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ADVANCES IN NEURODEGENERATIVE AND PSYCHIATRIC IMAGING SPECIAL FEATURE: REVIEW ARTICLE

Preclinical neuroimaging of gene–environment interactions in psychiatric disease

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ABSTRACT:

Psychiatric disease is one of the leading causes of disability worldwide. Despite the global burden and need for accurate diagnosis and treatment of mental illness, psychiatric diagnosis remains largely based on patient-reported symptoms, allowing for immense symptomatic heterogeneity within a single disease. In renewed efforts towards improved diagnostic specificity and subsequent evaluation of treatment response, a greater understanding of the underlying of the neuropathology and neurobiology of neuropsychiatric disease is needed. However, dissecting these mechanisms of neuropsychiatric illness in clinical populations are problematic with numerous experimental hurdles limiting hypothesis-driven studies including genetic confounds, variable life experiences, different environmental exposures, therapeutic histories, as well as the inability to investigate deeper molecular changes *in vivo* . Preclinical models, where many of these confounding factors can be controlled, can serve as a crucial experimental bridge for studying the neurobiological origins of mental illness. Furthermore, although behavioral studies and molecular studies are relatively common in these model systems, focused neuroimaging studies are very rare and represent an opportunity to link the molecular changes in psychiatric illness with advanced quantitative neuroimaging studies. In this review, we present an overview of well-validated genetic and environmental models of psychiatric illness, discuss gene–environment interactions, and examine the potential role of neuroimaging towards understanding genetic, environmental, and gene-environmental contributions to psychiatric illness.

Mental illness affects more than 450 million people worldwide[1] and nearly one in five adults in the United States.[2] With neuropsychiatric disorders now among the leading causes of worldwide disability,[1] there is renewed interest and urgency towards understanding how and why these diseases occur. Advances in neuroimaging, translational neuroscience, and emerging genetic, genomic, and molecular techniques have opened new avenues towards a greater understanding of the biological underpinnings of neuropsychiatric illness and new opportunities for improved diagnosis, therapeutics, and treatment monitoring. While still poorly understood, the neuropathogenesis of psychiatric disorders is thought to arise from the complex interplay of genotype and environment[3,4] that ultimately leads to changes in brain function.[5] The intricate relationship between genotype and environmental factors is thought to contribute to the marked heterogeneity and wide-spectrum of psychiatric disease presentation and treatment response that is observed clinically.[6] Dissecting the underlying biology and the genetic, environmental, and gene–environment contributions to psychiatric illness are challenging in human-only studies. Leveraging state-of-the-art genetic, genomic, and translational preclinical models of psychiatric illness affords unique opportunities to explore the neurobiology of mental illness, and to discover and test new hypotheses and treatment paradigms as we translate these discoveries and innovations at the bench to the bedside. Despite a wide array of available preclinical models, there is a conspicuous absence in the use of neuroimaging in these models to link findings across animals and subjects, thereby limiting the potential for translation of preclinical data. In this review, we aim to provide an overview of the existing genetic and environmental preclinical models of psychiatric illness (Table 1), discuss gene–environment interactions revealed by studies in these models, and finally stress the importance of utilizing neuroimaging in synthesizing the genetic, environmental, and gene-environmental contributions in neuropsychiatric disease.

Table 1. Summary of genetic, environmental, combined models, and other studies presented within.

