Review

Biological Psychiatry

Noncoding RNAs: Stress, Glucocorticoids, and Posttraumatic Stress Disorder

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a pathologic response to trauma that impacts ~8% of the population and is highly comorbid with other disorders, such as traumatic brain injury. PTSD affects multiple biological systems throughout the body, including the hypothalamic-pituitary-adrenal axis, cortical function, and the immune system, and while the study of the biological underpinnings of PTSD and related disorders are numerous, the roles of noncoding RNAs (ncRNAs) are just emerging. Moreover, deep sequencing has revealed that ncRNAs represent most of the transcribed mammalian genome. Here, we present developing evidence that ncRNAs are involved in critical aspects of PTSD pathophysiology. In that regard, we summarize the roles of three classes of ncRNAs in PTSD and related disorders: microRNAs, long-noncoding RNAs, and retrotransposons. This review evaluates findings from both animal and human studies with a special focus on the role of ncRNAs in hypothalamic-pituitary-adrenal axis abnormalities and glucocorticoid dysfunction in PTSD and traumatic brain injury. We conclude that ncRNAs may prove to be useful biomarkers to facilitate personalized medicines for trauma-related brain disorders.

Keywords: Glucocorticoids, Long-noncoding RNA, MicroRNA, Noncoding RNA, PTSD, Retrotransposons, Stress, TBI

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Posttraumatic stress disorder (PTSD) is the simultaneous presentation of four symptom clusters—intrusions, avoidance, negative cognitions, and hyperarousal—initiated after the experience of a traumatic event (1). It is a common condition with prevalence rates of 4% to 8% (2) and is highly comorbid with other psychiatric diagnoses and traumatic brain injury (TBI), particularly in military populations (3,4). The clinical definition is not rooted in biology, yet molecular (5,6) and circuit-defined (7,8) subtypes have been proposed, elucidating its biological heterogeneity. Historically regarded as a brain disease, PTSD affects whole body health (9,10), and its effects can potentially be measured peripherally (e.g., blood). In pursuit of biomarkers and a deeper understanding of PTSD pathophysiology, the role of noncoding RNAs (ncRNAs) is prime for exploration and should be studied together with alterations in coding RNAs (11).

The majority of the genome is transcribed, but until recently, research focused only on the 2% of the genome encoding proteins (12). The remainder constitutes the noncoding genome, which is widely transcribed into ncRNAs. In this review, we consider the role of three classes of ncRNAs in PTSD: the well-characterized microRNAs (miRNAs), which are 21 to 23 nucleotides in length; long-noncoding RNAs (lncRNAs), classified as RNA longer than 200 nucleotides; and retrotransposons, which range between 400 and 6000 nucleotides in length.

Functionally, the primary role of miRNAs is to regulate RNA stability and translation (13) (Figure 1A). lncRNAs interact with DNA, other ncRNAs, and proteins, and they are implicated in processes covering a wide range of transcriptional (e.g., guide, decoy, scaffold), posttranscriptional (e.g., miRNA sponges, RNA splicers), and posttranslational modifications (e.g., messenger RNA [mRNA] decay, cellular localization of RNA- or DNA-binding proteins) (14) (Figure 1B). Contrastingly, the function of most retrotransposons remains poorly understood. Many have been shown to regulate transcription and maintenance of heterochromatin structure and likely represent a bank of regulatory elements, such as alternative promoters. Also, due to their high interindividual variance, retrotransposons may represent useful biomarkers of disease susceptibility. ncRNAs are often classified as epigenetic mechanisms together with DNA methylation and histone modifications. This kind of molecular mechanism may be retained through meiosis and can lead to transgenerational or intergenerational epigenetic transmission, where epigenetic information transmits from parents to offspring (15,16).

The number of functional RNA units in mammalian genomes has been estimated as high as ~4 million (17). The number of annotated ncRNA genes exceeds that of protein-coding genes (18) (Table 1) and is constantly increasing as RNA sequencing identifies previously undetected RNA transcripts across various tissues. These estimates imply that most genomic functional complexity lies in genes that are largely unexplored. The prevailing theory is that the noncoding genome may be central to the evolution and development of multicellular organisms and cognition (19). The complexity of higher-level organisms seems to be driven by a more sophisticated regulatory architecture, relying on functional ncRNAs rather

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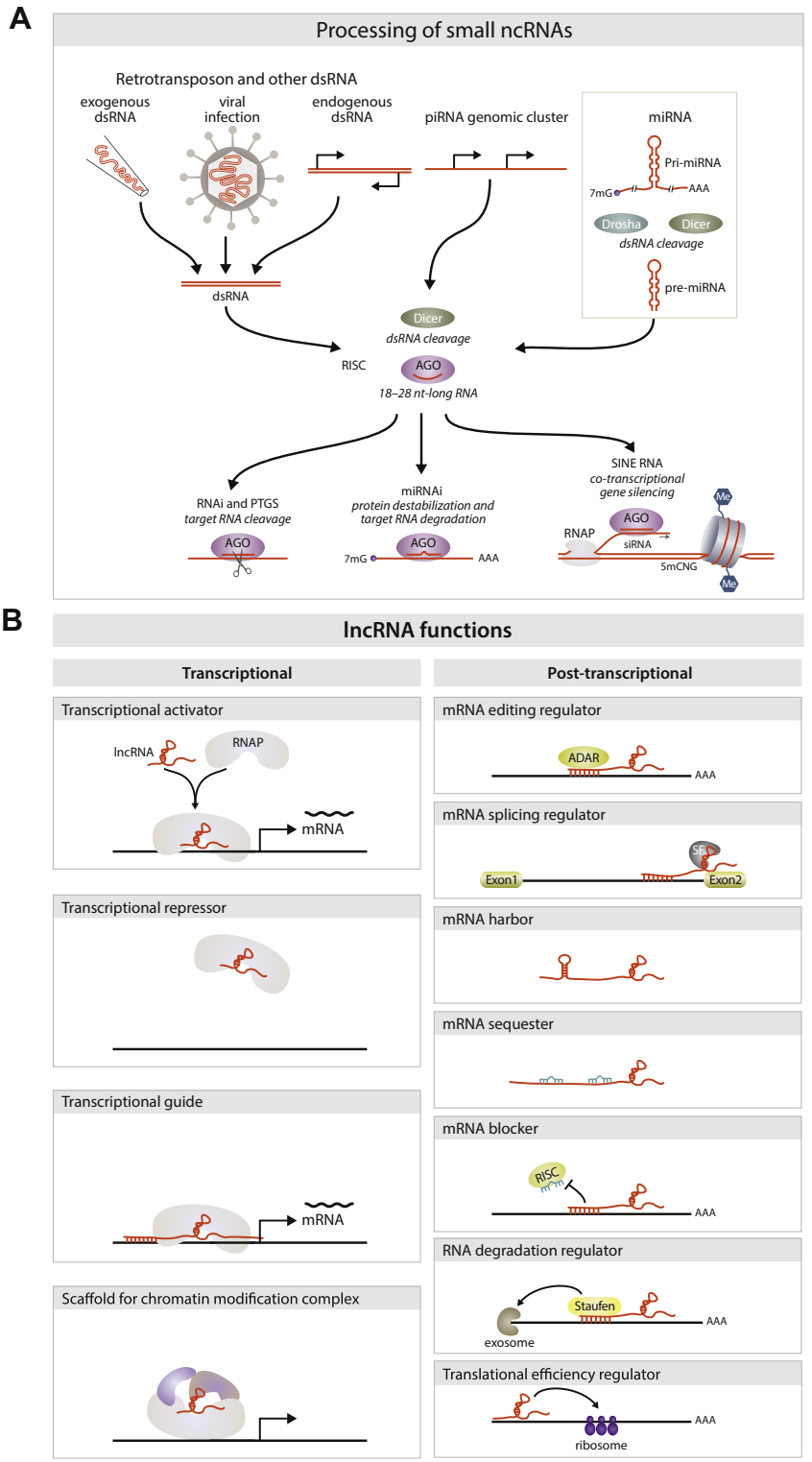

Figure 1. Noncoding RNA (ncRNA) mechanisms. **(A)** Processing of small ncRNAs from double-stranded RNA (dsRNA) by the Dicer and Drosha ribonucleases. A number of sources produce dsRNA, such as viruses (either endogenous or exogenous), microRNA (miRNA) genes, or the piwi RNA (piRNA) genomic cluster. Small ncRNAs are then able to target RNAs for cleavage or degradation, act as miRNAs on protein or RNA stability, as well as direct inhibition of transcription. [Adapted with permission from Sarkies and Miska (142).] **(B)** Known regulatory functions of long-noncoding RNAs (lncRNAs) include (clockwise from top right) interactions with the adenosine deaminase acting on RNA (ADAR) RNA editing complex, which converts adenosine to inosine; lncRNAs may interact directly with nascent messenger RNA (mRNA) to prevent splicing (and may be spliced in itself to produce hybrid transcripts); they may act as an miRNA sink or block miRNA from interacting with target RNAs (either regulatory or mRNA); they may regulate the degradation and transport of other RNAs through interactions with Staufen proteins; lncRNAs might also interact with mRNAs and ribosomes during translation to alter the efficiency of that process; lncRNA may help form scaffolds for epigenetic modification machinery, assist in targeting transcription factors to target sites in the genome, or repress transcription or activate it (143–145). [Adapted with permission from Yang *et al*. (143).] AAA, poly adenosine tail; AGO, argonaute; Me, methyl group; miRNAi, miRNA-mediated RNA interference; Pri-miRNA, primary miRNA; PTGS, posttranslational gene silencing; RISC, RNA-induced silencing complex; RNAi, RNA interference; RNAP, RNA polymerase; SF, splicing factor; SINE, short interspersed nuclear elements; siRNA, small interfering RNA; 5mCNG, methylated CpG site; 7mG, 7-methylguanine.

than an expansion of protein-coding genes. In contrast to protein-coding genes, ncRNAs are selected more by structure than sequence (20). The noncoding genome shows higher levels of interindividual (21), between-tissue (22), and interspecies (22) variability than the protein-coding genome does. Indeed, the difference between the noncoding genome of humans and chimpanzees is at least twice that found in their coding genome (23). Thus, pathophysiological research and

Table 1. Landscape of Noncoding RNAs

ncRNA Species	No. Gene/Sequences		
	Human (hg38)	Mouse (mm10)	Rat (rn6)
miRNA	1890	2254	1588
lncRNA (lncRNA and antisense)	24,229	11,544	3,379
Retrotransposons (LINE/LTR/SINE)[a]	1,570,523/754,264/1,852,583	989,435/973,534/1,533,283	1,007,640/914,902/1,517,721

This table reports the number of the three noncoding RNA (ncRNA) classes considered in this review according to release 91 of Ensembl Genes Database for Human, Mouse and Rat species (useast.ensembl.org/biomart). There are several other databases that report different numbers of ncRNAs, although some are species-specific, such as lncRNAdb (www.lncrnadb.org/), LNCipedia (https://lncipedia.org/), FANTOM CAT (fantom.gsc.riken.jp/cat/), and MiTranscriptome (mitranscriptome.org/), while other are more comprehensive, such as NONCODE (www.noncode.org/).

hg38, *Homo sapiens* reference genome version 38; LINE, long interspersed nuclear elements; lncRNA, long-noncoding RNA; LTR, long terminal repeat; miRNA, microRNA; mm10, *Mus musculus* reference genome version 10; rn6, *Rattus norvegicus* reference genome version 6; SINE, short interspersed nuclear elements.

