Early life exposures, neurodevelopmental disorders, and transposable elements

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ABSTRACT

Transposable elements make up a much larger portion of the genome than protein-coding genes, yet we know relatively little about their function in the human genome. However, we are beginning to more fully understand their role in brain development, neuroinflammation, and adaptation to environmental insults such as stress. For instance, glucocorticoid receptor activation regulates transposable elements in the brain following acute stress. Early life is a period of substantial brain development during which transposable elements play a role. Environmental exposures and experiences during early life that promote abnormal regulation of transposable elements may lead to a cascade of events that ultimately increase susceptibility to disorders later in life. Recent attention to transposable elements in psychiatric illness has begun to clarify associations indicative of dysregulation of different classes of transposable elements in stress-related and neurodevelopmental illness. Though individual susceptibility or resiliency to psychiatric illness has not been explained by traditional genetic studies, the wide inter-individual variability in transposable element composition in the human genome make TEs attractive candidates to elucidate this differential susceptibility. In this review, we discuss evidence that regulation of transposable elements in the brain are stage-specific, sensitive to environmental factors, and may be impacted by early life perturbations. We further present evidence of associations with stress-related and neurodevelopmental psychiatric illness from a developmental perspective.

1. Transposable elements in the brain

Originally termed "controlling elements" by their discoverer Barbara McClintock, transposable elements (TEs) constitute about half of the human genome and are becoming increasingly important to the field of neuroscience as their roles in mammalian development, immune response, and contributions to behavioral and cognitive domains continue to be uncovered (Lander et al., 2001). Given the significant amount of genomic real estate they occupy, it is surprising that research has focused on their roles in the central nervous system only in the last few decades. The repetitive nature of TEs presents technical challenges for identifying TEs in genomic and transcriptomic datasets but new advances in bioinformatics approaches are enabling a better understanding of TEs in the brain (Guffanti et al., 2018, 2016; Tokuyama et al., 2018). It is now well-accepted that TEs have played an integral role in the evolution of the primate genome, as shown by genes containing sequences with high homology to TEs and the role of TEs in mammalian development (Feschotte, 2008; Linker et al., 2017). There is greater individual variability in DNA polymorphisms in TE regions of the genome compared to exomes, so understanding TE function may give rise to a better understanding of individual susceptibility to early life disruptions and psychiatric illness not explained by traditional genetic studies (Mills et al., 2007). In this review we discuss the impact of environmental challenges, with a focus on stress, transposable elements in early life, and vulnerability to psychiatric illness with developmental origins.

1.1. Types of TEs

TEs likely integrated into the eukaryotic genome as parasites, but over evolutionary time have become tools for adaptive functions in the mammalian genome. TEs fall into two primary classes: DNA transposons, which mobilize around the genome through a "cut and paste" mechanism, and retrotransposons, which "copy and paste" to replicate themselves and insert their sequence into new areas of the genome (Fig. 1; Wicker et al., 2007). DNA transposons are not active in the human genome and will not be discussed further in this review (Lander et al., 2001). Retrotransposons can be further divided into long terminal repeat (LTRs)/endogenous retroviruses (ERVs) and non-LTRs (i.e. poly (A) retrotransposons). ERVs in humans are mostly mutated and cannot

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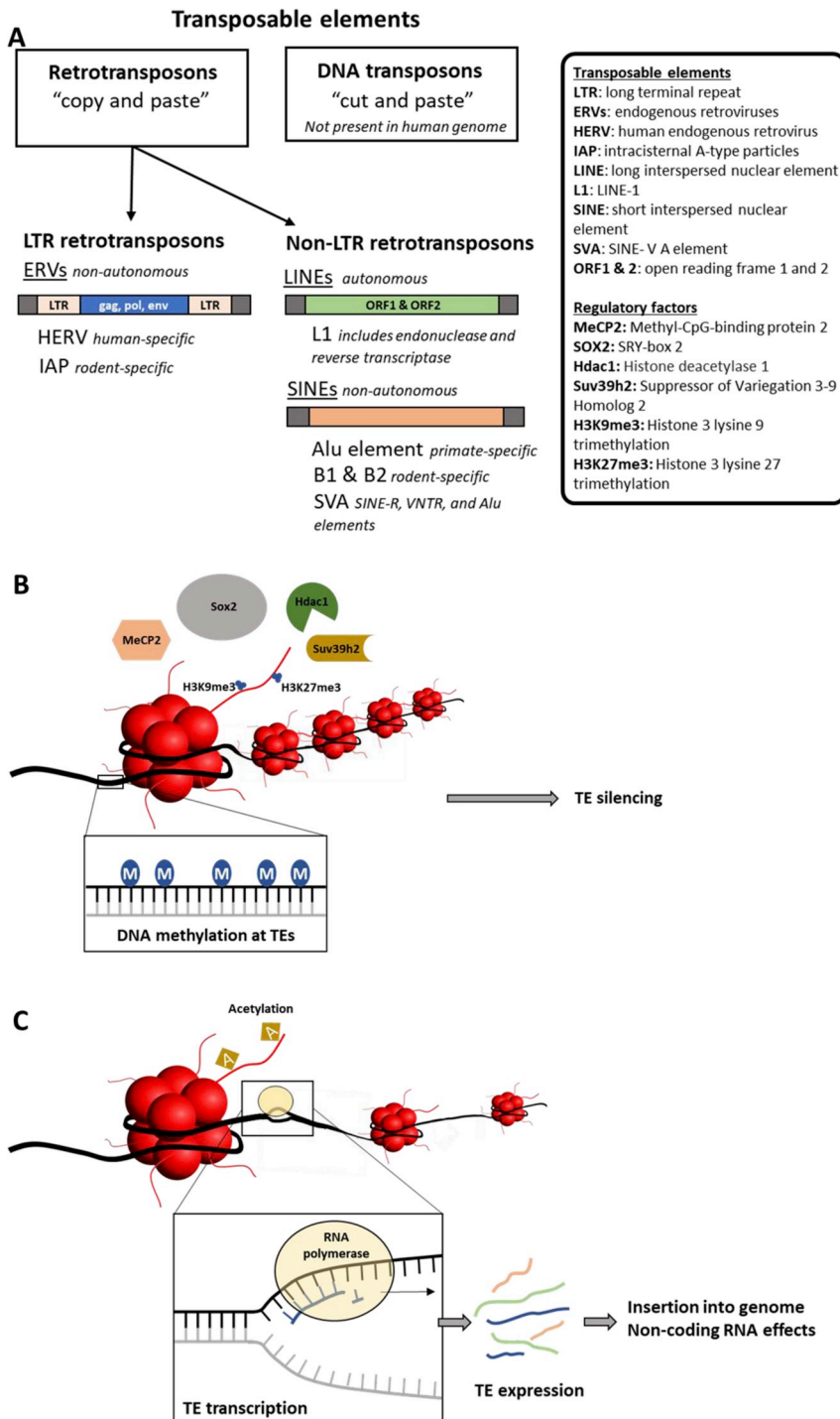
Fig. 1. A. Types of transposable elements. TEs can be classified into retrotransposons and DNA transposons. DNA transposons are not active in the mammalian genome. Retrotransposons can be further divided into LTR and non-LTR retrotransposons. LTR transposons include ERVs which contain the gag, pol, and env virus-like sequences flanked by LTR sequences. Types of ERVs include HERVs and the rodent-specific IAP element. Non-LTR retrotransposons include LINEs, such as L1 which is autonomous and contains ORF1 and 2, endonuclease, and reverse transcriptase within its sequence. SINEs are another type of non-LTR retrotransposon, and include the primate-specific Alu element, rodent-specific B1 and B2 elements, and SVA element. B. Several factors contribute to pre-transcriptional regulation of TEs including MeCP2, Sox2, Hdac1, Suvar39h2, and histone tail modifications H3K9me3 and H3k27me3. DNA methylation also contributes to TE silencing. C. Loss of regulatory factors, for example, after stress or during cell differentiation, can lead to TE transcription. Transcribed TEs can be inserted back into the genome at a new location or exert other effects in the cell as non-coding RNA.

