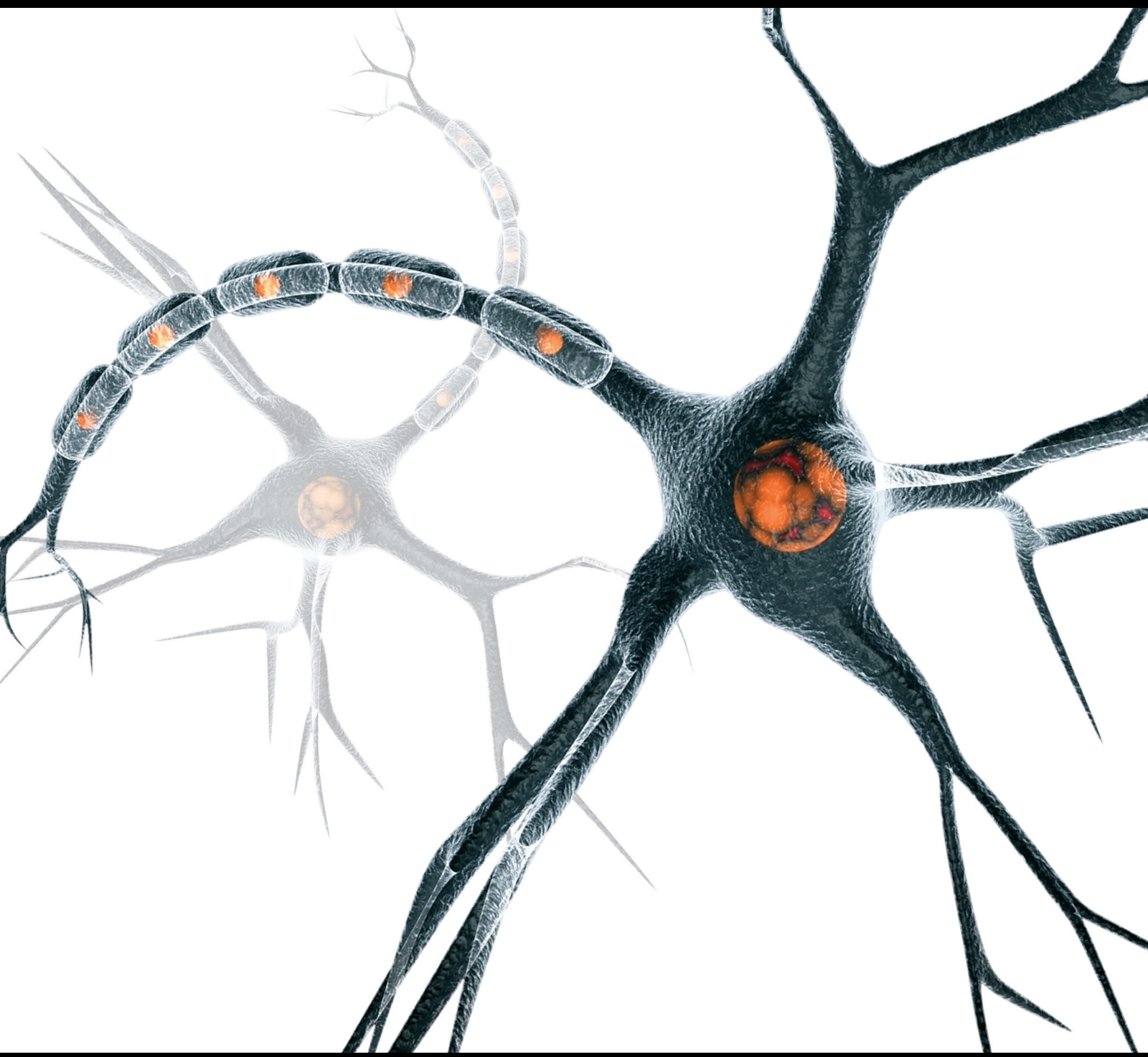
Neural Plasticity

Neural Plasticity in Mood Disorders

Lead Guest Editor: Bingjin Li
Guest Editors: Frank S. Hall and Aijun Li



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Editorial Board

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Volume 2018, Article ID 3745251, 2 pages
https://doi.org/10.1155/2018/3745251

Editorial
Neural Plasticity in Mood Disorders

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Received 2 April 2018; Accepted 2 April 2018; Published 9 May 2018

The contribution of differences in cellular and anatomical function to mood disorders has been a focus of research attention in biological psychiatry for a very long time. Some of the earliest structural imaging studies demonstrated differences in the size of certain brain structures in major depression, bipolar disorder, posttraumatic stress disorder, and drug dependence [1–4]. This led to the search for the cellular bases of these changes and how genetic and environmental factors contribute to these differences [5]. This is, of course, a topic of much ongoing research that seeks to identify these mechanisms at a cellular and anatomical level, as well as to relate these changes to both internal and external causal factors. An understanding of these factors will not only provide an understanding of the aetiology of affective disorders but will also inform efforts to develop new treatments for these conditions.

The contributions to this special issue address many aspects of this still-developing field, including summarizing changes in neural plasticity in brain regions important in depression, including the hippocampus, amygdala, and prefrontal cortex (W. Liu et al., "The Role of Neural Plasticity in Depression: From Hippocampus to Prefrontal Cortex"). New findings indicate that there are abnormalities in the functional connectivity of the anterior insula in depressed asthmatic patients (Y. Zhang et al., "Abnormal Functional Connectivity of Ventral Anterior Insula in Asthmatic Patients with Depression"). Differences in functional connectivity may influence brain activity involved in emotional states, as summarized in another review (R. Ding et al., "Emotion Processing by ERP Combined with Development and Plasticity"). Hypoxic injury associated with a variety of conditions has also been shown to contribute to the development of depression (F. Zhao et al., "Effect of Hypoxic Injury in Mood Disorder"), as summarized in another review, and in addition to hypoxic injury to neurons, such injury also affects neuroplasticity in many of these same brain regions.

As our understanding of the mechanisms underlying (generally) reduced neuroplasticity in many brain regions in depression evolves, efforts to normalize neural plasticity in depression continue to develop. Many of these new treatments, as well as a developing understanding of the mechanisms underlying the effects of older treatments, suggest that alterations in glutamatergic mediated neuroplasticity are critical for their antidepressant actions, including for the so-called "fast-acting" antidepressants (Y.-J. Huang et al., "New Treatment Strategies of Depression: Based on Mechanisms Related to Neuroplasticity"). A new report in this volume suggests that Yueju, a Chinese traditional medicine, not only has antidepressant effects in the learned helplessness model but also involves similar mechanisms to other antidepressants (e.g., PKA, CREB, BDNF, and NMDA receptors) (Z. Zou et al., "Neural Plasticity Associated with Hippocampal PKA-CREB and NMDA Signaling Is Involved in the Antidepressant Effect of Repeated Low Dose of Yueju Pill on Chronic Mouse Model of Learned Helplessness"). The effects of Yueju were greater than fluoxetine, and a previous report indicates that Yueju may be a fast-acting antidepressant [6]. Several other papers in this special issue address other understudied mechanisms that appear to contribute to neuroplasticity in mood disorders and related conditions.

These include the importance of zinc and how zinc might contribute to antidepressant actions through effects on monoaminergic systems (U. Doboszewska et al., "Zinc in the Monoaminergic Theory of Depression: Its Relationship to Neural Plasticity") and the role of histidine triad nucleotide-binding protein (P. Liu et al., "HINT1 in Neuropsychiatric Diseases: A Potential Neuroplastic Mediator").

Although most treatments for mood disorders emphasize pharmacological treatments, nonpharmacological treatments are of course important as well, particularly in combination with pharmacotherapy. As discussed in two reviews here, physical activity produces antidepressant-like effects that are mediated by differences in brain plasticity (C. Phillips, "Physical Activity Modulates Common Neuroplasticity Substrates in Major Depressive and Bipolar Disorder"), and these effects work through similar mechanisms to pharmacotherapies such as brain-derived neurotrophic factor (BDNF) (C. Phillips, "Brain-Derived Neurotrophic Factor, Depression, and Physical Activity: Making the Neuroplastic Connection"). Sleep is well known to be disrupted in depression, and sleep disturbances disrupt a number of neuroplastic mechanisms that are important for memory formation and other processes (M.-Q. Zhang et al., "Neural Plasticity Is Involved in Physiological Sleep, Depressive Sleep Disturbances, and Antidepressant Treatments"). These authors go on to consider the mechanisms underlying therapeutic sleep deprivation, which appears to involve at least some of the same mechanisms as other antidepressant treatments, including normalizing some aspects of neural plasticity that are disrupted in depression.

The link between depression and chronic pain is well known epidemiologically, but increased understanding of both neuropathic pain and the mechanisms of depressive disorders has identified substantial overlap in underlying mechanisms (J. Sheng et al., "The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain"). As discussed in this review, these mechanisms involve surprisingly similar alterations in glutamatergic synapses and similarities in the driving factors of these neuroplastic changes, including monoamines, BDNF, and inflammatory mechanisms. As synthetic opioids have become widely used for chronic pain, as well as widely abused, this raises important questions about the role of opioids in depression, the potential antidepressant actions of acute opioid treatments, and the potential for chronic opioid treatments to induce depression as a consequence of tolerance and withdrawal. The incidence of addiction is, of course, increased in patients with various pain conditions and mood disorders. Hypotheses about the causes of increased addiction in mood disorder patients include self-treatment for underlying mood and cognitive dysfunction [7], as well as more direct effects on drug actions or drug-related phenotypes. As discussed in a review in this volume, genome-wide association studies for drug dependence and genetic studies in mice have found that genetic variation or modifications of cell adhesion molecule genes may be a major contributor to addiction liability (D. E. Muskiewicz et al., "The Role of Cell Adhesion Molecule Genes Regulating Neuroplasticity in Addiction"). This indicates that there is a fundamentally important role for neural plasticity in addiction and in particular in the genetic liability for addiction. It remains to be seen to what extent this genetic contribution to addiction liability overlaps with genetic contributions to mood disorders.

Collectively, the articles presented in this special issue represent several novel research directions that are contributing to our understanding of the importance of neural plasticity in mood disorders and related conditions. This understanding will help lead to improved pharmacological and nonpharmacological treatments for these conditions.

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Hindawi
Neural Plasticity
Volume 2018, Article ID 9803764, 17 pages
https://doi.org/10.1155/2018/9803764

Review Article

The Role of Cell Adhesion Molecule Genes Regulating Neuroplasticity in Addiction

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Received 14 August 2017; Accepted 10 December 2017; Published 20 February 2018

Academic Editor: Michele Fornaro

A variety of genetic approaches, including twin studies, linkage studies, and candidate gene studies, has established a firm genetic basis for addiction. However, there has been difficulty identifying the precise genes that underlie addiction liability using these approaches. This situation became especially clear in genome-wide association studies (GWAS) of addiction. Moreover, the results of GWAS brought into clarity many of the shortcomings of those early genetic approaches. GWAS studies stripped away those preconceived notions, examining genes that would not previously have been considered in the study of addiction, consequently creating a shift in our understanding. Most importantly, those studies implicated a class of genes that had not previously been considered in the study of addiction genetics: cell adhesion molecules (CAMs). Considering the well-documented evidence supporting a role for various CAMs in synaptic plasticity, axonal growth, and regeneration, it is not surprising that allelic variation in CAM genes might also play a role in addiction liability. This review focuses on the role of various cell adhesion molecules in neuroplasticity that might contribute to addictive processes and emphasizes the importance of ongoing research on CAM genes that have been implicated in addiction by GWAS.

1. Introduction

Substance use disorder (SUD) [1] is a chronic disease characterized by compulsive drug seeking behavior, loss of control of drug intake, and the emergence of negative behaviors resulting from drug tolerance and withdrawal (e.g., anxiety, dysphoria, and other emotional, cognitive, and somatic symptoms [2]). Importantly, this description of SUD includes the persistence of symptoms beyond detoxification. The development of an SUD (herein, we will generally refer to the condition as drug dependence or drug addiction) involves a complex interplay between environmental and genetic factors. However, the genetic component of drug dependence liability is highly polygenic and heterogeneous, with each genetic locus contributing a rather small proportion of the overall genetic variance [3].

Early attempts to characterize the mechanisms underlying addiction liability focused primarily on twin studies, linkage studies, and candidate gene studies. These early studies established that a substantial genetic component contributed to addiction liability through the use of family, adoption, and twin studies, with estimates of the heritability of addiction ranging from 0.3 to 0.7 [4]. However, despite the apparent strength of the heritable component of addiction liability, the early phase of genetic research into the causes of addiction was plagued by a failure to produce a high degree of replication for specific genes or specific gene loci in candidate gene linkage and association studies. There are many reasons for this initial failure, including the often low number of subjects used in many studies, particularly early studies, which is especially problematic if there is a substantial heterogeneity of the underlying genetic architecture, as has been discussed

Table 1: Abbreviations used for cell adhesion molecules discussed in this review.

Cell adhesion molecule	Abbreviation
Neural cell adhesion molecule	NCAM
Polysialated neural cell adhesion molecule	PSA-NCAM
Neuronal cell adhesion molecule	NRCAM
Immunoglobulin super family	IGSF
Synaptic cell adhesion molecule	SYNCAM
Intercellular adhesion molecule 5	ICAM5
Cadherin 13	CDH13
Neurexin 3	NRXN3
Neurexin 2β	NRXN2β
Neuroligin 3	NLGN3
Neuroligan 1	NLGN1
Neurexin 3β	NRXN3β
Protein tyrosine phosphatase receptor D	PTPRD
Protein tyrosine phosphatase receptor B	PTPRB
CUB and Sushi multiple domains 1	CSMD1
Protein tyrosine phosphatase receptor Z 1	PTPRZ1

recently [5]. Locus and allelic heterogeneities are less of a problem for GWAS, but of course low numbers of subjects are certainly a problem, as well as low marker density, which also characterized early studies. Over time, the density of markers and the number of subjects included in addiction genetic studies increased, but another important strategy of these postgenomic studies was to look for replication across studies [6–8], the expectation being that if the contribution of each locus was small and heterogeneous it should not be expected that every study would produce identical results, but that positive identification of genes or loci would still reoccur at higher than chance rates across multiple studies in different samples. This did in fact occur. Moreover, analysis of the genes that were repeatedly identified in GWAS produced patterns that were initially unexpected, including a high proportion of CAMs compared to their representation in the genome overall [9, 10] (see Table 1 for the list of CAMs discussed in this review).

After the identification of so many CAMs in GWAS for addiction liability, one of the strategies used to confirm the potential role of these genes as addiction, that is, genes in which variation would affect addiction phenotypes, was to study them in genetically modified mice. Although the human variants likely contributed in more subtle ways to addiction liability, the use of gene knockout (KO) mice in which gene function was eliminated was considered, to some extent, to be a test of whether the identification of particular genes in GWAS was a false positive. Homozygous KO mice are a poor example of human genetic variation, but may still provide information about the potential involvement of genes in addiction. Indeed, given the high degree of genetic heterogeneity that was identified in GWAS, the finding of many positive effects in mice in which these CAMs have been deleted [11] provides strong support for the original GWAS findings as well as the overall concept based on those findings that allelic variation in CAM genes is an important part of the genetic component of addiction liability. Moreover, this suggests that neural plasticity, either during development, or later in life, plays an important role in the genetic component of addiction liability. In considering this idea in this review, we will focus on the potential roles of CAMs in brain function that may be relevant to addiction and then consider the evidence for particular CAMs in addiction.

2. Synaptic CAMs

2.1. Ig Superfamily

2.1.1. Structure and Function. The immunoglobulin superfamily (IgSF) is the largest and most well documented cell adhesion molecule subgroup, although not all genes in this family are cell adhesion molecules. IgSF contains over 700 genes of which at least 65 proteins are implicated in cell adhesion (for a recent review summarizing cell adhesion molecule classifications, structure, and known functions, see [12], as well as a reassessment of their classifications and potential signaling properties in the nervous system [9]). The Ig superfamily is largely characterized by a variable number of Ig modules, a subregion of the polypeptide chain essential to heterophilic and homophilic binding. Many of the members of the IgSF are built of homologous domains, ranging from 70–110 amino acid residues, with a structure formed by two β-sheets packed face-to-face [13]. However, individual members can differ by the number and size of the strands of the two β-sheets as well as the conformation of links between them [14]. Ig domains characteristically contain two cysteine residues, placed approximately 55–75 residues apart, and highly conserved tryptophan residues, approximately 10–15 residues downstream of the first cysteine [13]. The extracellular makeup of Ig CAMs can consist exclusively of either several Ig domains connected like beads on a string, as is the case for PECAM-1 and VCAM-1, or Ig connections followed by multiple copies of another molecular building block, such as fibronectin type III (Fn3), as is the case for NCAM and L1 [15]. The FN3 domain is found in most, but not all, IgSF members, and the number of domains often varies between members [13]. Extracellular modules are significantly variable from 1 in P0 to 17 in sialoadhesin. IgSF CAMs can be further subdivided by their membrane anchorage via a glycosylphosphatidylinositol- (GPI-) linked subgroup (e.g., F11, TAG-1, and BIG-1) as well as by their transmembrane subgroup (e.g., neurofascin, NgCAM, L1, and NCAM). Similar to the extracellular components, the cytoplasmic composition of IgSF CAMs also has significant heterogeneity, varying anywhere from 15 to 557 amino acid residues [15].

The wide variation in molecular composition of CAMs on the same general framework suggests their involvement in wide-ranging cellular functions, including different interactions with extracellular and intracellular biomolecules. Alongside indications of involvement of some CAMs in neuroplasticity that will be discussed in this review, members of the IgSF superfamily include many genes involved in immune function and other signaling pathways, including

major histocompatibility complex class I and II immunoglobulins, T receptor complex proteins, lymphocyte surface glycoproteins, virus receptors, tumor markers, and growth factor receptors. IgSF CAMs are involved in complex extracellular interactions involving both homophilic and heterophilic binding to CAMs as well as multiple cis and trans interactions [15]. TAG-1/axonin-1, NgCAM, NrCAM, gicerin, DM-GRASP, and NCAM have all been shown to have both homophilic and heterophilic interactions [16]. Several IgSF CAMs have been shown to be involved in axonal growth and guidance during the early development of the nervous system. This involvement is mediated by restricted expression patterns and ability to modulate cell interactions during development, particularly for certain isoforms, and does not exclude roles for the same genes later in life [13].

Our understanding of the physiological roles of CAMs and their interactions with each other and with other intracellular and extracellular proteins, as well as other types of signaling molecules, is still evolving. Indeed, one recent proposal [9], following on a series of clinical and preclinical studies of the role of CAMs in addiction, has completely reassessed the genes that should be classified as CAMs. This study has suggested that there should be a differentiation between CAMs that primarily play a role in information transfer between cells, or between cellular elements and extracellular matrix ("iCAMs"), and those that play primarily structural roles. Furthermore, they subdivided the types of structural CAM classes based on function and location as follows: interactions with cell matrix (mCAMs), tight junctions (tjCAMs), cell-cell interactions in the immune system (cCAMs), focal adhesions (faCAMS), axonal guidance (agCAMs), adherens junctions (ajCAMs), and myelin interactions (myCAMS). It was difficult to make clear distinctions between CAMs that had solely informational and primarily structural roles, and by far, the largest class of CAMs was iCAMs in their analysis. Moreover, this study reassessed gene classifications finding 474 likely CAM genes, of which 283 would be classified as iCAMs. Many of those are discussed in more detail below. This analysis supports previous emphases on the signaling aspects of synaptic formation played by several classes of CAMs [17].

2.1.2. NCAM1. Neural cell adhesion molecule 1 (NCAM1; see Figure 1 for a comparison of the structure of this CAM to other CAMs discussed in subsequent sections) is expressed across many cell types, including neurons, glial cells, cardiac muscle cells, and skeletal muscle cells, with as many as 27 distinct isoforms generated by alternative RNA splicing [15]. In general, NCAM can be expressed both pre- and postsynaptically and has three distinct classes of isoforms including transmembrane linked (seen in Figure 1), GPI anchored, and secreted or soluble NCAM. NCAM is composed of five Ig domains, encoded by two exons, and two fibronectin type III domains [18]. The role of NCAM1 in the brain was first characterized by Hoffman et al. [19], where it was shown to mediate retinal cell adhesion. Since then, NCAM1 has been shown to have roles in axonal development, involvement in signaling pathways, emotional function, and learning, as well as potential involvement in many neuropsychiatric and neurodegenerative disorders [20–25, 15]. More recent studies have indicated a role of NCAM1 in addiction, specifically the polysialylated form of NCAM1 (PSA-NCAM1), which commonly regulates the adhesive properties of the molecule and is critical for effects of NCAM on synaptic plasticity [25, 26]. The addition of the long linear homopolymers of alpha-2,8-linked sialic acid residues to NCAM1 produces antiadhesion properties. NCAM has been shown to mediate both pre- and postsynaptic scaffoldings that influences excitatory synapse formation and plasticity relevant to addiction. Studies have revealed that NCAM can effect postsynaptic scaffolding associated with β-spectrin and accumulation of PSD95, GluN1, GluN2B, and CaMKII [27]. In addition, PSA-NCAM was shown to increase AMPAR-mediated currents, although this was age dependent [28]. PSA-NCAM was also shown to affect NMDA receptor activity by inhibiting receptor currents in cultured hippocampal neurons at low, but not high, concentrations of glutamate, suggesting a role as a potential competitive antagonist at the glutamate binding site [29]. Given its substantial interaction with glutamate excitatory synapses, it is not surprising that PSA-NCAM has also been found to play a substantial role in many behavioral tests of addiction that involve the formation of drug-dependent memories. For instance, single cocaine administration decreases the number of PSA-NCAM1-positive neurons in the dentate gyrus (DG) of male Wistar rats, as well as decreasing the length of PSA-NCAM1-positive dendrites [30]. Similarly, amphetamine was shown to decrease the expression of 180–200 kDa isoform of PSA-CAM in the hippocampus of male C57BL/6 mice, although this appeared to occur regardless of whether drug exposure was specifically paired with a distinctive environment or not [31]. Thus, the role of PSA-NCAM1 may be specific to certain experimental circumstances not represented by the locomotor sensitization approach. Additional evidence supports a role of PSA-NCAM1 in other learning contexts. The cannabinoid receptor 1 agonist HU-210, an illicitly used synthetic cannabinoid, also antagonizes hippocampal synaptic plasticity associated with contextual fear conditioning, an effect that involves reversing the increases in PSA-NCAM1 expression involved in that type of learning [32]. Nicotine self-administration also reduces levels of PSA-NCAM1 in the DG of rats, in a dose-dependent manner [33]. PSA-NCAM1 levels in the ventromedial prefrontal cortex (vmPFC) are associated with the ability to transfer learning of a classically conditioned association to instrumental learning (Pavlovian-to-instrumental transfer (PIT)), and reduction in vmPFC PSA-NCAM1 levels by administration of endoneuraminidase reduced extinction behavior in a PIT task for ethanol reinforcement [34]. This study not only demonstrates the importance of PSA-NCAM1 in ethanol reinforcement, but also demonstrates its involvement in a specific behavior that has high relevance to drug dependence—extinction of drug reinforcer-mediated behavior.

In contrast to many of the findings discussed above, a clinical study found that PSA-NCAM1 levels were increased in the DG of heroin-addicted individuals [35]. The effects of opiates on *NCAM1* expression have not been studied, but

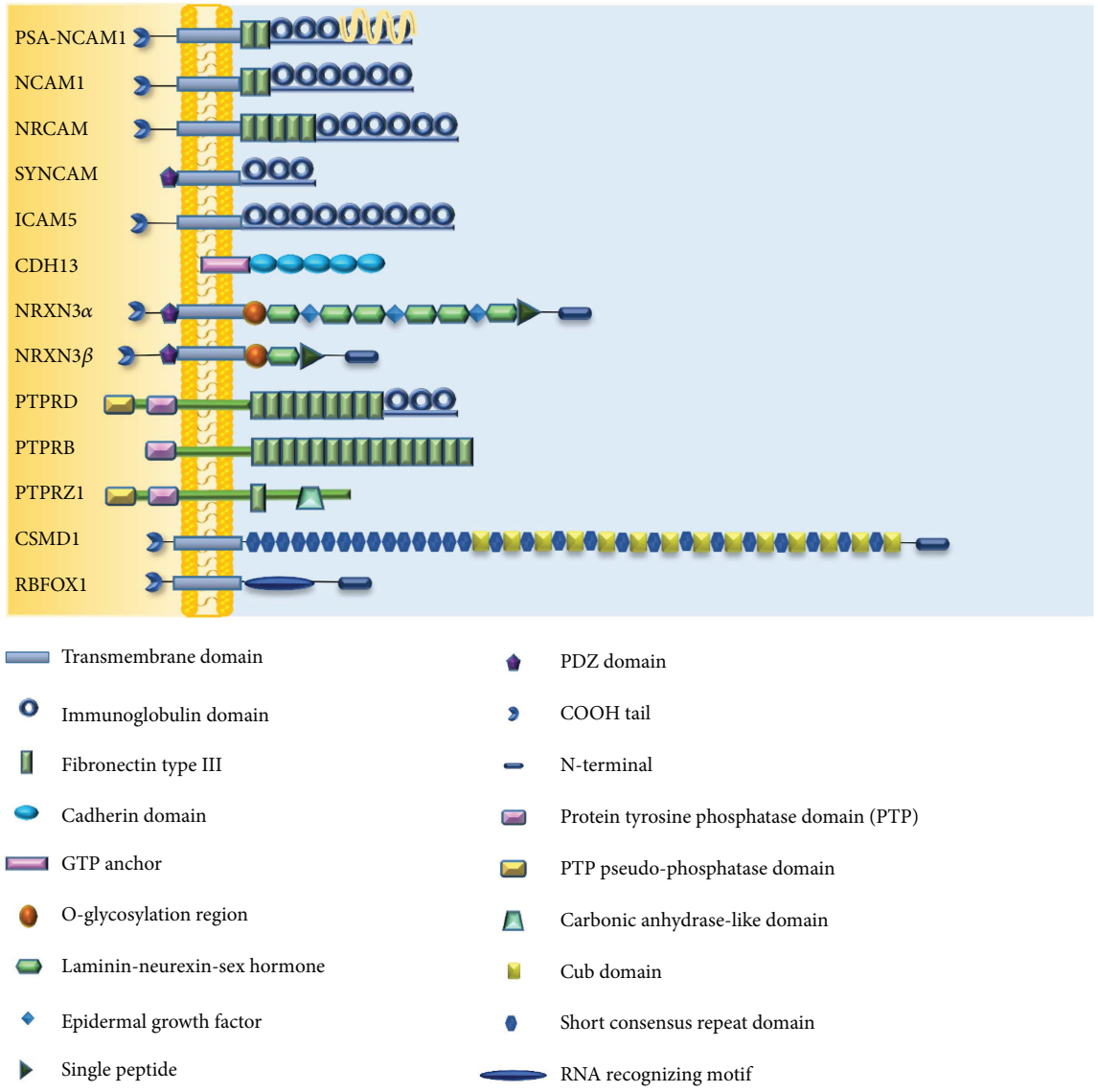

Figure 1: Schematic representation of the structural motifs of cell adhesion molecules discussed in this review.

presuming the acute effects of opiates are similar to those of other addictive drugs, this increase in PSA-NCAM1 might reflect a compensatory process associated with the repeated downregulation produced by acute effects of the drug, or an effect associated with drug withdrawal. As an additional piece in this still incomplete puzzle, neonatal nicotine exposure was found to reduce levels of *Ncam1* mRNA in the amygdala of female rats when assessed in early adolescence [36]. This study will be discussed in more detail throughout this review as it specifically addressed the effects of prenatal nicotine on the expression of a number of CAMs.

It is obvious that further studies are needed to fully elucidate the potential roles of NCAM1 in addictive processes under different conditions, including in response to different types of addictive drugs, at different ages and at different parts of the addiction cycle. However, it should be noted that the majority of the findings discussed in this section do not reflect changes in the expression of NCAM itself, but rather the levels of PSA-NCAM. Moreover, genetic associations for *NCAM* with drug dependence were not found in the majority of GWAS studies previously discussed, although *NCAM* has been recently associated with marijuana dependence [37]. One study did find that genes near *NCAM1* were associated with nicotine dependence [38]. However, this is a complex genomic area where *NCAM1* is part of a gene cluster with *TTC12*, *ANKK1*, and *DRD2*, and stronger associations have been found for markers within the other genes in this cluster [39, 40]. Nonetheless, an analysis of this region using a family-based association approach with denser marker coverage found an association of markers near the *NCAM1* exon 12/intron 13 border with alcohol dependence [41]. Although NCAM1 (as PSA-NCAM1) may have a role in certain aspects of the addictive process there is, thus far, less evidence that allelic variation in the *NCAM1* gene contributes to addiction liability. This may be because *NCAM1* allelic variation contributes more to certain aspects of the addictive process,

certain addiction phenotypes, or to addiction to particular substances. Indeed, a previous review of this subject has suggested that, although GWAS for drug dependence have been successful, this may be too broad of a phenotype and that stronger effects will be found for more specific drug addiction phenotypes [5]. It is also highly possible that only particular splice variants are associated with addiction, rather than *NCAM1* overall; a topic that will be considered again with respect to *A2BP1* (ataxin-2 binding protein 1).

2.1.3. NRCAM. *NRCAM* (neuronal cell adhesion molecule or *NgCAM*-related cell adhesion molecule; see Figure 1) belongs to the L1 family of IgSF CAMs and is composed of six Ig-like domains, five FN3 domains in its extracellular region, and a cytoplasmic region composed of approximately 110 amino acid residues [42]. NRCAM can interact with molecules both intracellularly and extracellularly. Several studies have indicated that the extracellular domain of *NRCAM* can interact with molecules on the cis- and transmembranes, as well as both homophilic and heterophilic binding with CAM and CAM-like molecules. *NRCAM* has been implicated in axonal growth and guidance, playing an important role in the development of cerebellar granule cells, dorsal and ventral spinal cord axonal development, optic chiasm formation, and the formation of thalamocortical projections [43].

Given its role in the development of thalamocortical projections and its general distribution in areas thought to be important in addiction [44], it is not surprising that *NRCAM* was hypothesized to play a role in addiction. Relationships between markers in or near the *NRCAM* gene and drug or alcohol dependence were found in genome-wide linkage studies for alcoholism [45–47] and early genome-wide association studies for drug dependence [48, 49]. Based on these findings, candidate gene approaches were used which found that *NRCAM* allelic variants were associated with drug dependence [44] and methamphetamine dependence [50]. In later GWAS studies, utilizing more subjects and greater marker density, *NRCAM* allelic markers were also associated with caffeine intake (Amin et al., 2012). However, the majority of later GWAS studies did not find significant associations of *NRCAM* variants with drug dependence. This may be because *NRCAM* variants are more closely related to particular endophenotypes that were better represented in some samples; in addition to an association with methamphetamine dependence, Yoo et al. [50] also found that *NRCAM* allelic markers were associated with specific measures of addictive behavior and personality traits thought to be a characteristic of drug abusers, including novelty seeking.

As discussed above, one of the reverse translational approaches used to confirm the possibility that variation in the *NRCAM* gene may contribute to addiction was the use of *Nrcam* KO mice. The logic behind this approach was specific; Ishiguro et al. [44] demonstrated that the same *NRCAM* markers associated with drug dependence were also associated with a 74% reduction in *NRCAM* expression. There was also a substantial upregulation of *Nrcam* gene expression after morphine treatment in rats. Thus, it might be expected that individuals with poorer expression might respond quite differently when taking drugs of abuse. On this basis, *Nrcam* KO mice were examined for condition place preference ((CPP) a measure of the reinforcing efficacy of drugs) produced by several drugs of abuse, including morphine, cocaine, and amphetamine. Reduced CPP was observed in both heterozygous and homozygous *Nrcam* KO mice. In a two-bottle free-access ethanol consumption paradigm, it was also found that male *Nrcam*+/− mice display reductions in ethanol consumption compared to wild-type littermates [51]. Furthermore, studies have shown that *Nrcam* KO mice have no general learning impairments that might confound CPP studies [44, 52]. However, other behavioral differences were observed, including a passive avoidance deficit interpreted as a result from poor impulse control [52]. Although the interpretation of that test is not certain, behavior seen in tests of responses to anxiety and novelty [51] could be interpreted in a similar manner. Certainly, examination of these mice in a circumstance that more specifically assesses impulsive behavior is warranted, although the general findings are consistent with those of Yoo et al. [50] in methamphetamine addicts.

2.1.4. Synaptic Cell Adhesion Molecules (SYNCAMs). The idea, developed from the results of a series of GWAS studies discussed above, that differences in the function of certain CAMs may contribute to addictive behavior has opened the door for the study of several other CAMs that were not implicated in GWAS studies. Obviously, from the name, the synaptic cell adhesion molecules ((SYNCAMs); see Figure 1) have prominent roles in synaptic cell adhesion, and synapse formation [53], as well as axon guidance during development [54]. SYNCAMs are IgSF/SYNCAM proteins that span the synaptic cleft and induce the formation of excitatory synapses *in vitro* [55], a process seen previously only with neuroligin [56]. Like NCAM1, polysialylation of SYNCAM1 is important to its function, with polysialylation of SYNCAM in the first Ig domain preventing homophilic binding [57]. As the formation of excitatory synapses has long been thought to be an important part of addictive processes, demonstrated by dendritic spine formation in several brain regions after exposure to drugs of abuse [58–60], along with increased surface expression of AMPA receptors [61–63], it would be natural to investigate SYNCAM1. Moreover, SynCAM1 was already known to influence synaptogenesis in the hippocampus and to be ubiquitously expressed throughout much of the brain, including the striatum and other structures know to exhibit synaptic plasticity after exposure to drugs of abuse. Consistent with this hypothesis, *Syncam1* KO mice showed decreases in the length of mushroom dendritic spines as well as impaired locomotor sensitization to cocaine [64].

However, with regard to the genetic basis of drug dependence liability, there is little evidence for contributions from allelic variation in *SYNCAM1*, judging from the GWAS studies mentioned above. A related family member, *CADM2*, was associated with marijuana dependence [37], but has not otherwise been investigated regarding the effects drugs of abuse or addiction.

2.1.5. Intercellular Adhesion Molecule 5 (ICAM5). ICAM5 (see Figure 1) is an immunoglobulin cell adhesion molecule highly expressed on the dendrites of neurons in the telencephalon that is known to have roles in immune and neural functions [65, 66]. Moreover, *in vitro* studies have indicated that the soluble form of ICAM5 may regulate glutamatergic neurotransmission [67, 68]. Not much is known about the ability of ICAM5 to affect addictive behavior through influences on glutamate function, but one study has shown that acute methamphetamine (MA) treatment stimulates cleavage of membrane-bound ICAM5 molecules, both *in vitro* and *in vivo*, via matrix metalloproteinase 9 (MMP9) [69]. *Mmp9* has been shown to have roles in alcohol seeking behavior and methamphetamine toxicity in rodents [70, 71]. Moreover, matrix metalloproteinases (and MMP9 in particular) have been suggested to affect neural plasticity and learning relevant to drug addiction [72, 73].

Genetic variation in ICAM5 has not been found to be associated with drug dependence in GWAS studies, and has not been a focus of other genetic approaches, although MMP9 has been associated with alcohol dependence [74], and was identified in the brains of cocaine abusers in a transcriptional study [75]. Based upon the role of ICAM5 in altering glutamatergic neurotransmission, including changes in response to methamphetamine, further research is warranted. The case of ICAM5, has an important implication: although some proteins may have roles in the circuitry underlying the effects of drugs of abuse, there may, for whatever reason, not exist genetic variation in the human genome that contributes to the genetic liability toward drug dependence.

2.2. Cadherins

2.2.1. Structure and Function. The cadherin superfamily of CAMs, consisting of more than 110 members, are transmembrane proteins defined by a repeated extracellular domain sequence, the cadherin EC domain [76, 77]. Each EC domain consists of seven β-strands, each forming two β-sheets, folding similarly to that of immunoglobulin domains, that play important roles in brain morphogenesis and wiring [76]. The stabilization of the extracellular domain in cadherins relies upon the presence of Ca^{2+}, which binds to the boundaries between EC domains, resulting in the formation of its rod-like structure [78]. EC domains containing several conserved Ca^{2+} binding sequences in cadherins include AXDXD, LDRE, and DXNDN domains. Cytoplasmic interactions of cadherins are essential to their cell-cell adhesion process [79]. Catenins have interactions with the cytoplasmic domain of cadherin molecules, and thus interactions between catenins and cadherins are important to their function [80–82]. These molecules included three different groups, α, β, and p120, which are essential in mediating linkage of the cytoplasmic components of cadherin molecules to the actin cytoskeleton of the cell. "Classical cadherins" have five EC domains, but the cadherin superfamily includes proteins with other numbers of domains as well (see [76] for a complete review of cadherin subtypes and classifications).

A number of classification schemes for cadherin have been proposed, but one clear division is between classical and nonclassical cadherins [76]. Nonclassical cadherins include a large number of cadherins, including CDH13, desmosomal cadherin, 7D family protocadherins, CDH23, fat-dachsous, CDH26, CDH28, flamingo, calsyntenins, and RET, which differ in a number of structural aspects, while still conforming to the basic cadherin structure. The size of cadherins differs substantially among nonclassical cadherins, particularly in terms of the size of the extracellular and intracellular domains. Structural variations in cadherins include differences in the number of cadherin (EC) motifs, as well as the presence/absence or number of several other intracellular and extracellular motifs, including the β-catenin binding site, p120 binding site, desmoglein repeats, and intracellular kinase domains. Classical cadherins belong to a group of type I transmembrane proteins containing five EC domains and a unique cytoplasmic domain. In humans, this class of cadherins consists of 18 members that are highly conserved and interact with β-catenin and p120-catenin. Classical cadherins can be further subdivided into the type I classical cadherins consisting of CDH1 (E-cad), CDH2 (N-cad), CDH3 (P-cad), CDH4 (R-cad), and CDH15 (M-cad); the type II classical cadherins include CDH5 (VE-cad), CDH6 (K-cad), CDH7, CDH8, CDH9 (T1-cad), CDH10 (T2-cad), CDH11 (OB-cad), CDH12 (N-cad-2), CDH18, CDH19, CDH20, CDH22, and CDH24.

Cadherins are thus a diverse class of molecules involved in many physiological functions, with diverse tissue-specific distributions [76]. Cell-cell interactions and cell adhesion are essential for the development of multicellular organisms, and especially in the development and plasticity of many complex organs such as the central nervous system. In particular, the formation of neural networks involves a series of processes that include cell fate determination, proliferation, migration, differentiation, axon elongation, pathfinding, target recognition, and synaptic plasticity, many of which rely on cell-cell adhesion and interaction. One of the more overlooked aspects of neural network formation and plasticity, however, is that many of these processes also involve cell signaling, which has been proposed to be an important criterion of CAM classification [9]. Cadherins have been implicated in a wide variety of these cellular processes that contribute to development and plasticity (for review see [76]). Certainly, not all cadherins may be involved in processes relevant to addiction, which means that those that do specifically play roles in addiction may constitute targets for antiaddiction drug development [10]. As an example of the specificity of the roles of these cadherins in neural function, the protocadherin class appears to regulate aspects of neural cell identity and diversity [83], rather than neuroplasticity. In the following section, only CDH13 will be considered, as it is the only cadherin for which there is strong evidence of a role in addiction, based upon neurobiological and genetic studies.

2.2.2. Cadherin 13 (CDH13). CDH13 (see Figure 1) is one of the genes that has been most often found to be associated with drug dependence or other addiction phenotypes in GWAS [6, 84–95]. Although many of these findings involve

dependence on particular addictive substances, or nicotine cessation, others involve general drug dependency, or responses that may be involved in the broad category of drug dependence. Prior to observation of these relationships in GWAS, there was no interest in CDH13 in the addiction field. However, CDH13 is glycosylphosphatidylinositol-anchored cell adhesion molecule, prominently expressed by ventral tegmental area and substantia nigra pars compacta dopamine neurons [96, 97], which are commonly associated with reward, locomotor control, and cognitive functions.

Some of the genetic markers used in association studies described above were also found to be associated with levels of CDH13 gene expression in human postmortem brain samples [98]. Using the same logic as was previously described for NRCAM [44], *Cdh13* KO mice were used to examine the effects of alterations in *Cdh13* expression on addiction-related phenotypes [98]. Firstly, cocaine CPP was examined in constitutive *Cdh13* KO mice, which showed evidence for a leftward shift in the dose-response curve—increased preference at 5 mg/kg s.c. and reduced preference at 10 mg/kg s.c. The reduction in cocaine CPP at 10 mg/kg was observed in both *Cdh13*+/− and *Cdh13*−/− mice. Furthermore, the same increase in preference for a low dose of cocaine was observed in conditional *Cdh13* KO mice, in which the transgene was activated in adulthood, thus negating the possibility that the effects in the constitutive KO mice were due to developmental effects.

For all of the CAMs discussed here, one of the most fundamental questions is whether the role that genetic variation plays in addiction liability is due to altered synaptic plasticity during development or in adulthood. The conditional knockout study strongly suggests that it is adult neuroplasticity that is affected. This argument was further assessed in (previously unpublished) gene expression data discussed below.

2.3. Neurexins/Neuroligins

2.3.1. Structure and Function. Other groups of CAMs that have been implicated in GWAS for addiction are neurexins (NRXNs) and neuroligins (NLGNs) [99], two classes of membrane-bound proteins involved in the central organization of glutamatergic and GABAergic synapses [100, 101], that have been implicated in a variety of neurodevelopmental disorders. This class of genes has been well described for some time, and their role in synapse formation has been well elaborated (for a more complete description see [102]). Briefly, in mammals, there are three neurexin genes, each with five alternative splicing sites, and three known extracellular binding partners (neuroligins, dystroglycan, and neurexophilins). Each gene has an upstream promoter, generating α-neurexin, and a downstream promoter which generates a smaller β-neurexin. Neurexins contain laminin, neurexin, and sex hormone-binding protein (LNS) domains which differ in number between α and β variants in addition to a highly glycosylated region, a transmembrane domain, and PDZ binding domain (PDZ-BD). Similar to neurexins, neuroligins are composed of a highly glycosylated region, a transmembrane region, and a PDZ-BD; however, their main extracellular domain is composed of a region homologous to acetylcholinesterase, but lacking cholinesterase activity. Neurexins are thought to localize to the presynaptic terminus and trigger postsynaptic differentiation while their binding partner, neuroligin, is thought to perform the opposite function, contributing to presynaptic differentiation via postsynaptic localization [103]. These CAMs are therefore thought to play an important role in synaptogenesis, and studies have shown that overexpression of neuroligins increases the number of synapses formed [104]. This role in synaptogenesis is not thought to be an exclusive role of these molecules, but to involve a number of CAMs [17]. Moreover, it would appear that specific CAM isoforms are involved in forming synapses in particular neural circuits (as well as initial circuit formation). This possibility of more specific roles in distinct brain regions has important implications for the potential roles of CAMs in addiction (as well as other functions and dysfunctional states).

2.3.2. Neurexin 3 (NRXN3) and Neuroligin 1/2/3 (NLG1/2/3). *NRXN3* (see Figure 1) has recently been implicated in addiction by GWAS studies of drug and nicotine dependence [99, 105], genome-wide linkage for opioid dependence [106], and with candidate gene approaches for alcohol, nicotine, or drug dependence [107–109], including smoking in schizophrenia patients [110]. Moreover, and again using the previous strategy of examining postmortem human tissue expression, in human studies revealing an association with a SNP potentially altering *NRXN3* gene splicing (rs8019381, located 23 bp from splicing site 5) and alcohol dependence, individuals with the addiction-associated rs8019381 T allele showed significantly lower levels of transmembrane NRXN3 isoforms [108]. There is also potential evidence for a relationship of *NRXN3* markers to addiction endophenotypes, including impulsivity [109].

As stated previously, NRXNs and NLGNs have important actions on both pre- and postsynaptic scaffolding and affect synaptic plasticity. Of importance for addiction phenotypes, these CAMs affect synaptic functions on both excitatory glutamate synapses as well as inhibitory GABA synapses. For instance, NRXN1β drives functional postsynaptic assembly of NMDARs and AMPARs on hippocampal neurons [111, 112]. Increased NLGN2 expression has also been found to increase GABAergic and glycinergic transmission, while NRXNβ has been shown to decrease $GABA_A$R-mediated transmission through extracellular binding to $GABA_A\alpha$R1 [113, 114]. The role of NRXNs and NLGNs in the development of addictive behaviors has also been examined in rodent studies, although to a limited extent. C57BL/6J mice, a strain commonly used in addiction studies due to their high levels of self-administration of most drugs of abuse, have lower levels of *Nrxn2β* and *Nlgn3* expression in the substantia nigra and increased expression of *Nlgn1* in the subthalamic nucleus compared to non-drug-preferring mice [115]. That same study also found that cocaine conditioning in a CPP procedure increased the expression of *Nrxn3β* in the globus pallidus. The combined human and animal data offer compelling evidence to support *Nrxn3* dysregulation as a potential mechanism contributing to addictive disorders. However, further research is

needed in both humans and animal models to solidify this potential role of NRXN3, and *NRXN3* genetic variance, in drug dependence.

2.4. Other CAM Classes. There are other CAM genes, from other CAM classes besides those discussed above, that have also been associated with addiction [8, 10]. These findings include the genes for several protein tyrosine phosphatase receptor type cell adhesion molecules ((PTPR); see http://www.genenames.org/cgi-bin/genefamilies/set/813 for a discussion of the nomenclature for this complex gene family), including *PTPRD* and *PTPRB*, as well as CUB and Sushi multiple domains 1 (*CSMD1*). Also included in this group of genes is *A2BP1*, which although it is not a cell adhesion molecule itself, has an important role in RNA splicing of cell adhesion molecules, including many discussed here that have been associated with drug dependence. PTPRs have both cell adhesion and catalytic activity that varies substantially across family members [116].

2.4.1. PTPRD. Many of the GWA studies discussed previously in this review identified clusters of SNPs with nominally significant associations ($10^{-2} > p > 10^{-8}$) with drug dependence and addiction-related phenotypes [6–8, 85, 88, 91, 92, 117–120]. Although the magnitude of the association in many of these studies did not reach "genome-wide significance," the repeated identification of an association in multiple samples suggested that this was indeed a real association, but with a small effect size as part of a highly polygenic genetic architecture. Subsequently, another laboratory has also found an association between *PTPRD* markers and opiate dependence in a GWAS for copy number variants in opiate-dependent individuals [121]. In a general way, these findings are consistent with the brain distribution of *PTPRD*, which is prominently expressed in ventral midbrain neurons implicated in reward, locomotor control, and sleep processes [122]. PTPRD forms both homodimers involved in the formation of neurites [123] and heterodimers, including PTPRD/SLITRK3 heterodimers that are involved in GABAergic synaptic plasticity [124]. Interestingly, SLITRK3 is from a family of Slit- and Trk-like proteins classified as "synaptic organizers."

PTPRD addiction-related haplotypes were shown to correlate with mRNA levels in human brain samples [125], providing the same sort of logic for examining drug responses in *Ptprd*-deficient mice (e.g., *Ptprd* KO mice) as for *Nrcam* and *Cdh13*. A leftward-shifted dose-response relationship for cocaine reward was observed in *Ptprd*+/− mice [125]. Heterozygous PTPRD KO displayed greater preference for places paired with 5 mg/kg cocaine as opposed to places with 10 or 20 mg/kg [125]. By contrast, cocaine preferences in *Ptprd*−/− mice were reduced at all doses. Obviously, much remains to be done in order to determine the role of PTPRD in response to drugs of abuse and for *PTPRD* variation in the genetic liability for drug dependence; a subsequent section presents additional data supporting this relationship based on cocaine regulation of *PTPRD* expression.

2.4.2. PTPRB. Protein tyrosine phosphatase receptor-type beta (*PTPRB*) is a part of the larger family of PTPRs which are known to regulate a variety of cellular processes including cell growth, differentiation, mitosis, and oncogenic transformation [126]. PTPRB contains extracellular fibronectin domains that interact with cell adhesion molecules such as contactin. To date, only a single study implicated PTPRB in substance abuse, finding significant associations for two *PTPRB* polymorphisms with alcoholism vulnerability in unrelated European-American individuals [127]. Additionally, mouse studies found that levels of *Ptprb* in the caudate putamen, midbrain, and hippocampus of C57BL/6J mice were significantly increased after both acute and chronic exposure to 20 mg/kg of morphine. It is obvious that further investigation is needed to elucidate and confirm the potential role of PTPRB in the neuroplasticity of addiction.

2.4.3. PTPRZ1. Ptprz1 (also called RPTPβ/ζ) is upregulated by acute morphine treatment and downregulated after chronic treatment in rodents [128]. Moreover, the PTPRZ1 ligand pleiotrophin [129] was also acutely upregulated by acute morphine treatment, but levels were normalized after chronic treatment, and upregulated by naloxone-precipitated withdrawal. These effects apparently involve signaling between astrocytes, which had elevated pleiotrophin expression, and midbrain dopamine neurons expressing PTPRZ1. Pleiotrophin is also upregulated by cocaine and amphetamine [130, 131] and may be involved in the extinction of cocaine-conditioned responses [132] and opiate withdrawal [133]. Adolescent amphetamine disruption of adult hippocampal plasticity is also dependent on pleiotrophin [134]. Some of these effects may be involved in the neurotoxic effects of these drugs as well [135–137].

Despite the accumulating evidence for a role of *Ptprz1* in addiction-related phenotypes from preclinical models, this gene was not identified in GWAS for addiction-related phenotypes. As mentioned before, there could be numerous reasons for why genetic variation in this gene in humans does not exist or has not been found to contribute to addiction-related phenotypes, not the least of which is the potential complexity of genetic contributions to addiction liability. Another PTPR family member, PTPRG, does not produce significant associations on its own with addiction-related phenotypes, but significant epistatic interactions of PTPRG markers with other genes were found in a recent GWAS examining alcohol dependence symptom counts [138].

2.4.4. CSMD1. CUB and Sushi multiple domains 1 (*CSMD1*) is a multiple domain complement regulatory protein that is highly expressed in the central nervous system [139]. CSMD1 consists of 14 CUB domains separated by short consensus repeat (SCR) domains (also called Sushi repeat domains), followed by 15 tandem SCR domains. Like many other cell adhesion molecules, CSMD1 is a type 1 membrane protein spanning the membrane once. It is enriched in nerve growth cones [139], and its cellular tissue distribution in the adult brain includes the ventral midbrain (Allen Mouse Brain Atlas), making it likely to be involved in processes associated with drug dependence. Indeed, *CSMD1* is among the most

highly replicated genes for drug dependence and related addiction phenotypes [6–8, 87, 88, 91, 92, 117–120]. Moreover, in a recent large GWAS study of cannabis dependence, a *CSMD1* marker was found to be associated with cannabis dependence at a genome-wide level of significance [140]. In a study of psoriasis, for which smoking is a risk factor, *CSMD1* variants were found to be associated with smoking and psoriasis in an interactive fashion [141]. In a similar manner, *CSMD1* copy number variants were found to be interactively associated with alcohol consumption as a risk factor for head and neck squamous cell carcinoma [142]. The mechanisms by which *CSMD1* variants may influence drug dependence liability are unknown and likely to be a part of broader effects on brain function as *CSMD1* markers have been associated with schizophrenia [143], autism [144], bipolar disorder [145], and general cognitive ability and executive function [146]. This later finding may suggest that the role of *CSMD1* variants in all of these conditions may result from impairments in executive function and decision making.