[a]Repbase: www.girinst.org/repbase/.

the pursuit of biomarkers and novel therapeutics for stress-related disorders, which present with substantial interindividual variation in susceptibility, would benefit by the inclusion of ncRNAs.

The role of ncRNAs in the pathophysiology of neuropsychiatric disorders has been thoroughly reviewed elsewhere (24–28). Despite compelling results implicating biological pathways such as the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid receptor (GR) signaling, the genetic determinants of PTSD and the molecular mechanisms underlying PTSD pathophysiology remain poorly understood (29). Here, we will consider evidence emerging from animal and clinical studies of trauma-related disorders and PTSD-like syndromes to illustrate the potential role of ncRNAs in PTSD pathophysiology. Evidence that GR signaling, along with other biological pathways, might be regulated by ncRNAs underscores their attractive potential as risk factors, diagnostic biomarkers, and drug targets, which have been successfully exploited in cancer, cardiovascular, and immune conditions (14).

MICRORNAs

miRNAs inhibit translation of 50% of the transcriptome and are highly conserved and abundant (13). There are specific chromosomes observed in each species where the numbers of miRNA genes are high; in humans, ~29% of miRNAs map on chromosomes 1, 2, 19, and X. After transcription, miRNAs undergo transcript-specific maturation steps (by Drosha in the cell nucleus; by Dicer in the cytoplasm) to become functional (Figure 1A). They bind to 3' untranslated region or non-3' untranslated regions of their target mRNAs to repress protein expression through a combination of translation silencing and mRNA destabilization (13) (Figure 1A).

miRNA Expression Profiles in Healthy Versus Pathologic States

miRNA expression profiles are widely distributed across human tissues, and while single miRNAs are not unique to individual tissues or cell types, they are more highly expressed in a subset of tissues (30–32), including different brain regions (33). This information is readily available through databases of miRNA target predictions and expression profiles (e.g., www.microrna.org) (34). In abnormal or dysfunctional tissue, individual miRNAs, usually retained in healthy tissue, can be selectively released (35). Since they can pass through the blood-brain barrier, due to their small size, and are stable in blood (36), they are relevant targets for peripheral measurement and have been a topic of recent interest in neuropsychiatry (24,26,28).

miRNA in Animal Studies

Validating animal models of PTSD with translational value has been challenging, similarly to most psychiatric disorders, where the primary focus has been face validity rather than etiologic or construct validity (37). Most models investigate biological responses to stressful stimuli (restraint stress, social defeat stress, predator exposure, foot shock, etc.), but they do not focus on individual differences of stress response (37). PTSD-specific models, such as single prolonged stress, have not measured ncRNAs, while models of anxiety, depression, and fear have reported on ncRNAs (Table 2). However, distinctions between animal models of specific psychiatric outcomes are likely artificial (38). All models probably map broadly onto stress-related psychopathology, including not only PTSD, but also depression, anxiety, addiction, and aggression, which often co-occur.

Prolonged activation of the HPA axis after chronic restraint stress (CRS), occurring only in Fischer 344 inbred rats, and not in control Sprague Dawley outbred rats, was associated with miR-18a-dependent GR downregulation (39). In stress-responsive regions of the rodent brain, acute restraint stress (ARS), compared with CRS, differentially affects the miRNA transcriptome. Meerson *et al.* (40) demonstrated miR-134 and miR-183 upregulation in the central nucleus of the amygdala (CeA) following ARS, compared with unstressed control animals, while CRS downregulated miR-134 in both the CeA and hippocampal CA1 region.

In adult mice, *Dicer1* ablation in CeA increased anxiety-like behavior, but it did not change the corticosterone response to ARS. ARS shifted the miRNA expression profile in the amygdala of wild-type mice and upregulated miR-34c. Subsequently, amygdala miR-34c overexpression prevented ARS-induced anxiety, possibly through downregulation of *Crhr1*, encoding corticotropin-releasing hormone receptor 1 (41). Another study revealed that ARS downregulates amygdala levels of miR-135a and miR-124 in parallel with upregulation of one of their target genes, *Nr3c2,* encoding the mineralocorticoid receptor, the other receptor for glucocorticoids (GCs) (42).

Table 2. Noncoding RNA Findings in Animal Stress Studies

Focus	Species	Sample Size	Tissue	Methods	No. of Hits	No. of Measured	Statistical Cutoff	Main Findings	Experiment for Causal Evidence	Ref.	GEO No.
miRNA											
CRS	Rat	Naïve: 6 Stress: 6	PVN	qRT-PCR	1	1	$p < .05$	miR-18a upregulated in F344 rats prestress and poststress	Transfected with miR-18a expression vector in SH-SY5Y cells	(39)	None
ARS	Rat	Naïve: pool of 3 or 4 Stress: pool of 3 or 4	Central amygdala	Customized spotted array	10	200	$p < .05$ and LR > 0.25	ARS differentially affects the miRNA transcriptome (miR-132, miR-134, miR-183, let-7a-a, miR-9-1, miR-124a-1) when compared with CRS	Overexpression or knockdown of miR-183 in CHO cells	(40)	None
ARS	Rat	Naïve: pool of 3 or 4 Stress: pool of 3 or 4	Hippocampal CA1	Customized spotted array	16	200	$p < .05$ and LR > 0.25				
CRS	Rat	Naïve: pool of 3 or 4 Stress: pool of 3 or 4	Central amygdala	Customized spotted array	28	200	$p < .05$ and LR > 0.25				
CRS	Rat	Naïve: pool of 3 or 4 Stress: pool of 3 or 4	Hippocampal CA1	Customized spotted array	22	200	$p < .05$ and LR > 0.25				
ARS	Mouse	Naïve: 2 Stress: 3	Amygdala	miRNA microarray (Agilent); miRNA microarray (Affymetrix); qRT-PCR validation	NR	350	$p < .05$ and LR > 0.20 for Agilent, $p < .05$ and LR > 0.40 for Affymetrix	miR-15a, miR-15b, miR-34c, miR-34a, miR-92a, and miR-100 were upregulated across platforms	Overexpression of miR-34c in the CA	(41)	None
ARS	Mouse	Naïve: pool of 12 Stress: pool of 12	Amygdala	Customized miRNA microarray; qRT-PCR validation	14	288	LR > 1 and log intensity >8 and <14	miR-135a and miR-124 were downregulated	Overexpression of miR-135a and miR-124 in N2a cells	(42)	None
CSDS	Mouse	GFP_Naïve: 12 GFP_Resilient: 12 GFP_Susceptible: 4 b-catenin-Cre_Naïve: 12 b-catenin-Cre_Susceptible: 8	NAc	Small-RNASeq (Illumina)	400	NR	$p < .05$ and foc > 1.3 (in any of the pairwise comparisons)	b-catenin-dependent microRNA regulation associated with resilience	For cell-type specific overexpression, an HSV carrying β-catenin in a lox-stop cassette was used in conjunction with D1- and D2-Cre transgenic mouse lines. Viral-Cre was used for local knockdown of β-catenin or Dicer1 in conditional floxed mice.	(43)	GSE61295

Table 2. Continued

Focus	Species	Sample Size	Tissue	Methods	No. of Hits	No. of Measured	Statistical Cutoff	Main Findings	Experiment for Causal Evidence	Ref.	GEO No.
CSDS	Mouse	Naïve: 10–11 Resilient: 10–11 Susceptible: 10–11	PFC	qRT-PCR	1	1	$p < .05$	miR-218 downregulation in susceptible mice	Transfection with a synthetic miR-218 in IMR-32 cells	(44)	None
CSDS	Mouse	Naïve: 4 pools of 3 Stress: 6 pools of 3	Amygdala	miRNA microarray (Affymetrix); qRT-PCR validation	NR	1412		miR-19b upregulated	Overexpression or knockdown of miR-19b in the BLA	(45)	None
CSDS	Mouse	Naïve: 4 pools of 3 Stress: 6 pools of 3	Amygdala	miRNA microarray (Affymetrix); qRT-PCR validation	NR	1412	$p < .01$ and foc > 1.75	miR-15a upregulated	Overexpression of miR-15a in the BLA	(46)	GSE87488
CSDS	Mouse	4 per group	Heart	miRNA microarray (Exiqon); qRT-PCR validation	3	2383	FDR < 0.1 and foc $>$ 1.5	3 miRNAs (miR-29b, miR-302a, and let-7d) downregulated in the short exposure and short rest group	Transcriptome analyses on a mouse fibroblast cell line that was transfected with a miR-29 miRNA mimic	(48)	GSE52869; GSE52872
Subchronic variable stress	Mouse	Naïve: 3 per gender Stress: 3 per gender	NAc	Small-RNASeq (Illumina)	70	NR	$p < .05$ and foc > 1.3 (in any of the pairwise comparisons)	Male and female mice show different NAc miRNA profiles following subchronic variable stress	None	(146)	GSE90962
Shock, odor-exposure	Mouse	Naïve: 12 Shock/stress: 5–6	Hippocampus	qRT-PCR	1	1	$p < .05$	Pri-miR-132 upregulated	Kinetics of pri-miR-132 induction	(49)	None
Shock	Mouse	No shock + vehicle: 6 No shock + fluoxetine: 6 Shock + vehicle: 6 Shock + fluoxetine: 6	PFC	miRNA microarray (Exiqon); qRT-PCR validation	2	2383	$p < .05$ and FDR correction	miR-3559-3p and miR-1971 were downregulated by fluoxetine in shocked mice	None	(57)	None
FC	Mouse	Naïve: 4 FC: 4	Amygdala	miRNA microarray (Exiqon); qRT-PCR validation	2	2383	$p < .01$ and dLMR = 0.5	miR-34a and miR-187 upregulated	Knockdown of miR-34a in the BLA	(51)	GSE59072