	Disease	Gene/ Paradigm	Behavioral symptoms	Neuroimaging phenotypes
Genetic models	Autism spectrum disorder	*FMR1*	Impaired cognition Locomotor hyperactivity Stereotypy Decreased anxiety Seizures	↑ Relative WM volume[7] ↑ Anatomic connectivity in V1[8] ↓ Anatomic connectivity of V1 with other neocortical regions[8] ↓ FA in corpus callosum[8] Functional decoupling[8] Changes in median effect size[9]
	Schizophrenia	*DISC1*	Hyperactivity Impaired pre-pulse inhibition	↑ Lateral ventricle volume[10]
Environmental models	Depression	Forced swim test Tail suspension test	Decreased latency to immobility	
		Learned helplessness	Anhedonia Weight loss Altered sleep pattern	
		Chronic mild stress	Anhedonia Decreased motivation, Decreased grooming Altered sleep pattern	Left-right asymmetrical and lateralized changes in glucose metabolism[11] ↓ MK and RK[12] ↑ metabolite:total creatine[12] ↑MD ↓FA ↑RD[13]
		Early-life stress	Impaired memory Increased anxiety Anhedonia Impaired social behaviors Learning deficits	↑ CBV, dmPFC, dACC volume[14] ↓ vmPFC, OFC WM volume[15] ↑AMYG-PFC and AMYG-HPC connectivity[16]
	PTSD	Single prolonged stress	Abnormal fear learning Hyperarousal Cognitive dysfunction	↓AMYG-mPFC connectivity[17]
Gene + environment models	Schizophrenia	*DISC1* +lead exposure	Changes in activity levels (sex-dependent) Impaired pre-pulse inhibition	↑ Lateral ventricle volume[18]

AMYG, amygdala; CBV, cerebellar vermis; FA, fractional anisotropy; HPC, hippocampus; MD, mean diffusivity; MK, mean kurtosis; OFC, orbitofrontal cortex; PTSD, post-traumatic stress disorder; RD, radial diffusivity; RK, radial kurtosis; V1, primary visual cortex; WM, white matter; dACC, dorsal santerior cingulate cortex; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

GENETIC MODELS OF NEURODEVELOPMENTAL AND PSYCHIATRIC ILLNESS

Genetic animal models of neuropsychiatric disorders harbor great potential for elucidating the pathophysiology and neurobiological basis of disease and for developing more efficacious pharmacologic interventions. With the introduction of numerous gene-editing technologies now allowing for the facile manipulation of genomes of not only mice but those of the rat, swine, and non-human primates, the generation and subsequent evaluation of genetic models of psychiatric and neurodevelopmental illness has never been more accessible. Researchers are now able to rapidly dissect and evaluate the role of genes on neurodevelopmental trajectories, brain microstructure, and brain function. The generation of these genetic models are largely informed by genomewide association studies (GWAS) completed in disorders such as autism spectrum disorder (ASD), which have identified numerous candidate gene-susceptibility factors as contributors to the overall disease state.[19] These include epigenetic and transcriptional regulators such as *Mecp2* (methyl CpG binding protein 2),[20] post-transcriptional protein modifiers and regulators such as *Fmr1* (Fragile X Syndrome),[7,8,21] *Tsc1/Tsc2* (tuberous sclerosis complex),[22] *Ube3a* (Angelman syndrome and non-syndromic ASDs),[23,24] *Pten* (Phosphatase and tensin homolog hamartoma tumor syndromes and non-syndromic ASDs),[25,26] synaptic organizing and scaffolding proteins such as Shanks, neurexins (*Nrxn*), and neuroligins (*Nlgn3, Nlgn4*).[27–29] While these analyses have not established any definitive causal genetic sequence variant for ASD, these mutations, which result in partial or total loss of function, have been consistently reported in individuals with ASD and serve as an experimental platform to investigate the neuropathogenesis of ASD. The generation of these preclinical models complement ongoing clinical research studies. Especially within neuroimaging, these models allow researchers to investigate the specific impact these genes can impart on morphometry, quantitative neural

microstructure, and brain function, absent potential confounding environmental factors. Though rare, these efforts critically complement and dovetail with clinical studies comparing functional and structural imaging data from patients with mental disorders and can pioneer and lead the validation of imaging biomarkers for diagnosis and evaluation of subsequent treatment response.[30,31]

