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Epigenetic mechanisms underlying enhancer modulation of neuronal identity and activity and neurodegeneration

Rafael Alcala Vida ^a, Ali Awada ^a, Anne-Laurence Boutillier ^a, Karine Merienne ^{a,*}

^a LNCA, CNRS UMR 7364, Strasbourg, France

^b University of Strasbourg, France

* Corresponding author

Dr. Karine Merienne

LNCA, University of Strasbourg/ CNRS UMR 7364, 12 rue Goethe, 67000 Strasbourg, France

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Abstract

Neurodegenerative diseases, including Huntington's disease (HD) and Alzheimer disease (AD), are progressive conditions characterized by selective loss of neuronal regions and/or subpopulations, in disease-dependent manner. Neuronal loss is preceded by a long period of neuronal dysfunction, during which glial cells also undergo major changes, resulting in particular in neuroinflammation. Those dramatic changes affecting both neurons and glial cells associate with epigenetic and transcriptional dysregulations, characterized by defined cell type-specific signatures. Notably, increasing studies support the view that altered regulation of transcriptional enhancers, which are distal regulatory regions of the genome capable of modulating the activity of promoters through chromatin looping, play critical role in transcriptional dysregulation in HD and AD. We review current knowledge on enhancers in HD and AD, and highlight challenging issues to better decipher the epigenetic code of neurodegenerative diseases.

1. Neuronal-specific enhancers: neuronal identity vs neuronal activity

Epigenetic regulations. Epigenetic mechanisms, including DNA methylation, some non-coding RNAs and various histone post-translational modifications acting through defined combinatorial rules, modulate the chromatin, which can be relaxed, a feature generally associated with transcriptionally active chromatin, or in a compact state, usually associated with transcriptional repression (Jenuwein and Allis, 2001). Epigenetic mechanisms also comprise regulation of 3D chromatin architecture, including chromatin loops modulating promoter-enhancer interactions and higher-order chromatin

organization, such as topologically associated domains (TADs)(de Laat and Duboule, 2013; Rowley and Corces, 2018). Histone acetylation, through the action of a family of histone acetyltransferases (HAT), plays a key role in chromatin relaxation. Histone acetylation at promoters and enhancers, corresponding to distal regulatory regions, is a prerequisite to target gene activation. Particularly, acetylation at lysine K27 of histone H3 (H3K27ac) by the HAT CBP/P300 is a mark of active enhancers (Tie et al., 2014). Mechanistically, transcriptional complexes comprising HAT, RNA polymerase II (RNAPII) and various transcriptional regulators, including transcription factors and proteins promoting chromatin loop formation such as CTCF and cohesin, are recruited at H3K27ac-enriched regions to facilitate enhancer-promoter interactions (Rowley and Corces, 2018) .

Super-enhancers and cellular identity. During cellular differentiation, H3K27ac signal undergoes massive changes and get particularly enriched at genes defining specific cellular identities (Whyte et al., 2013). Lineage-determining transcription factors, expressed in developmental- and cell type-dependent manners, provide specificity to the mechanism, driving the targeting of H3K27ac at selective genes in time and space controlled manners. Thus, H3K27ac is strongly cell type-dependent, and H3K27ac cellular profile at transcriptional enhancers reflects specific cellular identity. Cellular identity enhancers, regulating genes that specify cell type identity and function, are controlled by super enhancers, which are broad enhancers composed of multiple clusters of active enhancers (Heinz et al., 2015) (Figure 1). Super-enhancers, which generally encompass their target genes, are more highly enriched in H3K27ac when compared to classical enhancers (Heinz et al., 2015). Chromatin architecture at super enhancers displays extensive chromatin looping, enabling multiple promoter/enhancer interactions, thereby insuring elevated and sustained expression of cellular identity genes, a feature essential to cellular identity acquisition and maintenance (Nord and West, 2020; Yap and Greenberg, 2018).

Neuronal activity-regulated enhancers. Enhancers also display highly dynamic regulation since they respond to cellular stimulation, thereby integrating environmental signals and triggering adaptive genomic response. Dynamic regulation of enhancers is especially critical to neuronal function. In response to environmental stimuli, it drives transcriptional reprogramming promoting synaptic plasticity and adaptive behavior, including learning and memory (Campbell and Wood, 2019; Gräff and Tsai, 2013; Kim et al., 2010; Lopez-Atalaya and Barco, 2014; Yap and Greenberg, 2018). In response to stimulation, signaling cascades (e.g. cAMP- and Ras/MAPK-dependent pathways) are activated in neuronal tissue, which leads to the recruitment and/or activation of transcription factors and HAT (e.g. CREB and CBP) to enhancers and promoters of early response genes (ERGs), notably the transcription factor *Fos*. This first, rapid response leads to increased H3K27ac, enhancer RNA

transcription, strengthening of enhancer/promoter interaction and up-regulation of ERGs, thereby inducing a second regulatory wave, leading to activation of cell type-specific late response genes (LRGs). In brain tissue, LRGs are effector genes promoting synaptic plasticity. In response to neuronal stimulation, H3K27ac is increased at LRGs enhancers (Figure 2). LRGs are induced in time and cell type-specific controlled manners thanks to the cooperation between AP-1 proteins, especially FOS, cell type-specific pioneer transcription factors and factors regulating nucleosome eviction (Vierbuchen et al., 2017). It is noteworthy that, in contrast to activity-regulated enhancers, cellular identity enhancers did not show increased H3K27ac in response to cellular stimulation (Vierbuchen et al., 2017).

Thus, neuronal enhancers (and H3K27ac regulation) are critical for the acquisition and maintenance of stable neuronal identity, but also for the dynamic regulation of neuronal activity. While genome wide association studies (GWAS) provide increasing evidence that cell type-specific enhancers, especially super enhancers, are hotspots for risk variants modulating susceptibility to neurological diseases, fewer epigenomic studies have addressed the role of enhancers in brain diseases (Heinz et al., 2015; Nord and West, 2020; Nott et al., 2019). However, the advent of genome-wide scale approaches to investigate brain epigenome has made possible the identification of defined epigenetic signatures in neurological diseases, including neurodegenerative diseases such as HD and AD. Whereas genetic mouse models of these diseases have led to pioneered and critical exploratory studies, increasing data are currently being produced using human brain samples. Here we focus on epigenomic data generated using brain tissues from HD and AD mouse models, as well as post-mortem brain samples from patients. Remarkably, the data indicate that, in both HD and AD brains, neuronal- and glial-specific enhancers show distinct epigenetic signatures, which might stimulate the development of common innovative therapeutic strategies.