retrotranspose (Beck et al., 2011; Weiss, 2016), but some have known functions as long non-coding RNAs while the role of others is still not yet understood. Expression of some ERV elements in humans have been linked to several medical illnesses (Li et al., 2015; Mager and Stoye, 2015).

Non-LTR retrotransposons are subdivided into Long interspersed nuclear elements (LINEs) and short interspersed nuclear elements (SINEs). LINE elements in humans include LINE1 element (L1) which has about 500,000 copies in the human genome. SINE elements include the primate-specific Alu element, which has about 1 million copies in the human genome, and SINE -V A (SVA) elements, a SINE made up of pieces of SINE-R, VNTR and Alu which has about 3000 copies in the human genome (Cordaux and Batzer, 2009).

1.2. Transposition events

L1 is autonomous, meaning it contains all the necessary machinery to retrotranspose to a new location in the genome within its own sequence. L1 autonomy occurs through endonuclease and reverse transcriptase proteins to insert a new, often incomplete and retrotransposition-incompetent, copy of L1 elsewhere in the genome in a process known as cis-preference. Only about 100 copies of L1 are active in humans and an even smaller number, termed "hot L1s" are responsible for most transposition events (Brouha et al., 2003). Other retrotransposons, including Alu elements, rely on the endonuclease and reverse transcriptase encoded in L1 to retrotranspose, known as trans-retrotransposition (Dewannieux et al., 2003). An uncommon form of

retrotransposition is endonuclease-independent retrotransposition in which TEs are integrated back into the genome at existing DNA lesions (Morrish et al., 2007, 2002). Endonuclease-independent retrotransposition is traditionally considered a rare event and thought not to occur in the brain, although it has been recently suggested that these events occur commonly in the brain (Jacob-Hirsch et al., 2018). The frequency of retrotransposition events of each type of retrotransposon mirrors their relative abundance in the genome: 5% of live births for Alu, 0.5–5% for L1, and 0.1% for SVA elements (Cordaux and Batzer, 2009). Sites of insertions are often assumed to be stochastic depending on the epigenetic landscape, although this idea has been challenged with recent evidence that retrotranspositions may be inserted preferentially into existing TE sequences in the brain (Jacob-Hirsch et al., 2018).

1.3. Consequences of transposition

Transposition events can range from catastrophic to potentially beneficial depending on where in the genome the new copy is inserted. For example, Kazazian et al. (1988) was the first to show that TE insertions can lead to disease in a study that demonstrated a *de novo* insertion caused hemophilia A. Since that landmark study, more evidence has accumulated suggesting transpositions leading to genomic reshuffling can be detrimental to the organism (for a recent review on TE insertions relevance to disease, see Kazazian and Moran, 2017). Retrotransposition can also affect the genome in other ways since TEs can affect transcription of neighboring genes and TE sequences are contained in transcription factor binding sites and promoters (Faulkner and Carninci, 2009; Rebollo et al., 2012). The repetitive sequences that comprise TEs also provide opportunities for recombination events that may be disruptive to genomic stability (Konkel and Batzer, 2010; Lehrman et al., 1985). Recombination is also a driver of genomic shuffling that can contribute to evolutionary progress: there have been an estimated 500 Alu recombination events in the human genome since divergence from chimpanzees (Sen et al., 2006). Transposition events have been proposed to provide the capacity for genomic variability, which may provide a form of plasticity adaptive for responding to environmental changes (Lapp and Hunter, 2016; Muotri et al., 2009, 2005).

1.4. TE regulation

Transposable elements must be tightly regulated because uncontrolled regulation opens the possibility for transposition events that may have detrimental consequences for the organism through insertion into or altered transcription of genes needed for survival. Transcription factors may have originally evolved as regulators to silence transposable elements and only later became important for regulation of protein-coding genes (Bourque et al., 2008; Friedli and Trono, 2015). TE expression varies by tissue indicating that regulatory mechanisms are tissue-specific as opposed to global TE silencing (Dupressoir et al., 2012; Katsumata et al., 1998). Changes or deficits in one regulatory mechanism may only affect a specific cell population and have different downstream effects than changes to a different regulatory mechanism. Understanding specific mechanisms of TE regulation may help elucidate underlying individual differences in vulnerability to early life perturbations.

There are two primary pre-transcription types of silencing. (1) DNA methylation of cytosines at CpG sites within TEs enable transcriptional silencing in the same manner as DNA methylation of protein-coding genes and promoters and (2) histone modifications change chromatin shape to suppress TE transcription. Histone three lysine nine trimethylation (H3K9me3) and histone three lysine twenty-seven trimethylation (H3K27me3) are two histone tail modifications that have been implicated in TE silencing as discussed further in section 3.1.2 (Day et al., 2010; Hunter et al., 2012). A host of other factors have been

shown to mediate chromatin remodeling to affect L1 transcription including SOX2, histone deacetylase 1 (Hdac1), and Methyl-CpG-binding protein 2 (MeCP2), as well as transcription of other retrotransposons, including zinc finger proteins. It has been suggested that DNA methylation is not as effective as histone modifications in silencing TE transcription (Varshney et al., 2015), however it is commonly accepted that both epigenetic marks have the ability to repress TEs. In addition to pre-transcriptional silencing of TEs, there are several types of post-translational mechanisms of TE regulation including small interfering RNA (Robert et al., 2004), piwi-interacting RNA (Brennecke et al., 2007), and sequestration into stress granules (Goodier et al., 2007). These layers of TE regulation allow for dynamic and nuanced regulation of different classes of TEs (Fig. 1).

