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Invited review

Significance of higher-order chromatin architecture for neuronal function and dysfunction

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ABSTRACT

Recent studies in neurons indicate that the large-scale chromatin architectural framework, including chromosome territories or lamina-associated chromatin, undergoes dynamic changes that represent an emergent level of regulation of neuronal gene-expression. This phenomenon has been implicated in neuronal differentiation, long-term potentiation, seizures, and disorders of neural plasticity such as Rett syndrome and epilepsy.

This article is part of a Special Issue entitled 'Neuroepigenetic disorders'.

1. Introduction

Epigenetic phenomena are key regulators of gene expression orchestrating various forms of neuronal plasticity (Puckett and Lubin, 2011; Sweatt, 2013; Zovkic et al., 2013). Numerous studies have shown that covalent modifications of chromatin, e.g. DNA methylation and histone methylation/acetylation/phosphorylation (Day and Sweatt, 2011), as well as non-coding RNAs (Qureshi and Mehler, 2012), play key roles in neuronal plasticity underlying cognitive phenomena, and the pathogenesis of brain diseases (Kobow and Blumcke, 2011; Roopra et al., 2012; Sweatt, 2013; Urdinguio et al., 2009). However, there exist yet another class of epigenetic mechanisms, operating at the level of higher-order chromatin organization, and involving large-scale nuclear architectural remodeling (for general review see: (Bickmore and van Steensel (2013), Cavalli and Misteli (2013), Gibcus and Dekker (2013), Lanctot et al. (2007))). The early evidence suggesting that such phenomena can occur also in neurons, as a consequence of enhanced activity, has been brought by experiments of Barr and Bertram (1949, 1951), who studied nuclear structure in the neurons of the hypoglossal nucleus of female cats, upon electrical stimulation of the hypoglossal nerve. The authors noticed that enhanced neuronal activity was associated with nucleolar enlargement and the repositioning of a conspicuous roughly spherical body, formed by sex chromatin, from the nucleolar surface toward the nucleus periphery. These seminal observations were followed over the past decades by studies demonstrating the malleability of neuronal nuclear architecture. However, until recently, it was unknown whether the neuronal nuclear remodeling is merely a consequence of enhanced gene expression, or it has an instructive influence on this process. The present review summarizes available evidence for the importance of nuclear structure and its remodeling for the neuronal plasticity, including an activity-dependent plasticity of the adult brain.

2. Nuclear architecture, chromosome territories and transcription factories

According to the current model of nuclear organization, based on several decades of morphological studies, there are two main structural components of the cell nucleus: a chromatin and an interchromatin compartment (reviewed by Rouquette et al. (2010)). Such an arrangement was originally proposed by Monneron and Bernhard (1969) who distinguished the two components simply on the basis of the electron density (e.g. the dense chromatin and the lucent interchromatin space). Later studies, using more sophisticated methodology, including fluorescent in situ hybridization (FISH) and three-dimensional (3D) analysis by superresolution microscopy, fully supported the two-compartment model, and demonstrated its physiological relevance (Markaki et al., 2010, 2012; Schermelleh et al., 2008). Collectively, the data indicate that in the vast majority of mammalian cell types, chromatin comprises the shell located beneath the nuclear envelope, the clumps scattered throughout the interchromatin space, and the nucleolus-associated masses (Rouquette et al., 2010) (Fig. 1). The

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interchromatin compartment forms network of channels and wider lacunas separating the chromatin masses (Rouquette et al., 2010). It harbors the nucleolus, and a range of characteristic fibrillo-granular structures called nuclear bodies (Dundr, 2012; Mao et al., 2011; Meldi and Brickner, 2011; Morimoto and Boerkoel, 2013) (Fig. 1). There are several types of these inclusions having distinct ultrastructural appearance, or being identified based on their unique molecular composition: Cajal bodies (Cioce and Lamond, 2005; Nizami et al., 2010), interchromatin granule clusters (speckles) (Spector and Lamond, 2011), paraspeckles (Fox and Lamond, 2010), gems (Liu and Dreyfuss, 1996), PML bodies (Bernardi and Pandolfi, 2007), to name just a few. Although the present review is focused on the neuronal chromatin architecture, it should be noted that the studies in neurons contributed a lot to the description of nuclear bodies, starting from light-microscopic investigations of cortical neurons by Ramon y Cajal (Lafarga et al., 2009). One of the earliest, and a very detailed ultrastructural description of nuclear bodies were provided by Hardin et al. (1969) in peripheral sympathetic neurons. Also later, the composition and function of the neuronal nuclear bodies have been a subject of intense studies by Lafarga and colleagues, mainly in peripheral sympathetic and hypothalamic neurons ((Villagra et al., 2008) and references therein), and by other investigators (Clark et al., 1991). The continuing interest in these structures has been stimulated by their implication in the pathogenesis of various neurodegenerative disorders (Woulfe, 2008).

