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Epigenetic Mechanisms and Associated Brain Circuits in the Regulation of Positive Emotions: A Role for Transposable Elements

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ABSTRACT

Epigenetic programming and reprogramming are at the heart of cellular differentiation and represent developmental and evolutionary mechanisms in both germline and somatic cell lines. Only about 2% of our genome is composed of protein-coding genes, while the remaining 98%, once considered "junk" DNA, codes for regulatory/epigenetic elements that control how genes are expressed in different tissues and across time from conception to death. While we already know that epigenetic mechanisms are at play in cancer development and in regulating metabolism (cellular and whole body), the role of epigenetics in the developing prenatal and postnatal brain, and in maintaining a proper brain activity throughout the various stages of life, in addition to having played a critical role in human evolution, is a relatively new domain of knowledge. Here we present the current state-of-the-art techniques and results of these studies within the domain of emotions, and then speculate on how genomic and epigenetic mechanisms can modify and potentially alter our emotional (limbic) brain and affect our social interactions. J. Comp. Neurol. 524:2944–2954, 2016.

INDEXING TERMS: brain circuits; positive emotions; genomics; epigenetics; transposable elements

The completion of the human genome sequencing represents the beginning of a genetic and genomic revolution in health care. The pace of genomic medicine has moved at a surprisingly fast rate. Within 70 years, we have progressed from the foundational studies of Friedrich Miescher, Phoebus Levene, and Erwin Chargaff, and then Watson and Crick's seminal discovery of the double helix, to reading the whole genetic material in a human being with the possibility of using the genomic information for medical and health-related applications. However, even though we have obtained the complete sequence of our genome, we still need substantial new research to really understand the functional significance of the genome architecture, particularly within the context of neuroscience. While we have been developing a better knowledge of the most fundamental molecular mechanisms that regulate neuronal functions, we have recently, in parallel, been acquiring a better understanding of brain circuits and functions; the issue at stake is how to integrate these disparate pieces of information into a coherent framework.

Our understanding of the structural and functional composition of the genome, as well as the plasticity of gene regulatory pathways, has increased exponentially, through both technical developments and the resultant progressive understanding of common and complex diseases. Unexpectedly, however, the completion of the mapping and characterization of the human genome has revealed that the true complexity of the genome has little to do with the simple number, and even

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variability, of its coding genes. Only 2% of the human genome codes for proteins; the remaining 98% is represented by non–protein-coding sequences. For decades the noncoding genome was considered "junk" DNA without any functional significance, but deep sequencing analyses in recent years suggest that the whole human genome is transcribed into RNAs (Dunham et al., 2012; Harrow et al., 2012; Kundaje et al., 2015). The emerging pattern is that the vast majority of our genome is functional and regulates the gene-coding machinery by producing noncoding RNAs in a myriad of ways. Another level of complexity is related to the epigenetic interplay between genome activity and environmental influences: current research into functional genomics and individual deep sequencing is opening up new perspectives for our understanding of how genome and environment interact in complex diseases (Coop et al., 2010).

Here we present a short review of our current knowledge of the epigenetic mechanisms that functionally tune that part of our genome mostly involved in regulation of the central nervous system and that contribute to the proper, context-dependent functions of brain circuits involved in positive (or negative) emotions also via external (i.e., nongenomic) stimuli. For example, it is well known that social adversities, physical abuse, loneliness, and even grief are associated with increased susceptibility to disease. When such stressful events occur, they stimulate an adapted behavioral response where the environmental challenges can be viewed within the framework of the evolutionarily based adaptive match/mismatch hypothesis (Schmidt, 2011; Daskalakis et al., 2012, 2013). Under this scenario, the outcome of a stressful condition leading to either a physiological resilience or a psychopathological condition depends on the coping strategies that any individual has developed when faced with early life events. Coping strategies emerge as the result of the interaction between the "programmed" genomic-based adaptations and the constraints due to early, adverse events, especially in the perinatal and postnatal periods.

MOLECULAR ARCHITECTURE OF THE EMOTIONAL BRAIN: WHAT DO WE REALLY KNOW?