2. Transposable elements across the lifespan

2.1. Mammalian development

TEs are widely expressed in a stage-specific manner and play an integral role in early mammalian embryonic development. Regulation of TEs is also dynamic across development, involving DNA methylation, histone modifications, and mediators of histone modifiers such as Sebt1 and TRIM28 (Rowe and Trono, 2011). Global "erasing" of DNA methylation pre-implantation in embryos and pre-imprinting in germ cells presents the problem of TE regulation by other mechanisms to prevent unconstrained expression and transposition, followed by re-methylation programming of DNA to promote a more stable genome (Reik et al., 2001; Rowe and Trono, 2011). Strikingly, L1 in embryonic stem cells is critical in recruiting necessary machinery to direct a transcriptional program specific to the 2-cell stage (Percharde et al., 2018). A recent study assessing ERV expression across 8 stages of early embryonic development found the highest levels ERV expression in oocyte, zygote, and four-cell stages and gradual decline in ERV expression beginning at the 8-cell stage. TEs have also been implicated in placental formation and are highly expressed in the placenta (Dupressoir et al., 2012; Lynch et al., 2015). The specific roles of TEs and TE regulation across development is beyond the scope of this review, but can be found elsewhere for embryonic development (Gerdes et al., 2016; Rodriguez-Terrones and Torres-Padilla, 2018) and the placenta (Emera and Wagner, 2012; Finley, 2018).

Until relatively recently, transposition events were assumed to only take place during meiosis and early development in mammals when epigenetic silencing mechanisms were relaxed, creating a permissive state for DNA mobilization. It is now clear that retrotransposition in adult animals takes place as discussed in section 2.2. However, TE activity during development may have more widespread effects than during adulthood. Primordial germ cells are capable of L1 retrotransposition at a rate of about 1 per 8 births in mice, confirming the capacity for transposition events in early development to be passed on to future generations and may be acted upon by forces of natural selection (Richardson et al., 2017). Transposition events after specification into germ lineage will not be passed on to the future offspring, but somatic genomic mosaicism induced by TEs may still affect specific tissues or brain regions depending on timing of transposition (for in-depth discussion, see Richardson and Faulkner, 2018). The potential contributions of TEs to fetal development, neurogenesis, neural migration, neuronal growth and differentiation, synaptic pruning and cell death, and angiogenesis are largely unknown. Brain development is protracted in humans and continues in some areas post-parturition into the neonatal period, through childhood, and into early adulthood.

2.2. L1 transposition in the adult brain

In adulthood, the brain is privileged in terms of TE activity relative to peripheral tissues (Kurnosov et al., 2015). Seminal work by the Gage lab and collaborators have demonstrated that L1 retrotransposition not

only occurs in the adult brain, but also that the frequency of transpositions varies by brain region and cell type. The relative plasticity in TE expression and regulation in some regions and cell types suggests that TEs may serve important roles cellular or region-specific brain function and that loss of typical regulation may affect some areas while others are unaffected. Most work on L1 transposition in the adult brain has focused on the hippocampus and has highlighted the dentate gyrus as a hotspot for L1 retrotransposition (Muotri et al., 2005). The dentate gyrus is one of the only regions showing neurogenesis in the adult brain and the majority of L1 transposition events occur in neural progenitor cells in mice, suggesting that developmental processes in proliferation and differentiation provide a window of opportunity during which repressive regulators of L1, including SOX2 and Hdac1, are released allowing L1 activity (Muotri et al., 2005).

MeCP2 represses L1 expression and retrotransposition by interfering with promotor activity on the 5' end (Muotri et al., 2010; Yu et al., 2001). These findings have been expanded to the human brain using neural progenitor cells from human fetal brain tissue and embryonic stem cells (Coufal et al., 2009). It has been proposed that *de novo* L1 insertions in the adult brain may contribute to somatic mosaicism in the hippocampus that may be adaptive, such that new insertions offer the capacity for new genomic tools that may change neuronal phenotype in a direction that provides an adaptive advantage. This idea is supported by data indicating that new insertions are preferentially introduced near neuronal genes that are likely to be active (Bundo et al., 2014). *De novo* somatic insertions will not be passed on to offspring and therefore natural selection may not act on them directly, but perhaps the capacity for retrotransposition has been selected for because of its adaptive advantage to respond to change rather than natural selection working on individual somatic insertions as they can in the germline (Upton et al., 2011). Estimates of the level of transposition vary substantially between cell types, roughly 13 per cell in human cortical and hippocampal neurons as compared to 6 for glia and none in liver (Upton et al., 2011). Similarly, there is a contrast in the rate of transposition between labs, with a range from 16 events per neuron to 0.1 events (Upton et al., 2011; Evrony et al., 2012, 2016). Taking the lower bound means that 10% of neurons will show mosaicism, while the upper range of the estimates would mean that somatic mosaicism is ubiquitous in the cortex and hippocampus. For further information on L1 transposition in the brain, the reader is directed to Suarez et al. (2018).

2.3. Environmental adaptation in adulthood

Stress can be broadly defined as a stimulus or event that an organism must respond to on a behavioral or physiological level to maintain homeostasis and internal stability. Stressors include environmental perturbations like extreme thermal conditions or food scarcity, pharmacological challenges like drug or toxin exposure, and psychological challenges like perception of threat or social stress. TE activity in the brain has been shown to be affected by environmental challenges. For example, mice that experienced voluntary exercise, which is known to promote neurogenesis and therefore increase opportunities for *de novo* L1 insertions as described above, have more L1 insertions in the dentate gyrus of the hippocampus (Muotri et al., 2009). TE activity has also been shown to change with cocaine exposure (Maze et al., 2011), alcohol (Ponomarev et al., 2012), and heat shock (Allen et al., 2004). Derepression following environmental stressors may be a genomic adaptation that affords neural diversity potentially helpful in responding to environmental stimuli.

2.3.1. Glucocorticoid regulation of transposable elements

TEs have also been shown to be regulated by the more stringent definition of stress: an event that stimulates hypothalamic-pituitary-adrenal (HPA) axis activation resulting in elevated levels of glucocorticoids and glucocorticoid receptor (GR) activation. Simplistically, during the normal stress response glucocorticoids bind to GR in the cytosol, GR homodimerizes, and homodimer complex translocates to the nucleus where it binds to GR response elements and acts as a transcription factor to alter gene expression. Following an 1 h episode of acute restraint stress and a 45 min recovery period in adult male Sprague-Dawley rats, H3K27me3 was reduced and H3K9me3 elevated in the CA3 and dentate gyrus subregions of the hippocampus, areas rich in GRs and integral to HPA negative feedback (Hunter et al., 2009). These histone modifications are also associated with TE silencing in human and mouse cells and may silence different types of retrotransposons (Day et al., 2010). Chromatin immunoprecipitation sequencing analyses of hippocampi from rats that were stressed for 30 min and allowed to recover for 1 h revealed that epigenetic transcriptional silencing histone modification was selectively enriched in areas of the genome containing TEs (Hunter et al., 2012). Furthermore, there was significant GR binding near the *Suv39h2* gene, a histone methyltransferase, which was upregulated 1 h after corticosterone treatment (Hunter et al., 2012). Epigenetic silencing of TEs following stress is contrasted by the finding that heat shock stress increases the expression of Alu and B2 SINEs (Espinoza et al., 2004; Mariner et al., 2008). One explanation for the seemingly contradictory findings is that there is an immediate effect that increases TE expression followed by a compensatory H3K9me3 increase to silence TEs. The recovery period after restraint stress prior to sacrifice may have captured the second half of this response. Alternatively, these findings may indicate different adaptive responses to diverse stressors. The specific time course of TE expression and regulation following stressors currently remains an open question that is the subject of ongoing work in our laboratory.