ASD is one area of research where imaging studies in both clinical patients and preclinical genetic models of disease have revealed neural correlates that result from heritable disease factors. Disorders such as Fragile X Syndrome (FXS), which lie on the autism spectrum, is the most common form of inherited intellectual disability and results from a triple nucleotide CGG repeat expansion located in the 5'-UTR (untranslated region) of the *FMR1* gene with subsequent gene silencing.[32] Post-mortem stereology in male, adult patients with FXS have found that these males have a significantly increased volume in the caudate nucleus, parietal lobes and right brainstem, but decreased volume in the left frontal lobe compared to controls. Voxel-based morphometry analysis in the same study demonstrated specific regional differences in gray and white matter volumes when compared to neurotypical controls.[33] Furthermore, structural and functional MRI (fMRI) techniques have also identified changes in the brains of fragile X permutation carriers, who are at risk for fragile X-associated tremor/ataxia syndrome with these imaging findings now being used to non-invasively diagnose this disease.[34] Recent work by Lai et al has also shown that *FMR1* knockout mice bred in the FVB strain of mice show structural and volumetric changes in areas associated with frontostriatal circuitry that correlates to the human neuroimaging phenotype.[7] Another study that combined *in-vivo* ultra-high field diffusion tensor MRI, fMRI and viral tracing demonstrated a local over connectivity for the primary visual cortex, but low connectivity of other regions, along with defects in the structural integrity of the subcortical white matter in the forebrain. These defects could contribute to the functional decoupling across neocortical regions and more research in these mice may promote more understanding of sensory processing deficiencies and reduced functional connectivity in neocortical areas in FXS and ASD.[8]

Many other preclinical models of ASD exist and an MRI study that evaluated the neuroanatomical differences of mice across 26 different genetic and behavioral models of ASD found heterogenous, but distinct volumetric changes in the parietotemporal lobe, cerebellar cortex, frontal lobe, hypothalamus and the striatum. Clustering these 26 different mouse lines by median effect size difference in each anatomic structure between the different mouse models and their specific controls identified three large clusters, which differed in both volume difference as well as localization. Two of these circuits were linked to the under- and overconnectivity seen in ASD. While they were not able to show a single neuroanatomical pattern of autism, there was also no distinct pattern in any of the 26 models studied, which is reflected in the phenotypic heterogeneity of the human autism population. This study suggested that clustering may be important to increase diagnostic specificity and eventually help predict in treatment responses that can both guide and inform large cohort imaging studies of ASD.[9]

Another neuropsychiatric illness where neuroimaging and preclinical genetic models of disease may complement each other is schizophrenia. Schizophrenia is also recognized as a highly heritable illness with several scaffolding genes such as disrupted in schizophrenia 1 (*DISC1*)[35,36] and microtubule-associated protein 6 (MAP6)[37] implicated in the neuropathogenesis of disease. Researchers have found that patients diagnosed with schizophrenia have significantly reduced cortical thickness in comparison to age and sex-matched controls, which coincide with the reduction in cortical thickness seen in individuals who were carriers for the *DISC1* translocation.[38] These results suggest that the *DISC1* translocation may increase the risk of psychiatric disorders by affecting neurostructural phenotypes, such as cortical thickness. Another MRI study has demonstrated that patients who are *DISC1/TRAX* (translin-associated factor X) haplotypes are significantly over-represented among schizophrenic patients and have reduced gray matter density in the prefrontal cortex and display an association with reduced hippocampal volumes.[39] Several diffusion MRI studies have also shown a significant decrease in fractional anisotropy in multiple white matter fiber bundles relative to healthy controls, indicating abnormal white matter microstructural organization.[40–42] Recent longitudinal studies have uncovered the temporal changes in white matter microstructure that occur in schizophrenia, demonstrating that individuals experiencing their first psychotic episode harbor normal white matter microstructure in the corpus callosum relative to healthy controls,[43] but later demonstrate significantly reduced fractional anisotropy compared to controls.[44,45] Additionally, fMRI studies have been instrumental in elucidating what we currently know about neural bases of dysfunction in schizophrenia. Working memory impairment has been linked to disturbances in the dorsolateral prefrontal cortex[46] and facial emotion processing deficits have been associated with limbic abnormalities.[47] However, it is hypothesized that cognitive deficits result from diminished integration of local and global neural circuits, rather than singular deficits in specific areas.[48–50]

