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Review

Genoplasticity and neuropsychiatric diseases

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ABSTRACT

Adaptive capacity and the ability to sustain long-term changes as neural activity patterns are considered as the most critical and intriguing properties of the brain. This concept, called neuroplasticity, refers to the ability of the brain to adapt and change over time. Sometimes, re-organization or re-adaptation mediates crucial physiological events such as learning and memory by long-term potentiation, but sometimes, especially under heavily stressful internal or external conditions, contra-adaptation may underlie several neuropsychiatric diseases. Neuroplasticity is a continuous process that reacts to inter- and intraneuronal activity and neural injury, in parallel with apoptosis and structural or functional changes in neurites and synapses. Elements of signal transduction cascades (SDCs) between and within neurons include neurotransmitters, receptors, G proteins, secondary messengers, protein kinases, and transcription factors. If any of these elements fail, pathological conditions (contra-adaptation) occur in the brain. Each step of neurotransmission is influenced by changes in genes and DNA *via* SDCs. In fact, neuroplasticity is a result of adaptive genomic changes in SDC, and it is a product of gene plasticity or genoplasticity. At present, we do not yet have any radical solutions for the treatment of important neuropsychiatric diseases. Some external and internal factors may change the task definition of neurons by causing genomic changes and the resulting mutant or "terrorist" neurons may cause severe brain disorders.

KEYWORDS: adaptation, brain disorders, gene expression, genoplasticity, neuroplasticity, neuropsychiatric disorders.

ABBREVIATIONS

AD	:	Alzheimer's disease
ADHD	:	Attention deficit and hyperactivity disorder
APOE	:	Apolipoprotein E
BDNF	:	Brain-derived neurotrophic factor
CNS	:	Central nervous system
CREB	:	cAMP response element binding protein
EGF	:	Epidermal growth factor
GPER	:	G-protein-coupled estrogen receptor
GPCRs	:	G-protein-coupled receptors
HTR1B	:	Serotonin receptor 1B
IGF-1	:	Insulin-like growth factor-1
LTP	:	Long-term potentiation
miR	:	MicroRNA
MTHFR	:	Methyl tetrahydrofolate reductase
NAc	:	Nucleus accumbens
NCAM	:	Neural cell adhesion molecule
NGF	:	Nerve growth factor
PCNA	:	Proliferating cell nuclear antigen
PDGF	:	Platelet-derived growth factor
PFC	:	Prefrontal cortex
RDS	:	Reward deficiency syndrome
5-HTTLPR	:	Serotonin transporter gene-linked promoter region
SNPs	:	Single-nucleotide polymorphisms
VTA	:	Ventral tegmental area.

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1. Introduction

Our body consists of approximately 75 trillion cells. Although these cells have different tasks, they all display a common core structural feature. The cell nucleus contains chromosomal DNA, which, together with mitochondrial DNA, carries all of the hereditary information about the organism. The information that concerns our growth, development and health is found in DNA as a unique chemical code. This genetic code is determined as sequences of four nucleotide bases (adenine, thymine, cytosine, and guanine), which make up DNA together with the phosphate-sugar backbone [1]. Genes are small DNA segments that contain the directives necessary to produce the functional products (i.e., proteins) that are responsible for phenotypic features and characters. Genes direct cell function and the manifestation of phenotypes. Each gene contains a genetic code for one or more functionally related proteins. The process of generating proteins from genetic data encoded by the gene is called "gene expression." All essentially vital processes, such as growth, cell division, cell differentiation, and various adaptations, can be realized by gene expression [2].

Cells assemble to form tissues and organs. The systems created by organs turn into living organisms. Mammals are the most organized and complex living organisms. Whether they are single-celled or multi-cellular organisms such as mammals, all living organisms are influenced by internal and/or external environmental factors and must develop valid and sufficient adaptation mechanisms for survival. Only organisms that develop appropriate adaptations can preserve their species in the process of evolution. This is the basic principle of evolution, and life means appropriate adaptation. Although the living organism appears to be adapting, the process begins with DNA and the genes encoded by it. Although the original event is based on gene plasticity or genoplasticity, these terms are not frequently used in the related literature. For example, only one article on antifouling agents [3] is found under the keyword "genoplasticity" in the Web of Science, PubMed, and SCOPUS databases. In the same databases, only 17, 15, and 24 articles, respectively, are found for the keyword "gene plasticity". Even then, a search using the keyword "neuroplasticity" brings out more than 52,000 articles, and this number increases every year. Thus, we propose the following questions: Why are the terms "genoplasticity" or "gene plasticity" used so rarely? Does neuronal plasticity alone represent brain adaptation? While we discuss brain plasticity *via* neuroplasticity extensively, why do we not widely discuss the plasticity involved in other important organs such as the kidney, liver, and lungs? Is there a genetic basis of neuroplasticity, and if there is, what is the genetic basis of it?