Classic ultrastructural cytochemical studies demonstrated that electron-dense chromatin is transcriptionally silent, and thus appears to correspond mainly to heterochromatin (Fakan, 2004). In contrast, the transcriptionally active euchromatin is believed to reside at the surface of electron dense masses, extending into the interchromatin space in a poorly defined fibrillar form (Fakan and van Driel, 2007). Nevertheless, electron microscopy failed to reveal higher-order levels of chromatin organization in situ, beyond 10 nm- and 30 nm-thick fibrils. This fact, together with electron microscopic studies of isolated nuclear preparations, led, in early seventies, to the conclusion that chromatin resembles, in fact, an extensively interwoven amorphous tangle of fibers arising upon total decondensation of mitotic chromosomes (reviewed by Cremer and Cremer (2006)). However, a decade later, studies using selective irradiation of nuclei, or in situ hybridization, demonstrated that higher-order chromatin organization does exist in the form of well-defined chromosome territories that correspond to mitotic chromosomes which underwent decondensation, yet retained the structural integrity (for review see: Cremer and Cremer (2010), Meaburn and Misteli (2007)). Moreover, later it was found that the morphology of chromosome territories, and their dynamic interactions with one another and with the nuclear envelope, have profound relationship with gene expression (Geyer et al., 2011; Lanctot et al., 2007; Misteli, 2007). For example, a centromeric heterochromatin of different chromosomes tends to cluster within the nucleus, forming transcriptionally-silent masses called chromocenters (Manuelidis, 1984; Mayfield and Ellison, 1975; Weierich et al., 2003). The formation and the distribution of chromocenters is cell type- and species-dependent, and developmentally regulated (reviewed by Politz et al. (2013)). The most striking example of heterochromatin remodeling is the redistribution of chromocenters from the nucleus periphery to the nucleus center in the nuclei of rod photoreceptor cells, occurring during development in nocturnal animals (Solovei et al., 2009, 2013). Such an inversion of