As with other genes considered here, one of the approaches taken to consider the role that *CSMD1* may have in drug dependence was to examine the effect of its removal in mice. A *Csmd1* KO strain was created by Lexicon Pharmaceuticals in which the first exon was deleted and has been described in three studies to date. In the first study, no differences in any behavioral phenotypes relevant to schizophrenia were observed, including tests of prepulse inhibition of acoustic startle, social interaction, sucrose preference, and locomotor activity [147]. In a second study, *Csmd1* KO did produce changes in measures of affective behavior indicative of anxious and depressive phenotypes [148]. In the final study, homozygous *Csmd1* KO mice had impaired learning of the Morris water maze [149]. More importantly, for the present discussion, that study also found subtle, but significant, reductions in cocaine CPP in both heterozygous and homozygous *Csmd1* KO mice. In human postmortem brain samples, *CSMD1* variants were associated with differential gene expression, as has been found for several of the genes previously discussed here.

Although certainly encouraging, much more remains to be explored in order to confirm and extend the findings in genetically modified mice of phenotypes consistent with human clinical findings. Moreover, although it is quite logical based on the limited data available to hypothesize that *CSMD1* variation is influencing the development or plasticity of neural circuits relevant to these phenotypes, this remains to be studied in a specific manner.

2.4.5. RBFOX1. RNA binding protein fox-1 homolog (ataxin-2 binding protein 1 (A2BP1)) binds to the C-terminus of ataxin-2 [150, 151], but also has RNA-binding motifs recognizing the RNA element (U)GCAUG and is involved in alternative splicing [152] of many genes expressed in neural cells [153]. Moreover, the target specificity of RBFOX1 is tissue dependent [154]. CNS-specific deletion of *Rbfox1* in mice increases neuronal excitability in the dentate gyrus and produces spontaneous seizures [155]. Few changes in overall transcript expression were observed in these mice, but there were substantial changes in the relative abundance of particular transcripts, including genes involved in membrane excitability (*Gabrg2*, *Grin1*, *Scn8a*, and *Snap25*), but also the CAMs *Nrcam* and *Nrxn3*. The inclusion of these CAMs, in addition to alterations in neuronal excitability, would seem to indicate that RBFOX1 may affect synaptic plasticity as well as neuronal excitability. Indeed, the network of transcripts regulated by RBFOX1 has been implicated in the organization of neural circuits during development [156], particularly in the forebrain [157], and has been implicated in autism spectrum disorder in genomic and transcriptomic studies [158, 159].

Of particular relevance here, *RBFOX1* markers have been repeatedly associated with drug dependence and related phenotypes [6, 85–89, 92, 117, 119, 120, 160, 161], findings also supported by linkage analyses [47, 162, 163]. In support of these genetic findings, cocaine treatment has been found to substantially affect alternative splicing, effects hypothesized to involve RBFOX1 [164].

Table 2: Gene expression changes after repeated cocaine treatment.

	ST	vMB	CX	HC
RBFOX1a	0.99 ± 0.06	0.88 ± 0.05	$0.94 \pm 0.01^{*}$	1.05 ± 0.08
RBFOX1f	0.96 ± 0.04	0.95 ± 0.04	1.02 ± 0.02	1.01 ± 0.10
CDH13a	$1.14 \pm 0.05^{*}$	1.04 ± 0.03	$1.27 \pm 0.06^{**}$	1.26 ± 0.09
CDH13c	1.01 ± 0.13	1.36 ± 0.14	0.87 ± 0.10	0.94 ± 0.10
CDH13e	0.90 ± 0.05	1.23 ± 0.13	1.10 ± 0.08	1.07 ± 0.07
CSMD1g	$1.24 \pm 0.06^{*}$	1.06 ± 0.04	0.98 ± 0.05	1.17 ± 0.08
CSMD1h	1.10 ± 0.07	1.04 ± 0.08	0.92 ± 0.08	0.88 ± 0.06
PTPRDa	0.95 ± 0.03	1.02 ± 0.03	$0.82 \pm 0.03^{**}$	0.98 ± 0.08
PtPRDd	$1.39 \pm 0.07^{**}$	$1.25 \pm 0.09^{*}$	1.17 ± 0.07	0.97 ± 0.19

Data expressed as fold change as compared to saline controls ($N = 9$–12 per experimental condition). $^{*}p < 0.05$; $^{**}p < 0.005$. Note that the differences that are nominally significant at the $p < 0.05$ level might be false positives, while those that are significant at the $p < 0.005$ level are significant after a Bonferroni correction.

2.5. Regulation of CAM Expression by Cocaine. The specific role of CAMs discussed here in addiction and addiction phenotypes is not fully known. In particular, for the majority of these genes (except perhaps for *CDH13*), it is not known whether the role of polymorphisms is to influence CAM expression during development, or neural plasticity in response to exposure to drugs of abuse. If the primary role of CAMs is in neural plasticity occurring in response to drugs of abuse, it would be expected that drugs of abuse would alter the expression of the CAMs that GWAS (and mouse genetic studies) have shown are important for addiction liability and addiction phenotypes. Here, we report preliminary evidence that many of these CAMs are regulated by cocaine. The effect of cocaine on the expression of *CDH13*, *CSMD1*, *PTPRD*, and *A2BP1* transcripts was examined using rtPCR (see supplement for detailed methods). Multiple transcripts were examined (see Supplemental Table 1 for descriptions). Gene expression was examined in tissue samples (striatum, hippocampus, frontal cortex, and ventral midbrain) under

Table 3: Gene expression changes after cocaine CPP.

	ST	vMB	CX	HC
RBFOX1-a	$0.85 \pm 0.02^{**}$	0.95 ± 0.05	1.04 ± 0.03	0.98 ± 0.02
RBFOX1-f	0.96 ± 0.02	1.03 ± 0.08	1.04 ± 0.02	1.00 ± 0.04
CDH13a	1.09 ± 0.06	$1.12 \pm 0.04^{*}$	$1.14 \pm 0.04^{*}$	1.05 ± 0.06
CDH13c	0.93 ± 0.09	1.15 ± 0.06	—	$0.76 \pm 0.05^{*}$
CDH13e	0.88 ± 0.04	1.04 ± 0.07	—	$0.76 \pm 0.04^{*}$
CSMD1g	1.12 ± 0.06	$1.17 \pm 0.06^{*}$	$1.21 \pm 0.05^{*}$	0.98 ± 0.04
CSMD1h	1.07 ± 0.09	1.13 ± 0.08	$1.29 \pm 0.06^{**}$	0.81 ± 0.07
PTPRDa	0.89 ± 0.03	0.94 ± 0.03	—	$0.92 \pm 0.02^{*}$
PtPRDd	$0.51 \pm 0.05^{**}$	1.01 ± 0.13	1.26 ± 0.14	$0.71 \pm 0.04^{*}$

Data expressed as fold change as compared to saline controls ($N = 9$–12 per experimental condition). $^{*}p < 0.05$; $^{**}p < 0.005$. Note that the differences that are nominally significant at the $p < 0.05$ level might be false positives, while those that are significant at the $p < 0.005$ level are significant after a Bonferroni correction.

two conditions: after a regimen of repeated cocaine injections used to induce locomotor sensitization and after the cocaine treatment regimen used to induce cocaine-conditioned place preference. Both treatment conditions produced changes in CAM expression, although the pattern was somewhat different. Because this study is highly preliminary, the data is presented with uncorrected p values. Some of these are likely to represent false positives (those with p values between $p < 0.005$ and $p < 0.05$); something that will need to be addressed in additional, more comprehensive, studies.

Despite this, the tentative nature of these findings, the whole data set, representing examination of 4 genes chosen from the entire genome based on the GWAS and mouse genetic studies described in this review, provides strong evidence for the importance of alterations in the expression of these genes in response to cocaine. Although dependent on brain region, alterations in at least one transcript were found for all 4 genes after exposure to sensitizing regimen of cocaine (Table 2). In the striatum, cocaine increased the expression of *CDH13a*, *CSMD1g*, and *PTPRDd*. Increases in the expression of *PTPRDd* were also observed in the ventral midbrain and *CDH13a* in the cerebral cortex. Reductions in the expression of *RBFOX1a* and *PTPRDa* were observed in cerebral cortex. No changes were observed in the hippocampus. These changes were not large in magnitude, but as they would be expected to occur only within particular cell types, influencing particular synaptic connections, this is not surprising.

Even more changes were observed after conditioned place preference (Table 3). The expression of *RBFOX1a* was decreased in the striatum, as were the levels of *PTPRDd*. In the cerebral cortex, the levels of *CDH13a* were again increased, as they were after noncontextual cocaine treatments. The levels of *CSMD1g* and *CSMD1h* were also increased in cerebral cortex. *CDH13a* levels were also increased in the ventral midbrain, as were levels of *CSMD1g*. Perhaps, consistent with the greater contextual and spatial learning associated with the CPP procedure, changes in the expression of several CAMs were observed in the hippocampus, in contrast to what was observed after a simpler sensitization procedure. Reduced expression of the *CDH13c*, *CDH13e*, *PTPRDa*, and *PTPRDd* transcripts was observed. These appear to be prematurely terminated transcripts and may be a general indication that cocaine is altering RNA transcription of these genes. As with the sensitization data, none of these changes were terribly large, but again, this is not surprising since these changes were likely to have occurred in a relatively small subset of neurons within each of these brain regions and perhaps only within certain portions of the dissected regions.

Although these data are quite preliminary, they do support a role for these CAMs in the underlying cellular changes that occur in response to repeated cocaine treatments, including contextual learning associated with drug seeking as measured in the CPP procedure.

2.6. Implications of These Findings for the Role of Cell Adhesion Molecules in Addiction. Prior to the emergence of so many associations between markers in CAM genes and drug dependence in GWAS studies, these genes were not at all considered to be important in addiction or in the mechanisms underlying responses to addictive drugs. This is not surprising as little was known about the role of these genes in most neural functions prior to these studies. A growing appreciation has developed for the role of cell adhesion molecules not only in neural development, but also in neuroplasticity occurring throughout the lifespan.

A very important issue regarding the role of CAMs in addiction involves the cellular and anatomical distribution of CAMs, and whether these are found in regions of the brain that are likely to influence addiction phenotypes. For many of the CAMs discussed here, there is certainly evidence for localization in excitatory and inhibitory synapses, but there is certainly much work to be done to identify which particular CAMs associate with which synapses, as well as the specific regional distribution of CAMs. A complete consideration of this topic is beyond the scope of this review, but it has been noted that many of the cell adhesion molecules discussed here are located in portions of corticostriatal

circuitry involved in addiction on dopaminergic or glutamatergic neurons including CDH13, PTPRD, NLGN1, and NRXN3 [9]. It will be very important to separate the potential developmental roles of these genes from their roles in adult plasticity as well. For one addiction-associated CAM, CDH13 [98], a conditional knockout strategy, has suggested that the role of CDH13 influences adult plasticity. It is likely that many CAMs have developmental roles, or roles in both developmental and adult neural plasticity.

Not only have human studies repeatedly demonstrated the involvement of CAM variation in addiction, but mouse studies have now supported these findings. Studies in genetically modified mice have shown that reductions in the expression of several CAM genes, including NRCAM [44], CDH13 [98], CSMD1 [149], and PTPRD [125], affect responses to drugs of abuse, particularly cocaine, in standard animal models of psychostimulant responses that are important in the study of addictive properties of abused drugs. The levels of NRXN3 have also been shown to be upregulated in the globus pallidus during cocaine abstinence in mice [115]. Mechanistically, several CAMs have been shown to play integral roles in both postsynaptic and presynaptic differentiation and assembly in systems thought to be essential for the neuroplasticity of addiction. CAMs such as PSA-NCAM and SYNCAM, as well as several neurexins and neuroligins, differentially affect synaptic functions demonstrated by alterations in NMDA and AMPA receptor-mediated currents, as well as the expression of synaptic protein-mediated aspects of excitatory and inhibitory neurotransmission. These functions, when affected by drug exposure, may produce important neuroplastic changes fundamental to the development of addiction phenotypes. Thus, preclinical data supports GWAS findings suggesting a role of these genes in addiction, and by implication, that neural plasticity during development or after exposure to drugs of abuse is fundamental to the influence of variation in the function of these genes on addictive processes. Although certainly much remains to be done in this nascent field, the data also suggests that these molecules should be explored as potential targets of therapeutic interventions [10].

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

The authors would like to thank Jana Drgonova for her technical contributions to the gene expression studies and for her thoughtful comments on this manuscript. The authors wish to acknowledge financial support from the Intramural Research Program of the National Institute on Drug Abuse (FSH, GRU) and the University of Toledo.

Supplementary Materials

Supplemental Table S1: primers for rtPCR. *(Supplementary Materials)*

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Hindawi
Neural Plasticity
Volume 2017, Article ID 5181925, 9 pages
https://doi.org/10.1155/2017/5181925

Review Article

HINT1 in Neuropsychiatric Diseases: A Potential Neuroplastic Mediator

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Received 14 April 2017; Revised 23 August 2017; Accepted 18 September 2017; Published 30 October 2017

Academic Editor: Bingjin Li

Although many studies have investigated the functions of histidine triad nucleotide-binding protein 1 (HINT1), its roles in neurobiological processes remain to be fully elucidated. As a member of the histidine triad (HIT) enzyme superfamily, HINT1 is distributed in almost every organ and has both enzymatic and nonenzymatic activity. Accumulating clinical and preclinical evidence suggests that HINT1 may play an important role as a neuroplastic mediator in neuropsychiatric diseases, such as schizophrenia, inherited peripheral neuropathies, mood disorders, and drug addiction. Though our knowledge of HINT1 is limited, it is believed that further research on the neuropathological functions of HINT1 would eventually benefit patients with neuropsychiatric and even psychosomatic diseases.

1. Introduction to HINT1

Proteins containing the histidine triad (HIT) motif, a conserved HisXHisXHis sequence (in which X represents any hydrophobic amino acid), constitute an enzyme superfamily known as the HIT proteins [1]. According to enzyme activity classification, HIT proteins can be classified into three branches: nucleoside phosphoramidate hydrolases, dinucleotide hydrolases, and nucleotidylyl transferases. HIT proteins are conserved throughout evolution, and more than 35 members of this superfamily have been found in 29 species, including bacteria, archaea, yeast, plants, *C. elegans*, *Drosophila*, and mammals, implying that HINT1 exerts basic and essential physiological functions [2]. The human genome encodes seven HIT proteins, which mainly serve as nucleoside transferases and hydrolases and can be divided into five classes: histidine triad nucleotide-binding protein (HINT), galactosyl-1-phosphate uridine acyltransferase, aprataxin, DCPS/DCS-1, and the brittle histidine triad proteins [3–6].

The histidine triad nucleotide-binding protein (HINT) (including human HINT and nonhuman Hint) is the first class of HIT superfamily. It is now suggested that at least one *HINT* gene is thought to exist in all sequenced genomes. Three independent HINT genes encoding the HINT1, HINT2, and HINT3 proteins are found in the human genome. Genes encoding HINT1 proteins are localized on human chromosome 5q31.2, with a full length of 6160 bp, containing three exons. HINT1 mRNA is composed of 782 bp, encoding a 126-amino acid cytosolic protein molecule with a relative molecular mass of approximately 14 kDa (Figure 1) [3, 7]. According to nuclear magnetic resonance (NMR) and crystallography studies, HINT1 is one of the purine nucleotide-binding proteins. Two subunits constitute a homodimer structure with a binding site for purine bases and a binding site for ribose on each subunit (Figure 2) [1, 8, 9].

HINT1 was first described as a protein kinase inhibitor in 1990 [10] and supposed to be protein kinase C inhibitor 1 (PKCI-1) in early literature [11, 12]. Although direct or

```
1    atg gca gat gag att gcc aag gct cag gtc gct cgg cct ggt ggc  45
1    M   A   D   E   I   A   K   A   Q   V   A   R   P   G   G    15

46   gac acg atc ttt ggg aag atc atc cgc aag gaa ata cca gcc aaa  90
16   D   T   I   F   G   K   I   I   R   K   E   I   P   A   K    30

91   atc att ttt gag gat gac cgg tgc ctt gct ttc cat gac att tcc  135
31   I   I   F   E   D   D   R   C   L   A   F   H   D   I   S    45

136  cct caa gca cca aca cat ttt ctg gtg ata ccc aag aaa cat ata  180
46   P   Q   A   P   T   H   F   L   V   I   P   K   K   H   I    60

181  tcc cag att tct gtg gca gaa gat gat gat gaa agt ctt ctt gga  225
61   S   Q   I   S   V   A   E   D   D   D   E   S   L   L   G    75
                 ↑ Phosphorylation site
226  cac tta atg att gtt ggc aag aaa tgt gct gct gat ctg ggc ctg  270
76   H   L   M   I   V   G   K   K   C   A   A   D   L   G   L    90
                 ↑ Amidation site                    ↑ Myristyl site
271  aat aag ggt tat cga atg gtg gtg aat gaa ggt tca gat ggt gga  315
91   N   K   G   Y   R   M   V   V   N   E   G   S   D   G   G    105
                                    ↑ Myristyl site
316  cag tct gtc tat cac gtt cat ctc cat gtt ctt gga ggt cgg caa  360
106  Q   S   V   Y   H   V   H   L   H   V   L   G   G   R   Q    120

361  atg cat tgg cct cct ggt taa 381
121  M   H   W   P   P   G   *
```

Figure 1: DNA and protein sequences of human HINT1. Green boxes indicate the histidine triad (HIT) domain. The potential modification sites of the protein are shown, including the phosphorylation site, amidation site, and myristyl site.

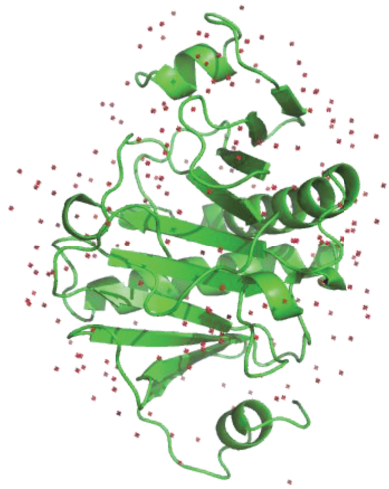

Figure 2: Crystal diffraction pattern of the HINT1 protein. HINT1 consists of a homodimer, each subunit of which contains two α-helices and three β-sheets. From http://www.rcsb.org/pdb.

indirect interactions between HINT1 and protein kinase C (PKC) were suggested, the inhibitory effects of HINT1 on PKC are still doubtful. Therefore, PKCI-1 was renamed to HINT1 [1]. The abbreviation PKCI is still occasionally used in the current literature with the altered meaning of protein kinase C interacting protein 1, which was indicated in Klein et al.'s study [13].

2. HINT1 in Tumorigenesis

Although HINT1 is known for its enzyme activity, studies have shown that it has additional functions unrelated to its enzymatic activity [14], such as tumorigenesis suppression [15, 16]. Accumulating evidence indicates that HINT1 plays a role as a haploinsufficient tumor suppressor in multiple malignant diseases, but little is known about the mechanism [15, 16]. Several recent studies demonstrated that by inhibiting the activities of transcription factors including AP1 [17], TFIIH [18], MITF [19], and USF2 [20], HINT1 could regulate gene expression in the Wnt/beta-catenin signaling pathway [21]. Therefore, it seems that HINT1 may exert potential anticancer effects as a gene transcriptional regulator. Currently, studies are focusing on the clinical relevance of HINT1 expression in several human specific cancers [22–24].

3. HINT1 in Neuropsychiatric Disorders

HINT1 has a wide range of distribution in various tissues including liver, kidney, stomach, and brain in humans and rodents [13]. HINT1 is expressed in the central nervous system (CNS) of mice and is particularly enriched in the olfactory sensory system, cerebral cortex, hippocampus, part of the thalamus, hypothalamus, midbrain, pons, and medulla oblongata [25]. The distribution of HINT1 in the CNS provides anatomical evidence for its potential importance in neuronal function.

3.1. Schizophrenia. The HINT1 gene is located on a genetic locus highly associated with schizophrenia (5q31.2) [26, 27]. Schizophrenia is a common psychiatric disease with manifestations of positive symptoms (hallucinations, delusions, disorganized speech, disorganized behavior, catatonic behavior, agitation, etc.) and negative symptoms (blunted affect, emotional withdrawal, apathetic social withdrawal, stereotyped thinking, attentional impairment, etc.), as well as cognitive, affective, and aggressive symptoms [28]. The etiology of schizophrenia is complicated, including epigenetic changes and interactions between genetic susceptibility and environment [29].

Vawter et al. found that HINT1 was significantly decreased in the dorsolateral prefrontal cortex (DLPFC) and prefrontal cortex in patients with schizophrenia [30–32]. Notably, the HINT1 gene is located in the SPEC2/PDZ-GEF2/ACSL6 region of 5q22-23, which is associated with schizophrenia [33]. The same team then evaluated eight single nucleotide polymorphisms (SNPs) in the HINT1 gene in Irish study of high-density schizophrenia families (ISHDSF, 1350 subjects and 273 pedigrees) and Irish case-control study of schizophrenia (ICCSS, 655 patients and 626 controls). They further compared expression levels of HINT1 in postmortem brain samples provided by the Stanley Medical Research Institute and concluded that mutations in the HINT1 gene were potentially correlated with schizophrenia [7]. Varadarajulu et al. [34] found that the expression of HINT1 protein was upregulated in the thalamus but downregulated in the DLPFC in postmortem brain samples of patients with schizophrenia compared to those of healthy controls, consistent with results from another study in 2011 [35]. Additionally, findings from the abovementioned studies suggest that the association between HINT1 and schizophrenia is gender-specific and may only exist in male patients [7, 32, 33].

The results obtained from clinical studies are further supported by studies of HINT1 knockout (KO) mice. Barbier and colleagues [36] demonstrated that compared with wild-type (WT) mice, HINT1 KO mice were more sensitive to acute amphetamine- (AMPH-) induced hyperlocomotor behavior. Quantitative microdialysis of the kinetics of dopamine (DA) in the striatum or nucleus accumbens (NAc) showed that presynaptic DA neurotransmission in these regions did not underlie the AMPH-induced behavioral phenotype of KO mice. However, systemic administration of apomorphine, a dopamine receptor agonist, significantly increased KO mouse locomotor activity, suggesting that the postsynaptic DA transmission may be dysregulated in KO mice. Considering that schizophrenia is often accompanied by dopaminergic system hyperfunction [37] and the hyperactivity induced by AMPH represents the positive symptom-like behavior in rodent models for schizophrenia [38], HINT1 KO mice appear to be a useful genetic animal model for studying schizophrenia. Furthermore, we found that HINT1 plays a role in a social isolation (SI) mouse model, characterized by behavioral abnormalities similar to those in schizophrenia, and potential interactions among HINT1, N-methyl-D-aspartate receptor (NMDAR), and DA type 2 receptor (D2R) may underlie the schizophrenia-like behavioral deficits induced by SI [39, 40].

3.2. Inherited Peripheral Neuropathies (IPNs). IPNs, which affect the peripheral nervous system (PNS), are neuromuscular and neurodegenerative disorders characterized by disrupted communication between the CNS and body. As one of the most common inherited neuromuscular disorders, the prevalence of IPNs is approximately 1 in 2500 [41]. IPNs include a large group of disorders involving multiple genes and complex phenotypes, so the correct diagnosis of each genetic subtype is a thorny problem for clinicians. At present, more than 100 different subtypes of IPNs have been identified, each with its own specific clinical features, pathophysiology, and prognosis. The unidentified mutations make it difficult to apply molecular diagnosis, and therefore, clinical features and developmental patterns are currently used to direct identification of genetic subtypes in patients with IPNs.

One study showed that mutations of HINT1 may be a cause of distal hereditary motor neuropathies [42]. In addition, Zimoń et al. [43] identified eight different mutations of the HINT1 gene in a cohort of 50 autosomal recessive axonal neuromyotonia (ARAN) patients with neuromyotonia (NM) from 33 unrelated nuclear families. NM is characterized by delayed muscular relaxation after voluntary contractions, induced by overexcited motor axons in the PNS [44]. In order to analyze the association between HINT1 and ARAN patients with NM, Zimoń and colleagues [43] screened patients and found a mutation rate at 11% in irrelevant patients with autosomal recessive peripheral neuropathy, which was 76% in ARAN patients with NM. Thus, there is a robust causal genetic association between HINT1 and ARAN patients with NM. However, Horga et al. did not detect variation of the HINT1 gene by direct sequencing of 152 patients with IPNs in England and Spain, indicating a regional specificity in this association [45–47].

Zimoń and colleagues also evaluated the expression levels of HINT1 in mouse tissues, such as heart, lung, and liver [43]. The results showed that HINT1 was enriched in the sciatic nerve in mice, indicating that HINT1 is a vital component of the function of PNS. Furthermore, they implemented *in vivo* genetic complementation analysis by using HINT1 deficit yeast strain (BY8-5c from *Saccharomyces cerevisiae* strain) and then analyzed HINT1 expression levels in lymphoblastoid cell cultures from affected individuals and irrelevant controls, respectively [43], identifying that mutations of HINT1 belong to loss-of-function mutations. Thus, a new genetic subtype was defined based on this functional mutation, namely, autosomal recessive axonal neuropathy with neuromyotonia (ARAN-NM) [43]. Even so, by using knockout mice, Seburn and colleagues demonstrated that HINT1 knockout mice may be useful for studying the biochemical activities of HINT1, but these mice do not provide a disease model or a means for investigating the basis of HINT1-associated neuropathy and neuromyotonia [48]. Therefore, further investigation is needed to determine whether HINT1 functions are species-specific.

3.3. Mood Disorders. Mood disorder is featured by obvious and sustained episodes of mania or depression with the clinical manifestations of major depressive disorder (MDD) and bipolar disorder (BP) [49].

Elashoff et al. [50] performed a meta-analysis of 12 microarray studies and concluded that expression of HINT1 was decreased in postmortem brains of patients with BP. A study using HINT1 KO mice demonstrated that KO mice showed decreased depression-like behavior and enhanced cognitive ability. Additionally, KO mice showed abnormalities in the tail suspension test (TST), which could be alleviated by acute administration of the mood-stabilizer valproic acid (VPA) [51]. Increased corticosterone secretion in HINT1 KO mice was also observed [51]. These behavioral and endocrine changes indicate that HINT1 participates in emotional regulation in the CNS, and its absence may lead to manic-like behavior. Furthermore, another study using HINT1 KO mice suggested HINT1 KO mice exhibited behavioral and molecular alterations paralleling those described in BP patients. Thus, HINT1 KO mice could be used as an appropriate model for studying BP and may help identify novel targets and drugs to treat this mental disorder [52].

Interestingly, Martins-de-Souza et al. [53] screened differential protein expressions in the DLPFC of postmortem brains from 24 patients with MDD and 12 controls and detected increased expression of HINT1 in patients with MDD without psychotic symptoms. Moreover, in a study using the chronic mild stress (CMS) depression model to explore the antidepressant effect of oleamide, proteomics analysis showed that the expression level of HINT1 protein in the hippocampus of the CMS group was increased [54]. These results indicate that in different episodes of mood disorders, HINT1 works exactly the opposite.

3.4. Anxiety Disorder. There is currently a shortage of clinical studies on the association between HINT1 and anxiety disorder, and results from preclinical studies are not consistent. Barbier et al. [36] conjectured that anxiolytic-like behaviors were included in HINT1 deficiency-induced emotional alterations [51]. While Varadarajulu et al. studied the behaviors of male HINT1 KO mice in a battery of tests. They concluded that *HINT1* KO mice exhibited increased anxiety-like behavior compared with that in WT mice [55]. What is more, Jackson et al. [56] found that in male HINT1 KO mice, the acute administration of nicotine resulted in production of anxiety-like responses rather than its anxiolytic effects, and administration of diazepam failed to induce anxiolytic responses. However, the anxiety-like behaviors described above were not observed in female *HINT1* KO mice, further supporting the aforementioned existence of gender differences in the behavioral impact of HINT1. All results from the anxiety studies were controversial, probably because of deviations in methods, experimental equipment, and animal age (e.g., Wang et al. often use older animals than Varadarajulu et al.).

3.5. Pain and Analgesia. The human μ-opioid receptor (MOR), a G protein-coupled receptor (GPCR), is the molecular target of morphine-induced analgesia and opiate-related addiction. Guang et al. [57] first discovered the specific interaction between HINT1 and the C-terminus of human MOR using a yeast two-hybrid system. This interaction reduced the desensitization and phosphorylation of MOR. Meanwhile, increased basic pain threshold and enhanced morphine-induced analgesic effects were found in *HINT1* KO mice. However, the dose-response curve indicated that KO mice exhibited a greater extent of tolerance to morphine-induced analgesia than WT mice. In addition, our group and Garzon's research team revealed that HINT1 deficiency could induce abnormalities in the hot-plate test, formalin-induced inflammatory pain, and CCI-induced neuropathic nociception [58–60]. In particular, Garzon and colleagues demonstrated that the inhibitor of HINT1 enzymatic activity, guanosine-5′-tryptamine carbamate (TpGc), significantly enhanced morphine antinociception and alleviated mechanical allodynia but prevented the development of tolerance to opioids [61]. These results show the negative regulatory effect of HINT1 in MOR-mediated morphine-induced analgesia. However, an association study of 2294 patients with cancer pain did not find a correlation between SNP mutations in the *HINT1* gene and opioid dose [62].

3.6. Drug Addiction. Association analysis from two independent samples indicates that mutations in the *HINT1* gene are associated with phenotypes of nicotine dependence. Further analysis of mRNA expression in human postmortem brain showed that smoking status and phenotype were associated with HINT1 expression [63]. Chronic nicotine administration elevated HINT1 expression in mouse NAc, which could then be reversed by a nicotine antagonist, mecamylamine, after 24 hours or drug withdrawal after 72 hours [63]. These results show a genetic association between HINT1 and nicotine dependence. Jackson et al. [64] employed the conditioned place preference (CPP) reward test and conditioned place aversion (CPA) test to evaluate emotional and somatic symptoms after nicotine withdrawal. Significant CPA after withdrawal was found in both *HINT1* KO and WT mice. In *HINT1* KO mice, however, nicotine failed to induce significant CPP and somatic withdrawal symptoms (e.g., hyperalgesia) were alleviated. This study could further support the conclusion that HINT1 plays a role in regulating behaviors associated with nicotine reward and withdrawal. However, in an open-label randomized trial of nicotine replacement therapy (NRT) covering 374 nicotine-dependent smokers, the results do not support the relationship between *HINT1* gene mutation and smoking cessation [65].

Relatively few studies have examined the role of HINT1 in addiction induced by other abused drugs. Romanova et al. [66] found that after a single injection of cocaine, HINT1 peak intensities increased significantly in the medial prefrontal cortex (mPFC) of low cocaine responder (LCRs) rats in the open field test. Previous studies showed that the LCRs were more sensitive to cocaine-induced behavioral sensitization compared to high cocaine responders (HCRs) [67, 68]. Increased cocaine CPP [69] and self-administration motivation [70] exhibited by LCRs suggests that LCRs are sensitive to cocaine addiction. Thus, HINT1 is highly expressed in the susceptible phenotype of cocaine addiction.

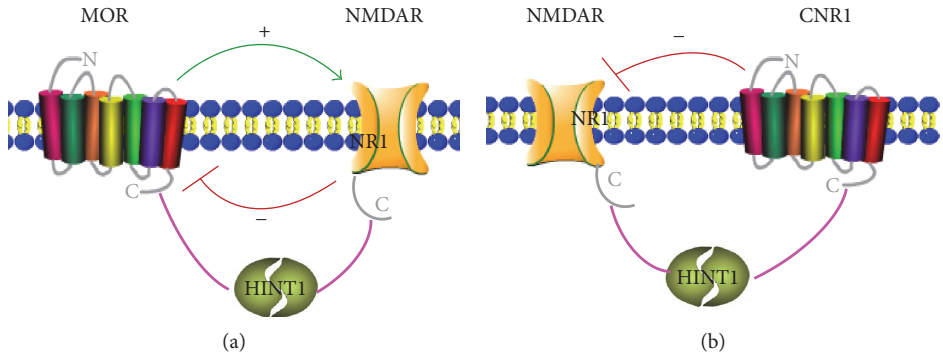

Figure 3: The pattern of HINT1 interacting with GPCRs. (a) HINT1 interacts with the C-terminus of μ-opioid receptor (MOR). HINT1 also interacts with the NR1 subunit of NMDAR. To prevent opioids from producing an excessive reduction of neuronal excitability, NMDARs are recruited to the MOR environment, where they become activated to restrain opioid signaling. In this context, HINT1 stabilizes the functional interaction between MOR and NMDAR. (b) HINT1 may also associate with cannabinoid receptor type I (CNR1). CNR1 can negatively regulate NMDAR function when the receptor is coupled to HINT1.

Our recent study has demonstrated that the HINT1 protein, particularly in the NAc, also plays a vital role in methamphetamine-induced CPP [71].

3.7. Down's Syndrome (DS). Weitzdoerfer et al. [72] used two-dimensional gel electrophoresis and mass spectrometry to analyze proteins in cortical tissue from aborted human fetus. They found that different kinds of early life proteins, including HINT1, that participate in neural differentiation, neural migration, and synaptic transmission were deficient in DS.

3.8. Brain Aging. Brain aging is one of the major high risk factors for many neurodegenerative disorders such as Alzheimer's disease (AD). Nevertheless, the molecular mechanisms of brain aging are complicated and still unclear. Rassoul et al. [73] analyzed differential transcriptome expression in the temporal cortex of the primate *Microcebus murinus*. Of 695 different genes identified among young healthy animals, old healthy animals, and AD-like animals, approximately 1/3 showed the same expression changes in healthy aging animals and AD-like animals, including the downregulation of HINT1 and HINT2. These findings indicate the possible contribution of HINT1 in the biological process of brain aging.

4. Potential Role of HINT1 in Neuroplasticity

As reviewed thus far, HINT1 is implicated in diverse neurological and neuropsychiatric diseases. Related to the latter, our studies have revealed that HINT1 is involved in SI mice model, which could induce behavioral abnormalities related to the core symptoms of certain neuropsychiatric disorders [39, 40]. Neuropsychiatric disorders are a class of diseases closely related to the environment and genetics. One of the core problems in neuropsychiatric disorders is abnormal changes in neuroplasticity [74]. Therefore, it could be hypothesized that HINT1 may play an important role related to neuroplasticity in neuropsychiatric disorders. Thus, HINT1 is a potential promising neuroplasticity mediator in neuropsychiatric diseases.

Actually, on one hand, HINT1 could trigger apoptosis independent of its enzymatic activity [14], while there is little research on the exact role of HINT1 in apoptosis. On the other hand, a growing body of evidence suggests that HINT1 acts as a molecular switch regulating the interaction and functional association between GPCRs and NMDARs. For example, HINT1 could stabilize the interaction between MOR/cannabinoid receptor type 1 (CNR1) and NMDARs, promoting (e.g., MOR) or reducing (e.g., CNR1) its glutamatergic activity (Figure 3) [57, 59, 60, 75–83]. HINT1 protein may also participate in conveying information mediated by GPCRs to different signaling pathways, especially the glutamate NMDAR-mediated neurotransmission and functional neural plasticity, such as long-term potentiation (LTP) [60, 76, 84]. Moreover, our accepted study indicated that under both basal and chronic immobilization stress conditions, compared to WT mice, HINT1 KO mice expressed more hippocampal BDNF [85], which is also a key molecule engaged in neuroplasticity [86, 87]. However, to understand the specific role of HINT1 in neuroplasticity, more in-depth study is needed.

5. Summary and Prospect

Since HINT1 was discovered to be involved in a variety of biological phenomena, the research interest in this protein has been increasing. Though many studies have aimed to elucidate its roles in cell physiology, the complete range of functions of HINT1 is yet to be determined. The known functions of HINT1, such as tumor suppression, nucleoside transferase, and hydrolase functions, are only a tiny fraction of the whole picture. Currently, treatments for human neuropsychiatric diseases rely on a very limited selection of drugs and therapies, primarily because of our superficial knowledge of the pathogenesis of these diseases. Reviewing the available literature on HINT1, we found that HINT1 is highly related to many neuropsychiatric diseases including schizophrenia, mood disorder, drug addiction, and so on, and HINT1 may participate in neuropsychiatric diseases as a potential neuroplastic mediator. While many studies describe the correlation

between HINT1 and neuropsychiatric diseases, few of them describe specific mechanisms. Thus, further study of HINT1 would be of potential value for expanding basic research, diagnosis, and treatment of neuropsychiatric and even psychosomatic diseases.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This research is supported by grants from the National Science Foundation of China (no. 81771435, no. 81371473, and no. 81171262), Natural Science Basic Research Plan in Shaanxi Province of China (no. 2016JM8078), and 2017 Open Research Fund of State Key Laboratory of Mechanical Manufacturing Systems Engineering (no. sklms2017002).

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Hindawi
Neural Plasticity
Volume 2017, Article ID 5870735, 16 pages
https://doi.org/10.1155/2017/5870735

Review Article

Neural Plasticity Is Involved in Physiological Sleep, Depressive Sleep Disturbances, and Antidepressant Treatments

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Received 6 April 2017; Revised 27 June 2017; Accepted 13 July 2017; Published 18 October 2017

Academic Editor: Bingjin Li

Depression, which is characterized by a pervasive and persistent low mood and anhedonia, greatly impacts patients, their families, and society. The associated and recurring sleep disturbances further reduce patient's quality of life. However, therapeutic sleep deprivation has been regarded as a rapid and robust antidepressant treatment for several decades, which suggests a complicated role of sleep in development of depression. Changes in neural plasticity are observed during physiological sleep, therapeutic sleep deprivation, and depression. This correlation might help us to understand better the mechanism underlying development of depression and the role of sleep. In this review, we first introduce the structure of sleep and the facilitated neural plasticity caused by physiological sleep. Then, we introduce sleep disturbances and changes in plasticity in patients with depression. Finally, the effects and mechanisms of antidepressants and therapeutic sleep deprivation on neural plasticity are discussed.

1. Introduction

Depression, which is characterized by a pervasive and persistent low mood and anhedonia, greatly impacts patients, their families, and society. It contributes largely to the global disease burden [1] and is associated with increased risks of several other diseases, which can further increase the economic burdens of individuals [2, 3]. In clinical practice, sleep disturbances are among the common complaints of depressed patients and negatively affect the quality of their lives. Studies demonstrated that sleep can facilitate neural plasticity, and changes in plasticity have been observed in depressed patients. However, therapeutic sleep deprivation exerts a rapid and robust antidepressant effect in patients with broadly defined depression. These facts raise the possibility that depression and accompanying sleep disturbances share a common origin. In other words, they may represent different phenotypes of the same pathophysiological process. To address this question, we first examine the macro- and microstructures of sleep and present evidence of how sleep facilitates neural plasticity. Then, we list the sleep disturbances and changes in neural plasticity in depression, including studies on humans and animals, and explain the common mechanisms. Next, we analyze the effects of antidepressants on neural plasticity and their mechanisms. Finally, we consider sleep deprivation as a therapy for depression and explain the consequences and mechanism in detail.

2. Sleep and Neural Plasticity

2.1. The Overall Structure of Sleep. Sleep or sleep-like state is ubiquitous to most living organisms. While awareness of the surroundings seems to be deliberately lowered or even blocked during the deepest stage of sleep, many processes continue to function. In terms of characteristics of the electroencephalogram (EEG), sleep in mammals can be divided into two distinct stages: rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM sleep in humans can be categorized further into 3 stages: stage 1 (N1), stage 2 (N2), and stage 3 (N3) [4]. N1 represents the transition from wake to sleep since predominant EEG activities shift from 14

to 30 Hz in wakefulness or 8–12 Hz in quiet rest to 4–7 Hz oscillations [5], while κ-complex events and sleep spindles occur in N2. κ-Complexes protect sleep from outside interference [6] and facilitate generation of sleep spindles [7], which usually last no more than 2 s and range from 11 to 15 Hz [8]. N3, which is a deeper NREM sleep stage compared with N1 and N2, is dominated by slow wave activity (SWA) ranging from 0.5 to 4 Hz that includes neocortical slow oscillations ranging generally from 0.5 to 1 Hz [5]. In addition, a special type of oscillation, known as sharp wave ripple (SWR) complexes, can be observed at the level of the hippocampus mainly during N3 [9, 10]. These SWR complexes, which range from 100 to 250 Hz, consist of sharp waves that originated in the CA3 region of the hippocampus and produce fast ripples in the CA1 region. In contrast, REM sleep is dominated by theta activity ranging from 4 to 8 Hz [11] and is associated with persistent muscle atonia and bursts of eye movement.

2.2. Generation of Different EEG Characteristics in Sleep. Our knowledge of intrinsic networks underlying different EEG activities grows as methodologies develop. For instance, SWA is a consequence of autonomous neocortical slow oscillations that result from interactions between excitatory and inhibitory neurons in the cortex [12]. Intracellular and extracellular recordings have demonstrated that the slow oscillation, which consists of up and down states, enters up state if an inside or outside signal stimulating the local cortical network is strong enough to counter local inhibition [13, 14] and the local network has passed its refractory period [14–16]. This local excitation spreads as positive feedback and leads to the synchronization visible in the EEG [12]. The thalamocortical neurons, which *in vitro* show strong intrinsic rhythms similar to the up and down states [8, 17, 18], are reciprocally connected with the cortex and depolarize in advance of the up states [14, 19–21]. Recent studies using optogenetics revealed that selective activation of thalamocortical neurons can induce the up state in the slow oscillation [22] and SWA [23]. These findings indicate that the thalamus is crucial in generating SWA [18] and implicate the thalamocortical network as an inseparable structure in regulating SWA [24]. Sleep spindles are generated by an interaction between thalamocortical relay cells and GABAergic neurons in the thalamic reticular nucleus [25–27]. Generation of theta activity, which is usually recorded at the hippocampus, involves the projection from the brainstem containing the center responsible for REM sleep [28] to the medial septum (MS) via the hypothalamus [29]. Pacemaker cells in the MS, which spontaneously fire in the valley of theta activity [30], provide inhibitory input to CA1 pyramidal cells [29]. The hippocampus also sends feedback to the medial and lateral septum [31], which synchronizes between the 2 structures. Conversely, the entorhinal cortex (EC) excites the hippocampus with cortical information via its direct glutamatergic projections to the CA1, CA3, and dentate gyrus [32, 33]. Recent studies showed that only the medial EC (MEC) appears related to generation of theta activity [34] and is also under control of GABAergic neurons in the MS [35]. Within the hippocampus, the oscillatory activation of the EC transmitted by the perforant path generates prominent theta activity in the dentate gyrus and then excites the CA3 and CA1 regions to compete with oscillatory inhibition driven by the MS. Furthermore, several other brain regions, such as the dorsal raphe nucleus (DRN), are also involved in control of theta generation through connections with the septal complex, which is composed of the MS as well as the vertical and horizontal limbs of the diagonal band of Broca [36]. In addition, pyramidal cells and interneurons in the medial prefrontal cortex (mPFC) can be excited by CA1 pyramidal cells from the ventral part of the hippocampus [37], and the amygdala complex, which is a critical interface for emotional responses, is reciprocally connected with the regions that are implicated in theta generation.

2.3. Implications of EEG Changes in Neural Plasticity. While the mechanisms of specific EEG activities have been elucidated, we still lack a universal theory to answer the mysterious question of why we sleep. One intriguing possibility is that sleep is needed because of neural plasticity, which is a process that fundamentally decides how we interact with the world [38, 39]. Neural plasticity is an umbrella term that may refer to structural alterations in the brain on a large scale, such as cortical remapping and changes in total weight, or on a microscopic scale, such as changes in size and density of neurons and glia. At the single cell level, synaptic plasticity describes the changes in strength of existing synapses, in synapse number or size, or in morphological structures that contain synapses [40].

The first line of evidence supporting a relationship between sleep and neural plasticity comes from patients suffering from insomnia. They exhibit reduced gray matter in subregions of the prefrontal cortex (PFC) [41, 42] and a smaller hippocampal volume [43, 44]. In addition, patients with primary insomnia show decreased sleep-dependent memory consolidation, which is commonly considered an indicator for neural plasticity, in procedural and declarative learning [45, 46].

Deeper examination of EEG studies, which directly and accurately reflect collective changes in the brain, reveals a profound link between sleep and neural plasticity. SWA is recognized as a measure of sleep need [47]. It increases with the prolongation of wakefulness and decreases gradually during sleep [48]. The increase of SWA during sleep has been shown to be directly associated with long-term potentiation (LTP) rather than prolonged wakefulness, since areas with increased LTP exhibit enhanced SWA while a reduction in LTP-related molecules blunts the SWA peak [49, 50]. Several studies have demonstrated that enhanced SWA is spatially and temporally associated with LTP during wakefulness [51, 52]. Computational studies indicate a relationship between stronger synaptic connections and higher SWA [53, 54]. Furthermore, studies found that approximately 5% of gene transcription in the rat cortex is under control of the sleep-wake cycle [55]. In particular, mRNA levels of genes associated with building new synapses and strengthening existing synapses increase in both cortical and hippocampal [55]. In addition, adenosine, which is closely associated with homeostatic regulation of sleep [56, 57],

has been reported to impact neural plasticity via adenosine A_1 receptors (A_1Rs) [58]. This is especially true in the hippocampus where extracellular levels of adenosine increase [59], and these increases colocalize with A_1Rs [60]. When the increase of extracellular levels of adenosine is attenuated, hippocampal LTP, which is low after sleep deprivation returns to normal. The same effect is observed when 8-cyclopentyl-1,3-dimethylxanthine, an A_1R antagonist, is chronically infused into the brain, which suggests that adenosine may play a role in regulation of hippocampal plasticity [61–63].

These lines of evidence give rise to the synaptic homeostasis hypothesis (SHY), which was developed by Tononi and Cirelli [64–66]. The main claims of the SHY are as follows: (1) Wakefulness is related to synaptic potentiation and increases in synaptic weight. (2) The amount of SWA during sleep adjusts according to the level of synaptic potentiation during preceding wakefulness in a spatiotemporal manner. (3) The increased SWA represents a generalized depression, namely downscaling [64–66]. This third claim is supported by reduced expression of synaptic markers [67, 68] and a net elimination of dendritic spines [69–71] during sleep. Indeed, when animals are placed in an enriched environment before sleep, expression of the immediate early gene, zif-268, is enhanced in REM and NREM sleep [72]. However, in comparison with activity-dependent synaptic scaling, this downscaling process should only affect recently potentiated synapses [65], which is conceptually different from long-term depression. A recent convincing study by de Vivo [73] using three-dimensional electron microscopy showed that the axon-spine interface (ASI) decreased by approximately 18% after sleep compared with during wakefulness. The animals were divided into 3 groups: (1) the spontaneous wake group in which brain tissues were obtained at 03:00, (2) the enforced wake group that was exposed to novel objects during day in which brain tissues were obtained at 15:00, and (3) the spontaneous sleep group in which brain tissues were obtained at 15:00. The ASI of animals in the spontaneous sleep group exhibited a significant reduction compared with the ASI of animals in the spontaneous wake and enforced wake groups, and the reduction was proportional to ASI size. This evidence is considered solid proof of the third claim in the SHY. Although some studies using sleep deprivation failed to find changes in markers of neuronal degeneration, stress, or apoptosis [74–76], there is certainly a mutual relationship between sleep and neural plasticity. However, a more elegant explanation is required to form a universal theory.

3. Mutual Mechanisms Underlying Sleep Disturbances and Neural Plasticity Anomalies within Depression

3.1. Sleep Disturbances and Neural Plasticity Anomalies within Depression. Depression is strongly associated with sleep disturbances [77]. Sleep disturbances are common complaints of patients suffering from depression, ranging from problems with falling asleep, frequent nocturnal awakenings, early morning awakenings, or a disturbed sleep duration [78, 79]. In turn, an epidemiological study showed that compared with persons free from sleep problems, individuals with insomnia are more likely to develop depression. The persistence of insomnia is associated with progress of new depressive episodes [80, 81].

Sleep EEG recordings provide more details on anomalies in sleep architecture. Delays in sleep onset, decreases in REM latency, and increases in REM sleep amounts along with sleep fragmentation are observed [82]. The cost of an increase in REM sleep is a reduction in NREM sleep, especially N3 [78]. Moreover, as an indicator of NREM sleep intensity, SWA should be highest in the first sleep cycle, and this is the case in the control subjects. However, in depressed patients, SWA is higher in subsequent sleep cycles [83], which suggests a suppressed generation of SWA.

In line with these findings, other studies indicate that depression is associated with changes in neural plasticity. The most concordant one is the observed decreased volume of the PFC and hippocampus [84–87]. Studies using rodent models revealed that stress can lead to atrophy and loss of neurons and glia in the PFC and hippocampus [88, 89], which is consistent with a decrease in synapse number in the PFC of patients with depression as demonstrated in postmortem studies [90]. In addition, repeated restraint stress induces a decrease in number and length of apical dendrites and spine synapses in pyramidal neurons of the mPFC [91]. Sleep fragmentation, which is a common sleep problem in depressed patients, causes a loss of N-methyl-d-aspartate (NMDA) receptor-dependent LTP in the hippocampal CA1 region [92]. Similarly, electrophysiological and immunoblotting studies indicate that insufficient sleep can impair LTP and facilitate LTD in the hippocampal CA1 area of mice, which is associated with selective augmentation of the number of NMDA receptor NR2A subunits and an increase in the NR1A/NR2B ratio [93, 94].

Recent studies suggest that the infralimbic PFC, which is responsible for processing emotional information, regulates the ventral tegmental areas (VTA) via the amygdala and ventral subiculum [95]. Thus, impaired functional connectivity of this circuit may lead to improper responses to rewards and anhedonia [96]. The ventral striatum is particularly crucial in coding and updating predictions about a reward based on previous experience, while the dorsal striatum is involved in defective action-reward contingency learning [97]. Therefore, it is not surprising to find aberrant activity in these 2 areas in depressed patients [98]. Interestingly, a recent study conducted by Oishi et al. using chemogenetics demonstrated that activation of VTA dopaminergic neurons induced a robust increase in wakefulness [99]. In contrast, the ventral striatum nucleus accumbens (NAc), which plays a key role in reward functions, has been found to increase sleep via dopamine D_2 receptors [100]. Moreover, the amygdala complex is known to regulate REM sleep based on reciprocal connections with ventrolateral periaqueductal gray (vlPAG) in the midbrain and the lateral pontine tegmentum (LPT) and sublaterodorsal nucleus (SLD) in the brainstem [101–103]. This overlap in neural circuitry of depression and sleep regulation may shed light on the mutual mechanisms that

account for genesis of depression, depressive sleep disturbance, and neural plasticity [58].