In this review, we aim to discuss gene plasticity, or genoplasticity, and to re-evaluate neuroplasticity in the framework of the above questions. At present, we do not yet have any radical solutions for the treatment of important neuropsychiatric diseases such as autism, schizophrenia, addiction, and Alzheimer's disease (AD). Thus, we also aim to approach these diseases with respect to genoplasticity.

1.1. Neuroplasticity

Adaptive capacity and the ability to sustain long-term changes as neural activity patterns are considered as the most critical and intriguing properties of the brain. This concept, called neuroplasticity or brain plasticity, refers to the ability of the brain to adapt and change over time [4]. Even though it was widely suggested again in the beginning of the new millennium, the first scientific data on neuroplasticity can be traced back to the early 19th century. Santiago Ramon Y Cajal, a Spanish neuroanatomist, histologist, and Nobel laureate, was the first to suggest that the neuron is the basic unit of the brain, and neurons connect and communicate with each other without having any physical contact [5]. This approach stands as the foundation of modern neuroscience and of the concept of synaptic transmission between neurons. Cajal also said, "*Everybody can become the sculptor of his own brain, if they want*." In this way, he was also the first to express the adaptive and changeable structural and functional properties of the brain. In 1949, Donald Hebb, a Canadian psychologist and behavioral neuroscientist, suggested that we can change our brain by learning something new, and these changes in the brain occur at the neuronal level.

The brain can continuously remodel itself *via* changes in connections at the synaptic level [6] and the Hebbian Theory forms the essential basis of synaptic plasticity, neuroplasticity, or brain plasticity. Terje Lømo from Oslo University and Timothy Bliss, a British Neuroscientist, described long-term potentiation (LTP) in 1973. LTP is a persistent increase in synaptic strength after high-frequency repeated stimulation of neurons [7]. The potentiation of the response is sustained for a long time, and it is the molecular basis of learning. LTP and its relationship to learning provide important support for the Hebbian Theory.

The continuous process of neural change in response to inter- or intraneural activities, together with structural and functional changes in the synapses between communicating neurons, can be defined as neuroplasticity. Neuroplasticity is responsible for the re-organization and re-adaptation of specific regions and connections within the brain. Sometimes the re-organization or re-adaptation mediates vital and important physiological events such as molecular encoding of long-term memory, e.g., through LTP. But sometimes, especially under heavily stressful conditions, these adaptive changes might act as a counter-adaptation, which might be responsible for several pathological conditions [8, 9]. Neuroplasticity is modulated by endogenous, exogenous, and environmental stress factors. The varied structural elements that embody plasticity include LTP and depression, synaptic remodeling, synaptic tagging, synaptogenesis, synaptic efficacy, neurite extension (including axonal sprouting and dendritic remodeling), neurogenesis, and recruitment. More inclusively, the processes underlying plasticity occur with the electrical, biochemical, and structural modulation of synapses; production of new synapses through generation of new axon terminals and dendritic spines; changes in the major metabolic activities in the somata, anterograde and retrograde transport, and interactions with neighboring cells; changes in the neural network/ pathway structure and function; and changes in behavioral, psychological, and sociological activities. Insufficient and/or disturbed organization of synapses or neural communication cause counter-adaptation and the emergence of several diseases of the central nervous system (CNS), such as AD, substance abuse and dependence, schizophrenia, depression, and autism [8-11]. Thus, neuroplasticity could be responsible for negative as well as positive changes in brain function. Recovery disorders may also be related to neuroplastic changes in the brain [12].

1.2. Genoplasticity

The term gene plasticity, or genoplasticity, refers to the adaptive state of genes. Genoplasticity adjusts the level of gene expression to adapt to changing environmental and internal conditions. Most of these adaptations have their roots in increasing the probability of survival; however, learning in general might present additional benefits to the organism and trigger genoplasticity.

One important source of adaptation is the level of energy expenditure. Just like corporations, our bodies have a profit-and-loss system that does not tolerate failures. Therefore, in order to preserve and enhance the probability of survival, our biology needs to endure a higher workforce with a limited energy budget. The adaptive changes of the heart muscles of astronauts in space are a striking example. Space conditions, such as microgravity, trigger various adaptive changes within the cardiovascular system. For example, the hearts of astronauts shrink after they arrive on the space station [13, 14].