Interestingly, repeated daily acute restraint stress for six days resulted in elevated basal H3K9me3 and a loss of H3K9me3 increase following acute stress (Hunter et al., 2009). This could indicate loss of homeostatic response to the stress events over time. The concept of allostatic load explains this phenomenon, where repeated or chronic stress can lead to an altered physiological "allostatic set point" that differs from the starting point of homeostasis with failure to recover to homeostasis between stress exposures (McEwen, 2000). Loss of dynamic regulation of TEs in the hippocampus could lead to aberrant TE activity with negative consequences for the organism over time, such as the hippocampal impairments related to memory and learning processes that accompany chronic stress (Kim and Diamond, 2002). Alternatively, animals may have habituated to the repeated acute restraint stress resulting in lower glucocorticoid levels with stress and attenuated H3K9me3 response. Future work should determine whether chronic variable stress also results in loss of H3K9me3 response and establish the time course for H3K9me3 and TE transcription following stressful events. These concerns are common not only to the examination of TEs, but to studies of gene expression in general. They are perhaps more acute in the study of TEs since the mechanisms by which TEs act remain unclear in many, if not most, cases. Thus, it is difficult to tease apart causal from compensatory phenomena. More work on molecular mechanisms of TE action will make these questions more tractable.

3. Early experiences affect transposable elements in the brain

Early life is a period when environmental perturbations can have particularly profound and enduring effects on brain development that can contribute to cognitive, emotional, and behavioral outcomes throughout the lifespan. The effects of early experience can vary by type of exposure, duration, and developmental stage during which it was experienced. However, even taking those variables into account, there is a substantial amount of variability in how individuals respond to any specific event or exposure in early life. Some individual variation can be accounted for by polymorphisms in protein-coding genes and interactions with the environment. While gene by environment interactions and polygenetic risk can explain some susceptibility to negative outcomes following early exposure to stress, it falls short in explaining

all individual variance. There is significantly more inter-individual variation in TEs in the genome compared to traditional polymorphisms in protein coding regions (Mills et al., 2007), and many if not most, polygenic risk loci are in non-coding regions of the genome (Ward and Kellis, 2012). Given this heterogeneity, it is plausible that interactions between TEs and environmental challenges in early life may help explain why some individuals become more susceptible to negative outcomes later in life compared to others.

Understanding TE activity in the hippocampus following early life perturbations will be especially informative as converging evidence suggests the hippocampus as a hub for dynamic TE expression and regulation: L1 retrotransposition during neurogenesis in neural progenitor cells, epigenetic changes in response to stress, and the exceptional predisposition of the hippocampus to be molded by early life experiences, especially stress. Changes in TE transcription and retrotransposition resulting from perturbations during periods of brain development in early life are just starting to be explored.

3.1. Retrotransposition and early life experience

There is exciting evidence that early experiences affect TE retrotransposition in the brain. In mice, total percent time of maternal care received during the first two weeks was negatively correlated with L1 copy number in hippocampal neurons of offspring on postnatal day 21 (Bedrosian et al., 2018). The association between maternal care and L1 copy number was not due to differences in rates of neurogenesis and maternal care was not related to copy number of other retrotransposons (SINEs B1 and B2, ERV IAP [intracisternal A-type particles]). Offspring receiving low maternal care also had less methylation at *YY1*, a transcription factor binding site necessary for L1 transcription, and lower levels of DNA methyl-transferase 31 at postnatal day 7 compared to offspring from high maternal care dams (Bedrosian et al., 2018). This study raises further questions about the effect of early experience on *de novo* TE insertions in the hippocampus: (1) As described above, GR activation via acute restraint stress or corticosterone injection in adult animals affects regulation and expression of TEs. However, it is unclear whether GR plays a role in regulating TE expression during the first two weeks of life when HPA development is mediated by maternal care. (2) Maternal care during the first two weeks of life programs GR methylation levels in the hippocampus with consequences for GR expression and HPA response to stress in adulthood (Weaver et al., 2004). Altered basal GR levels resulting from early experience may also alter the "normal" adaptive epigenetic silencing mark of TEs in the hippocampus when subsequent stressors are experienced in adulthood. (3) These findings were associations with naturally-occurring levels of maternal care in normal environmental exposures. It remains unknown whether more "extreme" and disruptive manipulations, such as predator threat, elevated maternal corticosterone via drinking water, or limited bedding and nesting material, would yield similar results or would affect nonautonomous types of TEs. (4) Finally, whether changes persist into adulthood and are causally related to hippocampal-dependent behaviors and cognitive process known to be affect by early life stress is an avenue for future studies.

3.2. Early life experience and epigenetic regulation

Although there is little research on the effects of exposure during early life on methylation of TE regions across the lifespan, there is some evidence that in utero exposures can affect TE DNA methylation in peripheral tissues. For instance, the yellow coat color and metabolic issues in agouti mice are caused by an IAP insertion into the agouti locus (Michaud et al., 1994). Maternal diet containing methyl donors and cofactors during pregnancy causes a shift toward increased methylation in the IAP mutation in offspring which is also associated with a corresponding change in phenotype including a shift toward brown coat color reminiscent of non-mutated phenotype (Cooney et al., 2002;

Wolff et al., 1998). Thus, maternal diet during gestation can affect methylation of TEs with functional consequences for offspring. In humans, levels of maternal monoethyl phthalate in maternal urine at 13 and 26 weeks gestation are negatively associated with methylation of Alu in cord blood (Huen et al., 2016). The same pattern, although weaker, exists for L1 methylation. Similarly, exposure to environmental pollutants during the first trimester are negatively associated with L1 methylation in newborn blood spots (Breton et al., 2016). There is also evidence that postnatal experiences can alter TE methylation; age 5 children with higher hair cortisol, a biomarker of chronic stress, had lower levels of methylation in SINEs in whole blood samples (Nätt et al., 2015). Early life experiences may also change histone modifications that control chromatin state near TEs and create permissive states for TE transcription and transposition. Although this has yet to be investigated directly in relation to TEs, there is evidence that developmental stressors can alter histone modifications (Kao et al., 2012; Xise et al., 2013).