3.2. Mutual Underlying Mechanisms. Depression is classified as a neurochemical disorder and has long been considered a mood disorder in which stress plays a vital role via an impaired monoaminergic neurotransmitter, usually serotonin (5-HT) [104–106]. The serotonergic system in the brain is located at the DRN and median raphe nucleus (MRN). These 2 nuclei project to many wake-promoting brain regions such as the basal forebrain, thalamus, hypothalamus, and cortex [107]. In addition, the extended amygdala and PFC are also innervated by the DRN and MRN [107]. Recent studies utilizing optogenetics found that activation of 5-HT neurons induced an increase in wakefulness and sleep fragmentation [108] partially due to corelease of glutamate [109]. Moreover, the DRN and MRN inhibit the SLD during NREM sleep and wakefulness, while this inhibition withdraws during REM sleep and gives rise to the glutamatergic projection in the SLD to generate muscle atonia [110, 111]. In addition, the decreased inhibitory inputs from the DRN and MRN also disinhibit the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT) [28] and result in generation of theta activity via the ascending pathway targeting the MS [29]. 5-HT also participates in tuning the balance between excitation and inhibition [112]. In the brain, 16 types of 5-HT receptors have been identified [113], and the metabotropic 5-HT_{1A} receptors (5-HT_{1A}Rs) are the dominant type in the PFC [114]. The layer 5 pyramidal neurons (L5PyNs) of the PFC express 5-HT_{1A}Rs in both soma, initial parts of axons and dendrites [114–116]. Moreau et al. showed that 5-HT_{1A}Rs in L5PyNs play an important role in controlling output signals of the PFC. Although most postsynaptic 5-HT_{1A}Rs are expressed in glutamatergic neurons in the PFC, GABAergic neurons also express 5-HT_{1A}Rs and project onto the dendrites of pyramidal cells [114]. This appears to explain the anomaly of SWA in depression, which may be due to an imbalance of 5-HT_{1A}R modulation of excitation and inhibition [117, 118].

Dopamine is another monoaminergic neurotransmitter that has attracted much attention. As the last fully developed monoaminergic system in the brain [119], the dopamine system plays roles in many brain functions including locomotion, reward, motivation, learning, and cognition [120]. Although 5-HT is traditionally linked with the pathophysiology of depression, it may not account for other key characteristics of depression, such as anhedonia and amotivation [121], whereas dysfunction in the dopamine system is consistent with these characteristics [122]. Excessive physiological or emotional stress and subsequent anxiety can give rise to major psychiatric disorders such as depression [123]. When subjects are exposed to transient stressors, dopaminergic neurons in the medial VTA exhibit short-term inhibition [124]. However, following exposure to a prolonged stressor, activity of dopaminergic neurons in the medial-lateral VTA increases briefly before a prolonged suppression, and the level of dopamine in the PFC and NAc increases [125, 126]. Abnormal neuronal activity of the dopaminergic system can be normalized by inhibiting the hippocampus, and decreased responsivity of the dopaminergic system is driven by the amygdala [127, 128]. Further investigations revealed that in animal depression models utilizing stress factors, the hyperactive infralimbic PFC activates the amygdala, which then suppresses the VTA, especially the medial part, through GABAergic neurons in the ventral pallidum and reduces normal reward-related activity in this brain region [95, 129, 130]. In addition, stressors, such as forced swimming, increase the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/NMDA ratio of excitatory synapses on VTA dopaminergic neurons [131, 132]. This process of potentiation is initiated as soon as 2 h after stressor delivery and maintained at least 1 d [132], and blockade of both AMPA and NMDA receptors in the VTA can prevent increased dopamine levels in the PFC [133]. However, the reaction of VTA dopaminergic neurons to stress differs based on the projection site of these neurons. An increased firing rate is only found in neurons projecting to the NAc [134–137], while those projecting to the PFC decrease firing rate in the social defeat animals [138]. Nonetheless, when firing rate is restored to normal, social interaction behaviors also normalize [135, 136, 138]. A study by Tye et al. [129] using optogenetics to stimulate VTA dopaminergic neurons while blocking the dopamine receptors in the NAc failed to reverse depressive behaviors induced using a chronic mild stress model, which suggests an essential role of the VTA-NAc circuit in stress- and depression-related behaviors such as anhedonia [139]. Interestingly, the same VTA-NAc circuit also plays an important role in the mesolimbic dopamine system in regulating the sleep-wake cycle as mentioned above. Substantial evidence has shown that the VTA promotes wakefulness by modulating the NAc and receives glutamatergic, GABAergic, serotoninergic, and cholinergic modulation from other brain regions such as the LDT, PAG, and DRN [100]. Sleep-wake regulation of the NAc is under control of the PFC, ventral hippocampus, VTA, thalamus, and amygdala and is achieved by traditional direct/indirect pathways of the basal ganglia [100].

Adenosine, as an endogenous sleep promoter, is also involved in neural plasticity, and activation of A_1Rs suppresses LTP [140]. Zgombick et al. [141] proposed that since A_1Rs and 5-HT_{1A}Rs are colocalized and share G proteins in several brain regions, they may affect intracellular signaling cascades together. These effects are mediated by the cyclic adenosine monophosphate (cAMP) signaling pathway since A_1Rs are inhibitory G protein-coupled receptors. The cAMP-response element binding protein (CREB), which can be activated by the cAMP-protein kinase A (PKA) signaling pathway [9, 142], is vital to long-lasting hippocampal synaptic plasticity [143, 144]. In addition, expression of brain-derived neurotrophic factor (BDNF), which is a critical promoter of neurogenesis, neuronal survival and synaptic plasticity [145, 146], is under control of CREB [147]. BDNF decreases in expression and function in the PFC and hippocampus in animal models, which is crucial in the genesis of depression, as well as in the blood of patients with depression [148–150]. Blockade of BDNF release causes atrophy of neurons in the hippocampus [151] and mPFC [152] in mice, while heterozygous deletion of BDNF reduces spine density

and dendrite of neurons in the hippocampus and PFC along with a decreased volume of the hippocampus [153, 154]. Recent research suggests that adenosine A_{2A} receptors (A_{2A}Rs) are arguably more important than A_1Rs in homeostatic regulation of sleep [56]. However, little is known about their role in neural plasticity. Our work has demonstrated that increased REM sleep induced by bilateral olfactory bulbectomy is associated with A_{2A}Rs in the olfactory bulb and can be normalized by acute administration of fluoxetine, but depressive behaviors remain the same [155, 156]. While the REM-suppressing role of A_{2A}Rs in the olfactory bulb can be explained by mutual connections with REM-regulating nuclei in the brainstem via the piriform cortex and amygdala, depressive behaviors induced by bilateral olfactory bulbectomy seem to be long-lasting and need further investigation. Answering this question should increase our understanding of how adenosine regulates neural plasticity.

The largely overlapping mechanisms of sleep regulation and genesis of depression suggest that they may share common mechanisms, one of which, as we suggest in the current review, may be neural plasticity. Sleep dysfunction impairs neural plasticity and vice versa. Human patients who suffer from depression, as well as animal depression models, show changes in neural plasticity. However, it is unlikely that sleep disturbances lead to genesis of depression, because many other neurological disorders also involve sleep disturbance. In our point of view, genesis of depression changes neural function in regions of the brain that are important for sleep regulation. This then leads to sleep disturbances, which reduces sleep quality and further facilitates depression.

4. Neural Plasticity Involved in Antidepressant Treatment

4.1. Typical Antidepressants Restore Neural Plasticity. Despite the high rate of resistance and notably long delay before taking effect, typical monoamine-based antidepressants are still the first choice in treatment of depressed patients since they were discovered fortuitously more than 50 years ago [157]. Their appearance provided a possible interpretation of the biological basis of depression and guided development of a series of more specific medications in the following decades, including tricyclic antidepressants (TCAs), monoamine-oxidase inhibitors (MAOIs), selective norepinephrine reuptake inhibitors (NARIs), selective 5-HT reuptake inhibitors (SSRIs), 5-HT/NE reuptake inhibitors (SNRIs), and 5-HT2 receptor antagonist/reuptake inhibitors. However, the discrepancy between acute changes of extrasynaptic monoamine levels and their delayed onset of action implicates other more direct and rapid changes in addition to the altered monoamine neurotransmitter system in the neurobiological basis of depression.

Growing evidence indicates that chronic treatment with antidepressants enhances neural plasticity at both cellular and functional levels. Chronic treatment with the SSRI, fluoxetine, enhances LTP and synaptic transmission in the dentate gyrus of the hippocampus, upregulates dendritic spine density in the cerebral cortex and hippocampal CA1 and CA3 fields, and blocks atrophy of dendrites and spines caused by chronic stress exposure [158–160]. It also restores neuronal plasticity in the adult visual system of rats [161]. The change in synaptic plasticity may act through local BDNF and contribute to extinction of conditioned fear by remodeling memory circuitry [162]. Administration of fluoxetine and imipramine has been reported to remodel dendritic and synaptic contacts in the hippocampus and PFC after chronic stress exposure [163]. In addition, evidence suggests that treatment with tianeptine overcomes blocking of LTP induction caused by inescapable stress [164]. Moreover, amitriptyline and mianserin have been reported to reverse bulbectomy-induced reduction in dendritic spine density in the hippocampus [165]. These studies implicate an important role of neural plasticity in antidepressant effects of these conventional medications.

4.2. Mechanisms Underlying Changed Neural Plasticity

4.2.1. BDNF. BDNF is thought to play a pivotal role in the pathophysiology of depression and the neuroprotective effects of conventional antidepressants. It has been shown clearly that stress and glucocorticoids downregulate the expression of neurotrophins including BDNF and their receptors in the hippocampus [166, 167]. Postmortem studies also showed a decrease of BDNF protein and mRNA expression in the hippocampus of depressed suicide patients [168, 169], and this decrease can be reversed after chronic treatment with many different classes of antidepressants, including MAOIs, NARIs, SSRIs, and some atypical antidepressants [170, 171]. Furthermore, reduction of serum levels of BDNF in depressed patients can be partially normalized after administration of antidepressants [172, 173].

It is expected that BDNF can affect neural plasticity. Haploinsufficient BDNF mice have shorter and simplified CA3 dendrite spines [153]. Mice with a human loss-of-function BDNF gene variant, Val66Met, exhibit an impaired synaptogenesis in the PFC [152] and more prominent changes in dendritic spine density in the PFC and amygdala after stress [174]. In addition, their anxiety-related behaviors are increased and cannot be normalized by treatment with the antidepressant fluoxetine [174, 175]. Volunteers with the Val66Met polymorphism are more vulnerable to depressive symptoms if they are exposed to early-life stress [176]. Furthermore, heterozygous BDNF knockout mice show a blunted antidepressant effect of imipramine in the forced swim test [177]. Taken together, these studies support BDNF involvement in antidepressant effects and modulation of neural plasticity by conventional antidepressants.

4.2.2. Neuroplasticity-Related Signaling Pathways. The delayed action of typical antidepressant treatments suggests a role of receptor-coupled signal transduction proteins and their genes. Stress and depression disrupt BDNF, and tyrosine kinase B (TrkB) receptor mediated extracellular signal-regulated kinase (ERK) and thymoma viral proto-oncogene (Akt) pathways in the hippocampus and PFC [178]. Administration of antidepressants can rapidly activate TrkB, which is required for behavioral effects [179], and increase levels of

ERK1 and ERK2 in the hippocampus and PFC [180, 181]. Reduction in Akt activity in ventral tegmental dopamine neurons is associated with increased susceptibility to social defeat stress, while chronic antidepressant treatment increases active Akt levels [182]. Furthermore, evidence suggests that mitogen-activated protein kinase (MAPK) modulation plays an important role in the antidepressant response. Administration of a MAPK pathway inhibitor produces depressive-like behavior and blocks effects of antidepressants in rodents [183]. Postmortem studies revealed increased expression of a negative regulator of MAPK, MAPK phosphatase-1, in the hippocampus of patients with major depressive disorder. Similar results were observed in rat and mouse models of depression, and levels could be normalized by chronic antidepressant treatment [184].

Postmortem studies on depressed suicide patients have suggested a significant reduction in mRNA and protein levels of PKA and CREB in the hippocampus and orbitofrontal cortex [185]. Overexpression of CREB in the hippocampus of rats produces an antidepressant effect in learned helplessness and forced swimming tests [186]. Chronic administration of different classes of antidepressants increases levels of cAMP production, PKA activation, and expression of CREB in the PFC and hippocampus [171, 187, 188]. In addition, CREB phosphorylation and CREB-mediated gene transcription are upregulated by chronic antidepressant treatment [180, 189]. These observations suggest an important role of the cAMP-PKA-CREB pathway in antidepressant effects.

4.2.3. Glutamate Receptors (GluRs). Stress and depression can cause dendritic remodeling and reduction in synaptic spines, while enhancement of glutamate seems crucial for these structural and functional changes [190]. GluRs are involved in modulation of neural plasticity after chronic treatment with antidepressants. Chronic administration of antidepressants fluoxetine, desipramine, and reboxetine reduces depolarization-evoked glutamate release in the hippocampus [191]. Fluoxetine increases the phosphorylation of the AMPA receptor GluR1 subunit [192] and upregulates the expression of the NMDA receptor NR2A subunit, GluR1, and GluR2 in the forebrain [159]. An AMPA receptor antagonist can reverse most antidepressant actions of fluoxetine in stressed mice [193]. A similar effect was found in the antidepressant-like effect caused by administration of lithium in the mouse tail suspension and forced swimming tests [194]. Imipramine alters ligand binding to the NMDA receptor complex in the cerebral cortex and enhances the synaptic expression of GluR1 in the hippocampus, but attenuates glutamatergic transmission and field potentials in ex vivo rat frontal cortex slices [195–198]. These data suggest an important involvement of the glutamatergic system in antidepressant action. Therefore, GluRs may represent promising targets for antidepressant development.

4.3. Rapid-Acting Antidepressant Ketamine. Discovery of the noncompetitive NMDA receptor antagonist, ketamine, urges us to conduct further research on the mechanisms involved in depression and to develop novel fast-acting antidepressants. Compared with classical antidepressants, ketamine exerts a robust, rapid (within a few hours), and sustained (lasts for 1 week) antidepressant effect that can be induced by a single dose in patients with treatment-resistant depression [199, 200] and in animal models of depression [177, 201, 202].

4.3.1. Increased Neural Plasticity Caused by Ketamine and the Underlying Mechanism. Compared with traditional monoamine-based antidepressants, ketamine has a more direct and rapid influence on the glutamatergic system and synaptic plasticity. Ketamine rapidly reverses decreased expression of synaptic proteins and spine numbers as well as the frequency and amplitude of excitatory postsynaptic currents in PFC neurons caused by chronic stress exposure [203, 204]. Stimulus-evoked somatosensory cortical responses increase after ketamine infusion in patients with treatment-resistant depression, which suggests increased cortical excitability [205, 206].

Antidepressant effects of ketamine might be related to enhanced expression of AMPA receptors and BDNF [207, 208]. It was reported that ketamine reduced phosphorylation of eukaryotic elongation factor 2 kinase and disinhibited translation of BDNF [202]. However, another study showed that ketamine produced similar antidepressant-like responses in wildtype and heterozygous BDNF knockout mice, and it did not influence levels of BDNF or TrkB phosphorylation in the hippocampus [177]. The mammalian target of rapamycin (mTOR) pathway, as a downstream signaling cascade of BDNF, has been implicated in protein synthesis-dependent synaptic plasticity and can be interrupted in depression. Compared with healthy controls, expression levels of mTOR and its core downstream signaling target proteins, p70S6K, elF4B, and p-elF4b, are reduced significantly in depressed individuals [209]. Levels of regulated in development and DNA damage responses-1, an inhibitor of mTOR, increase in the PFC of patients with depression, along with a concurrent decrease in phosphorylation of signaling targets of mTOR [210]. Ketamine can activate the mTOR pathway, which leads to an increase in synaptic signaling proteins and new spine synapses. Blockade of mTOR signaling can completely block ketamine-induced synaptogenesis and behavioral responses in models of depression [203].

As a key component of the Wnt pathway and upstream of the mTOR signaling cascade, glycogen synthase kinase 3-β (GSK3-β) plays major roles in gene expression, cell behaviors, neurodevelopment, and regulation of neuronal plasticity [211]. It contributes to synaptic deconsolidation and shows increased levels in brains of patients with major depressive disorder [212]. A promoter single nucleotide polymorphism of GSK3-β (rs334558) is associated with delayed onset of depression [213] and an improved response to lithium salt therapy [96]. Antidepressant effects of ketamine require an inhibitory phosphorylation of glycogen synthase kinase-3 (GSK3) and can be potentiated when administered with the nonselective GSK3 inhibitor lithium chloride [154, 214].

4.3.2. SWA Changes as a Predicator of Ketamine-Induced Plasticity and Antidepressant Effects. SWA is considered a

sensitive marker of cortical synaptic strength and synchronization [215–217]. In patients with depression, SWA and delta sleep ratio (DSR, the ratio of SWA between the first 2 NREM sleep episodes) tend to be lower [83, 218]. Reduction in delta power during NREM sleep is linearly associated with improved negative affect in major depressive disorder [219]. The measure of distribution of SWA and DSR might be a more robust predictor of clinical response and recurrence to antidepressant therapy than REM sleep latency. A higher DSR may indicate more favorable therapeutic outcomes [83, 218]. Similar to some conventional antidepressants [218, 220], administration of ketamine increases SWA and DSR in rats [221] and individuals with depression [222, 223]. It is noteworthy that the decrease in plasma BDNF levels of depressed patients is proportional to the change in EEG parameters [223]. These studies suggest a role of SWA and DSR in predicating ketamine-induced neural plasticity changes and antidepressant effects.

5. Neural Plasticity Involved in Antidepressant Effects of Therapeutic Sleep Deprivation (SD)

5.1. SD Therapy for Depression. Since it was first found to benefit depressed patients in the 1970s, therapeutic SD has been widely used as a rapid antidepressant treatment. SD shows a rapid and robust antidepressant effect in patients with broadly defined depression, including some difficult-to-treat conditions [224, 225]. The effect of therapeutic SD is highly reproducible and substantial, but transient. Most patients relapse after 1 night of sleep or even short naps [225, 226], which limits SD as the first-line treatment for depression. Some new clinical strategies have been developed to sustain the efficacy of SD, including combining SD with chronobiological techniques (light therapy and sleep-phase advance) or antidepressants [227–229].

5.2. SD and Neural Plasticity

5.2.1. Changed Sleep Homeostasis and Neural Plasticity. Similar to other rapid-acting antidepressant treatments such as rapid-acting NMDA receptor antagonist or electroconvulsive therapy, SD regulates neuronal inhibition-excitation balance in the brain. Nocturnal sleep following SD in patients who respond positively to SD therapy show a higher rebound of sleep wave sleep (SWS) compared with those that respond negatively [88]. Studies have suggested that changes in SWA may be associated with the therapeutic outcome of SD, and a high baseline DSR is a positive predictor for SD response [230]. A SWS deprivation test proved that a reduction in depressive symptoms was correlated with overnight dissipation of frontocentral SWA on baseline sleep, rebound in right frontal all-night SWA on recovery sleep, and amount of REM sleep on the deprivation night [231]. These data indicate a change in sleep homeostasis of depressed patients during SD therapy.

Neuroplasticity also contributes to antidepressant effects of therapeutic SD. SD was reported to increase dendritic spine density in the dentate gyrus of the hippocampus, which was associated with upregulation of Wnt signaling gene Wnt 7a and activation of the innate immune system of the brain. Increased expression of the immediate early Arc/Arg3.1 suggests an increased neuroplasticity [232]. In addition, similar to the rapid-acting NMDA receptor antagonist ketamine, an increase in inhibitory phosphorylation of the signaling protein GSK3-β contributes to the antidepressant effect and synaptic potentiation of therapeutic SD [67]. Its single nucleotide polymorphism, rs334558, influenced acute antidepressant response of SD and showed a better mood elevation [233]. A role for glutamatergic neurotransmission has also been reported. A molecular imaging study demonstrated that therapeutic SD induced an increase of cerebral functional mGluR5 availability, which is consistent with reduced density of mGluR5 in depressed patients [234]. Moreover, increased cortical plasticity, indicated by increasing cortical excitability, was reported during repeated SD in patients with bipolar disorder, which paralleled and predicted the antidepressant response to SD. This may be a major effect of successful antidepressant treatments, and patients who do not respond may experience persistent impairment in neuroplasticity mechanisms [235].

5.2.2. A Synaptic Plasticity Model of SD in Depression. According to the classic 2-process model of sleep regulation, depression develops because of a deficient build-up of homeostatic process S with an unaffected circadian process C. Therapeutic SD benefits from a transient increase of process S [236]. When linked to the recent SHY where synaptic strength changes during the sleep/wake cycle, the therapeutic effect of SD is likely due to changed synaptic potentiation [65, 71].

A rat study showed that electrically induced LTP was occluded partially during prolonged SD and restored after sleep [237]. However, prolonged wakefulness beyond a physiological duration did not further increase spine density [69]. Therefore, Wolf et al. [238] concluded that SD might lead to excessively high cortical excitability and saturation of synaptic strength and, consequently, to partial occlusion of LTP inducibility. They further postulated a window of optimal associative synaptic plasticity (LTP inducibility) during wakefulness. After sleep (insufficient upscaling) and extended periods of sleep deprivation (saturation), LTP inducibility is reduced. Based on this, a synaptic model was proposed. It was hypothesized that in patients with depression, LTP inducibility is impaired and the window of optimal associative plasticity may not extend through a normal waking period because the ability to generate cortical LTP diminishes. Therapeutic SD enhances cortical synaptic strength and therefore shifts deficient LTP inducibility in depressed patients to a more favorable window of associative plasticity. Namely, in healthy controls, SD leads to synaptic saturation and deficient LTP inducibility, but it compensates for attenuated synaptic plasticity in the brains of patients with depression and finally evokes an antidepressant effect. The model builds on changed synaptic strength and cortical excitability in healthy people and depressed patients during different stages of wake/sleep cycles. It explains the paradoxical role of SD in dampening neural plasticity in healthy controls and improving clinical symptoms in patients with

depression. Further research must be done to evaluate the validity of this model.

6. Conclusion

In this review, we summarize the latest progress on the mechanisms of interactions between sleep, depression, and neural plasticity. Although there have been much excitements with recent progress in sleep-related methods to treat depression via regulation of neural plasticity, further development and clinical application are needed to elucidate the mechanisms and their effects.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Meng-Qi Zhang and Rui Li contributed equally to this work.

Acknowledgments

This study was supported in part by grants-in-aid for scientific research from the National Natural Science Foundation of China (81571295, 31530035, 31271164, and 81420108015); the National Basic Research Program of China (2015CB856401); a key laboratory program of the Education Commission of Shanghai Municipality (ZDSYS14005); and the Shanghai Committee of Science and Technology (14JC1400900).

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Hindawi
Neural Plasticity
Volume 2017, Article ID 9160515, 11 pages
https://doi.org/10.1155/2017/9160515

Research Article

Neural Plasticity Associated with Hippocampal PKA-CREB and NMDA Signaling Is Involved in the Antidepressant Effect of Repeated Low Dose of Yueju Pill on Chronic Mouse Model of Learned Helplessness

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Received 15 April 2017; Revised 16 July 2017; Accepted 3 August 2017; Published 17 September 2017

Academic Editor: Bingjin Li

Yueju pill is a traditional Chinese medicine formulated to treat syndromes of mood disorders. Here, we investigated the therapeutic effect of repeated low dose of Yueju in the animal model mimicking clinical long-term depression condition and the role of neural plasticity associated with PKA- (protein kinase A-) CREB (cAMP response element binding protein) and NMDA (N-methyl-D-aspartate) signaling. We showed that a single low dose of Yueju demonstrated antidepressant effects in tests of tail suspension, forced swim, and novelty-suppressed feeding. A chronic learned helplessness (LH) protocol resulted in a long-term depressive-like condition. Repeated administration of Yueju following chronic LH remarkably alleviated all of depressive-like symptoms measured, whereas conventional antidepressant fluoxetine only showed a minor improvement. In the hippocampus, Yueju and fluoxetine both normalized brain-derived neurotrophic factor (BDNF) and PKA level. Only Yueju, not fluoxetine, rescued the deficits in CREB signaling. The chronic LH upregulated the expression of NMDA receptor subunits NR1, NR2A, and NR2B, which were all attenuated by Yueju. Furthermore, intracerebraventricular administration of NMDA blunted the antidepressant effect of Yueju. These findings supported the antidepressant efficacy of repeated routine low dose of Yueju in a long-term depression model and the critical role of CREB and NMDA signaling.

1. Introduction

Major depressive disorder (MDD) is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being [1]. MDD afflicts approximately 16 percent of the world's population at some point in their lives [2, 3]. Although a number of antidepressants, such as the first-line selective serotonin reuptake inhibitors (SSRIs), are available, a remarkable population of patients never attain sustained remission of their symptoms [4, 5]. These and other disadvantages such as delayed onset of efficacy of SSRIs challenge the traditional monoamine-based hypothesis of depression, and emerging evidence favors the neural plasticity hypothesis which proposes an important role of the impaired neural plasticity including neurotrophic factors, cAMP response element binding protein (CREB) signaling, synaptic plasticity influenced by N-methyl-D-aspartate (NMDA) signaling, adult neurogenesis in depression, and neural plasticity as the crucial targets for antidepressant action [6, 7].

CREB signaling, activated by one of the classic upstream activator protein kinase A (PKA), regulates expression of genes that promote synaptic and neural plasticity, including proteins for spine formation [8, 9]. Both human and experimental studies supported the link of PKA-CREB signaling to depression and its treatment [10].

Brain-derived neurotrophic factor (BDNF) is one of the best studied neurotrophic factors implicated in depression and antidepressant effect [11]. Activation of PKA-CREB signaling is also capable to upregulate BDNF expression. Additionally, Increasing number of studies suggest *N*-methyl-D-aspartate (NMDA) receptors (NMDAR) are profoundly associated with depression [12, 13]. NMDARs are glutamate ionotropic receptors that play an important role in synaptic transmission and plasticity. Some NMDAR antagonists were identified to rapidly induce antidepressant effect by instant upregulation of expression of BDNF and spine formation [14, 15]. Therefore, enhancement of neural plasticity can result from activation of PKA-CREB or inhibition of NMDA signaling.

The learned helplessness (LH) procedure is one of the validated animal models of depression, extensively used to model stress-induced depression-like behavior in rodents [16–19]. It represents a model with good face, construct, and predictive validity [20] and has been shown in subpopulation of MDD patients. In the model, animals are exposed to unpredictable and uncontrollable stress, such as electroshocks, and then develop coping deficits in aversive but escapable situations [21]. As a relatively short and reliable stress-induced model, a variety of LH procedures have been developed. However, few of previous studies investigated the validity of a model with long-term depressive-like symptoms, which is a typical and obligatory feature for clinical depression. Long-term model is relatively more informative to uncover the mechanisms of the disorder and long-term efficacy of antidepressants.

To develop novel antidepressant therapy, some attention has been paid to integrative medicine [22]. Yueju pill, a traditional Chinese herbal medicine formulated 800 years ago to treat mood disorders related syndromes has been used to treat MDD and contain multiple compounds with antidepressant potential [23–25]. More recently, a relative high dose of Yueju demonstrated rapid antidepressant efficacy in both preclinical and clinical studies [26, 27]. However, as a nonprescription drug in oriental medicine, the routine dose of Yueju has not been tested scientifically for antidepressant effect previously. Here, we developed a long-term learned helplessness depression model to test the therapeutic effects of Yueju. Additionally, PKA-CREB and NMDA signaling, as well as BDNF was examined in the mice subjected to routine dose of Yueju following chronic learned helplessness procedure. Finally, the role of NMDA signaling in Yueju's action was further verified by using intracerebroventricular pharmacological infusion approach.

2. Materials and Methods

2.1. Animals. Male and female Kunming mice were obtained from the China Academy of Military Medical Sciences (Beijing). Mice aged approximately 6 weeks old (18–24 g) were habituated to animal facilities for 7 days prior to behavioral testing. All animal experiments were in accordance with the Guide for the Care and Use of Laboratory Animals approved by the Institutional Animal Care and Use Committee at Nanjing University of Chinese medicine.

2.2. Drugs. Fluoxetine (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in 0.9% saline. The OCT Yueju pills (Jiangsu 707 Natural Pharmaceutical Co. Ltd., lot number 150801) were ground into powder and dissolved with 0.9% saline with different doses. The solutions of the Yueju, fluoxetine, and vehicle were administered to the mice via intragastric administration, and the concentration of the solution was 1 mg/ml. The dose for fluoxetine was 18 mg/kg/day, and N-Methyl-D-aspartic acid (Sigma-Aldrich, St. Louis, MO, USA) was administered by intracerebroventricular infusion (i.c.v.), 1 pmol/3 μl. All drugs were dissolved in 0.9% saline.

2.3. Behavioral Tests. All behavioral tests were performed during the late light phase. Animals were transferred to the testing room and habituated to the room conditions for at least 1 hour before the beginning of the behavioral experiments. Behavioral testers were blinded for experimental groups.

2.3.1. Open Field Test. Mice were placed in individual open field arena ($40 \times 40 \times 40$ cm) and allowed to freely explore for 2 hours. A camera was mounted above the open box for recording locomotor activity. The entire test arena was adjusted to even illumination. Mice were placed in the center of the arena and all owed to freely explore for 5 minutes. The total distance traveled and time spent in the central area was measured. The testing apparatus was thoroughly cleaned before each animal using 70% ethanol.

2.3.2. Tail Suspension Test. The apparatus is consisted of four chambers. The front of the box was open, and a bar was placed horizontally 1 cm from the top with an attached vertical bar hanging down in the center. Mice were individually suspended 1 cm from the tip of the tail to the vertical bar with adhesive tape. A camera positioned in front of the TST box was used to record the animals' behavior for 6 minutes. The software analysed the Immobility time of the last 4 minutes. Mice were returned in individual cages and remained so until the end of the experiment.

2.3.3. Forced Swim Test. Mice were placed in a clear Plexiglas cylinder (25 cm high; 10 cm in diameter) filled to a depth of 10 cm with 23–25°C water. A camera recorded the 6-minute swim session. The immobility of the mice was measured during the last 4 minutes of the test. Immobility in this test was defined as they floated passively in water.

2.3.4. Novelty-Suppressed Feeding Test. After fasting for 24 hours, the mice were habituated for 2 hours in the experimental environment and placed in a new cage. The center of the cage placed an already weighed grain. Each mouse was placed in a corner of the box and allowed to explore for up to 10 minutes. The trial ended when the mouse chewed a part of the chow. The amount of food consumed in the home cage was taken as the weight of chow consumed in 10 minutes. Food consumption is the weight of chow consumed divided by the weight of the mice. The time the mouse

first started to consume the food pellet was recorded as the latency.

2.3.5. Learned Helplessness (LH) Test. LH consists of two stages: training stage and testing stages.

In the training stage, regular LH paradigm was carried out as described previously [28]. LH was performed in a shuttle cage ($40 \times 10 \times 13$ cm) that was divided equally into two chambers. Learned helplessness was induced in mice by administering 120 scrambled, inescapable foot shocks (0.45 mA shock amplitude, 15 s duration, 18–44 s average interval) over a 1 h session. For chronic LH paradigm, mice were trained for 3 consecutive days as described, followed by two additional intermittent training on day 8 and day 13. Control animals were exposed to the apparatus for the same period without receiving foot shocks.

In the testing stage, each mouse was given 30 shuttle escape trials with 3 s duration and 18–44 s intervals. The door was raised at the beginning of the shock, each trial was terminated when the mouse crossed into the nonshock compartment. Latency to escape and the number of escape failures were recorded automatically by software.

2.4. Stereotaxic Surgery and Microinjection. Mice were anesthetized and implanted with a guide cannula (3.3 mm) into lateral ventricle using a procedure described previously with some modifications [29]. The skull surface was first coated with 3% hydrogen peroxide. After the guide cannula was inserted into the lateral ventricle (coordinates: 0.6 mm posterior, 1.1 mm lateral, and −2.5 mm ventral to the bregma), Kerr Prime was applied onto the skull and cannula surface. Finally, the dental cement was used to fill the area around the cannula, and a dummy cannula was inserted into the guide cannula to maintain the cannula patency. Animals were individually housed, handled daily, and allowed to recover for 7 days after surgery.

All microinjections were performed on conscious, unrestrained, and freely moving mice in the cage. On the experimental day, a PE tubing connected to a 5 μl syringe was inserted into the guide cannula and extended 1 mm beyond the tip. Drugs or vehicle was infused laterally in a volume of 3 μl over 2 minutes. An additional 5 minutes was allowed for diffusion and prevention of backflow through the needle track before the injector was withdrawn. Mice were divided into four different treatment groups, including vehicle + saline, YJ + saline, YJ + NMDA, and vehicle + NMDA. Mice first received intracerebroventricular injection of NMDA (1 pmol/3 μl) or vehicle and 30 minutes later were given intragastric administration of YJ (2 g/kg) or saline. Thirty minutes after YJ administration, mice were subjected to the OFT, TST, FST, and NSF.

2.5. Western Blot. The whole hippocampus was lysed in RIPA buffer containing protease inhibitors and phosphatase inhibitors. Protein concentration was determined colorimetrically by BCA assay (Pierce, Rockford, IL, USA). Protein lysates were separated by 12% SDS-PAGE electrophoresis and were transferred onto polyvinylidenedifluoride (PVDF) membranes. After blocking with 1% BSA for 1 hour, the membranes were incubated with primary antibodies. BDNF (SantaCruz Biotechnology, sc-546, 1 : 200), P-CREB (Cell Signaling Technology, 9198s, 1 : 500), CREB (Cell Signaling Technology, 9197, 1 : 500), PKA (Proteintech, 55388-1-AP, 1 : 1000), NMDAR1 (Cell Signaling Technology, 5104s, 1 : 1000), NR2A (Cell Signaling Technology, #4205, 1 : 1000), NR2B (Cell Signaling Technology, 4212s, 1 : 1000), and tubulin (Proteintech, 10094-1-AP, 1 : 2000) were used at 4°C overnight. The next day, blots were washed 3 times in TBST, followed by incubation with horseradish peroxidase-conjugated secondary antibodies for 1 hour. After the last wash for 3 times, the blots were visualized using the SuperSignal West Pico Chemiluminescent Substrate (Thermo Fisher Scientific Inc.). BDNF and pro-BDNF were normalized to tubulin bands, and P-CERB and total CREB bands were taken as a ratio of tubulin bands. All experiments were performed 3 times.

2.6. Statistics Analyses. Two-sample comparisons were carried out using two-tailed Student's *t*-test; multiple comparisons were made using one-way ANOVA, followed by the Bonferroni multiple comparison tests. Two-way ANOVA was used for the analysis of behavioral effects of NMDA, and Yueju in the TST, FST, and OFT. Analyses of variance with repeated measures were used in LH treatment at different time points. All data are presented as mean ± SEM, and statistical significance was accepted at the 5% level unless otherwise indicated.

3. Results

3.1. 2 g/kg Yueju Was Effective in Inducing Antidepressant Effect. The dose range from 1 g to 3 g/kg in mice was approximate to the routine use of Yueju nonprescriptively, and they were selected for testing antidepressant effect using TST, FST, and NSF. Only 2 g/kg of Yueju significantly reduced immobility time in the TST ($p < 0.05$) at 1 hour and FST ($p < 0.05$) at 3 hours post administration (Figures 1(a) and 1(b)). This dose of Yueju also reduced the latency to eat in NSF ($p < 0.05$, Figure 1(c)) at 24 hours and increased the food consumption ($p < 0.05$, Figure 1(d)) at 72 hours. Interestingly, it did not alter food consumption at 24 hours or latency at 72 hours (both $p > 0.05$). The dose of 1.5 g/kg effectively decreased the immobility time in the FST ($p < 0.05$) but not TST (Figure 1(b)). Collectively, 2 g/kg Yueju was an optimal dose that effectively elicits antidepressant response. To confirm the effect, an independent cohort of animals were tested for TST and FST quickly and one day after Yueju administration. The effect on TST ($p < 0.05$) at 1 hour and FST ($p < 0.05$) at 3 hours was replicated. Furthermore, the antidepressant effect was also detected at 24 hours for TST ($p < 0.05$) and 26 hours for FST ($p < 0.05$). Administration of Yueju did not affect the time spent in central area or total distance in the open field test (data not shown). Therefore, the dose of 2 g/kg was an effective dose and used in the following experiments.

3.2. An Intermittent Training following a 3-Day Training Period Resulted in a Long-Term Learned Helpless Activity. Firstly, we tested the persistent time of learned-helpless

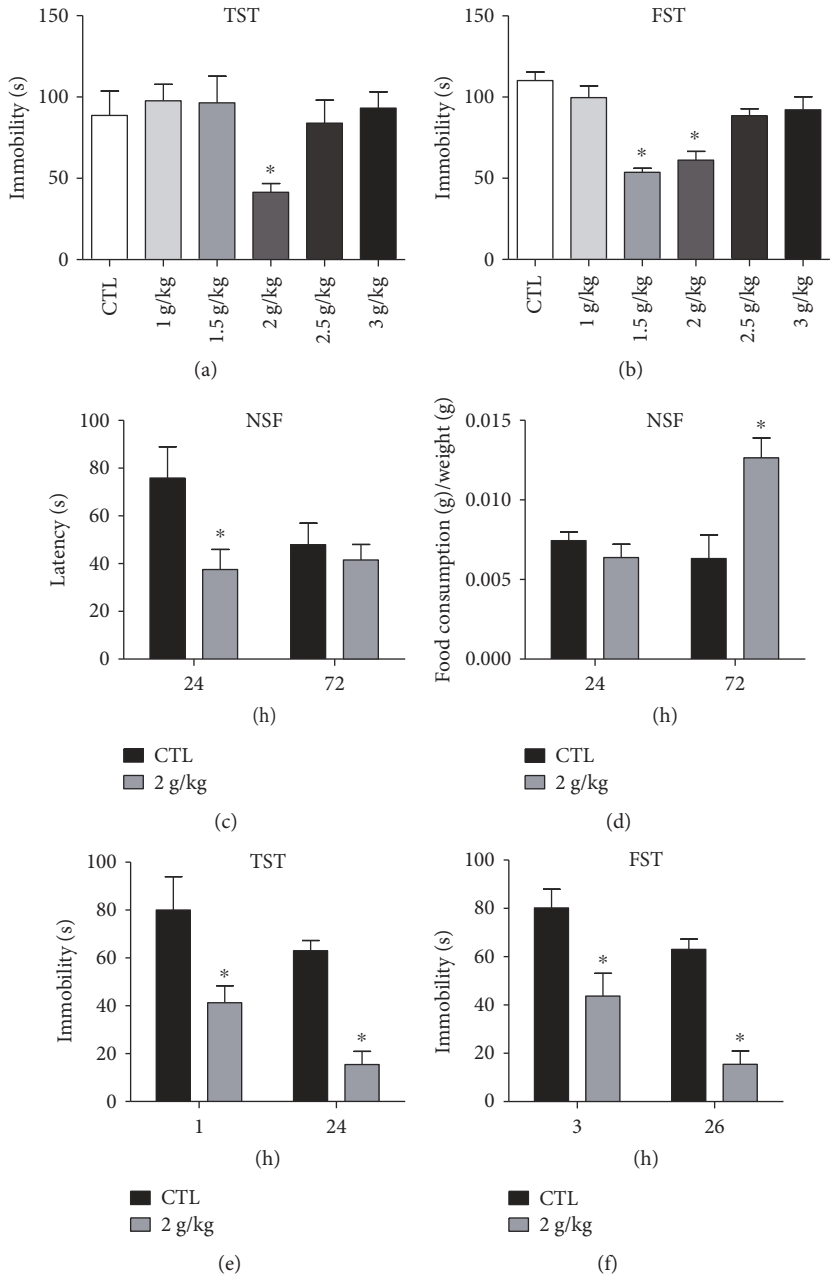

Figure 1: Screen of effective antidepressant dose of Yueju. The doses of YJ with 1 g/kg, 1.5 g/kg, 2 g/kg, 2.5 g/kg, and 3 g/kg were used for test. (a) There was significant treatment effects on tail suspension test (TST) performed 1 hour after a single administration of YJ (ANOVA, $F(5, 51) = 2.918$, $p < 0.05$) and (b) on forced swimming test (FST) carried out at 3 hours post administration (ANOVA, $F(5, 49) = 15.05$, $p < 0.01$). Mice were also tested for NSF at 24 h and 72 h after administration of 2 g/kg YJ (c, d). In the separate group of animals, animals were treated with 2 g/kg and tested with TST at 1 h and 24 h (e), as well as FST at 3 h and 26 h after administration YJ (f). Immobility time was measured for the last 4 min during the 6 min testing time for TST or FST. Data are means ± SEM. $^*p < 0.05$, compared with control group.

activity following the regular 3-day training paradigm. Animals were tested at 3 days and 6 days after the termination of training (Figures 2(a) and 2(b)). The repeated measures with the regular 3-day training did not show significant effects for time ($F(1, 12) = 0.039$, $p > 0.1$ for escape failure, $F(1, 12) = 2.995$, $p > 0.1$ for latency). The interaction between treatment and time had no difference ($F(1, 12) = 0.852$, $p > 0.1$ for escape failure, $F(1, 12) = 0.013$, $p > 0.1$ for latency). Post hoc analyses showed that both the latency to escape ($p < 0.05$) and frequency of escape failure ($p < 0.05$) was significantly different between the model and control animals at 3 days post training. However, after 6 days, only frequency of escape failure remained a deficit whereas there was no difference in latency to escape (Figures 2(a) and 2(b)), indicating that the learned helpless response has begun to diminish. To extend the duration of learned helplessness, a cohort of animals received two additional trainings 5 and 10 days posttermination of 3 days training. Animals were

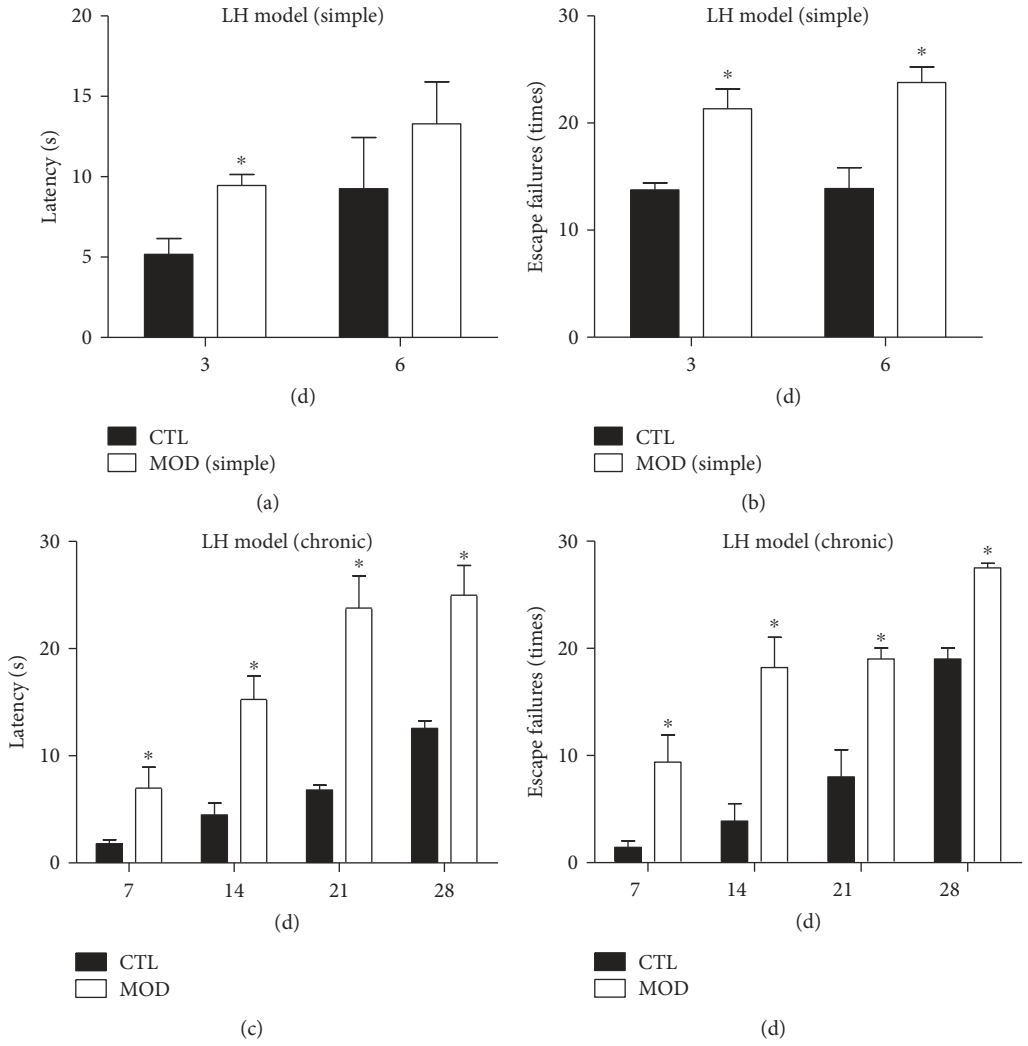

Figure 2: Duration of learned helpless response in two different models. On the top panel, escape failures and latency to escape was measured at 3 and 6 days post regular 3-day training paradigm (a, b). On the bottom panel, escape failures and latency to escape was measured weekly for 4 weeks following the 3-day plus 2 intermittent training paradigm (c, d). Control animals (CTL) received no training, MOD-simple group received 3-day training, and MOD received 3 days plus 2 intermittent training. Data are means ± SEM. $^*p < 0.05$, compared with control group at the same time points, repeated measures, followed by t-test.

tested weekly until the fourth week post the last training (Figures 2(c) and 2(d)). The repeated measures showed significant effects for latency ($p < 0.01$) but not escape failure ($p > 0.05$). The analysis with the latency showed significant effects for time ($F(3, 36) = 6.996$; $p < 0.05$). Post hoc analyses showed that, from 7 to 28 days, both latency to escape and frequency of escape failure was significantly increased ($p < 0.05$), indicating the deficits lasted at least for 4 weeks.

3.3. Chronic Administration of Yueju Reversed the Learned Helplessness and Depressed Phenotype of Mice. Animals received 2 weeks administration of Yueju (YJ) or fluoxetine (FLX) following the chronic learned helpless paradigm and tested for LH, as well as OFT, TST, FST, and NSF (Figure 3(a)). The four groups have no difference in the total distance traveled or central time (data not shown). In the LH test, animals still demonstrated learned helpless behavior, and Yueju restored it in terms of both latency ($p < 0.05$ versus Veh) and escape failure ($p < 0.001$ versus Veh), without difference from the control group (Figures 3(b) and 3(c)). In contrast, chronic administration of fluoxetine failed to reverse either measurement in learned helplessness (both $p > 0.05$ versus Veh) and remained deficient (both $p < 0.05$ versus CTL). Additionally, animals also displayed other depressive responses, indicated by increase in immobility time in TST and FST, increased latency to eat in NSF, and reduced food consumption in NSF (all $p < 0.05$ versus CTL). Compared to the vehicle group, YJ significantly reduced the immobility time in TST ($p < 0.001$) and FST ($p < 0.05$), decreased latency to eat ($p < 0.01$), and increased food consumption ($p < 0.01$) in NSF. Chronic fluoxetine only restored TST ($p < 0.05$) and latency to eat ($p < 0.01$) in NSF. It did not improve the learned helplessness, neither did it alter immobility time in FST or food consumption in NSF (Figures 3(d), 3(e), 3(f), and 3(g)). In summary, repeated administration of 2 g/kg Yueju displayed full spectrum of

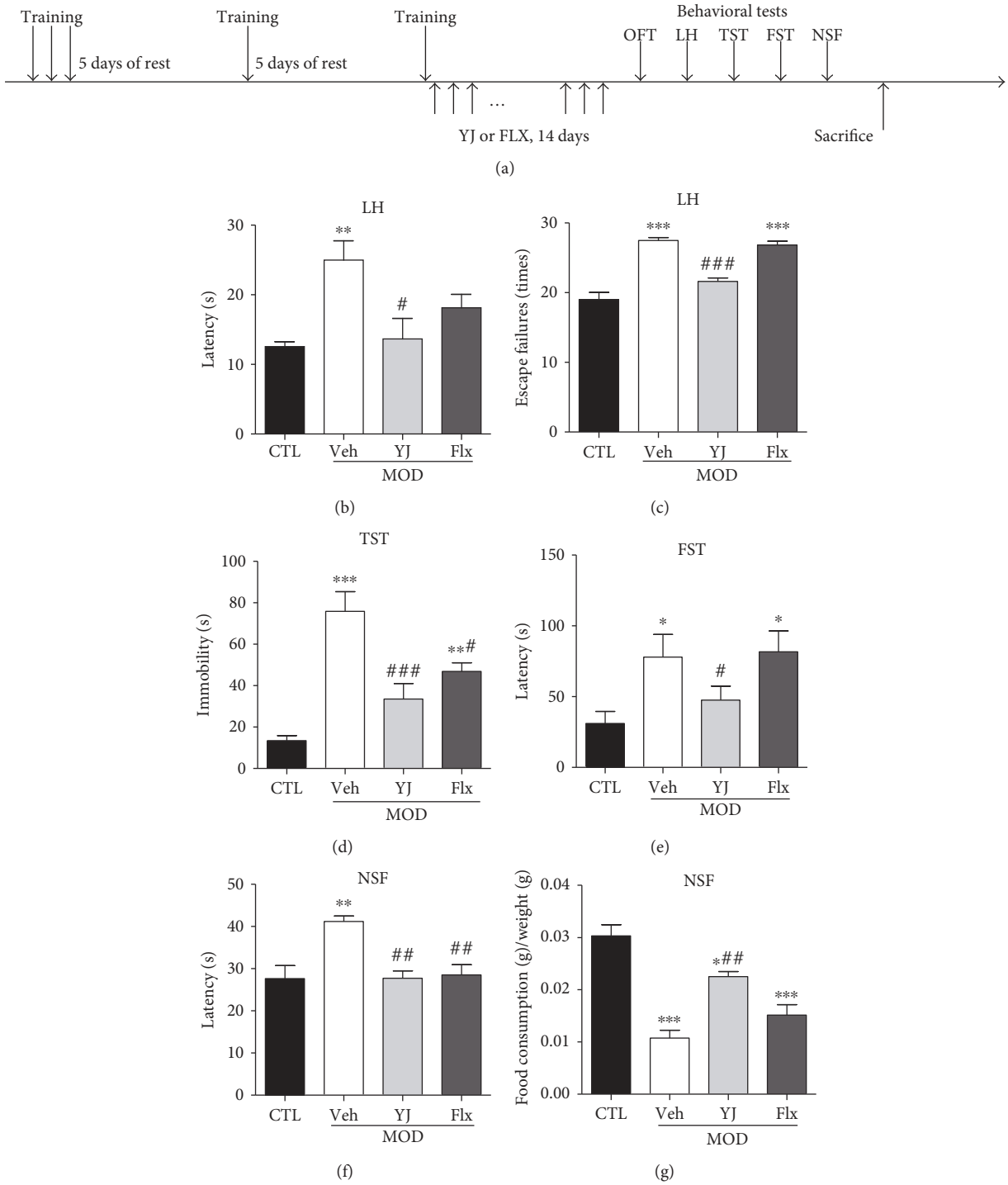

Figure 3: Behavioral effects after fluoxetine and Yueju treatment following chronic learned helplessness procedure. The timeline of the procedure is illustrated (a). Control animals (CTL) received vehicle treatment and no training, and animals exposed to chronic LH received administration of vehicle (Veh), Yueju (YJ), or fluoxetine (Flx) for 14 days. There were significant treatment effects on escape failures (ANOVA, $F(3, 31) = 6.526$, $p < 0.05$) and latency (ANOVA, $F(3, 31) = 44.98$, $p < 0.05$) (b, c). TST (ANOVA, $F(3, 31) = 16.77$, $p < 0.05$) and FST (ANOVA, $F(3, 31) = 3.624$, $p < 0.05$) were tested at 28 hours and 30 hours after drug treatment, respectively (d, e). NSF was tested at 48 hours after drug treatment. Food consumption (ANOVA, $F(3, 31) = 23.23$, $p < 0.05$) and latency (ANOVA, $F(3, 31) = 8.73$, $p < 0.05$) were measured for 10 minutes (f, g). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, compared to CTL; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, compared to Veh.

antidepressant effect, whereas fluoxetine failed to improve the learned helplessness response, with success in only a minor part of the measurements.