Examples of genoplasticity can even be derived from simpler organisms, such as plants. The habitats of buttercups (*Ranunculus acris*) are usually on the banks of rivers. As the rivers flood seasonally, these plants will be at risk. Interestingly, buttercups can completely change the shape of their leaves adaptively *via* altered gene expression when the river floods [15]. Although the buttercup looks like a different plant after this adaptation, only the expressed phenotype changes, without any changes in its genome, increasing the chances of survival.

Phenotypic adaptations of honeybees might present a different example. Different phenotypes are displayed by honeybees of the same genotype, which point to epigenetic modifications underlying the observed phenotypic variation. When field bees search for nectar, nurse bees are taken away by explorer bees. Field bees do not consent to

neglecting the baby bees, and they assume the nurse assignment, altering the genetic labeling of these bees [16]. Although the previously expressed genes are now silent, the genes that were previously silent are now expressed. Thus, field bees are transformed into nurse bees by an epigenetic mechanism. These adaptive changes in bee societies can exhibit general behaviors such as aggression [17].

Like those of bees, our lives are seriously influenced positively or negatively by altered gene expression. The expression patterns of our genes are not in a constant and stable state. They can be influenced and changed under the effect of several environmental factors. These changes in gene expression and genomic plasticity are important strategies for the survival of mammals and other organisms. Our genes work as part of a flexible or plastic network. In contrast to old beliefs in the scientific literature, gene expression, like the neural response and structure, are not constant and inflexible [18-20].

2. Gene expression and neuroplasticity

Neuroplasticity represents adaptation of the brain. It underlies all memory processes and is principally based on altered gene expression on the neuronal level [21]. Knowledge based on accurate information and adaptation is crucial for survival. Learning and memory, which are two of the most important activities on the neuronal level, are of key importance to accurate information processing (Figure 1). Creating memories of a stressful life event is critical to an organism's survival, as it allows for its adaptation and response in a more appropriate manner should the conditions reoccur [22]. If organisms cannot form accurate memories or if heavily stressful conditions lead to the formation of traumatic memories, the result can be one of several disorders or illnesses or damage to brain function, as well as functions of the peripheral areas of the body.

As seen in Figure 1, sustainable attention is critical for learning and memory, and any problem in this area of the brain might lead to disorders such as attention deficit and hyperactivity disorder (ADHD) [23, 24]. The cingulum is a group of white matter fibers that arise from the cingulate gyrus to innervate the neurons in the entorhinal cortex, creating a path for communication between the prefrontal cortex and hippocampus, both of which are parts of the limbic system [25]. Thus, besides attention, the cingulum has a crucial role in visual and spatial skills and memory.

In Figure 2, some important events of neuroplasticity at the molecular level are summarized. Post synaptic events following the release of a neurotransmitter from the presynaptic nerve terminal to the synaptic cleft are depicted in the figure. As a well-known fact, when an internal or external stimulus arrives at the presynaptic terminal *via* action potentials, neurotransmitters are released to the synaptic cleft as quanta. These neurotransmitters pass the synaptic cleft and bind ionotropic or metabotropic receptor proteins located on the neural membrane. The majority of metabotropic receptors are also connected with specific membrane-bound elements called G proteins. G-protein coupled receptors (GPCRs) conduct the message *via* activation of membrane-bound first effector proteins, such as adenylyl cyclase and phospholipase C (PLC), which in turn synthesize secondary messengers, such as hydrophilic cAMP, IP3, and hydrophobic DAG. These secondary messengers further trigger the activity of protein kinase systems or directly regulate the activity of ion channels. The increased intracellular calcium ion concentration, either through the activity of ionotropic receptors, such as the NMDA receptor, or through indirect release from the intracellular stores, such as through IP3 signaling, can also act as an important secondary messenger itself and trigger the activity of Ca-dependent kinases. The major secondary messengers that can trigger the downstream pathways ending with gene plasticity are the water-soluble secondary messengers cAMP and Ca^{2+}. The message is finally transported to the neural nucleus by the chain reaction of protein kinases and the activation of transcription factors, such as cAMP response element binding protein (CREB). In the nucleus, the binding of transcription factors to regulatory sequences causes enhanced or suppressed activity of genes involved in plasticity, which leads to increased or decreased expression of plasticity-related proteins [26-29].