2. Epigenetic dysregulation and enhancer regulation in HD

Etiology and neuropathology of HD. HD is a progressive neurodegenerative disease, usually characterized by adult onset, though rare juvenile forms of the disease also exist that display severer clinical presentation and faster progression when compared to the adult form. The disease is caused by an unstable CAG triplet repeat expansion in the first exon of the *HTT* gene, which results in the production of mutated protein with toxic polyglutamine (polyQ) expansion, highly prone to aggregation. The number of CAG repeats at *HTT* is polymorphic in the normal population and does not exceed 36-39 CAGs. Above this threshold, the CAG repeat is pathogenic, and since longer repeats are more toxic, there is an inverse correlation between the number of repeats and age of disease onset (Bates et al., 2015). Moreover, the HD mutation is unstable in the germline and in somatic

tissues, which results in increasing numbers of CAG repeats in successive generations and in somatic tissues with age (López Castel et al., 2010). GWAS showed that genetic modifiers in HD predominantly target DNA repair genes implicated in CAG repeat instability (Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium, 2019, 2015; Jones et al., 2017). Despite ubiquitous expression of the *HTT* gene, polyQ-HTT is predominantly toxic to specific neurons of the striatum, e.g. medium spiny neurons (MSNs). However, as disease progresses, additional brain regions are affected, including cortical regions. Microglia and astrocytes also contribute to the pathogenic process through astrogliosis and inflammatory response, as observed in several neurodegenerative diseases. Neurodegeneration results from a long period of brain cell dysfunction, characterized by multiple cellular defects, resulting from both gain- and loss-of function mechanisms (Bates et al., 2015; Saudou and Humbert, 2016). Particularly, the HD mutation induces large-scale transcriptional and epigenetic dysregulation in HD brain (Francelle et al., 2017).

HD transcriptomic signatures. A numbers of transcriptomic studies were performed using brain tissues of HD mice and post-mortem brain tissues (Francelle et al., 2017; Hodges et al., 2006; Kuhn et al., 2007; Labadorf and Myers, 2015; Luthi-Carter et al., 2000; Seredenina and Luthi-Carter, 2012). Specifically, comprehensive transcriptomic profiling using HD knockin mice expressing mutated *Htt* with different CAG repeat lengths indicated that transcriptional dysregulation in HD is CAG length-, age- and tissue-dependent, being most extensive in the striatum, and thus correlated with disease progression (Langfelder et al., 2016). Dysregulated genes in HD striatal tissue display characteristic signature that is conserved across mouse models, including knockin and transgenic mice, and also in post mortem brain tissues from HD patients (Achour et al., 2015; Kuhn et al., 2007; Langfelder et al., 2016; Luthi-Carter et al., 2000; Vashishtha et al., 2013). Specifically, down-regulated genes in HD striatum are enriched in neuronal function genes, particularly in genes that specify striatal identity (Achour et al., 2015; Hervás-Corpión et al., 2018; Langfelder et al., 2016; Vashishtha et al., 2013). These genes include typical markers of mature MSNs, including dopamine D1 receptor (*D1R*), dopamine D2 receptor (*D2R*), *RGS9*, *DARPP32*... (Francelle et al., 2017). Data analyses indicate that gene down-regulation in HD striatal tissue is not just the consequence of neuronal death (Kuhn et al., 2007). Furthermore, mouse data generated at different time points, including presymptomatic age, suggest gene down-regulation in HD is an early process (Langfelder et al., 2016). In contrast, up-regulated genes in HD brain tissue are enriched in immune and developmental genes, and thus display distinct functional signature (Achour et al., 2015; Kuhn et al., 2007; Labadorf and Myers, 2015; Langfelder et al., 2016).

HD epigenomic signatures. Several epigenomic studies have been generated using brain tissues of HD mice and HD patients (Achour et al., 2015; Bai et al., 2015; Dong et al., 2015; Horvath et al., 2016; McFarland et al., 2012; Merienne et al., 2019; Ng et al., 2013; Valor et al., 2013; Vashishtha et al., 2013). Histone acetylation, including H3K27ac, H3K9,14ac, H4K12ac and H2Aac, was a major focus in those studies. CHIP-seq analyses indicated that changes in H3K9,14ac and H4K12ac were limited in the hippocampus and cerebellum of the HD transgenic mouse N171-82Q, and did not particularly correlated with transcriptional changes (Valor et al., 2013). In contrast, extensive changes in H3K27ac were observed in the striatum of HD R6/1 transgenic mice, which correlated with RNAPII and transcriptional changes (Achour et al., 2015; Le Gras et al., 2017). Similar results were found analyzing H3K27ac ChIPseq data generated using post mortem striatal tissue of HD patients at early symptomatic stage (Merienne et al., 2019). Although the bulk of striatal tissue was used in these studies, integrated analysis with cell type-specific transcriptomic striatal database allowed specifying the contribution of neurons and glial cells to H3K27ac changes: H3K27ac was depleted at neuronal super enhancers in HD vs controls, while it was increased at glial-specific enhancers (Figure 3). Moreover, those cell type-specific H3K27ac changes positively correlated with cell type-specific transcriptional changes, indicating that the HD mutation leads to opposite transcriptional and epigenetic reprogramming in neurons and glial cells (Merienne et al., 2019). Whether maintenance or acquisition of striatal cell identity is compromised in HD is an intriguing possibility that could underlie the mechanism.

HD promoter features were also investigated targeting H3K4me3, a mark enriched at active promoters (Bai et al., 2015; Dong et al., 2015; Guiretti et al., 2016; Vashishtha et al., 2013). CHIP-seq data generated using the striatum and cortex of HD R6/2 transgenic mice indicated that H3K4me3 was widely depleted at neuronal identity gene promoters, which displayed broad H3K4me3 profile, while genes showing increased H3K4me3 showed developmental signature (Vashishtha et al., 2013). H3K4me3 was also investigated using post mortem prefrontal cortex from HD patients, a region however showing mild neuropathological involvement in HD (Bai et al., 2015; Dong et al., 2015). These studies specifically analysed cortical neurons after nuclei sorting using fluorescently activated nuclei sorting (FANS), and identified hundreds of regions differentially enriched in H3K4me3 in HD vs control samples, which were preferentially depleted in H3K4me3. Although the connection between increased H3K4me3 and transcription in HD brain remains elusive, depleted H3K4me3 in HD vs control samples correlated with reduced transcription (Dong et al., 2015).

