberty onset itself as an experimental variable have made it difficult to study the consequences of pubertal timing, although current evidence points to a role for pubertal onset on later cognitive function (Juraska and Willing, 2017).

In human females, puberty has been investigated in the impact of pubertal timing on later life mental health concerns. Pubertal status, and particularly levels of estradiol, in girls has been associated with activation of reward cue processing brain regions, including the nucleus accumbens and medial prefrontal cortex, which may have important implications for future vulnerability to depression (Ladouceur et al., 2019). Evidence from animal models also suggests that puberty is a period of particular vulnerability to long-term programming of the brain by external insults (Holder and Blaustein, 2014). Pubertal manipulations can be combined with a lifespan approach to understand how experiences during this time period can influence later responses to stimuli in adulthood. In our own work, we generated a novel mouse model to examine the impact of adversity during the pubertal transition on later life stress responsiveness in both humans and mice (Morrison et al., 2020a, 2017). We found that not only does stress during puberty leave a lasting effect at the level of chromatin regulation in the brain, but that the negative consequences were uncovered in females only when they were pregnant or postpartum. Another recent study demonstrated that chronic stress during adolescence led to shifts in the mitochondrial function at the synapse in a sex-specific manner (Shaw et al., 2020). Together, these findings suggest that future work in animal

models relevant to female brain health could benefit from expansion out of the traditionally hormone-focused outcomes.

As females age, the majority will encounter the experience of pregnancy and postpartum. In neuroscience, many studies have just looked at the consequences of maternal exposures to stress, infection, or diet only on offspring, but mom is not simply a vessel for the next generation. Understanding the impact of pregnancy on mom's brain and biology is important as well. The impact of pregnancy and parity is not uniform across neurological conditions, and this differential role of pregnancy as a risk factor versus a protective factor has recently been reviewed in depth (Deems and Leuner, 2020). One of the considerations of pregnancy and postpartum, especially in the relatively short gestational periods of most laboratory animals, is that the milieu of hormones, immune cells, and microbiota change on a nearly daily basis during this dynamic period. Work in rats has demonstrated that microglia, important innate immune cells in the brain, go through changes in number and state within the brain in a region-specific manner during pregnancy and postpartum (Haim et al., 2017). These changes are functionally relevant in modulating the immune response during pregnancy and postpartum (Sherer et al., 2017). In the area of animal models of the impact of pregnancy and postpartum on mood disorders, there were early innovators such as Liisa Galea and colleagues, who developed the first animal model of postpartum depression (Brummelte et al., 2006). Their work and the work of others has illuminated the impact of parity on cognition, neuroplasticity, and immune signaling in the brain (Duarte-Guterman et al., 2019; Haim et al., 2014). Work by Jamie Maguire and colleagues has been critical in the advancement of a pharmacological treatment for postpartum depression (Maguire and Mody, 2008; Melón et al., 2018; Meltzer-Brody et al., 2018). Brexanolone, which is the synthetic analog of the endogenous steroid hormone allopregnanolone, is the first drug specifically for postpartum depression and has been hailed as a breakthrough not only in pharmacological treatments but also because the focus of drug development was specifically on women's mental health (Morrison et al., 2019). Interestingly, for some disorders, the hormonal changes of pregnancy and parity have been associated with a protective effect. For multiple sclerosis, higher parity has been associated with decreased risk of the first demyelinating event (Ponsonby et al., 2012).

Animal models have also been used to address women's brain health during menopause, or reproductive senescence. One of the challenges of aging research in animals is simply the cost associated with either purchasing aged animals, who would necessarily have had a life experience outside of the control of the researchers, or aging them within the lab, which can be cost- and space-prohibitive. A minireview covering both the strengths and weakness of animal models of reproductive senescence pointed out that a major translational gap existing for animal models of aging is between the surgical interventions experienced by women and those used in animal models (Diaz Brinton, 2012). Indeed, many animal models elect to ovariectomize young animals as a way to mimic reproductive senescence, when a more translationally relevant model would be to perform these surgical interventions in aged mice. Laboratory rat and mouse menopause models have also been reviewed in depth elsewhere, with the conclusion that while there are several areas where optimizations can be made to the preclinical work, animal models provide powerful insight into the impact of menopause on women's health (Koebele and Bimonte-Nelson, 2016).

