

# World Journal of *Psychiatry*

*World J Psychiatr* 2021 October 19; 11(10): 681-914



**FRONTIER**

- 681 Framework for internal sensation of pleasure using constraints from disparate findings in nucleus accumbens  
*Vadakkan KI*

**REVIEW**

- 696 Metabolic disturbances associated with antipsychotic drug treatment in patients with schizophrenia: State-of-the-art and future perspectives  
*Chang SC, Goh KK, Lu ML*
- 711 Alternative models for transgenerational epigenetic inheritance: Molecular psychiatry beyond mice and man  
*Hime GR, Stonehouse SL, Pang TY*
- 736 Antipsychotics cardiotoxicity: What's known and what's next  
*Li XQ, Tang XR, Li LL*
- 754 Therapeutic role of yoga in neuropsychological disorders  
*Nourollahimoghdam E, Gorji S, Gorji A, Khaleghi Ghadiri M*
- 774 'Omics' of suicidal behaviour: A path to personalised psychiatry  
*Kouter K, Videtic Paska A*

**MINIREVIEWS**

- 791 Environmental pollution with psychiatric drugs  
*Argaluz J, Domingo-Echaburu S, Orive G, Medrano J, Hernandez R, Lertxundi U*
- 805 Connecting brain and body: Transdiagnostic relevance of connective tissue variants to neuropsychiatric symptom expression  
*Sharp HEC, Critchley HD, Eccles JA*
- 821 Psychiatric sequelae in COVID-19 survivors: A narrative review  
*Putri C, Arisa J, Hananto JE, Hariyanto TI, Kurniawan A*
- 830 Metabotropic glutamate receptors and nitric oxide in dopaminergic neurotoxicity  
*Bashkatova V*

**ORIGINAL ARTICLE**

**Retrospective Cohort Study**

- 841 Factors causing a relapse of major depressive disorders following successful electroconvulsive therapy: A retrospective cohort study

*Kurimoto N, Inagaki T, Aoki T, Kadotani H, Kurimoto F, Kuriyama K, Yamada N, Ozeki Y*

**Retrospective Study**

- 854 Determinants of mechanical restraint in an acute psychiatric care unit

*El-Abidi K, Moreno-Poyato AR, Toll Privat A, Corcoles Martinez D, Aceña-Domínguez R, Pérez-Solà V, Mané A*

- 864 What factors explain anger and mental health during the COVID-19 pandemic? The case of Israeli society

*Braun-Lewensohn O, Abu-Kaf S, Kalagy T*

**SYSTEMATIC REVIEWS**

- 876 Measures of empathy in children and adolescents: A systematic review of questionnaires

*Sesso G, Brancati GE, Fantozzi P, Inguaggiato E, Milone A, Masi G*

- 897 Neurofeedback for insomnia: Current state of research

*Lambert-Beaudet F, Journault WG, Rudziavic Provençal A, Bastien CH*

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## Alternative models for transgenerational epigenetic inheritance: Molecular psychiatry beyond mice and man

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### Abstract

Mental illness remains the greatest chronic health burden globally with few inroads having been made despite significant advances in genomic knowledge in recent decades. The field of psychiatry is constantly challenged to bring new approaches and tools to address and treat the needs of vulnerable individuals and subpopulations, and that has to be supported by a continuous growth in knowledge. The majority of neuropsychiatric symptoms reflect complex gene-environment interactions, with epigenetics bridging the gap between genetic susceptibility and environmental stressors that trigger disease onset and drive the advancement of symptoms. It has more recently been demonstrated in preclinical models that epigenetics underpins the transgenerational inheritance of stress-related behavioural phenotypes in both paternal and maternal lineages, providing further supporting evidence for heritability in humans. However, unbiased prospective studies of this nature are practically impossible to conduct in humans so preclinical models remain our best option for researching the molecular pathophysiology underlying many neuropsychiatric conditions. While rodents will remain the dominant model system for preclinical studies (especially for addressing complex behavioural phenotypes), there is scope for current research of the molecular and epigenetic pathologies by using invertebrate models. Here, we will discuss the utility and advantages of two alternative model organisms—*Caenorhabditis elegans* and *Drosophila melanogaster*—and summarise the compelling insights of the epigenetic regulation of transgenerational inheritance that are potentially relevant to human psychiatry.

**Key Words:** Transgenerational inheritance; Epigenetics; Invertebrate models; *Caenorhabditis elegans*; *Drosophila melanogaster*; Environmental stress

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**Core Tip:** Psychiatry research is only beginning to identify the complex epigenetic pathologies across various conditions that may regulate symptomatology. Epigenetics may account for certain conditions that are highly heritable but are not fully accounted for by genetics. Preclinical animal models are a necessary tool to accelerate our understanding of molecular mechanisms and for developing new therapeutic options. Simple behavioural and neurobiological assays combined with high levels of functional gene conservation and rapid generation time in easily genetically manipulated organisms make *Caenorhabditis elegans* and *Drosophila melanogaster* excellent systems to model transgenerational epigenetic inheritance phenotypes.

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## INTRODUCTION

Advances in genomic technologies have led to a rapid increase in the number of known genomic variants linked to human psychiatric illnesses. However, we still know little of the molecular and genetic functions of many of these genes or their mode of inheritance. The wealth of genetic information and experimental techniques associated with laboratory model organisms that have not been traditionally utilised for analysis of psychiatric illnesses provide an untapped resource that promise to revolutionise our understanding of these conditions.

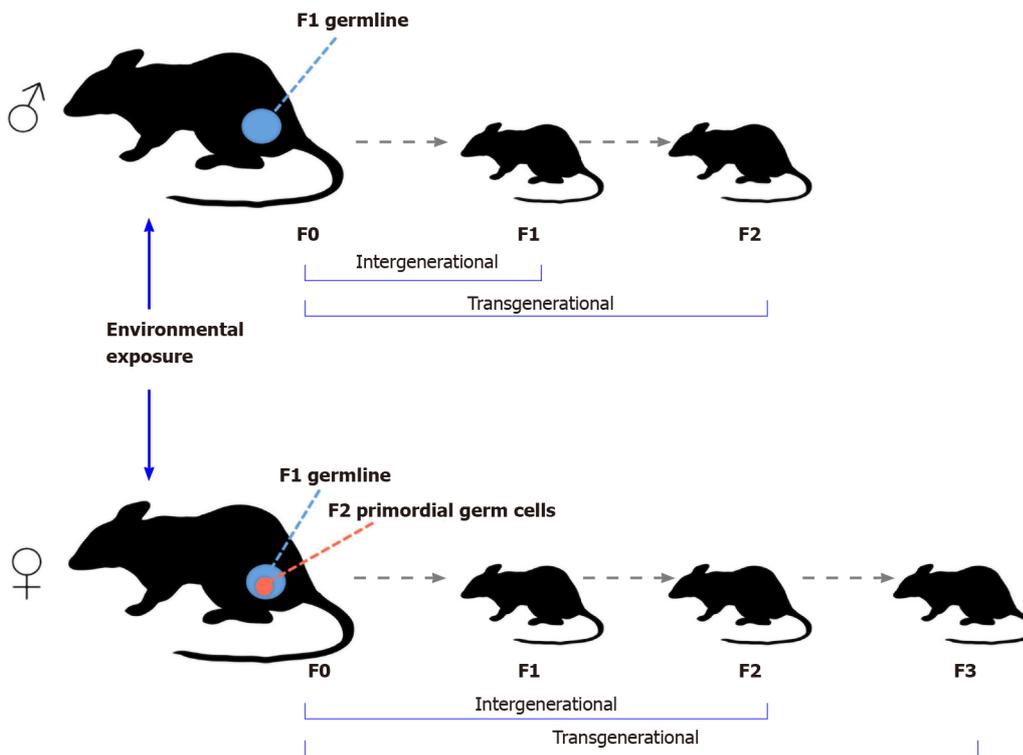
At the turn of the 18<sup>th</sup> century, the French naturalist Jean-Baptiste Lamarck proposed that environmentally adaptive traits could be acquired by an individual over a lifetime and, more importantly, inherited by their progeny. It was not until the 21<sup>st</sup> century that Lamarckian theory re-emerged from the shadows of Darwin's theory of natural selection and the principles of genetic inheritance. This recent revival has been driven by growing evidence of unusual inheritance patterns across a wide number of species, which collectively indicate the presence of biological mechanisms that govern how the physical environment, diet and individual experiences not only influence our individual constitution, but the health of our descendants as well. In the past decade, preclinical studies of mammalian models of human disease have uncovered robust evidence of transgenerational shifts in health. However, alternative animal models should be considered as a means of conducting more time- and cost-effective transgenerational research. Here, we summarise recent advances in transgenerational epigenetic inheritance stemming from non-mammalian models that have revealed epigenetic processes potentially relevant to psychiatry. We hope to convince readers that research based on these non-mammalian organisms have the capacity to provide novel insights into the molecular pathologies of different neuropsychiatric conditions.