A vast body of literature in the last decade attests to the renewed and increased interest in the study of the neural bases of affections or emotions. New analytical strategies that combine refined brain imaging and genomic methods, together with psychometric and clinical quantitative traits, are allowing for the current research in neuroscience to clarify how our brain and our behavior are shaped both phylogenetically and evolutionarily. As thoroughly reviewed by Panskepp and Biven (2012), the "emotional" (primarily composed of the limbic system) and the "social" brain (primarily composed of the prefrontal and anteromedial temporal systems) are privileged targets for these studies, but they represent more difficult objectives than, say, the more accessible and long-studied cognitive and executive functions of the dorsal and lateral neocortical systems. To explore the world of human emotions, we need both theoretical and operational improvements. Theoretically, we have already made substantial improvements, shifting from a purely psychological to a more integrated neurobiological/cognitive framework that can help evince a clearer understanding of experimental findings. Operationally, sophisticated investigations are required to understand how genomic and epigenomic mechanisms that regulate brain circuits controlling for emotions and social behaviors work day to day and over the full lifetime in living humans. Other reports in a special issue of this journal have presented in detail the current hypotheses of brain circuits and neurotransmitter pathways that control for positive emotions, but here we are interested in speculating on a model that integrates the functional and the molecular architecture of the emotional brain.

In short, we know that both subcortical and cortical structures are relevant in controlling for affects and emotions in humans, including the orbitofrontal cortex, the amygdala, the hippocampus, the limbic system and its associated cortico-subcortical loops in the basal ganglia, the limbic thalamus, and the brainstem monoaminergic nuclei. Our knowledge of the functional anatomy of these brain regions has steadily progressed in the last 30 years, but other brain regions also considered relevant, like the periaqueductal gray, the septum, and a few non-monoaminergic brainstem nuclei are still poorly understood. Moreover, little is known about the developmental mechanisms that control for the proper circuital organization of these structures and of their neuronal connections. We have known for quite a long time the essential role played by dopamine in the "reward" system (Schultz, 2011; Russo and Nestler, 2013) and the key role played by other neurotransmitters like the opioid peptides and endocannabinoids. Experimental support for the relevance of these systems is increasing: for example, a frequent DNA variant in the fatty acid amide hydrolase (FAAH) gene that reduces the amount of deactivation of anandamide, a naturally occurring human cannabinoid, correlates with lower levels of anxiety and fear. The reduced FAAH expression associated with the variant allele also "selectively enhances prefronto-amygdala connectivity and fear extinction learning ... suggest[ing] a gain of

function in fear regulation" (Dincheva et al., 2015). This mechanism may represent an adaptive function for a primary process of positive emotion that humans share with other mammals, in this case mice.

It is possible, however, that different mutational mechanisms other than nucleotide substitutions must be invoked to explain how gene networks have been (re)wired during human evolution to deal with environmental, primarily intraspecies, control of emotions and hence have shaped our emotional and social brain. Widespread epigenetic changes have been proposed to underlie alterations in gene expression associated with gene networks and brain circuits that control for positive emotions. Modular gene networks that are coexpressed in anatomically different, but functionally related, brain regions can represent the backbone of a circuital organization that modulates our ability to deal with emotions. Under this scenario, genes that belong to the same network or genes that follow a hierarchical time-dependent expression developmental pattern must be activated in a coordinated way across different and somewhat distant brain regions. This coordinated molecular/functional activity across brain regions is similar to the mechanisms that are putatively at work in complex neuropsychiatric disorders, including schizophrenia and affective disorders, i.e., in all cases in which scores of genes must be jointly implicated epistatically. However, how both normal and pathological neuronal circuitry depends on the specificity and extent of epigenetic programs has not yet been fully elucidated.