Looking forward

The use of animal models is poised to provide important innovation in understanding women's brain health. Critical in that innovation is to utilize animal models to go beyond SABV to address questions that are relevant specifically for women. There are several ways in which animal models can be enhanced to improve translatability (Figure 2). These recommendations have in common the need to potentially expand a researcher's comfort zone in terms of collaborations, techniques, and theoretical approaches.

Collaboration

If the end goal of preclinical research is to inform clinical research and to make gains for women's brain health, the involvement and collaboration of clinicians is a critical component. Clinicians who work with the group of interest have tremendous insight into what these individuals experience and how any symptoms manifest. The best version of this type of collaboration will involve regular sharing of data. Consistent communication about findings in both humans and animals allows for more flexibility in the types of experiments that are planned and the interpretation of the findings. This type of collaboration can also help to avoid one of the common pitfalls of validating animal models, which is to do so based on how animals respond to pharmacological therapies that are already approved in humans (Sarter and Bruno, 2003; van der Staay et al., 2009). This practice is especially problematic when there are few pharmacotherapies or when those therapies are not highly effective in humans. Working directly with clinicians to better understand the discrete, translatable symptoms that are observed in their patient population can sidestep this problem. Animal experts can then leverage their knowledge of their study species to design analogous, relevant testing for that species. Together, this can lead to the discovery of novel mechanisms and therapeutics.

Translatable Outcomes

An approach that facilitates rapid translation of findings from bench to bedside and vice versa is the measurement of easily translatable outcomes. Measurement of outcomes that are more closely related, often due to similar regulation in animals and humans, requires less extrapolation on how preclinical and clinical findings map onto one another. This also helps to sidestep the serious criticism that has been levelled at the lack of validity in many of the 'standard' laboratory mouse and rat behavioral tasks for understanding human brain disorders, especially those related to mental health (Nestler and Hyman, 2010). This is not to suggest that behavioral tasks should not be used. Assessing the behavior of animals is critical for giving context to any biochemical or molecular findings. However, a single behavior or a highly contrived behavioral task can provide difficulty of interpretation and translation. Behaviors that are closer to what an animal might perform in the wild, or those that are more ethologically relevant, are ideal. This is not to suggest that an ethologically-relevant task necessarily makes for simple design or interpretation, as these behaviors are also context specific (Bredewold et al., 2014; De Lorme and Sisk, 2013). Here, too, it is important to consider the types of experiences females have and how they may have different behavioral expression of internal states compared to males. As male animals have been primarily used in neuroscience, the behavioral tasks were often designed and

interpreted based solely on male behavior. For example, fear conditioning is a widely used paradigm that examines the effectiveness of learning by quantifying the amount of freezing to a previously neutral stimulus. Classically, the greater the freezing during these tasks, the more intense the fear and effective the learning. However, it was recently found that female rats do not necessarily express fear by freezing, but instead by utilizing a more active fear response that has been termed ‘darting’ (Gruene et al., 2015).

Another highly translatable set of outcomes are those related to the autonomic nervous system (ANS), the function of which is conserved across species. To facilitate rapid translation between animal models and human studies, these outcomes are relatively easy to obtain, have a high degree of homology, and have been previously associated with more direct brain measures such as functional and anatomical imaging. For example, the measurement of the stress response, typically via evaluation of the hypothalamic-pituitary-adrenal (HPA) axis, is a rapid and reliable method to measure the acute stress hormone response to stimuli (McCormick et al., 2016). Assessment of HPA axis function is also relevant because disruption of this axis is a common endophenotype of a variety of neurological conditions, especially mood disorders (Watson and Mackin, 2006). Similarly, noradrenergic signaling represents an easily tractable system in animals, as it exerts effects related to alertness and arousal, which are easily measured in laboratory mice and rats (Bushnell and Strupp, 2009). The startle reflex and its modulation by external stimuli, such as a prepulse, is another output of the ANS that has been successfully used to rapidly translate animal models to clinical work (Fendt and Koch, 2013; Glover et al., 2011; Jovanovic et al., 2013). The bidirectional communication between the brain and the gut microbiome has also emerged as an important consideration for brain health that is dependent upon both age and exposure to external stimuli such as trauma (Jašarević et al., 2016).