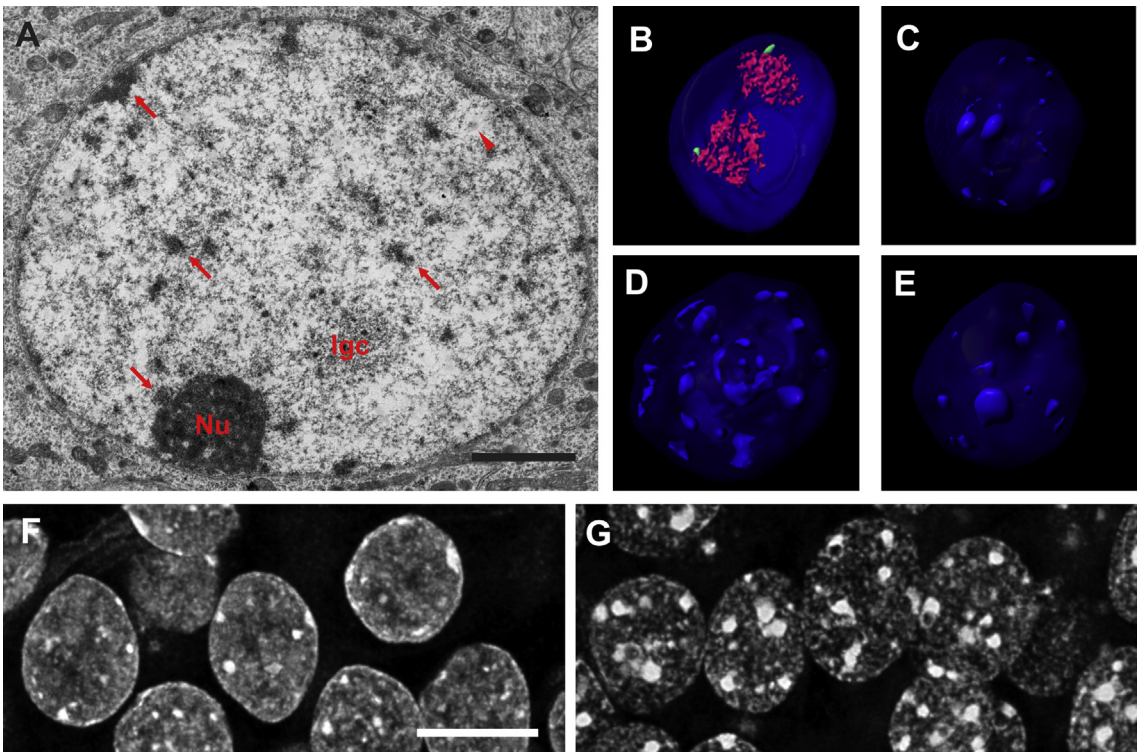

Fig. 1. Higher-order chromatin architecture in neurons. A) Electron-microscopic image of the nucleus of the rat dentate gyrus granule neuron. Arrows point to the electron-dense chromatin clumps; Nu – nucleolus; Igc – interchromatin granule cluster; Arrowhead – a simple nuclear body. The electron-lucent area harboring aforementioned objects corresponds to the interchromatin space. Bar – 2 μm. B) Three-dimensional reconstruction of the granule cell nucleus from the specimen subjected to the double fluorescent in situ hybridization for chromosome 3 territory (red) and Bdnf alleles (green); DNA is counterstained with TOPRO-3. C–E) Three-dimensional reconstructions of the nuclei fluorescently stained for DNA (Hoechst 33342), demonstrating the variability of chromocenter size and distribution among the neurons from the rat dentate gyrus (C), hippocampal CA1 area (D), and layer V of the cerebral cortex (E). F–G) Confocal images of the rat (F) and mouse (G) dentate gyrus stained for DNA with Hoechst 33342, demonstrating the prominent interspecies difference in neuronal nuclear architecture. Bar – 10 μm.

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nuclear architecture has a pivotal role for vision under low light conditions, in which rod nuclei are considered to act as microlenses to better propagate light towards the photoreceptors (Solovei et al., 2009). Another type of nuclear remodeling involving chromosome territories is associated with gene looping. It was shown that chromatin loops containing active genes originating from sites that are distant from each other, in terms of DNA sequence, even belonging to different chromosome territories, can make contacts in the three-dimensional space to establish a common transcription factory (Branco and Pombo, 2007; Edelman and Fraser, 2012; Papantonis and Cook, 2011). Most recently, a range of chromosome conformation capture techniques, combining chromatin cross-linking, with massive sequence analysis has emerged, and rendered a global view of spatial interactions among genes in the cell nucleus (Bickmore and van Steensel, 2013; Gibcus and Dekker, 2013). Together with biophysical modeling these results rendered a model of higher-order chromatin structure called a fractal globule (Fudenberg and Mirny, 2012).

In neurons, the light-microscopic appearance of chromatin changes substantially during development (Aoto et al., 2006; Martou and De Boni, 2000; Solovei et al., 2013). In vitro, stem cells have large nuclei containing virtually no condensed chromatin (Aoto et al., 2006). At the stage of differentiation to the neuronal progenitors, the nuclei shrink and become populated by numerous small chromocenters. These chromocenters coalesce into a few large masses as the progenitors differentiate into mature neurons (Aoto et al., 2006). A trend toward fusion of interphase centromeric regions was observed during early postnatal development of the mouse cerebellar Purkinje neurons, with the decrease in the number of chromocenters from about 8 per nucleus at P0, to about 5 per nucleus at P6 (Martou and De Boni, 2000; Solovei et al., 2004). Although subsequently the number of chromocenter increases to about 10 per nucleus, it remains much smaller than the chromosome complement for the species, e.g. 40. The exact number, size, and distribution of the chromocenters vary among different types of neurons and different anatomical locations (Billia and de Boni, 1991; Manuelidis, 1984; Solovei et al., 2013; Vadakkan et al., 2006) (Fig. 1). For example, mouse cerebellar Purkinje cells have typically two large chromocenter clusters capping opposite sides of the centrally positioned nucleolus, as well as several small clusters attached to the nuclear envelope. Similar arrangement appears to be present in Lugaro interneurons, except that they have only a single central cluster. In contrast, in adult cerebellar granule neurons there are only clusters located peripherally (Manuelidis, 1984; Solovei et al., 2013). Perhaps the most prominent example of developmentally-regulated chromatin rearrangement in neurons is the case of the mouse olfactory sensory neurons, in which 92 olfactory receptors gene clusters join to form about 5 heterochromatic higher-order clusters located centrally in the nucleus (Clowney et al., 2012). This phenomenon allows for a concerted silencing of all, except one, olfactory receptor genes, and was shown to depend on developmental downregulation of lamin B receptor (LBR) (Clowney et al., 2012).