Development of the CNS depends on the extracellular and intracellular signals that instruct

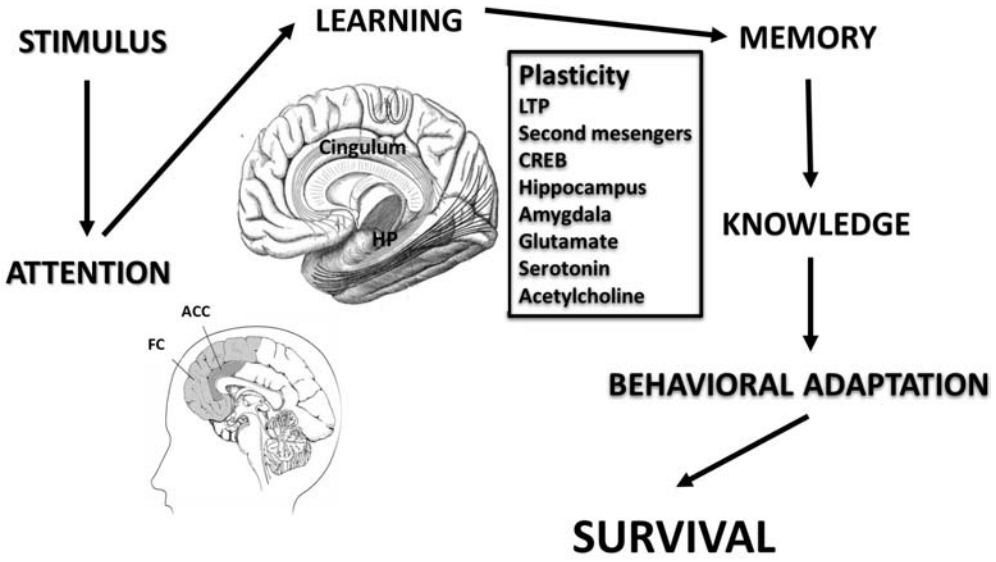

Figure 1. Knowledge and adaptation according to accurate information are everything for survival. This process is carried out by neuronal plasticity modulated by several factors, such as second messengers, various neurotransmitters, and proteins, on the molecular level. ACC and FC are important brain areas for continuing and interpreting of attention to any internal or external stimuli that enter the brain. The dense neuronal circuit called the cingulum, which reaches out from the septum to the hippocampus, makes a significant contribution to producing several memories. These memories are converted to available behaviors that support adaptation and survival (ACC: anterior cingulate cortex; FC: frontal cortex; Hp: hippocampus; LTP: long-term potentiation; CREB: cAMP response element binding protein).