Collectively, H3K4me3 and H3K27ac epigenomic data indicate that the HD mutation induces loss of activity of neuronal-specific enhancers and promoters implicated in the control of neuronal identity genes. Whether the HD mutation also affects activity-driven epigenetic regulation of

neuronal-specific genes implicated in neuronal plasticity is yet unknown, since none of epigenomic studies above described were performed using behavioral paradigm challenging the brain.

Abnormal epigenetic aging vs development. On the one hand, HD is an age-related disease that is progressive in nature and generally characterized by adult onset, which might suggest that epigenetic aging is altered in HD. This question was addressed assessing the epigenetic clock, which compares biological and chronological clocks through analysis of hundreds of defined DNA methylation sites (Horvath, 2013). Analysis of frontal lobe, parietal lobe and cingulate gyrus of HD patients revealed significant acceleration of epigenetic age (Horvath et al., 2016). Moreover, a negative correlation was observed between CAG repeat length in *HTT* and the epigenetic age. Although epigenetic age was not accelerated in striatal tissue of HD patients, likely due to neuronal loss, these data suggest that accelerated aging contributes to dysregulation of HD epigenome (Horvath et al., 2016). Whether enhancers and/or promoters would be more particularly targeted by such a mechanism is an intriguing hypothesis.

On the other hand, increasing evidences indicate that HD comprises a neurodevelopmental component, likely due to partial loss of physiological neurodevelopmental function of normal *HTT* (Barnat et al., 2017; Mehler et al., 2019; Molero et al., 2016, 2009). More specifically, several studies using human and mouse stem cells differentiated into neurons, including striatal-like cells, show that mutated *HTT* leads to defects in neuronal specification and maturation (Conforti et al., 2018; HD iPSC Consortium, 2017; Molero et al., 2009; Ring et al., 2015; Ruzo et al., 2018; Smith-Geater et al., 2020). Using induced pluripotent stem cells (iPSC) differentiated in MSN-like neurons showed delayed differentiation in the HD background, which correlated with altered epigenetic and transcriptional reprogramming (HD iPSC Consortium, 2017; Smith-Geater et al., 2020). Specifically, persistent expression of developmental genes, including *OCT4*, was observed during striatal neuron differentiation of HD iPSCs, together with abnormal H3K27ac and H3K4me3 profiles, which reflected more immature neuronal state than in controls (HD iPSC Consortium, 2017; Smith-Geater et al., 2020). Thus, abnormal epigenetic regulation during neurodevelopment might compromise proper acquisition of cellular identity of HD terminally differentiated neurons. It is possible, however, that HD-mediated epigenetic alterations during development render neurons more vulnerable to environmental stressors, which may be compensated during early life, but not at later stage, due to cellular aging. Thus, HD epigenetic neurodevelopmental and aging-related components may be related.

Dysregulation of epigenetic regulators by mutated *HTT*. A number of studies have provided evidence for dysregulation of specific chromatin regulators in HD, which may contribute to disruption

of HD epigenetic landscape. It was found in early studies that the HAT CBP is recruited in polyQ-HTT aggregates in HD neurons (Nucifora et al., 2001; Seredenina and Luthi-Carter, 2012; Steffan et al., 2001). Since H3K27ac is a bona-fide target of CBP (Tie et al., 2014), titration of CBP by HD neuronal aggregates could lead to neuronal-specific depletion of H3K27ac. Noticeably however, mutant HTT aggregate formation is a rather late event with respect to HD pathogenesis. Thus, sequestration of CBP in polyQ-HTT aggregates is unlikely to explain epigenetic dysregulation during neuronal differentiation. Nonetheless, a numbers of studies indicate that targeting histone acetylation in HD is beneficial, at least in animal models (Butler and Bates, 2006; Francelle et al., 2017). Specifically, several histone deacetylase inhibitors (HDACi) have been used to treat HD mice and drosophila models, which led to partial recovery of HD-like phenotypes (Ferrante et al., 2003; Gardian et al., 2005; Hockly et al., 2003; Jia et al., 2016; Naia et al., 2017; Siebzehnrübl et al., 2018; Steffan et al., 2001; Suelves et al., 2017; Thomas et al., 2008). Interestingly enough, the HDACi LBH589 improved HD neuronal differentiation (Siebzehnrubl et al., 2007; Siebzehnrübl et al., 2018). However, since no epigenomic data have been generated on HDACi treated animals, it is unclear whether histone acetylation is restored at neuronal super enhancers upon treatment. Moreover, the few transcriptomic data do not support complete rescue of neuronal identity gene transcription, and rather suggest that HDACi modulate metabolic genes (Naia et al., 2017). Yet, in mature neurons, histone acetylation is critical to activity-driven transcription, i.e. to the dynamic regulation of plasticity genes in response to neural stimulation. Thus, it would be interesting to test whether compounds that target histone acetylation affect activity-driven genes in the context of HD.

Additional pieces of evidence indicate that protein complexes and/or enzymes facilitating repressive chromatin are activated by the HD mutation, which could impair the balance between euchromatin and heterochromatin. For example, the activity of polycomb repressive complex 2 (PRC2) was enhanced by mutant HTT, and during neuronal differentiation, HTT was required for proper regulation of H3K27me3, a PRC2 target, enriched in facultative heterochromatin (Biagioli et al., 2015; Seong et al., 2010; Song et al., 2018). However, the effect of mutant HTT on H3K27me3 in mature neurons remains elusive. Other studies showed that the histone H3K9 methylase ESET/SETDB1 was increased in the striatum of HD transgenic mice, a feature correlating with dysregulation of H3K9me3, a marker of constitutive heterochromatin (Lee et al., 2017; Ryu et al., 2006). Underlying mechanism might involve impaired interaction between mutant HTT and ATF7IP-ESET/SETDB1 complex (Irmak et al., 2018). Finally, using a genetic screen in a drosophila model system indicated that HTT physiological function includes chromatin re-organization through regulation of H3 methylation at heterochromatin-euchromatin boundaries (Dietz et al., 2015). While these studies support the notion that HTT is an epigenetic regulator contributing to reprogramming of facultative and/or constitutive heterochromatin during neurodevelopment, the direct effect of

mutant HTT on repressive histone marks in mature neurons and their impact on transcriptional regulation remains unclear.