Epigenetic inheritance drives the adaptation of phenotypic traits and plays a significant role in directing human health outcomes across generations. For example, the accumulation of specific epigenetic modifications is proposed to contribute to the increasing prevalence of cardiovascular and metabolic diseases[1,2]. Separately, epigenetic modifications have been demonstrated in the transgenerational transmission of risk for mental illness, and possibly contributing to the increasing prevalence of a range of psychiatric disorders[3-6]. However, non-mammalian models have also contributed by extending our understanding of the molecular pathologies in human disease. For example, studies of the nematode *Caenorhabditis elegans* (*C. elegans*) have not only provided us enlightening perspectives on the molecular regulation of aging[7,8] but also revealed how stress and nutrition are transgenerational modifiers of progeny survival[9-11].

Briefly, transgenerational inheritance broadly describes the process of a parental generation undergoing experiences and exposures that are subsequently linked to altered phenotypes and behaviours in future generations (in F2s at the very least). Note that the phrase 'intergenerational inheritance' describes transmission that is

limited (or only studied up till) to the very next F1 generation (see [Figure 1](#) for further patrilineal and matrilineal distinctions). While the full spectrum of biological processes underlying transgenerational inheritance is yet to be fully elucidated, a multiplex of epigenetic modifications has been implicated. Importantly, epigenetic inheritance specifically excludes the reorganisation of genome sequence through DNA mutations, and some epigenetic marks are species-specific (further emphasizing the importance of multi-species research). The most widely studied epigenetic modifications include DNA methylation, histone protein modifications (such as methylation, acetylation), as well as short and long non-coding RNAs (sncRNAs and lncRNAs, respectively) that moderate transcriptional activity. Due to space constraints, we refer readers to the following reviews that comprehensively discuss the biochemistry of epigenetic modifications relevant to the neuropsychiatric field[12-16]. The epigenome is subject to modification following exposure to stressors that challenge survival, ranging from environmental (exposure to toxic chemicals)[17] to physical (heat stress) to psychological (fear of predation)[18,19]. We now know that offspring can inherit a range of epigenetic modifications that alters their physical or behavioural traits. Over the past decade, preclinical studies of rodent models of chronic stress[20,21] and trauma[22-24] have demonstrated this phenomenon, but could alternative non-mammalian models of stress offer further insight into the relevant epigenetic pathologies? These tools offer the field of psychiatry the opportunity to clarify the extent to which the risk for mental illness may be moderated by parental or ancestral exposures to such stressors and life events, and understand the molecular mechanisms mediating such forms of transgenerational inheritance. Epidemiological studies have reported a range in heritability of neuropsychiatric disorders (although readers should note that there have been relatively few studies given the challenges of conducting such large-scale research). For example, a high degree of heritability (81%) was initially estimated for schizophrenia (SZ) based on twin studies[25], while subsequent estimates based on the Danish and Swedish populations were comparatively lower at approximately 60%[26, 27]. Those latter studies also estimated that heritability of bipolar disorder (BP) was similar to SZ. However, the potential that epigenetic inheritance moderates the heritability of certain neuropsychiatric conditions has yet to be thoroughly investigated. Of course, in contrast, other psychiatric disorders such as alcohol dependence or major depression display low-moderate degrees of heritability[28] so while those disorders may involve aspects of epigenetic pathology, it is less likely that epigenetic inheritance would be a significant causal factor.

While studies of *C. elegans* and *Drosophila melanogaster* (*D. melanogaster*) may be initially dismissed as far removed from relevance to human physiology, and although most preclinical drug testing is performed with rodent models, these invertebrate model systems provide alternative approaches to conducting complementary research of common epigenetic mechanisms and biochemical processes that may be fundamental to neuropsychiatric pathologies. One should not forget that mammalian transgenerational research can trace its roots to historically rich and revealing studies of plants. Some of the earliest evidence for the phenomenon include Barbara McClintock's ground-breaking studies of retrotransposition in maize and the transgenerational inheritance of transposon phases. While we tend to associate 'stress' with the notion of psychosocial stress, this term can be used to encompass any extrinsic condition that disturbs the normal function of the biological system, or a condition that decreases fitness, including thermal stress, desiccation, UV stress, starvation, chemical exposure and overcrowding. In using alternative animal models, it is crucial that etiologically relevant stressors are applied in the appropriate manner. Heat stress is well known to impact a wide range of physiological and behavioural parameters, which can result in gastrointestinal dysfunction[29], increased blood pressure and disordered metabolic function[30]. In particular, elevated temperatures cause profound disruptions to various aspects of reproduction in both mammals and invertebrates including mating behaviours[31,32], spermatogenesis and oogenesis, egg/foetal development and viability, and offspring body size[33,34]. With mounting concerns about climate change, and recent increases in unusual climate events, understanding how we adapt to such environmental changes and the implications for global population health trends have become more important than ever. A recent systematic review of the impacts of climate change on mental health reported on the complexities in attempting to consolidate the data, but highlighted more common psychopathologies such as anxiety and trauma[35]. It is unclear if and how climatic factors could influence human health outcomes through epigenetic modifications. Understandably, designing and conducting human studies of this nature would be highly challenging due to the inherent complexities *e.g.* having to account for geographical and ethnic diversities. However, research based in the primary



**Figure 1** Differences between the definition of transgenerational and intergenerational inheritance through the male and female germ lines.

production industries may be an unexpected source of early clues as to how these occur. After all, developing the knowledge to control the effects of heat stress has been crucial to the field of agriculture for maximising crop yield[36,37] and maintaining livestock fecundity and fitness[38,39].

There are mounting calls to recognize that ancestral health is a significant contributing factor of current day human health and phenotypes, and this would require maintaining detailed individual medical records for longitudinal epidemiological studies. On a large scale, such a perspective shift would aid us in identifying the determinants of public health issues and evaluating possible interventions and treatments. Furthermore, elucidating the mechanisms driving environmentally-induced epigenetic changes linked to specific aspects of health and disease may promote a shift towards the development of personalised treatments and drugs based on these signatures[40]. With numerous epigenetic processes conserved from invertebrates to humans, it is unsurprising that many fundamental epigenetic processes are also shared by humans and non-mammalian animals. Therefore, there is valid argument for utilising non-mammalian species as viable alternative animal models to investigate environmentally induced changes in human health, stress response and behavioural adaptations. We will now summarise recent evidence from transgenerational studies of key two non-mammalian models-*C. elegans* and *D. melanogaster*-focussing on environmental stressors and highlight their potential utility for investigating the molecular pathologies of psychiatric conditions.