Translational potential is also driven by direct comparisons of molecules and tissues from humans and animals. Thus, assaying easily accessible biofluids is a way to assess the validity of animal models that might have behavioral face validity. Fluids such as blood, saliva, and breastmilk can be relatively easily collected and repeated within the same individual. As molecular profiling capabilities of biofluids has improved, so too has the search for potential biomarkers of the state of the brain. Both our understanding of and the toolkit for assessing these fluids have become increasingly sophisticated, including more advanced measurement of proteins, extracellular vesicles, and nucleic acids. For example, the study of extracellular vesicles in biofluids for understanding brain health has expanded due in part to advancements in benchtop isolation methods (Roy et al., 2018). Another recent molecule of interest is circulating cell-free mitochondrial DNA, which is fragments of DNA from mitochondria that have been expelled from cells and freely float in blood. Increased ccf-mtDNA in blood has been observed in individuals with major depressive disorder and individuals who attempted suicide, while subjects who responded to SSRI treatment also had a decrease in ccf-mtDNA (Lindqvist et al., 2018, 2016). Important for considering measurements in the periphery, whether these molecules are merely indicators of the state of the brain or whether they are thought to have a mechanistic role in the brain, is that there have been associations of markers such as peripheral cytokines and brain function (Mehta et al., 2020).

Complexity of Models

One of the criticisms of animal models of brain health has been the lack of complexity in these models compared to the intricacy that underlies many brain health issues in humans, especially mental health (Neigh et al., 2013; Richter-Levin et al., 2019). Humans have a lifetime of experiences that compound in various ways. Animal models that shift towards increasing complexity of experiences, genetic backgrounds, and developmental periods are poised to provide powerful insight into the heterogeneity observed in women. Epidemiological and clinical literature can provide key information about both the factors that confer increased risk and those that confer resilience or protection. Among the complexity of experiences that should be considered include social interactions and social context. It is well established in humans that social support can provide resilience to the consequences of traumatic events, and this has also been demonstrated in animals (Kaufman et al., 2004; Morrison et al., 2016; Schulz et al., 2014; Wingo et al., 2010; Wrenn et al., 2011). Animals also experience important social development, the disruption of which has lasting neurobiological and behavioral consequences. For example, play behavior, which peaks around puberty, is an important social experience that facilitates adult cognitive and social skills in rats and mice (Papilloud et al., 2018; Schneider et al., 2016). Inclusion of factors such as prior social experience, current social structure or complexity, and environmental enrichment are key avenues for increasing complexity of animal models in a human-relevant manner. Some increases in complexity can be driven by the types of experiences that an animal receives in their environment, and others can be driven by molecular manipulations. For example, next generation sequencing results have broadly shown that mood disorders are likely the result of genetic alterations to many genes and that the candidate-gene approach cannot fully explain the genetic risk for neuropsychiatric disorders (Bray and O'Donovan, 2018). Candidate genes are appealing, especially in mouse studies, as the technology to robustly alter the expression of one gene in a tissue-specific manner is well-established. Newer CRISPR-based technology is showing promise for the ability to simultaneously manipulate a set of genes of interest, which may provide a more translationally-relevant manipulation, both as a proof of concept and as applied to a mouse model of cocaine response (Savell et al., 2020; Zhou et al., 2018).