3. Epigenetic dysregulation and enhancer regulation in AD

Etiology and neuropathology of AD. AD is an aging-related neurodegenerative disease characterized by the accumulation of amyloid beta peptides (A β) and neurofibrillary tangles, which are composed of abnormally phosphorylated Tau protein. AD leads to progressive synaptic and neuronal loss, most particularly in the prefrontal cortex and hippocampus, thereby resulting in memory decline (Serrano-Pozo et al., 2011). Neuroinflammatory response is also a major hallmark of AD. A minority of cases, usually characterized by early onset (i.e. <65 years), is caused by mutations in genes implicated in A β processing, including APP and presenilins. However, the vast majority of cases is sporadic (>95%) and late onset, and results from more complex etiology implicating both environmental and genetic risk factors. While aging is the strongest environmental risk factor, GWAS studies revealed several genetic risk variants, including variants associated with *APOE* and *BIN1* (Bellenguez et al., 2019; Jansen et al., 2019).

Brain enhancers, hotspots for AD-risk variants. Consistent with AD pathogenesis, genes associated to AD-risk variants are enriched in 4 major functions, including A β formation, tau, lipid metabolism and immune response (Jansen et al., 2019). Thus, it is believed that risk variants play causal role, modulating transcription of associated genes (Grubman et al., 2019; Jansen et al., 2019; Klein et al., 2016; Nott et al., 2019). However, the interpretation of risk variants remains elusive in many instances, since they are often located in non-coding regions of the genome that may be distant to the gene(s) they modulate (Maurano et al., 2012; Nott et al., 2019). Analysis of GWAS catalog database showed that nearly 30% of non-coding AD SNPs are located in enhancers, with 95% of the AD SNPs located in enhancers co-localizing with their expressed quantitative trait locus (eQTL) genes in TADs (Kikuchi et al., 2019). Epigenome-wide studies using post mortem brain tissues of AD patients further point to a critical role for enhancers in AD-risk variants, since differential DNA methylation patterns between AD and control individuals were enriched at enhancers (De Jager et al., 2014; Li et al., 2019; Lunnon et al., 2014). The role of enhancers and DNA methylation in mediating the effect of risk factors in AD was further supported by a study showing that the AD-risk associated haplotype at PM20D1 locus leads to altered enhancer-promoter interaction in a CTCF-dependent manner (Sanchez-Mut et al., 2018) (Figure 4).

The heterogeneity of cerebral tissues represents another limitation to the interpretation of risk variants, especially since increasing evidence indicates that functional consequences of risk

variants are cell type-specific (Yeh et al., 2017; Tansey et al., 2018; Nott A et al., 2019). Network analysis of bulk AD brain transcriptome indicated gain of microglial gene connectivity and loss of neuronal connectivity (Zhang et al., 2013). Moreover, studies using single-nucleus/cell RNA sequencing on AD and control cortices provided additional insights, showing that *APOE* is upregulated in an AD-specific microglial subpopulation, while repressed in AD oligodendrocyte progenitor cells and astrocyte subpopulations (Grubman et al., 2019; Mathys et al., 2019). To interpret the effects of AD risk variants in cell type-specific manner, Nott et al. performed cell type-specific epigenomic analysis using human resected cortical brain tissues and found that microglia-specific enhancers were more particularly enriched in AD risk variants (Nott et al., 2019). Using proximity ligation assisted ChIP-seq (PLAC-seq) to establish cell type-specific enhancer-promoter interactome maps and CRISPR/Cas9 technology, they further showed that risk variant rs6733839, the second highest AD-risk variant, is located in microglia enhancer controlling microglia-specific transcription of *BIN1* (Nott et al., 2019). Thus, increasing evidence indicates that brain-specific enhancers, most particularly microglial-specific enhancers, are hotspots for genetic and/or epigenetic variations in AD, thereby contributing to AD pathogenesis in cell type-specific manner (De Jager et al., 2014; Jansen et al., 2019; Kikuchi et al., 2019; Nott et al., 2019).

Genome-wide scale enhancer dysregulation in AD. Several studies indicate disruption of transcriptional enhancers in AD brain tissue, correlating with transcriptional alterations (Benito et al., 2015; Chatterjee et al., 2018; Gjoneska et al., 2015; Klein et al., 2016; Li et al., 2019; Marzi et al., 2018). First evidence came from studies using AD mouse models (Benito et al., 2015; Gjoneska et al., 2015). Transcriptomic and epigenomic profiling using the hippocampus of CK-p25 mouse model, showing amyloid and tau pathologies, revealed coordinated downregulation of synaptic plasticity genes and associated enhancers and promoters and, in contrast, upregulation of immune response genes and regulatory regions (Gjoneska et al., 2015). H3K27ac and H3K4me3 were reduced at neuronal-specific enhancers and promoters, respectively, which correlated with down-regulation of their target genes, whereas the direction of epigenetic and transcriptional changes at glial-specific regulatory regions/genes was opposite (Gjoneska et al., 2015). Consistently, decreased and increased-level regulatory regions were enriched in distinct DNA motifs, recognized by neuronal- and glial-specific transcriptional regulators, respectively (Gjoneska et al., 2015). H3K27ac profiling of AD post-mortem entorhinal cortex samples supported mouse data, showing that enhancer dysregulation is a major hallmark of AD brain (Marzi et al., 2018). Comparing samples of AD patients vs control individuals, thousands of genes were identified that associated with hyper- or hypo-acetylated peaks, and the direction of change in acetylation positively correlated with transcriptional changes (Marzi et al., 2018). Gene ontology analysis further indicated that genes nearby increased H3K27ac in AD

samples were enriched in metabolic/glial functions, while neuronal processes associated with regions depleted in H3K27ac (Marzi et al., 2018). This suggests that AD, similar to HD, leads to opposite H3K27ac changes at neuronal- and glial-specific enhancers. Although super enhancers and identity genes have not been specifically investigated in AD studies, one cannot exclude that comparable genome-wide scale reprogramming of neuronal and glial cell identity operates in AD and HD brains.