While neuroimaging studies in human patients have increased our understanding of the structural and functional consequences of schizophrenia, evaluating the role of these genes in preclinical models would provide new insights to explore the genetic contribution to the overall disease process in a more direct and controlled manner absent the numerous confounding factors that mitigate clinical neuroimaging trials.[51] To date, there is a paucity of neuroimaging studies conducted on existing genetic models of schizophrenia. In one of the only preclinical imaging studies conducted in relation to schizophrenia, Hikida et al conducted an MRI study on dominant-negative *DISC1* transgenic mice and showed that they displayed schizophrenia-associated phenotypes, including asymmetrically enlarged lateral ventricles and interneuron deficits that may contribute to cortical asynchrony, which translated to structural changes seen in human patients.[10] Although numerous other genetic models of schizophrenia exist, a detailed morphometric and microstructural evaluation of brain structure have not been undertaken in these models, greatly limiting the potential of these animal studies to serve as better tools for understanding the biological underpinnings of human

disease. The absence of data and active investigation in this realm presents a unique opportunity to explore the role of salient genes implicated in schizophrenia, their impact of neural structure and organization, and preclinical opportunities to assess and evaluate pharmacologic and environmental interventions and their commensurate impact on neural structure.

Environmental models of psychiatric illness

In addition to genetic factors, many studies have shown how environmental influences play an important role in the development of psychopathology in humans.[52–58] However, these studies are limited by the presence of confounding factors, including different genetics, treatment, upbringing, socioeconomic status, difference in nature of stress experienced, geographic location, and culture, as well as the inability to further manipulate the experiment or dissect the results. Thus, studies using environmental models are important because they can control for the many confounds inherent in human studies and allow deeper probing of the intrinsic molecular mechanisms at play. A wide array of preclinical environmental models for psychiatric disorders exist and have been crucial in gaining more understanding about the molecular changes and processes that underlie atypical behavior, as well as serving as a platform for testing the efficacy of potential therapeutics. Despite the large amount of research conducted in these preclinical environmental models, neuroimaging studies in these animals are very rare. Neuroimaging studies in preclinical models can provide valuable information that helps pinpoint mechanisms of disease by shedding light on changes in neural circuitry and connectivity associated with atypical behavior, as well as potentially identify neuroimaging biomarkers that aid in early detection of at-risk individuals. In this section, we discuss key studies conducted in environmental models of depression, at-risk populations, and post-traumatic stress disorder (PTSD) and relay the current research on how certain environmental factors can influence psychiatric illness as well as highlight potential opportunities for neuroimaging research within this field.

Depression is a mental illness that can be reliably modeled with environmental simulations. There are a number of different experimental paradigms that have been shown to induce depression-like symptoms in animals including models of acute stress,[59–61] and chronic stress.[14,62–64] In acute stress models, tests such as the forced swim test or the tail suspension test cause animals to struggle as they are placed in a situation or position that they perceive as threatening.[60] These animals eventually cease struggling and the immobility displayed is interpreted as an expression of behavioral despair or entrapment[65] with decreased latency to immobility as a proxy of increased depressive behavior. Learned helplessness models apply a chronic, uncontrollable, and inescapable stress, such as electric foot shock, until even when provided with an easy escape route, animals will be slow or fail to escape altogether.[59] Other sequelae of these inescapable shock sessions include weight loss, altered sleep patterns and hypothalamic–pituitary–adrenal axis activity, and loss of dendritic spine synapses in the hippocampal regions.[61,66] Although these models have been key in evaluating phenotypes of transgenic models of psychiatric disease, as well as the efficacy of potential pharmacologic interventions, there are very few neuroimaging studies conducted on models of acute stress.

