Review

Pharmaceutical Implications of Sex-Related RNA Divergence in Psychiatric Disorders

Alon Simchovitz-Gesher¹ and Hermona Soreq¹,²,*

Male–female differences have long been observed in the epidemiology and clinical presentation of psychiatric disorders. Current understanding is based on sex hormones and on transcription patterns governed by the sex chromosomes, and specific sexually dimorphic pathways were only recently identified. However, the underlying molecular mechanisms and pharmaceutical implications remain unclear. We highlight the importance of studying the sex-specific patterns of mental diseases at all levels from genomics to pharmaceutics. In particular, we discuss transcriptional level differences between the sexes in psychiatric disorders and outline the possible impact of such research on future pharmaceutical developments.

Differences between Sexes in Psychiatric Disorders

The fact that psychiatric disorders display different prevalences between the sexes is not new. Whereas anxiety and stress-related disorders such as post-traumatic stress disorder (PTSD) [1,2] and major depressive disorder (MDD) [3] are more common in females, addiction is more common in males [4]. Disease characteristics may also vary between the sexes, including earlier age of schizophrenia (SCZ) onset in males [5], and different suicidal tendencies between the sexes. Females show a higher rate of suicide attempts, whereas males present higher suicide rates. A recent cross-national study identified increased suicidal intent in males as a possible contributing factor to this difference [6]. Sociological factors may explain some of these gaps. For example, females are more likely to be exposed to specific stressors that cause PTSD, such as sexual violence [2]. However, these factors fail to fully explain the epidemiological variability between the sexes. This indicates that biological differences also participate in defining the sexually dimorphic nature of many psychiatric disorders [2,3].

The association of mental conditions with hormonal changes supports this claim. Examples include depression associated with antiandrogen therapy in males [7] and with menopause in females [8]. In addition, premenstrual dysphoric disorder is associated with both sex hormone levels and so far unidentified genetic and epigenetic mechanisms [9]. Animal models have also revealed effects of sex hormones on a plethora of brain-related attributes such as neurotransmitter levels [10], fear extinction [2] and hypothalamic–pituitary–adrenal axis activation [11] that is known to be related to the development of psychiatric disorders.

More recently, genome-wide association studies (GWAS, see Glossary) in humans have identified sex-specific genetic risk factors for PTSD [12] and for risky sexual behavior [13]. However, some psychiatric disorders do not show a genetics-based sex bias. Comparison of GWAS and population data for attention-deficit hyperactivity disorder (ADHD) revealed no sex-dependent genetic risk factors despite the higher prevalence of ADHD in males compared with females [14]. Continued sex-based analyses of epidemiologic studies are therefore called for, and accumulating GWAS data on psychiatric disorders will hopefully assist in such analyses.

Highlights

Sex differences in various epidemiological features of psychiatric diseases may have both sociological and biological etiologies.

General and psychiatric drugs demonstrate sexually dimorphic pharmacokinetics and pharmacodynamics. Research on sex differences in disease mechanisms and drug therapies is necessary.

Brain transcriptome profiling has revealed many sex- and disease-specific expression patterns. These include regulatory pathways in major depressive disorder, bipolar disorder, and schizophrenia.

Brain long noncoding RNA (IncRNA) expression patterns are often sex-biased.

IncRNAs are prominent at the interface between psychiatric and neurodegenerative disease, such as in the case of NEAT1.

IncRNA expression is often affected by drugs. Pharmacotranscriptomic aspects of common drugs may have a sex-specific role involving IncRNA expression. Further study is needed in this developing field.

¹The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel
²The Edmond and Lily Safra Center for Brain Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel
*Correspondence: hermona.soreq@mail.huji.ac.il (H. Soreq).

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Notably, both drug efficacy and the nature and prevalence of side effects in response to treatment with neurotrophic and nonneurotrophic drugs differ between males and females, reflecting both differences in basic physiology and different disease mechanisms [15,16]. For example, sex-related differences have been observed in the pharmacokinetics of several neurotrophic drugs (Figure 1). Several antipsychotics such as clozapine, olanzapine and amisulpride were demonstrated to reach higher concentrations in the plasma of female patients, whereas ziprasidone and quetiapine did not exhibit such differences, and others such as risperidone exhibited conflicting trends in different studies [17].