Comprehensive fine-mapping of DNA methylation further suggests a crucial role for enhancer dysregulation in AD neuronal pathogenesis, since thousands of differentially methylated enhancers were identified in neurons isolated from prefrontal cortex of AD patients vs control individuals (Li et al., 2019). Surprisingly however, most of these regions were hypomethylated non-CpG sites (e.g. CpH sites), a result that correlated with increased transcriptional activity of closest genes (Li et al., 2019). The role of these non-canonical methylation sites in AD is yet to be uncovered. Finally, changes in additional histone modifications, particularly histone acetylation, including H3K9ac, H3K14ac, H4K5ac, H4K12ac, H4K16ac and H2Bac were also observed in brain tissues of AD mouse models and/or post mortem AD brain cells. While it is not clear whether those acetylation changes were enriched in specific regulatory regions, these results indicate a degree of complexity of AD epigenetic signature (Benito et al., 2015; Chatterjee et al., 2018; Gräff et al., 2012; Klein et al., 2019; Nativio et al., 2018). Collectively, those epigenomic data show that AD leads to significant cell type-specific epigenetic dysregulation of brain enhancers. While histone acetylation remains a major focus in AD epigenomic studies, H3K4me3 was found dysregulated in AD mice, indicating that epigenetic regulation of promoters might also be impaired in AD (Gjoneska et al., 2015; Kerimoglu et al., 2017).

Epigenetic control of activity-regulated genes in AD. The dynamic epigenetic control of gene program regulating neuronal plasticity is critical to memory formation and maintenance, and histone acetylation plays a central role in this mechanism (Yap and Greenberg, 2018). Several studies suggest that altered regulation of histone acetylation contributes to memory decline in AD (Fischer, 2014a). Early study revealed that histone deacetylase 2 (HDAC2) was increased at neural plasticity genes, both in brain tissues of AD mice and in post-mortem brains from AD patients (Gräff et al., 2012). Consequently, AD mice were treated with HDAC inhibitors (HDACi), which generally improved memory function and, when tested, also ameliorated synaptic plasticity (Fischer, 2014; Gräff et al., 2012). Interestingly enough, memory function and synaptic plasticity were restored in tauopathic mice treated with an activator of the HAT CBP/P300, the compound CSP-TTK21 (Chatterjee et al., 2018, 2013). Epigenomic and transcriptomic analyses using the dorsal hippocampus of tauopathic mice further showed that functional amelioration associated with transcriptional rescue of activity-regulated genes and increased H2B acetylation at CBP-regulated enhancers, while H3K27Ac

remained unchanged (Chatterjee et al., 2018). In addition, CBP levels were decreased in the hippocampus of tauopathic mice as well as in postmortem prefrontal cortices of AD patients (Bartolotti et al., 2016; Schueller et al., 2020), suggesting a role for CBP in dysregulation of these genes (Chatterjee et al., 2018), an hypothesis supported by an earlier study showing that gene transfer delivery of CBP in the hippocampus of AD mice improves memory processes (Caccamo et al., 2010).

Epigenetic aging in AD. Altered epigenetic aging may be another mechanism driving epigenetic defects in the AD brain. Whether epigenetic aging is accelerated and/or dysregulated was recently addressed through epigenomic studies using post mortem brain tissues of AD patients (Li et al., 2019; Nativio et al., 2018). Investigating H4K16ac, a promoter mark linked to DNA damage repair and increased in senescent cells (Dang et al., 2009; Kozak et al., 2010), Nativio et al. identified 3 types of changes in the lateral lobe of AD patients: disease-specific changes were observed in AD patients vs age-matched individuals, age-dysregulated changes were observed in aged vs young individuals but not in AD vs young individuals, and age-regulated changes were observed in both aged control and AD individuals (Nativio et al., 2018). Interestingly, disease-specific changes affected genes enriched in neuronal functions, while age-dysregulated changes implicated immunity and stress response genes, reflecting glial responses. Age-dysregulated changes were predominantly characterized by age-dependent increase in H4K16ac in control individuals, but age-dependent H4K16ac depletion in AD individuals, suggesting AD leads to dysregulated aging and is not simply accelerated aging (Nativio et al., 2018). However, cell type-specific epigenomic analysis focusing on H4K12ac indicated aging-related acceleration of decreased H4K12ac in hippocampal neurons of AD mice modeling amyloid pathology, and the mechanism correlated with down-regulation of target genes, which were enriched in neuronal plasticity genes (Benito et al., 2015). Also, using the epigenetic clock, Li et al. found that neurons of advanced AD cases show significant acceleration of epigenetic aging (Li et al., 2019). Thus, current studies provide rather complex picture of the interplay between AD and epigenetic aging. Undoubtedly, investigating the impact of aging on additional epigenetic marks, including H3K27ac, and at cell type-specific resolution should help refine the conclusions and specify the role of epigenetic aging in AD. It is noteworthy that H3K27ac was found to be a key predictor of age-related transcriptional changes in various mammalian tissues (Benayoun et al., 2019). Finally, recent evidence suggests that tau-related alteration induce widespread reorganization of chromatin architecture and TADs, which could contribute to aging-related mechanisms (Klein et al., 2019). Remarkably, neurons appear to be more specifically affected by the mechanism (Klein et al., 2019). Altered maintenance and regulation of heterochromatin due to pathologically phosphorylated tau

would be the driving force, through impairment of nuclear lamina organization (Chang et al., 2010; Klein et al., 2019; Mansuroglu et al., 2016).

Several mechanisms might contribute to large-scale dysregulation of epigenetic landscape in AD. Yet, it is unclear whether enhancer dysregulation is a primary defect driving other epigenetic changes or is secondary to earlier mechanisms.

Conclusions and perspectives

Epigenomic and transcriptomic data generated on animal models and tissues from HD and AD patients revealed epigenetic changes in affected brain tissues, for both diseases. Remarkably, despite different etiologies between HD and AD, current data indicate that HD and AD pathogenesis associate with large-scale dysregulation of enhancers and promoters, which positively correlates with transcriptional alterations. Although additional studies are required to specify temporal dynamics, spatial chromatin re-organization and cell type-specificity of changes at HD/AD enhancers and promoters, a picture emerges from current data. Neuronal- and glial-specific regulatory regions and their associated genes show lower and increased activities, respectively, in disease vs control brains, which might contribute to loss of neuronal function and inflammatory responses, two major pathological hallmarks. Microglial enhancers appear more specifically dysregulated in AD, whereas HD data indicate that neuronal super enhancers are particularly vulnerable, suggesting loss of neuronal identity in HD brain. Yet, the role for super enhancers in AD remains unclear. However, the regulation of activity-driven regulatory regions and their associated genes is impaired in AD, supporting the notion that dynamic regulation of neuronal activity is more specifically altered in AD.