4. Transposable elements in neurodevelopmental disorders

The concept that many psychiatric illnesses have developmental origins is well established in neurobiology (Bale et al., 2010). Research on fetal and early-life exposures such as diet, toxins, infection/inflammation, drug exposure, and aberrant HPA activation demonstrate lasting effects on the developing organisms, some of which are sustained into adulthood and increase the susceptibility for psychiatric illness. Autism Spectrum Disorders (ASD) has been linked to various maternal infections and illnesses during pregnancy, suggesting maternal immune response to infections may increase risk of ASD in offspring (Estes and McAllister, 2015). Along with genetic factors, it is likely that ASD results from a combination of genetic susceptibility and changes driven by maternal immune activation (MIA) during early prenatal development. Anatomical differences in brains of individuals with ASD, such as the microstructure differences in stacks of neuronal cell bodies (minicolumns) in the neocortex, can be attributed to various stages of development during the prenatal period (Casanova et al., 2002; Gottfried et al., 2015; Zikopoulos and Barbas, 2013). Changes in anatomical structure of minicolumns may contribute to ASD pathology such as language processing (Chance, 2014; McKavanagh et al., 2015). Like ASD, schizophrenia is thought to have developmental origins driven by environmental exposures. Risk of schizophrenia is elevated with maternal stress during pregnancy (Khashan et al., 2008), maternal infection and altered cytokine profiles (Buka et al., 2001a; Buka et al., 2001b), hypoxia (Cannon et al., 2002, 2002; Zornberg et al., 2000), and prenatal malnutrition (Hoek et al., 1998; Susser et al., 2008).

Postnatal experiences can also affect susceptibility to neurodevelopmental and stress-related disorders. The Adverse Childhood Experiences studies demonstrate the connection between early life adversity and illness later in life, showing graded increases in mental illness, medical illness, and risky behaviors associated with increases in types of traumatic events experienced during childhood and adolescence (Anda et al., 2010, 2006; Felitti et al., 1998). There is a relationship between Adverse Childhood Experience scores and risk of psychiatric symptoms including depressed affect, anxiety, hallucinations, and panic reactions, and risk for diagnosis of mental disorders including depression, anxiety, post-traumatic stress disorder (PTSD), and suicide attempts (Anda et al., 2008, 2006; Brown et al., 2005; Cabrera et al., 2007; Chapman et al., 2004; McCauley et al., 1997). Other studies of early life adversity, such as parental loss or separation, have supported these findings (Agid et al., 1999; Kendler et al., 1992; Morgan et al., 2007). These and other measures of early adversity show associations with generalized anxiety disorder, major depression, bipolar disorder, social anxiety disorder, schizophrenia, PTSD, and alcohol abuse (Agid et al., 1999; Bailer et al., 2014; Hemmingsson et al., 2014; Kendler et al., 1992; MacMillan et al., 2001; Morgan et al., 2007; Perroud et al., 2016; Roth et al., 2014; Simon et al., 2009; Stein et al.,

1996; Varese et al., 2012).

The prevalence of many developmental disorders varies by sex, but sex differences in TE regulation, expression, and transposition are not understood. Furthermore, there are known sex differences in stress response, which affects TE regulation (Bale and Epperson, 2015). Other steroid receptors are also regulators of TE expression, which could help explain tissue differences, sex differences, and emergences of developmental disorders at and after puberty (Gore et al., 2014). In the same vein, changes in TE activity are likely to vary by age just as early life perturbations on the transcriptome and epigenetic machinery are temporally distinct (Suri et al., 2014).

4.1. Developmental disorders caused by genetic mutations

TEs have been shown to play an important role in some developmental psychiatric disorders (Guffanti et al., 2014). Rett syndrome is characterized by developmental delay, seizures, and intellectual disability with developmental onset between 6 and 18 months of age that results from mutations in the *MeCP2* gene (Amir et al., 1999; Hagberg et al., 1983). Neural progenitor cells from an individual with Rett syndrome show increased L1 transposition susceptibility (Muotri et al., 2010). Similarly, L1 copy number was increased in postmortem hippocampal neurons of individuals with ataxia telangiectasia (Louis-Bar syndrome), which is a progressive neurodevelopmental disorder that emerges in early childhood and leads to immune dysfunction, cerebellar ataxia, and neurological impairment resulting from a mutation in the *ATM* gene (Coufal et al., 2011; Savitsky et al., 1995). Most recently, a whole-genome mapping approach was used to investigate retrotransposition events in the brain and blood of individuals with the disorders mentioned above in addition to tuberous sclerosis complex, which is characterized by seizures, developmental delay, and intellectual disability and results from mutation in *TSC1* or *TSC2* genes, and nonsyndromic autism (Jacob-Hirsch et al., 2018; Orlova and Crino, 2010). Confirming previous findings, there were more L1 insertions in brain samples compared to non-brain samples (peripheral blood and lymphoblastoid cell lines). Brain tissue from individuals with neurodevelopmental disorders had 14.7-fold higher levels of L1 and Alu insertions compared to non-pathological brains. Interestingly, about 93% of new L1 insertions occurred in pre-existing L1 sequences and the authors suggest that shuttling new insertions into existing L1 sequences may help constrain some possible disruptive effects of *de novo* retrotranspositions. Finally, 76.8% of L1 insertions were truncated at the 3' and 5' ends in brains from individuals with neurodevelopmental disorders, which may be indicative of non-classical endonuclease-independent transposition (Jacob-Hirsch et al., 2018). The pathological brain tissue samples were from cerebellar, occipital, and frontal cortices, and future work will need to assess other brain areas and draw comparisons between them to determine if the increase in L1 insertions is a global phenomenon or varies by brain region.

4.2. Autism spectrum disorder

Autism Spectrum Disorders (ASD) are pervasive neurodevelopmental disorders first described by Eugen Bleuler in 1911. Since the addition of ASD to the DSM III in 1980, the diagnostic criteria for ASD has changed with each DSM revision. Most recently, ASD is defined by two core symptoms: 1) social communication and social interaction impairment and 2) restricted interest and repetitive behaviors (American Psychiatric Association, 2013). ASD symptoms start in early childhood and interfere with everyday life. Early twin studies suggested a strong genetic component in the etiology of ASD (Bailey et al., 1995; Steffenburg et al., 1989; Tchaconas and Adesman, 2013). Several genes (e.g. *MET, TSC1, MECP2, NF1, TSC2, MIF, C4B,* among others) and single nucleotide polymorphisms have been linked to ASD, but studies have shown that ASD can be attributed to genetic causes only in a limited number of cases (Estes and McAllister, 2015; Gaugler et al.,

2014; Gottfried et al., 2015; Jiang et al., 2013). Copy number variants have also been identified as a contributing factor to ASD risk for up to 20% of cases (Luo et al., 2012; Marshall et al., 2008). While evidence supports some genetic cause, much risk of ASD is still unaccounted for, suggesting that environmental factors play a critical role in ASD etiology (Estes and McAllister, 2015). There is a great deal of heterogeneity in symptom presentation among individuals diagnosed with ASD, and different disorder subtypes likely correspond to different underlying causes. Understanding the role of TEs in ASDs may reveal biological underpinnings of ASD heterogeneity.