Similar observations were also made for antidepressants. For example, the tricyclic antidepressant clomipramine reaches higher concentrations in the plasma of females [18], as do many antidepressants of the selective serotonin reuptake inhibitor (SSRI) class [19]. Although some studies mark the difference in SSRI levels as more prominent in young patients [20], others point to elderly patients [19], stressing the need for additional research on larger populations. Conversely, low-dose ketamine, which is also used as an antidepressant, reached higher levels in the plasma and brain of male compared with female rats [21]. Inhaled substances may also have sex-biased pharmacokinetics, as observed for smoked cannabis. Plasma concentrations of the active component tetrahydrocannabinol (THC) were higher in males compared with females [22].

Sex-specific differences in drug efficacy have also been observed in diseases such as Alzheimer’s disease (AD) and MDD. A study of 184 AD patients revealed a stronger response of females to treatment with cholinesterase inhibitors, possibly mediated through specific genotypes of the estrogen receptor ESR1 [23]. The underlying sex-related differences in cholinergic brain circuits [24] may mediate this effect. In addition, comparing electroencephalography (EEG) patterns and drug responses in MDD identified a female–specific association between particular EEG patterns and drug response. Specifically, females with specific EEG patterns displayed remission in response to the SSRIs escitalopram and sertraline, but not to the selective serotonin/noradrenaline reuptake inhibitor (SNRI) venlafaxine [25].

Importantly, sex-biased side effects include psychosis induced by antiepileptic drugs, which is more common in females [26]. In addition, many widely used antipsychotics cause depletion of bone mineral density (BMD), which may result in osteoporosis. Recent reports identify greater antipsychotic-induced BMD decline in males compared with females [27]. This is accompanied by sex-biased risk factors for BMD depletion (such as concomitant SSRI use in females) [28]. Together, this growing body of evidence reinforces the importance of taking sex differences into account when selecting treatment modalities in patients with psychiatric disease. However, a recent meta-analysis demonstrated that women were under-represented in most clinical trials of new long-acting antipsychotic drugs. Consequently, both main and secondary variables were generally not analyzed separately by sex [29], which calls for amendments.

Sex Chromosome-Driven Transcriptional Differences between Males and Females
The basic biological difference between males and females stems from two general mechanisms. One is the activation of the sex-determining region Y (SRY) gene in the gonads during embryogenesis, which initiates the formation of testicles (or ovaries in the absence of SRY) and results in differential sex hormone secretion patterns [30]. The sex hormones themselves then exert numerous effects on various aspects of cell function including transcription [31], mitochondrial activity [32], and activation of signaling via cell surface and intracellular receptors [33], among others. The second mechanism lies in the sex chromosomes, X and Y: males carry one X and one Y chromosome, whereas females carry two copies of the X chromosome (Figure 2A).
females, one X chromosome is largely inactivated by the X-inactive specific transcript (XIST) **long noncoding RNA (lncRNA)** [34], although, importantly, some areas on the X chromosome do escape inactivation [35], thus producing a sexually dimorphic transcription pattern [36]. Notably, XIST is regulated by the small microRNAs (miRs), and subsequent ‘sponging’ of these miRs draws them away from their other targets, thus reducing their regulatory effects on these targets [37,38]. This in turn suggests that XIST, that is also expressed in the brain, may exert substantial effects on the female transcriptome in general. Recent research has identified the transcription of male-specific lncRNAs such as TTTY15 and Inc-KDM5D-4 from the Y chromosome as well [39,40]. Another group of small noncoding RNAs includes the recently rediscovered **tRNA fragments (tRFs)** that may function like miRs and whose levels changes in the plasma of pre-seizure epileptic patients [41], in blood cells of ischemic stroke patients [42], and in a sex-dependent manner in the serum of Parkinson’s disease (PD) patients, suggesting that they are relevant for brain activities and for sex differences.