Intriguing studies suggest that epigenetic alterations in HD/AD might interplay with epigenetic aging, which may be accelerated and/or dysregulated. Moreover, HD studies using ESCs or iPSCs suggest early epigenetic dysregulation originating from abnormal neurodevelopmental process. In fact, a unifying mechanism that would underlie epigenetic defects in HD or AD remains to be uncovered, despite studies indicating that the regulation of specific chromatin regulators -that may be common to both diseases, e.g. CBP- is impaired in HD and/or AD. Understanding the mechanism(s) driving epigenetic dysregulation is a current challenge, with potentially major therapeutic implications.

Major limitations to take up the challenge include the brain complexity and the difficulty to address causal relationships between epigenetic changes and functional consequences. However, the current development of innovative deep sequencing methods, together with new genome editing tools and behavioral paradigms allowing to characterize and manipulate epigenomic and transcriptomic signatures of particular neural cell populations in specific activation states and at

single cell resolution will undoubtedly overcome these issues (Grubman et al., 2019; Liu and Jaenisch, 2019). Also, advanced methods (e.g. Hi-C) to establish 3D maps of enhancer-promoter interactions in vivo at genome-wide and cell type-specific levels will be critical to decipher causal roles of enhancers in neurodegenerative diseases (Nott et al., 2019). Finally, the generation of multi-omic atlas and databases using diseased brains together with the development of bioinformatics methods will also be essential to provide comprehensive picture and build accurate models with predictive or instructive values (De Jager et al., 2018 ; Gosselin Science 2017). Yet, brain tissue availability from individuals at early disease stages, including pre-symptomatic and prodromal stages, represents a limitation to assess early temporal dynamics of epigenetic and transcriptional changes. In this context, mouse models will remain instrumental.

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Figure legends

Figure 1. Regulation of brain cell-identity through super-enhancers. **a**, schematic representations of super-enhancer-regulated gene (top), conventional enhancer-regulated gene (middle) and repressed gene (bottom). Super-enhancers consist of dense clusters of enhancers and are highly enriched in H3K27ac (green circle), RNAPII and transcription factors (TF), including the mediator and cell type-specific TFs. Super-enhancers regulate genes that define cell-type specific identity and function. In contrast, conventional enhancers display more discrete features. Finally, repressed genes are enriched in histone modifications associated with compact chromatin state (red circles), such as H3K9me3 and/or H3K27me3, leading to the inability to recruit transcription factor and form RNAPII complexes. **b**, schematic representation of cell type-specific epigenetic signature of striatal super enhancers. The striatum comprises different cell types, including neurons (purple) and glial cells (green), expressing cellular identity genes regulated by super-enhancers. Identity genes may be neuronal-specific or glial-specific (e.g. neuronal SE, glial SE). The picture is even more complex since different subpopulations of neurons and glial cells are present in the mammalian striatum, expressing each specific subsets of cellular identity genes, controlled by specific super enhancers (for example D1 and D2 MSNs as compared to calretinin (*Calb2*) expressing interneurons, astrocytes expressing *S100b*, oligodendrocytes expressing the myelin basic protein (*Mbp*) or microglia expressing *Cx3cr1*).

Figure 2. Neuronal activity modulation of chromatin loops in early and late response genes.

Scheme representing the dynamics of chromatin changes at activity-driven genes, including early and late response genes (ERG and LRG, respectively), in response to neural stimulation. In top panels, from the left to the right, the pictures illustrate physiological neuronal state, starting with basal condition (left), followed by early state of neuronal activation (middle) and ending with late stage of neuronal activation (right), leading to neuronal plasticity. At the molecular level (bottom panels), the induction of ERGs is a crucial event initiating neuronal transcriptional cascade leading to the induction of LRGs implicated in synaptic plasticity. In basal condition (bottom, left panel), ERG promoters already display transcriptionally active features, including the binding of transcription factors (TFs) such as CREB and SRF/ELK1, RNAPII and chromatin loop formation components such as CTCF and cohesin, but also the histone lysine deacetylase 2 (HDAC2), which negatively regulates their expression. Upon neuronal activation, chromatin re-arrangement allow for a proper enhancer-promoter interaction and the histone acetyltransferase CBP is recruited, increasing the levels of H3K27ac (green circles). Altogether, these chromatin changes lead to the transition of RNAPII from a paused state to a transcriptional elongating state, ensuring the induction of ERGs. At late stages of neuronal activation (bottom right), the coordinated activity of ERGs and cell-type specific factors (CTSF) orchestrate the chromatin remodelling of late response gene (LRGs) promoters, triggering their expression and contributing to the final transcriptional wave enriched in synaptic plasticity genes.

Figure 3. Cell type-specific dysregulation of super-enhancers in HD. Scheme illustrating epigenetic signatures in HD striatum. Super-enhancers regulating neuronal identity genes (purple) and glial identity genes (green) are differentially impaired in HD. In control striatum (top panels), both neuronal and glial super-enhancer regulated genes are highly enriched in H3K27ac (green circles), leading to extensive promoter-enhancer interactions and high transcriptional rates. In HD striatum (bottom panels), neuronal super-enhancers (bottom left panel) are depleted in H3K27ac, correlating with down-regulation of neuronal identity genes. In contrast, glial super-enhancers in HD (bottom right panel) show increased H3K27ac, associated with increased transcription.

Figure 4. Disruption of promoter-enhancer chromatin loop at AD risk variant. On the left, an illustration of how Genome Wide Association Studies (GWAS), based on the comparison of Single Nucleotide Polymorphisms (SNPs, horizontal stripes) enriched in thousands of individuals corresponding to a healthy reference group (CTRL, grey) or presenting Alzheimer's disease (AD, red) can identify disease-associated risk variants (yellow horizontal stripes). On the right, a scheme

illustrating the effect of AD genetic risk variant rs708727 located in an enhancer-like region interacting with *PM20D1* (Sanchez-Mut et al. 2018). In control individuals (CTRL, right upper panel), *PM20D1* promoter-enhancer interaction results from the recruitment of CTCF at *PM20D1* promoter and enhancer region, together with additional transcription factors (TF) and Mediator (Med1), establishing the mediator complex, which stimulates enhancer transcription (eRNA) and *PM20D1* mRNA transcription. The presence of the AD associated rs708727 SNP (AD, bottom right panel) in the cis regulatory region of *PM20D1* gene (white mark) impairs promoter chromatin interaction, enhancer CCCTC-binding factor (CTCF) recruitment and leads to *PM20D1* promoter methylation (red M circles) and, as a consequence, a significant impairment of *PM20D1* expression.