Table 2. Continued

Focus	Species	Sample Size	Tissue	Methods	No. of Hits	No. of Measured	Statistical Cutoff	Main Findings	Experiment for Causal Evidence	Ref.	GEO No.
FC	Mouse	Naïve: 2 (in triplicate) FC: 2 (in triplicate)	Dorsal hippocampus	miRNA microarray (Exiqon); qRT-PCR validation	19	2383	foc > 0.5	5 miRNAs (miR-33, miR-381-5p, miR-136-5p, miR-144-39, miR-494-3p) predicted to target mRNAs encoding $GABA_A$ receptors	Overexpression or knockdown of miR-33 in the dorsal hippocampus	(52)	None
FC	Mouse	Naïve: 8 FC: 30 min: 8 FC: 2 hours: 8	Hippocampus	qRT-PCR	NA	NA	$p < .05$	miR-132 was upregulated 30 min after FC and returned to baseline in 2 hours	Knockdown of miR-132 in the hippocampus	(53)	None
FC	Rat	Naïve: 4 pools of the same 8 Unpaired: 4 pools of the same 8 Paired: 4 pools of the same 8	Lateral amygdala	miRNA microarray (Affymetrix); qRT-PCR validation	1	350	miRNAs predicted to target ≥1 of several ARPs and downregulated 2.0-fold in the paired group relative to naïve group	miR-182 downregulated	Overexpression of miR-182 in the lateral amygdala	(50)	None
FC	Rat	Naïve: 4 FC: 4	Hippocampus	miRNA microarray (Miltenyi); qRT-PCR validation	21	2063	$p < .05$ and foc > 1.5	Vesicular transport and synaptogenesis pathways as the major targets of the fear-induced miRNAs	Overexpression or knockdown of miR-153 in the hippocampus	(147)	GSE84262
Fear extinction	Mouse	Naïve: 5 FE: 5	Infralimbic PFC	qRT-PCR	2	3	$p < .05$	miR-128b upregulated	Overexpression or knockdown of miR-128b in the ILPFC	(55)	None
lncRNA											
SEFL	Rat	Naïve: 10 Stress: 10	Hippocampus	RNA microarray	769	38237	$p < .05$	143 lncRNAs and 167 mRNAs were upregulated and 150 lncRNAs and 309 mRNAs were downregulated	No	(90)	None
FC	Mouse	Naïve: 6 Context only: 6 FC: 5	mPFC	RNAseq	53	~30545	$p < .03$	53 loci were altered in either context-exposed or FC mice; *Gomafu* downregulated after FC	Knockdown of *Gomafu* in mPFC	(91)	None

Table 2. Continued

Focus	Species	Sample Size	Tissue	Methods	No. of Hits	No. of Measured	Statistical Cutoff	Main Findings	Experiment for Causal Evidence	Ref.	GEO No.
Retrotransposon RNA											
ARS	Rat	Naïve: 12 Stress: 12	Hippocampus	qRT-PCR	2	2	$p < .005$	Acute stress downregulation of IAP-ERV/LTR and B2 SINE RNA in the hippocampus but not other brain regions examined	No	(111)	GSE41217
SEFL	Rat	Naïve: 8 Stress: 8	Amygdala	RNA microarray (Illumina); qRT-PCR validation	1	22500	$p < .05$ and FDR correction	L1 transposase transcript upregulation by SEFL	No	(117)	None

ARP, actin regulatory proteins; ARS, acute restraint stress; BLA, basolateral amygdala; CA, central amygdala; Cre, Cre recombinase transgene; CRS, chronic restraint stress; CSDS, chronic social defeat stress; dLMR, difference in average expression levels between sample groups, log2 scale; ERV, endogenous retrovirus; FDR, false discovery rate; FC, fear conditioning; FE, fear extinction; foc, fold change; $GABA_A$, gamma-aminobutyric acid A; GEO No., Gene Expression Omnibus accession number; GFP, green fluorescent protein; HSV, herpes simplex virus; IAP, intracisternal-A particle; ILPFC, infralimbic prefrontal cortex; lncRNA, long-noncoding RNA; LR, log ratio; LTR, long terminal repeat; miRNA, microRNA; mPFC, medial prefrontal cortex; mRNA, messenger RNA; NA, not applicable; NAc, nucleus accumbens; NR, not reported; PFC, prefrontal cortex; qRT-PCR, quantitative real-time reverse transcription polymerase chain reaction; RNAseq, RNA sequencing; SEFL, stress-enhanced fear learning; SINE, short interspersed nuclear element.

miRNA biogenesis in the nucleus accumbens appears crucial for differences in the behavioral response to chronic social defeat stress (CSDS) as *Dicer1*-deficient animals were vulnerable to milder versions of this stress paradigm (43). Upregulation of *Dcc*, encoding for deleted in colorectal cancer, and reduced levels of miR-218 in the prefrontal cortex (PFC) are molecular signatures of murine CSDS susceptibility (44). CSDS-exposed mice showed miR-19b and miR-15a upregulation. These are both essential elements of the RNA-induced silencing complex–Ago2 complex in the amygdala concomitant with protein reduction of their putative target genes, *Adrb1* (45), encoding the adrenergic receptor beta-1, and *FKBP51* (46), encoding FK506 binding protein 5. Also, miR-135a upregulation in the raphe nuclei was involved in the prevention of post-CSDS social avoidance, by imipramine, a selective serotonin reuptake inhibitor (47). Post-CSDS behavioral phenotypes were also associated with heart injury and downregulation of miR-29b, miR-302a, and let-7d (48).

In the context of fear conditioning (FC), hippocampal pre-miR-132 was upregulated after contextual FC (49). Array-based analyses identified miR-182 downregulation in the lateral amygdala 1 hour after auditory FC in rats and its overexpression disrupted long-term, but not short-term, fear memory (50). miR-34a upregulation in mouse basolateral amygdala, which targets *Crhr1*, 30 minutes after auditory FC, was reversed by inhibition of Notch signaling, producing an impairment of fear memory (51). Array-based discovery of miR-33 upregulation 24 hours after auditory FC was validated with overexpression and knockdown experiments (52). Mature miR-132 is upregulated and peaks at 30 minutes after trace FC and returns to the baseline in 2 hours, while pre-FC hippocampal knockdown impairs memory acquisition (53). In another study, infralimbic PFC miR-128b increased after extinction learning, and its knockdown impairs extinction recall, while miR-144-3p decreases in mice with fear extinction deficits and its overexpression can prevent those deficits (54,55). Mice lacking SIRT1 catalytic activity in a brain-specific manner (SIRT1Δ) showed decreased freezing and CA1 synaptic plasticity linked to hippocampal differential expression of brain-enriched miRNAs. Reversing the upregulation of miR-134 in SIRT1Δ rescued the behavioral and neuronal phenotypes (56). Finally, in a mouse model of PTSD that distinguishes between conditioned and sensitized fear 4 weeks after conditioning, fluoxetine in shocked mice was associated with a miR-1971 downregulation in PFC (57).

Putative Role of miRNAs in Early-Life and Transgenerational Stress Effects

Early-life trauma is a risk factor for PTSD and other behavioral disorders. Many studies of early-life stress in rodents reveal long-lasting effects, depending on both genetic background and adult stress exposures, likely conferring epigenetic changes in genes involved in the stress circuitry (58).

Uchida *et al.* (59) reported that rats that underwent maternal separation for 3 hours in the first 2 postnatal weeks, compared with nonrestrained rats with and without early-life stress, showed increased depression-like behaviors in adulthood following CRS. Furthermore, the maternally separated rats exhibited medial PFC upregulation of *Rest4*, a neuron-specific

splicing variant of the transcriptional repressor element-1 silencing transcription factor, and a variety of repressor element-1 silencing transcription factor target mRNAs and miRNAs (59).

Maternal separation for 6 hours in the first postnatal week induced depression-like behaviors and downregulation of *Bdnf,* encoding for brain derived-neurotrophic factor, and miR-16 upregulation in the hippocampus (60). After chronic unpredictable stress in adulthood, maternally separated rats displayed depressive-like phenotypes along with upregulation of miR-504, linked to a downregulation of dopamine receptor genes (*Drd1* and *Drd2*) in the nucleus accumbens, and miR-9 downregulation, linked with *Drd2* upregulation, in the striatum (61).

Emerging evidence in animal models of stress reveals that stress-induced changes in miRNA expression can be transmitted from one generation to another, opening the possibility of transgenerational epigenetic inheritance. In the sperm of male mice exposed to prenatal or chronic stress, either in puberty or as adults, specific miRNAs were altered and were predictive of offspring with HPA-axis dysregulation (62,63). Similarly, another study showed that postnatal maternal separation increased anxiety and depression-like behavior; altered blood glucose and insulin levels; and modified sperm, hippocampal, and hypothalamic RNA levels—including miRNA profiles—in male mice. Furthermore, injecting sperm miRNA from a stressed male into oocytes fertilized by nonstressed parents generated the stress-induced phenotype in offspring, who exhibited altered metabolism and behavior akin to those observed in the stressed father (64). The review by Chan *et al.* (65) provides an overview of the intergenerational stress effects.

miRNA in Human Studies

While animal studies of stress measure miRNAs in the brain, human studies rely primarily on blood. Four cross-sectional miRNAs studies in PTSD patients and control subjects and one array-based total RNA study yielded divergent results, with little overlap in modulated miRNAs between studies (Table 3). First, a miRNA signature in military PTSD, comprising 8 significant multiple-comparison corrected hits, was discovered, with hits associated with biological pathways involved in axonal guidance and cancer (66). Second, 71 miRNAs, exhibiting differential regulation in control subjects versus PTSD patients, some of whom also had depression, were reported (67). Pathway analysis revealed an association with inflammation. Third, downregulation of miR-3130-5p in PTSD across two independent populations was reported (68). Fourth, an additional study revealed 190 dysregulated miRNAs in PTSD subjects, many with comorbid depression, versus control subjects (69). Fifth, miR-21 upregulation in veterans with PTSD was reported in a non-miRNA-specific microarray study (70). Among these studies, miR-15b downregulation was reported by two studies (66,67). miR-15b is also associated with multiple cancers (71); is a potential biomarker for Alzheimer's disease (72), which is interesting as PTSD increases risk for dementia (73); and is involved in GC signaling (see Putative Role of ncRNAs in GR Signaling in PTSD). The divergent results above may be due to differences in study design and assays as well as to inadequate statistical power due to relatively small sample sizes (74).

DICER1 expression decreases in PTSD (68), perhaps related to the increased vulnerability described in the animal model above (43), leading to lower concentrations of miRNAs in case versus control subjects overall when measured via RNA sequencing. Supporting this, the majority of PTSD blood-based miRNA studies report reduced miRNA expression in PTSD (Table 3). Reduced *DICER1* expression levels are also associated with positive affect (75), which is indicative of the cross-disorder role of DICER and possible reduced miRNA concentration across multiple psychiatric disorders (75). Functionally, miRNAs regulate posttranscriptional gene expression, and while any single miRNA's influence is small, the overall reduction in miRNAs may lead to "decreased buffering" of gene expression, allowing large fluctuations in transcript levels and downstream protein expression, potentially permitting pathogenic processes to take over.