The first study to draw connections between ASD and TEs demonstrated differential expression of human ERV (HERV) elements in peripheral blood mononuclear cells (PMBCs) in individuals with ASD (Balestrieri et al., 2012). In a more recent study, L1 open reading frame (ORF) 1 and 2 mRNA were measured in postmortem brain tissue of individuals with ASD and matched controls. ORF1 and 2 expression was significantly upregulated in the cerebellum in the ASD samples, with no difference in the three cortical brain regions measured (Shpyleva et al., 2018). In the ASD sample but not healthy controls, there was a significant relationship between MeCP2 binding to the 5′UTR and ORF 1 expression accompanied by a reduction in H3K9me3 levels in the cerebellum in the ASD group, suggesting these factors may play a role in creating a permissive state for L1 activity in the cerebellum in ASD (Shpyleva et al., 2018). Using existing transcriptome profiles of individuals with ASD, L1 insertion, primarily in intronic regions, was associated with differentially expressed genes, and pathway analysis revealed these genes were involved in sex hormone receptor signaling and axon guidance. L1 was hypomethylated in lymphoblastoid cell lines derived from a subset of ASD individuals with severe language impairment and methylation levels were negatively associated with L1 expression (Tangsuwansri et al., 2018). In a similar study by the same group, pathway analysis revealed differentially expressed genes associated with Alu were involved in signaling pathways including IL-6, axon guidance, estrogen and androgen signaling, CREB, neurotrophin/TRK, and ERK/MAPK and *Alu* methylation status varied by ASD subtype (Saeliw et al., 2018).

4.3. Schizophrenia

Schizophrenia is a psychotic disorder characterized by neurocognitive deficits including delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms (American Psychiatric Association, 2013). Schizophrenia is associated with disruptions to several domains of brain function, including structural abnormalities (Lawrie and Abukmeil, 1998) and altered gene expression patterns in specific cell populations (Harrison and Weinberger, 2005; Lawrie and Abukmeil, 1998). Functional, structural, and transcriptional abnormalities may converge to change connectivity and synaptic functions which contribute to the disorder's symptoms. The onset of schizophrenia is during puberty or early adulthood, suggesting a role for gonadal hormones in schizophrenia ontogeny. Males tend to have earlier onset and differences in prevalence of certain symptoms between males and females have been described (Leung and Chue, 2000). Given the resemblance of many TEs to retroviruses, it is plausible that TE overexpression resulting from abnormal regulation might contribute to the neuroinflammation observed in the disease (see section 4.5).

The first studies to find a connection between TEs and schizophrenia demonstrated expression of ERVs in blood and cerebral spinal fluid from individuals with schizophrenia (Huang et al., 2011, 2006; Karlsson et al., 2001; Perron et al., 2012). In a pioneering study, Bundo et al. (2014) demonstrated increased L1 copy number in dorsolateral prefrontal cortex (PFC) neurons of individuals with schizophrenia. L1 insertions were preferentially found near genes previously implicated in schizophrenia etiology and involved in synapse formation. Importantly, increased L1 copy number was also found in offspring of two different animal models whereby environmental factors during early life lead to

schizophrenia endophenotypes: prenatal polyI:C injection in pregnant dams to induce maternal immune activation and chronic epidermal growth factor administration to neonatal macaques (Bundo et al., 2014). These findings have been confirmed by a recent study that used different methods and pathway and ontological analyses that showed increased L1 insertions in dorsal lateral PFC neurons of individuals with schizophrenia, preferentially in genes involved in cell projection and post-synaptic membrane (Doyle et al., 2017). Additionally, childhood total trauma and emotional abuse influence L1 methylation in adults with schizophrenia such that patients who experienced childhood trauma had lower DNA methylation in L1 compared to patients that did not experience trauma and healthy controls (Misiak et al., 2015). Li et al. (2018) also found hypomethylation of L1 at two CpG sites in a Han Chinese cohort, although childhood adversity was not examined in that study (Li et al., 2018). These experiments confirm an association between L1 activity and schizophrenia and demonstrate that environmental factors during early life can have lasting effects on L1 copy and methylation.

4.4. Stress-related psychiatric disorders

The HPA axis is responsible for the physiological stress response and provides a common pathway through which perinatal stress may increase susceptibility to stress-related mental illness. Early life stress leads to HPA dysregulation, which is hypothesized to be a key contributor to early life stress-induced illness vulnerability (Lapp et al., 2018). Abnormal HPA activity has also been described in individuals with psychological disorders, further supporting this hypothesis (Borges et al., 2013; Bradley and Dinan, 2010; Jansen et al., 1998). Reductions in hippocampal volume, an area important to the HPA negative feedback and privileged in terms of TE activity in the adult brain, are associated with early life stress (Bremner et al., 1997; Jackowski et al., 2011; Stein et al., 1997; Vythilingam et al., 2002) and are implicated in depression (Sheline et al., 1996) and PTSD (Bremner et al., 1995).

4.4.1. PTSD

PTSD inherently involves dysregulation of the adaptive stress response in returning to homeostasis following exposure to trauma as part of its diagnosis. While many individuals are exposed to trauma at some point in their lives, only a fraction develop PTSD. At least some individual variance has been traced back to early life adversity, and individuals with PTSD and early life trauma may have a different endophenotype than other types of PTSD. Furthermore, both early life adversity and PTSD are associated with HPA dysregulation, including reduced GR responsiveness (Yehuda et al., 2010). Many TE-derived non-coding RNAs have emerged in PTSD genomic studies (Daskalakis et al., 2018) and failure of epigenetic silencing of TEs during trauma might contribute to the disorder (Hunter et al., 2012).

In the only study of TEs in PTSD in humans to date, L1 was hypomethylated in military service members diagnosed with PTSD post-deployment while *Alu* was hypermethylated prior to deployment (Rusiecki et al., 2012). With the idea that exposure to stressful experiences early in life can predispose an individual to exaggerated fear response to a later stressor, stress enhanced fear learning has been used as an animal model of PTSD where prior stress (i.e. foot shocks) facilitates subsequent fear learning (Rau et al., 2005). Transcriptome network analysis following stress-enhanced fear learning in the basolateral amygdala found upregulation of elements containing L1 domains, which was blocked with exposure to a sub-anesthetic dose of isoflurane (Ponomarev et al., 2010).