Imaging studies in models of chronic stress are more readily available but remain relatively rare. In contrast to models of acute stress, chronic stress models are more nuanced and thought to better recapitulate stressors that are more translatable to clinical populations. A well-established model of chronic stress is chronic mild stress (CMS) in which animals are continuously exposed to a variety of mild stressors, such as periods of food or water deprivation, small changes in temperature, changing cage mates, etc. over a prolonged period of time, ranging from 1 to 7 weeks.[62] These animals display a variety of anhedonic behaviors, including decreased sucrose intake,[67] food intake[68] and decreased male sexual behavior.[69] Other tests also reported other depression-related behaviors such as decreased motivation, reduced self-care and changes in sleep patterns via increased immobility in the forced swim test,[70] decreased grooming[71] and decrease in REM sleep latency.[72,73] A study using positron emission tomography has shown that CMS activated the left auditory cortex, while deactivating the left piriform cortex, left inferior colliculus, septal nuclei and periaqueductal gray, while no significant changes in the glucose metabolism of the hippocampi or amygdala were seen.[11] However, a 2011 study using diffusion kurtosis imaging was able to detect substructural changes in the hippocampi of both anhedonic and resilient animals following exposure to CMS with MRI, with resilient animals showing significant inward or outward displacement of the hippocampal tips compared to anhedonic and control animals. Furthermore, MR spectroscopy was able to differentiate between the anhedonic and resilient animals via significantly increased glutamate to total creatine ratios.[12] Finally, a diffusion tensor imaging study showed signs of demyelination in various brain regions like the frontal cortex, hippocampus, hypothalamus, thalamus, corpus callosum and sensory motor cortex, suggesting that disrupted connectivity between the prefrontal cortex and the limbic area plays an important role in the development of anhedonic behaviors.[13]

Another important model of chronic stress is early-life stress (ELS). In contrast to other chronic stress models, ELS models focus less on immediate disease generation and instead focus on recapitulating early life experiences that have been implicated in mental health outcomes later in life. It is well established that consistent maternal care contributes to normal development of the stress response whereas deficient or abnormal care has been linked to human affective disorders.[74–77] There are multiple ELS models that aim to recapitulate the hallmarks of abnormal maternal care or fragmented or erratic behavior.[78] ELS has most commonly been modeled by maternal separation with numerous examples demonstrating subsequent behavioral, molecular, and microstructural changes in the brain with ELS. These include studies of rhesus monkeys that were raised with their mothers with another group of age-matched monkeys who were raised only with their peers. Anatomical images acquired from the juvenile monkeys showed an enlarged vermis, dorsomedial prefrontal, and dorsal anterior cingulate cortex in peer-raised monkeys when compared to maternal-rated monkeys.

These findings suggest that peer-raising during infancy can induce hypertrophy of stress-sensitive regions in the brain, which may be a structural phenotype for humans at increased risk of neuropsychiatric disorders.[14] A study examining a rodent model of parental separation reflected similar neural changes in the amygdala and behavioral patterns of children adopted from orphanages abroad. The neural changes persisted until adulthood, highlighting how early-life stress can lead to altered brain circuitry and increase risk for psychopathology down the line.[64] Recent work has also found that maternal separation is associated with volumetric reduction of the prefrontal cortex and the orbitofrontal cortex, with decreases in white matter volume within these regions. Interestingly, treatment with mifepristone, a glucocorticoid receptor blocker known to mitigate behavioral changes found with the model, did not alter the lasting volumetric and structural changes within the brain further suggesting that these are durable imprinted changes in brain structure.[15]