Interdisciplinary Approaches

Finally, while the main focus here is women's brain health, the true health of the brain needs to be assessed in the larger context of the whole body. Neuroscientists are often lacking in a whole-body systems background, including important facets of biology such as the immune system and the microbiome. Many eschew even considering the roles of systems such as the endocrine and circadian systems as critical parts of animal experiments, which is often evident by the random timing of behavioral testing within the light/dark cycle. Establishing an interdisciplinary team where subject matter experts can provide nuance will facilitate progress on the use of animal models. For example, the role of the microbiome in human health is becoming more widely appreciated (Young, 2017). The microbiome is also easily sampled and manipulated in humans, making it a readily tractable translational outcome. However, participation in this type of work should involve microbiologists and others who specialize in understanding the microbiome. The same could be said for the rapidly increasing use of next generation sequencing to understand the brain. While many

sequencing approaches have become fairly easy to use ‘out of the box’, the best version of incorporating these techniques involves collaboration with expert molecular biologists and bioinformaticians. Together, an interdisciplinary team of experts can make greater leaps in our understanding than we could hope to accomplish alone.

The type of interdisciplinary work and collaborations that lead to the best chance of success in translation are not likely to flourish without direct grant funding. The ability to spend time on any research is ultimately driven by resources, and scientists and clinicians are more likely to be able to participate in these types of collaborative endeavors when they have the resources to prioritize the work. A successful example is the National Institutes of Health Office of Research on Women’s Health program to fund multi-investigator Specialized Centers of Research Excellence (SCORE) on Sex Differences. In an effort to make more progress in stemming the opioid health crisis, the NIH has recently established the Helping to End Addiction Long-term (HEAL) Initiative, which funds both preclinical and clinical work. Both of these examples are trans-agency initiatives that allow for the marshalling of significant expertise and financial resources to facilitate interdisciplinary bench-to-bedside science.

Conclusion

A significant goal of the medical and biomedical communities is to have precision or personalized medicine. For women, this goal will not be realized until both clinical and preclinical research consider research questions that are specific to women’s brain health. Animal models hold tremendous promise in unlocking the mechanisms underlying these clinical disorders, although to date there has been little focus on using female animals to address issues specific to women. True breakthroughs in the area of animal models for women’s brain health will take effort from all stakeholders: preclinical researchers need to be willing to expand the types of questions they ask, clinicians need to be willing to work with basic researchers to develop these models, and funding agencies need to be willing to fund larger grant mechanisms to support these collaborations.

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Figure 1. Risk factors for brain disorders that are specific to women.

Women have unique biological and experiential factors that alter their risk for negative outcomes in brain health. These include dynamic periods of hormonal change, such as puberty and ensuing menstruation, pregnancy and postpartum, and menopause, sex chromosome and epigenetic, and societal considerations, such as increased risk for trauma and increased burden of caregiving stress. These factors can have both individual and interacting effects on the brain that will depend on the developmental period during which they occur.

Figure 2. Approaches to maximize translational potential of animal models.

Animal models have tremendous promise for illuminating women's neurological conditions. There are several approaches that can be taken alone or in combination that can take full advantage of this promise. Collaboration and communication with clinicians is a way to rapidly translate findings from the bench to the bedside in an iterative manner, refining both clinical and preclinical work more rapidly. Another approach that will increase the speed of translation is the measurement of outcomes that are as closely matched as possible, including female-relevant behavioral tasks, autonomic nervous system outcomes, and assessment of easily accessed biofluids. As women have complex life experiences that interact and compound to dictate future outcomes, the translation of animal models would benefit from increased complexity. This includes taking a lifespan approach and examining how multiple life experiences interact to produce risk or resilience for brain health issues. Finally, an interdisciplinary approach can also increase translational potential. Including experts outside of the neurosciences, including those with expertise in the microbiome, circadian biology, imaging technology, next generation sequencing, and mitochondrial, and taking a whole body systems approach to brain health can enhance the meaningfulness of findings from any one animal model.