## EPIGENETIC MODIFICATIONS IDENTIFIED BY TRANSGENERATIONAL STUDIES OF *C. ELEGANS* RELEVANT TO PSYCHIATRY

In contrast to mammalian models where multigenerational studies are impeded by long generational times, logistical difficulties and confounding factors, invertebrate models breed rapidly with large progeny cohorts, making them ideal models for performing multi-generational studies. There are the obvious limitations of *C. elegans* as a model, primarily that it is a relatively simple organism lacking many organ systems found in vertebrates. However, the *C. elegans* genome possesses homologs of about two-thirds of all human disease genes. Thus, it is widely used as a model system for studying aging, age-related diseases[41] and neurodegenerative conditions[42].

Transgenerational studies of *C. elegans* could therefore provide insight into the molecular pathologies and epigenetic modifications that could be accumulating across generations in humans. Here, we will summarise recent advances in our understanding of the transgenerational responses of *C. elegans* involving thermal stress and starvation and highlight their relevancy to human psychopathologies (Table 1).

The most impressive finding to-date was that exposure of a single progenitor generation to an elevated rearing temperature (25 °C instead of 20 °C) caused transcriptome-wide expression changes that persisted for a further seven generations after temperature normalisation[43]. Importantly, it was identified that the ancestral exposure to a higher temperature was associated with a reduction in the repressive histone modification H3K9me3 (trimethylation of lysine 9 residue in histone H3) in both oocytes and sperm, before onset of zygotic transcription. What could be of importance to the psychiatry field was the revelation that there was de-repression of endogenously repressed repeat sequences, and increased expression of two DNA transposons remained for up to five generations. The role of repetitive elements in human health and disease is still unclear but they have been speculated to be potential etiological factors for SZ, BP and major depressive disorder (MDD)[44], despite a present lack of consistent evidence. For example, there has only been a single report of a repetitive element insertion in three monozygotic twin pairs discordant for SZ[45] but similar observations have not been detected in other studies. However, subsequent studies have reported elevated levels of Class I retrotransposon RNA in cerebrospinal fluid, whole blood and serum samples from SZ patients[46-48]. It should be noted that these latter studies were conducted by the same research group and further independent verification is still required. At the present time, there are also no available rodent models of abnormal repetitive element expression so determining its relevance to neuropsychiatric pathologies is impossible. *C. elegans* would therefore be a prime model organism to investigate environmental factors associated with the aforementioned psychiatric conditions, with the dysregulation of repetitive element expression as a primary outcome measurable. Such studies would either cement their causal roles or establish them as secondary molecular pathologies.

Separately, another repressive histone mark linked to *C. elegans* lifespan[49], di methylation of lysine 9 residue in histone H3 (H3K9me2), has also been implicated in various psychiatric conditions. Increased levels of H3K9me2 were found in post mortem SZ brains and in peripheral blood cells[50]. However, the directionality of this change in expression may vary depending on the specific psychopathology, according to evidence from rodent studies. For example, stress-induced depression was associated with reduced H3K9me2 occupancy at the oxytocin and arginine vasopressin gene promoters, both of which were normalised by physical exercise[51]. Thus, the outcomes linked to the manipulation of H3K9me2 levels are also gene specific. This is further exemplified by the capacity for Cdk-5 targeted H3K9me2 to attenuate cocaine-induced locomotor behaviour and conditioned place preference[52]. These clearly showcase the complexity to epigenetic regulation of gene transcription and the significant challenges faced when attempting to treat psychiatric conditions by targeting a single histone modification. However, armed with precise knowledge of the molecular pathologies, aiming to modify negative behaviours in addiction through gene-targeted histone modification could be an intriguing prospect for the future.

A recent study examined a more severe temperature perturbation through acute heat shock (34 °C for 5 min) and discovered that this caused maternal neurons to release the neurotransmitter 5-HT, which facilitated transcription factor heat shock factor 1 (HSF-1)-mediated mRNA production in soon-to-be fertilized germ cells[9]. The authors proposed that this timely activation of HSF-1 in germ cells ensures viability and future stress tolerance since embryos that arose from heat-shocked mothers contained an excess of protective mRNA and their F1 progeny were more resilient to subsequent temperature insults. It was found that HSF-1 recruited the histone chaperone FAcilitates Chromatin Transcription (FACT) complex to alter histone dynamics and promote transcription of the heat shock protein Hsp70. Interestingly, several studies have identified an accumulation of Hsp70 associated with MDD. In a study of post-mortem brain samples from patients with MDD, Hsp70 was significantly elevated in the dorsolateral prefrontal cortex, while antidepressant treatment did not have any modulatory effect[53]. Separately, elevated serum Hsp70 levels were reportedly predictive of premenopausal women who would go on to develop MDD [54], although Hsp70 levels subsequently decreased for women who did not develop MDD. Collectively, this suggests that Hsp70 could be a useful biomarker for MDD risk but it remains to be verified in a younger, or even a healthy, population.

**Table 1 Studies of transgenerational epigenetic inheritance in *Caenorhabditis elegans* of relevance to neuropsychiatric conditions and mammalian preclinical models**

Type of stress (if applicable to study)	Transgenerational shifts in progeny phenotypes	Epigenetic modifications implicated in the inheritance process	Ref.	Psychiatric conditions with similar epigenetic pathology	Ref.	
Elevated temperature	Temperature-induced transcriptome changes potentially up to F14 generation	Heat shock reduces H3K9me3 to facilitate de-repression of endogenously repressed repeats (DNA transposons)	Klosin <i>et al</i> [43], 2017	Repetitive elements as etiological factors for schizophrenia (SZ), bipolar disorder and major depression (review)	Darby and Sabunciyar 2014[44]	
		No difference in another repressive mark, H3K27me3		Altered expression of human endogenous retroviruses associated with autism spectrum disorder and SZ (review)		Misiak <i>et al</i> [169], 2019
		Active histone marks H3K36me3 and H3K4me2 both unchanged		Tissue-specific repetitive elements expression differences in Parkinson's disease		Billingsley <i>et al</i> [170], 2019
Heat shock	Maternal heat shock altered survival of F1 progeny through 5-HT dependent HSF-1 recruitment to heat shock protein gene promoters. Persistence of phenotypic changes not investigated	Histone H3 occupancy at <i>hsp70</i> genes decreased following heat shock	Das <i>et al</i> [9], 2020	MDD associated with increased <i>hsp70</i> expression in post mortem dorsolateral prefrontal cortex	Martín-Hernández <i>et al</i> [53], 2018	
				Elevated serum HSP70 levels predicted development of MDD for premenopausal women. Serum HSP70 decreased over time for women who did not develop MDD		Pasquali <i>et al</i> [54], 2018
				Decreased Hsp70 expression in CA4 associated with complete seizure remission for temporal lobe epilepsy		Kandratavicius <i>et al</i> [171], 2014
NA	NA	Transgenerational inheritance of H3K36me3 is regulated by two distinct histone methyltransferases, MES-4 and MET-1	Kreher <i>et al</i> [172], 2018	H3K36me3 implicated in SZ susceptibility SNPs. But histone lysine methyltransferases yet to be investigated in the context of SZ	Niu <i>et al</i> [65], 2019	
NA	NA	Lifespan regulated by the H3K9me2 methyltransferase MET-2	Lee <i>et al</i> [49], 2019	H3K9me2 elevated in post-mortem SZ brains and peripheral blood cells. Treatment with histone methyltransferase inhibitor BIX-01294 decreased H3K9me2 levels and rescued expression of SZ risk genes	Chase <i>et al</i> [50], 2019	
				Reduced H3K9me2 at oxytocin and arginine vasopressin gene promoters in a rodent model of stress-induced depression. Rescued by physical exercise		Kim <i>et al</i> [51], 2016
				Cdk-5 targeted H3K9me2 attenuates cocaine-induced locomotor behaviour and conditioned place preference in a rodent model of addiction		Heller <i>et al</i> [52], 2016
NA	Decline in fertility	H3K4me2 demethylase <i>spr-5</i>	Greer <i>et al</i> [173], 2014	Treatment with antipsychotic drug olanzapine increased H3K4me2 binding on gene loci associated with adipogenesis and lipogenesis in a rat model	Su <i>et al</i> [174], 2020	
				<i>KDM5C</i> gene that encodes the H3K4me2/3 histone demethylase linked to autism and intellectual disability		Vallianatos <i>et al</i> [175], 2018
Heavy metal (arsenite) stress	Increased resistance to oxidative stress up to F2 generation; no change in reproduction or lifespan	H3K4me3 complex components ( <i>wdr-5.1</i> , <i>ash-2</i> , <i>set-2</i> ), and transcription factors <i>daf-16</i> and <i>hsf-1</i>	Kishimoto <i>et al</i> [10], 2017	Increased H3K4me3 associated with three <i>synapsin</i> gene variants in bipolar disorder and major depression	Cruceanu <i>et al</i> [63], 2013	
				SZ risk variants are over-represented in association with		Girdhar <i>et al</i> [64], 2018