Additional complexity is added by the existence of gametologs – pairs of **homologous genes** on the X and Y chromosome which exert similar functions, and whose activities lead to similar combined protein levels in males and females (because they escape X inactivation) [35]. Although the...
protein coding sequence of homologs is generally conserved, miR regulation of their untranslated regions sometimes differs [43,44]. The same is likely to also apply to gametologs (Figure 2B). For example, bioinformatic predictions of miR regulation using the miRWalk 2.0 algorithm [45] display very little overlap for the gametologs KDM5C and KDM5D, but substantial overlap for the gametologs DDX3X and DDX3Y, indicating distinct regulation patterns of such gametologs by miRs. This mechanism of transcriptional variance, based on differential miR ‘sponging’ and consequent effects on large transcriptional networks, awaits investigation.

The relevance of sex chromosome-driven transcriptional changes to the human brain has only been shown in a handful of cases, including the expression of Y-chromosome IncRNAs in the developing human brain [46], elevated XIST levels in post-mortem brains of female bipolar disorder (BD) and MDD patients [47], and the involvement of SRY expression in the substantia nigra dopaminergic cell death in PD, which often involves mental impairments [48] (Figure 2C). Notably, syndromes with characterized karyotype alterations in sex chromosomes (such as XO, XXY, XYY, and others) could be helpful in studying the effects of the sex chromosomes on transcription, including large regulatory autosomal networks [96]. Further research into these syndromes may help to elucidate the interactions between noncoding RNAs and gametologs and the potential transcriptome-wide effects of differential miR regulation over gametologs.

**Differences in Transcription Patterns between Male and Female Brains**

Discoveries of brain transcriptomic differences between sexes have been fueled by the recent blossoming of ‘big-data’ studies characterizing the entire molecular landscape of various tissues,
organisms, and diseases (often referred to as 'omic' studies – transcriptomics, proteomics, metabolomics, and others). These studies present an outstanding opportunity for scientists to coanalyze their biomedical findings with large web-available datasets and reach novel, well-substantiated conclusions. Indeed, careful comparison has revealed substantial differences between brain transcription patterns from healthy male and female donors [49], and some genes also display conserved sex-biased expression patterns across mammalian species [50]. Moreover, microglia from murine male and female brains display different transcription patterns. Ovariectomy does not reverse these patterns entirely, thus indicating the involvement of additional causes apart from circulating estrogens [51]. Transcriptomic analyses further revealed delayed microglial maturation in developing male compared with female mice [52]. Proteomics, morphological features, and the distribution of microglia in different brain regions also revealed sexually dimorphic properties [53]. Likewise, the developing mouse hippocampus showed sexually distinct transcription patterns [54].

Although comparisons of the molecular landscapes in male versus female brain disease are still rare, probably because of low tissue accessibility, several such comparisons have recently been published that report sex-related transcriptomic differences in psychiatric diseases. Specifically, brain transcriptome differences suggest sex-biased mechanisms associated with MDD. In stressed mice, which serve as a model for depression, inhibitory interneurons in the prefrontal cortex display sexually dimorphic transcriptional changes [55]. Supporting this notion, miR–mRNA network analysis in the nucleus accumbens of similarly stressed mice revealed mostly nonoverlapping pathways between males and females [56]. In addition, whole-tissue transcriptomes of mRNA across six human brain regions revealed distinct male and female MDD networks [57]. Cortical transcriptomes from SCZ and BD patients have also revealed sex-biased pathways. Although some BD pathways were enriched for both male- and female-specific transcripts, a larger sex-bias was observed in SCZ where different pathways were enriched for transcripts that change differently in males and in females [58]. Sex-specific transcription patterns in the brain have therefore been identified in several psychiatric diseases, although the underlying mechanisms often remain obscure.

The dual roles of the neurotransmitter acetylcholine as both a neuromodulator [59] and a modifier of inflammation [60] make it a potential mediator of such sex differences. A prominent example can be seen in the metabolic side effects of antipsychotic drugs in patients with SCZ. These side effects have been shown to involve the histaminergic and cholinergic systems [61], and appeared to affect males and females to a different extent [62,63]. Intriguingly, short RNA-Seq from neuroblastoma-derived cell lines of human male and female origin revealed sexually dimorphic miR profiles upon cholinergic differentiation. Specifically, that analysis highlighted female-biased expression of the miR-10 family and male-biased expression of the miR-199 family, both of which regulate cholinergic activities [58]. This suggests that the cholinergic system may be involved in some of the observed sex differences in these and possibly other psychiatric disorders through sex-specific miR regulation, with possible implications for studying and understanding disease development, progression, and treatment.