PTSD and TBI Comorbidity and miRNA Regulation

PTSD is highly comorbid with depression and mild TBI (mTBI) (76). For an overview of miRNAs in PTSD and depression, we refer readers to a recent review by Giridharan *et al.* (77). mTBI is a head injury leading to brief loss of consciousness and changes in mental status that can lead to headaches, sleep disruption, and neurocognitive symptoms, sometimes lasting years. Many mTBI symptoms overlap with aspects of PTSD (78). Notably, PTSD and TBI are frequently studied in parallel in military cohorts but generally are not considered together in civilian studies. For instance, only two of the five PTSD miRNA studies discussed herein reported TBI status of subjects.

mTBI patients with neurocognitive deficits exhibited an overall decrease in miRNA expression (79), similar to the PTSD studies described above. The downregulation of 4 of 13 miRNAs was replicated in an independent sample of mTBI patients with neurocognitive deficits (80). Notably, both case and control subjects could be PTSD positive, and the signature was not translatable to TBI alone. Another hallmark of PTSD and mTBI is dysregulation of the HPA axis (81). Taheri *et al.* (82) explored predictors of hypopituitarism in TBI subjects, as determined by low cortisol levels in acute TBI cases, and found two miRNAs systematically upregulated at multiple time points. Notably, peritraumatic low cortisol is associated with higher risk for PTSD (81). Given how closely related hypocortisolemia is to both PTSD-associated and TBI-associated hypopituitarism, it is possible that the identified miRNAs are also suggestive of PTSD risk. Supplemental Table S1 summarizes miRNA studies in human TBI, beyond what is discussed here.

Future Directions for miRNA Studies

miRNA characterization may shed light on the joint pathogenic processes of PTSD and mTBI and yield biomarkers for disease diagnosis and monitoring (e.g., see www.google.com/patents/US20140073524). Current data is difficult to interpret for several reasons. Firstly, studies are underpowered, and power is critical for robust results. Collaborative, large, well-powered discovery studies of miRNAs and other blood-based biomarkers are necessary to uncover reliable, reproducible hits for translation into clinically significant biomarkers. Secondly, it is difficult to compare across miRNA studies because different

blood preparations and assays were used. For instance, PTSD studies primarily use whole blood while TBI studies focus on cell-free portions of blood. Understanding which blood fractions exhibit the best signal to noise for abnormal miRNA measurement is key. Moreover, understanding which miRNAs are highly expressed in dysfunctional neural circuits in PTSD and mTBI postmortem brains will elucidate biological mechanisms and reveal putative biomarkers to measure in the cell-free portions of blood. Lastly, biomarker studies are correlational and must be validated through functional studies. A key divide between preclinical and human studies is the divergence in tissues of study—preclinical studies generally focus on brain tissues while human research is limited to blood. Bridging between the two spheres by pursuing animal studies of brain and blood and then pursuing brain-enriched candidate markers in human studies, may lead to biomarkers of PTSD pathophysiology.

LONG-NONCODING RNAs

Most lncRNAs are RNA species characterized by polyadenylation, splicing of multiple exons, promoter trimethylation of histone H3 at lysine 4, and transcription by RNA polymerase II (83). lncRNAs are transcripts that lack protein-coding potential, characterized by the presence of open-reading frame length >100 amino acids. Although generally lncRNAs are generated and processed in the nucleus, most lncRNAs function in the cytoplasm, but some operate in the nucleus such as *XIST* (X inactive specific transcript) (83,84). Functional conservation across species (Table 1) is emerging to be a key feature of lncRNAs akin to protein-coding genes (83,85,86). To date, <50 lncRNAs have been functionally characterized, most in the context of cancer (87). These examples provide the foundational landscape of lncRNA-mediated biology and its implications in a variety of processes, including differentiation, apoptosis, development, and neurogenesis (88).

The role of lncRNAs in trauma-related mental disorders remains poorly characterized, despite their high expression in the brain (89). Here, we review the limited evidence of lncRNAs association with stress and PTSD-like disorders in animal and human studies (Tables 2 and 3, respectively).

lncRNAs in Animal Studies

In 2015, two studies reported a correlational link between lncRNAs and PTSD-like syndromes in rats (90) and mice (91).

Microarray analysis in rats exposed to stress-enhanced fear learning (SEFL), a PTSD model, showed differential hippocampal expression of lncRNAs in SEFL rats versus control rats (90). Enrichment analysis implicated many biological functions, including neuroactive ligand-receptor interaction, calcium signaling, PI3K-Akt pathway, and Ras signaling. Specifically, *Fos* gene-associated lncRNA *MRAK159688* was downregulated and lncRNA EU056364.1, associated with calcium-calmodulin kinase II (*Camk2a*), was upregulated in SEFL rats. Because FOS and CAMK2A are strongly associated with learning and memory, one may hypothesize a role for lncRNAs in memory regulation.

Spadaro *et al.* (91) used RNA sequencing to profile lncRNAs expression in the medial PFC and detected a significant downregulation of lncRNA *Gomafu* in adult mice after FC (91). They also reported stress reactivity and anxiety-like behaviors in knockdown of this lncRNA. *Gomafu* downregulation in the cortex was previously reported in schizophrenia (92). In this study, the authors showed the regulatory function of *Gomafu,* through recruitment of the BMI1 proto-oncogene, associated with polycomb repressive complex 1, to the site of transcription of *Crybb1*, repressing its expression at basal conditions. In response to FC, downregulation of *Gomafu* led to BMI1–polycomb repressive complex 1 release and upregulation of *Crybb1* in fear-conditioned mice. This adds to the emerging evidence that lncRNAs are key epigenetic modifiers of gene expression and, for the first time, implicates this mechanism in anxiety-related phenotypes.

Additionally, *Dicer1* knockout in mouse embryonic stem cells resulted in lower expression of hundreds of lncRNAs (93), implicating DICER not only in the biogenesis of miRNAs but also in downstream activation of lncRNAs.

lncRNAs in Human Studies

To date, there are three genome-wide studies reporting a correlative link between lncRNAs and PTSD. First, Guffanti *et al*. (94) reported an lncRNA-associated single nucleotide variant (SNV) mapping to a novel RNA gene, lncRNA *LINC01090* (previously called *AC068718.1*), which reached genome-wide significance in a genome-wide association study (GWAS) of PTSD in >400 African American women. Second, Almli *et al.* (95) reported a GWAS–threshold-significant SNV, mapping to a regulatory region likely in linkage disequilibrium with SNVs mapping to ncRNA *RP11-79E3.2* (previously called *BC036345*) of unknown function, in association with PTSD in combat-exposed veterans. Third, in another veteran cohort, Logue *et al.* (96) identified *LINC01137* (*LOC728431*) to be downregulated in the blood by PTSD, although it did not replicate in two independent samples. In each case, the identified lncRNAs are not yet functionally characterized, making it difficult to understand the pathogenic contribution of lncRNAs. An additional gene-based GWAS analysis from a civilian trauma study of African American women uncovered a PTSD association with the antisense lncRNA, *ZNRD1-AS1*, although this did not replicate in an independent sample. *ZNRD1-AS1* is located in the major histocompatibility complex locus, which has been associated with schizophrenia (97). lncRNA findings have been mostly coincidental to date, but as more evidence emerges, focused studies are warranted.

Apart from genome-wide studies, Rusiecki *et al.* (98) explored methylation of the well-characterized lncRNA, *H19*, in military personnel before and after deployment to combat zones. They found the percentage of methylation decreased postdeployment in individuals who never received a PTSD diagnosis (98). *H19* is an imprinted gene that might influence trauma response through multiple mechanisms given its involvement in a multitude of functions from embryogenesis (99) to tumor growth (100) and miRNA regulation (101).

RETROTRANSPOSONS

Transposable elements compose roughly 45% of the human genome, and >90% of these are retrotransposons (102). Transposons are a class of genomic elements capable of

Table 3. Noncoding RNA Findings in Human PTSD Studies

Focus/Study Design	No. of Case Subjects	No. of Control Subjects	Tissue	Methods	No. of Hits	No. Measured	Statistical Cutoff	Replicated in Distinct Cohort?	Main Findings	Ref.	GEO No.
miRNA											
PTSD cross-sectional	15	9	Blood, whole (Paxgene)	RNAseq	8	2578	FDR < 0.05	No	4 miRNAs were downregulated (miR-486-3p, miR-128-3p, miR-15b-3p, miR-125b-5p), and 4 were upregulated (miR-19a-3p, miR-101-3p, miR-20b-5p, miR-20a-5p). Note some PTSD case subjects also had comorbid TBI; control subjects did not have TBI.	(66)	GSE87768
PTSD cross-sectional	8	4	Blood, PBMC	miRNA microarray (Affymetrix)	71	1163	BH-adjusted $p < .05$	No	7 miRNAs were upregulated and 64 miRNAs were downregulated in PTSD. In PBMC cultures, addition of pre-miR125a decreased IFNγ release. Note TBI not measured, some case subjects had comorbid depression.	(67)	None
PTSD + MDD cross-sectional	17	7	Blood, whole	RNAseq	2	2588	FDR < 0.05	Yes	*DICER* expression is lower in case subjects. miR-3130-5p and miR-212-3p were downregulated in case subjects; the former replicated in a distinct cohort.	(68)	GSE67663
PTSD cross-sectional	28	27	Blood, whole	RNA microarray (Affymetrix)	203	54,675	FDR < 0.05	No	miR-21 was upregulated among the 203 mRNAs found to be changed in PTSD; some PTSD case subjects are comorbid for TBI. Note this is a total RNA discovery paper with a single miRNA hit.	(70)	None
PTSD cross-sectional	8	4	Blood, PBMC	miRNA microarray (Affymetrix)	190	847	$p < .05$	No	7 miRNAs were upregulated and 183 were downregulated; TBI not measured, some comorbid depression in case subjects.	(69)	GSE83601

Table 3. Continued

Focus/Study Design	No. of Case Subjects	No. of Control Subjects	Tissue	Methods	No. of Hits	No. Measured	Statistical Cutoff	Replicated in Distinct Cohort?	Main Findings	Ref.	GEO No.
lncRNA/Retrotransposon											
PTSD cross-sectional	63	84	Blood	GWAS	1	730,493	$p = 1.28e^{-8}$	Yes, replicated when female subjects excluded	T allele of rs717947 (*BCO36356*), an uncharacterized lncRNA) associated with elevated PTSD symptoms; TBI was not reported.	(95)	NA—GWAS dataset
PTSD cross-sectional	94	319	Blood or saliva	GWAS	1	730,525	$p = 5.09e^{-8}$	Yes	*ACO68718.1* is associated with higher incidence of PTSD; TBI was not reported.	(94)	NA—GWAS dataset
PTSD cross-sectional	1158	2520	Blood or saliva	GWAS (gene-based analysis)	2	634,854	$p = 1.55e^{-06}$	Yes, one hit replicated only	*ZNRD1-AS1*, a lncRNA, was discovered using an array of gene-based methods. *NLGN1* was also discovered and nominally replicated in a replication study, but *ZNRD1-AS1* was not replicated.	(148)	NA—GWAS dataset
PTSD cross-sectional	115	28	Blood, whole (Paxgene)	RNA microarray (Illumina)	41	10,264	$p < .05$, multiple testing correction	Yes, lncRNA did not replicate	41 transcripts were identified in this mRNA screen; lncRNA, *LINC01137* (*LOC728431*), was discovered in the initial cohort, but it was not replicated.	(96)	None
PTSD longitudinal	75	75	Blood, serum	Bisulfite treatment, PCR, and pyrosequencing	4 loci	7 loci	$p < .05$	No	4 loci were identified with differences in methylation between cases and controls; lncRNA, *H19* locus: Individuals who developed PTSD showed an increase in methylation from predeployment to postdeployment when compared with others who did not develop PTSD; retrotransposon, *LINE-1* locus was hypermethylated in controls postdeployment; retrotransposon, *Alu* locus (retrotransposon) was hypermethylated in cases postdeployment.	(98,119)	None