				H3K4me3 in human frontal lobe	
				H3K4me3 implicated in SZ susceptibility SNPs	Niu <i>et al</i> [65], 2019
				Increased H3K4me3 associated with increased <i>Oxtr</i> gene expression in a rat model of methamphetamine addiction	Aguilar-Valles <i>et al</i> [68], 2014
Hyperosmotic stress	Increased resistance to oxidative stress up to F2 generation	Not further investigated in study	Kishimoto <i>et al</i> [10], 2017	Relevance to human health presently unclear	
Larval starvation	Increased resistance to oxidative stress up to F2 generation	Not further investigated in study	Kishimoto <i>et al</i> [10], 2017	Relevance to human health presently unclear	
Larval starvation	NA	Thirteen miRNAs up-regulated (miR-34-3p, the family of miR-35-3p to miR-41-3p, miR-39-5p, miR-41-5p, miR-240-5p, miR-246-3p and miR-4813-5p); Two miRNAs down-regulated (let-7-3p, miR-85-5p)	Garcia-Segura <i>et al</i> [77], 2015	Eight differentially expressed blood miRNAs linked to PTSD. Four up-regulated (miR-19a-3p, miR-101-3p, miR-20a-5p, miR-20b-5p). Four down-regulated (miR-486-3p, miR-125b-5p, miR-128-3p, miR-15b-3p)	Martin <i>et al</i> [78], 2017
				Deletion of miR-34 family in mice facilitates resilience to stress-induced anxiety and extinction of fear memory	Andolina <i>et al</i> [84], 2016
				miR-34 differentially expressed in induced pluripotent stem cells derived from schizophrenia patients	Zhao <i>et al</i> [176], 2015
				miR-34a regulates expression of p73, a p53-family member, that is implicated in neuronal differentiation	Agostini <i>et al</i> [86], 2011
Starvation	Increased longevity of progeny up to F3 generation	Inheritance of small RNAs through at least 3 generations.	Rechavi <i>et al</i> [11], 2014	miRNAs and rRNAs make up the majority of exRNAs in human plasma	Danielson <i>et al</i> [91], 2017
		Small RNAs regulating expression of genes involved in nutrition, metabolic health and lipid transport		1 specific exRNA predicted diagnosis of Alzheimer's disease	Yan <i>et al</i> [94], 2020
				exRNAs are potentially involved in the paternal intergenerational influence on offspring metabolic health (mouse model)	van Steenwyk <i>et al</i> [93], 2020

HSF-1 activity is also associated with elevated histone H4 protein levels in somatic tissue during development, leading to reduced transcription of mitochondrial complex IV genes and decreased respiratory capacity[55]. While it has not been linked specifically to histone H4 only, a similar role of neuronal heat shock proteins in moderating the response to oxidative stress is evidenced in *D. melanogaster* with increased resistance to oxidative stress and extended organismal lifespan, in addition to ameliorating phenotypes associated with Parkinsonism-type genetic models[56]. Collectively, it emphasizes the conserved association between heat shock proteins, oxidative stress and neuronal damage. However, the precise regulatory roles that histone H3 and H4 proteins provide independently to the overall oxidative stress response remain unclear and warrants further investigation. Mitochondrial dysfunction and the accumulation of oxidative stress are crucial factors in the pathophysiology of MDD[57-59], and biomarkers of oxidative stress are elevated in drug-naïve first episode SZ patients[60]. Thus, there is strong interest in targeting oxidative stress deficiencies in MDD, BP and SZ[61] through antioxidant treatments such as N-acetylcysteine[62]. Future studies could use *C. elegans* to explore the efficacies of various antioxidant compounds in treating heat shock-induced oxidative stress, as well as their underlying modes of action. Studies could also be extended to heat shocking *C. elegans* pre-treated with antioxidants to better understand the epigenetic regulation of 5-HT neurotransmission.

The dysregulation of transcriptional activity is widely reported in a swathe of psychiatric conditions but the causes have yet to be precisely identified. For example, H3K4me3 has been implicated in the pathophysiology of SZ, BP and MDD, with increased H3K4me3 is associated with three *synapsin* gene variants in BP and MDD[63] while SZ risk variants are over-represented in association with H3K4me3 in human frontal lobe samples[64]. The latter is consistent with a separate study examining H3K4me3 association with SZ susceptibility SNPs[65]. While there have been several independent GWAS studies of SZ, there has yet to be an attempt to reconcile the genomic data with epigenomic variation. That would undoubtedly be a tremendous undertaking, but it could further streamline and identify more robust gene candidates in our attempts to pinpoint the primary molecular pathologies underlying SZ. *C. elegans* could be used to first establish the molecular consequences of such an abnormal epigenetic landscape and resulting transcriptional dysregulation (matched to existing human data), before further behavioural studies are extended to mammalian models. Incidentally, H3K4me3 was identified by Kishimoto *et al*[10] as being involved with the transgenerational adaptations to other forms of environmental stressors aside from thermal stress, namely heavy metal exposure, hyperosmotic conditions, and transient starvation[10]. Following progenitor exposure to all three stressors, there were consistent increases in progeny fitness up till the F2 generation; however only the epigenetic mechanism mediating adaptation to arsenite exposure was further investigated. Unlike the repressive histone modifications mentioned above, H3K4me3 predominantly marks transcriptional start sites and is part of a regulatory complex that facilitates access and assembly of RNA polymerase 2[66,67]. Kishimoto *et al*[10] reported that the genetic components (*wdr-5.1*, *ash-2* and *set-2*) of the H3K4me3 regulatory complex were required to manifest the transgenerational adaptations, implicating histone H3-dependent gene transcription in transgenerational inheritance. Therefore, future work on H3K4me3-regulation transcriptional activity could provide new insight into the molecular pathways affected in SZ, BP and MDD by targeting *C. elegans* homologs of human risk genes for more specific investigations.

Finally, in a rat model of methamphetamine addiction, there was greater H3K4me3 association with the oxytocin receptor gene that corresponded to increased *Oxtr* gene expression[68]. As discussed above, strategies to treat addiction-related molecular pathologies by targeting histone modifications will be challenged by having to account for both active and repressive histone marks. The viability of such interventions and their molecular consequences would be ideally be first tested in *C. elegans* before proceeding to trials in mammalian models.