NEW INSIGHTS FROM GENOMIC STUDIES

One of the surprises of the genomic era is the relatively small number of protein-coding genes in the human genome. Before completion of the Human Genome Project, indirect estimates for the number of protein-coding genes were ranging from 35,000 to 100,000 (Ohno, 1972; Lander et al., 2001). To date, the number of protein-coding genes has been experimentally reduced to 20,000–25,000, and we expect it to be further revised (International Human Genome Sequencing Consortium, 2004). Current evidence shows that many regulatory complexes are needed for the development and function of the vertebrate brain (Yoo and Crabtree, 2009; Yoo et al., 2009): recent progress from the ENCODE project has begun to reveal the complexities of the noncoding human genome, beginning with the functional characterization of an unprecedented number of elements previously considered nonfunctional (Kundaje et al., 2015). These efforts have lead to the generation of an extensive catalog of more than four million noncoding elements that regulate the dynamics of gene expression, frequently, but not exclusively, via chromatin (re)modeling (Harrow et al., 2012; Maurano et al., 2012). Noncoding regulatory elements include several families of noncoding RNA molecules such as long intergenic noncoding RNAs (lncRNA), and short RNA molecules, including microRNA (miRNA), short interfering RNA (siRNA), Piwi-interacting RNA (piRNA), regulatory DNA sequences (i.e., transcription factors), and other sequences with yet unknown functions. In addition to this network of regulatory "switches," the genomic architecture is also characterized by low-complexity regulatory elements (e.g., long interspersed elements [LINEs], short interspersed elements [SINEs], human endogenous retroviruses [HERVs], and SINE-R/variable number tandem repeat [VNTR]/Alu-like [SVAs]) that compose ~45–62% of our genome, and consist of repeated transposable elements (TEs; DNA elements that have the ability to move, i.e., transpose, within the genome) that make humans unique in having the largest ratio of noncoding to coding DNA, specifically in central nervous system–related genes (Taft et al., 2007; de Koning et al., 2011) (Fig. 1).

TRANSPOSABLE ELEMENTS INTRODUCE GENETIC VARIABILITY IN THE HUMAN GENOME

The retrotransposition rate of still active TEs has been estimated to range between 0.8 to 0.6 somatic L1 insertions per neuron in the human brain (Coufal et al., 2009; Evrony et al., 2012), while the transposition rate is higher in germline cells. Not surprisingly, then, cells evolved self-defense machineries to regulate the activity of TEs through epigenetic mechanisms, such as DNA methylation (TEs account for one-third of all CpG sites) and histone modification (Slotkin and Martienssen, 2007), and also by post-transcriptional mechanisms. Methylation of CpG sites results in effectively repressing the transcription of nearby genes (*cis* mechanism). Despite the machinery used by the cell to regulate TE activity, some TEs escape repression and generate new insertions in germline cells and during early embryonic development, as well as in somatic tissues later in life (Baillie et al., 2011; Kazazian, 2011; Lee et al., 2012), affecting the genome in different ways, as explained in the next paragraphs. The human genome has accumulated ~970,000–1.5 million LINE1s (L1s), the majority of which are retrotranspositionally inactive. The still active LINEs belong to the L1HS family (Brouha et al., 2003) and are responsible for the majority of the ongoing retrotransposition in the human populations. These variations are called *retrotransposon*

insertion polymorphisms (RIPs) or *mobile element insertions* (MEIs) (Ewing and Kazazian, 2010, 2011; Schmitz, 2012). At least four studies in different populations have been conducted using next-generation (i.e., short reads-based) sequencing to investigate the specific content of de novo retrotransposition (Beck et al., 2010; Ewing and Kazazian, 2010; Huang et al., 2010; Iskow et al., 2010). The main findings were that individual genomes are highly variable in the specific locus position of individual nonreference (i.e., polymorphic) L1 insertions and that de novo retrotransposition are much more frequent than previously thought. However, TEs do not transpose within the genome in an exclusive random mode: LINEs tend to reinsert into GC-poor, and SINE/Alus into GC-rich, regions (Pavlicek et al., 2001). This evidence provides a highly dynamic portrait of the genome, whereby individuals differ not only with respect to the presence or absence of various L1 insertions, but also with respect to the relative position of the insertion (Lupski, 2010). (See Fig. 1 for a classification and schematic representation of the molecular structure of TEs.)