3.4. Yueju Treatment Induced an Upregulation of BDNF Expression and PKA-CREB Signaling and Decreased the Upregulation of NR1, NR2A, and NR2B Expression in

Learned Helplessness Mice. The molecular signaling responsible for neural plasticity in the hippocampus associated with depression and antidepressant activity was examined. There was reduced signaling of PKA, CREB, and BDNF. Chronic Yueju restored CREB signaling (Figure 4(b), $p < 0.05$), whereas fluoxetine failed to alter it ($p > 0.05$). However, both Yueju and fluoxetine restored PKA and BDNF expression (Figures 4(a) and 4(c)). Additionally, there was significant increase in expression of NMDA subunits NR1, NR2A, and NR2B in the chronic learned helpless mice, which were reversed by either repeated treatment of Yueju or fluoxetine (Figures 4(d), 4(e), and 4(f)).

3.5. Inhibition of NMDA Signaling Was Required for the Antidepressant Effect of Yueju. The molecular analysis indicates the association of inhibition of NMDA receptor subunit expression with antidepressant effect of Yueju. To further assess the role of NMDA signaling in antidepressant effect of Yueju, animals were pretreated with NMDA at 30 minutes before YJ or vehicle. Only Yueju ($F(1, 31) = 4.31$, $p < 0.05$ for TST at 1 hour; $F(1, 30) = 4.232$, $p < 0.05$ for TST at 24 hours; $F(1, 29) = 4.941$, $p < 0.05$ for FST at 3 hours; $F(1, 29) = 22.944$, $p < 0.05$ for FST at 26 hours) but not NMDA ($F(1, 31) = 0.079$, $p > 0.1$ for TST at 1 hour; $F(1, 30) = 1.333$, $p > 0.1$ for TST at 24 hours; $F(1, 29) = 2.846$, $p > 0.1$ for FST at 3 hours; $F(1, 29) = 2.522$, $p > 0.1$ for FST at 26 hours) showed the main effect on TST or FST at each individual times. There was an approaching significant interaction between Yueju and NMDA treatment in the TST ($F(1, 31) = 9.099$, $p < 0.01$ at 1 hour; $F(1, 30) = 14.411$, $p < 0.01$ at 24 hours) and significant interaction in the FST ($F(1, 29) = 8.001$, $p < 0.05$ at 3 hours; $F(1, 29) = 9.129$, $p < 0.01$ at 26 hours). Post hoc analyses showed that microinfusion of NMDA did not alter the immobility time in TST (1 hour, $p > 0.05$; 24 hours, $p > 0.05$) or FST (3 hours, $p > 0.05$; 26 hours, $p > 0.05$) in animals receiving oral dose of vehicle. However, it blunted the reduction of immobility time in TST (1 hour, $p < 0.05$; 24 hours, $p < 0.05$) or FST (1 hour, $p < 0.05$; 24 hours, $p < 0.05$) by Yueju (Figures 5(a) and 5(b)). The four groups have no main effect in open field test for total distance ($p > 0.05$) and time spent in central area ($p > 0.05$) (Figures 5(c) and 5(d)).

4. Discussion

In this study, we first identified optimal dose of Yueju within the routine use range that conferred antidepressant activity. A chronic learned helplessness protocol was established to elicit a long-term depressive symptoms, which was used to test the therapeutic effect of repeated administration of Yueju or fluoxetine. Yueju reversed all behavioral deficits, in contrast to only partial recovery by fluoxetine. Interestingly, CREB activation was increased by Yueju but not fluoxetine, although they both normalized BDNF and PKA level. Yueju also attenuated the expression of NMDA subunits that was upregulated by the chronic LH. In agreement with it, NMDA pretreatment blocked the antidepressant effect of Yueju.

Previously, we found that relative high dose of ethanol extract of Yueju (equivalent to 10 g/kg raw herbal mixture followed by ethanol extract) alleviated the depressive symptoms in a rapid and lasting manner [30, 31]. The present study showed that 2 g/kg of the raw herbal mixture of YJ was also effective to elicit an antidepressant effect. However, the duration of the antidepressant effects lasted for less than 2 days after a single dose of 2 g/kg, whereas with high dose, the duration of antidepressant effect was as long as 5 days, much longer than the present dose in the same tests using same strain of animals [32]. Nonetheless, the routine dose of YJ is still significant for antidepressant effect. The long-term administration of the routine dose of Yueju is very safe, which is very important for the practice of clinical treatment of depression. Furthermore, this repeated Yueju was very efficacious to alleviate the long-term depressive symptoms that fluoxetine, a mainstream antidepressant, largely failed. The oral dose of fluoxetine for 14 days are sufficient to induce antidepressant effects when administered chronically in some animal models of depression [33]. However, some other studies showed no effects on some paradigm of depression in certain models or animal strains [34, 35]. This may reflect the fact to some degree that many patients are not responsive to conventional SSRIs including fluoxetine. Alternatively, this model may recapitulate the so called treatment-resistant depression. Nonetheless, routine dose of Yueju was found to be effective in the model that mimics the long-term depression and support the utility of Yueju on treatment of depression.

The present study developed and investigated the temporal profile of learned helpless response following a short training period. It has been shown that LH paradigm is an animal model widely used for the study of neural changes underlying behavioral phenotypes related to mood disorders [36, 37]. One day or two consecutive days after LH training, the depression phenotype duration was short in some strain of mice. Four consecutive days of induction training induced the phenotype of depression lasting for 1 week [38, 39]. Our data suggests that the depression phenotype already declined between 3 and 6 days after 3 consecutive training, but only two additional intermittent training evoked the depression behavior at least lasting for 28 days, which allows to evaluate the treatment effect on persistent depression status.

The present study examined several factors involving neural plasticity, but only found that CREB signaling was more closely related to the therapeutic effect of Yueju, as all other molecules examined including CREB activator PKA, downstream effector BDNF, and NMDA receptor subunits were similarly restored by fluoxetine as well. The decrease of CREB expression is associated with depression [40, 41]. Depressed rats with an overexpression of CREB in the dentate gyrus behaved similarly to rats treated with antidepressants [42]. Although the persistent antidepressant effect of a single high dose of Yueju was specifically dependent on PKA-CREB signaling [9], the restoration of CREB level in the present study was more likely contributed by chronic and accumulating effect of repeated low dose of Yueju. The crucial upstream and downstream signaling related to CREB for action of repeated routine dose of Yueju warrants further investigation.

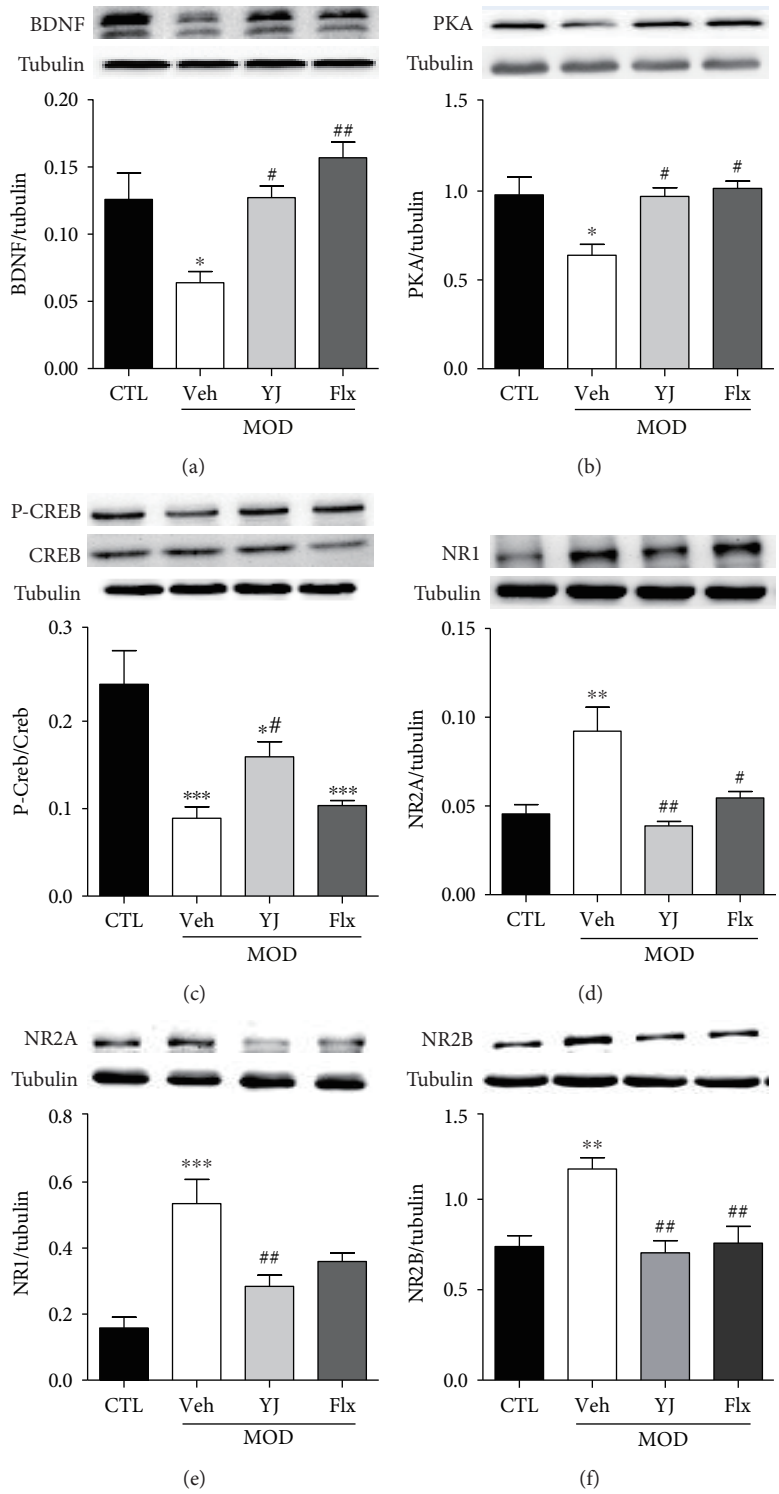

Figure 4: Western blots of CREB signaling and NMDA receptor subunits in the hippocampus in chronic LH animals receiving drug treatments. Mean ± SEM of protein expression levels of BDNF (ANOVA, $F(3, 15) = 8.566$, $p < 0.05$), PKA (ANOVA, $F(3, 16) = 5.899$, $p < 0.05$, P-CREB/CREB (ANOVA, $F(3, 20) = 15.68$, $p < 0.05$), NR1 (ANOVA, $F(3, 16) = 10.54$, $p < 0.05$), NR2A (ANOVA, $F(3, 15) = 10.54$, $p < 0.05$), and NR2B (ANOVA, $F(3, 17) = 9.188$, $p < 0.05$) in the hippocampus of CTL, Veh, YJ, and Flx groups. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$, compared to CTL; $^{\#}p < 0.05$ and $^{\#\#}p < 0.01$, compared to Veh.

Previously, it has been demonstrated that the antidepressant effect of a single high dose of Yueju is closely related to NMDA receptor subunit, especially NR1 [32, 43]. Dysfunction of NMDA receptors is implicated in mood disorders, demonstrating the importance of these receptors in depression [44, 45]. NMDA receptors consist of different subunits to

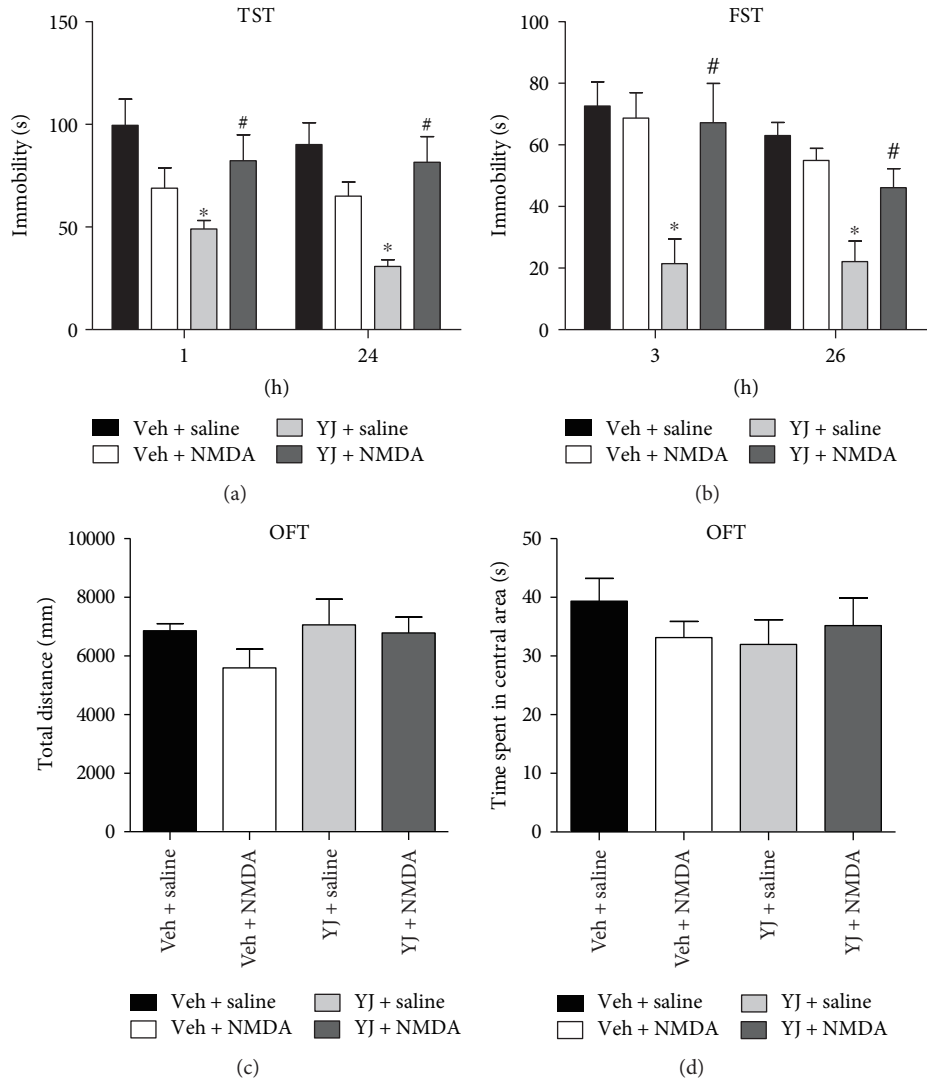

Figure 5: Intracerebroventricular microinjection of NMDA blocked Yueju (YJ) induced antidepressant effect. Mice received intracerebroventricular injection of vehicle or NMDA (1 pmol/site) 30 min prior to YJ (2 g/kg) or saline. TST was tested at 1 hour (two-way ANOVA, $F = 4.476$, $p < 0.05$) and 24 hours (two-way ANOVA, $F = 6.572$, $p < 0.01$) after the administration (a). FST was tested at 3 hours (two-way ANOVA, $F = 4.783$, $p < 0.01$) and 26 hours (two-way ANOVA, $F = 12.472$, $p < 0.01$) after the administration (b). OFT was performed 30 minutes post administration of YJ or Veh (c, d). $^{*}p < 0.01$ compared with Veh-saline group; $^{\#}p < 0.05$ compared with Veh-Yueju group.

form three subtypes: NR1, NR2, and NR3 [46, 47]. In the regular model of LH, the expression of NR1 subunit in the hippocampus also increased and sustained for several days, whereas a single high dose of Yueju reverses this effect in a persistent manner. In comparison, there was only temporal or no effect on NR2B or NR2A expression [32]. In this study, chronically learned helpless mice showed long-term abnormal upregulation of NR1, NR2B, and NR2A and repeated treatment of Yueju, as well as fluoxetine decreased their expressions, suggesting that the inhibition of NMDA signaling was associated with antidepressant action. The present study further demonstrated that inhibition of NMDA signaling is required by using intracerebroventricular pharmacological manipulation, confirming that NMDA signaling is an obligatory target of Yueju.

In summary, the present study demonstrated that the routine dose of Yueju has significant antidepressant efficacy and effectively attenuated behavioral deficits in chronic learned helpless animals. Restoration of neural plasticity via CREB signaling is crucially involved in the antidepressant effect of Yueju, whereas the inhibition of NMDA signaling is required and part of the mechanism of antidepressant efficacy of Yueju.

Ethical Approval

All animal experiments were in accordance with the Guide for the Care and Use of Laboratory Animals approved by the Institutional Animal Care and Use Committee at Nanjing University of Chinese medicine.

Conflicts of Interest

The authors declare that they have no competing interests in this paper.

Acknowledgments

The study was supported by the National Science Foundation of China (81673625) and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD). The study was also supported by the Natural Science Foundation of Jiangsu Province (BK20140962, BK20151568, and BK20161040) and the Collegiate Natural Science Foundation of Jiangsu Province (15KJB180011).

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Hindawi
Neural Plasticity
Volume 2017, Article ID 7260130, 17 pages
https://doi.org/10.1155/2017/7260130

Review Article

Brain-Derived Neurotrophic Factor, Depression, and Physical Activity: Making the Neuroplastic Connection

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Received 14 April 2017; Accepted 18 July 2017; Published 8 August 2017

Academic Editor: Frank S. Hall

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that is vital to the survival, growth, and maintenance of neurons in key brain circuits involved in emotional and cognitive function. Convergent evidence indicates that neuroplastic mechanisms involving BDNF are deleteriously altered in major depressive disorder (MDD) and animal models of stress. Herein, clinical and preclinical evidence provided that stress-induced depressive pathology contributes to altered BDNF level and function in persons with MDD and, thereby, disruptions in neuroplasticity at the regional and circuit level. Conversely, effective therapeutics that mitigate depressive-related symptoms (e.g., antidepressants and physical activity) optimize BDNF in key brain regions, promote neuronal health and recovery of function in MDD-related circuits, and enhance pharmacotherapeutic response. A greater knowledge of the interrelationship between BDNF, depression, therapeutic mechanisms of action, and neuroplasticity is important as it necessarily precedes the derivation and deployment of more efficacious treatments.

1. Introduction

Major depressive disorder (MDD) is a leading cause of global disease burden that affects over 300 million persons worldwide [1–3]. Pathognomonic features of this complex mental illness include the persistence of one or more episodes of sadness or anhedonia in a two-week period, along with the manifestation of cognitive and somatic symptoms (e.g., changes in appetite, sleep patterns, energy level, concentration, or physical activity; feelings of worthlessness and guilt; and suicidal thoughts or behaviors) [4]. The disorder can consist of a single episode or several recurrent episodes. Direct and indirect costs of treating MDD in the United States exceed $210 billion annually [5]. The high costs to individuals and society demand efficacious treatments, yet 30% of patients fail to respond to current pharmacotherapeutics and 70% do not achieve complete remission [6]. Disenchantment with the ability of extant drugs to mitigate symptoms in a significant proportion of persons, the undesirable side effects, and the high economic and social cost to society have prompted a diversification of the search for effective treatment options. Of the alternative therapeutics garnering attention, physical activity (PA) has shown clear and consistent promise for mitigating depressive neurobiology through mechanisms that involve brain-derived neurotrophin factor (BDNF).

Because it is important that clinicians and scientists understand the means by which PA can be used to optimize BDNF levels and mitigate pathophysiological substrates of depression, from both a self- and patient-education perspective, the aims of this review are to (1) explicate the putative neurobiological mechanisms involved in MDD and how trophic factors relate to those mechanisms, (2) review clinical and preclinical evidence of altered BDNF in persons with MDD, (3) discuss the relationship of BDNF to neuroplasticity, (4) discuss the effect of PA on BDNF, and (5) highlight current and future implications for clinicians and scientists.

2. Neurobiology of Depression

Neuroimaging studies of depression and surgical lesion studies that induce or mitigate depressive symptoms have been used to elucidate mood circuits [7, 8]. Comprising these circuits are several brain structures and regions, particularly the dorsal prefrontal cortex, ventral prefrontal cortex, anterior cingulate gyrus, amygdala, hippocampus, striatum, and thalamus [9–11]. Several pathophysiological processes are

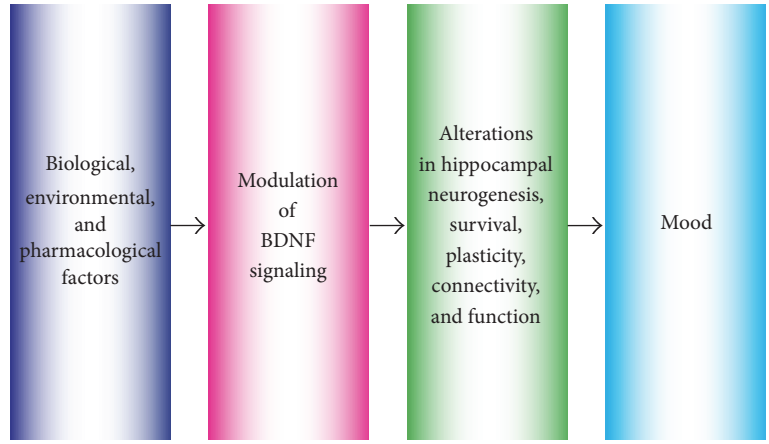

Figure 1: Endogenous and exogenous factors modulate BDNF levels to effectuate changes in the hippocampus and mood. Environmental stress—along with biological, genetic, and pharmacological factors—modulates BDNF levels and synaptic plasticity in various regions of the brain, including the hippocampus. Decrements in BDNF levels can confer vulnerability for hippocampal dysfunction and loss of emotional regulation. Conversely, antidepressant administration and voluntary PA optimize BDNF levels in the hippocampus and mitigate mood symptoms.

implicated in mood circuit and structure dysfunction [7, 12], including those related to genetic, epigenetic, and environmental factors. Results from a twin study suggest that the heritability of MDD is approximately 40% [13]. Preclinical studies have implicated epigenetic mechanisms by demonstrating that maternal behavior alters the function of stress-related genes [14] just as the administration of antidepressant drugs alters DNA regulation [15]. Other studies have shown that the depletion of neurotransmitters (e.g., dopamine, serotonin, and norepinephrine) contributes to depressive symptoms [16, 17] by altering glutamate and γ-aminobutyric acid (GABA) signaling. Accordingly, therapeutic agents were derived to either inhibit neuronal reuptake or inhibit degradation of monoamines in the synaptic cleft, actions aimed at increasing monoamine transmission. Yet monoamine depletion failed to produce depressive symptoms in persons who were healthy or worsen the severity of symptoms in persons with MDD [18]. Moreover, recent preclinical and clinical investigation demonstrated that ketamine, an NMDA receptor antagonist, induced rapid antidepressant effects through different mechanisms than monoamine reuptake inhibitors [18]. Subsequent study of signaling mechanisms that underlie the rapid antidepressant effects of ketamine has implicated BDNF and its ability to induce neuronal network alterations [18, 19].

The neurotrophic hypothesis of depression proposes that stress-related alterations in BDNF levels occur in key limbic structures to contribute to the pathogenic processes in MDD [19]. This notion is prefaced on evidence that neurotrophins are growth factors that play pivotal roles in the formation and plasticity of neuronal networks [20], and yet persons with MDD exhibit region-specific alterations in the level and function of BDNF. Upregulation of BDNF occurs in the amygdala and nucleus accumbens of persons with MDD whereas downregulation of BDNF occurs in the hippocampus and medial prefrontal cortex (mPFC) [21]. BDNF abnormalities also contribute to dysfunction of astrocytes and microglia in depression circuits. It has been shown that (1) persons with MDD exhibit decreased expression of glial fibrillary acidic protein and mRNA in the frontolimbic cortical region, (2) BDNF modulates glial function, and (3) antidepressant administration and deep brain stimulation mitigate glial deficits [22]. Finally, upregulation of BDNF occurs following chronic administration of antidepressants or voluntary participation in PA, consistent with the time course for the therapeutic action of antidepressants and PA [23]. Taken together, this evidence suggests that altered level and function of neurotrophins contributes to the atrophy, synaptic disconnection, and dysfunction of MD-related circuits [24, 25]. Conversely, optimization of BDNF levels facilitates synaptic plasticity and remodeling, induction of long-term potentiation (LTP), modulation of gene expression for plasticity, resilience to neuronal insults [24–26], and alleviation of depressive symptoms [27] (see Figure 1). This evidence has led to concerted efforts to better understand the actions of BDNF and how these actions can be harnessed to maintain, repair, and reorganize damaged emotional and cognitive circuits, a central goal for MDD treatment and rehabilitation.

3. Brain-Derived Neurotrophic Factor: Localization, Synthesis, Release, and Binding

Neurotrophins are a closely related family of proteins in the brain that contributes to the survival, growth, and maintenance of neurons [28] and participate in a variety of learning and memory functions [29]. The mammalian neurotrophins include BDNF, nerve growth factor, neurotrophin 3, and neurotrophins 4-5. Undoubtedly, the majority of the literature linking neurotrophins with depression involves the study of BDNF. BDNF has proven to be one of the most highly inducible neurotrophins with PA, prompting the focus on this neurotrophin herein.

The synthesis of BDNF occurs in both the central and peripheral nervous system by target neurons under physiologic conditions and by astrocytes following injury, inflammation, or administration of antidepressants [30–32]. In the brain, neurons are considered a significant cellular source of BDNF, and synthesis occurs in regions that participate in emotional and cognitive function (e.g., hippocampus and frontal, parietal, and entorhinal areas). Gene expression studies in humans have revealed that central BDNF is highest in the cortex, hippocampus, amygdala, basal forebrain, dorsal vagal complex, hindbrain, and midbrain [33, 34]. Several brain regions retrogradely transport BDNF from their projection areas. Raphe nuclei in the brainstem of rodents do not contain BDNF mRNA [35], but serotonergic neurons in these nuclei retrogradely transport BDNF from the frontal cortex, occipital cortex, entorhinal cortex, and amygdala (their projection areas) to their cell bodies [36, 37]. Noradrenergic neurons of the locus coeruleus retrogradely transport BDNF from the frontal and entorhinal cortex. It appears that nine different gene promoters induce the tissue-specific expression of 24 different BDNF transcripts, suggesting multilevel regulation of expression across brain regions [38]. The use of different promoters can facilitate the involvement of a myriad of transcription regulatory factors and mRNA-targeting signals, factors that shunt the translation of BDNF towards activated synaptic sites [39–41].

BDNF is synthesized as a precursor (pre-pro-BDNF protein) that results from cleavage of a 32 kDa pro-BDNF protein. Pro-BDNF can be proteolytically cleaved intracellularly by enzymes (e.g., PC7, furin, and proconvertases) and secreted as the 14 kDa mature form [42, 43] or it can be secreted as pro-BDNF and subsequently cleaved extracellularly by proteases (e.g., metalloproteinases and plasmin) [44]. Both forms of BDNF (pro-BDNF and mature) are sorted and packaged into vesicles for activity-dependent secretion [36, 45, 46]. Pro-BDNF can be internalized and stored by astrocytes and later released as the immature (pro-BDNF) or mature (BDNF) form [47].

Pro-BDNF mediates its biological actions through binding to low-affinity p75 neurotrophin receptors, whereas mature BDNF binds with higher-affinity tropomyosin-related kinase family (Trk) receptors [48]. Once bound to its cognate receptors, BDNF is internalized along with its receptor and transported via retrograde axonal transport mechanisms to the soma wherein it can initiate a multiplicity of effects within the nucleus [49]. The functional importance of differential binding to either p75 or Trk receptors is underscored by their opposing effects. Proneurotrophin binding to p75 reduces spine complexity and density [50], induces long-term depression (LTD) [51], promotes neuronal cell death [52], and facilitates the resculpting of neuronal circuits [48]. These biological actions are accomplished via activation of a receptor complex that is composed of p75 and sortilin [52, 53]. In contrast, mature neurotrophin binding to Trk receptors increases cell survival and differentiation, dendritic spine complexity, long-term potentiation (LTP) [54, 55], synaptic plasticity [56], and the resculpting of networks [57]. Localization of TrkB receptors significantly increases at synaptic sites following neuronal activity [58].

4. BDNF Abnormalities in Persons with Depression

There is a well-established body of clinical evidence implicating the involvement of BDNF in the pathobiology of depression [59]. Peripheral reductions in mature BDNF in serum and plasma have been noted in persons with depression [60, 61] and in cases of suicide [62, 63], and psychosocial stress appears to exert a role in these decrements [64]. Findings from a recent meta-analysis and systematic review showed significantly lower levels of serum mature and pro-BDNF in antidepressant-free patients with MDD as compared to healthy controls [65]. Notwithstanding, serum levels of BDNF tend to normalize in response to several treatments (e.g., antidepressants [66], electroconvulsive therapy [67], and PA [68]).

Central reductions in BDNF in specific brain regions have been reported also. A postmortem study of persons with MDD reported decrements in BDNF protein in the hippocampus [19], along with smaller hippocampal volumes [69]. Dunham and colleagues reported a reduction of pro-BDNF in all layers of the right hippocampus in persons with depression [70]. Postmortem hippocampal samples taken from suicide completers exhibited increased mRNA for the p75 receptor [71], intimating that LTD and pruning may underlie hippocampal pathology. Thompson and colleagues reported a reduction of BDNF mRNA in layer II of the entorhinal cortex relative to controls [72]. BDNF levels were reduced in the hippocampus of postmortem samples taken from suicide completers [71, 73]. The activity of MAP kinase signaling, a major downstream signaling pathway associated with TrkB, was reduced in persons with depression [74, 75]. Conversely, persons treated with antidepressant drugs exhibited increased BDNF expression and CREB in certain regions of the brain [76].

Further implicating BDNF with MDD are genetic [73, 77] studies demonstrating that depressive behavior is associated with altered BDNF functioning [78]. The Val66-Met polymorphism in the *BDNF* gene is a common single-nucleotide variant associated with MDD [79, 80]. It has an allele frequency of 20 to 30% in Caucasian populations [81]. The Val66Met polymorphism affects intracellular packaging of the pro-BDNF polypeptide and activity-dependent release [82, 83]. This polymorphism is associated with decreased hippocampal volume in healthy persons [84–86], persons with MDD [87], and persons suffering an adverse response to stress [88]. Also, it has been shown that persons who experience early-life stress and carry the Val66Met polymorphism exhibit significantly less grey matter in the subgenual anterior cingulate cortex [89] and are at increased risk for depression [90]. The Val66Met polymorphism is also a risk factor for geriatric depression [91] and has been shown to modulate antidepressant drug efficacy in Asians [92]. Thus, this naturally occurring genetic variant of the BDNF gene may contribute to a genetic predisposition for depressive disorder.

In addition to associations of the Met66 allele with decreased hippocampal size, other studies have demonstrated reduced hippocampal activation and poorer episodic

memory [83, 93]. The contribution of BDNF to mechanisms of learning and memory involves the modulation of synaptic transmission and plasticity [94, 95] and refinement of synaptic architecture [94, 96, 97] as well as activity-dependent transcription. It is generally held that activity-dependent transcription provides a mechanism by which neurons convert transient cellular changes to stable changes in brain function, particularly in memory formation. Increased calcium influx via voltage-gated Ca^{2+} channels and NMDA receptors is vital for neuronal plasticity mechanisms [98, 99]. NMDA receptor activation is particularly important for hippocampal synaptic plasticity [100] and modulation of BDNF [101], given that the latter determines the strength of existing synaptic connections and promotes the formation of new synapses. Together, this evidence suggests that alterations in BDNF function may affect activity-dependent plasticity in the hippocampus and thereby learning in memory and emotions in persons with MDD.

Knowledge of BDNF level and function is relevant for MDD research and treatment purposes for the several reasons listed.

(i) Altered BDNF function can contribute to an increased risk of depression and suicidal behavior [102].

(ii) With refinement of current knowledge, BDNF may eventually serve as a biomarker of depression and suicidal behavior in persons with depression and enhance diagnostic and treatment efforts [103, 104].

(iii) Treatment-induced normalization of BDNF may promote neural health and recovery of function from illness [105]. Additionally, the administration of BDNF-enhancing techniques (e.g., PA and transcranial stimulation) may enhance pharmacotherapeutic response [106].

5. BDNF in Animal Models of Depression

Stress is a well-known harbinger of depression in persons with genetic vulnerability [13, 107]. Evidence of the link between stress and depression has prompted investigators to derive animal research models of stress (e.g., immobilization, unpredictable chronic stress, foot shock, social isolation, social defeat, restraint, forced swim, and maternal deprivation) to determine a cause and effect relationship between pathology, interventions, BDNF, and depressive symptoms (for excellent reviews of depression metrics in animals, see [108–114]).

Preclinical studies have demonstrated that chronic stress and depressive-like symptoms are associated with reduced BDNF synthesis and activity of TrkB in the hippocampus and frontal cortex [19, 115, 116], making it seem plausible that decreased levels of BDNF induce a state of increased vulnerability to stress and depression. Conversely, direct infusion of BDNF into the hippocampus or midbrain yields antidepressant-like effects [117, 118]. Other studies have shown that chronic administration of antidepressants increases BDNF mRNA protein in the hippocampus and cerebral cortex [19, 119–121], but these effects can be blocked in mice with a conditional knockout that reduces levels of BDNF in forebrain regions [122]. Similarly, chronic peripheral subcutaneous administration of BDNF to rats effectuated increased levels and signaling of BDNF along with antidepressant effects, that is, increased mobility in the forced swim test, increased sucrose consumption, decreased latency in the novelty-induced hypophagia test, and increased time spent in the open arms of an elevated plus maze [123]. Rodents overexpressing BDNF or TrkB also exhibit increased resistance and resilience to stress and depressive-related symptoms, that is, decreased immobility in forced swim [124, 125].

The robust effects between stress and BDNF levels are clearly apparent in the hippocampus in the subgranular zone [126]. Neurogenesis in the adult brain is a form of experience-dependent plasticity whereby stem cells within distinct regions (the subgranular zone of the hippocampus and subventricular zone) give rise to new neurons [127]. The 20,000,000 neurons generated over the course of a lifetime have different fates. Some newly born neurons migrate to the granule cell layer, develop a dendritic tree, and send their axon into the mossy fiber pathway [127, 128] to enhance the functional capacity of neural circuitry that is important for learning, memory, and emotional regulation [129–131] in an environmentally dependent manner [132]. Neurons that fail to accomplish this experience a different fate: death. Thus, the proliferation and survival of new neurons in the hippocampus is vitally important for persons with MDD [133], particularly given that the elevations in glucocorticoid levels that cooccur with MDs reduce levels of BDNF and rate of neurogenesis and induce the retraction of dendrites [64].

Fortunately, antidepressant drugs increase levels of BDNF in the hippocampus [19, 21], neurogenesis [134], and hippocampal cell survival rates [135]. The temporal profile of these effects is congruent with the temporal profile of clinical effectiveness of antidepressant drugs, suggesting a similarity between mechanisms [19, 35]. Other preclinical studies suggest that the degree of dendritic branching and the number of spines in hippocampal neurons increase following the restoration of BDNF levels [19, 35, 136–138]. Interestingly, selective deletion of the BDNF gene in the rodent hippocampus attenuates antidepressant efficacy as measured by the elevated plus maze, fear conditioning, sucrose preference, and forced swim tests [139]. Together, these findings suggest that altered expression of BDNF and dysregulation of neurogenesis in the hippocampus may effectuate maladaptive changes in neural networks that are implicated in MDD pathophysiology and, by corollary, that antidepressants may reverse these maladaptive changes.

Subsequent study has revealed that the relationship between BDNF and depressive symptoms is more nuanced in other brain regions. In contrast to the effects seen in the hippocampus, infusion of BDNF to the ventral tegmental/nucleus accumbens area increased depression-like behavior (shorter latency to immobility in the forced swim test) [140] through mechanisms that may involve maladaptive learning. Berton and colleagues demonstrated that chronic

stress increased BDNF levels within the nucleus accumbens [141], whereas virally mediated knockdown of BDNF in this region reduced social aversion following chronic social defeat [141], suggesting that increased BDNF in the ventral tegmental area and nucleus accumbens is positively associated with plasticity-induced aversive learning [142–144]. Finally, rodents with a knockdown of the BDNF gene in the ventral tegmental area consumed greater amounts of high-fat diet foods [145], whereas Goto-Kakizaki rats administered intracerebroventricular injections of BDNF exhibited suppressed feeding [146], a finding that underscores the modulating effects of BDNF on feeding behaviors and its interactions with the mesolimbic dopaminergic reward system [147].

Admittedly, central reductions in BDNF are not sufficient to produce depressive-like behaviors in all animals. Rather, reductions of BDNF appear to increase susceptibility to the deleterious effects of stress: exposure of BDNF heterozygous knockout mice to stress induces depressive-like behavior, as does the blockade of BDNF-TrkB signaling following stress [148]. These studies suggest that the anti- or prodepressive effects of BDNF depend upon the brain region affected and offer evidence that selectively targeting BDNF levels in key brain regions may benefit patients affected by MDs. These studies also demonstrate that the effects of BDNF are region- and circuit-specific and cannot be extended arbitrarily to other brain regions.

6. BDNF, Plasticity, and Neuroprotection in MDD

It has been proposed that BDNF signaling is a prime mediator of activity-dependent neural plasticity and the resculpting of MD-related circuits [149–151]. Neuroimaging studies have revealed functional deficits in cognitive and affective processing during the early phases of illness [152–155], changes that become increasingly impaired with illness progression [156], and the emergence of structural impairments in the frontal cortex and hippocampus [157–160]. Together, the functional and structural deficits disrupt cognitive and affective regulation that is dependent upon circuit-level integrity of the prefrontal-thalamo-limbic and limbic-striatal-pallidal-thalamic systems [161]. By corollary, circuit level disruption can impede future learning [162]. Cortical regions (e.g., dorsolateral prefrontal cortex [163, 164] and anterior cingulate cortex [165]) comprise the cognitive control network, whereas the subcortical regions (e.g., hippocampus [166], amygdala [167], parahippocampal gyrus [168], caudate nucleus [169], posterior cingulate cortex [168], and thalamus [170]) comprise the affective processing network. Persons who are depressed exhibit impairments in the cognitive control network as evidenced by their inability to disengage from negative stimuli, a task that requires top-down regulation by cortical regions [164, 171]. They may also exhibit impairments in the affective control network as evidenced by hyperactivity of the amygdala [156, 172] and hippocampus [163] to negative stimuli and recall.

The impairments in structure and function in these areas and circuits putatively arise from a myriad of contributing factors, including altered trophic factor level and function, neurotransmitter level and function, stress regulation, peroxisome proliferator-activated receptor C coactivator alpha, neurogenesis, immune function, antioxidant defense, circadian rhythms, epigenetic modifications, and maintenance of telomere length [173]. Within this context, decrements in BDNF are not sufficient to effectuate depression in humans per se. Rather, adequate levels of BDNF effectuate activity-dependent neuronal plasticity that is requisite for the maintenance of basal neuronal and circuit function [174] and for making adaptive responses to endogenous and exogenous stressor challenges [27, 175], particularly during chronic stress [88] and depressive states [87].

Inherent to the depressive state is the inability to return to normal circuit function following the abatement of stressful situations (either psychological or physical in nature), a phenomenon that likely reflects reduced plasticity. Hippocampal atrophy and disconnected brain circuits become increasingly resistant to change in the absence of exogenous interventions that promote recovery. Part of this resistance is the result of the disconnection and loss of function that occurs [19, 24, 176, 177] secondary to synaptic decrements [178, 179].

Synapses typically exhibit plasticity, a state where their function and structure are modified in response to activity and factors in the cellular milieu. LTP is one form of functional synaptic plasticity, wherein connections between synapses become strengthened with activity, a process that is fundamental to learning and memory [180]. Yet, requisite for the strengthening of LTP is the presence of mature BDNF [181]. LTD is another form of functional plasticity, where a set of synapses display a reduced capacity to elicit a response in one another, a process that is vital to forgetting [182]. Requisite for LTD are adequate levels of pro-BDNF [181]. Working in concert, LTP and LTD regulate homeostatic plasticity and the function of neuronal circuits [149, 183] in emotional circuits. This regulation is accomplished by the ability of high-frequency (but not low-frequency) stimulation to induce the secretion of tissue plasminogen activator, a protease that converts extracellular pro-BDNF to mature BDNF [181]. Not surprisingly, the study of hippocampi in persons with MDs has revealed that decreased volumes are positively associated with symptom severity, duration, and treatment outcomes [184–187].

Fortunately, antidepressant drug administration enhances synaptic turnover [188–190], increases synaptic plasticity gene activation [191], and promotes functional connectivity in the hippocampus [192] following stress, processes that are dependent upon TrkB signaling [188]. Also, antidepressant administration increases phosphorylation of TrkB receptors in the rodent hippocampus and cortex within hours [193, 194] and increases the translocation of TrkB receptors to synaptic sites [195]. Via phosphorylation of BDNF and other mechanisms, antidepressant drugs appear to reactivate neuroplasticity.

Maya Vetencourt and colleagues previously reported that chronic administration of fluoxetine, at a dosage that produced serum fluoxetine levels within the therapeutic range in humans, reinstated ocular dominance plasticity in adulthood and promoted visual recovery in amblyopic adult

animals. These effects were accompanied by reduced intracortical inhibition and increased BDNF expression in the visual cortex [196]. Similarly, direct infusion of BDNF into the visual cortex recapitulated the effects of fluoxetine [196], suggesting that the antidepressant drug reinstated critical period-like plasticity in the visual cortex [197].

Kobayashi and colleagues demonstrated that chronic treatment of adult mice with fluoxetine greatly reduced expression of calbindin, a marker for mature granule cells in the hippocampus. Additionally, chronic administration of fluoxetine induced active membrane properties that resembled immature granule cells and concomitantly reduced the synaptic facilitation that is characteristic of mature dentate-to-CA3 signal transmission, suggesting that the drug reversed the established state of neuronal maturation in the adult hippocampus [198].

Karpova and colleagues investigated the effects of antidepressants on behavioral experience by using a fear-conditioning and fear-extinction paradigm in rodents. They combined extinction training with chronic fluoxetine and induced an enduring loss of conditioned fear memory in adult animals, an effect that could not be produced without the drug. Strikingly, fluoxetine administration effectuated synaptic plasticity and facilitated the conversion of the fear memory circuitry to an immature state, effects that were mediated by BDNF. The authors concluded that fluoxetine-induced plasticity permits fear erasure by extinction-guided remodeling of the memory circuitry, suggesting that antidepressant drugs may be used to prime plasticity in circuits prior to psychological rehabilitation to facilitate the reorganization and proper function of MDD networks [199].

In another study, Chollet and colleagues administered patients who suffered a stroke add-on fluoxetine to physical therapy. The results of their double-blind, placebo-controlled trial demonstrated that persons who received early prescription of fluoxetine with physical therapy had enhanced motor recovery after 3 months [200].

These findings support the notion that antidepressant drug mechanisms involve the reactivation of neuroplasticity and facilitation of functional reorganization of the neuronal network when accompanied by environmental enrichment [175, 201]. By corollary, they underscore the importance of resolving stressful situations that initially induced functional and structural impairment in mood-related circuits and of deriving biomarkers that facilitate earlier detection and rehabilitation before the illness gains a strong foothold [202]. Also, this evidence highlights a critical unmet need for new antidepressant therapeutics that exert faster onset of action and greater efficacy. Accordingly, a multiplicity of preclinical and clinical investigations has aimed to understand how therapeutics can be used to harness homeostatic mechanisms that regulate neurotrophin release and function to mitigate MDD-related disease, particularly aerobic PA [129, 173, 203].

7. Physical Activity, BDNF, and Neuroplasticity

Convergent evidence demonstrates the positive effects of PA in persons with MDD. PA refers to activities that require energy expenditure and involve bodily movements produced by skeletal muscles [204]. Exercise is a subcategory of PA that entails purposeful, planned, and structured endeavors undertaken to improve physical fitness or skill level [204]. Evidence suggests that PA reduces the risk for MDD [205, 206], mitigates symptoms [207], facilitates recovery [208, 209], lowers the incidence of relapse [210, 211], and decreases overall caregiver burden [212]. Undoubtedly, many of the positive effects of PA on brain health and function derive from its ability to optimize central levels of BDNF, particularly in the hippocampus [130].

Preclinical work demonstrates that chronic PA upregulates the expression of BDNF in the hippocampus of rodents for days [116, 213]. Concomitantly, endurance exercise induces elevations of muscle-derived proteins [proliferator-activated receptors (PGC-1α) and FNDC5] that regulate BDNF expression in the rodent hippocampus. The ability of PA to modulate changes in BDNF and PGC-1α is relevant for stress-induced depression given their interaction with neuroinflammatory and neuroplasticity pathways [214] via alterations in tryptophan degradation [204, 215] and 5-HT_{1A} receptor activation [216].

A bevy of other work underscores the inextricable relationship between PA, BDNF level optimization, and downstream factors. PA optimizes neurotransmitter system level and function (e.g., glutamate, GABA, serotonin, dopamine, and noradrenaline) [173]. In turn, changes in neurotransmission mediate changes in BDNF gene expression in various brain regions (e.g., hippocampus, nucleus accumbens, and amygdala) [217]. Robust preclinical and clinical work demonstrates that PA increases neurogenesis and plasticity via BDNF-dependent mechanisms, particularly when paired with environmental enrichment [173, 218]. Other work demonstrates that PA attenuates the inflammatory process and induces a more resilient stress response [173]. The ability of PA to mitigate HPA dysregulation is especially important for preventing hippocampal atrophy [219, 220] in persons with affective disorders [221] because chronic exposure of hippocampal neurons to elevated glucocorticoid levels induces a retraction of dendrites and reduction of dendritic spines [222].

Emerging preclinical evidence suggests that PA can mitigate the astrocytic dysfunction seen in MDD. Early work in rodents demonstrated that ablation of astrocytes effectuated a reduction of dentate granule cell density and glutamate transporter expression, changes that negate the ability of these cells to effectively remove glutamate excess from the synaptic milieu [223]. Later work demonstrated that chronic stress reduced the number of astrocytic projections in rodents, whereas environmental enrichment increased the number of astrocytic projections [224], a significant finding given that the extent of astrocyte projections is a marker of well-being in these cells. Bolstering the notion of a link between astrocytic function and BDNF is a preclinical work showing that BDNF infusion attenuates hippocampal glial fibrillary acidic level reductions that were a consequence of chronic unpredictable stress [225]. More recent work showed that rodents exposed to long-term PA (5 days per week $\times$ 4 weeks) demonstrate increased BDNF synthesis and release

Table 1: Effects of physical activity on brain-derived neurotrophic factor (BDNF).

Reference	Sample	Treatment	Assessment outcome
[233]	13 young, healthy men	Moderate-intensity aerobic PA 4 d/wk for 5 wks	↑ plasma BDNF
[234]	7 healthy, sedentary males	Aerobic PA 7 d/wk for 12 wks	↑ plasma BDNF
[238]	60 older adults	Aerobic PA 3 d/wk for 60 wks	↑ BDNF and ↑ hippocampal volume
[236]	47 healthy, sedentary males	Aerobic PA 3 d/wk for 5 wks	↑ serum BDNF following PA and ↑ memory on face name matching
[235]	62 healthy, sedentary males	Moderate-intensity aerobic PA for 2 wks	↑ serum BDNF following PA and ↑ memory on face name matching
[247]	104 persons with partial response to antidepressants	Add-on high (16 kcal/kg/week) or low (4 KKW) PA for 12 wks to standard depression care	Persons entering with ↑ BDNF levels exhibited ↑ rate of response to antidepressants
[248]	15 severely depressed adults	Add-on aerobic PA 16 kcal/kg/week for 3 d/wk for 3 wks to standard care for depression or medication-only group	Similar ↑ in BDNF in aerobic PA and medication-only group, but ↓ in oxidative stress markers seen only in PA group

in the dentate gyrus along with altered orientation and morphology of astrocytes, effects that are TrkB-signaling dependent [226]. The latter findings suggest that PA-induced changes in astrocytic projection length and density might enhance glutamate clearance from the synapse and mitigate glutamate excitotoxicity in models of MDD, a notion that awaits further study.

Some evidence suggests a synergistic effect of PA and restricted dietary intake on BDNF upregulation. Alomari and colleagues examined the effects of aerobic PA (voluntary wheel running or forced swimming) plus caloric restriction versus dietary restriction alone on BDNF and learning and memory in rodents. Their results demonstrated that the combination of voluntary PA and caloric restriction effectuated greater increases in BDNF levels in the hippocampus, even though improvements in spatial learning and memory occurred in both the combination and dietary restriction groups [227]. Thus, it seems plausible that multidomain treatments such as PA and dietary modification may be particularly beneficial in persons with MDD who exhibit stress-induced decrements in central and peripheral BDNF levels and carry gene-copy-number variants in the BDNF gene.