Malnutrition and starvation at different stages of life have a dramatic impact on mental health. For example, famine exposure *in utero* was associated with an increased risk for mental illness in females, though surprisingly with no apparent significant effect on males[69]. Developmental malnutrition driven by abnormalities in oxidative stress pathways has been linked to an increased risk for SZ and other psychiatric illness later-in-life[70]. Nutrition ultimately dictates metabolic health and more recent studies reported that fasting insulin levels and body mass index at different ages were predictive of at-risk status for psychosis or depression[71], while fasting blood glucose and serum lipid levels predicted suicide attempters in young patients with MDD[72]. At the opposite end of the age spectrum, geriatric deficiencies in micronutrients such as folic acid, thiamine or cobalamin have been linked to worsened mental health symptoms[73,74]. However, careful regulation of nutrition through caloric restriction or fasting has been proposed to be effective in improving symptoms of MDD[75], indicating that dietary interventions where appropriate would benefit patients. This could be particularly important in conditions whereby medications could have unavoidable metabolic side effects[76]. While epidemiological data flags the importance of nutrition for mental health, we continue to have a very poor understanding of this interactive relationship in the absence of evidence of causality and the underlying molecular mechanisms. Human studies of that nature would be severely limited by inherent genetic and cultural heterogeneities within populations, and there would be strong ethical arguments against the manipulation of subjects' diets. These issues are circumvented in studies of *C. elegans* wherein genetic homogeneity is controlled and dietary manipulations are feasible, although as *C. elegans* feed upon bacteria subtle dietary manipulations may be more easily accomplished using the chemically controlled diets that have been formulated for *D. melanogaster*. Transgenerational studies of starvation in *C. elegans* have already been conducted with clear evidence of downstream impacts on progeny fitness. More importantly, these studies have identified epigenetic mechanisms regulating the transgenerational adaptations, and these could potentially be regulating the molecular pathologies driving the malnutrition-related increase in risk for mental illness.

Kishimoto *et al*[10] reported that progenitor larval starvation triggered increased resistance to oxidative stress of two generations of progeny[10] but did not pursue the underlying epigenetic mechanisms and their associated molecular adaptations. However, previously, it was reported that starvation during the early L4 Larval stage altered the expression of 13 miRNAs in *C. elegans*[77]. Of the 13, only 2 were downregulated while the miRNAs of the miR-35 family were most highly upregulated. Being a simple organism, there are only 302 known miRNAs in *C. elegans* compared to over 2000 human miRNAs, so studying their role in transgenerational inheritance and phenotype adaptations is comparatively straightforward. miRNAs are now established to be dysregulated in different human conditions and are the subjects of interest for severe stress-related anxiety disorders such as post-traumatic stress disorder and SZ, as prognostic biomarkers and therapeutic targets. However, their role as epigenetic regulators of pathogenesis are unclear and systematic profiling of individual miRNAs to neuronal circuitry could be one approach to identifying their potential pathogenic roles in psychiatric conditions.

In a cohort study of military combat veterans, 8 differentially expressed blood miRNAs were associated with the diagnosis of post-traumatic stress disorder (PTSD) [78], and their predicted gene targets were implicated in neurotransmission and maintenance of the neural circuitry. Indeed, multiple functional magnetic resonance imaging studies have clearly demonstrated that brain function is compromised in PTSD[79,80]. There is initial evidence to suggest that paternal PTSD may also have the capacity to influence the neural function and behaviour of progeny, and that this is through the inheritance of sperm-borne miRNAs. In the social defeat mouse model of PTSD, both male and female progeny displayed significant anxiety and depression-related behaviours despite themselves not having been subject to stressful interventions[81,82]. It was later independently reported that modelling paternal early life trauma alters sperm miRNAs and exerts significant intergenerational alterations of target genes in the brains of progeny (*e.g. cttnb1*, catenin  $\beta$ 1 in the hippocampus)[22]. Our own studies have extended that line of evidence by demonstrating the transgenerational effects of paternal stress exposure and altered sperm miRNAs resulting in significant expression differences of the imprinted gene insulin-like growth factor 2, *Igf2* in the hippocampus of two generations of progeny[21]. While their downstream target genes may have been discovered to be dysregulated, there is still some controversy regarding the intergenerational inheritance of sperm miRNAs because having altered levels of miRNAs in sperm does not translate to those same miRNAs being dysregulated in offspring brains[23]. Despite the transgenerational implications of paternal PTSD on brain function of their children remaining unknown at this time, a bigger unresolved question is how traumatic stress alters miRNA expression, with one possibility being dysregulation of histone protein modifications and altered chromatin state. Unlike PTSD, which is caused by an external trigger, miRNAs appear to be co-regulated with susceptibility risk genes in SZ. For example, one study has reported an over-representation of miR-9-5p-targeted risk genes while miR-9-2 is located in a genomic region strongly associated with SZ[83]. Given the strong environmental component to both PTSD and SZ, continuing research into stress-induced miRNA changes in *C. elegans* could be used to further our understanding of the relevant environment x gene interactions underlying the molecular pathogenesis of PTSD and SZ. Other miRNAs have been implicated in stress-related disorders such as members of the miR-34 family, which are differentially expressed in induced pluripotent stem cells derived from SZ patients[41,84]. Among these, and consistent with the neurodevelopmental hypothesis of SZ[85], miR-34a is a key regulator of p73 expression, a p53-family member that is implicated in neuronal differentiation[86]. However, causal evidence is lacking to demonstrate that miR-34a is an epigenetic conduit for environmental stress to impact on brain development resulting in a schizotypy brain phenotype. One feasible experiment to propose would be ablating expression of the *C. elegans* homolog of miR-34a or the miR-34 family and study the impacts on neuronal differentiation, development and circuit maturation.

Interestingly, Rechavi *et al*[11] report that progenitor larval starvation was associated with extended longevity in three generations of progeny through the inheritance of small RNAs that regulate genes involved in nutrition, metabolic health and lipid transport[11]. It has been demonstrated in *C. elegans* that extracellular RNAs (exRNAs) are transported from one generation to the next through intracellular vesicles or even as unpackaged extracellular material[87]. The transgenerational effects of paternal stress exposures[21-23] involve altered small non-coding RNA content of sperm transmitted in microvesicles within the male reproductive organs[88,89], but so far this has only been demonstrated in mouse models[90]. Perhaps not so coincidentally, miRNAs are one of two major exRNA species in human plasma (the other

being ribosomal RNAs)[91]. Their presence and relative stability have led to an emerging recognition of their promise as ‘liquid biopsies’ for diseases, but while early adoption has targeted metabolic pathology[92], the correlation of biofluid exRNA levels with psychiatric conditions remain untested. Interestingly, it was reported that chronic injection of serum from a mouse model of trauma into healthy controls was sufficient to recapitulate the intergenerational impact on offspring metabolism[93]. However, miRNA profiling of the serum content was not performed in that study. Very recently, an investigation profiling exRNAs isolated from the plasma of elderly individuals up to 15 years prior to death revealed that the early presence and progressive increase of phosphoglycerate dehydrogenase (PHGDH) exRNA predicted eventual diagnosis of Alzheimer’s disease (confirmed with post mortem pathology testing)[94]. Studies of *C. elegans* could be used to first determine how stress triggers an elevation of circulating exRNAs. Subsequently, given that biofluid screening of exRNAs is already being used to aid diabetes and AD diagnoses, there appears to be untapped potential for this methodology as a presymptomatic screening tool in psychiatry.

Overall, recent studies have demonstrated the complexity of epigenetic responses implicated in the transgenerational responses to progenitor stress exposure. These include histone modifications, dysregulation of DNA repetitive elements and altered expression of non-coding RNAs. These are also molecular processes shared by humans and have been identified as molecular pathologies of various psychiatric conditions. Thus, studying the epigenetic response of *C. elegans* to etiologically relevant environmental stressors and the corresponding physiological and behavioural responses will continue to provide further insight into human molecular psychiatry.