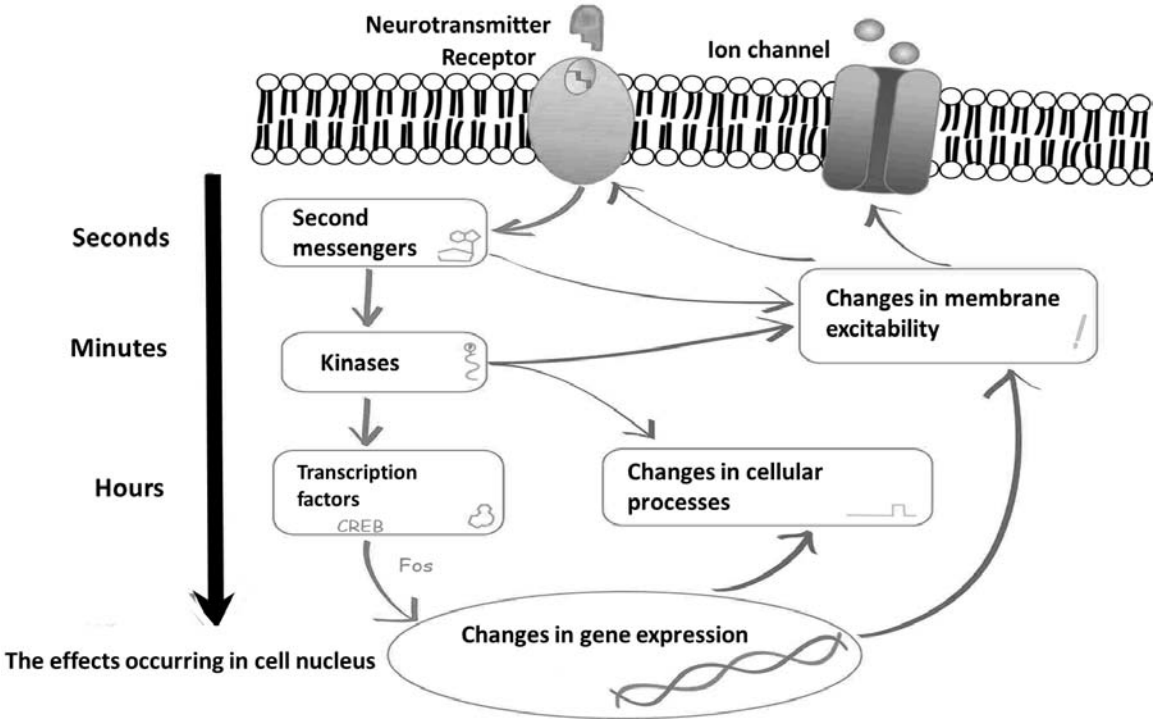

Figure 2. Signal transduction cascade on the synaptic level.

neural precursor cells when to divide, differentiate, survive, or die. Neurochemical regulators, known as neurotrophins or neurotrophic factors, were first described for their neurotrophic activities. Neurotrophic factors prevent neuronal apoptosis and deterioration during brain development and aid in neuronal recovery from injuries and age-related atrophies, which make them natural target-derived molecules in the brain [30, 31]. Among these neurotrophins, nerve growth factor (NGF) was the first member, discovered in 1952 by Levi-Montalcini [32]. Other important members of neurotrophins include brain-derived neurotrophic factor (BDNF), NT-3, NT-4 (NT-4/5 or NT-5), and NT-6. These neurotrophins are released in small concentrations and act as the brain's immune system [33, 34].

BDNF is a neurotrophin that regulates synaptic function and axonal and dendritic branching, affecting the survival, growth, and function of neurons in the central and peripheral nervous system and stabilizing synapses. In the CNS, it helps the neurons to develop and remodel themselves. In addition, it contributes to the structural integrity and healthy functioning of major nerve pathways. [35-37]. The findings suggest that deficiency or incapacity of BDNF synthesis increases susceptibility to neurobehavioral and neurodegenerative diseases such as depression and AD [38, 39]. Important findings suggest that BDNF can contribute to the treatment of such diseases by repairing neurodegeneration [40, 41].

CREB, a transcription factor regulating the processes of neuronal survival and restraining genes involved in synaptic plasticity, has a key role in the regulation of BDNF expression. When phosphorylated, CREB is transcriptionally activated and responds to stimuli such as neuronal activity, hormones, and growth factors [42]. Thus, the BDNF gene is of critical importance for neuronal survival and synaptic plasticity. Overall, these findings imply that neuroplasticity is actually based on gene plasticity or gene expression in the CNS.

According to the quality of incoming messages and related internal and external conditions, a new, healthy neuron with adequate synaptic development can be produced through neurogenesis, but a defective or mutant neuron or an incapable neuron can also be produced. According to their status, substantial synapses can be strengthened, be weakened, or become dysfunctional. All elements of the signal transduction cascade, including neurotransmitters, receptors, G proteins, second messengers, protein kinases, and transcription factors, are critical during the process. If any of them fails to function properly in this system, it may result in pathological conditions or counter-adaptation.

Finally, neuroplasticity based on all these signal transduction events occurs on the synaptic level in the CNS. The steps of signal transduction cascades are carried out on the molecular level, and they are influenced directly by genes and DNA. In fact, synaptic plasticity, the events that are explained by neuroplasticity in the brain, is a result of genomic changes that occur through signal transduction cascades at synapses. In short, neuroplasticity actually originates from the flexibility of gene expression and the interaction of genes with the environment. It results from the plasticity of many genes that direct the process in the signal transduction cascade; therefore, all cases of neuroplasticity, primarily learning, are in fact based on gene plasticity or genoplasticity.

3. What is genoplasticity in terms of CNS diseases?

3.1. Genetic basis of neuropsychiatric diseases

We had another opportunity to learn about DNA sequences and to make additional comparisons with the development of sequencing technology, single-nucleotide polymorphism arrays, or whole-genome array comparative genome hybridization. The advancement of technology provided us with information about DNA sequencing by statistical methods and allowed sequencing of the genome [43]. Many polymorphisms scattered throughout the genome are complex and exhibit polygenic properties. When alleles are examined according to their associated diseases, more information about epistatic interactions can be obtained [44]. Explaining the effects of the allele frequencies gives us the opportunity to learn more about the variations [45]. Elucidation of the molecular mechanisms controlling the activity-dependent

transcription of synaptic plasticity-related genes has paved the way to understanding neuronal function and disorders, together with the identification of new target molecules for pharmacological design [46]. By altering gene expression, the epigenetic arrangements that allow the integration of internal and external signals into the genome can play an active role in the development of psychiatric diseases and guide the setting of targets for new treatment options. It has been shown that functional polymorphisms in the serotonin transporter gene-linked promoter region (5-HTTLPR) and BDNF val66met interact with childhood adversities, where having at least one 5-HTTLPRs' or BDNF val66met allele led to sensitivity to childhood events [47].