The overall spatial distribution of heterochromatin in the neuronal nuclei of various species appears to be similar (Berchtold et al., 2011; Manuelidis, 1985; Solovei et al., 2013), although there exist species-dependent differences in the shape and size of neuronal chromocenters; for example, human and rat neurons have smaller and more irregular heterochromatin clusters than mouse neurons of the same type and location, leading to the dramatically distinct visual appearance of neuronal nuclei in mouse, compared to the two other species (Fig. 1). This difference, which is well known with regards to other cell types (Weierich et al., 2003), appears to be related to the presence of very large pericentromeric heterochromatin arrays in mouse chromosomes (Vissel and Choo, 1989). An especially prominent common feature of the nuclei of neurons is the presence of sex chromatin as a roughly spherical globule having up to 1 μm in diameter (Barr and Bertram, 1949). The size of sex chromatin is, however, also species-dependent; for example it is much more prominent in *Carnivora* than in *Rodentia* species (Hardin et al., 1969; Moore and Barr, 1953).

A few reports indicate that the rearrangement of chromosome territories may also occur as a result of enhanced neuronal activity. The evidence for this phenomenon was provided by Billia et al. (1992) who showed the spatial rearrangement of centromeres, identified by FISH, upon the induction of long-term potentiation (LTP) in acute slices of the rat brain. This was in line with the earlier studies by Barr and Bertram (1949, 1951). Likewise, Borden and Manuelidis (1988) demonstrated that the position of the X chromosome territory is different, e.g. more internal, in the neurons from human cortical epileptic foci, compared to the neurons of the healthy cortex bordering the lesion. The three-dimensional curvilinear movement of chromocenters was also observed in live cultured dorsal root ganglion neurons, at a rate of about 2 degrees per minute, as a result of intriguing, yet poorly understood, phenomenon of the nuclear rotation (called also the karyoplasm streaming) (De Boni and Mintz, 1986). The speed of such movements was increased by NGF, GABA, calcium ionophore, or calcium chelator, by up to 50%, however depolarization had no effect (Fung and De Boni, 1988). The existence of nuclear rotation has recently been confirmed by the state-of-art methodology (Strickfaden et al., 2010).

Most recently, Crepaldi et al. (2013) demonstrated an activation-dependent relocation of some immediate-early genes (IEGs) (including c-Fos) to transcription factories in cultured cortical neurons. Most importantly, the authors found that this phenomenon depends on TFIIIC, which binds to transposon-like short-interspersed repeats (SINEs) located in the vicinity of activity-dependent genes. Silencing TFIIIC lead to uncontrolled association of IEGs with transcription factories, resulting in profound morphological consequences to the cell, namely the prominent elaboration of its dendritic tree (Crepaldi et al., 2013).