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## EPIGENETIC MODIFICATIONS IDENTIFIED BY TRANSGENERATIONAL STUDIES OF *D. MELANOGASTER* RELEVANT TO PSYCHIATRY

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*D. melanogaster* has been established as an invertebrate model organism for studying human neurological disorders due to the remarkable evolutionary conservation of multiple human disease-causing genes. *D. melanogaster* have a higher degree of concordance with humans than *C. elegans*, with 75% of human diseases estimated to have a *D. melanogaster* homologue[95]. While also displaying sexual dimorphism in its physiology and behaviour, *D. melanogaster* have a generational time of only 10-12 d as opposed to approximately 6-9 wk for mice. Thus, in a protracted timeframe and at much lower cost compared to using rodents, multi-generational studies can also be performed to assess transgenerational effects and adaptations of *D. melanogaster* offspring to various environmental stressors. Additionally, a wide range of established transgenic strains, gene manipulation techniques and tools are readily available[96]. Here, we refer readers to several broad reviews discussing the utility of *D. melanogaster* research in advancing the understanding of the complex genetic basis for human traits, psychiatric disorders, neurodegeneration, and for drug discovery and screening[97-100]. Of course, the significant limitations of modelling complex neuropsychiatric conditions in *D. melanogaster* must also be acknowledged. Despite the relative ease in genetic manipulation, neuropsychiatric conditions such as SZ are driven by a combination of multiple genetic and environmental factors, and cannot be simply reduced to and reproduced in single, double or even triple transgenic knockout strains. Furthermore, the myriad of behavioural symptoms requires higher brain function to manifest, for which only mammalian models could be considered as appropriate. However, these reasons should certainly not diminish the utility value of *D. melanogaster* as a high throughput screening tool for basic neuropathological, molecular or epigenetic markers of disease. Most recently, *D. melanogaster* have even been used to model insomnia in order to examine the effectiveness of sleep restriction therapy[101]. However, despite these advantages, transgenerational studies in *D. melanogaster* aimed at examining mechanisms of epigenetic inheritance remain relatively sparse. Yet, the limited research has produced some compelling evidence, nonetheless. In this section, we will summarise key findings by highlighting the transgenerational outcomes of environmental and chemical stress exposures on offspring phenotypes paired with the reported epigenetic processes implicated. We will then flag the neuropsychiatric conditions for which further *D. melanogaster* research could potentially shed new light on the pathological origins.

*D. melanogaster* are sensitive to the climate and temperature fluctuations[102,103] and have been instrumental in advancing our understanding of the heat stress response. Heat stress-associated deleterious effects on physiology and behaviour are

largely attributed to its denaturing effect on proteins, which undergo abnormal folding, entanglement and unspecific aggregation[104]. In addition to the disruption of singular proteins, heat stress can also disrupt other cellular mechanisms with the culmination of these individual disruptions being cell death[105]. The ubiquitous and highly conserved heat shock response is a complex cascade of different processes, the most central being the transcriptional up-regulation of genes coding for the family of heat shock proteins that were in fact first discovered in *D. melanogaster*[106,107]. In addition to the metabolic and physiological effects on the exposed organism[108,109], selective thermal variations can dramatically shift *D. melanogaster* physical phenotypes such as flight ability over generations (impaired by F2 generation and maintained till the F4 generation) in a sex-dependent manner[110,111]. Thus, imposing a suboptimal ambient environment for survival either by changing the housing temperature or through a transient shift of temperature represents the most etiologically relevant approaches to stressing *D. melanogaster*. These encapsulate studies of both cold tolerance[112] and heat tolerance (discussed in detail below, Table 2), and these allow us to investigate how genetic variation dictates response to the environment or *vice versa*. Research into the transgenerational effects of heat stress in *D. melanogaster* have yielded intriguing and robust evidence of altered offspring physiology and heat stress responses. More importantly, those studies have also revealed epigenetic mechanisms that are of particular interest to psychiatry. Perhaps the most compelling demonstrations of environment-directed modifications of *D. melanogaster* epigenetics resulting in altered gene expression are the transgenerational studies of *white* gene expression following heat stress. The X chromosome residing *white* gene encodes for an ATP-binding cassette transporter that facilitates transport of the eye pigment precursors, guanine and tryptophan (red and brown pigment precursors, respectively) into the developing eyes during pupation[113]. Repression of *white* achieved by inserting the cellular memory module Fab-7 upstream of *white* to enhance chromatin silencing results in the loss of eye pigmentation[114]. Importantly, the Fab-7-mediated silencing process involves recruitment of Polycomb Group (PcG) proteins, which are essential in the propagation of chromatin structures and regulate gene silencing through S-phase of the cell cycle[115-117]. The mere developmental exposure to a mildly stressful temperature of 29 °C (typical housing temperature is 25 °C) suppressed Fab-7 expression, resulting in the de-repression of *white* and recovery of red eye pigmentation[118]. Importantly, that de-repression event was heritable down both male and female germ lines up till the F4 generation. That “founder effect” and maintenance of a de-repressed state across multiple generations indicates that inheritance of the temperature-modified chromatin state is maintained by the PcG protein complex. Of relevance to the human epigenome, the PcG protein complexes catalyse the formation and maintenance of the inactive histone mark H3K27me3[118], which as previously mentioned, is widely associated with neuropsychiatric conditions with abnormal histone modification patterns and aberrant gene transcriptional profiles [119]. Yet, the regulation of differentially expressed genes by PcG protein complexes in neuropsychiatric conditions has not been reported. While PcG protein complex function has been of great interest to the oncology field given the tell-tale features of DNA hypermethylation and aberrant transcriptional silencing of tumour suppressor genes[120], a causative role in psychiatric disorders has yet to be established. PcG protein complexes serve as a master regulator of active gene transcription so understanding the intricacies of PcG regulation of chromatin states will be essential if targeting aberrant histone modifications are to be a major therapeutic focus of the future. Aside from changes at the *white* gene locus, the multi-generational effects of heat shock on other behavioural (social interaction, mating) and physiological (metabolic and endocrine health) parameters in *D. melanogaster* are yet to be comprehensively studied. It would be very interesting to investigate if PcG protein complexes also have the capacity to affect the social behaviour, cognition and physical attributes of *D. melanogaster* by manipulating the extent of histone methylation associated with neuropsychiatric risk genes.

Interestingly, and in contrast to the stable inheritance pattern mediated by PcG protein complexes, heat shock-induced de-repression of *white* gene expression involving disruption of the heterochromatin assembly was maintained through three generations of embryos but contingent on repeated exposure of the offspring themselves to heat stress[121]. In that study, the transgenerational effects of heat shock were associated with increased phosphorylation of ATF-2, a member of the CREB/ATF family of transcription factors. Interestingly, levels of phosphorylated ATF-2 are reported to be increased in the ventral parieto-occipital region of post-mortem human brains when comparing between medicated and unmedicated patients with depression[122]; it is unknown if pATF-2 Levels could be predictive of a familial

**Table 2 Studies of transgenerational epigenetic inheritance in *Drosophila melanogaster* of potential relevance to psychiatric conditions and mammalian preclinical models**