A more sophisticated model of ELS is limited bedding (LB), where dams and her pups are housed with minimal bedding for a short period of time following birth.[63,79] The key finding in the work done by Ivy et al is that limited access to nesting materials chronically stressed rat dams and resulted in them leaving their pups alone more frequently and decreased nurturing behaviors like grooming. The LB dams showed more anxiety-like behavior in certain behavioral tests and had elevated morning plasma corticosterone accompanied with a reduction in corticotropin releasing hormone mRNAs. This fragmented maternal care is transmitted onto her pups with a study demonstrating that these pups later developed severely impaired memory with compromised long-term potentiation, which is critical for encoding memory. These defects were selective to the CA1 and CA3 regions of the hippocampus and were also accompanied by abnormal dendritic morphology.[80] Subsequent work was able to demonstrate rescue of memory impairment and long-term potentiation effects with corticotropin releasing hormone receptor antagonists if they were administered following the stress period.[81] Additional work has also demonstrated a wide range of longlasting emotional and cognitive outcomes, including increased anxiety, anhedonia, impaired social behaviors, and learning deficits[82] including recent work comparing behavior and neural connectivity between an unpredictable maternal separation stress paradigm with the LB paradigm. In this study, researchers found that only maternal separation created an increase in anxiety-like behavior in juvenile and adult mice. Resting state fMRI was then used to compare frontolimbic connectivity in the maternal separation mice versus controls, and the ELS mice were found to have amygdala hyperconnectivity to the prefrontal cortex and hippocampus, which was highly correlated with anxiety-like behavior.[16] Altogether, these studies show that "acquired" contributing factors in life can fundamentally alter neuronal circuits within the brain that can result in higher susceptibility to psychiatric illness.

Other environmental paradigms of stress include models of PTSD that are commonly modeled with single-prolonged stress (SPS). SPS introduces a single type of stress or sequential stress events in one long session.[83–85] This produces a wide array of abnormal behaviors that reflect behavior patterns in human PTSD patients, including abnormal fear learning, as demonstrated with defensive reactions and avoidance of trauma cues including restraint apparatuses, swim tanks, holding chambers, as well as any tones or scents related to the SPS,[84,86] hyperarousal,[86] and cognitive dysfunction.[87–89] Only one imaging study has been reported on this preclinical model, but they found that intrinsic functional connectivity within the amygdala–prefrontal cortex circuit was compromised 7 days following the traumatic event, which correlates with the usual timing of abnormal behavior onset.[17] A particularly interesting aspect of this study was the usage of resting-state fMRI in awake rats, which allows long-term ongoing evaluation of these animals and a new opportunity in examining stress-related mental disorders beyond static structural neuroanatomy. Furthermore, as only a subset of individuals exposed to trauma develops PTSD, SPS models can be used to model pre-existing or post-trauma factors to identify protective and deleterious contributors, as well as predict enduring behavioral effects of traumatic stress.

Gene–environment interactions of neuropsychiatric illness

Despite a wide array of reports available describing both genetic and environmental influences in the development of neuropsychiatric illness, we remain far removed from a fundamental understanding of how genetic background and subsequent environmental exposures ultimately influence neuropsychiatric illness through effects on brain structure and function. While we have begun to tentatively explore this topic in clinical populations with a number of studies finding certain genotypes more susceptible to psychiatric illness following environmental changes,[90–93] there remain too many confounding factors to truly ascertain the connections and mechanisms underlying the mechanism of these presumed gene–environment interactions. Therefore, a closer examination marrying genetic models of psychiatric disease with environmental paradigms must be conducted, especially using neuroimaging techniques, as clinical studies have shown that development of psychiatric disease is accompanied by concomitant changes in neural structure.

With many preclinical models of schizophrenia now available[94,95] and with many well-described environmental paradigms of CMS and ELS that share face validity with clinical exposures known to be associated with schizophrenia, the field is primed for a detailed examination and exploration of how gene–environment interactions impact measures of neural morphometry and microstructure and later, how interventions (both behavioral and pharmacologic) an blunt and/or rescue these interactions. Other clinical studies have suggested an association between environmental toxins such as air pollution[96,97] and lead exposure,[98] and the increased likelihood of schizophrenia later in life and preclinical models would represent a natural opportunity to more closely explore these described associations. In particular, as lead is a known potent N-methyl-D-aspartate receptor (NMDAR) antagonist, and hypoactivity of the NMDAR is currently though to play an important role in the pathophysiology of schizophrenia, preclinical studies examining how environmental exposures, such as those to lead, and how lead can impact differentially