Transcriptional networks revolve around hub genes whose expression patterns correlate best with the network and that are often regulatory genes in these networks; in human MDD patients, different hub genes were identified for each sex, including DUSP6 in females and EMX1 in males. In a mouse model, these genes demonstrated sex-specific functional roles in the susceptibility to depression [57]. Furthermore, pathway analysis of MDD brain transcriptomes revealed male-associated enrichment of pathways linked to neurological and psychiatric disorders [64]. The traditionally biased male-centric preclinical research [65] may hence lead in some cases to the identification of 'disease-associated genes' which might actually be 'male disease-associated
genes’. Comparative analysis of transcription patterns in male and female brains with or without disease may resolve this issue.

Lack of Correlation between the Brain Transcriptome and Proteome
Although transcriptome differences between male and female brains of patients with psychiatric diseases are relatively well established, it is important to note that transcriptome–proteome correlations in general are only modest [66], affecting the validity of the observed transcriptional changes in protein-coding genes. Specific transcriptome–proteome inconsistencies have been observed in multiple datasets, including in the brain, for example, in the developing murine hippocampus [54]. In another example, meta-analysis of synaptic proteins in the brains of SCZ patients revealed several proteome–transcriptome inconsistencies, including changes in the mRNA levels of CPLX1 and CPLX2 but not in the levels of the proteins they encode – complexin I and complexin II [67]. In addition, the levels of brain-derived neurotrophic factor (BDNF) mRNA but not its protein product displayed sexually dimorphic behavior in MDD brain, indicating that transcriptome–proteome inconsistencies may also be relevant for sex differences in psychiatric diseases [68]. These studies stress the importance of performing both RNA and protein measurements in brain disorders to fully understand the functionality of the transcriptome of coding genes. However, proteomic characterizations pose distinct challenges and require considerably larger amounts of biological material compared with transcriptomic analysis. This complicates studies of brain disorders, where biological material is often very scarce.

The Potential of IncRNAs for Studying Sex-Specific Differences in Brain Disorders
Apart from protein-coding genes and transcriptional networks, transcriptomic analysis can also identify deregulation of noncoding RNAs such as IncRNAs [69]. Unlike coding transcripts, IncRNAs are functional at the RNA level [70], simplifying the interpretation of their activities based on transcriptomic data alone and making their study in such methods more revealing.

Recent research has identified the expression of IncRNAs from the Y chromosome in the developing human brain [46]. Similarly, a nonbiased transcriptomic analysis of several areas from the macaque brain revealed substantial sex-biased IncRNA changes. Interestingly, the observed sex bias was larger for IncRNAs than for mRNAs [71], although the underlying mechanism(s) is unknown. IncRNAs were also identified at the intersection of psychiatric disease and sex differences, in both peripheral tissues and the brain. A recent survey of six candidate IncRNAs in peripheral blood cells from SCZ patients and controls revealed a female-specific change in the expression of five of those IncRNAs – HOXA-AS2, Linc-ROR, MEG3, SPRY4-IT1, and UCA1 [72]. However, 83 other peripheral blood IncRNAs showed no sex-specific expression differences in MDD patients compared with controls [73], indicating that this difference is not global. In human brain, recent research has identified an important role for IncRNAs in sex differences. An example is NEAT1, an IncRNA that forms the scaffold enabling the formation of nuclear paraspeckles that bind transcription factors, miRs, and other small molecules to regulate their function [74]. Interestingly, NEAT1 levels are reduced in the cortex of patients with SCZ [75], whereas they are elevated in the caudate nucleus of Huntington’s disease patients [76], as well as in the substantia nigra of PD patients [77], neurodegenerative conditions that both often involve mental impairments and dementia [78,79]. Notably, NEAT1 is regulated by the estrogen receptor [31], suggesting a potential sexual dimorphism for its function and/or its manipulation. In addition, NEAT1 levels are modified under treatment with a variety of drugs, including lipid-lowering agents [77] and psychotropic drugs [80]; such changes may affect the various functions of NEAT1, including those involving psychiatric disorders.