Type of stress (if applicable to study)	Transgenerational shifts in progeny phenotypes	Epigenetic processes implicated in the inheritance process	Ref.	Potentially relevant psychiatric conditions	Ref.
Thermal stress (selection based on intolerance to heat stress)	Reduced ability to fly by F2 generation, maintain through to F4 generation	Epigenetic mechanism not investigated; aspects of stress physiology that affect flight still unclear	Krebs and Thompson [111], 2006	Relevance to human health presently unclear.	
Mild heat stress(embryos maintained at 29 °C)	De-suppression of <i>white</i> gene up to F4 generation	Disruption of polycomb group (PcG) protein complex affecting H3K27me3	Bantignies <i>et al</i> [114], 2003	Despite multiple reports of altered H3K27me3, the involvement of PcG protein complexes in human psychopathologies has not been established	
Heat shock (flies exposed to 37 °C for 1 h)	De-suppression of <i>white</i> gene sustained up to F3 generation required repeated exposure to the same paternal stressor. Gradual return to normal upon removal of heat shock	Disruption of pATF-2 mediated heterochromatin assembly	Seong <i>et al</i> [121], 2011	Rat model of chronic stress reported increased ATF-2 gene expression in the frontal cortex of chronically stressed rats, which is decreased following chronic antidepressant treatment	Laifenfeld <i>et al</i> [122], 2004
				pATF-2 levels are increased in post mortem samples of unmedicated <i>vs</i> medicated patients with MDD. No differences detected for bipolar disorder or schizophrenia	Gourzis <i>et al</i> [177], 2012
				Case report of decreased chromosome 1 heterochromatin in FTLD, misdiagnosed as SZ. Altered size distribution of chromosome 1 heterochromatic region in unrelated SZ patients compared to controls	Kosower <i>et al</i> [178], 1995
				Risperidone inhibition of heterochromatin formation in human liposarcoma cells <i>in vitro</i> , in a process involving PKA signalling; extent of dysregulated heterochromatin in psychosis yet to be explored	Feiner <i>et al</i> [125], 2019
				Parental exposure to risperidone led to intergenerational effects on F1 predator avoidance behaviours in zebrafish; potential human effects have not been investigated	Kalichak <i>et al</i> [179], 2019
Heat stress (flies raised at 29 °C)	Suppression of BX2 transgene cluster over multiple (50) generations	Paramutation of BX2 <i>via</i> maternally inherited piRNAs, triggered by heat stress which resulted in active transcription of piRNAs within that gene locus	de Vanssay <i>et al</i> [126], 2012	Paramutation is not regarded as an established epigenetic process in mammals	
				However, readers should be aware of this proof-of-concept study in mice	Yuan <i>et al</i> [180], 2015
			Casier <i>et al</i> [127], 2019	Paternal transmission of “white-tail-tip” phenotype caused by paramutant allele in mice limited to one generation. Maternal miRNAs and piRNAs regulate (inhibit) germline transmission of paramutation	
				14 piRNAs differentially expressed in AD prefrontal cortex samples <i>vs</i> controls	Qiu <i>et al</i> [128], 2017
				Sequencing of CSF-derived exosome sncRNA revealed combination of 3 miRNAs and 3 piRNAs detected AD and predicted the conversion of mild-cognitive impaired (MCI) patients to AD dementia. Greater predictive confidence when combining the smallRNA signature with pTau and Aβ 42/40 ratio pathology	Jain <i>et al</i> [129], 2019
Forced cohabitation with predator or	Stressed females shift behaviour to laying eggs on	Maternal inheritance of chromosome III and NPF (	Bozler <i>et al</i> [136], 2019	Dysregulation of NPY levels in the brain is a key pathophysiology of drug	Gonçalves <i>et al</i> [181], 2016

endoparasitoid wasps	food rich in ethanol, and that preference is inherited through five generations	<i>Drosophila</i> homolog of NPY) gene locus, reduced NPF expression in the fan shaped body of the adult brain drives ethanol preference		addiction. Manipulation of NPY neurotransmission has potentially beneficial behavioural outcomes, depending on the drug in question  NPY is implicated in human alcohol misuse disorders  NPY is also implicated in rodent models of alcohol misuse disorder	Mayfield <i>et al</i> [137], 2002  Mottagui-Tabar <i>et al</i> [138], 2005  Thorsell and Mathe[139], 2017  Badia-Elder <i>et al</i> [140], 2003  Schroeder <i>et al</i> [142], 2005  Robinson <i>et al</i> [141], 2019
Restraint stress	Paternal restraint stress affects epigenome, transcriptome and metabolome of F1 progeny	Stress-induced up-regulation of <i>Upd3</i> ( <i>Drosophila</i> homolog of IL-6) in somatic cells and testes, activating JAK/STAT pathway  Subsequent p38 activation results in dATF-2 deactivation in germ cells leading to decreased H3K9me2 (repressive mark) at target genes. Repressive histone marks inherited by F1 progeny	Seong <i>et al</i> [145], 2020	Metabolic dysregulation in the F1 offspring derived from male breeders exposed to early postnatal stress  Review of epigenetic mechanisms proposed to underlie intergenerational transmission of paternal trauma  Childhood adversity associated with altered DNA methylation of HPA axis and immune system genes; potentially inherited by offspring	van Steenwyk <i>et al</i> [146], 2018; van Steenwyk <i>et al</i> [93], 2020  Yehuda and Lehrner[182], 2018  Bick <i>et al</i> [154], 2012
Methylphenidate (MPH) treatment	Behavioural response to MPH is genetically variable and intergenerational effects can be observed in F1 offspring	Mechanism is unknown but MPH resulted in alterations to expression of many histone modifying genes	Rohde <i>et al</i> [158], 2019	ADHD is highly heritable, but the reasons are unclear despite the identification of candidate genes. Future studies should attempt to identify transgenerationally heritable epigenetic modifications as the basis for genetic vulnerability  Non-human primate studies indicate that MPH treatment affects normal puberty. The transgenerational implications of this finding for humans needs to be followed-up	Mattison <i>et al</i> [155], 2011
G418 treatment (toxic stress)	Exposure of F0 females to G418 resulted in reduction of <i>Polycomb</i> group gene expression in up till F3 generation	Maternal <i>Polycomb</i> group expression in early embryogenesis affects expression of the zygotic genome, which can be inherited	Stern <i>et al</i> [168], 2014	G418 has been successfully used to rescue PTC deficiencies in a cell culture model for frontotemporal dementia. However, its broader utility for treating neuropsychiatric conditions remains unknown  PTC mutations of neuronal <i>UPF3B</i> gene associated with nonspecific mental retardation with or without autism	Kuang <i>et al</i> [164], 2020  Laumonnier <i>et al</i> [183], 2010

PTC: Premature termination codon; IL: Interleukin.

history of MDD or other forms of stress-related psychopathology. The *D. melanogaster* ATF-2 is known to be an essential regulator of heterochromatin assembly through its co-localisation with HIP1, a crucial adaptor molecule for DNA methyltransferases that are recruited along the heterochromatin assembly by H3K9me marks. Thus, despite the lack of evidence at this time, it has been speculated that the general disruption of gene expression in psychiatric conditions such as SZ involves a combination of abnormal DNA methylation and histone methyltransferase activity[123,124], and that recurring environmental stress could be key triggers for the familial manifestations of psychosis. It is especially important that this aspect of epigenetic pathology be examined given more recent *in vitro* evidence that antipsychotics such as risperidone

have the capacity to inhibit heterochromatin formation[125].

Studies of heat stress have also uncovered other heat-induced epigenetic responses involving paramutation and the resulting transgenerational inheritance of small non-coding RNAs *via* the maternal lineage. de Vanssay *et al*[126] described a paramutation event involving P-transposable-element repression in the germ line (termed trans-silencing effect, TSE) that converted other homologous clusters typically incapable of TSE into strong silencers[126]. The transgenerational effects of this paramutation persisted through 50 generations of progeny and was found to specifically require *aubergine* gene-mediated piRNA biogenesis but not Dicer-2 mediated siRNA production. Interestingly, this paramutation is triggered by heat stress and the pattern of piRNA up-regulation is transmitted *via* the maternal lineage[127]. Thus, one of the persistent epigenetic modifications in response to stress in humans could be the emergence of actively transcribed piRNA loci. While piRNAs are not a core focus of molecular psychiatry, piRNAs have started to gain attention in the domain of neurodegenerative diseases after having been found to be differentially expressed in prefrontal cortical tissue of post-mortem AD brains[128]. That has led to questions of their role in disease pathogenesis and the possibility of using them as a reliable biomarker for human disease. In support of the latter notion, miRNA and piRNA profiling of human cerebrospinal fluid-derived exosomes has more recently been proposed to have utility in diagnosing AD, as well as predicting the conversion from mild cognitive impairment to AD dementia[129]. There is sexual dimorphism in the clinical manifestation of AD with more women than men being diagnosed and maternal transmission is more frequently observed than paternal transmission[130]; but the potential involvement of maternally inherited miRNAs or piRNAs to confer AD risk is completely unknown at this time. In *D. melanogaster* it has been established that piRNAs are maternally inherited and aging is associated with an increased presence of novel heterochromatic-only secondary piRNAs[131-134]. However, evidence of a similar pattern of inheritance role in humans has yet to be discovered. Our understanding of piRNA in the context of psychiatry and behaviour is barely in its infancy, and there remains much to be uncovered regarding the piRNA pathogenesis and its direct consequences across the range of neuropsychiatric diseases. Perhaps further studies in *D. melanogaster* can uncover novel piRNA-mediated disease mechanisms for psychiatry conditions that are skewed to maternal transmission.