Transposable elements induce transcriptome diversity

TEs can affect genomic integrity in many ways through de novo insertions and postinsertional rearrangements, resulting in deleterious mutations in the open reading frames of a gene, leading to protein disruption and/or aberrant expression (Goodier and Kazazian, 2008). Even if transposon-mediated mutagenesis is extensive in the human genome (Cordaux et al., 2006), this is not the only mechanism by which TEs can influence cellular functions. Contrasting with the hypothesis that retrotransposons are disruptive and negatively affect genomic integrity (Goodier and Kazazian, 2008) is the finding in many cases that they have rather been exapted as transcriptional start sites (TSS) or enhancers (Huda et al., 2010), and have significantly and positively contributed to the evolution of the human genome (Cordaux et al., 2006).

TE nonreference or de novo insertions may be beneficial to gene expression in inducing transcript diversity (Cowley and Oakey, 2013). TE insertions can generate *alternative splice sites*, causing the splicing system to include new sequences as exons or to elongate existing ones (Schmitz and Brosius, 2011). They can also introduce *poly(A) signals*, causing premature termination of transcription of the host gene, and also generate *new transcription start sites* (Faulkner et al., 2009). All these mechanisms have a clear role in promoting transcript diversity. Furthermore, recent genome-scale studies

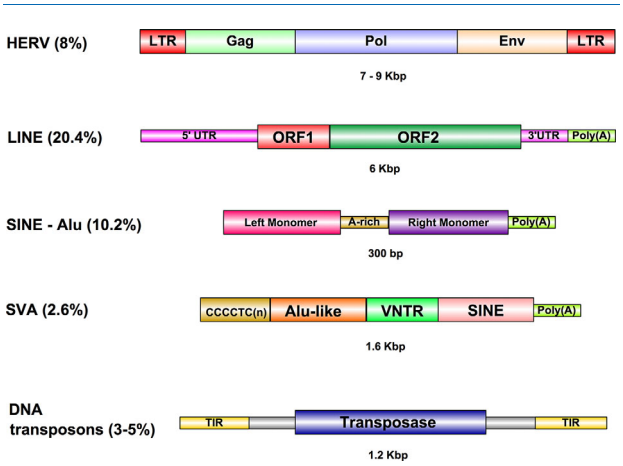

Figure 1. Transposable element (TE) classification and molecular structure. In this schematic representation, different TEs are not shown to scale. Long terminal repeat (LTR)-transposons or human endogenous retroviruses (HERVs) include two LTR sequences flanking the coding sequences of the functional polyproteins capsid (gag), protease, polymerase and reverse transcriptase (pol), and envelope (env). Non–LTR-retrotransposons include long interspersed elements (LINEs), short interspersed elements (SINEs), and SVAs (SINE-R/VNTR/Alu-like). L1 elements consist of an intact 5′ untranslated region (UTR) that functions as an internal promoter and full-length L1 mRNA of functional open reading frame (ORF1 and ORF2) proteins, encoding for a reverse transcriptase. Alus consist of a tRNA-related region that represents the internal promoter stretch, followed by a tRNA-unrelated region and a LINE-related region, which is used by the SINE element to bind LINE-encoded proteins to complete LINE-1–mediated retrotransposition. SVAs consist of four domains including a CT-rich repeat at the 5′ end, commonly referred to as CT-hexamer, an Alu-like sequence, so-called for homology with two antisense Alu-like fragments, a GC-variable number tandem repeat (VNTR), whose length determines variation of the full-length SVA elements, a sequence derived from the envelope gene (env), and a SINE-R, an LTR of an extinct HERV-K10. In the DNA transposons a protein called transposase is bound by terminal inverted repeats (TIRs) that flank the TE, excise the TE out of the donor position, and reintegrate it into the genome. The schematic representation was inspired by images in Guffanti et al. (2014).

have revealed the importance of TEs in dispersing *transcription factor binding sites* (TFBS). The effects of the dispersion of TE-derived TFBS are multiple. In normal tissues, they contribute to the generation of tissue-specific (e.g., brain-specific, and brain area-specific) expression profiles (Faulkner et al., 2009), while the inappropriate activation of these TE-derived transcription factor binding sites seem to be responsible for driving ectopic gene expression, which has been implicated in human diseases (Faulkner et al., 2009). Moreover, TEs can coordinate the activation of gene expression throughout the genome, co-orchestrating the activity of functionally related genes, i.e., within the same pathway, but not necessarily physically clustered

(Britten and Davidson, 1971; Lynch et al., 2015). For this fundamental activity of coordinators of global patterns of gene expression, TEs have been defined as the "engineers" of transcriptional networks (Cowley and Oakey, 2013).