Although IncRNAs may readily be investigated using transcriptome data, several aspects of their biology pose particular research challenges. For example, the function of many IncRNAs remains
unknown, precluding further follow-up such as pathway analysis [81]. In addition, lncRNAs show high interindividual variability [82], which translates to lower $P$ values for similar fold changes of transcript levels when interrogating their differential expression between groups. Further, many lncRNAs show very low evolutionary conservation and are expressed at very low levels that are considered by some to be ‘transcriptional noise’ [70]. The combination of these challenges

Figure 3. Screening for Long Noncoding RNA (lncRNA) Roles in Psychiatric Disease. (A) A three-stage approach to identifying sex-specific gene expression patterns; the first two steps are also applicable to lncRNA analysis. (B) lncRNAs show higher variability and lower expression levels compared with protein-coding mRNAs. (C) The main challenges to lncRNA analysis are high variability, low expression levels, and unknown biologically significant functions. The combined calculated score (CCS), based on combined global expression level and $P$ values, can overcome part of these difficulties and provide a more reproducible prediction of the roles of lncRNAs than the $P$ value alone. Abbreviation: DE genes, differentially expressed genes.
impedes identification of specific lncRNAs that are involved in particular conditions using traditional analysis based on $P$ values alone. To address this issue, we propose that combining expression levels and $P$ values would enable better identification of sexually dimorphic lncRNAs. To challenge this concept, we analyzed lncRNA expression via a scoring approach which ranks lncRNAs by both the $P$ values of their expression differences and their expression levels. This combined calculated score (CCS) \[83,84\] provides more reproducible results than those achieved by $P$ value alone \[84\] (Figure 3). Using this method, we found that RP11-386G11.10

| Gene Expression Omnibus identifier | Disease   | Tissue (as defined by data submitter) | Number of samples available |
|-----------------------------------|-----------|---------------------------------------|-----------------------------|
|                                   |           |                                       | Control male | Control female | Diagnosed male | Diagnosed female |
| GSE125583                         | AD        | Fusiform gyrus                        | 37           | 33            | 121           | 97             |
| GSE102741                         | ASD       | Dorsolateral prefrontal cortex (DLPFC) | 30           | 8             | 10            | 3              |
| GSE9288 + GSE51264                | ASD       | Prefrontal cortex (PFC)               | 27           | 12            | 18            | 7              |
| GSE80655                          | BD        | Anterior cingulate cortex              | 27           | 3             | 19            | 9              |
| GSE80655                          | BD        | DLPFC                                 | 27           | 3             | 20            | 8              |
| GSE80655                          | BD        | Nucleus accumbens (Nac)                | 25           | 2             | 21            | 10             |
| GSE112523                         | BD        | Frontal cortex                        | 14           | 3             | 5             | 5              |
| GSE80336                          | BD        | Dorsal striatum                       | 7            | 11            | 6             | 12             |
| GSE53239                          | BD        | DLPFC                                 | 6            | 5             | 6             | 5              |
| GSE78306                          | BD        | BA11                                  | 9            | 3             | 8             | 8              |
| GSE42546                          | BD        | Dentate gyrus granule cells           | 17           | 12            | 9             | 7              |
| GSE80655                          | MDD       | Anterior cingulate cortex              | 27           | 3             | 24            | 6              |
| GSE80655                          | MDD       | DLPFC                                 | 27           | 3             | 22            | 9              |
| GSE80655                          | MDD       | Nucleus accumbens                     | 25           | 2             | 25            | 8              |
| GSE42546                          | MDD       | Dentate gyrus granule cells           | 17           | 12            | 10            | 7              |
| GSE102556                         | MDD       | Nac                                   | 13           | 9             | 15            | 13             |
| GSE102556                         | MDD       | Orbitofrontal cortex (OFC; BA11)      | 13           | 9             | 13            | 13             |
| GSE102556                         | MDD       | DLPFC (BA8/9)                         | 13           | 9             | 13            | 13             |
| GSE102556                         | MDD       | Cingulate gyrus 25 (Cg25)             | 8            | 7             | 3             | 10             |
| GSE102556                         | MDD       | Anterior insula (aINS)                | 13           | 9             | 13            | 13             |
| GSE102556                         | MDD       | Subiculum (Sub)                       | 12           | 7             | 12            | 12             |
| GSE101521                         | MDD       | DLPFC (BA09)                          | 23           | 6             | 19            | 11             |
| GSE114517                         | PD        | Substantia nigra                      | 4            | 5             | 10            | 4              |
| GSE110716 (Coding exome only)     | PD        | Cingulate gyrus                       | 4            | 4             | 4             | 4              |
| GSE80655                          | Schizophrenia | Anterior cingulate cortex            | 27           | 3             | 25            | 3              |
| GSE80655                          | Schizophrenia | DLPFC                            | 27           | 3             | 25            | 4              |
| GSE80655                          | Schizophrenia | Nac                            | 25           | 2             | 23            | 4              |
| GSE107638                         | Schizophrenia | BA46 (neuronal nuclei)             | 18           | 9             | 11            | 12             |
| GSE107638                         | Schizophrenia | BA46 (oligodendrocyte nuclei)        | 15           | 7             | 7             | 10             |
| GSE78336                          | Schizophrenia | BA11                         | 9            | 3             | 11            | 5              |
| GSE42546                          | Schizophrenia | Dentate gyrus granule cells          | 17           | 12            | 9             | 8              |