BH, Benjamini and Hochberg; FDR, false discovery rate; GEO No., Gene Expression Omnibus accession number; GWAS, genome-wide association study; IFNγ, interferon gamma; IL, interleukin; lncRNA, long-noncoding RNA; MDD, major depressive disorder; miRNA, microRNA; mRNA, messenger RNA; NA, not applicable; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; RNAseq, RNA sequencing; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

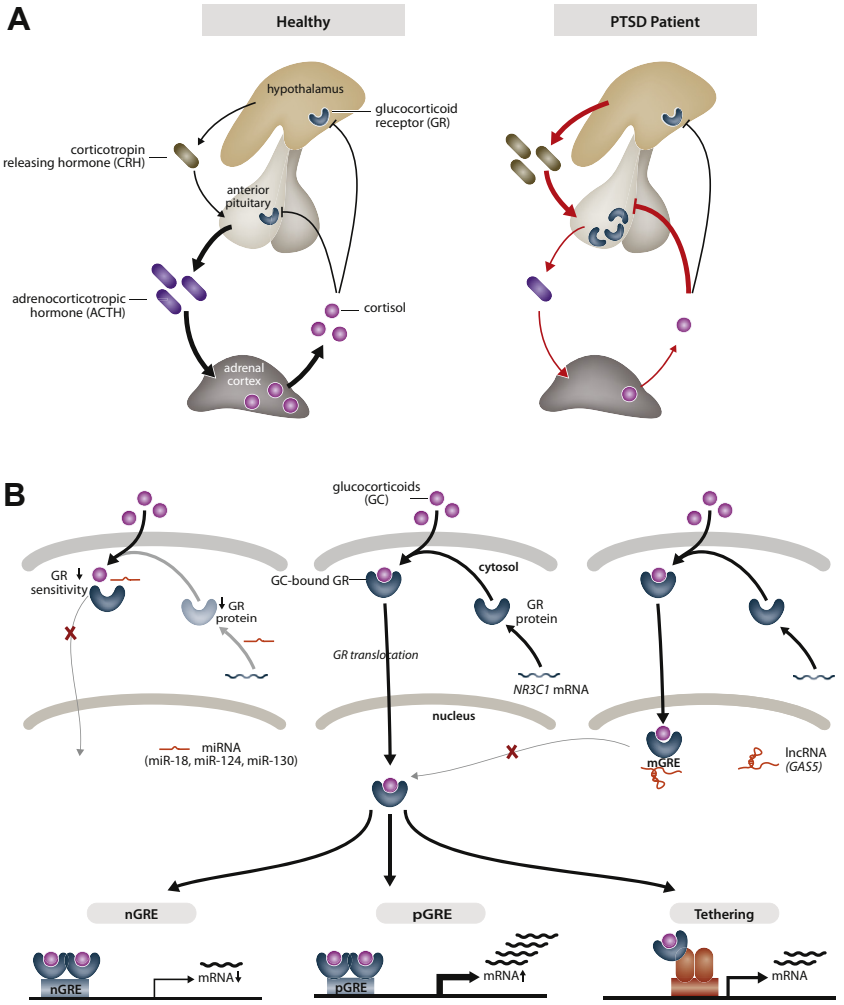

Figure 2. Glucocorticoids (GCs) and noncoding RNAs. **(A)** The function of the hypothalamic-pituitary-adrenal axis in healthy and posttraumatic stress disorder (PTSD) patients. Hypothalamic-pituitary-adrenal axis basal tone and responses to stress are altered in PTSD (149). The increased secretion of corticotropin-releasing hormone (CRH) from the hypothalamus in PTSD is represented by a thick red line. The decreased anterior pituitary release of adrenocorticotropic hormone (ACTH) and adrenal secretion of cortisol in PTSD is represented by thin red lines. The increased negative feedback inhibition of the hypothalamic-pituitary-adrenal axis at the pituitary level in PTSD is represented by thick red lines and is due to possibly higher glucocorticoid receptor (GR) function (increased receptor number or sensitivity). CRH receptors at the pituitary, ACTH receptors at the adrenal or differences in arginine vasopressin secretion might be also involved in the GC alterations in PTSD. It should be noted that this a working model and has not been proven by definitive data. The GC tone in PTSD, for instance, was investigated by many studies showing all the spectrum of responses from low to not altered to higher levels of cortisol. Explanations have been discussed for these discrepancies relating to gender, childhood trauma history, comorbidities (depression, traumatic brain injury, etc.), stress context, and circadian time point of sampling. **(B)** Transcriptional responses elicited by the GR affected by microRNA (miRNA) and long-noncoding RNA (lncRNA) species. In the center, key molecular factors affecting genomic sensitivity to GC signaling are shown. GCs (like cortisol) bind to the GR in the cytoplasm, which is coded by nuclear receptor subfamily 3 group C member 1 (*NR3C1*) and is part of a complex. Other members of the GR complex include chaperone proteins heat shock protein 90 and immunophilins such as FK506 binding protein 5. The GC-bound GR complex is translocated into the nucleus and it can bind to GC response elements (GRE) as a homodimer in simple GRE sites, in combination with other transcription factors in composite GRE sites, or finally via interaction with other transcription factors without DNA binding [i.e., tethering; right bottom panel (150)]. The bottom left and bottom center panels depict only simple GREs for simplicity: binding to positive GREs ([pGREs]; center bottom panel) leads to upregulation of target genes, while binding to negative GREs ([nGREs]; left bottom panel) leads to downregulation (150). Ultimately, the transcription of a myriad of genes is affected by GR in multiple cell types and tissues. Specific miRNAs can affect GR signaling by reducing GR protein levels or sensitivity to GCs, leading to a reduced translocation of GC-bound GR to the nucleus. lncRNAs interfere with the nuclear binding of GR to DNA sites by providing alternative sites for GR-binding. These "decoy" GREs mimic the sequence of consensus GRE (mGRE). It should be noted that the proposed model in not relevant to a specific tissue type in the brain or in the periphery. For instance, the other corticosteroid receptor, the mineralocorticoid receptor is not included. Mineralocorticoid receptor does not always co-localize with GR because mineralocorticoid receptor is present in specific brain regions such as the hippocampus and specific peripheral tissues such as the kidney, while GR is more abundant. Additionally, the other members of the GR complex might also be regulated by noncoding RNAs. *GAS5*, growth arrest specific 5; mRNA, messenger RNA.

moving (transposing) themselves around the genome. Retrotransposons transpose via a copy and paste mechanism using RNA intermediates. Retrotransposons are further subdivided into three major taxa: the long interspersed nuclear elements (LINE), the short interspersed nuclear elements, and the endogenous retrovirus/long terminal repeat class (103). Transposons were initially described as "controlling elements" (104), appearing to be responsive to stressful events (105).

With the capacity to transpose a defining feature of retrotransposons, they are commonly transcribed and provide a diversity of regulatory RNA motifs. Most lncRNAs derive form transposons, which have little impact on protein-coding sequence (106). There is far higher interindividual diversity in retrotransposon sequence relative to protein-coding sequence; it is thought each person carries at least one "private" retrotransposon, unique to their genome (107). Other observations have confirmed the expression of transposons in the brains of healthy and stressed rodents, primates, and humans under normal conditions. Changes in their expression occur in many disorders of the nervous system, including amyotrophic lateral sclerosis, depression, and schizophrenia (108–114). Thus, the importance of these elements to understand complex disorders such as PTSD is apparent (115,116).

Retrotransposons in Animal and Human Studies

Recent findings in human and animal models implicate retrotransposons in PTSD. In the SEFL model, exposure to repeated shock upregulated the expression of LINE-1s in the rat amygdala, while exposure to nonsedating doses of anesthetic that block SEFL caused a decrease in the expression of *LINE-1* RNA (117). A study by the same group showed that in the brains of patients with alcoholism, a common comorbidity of PTSD (2), multiple classes of retrotransposons showed upregulation and hypomethylation in cortex, basolateral amygdala, and CeA (118). Perhaps the most significant finding to date is the observation that *LINE-1* was hypomethylated after deployment in soldiers who developed PTSD, while *Alu* was hypermethylated in affected soldiers before combat exposure, indicating *Alu* hypermethylation as a potential PTSD susceptibility factor (119). Poorly controlled expression of *Alu* elements is a causal factor in macular degeneration (120), qualifying these elements as possible epigenetic regulators in other disorders such as PTSD. We have hypothesized elsewhere that part of the neuropsychiatric inflammatory signature might result from ectopic expression of retrotransposons that activate innate immune responses (121,122). Elevated inflammatory markers are a characteristic of PTSD, particularly in its more chronic manifestations (123,124). The evidence of retrotransposons involvement in PTSD remains correlational, but suggestive enough to warrant future functional validation.

PUTATIVE ROLE OF ncRNAs IN GR SIGNALING IN PTSD

Given that stress is, by definition, implicated in the development of PTSD, the primary stress systems, the fight-or-flight autonomic system, and the HPA axis have been a natural target of biological studies of PTSD, as reflected in the previous sections. PTSD was initially assumed to be a response to extreme or prolonged trauma with the expectation of increased levels of the major stress mediators, catecholamines, and GCs (81). However, PTSD epidemiology revealed that traumatic events are common (2).

Against expectation, PTSD patients displayed low basal cortisol, and an exaggerated HPA-axis GR-mediated negative feedback (Figure 2A), measured most commonly by the dexamethasone suppression test, while peripheral and central catecholamine levels were increased (125,126). The reduced GC tone in PTSD is accompanied by increased levels of corticotropin-releasing hormone, proinflammatory cytokines, norepinephrine (127–129), and downregulation of genes associated with GC signaling (96). Genetic and environmental factors that diminish GC signaling before and after trauma also associate with PTSD risk (130). Dexamethasone suppression test findings revealed increased GR sensitivity in the pituitary, while in vitro assays of GC sensitivity (mainly in lymphocytes) revealed that increased GR sensitivity in PTSD might not be specific to a single tissue (131). This was confirmed in a rat study where limbic brain and blood GR signaling were shown to associate with individual differences in behavioral responses to predator-scent stress (132).

miRNA might contribute to GC alterations in PTSD and stress-related psychopathology. miR-18, miR-124a, and miR-130b decrease GR (39,133,134) (Figure 2B). miR-15a, miR-15b/16, miR-223, and miR-379 are induced by GCs, while miR-15b/16 increases GC sensitivity in leukemia cell lines (135). In the context of animal models of stress, chronic corticosterone-mediated depressive-like phenotypes in rats resulted in 19 upregulated and seven downregulated miRNAs in the PFC with miR-124 and miR-218 most prominently affected (136).