3.1.1. Schizophrenia

Monoamines such as dopamine, serotonin, and noradrenaline are directly related to the action mechanism of drugs used in the treatment of neuropsychiatric disorders [48]. Genotyping by referring to the allele distribution frequencies of genes involved in the treatment of CNS diseases, particularly genomics, plays an important role in the assessment of susceptibility to neuropsychiatric diseases such as bipolar disorder, schizophrenia, and major depression through single-nucleotide polymorphisms (SNPs) [49, 50]. Recently, it has been suggested that the histone H3K4 methylation pathway contributes to the etiology of schizophrenia [51]. Variations in the expression of the mRNAs of neurotransmitters, their transporters and their receptors may also cause some important negative changes in synaptic activity in patients with schizophrenia. These variations may also switch some basic developmental processes, such as neuronal migration and axonal growth, involved in schizophrenia [51]. Because schizophrenia has been accepted as a neurodevelopmental disorder, this statement could be critical to the developmental progression of schizophrenia.

3.1.2. Attention deficit hyperactivity disorder (ADHD)

Studies on genetic background accompanied by brain imaging showed that there is a significant relationship between polymorphisms in various genes such as serotonin receptor 1B (HTR1B), dopamine beta-hydroxylase (DBH), the dopaminergic catechol-*O*-methyltransferase (*COMT*) Val158Met, the TC genotype of the G-protein-coupled estrogen receptor (GPER), and the gene encoding methyl tetrahydrofolate reductase (MTHFR) in ADHD and impulsivity [52-56]. Recently, Ghirardi *et al*. (2018) found dimension-specific etiological and phenotypic overlap between ADHD and autism spectrum disorder traits in adults [57]. Considering genetic profiles has also been helpful for effective pharmacotherapy of impulsivity and ADHD in children [58].

3.1.3. Depression

Chronic internal or external stressful events such as aging, exposure to chemical toxic agents, and trauma (i.e., stroke) have intense and damaging effects on the hippocampus [59]. Through studies of depression models that utilize stress as a trigger, chronic exposure to stress was shown to cause attenuated BDNF expression [60, 61] and neuronal atrophy of the hippocampus [62]. The volume of the hippocampus was also shown to be reduced in patients with chronic depression [63, 64] or post-traumatic stress disorder [65-68]. Conversely, the expression of BDNF in the hippocampus was increased by antidepressants [69-72]. Moreover, it has been shown that antidepressants enhanced glutamate-1 transporter mRNA levels and protein expression [73], excitatory postsynaptic potentials [74], neurogenesis [75, 76], apoptosis [77], and BDNF mRNA expression and protein levels [78] in the brains of stress-induced depressive animals. It appears that drug-induced genoplasticity contributes to the treatment of depression or the beneficial effects of antidepressants.

3.1.4. Alzheimer’s disease

Neurodegenerative diseases such as AD and Parkinson’s disease (PD) have a strong association with gene expression and genoplasticity. Three relevant genes and one susceptible gene have been described for AD. The relevant genes are the presenilin-1 gene on chromosome 14, the amyloid precursor protein gene on chromosome 21, and the presenilin-2 gene on chromosome 1. The susceptibility gene is the apolipoprotein E (APOE) gene on chromosome 19 [11, 79]. Three common polymorphisms in the APOE gene, ε2, ε3, and ε4, which create single amino acid changes,

strongly alter the likelihood of developing AD in a dose-dependent manner. APOEε2 is associated with a decreased risk for AD, and APOE ε4 is especially associated with an increased risk [80].

Ectopic cell cycle proteins, such as proliferating cell nuclear antigen (PCNA), were found in sites vulnerable to apoptosis when postmortem brain tissue from AD patients was examined [81, 82]. PCNA is known to be involved in DNA repair mechanisms; however, it was also shown that DNA replication actually occurs in at-risk neurons, indicating true re-entry into the cell cycle [83]. This abnormal cell cycle entry, which is ultimately fatal, was found to be driven by β-amyloid (Aβ). Cultured neurons treated with Aβ displayed increased expression of cyclins, initiated DNA replication, then underwent apoptosis in a cyclin-dependent manner [84, 85].