TEs might also impact gene expression indirectly, when the retrotransposition machinery is used by non-TE genes to retrotranspose protein-coding mRNAs, leading to the creation of a copy of the original gene. While these copies are mostly nonfunctional, sometimes they can evolve into retrogenes with novel functions. Retrogenes, when embedded in the introns of genes, have the potential to induce premature termination of transcription by causing upstream transcript polyadenylation. This particular mechanism affects only one of the two parental alleles (Cowley and Oakey, 2013), and creates a polymorphic effect similar to that shown for intronic HERVs (Ward et al., 2013). On the basis of an increasingly overwhelming body of evidence, it is reasonable to believe that the study of the "mobilome" may transform our understanding of the mechanisms of coordination responsible for gene expression throughout transcriptional networks, leading to a better understanding of the functional architecture of the normal brain, as well as the etiopathogenesis of many neuropsychiatric diseases (Erwin et al., 2014; Guffanti et al., 2014; Insel, 2014).

An impressive level of TE transcription is present in both evolutionarily conserved and accelerated genome regions. Many evolutionarily "old" L1s show an intense expression even when severely truncated, while L1s other than L1HS are also present in rapidly evolving regions. For example, there are several almost intact L1s (L1PA3, L1PA2, and L1PA4s) that show a high level of expression in positively swept regions. Many TEs seem to be unique to humans compared with other primates or vertebrates, suggesting a more recent than expected evolutionary time, or representing relatively "new" polymorphic insertions in the human genome. Despite the current evidence for the relevance of human accelerated regions (HARs) in shaping the human genome (Gilad et al., 2006; Pollard et al., 2006; Lindblad-Toh et al., 2011; Burbano et al., 2012), the real modes of evolution are not yet definitively known (Hernandez et al., 2011; McLean et al., 2011). It is possible that a polygenic combination of "soft" sweeps in networks of genes (Cordaux and Batzer, 2009; Erwin and Davidson, 2009; Pritchard et al., 2010) rather than a positive selection at single loci may be one of the major mechanisms regulating the evolution of expression (Khaitovich et al., 2006; Feschotte, 2008), especially for the developmentally relevant regulatory elements (Matlik et al., 2006).

Frequently, L1s (or Alus or HERVs) that are consistently expressed overlap with transcription signals detected by the ENCODE Consortium (Kundaje et al., 2015), including transcription factors (TFs) and TFBS. Frequently these transcription signals also disperse within H3K4me1 and -3 histone marks, suggesting promoter or regulatory functions (as enhancers). The pervasive pattern of TE transcription at a whole-genome level nonetheless is not uniform: some genes have almost no TEs across their entire open reading frame (ORF), whereas others show an extremely dense pattern of TEs across the entire gene structure, including introns (3′ and 5′ untranslated regions [UTRs]).

Thus, it is becoming clear that the noncoding genome has a critical epigenetic role in controlling for the complex pattern of tissue and time-specific patterns of gene expression; it is also becoming more and more evident that genes do not work in isolation, but only as part of gene networks.

We are just beginning to understand the complexity of such a regulatory genome and its epigenetic mechanisms. Epigenetics/regulatory mechanisms can work either locally—through promoters, enhancers, insulators, and other elements controlling for the expression of nearby genes—or distantly—through a variety of other mechanisms, like methylation-silencing gene promoters, transcription factors, short and long noncoding RNAs, TEs, and chromatin modifiers.

TRANSPOSON-MEDIATED EPIGENETIC MODEL FOR POSITIVE EMOTIONS

A great deal of work has been performed on negative emotions such as fearful behaviors, but information about the neurobiological mechanisms underlying positive emotions is still relatively limited (Burgdorf and Panksepp, 2006). As a consequence, much of what we know about epigenetic mechanisms promoting the transduction of environmental inputs into affective states derives from the stress–fear–response model.