3. Nuclear lamina and its influence on gene-expression

Another important nuclear architectural element having profound influence on gene expression is nuclear lamina (Gerace and Huber, 2012; Zuleger et al., 2011). This is a fibrous sheath attached to the inner surface of the nuclear envelope, composed primarily of type A and type B lamins (Burke and Stewart, 2013). Other important components of the lamina are membrane proteins of the inner leaflet of the nuclear envelope, such as emerin or LBR (Berk et al., 2013; Brachner and Foisner, 2011; Olins et al., 2010). These proteins ensure an anchoring of the phospholipid bilayer to the lamin fibrils and chromatin. The lamina was demonstrated to provide a mechanical stability for the nucleus, it is also believed to provide an important structural framework organizing the genome (de Las Heras et al., 2013; Gerace and Huber, 2012; Zuleger et al., 2011). The mechanical functions of lamins occurred to be very important for proper neuronal migration in the developing brain (Coffinier et al., 2011; Jung et al., 2013). A key role of lamina in organizing higher-order chromatin architecture was supported by tiling microarray sequence analysis of lamina-associated chromatin which demonstrated the existence, in mammalian cells, of about 1000 discrete 50 kb- to 10 Mb-large lamina-associated domains, which cover 30%–40% of the genome (Gibcus and Dekker, 2013; Peric-Hupkes and van Steensel, 2010). However, due to the variability in the chromosomal positioning among individual cells, that could result at least in part, from rotational movements of large chromatin assemblies (Strickfaden et al., 2010), only a fraction of

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these sequences is expected to represent actual LADs in a given nucleus.

In mammals, nuclear lamina is known to exert strong inhibitory effect on the expression of genes located in its vicinity. Such an activity is fully consistent with an electron-microscopic images of the cell nucleus showing typically a rim of condensed chromatin beneath the nuclear envelope. More importantly, it was demonstrated explicitly that tethering of genes to the nuclear lamina, using LacO/LacL tethering technology induces gene silencing (Peric-Hupkes and van Steensel, 2010; Zuleger et al., 2011). The molecular mechanisms of the transcription suppression by the lamina are poorly understood. It was demonstrated that histone deacetylase 3 (HDAC3) binds, both to lamina-associated polypeptide 2β and emerin, thereby leading to deacetylation of the adjacent chromatin (Demmerle et al., 2012; Somech et al., 2005). Consistently, hepatocytes of HDAC3 knockout mice have strongly reduced content of lamina-associated condensed chromatin (Bhaskara et al., 2010). A number of studies have shown that the interactions of chromatin with the nuclear lamina can change during cellular differentiation, and that this is correlated with the chromatin's transcriptional activity in a variety of cell types (Kosak et al., 2002; Peric-Hupkes et al., 2010; Ragoczy et al., 2006; Szczerbal et al., 2009; Williams et al., 2006; Zink et al., 2004). With regards to neuronal lineage, a repositioning of a gene encoding for Mash1 transcriptional regulator away from the nuclear lamina was demonstrated using fluorescent in situ hybridization (FISH) to occur during differentiation of embryonic stem cells (ES) into the neurally-committed progenitors (Williams et al., 2006). Moreover, with the use of a methylation-based tagging method (DamID) (Orian et al., 2009), followed by massive sequence analysis, Peric-Hupkes et al. (2010) showed, that during differentiation from neuronal stem-cells via lineage committed neural precursor cells into terminally differentiated astrocytes, there is a relationship between gene–lamina interaction and the level of the expression of the particular gene. (Peric-Hupkes et al., 2010).

The two most recent developmental studies have provided an unprecedented insight into the mechanisms of lamina-dependent chromatin organization in neurons (Clowney et al., 2012; Solovei et al., 2013). The study on olfactory sensory neurons (OSNs) by Clowney et al. (2012) demonstrates that LBR plays a key role in developmentally regulated spatial distribution of heterochromatin in these cells. Similarly to mature rod cells, OSNs have an inverted heterochromatin arrangement, with a centrally positioned heterochromatin and peripheral euchromatin. Such a nuclear architecture arises during differentiation and is coincident with a downregulation of LBR expression. Importantly, ectopic expression of LBR in mature OSN leads to a profound remodeling of the nucleus with an eccentric redistribution of heterochromatin. Concomitantly, the developmentally determined silencing of about 2800 olfactory receptor genes (except one), that occurs in each OSN, became disrupted, demonstrating the significance of an inverted heterochromatin arrangement for SON function. The paper by Solovei et al. (2013) demonstrates that LBR and lamin A/C are the proteins playing key role in tethering of the heterochromatin to the nuclear envelope in a variety of cell types, including neurons. Interestingly, LBR and lamin A/C function sequentially during development. In general, LBR proceeds, and is replaced by, lamin-A/C. Among neurons, some cell types lack LBR already at birth (cerebellar Purkinje cells, cortical neurons) whereas some switch to lamin A/C-dependent tether later (P5) (retinal bipolar, amacrine, horizontal and ganglion neurons, cerebellar granular cells). As a consequence, the neuronal nuclear architecture of the adult animals is not affected by LBR knockout. Interestingly, lamin A/C knockout also does not affect neuronal nucleus, being compensated by prolonged expression of LBR. Nevertheless, LBR and lamin A/C double knockout induces an inversed nuclear architecture in all cell types in the body, including neurons (Solovei et al., 2013).