In the early stages of AD, the upregulation of several growth-related proteins may trigger genoplasticity. Some of these proteins include neural cell adhesion molecule (NCAM), myristoylated alanine-rich C kinase substrate, growth-associated protein 43 (GAP-43), heparan sulfate, laminin, spectrin, various cytokines and neurotrophic factors including fibroblast growth factor (bFGF), NGF, interleukin 1, 2, and 6, insulin-like growth factor 1 (IGF-1), IGF-2, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), hepatocyte growth factor, and several growth factor receptors [84]. An increased NCAM/SNAP-25 ratio can be used to detect the level of synaptic remodeling in AD [86, 87].

Downregulated expression of BDNF is observed in the hippocampus and neocortex during AD [88]. Together with BDNF, the expression of its TrkB receptor is also reduced in the frontal cortex and hippocampus in AD, while truncated TrkB receptors are upregulated in association with senile plaques [89, 90]. Furthermore, BDNF was upregulated in dystrophic neurons around senile plaques, and full-length TrkB was upregulated in the hippocampus, especially in glia [89]. BDNF polymorphisms are also associated with higher risk for AD, i.e., for specific ethnic groups and non-ApoE4 carriers [91, 92]. In addition to the Aβ pathology-driven disturbances, interestingly, tau pathology is first observed in the entorhinal cortex, followed by the subiculum and CA1 through the retrograde transport pathways of BDNF. The basal forebrain, amygdala, and several cortical regions follow this progress of tau pathology successively [86]. NMDA receptors are the predominant source for the maintenance of normal BDNF expression, whereas the overexpression of BDNF is mediated by non-NMDA receptors [93, 94]. Memantine, an NMDA-receptor antagonist commonly used for the treatment of AD, upregulates BDNF and TrkB expression in rats [95]. BDNF, in turn, has protective effects against Aβ-induced toxicity [96].

Fibroblast growth factor-2 (FGF-2), which also regulates BDNF levels, is important in neuronal development and neuroprotection after neuronal loss [97]. During AD, increased expression and binding of FGF-2 were observed in the presence of neurofibrillary tangles and senile plaques [98, 99], promoting the neurotic involvement of plaques [100]. Cultured neurons that are treated with FGF-2 displayed increased levels of tau phosphorylation [101] and increased levels of tau kinase and glycogen synthase kinase 3β (GSK-3β) [102, 103].

3.1.5. Parkinsonism

Small non-coding RNA molecules that are involved in RNA silencing and post-transcriptional regulation are called microRNAs (miRNAs). Various mammalian cells have miRNAs, which appear to target approximately 60% of human and other mammalian genes [104-106]. Specific miRNAs were associated with the progression of several diseases, e.g., PD. It is highly possible that these miRNAs can be used as potential markers to distinguish subsets of Parkinson's patients, as they are known to be involved in mitochondrial dysfunction, oxidative stress, and the maintenance of neural development. The late diagnosis of PD, usually at the stage where the majority of dopaminergic neurons are lost, makes the identification of molecular biomarkers for early detection of PD very important. Since miRNAs are thus critical for the post-transcriptional regulation of gene expression, they can be used as biomarkers, together with their target genes, for the early diagnosis of PD [107]. Furthermore, the exact expression of microRNA-7 (miR-7) is crucial

for normal brain development and neurogenesis, also keeping alpha-synuclein (α-Syn) at the physiological level. PD patients and animal models of MPTP-induced PD show a significant attenuation of miR-7 in regions related to neurodegeneration of dopaminergic neurons. Depletion of miR-7 in the substantia nigra is also associated with α-Syn accumulation, loss of dopaminergic cells, and reduction of dopamine in the striatum. Thus, it has been predicted that miR-7 replacement may be beneficial in the treatment of PD [108]. miRNAs have a crucial role not only in PD but also in AD. Recently, it has been suggested that miRNAs significantly decreased β-amyloid accumulation *via* reduction of β-secretase 1 enzyme expression [109].