First we review a working example of the interaction among stress, epigenetics, and emotions specifically involving TEs as "controlling elements." Second, we review a working example of the interaction among neuroimaging, epigenetics, and emotions involving brain regions associated with emotion regulation. It is plausible to argue that positive emotions might be mediated by the same biological mechanisms reviewed in these two experimental frameworks. Finally, we discuss how transposon-mediated epigenetic control in a stress–response model may provide us with an explanation for brain plasticity as the basis of positive emotions.

Transposable elements, stress, and emotions

Initial evidence that epigenetic regulation of TEs mediates the effects of stress on neural plasticity came from work by Hunter and colleagues (2013). In rats, acute stress induces increased hippocampal levels of the histone H3 lysine 9 trimethylation (H3K9me3), whose function is mainly associated with repression of gene expression (Hunter et al., 2009). Further research illustrated that increased levels of this epigenetic

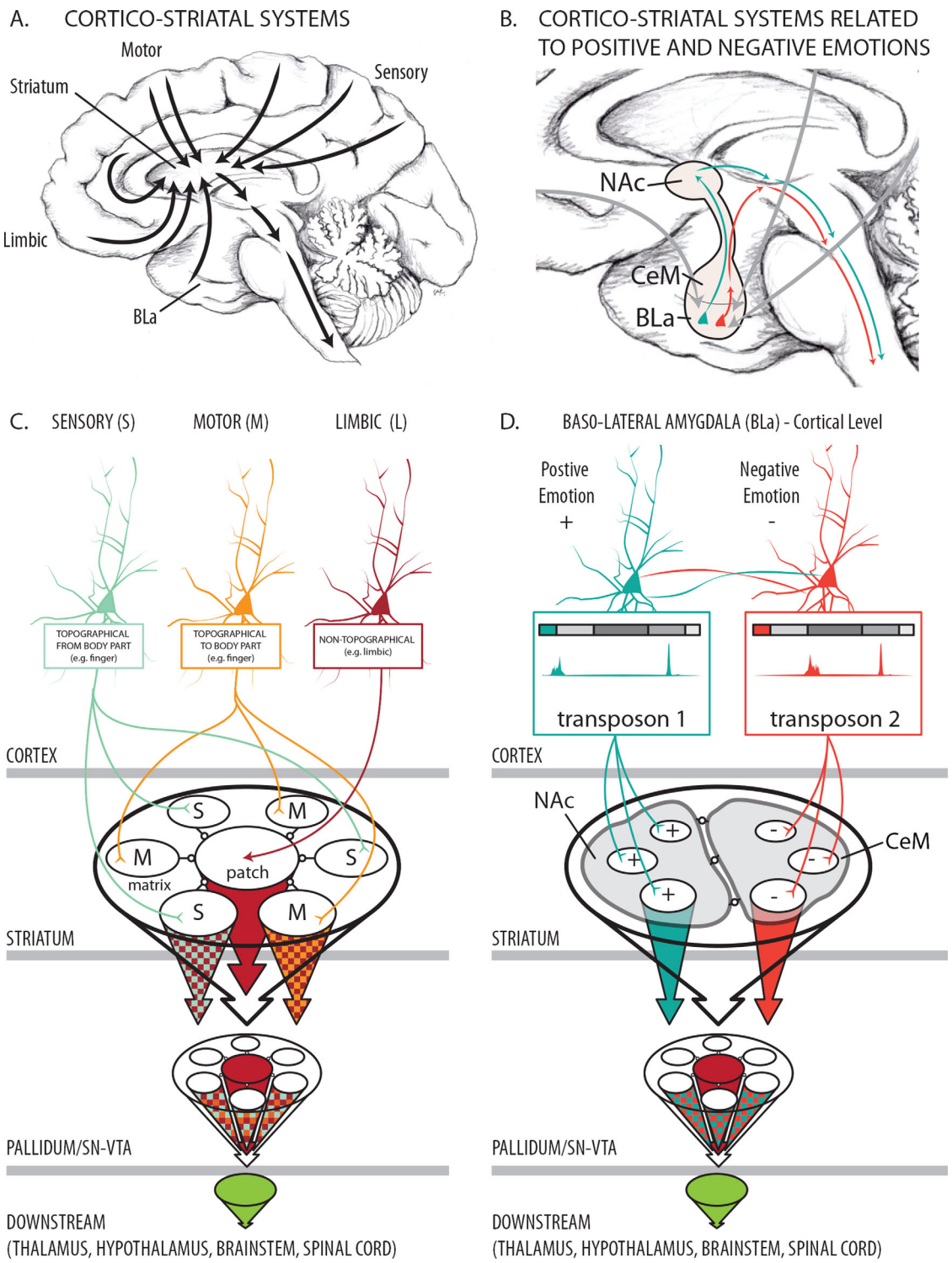

Figure 2.