Carriers of the BDNF Val66Met polymorphism exhibit decreased activity-dependent secretion in comparison to Val/Val carriers, although the level of constitutive secretion of BDNF protein in hippocampal neurons remains the same [83]. Decreased activity-dependent secretion from the neurons of BDNF Met carriers is functionally significant because most BDNF protein is released from the activity-dependent pathway [83, 228]. The fact that PA modulates BDNF levels and symptoms of depression [229, 230] suggests that BDNF gene interactions with PA may influence depressive symptoms [231]. Bolstering this notion is recent work showing that the BDNF polymorphism moderates the association between PA and depressive symptoms. Higher levels of PA were protective against depressive symptoms for girls with the BDNF Met allele, but not for girls with the Val/Val polymorphism [232].

Further elucidating the association between PA and BDNF are clinical investigations of brain structure and function (see Table 1). These studies reaffirm that chronic aerobic exercise increases peripheral levels of BDNF [233–236], blood volume in the dentate gyrus [237], grey matter in the prefrontal and cingulate cortex [235], size of the right and left hippocampus [238], and memory performance [235, 236] in humans. Encouragingly, increases in hippocampal size are correlated with increased spatial memory performance in persons who are healthy and experiencing neurodegenerative changes [238], suggesting that PA might mitigate the cognitive deficits experienced in MDD. Moderate to high training intensity PA appears requisite for maximal PA effects [239, 240]. Clinical studies have demonstrated that acute aerobic PA at 85% of maximal capacity increased plasma BDNF levels, which is important because plasma BDNF levels are linked to alterations in BDNF levels [241, 242], synaptic plasticity, and learning ability [243], whereas blockade of BDNF on TrkB receptors reduced the effects of PA on synaptic plasticity [244].

Parallel studies have investigated the relationship of PA, BDNF, and depressive symptoms. It has been shown that PA increases BDNF in unmedicated patients with MDD [245] and elderly persons with remitted depression [246]. Examining the effects of exercise augmentation (16 kcal/kg/week × 12 weeks) in persons who experienced a partial response to antidepressants, Toups and colleagues found that persons with higher BDNF levels experienced more rapid symptom relief, suggesting that pretreatments with exercise might improve antidepressant efficacy [247]. Schuch and colleagues investigated the effects of add-on PA (16.5 kcal/kg/week of aerobic exercise 3× per week for approximately 3 weeks) with treatment as usual. They found no additional increase of BDNF in the exercise plus medication group relative to the medication-only group, suggesting a plateau

effect of antidepressant drugs on BDNF levels in persons with depression [248]. What remains to be determined is whether this plateau effect exists in carriers of the Met allele.

While it is known that PA increases circulating BDNF levels in healthy humans [249] and that BDNF is vitally important for maintaining affective and cognitive circuit function during health and disease, the source of these increases remains unclear. Some have proposed that platelets are the origin of serum BDNF following exercise [250], but BDNF is also increased in plasma samples, a finding that implicates other sources. Krabbe and colleagues demonstrated cerebral output of BDNF in healthy humans at rest [251], suggesting that exercise-induced alterations in plasma BDNF levels reflect altered release of BDNF from the brain [252]. Exploring the latter notion further, Rasmussen and colleagues used arterial-to-internal jugular venous measurement differences to analyze the contribution of the human brain to plasma BDNF levels at rest and during prolonged whole-body exercise. Their results show that the brain is a significant source of BDNF production at rest and during prolonged exercise, contributing approximately three-quarters of the BDNF to venous circulation [253]. Part of the increase in central BDNF may be a consequence of activated platelets in the cerebral circulation [254] or activity-dependent function in other brain structures (e.g., hippocampus and cortex) [253].

These results suggest that PA effectuates central neuroplastic adaptations via optimization of BDNF levels. The ability of PA to enhance BDNF release and function in the synapse, promote dendritic spine integrity, and activate other cellular pathways that contribute to plasticity [19, 24, 255] is vital for homeostatic processes that are necessary for the maintenance, repair, and reorganization of circuits damaged during depression, effects that recapitulate those of antidepressant drugs. While it remains to be determined whether PA can reactivate neuroplasticity, preliminary work by Eadie and colleagues has demonstrated that long-term PA significantly increased total length and complexity of dendrites, increased the spine density on dendrites, and induced a more immature state of dentate granule cells [137].

8. Conclusions and Future Directions

The derivation of an effective treatment for MDD represents an unmet goal. Notwithstanding, considerable progress has been made in better understanding the pathobiological features and processes that contribute to the structural, functional, and circuit disruptions that are endemic to MDD. Herein, biomedical evidence demonstrated that stress-induced depressive pathology contributes to altered BDNF level and function in persons with MDD and, thereby, disruptions in neuroplasticity at the regional and circuit level. By corollary, effective therapeutics that mitigate depressive-related symptoms (e.g., antidepressants and physical activity) will optimize BDNF in key brain regions to promote neuronal health and recovery of function in MDD-related circuits. A better ability to deploy therapeutics that optimize BDNF is needed given evidence that intervention in neurodegenerative processes is more likely to achieve disease modification, while ones deployed later demonstrate a significant but more limited effect after the emergence of neuronal degeneration [256].

Clearly, there is an urgent need to identify how PA can best be translated operationally to influence the health and wellness of brain structure and function [173], particularly by optimizing neuroplasticity mechanisms. This challenge will necessarily entail a better understanding of how the optimum mode, intensity, and duration of PA might alter MDD-related symptoms and pathology. Several studies suggest that exercise interventions that combine multiple modalities (e.g., aerobic and strength-training activities) are more effective at enhancing emotional and cognitive health in humans in comparison to those that emphasize aerobic activities alone. Colcombe and Kramer reported that persons who participated in aerobic and strength-training activities exhibited higher gains in cognition in comparison to those who participated in aerobic activities alone [257]. Smith and colleagues reported that interventions that consisted of aerobic and strength-training activities improved attention, processing speed, and working memory to a greater extent than aerobic exercise alone in both healthy individuals and those with neurodegeneration [258], an effect putatively linked to alterations in hippocampal volume [238, 259]. Supporting the latter notion is evidence that decrements in hippocampal size are linked to neurodegenerative progression, whereas the reversal of neurodegenerative progression has been linked to improvements in hippocampal volume [219, 220]. Indeed, aerobic exercise of moderate intensity for 12 months improved memory and hippocampal size in healthy older adults, effectively reversing age-related loss of volume by one to two years [238]. Directly applying the aforementioned, Makizako and colleagues demonstrated that hippocampal volume was directly linked to improved memory in humans and that greater durations of moderate PA could effectuate greater increases in hippocampal volume and memory [259].

Altogether, the data presented here suggests that moderate PA—a target that is practical, well tolerated, and likely to optimize exercise adherence—optimizes BDNF and plasticity, particularly in persons with depression. PA's relative low-risk profile, ease of implementation, and absence of side effects [260] have led to the incorporation of PA into basic clinical management protocols for MDs [261, 262]. Undoubtedly, future efforts to improve population health should consider the ability of lifestyle factors to prevent and treat mental disorders [263] by optimization of neuroplasticity substrates, particularly when coupled with rehabilitation.

Abbreviations

BDNF: Brain-derived neurotrophic factor
GABA: γ-Aminobutyric acid
LTD: Long-term depression
LTP: Long-term potentiation
MDD: Major depressive disorder
NMDA: N-Methyl-D-aspartate
PA: Physical activity
TrkB receptors: Tropomyosin receptor kinase B.

Conflicts of Interest

The author declares that she has no conflicts of interest.

Acknowledgments

The author would like to thank Ms. Cindy Ferrell for professional graphic work.

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Hindawi
Neural Plasticity
Volume 2017, Article ID 5282670, 15 pages
https://doi.org/10.1155/2017/5282670

Review Article

Emotion Processing by ERP Combined with Development and Plasticity

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Received 12 April 2017; Accepted 9 July 2017; Published 31 July 2017

Academic Editor: Bingjin Li

Emotions important for survival and social interaction have received wide and deep investigations. The application of the fMRI technique into emotion processing has obtained overwhelming achievements with respect to the localization of emotion processes. The ERP method, which possesses highly temporal resolution compared to fMRI, can be employed to investigate the time course of emotion processing. The emotional modulation of the ERP component has been verified across numerous researches. Emotions, described as dynamically developing along with the growing age, have the possibility to be enhanced through learning (or training) or to be damaged due to disturbances in growth, which is underlain by the neural plasticity of emotion-relevant nervous systems. And mood disorders with typical symptoms of emotion discordance probably have been caused by the dysfunctional neural plasticity.

1. Introduction

Emotion, as a form of information delivery, serves as a critical role in human survival and social communication, from which humans can receive the signals of threats and messages individuals would use to correspond in correct ways. Thus, the emotion processing has been attracting numerous researchers into the exploration of it (for more details, see LeDoux et al. [1], Phan et al. [2], Russel [3], Ochsner and Gross [4], Lindquist et al. [5], and Olofsson et al. [6]). Especially, the application of event-related potential (ERP) and functional magnetic resonance imaging (fMRI) techniques into psychological and neurological science enables the assessment of affective responses with millisecond temporary resolution and high spatial resolution, respectively, with increasing emergence of studies for emotion processing. Through functional imaging, studies have depicted extensive emotion-relevant brain networks involved in emotion processing in human subjects, regions of which include traditional visual cortices (e.g., the face-selective fusiform gyrus, superior temporal gyrus) [7–10], amygdala [11–13], orbitofrontal cortex [9, 14, 15], right frontal-parietal cortices [9, 16], somatosensory related cortices (i.e., insula cortex) [17, 18], and basal ganglia [19–21] and maybe auditory cortices for processing emotion-related prosy [22, 23]. Likewise, the electrophysiological studies for processing affective stimuli have offered us various insights into emotion processes from the temporal dimension. An early study by Begleiter et al. in late 1960s already demonstrated the amplitude variability with emotion category, in which stimuli conditioned by unpleasant words elicited larger peak-to-peak amplitude, compared to those associated with neutral and pleasant words [6]. More recently, the ERP studies have consistently confirmed the ERP components which are sensitive to processing the emotional stimuli, such as N100, P100, N170, vertex positive potentials (VPP), N250, N300, P300, late positive potentials (LPP; or as late positive complex (LPC)), and early posterior negativity (EPN) [24–28]. However, the magnificent achievements in spatially localizing the emotion processing, as well as the enthusiasm for assessing emotion processes by means of fMRI, contrast vividly with modest progress in the temporal course of processing emotion.

fMRI using BOLD (blood oxygenation level-dependent effect) contrast, since firstly applied into exploring functions

of human cortex in 1992 [29, 30], has been receiving welcome from neuroscience and psychological researchers. fMRI technique with its high spatial resolution and noninvasiveness has exhibited an immense advantage in exploring the relationship between neuroanatomy and cognitive processes, compared to other functional imaging methods. The subsequent event-related design fMRI approach [31, 32], conforming to the logic ERP studies adopted, allows randomly the presentation of experimental trials and controlled trials, which creates a higher level of assurance that experiment hypothesis reflects the differences between contrasts (i.e., conditions) than the block design. Additionally, functional connectivity (FC) analytical methods [33, 34] can be applied to explore whether changes of certain brain region activity contact with others or not, and in that way, we can confirm the cognition and emotion-relevant neural network. Using the FC method, researchers have investigated and endeavored to identify the emotion-relevant network in healthy individuals and in mental disorder populations [5, 35–37]. Still, the shortcomings exist in fMRI studies. Unlike ERP directly measuring the evoked potentials by brain activity, the fMRI method utilizes the hemodynamic property of the brain and surveys the indirect metabolism signals induced by cerebral activities, leading to delayed rising of BOLD with several seconds after stimulus presentation or cognitive manipulation (i.e., the temporal resolution of fMRI is lower than that of ERP). Despite the terrible spatial resolution, the ERP technique allows researchers to assess emotion processing with millisecond temporal resolution. Thus, ERP provides us with an excellent tool to look into the temporal course of emotion processing, which fMRI lays its deficits on. Given the shortcomings of fMRI and the modest progress in the time course of emotion processing, it is imperative to further investigate when experience evoked by emotional stimulus affects event-related potentials and even deep into how emotion signals are processed in the brain through the combination of the fMRI and ERP methods.

Emotion, as acknowledged, is more than the statical innate ability to deliver information about survival and threats, but also a competence of developmental attributes, by which ones can respond to diverse situations with increasing properly emotional-expressive behaviors [38]. Thus, emotion to be developmentally investigated is what we should consider when exploring the mechanism for emotion processing. The longitudinal studies using fMRI have verified the brain regions of neural plasticity for emotion processes [39–41]. In addition to neural imaging method, ERP could be utilized to characterize the temporal changes of emotion processing along with the growing of individuals. It is legitimately expected that more refined developments in emotion-relevant areas could be localized through the combination of ERP and fMRI. Moreover, the ERP technique can induce and measure the long-term potentiation (LTP), as a correlate of neural plasticity, in the human visual and auditory cortex, and provide a noninvasive instrument to assess LTP-associated plasticity in human beings [42, 43]. From another point of view, the disturbances of such neural plasticity contribute, at least partly, to the generation of mental disorders of emotional deficits, for instance mood disorders and schizophrenia [44]. The researches using the ERP technique endeavored to assess the impaired neural plasticity in patients with these disorders and obtained significant results [45, 46]. It is therefore feasible and required to probe the neural plasticity for emotional development by means of ERP.

To sum up the above arguments, the present review collected the emotional ERP studies from the recent 10 years (2007–2016) and integrated the emotional effects on ERP components, combined with the review of emotional development studies and studies regarding neuropsychiatric disorders for emotional neural plasticity. Additionally, this review discusses the issues that may contribute to emotional effects on ERPs, including methodology, stimuli characteristics, and emotion categories.

2. Exploring Emotion Processing by Means of the ERP Technique

2.1. Categories and Dimensions of Emotion. According to the studies by Osgood et al., Russel et al., and Lang's discourse on emotional dimensions [47–50], emotion could be viewed as a continuum of two dimensions, namely, valence and arousal. The valence dimension refers to the degree in which individuals feel pleasant or unpleasant, and arousal dimension denotes the subjective state of feeling activated or deactivated (i.e., denoting the intensity of internal emotion response) [51]. Based on the cross-culture study of facial expressions, Ekman and his colleagues proposed that happy, sad, fear, anger, disgust, and surprise represented the six basic affective states of emotion [52, 53]. The six basic affective states could be placed into the circumplex model of affect by Russel, with the respective values of valence and arousal [48]. Lang et al. hold the position that the valence viewed as a manifestation of motivational systems in the brain and the arousal denoting the intensity of the motivational systems would to some extent interact with each other [54]. Thus, the level of arousal should be controlled when valence effect is the research target. Apart from the six basic emotional states, one class of emotions which we called the social emotions plays a critical role in social interactions. Social emotions including pride, guilt, jealousy, shame, and embarrassment develop later than the above basic emotions and are more dependent on social context [55].

2.2. Issues Accompanied with ERP Application into Emotion Study. ERP, as an experimental tool to temporally explore cerebrum processing, is sensitive not only to properties of stimulus presented to subjects but also to mental states of subjects [56, 57]. Especially, when investigating affective processing, it is critical to avoid the confounding between stimulus and emotional effects on ERP components. Additionally, ERP extracts event-related signals from the background rhythms of brain electric activity [56], and in consequence, the methodology for ERP studies of emotion processing requires considerations. As the above review suggests, affective states correlate with a distributed network of brain areas, with differential cerebral localizations responding to different emotions. Reflected in ERPs, various

emotions might exert distinct temporal dynamics. In conclusion, emotion categories as well as methodological considerations and stimuli characteristics will be discussed in the subsections below to elucidate how to elicit reliable emotional response/experience and how to ensure the real effects of emotion on ERPs.

2.2.1. Methodological Considerations. Most ERP studies of emotion processing generally employ the facial affective pictures as stimuli to elicit emotional response/experience, and these affective stimuli were mainly extracted from the standardized datasets, such as the International Affective Picture System (IPAS) and Chinese Facial Affective Picture System (CFAPS) [58–60]. Take IPAS as an example, the system received ratings of valence and arousal from subjects during free view [58, 61]. ERP studies however are overtly distinct from free view situations where the level of arousal for identical emotional stimulus differed from the former, especially when the experiments confine the stimulus duration/presentation velocity [62–64]. It is consequently essential to execute the prudent and rigorous manipulations of the two emotional dimensions, namely, valence and arousal, in which arousal influence could be measured and analyzed to disentangle effects of valence and arousal on ERPs. Available adoptions like subjective ratings of valence and arousal within the ERP programs could be applied. Or like Aguado et al. and Utama et al. implemented in their studies [65, 66], the same population of subjects was requested to rate the intensity of stimuli in psychological experiment followed by the electrophysiological experiment with selected stimuli based on previous ratings and with similar program of evaluating the intensity level as in the former experiment.

In order to obtain the reliable ERP components with high signal-to-noise ratio, a large scale of trials constituted by visual or auditory stimuli is needed [56]. In ERP studies of emotion processing, the trials of stimuli should be repeated for enough times to insure reliable and steady ERP components extracted from electroencephalographical (EEG) signals. However, the repeated experience of an identical visual stimulus would suppress the intensity of stimulus-related neuronal responses, namely, repetition suppression effect [67]. Fiebach et al. and Matsumoto et al. explored the ERP evidence of whether repetition suppression phenomenon existed during processing the repeated stimuli and found that N400 reduced significantly when stimulus-related information was repeatedly presented to subjects [68, 69]. Thus, using ERP to research emotion processing should endeavor to avoid the decreasing response to affective stimuli, which to some extent contradicts with the practice that repetition of stimuli-involved trials enables reliable and stable ERPs. Carefully, experimental design, with random and pseudorandom allocation of sequence of the emotional stimuli as well as trials, is necessarily considered to lower the subjects' familiarity with stimuli, especially faces and words. Moreover, just like Olofsson et al. proposed [6], researchers can assess the repetition effect evoked by repeated stimuli, with the purpose to evaluate whether repetition of stimuli changes over valence and arousal conditions.

As we reviewed above, emotion processing involves a complex and distributed network of cerebral regions. Consequently, assessing the spatial distribution of emotion-evoked ERPs is necessary. With the increasing complexity of ERP datasets obtained by high-density electrode arrays, the analysis method like principle component analysis (PCA) and independent component analysis (ICA) with more reliability can be employed into analyzing the ERP datasets obtained by high-density device. Meanwhile, it is partly helpful for circumventing certain restrictions of conventional ERP analytical methods, like insensitivity to brain activity indicated by low ERP signal and reference dependence (i.e., ERP amplitude varies with selections of reference electrodes) [70, 71]. Another advanced method called low-resolution brain electromagnetic tomography (LORETA) could combine with a head model constructed by the previous scanned MRI structural images to assess the spatial dynamics of emotion processing [56, 72, 73].

2.2.2. Stimulus Considerations. Emotion, as a systematical behavior with complex brain activities, incorporates various expressing modalities. As Adolphs reviewed, individuals can recognize emotions from multiple sensory modalities, including facial expressions, emotional prosody, and body expressions, or from the integration of multiple modalities [74]. When studying emotion processing, systematical investigation of emotion recognition from multiple modalities cannot be ignored, where temporal dynamics of emotion processes probably are affected by modalities due to the differential sensory pathways. However, the ERP studies for emotion processing mainly employed the facial expressions as emotion-eliciting stimuli. Compared with the extensive investigation into emotion triggered by visual modality, the ERP studies regarding affective processing seldom involve other modalities, while utilizing ERP into emotion response/experience elicited by vocal, bodily, and touching stimuli earned significant results [75–77]. What we elaborated above is for the one hand, and on the other hand, the integrality of emotion perception should be taken into account. Simultaneously, perception of emotional information comes from multiple sensory modalities, that is, individuals perceive and process concurrent input of affective cues including facial expressions, voice, and body expressions. And this concurrent input of multimodal information generally enhances the emotion perception and recognition [78, 79]. The ERP studies therefore should further involve exploration into the temporal integration of multimodal affective info, which even though have already found the interaction between facial and body expressions as well as between emotional prosody and body expressions [79, 80]. Moreover, integration of multisensory modalities adheres to demand for improving the ecological validity.

The reason why ERP researchers attended less to emotion-expressing modalities of voice, body, and touching may lead to less compatibility with complex physical properties of stimulus. ERP waves are sensitive to physical attributes of stimulus and changes of environment [56, 81]. And such fact necessitates the premeditation of controlling and maybe

evaluating stimulus physical properties and environmental variables. In addition, a certain number of researches probed into whether the physical properties of stimulus would affect the effects of emotional dimensions on ERP components, and found featural size, color, spatial frequency, and complexity as confounding factors in explaining the emotional effects on ERPs [82–85]. Thus, ERP studies of emotion processing have to strictly control the physical variables or to assess the overall complexity towards subjects as Carretié et al. performed in their study [86]. Numerous studies have shed light on the interaction and integration between emotion and sensory processing (e.g., emotional stimuli gain more rapidly processing relative to nonemotional ones) [87], yet few are known about how perceptual information interacts with processing emotional stimuli. The relationship between emotion processing and selective attention towards more salient stimulus will enlighten us in exploring the mechanism by which the stimulus physical properties modulate emotional response/experience [88].

Various affective systems have been developed for emotion elicitation and measurement based on differed cultural populations which been validated, such as IAPS [58], CFAPS [59], the Geneva Affective Picture Database (GAPED) [89], the Karolinska Directed Emotional Faces (KDEF) [90], NimStim Face Stimulus Set [91] for visual elicitation, and the International Affective Digital Sounds (IADS) [92], the Montreal Affective Voices (MAV) [93], and the Acoustic Profiles in Vocal Emotion Expression [94] for auditory elicitation. According to the discrete emotional model by Ekman [53], the basic emotions are ubiquitous through all cultures. Nonetheless, the cultural differences were still observed in recognition of emotions [95–97]. ERP study by Hot et al. found the electrophysiological evidence for cultural differences during emotional processing, in which the later components' amplitudes significantly decreased for Japanese subjects relative to French ones [98]. The databases based on the specifically cultural population necessitate the consideration of applicability towards current subjects. For further assurance of stability in evaluating valence/arousal, pilot study could be performed to have subjects voluntarily assess the dimensions. Another way to select the stimuli that we can produce on our own however arises another trouble that these made-up stimuli receive no validations and standardizations. The real-life emotion perception and production is a continuing affective processing. Studies regarding the sustained processing of emotion ordinarily employed the film clips as eliciting stimuli, instead of static pictures. This practice could supply individuals with more real-life accordant scenarios and more authentic emotional response/experience. The film clips databases have therefore been exploited to improve ecological validity. The current existed databases like IAPS and GAPED have been already added with film clips [61, 89]. It is worth noting that most of film clips databases could elicit discrete affective states [99]. On the other hand, IAPS validated the validity of film clips in eliciting emotional experience measured by valence and arousal, and so as the Emotional Movie Database (EMDB) [61, 99]. Although low numbers of ERP studies were reported with the emotion elicitation by film clips, yet like Chwilla et al. performed [100], reasonable and cautious experimental design would enable such method possible in ERP studies.

2.2.3. Emotion Categories. Most of the studies using ERP into emotion processing targeted the six basic emotional states, especially happy, sad, and fear, which is independent of social concerns (e.g., situation where emotions happen). However, emotion is generally, as acknowledged, the result of social events and interacts with social processes [101–103], which cannot be overlooked when considering conceptual emotions from the perspective of functionalism [104]. The researches need considerations of socially elicited emotions, especially when we take development of emotion processing into consideration. Some theorists, from another point of view, distinguish the two groups of elicited emotions into separate categories [105, 106]. The social emotions defined as a specific subset of emotions, compared to basic emotions, commonly incorporate envy, jealousy, shame, guilty, embarrassment, admiration, and so on. Norris et al. examined and verified the significant interaction between social and emotional processes [107], and the recent ERP study regarding the emotion recognition investigated and showed the significant difference of slow positive wave (SPW) on recognizing happiness and pride [108]. Even so, the social emotional processes are still much less well investigated than the basic emotional processing, possibly due to its inherent complexity, subjectivity, and prolonged experience [109]. And it remains to be resolved in the future.

2.2.4. Other Considerations. Based on James' peripheral perception theory and basic emotion theory by Ekman et al. [52], the emotion response is a systematical behavior incorporating psychological experience as well as physiological reflections which could be indexed by heart rate (HR), skin conductance level (SCL), respiratory rate (RR), and so on. And these indexes have been validated to be correlated with assessing the affective valence and arousal ratings [110–113]. Moreover, the physiological patterns accompanied with emotion response/experience have been utilized to classify the emotion categories, with high accuracy even in identifying the emotion of unknown individuals [114]. On the other hand, the physiological indexes, like HR, SCL, and RR, would also affect the electrophysiological signals, leading to interference with ERPs. Altogether, it is worth a try to measure these indexes and evaluate the influence on ERPs mirroring emotional processing other than removing and correcting artifacts based on certain algorithms (e.g., ICA).

3. Emotion Processing Revealed by ERPs

Numerous studies have been performed to answer the anatomical questions about emotion processing (for review, see Lindquist et al. and Dricu and Frühholz [5, 115]), especially for the six basic emotional states. However, answering the question like how cerebrum processes the affective information not only needs the studies of spatial properties but also needs investigating the temporal dynamics of processing emotion. With high temporal resolution, the ERP technique would perform surpassingly in temporally characterizing

the emotion processes, which will improve the understanding of when emotion recognition happens. And characterizing the temporal order of emotional ERPs would help to further investigate and speculate the specific ERP components responding to the specific emotions' recognition. It is therefore in demand, for further researching emotion processing temporally, to integrate the findings of ERP studies on emotion. In the following section, we would collect emotion-relevant studies using ERP and discourse the emotional effects on ERP components. Given the previous review by Olofsson et al. based on literatures of 1966–2007, we searched the studies published during 2007–2016. Based on past ERP studies and their own works, Luo et al. proposed the three-stage model to describe the time course of emotion processing. The model holds that the ERP components have differential preference for distinct emotional facial expressions [25]. And the various ERP components could contribute to emotion distinguishing in three stages: the first stage for automatic but coarse processing (N100 and P100), the second stage for distinguishing emotional and neutral facial expressions (N170 and VPP), and the third stage for distinguishing various emotional facial expressions (N300 and P300). The model has been extended to processing emotional words by Zhang et al. [116]. The following review mainly focus on the above ERP components with the additional EPN and LPP.

3.1. P100 and N100. P100 with an onset latency of 60–80 ms is a positive-direction component which peaks at around 100–130 ms after stimulus onset and generally is detected at the parieto-occipital electrodes. There exist recently ERP studies investigating the modulation of P100 by emotionality including valence and arousal factors. Luo et al. employed rapid serial visual presentation (RSVP) paradigm to explore the electrophysiological correlates of facial expression processing as well as the attentional blink effects on emotional facial expressions and found that P100 was significantly affected by facial emotions (i.e., fearful facial expressions elicited higher P100 than happy and neutral ones) [25]. And the results are consistent with the previous study by Utama et al. and the subsequent study by Aguado et al. [65, 66]. The latter two studies, respectively, manipulated the arousal and valence of stimuli to discuss whether the two dimensions correlated with P100 and returned with results of significant correlations for valence yet insignificant for arousal. Some ERP studies meanwhile applied other emotion-eliciting stimuli which include emotional words, emotional sentences, and emotional scenes [117–119]. Especially worth to note, the study by Rochas et al. combined EEG and transcranial magnetic stimulation (TMS), in which TMS was used to interfere the word-reception region, at the time when emotion significance was processed (i.e., between 70 and 200 ms). And the results showed slower detection of emotional words as compared to neutral words [117]. Moreover, Conty et al. assessed the interaction among gaze direction, body gesture, and facial expressions and also found the main effect of anger expressions on P100 activity except from the significant interaction [120]. Thus, based on the above sum-up, it is probably concluded that emotion processing starts at around 100 ms after stimulus onset but no integration of emotion significance and other social information.

For N100 considered as a sensory component, the work by Luo et al. indicated the significant emotion modulation of N100, in which fearful faces elicited larger N100 amplitudes than happy and neutral faces [25]. The results are in accordance with the previous studies [121, 122] and with the theoretical consideration that unpleasant stimuli can more easily capture the attention resources relative to pleasant and neutral ones [123]. Another study by Pell et al. with nonlinguistic vocals involved found that happy vocal stimuli significantly reduced the N100 latencies as compared to sad and anger stimuli but no significant main effect of emotion on N100 amplitudes [124], which may suggest the differences between processing emotional faces and emotional vocals. Some of the researches with emotional words also test the N100 differences elicited by emotionality, few of which reported significant effect of emotions on N100 amplitudes and latencies [116, 125]. And regarding the reason, this may lead to the visual fields of word presentation [126, 127]. Additionally, the integration of emotion modalities to some extent has been explored. Jessen and Kortz combined vocal, facial, and body expressions into the experimental paradigm and showed us the interaction between auditory and visual modalities reflected by N100 (i.e., N100 amplitudes were elicited smaller at audiovisual condition compared to unimodal condition) [79]. Combined with the unanimous findings about emotional effects on N100, conclusion could be made that N100 is probably influenced by complex factors to be dissociated and maybe indicate the interaction among various modalities.

3.2. N170 and VPP. N170 is a negative-going ERP component detected at the lateral occipitotemporal electrodes, which peaks around 170 ms after stimulus onset. This component has been found to be sensitive to face stimuli rather than nonface stimuli [128]. Most ERP studies about emotion processing involved the analysis of N170 component. In study by Luo et al., experimenters recorded the electroencephalographic signals locked to emotion response and obtained the significant emotional modulation of N170, in which happy and fearful facial expressions elicited larger N170 amplitudes and shorter latencies than the neutral faces [25]. This study employing the RSVP also found the significant differentiation between fearful and happy expressions by N170, which indicated that N170 may contribute to distinguishing the emotional facial expressions. Such findings received supports from other studies [129–132]. Moreover, another supporting study with magnetoencephalography (MEG), in which a sphere head model was scanned by MRI and fitted to the inner skull surface, in the fusiform gyrus, showed larger amplitude elicited by fearful expressions than by neutral faces at 170 ms [133]. However, some researches yielded contradicting outcomes. Like Leppänen et al., they manipulated the intensities of fearful and happy emotional expressions and found no significant emotion effect on N170 amplitudes [134], which other studies agreed with [135–137]. A meta-analysis included 57 emotion studies and calculated the overall effect size describing N170

responses to emotional faces, which exhibited larger N170 amplitudes elicited by anger, fear, and happy facial expressions relative to neutral faces [138]. The meta-analysis also investigated the moderators that may affect N170 differentiation between emotional faces and neutral ones and suggested that N170 was sensitive to unattended stimuli and was a subject to the reference electrodes. To sum up, N170 as a valuable instrument can be effectively applied to study the neural processing of emotion, but modulatory factors need further consideration and investigation.

VPP is a positive component with a peak latency similar to that of N170 and is detected at the frontocentral electrodes. Rossion et al. verified VPP's sensitivity to face stimuli processing other than N170 [128]. The ERP researches regarding the N170 component generally report the analytical results of the VPP component. Consistent with the previous studies [139–141], Luo et al. obtained the significant emotional effect on VPP amplitudes as well as on VPP latencies, in which happy and fearful faces elicited larger VPP amplitudes than neutral facial expressions. Contrasted with the facts that few studies included in this review reported the significant emotional modulation of VPP latencies (or chose not to report the results about VPP latencies), Luo et al. also showed that shorter latencies were elicited by fearful facial expressions than by happy and neutral faces [25]. The subsequent studies additionally provided the support for findings obtained by Luo et al. [142–144]. It is evidenced that early processing indicated by N170/VPP occurs in discriminating fearful/happy facial expressions and neutral faces [145]. Other than such point of view, the studies contrasting positive and negative emotions suggested the possible differentiation between positive and negative facial expressions by VPP. For instance, Willis and Rburke involved anger and happy faces in the study and detected the significant ERP difference between two emotions with larger VPP amplitudes elicited by angry blocks than by happy blocks [144]. And in another study, the disgust facial expressions evoked larger VPP amplitudes than the happy faces [142]. Agreement therefore could be made that negative facial expressions receive perhaps more early processing as compared to other facial expressions.

3.3. EPN. EPN, namely, early posterior negativity, peaks at 210–350 ms with a topographical distribution over occipitotemporal sites. The EPN effect for emotionality has been normally reported in studies using emotional faces and words to elicit emotion response/experience. The very recent study by Calvo et al. assessed the emotion effect on ERPs with the emotion-eliciting stimuli of whole faces and half faces employed, in which the EPN amplitudes for angry expressions were larger than those elicited by other facial expressions in the right hemisphere and were larger than those for neutral faces in the left hemisphere, but the above effects were only seen in whole face condition [146]. And the results indicate that the early lateralized processing (e.g., brain activity reflected by N170 and VPP) possibly encodes the holistic features of emotion. The work by Zhang et al. obtained significantly larger EPN amplitudes for positive and negative words than for neutral words. In this study, hemisphere effect on EPN amplitudes was observed as well, with more negative-going EPN for emotional words than the neutral ones in the left hemisphere [116], which is consistent with the abovementioned study. But unlike the study by Calvo et al., Zhang et al. reported no significant difference of EPN amplitudes between negative and positive emotional words, and this could be contributed to the delayed access to the emotion value of words relative to facial expressions [131, 147]. Other researches regarding the emotion processing also illustrated the evidence for modulation of the EPN component by facial expressions [65, 148], emotional pictures [64, 149], and emotional words [122, 150, 151]. Combined with the findings that angry faces elicit larger EPN components than happy facial expressions [148, 152], it is therefore concluded that the EPN occurring after N170 may discriminate the discrete emotions.

3.4. P300 and LPP (or as LPC). P300 is a positive-going deflection detected at parieto-occipital electrodes, with sthe peak latency after 300 ms. The P300 discussed here refers to the component extracted from the 300–450 segmentation rather than P300 family. This component has been referred to as indicating the high order cognitive operations associated with attention performance, which may respond to the attentional allocation towards the motivationally salient stimuli. Consistent with such theoretical considerations that the P300 is also sensitive to the stimuli of emotional salience, the early studies regarding emotion processing primarily focus on the P300 effect for emotional valence and arousal and found the significant modulation of P300 amplitudes by the two dimensions [24, 141, 153–155]. For discrete emotions, the recent studies incorporating the P300 analysis also obtained promising results. In a study by Luo et al., the P300 amplitudes for facial expressions showed difference between the fearful and the happy as well as the emotional faces and neutral faces [25], which to some degree extended the previous findings that angry faces elicited larger P300 than happy and neutral faces [156]. Schupp et al. attributed the P300 difference between anger and happy to a more arousal for anger than happy. By contrast, the study by Luo et al. controlled the level of arousal for emotional faces, which would lead to a more convincing conclusion. As we all know, the P300 can be divided into two subcomponents, namely, P3a and P3b. The recent study, respectively, analyzed the two subcomponent amplitudes responding to angry and happy faces and suggested opposite patterns towards emotionality, in which angry elicited smaller P3a amplitudes than happy and larger P3b amplitudes for angry than for happy [144]. The findings about P3b additionally received the support from a subsequent study [143]. This may be due to the less attention orienting towards happy than angry [157]. In a word, P300 can be a valuable tool to explore emotion processing, especially for relationship between emotion and attention.

LPP, also known as LPC, is a positive-going ERP component peaking as early as 300 ms and is generally detected at parietal sites lasting for hundreds of milliseconds after stimulus presentation. LPP is evident at central and frontal midline sites as compared to the earlier parietal positivities, and the component could even persist for several seconds

[158, 159]. Especially in studies regarding emotion processing, the PCA analytical method revealed that the LPP significantly differed from the early parietal activities (the activities could be indexed by P300) responding to emotional stimuli [160]. The emotion effect on LPP has received ample supporting evidence from the existent studies. The recent study performed by Zhang et al. verified markedly the modulation of LPC by emotional adjectives, reflecting the larger LPC amplitudes elicited by positive words than the ones by negative words and neutral words [116]. The results are consistent with the previous studies and a subsequent study using emotional nouns [131, 150, 161–163]. For emotional faces, Calvo et al. equally analyzed the LPP response to emotional faces, but the emotion modulation of the component was only seen in upper face half condition with an augmented LPP amplitudes for angry faces than those for the other expressions (neutral, happy, and surprise) [146]. The results supplied a further support for the previous findings regarding the relationship between emotion processing and LPP and additionally to some extent are supported by a subsequent study with RSVP involved [131, 134, 147, 164]. Another ERP study employed the dynamical emotional faces which constituted emotional clips and also found the significant LPC difference among fear, anger, surprise, disgust, sad, and neutral (fear > the rest; anger and surprise > happy) [165]. Combined with the above review, it could be concluded that LPP, mirroring the more elaborative processing of emotion than early and midlatency components, is sensitive to discriminate the discrete emotions.

4. From Developmental Emotion and Mental Disorders to Neural Plasticity

In the above section, we reviewed recent decade's progresses in emotion processing investigated by ERP, which indicated the temporal characteristics of emotion processing described by ERP components. On the other hand, emotions cannot be treated as a static competence, but of dynamical developmental properties which are usually accompanied with development of sociality. The development of emotion processing could lead to more appropriate emotional experience and response and also could lead to dysfunctions of emotion processes (like mood disorders), which may be reflected through changes of neural plasticity. Thus, in the following parts, the studies regarding the emotion development and mood disorders will be collected and reviewed, which future researches might put their emphasis on.

4.1. Emotion Development and Neural Plasticity. As mentioned in the Introduction, emotion of developmental feasibility could be enhanced through learning (or training) and growing ages or suffers from deficits due to malfunctions of emotion-related neural basis and alternatively disturbances in environmental factors [166, 167]. Researches have investigated these developmental changes of affective processing, by means of behavioral, psychophysical, and neural imaging (fMRI) methods, in humans including healthy normal and patients with mental disorders. Even in adulthood, the emotional competence can be boosted through intervention [168]. And these researches have in turn identified attainable development-dependent changes of emotion processes and cerebral regions that develop along with the growing age or after training. These region changes include greater medial prefrontal control over negative inputs, increased activations in medial orbitofrontal cortex, and putamen for empathy [40, 169]. ERP, despite its incapability to localize the brain regions of developmental changes, could also be employed to explore the developments of emotional processing, which offers an effective instrument for evaluating the changes of processing course of emotion. In the study by Williams et al., advancing age was found to be associated with the decrease of early ERPs over the medial frontocentral electrodes that are supposed to be responsible for happiness [169]. The above changes in the behavior level and cerebral regions to some extent approve the neural plasticity for emotion processing.

From the perspective of psychopathology, the patients with mental disorders who generally somehow manifest the deficits in affective processing should be the targets of emotional investigation, especially affective and mood disorders, alexithymia, autism spectrum disorders, and schizophrenia. Compared to healthy controls, the patients commonly showed significant discrepancy in emotional processes measured with the ERP method, with the detailed results that for instance schizophrenics both suffered disruption of early processes (P100, N170, and N250) and late emotional processing (P300 and LPP) modulated by attention [170–173] and that P100 and P200 for depression were higher evoked by identical sad-eliciting stimuli than for normal people and larger P200 for neutral expressions relative to the positive ones might suggest the diminished perceptual processing of emotion information [174, 175]. These comparative studies between the mental disorders and the healthy could provide exploration of emotion mechanism with the potent and diversified evidences that deficits in emotion processing possibly suggest the disruption of essential mechanism for emotion, which the analysis of localizing the disruption mirrored by ERP discrepancies would serve beneficially to. It is hence critical to emphasize and integrate both emotional findings about normal populations and psychiatric ones.

Unlike organic diseases, mental disorders cannot be attributed to the specific pathogenesis. Especially, for mood disorders of emotion deficits, it meets mass difficulties in locating specifically consistent heterogeneous brain lesions across countless studies, from which the steady and efficient biomarkers could not be easily defined. It is commonly acknowledged nowadays that mood disorders result from the combined influences of physiological and environmental factors (including psychological and social factors). Consistent with such consideration, mood disorders have been attributed to the disturbances in neural plasticity [44]. The neural plasticity refers to a fundamental attribute of nervous systems, the structures and dynamics of which could be altered corresponding to continuing inputs into the systems. And this neural property hence underlies learning. Neural plasticity is a double-edged sword which would lead to the enhancement of related functions owing to the accommodative inputs or would lead to the functional deficits due to the

inputs of maladjustments. And such property possibly causes malfunctional psychosomatical symptoms that are behaved by patients with mental disorders, like mood disorders and schizophrenias [44].

Neural plasticity can be assessed by longitudinal studies using fMRI and other techniques, which is an indirect means to investigate the changes of cerebral processing and related regions. Neural plasticity additionally can be measured by LTP and long-term depression (LTD) methods [176], which have been effectively used in animal experiments [177]. And subsequent researchers successfully applied the ERP technique, in which stimulus-specific paradigm (SSP) was employed, to induce the LTP [42]. Other than the SSP method, the ERP component, namely, mismatch negativity (MMN), was confirmed with the capability to index the neural plasticity [178]. On the other hand, N100 repetition reflecting neural adaption also was utilized to investigate the health of plasticity mechanisms required for normal development [179]. Plasticity changes in humans can hence be detected using the noninvasive means of the ERP technique. There exist studies using this method to assess the impaired plasticity of visual and auditory systems in patients with schizophrenia and obtained the significant results [45, 180]. However, seldom studies were reported with the application into emotion processing and patients with mood disorders. Still, we suppose that this plasticity-assessing method with an appropriate improvement might have the potential in assessing the neural plasticity in mood disorders as well. For further study of emotion-related neural plasticity in mood disorders, it is necessary to review the recent progress from the studies regarding emotion processing and neural plasticity in mood disorders, which is expected to offer enlightening for the pathogenesis of mood disorders and offer the potential targets for therapy.

In the following section, we reviewed the emotional studies which emphasized the developmental properties of emotion processing and the studies that focused on mood disorders suffering emotional deficits. Then the neural plasticity for emotion processing was summarized.

4.2. Normal versus Mood Disorders. William et al. administered a test to 1000 healthy individuals whose ages cover the lifespan period from 6 to 91 and assessed the explicit as well as implicit recognition of facial emotions, which obtained the result that performance in recognition of emotions improved from childhood through adolescence to early adulthood and then declined in later adulthood [181]. This study provides a powerful evidence for emotion development along with advancing age. Researchers employed the ERP method to investigate the relationship between emotion processing and ages, with the offer of electrophysiological evidence for developing emotion processes. In the study by Kisley et al. [182], the subjects between 18 and 81 years old were asked to categorize the images as positive, negative, or neutral emotion and were simultaneously recorded with EEG device for ERP signals. And the study verified the significant variation of LPP amplitudes with advancing age, in which the LPP amplitudes elicited by negative stimuli were reversely significantly correlated with age while the amplitudes of LPP elicited by positive and neutral ones were not. Such findings regarding the LPP component to some extent reflected the development of top-down regulation for emotion response/experience. Another study performed by Wieser et al. investigated the EPN changes responding to the arousal of emotional stimuli along with the growing age, in which EPN was slightly delayed in elder subjects relative to the younger subjects [183]. The reduction in emotional modulation of the EPN component observed in elderly subjects probably indicates an age-related delay of early visual emotion discrimination. However, Wieser et al. emphasized no influence of this delay on further evaluative processing of emotional stimuli. Combined with the abovementioned study, it could be concluded that the speed of emotion discrimination might decrease from younger adulthood to elderly ones but increased the top-down modulation of emotion response/experience with increasing age to the elderly.

Through training, the process of emotional information gets impacted as well. Especially, in musical training, with accumulated evidences from EEG and fMRI, its capability in changing brain neural plasticity has been verified (for review, see Herholz et al. [184]). ERP as a means also can be employed to assess the plasticity changes related with training. Pinheiro and colleagues compared musicians and nonmusician healthy controls when they listened to sentences with two conditions: sematic content (neutral versus happy versus angry) and pure prosody. The results showed that musicians differed in P200 amplitudes between two conditions, whereas the P200 amplitudes of nonmusicians remained unchanged. And the participants with musical training were more accurate in recognizing angry prosody involved in the sematic sentences [185]. Not only musical training but also mental training, such as meditation, affects significantly neural plasticity and brain functions as well [186]. The ERP study exploring the effects of meditation on emotional processes also offers the evidence for emotional development, in which meditators are less affected by negative stimuli and the influence of positive ones remains unchanged [187]. The above electrophysiological variations with advancing age mirrored the plasticity for neural basis underlying emotion processing, which has been approved by fMRI studies [169, 188].

As mentioned above, the patients with mood disorders, like depression, showed main symptoms manifested in affective deficits mirrored by ERP components compared to healthy controls [189]. And the causes of such disorders have been availably explained towards the damage in neural plasticity, which enables the incapability to harmonically coordinate with experimental inputs, vice versa [190, 191]. A very recent multicenter study enrolled 3036 participants and found the significant association between childhood adversity and subcortical abnormalities, in which increased exposure to childhood adversity led to the smaller caudate volumes in females [192]. It could legitimately be deduced that exactly the subcortical areas of neural plasticity, as a double-edged sword, give rise to the abnormality-orienting changes. Studies using the ERP method found the high-risk individuals (high risk for mood disorders) showing abnormalities in ERP components responding to threatening and

negative stimuli compared to the age- and gender-matched low-risk individuals. In studies by Nelson et al. and Kujawa et al., the offspring of depressed parents relative to the offspring of healthy parents demonstrated decreased LPP amplitudes in response to negative and threatening faces and threatening scenes [193, 194]. This discrepancy in emotional response may be due to the dysfunctional plasticity that was inherited from parents of mood disorders [195]. And the neural plasticity additionally is embodied in the invertible properties of such changes. Hetzel et al. assessed the astroglial protein S100B and visually evoked ERPs before and after antidepressant treatment, in which S100B concentration increased as well as that P300 latency was normalized and P200 latency significantly decreased after weeks of treatment [196]. The results are consistent with the subsequent studies using the ERP, MEG, and fMRI methods [197–199].

Neural plasticity, other than the abovementioned cross-sectional and longitudinal studies, could be assessed by LTP or LTD induced by SSP involved in ERP design and could even be assessed by the MMN component evoked in auditory cortex. But unlike the application of LTP into schizophrenia plasticity, few studies were seen to investigate the neural plasticity in mood disorders. As evidenced by the previous studies [42, 43], LTP measured by the ERP technique could be employed to evaluate the neural plasticity of visual and auditory cortex. From this perspective, researchers at least could explore the plasticity of perceptual processing for visual and auditory emotional information through such means. It is therefore noteworthy that future studies regarding dysfunctional neural plasticity associated with mood disorders could consider the practical feasibility of employing the noninvasive ERP technique, which could be combined with PCA and LORETA analytical methods, to define the sources of potential neural plasticity.

5. Conclusion

ERP, as a high temporal resolution method, has demonstrated its advantage, compared with the fMRI method, in exploring the temporal dynamics of cerebral activities. Emotion is a complex systematical behavior consisting of peripheral expressions and internal experiences. Compared with its cerebral spatial localization obtaining extremely high-speed progress, the temporal course of emotion processing remains unclear. It is therefore requisite and urgent to push the demand for temporally investigating the mechanism of emotion processing, which application of ERP to some extent could fit. And based on the ERP researches, the three-stage model for processing emotional facial expressions has been proposed by Luo et al.

The neural plasticity enables the emotional development along with the advancing age. And the dysfunctions of neural plasticity for emotion processing have been explained as the causes of mood disorders. ERP, in which the SSP is included, can be employed to investigate the neural plasticity of nervous system. However, such method seldom was applicated into mood disorders, which is waited to be explored in future researches.

Nonetheless, plenty of puzzles with respect to emotion processing remain to be resolved. As reviewed above, most of ERP studies about emotion processing employed the emotional picture, facial expressions, and emotional words as stimuli to elicit emotion response/experience. Other stimulus modalities, like voice, body, and gesture, triggering the emotion response/experience, should receive more attention. The time course of the integration of various emotional modalities is still unclear and needs more consideration. Other issues, for instance the temporal mechanism of social emotion beyond basic emotions and development of emotions, are all worth the efforts, which will be helpful for comprehending what emotion is.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Rui Ding, Ping Li, and Wei Wang contributed equally to this work.

Acknowledgments

The work was supported by the National Natural Science Foundation of China (Grant no. 31371033).

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Hindawi
Neural Plasticity
Volume 2017, Article ID 6986983, 10 pages
https://doi.org/10.1155/2017/6986983

Review Article

Effect of Hypoxic Injury in Mood Disorder

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Received 24 March 2017; Revised 26 May 2017; Accepted 6 June 2017; Published 22 June 2017

Academic Editor: Aijun Li

Hypoxemia is a common complication of the diseases associated with the central nervous system, and neurons are highly sensitive to the availability of oxygen. Neuroplasticity is an important property of the neural system controlling breathing, memory, and cognitive ability. However, the underlying mechanism has not yet been clearly elucidated. In recent years, several pieces of evidence have highlighted the effect of hypoxic injury on neuronal plasticity in the pathogenesis and treatment of mood disorder. Therefore, the present study reviewed the relevant articles regarding hypoxic injury and neuronal plasticity and discussed the pathological changes and physiological functions of neurons in hypoxemia in order to provide a translational perspective to the relevance of hypoxic injury and mood disorder.

1. Introduction

The ability of the brain to absorb internal and external information, learn new skills, and form new memories is dependent on neural functions. Neurons are the fundamental structural and functional units in the neural information network. The neural plasticity might be an ability of the nervous system to adapt in response to intrinsic and extrinsic stimuli [1]. A large number of studies demonstrate that neural circuits, synaptic connections, morphology, and the biochemical components (including nucleic acids, enzymes, and neurotransmitters) of a single neuron may exhibit a certain degree of plasticity. This phenomenon explicates why dysregulation or disruption of neural plasticity may be associated with neurodegenerative and neuropsychiatric disorders, such as mood disorders. Mood disorders are known as mental disorders characterized by periodic elevation of the mood, which might sometimes alternate with the periodic depression. The pathogenesis of mood disorders is yet uncertain, and the role of neural plasticity in mood disorder has been widely evaluated.

Recently, a large number of factors have been identified that can affect neural plasticity; the correlation between hypoxic injury and neural plasticity has been under intensive focus. In this article, we review some of the recent studies on the relationship of hypoxic injury and neural plasticity in mood disorders and explore the mechanism underlying the hypoxic damage leading to mood disorders.