impact animals with different genetic backgrounds and genetic susceptibilities would also represent another novel avenue of investigation. These lines of inquiry are already underway with groups examining the interaction between lead exposure and a DISC1 mutation by feeding DISC1 mutant mice and controls lead-laced diets. Although there were no gross developmental abnormalities, chronic lead exposure produced gene and sex-dependent hyperactivity, where lead exposure caused decreased activity in male controls, but increased activity in male DISC1 animals, and increased activity in female controls, but no significant change in female DISC1 animals. Other behaviors found included exaggerated responses to the NMDAR antagonist MK-801, and mildly impaired pre-pulse inhibition. MRI findings also included enlarged lateral ventricles.[18] New investigative opportunities such as this—systematically coupling gene–environment interactions with molecular and behavioral neuroscience with advanced neuroimaging represents the vanguard of translating bench findings to the patient and the clinic.

In addition to various susceptibility genes and environmental effects, there is increasing evidence that epigenetic signaling plays a significant role in the development of psychiatric disease via influences on neuronal growth, communication, differentiation and synaptic plasticity.[99] Histone acetylation has been shown to be important for long-term memory as well as contextual fear memory,[100] and is therefore implicated in PTSD[101] and substance use disorders.[102] Both histone acetylation and methylation has been shown to influence symptoms of depression and response to antidepressants in various animal models.[103] Furthermore, the fragmented maternal care caused by the limited bedding paradigm leads to lasting epigenetic changes in offspring that alters glucocorticoid receptor expression and stress responses.[104] Epigenetic modifications have also been shown to affect patients with psychosis and autism. However, neuroimaging studies have not been well integrated with epigenetic studies in either human patients or preclinical models, which represents another opportunity for future research to explore.

CONCLUSION

Psychiatric illness exerts a tremendous burden worldwide and currently stands as the leading disability in the USA. Despite this broad recognition, mental illness is still stigmatized, poorly understood, and remains as one of the most neglected areas of modern medicine. New research tools spanning the entirety of the multiomics spectrum as well as advanced gene editing technologies now allow for an unprecedented opportunity to dissect and examine the molecular underpinnings of psychiatric illness and in efforts to destigmatize mental illness, have begun to help us understand and cast neuropsychiatric disorders first and foremost as a biological disorder. These biological investigations are largely centered on preclinical models of disease, both genetic, epigenetic, and environmental, and are crucial facets of research aimed towards understanding the molecular mechanisms of disease pathogenesis.

Before considering the translational efficacy of a treatment first utilized in an animal model, it is important to highlight that psychiatric illness will never be fully recapitulated in animal models. The core symptoms of these illnesses involve complex mental states, percepts, and motivations that cannot be interrogated in an animal model. As such, animal models' primary utility is to provide insight into the dimensions of neural circuits and mechanisms driving disease phenotypes. These preclinical research models require the use of proper sample size calculation, well-reasoned inclusion and exclusion criteria, randomization methods, experimenter blinding, and validated outcome measures. In addition to these steps towards improving experimental rigor and reproducibility, a technique that is gaining traction in the psychology field among others is preregistration, which requires specifying the experimenter's research plan and hypothesis in public form prior to gathering data. The literature for animal models in psychiatric research also puts forward recommendations to focus on experimental paradigms which interrogate the same endophenotypes in both animals and humans, validate the meaningfulness of a given behavioral trait, and place value on differences in species-specific social and environmental cues. Even as these recommendations are applied to ongoing research efforts, there is still a significant gap in translating preclinical data to human disease, and concurrent neuroimaging is an underutilized tool that could help remove these limitations by increasing early recognition of phenotypic risk, accelerating the development of new and improved therapeutics, and understanding the origins of psychiatric disorders.

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