*Abbreviations: AD, Alzheimer's disease; ASD, autism spectrum disorder; BA, Brodmann area; BD, bipolar disorder; MDD, major depressive disorder; PD, Parkinson's disease. [www.ncbi.nlm.nih.gov/geo].
is involved in autism, compatible with other reports [85], and identified functionally important lncRNAs in PD brain [84].

Concluding Remarks and Future Perspectives

Sexual dimorphism in psychiatric disorders is repeatedly observed in epidemiology, drug efficacy, and side-effect studies. However, both preclinical and clinical trials largely fail to balance the male and female participants, and further often neglect to analyze the results in a sex-separated manner, hindering proper characterization of such sex differences.

Recent developments have changed our understanding of the molecular mechanisms underlying sex differences in mental disorders. In particular, studies have identified sex-dimorphic transcriptomic networks in MDD, SCZ, and BD. In the latter two cases, the cholinergic system is involved both in disease pathology and in drug response, and the findings associated sex differences with impaired cholinergic regulation.

The recent emergence of lncRNAs as pivotal to sex-related differences calls for focusing on these transcripts in the context of mental diseases: because some lncRNAs display sexually dimorphic properties, they constitute a possible mechanism by which drugs may cause sexually dimorphic outcome and/or side effects. However, the scarce data on the differential functions of lncRNAs in male and female disease patterns complicates that goal.

Our review suggests several avenues for studying the sex-specific divergence of RNA expression patterns in psychiatric disease between male and female brains that have effects on treatment (see Outstanding Questions), focusing on noncoding RNA species such as lncRNAs and tRFs. Importantly, we stress the need for awareness of the pressing issue of balancing male and female participants in preclinical and clinical trials for psychiatric disorders.

We also call for studying selective sex-related targeting of cholinergic networks. New insights into these networks may assist in disease treatment, fine-tuning of drug efficacy, and reducing side effects. Future transcriptome-wide analysis of sex differences in lncRNA expression patterns in disease may also be of value, and we have compiled a list of web-available datasets that can be reanalyzed towards that goal (Table 1). Finally, correct pharmacotranscriptomic analysis can identify sex-related effects of commonly used drugs on the transcription of brain lncRNAs and shed new light on the clinical relevance of such effects.

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Outstanding Questions

What can be done to facilitate sex-related preclinical research and ensure the performance of clinical trials that analyze drug efficacy, side effects, and impact on disease pathology in men and women separately?

In which ways does miR and lncRNA regulation of gametologs affect the brain transcriptome in health and disease, and in males compared with females?

Does sexually dimorphic cholinergic signaling selectively modulate psychiatric disorder symptoms and the side effects of therapeutics?

To what extent does sexual dimorphism affect the expression patterns of brain lncRNAs in psychiatric diseases, and does it relate to patient responses to therapeutics?

What is the clinical significance of sex-related drug effects on lncRNA transcription?

Do the recently rediscovered tRNA fragments show sex-related differences in specific brain regions and responses to pharmacology?
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