2. The Main Mechanism of Hypoxic Injury

Hypoxemia refers to insufficient oxygen in the circulating blood. However, the general term hypoxia indicates an abnormally low concentration of oxygen in any tissue, organ, or the body as a whole. Hypoxia has been implicated in a large number of pathologies, including head trauma, stroke, neurodegenerative diseases, obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD), which are related to the central nervous system (CNS) and respiratory system. Thus, any factors that affect the volume or rate of oxygen reaching the lungs or any causes that lessen the transfer of oxygen from the lungs to the blood might result in hypoxemia. The brain is highly sensitive to the oxygen concentration in the artery [2]. Any disease that affects the airflow and blood perfusion could cause decreased oxygen supply to the brain [3] that might alter the neuronal function, leading to cell injury and death. Spatial memory and learning deficits caused by long-term intermittent hypoxia (IH) are accompanied by an increase in oxidative stress in the brain areas, such as the

hippocampus, involved in cognition and memory [4]. Hypoxia causes the enhanced anaerobic glycolysis in cells [5, 6], which led to aberrant oxidative phosphorylation and energy supplement in cells. In addition, patients with COPD and obstructive sleep apnea are often accompanied by systemic inflammation [7, 8], which might aggravate the neuronal damage. Hypoxia-induced neurodegeneration and apoptosis may also play a vital role in mood disorder. Protocatechuic acid (PCA) was noted to alleviate the oxidative stress, apoptosis, and glial proliferation; moreover, it also decreased the level of IL-1β in the brain following chronic intermittent hypoxia, further enhancing the learning and memory ability [9].

In addition, ischemia is commonly a restriction in blood supply to tissues, which result in the deficiency of glucose and oxygen needed for cellular metabolism. Ischemia includes insufficiency of oxygen, decreased availability of nutrients, and inadequate discharge of metabolic rubbish. Both hypoxic injury and ischemic damage effectuate in coordination during the pathogenic process of different diseases, such as stroke.

2.1. Oxidative Stress. Oxidative stress is caused by increased production of both reactive oxygen species (ROS) and reactive nitrogen species (RNS) or decreased antioxidant ability and the capacity of elimination of free radicals. When the oxygen supply is not sufficient, the electron transport chain is impeded, and oxygen radicals and peroxynitrite can be produced, including hydrogen peroxide, superoxide, perhydroxyl, and hydroxyl radicals. This process can be aggregated by Ca^{2+} accumulation in the mitochondria that results in mitochondrial dysfunction which, in turn, increases the production of reactive oxygen radicals. All these ROS/RNS can alter the structure of DNA by direct interaction and lead to cell injury and apoptosis [10]. Hypoxia also induces the cells to undergo oxidative stress from the uncontrolled generation of ROS in the mitochondrion that might lead to cell death in the tissue [6, 11, 12]. The hypoxia and ischemia-reperfusion injury are severe in some brain injury patients; the abundant production of ROS/RNS and inadequate supply of antioxidants is primarily responsible for the subsequent brain pathology, as the balance between the oxidative and antioxidative systems is disrupted in the brain [13, 14]. However, the chronic intermittent hypoxia (CIH) is shown to occur in the respiratory diseases, causing an increase in ROS/RNS and the overall oxidative stress [13, 14]. Furthermore, oxidative stress is associated with the development of CNS diseases involving cognitive function and memory processes [15–17], such as hippocampal synaptic plasticity. Hypoxia-induced oxidative stress also contributes to neurodegeneration and apoptosis [18], as well as spatial memory impairment [11].

2.2. Systemic Inflammation. Systemic inflammation is crucial for the mechanism of hypoxic brain injury [19, 20]. The acute and chronic inflammation event that occurs during and following hypoxia may be involved in secondary neuronal injury processes [10]. The process of inflammation is characterized by the infiltration of inflammatory cells, production of inflammatory mediators, and activation of resident cells. The activation and infiltration of inflammatory cells into a functional brain area is the interactive effect of a series of adhesion molecules, chemokines, and cytokines. The cytokines involved in the process of hypoxic injury include tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), interleukin-6 (IL-6), and other factors. Various cytokines and chemokines have been produced and released during the inflammatory process; furthermore, neutrophils, macrophages, T cells, and other cells, have been activated, which could aggravate the secondary injury of the tissue [10]. The prognosis of acute and prolonged inflammatory process in the brain may be different depending on the ether interaction between the inflammatory cells and mediators or the compensatory capacity of the body.

Overall, the chronic systemic inflammation may result in cognitive function impairment by the following aspects: (1) persistent activation of microglia induces neuronal injury [21]; (2) inflammation leads to the morphological changes in neuronal dendritic spines in susceptible regions in the brain [22]; and (3) inflammation downregulates the expression of the genes associated with growth factors that are involved in cognitive and memory ability [22].

2.3. Apoptosis. Apoptosis is a genetically programmed cell death occurring at specific developing stages in plants and animals; it is an active death-related process of the cells and is controlled by specific genes [23, 24]. The biochemical events lead to characteristic morphological changes and death in the cells. These characteristic changes include cell blebbing, cell shrinkage, nuclear chromatin condensation and fragmentation, chromosomal DNA fragmentation, and mRNA decay [10]. In normal physiological conditions, apoptosis is a homeostatic mechanism maintaining the cells in different tissues. Apoptosis also occurs as a protective response in the case of cell damage in abnormal pathological conditions. Apoptosis is an energy-dependent coordinated process that involves the activation of a series of cysteine proteases and a complex cascade of events that link the initiating stimuli to the final cell death [23]. In some cells, radiation treatment can lead to apoptosis through a p53-dependent pathway-mediated DNA damage, as well as other cellular apoptosis reactions induced by expressing Fas or TNF receptors [23]. A recent study suggests that delayed hyperbaric oxygen can enhance neurogenesis and improve neuronal function by ROS/HIF-1α/β-catenin pathway [25].

2.4. Endoplasmic Reticulum and Excitotoxicity. The endoplasmic reticulum (ER) is a locus where proteins are modified, folded, and calcium-modulated. Reportedly, ER can prevent oxidative stress and aberrant Ca^{2+} regulation from killing the neurons in vivo and in vitro [26–28]. ER stress is initiated in the early stage of hypoxic-ischemia, and the activation of ER stress response is a grave consequence of enhanced oxidative stress, which could result in a series of cellular malfunctions as well as neuronal apoptosis [29, 30]. ER stress can cooperate with autophagy in the process of neurodegeneration with the morphological changes in the ER structure [31]. Regular exposure to the intermittent hypoxic environment can cause dilation and distortion of ER in

the hippocampus of mice that is accompanied by excessive expression of Grp78 [32], caspase-12, and CHOP; caspase-12 and CHOP are the two mediators associated with ER-induced apoptosis [33, 34].

CIH exposures lead to upregulation of the unfolded protein response (UPR) in the brain prefrontal cortex and hippocampus by enhanced phosphorylation of PKR-like ER kinase, which indicates that a specific ERS inhibitor, salubrinal, protects the neurons against CIH-induced injury [35]. The short-lasting activation of UPR can prevent its further accumulation by inhibiting the synthesis of protein, and the sustained activation of UPR might be associated with the neurodegeneration in hypoxia-ischemia [36].

Thus, the above findings suggest that ER is a valuable biomarker of the severity of hypoxia-ischemia injury.

3. Hypoxic Injury and Neuronal Plasticity

The brain is highly sensitive to the change in the arterial concentration of oxygen [2]; it ineluctably sustains the hypoxic stress. Decreased oxygen content might lead to neuronal injury in the brains of COPD patients, which is demonstrated by clinical symptoms such as mood disorders and neuropsychological deficits [3]. Furthermore, the systemic inflammation is accompanied by a hypoxic injury that may exacerbate the neuronal injury. A large number of patients with intermittent hypoxia manifest a series of symptoms related to the injury to the nervous system, which is exhibited as a deficiency in memory, learning, and decision-making ability [37]. In addition, the hypoxic damage in the brains of other patients is manifested as depression, anxiety, physical disabilities [7], and neuropsychological deficits [2, 38–41]. Compared to the controls, patients with COPD displayed a poor performance in the figure memory test, mini-mental state examination, and visual reproduction [3]. Some studies demonstrate that hypoxia is associated with the changes in the brain structure, including volume atrophy and a decrease in the gray matter in the amygdala, hippocampus, anterior cingulate cortex, prefrontal cortex, and other regions [42, 43]. Different degrees of IH-induced irreversible damage to the neural cell ultrastructure and loss of nerve cells, which could cause various degrees of nervous system disorders. The neuronal plasticity plays a critical role in brain function. The hypoxic injury affects the neuronal plasticity in the brain through different mechanisms, thereby affecting the brain in response to intrinsic and extrinsic stimuli. Moreover, several regions of the brain, such as the hippocampus, frontal cortex, amygdala, insula, anterior cingulate, fornix, mammillary bodies, and cerebellum, are impaired during and after sleep-disordered breathing, and all these structures are altered in depression patients [44]. The different kinds of changes of neural plasticity induced by hypoxic-ischemic injury in various brain regions are shown in Table 1.

3.1. The Hypoxic Injury in the Hippocampus. In the brain, the hippocampus has an affinity with learning and memory, and the hippocampal synapse is a model system to study the mechanisms of learning and memory [45]. The hippocampal synaptic plasticity is considered as important for the formation of hippocampus-dependent explicit memory [46]. A previous study on quantum dots proved that nanoparticle impaired the synaptic transmission and plasticity in the hippocampus dentate gyrus area of rats via oxidative stress [47]. The long-term synaptic plasticity is an essential property of the nervous system and a critical mechanism for memory and learning, which can bidirectionally modify the synaptic strength—either depressing (long-term depression (LTD)) or enhancing (long-term potentiation (LTP)) [48]. Some studies show that NO affects the hippocampal synaptic plasticity, including LTD and LTP, and consequently learning and memory [49–54]. Also, NO serves as a retrograde messenger and acts directly on the presynaptic neurons to produce LTP [48, 55–57] and then suppresses the synaptic plasticity [58]. Other studies have shown that some drugs could protect the hippocampal neurons by inhibiting the NOS activity and expression in the hippocampus [58–60]. The ER stress induced by chronic IH resulted in apoptosis and fine structural changes in the synapses in the hippocampal CA1 region [61], which might inhibit the transfer of Schaffer collaterals from CA3 to CA1 neurons [62]. Hypoxia and inflammation act in synergy to trigger the long-term synaptic depression (LTD), which might contribute towards synaptic disruptions and memory impairments in neuroinflammation-related brain disorders [63].

MAPK phosphorylation is enhanced following IH. The overstimulation of MAPK signaling pathways by IH induces the abnormal expression of Bax and Bcl-2, resulting in a severe loss of hippocampal neurons. This phenomenon was correlated to oxidative stress, inducing the upregulation of malondialdehyde (MDA) and the downregulation of superoxide dismutase (SOD) [64]. Accumulating evidence demonstrate that the production of ROS is closely related to protein folding [65, 66], and the accumulation of misfolded or unfolded protein could cause increased ROS production [29]. The present study suggests that the aberrant energy metabolism might be an alternative mechanism underlying depression.

In addition, the volumetric changes of the hippocampus are also critical to mood regulation. Reportedly, the cognitive disabilities in hypoxia-ischemic encephalopathy patients are also accompanied by hippocampal atrophy; the white matter density is decreased in the frontal gyrus [67, 68]. In the event of hypoxia induced by central hypoventilation syndrome (CHS), the hippocampus shows a reduced volume [69]. Smaller hippocampal volumes have also been reported in schizophrenic individuals who suffered pre- and perinatal hypoxia [70]. Additionally, some studies postulate that hippocampal apoptosis is a causative factor in hippocampal volumetric changes [71].

3.2. The Hypoxic Injury in the Prefrontal Cortex. The prefrontal cortex (PFC) is a crucial nerve center of thinking and behavior regulation in the brain [72] and is divided into two subregions: ventromedial prefrontal cortex (vmPFC) for regulating the affection and dorsolateral sectors (dlPFC) for mediating the cognitive functions [73, 74]. The interactions within the neuronal networks centered on the hippocampus and PFC are closely related to information transfer

and storage [75–77]. The PFC receives strong monosynaptic projections from the intermediate and ventral hippocampus [78, 79]. The hypoxia-ischemic injury causes the disruption of interactions within the prefrontal-hippocampal networks [80], which could affect the thinking and behavior. Several studies reported that the frontal lobe dysfunction led to various degrees of cognitive impairments such as inattention, hyperactivity, impulsiveness, and changes in the personality [81].

PFC is a region contributing towards the behavioral regulation and neuroendocrine responses to stress and can be injured by excessive exposure to a stimuli-induced release of inflammatory mediators and steroid molecules [82–84]. A previous study reported that animals exposed to IH presented impaired executive function associated with dopaminergic disturbance and tissue atrophy in the PFC [85]. The increased density of GABAergic neurons in the PFC during and after IH disrupts the balance between excitation and inhibition which, in turn, impairs the network activity within PFC [80]. Since the thalamic burst spikes are efficient in exciting the postsynaptic neurons [86], the activation of T-type Ca^{2+} channels in the MD might specifically stimulate the PFC neurons and then lead to frontal lobe-specific seizures [81]. In the mouse model, PFC damage induced by hypoxic conditions including ghost cells, increased the neuronal death and upregulated the expression of molecules such as VEGF, Glut1, Hif-1, and lactate dehydrogenase A, which might cause a local excitability in PFC neurons [81, 87]. In addition, NADPH oxidase-2 induced the oxidative stress that might contribute to the developmental loss of parvalbumin- (PV-) positive cells (PV-cells) in the PFC and progression of psychiatric anxiety in rat models [72, 88]. Moreover, the loss of PV-cells in the PFC and the IH-induced psychiatric anxiety can be alleviated by inhibiting the NADPH oxidase-2-induced oxidative stress [88].

Acetylcholine is an indispensable element for memory and learning [89]. IH could induce spatial learning deficits, and the expression of choline acetyltransferase in the basal forebrain decreased in rats [90, 91]. Muscarinic cholinergic receptors are coupled to G proteins [92], and M2-muscarinic receptor regulates the release of acetylcholine in PFC in mouse [93]. G proteins constitute a functionally complex network that enhances the transmembrane signaling. A few changes in the activation of G proteins can dramatically cause distal signal transduction cascades. Hypoxia enhanced the cholinergic activation and mu-opioid activation of G proteins in the PFC, thereby increasing the acetylcholine release of PFC neurons; thus, the functions of PFC is altered [94].

3.3. The Hypoxic Injury in the Amygdala. The amygdala is closely associated with emotion, learning, attention, and memory, especially its role in the correlation between negative emotion and learning ability as well as memory [95]. The disturbances to the amygdala constitute the primary features of bipolar disorder [96]. The various changes in the morphology and function of amygdala might be related to mood disorders such as depression [97, 98]. The hypoxic injury arising from diverse factors might cause serious changes in the amygdala and has been demonstrated in several animal models. Carty et al. found a significant decrease in the cell size and axonal degeneration of corticotropin-releasing factor-positive neurons in the amygdala of the rat after undergoing neonatal hypoxia-ischemia [99]. The gray matter in the amygdala is reduced in children who suffered from neonatal hypoxia-ischemia [100], and the volume of the left amygdala is reduced in patients with COPD [3]. The number of corticotropin-releasing factor- (CRF-) and neuropeptide-Y- (NPY-) positive neurons were found to be decreased distinctly in the amygdala after postnatal day 3 hypoxia-ischemia [99], and c-fos protein expression increased in the nc. accumbens and the anterior amygdaloid area in the rat brain exposed to hypoxic injury [101]. These long-term changes in the amygdala may be functionally associated with the specific behavioral disorders including bipolar disorder [102].

However, some researchers found that perinatal hypoxia does not change the susceptibility to amygdaloid-induced seizures in the adult rabbits [103].

3.4. The Hypoxic Injury in Other Structures of the Brain. Heart failure (HF), OSA, and congenital central hypoventilation syndrome (CCHS) occur as a result of insular and cingulate cortex injury [62]. Damage in those regions apparently contributes towards inhibiting or enhancing the sensation. The extent of injury in the insula shows the loss of tissue in HF, increased mean diffusivity in OSA, and axial and radial diffusivity changes in CCHS as well as in anterior cingulate [62]. Other studies have shown that the cortical thinning and white matter loss also occurs in the brain after the repeated chronic exposure to hypoxia and hypercapnia in CHS [104, 105]. Based on the fMRI study, significant differences were observed in the magnitude and timing of responses in specific regions of the brain between groups induced by hypoxia; these regions included the cerebellar cortex, deep nuclei, and posterior thalamic structure, as well as the amygdala and hippocampus. These finds emphasize the important roles of posterior thalamus, midbrain, and cerebellum in normal hypoxic conditions [106].

3.5. The Related Signaling Pathway in Hypoxia/Hypoxic-Ischemia Injury. Several pathways, regulators, and effectors participate in the pathological process of the secondary injury of brain hypoxia/hypoxia-ischemia reperfusion. The damage to blood-brain barrier (BBB) also plays a critical role in the initiation of the reoxygenation/reperfusion injury and development.

Hypoxia/reoxygenation (H/R) stress can induce the upregulation of the mRNA expression of Abcc1, Abcc2, and Abcc4 at the BBB. This upregulation is regulated by the activation of nuclear factor E2-related factor (Nrf2) signaling. The Mrp isoforms belong to the ABCC group of proteins, and the enhanced functional expression of Mrp isoforms at BBB could induce the neural cell injury and death by reducing the concentrations of antioxidant glutathione (GSH) in the endothelial cell [107]. Another study demonstrated that the upregulation of Nrf2 by hyperbaric oxygen preconditioning (HBO-PC) might alleviate the hypoxia-ischemia brain damage (HIBD) [108]. Brain-derived neurotrophic factor

Table 1: Changes of neural plasticity induced by hypoxic-ischemic injury in various brain regions.

Brain region	Changes of neural plasticity	Mechanisms
Hippocampus	Synaptic plasticity	(1) Triggering of LTD via ROS and NOS (2) Impairment of LTP in presynaptic neurons (3) Impaired synaptic transmission and plasticity in dentate gyrus area of rats (4) Fine structural changes of synapses in CA1 region
	Volumetric changes	(1) Hippocampal atrophy and neurons apoptosis (2) White matter density decreased
	Apoptosis	(1) A severe loss of neurons induced by activation of MAPK signaling pathways (2) ER stress and oxidative stress
	Misfolded/unfolded protein	(1) Increased production of ROS
Prefrontal cortex	Synaptic plasticity	(1) Increased density of the GABAergic neurons impair the network activity within PFC (2) Increased neuronal death (3) Activation of T-type Ca^{2+} channels in the MD
	Activity in vmPFC and dlPFC	(1) Increasing the acetylcholine release by enhancing the activation of G protein
	Immunoreactive cells and cytokine changes	(1) Upregulated expression of molecules such as VEGF, Hif-1, and Glut1 (2) PV cells loss induced by the NOX2-derived oxidative stress
	Volumetric changes	(1) Increased neuronal death and ghost cells (2) Tissue atrophy
Amygdala	Synaptic plasticity	(1) Decreased expression of NPY (2) Increased expression of c-fos protein
	Volumetric changes	(1) Smaller gray matter volume in the amygdala and decreased volume of the left amygdala (2) Significant shrinkage of cell size and axonal degeneration of corticotropin-releasing factor-positive neurons
Signaling pathways	Upregulation of Abcc1, Abcc2, and Abcc4 mRNA expression at the BBB	(1) Regulated through Nrf2 signaling
	Activation of BDNF-TrkB signaling pathway	(1) The circulating levels of BDNF increased
	Enhancement of ERK1/2-CREB-BDNF signaling pathway	(1) The circulating levels of BDNF increased
	Activation of STAT3 signaling pathway	(1) Phosphorylation of STAT3
	Triggering cAMP/PKA signaling pathway	(1) Increased release of CRF
	Dysregulation of NMDARs-Wnt-catenin signaling	(1) Decreased expression of NMDARs

(BDNF) is another critical molecule that promotes the growth and survival of nervous cells as well as the communication between neurons. In addition, it plays a major role in long-term memory and cognitive function. The circulating levels of BDNF in humans have been shown to increase dramatically during hypoxic stress, both in the perinatal period [109] and adulthood [110, 111] which, in turn, inhibits the ER stress activation as well as ROS production [112]. BDNF can regulate the ion channel activity and synaptic transmission in different regions of the brain by interacting with the TrkB receptor [113]. BDNF-TrkB signaling pathway has a precedent role in modulating the synaptic plasticity in the CNS [114]. During chronic hypoxia, the activation of BDNF-TrkB signaling pathway increases the voltage-dependent Ca^{2+} influx and catecholamine secretion in chromaffin cells [114]. Furthermore, CIHH pretreatment improved the ischemia-induced cognitive dysfunction by the activation of ERK1/2-CREB-BDNF signaling pathway [115].

As demonstrated above, BDNF not only plays a crucial role in the development of CNS but also regulates the plasticity of neurons during hypoxic stress.

STAT3 signaling pathway has also been shown to play a role in the hypoxic injury of neural cells. The hypoxic-ischemia damage may cause the phosphorylation of STAT3, and the activation of STAT3 signaling pathway might be involved in the apoptosis-mediated regulation of nerve cells [116], tissue loss, and gliosis following neonatal hypoxia-ischemia stress [117]. Hypoxia triggers cAMP/PKA signaling pathway in cortical astrocytes by releasing CRF, thereby leading to the activation of aquaporin-4 and cerebral edema [118]. In addition, the dysregulation of

N-methyl-D-aspartate receptors (NMDARs)-Wnt-catenin signaling in the hippocampus may participate in the process of prenatal hypoxia that induces the spatial acquisition and retrieval deficits in adolescent offspring [119].

4. Summary and Conclusion

Neuronal plasticity is a critical property of the neural system regulating and coordinating mood and behavior. There are various intrinsic and extrinsic stimuli, which could affect the neuroplasticity in several aspects, such as the volume of nuclei, regulation of neuronal apoptosis and neurodegeneration, secretion of neurotransmitter, and any other forms of changes. Oxidative stress, inflammation, apoptosis, and excitotoxicity are the primary mechanisms underlying hypoxic-ischemic brain injury [10]. Various degrees of improvements were found in oxidative stress markers, cell density, the rate of neuronal apoptosis, and caspases in hypoxia-ischemia model of the rat after treatment with hyperbaric oxygen [120] and antioxidants. The goal was to explore the mechanism of hypoxic injury on the brain in order to focus on the long-term functional recovery in both injured and uninjured brain regions, and the neuronal plasticity might serve as the vital target.

Conflicts of Interest

The authors confirm no conflict of interest with respect to the present study.

Acknowledgments

This work was supported by grants from the Natural Science Foundation of China (NSFC: 31471120, 31540076, and 31171123).

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Hindawi
Neural Plasticity
Volume 2017, Article ID 9724371, 10 pages
https://doi.org/10.1155/2017/9724371

Review Article

The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain

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Received 25 March 2017; Revised 4 May 2017; Accepted 24 May 2017; Published 19 June 2017

Academic Editor: Aijun Li

Chronic pain, as a stress state, is one of the critical factors for determining depression, and their coexistence tends to further aggravate the severity of both disorders. Unfortunately, their association remains unclear, which creates a bottleneck problem for managing chronic pain-induced depression. In recent years, studies have found considerable overlaps between pain- and depression-induced neuroplasticity changes and neurobiological mechanism changes. Such overlaps are vital to facilitating the occurrence and development of chronic pain and chronic pain-induced depression. In this review, we summarized the role of neuroplasticity in the occurrence and development of the two disorders in question and explored individualized application strategies of analgesic drugs and antidepressants that have different pharmacological effects in the treatment of chronic pain-induced depression. Therefore, this review may provide new insights into the understanding of association between chronic pain and depression.

1. Introduction

Chronic pain is usually defined as any persistent or intermittent pain that lasts more than 3 months, which can be categorized along a variety of dimensions, including one of the most important divisions, neuropathic versus nociceptive pain [1, 2]. Neuropathic pain is induced by a lesion or disease involving the nervous system [3], and nociceptive pain occurs as a consequence of actual or threatened damage to nonneural tissue [4]. Chronic pain is a major public health problem, with epidemiological studies reporting that in the USA and Europe, approximately one fifth of the general population are affected [5]. Additionally, as one of the most common and disabling mental disorders, depression has been reported to be the third leading contributor to the global disease burden [6, 7]. Clinical studies have revealed that chronic pain, as a stress state, often induced depression [8–10] and that up to 85% of patients with chronic pain are affected by severe depression [11, 12]. Patients suffering from chronic pain-induced depression exhibit a poorer prognosis than those with chronic pain only; and chronic pain and depression are closely correlated in terms of occurrence and development and are able to mutually promote their own severity progress [13].

To date, neither the corresponding pathophysiological mechanisms of chronic pain and depression nor their mutual correlation has been identified, which poses a huge challenge for the treatment of pain accompanied by depression. However, in recent years, studies have revealed considerable overlaps between pain- and depression-induced neuroplasticity changes and neurobiological mechanism changes. Such overlaps are vital to facilitating the occurrence and development of chronic pain-induced depression. In particular, injury sensory pathways of body pains have been shown to share the same brain regions involved in mood management, including the insular cortex, prefrontal cortex, anterior cingulate, thalamus, hippocampus, and amygdala, which form a histological structural foundation for the coexistence of pain and depression [14]. Furthermore, the volumes of the prefrontal cortex (PFC) and hippocampus have been reported in many studies to be significantly smaller in depressed patients and to be closely related to depression severity [15–17]. In addition,

individuals with depression in postmortem studies have also been observed to have a significantly reduced number of PFC synapses, which thus decreases synaptic functions [18]. Meanwhile, the effect of PFC on pain development via the nucleus accumbens has also been verified [19], thus indicating that the occurrence and development of pain and depression may be associated with some identical neuroplasticity changes. Furthermore, maladaptive plasticity changes, which refer to the plasticity in the nervous system that leads to a disruption of the function and may be considered a disease state, have also been indicated in a large number of clinical trials and animal studies [20]. Additionally, these maladaptive plasticity changes may also occur in sensory conduction pathways from the peripheral to the central nervous system and participate in the occurrence, development, and maintenance of chronic pain [3]. In summary, chronic pain and depression may be based on common neuroplasticity mechanism changes, which are a potentially important route for the onset and aggravation of chronic pain and depression. Reviewing the role of neuroplasticity in chronic pain and depression, this paper explores the influence of analgesic drugs and antidepressants with different pharmacological effects on neuroplasticity as well as their contribution to individualized application strategies in the treatment of chronic pain-induced depression.

2. Molecular Mechanisms Associated with Chronic Pain and Depression-Induced Neural Plasticity Changes

2.1. Monoamine Neurotransmitters. Monoamine neurotransmitters, including serotonin (5-HT), dopamine (DA), and norepinephrine (NE), have been studied in molecular mechanisms involved in chronic pain and depression. The classical monoamine hypothesis proposes that depression may occur as a result of decreased availability of monoamine neurotransmitters such as 5-HT and NE in the central nervous system (CNS) [21], which is supported by strong evidence from many studies [22–24]. Monoamine neurotransmitters are also vital to the occurrence and development of pain. Additionally, electrical stimulation either in the periaqueductal gray or in the rostral ventrolateral medulla may elevate NE levels in cerebrospinal fluid and thus achieve an analgesic effect, which in turn can be blocked by spinal adrenergic antagonists [25].

In exploring the common neuroplasticity changes of chronic pain and depression, attention should also be paid to the midbrain dopaminergic system because it exerts an indispensable role in the control of forebrain functions. In fact, chronic pain has been shown to have the potential to significantly damage DA activity in the limbic midbrain area according to a large body of evidence [26]. The reactivity of the DA system in the limbic midbrain area to significant stimuli has been observed in imaging studies to be reduced in patients with chronic pain [27, 28]. In particular, the DA receptor D2, also known as D2R, is a protein that is known to be involved in the occurrence and development of depression [29]. Reduced overall DA levels and significantly lowered D2R expression were found in Sagheddu et al.'s chronic neuropathic pain rat model [30], which provides possible new neuroplasticity targets for the treatment of chronic pain-induced depression.

2.2. Brain-Derived Neurotrophic Factor (BDNF). As a precursor protein, pro-BDNF can be processed into a mature BDNF through intracellular and/or extracellular proteases [31]. BDNF belongs to the family of neurotrophic factors and is not only involved in the signaling pathways of the PFC and hippocampal dentate gyrus together with its receptor tropomyosin receptor kinase B (TrkB) but is also important in regulating neuroplasticity [32, 33]. Aside from decreasing BDNF expression and function in the PFC, the hippocampus, and other depression-related structures, depression has been found to reduce the blood BDNF levels in affected patients [34–36]. The crucial function of BNDF in pain occurrence and development has also been confirmed by extensive studies. In particular, Yajima et al. found that BDNF released from the spinal cord can form signaling pathways by binding to TrkB, thereby activating the expression of spinal protein kinase C in spinal neurons, which can regulate hypersensitivity to pain and further influence the progression of neuropathic pain [37, 38].

2.3. Inflammatory Factors. The association between inflammatory factors and the CNS has become increasingly clear in recent decades. The surrounding inflammatory response has been shown to cause pain and depression; thus, inflammatory response-mediated pain may be more strongly associated with depression [39–41]. By affecting depression-related pathophysiological functional areas via the blood-brain barrier, inflammatory signals can induce changes in neurotransmitter metabolism, neuroendocrine function, and neuroplasticity [40]. Additionally, the depressive symptoms of affected patients receiving systemic treatment for malignant melanoma or hepatitis C virus infection with INF-α have been found to be aggravated in several studies, where major depressive disorder (MDD) was clinically diagnosed in up to 45% of sufferers [42–45]. Furthermore, a high ratio of plasma kynurenine and tryptophan in patients undergoing IFN-α therapy has been shown to predict depression severity [42, 46, 47].

2.4. Glutamate and Its Receptor Subtypes. Glutamate functions as one of the main excitatory neurotransmitters in the CNS and exists in synapses throughout the brain [48]. Furthermore, glutamate and its receptor subtypes, N-methyl-D-aspartic acid (NMDA) receptor and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, have been found to be involved in the occurrence and development of chronic pain and depression [49–51]. In the spinal cord, both increased excitatory system activity and the accompanying reduced inhibitory system are known to contribute to central hyperalgesia and to ultimately lead to the progression of pathological pain [52]. Glutamatergic activity can be promoted through the breakdown of efficient inhibition of the actions of glutamate by GABA. GABAergic transmission is excitatory during fetal early

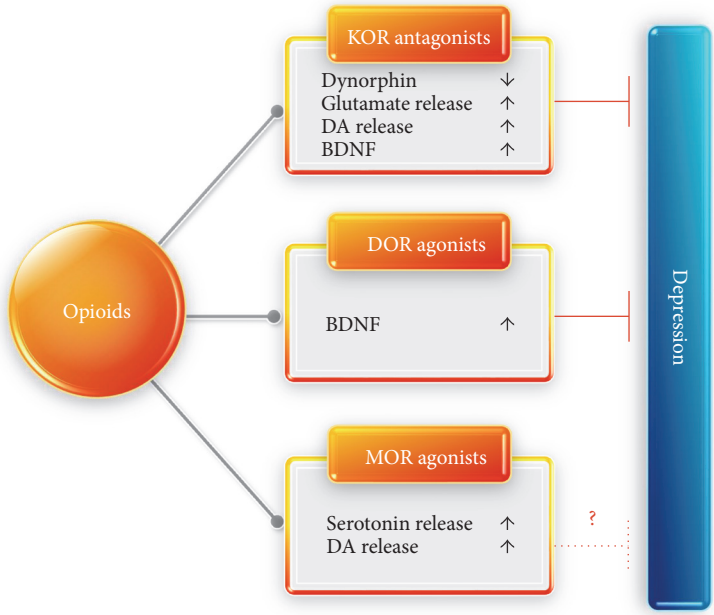

Figure 1: Potential mechanisms of opioids in chronic pain-induced depression therapy.

development but becomes inhibitory during late pregnancy, which results from the depolarization caused by the dominance of Na-K-Cl-cotransporter-1 (NKCC1) and K-Cl-cotransporter-2 (KCC2), which are proteins that aid in the active transport of sodium, potassium, and chloride into and out of cells during early fetal development. Similarly, the return of NKCC1 and KCC2 levels to those of the immature state under pathological conditions increases the excitability of GABAergic transmission, thereby weakening the inhibitory effect [53, 54]. Low-dose diazepam (an NKCC1 inhibitor) was administered to the unipolar depression genetic model in Flinders Sensitive Line (FSL) rats in Matrisciano et al.'s study, which found significantly increased behavioral response compared with that of the control group. In the FSL rats, dramatically elevated KCC2 expression, especially in their cerebellum, was revealed via Western blotting and immunohistochemical data. These data suggest that spontaneous depression in animals is associated with amplified GABAergic transmission in the CNS as a result of enhanced KCC2 expression [55]. Similarly, glutamate and its receptors have an important function in pain and its chronification as well. Increased sensitivity to pain may be due to the absence of a GABAergic region in the spinal cord, especially in the dorsal horn [40].

In conclusion, neuroplasticity crucially affects the occurrence and development of chronic pain and depression and may involve the same brain structures, neurotransmitters, and signaling pathways. Through exploring the common neuroplasticity changes of these two disorders, new targeted therapeutic drugs should be able to be developed or these disorders' common targets should be able to be identified for precise treatment of chronic pain-induced depression, which will surely contribute to the improvement of life quality and prognosis in patients suffering from these disorders.

3. Analgesic Drugs to Treat Chronic Pain-Induced Depression

3.1. Opioids. Opioids are the most effective drugs for treating chronic pains. By combining with the opioid receptor to relieve patients' pain, opioids have been widely applied to treat various chronic pains, such as cancer pain, nociceptive pain, and neuropathic pain.

In recent years, research into the role of opioid receptors in antidepressant therapy has been emerging, with increased concern centered around the potential of opioids in antidepressant therapy. Lots of research suggest that there are three classical types: μ, δ, and κ receptors, all of which involve in regulating mood [56], and some potential mechanisms have been studied (Figure 1) [57–61]. The combined effect of the μ receptor agonist and κ receptor antagonist was found to have the potential to reduce the occurrence of dysphoria-like behaviors in a study by Tenore [62]. Moreover, the κ receptor antagonist has been indicated to have a possibly antidepressant effect in Mague et al.'s animal experimental study [63].

As mentioned earlier, the occurrence and development of depression involve many neurotransmitter systems that are associated with changes in neuroplasticity. The opioid receptor may achieve antidepressant effects by regulating these neurotransmitter systems; this finding has been supported by several studies [56, 64]. Systemic acute morphine injection into mice has been found to have the potential to increase the release of 5-HT in several limbic systems, such as the nucleus accumbens and dorsal striatum. Thus, the finding that the μ receptor can achieve an antidepressant effect by controlling the activity of 5-HT neurons is laterally supported [61]. The κ receptor is expressed in the nucleus accumbens presynaptically by DA neurons. It can relieve emotions by directly

inhibiting the release of DA [65]. Numerous studies shows that δ receptor-knockout mice exhibit increased depressive-like behaviors, which indicates that δ receptor may become a potential antidepressant target [66–68].

Some animal experiments and clinical studies have demonstrated the effectiveness of some opioids in treating depression [69, 70]. Buprenorphine is a partial agonist of the μ receptor and an antagonist of the κ receptor and has a good affinity for the δ opioid receptor. Because its pharmacokinetics is not influenced by age and renal function, buprenorphine can be used for the middle-aged and the elderly who suffer from refractory depression [71]. A low dosage of buprenorphine for refractory depression in the first 3 weeks was found to significantly reduce depression severity but required long-term maintenance in clinical studies conducted by Karp et al. [70]. The role of buprenorphine in antidepressant therapy, together with samidorphan (an effective μ opioid receptor antagonist), was demonstrated via a multicenter, double-blind, and randomized clinical test by Fava et al. [72]. Tramadol is a weak nonopioid agonist of the μ receptor and displays properties of TCAs that inhibit the reuptake of 5-HT and NE. Tramadol was found to improve behaviors related to depression and anxiety caused by sciatic nerve injury in Caspani et al.'s examination of a chronic neuropathic pain mouse model [73]. This indicates that certain opioids may enhance synaptic plasticity and achieve the purpose of antidepressant therapy by adjusting neurotransmitter systems.

The potential of opioids in treating chronic pain-induced depression is established; however, application of opioids to antidepressant therapy has been controversial because of patients' severe dependence and addiction to them [74]. The long-term use of opioids has been shown to increase the risk of depression [75] and to even cause hyperalgesia, which can lead to depression [76]. By statistically analyzing the opioid treatment of pain in three independent American health systems, Scherrer et al. found that in the Veterans Health database, patients taking opioids for 31–90 days were found to be at an 18% higher risk for depression than those taking opioids for 1–30 days [77]. Additionally, depression may prolong the duration of opioid use [78]. The duration of opioid use in patients with a history of depression was found to be three times longer than that in patients without depression according to Braden et al.'s study [79]. Therefore, the extensive application of opioids for treating chronic pain-induced depression remains to be further studied and explored.

3.2. Benzodiazepines. Benzodiazepines have been demonstrated to have a certain therapeutic effect in treating chronic pains, including neuropathic pain or inflammatory pain [80]. The analgesic mechanism of the benzodiazepines may be associated with the antihyperalgesic effect of the $GABA_A$ receptor, which is a molecular target of the benzodiazepines in the spinal cord [81]. Because the $GABA_A$ receptors, including the $\alpha1$, $\alpha2$, $\alpha3$, or $\alpha5$ subunit, have also been found to be involved in mood regulation [82], the benzodiazepines have a potential in antidepressant therapy. By studying the $GABA_A$ receptor $\alpha2$ subtype homozygous gene-knockout mouse, anxiety and depression-like behaviors of the mouse were markedly increased in the conflict-based novelty-inhibited feeding test and increased in despair-based forced swim test and tail suspension tests in a study by Vollenweider et al. [83]. This result suggests that the benzodiazepines can potentially treat chronic pain-induced depression.

4. Antidepressant Drugs for Treating Chronic Pain-Induced Depression

4.1. Monoamine Oxidase Inhibitor. Monoamine oxidase (MAO) is an important enzyme in the biogenic amine degradation pathway. MAO can be classified into two types: the type A MAO degrades NE and 5-HT and the type B MAO degrades phenylethylamine and benzydamine [84]; however, evidence suggests that type A MAO is more often implicated in mental disorders, including major depressive disorder [85]. Because clinical depression is associated with a decreased system of NE and/or 5-HT content in some regions of the CNS, the antidepressant effect of the classical monoamine oxidase inhibitor (MAOI) might be related to its ability to increase the NE and/or 5-HT levels of these sites [21, 85]. The mechanism of the classical MAOI is irreversible inhibition of MAO by covalent binding to the active site of the enzyme, but it is nonspecific and can inhibit the liver microsomal enzyme system, which affects the metabolism of many drugs. In addition, some classic MAOI themselves have hepatotoxicity [86], so they are clinically no longer used for treating depression at present. In recent years, the MAOI has been represented by moclobemide, which selectively reversibly inhibits type A MAO and has been attracting attention again due to its side effects. This drug can increase NE, 5-HT, and DA levels in the tissues, which has been confirmed by in vitro and in vivo tests [87]. Its antidepressant effect on the elderly has also been verified by clinical studies [88]. The effect of such drugs on pain treatment has been also confirmed in other clinical studies [89]. Mattia and Coluzzi found that indantadol as an oral and nonselective monoamine oxidase inhibitor and NMDA antagonist had the potential to treat neuropathic pain due to its antihyperalgesic activity [90]. However, the application of monoamine oxidase inhibitors in the treatment of chronic pain-induced depression still requires confirmation through a large number of clinical trials and animal experiments.

4.2. Tricyclic Antidepressant Drugs. Tricyclic antidepressant drugs are traditional antidepressant drugs, commonly including amitriptyline, imipramine, nortriptyline, and desipramine. The action mechanism of tricyclic antidepressant drugs may be to first inhibit 5-HT and NE reuptake at the synapse site and then enhance endogenous pain inhibition of the CNS. They are helpful for easing many chronic pains, especially neuropathic pain [91]. Because similar neuroplasticity changes occur during the experience of pain and depression in the monoamine neurotransmitter system, studies focused on the application of tricyclic antidepressant drugs in pain management have emerged unceasingly in recent years. For example, a clinical study by Kopsky and Hesselink indicated that local high doses of amitriptyline

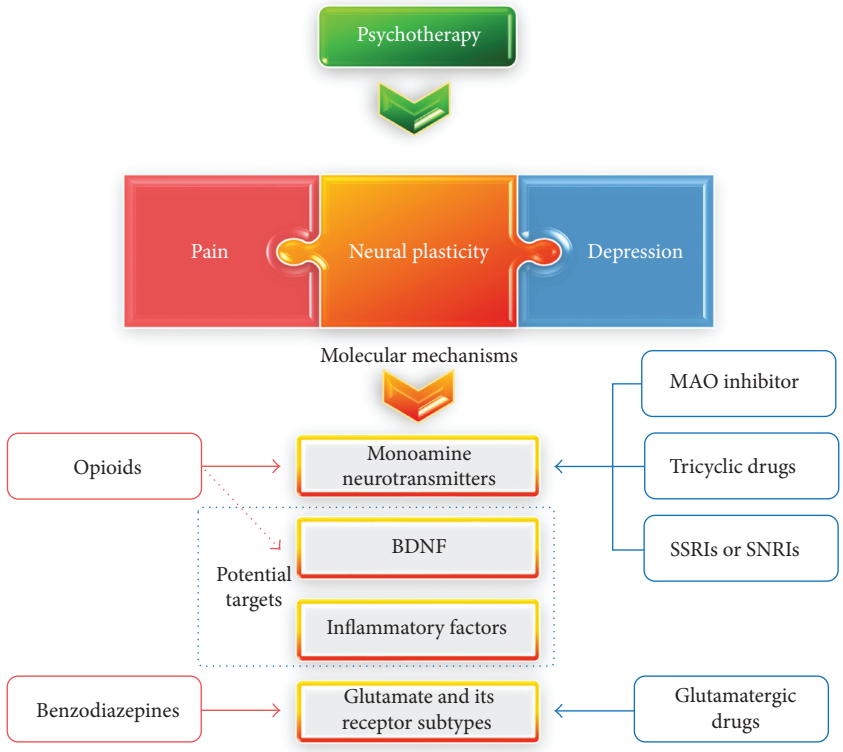

Figure 2: The treatment of chronic pain-induced depression.

were effective for treating neuropathic pain [92]. Furthermore, Rowbotham and colleagues, through a clinical trial of 47 neuropathic pain patients comparing three antidepressants, that is, desipramine, amitriptyline, and fluoxetine, confirmed that all three drugs can reduce pain experienced by postherpetic neuralgia patients, and the tricyclics desipramine and amitriptyline were well tolerated and provided more meaningful pain relief in 53%–80% of all subjects [93].

4.3. Monoamine Reuptake Inhibitors. For monoamine neurotransmitters, neurotransmitter reuptake is one of the most important determinants of signal kinetics and regulation of neurotransmitter reuptake also helps regulate the activity of the nervous network across the CNS, thus achieving an antidepressant effect [94]. With more in-depth studies on the treatment mechanism of monoamine neurotransmitters in antidepression and pain relief, inhibitors including selective 5-HT reuptake inhibitors (SSRIs) and 5-HT and NE reuptake inhibitors (SNRIs) have emerged unceasingly and have gradually become first-line drugs for clinical antidepressant therapy [95]. Antidepressant pharmacological mechanisms of SSRIs and SNRIs are to selectively act on some 5-HT and/or NE receptor subtypes and block their reuptake to increase 5-HT and/or NE that are available for biological uses in the synaptic cleft of nerve cells, thus further enhancing monoamine neurotransmission and having an antidepressant effect. The 5-HT and NE reuptake inhibitor antidepressants have been confirmed by numerous studies to be efficacious in chronic neuropathic pain patients [96–98]. Furthermore, average pain relief (recorded via a diary) and maximum pain intensity (retrospective assessment via a computer program) in patients with chronic neuropathic pain were found to be significantly lower with antidepressant venlafaxine, a 5-HT and SNRI, compared with a placebo in Tasmuth et al.'s randomized, double-blind study [99].

4.4. Glutamatergic Antidepressant Drugs. As mentioned previously, studies have demonstrated the role of glutamate and its NMDA receptor subtypes in analgesia and antidepressant therapy [100–104]. As a noncompetitive NMDA receptor antagonist, ketamine has been used for anaesthetization since the 1960s and was reported in 2000 to rapidly improve depressive symptoms, including refractory depression within several hours. It has become a new type of antidepressant drug for targeting the glutamatergic system [105]. More importantly, studies have found that ketamine not only increased the number of synaptic connections in the PFC but rapidly improved deficits caused by chronic stress [106, 107]. Furthermore, by antagonizing the glutamatergic NMDA receptor, ketamine was found to accelerate the release of presynaptic glutamate, thereby enhancing the regional activity of the excitatory network, and eventually leading to a significant change in synaptic plasticity and connectivity [108, 109]. This achieves the purpose of analgesia and antidepressant therapy [107]. However, such drugs have side effects such as dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, and restlessness [110]. Therefore, the safety and efficacy of ketamine and other NMDA receptor antagonists for

treating chronic pain-induced depression remain to be further explored.

4.5. Potential Therapy Methods. Although we have summarized clinical drugs that may be therapeutically applied to treat chronic pain-induced depression, their selection for use in therapy is currently still limited. Based on our summary of common neuroplasticity changes in pain and depression, many new therapy targets may provide new future therapy directions for treating chronic pain-induced depression.

The fact that dopaminergic drugs, such as pramipexole, are effective drugs for depression inhibition suggests that enhancing DA function may form at least a partial basis for treatment response of MDD [111]. A change in the function of the DA system in the midbrain margin and the fact that certain antidepressant drugs also had a function in enhancing DA transmission have been demonstrated in studies with rodent depression models [112, 113]. Furthermore, treatment methods for chronic depression including electroconvulsive stimulation, sleep deprivation, and almost all antidepressant drugs have been shown to enhance the role of the DA receptor agonist in motion stimulation [111]. Additionally, data and gene-related animal model studies concluded that DA could relieve pain via the D2 receptor [26]. Also supporting the claim that DA has an analgesic effect, some human studies found an increase in emotional pain rating after DA was exhausted and an improvement in conditional pain after the D2 receptor was activated [114, 115]. Thus, the D2 receptor may serve as a new therapeutic target for chronic pain-induced depression.

The activity-dependent regulation expressed by the early BDNF is associated with neuronal plasticity [31]. The BDNF level of patients with depression has been found to be significantly reduced in several studies [116, 117]. Additionally, a reduced BDNF receptor TrkB level in the brain has also been reported [118]. Activation and phosphorylation of TrkB are also known to be significantly reduced in suicide victims [119, 120]. Furthermore, a decrease in BDNF level can lead to a decrease in hippocampal volume and number of nerves, dendritic reconstruction, loss of glial cells, increasing neurotoxicity, and increasing susceptibility to depression [121]. Meanwhile, the BDNF has been shown to be a crucial signal molecule between microglia and neurons, which is an essential link in neuropathic pain transmission, and blocking this pathway may represent a therapeutic strategy for treating neuropathic pain [122]. Therefore, the BDNF could become a new target for treating chronic pain-induced depression in the near future.

4.6. Adjuvant Psychotherapy. In addition to the neural plasticity mechanism described above, psychosocial factors also have a significant effect on the occurrence and development of chronic pain-induced depression [123, 124]. Therefore, appropriate adjuvant psychotherapy also has a crucial role in treating chronic pain-induced depression, which has been confirmed in many clinical investigations [125–127]. For example, by means of randomized clinical trials of 342 patients with chronic back pain between 20 and 70 years of age, the group that received cognitive behavioral therapy versus usual care showed greater improvement in function (adjusted mean difference in range) [128]. Furthermore, Eccleston et al., through a retrospective analysis of 37 clinical randomized trials, found that, for children and adolescents with headache, psychological therapy decreased treatment pain and follow-up pain [129]. Thus, psychotherapy contributes to the relief from clinical symptoms, shortens the duration of the recovery cycle, improves patients' prognosis, and is recommended as a necessary adjuvant therapy for chronic pain-induced depression.

5. Summary and Prospects

In conclusion, pain and depression are closely correlated from the perspectives of both brain regions and the neurological function system, whereby chronic pain may lead to depression. One of the important causes for chronic pain leading to depression appears to be the crucial effect of common neuroplasticity changes on the occurrence and development of the two disorders in question (Figure 2). Nevertheless, current efforts in this field fail to sufficiently and explicitly explain their connection. Further investigations into the common neuroplasticity changes shared by pain and depression are warranted to promote the identification of new drug targets and to free patients from chronic pain-induced depression.

Conflicts of Interest

The authors confirm no conflicts of interest regarding the publication of this article.

Acknowledgments

This work was supported by grants from the Natural Science Foundation of China (NSFC: 31471120, 31540076, and 31171123).

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Hindawi
Neural Plasticity
Volume 2017, Article ID 7838035, 11 pages
https://doi.org/10.1155/2017/7838035

Research Article

Abnormal Functional Connectivity of Ventral Anterior Insula in Asthmatic Patients with Depression

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Received 10 January 2017; Revised 24 March 2017; Accepted 9 April 2017; Published 7 June 2017

Academic Editor: Bingjin Li

Objective. To explore the underlying mechanism of depression in asthmatic patients, the ReHo in the insula and its FC was used to probe the differences between depressed asthmatic (DA) and nondepressed asthmatic (NDA) patients. *Methods*. 18 DA patients, 24 NDA patients, and 60 healthy controls (HCs) received resting-state fMRI scan, severity of depression, and asthma control assessment. *Results*. DA patients showed increased FC between the left ventral anterior insula (vAI) and the left middle temporal gyrus compared with both NDA and HC groups. In addition, compared with HCs, the DA and NDA patients both exhibited increased FC between the left vAI and the right anterior cingulate cortex (ACC), decreased FC between the left vAI and the bilateral parietal lobe, and increased FC between the right vAI and the left putamen and the right caudate, respectively. Furthermore, the increased FC between the left vAI and the right ACC could differentiate HCs from both DA and NDA patients, and the increased FC between the right vAI and both the left putamen and the right caudate could separate NDA patients from HCs. *Conclusions*. This study confirmed that abnormal vAI FC may be involved in the neuropathology of depression in asthma. The increased FC between the left vAI and the left MTG could distinguish DA from the NDA and HC groups.

1. Introduction

Bronchial asthma is a common chronic inflammatory condition that swelled and narrowed the airways, leading to dyspnea, coughing, and tightening of the chest. Asthma is significantly associated with psychiatric disorders [1], especially depression that has been consistently reported to be prevalent in asthmatic patients [2–4]. Adeyeye et al. [5] indicated that depression is the most important factor independently associated with asthma-related quality of life. And an epidemiology study found asthma per se may be an independent risk factor for suicidality [6]. Inflammation-associated mood deterioration was reflected in changes in brain function during evoked responses to emotional stimuli [7].