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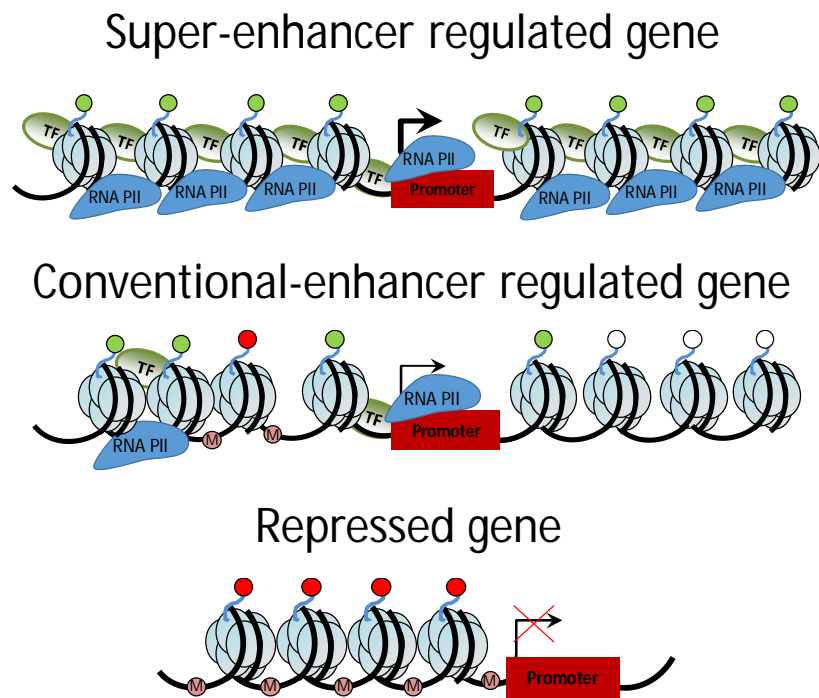
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Figure 1