Recently, increasing evidence supports the role of lncRNA, growth arrest specific 5 (*GAS5*) in the regulation of GC signaling. Initially associated with cancer (137,138), functional studies characterized *Gas5* as a suppressor of transcriptional activity of GC-responsive genes in mice (139,140). *GAS5* contains a GR-binding site that "mimics" the sequence of a GC response element, which allows direct competition for the DNA-binding domain of the GR itself. By acting as a "decoy" GC response element, *GAS5* inhibits the transcriptional activity of GR with widespread consequences on transcription of GR target genes (Figure 2B). To date, there is not a direct link between *GAS5* and PTSD, but the hypothesized mechanism directly targeting one of the principal pathways implicated in HPA-axis regulation, make this lncRNA attractive for further investigation.

FUTURE DIRECTIONS AND OTHER POTENTIAL MECHANISMS

Here, we presented developing evidence that ncRNAs are involved in key aspects of PTSD pathophysiology and may be evaluated as biomarkers and therapeutic targets for trauma-related brain disorders. As the functions of many ncRNAs remain poorly understood, modeling their role in pathology remains a hurdle. For this, we identify several avenues for further research of ncRNAs. First, the identification of risk-associated ncRNA variants, using both SNVs derived from GWAS and whole genome sequencing approaches, is the most attainable goal with present technology. Second, the identification of pathways regulating or regulated by identified risk-associated ncRNAs can be facilitated by leveraging epigenomic and transcriptomic data. Third, novel RNA-targeted therapeutics, beyond current gene therapy approaches, can be developed and possibly involves CRISPR/CAS9 gene editing (141). Lastly, noting some of the challenges the field faces, future studies will need to be well powered to improve reproducibility and the chance for success of functional validation experiments.

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REFERENCES

1. American Psychiatric Association (2013): Diagnostic and statistical manual of mental disorders, 5th ed. Washington, DC: American Psychiatric Association.
2. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (1995): Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52:1048–1060.
3. Jaffee MS, Meyer KS (2009): A brief overview of traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) within the Department of Defense. Clin Neuropsychol 23:1291–1298.
4. Tanev KS, Pentel KZ, Kredlow MA, Charney ME (2014): PTSD and TBI co-morbidity: Scope, clinical presentation and treatment options. Brain Inj 28:261–270.
5. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, *et al.* (2008): Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA 299:1291–1305.
6. Zhang L, Benedek DM, Fullerton CS, Forsten RD, Naifeh JA, Li XX, *et al.* (2014): PTSD risk is associated with BDNF Val66Met and BDNF overexpression. Mol Psychiatry 19:8–10.
7. MacNamara A, Rabinak CA, Kennedy AE, Fitzgerald DA, Liberzon I, Stein MB, Phan KL (2016): Emotion regulatory brain function and SSRI treatment in PTSD: Neural correlates and predictors of change. Neuropsychopharmacology 41:611–618.
8. Lanius RA, Vermetten E, Loewenstein RJ, Brand B, Schmahl C, Bremner JD, Spiegel D (2010): Emotion modulation in PTSD: Clinical and neurobiological evidence for a dissociative subtype. Am J Psychiatry 167:640–647.
9. Wolf EJ, Schnurr PP (2016): PTSD-related cardiovascular disease and accelerated cellular aging. Psychiatr Ann 46:527–532.
10. Cordova MJ, Riba MB, Spiegel D (2017): Post-traumatic stress disorder and cancer. Lancet Psychiatry 4:330–338.
11. Girgenti MJ, Duman RS (2018): Transcriptome alterations in posttraumatic stress disorder. Biol Psychiatry 83:840–848.
12. Maher B (2012): ENCODE: The human encyclopaedia. Nature 489:46–48.
13. Pasquinelli AE (2012): MicroRNAs and their targets: Recognition, regulation and an emerging reciprocal relationship. Nat Rev Genet 13:271–282.
14. Tay Y, Rinn J, Pandolfi PP (2014): The multilayered complexity of ceRNA crosstalk and competition. Nature 505:344–352.
15. Klengel T, Dias BG, Ressler KJ (2016): Models of intergenerational and transgenerational transmission of risk for psychopathology in mice. Neuropsychopharmacology 41:219–231.
16. Bohacek J, Mansuy IM (2015): Molecular insights into transgenerational non-genetic inheritance of acquired behaviours. Nat Rev Genet 16:641–652.
17. Smith MA, Gesell T, Stadler PF, Mattick JS (2013): Widespread purifying selection on RNA structure in mammals. Nucleic Acids Res 41:8220–8236.
18. Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, *et al.* (2015): The landscape of long noncoding RNAs in the human transcriptome. Nat Genet 47:199–208.
19. Mattick JS (2011): The central role of RNA in human development and cognition. FEBS Lett 585:1600–1616.
20. Nitsche A, Stadler PF (2017): Evolutionary clues in lncRNAs. Wiley Interdiscip Rev RNA 8.
21. Kornienko AE, Dotter CP, Guenzl PM, Gisslinger H, Gisslinger B, Cleary C, *et al.* (2016): Long non-coding RNAs display higher natural expression variation than protein-coding genes in healthy humans. Genome Biol 17:14.
22. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, *et al.* (2012): The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res 22:1775–1789.
23. Chimpanzee Sequencing and Analysis Consortium (2005): Initial sequence of the chimpanzee genome and comparison with the human genome. Nature 437:69–87.
24. O'Connor RM, Gururajan A, Dinan TG, Kenny PJ, Cryan JF (2016): All roads lead to the miRNome: miRNAs have a central role in the molecular pathophysiology of psychiatric disorders. Trends Pharmacol Sci 37:1029–1044.
25. Schouten M, Aschrafi A, Bielefeld P, Doxakis E, Fitzsimons CP (2013): microRNAs and the regulation of neuronal plasticity under stress conditions. Neuroscience 241:188–205.
26. Issler O, Chen A (2015): Determining the role of microRNAs in psychiatric disorders. Nat Rev Neurosci 16:201–212.
27. Barry G (2014): Integrating the roles of long and small noncoding RNA in brain function and disease. Mol Psychiatry 19:410–416.
28. Schmidt U, Keck ME, Buell DR (2015): miRNAs and other non-coding RNAs in posttraumatic stress disorder: A systematic review of clinical and animal studies. J Psychiatr Res 65:1–8.
29. Daskalakis NP, Rijal CM, King C, Huckins LM, Ressler KJ (2018): Recent genetics and epigenetics approaches to PTSD. Curr Psychiatry Rep 20:30.
30. Fehlmann T, Ludwig N, Backes C, Meese E, Keller A (2016): Distribution of microRNA biomarker candidates in solid tissues and body fluids. RNA Biol 13:1084–1088.
31. Ludwig N, Leidinger P, Becker K, Backes C, Fehlmann T, Pallasch C, *et al.* (2016): Distribution of miRNA expression across human tissues. Nucleic Acids Res 44:3865–3877.
32. Castellano L, Stebbing J (2013): Deep sequencing of small RNAs identifies canonical and non-canonical miRNA and endogenous siRNAs in mammalian somatic tissues. Nucleic Acids Res 41:3339–3351.
33. Olsen L, Klausen M, Helboe L, Nielsen FC, Werge T (2009): MicroRNAs show mutually exclusive expression patterns in the brain of adult male rats. PLoS One 4:e7225.
34. Betel D, Wilson M, Gabow A, Marks DS, Sander C (2008): The microRNA.org resource: Targets and expression. Nucleic Acids Res 36:D149–D153.
35. Pigati L, Yaddanapudi SC, Iyengar R, Kim DJ, Hearn SA, Danforth D, *et al.* (2010): Selective release of microRNA species from normal and malignant mammary epithelial cells. PLoS One 5:e13515.
36. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, *et al.* (2008): Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci U S A 105:10513–10518.
37. Daskalakis NP, Yehuda R, Diamond DM (2013): Animal models in translational studies of PTSD. Psychoneuroendocrinology 38:1895–1911.
38. Nestler EJ, Hyman SE (2010): Animal models of neuropsychiatric disorders. Nat Neurosci 13:1161–1169.
39. Uchida S, Nishida A, Hara K, Kamemoto T, Suetsugi M, Fujimoto M, *et al.* (2008): Characterization of the vulnerability to repeated stress in Fischer 344 rats: Possible involvement of microRNA-mediated down-regulation of the glucocorticoid receptor. Eur J Neurosci 27:2250–2261.
40. Meerson A, Cacheaux L, Goosens KA, Sapolsky RM, Soreq H, Kaufer D (2010): Changes in brain MicroRNAs contribute to cholinergic stress reactions. J Mol Neurosci 40:47–55.
41. Haramati S, Navon I, Issler O, Ezra-Nevo G, Gil S, Zwang R, *et al.* (2011): MicroRNA as repressors of stress-induced anxiety: the case of amygdalar miR-34. J Neurosci 31:14191–14203.
42. Mannironi C, Camon J, De Vito F, Biundo A, De Stefano ME, Persiconi I, *et al.* (2013): Acute stress alters amygdala microRNA miR-135a and miR-124 expression: Inferences for corticosteroid dependent stress response. PLoS One 8:e73385.