The development of brain functional magnetic response imaging (fMRI) has been a useful technique to explore the neurobiological mechanisms of asthma and emotion. Rosenkranz et al. [8–10] detected the neural circuitry underlying the interaction between emotion and asthma symptoms used task fMRI, and the findings consistently indicated that neuron phenotypes of asthma might be identified by neural activity of brain circuits previously implicated in emotion regulation, especially the insula.

The insula may modulate inflammatory processes by the influence on neuroendocrine responses to stress, including extensively studied effects on the HPA axis and its physiological responses [11]. As a "cortical hub," the insula carries information of dyspnea and has strong connections with neural structures important in processing emotional information

[8, 12–14]. However, to our knowledge, only one research explored the underpinnings of depression with the method of fMRI in female asthmatic patients, in which depressed asthma (DA) patients showed a decreased spontaneous activity in the right insula [15]. Furthermore, the functional connectivity (FC) between the insula and other brain regions was not clear. Therefore, we selected the insula as a region of interest (ROI) to explore whether its regional homogeneity (ReHo) and FC changes occur with depression in asthma. We hypothesized that DA and nondepressed asthma (NDA) patients would show abnormal spontaneous activity in insula and abnormal insula FC compared with that of healthy controls (HCs).

2. Materials and Methods

2.1. Participants. After attrition and data screening, the sample included 42 patients with a diagnosis of bronchial asthma with nonacute attacks and 60 HCs. 18 of the included asthmatic patients (12 patients with steroid treatment) entered into the DA group and the other 24 patients (18 patients with steroid treatment) entered into the NDA group according to the scores of the 17-item Hamilton Depression Rating Scale (HDRS-17). There was no statistical difference between the DA and NDA patients ($\chi^2 = 0.350$, $P = 0.554$). All participants signed a written informed consent form, as required by the ethics committee (Zhongda Hospital, Southeast University, Nanjing, People's Republic of China). The clinical trial registration number was ChiCTR-COC-15007442.

2.2. Inclusion/Exclusion Criteria. Participants were all at least 18 years old, right-handed, and had an educational level of junior high school or higher. Asthmatic patients were diagnosed as bronchial asthma with nonacute attacks. The HCs were required to have a score below 7 on the HDRS-17.

Participants were excluded if they are presented with other serious physical diseases, psychotic disorders, and alcohol or drug dependence; were pregnant or lactating; and had electronic or other metal equipment that was surgically implanted (such as a cardiac pacemaker, defibrillator, and stent).

2.3. Evaluations

2.3.1. HDRS-17. In the current study, all subjects received HDRS-17 evaluation by researchers. HDRS-17 [16] contains 17 variables which are measured on five-point scales, and it is used to assess the depression severity. Participants with a score equal or above 7 are recognized having depression possibly.

2.3.2. Asthma Control Test (ACT). All asthmatic patients completed ACT by themselves. ACT [17] contains 5 items with a total score arranging from 0 to 25. Patients with a total score below 20 are thought to have no control for their asthma.

2.4. Brain Image Acquisition. Imaging was performed on a 3-Tesla Scanner using a homogeneous birdcage head coil. Participants were required to keep their eyes closed, awake, and not think of specific things during scanning. Participants lay supine with the head snugly fixed by a belt and foam pads to minimize head motion. A gradient-recalled echo-planar imaging (GRE-EPI) pulse sequence was set up to acquire resting-state images. For each data volume, we acquired 36 continuous axial slices in descending order with 3.75 mm × 3.75 mm in-plane resolution parallel to the anterior commissure-posterior commissure line, 3 mm slice thickness, and a 0 mm gap using resting-state imaging (TR = 2000 ms, TE = 25 ms, flip angle = 90°, acquisition matrix = 64 × 64, field of view = 240 mm × 240 mm). This acquisition sequence generated 240 volumes in 8 minutes.

2.5. Functional Imaging Preprocessing. All the image data were reconstructed and inspected by two experienced radiologists. Image preprocessing was performed using the DPARSF software [18]. The first 10 time points were discarded for scanner calibration and for subjects to get used to the circumstance. The remaining time points were corrected for timing differences between slices and for motion effects (six-parameter rigid body) using a reference volume in the center of the run. After head motion correction, participants with head motion of more than 2.5 mm of maximum displacement in any direction (x, y, or z) or 2.5° of angular motion were ruled out. The resulting images were spatially normalized into a standard stereotaxic space using a 12-parameter affine approach and an EPI template image that was resampled to $3 \times 3 \times 3\,mm^3$ voxels. Following this, temporal filtering (0.01 Hz < f < 0.08 Hz) was applied to the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency noise. Any linear trend was then eliminated.

2.6. Selection of Region of Interest (ROI). The regions of interest (ROIs) of insula were defined according to the automated anatomical labeling (AAL) template [19] in the REST tool kit (http://www.resting-fmri.sourceforge.net) [20]. Then, the insula-ROIs were resampled to $3 \times 3 \times 3\,mm^3$ as a mask for the further ReHo analysis.

In order to explore the FC between the insula and the whole brain, we divided the insula into three subregions for both right and left referenced to the previous research [21], including the ventral anterior insula (vAI), dorsal anterior insula (dAI), and posterior insula (PI). The bilateral insula subregions were defined anatomically by drawing insula gray matter on the Montreal Neurological Institute (MNI) 152 standard brain. Each voxel in the insula subregion ROIs (converted to 3 mm resolution) was used as a seed in a whole-brain FC analysis in the DA, NDA, and HC groups.

2.7. ReHo Analysis. DPARSF software was used to analyze ReHo maps. Individual ReHo maps were generated by calculating the Kendall coefficient [22] concordance of the time series of a given voxel with those of its nearest neighbors (27 voxels) in a voxel-wise manner. ReHo maps were normalized transformed to standard zReHo maps and then smoothed with a Gaussian kernel of 6 mm (full width at half maximum; FWHM), in order to reduce the effect of

Table 1: Demographics and clinical characteristics of participants.

	DA ($n = 18$)	NDA ($n = 24$)	HCs ($n = 60$)	P value
Age (years)	$53.61 \pm 9.08^{*}$	50.58 ± 10.57	45.78 ± 14.49	0.051[a]
Gender (male/female)	9/9	9/15	24/36	0.688[b]
Education (years)	11.89 ± 2.56	11.75 ± 2.64	12.42 ± 3.57	0.639[a]
Duration of asthma (years)	22.86 ± 20.19	21.42 ± 19.27	—	0.815[c]
HDRS-17 scores	$11.06 \pm 4.40^{**\dagger\dagger}$	$2.21 \pm 1.47^{\#}$	0.93 ± 1.34	<0.001[a]
ACT scores	15.00 ± 4.38	19.58 ± 4.31	—	0.002[c]

Note: data are expressed as mean ± standard deviation. [a]One-way ANOVA; [b]Chi-square test; [c]Independent-sample t-test. DA versus HC, $^{*}P < 0.05$, $^{**}P < 0.001$; DA versus NDA, $^{\dagger\dagger}P < 0.001$; NDA versus HC, $^{\#}P < 0.05$. DA: depressed asthma; NDA: nondepressed asthma; HCs: healthy controls; HDRS-17: 17-item Hamilton Depression Rating Scale; ACT: asthma control test.

individual variations on the Kendall coefficient of concordance value.

2.8. FC Analysis. The FC analysis was supported by REST tool kit (http://www.resting-fmri.sourceforge.net) [20]. Global trend, white matter (WM), and cerebrospinal fluid (CSF) were obtained by averaging the time series within the whole brain, WM, and CSF masks, respectively. For each insula-ROI, a seed referenced time course was obtained by averaging the time series of all voxels in the ROI. Then, Pearson's correlation analysis was performed between the seed reference time course and time series of each voxel in the brain in a voxel wise way. And a Fisher's z-transform was applied to improve the normality of the correlation coefficients [23]. Six head motion parameters and the mean time series of global signals, WM signals, and CSF signals were introduced as covariates into a random effects model to remove possible effects of head motion, global signal, WM signal, and CSF signals on the results.

2.9. Statistical Analysis. Predictive Analytics Software (PASW) Statistics 18 package was employed (IBM Corporation, Armonk, NY, USA) to complete the analyses. Age, education, and HDRS-17 scores were performed by one-way analysis of variance (ANOVA). Gender was compared by means of the chi-square test. Duration of illness and ACT scores were analyzed by independent samples t-test. P values less than 0.05 were considered to indicate statistical significance.

Insula zReHo values and its subregions FC comparisons were also processed with REST software. Statistical tests across groups were performed using a voxel-based, one-way analysis of covariance (ANCOVA), with age, gender, and education level as covariates. We used AlphaSim correction based on the Monte Carlo simulation algorithm to correct for multiple comparisons, using the following parameters for zReHo: single voxel P value = 0.01, FWHM = 6 mm, with $61 \times 73 \times 61\ mm^3$ insula mask, which yielded a corrected threshold of $P < 0.01$, and cluster size >375 mm^3 (https://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf) and the following parameters for FC: single voxel P value = 0.01, FWHM = 6 mm, with $61 \times 73 \times 61\ mm^3$ grey matter mask, which yielded a corrected threshold of $P < 0.01/6$, and cluster size >1431 mm^3. The post hoc independent samples t-test of FC was conducted within a mask showing significant differences obtained from the ANCOVA analysis, with AlphaSim corrections (single voxel P value = 0.01, FWHM = 6 mm, which yielded a corrected threshold of $P < 0.01$, and cluster size >216 mm^3/135 mm^3 for the left and right vAI, resp.).

Brain regions which exhibited difference among the three groups were further selected as ROIs. Mean FC values were extracted within each of these ROIs for further receiver operating characteristic (ROC) curve analyses. Furthermore, Pearson correlation coefficients were computed between the extracted insula subregions FC values within these ROIs and the clinical assessments of DA patients by PASW 18.0, and the significance level was set at $P < 0.05$ (two tailed).

3. Results

3.1. Demographic and Clinical Data. As shown in Table 1, DA patients showed significantly lower scores in ACT ($P < 0.01$) compared with NDA patients. There were no significant differences in the age, gender, education, and durations between the groups.

3.2. Insula ReHo Results. In the current study, significant differences of zReHo values in the insula between DA, NDA, and HCs were not found.

3.3. Insula Subregions FC Results. In the left insula, vAI showed significant altered whole-brain connections among the DA, NDA, and HC groups (see Table 2 and Figure 1). Compared with NDA, DA patients showed decreased connectivity between left vAI and the left cerebellum posterior lobe and right parietal lobe, respectively, and increased connectivity between left vAI and the left middle temporal gyrus (MTG). In addition, compared with HCs, DA patients exhibited increased left vAI FC and both left MTG and bilateral anterior cingulate cortex (ACC) and decreased left vAI FC and the bilateral parietal lobe. Compared with HCs, increased left vAI FC with the left cerebellum posterior lobe and right ACC and decreased left vAI FC with the bilateral parietal lobe were found in NDA patients.

In terms of the right insula (see Table 2 and Figure 1), decreased FC between right vAI and both left putamen and right caudate were found in the DA patients compared with that in the NDA patients. Compared with HC, DA, and NDA patients, both showed increased right vAI FC with the left putamen and right caudate.

Table 2: The FC between vAI with the whole brain among DA, NDA, and HCs.

Peak area	BA	Side	MNI coordinates			Voxels	Peak t-value
			X	Y	Z		
FC between left vAI and following brain regions							
ANCOVA							
Cerebellum posterior lobe	—	L	−39	−69	−39	66	12.857
Middle temporal gyrus	21	L	−51	−21	−6	77	10.0207
ACC	32	B	3	42	0	107	10.4837
Parietal lobe	7	R	15	−66	51	161	20.4306
Parietal lobe	7	L	−18	−63	54	79	13.9602
DA-NDA							
Cerebellum posterior lobe	—	L	−36	−72	−42	23	−3.6785
Middle temporal gyrus	21	L	−66	−12	−6	28	4.4333
Parietal lobe	7	R	15	−66	51	52	−4.8216
DA-HCs							
Middle temporal gyrus	20	L	−39	−12	−6	77	4.4481
ACC	32	B	−3	39	3	107	4.5744
Parietal lobe	7	R	15	−66	51	161	−6.2223
Parietal lobe	7	L	−18	−63	54	79	−5.2783
NDA-HCs							
Cerebellum posterior lobe	—	L	−39	−69	−39	66	4.7411
ACC	32	R	6	36	6	62	3.862
Parietal lobe	7	L	−18	−63	48	20	−3.2677
Parietal lobe	7	R	30	−45	60	24	−3.6245
FC between right vAI and following brain regions							
ANCOVA							
Putamen	—	L	−21	9	0	54	10.0985
Caudate	—	R	15	12	15	82	13.983
DA-NDA							
Putamen	—	L	−21	15	0	7	−3.2276
Caudate	—	R	15	12	18	12	−3.55
DA-HCs							
Putamen	—	L	−15	18	9	7	4.0056
Caudate	—	R	21	6	9	6	2.8772
NDA-HCs							
Putamen	—	L	−21	9	0	52	4.6445
Caudate	—	R	15	12	15	82	4.985

Note: ANCOVA threshold was set at $P < 0.01/6$ (AlphaSim-corrected, cluster size >1431 mm^3). The independent t-test threshold was set at $P < 0.01$ (AlphaSim-corrected, cluster size >216 mm^3 for left vAI and 135 mm^3 for right vAI). X, Y, Z: coordinates of primary peak locations in the MNI space; MNI: Montreal Neurological Institute space; BA: Brodmann area; vAI: ventral anterior insula; L: left; R: right; B: bilateral; DA: depressed asthma; NDA: nondepressed asthma; HCs: healthy controls; ANCOVA: one-way analysis of covariance.

3.4. Correlations between FC and Scales. The present study used partial correlation analysis to explore the relationships between mean FC values in ROIs (brain regions showed differences among the three groups by ANCOVA) and clinical assessments. No significant correlations were found between FC values in ROIs and HDRS-17, ACT scores, respectively, either in DA or in NDA group.

3.5. ROC Analyses. The mean FC values between left vAI and left cerebellum posterior lobe, left MTG, bilateral ACC, and bilateral parietal lobe were extracted, respectively, for the further ROC analyses (see Table 3 and Figure 2). The area under the curve (AUC) in FC between left vAI and left cerebellum posterior lobe was 0.7 ($P < 0.01$) which distinguished DA from HCs preferably (Table 3, Figure 2(b)), and it also differentiated NDA from HCs with an AUC of 0.82 ($P < 0.001$) (Table 3, Figure 2(c)). Similarly, FC between left vAI and bilateral ACC also significantly distinguished HCs from the DA and NDA groups (Table 3, Figures 2(b) and 2(c)). And the FC between left vAI and left MTG significantly distinguished DA from the NDA and HC groups (Table 3, Figures 2(a) and 2(b)). In addition, both the FC

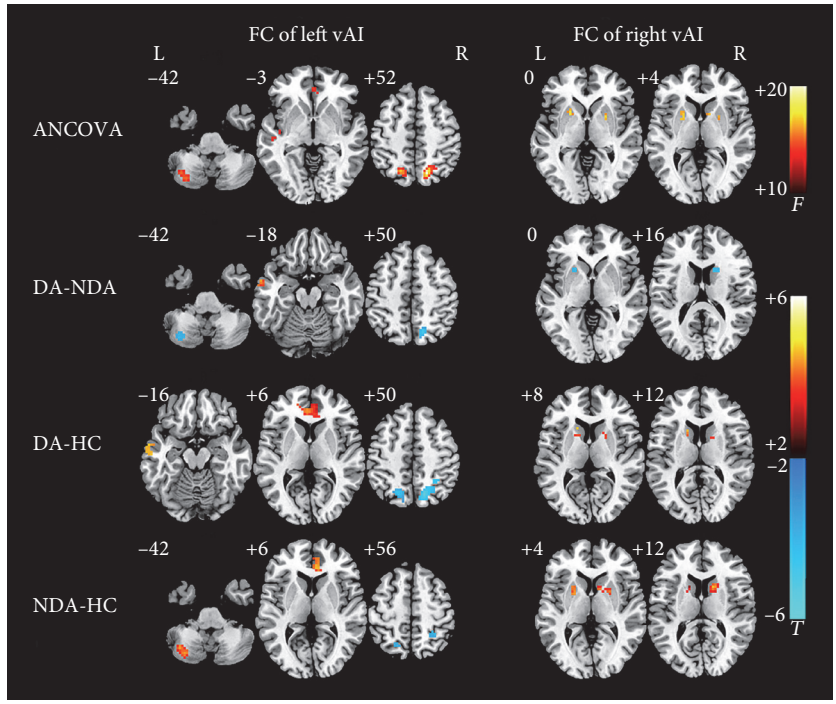

Figure 1: Statistical maps showing vAI FC differences in different brain regions between the DA, NDA, and HC groups. ANCOVA significantly increased in vAI FC among the DA, NDA, and HCs groups ($P < 0.01/6$, AlphaSim corrected). The FC between left vAI with left cerebellum posterior lobe, left MTG, bilateral ACC, and bilateral parietal lobe were increased; the FC between right vAI with the left putamen and right caudate were also increased; the red color bar indicates the F value from ANCOVA among the three groups. DA-NDA significantly altered in vAI FC of DA patients compared with that of NDA patients ($P < 0.01$, AlphaSim corrected). DA patients showed increased left vAI FC with MTG, decreased left vAI FC with left cerebellum posterior lobe and right parietal lobe, and decreased right vAI FC with the left putamen and right caudate. DA-HC significantly changes in vAI FC of DA patients compared with that of HCs ($P < 0.01$, AlphaSim corrected). DA patients showed increased left vAI FC with left MTG and bilateral ACC, decreased left vAI FC with bilateral parietal lobe, and increased right vAI FC with the left putamen and right caudate. NDA-HC significantly altered in vAI FC of NDA patients compared with HCs ($P < 0.01$, AlphaSim corrected). The NDA patients showed increased left vAI FC with left cerebellum posterior lobe and right ACC, decreased left vAI FC with bilateral parietal lobe, and increased right vAI FC with the left putamen and right caudate. The color bar indicates the t value from independent samples t-test between the three groups. ANCOVA, analysis of covariance; DA, depressed asthma; NDA, nondepressed asthma; HCs, healthy controls; FC, functional connectivity; vAI, ventral anterior insula; MTG, middle temporal gyrus.

between right vAI and both the left putamen and the right caudate only significantly differentiated NDA from HCs (Table 3, Figure 2(f)), without distinguishing DA from NDA or DA from HCs (Table 3, Figures 2(d) and 2(e)).

4. Discussions

In the present study, we employed the method of ReHo to measure the spontaneous activity of insula, as well as to investigate the relationship between insula subregions FC with whole brain in DA, NDA, and HCs. The results demonstrated that compared with HCs, both DA and NDA patients have no significant differences in spontaneous activity in the insula. However, to the best our knowledge, we demonstrated for the first time that asthmatic patients displayed altered insula FC compared with HCs. The present study found that DA patients showed increased FC between left vAI and left MTG compared with both the NDA and HC groups, and it could separate DA patients from NDA and HCs. In addition, when compared with HCs, the DA and NDA patients both exhibited increased FC between left vAI and right ACC, decreased FC between left vAI and bilateral parietal lobe, increased FC between right vAI and left putamen, and increased FC between right vAI and right caudate. Furthermore, the increased FC between left vAI and right ACC could differentiate HCs from both the DA and NDA patients. And the increased FC between right vAI and both the left putamen and the right caudate could separate NDA patients from HCs.

In the current study, compared with HCs, both the DA and NDA patients did not show significant differences of ReHo in the insula, which was consistent with the finding in our previous study that asthmatic patients did not exhibit abnormal ReHo in the insula [24]. Many studies indicated that the insula is associated with the perception of dyspnea both in patients with respiratory diseases [11, 25, 26] and healthy subjects [13], because dyspnea has a sensory and an effective dimension [27]. However, Peiffer et al. [28] explored dyspnea-related brain activation in healthy subjects, and the altered activity in the insula was not found during dyspnea. Although the anterior insula is a critical brain region involved in the experience of negative emotions [29], many

Table 3: ROC analyses for separating different groups.

Brain regions	AUC	*P* value	95% CI	Sensitivity	Specificity	Cut-off point
FC between the left vAI and the following brain regions						
Left cerebellum posterior lobe						
DA-NDA	0.194	0.001	0.058–0.331	0.056	0.333	−0.0095[a]
DA-HCs	0.700	0.010	0.588–0.812	0.944	0.583	−0.1290
NDA-HCs	0.820	<0.001	0.720–0.920	0.917	0.683	−0.0808
Left middle temporal gyrus						
DA-NDA	0.759	0.004	0.606–0.912	0.778	0.708	0.0932
DA-HCs	0.831	<0.001	0.709–0.952	0.778	0.833	0.0941
NDA-HCs	0.599	0.157	0.465–0.733	0.458	0.767	0.0632
Bilateral anterior cingulate cortex						
DA-NDA	0.623	0.178	0.450–0.796	0.833	0.458	0.1389
DA-HCs	0.828	<0.001	0.721–0.935	0.833	0.783	0.1450
NDA-HCs	0.709	0.003	0.586–0.833	0.542	0.800	0.1554
Right parietal lobe						
DA-NDA	0.257	0.008	0.102–0.412	0.278	0.292	−0.1453
DA-HCs	0.129	<0.001	0.024–0.233	0.222	0.083	−0.1336
NDA-HCs	0.301	0.005	0.173–0.429	0.500	0.150	−0.1057
Left parietal lobe						
DA-NDA	0.294	0.024	0.134–0.454	0.444	0.167	−0.2058
DA-HCs	0.159	<0.001	0.057–0.262	0.333	0.117	−0.1446
NDA-HCs	0.314	0.008	0.189–0.438	0.542	0.117	−0.1489
FC between right vAI and following brain regions						
Left putamen						
DA-NDA	0.336	0.071	0.170–0.502	0.111	0.542	0.3462
DA-HCs	0.644	0.066	0.510–0.777	0.778	0.550	0.2277
NDA-HCs	0.760	<0.001	0.651–0.868	0.667	0.800	0.3013
Right caudate						
DA-NDA	0.306	0.033	0.141–0.470	0.389	0.250	0.2506
DA-HCs	0.599	0.204	0.459–0.739	0.833	0.367	0.1431
NDA-HCs	0.778	<0.001	0.677–0.880	0.875	0.617	0.2381

Note: [a]This cut-off point resulted in a sensitivity of 5.6% and a specificity of 33.3% while DA patients separating from NDA patients. The means of other cut-off points were similar. ROC: receiver operating characteristic; AUC: area under the curve; CI: confidence interval; DA: depressed asthma; NDA: nondepressed asthma; HCs: healthy controls.

fMRI research of depression did not report abnormal activity in the insula [30, 31]. These findings further supported our study that significant differences of ReHo in the insula were not found between the DA and NDA patients. Thus, the relationship between spontaneous activity of the insula with asthma-specific symptoms and emotions needs further study.

A functional imaging study indicated that MTG belongs to the visual recognition circuit, which is assumed to play an important role in processing facial stimuli [32]. Further, it also regulates semantic processing, the processing of emotional information and cognitive regulation [33]. Cao et al. [33] reported that increased spontaneous brain activity in the left MTG may cause emotional dysregulation, thus increases the vulnerability to impulsive and suicidal behavior in major depression disorder. Increased gray matter volume in the MTG was also found in the late onset depression, which suggested that it would be an anatomical basis for emotional dysregulation and impaired decision making [34]. In addition, neuroimaging revealed that vAI is connected to regions representing sensory inputs associated with affective experience [21, 35]. In the current study, ROC analyses demonstrated that the increased FC between left vAI and left MTG as an independent variable performed well in differentiating DA from both the NDA and HC groups. The previous study also reported decreased neural activity in MTG in patients with depression disorder [36]; however, the similar finding was not found in DA patients. Therefore, the increased FC between left vAI and left MTG in DA patients would be associated with emotional dysregulation.

Rosenkranz and Davidson [10] demonstrated that the anatomical projections of ACC and insula implicate these structures in monitoring changes in physiological status, integrating this information with external sensory, cognitive, and emotional information and directing the appropriate behavioral and peripheral physiological responses. ACC and insula may be hyperresponsive to asthma-specific

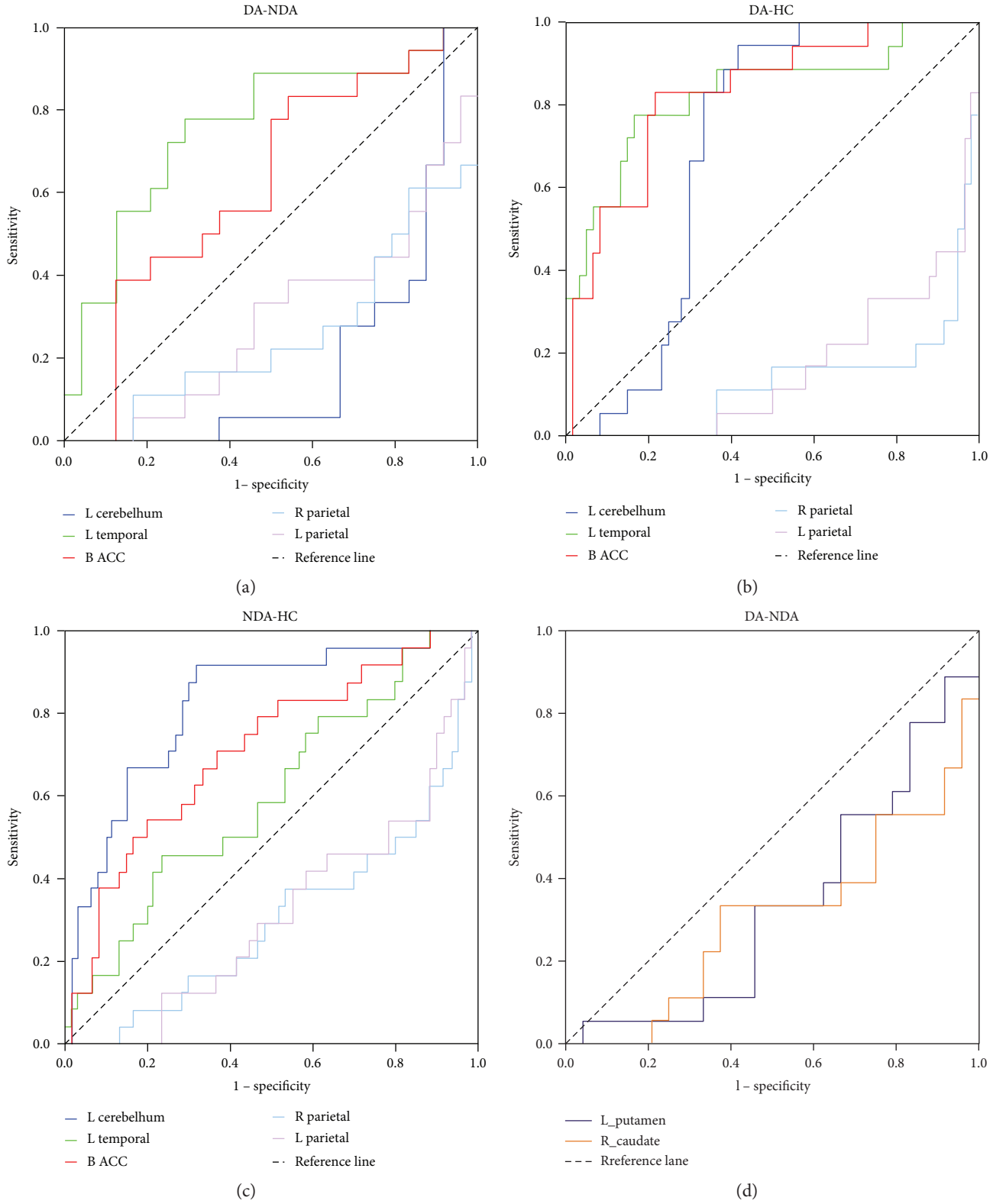

Figure 2: Continued.

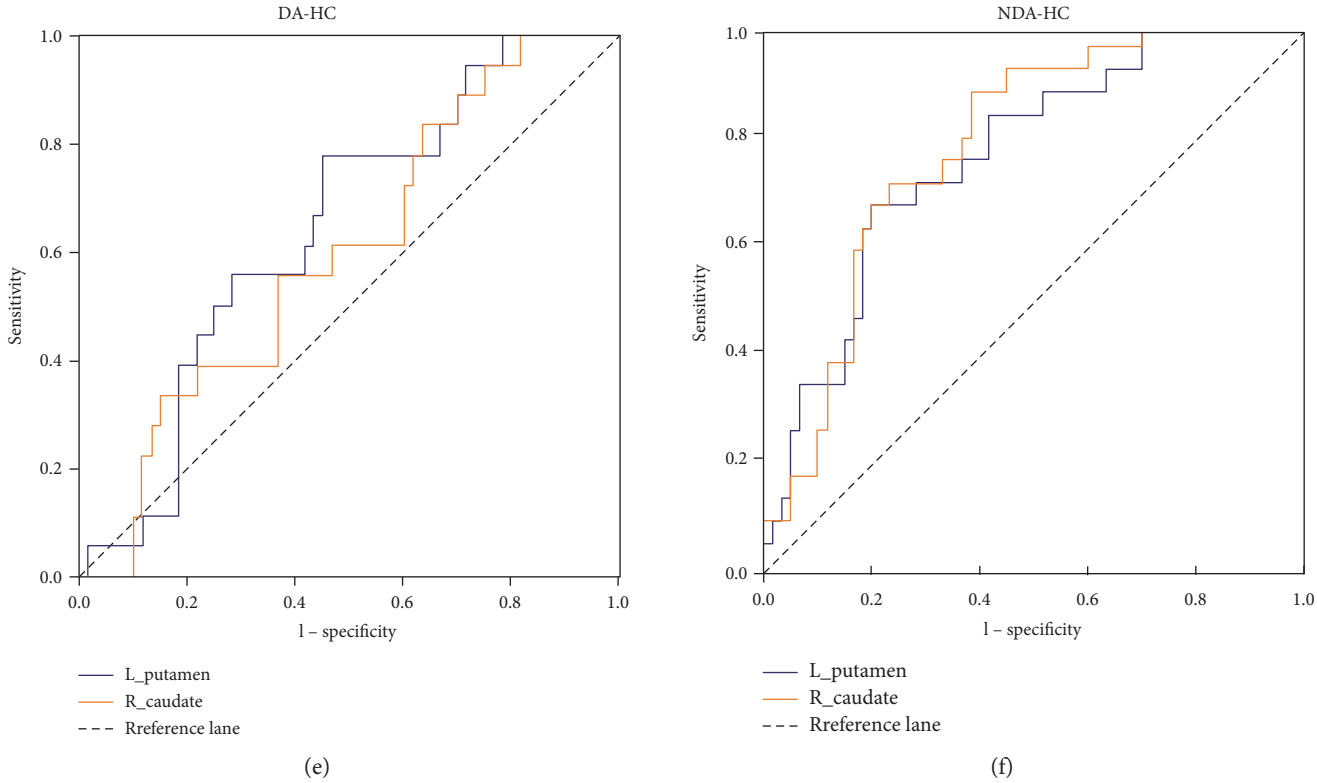

Figure 2: ROC analyses. (a) ROC analyses differentiate DA from NDA patients by using FC values between left vAI with left cerebellum posterior lobe, left MTG, bilateral ACC, right parietal lobe, and left parietal lobe. The areas under the ROC curve for FC between left vAI with left cerebellum posterior lobe, left MTG, bilateral ACC, right parietal lobe, and left parietal lobe were 0.194 ($P < 0.001$; 95% CI: 0.058–0.331), 0.759 ($P < 0.01$; 95% CI: 0.060–0.912), 0.632 ($P > 0.5$; 95% CI: 0.450–0.796), 0.257 ($P < 0.01$; 95% CI: 0.102–0.412), and 0.294 ($P < 0.05$; 95% CI: 0.134–0.454), respectively. (b) ROC analyses differentiate DA from HC by using FC values between left vAI with left cerebellum posterior lobe, left MTG, bilateral ACC, right parietal lobe, and left parietal lobe. The areas under the ROC curve for FC between left vAI with left cerebellum posterior lobe, left MTG, bilateral ACC, right parietal lobe, and left parietal lobe were 0.700 ($P < 0.01$; 95% CI: 0.588–0.812), 0.831 ($P < 0.001$; 95% CI: 0.709–0.952), 0.828 ($P < 0.001$; 95% CI: 0.721–0.935), 0.129 ($P < 0.001$; 95% CI: 0.024–0.233), and 0.159 ($P < 0.001$; 95% CI: 0.057–0.262), respectively. (c) ROC analyses differentiate NDA from HC by using FC values between left vAI with left cerebellum posterior lobe, left MTG, bilateral ACC, right parietal lobe, and left parietal lobe. The areas under the ROC curve for FC between left vAI with left cerebellum posterior lobe, left MTG, bilateral ACC, right parietal lobe, and left parietal lobe were 0.820 ($P < 0.001$; 95% CI: 0.720–0.920), 0.599 ($P > 0.5$; 95% CI: 0.465–0.733), 0.709 ($P < 0.01$; 95% CI: 0.586–0.833), 0.301 ($P < 0.01$; 95% CI: 0.173–0.429), and 0.314 ($P < 0.01$; 95% CI: 0.189–0.438), respectively. (d) ROC analyses differentiate DA from NDA patients by using FC values between right vAI with the left putamen and right caudate. The areas under the ROC curve for FC between left vAI with the left putamen and right caudate were 0.336 ($P > 0.05$; 95% CI: 0.1700.502) and 0.306 ($P < 0.05$; 95% CI: 0.141–0.470), respectively. (e) ROC analyses differentiate DA patients from HC by using FC values between right vAI with the left putamen and right caudate. The areas under the ROC curve for FC between left vAI with the left putamen and right caudate were 0.644 ($P > 0.05$; 95% CI: 0.510–0.777) and 0.599 ($P > 0.05$; 95% CI: 0.459–0.739), respectively. (f) ROC analyses differentiate NDA patients from HC by using FC values between right vAI with the left putamen and right caudate. The areas under the ROC curve for FC between left vAI with left putamen and right caudate were 0.760 ($P < 0.001$; 95% CI: 0.651–0.868) and 0.778 ($P < 0.001$; 95% CI: 0.677–0.880), respectively. DA, depressed asthma; NDA, nondepressed asthma; HC, healthy controls; ACC, anterior cingulate cortex; FC, functional connectivity; vAI, ventral anterior insula; MTG, middle temporal gyrus.

emotional and afferent physiological signals, which may contribute to the dysregulation of peripheral processes [11]. In the current study, both DA and NDA patients showed increased FC between left vAI and ACC compared with HCs. It was consistent with the findings of von Leupoldt and Dahme [37, 38] that patients with dyspnea show increased activity in the ACC. Furthermore, greater activity in the perigenual ACC seems to reflect greater reactivity and is associated with greater airway inflammation, a more robust alpha amylase response, and a greater stress-induced increased in proinflammatory cytokine mRNA expression in airway cells [39]. Thus, the increased FC between left vAI and ACC in asthmatic patients would be possible to be associated with asthma-specific inflammation and emotions.

The parietal lobe is primarily responsible for the integration of sensory information, both tactile and perceived, as well as spatial recognition and processing of both language and memory [40]. Zhang et al. [41] explored the brain activity in healthy subjects that experienced experimentally induced low back pain and found that the right inferior parietal lobe of these subjects showed a decreased spontaneous activity. Moreover, they suggested that these changes

may account for the recognition, execution, and emotional and memory process involved in acute pain [41]. In patients with headache, the gray matter density in the bilateral parietal lobe was also decreased [42]. In the present study, asthmatic patients showed decreased FC between left vAI and bilateral parietal lobe, which was similar to above findings. The neural structures that promote dyspnea and pain are shared [27], we deduced that the decreased FC between left vAI and bilateral parietal lobe would be the underpinning of cognitive in asthma.

The putamen and caudate are believed to contribute to sensorimotor activity and cognition, respectively [43]. An fMRI study of the normal fear response in healthy subjects revealed increased putamen activation in response to a fearful situation [44]. In patients with panic disorder, the putamen also showed abnormal function indicating that the subcortical mediated panic-related fight or flight response may be abnormal [45]. In addition, the putamen also plays a critical role in gating respiratory information to the cortex [46]. Since vAI is connected with visceromotor regions [21, 35], thus, we speculated that the increased FC between right vAI and left putamen in asthmatic patients may involve in the asthma-specific fear. Furthermore, in the present study, this increased FC differentiated NDA patients from HCs. It further supported our speculations.

Previous studies reported that caudate nucleus has stronger anatomical links with the prefrontal cortex, and caudate is demonstrated to be involved in more cognitive tasks [47, 48]. For example, Quevedo et al. [49] found patients with depression showed heightened caudate and insula to ventral striatum connectivity, which suggested that these patients may intend to have more behavioral planning and goal-oriented cognitions for negative outcomes. Therefore, the increased FC between right vAI and right caudate in the current study was possibly associated with the hyperattention of asthma symptoms.

On the basis of previous studies, these abnormal vAI FC are involved in asthma-specific symptoms including inflammation, cognition, fear, hyperattention, and emotion. Whether these abnormal FC could be used as biomarkers to predict depression in asthma needs to be further demonstrated with large samples in the future study.

There were some limitations in the current study. First, it was a nonrandomized study with a relatively small sample size. Since all asthmatic patients received the same kind of pharmacotherapy, the effect of antiasthma drugs on brain functions needs further exploration. Second, the generalizability of the results might have been reduced due to the sampling strategy. Third, we just assessed the depression severity and asthma control level in the present study; more cognitive-related tests were required adequately to describe the patients' cognitive profile. To overcome these limitations, studies with larger sample sizes are needed in the future.

5. Conclusions

The current study showed for the first time the evidence of altered vAI FC of depression that would be involved in the neuropathology of depression in asthma.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors thank Professor Huanxin Chen (from Key Laboratory of Cognition and Personality, Ministry of Education; School of Psychology, Southwest University, Chongqing 400175, PR China) who help edit the language. This work was supported by the National Natural Science Foundation of China (Grant no. 81371488, Yonggui Yuan), the Fundamental Research Funds for the Central Universities (Southeast University, Grant no. 2242016K41053), and the National Key Research and Development Program of China (2016YFC1306702).

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Hindawi
Neural Plasticity
Volume 2017, Article ID 7014146, 37 pages
https://doi.org/10.1155/2017/7014146

Review Article

Physical Activity Modulates Common Neuroplasticity Substrates in Major Depressive and Bipolar Disorder

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Received 4 November 2016; Revised 10 February 2017; Accepted 16 March 2017; Published 26 April 2017

Academic Editor: Frank S. Hall

Mood disorders (MDs) are chronic, recurrent mental diseases that affect millions of individuals worldwide. Although the biogenic amine model has provided some clinical utility, a need remains to better understand the interrelated mechanisms that contribute to neuroplasticity deficits in MDs and the means by which various therapeutics mitigate them. Of those therapeutics being investigated, physical activity (PA) has shown clear and consistent promise. Accordingly, the aims of this review are to (1) explicate key modulators, processes, and interactions that impinge upon multiple susceptibility points to effectuate neuroplasticity deficits in MDs; (2) explore the putative mechanisms by which PA mitigates these features; (3) review protocols used to induce the positive effects of PA in MDs; and (4) highlight implications for clinicians and researchers.

1. Introduction

Major depressive disorder (MDD) and bipolar disorder (BP) are chronic mood disorders (MDs) that adversely affect over 400 million persons worldwide [1]. Pathognomonic features of MDD include the persistence of one or more episodes of sadness or anhedonia in a two-week period, together with a range of cognitive and somatic symptoms (e.g., changes in appetite, sleep patterns, energy level, concentration, or physical activity and feelings of worthlessness and guilt) [2]. In BP, persons exhibit similar symptoms in the depressive phase but alternate to euphoric states during the manic phase—a state characterized by excessive activity and libido and grandiose thinking [2]. Recent attention has focused on the inability of extant treatment approaches to induce remission of symptoms in a significant number of affected persons [3, 4], prompting the diversification of efforts to derive more effective treatment strategies.

Fortunately, convergent evidence demonstrates that physical activity (PA) confers neuroplastic effects [5, 6] and may serve as an effective intervention for MDs [7–12]. Physical exercise is a subcategory of PA that connotes purposeful, planned, and structured endeavors undertaken to improve skill or physical fitness level [12]. PA alters the progression of MD neuropathology by optimizing the levels of neurotransmitters [13], neurotrophic factors [13, 14], beta-endorphins [15], cortisol [16, 17], and muscle-derived protein (peroxisome proliferator-activated receptor gamma coactivator 1-α [PGC-1α]) [18]. Moreover, regular PA optimizes processes involved in neurogenesis [19, 20], immune function [21, 22], stress regulation [23, 24], antioxidant defense [25, 26], circadian rhythms [27–29], epigenetic modifications [30, 31], and the maintenance of telomere length [32–35].

Via these complex and interrelated mechanisms, PA may reduce the risk for MDs [36–38], the degree of symptoms [10, 39], the incidence of relapse [40, 41], and caregiver burden [42]. This evidence, along with its relatively low-risk profile and ease of implementation [43], has led to the incorporation of PA into basic clinical management protocols for MDs [44, 45]. Because it is important that clinicians and scientists understand the means by which PA can alter pathophysiological substrates, from both a self- and patient-education perspective, the aims of this review are to (1) elucidate key substrates implicated in MD pathobiology, (2) explore the mechanisms by which PA can mitigate them, (3) examine protocols used to effectuate the positive effects of PA in MDs, and (4) highlight implications for clinicians and scientists.

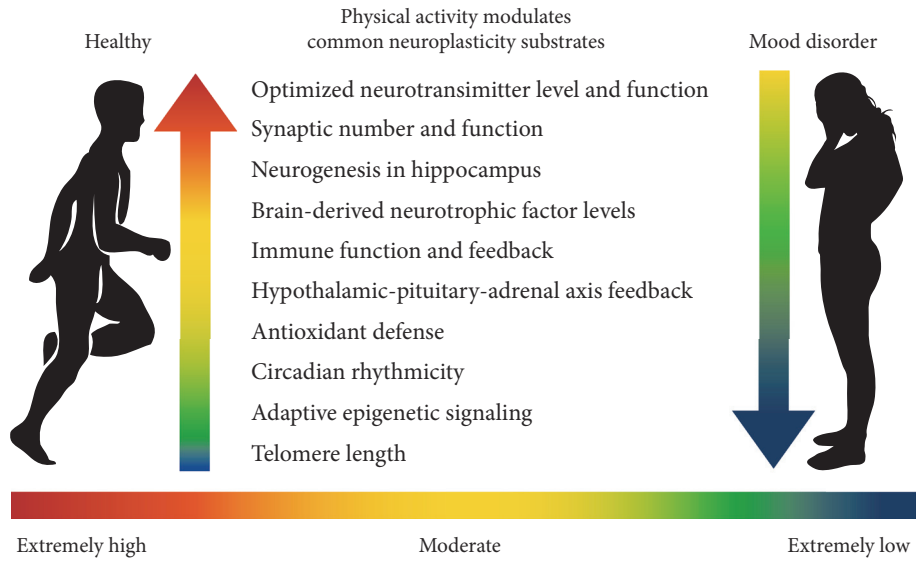

Figure 1: Physical activity modulates common neuroplasticity substrates in the brain. Here, the effects of various levels of PA are illustrated for the person who is healthy and the person with a MD.

2. The Neurobiology of Major Depressive and Bipolar Disorders

Recent decades have noted dramatic progress in the neurobiological understanding and treatment of psychiatric conditions. On the one hand, psychiatrists have refined diagnostic categories based on clinical symptoms [46, 47]. On the other hand, neuroscientists have derived evidence of transdiagnostic biomarkers across psychiatric conditions [48–50], including those that modulate neuroplasticity substrates in MDs [51–54]. Early biologic theories focused upon neurotransmitters, particularly the biogenic amines [55]. Subsequent advances in technology heralded new abilities to characterize general and distinctive cellular and molecular mechanisms, genetic contributions, and structural correlates of psychiatric disease [56, 57]. Although a complete description of these advances is beyond the scope of this article, a cursory review of MD neurobiology will be presented before focusing on neuroplasticity substrates. The reader is referred to the following excellent reviews for a more comprehensive presentation on the neurobiology of MDD [3, 58–60] and BP [61–64].

2.1. Major Depressive Disorder. Neuroimaging studies of depression and analysis of surgical lesions (that induce or reverse depressive symptoms) have revealed mood circuits [65, 66]. Implicated in these circuits are several brain structures and regions, including the dorsal prefrontal cortex, ventral prefrontal cortex, anterior cingulate gyrus, amygdala, hippocampus, striatum, and thalamus [67–69]. Drevets et al. have emphasized the pathophysiological processes and dysfunction of multiple pathways that adversely affect mood circuits and structures [66, 70], including those related to genetic, epigenetic, and environmental factors. Results from a twin study suggest that the heritability of MDD is 38% [71]. Preclinical studies implicating epigenetic mechanisms have shown that maternal behavior alters the function of stress-related genes [72] and that antidepressants alter the regulation of DNA [73, 74]. Other studies have shown that depletion in neurotransmitter levels contributes to depressive symptoms [55, 75]: slow-acting neurotransmitters (e.g., dopamine, serotonin, and norepinephrine) appear to interact with signaling proteins found inside the cell membrane in a way that allows the receiving cells to process signals from glutamate and γ-aminobutyric acid (GABA). Accordingly, therapeutic agents for MDs were derived to increase monoamine transmission acutely, either by inhibiting neuronal reuptake or by inhibiting degradation in the synaptic cleft. While this strategy has demonstrated some utility in the alleviation of symptoms, the fact that monoamine depletion fails to produce depressive symptoms in healthy individuals [76] or worsen depressive symptoms in persons with MDD [77, 78] induced a more comprehensive search for mechanisms. Subsequent work has implicated general disruption in neurogenesis [79], trophic factor level and function [80], antioxidant defense [81], hypothalamic-pituitary-adrenal (HPA) axis function [82], immune regulation [83], neuroplasticity [84], and circadian rhythms [85, 86], changes that collectively contribute to neuronal network alterations [84, 87]. Interestingly, the patterns of disruption to neurogenesis, immune system function, and antioxidant defense in MDD are similar in many respects to the patterns of disruption that are seen in BP. Also notable is evidence that has suggested a "kindling process" wherein depressive episodes are triggered more readily over time [88] and the number of prior episodes is a better predictor of future episodes than life stress is [89].

2.2. Bipolar Disorder. The complex pathophysiology of BP is undoubtedly mediated by genetic and epigenetic factors acting in concert with environmental stressors [90] to effectuate functional and structural abnormalities in the interconnected limbic, striatal, and fronto-cortical neurotransmitter neuronal circuits [91] and in plasticity substrates [51–54]. A robust

genetic basis for BP has been derived from familial and identical twin studies: concordance rates for BP among identical twins typically range from 40 to 70%, with the estimated heritability reaching as high as 90% [92]. Notwithstanding, genome-wide studies have failed to detect single-gene contributions, supporting the premise that BP is a polygenic condition [92]. Strikingly, while some distinctions in genetic risks exist between BP and other psychiatric conditions, a high degree of genetic overlap has been reported among BP, MDD, and schizophrenia [48, 93]. Putative interactions between genes and life stresses are thought to effectuate disruptions in homeostatic and neuroplastic mechanisms [94, 95] and increase the severity of symptoms [95]. Parallel work has demonstrated disruption of glucocorticoid signaling [96], neurogenesis [97], immune-inflammatory imbalance [98], and antioxidant defense [99], changes that contribute to increased loss of volume in brain regions vital for mood regulation and cognitive function [65]. The identification and understanding of mechanistic pathways common to BP and MDD offer an opportunity to deploy novel lifestyle interventions such as PA to target these disorders in an integrated fashion.

3. Neuroplasticity

The ability of the central nervous system to continuously adapt to challenges is accomplished by neuroplasticity, a process wherein neurons change and reorganize to meet the demands of the environment [100]. Neuroplasticity is dependent upon stimulus-induced synaptic activity and membrane depolarization which, in turn, induce receptor trafficking, the activation of a multiplicity of genes, and the release of neurotransmitters. The secondary messengers effectuate downstream changes in the brain that permit its resculpting. Emotional and cognitive learning, neural homeostasis, and adjustments in behavior rely on biological correlates of neural plasticity for adaptation [53, 101]. Plastic changes in the brain can be maladaptive wherein a net loss of function occurs [102], a situation that reifies in MDs [103, 104]. On the other hand, brain plasticity can be adaptive when a gain of function occurs [105]. That is, PA can modulate common neuroplasticity substrates in the brain (as described in Figure 1) and then cognitive stimulation (e.g., cognitive behavioral therapy) can increase the likelihood of behavioral change in MDs [106].

4. Measurement of Voluntary Physical Activity in Humans

Voluntary PA refers to locomotor activity that is not directly required for survival or motivated by an external factor (such as searching for food, shelter, or mates; interacting with competitors; or avoiding predators) [107]. Human voluntary PA occurs in a multiplicity of ways and varies tremendously in both intensity and duration, both of which modulate its physiological consequences. Several indirect and direct assessment methods have been used to investigate the effects of voluntary PA in humans—including retrospective questionnaires, surveys, activity logs, motion sensors, heart rate monitors, calorimetry, and direct observation [108]—with different methods possessing unique strengths and weaknesses. The majority of early studies used self-reports of PA, particularly given their ease of administration, cost effectiveness, positive acceptance, and lack of intrusiveness on personal habits [109, 110]. Yet, while the administration of questionnaires at the population level has proved to be a feasible method of assessment, some evidence suggests that they are the least valid and reliable measure [107, 110–112]. In contrast, direct measures of voluntary PA assess energy expenditure [113] or actual movement [114] and are less susceptible to response and recall biases [113, 115, 116]. Notwithstanding, large-scale studies using direct measures have not been feasible in the general population [117]. Additionally, it seems plausible that long-term monitoring of PA with direct measures would sacrifice face validity by increasing intrusiveness and burden on participants [107, 116]. The inverse relationship between the validity and feasibility of assessment methods [107] has prompted recent investigations to use direct measures and standardized interventions in smaller populations. Studies of this type are vital because direct measures provide a means to examine a cause and effect relationship between PA and neuroplasticity substrates. Accordingly, several investigations that aim to determine the neurobiological, psychological, and physiological effects of PA on humans are systematically reviewed in Table 1. Analysis of these investigations reveals that PA generally produces antidepressant effects and improves cognitive function, enhances quality of life, improves sleep, optimizes brain-derived neurotrophic factor (BDNF) levels and function in the hippocampus, and enhances fitness measures.