a



b

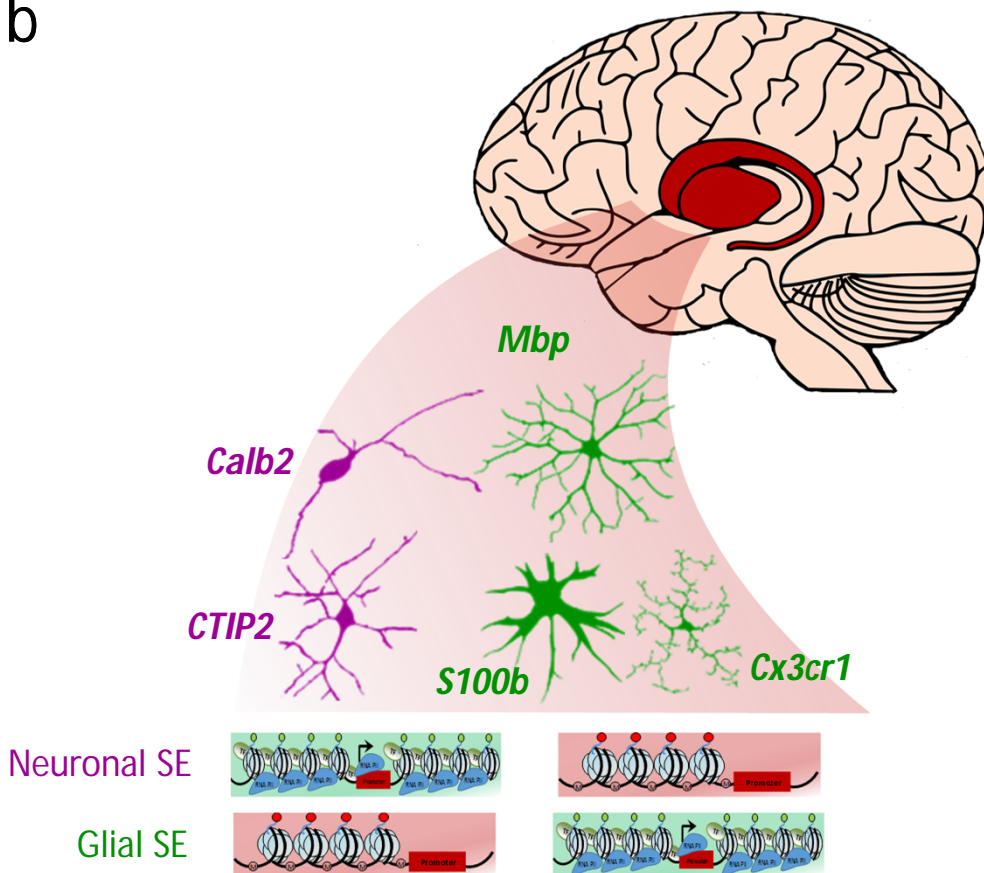


Figure 2

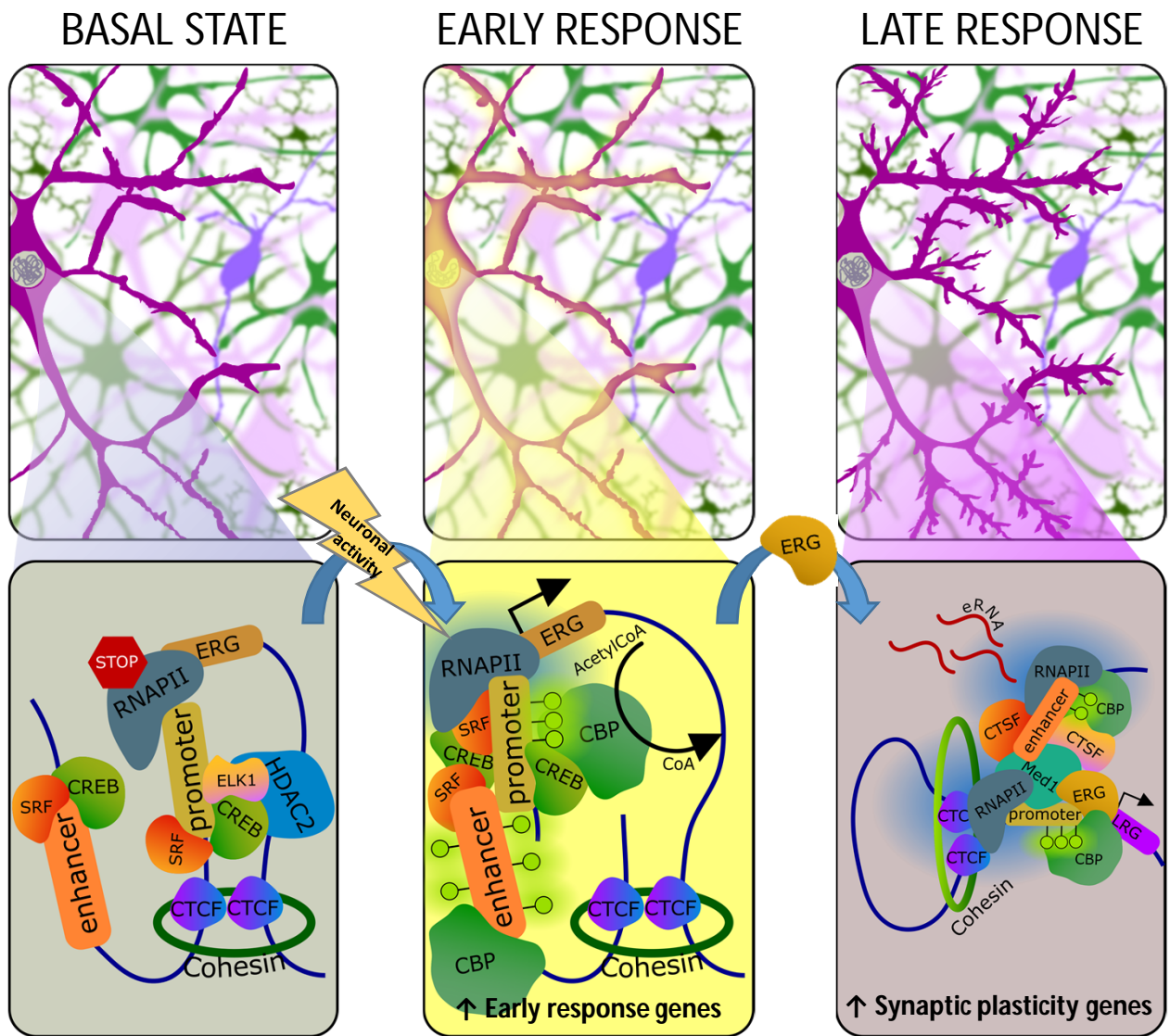


Figure 3

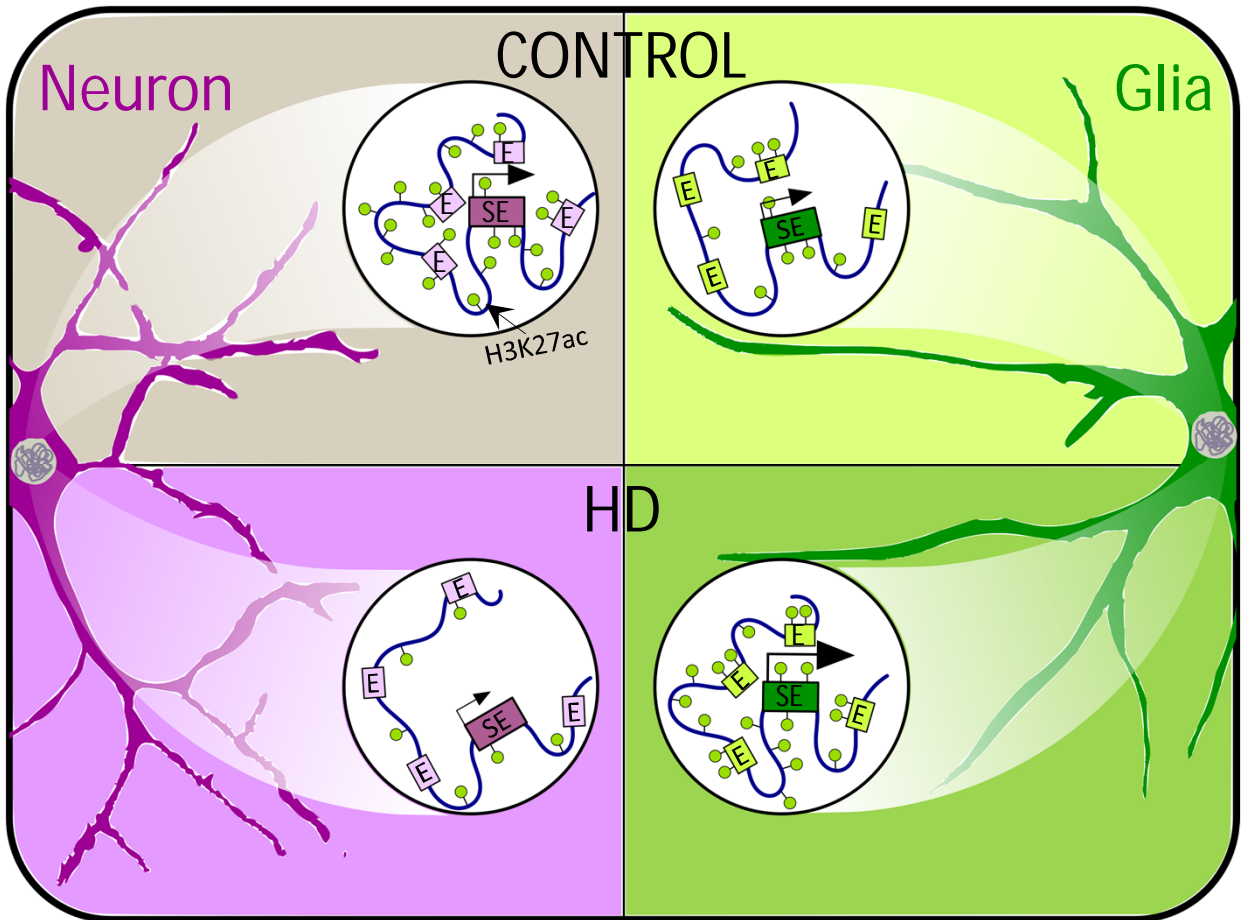


Figure 4