marker were specifically localized to active classes of TEs, namely, LINEs, SINEs, and ERV/LTR, leading in turn to their reduced transcriptional levels. Such a response to stress initially revealed a high hippocampal specificity, although more comprehensive investigations are needed before ruling out similar effects in other brain regions similarly known for their role in stress sensitivity, such as the amygdala, septum, bed nucleus of the stria terminalis, nucleus accumbens, and limbic thalamus. In an effort to further explain the mechanism by which stress induces epigenetic alterations in the brain, the authors examined the expression of several methyltransferases, the enzymes that allow methylation (and therefore transcriptional repression) of their molecular targets, in this case the aforementioned active classes of TEs. Upregulation of one of these enzymes (*Suv39h2*) was found to be associated with increased binding of the glucocorticoid receptor (GR), consistent with higher expression in the hippocampus (Hunter et al., 2012, 2015). The GR is a known stress-related hormone-dependent transcriptional regulator previously implicated in epigenetic mediation of stress exposure, with particular emphasis on the effects of maternal care on an individual's behavior (Meaney and Szyf, 2005).

Overall, these findings supported an active role for TEs in the epigenetic mechanisms underlying the biological response to environmental stress exposure. The downstream effects of such epigenetic response in shaping the programming and reprogramming of neural circuitry of emotional regulation remain to be fully elucidated. In other words, the direction in which repression of transcriptional activity of large portions of the noncoding genome is capable of influencing widespread transcriptional activity in the brain has not yet been the object of thorough investigation. Recently, work by Fasching and colleagues (2015) illustrated a potential mechanism that could explain the complex relationship between stress-mediated epigenetic regulation of TEs and transcriptional plasticity of neural circuitry. The authors reported that deletion of the gene *TRIM28*, a transcriptional regulator, in neural progenitor cells determines loss of the H3K9me3 epigenetic marker localized on HERVs, ultimately leading to their transcriptional reactivation. Interestingly, reactivation of HERVs revealed exaptation properties of this class of TEs by influencing expression levels of nearby genes and the production of long noncoding RNAs, which are also known for *cis*- and *trans*-regulatory functions (Guttman and Rinn, 2012). Upon loss of repressive epigenetic markers, HERVs were capable of acting as promoters/enhancers, inducing gene expression of other genes, and potentially reconfiguring the whole transcriptional network (Feschotte, 2008). Although far from conclusive, these findings encourage further explorations of TEs and their exaptation into *cis*-regulatory elements of transcriptional activity.

Epigenetics, brain circuits, and emotions

Studies related to the genomic/epigenomic regulation of positive emotions are just beginning to appear in the literature (Puglia et al., 2015). These authors provide evidence of the association of higher levels of oxytocin receptor gene methylation with higher activation