3.1.6. Addiction

Drug addiction is characterized by compulsive drug seeking and a high tendency to relapse following drug cessation. The brain reward system is a crucial network in the development of addiction. Drug- or substance-induced alterations in gene expression in the neural substrates for reward and motivation, e.g., the nucleus accumbens (NAc), ventral tegmental area (VTA), and prefrontal cortex (PFC), represent an important mechanism that contributes to addiction. For the molecular substrates that underlie long-lasting changes in these regions, epigenetic mechanisms appear to be attractive candidates. Reversing the epigenetic signature of addiction could present fundamentally new approaches for more efficient treatment of drug relapse [110].

Reward deficiency syndrome (RDS) was suggested to arise from defects in combinations of several genes encoding neurotransmitters involved in the brain reward system. Individuals with such defects are generally at risk for abuse of unusual rewards. The dopamine D2 receptor (DRD2) appears to be one of the major targets in such cases. It has been associated with pleasure, and the DRD2 A1 allele was also referred to as a reward gene. It has been shown that a person who has the A1 allele of the gene displays decreased D2 receptor binding affinity. Recent studies associated the TaqI A1 allele of the DRD2 gene with drug abuse, alcoholism, smoking, compulsive gambling, obesity, and several personality traits in various subject groups. RDS may also be related to ADHD, Tourette's syndrome, schizophrenia, and antisocial behaviors [111-113].

The expression or activity of numerous transcription factors, such as CREB, ΔFosB, MEF2 (myocyte-enhancing factor-2), and NFκB (nuclear factor κB), can be altered under chronic exposure to addictive drugs. When these factors, i.e., in the brain's reward circuitry, were modulated in experimental models of substance abuse and dependence, the molecular, cellular, and behavioral responses could be altered, defining the functional role of these factors and their target genes in dependence. Epigenetic regulation is an underlying source of various cases of adaptations observed in an adult organism to environmental stimuli, e.g., during drug addiction. The ability of drugs of abuse to alter the expression of specific genes in the reward system after chronic exposure can be mediated by the post-translational modification of histone tails, the altered activity of a host of chromatin remodeling proteins, and direct modification of DNA. The expression of several addiction-linked proteins was shown to be regulated by several specific miRNAs, whose expression is altered by drugs of abuse in brain reward regions [114].

Addictive substances do not only affect a specific point in the signal transduction cascade. The affected stage or region may vary depending on the drug, or an agent may affect multiple stages. Substance addiction is also a polygenic disease similar to schizophrenia and many other important brain diseases. This situation is the most important problem, and it points to the fundamental solution. As mentioned before, on the molecular and cellular levels, addiction is a negative neuroadaptation in specific structures or pathways such as the dopaminergic system in the brain. This state may be related to neurodegeneration or generate unusual, mutant, or "terrorist" neurons in these specific brain regions. The process is directly generated and/or supported by chronic use of addictive agents. A treatment that inhibits neurodegeneration and stimulates healthy neurogenesis in damaged areas and/or prevents the generation of "zombie"/"terrorist" neurons or converts them to normal neurons may provide a radical solution for this serious public health problem [115].

4. Conclusion

Neuroplasticity is actually a gene plasticity, and it can be described as genoplasticity. Because the brain is changed and reorganized constantly by genoplasticity on the neuronal level, genoplasticity has key importance in learning and memory, adaptation, and survival. It is also affected by internal and external factors; negative genoplasticity or counter-adaptation may be responsible for neuropsychiatric disorders, and this statement is also associated with individuals' genetic backgrounds. Negative genoplasticity results in neurodegeneration or generation of "terrorist" neurons that are falsely coded and have a new confused mission. Neurodegeneration may appear in many chronic brain disorders such as schizophrenia, major depression, and addiction, as well as Parkinsonism and Alzheimer disease. However, all brain problems can also be triggered with the appearance of "terrorist" neurons. These neurons can be generated by some genoplasticity-induced changes in the signal transduction cascade in synapses. Omalu described a neurologic problem called "chronic traumatic encephalopathy" in some American footballers with a head-to-head collision history [116, 117]. These players displayed personality disorders. They were impulsive, aggressive, could not make sensible decisions, and had attention deficits. Some of them were drug addicted, and the cause of death in some cases, according to autopsies, was suicide. In postmortem autopsies, Omalu detected some transformations and deformations, like the definition of "terrorist" neurons in the frontal cortex neurons of these players. If we can detect other specific "terrorist" neurons located in some specific regions of the brain in the beginning of several disorders by non-invasive imagination techniques and develop these kinds of techniques, we can provide great development in the early diagnosis of neuropsychiatric disorders. Drugs or treatment strategies that can reverse negative genoplasticity or change "terrorist" neurons to the normal form may be helpful for prevention or radical treatment of important neuropsychiatric illnesses.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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