The recent paper by Walczak et al. (2013) demonstrated that the dynamic association-dissociation of the genes to/from the nuclear lamina can occur also as a result of neuronal activity. In a rat model of massive neuronal activation upon kainate-induced seizures, the authors found, using FISH-based innovative image analysis, and chromatin immunoprecipitation, that elevated neuronal expression of the Bdnf gene is associated with its detachment from the nuclear lamina, and translocation toward the nucleus center. In contrast, the position of stably expressed Trkb remains unchanged after seizures. This study demonstrated that activation-dependent architectural remodeling of the neuronal cell nucleus in vivo contributes to activity-dependent changes in gene expression in the adult brain.

4. Higher-order chromatin architecture in neuropsychiatric disorders

Recently, an important pathogenic role in disorders of the nervous system has been ascribed to epigenetic mechanisms. With regards to the higher order chromatin structures, the two recent studies point to the involvement of this phenomenon in the pathogenesis of Rett syndrome (Agarwal et al., 2011; Singleton et al., 2011). The disease is an X-liked mental retardation syndrome occurring due to the loss-of-function mutations of the gene encoding Methyl-Cytosine binding Protein 2 (MeCP2) (Berger-Sweeney, 2011). Agarwal et al. (2011) found that various mutations causing abnormal interactions of MeCP2 protein with chromatin lead to large-scale alterations in chromocenter number and size in cultured cells. The authors hypothesized, that subtle transcriptional changes detected in MeCP2 mutant mice might results from the remodeling of the higher-order chromatin structure, independently of MeCP2 role as a transcriptional repressor. In addition, Singleton et al. (2011) showed that MeCP2 knockout mice have developmental abnormalities in chromocenter size and distribution, resulting in larger and more numerous chromocenters in the adult mutants. Another brain disease that has strong links to higher-order chromatin architecture is epilepsy, as demonstrated by an early study of human brain (Borden and Manuelidis, 1988). However, also a recent study by Walczak et al. (2013) can have some implications related to epilepsy pathogenesis. The kainate-induced status epilepticus model, utilized by Walczak et al. (2013), is also a model of epileptogenesis, for about 50% of experimental animals develop chronic limbic epilepsy resembling human temporal epilepsy (Ben-Ari, 2001; Morimoto et al., 2004). Our unpublished results indicate that among epileptic animals the percentage of nuclei in which the Bdnf gene detaches from the nuclear lamina positively correlates with the degree of both behavioral alterations and histological alterations in the form of mossy fibers sprouting (Walczak et al., in preparation).

5. Higher-order chromatin architecture as both, the effect and the cause, of gene expression

The fact that the architecture of the neuronal nucleus depends on ongoing gene-expression orchestrated by molecular machinery is a reductionist concept very much consistent with the knowledge accumulated throughout many decades. However, it is less obvious that the reverse is also true, e.g. that nuclear architecture is an independent, emergent mechanism governing the gene expression. Regarding neurons, the studies on the interactions of genes with the nuclear lamina provide some evidence that actually both the aforementioned views are correct. Peric-Hupkes et al. (2010) demonstrated that although during neuronal differentiation

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plenty of genes that move away from lamina are concomitantly activated, many others remain inactive but are unlocked for activation in the next differentiation step. Thus the architectural change is a priming event that happens ahead of subsequent changes in expression. Similar conclusion comes from the study of Clowney et al. (2012) on olfactory sensory neurons. Likewise, Walczak et al. (2013) showed that although the Bdnf allele that had dissociated from the lamina upon seizures, loosed, over several weeks, its enhanced expression, yet the allele remained sensitized to the incoming activation. It is tempting to speculate that architectural changes represent an exceptionably long-lasting epigenetic alterations underlying long-term cellular memory, that upon pathologic conditions transforms to a form of durable molecular scar. Altogether, the aforementioned evidence points to the bidirectional relationship between gene expression and large-scale chromatin architecture, as an attractive research line for the future.

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