Figure 2. Functional circuits of positive emotions. **A,C:** A general model of the cortico-striato-pallido-SN-VTA downstream systems in the human brain. **B,D:** The specific case of the cortico-striato-pallido-SN-VTA systems that regulate positive and negative emotions. In both cases, the systems are made up of parallel, hierarchical, interacting cortico-subcortical modules that ultimately control behavior through downstream control of skeletal, autonomic, and endocrine motor systems, but also involve recurring loops back to both neocortex and limbic cortices, primarily through ascending thalamo-cortical and monoaminergic projections (not shown). In the general forebrain cortico-striatal originating channels in **A** and **C**, the sensory cortices provide topographical inputs (S for sensory) to the matrix compartments of the caudate-putamen, while premotor and motor cortices innervate adjacent matrix compartments (M for motor). Nontopographical inputs from limbic cortices primarily innervate the "patch" striatal compartment. Interneurons, including tonically active neurons, interconnect these compartments. These compartments then project to either the internal or external segment of the globus pallidus, and/or different sectors of the substantia nigra–ventral tegmental area. Further downstream convergence occurs on thalamic, hypothalamic, brainstem, and spinal cord cell columns and nuclei that control movement, the autonomics, pituitary, and preganglionics. In **B** and **D,** a similar set of cortico-striatal systems originating in the main cortical-like nucleus of the amygdala, the basolateral amygdaloid nucleus (BLa), innervate striatal-like targets in the central nucleus of the amygdala (CeM) for the control of negative emotions (in red) or the medial sector of the nucleus accumbens (NAc) containing the hedonistic hot spot for the control of positive emotions (in green). These limbic striatal-like targets in turn project to their respective ventral pallidal and SN-VTA targets, and further to downstream targets that regulate motor outputs related to emotionally dominated complex adaptive behaviors. As in the case of the general forebrain schema of cortico-striatal connectivity (**A,C**), the adjacent neurons at the cortical, striatal, and pallidal levels subserving different functionality in the emotional circuitry (**B,D**) (e.g., positive vs. negative emotions) are linked by direct connections (e.g., between neighboring pyramidal neurons at the cortical levels), as well as by indirect, interneuron-mediated connectivity. These close interneuronal interactions at each level also allow for epigenetic tuning of the two different functional systems, in part mediated by plastic control of transposon-mediated regulation of promoters and enhancers of coding genes characteristic of each neuron at each level of the system.

of brain areas involved in emotional regulation, namely, the amygdala, fusiform gyrus, and insula, and with "decreased functional coupling of amygdala with the rest of the regions involved in emotional regulation" (Puglia et al., 2015), ultimately leading to increased anxiety. Although preliminary, these findings support the relevance of epigenetic regulation in shaping the neural circuitry of emotional regulation.

The integration of epigenetics and brain circuitry of emotional regulation extends efforts to include epigenetics in the framework of genome-wide association studies rather than simply inspecting candidate genes. Although the era of "large-scale studies of human disease-associated epigenetic variation, specifically variation in DNA methylation" (Rakyan et al., 2011) has started to deliver the first wave of results, this neuroepigenetics study offers an example of an alternative and complementary approach to epigenome-wide association studies (EWAS) while providing an additional level of functional characterization of candidate genes findings.

In parallel, refinement of our understanding of pleasure mechanisms in the brain via imaging studies (Berridge and Kringelbach, 2015) is building up a better systematic knowledge of emotional mechanisms. These investigations suggest the existence of a neural circuit common to diverse pleasures, with specific "hot-spots" in the limbic circuitry (e.g., the dorsomedial notch of the nucleus accumbens) and other subcortical regions mostly localized in the right (nondominant) hemisphere for well-defined "hedonic" phenotypes. Two recent studies (Berridge and Kringelbach, 2015; Namburi et al., 2015) are suggesting an interesting neural mechanism possibly controlling for positive emotions. Neurons from the basolateral amygdala complex (BLA) can control for either positive or negative associations (pleasure compared with fear, for example), projecting to either mesolimbic or subcortical structures, based on the specific stimuli that come from the environment. Figure 2 shows a detailed vision of the functional circuits involved in such control, with a speculative interpretation of the role that TEs can play in driving the fate of otherwise indistinguishable neurons toward responding to either positive or negative emotions.

CONCLUSIONS

We argue that integration of the application of these neurobiological approaches suggests a major epigenetic role of regulatory mechanisms of the neural genome, hence including TEs, in explaining the biological mechanisms underlying emotions. The genome responds to environmental inputs via dynamic regulation of the expression of TEs in the brain, which in turn has an impact on protein-coding mRNA transcription and/or post-translational mechanisms. These would ultimately modulate behavioral phenotypes such as positive emotions. Because of the high level of interindividual variation in TE-derived regulatory elements in the human genome, their ability to modulate both positive and negative exposure through epigenetic mechanisms, and their emerging role as regulatory elements of transcriptional activity, TEs can have a central role in coorchestrating the dynamic neural circuitry processes underlying emotional regulation.

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