4.4.2. Affective disorders

Affective disorders not only have connections with postnatal early life stress and the HPA axis, but have also been associated with prenatal stress, maternal diet during pregnancy, and prenatal maternal immune activation (Brown et al., 1995; Machón et al., 1997; Van Os and Jones,

1999). Few studies have examined TEs in individuals with affective disorders and none have in the context of early exposures. One study found hypomethylation at two CpG sites in L1 in Han Chinese individuals with bipolar disorder (Li et al., 2018). Similarly, DNA methylation in L1 was decreased and L1 copy number was increased in peripheral blood in patients with major depressive disorder (Liu et al., 2016). In mice that underwent chronic unpredictable mild stress, a manipulation thought to induce a depressive-like state, L1 copy number was elevated in peripheral blood in concordance with the human findings, but was reduced in the prefrontal cortex and unaffected in the hippocampus, amygdala, nucleus accumbens, and paraventricular nucleus of the hypothalamus (Liu et al., 2016). Methylation of an AluJb element found in the serotonin transporter promoter in peripheral blood was significantly lower in individuals with major depression and in participants reporting higher stress (Schneider et al., 2018). In individuals with major depression, AluJb methylation was positively associated with amygdala reactivity to emotional faces (Schneider et al., 2018). These findings draw connections between differential methylation of a TE subregion of a promoter for a protein-coding gene, brain activity, and depression diagnosis, an approach that may help clarify how differential methylation of TEs in psychiatric illness contribute to functional differences in brain networks.

4.5. Transposable elements in inflammatory pathways

Many disorders described above also have a known immune component. For example, individuals with ASD have dysregulated immune factors in the periphery; analysis of plasma and peripheral blood mononuclear cells show elevated levels of interleukin-1β, interleukin-4, interleukin-5, interleukin-6, interleukin-8, and interleukin-12, among other immune factors (Ashwood et al., 2011; Careaga et al., 2015; Krakowiak et al., 2017; Suzuki et al., 2011). These elevations are mirrored by similar elevations in postmortem brains of individuals with ASD (Li et al., 2009; Wei et al., 2011). Other assessments of postmortem brain tissue have found differences in microglia and astrocytes (Edmonson et al., 2014) and increased numbers of active microglia (Bailey et al., 1998; Vargas et al., 2005). In line with these known risk factors, familial history of autoimmune disorders is an established risk factor for ASD (Estes and McAllister, 2015; Keil et al., 2010) and individuals with ASD are more likely to have an autoimmune disorder themselves (Comi et al., 1999). Altered immune components have also be described in PTSD (Lindqvist et al., 2014), depression (Howren et al., 2009), and schizophrenia (Tomasik et al., 2016).

TEs have known interactions with immune components since the discovery of their role in V(D)J recombination adaptive immunity (Teng and Schatz, 2015; van Gent et al., 1996). One of the best characterized role of TEs in the inflammatory pathways comes from a line of research in age-related macular degeneration, where reduced levels of DICER1, which normally regulates Alu transcripts through degradation into smaller non-toxic components, leads to NLRP3 inflammasome activation (Kaneko et al., 2011). This initiates toll-like receptor independent MyD88 signaling via the proinflammatory cytokine interleukin-18 (Tarallo et al., 2012). Subsequent activation of Capsase-8 eventually leads to apoptotic cell death in retinal pigmented epithelium and contributes to progression of macular degeneration (Kim et al., 2014). TEs also have a demonstrated role in autoimmune disease. For example, excess nucleic acid accumulation, primarily L1 DNA, in neuronal cytosol due to three-prime repair exonuclease I (TREX1) deficiency, which normally degrades nucleic acids, results in type 1 interferon inflammatory response and ultimately apoptosis. TREX1 deficiency also leads to abnormal cortical organoid development and may have implications for Aicardi-Goutières syndrome autoimmune disease which has been associated with impaired TREX1 function (Thomas et al., 2017). Similarly, it has been suggested that L1 may activated toll-like receptor pathways that lead to activation of type 1 interferons (Crow, 2010).

Table 1
TE copy number, DNA methylation and expression in neurodevelopmental and psychiatric disorders.

Disorder	Tissue/sample[a]	Sample size	Method	TE copy number	TE DNA methylation	TE expression	Reference
Rett syndrome	Neural progenitor cells derived from induced pluripotent stem cells	Rhett syndrome: n = 5 Control: n = 5	L1 5'UTR-Luciferase plasmid	Increased L1 retrotransposition			Muotri et al. (2010)
Ataxia telangiectasia (Louis-Bar syndrome)	Post-mortem hippocampal tissue	Ataxia telangiectasia: n = 7 Control: n = 7	Taqman q-PCR	Increased L1 ORF2 copy number			Coufal et al. (2011)
Rett syndrome, Ataxia telangiectasia, tuberous sclerosis complex, nonsyndromic autism	Post-mortem cerebellar, occipital, and frontal cortex tissue	Pathologic: n = 17 Non-pathologic: n = 5 (various areas)	Whole-genome mapping	Increased L1 and Alu retrotransposition			Jacobs-Hirsh et al. (2018)
ASD	Peripheral blood	ASD: n = 28 Control: n = 28	PCR amplification, gel electrophoresis for presence/absence detection			More individuals with ERV-H and HERV-W expression	Balestrieri et al. (2012)
ASD	Post-mortem cerebellum, BA9, BA22, and BA24	ASD: n = 13 Control: n = 13	Taqman q-PCR			Higher L1 in cerebellum, no difference in other regions	Shpyleva et al. (2018)
ASD	Existing peripheral blood transcriptome data from NCBI Gene Expression Omnibus DataSets	ASD: n = 465 Control: n = 256	Ingenuity Pathway Analysis of differentially expressed genes	Increased L1 insertions near genes involved in sex hormone receptor signaling and axon guidance			Tangsuwansri et al. (2018)
ASD	Existing peripheral blood transcriptome data from NCBI Gene Expression Omnibus DataSets	ASD: n = 36 Control: n = 20	Ingenuity Pathway Analysis of differentially expressed genes		Alu methylation varied by ASD subtype		Saeliw et al. (2018)
ASD with severe language impairment	Lymphoblastoid cell lines	ASD: n = 36 Control: n = 20	Combined bisulfite restriction analysis, qPCR		L1 hypomethylation	L1 methylation negatively associated with L1 expression	Tangsuwansri et al. (2018)
Schizophrenia	Cell-free cerebrospinal fluid, postmortem frontal cortex	Schizophrenia (CFS): n = 55 Control (CFS): n = 12 Schizophrenia (brain): n = 5 Control (brain): n = 6	Nested PCR & gel electrophoresis visualization, sequencing			More individuals with HERV-W expression in CFS, increased HERV-W expression in frontal cortex	Karlsson et al. (2001)
Schizophrenia & Bipolar disorder	Peripheral blood	Bipolar disorder: n = 110 Schizophrenia: n = 59 control: n = 105	Taqman q-PCR, sequencing	Decreased HERV-W copy number		Elevated ERV-W expression	Perron et al. (2012)
Schizophrenia	Serum	Schizophrenia: n = 118 Control: n = 106	Nested PCR & gel electrophoresis visualization, sequencing			More individuals with HERV-W evn expression	Huang et al. (2011)
Schizophrenia	Peripheral blood	Schizophrenia: n = 58 Control: n = 38	Nested PCR & gel electrophoresis visualization, sequencing			More individuals with ERV9 pol expression	Huang et al. (2006)
Schizophrenia	Postmortem dorsolateral PFC tissue	Schizophrenia: n = 13, n = 35 Control: n = 13, n = 34	Taqman q-PCR	Increased L1 copy number			Bundo et al. (2014)
Poly:IC maternal immune activation (mice), chronic epidermal growth factor (macaque) models of schizophrenia	PFC	Poly:IC (mice): n = 8 Control (mice): n = 8 EGF (macaques): n = 2 Control (macaques): n = 3	SYBR green q-PCR	Increased L1 copy number			Bundo et al. (2014)
Schizophrenia	Postmortem dorsolateral PFC tissue	Schizophrenia: n = 36 Controls: n = 26	L1-seq	Increased L1 insertions near genes involved in cell projection and post-synaptic membrane			Doyle et al. (2017)
Schizophrenia with childhood trauma	Peripheral blood leukocytes	Schizophrenia w/trauma: n = 18 Schizophrenia w/o trauma: n = 18 Control: n = 46	Combined bisulfite restriction analysis, PCR, gel electrophoresis visualization		L1 hypomethylation		Misiak et al. (2015)