43. Dias C, Feng J, Sun H, Shao NY, Mazei-Robison MS, Damez-Werno D, *et al.* (2014): Beta-catenin mediates stress resilience through Dicer1/microRNA regulation. Nature 516:51–55.
44. Torres-Berrio A, Lopez JP, Bagot RC, Nouel D, Dal Bo G, Cuesta S, *et al.* (2017): DCC confers susceptibility to depression-like behaviors in humans and mice and is regulated by miR-218. Biol Psychiatry 81:306–315.
45. Volk N, Paul ED, Haramati S, Eitan C, Fields BK, Zwang R, *et al.* (2014): MicroRNA-19b associates with Ago2 in the amygdala following chronic stress and regulates the adrenergic receptor beta 1. J Neurosci 34:15070–15082.
46. Volk N, Pape JC, Engel M, Zannas AS, Cattane N, Cattaneo A, *et al.* (2016): Amygdalar MicroRNA-15a is essential for coping with chronic stress. Cell Rep 17:1882–1891.
47. Issler O, Haramati S, Paul ED, Maeno H, Navon I, Zwang R, *et al.* (2014): MicroRNA 135 is essential for chronic stress resiliency, antidepressant efficacy, and intact serotonergic activity. Neuron 83:344–360.
48. Cho JH, Lee I, Hammamieh R, Wang K, Baxter D, Scherler K, *et al.* (2014): Molecular evidence of stress-induced acute heart injury in a mouse model simulating posttraumatic stress disorder. Proc Natl Acad Sci U S A 111:3188–3193.
49. Nudelman AS, DiRocco DP, Lambert TJ, Garelick MG, Le J, Nathanson NM, Storm DR (2010): Neuronal activity rapidly induces transcription of the CREB-regulated microRNA-132, in vivo. Hippocampus 20:492–498.
50. Griggs EM, Young EJ, Rumbaugh G, Miller CA (2013): MicroRNA-182 regulates amygdala-dependent memory formation. J Neurosci 33:1734–1740.
51. Dias BG, Goodman JV, Ahluwalia R, Easton AE, Andero R, Ressler KJ (2014): Amygdala-dependent fear memory consolidation via miR-34a and Notch signaling. Neuron 83:906–918.
52. Jovasevic V, Corcoran KA, Leaderbrand K, Yamawaki N, Guedea AL, Chen HJ, *et al.* (2015): GABAergic mechanisms regulated by miR-33 encode state-dependent fear. Nat Neurosci 18:1265–1271.
53. Wang RY, Phang RZ, Hsu PH, Wang WH, Huang HT, Liu IY (2013): In vivo knockdown of hippocampal miR-132 expression impairs memory acquisition of trace fear conditioning. Hippocampus 23:625–633.
54. Murphy CP, Li X, Maurer V, Oberhauser M, Gstir R, Wearick-Silva LE, *et al.* (2017): MicroRNA-mediated rescue of fear extinction memory by miR-144-3p in extinction-impaired mice. Biol Psychiatry 81:979–989.
55. Lin Q, Wei W, Coelho CM, Li X, Baker-Andresen D, Dudley K, *et al.* (2011): The brain-specific microRNA miR-128b regulates the formation of fear-extinction memory. Nat Neurosci 14:1115–1117.
56. Gao J, Wang WY, Mao YW, Graff J, Guan JS, Pan L, *et al.* (2010): A novel pathway regulates memory and plasticity via SIRT1 and miR-134. Nature 466:1105–1109.
57. Schmidt U, Herrmann L, Hagl K, Novak B, Huber C, Holsboer F, *et al.* (2013): Therapeutic action of fluoxetine is associated with a reduction in prefrontal cortical miR-1971 expression levels in a mouse model of posttraumatic stress disorder. Front Psychiatry 4:66.
58. Daskalakis NP, Bagot RC, Parker KJ, Vinkers CH, de Kloet ER (2013): The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome. Psychoneuroendocrinology 38:1858–1873.
59. Uchida S, Hara K, Kobayashi A, Funato H, Hobara T, Otsuki K, *et al.* (2010): Early life stress enhances behavioral vulnerability to stress through the activation of REST4-mediated gene transcription in the medial prefrontal cortex of rodents. J Neurosci 30:15007–15018.
60. Bai M, Zhu X, Zhang Y, Zhang S, Zhang L, Xue L, *et al.* (2012): Abnormal hippocampal BDNF and miR-16 expression is associated with depression-like behaviors induced by stress during early life. PLoS One 7:e46921.
61. Zhang Y, Zhu X, Bai M, Zhang L, Xue L, Yi J (2013): Maternal deprivation enhances behavioral vulnerability to stress associated with miR-504 expression in nucleus accumbens of rats. PLoS One 8:e69934.
62. Rodgers AB, Morgan CP, Leu NA, Bale TL (2015): Transgenerational epigenetic programming via sperm microRNA recapitulates effects of paternal stress. Proc Natl Acad Sci U S A 112:13699–13704.
63. Morgan CP, Bale TL (2011): Early prenatal stress epigenetically programs dysmasculinization in second-generation offspring via the paternal lineage. J Neurosci 31:11748–11755.
64. Gapp K, Jawaid A, Sarkies P, Bohacek J, Pelczar P, Prados J, *et al.* (2014): Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nat Neurosci 17:667–669.
65. Chan JC, Nugent BM, Bale TL (2018): Parental advisory: Maternal and paternal stress can impact offspring neurodevelopment. Biol Psychiatry 83:886–894.
66. Martin CG, Kim H, Yun S, Livingston W, Fetta J, Mysliwiec V, *et al.* (2017): Circulating miRNA associated with posttraumatic stress disorder in a cohort of military combat veterans. Psychiatry Res 251:261–265.
67. Zhou J, Nagarkatti P, Zhong Y, Ginsberg JP, Singh NP, Zhang J, Nagarkatti M (2014): Dysregulation in microRNA expression is associated with alterations in immune functions in combat veterans with post-traumatic stress disorder. PLoS One 9:e94075.
68. Wingo AP, Almli LM, Stevens JS, Klengel T, Uddin M, Li Y, *et al.* (2015): DICER1 and microRNA regulation in post-traumatic stress disorder with comorbid depression. Nat Commun 6:10106.
69. Bam M, Yang X, Zumbrun EE, Zhong Y, Zhou J, Ginsberg JP, *et al.* (2016): Dysregulated immune system networks in war veterans with PTSD is an outcome of altered miRNA expression and DNA methylation. Sci Rep 6:31209.
70. Guardado P, Olivera A, Rusch HL, Roy M, Martin C, Lejbman N, *et al.* (2016): Altered gene expression of the innate immune, neuroendocrine, and nuclear factor-kappa B (NF-kappaB) systems is associated with posttraumatic stress disorder in military personnel. J Anxiety Disord 38:9–20.
71. Schee K, Lorenz S, Worren MM, Gunther CC, Holden M, Hovig E, *et al.* (2013): Deep sequencing the microRNA transcriptome in colorectal cancer. PLoS One 8:e66165.
72. Cheng L, Doecke JD, Sharples RA, Villemagne VL, Fowler CJ, Rembach A, *et al.* (2015): Prognostic serum miRNA biomarkers associated with Alzheimer's disease shows concordance with neuropsychological and neuroimaging assessment. Mol Psychiatry 20:1188–1196.
73. Yaffe K, Vittinghoff E, Lindquist K, Barnes D, Covinsky KE, Neylan T, *et al.* (2010): Posttraumatic stress disorder and risk of dementia among US veterans. Arch Gen Psychiatry 67:608–613.
74. Ioannidis JP (2005): Why most published research findings are false. PLoS Med 2:e124.
75. Wingo AP, Almli LM, Stevens JS, Jovanovic T, Wingo TS, Tharp G, *et al.* (2017): Genome-wide association study of positive emotion identifies a genetic variant and a role for microRNAs. Mol Psychiatry 22:774–783.
76. Haarbauer-Krupa J, Taylor CA, Yue JK, Winkler EA, Pirracchio R, Cooper SR, *et al.* (2017): Screening for post-traumatic stress disorder in a civilian emergency department population with traumatic brain injury. J Neurotrauma 34:50–58.
77. Giridharan VV, Thandavarayan RA, Fries GR, Walss-Bass C, Barichello T, Justice NJ, *et al.* (2016): Newer insights into the role of miRNA a tiny genetic tool in psychiatric disorders: Focus on post-traumatic stress disorder. Transl Psychiatry 6:e954.
78. Bryant R (2011): Post-traumatic stress disorder vs traumatic brain injury. Dialogues Clin Neurosci 13:251–262.
79. Pasinetti GM, Ho L, Dooley C, Abbi B, Lange G (2012): Select non-coding RNA in blood components provide novel clinically accessible biological surrogates for improved identification of traumatic brain injury in OEF/OIF Veterans. Am J Neurodegener Dis 1:88–98.
80. Ho L, Lange G, Zhao W, Wang J, Rooney R, Patel DH, *et al.* (2014): Select small nucleolar RNAs in blood components as novel biomarkers for improved identification of comorbid traumatic brain injury