Predator stress is another form of environmental stress that applies to *D. melanogaster* and studies have revealed that it is sufficiently severe to induce shifts in reproductive behaviours. Females housed in cohabitation conditions with endoparasitoid wasps develop a preference to lay eggs on ethanol-rich food as ethanol protects the larvae from wasp infection[135]. That change in oviposition behaviour was found to be driven by neuropeptide F (the *D. melanogaster* homolog of Neuropeptide Y, NPY) and persisted despite removal of the endoparasitoid wasps. More impressively, a recent study reported that exposure to predatory wasps is also an environmental stressor that triggers a similar transgenerational modification of egg laying behaviour over five generations[136]. That shift towards ethanol-rich substrates was established to be superficially maternally transmitted and involved inheritance of Chromosome III within which resides the *NPF* gene that is differentially expressed in the fan shaped body of the adult female brain. Here, it is worth noting that NPY is of major interest to substance misuse disorders and has been implicated in human alcohol use disorder [137-139] as well as in rodent models[140-142]. Since genetic vulnerability remains the core disease-causing factor for humans, and given that unbiased genetic screening, QTL analyses or GWAS studies are easily paired with functional studies in *D. melanogaster*[143,144], the latter presents as a viable alternative organism to study gene-environment interactions and the triggers that drive alcoholism, with perhaps the next step being a pursuit of the epigenetic mechanisms underlying those pathologies.

Interestingly, by using restraint stress to model strong psychological stress, Seong *et al*[145] found that paternal stress altered the epigenome, transcriptome, and metabolome in a dATF2 pathway-dependent manner[145]. A host of genes involved in metabolic health (amino acid metabolism, glycolysis, TCA cycle) were differentially expressed in the F1 offspring, which is consistent with the observations of similar paternal stress studies in mice[93,146]. The intergenerational effects in *D. melanogaster* were proposed to be caused by stress-induced up-regulation of *Upd3* gene in the testes [the *D. melanogaster* homolog of the pro-inflammatory cytokine Interleukin-6 (IL-6)], which was confirmed by overexpression studies of *Upd3* in paternal somatic cells with corresponding studies of the offspring outcomes. The overall intergenerational effects were proposed to be mediated by stress-induced increases in *Upd3* that causes abnormal phosphorylation of dATF-2 in *D. melanogaster* germ cells, resulting in decreased H3K9me2 repressive marks that are inherited by the F1 offspring to

ultimately disrupt heterochromatin assembly and gene transcription. In humans, it remains to be clarified whether IL-6 (or other pro-inflammatory cytokines) correlates with sperm DNA damage[147,148]. However, it is well-established that inflammation has a significant role in the pathogenesis of various neuropsychiatric conditions including MDD[149-151] and SZ[152,153]. It would be interesting to elucidate the relationship of SNPs and risk gene loci with H3K9me2 repressive marks, and its contribution to the development of those conditions especially in familial cases. Additionally, given initial evidence suggesting that traumatic stress has long-term epigenetic consequences including altering the DNA methylation patterns of genes relevant to HPA axis function and the immune (inflammation) response[154], future *D. melanogaster* studies should also focus on DNA methylation as a key epigenetic mechanism mediating the transgenerational inheritance of stress-induced pathologies.

Methylphenidate (Ritalin) is a frontline prescription psychostimulant for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. The increasing frequency of prescription has been the cause for concern regarding over-prescription and overdiagnosis. Methylphenidate treatment has been reported to result in significant developmental delay to puberty with hormonal imbalance in non-human primates[155]. While the impacts on spermatogenesis or sperm health were not investigated in that study, separate work on the major metabolite of methylphenidate, ritalinic acid, has found a significant increase of human sperm motility and viability *in vitro*[156]. However, any effects of long-term methylphenidate treatment on pubertal growth, sperm development *in vivo* and the sperm epigenome are unknown presently. *D. melanogaster* studies have contributed tremendously to advancing our understanding of the genetics of neuropsychiatric conditions. A prime example is they have been used to identify ADHD candidate genes[157] and to determine the transcriptomic response to methylphenidate, which correlate to their locomotor responses to drug treatment[158]. The latter study also identified putative candidate genes through whole genome transcriptomic analysis that accounted for the variability in drug response. Collectively, that body of work establishes *D. melanogaster* as a valid organism to further probe the transgenerational effects of methylphenidate exposure on male reproductive health and progeny behaviours. The aetiology of ADHD remains poorly understood but epidemiological data indicates approximately 80% heritability for both adults and children[159,160] despite only 22% of the disease liability being linked to common gene variants[161]. Given that knockdown of *D. melanogaster* homologues of ADHD candidate genes produces abnormal locomotor phenotypes that are also responsive to treatment by ADHD prescription compounds [162,163], *D. melanogaster* would continue to serve as an ideal organism for future investigations into the epigenetic factors underlying the high degree of heritability of ADHD.

Recently, one study investigating new therapeutic options for treating frontotemporal dementia (FTLD)[164] explored the use of aminoglycosides—a class of gram-negative bacilli antibiotics that have the capacity to induce eukaryotic ribosomal readthrough of premature termination codon (PTC) sequences to yield a full-length protein. Aminoglycosides have successfully been used to treat various diseases involving PTC mutations such as cystic fibrosis[165], Duchenne muscular dystrophy [166] and Rett syndrome[167], but have yet to be employed for neuropsychiatric conditions. In using a cell culture screening assay to conduct proof-of-principle studies with non-sense mutations of *progranulin* associated with FTLD, Kuang *et al*[164] identified two aminoglycosides that rescued the expression of the *progranulin*. It is worth noting that one of those aminoglycosides, G418 (also known as geneticin), has previously been reported to exert transgenerational effects on maternal *Polycomb* levels in *D. melanogaster* F2 embryos that persisted into the F3 generation[168]. Importantly, G418 exposure lead to growth retardation and delay in pupation times. While the transgenerational implications of G418 would be minimal since FTLD is associated with advanced aging, we believe it is important that readers be aware of such potential risks to offspring should aminoglycosides continue to be explored as therapeutic options for conditions in a younger fertile population.

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## CONCLUSION

Looking towards the future, improving the prospects for neuropsychiatric patients requires the field of psychiatry to have a more comprehensive understanding of the causes of various conditions, especially regarding how basic molecular and epigenetic pathologies interact and contribute to the overall disease phenotype. A major step

would be the incorporation of epigenome profiling since it is the key molecular intermediary linking genetics (susceptibility) to the environment (stress-related triggers). In highlighting the key findings of studies of *C. elegans* and *D. melanogaster*, we hope readers can come to appreciate the value of conducting basic research employing these two key non-mammalian organisms to potentially uncover novel molecular and epigenetic pathologies. Multiple stress-induced epigenetic modifications that affect the individual have significance in a variety of human neurological conditions, but further findings that progeny are also transgenerationally affected will have broader implications for health projections for future generations. At a time when stress (physical and mental) is prevalent and largely unavoidable, there is great urgency to understand the current mental health crisis and work towards new approaches for treatment and prevention. Of course, it is openly acknowledged that complex human behavioural responses and adaptations related to psychopathologies cannot be modelled in simple organisms. However, many fundamental molecular mechanisms that regulate neuronal behaviour have been conserved across phyla, and those molecular and neuronal circuitries can be interrogated in a rapid manner in simple model organisms. Therefore, invertebrate research should be regarded as being tremendously beneficial and highly complementary to human and mammalian model research, and further investments should be made in this regard. An expanded combination of clinical studies, rodent models and molecular studies in model organisms provides an extremely powerful multi-tiered approach to understanding the molecular basis of psychiatric disorders. Focusing on the epigenetic pathologies associated with neuropsychiatric conditions will undoubtedly lead to the development of novel approaches for treatment.

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