Table 1 (*continued*)

Disorder	Tissue/sample[a]	Sample size	Method	TE copy number	TE DNA methylation	TE expression	Reference
Schizophrenia	Peripheral blood, Han Chinese cohort	Schizophrenia: n = 92 Control: n = 92	Bisulfite conversion-specific one-label extension		L1 hypomethylation		Li et al. (2018)
PTSD	Serum, military service members	PTSD: n = 75 Control: n = 75	Pyrosequencing		L1 hypomethylation post-deployment, Alu hypermethylation pre-deployment		Rusiecki et al. (2012)
Stress-enhanced fear learning model of PTSD	Rat basolateral amygdala	n = 7–8	Transcriptomic network analysis			Higher expression of elements containing L1 domains	Ponomarev et al. (2010)
Bipolar disorder	Peripheral blood, Han Chinese cohort	Bipolar: n = 99 Control: n = 92	Bisulfite conversion-specific one-label extension		L1 hypomethylation		Li et al. (2018)
Major depressive disorder	Postmortem dorsolateral PFC tissue	MDD: n = 12 Control: n = 13	Taqman q-PCR	Non-significant increase in L1 copy number			Bundo et al. (2014)
Major depressive disorder	Peripheral blood	MDD: n = 105 Control: 105	Taqman q-PCR, methylation sensitive restriction enzymes		L1 hypomethylation	Higher L1 expression	Liu et al. (2016)
Chronic unpredictable mild stress model of depression	Peripheral blood, PFC, hippocampus, nucleus accumbens, paraventricular nucleus of hypothalamus of mice	Depression model: n = 22 Control: n = 12	SYBR green q-PCR	L1 copy number increased in blood, reduced in PFC, unaffected in other areas			Liu et al. (2016)
Major depressive disorder	Peripheral blood	MDD: n = 122 Control: n = 176	Bisulfite conversion, PCR amplification, sequencing		*Alu*Jb element in serotonin transporter promoter hypomethylation		Schneider et al. (2018)

[a] All tissues are human unless otherwise specified.

Elevated glucocorticoids following stress exposure have regulatory functions over downstream physiological processes including the immune function, so it is reasonable to assume that HPA dysregulation triggered by early life stress also affects immune function (Juster et al., 2010). Stress leads to increases in proinflammatory cytokines, which are associated with psychological disorders as described above. Inflammatory pathways are an indirect pathway through which HPA dysregulation can lead to poor mental and medical health outcomes that may involve TEs (Seeman et al., 2010).

5. Conclusions

A surge of interest in the role of TEs in psychiatric illness in the past few years has provided a better understanding of the role of TEs in the brain across the lifespan and in developmental disorders. There is evidence that TEs in the brain are affected by environmental influences and it is well-established that the risk for several disorders, including autism, schizophrenia, and stress-related disorders, is increased by exposure to certain environmental influences in early life, possibly through interaction with inflammatory pathways. Whether environmental perturbations change TE activity during development is understudied. Remarkably, there is agreement across most studies of TEs in mental disorders where pathological individuals show hypomethylation, increased expression, and increased copy number of TEs compared to healthy individuals in various tissues (see Table 1). This suggests poor regulation of TEs in these disorders, although whether TEs play a causal role in disorder development, specific symptomology, or behavior in general remains undetermined. Though many of the studies to date suffer from limitations of methodology or statistical power as is expected early in the development of a line of inquiry, a general trend is evident across them. This agreement argues for larger studies at the epidemiological level and more rigorous mechanistic studies in vitro and in in animal model systems. Functions of transcribed TEs are still being discovered, but it is likely that TE overexpression results in a multiplicity of effects that will interact with other risk factors to give rise to psychiatric symptoms.

Future work will need to focus on establishing a causal framework for TE actions in the nervous system. At present, this effort is hampered by the fact that rules governing transposon derived non-coding RNA are not as well understood as those governing the function of protein coding genes. Similarly, the complexity and variety of the mechanisms by which a single TE might interact with the rest of the genome and the cell offers challenges to experimental design. Further, most TEs exist in multiple copies, meaning that traditional molecular genetic techniques become more challenging to use. Lastly, TEs are poorly conserved across taxa so making translational analogies across species lines is more problematic than with protein coding genes. These caveats aside, there are clear examples, such as SINE regulation of transcription during heat shock, that show that mechanistic work can be done in the field and that TEs have a functional role. The field will be strengthened by a move in this direction. Work has already established the necessity of TE RNA for transition past the two-cell stage of development (Percharde et al., 2018), and future work should extend these findings to later stages of development, including neural development. Further, it is evident that recent human and primate-specific TEs are differentially expressed in regions such as the prefrontal cortex (Guffanti et al., 2018). Mechanistic experiments to establish what role they play in the development and function of these regions are likely to open new vistas for understanding mental disorders, which are in many ways unique to our species. In vitro examination of the molecular interactions of TE derived RNA and proteins are also needed to build a genuine mechanistic picture of TE function both in the brain and other tissues. Animal models will continue to serve a role in experiments demonstrating proof of principle and general mechanisms. However, given the wide divergence of the transposome across species, translational arguments must be made with greater care and forethought than has

typically been the case with genetic models in the past. TEs represent perhaps the last great genomic terra incognita, and dead ends and spurious conclusions are an ever-present danger. However, the idea that our genome might be orders of magnitude more complex than we imagined even a decade ago is a prospect worth exploring vigorously.

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Conflicts of interest

The authors declare no competing interests.

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