and post-traumatic stress disorder in veterans of the conflicts in Afghanistan and Iraq. Am J Neurodegener Dis 3:170–181.
81. Daskalakis NP, Lehrner A, Yehuda R (2013): Endocrine aspects of post-traumatic stress disorder and implications for diagnosis and treatment. Endocrinol Metab Clin North Am 42:503–513.
82. Taheri S, Tanriverdi F, Zararsiz G, Elbuken G, Ulutabanca H, Karaca Z, *et al.* (2016): Circulating microRNAs as potential biomarkers for traumatic brain injury-induced hypopituitarism. J Neurotrauma 33:1818–1825.
83. Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, *et al.* (2009): Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature 458:223–227.
84. Lee JT (2012): Epigenetic regulation by long noncoding RNAs. Science 338:1435–1439.
85. Ulitsky I, Shkumatava A, Jan CH, Sive H, Bartel DP (2011): Conserved function of lincRNAs in vertebrate embryonic development despite rapid sequence evolution. Cell 147:1537–1550.
86. Taft RJ, Pheasant M, Mattick JS (2007): The relationship between non-protein-coding DNA and eukaryotic complexity. Bioessays 29:288–299.
87. Sahu A, Singhal U, Chinnaiyan AM (2015): Long noncoding RNAs in cancer: from function to translation. Trends Cancer 1:93–109.
88. Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A, Rinn JL (2011): Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes Dev 25:1915–1927.
89. Wu P, Zuo X, Deng H, Liu X, Liu L, Ji A (2013): Roles of long noncoding RNAs in brain development, functional diversification and neurodegenerative diseases. Brain Res Bull 97:69–80.
90. Qingzhen L, Jiehua M, Zhiyang Y, Hongjun L, Chunlong C, Weiyan L (2016): Distinct hippocampal expression profiles of lncRNAs in rats exhibiting a PTSD-like syndrome. Mol Neurobiol 53:2161–2168.
91. Spadaro PA, Flavell CR, Widagdo J, Ratnu VS, Troup M, Ragan C, *et al.* (2015): Long noncoding RNA-directed epigenetic regulation of gene expression is associated with anxiety-like behavior in mice. Biol Psychiatry 78:848–859.
92. Barry G, Briggs JA, Vanichkina DP, Poth EM, Beveridge NJ, Ratnu VS, *et al.* (2014): The long non-coding RNA Gomafu is acutely regulated in response to neuronal activation and involved in schizophrenia-associated alternative splicing. Mol Psychiatry 19:486–494.
93. Zheng GX, Do BT, Webster DE, Khavari PA, Chang HY (2014): Dicer-microRNA-Myc circuit promotes transcription of hundreds of long noncoding RNAs. Nat Struct Mol Biol 21:585–590.
94. Guffanti G, Galea S, Yan L, Roberts AL, Solovieff N, Aiello AE, *et al.* (2013): Genome-wide association study implicates a novel RNA gene, the lincRNA AC068718.1, as a risk factor for post-traumatic stress disorder in women. Psychoneuroendocrinology 38:3029–3038.
95. Almli LM, Stevens JS, Smith AK, Kilaru V, Meng Q, Flory J, *et al.* (2015): A genome-wide identified risk variant for PTSD is a methylation quantitative trait locus and confers decreased cortical activation to fearful faces. Am J Med Genet B Neuropsychiatr Genet 168B:327–336.
96. Logue MW, Smith AK, Baldwin C, Wolf EJ, Guffanti G, Ratanatharathorn A, *et al.* (2015): An analysis of gene expression in PTSD implicates genes involved in the glucocorticoid receptor pathway and neural responses to stress. Psychoneuroendocrinology 57:1–13.
97. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, *et al.* (2016): Schizophrenia risk from complex variation of complement component 4. Nature 530:177–183.
98. Rusiecki JA, Byrne C, Galdzicki Z, Srikantan V, Chen L, Poulin M, *et al.* (2013): PTSD and DNA methylation in select immune function gene promoter regions: A repeated measures case-control study of U.S. military service members. Front Psychiatry 4:56.
99. Gabory A, Ripoche MA, Yoshimizu T, Dandolo L (2006): The H19 gene: Regulation and function of a non-coding RNA. Cytogenet Genome Res 113:188–193.
100. Matouk IJ, DeGroot N, Mezan S, Ayesh S, Abu-lail R, Hochberg A, Galun E (2007): The H19 non-coding RNA is essential for human tumor growth. PLoS One 2:e845.
101. Cunningham MD, Kassis JA, Pfeifer K (2010): Chromatin modifiers, cognitive disorders, and imprinted genes. Dev Cell 18:169–170.
102. Cordaux R, Batzer MA (2009): The impact of retrotransposons on human genome evolution. Nat Rev Genet 10:691–703.
103. Jurka J, Kapitonov VV, Kohany O, Jurka MV (2007): Repetitive sequences in complex genomes: structure and evolution. Annu Rev Genomics Hum Genet 8:241–259.
104. McClintock B (1951): Chromosome organization and genic expression. Cold Spring Harb Symp Quant Biol 16:13–47.
105. McClintock B (1984): The significance of responses of the genome to challenge. Science 226:792–801.
106. Kelley D, Rinn J (2012): Transposable elements reveal a stem cell-specific class of long noncoding RNAs. Genome Biol 13:R107.
107. Mills RE, Bennett EA, Iskow RC, Devine SE (2007): Which transposable elements are active in the human genome? Trends Genet 23:183–191.
108. Alfahad T, Nath A (2013): Retroviruses and amyotrophic lateral sclerosis. Antiviral Res 99:180–187.
109. Hunter RG, McEwen BS, Pfaff DW (2013): Environmental stress and transposon transcription in the mammalian brain. Mob Genet Elements 3:e24555.
110. Reilly MT, Faulkner GJ, Dubnau J, Ponomarev I, Gage FH (2013): The role of transposable elements in health and diseases of the central nervous system. J Neurosci 33:17577–17586.
111. Hunter RG, Murakami G, Dewell S, Seligsohn M, Baker ME, Datson NA, *et al.* (2012): Acute stress and hippocampal histone H3 lysine 9 trimethylation, a retrotransposon silencing response. Proc Natl Acad Sci U S A 109:17657–17662.
112. Bundo M, Toyoshima M, Okada Y, Akamatsu W, Ueda J, Nemoto-Miyauchi T, *et al.* (2014): Increased l1 retrotransposition in the neuronal genome in schizophrenia. Neuron 81:306–313.
113. Guffanti G, Gaudi S, Klengel T, Fallon JH, Mangalam H, Madduri R, *et al.* (2016): LINE1 insertions as a genomic risk factor for schizophrenia: Preliminary evidence from an affected family. Am J Med Genet B Neuropsychiatr Genet 171:534–545.
114. Liu S, Du T, Liu Z, Shen Y, Xiu J, Xu Q (2016): Inverse changes in L1 retrotransposons between blood and brain in major depressive disorder. Sci Rep 6:37530.
115. Guffanti G, Gaudi S, Fallon JH, Sobell J, Potkin SG, Pato C, Macciardi F (2014): Transposable elements and psychiatric disorders. Am J Med Genet B Neuropsychiatr Genet 165B:201–216.
116. Gaudi S, Guffanti G, Fallon J, Macciardi F (2016): Epigenetic mechanisms and associated brain circuits in the regulation of positive emotions: A role for transposable elements. J Comp Neurol 524:2944–2954.
117. Ponomarev I, Rau V, Eger EI, Harris RA, Fanselow MS (2010): Amygdala transcriptome and cellular mechanisms underlying stress-enhanced fear learning in a rat model of posttraumatic stress disorder. Neuropsychopharmacology 35:1402–1411.
118. Ponomarev I, Wang S, Zhang L, Harris RA, Mayfield RD (2012): Gene coexpression networks in human brain identify epigenetic modifications in alcohol dependence. J Neurosci 32:1884–1897.
119. Rusiecki JA, Chen L, Srikantan V, Zhang L, Yan L, Polin ML, Baccarelli A (2012): DNA methylation in repetitive elements and post-traumatic stress disorder: A case-control study of US military service members. Epigenomics 4:29–40.
120. Tarallo V, Hirano Y, Gelfand BD, Dridi S, Kerur N, Kim Y, *et al.* (2012): DICER1 loss and Alu RNA induce age-related macular degeneration via the NLRP3 inflammasome and MyD88. Cell 149:847–859.
121. Hunter RG, Gagnidze K, McEwen BS, Pfaff DW (2015): Stress and the dynamic genome: Steroids, epigenetics, and the transposome. Proc Natl Acad Sci U S A 112:6828–6833.
122. Lapp HE, Hunter RG (2016): The dynamic genome: transposons and environmental adaptation in the nervous system. Epigenomics 8:237–249.

123. McFarlane AC, Lawrence-Wood E, Van Hooff M, Malhi GS, Yehuda R (2017): The need to take a staging approach to the biological mechanisms of PTSD and its treatment. Curr Psychiatry Rep 19:10.
124. Mendoza C, Barreto GE, Avila-Rodriguez M, Echeverria V (2016): Role of neuroinflammation and sex hormones in war-related PTSD. Mol Cell Endocrinol 434:266–277.
125. Mason JW, Giller EL, Kosten TR, Ostroff RB, Podd L (1986): Urinary free-cortisol levels in posttraumatic stress disorder patients. J Nerv Ment Dis 174:145–149.
126. Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL Jr, Mason JW (1990): Low urinary cortisol excretion in patients with posttraumatic stress disorder. J Nerv Ment Dis 178:366–369.
127. Baker DG, Ekhator NN, Kasckow JW, Hill KK, Zoumakis E, Dashevsky BA, *et al.* (2001): Plasma and cerebrospinal fluid interleukin-6 concentrations in posttraumatic stress disorder. Neuroimmunomodulation 9:209–217.
128. Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, *et al.* (1999): Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry 156:585–588.
129. Geracioti TD Jr, Baker DG, Ekhator NN, West SA, Hill KK, Bruce AB, *et al.* (2001): CSF norepinephrine concentrations in posttraumatic stress disorder. Am J Psychiatry 158:1227–1230.
130. van Zuiden M, Kavelaars A, Geuze E, Olff M, Heijnen CJ (2013): Predicting PTSD: Pre-existing vulnerabilities in glucocorticoid-signaling and implications for preventive interventions. Brain Behav Immun 30:12–21.
131. Yehuda R, Golier JA, Yang RK, Tischler L (2004): Enhanced sensitivity to glucocorticoids in peripheral mononuclear leukocytes in posttraumatic stress disorder. Biol Psychiatry 55:1110–1116.
132. Daskalakis NP, Cohen H, Cai G, Buxbaum JD, Yehuda R (2014): Expression profiling associates blood and brain glucocorticoid receptor signaling with trauma-related individual differences in both sexes. Proc Natl Acad Sci U S A 111:13529–13534.
133. Vreugdenhil E, Verissimo CS, Mariman R, Kamphorst JT, Barbosa JS, Zweers T, *et al.* (2009): MicroRNA 18 and 124a down-regulate the glucocorticoid receptor: implications for glucocorticoid responsiveness in the brain. Endocrinology 150:2220–2228.
134. Tessel MA, Benham AL, Krett NL, Rosen ST, Gunaratne PH (2011): Role for microRNAs in regulating glucocorticoid response and resistance in multiple myeloma. Horm Cancer 2:182–189.
135. Rainer J, Ploner C, Jesacher S, Ploner A, Eduardoff M, Mansha M, *et al.* (2009): Glucocorticoid-regulated microRNAs and mirtrons in acute lymphoblastic leukemia. Leukemia 23:746–752.
136. Dwivedi Y, Roy B, Lugli G, Rizavi H, Zhang H, Smalheiser NR (2015): Chronic corticosterone-mediated dysregulation of microRNA network in prefrontal cortex of rats: relevance to depression pathophysiology. Transl Psychiatry 5:e682.
137. Mourtada-Maarabouni M, Pickard MR, Hedge VL, Farzaneh F, Williams GT (2009): GAS5, a non-protein-coding RNA, controls apoptosis and is downregulated in breast cancer. Oncogene 28:195–208.
138. Pickard MR, Mourtada-Maarabouni M, Williams GT (2013): Long non-coding RNA GAS5 regulates apoptosis in prostate cancer cell lines. Biochim Biophys Acta 1832:1613–1623.
139. Hudson WH, Pickard MR, de Vera IM, Kuiper EG, Mourtada-Maarabouni M, Conn GL, *et al.* (2014): Conserved sequence-specific lincRNA-steroid receptor interactions drive transcriptional repression and direct cell fate. Nat Commun 5:5395.
140. Lucafo M, De Iudicibus S, Di Silvestre A, Pelin M, Candussio L, Martelossi S, *et al.* (2015): Long noncoding RNA GAS5: A novel marker involved in glucocorticoid response. Curr Mol Med 15:94–99.
141. Dominguez AA, Lim WA, Qi LS (2016): Beyond editing: repurposing CRISPR-Cas9 for precision genome regulation and interrogation. Nat Rev Mol Cell Biol 17:5–15.
142. Sarkies P, Miska EA (2014): Small RNAs break out: The molecular cell biology of mobile small RNAs. Nat Rev Mol Cell Biol 15:525–535.
143. Yang G, Lu X, Yuan L (2014): LncRNA: A link between RNA and cancer. Biochim Biophys Acta 1839:1097–1109.
144. Wang KC, Chang HY (2011): Molecular mechanisms of long noncoding RNAs. Mol Cell 43:904–914.
145. Geisler S, Coller J (2013): RNA in unexpected places: long non-coding RNA functions in diverse cellular contexts. Nat Rev Mol Cell Biol 14:699–712.
146. Pfau ML, Purushothaman I, Feng J, Golden SA, Aleyasin H, Lorsch ZS, *et al.* (2016): Integrative analysis of sex-specific microRNA networks following stress in mouse nucleus accumbens. Front Mol Neurosci 9:144.
147. Mathew RS, Tatarakis A, Rudenko A, Johnson-Venkatesh EM, Yang YJ, Murphy EA, *et al.* (2016): A microRNA negative feedback loop downregulates vesicle transport and inhibits fear memory. Elife 5:pii:e22467.
148. Kilaru V, Iyer SV, Almli LM, Stevens JS, Lori A, Jovanovic T, *et al.* (2016): Genome-wide gene-based analysis suggests an association between Neuroligin 1 (NLGN1) and post-traumatic stress disorder. Transl Psychiatry 6:e820.
149. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, *et al.* (2015): Post-traumatic stress disorder. Nat Rev Dis Primers 1:15057.
150. Newton R, Holden NS (2007): Separating transrepression and transactivation: a distressing divorce for the glucocorticoid receptor? Mol Pharmacol 72:799–809.