5. Measurement of Voluntary Physical Activity in Animal Models

Multiple animal studies have been conducted to ascertain the effects of PA on brain structure and function. Specifically, investigators have deployed a voluntary wheel-running model in rodents to simulate PA in humans [118, 119], an avenue that provides unfettered hypothesis-driven discovery. Bolstering support for the model is evidence that (1) voluntary wheel running is a self-rewarding behavior that allows rodents to choose how much to run while avoiding the stress of forced running or investigator handling [107, 120, 121], (2) rodents show a conditioned preference to the place associated with wheel running [122] and can perform an instrumental reaction to garner access [123], (3) age-related decrements in PA occur in both rodents and humans [124, 125], (4) both running wheel access in rodents and voluntary PA in humans induce changes in brain reward systems [107], and (5) voluntary wheel running and voluntary PA occur in low-energy expenditure contexts such as laboratory housing and industrialized Western society [107, 126].

The historical preference for voluntary wheel running as opposed to forced treadmill running has derived from the notion that forced running on motorized treadmills may cause the release of stress-linked hormones, which could

Table 1: Clinical trials of physical activity in persons with mood disorders. To determine the effects of PA on the brain in humans affected by MDs, a computer search of MEDLINE using the terms "mood disorder," "physical activity," and "exercise" was used to produce a list of interventional studies. Then, manual searches of key references were performed to identify additional studies. Articles met inclusion criteria if they were peer-reviewed interventional studies in persons diagnosed with MDD or BP. Articles were excluded if they were reviews, case reports, conference abstracts, expert opinions, or clinical studies of adolescents. Duplicate articles and those not available in English language were excluded also. Based on this search and subsequent screening, 37 articles that spanned from 1987 to 2016 were identified. Whereas extensive variations existed in the studies with regard to age, sex, degree of symptoms, phase of disease, and setting, 97% of RCTs (31 out of 32) that measured behavioral outcomes reported positive associations between PA and recovery from depressive symptoms [40, 41, 267, 316, 463–489] by utilizing training ranges of 100–250 min per week for a duration of 2–6 months [40, 41, 316, 463–468, 472–474, 476–485, 487, 488]. One report achieved relief of depressive symptoms following 60 minutes of PA for a duration of 5 weeks [489], whereas another study reported that participants obtained relief following PA 30 min/day for a duration of 1 week [470]. The modalities used in the programs varied, but most of the programs deployed some form of aerobic activity as a core component [40, 41, 96, 464–483, 485–488, 490, 491]. Notably, the one study that failed to find an association between PA and depressive symptoms used a relaxation group as a control [492], a fact that may be problematic given preliminary evidence that stress reduction activities reduce cortisol abnormalities and, in turn, may mitigate depressive symptoms [489]. The remaining studies reported that PA reduced sleep problems [382, 383, 487]; normalized BDNF levels in some studies [267, 268], but failed to do so in others [490]; and reduced cortisol levels [489]. Nevertheless, extant RCTs are still few and leave many questions unresolved.

References	Sample	Modality	Frequency & duration of PA	Assessment
[463]	Mean age of 75 y/o with MDD ($n = 121$)	Sertraline only; sertraline + supervised nonprogressive PA (<70% peak heart rate); sertraline + supervised progressive aerobic activity (60% peak heart rate)	60 min/session 3 d/wk for 24 wks	Reduced depressive symptoms on HAM-D and CGI in all groups, but earlier and higher remission rates in exercise groups at 4, 8, and 12 wks
[464]	50 y/o or greater with MDD ($n = 156$)	Aerobic exercise (70–85% max HR); aerobic exercise (70–85% max HR) + standard medication; or standard medication only	Supervised 45 min sessions 3 d/wk × 16 wks	Reduced depressive symptoms on BDI and HAM-D in all groups, but response was quicker in medication-only group
[465]	19–78 y/o with depressive symptoms ($n = 112$)	Aerobic exercise outside during daylight hours (60% max HR) + prompts to take a specific vitamin regimen or control	20 min per session 5 d/wk × 8 wks	Reduced depressive symptoms in both groups, but more so in exercise group; specifically, ↓ depressive symptoms on CES-D in exercise group; ↓ anger and tension on POMS in exercise group; ↑ vitality in exercise group
[466]	18–65 y/o with MDD ($n = 62$)	Add-on aerobic exercise × 10 wks; add-on basic body awareness therapy × 10 wks; or single consult for advice on PA + care as usual	55–60 min session 2 d/wk × 10 wks; group basic body awareness therapy 2 d/wk × 60 min; or advice on PA on one occasion	Reduced depressive symptoms on MADRS in all groups (−10.3 in aerobic PA, −5.8 in body awareness, and −4.6 in advice only group); ↑ cardiovascular fitness gains in aerobic exercise group; ↓ self-rated depression symptoms in PA and basic body awareness groups
[41]	50 y/o or greater with MDD ($n = 133$)	Aerobic activity (70–85% max HR); aerobic activity (70–85% max HR) + sertraline; or sertraline only	Supervised 45 min sessions 3 d/wk × 16 wks then follow-up 24 wks after study conclusion	Reduced depressive symptoms on HAM-D; ↑ rate of partial or full recovery from depressive symptoms on HAM-D in exercise group; and ↓ rate of relapse for MDD in exercise group
[316]	18–20 y/o with mild to moderate depression ($n = 28$)	Exercise regimen or usual daily activities	50 min sessions 5 d/wk × 8 weeks for each regimen	Exercise regimen reduced depressive symptoms on CES-D; ↓ cortisol; and ↓ urinary secretion of epinephrine

Table 1: Continued.

References	Sample	Modality	Frequency & duration of PA	Assessment
[467]	20–64 y/o with MDD ($n = 82$)	Aerobic exercise + care as usual or care as usual only	Progressive exercise 45–60 min per session 3 d/wk × 8 wks	Combination of exercise + fluoxetine group exhibited greater reduction in depressive symptoms on BDI and ICD-10 than fluoxetine alone
[468]	18–35 y/o with MDD or minor depression ($n = 40$)	Aerobic (80% max HR); strength training (50–60% max HR); or control	Supervised sessions 4 d/wk × 8 wks	Reduced depressive symptoms on BDI and HAM-D in both exercise groups following intervention and at 12 mo follow-up
[469]	20–45 y/o with diagnosis of MDD ($n = 80$)	4 aerobic exercise treatment groups that varied according to intensity: low dose (7.5 kcal/kg/wk for 3 or 5 d/wk × 12 wks); high dose (17.5 kcal/kg/wk for 3 or 5 d/wk × 12 wks); or control	Supervised aerobic activity × 12 wks	Reduced depressive symptoms on HAM-D for high-dose aerobic exercise (17.5 kcal/kg/wk 3–5 d/wk)
[470]	20–53 y/o with MDD ($n = 38$), somatization syndrome ($n = 26$), or healthy controls ($n = 47$)	Aerobic exercise or control	30 min/d for 1 wk or reduced PA for 1 wk	Reduced depressive symptoms on BDI 2 following 1 wk of exercise in persons with MDD, but not other groups; ↑ monocytes in healthy controls, but not in persons with MDD or somatization syndrome
[471]	18–65 y/o with MDD and sedentary lifestyle and with residual cognitive or attention impairments following tx with SSRIs for 8–12 wks ($n = 39$)	High-dose aerobic exercise (target of either 16 KKW—the equivalent to walking 4 mph × 210 min/wk) or low-dose aerobic control (4 KKW—the equivalent to walking 3.0 mph for 75 min/wk)	Initial supervision during sessions then transition to home-based program × 12 wks	Reduced depressive symptoms in both groups on IDS-C, but greater effect in high-dose exercise group; high dose PA ↑ spatial working memory and both groups ↑ cognitive function (psychomotor speed and executive function)
[472]	60 y/o or greater women who were overweight or moderately depressed ($n = 106$)	Add-on supervised aerobic exercise + strengthening activities or usual care	Supervised 50 min session 3 d/wk × 24 wks	Reduced depressive symptoms and anxiety on GDS, STAI, and EQ-5D in intervention group; ↓ BMI in intervention group
[473]	40 y/o or greater with diagnosis of MDD ($n = 102$)	Supervised aerobic exercises (70–85% of max HR); sertraline; or placebo	45 min session 3 d/wk × 16 wks	Reduced depressive symptoms in both groups on HAM-D and BDI along with higher remission rates compared to placebo; ↔ between groups in verbal memory, verbal fluency, or working memory
[40]	Mean age of 51 y/o with MDD and sedentary ($n = 202$)	Supervised aerobic exercise (70–80% of max HR); home-based exercise; sertraline; or placebo	45 min session 3 d/wk × 16 wks	At 12 mo follow-up, exercisers who reported 180 min/wk exhibited reduced depressive symptoms on HAM-D scores and a ↓ risk for relapse in comparison with persons who reported 0 min of exercise

Table 1: Continued.

References	Sample	Modality	Frequency & duration of PA	Assessment
[474]	18 y/o or greater with MDD ($n = 42$)	Structured group exercise (50% max HR) or usual care	45 min session 3 d/wk × 6 wks	Reduced depressive symptoms on MADRS and BDI-2 in both groups, but ↑ response (> 50% decrease of symptoms on MADRS) in exercise group; ↓ diastolic blood pressure in exercise group; ↓ waist circumference in exercise group; ↑ HDL in exercise group; ↑ cardiorespiratory capacity in exercise group
[475]	75 y/o or greater with depressive symptoms ($n = 193$)	Individualized; home-based exercise program (i.e., balance, strength, and aerobic activity); or control	52 wks	Reduced depressive symptoms on GDS and ↑ mental health-related quality of life in both groups, but no difference between groups
[476]	18 y/o or greater with depressive symptoms ($n = 23$)	Low-frequency aerobic exercise (within target HR); high-frequency aerobic exercise; or high-frequency aerobic exercise + group team building intervention	1 aerobic activity 30 min session 1 d/wk × 8 wks; 30 min session 3–5 d/wk × 8 wks; 30 min session 3–5 d/wk + group team building × 8 wks	Persons in high-frequency aerobic groups exhibited reduced depressive symptoms on BDI-2, but team-building intervention ↔ depressive symptoms
[477]	22–63 y/o with depressive symptoms ($n = 80$)	Aerobics + bright light or aerobics + normal light	Individualized aerobic training 2-3 d/wk × 8 wks	At 8 wks, reduced depressive symptoms on HAM-D and ATYP in both groups, but greater effect in aerobics + bright light group; ↑ in vitality on RAND in both groups, but more so in bright light group
[478]	26–63 y/o with depressive symptoms ($n = 98$)	Aerobics + bright light; aerobics + normal light; or stretching in bright light	Supervised sessions 2 d/wk × 8 wks	Reduced depressive symptoms on HAM-D in both aerobic groups; reduced depressive symptoms on SIGH-SAD-SR in aerobic + bright light group; ↔ in serum lipid levels or BMI in any group
[485]	31–52 y/o with dysthymia and MDD ($n = 99$)	Add-on aerobic exercise (70% max HR); nonaerobic exercise; or usual care	Supervised 60 min sessions 3 d/wk × 8 wks	Reduced depressive symptoms on BDI in both exercise groups; ↑ VO_2 max in aerobic exercise group
[479]	21–70 y/o or greater with MDD or BD ($n = 75$)	Chronotherapeutic intervention (consisting of wake therapy, bright light therapy, sleep phase advance, and sleep time stabilization) or individualized aerobic exercise plan	30 min sessions 5 d/wk × 29 wks	Reduced depressive symptoms on HAM-D in both groups, but even greater response in chronotherapy group—at 9 wks remission rate was 45% for chronotherapy group versus 23% for PA group and at 29 wks remission was 62% for chronotherapy group versus 38% for PA group
[480]	53 y/o or greater with mood disorder who were poor responders to antidepressant meds ($n = 86$)	Add-on exercise (aerobic, strengthening, and stretching) or health education talks	Supervised activity for 60 min session 2 d/wk × 10 wks	Reduced depressive symptoms on HAM-D in both groups, but response more positive in exercise group

Table 1: Continued.

References	Sample	Modality	Frequency & duration of PA	Assessment
[487]	65 y/o or greater with and without depressive symptoms who are sedentary ($n = 451$)	Aerobic exercise (60 to 80% max HR) or progressive strength training (50–75% 1 rep max)	Supervised training 60 min session 3 d/wk × 10/wks	Reduced depressive symptoms on GDS in both strength training and aerobic exercise groups; ↑ plasma BDNF in strength training group
[481]	60 y/o or greater with osteoarthritis of knee and depressive symptoms ($n = 438$)	Aerobic exercise (50–70% max HR); strength training; or health education	Supervised walking 60 min session 3 d/wk then home-based aerobic activity × 15 mo or supervised progressive strength training 60 min session 3 d/wk × 3 mo + home-based continuation of training × 15 mo	Reduced depressive symptoms on CES-D in aerobic exercise group; ↔ depressive symptoms on CES-D in strength training group; both aerobic and strength training ↓ pain, ↓ self-reported disability, and ↑ walking speed
[486]	50 y/o or greater with MDD ($n = 200$)	Add-on aerobic home-based program (target of 150 min per wk) and strength training + usual care or usual care only	Exercise 3 d/wk for strength training for all major muscle groups + 30 min session aerobic activity 5 d/wk × 12 wks	Reduced depressive symptoms on MADRS in both groups at 12-, 26-, and 52-week follow-up assessments
[489]	18–65 y/o with MDD ($n = 60$)	Add-on yoga to quetiapine fumarate or escitalopram or no yoga	Supervised 60 session 1 d/wk × 5 wks	Reduced depressive symptoms on HAM-D; trend towards ↓ cortisol secretion in both groups
[482]	18–60 y/o with MDD ($n = 26$)	Add-on aerobic exercise at patient selected intensity + usual care or usual care only	16.5 kcal/kg/wk × 3 d/wk	Reduced depressive symptoms on HAM-D and QoL measure in psychological domain
[483]	18–60 y/o severely depressed inpatients with MDD ($n = 50$)	Add-on aerobic PA (with goal of 15.5 kcal/kg/wk) + usual care or usual care only	Supervised session 3 d/wk (mean length 23.36 days ± 9 days)	Reduced depressive symptoms on HAM-D and ↑ quality of life (World Health Organization Quality of Life Assessment Instrument-Brief version (WHOQOL-BREF) during second wk of treatment and at discharge
[484]	69–73 y/o with MDD, minor depressive symptoms, or dysthymia ($n = 32$)	Progressive resistance training (3 sets of 8 repetitions of 80% 1 rep max) × 10 wks + unsupervised exercise or health education	Supervised 45 min sessions 3 d/wk × 10 wks followed by unsupervised resistance training 2-3 d/wk × 10 wks	Reduced depressive symptoms in exercise group on BDI at 20 wks and 26 mo follow-up; ↑ morale on measures of aging on the Philadelphia Geriatric Morale Scale
[488]	18–55 y/o with MDD ($n = 57$)	Add-on aerobic exercise (60–85% VO_2 max) + sertraline or sertraline only	Supervised sessions 4 d/wk × 4 wks	Reduced depressive symptoms on HAM-D in both groups, but response occurred with lower dosage in exercisers; ↑ VO_2 max in exercisers

Table 1: Continued.

References	Sample	Modality	Frequency & duration of PA	Assessment
[492]	18–55 y/o with MDD who were medicated and unmedicated and received psychotherapy ($n = 165$)	Strength training (2 or 3 trials of 12 reps at 50% max and increasing to 8 reps of 75% max); aerobic exercise (70% max heart rate); or control (stretching and relaxation groups ($n = 55$ for each)	Supervised training 90 min per session 2 d/wk × 16 wks	↔ in depressive symptoms between three groups on HAM-D at 4 mo and 12 mo; ↔ in cognitive symptoms between the three groups at 4 mo and 12 mo
[268]	50 y/o or greater with remitted MDD ($n = 35$)	Modified incremental walking protocol	Supervised single 30 min exercise bout	↑ BDNF towards levels comparable to healthy controls
[267]	22 y/o or greater with MDD ($n = 18$)	Progressive exercise until 125 beats per minute	Supervised single aerobic exercise bout	↑ BDNF
[383]	18–70 y/o with nonremitted MDD ($n = 126$)	Augmentation of SSRI with 16 kilocalories per kilogram of body weight per wk × 12 wks (equivalent to 150 min per wk at moderate intensity) or 4 kilocalories per kilogram of body weight per wk × 12 wks	Sensor monitored and partially supervised × 12 wks	↓ in hypersomnia on IDS-C, a change that was correlated with ↓ BDNF and ↓ IL-1β; lower baseline levels of IL-1β predicted greater improvements in insomnia
[490]	18–60 y/o with MDD ($n = 79$)	Aerobic exercise (80% aerobic capacity) or control	Supervised 45 min sessions 3 d/wk × 3 mo	↔ hippocampal volume; BDNF; VEGF; or IGF-1 in exercise group
[382]	18–70 y/o with nonremitted MDD ($n = 122$)	Augmentation of SSRI with 16 kilocalories per kilogram of body weight per wk × 12 wks (equivalent to 150 min per wk at moderate intensity) or 4 kilocalories per kilogram of body weight per wk × 12 wks	Sensor monitored and partially supervised × 12 wks	↓ insomnia as measured on IDS-C in both groups
[491]	18–60 y/o with MDD ($n = 53$) versus healthy controls ($n = 58$)	Aerobic exercise (80% max heart rate) or control	Supervised sessions 45 min session 3 d/wk × 3 mo	↓ at-rest levels of copeptin in participants with high exercise compliance

ATYP: Atypical Depression Symptoms Addendum to Hamilton Depression Rating Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CES-D: Center for Epidemiologic Studies Depression; GWB: General Well-Being Schedule; GDS: Geriatric Depression Scale; HAM-D: Hamilton Depression Rating Scale; ICD-10-D: International Classification of Diseases-Depression; IDS-SR: Inventory of Depressive Symptomatology-Self Reported; POMS: Profile of Mood States; GCPS: Graded Chronic Pain Scale; CGI: Global Improvement of Depression; MADRS: Montgomery and Asberg Depression Rating Scale; QoL: quality of life; QALY: quality-adjusted life years using EuroQol (EQ-5D); RAND: RAND 36-Item Health Survey; SIGH-SAD-SR: Seasonal Affective Disorders Version Self-Rating Format; STAI: State-Trait Anxiety Inventory; WHOQOL-BREF: World Health Organization Quality of Life Assessment Instrument-Brief version.

negate neuroplastic mechanisms. Bolstering this idea are preclinical and clinical studies that have shown that restriction of control during activity is deleterious [127–129], whereas the ability to exert control is beneficial for neurobiology and mental health [130]. Recently expanding on this notion, Greenwood and colleagues [131] sought to investigate the effects of forced and voluntary PA on emotional resilience. To do so, they designed a set of experiments with five exercise conditions: sedentary controls, forced treadmill training with motion initiated by foot shock, forced running on motorized wheels designed to approximate rats' voluntary running behavior, voluntary wheel running, and voluntary wheel running in an environment matched to the forced-wheel group. Then, all animals were exposed to stress-inducing conditions (restrained in Plexiglas tubes and exposed to uncontrollable tail shock), and their escape and fear responses were monitored. Interestingly, both forced and voluntary PA on running wheels prevented the behavioral consequences of stress, but forced treadmill training with foot shocks did not. The fact that wheel runners whose activity was forcibly started and stopped in naturalistic patterns (a model that mimics circuit training) also exhibited increased stress resistance [131] suggests that the ability of PA to regulate emotion and stress resilience may be modulated by the pattern of aerobic activity as long as (1) intensity, duration, and distance thresholds are sufficient; (2) the pattern of activity is naturalistic; and (3) the degree of stress is minimized [132].

While the study of affective symptoms in rodents is difficult, well-developed behavioral assays exist, as thoughtfully characterized in a review by Holmes [133]. From these studies, it has been shown that running reverses stress-related deficits and mitigates depressive and manic behavioral outcomes. Also, most of these studies report that PA increases neurogenesis in the hippocampus, reduces the length of corticosteroid exposure following stress, improves circadian rhythmicity, increases synaptic plasticity gene activity, and increases hippocampal BDNF in models of depression. A summary of preclinical studies that investigated the effects of voluntary wheel and motorized treadmill running on neurobiological, psychological, and physiological outcomes in rodents is systematically presented in Table 2.

Evidence that impairments in neural plasticity are implicated in MDs [103] and that PA modulates common neuroplasticity substrates (neurotransmitters, synaptic number and function, neurogenesis, BDNF, inflammation, stress reactivity, antioxidant defense, circadian rhythm, epigenetic modifications, and alteration of telomere length) in MDD and BP has led to numerous attempts to harness neuroplasticity to promote healing and recovery [134], particularly as it applies to psychiatric disease [135, 136]. Fortunately, convergent evidence suggests that long-term PA is positively correlated with positive neurobiological, affective, and cognitive outcomes, as reviewed below.

6. Neurotransmitter Levels and Function and Physical Activity

A pathognomonic feature of MDD [55, 137] and BP [137–139] is aberrant neurotransmitter level and function, a situation that can adversely affect synaptic plasticity. It has been suggested that depressive symptoms are caused in part by a deficiency in neurotransmitter levels (serotonin, norepinephrine, and dopamine), whereas manic symptoms are caused by excess levels, a notion premised on the study of psychological and cellular actions of several psychotropic agents [140]. Both types of fluctuation are problematic given the inverted U-shaped function of neurotransmitters: moderate levels are required for optimal emotional and cognitive function [141]. Fortunately, PA can optimize the synthesis, metabolism, and release of serotonin [142–146], norepinephrine [143, 147, 148], dopamine [143, 149, 150], and glutamate [151–153].

In the serotonergic system, the ability of PA to restore depleted neurotransmitter levels in the cerebral cortex, hypothalamus, brainstem, and hippocampus [143, 154] occurs via three primary mechanisms. PA increases the relative proportion of free tryptophan peripherally [155], a condition which favors influx across the blood-brain barrier [156]. Also, PA modulates the activity of tryptophan hydroxylase [157, 158] and inactivates indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase, which are rate-limiting enzymes that, following stress, shunt metabolism of tryptophan towards the kynurenine pathway in lieu of the serotonin pathway [156, 159, 160].

In the noradrenergic system, PA's neuroprotective effects stem from an adaptive response [145] wherein upregulated galanin expression hyperpolarizes noradrenergic neurons and thereby inhibits excessive norepinephrine release from the locus coeruleus [161–164]. Moreover, PA increases the conversion of cortisol to its inactivated form (cortisone) [165] to dampen an individual's reactivity to stress [166–168].

In the dopaminergic system, long-term PA optimizes dopamine metabolism [149, 169] via putative mechanisms that modulate tyrosine hydroxylase activity [170], rate of dopaminergic turnover [171], and calcium levels [172, 173]. The optimization of dopamine levels is important because dopamine levels modulate motivation and reward behavior [174]. That is, deficiencies in dopamine have been related to depression [175, 176], whereas excess dopamine levels have been related to mania [98].

Recently, considerable work has focused on the putative role of glutamate and the N-methyl-D-aspartate receptor (NMDAR) in the pathophysiology of MDs. Physiologic modulation of glutamate is imperative given its central role in synaptic strength and plasticity [177–179], yet alterations in plasma, serum, and cerebrospinal fluid have been reported in MDs [180]. Notably, PA enhances glutamate turnover and prevents excitotoxicity [151, 181] by improving calcium regulation [182]. The former mechanisms reciprocally interact with corticosteroid signaling and neural plasticity processes. Conversely, PA can mitigate glutamate hypofunctioning [183]. Maddock and colleagues [152] demonstrated that long-term PA increases glutamate in the anterior cingulate cortex, a significant finding given that glutamate contributes to the production of glutathione, a pervasive antioxidant in the central nervous system. Finally, PA increases the expression of NR2A and NR2B glutamatergic receptors in the hippocampus,

Table 2: Preclinical studies of physical activity in rodent models of mood disorder. To determine the effects of PA on the brain of rodents, a computer search of MEDLINE using the terms "voluntary wheel running," "rodents," "depression," and "mania" was used to produce a list of studies. Then, manual searches of key references were performed to identify additional studies. Articles met inclusion criteria if they were peer-reviewed and performed in rodent models of depression or bipolar disorder. Articles were excluded if they were reviews, conference abstracts, or expert opinions. Duplicate articles and those not available in English language were excluded also. Based on this search and subsequent screening, a total of 28 articles that spanned from 2001 to 2016 were identified. Of those studies, 20 examined the effects of PA on behavioral outcomes. Strikingly, PA mitigated adverse outcomes in 95% (19 out of 20) of the studies that utilized behavioral measures, including those that examined depressive [493–508], anxiety [493, 496], and social-[495] and fear-avoidant behaviors [131, 509]. Another study reported that exercise mitigated manic-like behavior [250]. The remaining studies generally reported that exercise mitigated cognitive impairments [131, 499, 509], optimized the glucocorticoid response [500, 501, 509, 510] and neurotransmitter levels [497, 498, 511], optimized BDNF in the hippocampus [251, 493, 499, 500, 504, 505, 512, 513], increased neurogenesis [251, 502, 505, 506, 513], enhanced sleep [250, 514], and increased synaptic markers [508].

References	MD model	Age (wks)	Treatment modality	Duration (wks)	Measure	Outcome
[496]	Wistar rats exposed to chronic unpredictable stress	8	Voluntary wheel running	4	Sucrose preference, elevated plus-maze, elevated T-maze, and forced-swim test	Reduced depressive-like symptoms and ↓ anxiety symptoms in stressed rats
[499]	C57BL/6 mice exposed to chronic uncontrollable stress	8-9	Voluntary wheel running	4	Forced swim, tail suspension, water maze, and BDNF	Reduced depressive-like symptoms, ↑ spatial memory, ↑ mature BDNF
[493]	C57BL/6 mice exposed to chronic uncontrollable stress	"Adult" status, but actual age not specified	Voluntary wheel running	3-4	Learned helplessness, forced swim, tail suspension, elevated plus maze, and BDNF	Reduced depressive-like symptoms and ↓ anxiety symptoms in wheel runners, ↑ hippocampal BDNF mRNA
[500]	Sprague-Dawley rats exposed to chronic uncontrollable stress	Not specified	Voluntary wheel running	4 wks	Sucrose preference test, open field test, Morris water maze, corticoste rone, BDNF RNA, and glucocorticoid receptor RNA	Reduced depressive-like symptoms, ↑ hippocampal BDNF RNA following stress, ↓ corticosterone following stress, ↑ glucocorticoid RNA receptor following stress
[501]	Sprague-Dawley rats exposed to chronic uncontrollable stress	"Adult" status, but actual age not specified	Voluntary wheel running	4 wks voluntary wheel running prior to stress followed by 4 wks voluntary wheel running after stress	IgM antibodies, IgG2a antibodies, and distance ran	Voluntary wheel running reduced stress-induced depressive-like symptoms and ↓ stress- induced alterations in immune function
[503]	Fischer F344 rats exposed to chronic uncontrollable stress	"Adult" status, but actual age not specified	Voluntary wheel running	2 and 6	Freezing behavior and shuttle-box escape learning	6 wks running after exposure to uncontrollable stress reduced depressive-like symptoms and anxiety symptoms in runners
[515]	Fischer F344 rats exposed to chronic uncontrollable stress	8	Voluntary wheel running	5	Social exploration, shock-elicited freezing, escape behavior, corticosterone, and body weight	Runners exhibited ↓ body weight, ↓ anxiety and reduced depressive-like symptoms, and ↓ corticosterone response to stress

Table 2: Continued.

References	MD model	Age (wks)	Treatment modality	Duration (wks)	Measure	Outcome
[505]	C57BL/6 mice exposed to chronic uncontrollable stress	8	Stressed animals with no treatment, a dietary supplement (antioxidants), voluntary wheel running, or both dietary supplement & free access to running wheel	4	Neurogenesis, hippocampal BDNF mRNA, VGF serum, and saccharin preference	Combination of diet and exercise (but neither alone) reduced depressive-like symptoms, ↑ neurogenesis in dentate gyrus in diet + exercise group, ↑ BDNF mRNA in hippocampus of exercise + diet group, and trend towards ↑ VGF in exercise + dietary supplement group only
[506]	ICR mice exposed to chronic uncontrollable stress	8	Treadmill running 60 min, treadmill running + SU1498 [a VGF receptor (Flk-1) inhibitor], and control	2	Open-field test, forced swim test, open-field test, BrdU, Ki67, and CD31 immunohistochemistry	Treadmill group exhibited ↑ hippocampal neurogenesis in dentate gyrus and ↓ anxiety and reduced depressive-like symptoms in a manner that is dependent on VEGF-Flk-1 signaling
[498]	Swiss mice	Age not specified	Voluntary wheel running	3	Forced swim, tail suspension, and open-field test	Reduced depressive-like symptoms, an effect that appeared related to availability of bioamines
[507]	Diurnal sand rats housed in either short photoperiod (SP) (5 hr light/19 hr dark) or neutral light (12 light/ 12 dark)	24	Voluntary wheel running	3	Elevated plus-maze, forced-swim test, and social interaction	↓ disruptions in activity rhythms of SP/exercise animals, ↓ anxiety and reduced depressive- like symptoms for SP/running wheel group, ↑ number and duration of social interaction for SP/running wheel group
[504]	C57BL/6J mice	6-7	Voluntary wheel running	4	VGF protein, BDNF protein, plasticity genes (Egr2, Grb2, ornithine decarboxylase-1, synapsin-1, and synCAM), forced-swim, and tail-suspension tests	Reduced depressive- like symptoms, ↑ in VGF protein and ↑ in BDNF protein in hippocampus, altered synaptic plasticity gene profile activity
[502]	Flinders Sensitive Line (FSL) rat	22	Administered escitalopram, escitalopram + voluntary wheel running, vehicle diet, or vehicle diet + voluntary wheel running	4	BrdU immunohistochemistry and forced-swim test	↑ in hippocampal neurogenesis in escitalopram, escitalopram + wheel running, and wheel running only, reduced depressive-like symptoms in wheel runners and escitalopram + wheel running groups

Table 2: Continued.

References	MD model	Age (wks)	Treatment modality	Duration (wks)	Measure	Outcome
[497]	SwHi rats and SwLo rats	6–14	Voluntary wheel running	3	Forced-swim test	Reduced depressive-like symptoms in SwLo wheel runners with concomitant ↑ galanin mRNA in locus coeruleus
[508]	Sprague-Dawley rats	"Adult" status, but actual age not specified	Voluntary wheel running wheel during CORT administration; voluntary wheel running wheel prior to CORT administration; voluntary wheel running prior to and concurrent with CORT administration	2	Forced-swim test, sucrose- preference test, BrdU immunohistochemistry, synaptophysin, and BDNF	Reduced depressive-like symptoms in animals that ran prior to and concurrent with CORT administration, ↑ neurogenesis and cell survival in animals that ran prior to and concurrent with CORT administration, ↔ BDNF or IGF-1 in animals running prior to and concurrent to CORT administration, ↑ synaptophysin proteins in animals running prior to and concurrent to CORT administration
[131]	Fischer 344 rats exposed to chronic uncontrollable stress	"Adult" status, but actual age not specified	Treadmills, motorized running wheels, or voluntary wheel running	6	Shock-elicited freezing and shuttle-box escape	Both forced and voluntary wheel running reduced fear conditioning and ↓ cognitive impairments
[515]	Fischer 344 rats exposed to chronic uncontrollable stress	"Adult" status, but actual age not specified	Voluntary wheel running	6	Shuttle-box escape	Running reduced fear conditioning and cognitive learning, ↓ 5-HT_{2C}R mRNA in basolateral amygdala and dorsal striatum
[495]	C57BL/6 mice exposed to chronic social defeat stress	10	Voluntary wheel running	<1	Social-interaction test, open-field test, monoamines	Reduced social avoidance in those that ran 2 hours after stress, ↔ anxiety levels, ↔ in depressive symptoms
[250]	Myshkin mice (Myk/+)	6–12	Administered melatonin or voluntary wheel running	6	Open-field test, elevated plus-maze, light–dark box, accelerating rotarod, EEG and EMG recordings during sleep, and BDNF protein	Both melatonin and PA reduced manic behaviors, melatonin ↑ sleep duration, ↔ in hippocampal BDNF mRNA following exercise
[516]	C57BL/6 mice exposed to lipopolysacharide	16 and 88	Voluntary wheel running	4 for young mice and 10 for aged mice	Tail-suspension, sucrose preference, TNF-a, IL-1B, IL-6, and IFN-γ	↔ in depressive- like behavior in presence of ↑ TNF-a, IL-1B, IL-6, and IFN-γ

Table 2: Continued.

References	MD model	Age (wks)	Treatment modality	Duration (wks)	Measure	Outcome
[511]	Fischer 344 rats exposed to acute uncontrollable stress	"Adult" status, but actual age not specified	Voluntary wheel running	6-7	Serotonin and dopamine in striatum	Running prevented stress-induced elevation of extracellular serotonin and potentiated dopamine concentration in the dorsal striatum
[494]	Outbred Hsd:ICR mice stressed by wheel removal	7–9 wks	Voluntary wheel running	6 days	Forced swim, tail-suspension, and behavioral despair	High CORT males deprived access to running wheel showed ↑ depressive symptoms
[510]	C57BL/6 mice exposed to chronic uncontrollable stress	6	Voluntary wheel running	4	Corticosterone and adrenal weight	More rapid corticosterone response but returned to baseline more quickly in wheel runners, ↑ adrenal weight
[513]	C57BL/6 mice exposed to chronic uncontrollable stress	8	Voluntary wheel running	3–6	Corticosterone, BDNF, neurogenesis, open-field, elevated O-maze, dark-light box, forced swim, and learned helplessness	↑ hippocampal BDNF, ↑ neurogenesis, ↑ cortico-sterone metabolites, ↑ anxiety-like behavior in novel and aversive environments
[512]	Fischer F344 rats exposed to chronic uncontrollable stress	"Adult" status, but actual age not specified	Voluntary wheel running	3 and 6	Shuttle-box escape and conditioned fear	6 wks of running ↑ hippocampal BDNF mRNA and protein following stress
[251]	C57Bl/10 mice	8	Voluntary wheel running, fluoxetine, or combination of fluoxetine and voluntary wheel running	3	BDNF, IGF-1, and BrdU immunohistochemistry	↑ in hippocampal BDNF in fluoxetine group only, and ↑ in neurogenesis with fluoxetine group only
[517]	$TrkB^{hGFAP}$ and TrkB Nestin mice that were conditionally ablated for the gene encoding TrkB, the high affinity receptor for BDNF, in a regional and cell-type-specific manner	Postnatal day 15 and "adult" status specified, but not actual age	Voluntary wheel running	6	Dark light test; open-field test; forced swim test, BrdU incorporating cells	neural Progenitor cell deletion of trkB, both in embryos and in the adult, causes ↓ hippocampal neurogenesis and ↓ behavioral improvements following chronic antidepressant administration or wheel running
[514]	F344 rats exposed to chronic uncontrollable stress	8	Voluntary wheel running prior to stress exposure	6	Sleep and temperature rhythms	↑ entrainment of sleep/wake behavior and ↓ disruption of diurnal rhythms of sleep and temperature following stress

PA and MDs in preclinical studies. BDNF: brain-derived neurotrophic factor; CORT: corticosterone; CUS: chronic unpredictable stress; SP: short photoperiod; STAT3: signal transducer and activator of transcription pathway 3; tx: treatment; VEGF: vascular endothelial growth factor.

receptors that are associated with neurogenesis and synaptic plasticity [184, 185].

Altogether, these studies suggest that PA modulates the underlying pathobiology of MDD [186] and BP [187] by altering the levels of key neurotransmitters that regulate emotional and cognitive health. In turn, the modulation of these neurotransmitters promotes the maintenance, repair, and survival of neurons and induces changes in molecular and cellular plasticity [188–190], effects similar to those exerted by antidepressants and antipsychotics.

7. Synaptic Number and Function and Physical Activity

As fundamental sites of communication between a neuron and its partner cell, synapses play an important role in emotion and cognition. Synapses exhibit plasticity, wherein synaptic function and structure are modified in response to activity and factors in the cellular milieu. Long-term potentiation is one form of functional synaptic plasticity, wherein synaptic connections between synapses are strengthened following activity, a process that is fundamental to learning and memory [191]. Long-term depression is another form of functional plasticity, one that is associated with the process of forgetting, where a set of synapses display a reduced capacity to elicit a response in one another [192]. Working in concert, long-term potentiation and long-term depression regulate homeostatic plasticity and the function of neuronal circuits [193]. Structural plasticity refers to changes in the 3-dimensional structure of neurons and their connections.

Convergent evidence suggests that changes in structural and functional plasticity at the synapse are relevant to MDs [194–198] and can adversely affect emotional [199] and cognitive function [200]. Indeed, loss of synapses is a common characteristic of MDD [201, 202], resulting in disconnection and loss of function in key brain regions [80, 203, 204] such as the association cortices and hippocampal region [205]. Rodent models of BP have revealed concentrated levels of ankryin-G at the synapse (which is vital for AMPAR-mediated synaptic transmission and maintenance of spine morphology), an intriguing finding given that this gene is robustly associated with the disorder [206].

The lack of noninvasive methods for the study of synaptic function precludes direct examination in humans in vivo, prompting the use of proxy measures. Accordingly, neuroimaging studies have revealed smaller hippocampal volume in persons with MDD and BP [194–198, 207]. Moreover, the study of the hippocampus in persons with MDs has revealed that volumes are inversely associated with symptom severity and duration, but positively associated with treatment outcomes [196, 208–210].

Fascinatingly, studies have shown that PA mitigates deficits in synaptic plasticity in the hippocampus. It has been shown that for aging adults, long-term exercise counters age-related decrements in hippocampus size and protects against memory impairment [211–214]. Another study has demonstrated that healthy people who participated in long-term PA (e.g., aerobic exercise 3 times per week, 30 minutes per session, for 12 weeks) exhibited increased hippocampal volume [214], a finding that could be attributed to an increase in the number of synapses, their projections, or a combination of both. Erickson and colleagues [212] demonstrated that 1 year of aerobic exercise of moderate intensity improved memory and hippocampal volume in healthy older adults, effectively reversing the age-related loss of volume by 1-2 years. Extending these studies, Makizako and colleagues [20] demonstrated that hippocampal volume was the link between moderate PA and memory augmentation in people with mild cognitive impairment and that greater durations of moderate PA resulted in increased hippocampal volume and improved memory. Also, preclinical work has demonstrated that aerobic exercise reverses age-related decrements in long-term potentiation in the dentate gyrus region of the hippocampus [215, 216] and increases spine density in the entorhinal cortex and CA1 region [217]. Moreover, voluntary wheel running by rodents for 3 weeks changes the level of several gene transcripts known to be associated with synaptic structure and plasticity, indicating that PA elicits different gene expression profiles relevant for brain function [31]. Together, these studies suggest that PA promotes structural and functional plasticity in key regions of the brain that are adversely affected by MDs and, thereby, may be used to promote functional connectivity in persons with MDs [215, 216, 218].

8. Neurogenesis and Physical Activity

Neurogenesis in the adult mammalian brain is a form of experience-dependent plasticity wherein stem cells within distinct regions of the brain give rise to new neurons [219, 220] that then migrate to the dentate gyrus of the hippocampus to become integrated into circuits important for learning, memory, and emotional regulation [5, 6, 221, 222]. The 20,000,000 neurons generated over the course of a lifetime replace dead or dying neurons [219] and, in turn, enhance functional capacity to modify neural circuitry in an environmentally dependent manner [223] as both intrinsic and extrinsic factors alter the rate of neurogenesis [223, 224]. Such is relevant for persons with MDD [79] and BP [97] because the elevations in glucocorticoid levels that frequently accompany MDs reduce neurogenesis rates and effectuate volumetric decrements in the hippocampus [225]. Conversely, pharmacological blockade of glucocorticoid receptors [226] blocks decrements in hippocampal size, as can antidepressant [227] or lithium [207] administration.

Also, preclinical and clinical work suggest that rates of neurogenesis can be optimized with exercise. Voluntary wheel running in rodents potently induces neurogenesis in the dentate gyrus, changes that result from increased proliferation and differentiation of neurons [228–230]. The newly born neurons can then integrate into the hippocampal architecture, a process that takes 4–8 weeks [231]. Interestingly, the newly integrated hippocampal neurons exhibit a lower excitability threshold and enhanced neuroplastic capabilities [223]. The latter fact suggests that PA not only mitigates volumetric decrements but also may contribute to neuroplastic changes that enable the reversal of MD-related emotional and cognitive deficits. Indeed, enhanced neurogenesis in

animal models has been positively correlated with improvements in learning and memory [19, 232]. A clinical study has demonstrated that regular aerobic exercise of moderate intensity (as measured by an accelerometer worn on the hip for 2 weeks) was associated with increased hippocampal volume in older adults, findings positively associated with the encoding of new memories [233]. Thus, PA-induced hippocampal neurogenesis offers considerable hope for exploiting newly born cells and their heightened plasticity to reestablish hippocampal brain circuits that have been damaged as a result of the neuroprogression of MDs [224, 228–230, 234, 235], particularly when paired with environmental enrichment (e.g., cognitive behavioral therapy).

9. BDNF and Physical Activity

Neurotrophins—vital proteins in the brain—contribute to the survival, growth, and maintenance of neurons [218, 236] and participate in a variety of learning and memory functions [237]. BDNF, one of the most widely distributed neurotrophins in the brain, plays a vital role in the maintenance of neurons that underlie emotion and cognition, including those adversely affected in MDs [238, 239]. The neuronal atrophy and dysfunction incurred during the course of MDs effectuate disruptions in neurotrophic support, particularly BDNF. A bevy of BDNF-related abnormalities have been associated with MDs. It has been shown that (1) serum levels of BDNF are reduced in persons with BP [240, 241] and MDD [242, 243]; (2) reductions of BDNF occur in the hippocampus in MDD and BP [244]; (3) serum levels of BDNF normalize in response to several treatments (e.g., antidepressants in MDD [242, 245], mood stabilizers and antipsychotics in BP [246–248], electroconvulsive therapy in MDD and BP [249], and PA in models of BP [250] and depression [251]); (4) polymorphisms in the *BDNF* gene are associated with MDD [252, 253] and BP [254, 255]; and (5) mature BDNF plays a critical role in brain plasticity and is intimately involved in cognitive and mood-related behaviors [236]. Accordingly, BDNF is generally regarded as a putative biomarker for BP [239, 256] and MDD [239, 257].

Recognition of the aforementioned facts, along with the fact that BDNF is highly inducible by PA, has piqued the interest of multiple laboratories in recent years [6]. Accordingly, it has been shown that PA robustly upregulates the expression of BDNF in the hippocampus of rodents [258–261], changes that endure for days [261]. Moreover, recent work has demonstrated that peroxisome proliferator-activated gamma receptor coactivator 1-alpha (PGC-1α) and FNDC5, muscle-derived proteins that increase following endurance exercise, regulate BDNF expression in the brain in the hippocampus of mice [262]. Such is relevant for stress-induced depression given the interaction with neuroinflammatory and neuroplasticity pathways [263, 264] via alterations in tryptophan degradation [264, 265] and 5-HT_{1A} receptor activation [266]. Thus, PA may protect against stress-induced depression by altering kynurenine metabolism [18] and, thereby, modulating BDNF levels.

Notably, PA-induced increases in BDNF have been recapitulated in unmedicated patients with MDD [267], elderly persons with remitted depression [268], and women with BP [269]. Moreover, parallel clinical studies in elderly adults have linked acute aerobic PA (until heart rate reached 85% of max capacity) with alterations in frontal cognitive functions [270], changes that may be particularly beneficial for the domains of attention, processing speed, and memory [271].

Together, these results suggest that PA may effectuate central neuroplastic adaptations via optimization of BDNF levels in persons with MDD and BP. The ability of PA to enhance BDNF release and function in the synapse, promote dendritic spine integrity, and concomitantly activate other cellular pathways [80, 179, 203, 272] is a cornerstone for neuroplastic processes that are necessary to repair and reorganize circuits damaged during the course of MDs.

10. Inflammation, Immune Function, and Physical Activity

The dramatic release of inflammatory cytokines following chronic mental or physical stress is a well-known harbinger of MDD [83, 273] and BP [98, 274] through mechanisms involving neuroplasticity, cell resilience, and neuronal survival [275, 276]. It has been shown that persons with MDD exhibit elevated levels of inflammatory cytokines including C-reactive protein (CRP), interleukin- (IL-) 1, IL-6, and tumor necrosis factor-α (TNF-α) [277, 278]. Yet, the most robust evidence for the role of inflammation in the causation of MDD derives from evidence that chronic cytokine immunotherapy induces depression in a significant number of patients [279, 280]. This trend is also seen in BP. Persons who were in the depressive phase exhibited increased IL-2, IL-6, IL-8, CRP, and TNF-α [274, 276]. Persons with BP in the manic phase exhibited increased proinflammatory markers (CRP, IL-2, IL-4, IL-6, and TNF-α) [274, 276], and mood symptoms have been positively correlated with IL-6 and IL-2 [276]. Fortunately, administration of cyclooxygenase-2 inhibitors and antagonists of TNF-α inhibits inflammatory markers in persons with MDD and BP [281–284]. Moreover, chronic lithium treatment (over 3 months) in euthymic persons with BP resulted in lower levels of peripheral blood lymphocytes secreting IL-2, IL-6, IL-10, and IFN-γ [285]. Another study has demonstrated that inflammatory factors were associated with cognitive performance in euthymic persons with BP. That is, TNF-α was associated with intrusions on the California Verbal Learning Test, IL-8 was associated with repetitions, and IFN-γ was negatively correlated with recollection deficits [286]. Whether the relationship of the immune response with MDD and BP is primary or secondary has yet to be determined. Nevertheless, the suggestion that PA may play an anti-inflammatory role and mitigate pathobiology in the brain warrants close consideration.

Notably, clinical studies demonstrate that PA attenuates the inflammatory process and provides a more resilient stress response [21, 22, 287, 288]. A randomized controlled trial (RCT) in healthy aging adults demonstrated that those who participated in progressive aerobic activity (15 minutes increasing to 40 minutes) twice per week for a 6-month duration exhibited a significant improvement in immune system

function [287]. Similar results were found in a study of elderly women undergoing aerobic exercise (60 minutes per session, 3 times per week, for 16 weeks) [288]. Another study of fitness level (as denoted by heart rate) was associated with IL-6 and TNF-α response following stress [22], which is important because cytokines may adversely alter glucocorticoid receptor function to contribute to an excessive inflammatory response in MDs [289]. Finally, a study in healthy men demonstrated that PA directed monocytes towards anti-inflammatory pathways [290], a mechanism that likely supports plasticity in the brain [291]. Together, this evidence makes it seem plausible that PA induces an adaptive immune response and mitigates an exaggerated inflammatory response that can be deleterious to brain plasticity.

Admittedly, findings from human studies relating PA and immune function have varied, a situation that likely reflects unaccounted-for influences. Nevertheless, current exercise guidelines issued by the American College of Sports Medicine and the Surgeon General suggest that moderate exercise (150 minutes per week at 40% to 60% of aerobic capacity) can be deployed to induce positive immune health [292]. This notion is reaffirmed by a consensus statement drafted by international experts in the field of exercise immunology that states moderate levels of regular exercise optimize immune function [21].

11. HPA Function and Physical Activity

The HPA axis is an adaptive mechanism designed to respond to stress. Chronic stress is associated with hyperactivity of the HPA axis and increased levels of glucocorticoids [293, 294], even in the absence of external stressors. Several lines of evidence have implicated stress-related hyperactivity and dysregulation of the HPA axis with MDD [295, 296] and BP [62, 96]. Persons with MDD exhibit excessive HPA activity as measured by increased CRH in cerebrospinal fluid; increased cortisol in plasma, urine, and cerebrospinal fluid [297]; and increased rates of nonsuppression following administration of the synthetic glucocorticoid, dexamethasone (known as the dexamethasone suppression test) [298–300]. Persons with BP exhibited increased levels of ACTH and cortisol (basal and postdexamethasone), but not of CRH [96]. Euthymic persons with BP exhibited a flatter diurnal slope of cortisol secretion than healthy persons. Moreover, persons with a history of many episodes exhibited higher cortisol levels, reduced cortisol reactivity to daily stress, and a flatter diurnal slope than persons with fewer episodes [301]. Persons with psychotic and nonpsychotic major depression exhibited distinct patterns of HPA axis reactivity—a combination of depressive and psychotic symptoms induced a greater nadir in evening cortisol than depressive symptoms in isolation [302]. Investigation of a rodent model of BP reports stress-induced hypersecretion of glucocorticoids [303]. The relentless dysregulation of glucocorticoids in MDs can effectuate neuronal atrophy secondary to changes in neurochemistry, neuronal excitability, resilience, and plasticity of the hippocampus [196, 304–306]. In turn, these changes contribute to neurotoxicity [294] and can promote neuroprogression in MDD [307] and BP [308]. Also noteworthy is the fact that cytokines disrupt neuroendocrine function (e.g., IL-1, TNF-α, and interferon-α) by inhibiting glucocorticoid receptor signaling [275, 309] as reflected by decrements in glucocorticoid translocation and activation of glucocorticoid receptor-inducible enzymes [309, 310].

Although acute PA sharply increases levels of cortisol, regular PA mitigates an overactive stress response [23, 311]. Following stimulation, the hypothalamus secretes CRH, which then induces the release of ACTH from the pituitary gland. In turn, ACTH interacts with the adrenal gland to initiate the release of cortisol in humans and corticosterone in some animals (e.g., rodents, amphibians, reptiles, and birds) [312]. Within this context, acute exercise functions as a stressor, but regular exercise initiates neuroprotective effects. Bolstering the latter notion is evidence that long-term training reduces the response to both physical exercise [312] and other forms of stressor challenge [24], effects that may stem from altered density and efficiency of mineralocorticoid receptors, lower levels of circulating cortisol, and inhibition of cortisol synthesis [24, 312]. The ability of PA to attenuate HPA dysregulation is especially important for preventing hippocampal atrophy [313–315] and reversing cognitive deficits in aging populations [20, 212] and those with affective disorders [316], as hippocampal neurons persistently exposed to elevated glucocorticoids retract their dendrites and exhibit fewer dendritic spines [317]. Fortunately, the degree of dendritic branching in hippocampal neurons and the overall number of dendritic spines increase when animals are exposed to voluntary wheel running [217, 318, 319], alterations that enhance neuroplasticity and that mimic antidepressant actions. Translating these findings to humans at the behavioral level, it has been shown that 8 weeks of exercise improved depressive symptoms and levels of 24-hour urinary cortisol [316]. Another study demonstrated that 12 weeks of high-intensity aerobic exercise enhanced mood and optimized responsiveness of the HPA to the dexamethasone responsiveness test in persons experiencing chronic pain [320]. Altogether, these studies suggest that PA may mitigate HPA dysregulation in persons with MDD or BP, a notion that requires a further study.

12. Antioxidant Defense and Physical Activity

Oxidative stress is an imbalance between antioxidants and reactive oxygen species (ROS) (e.g., superoxide, hydrogen peroxide, and hydroxyl radical) [321], a problematic situation in the brain given high metabolic demands and low antioxidant capacity [322]. Oxidative stress is particularly germane to the topic of MDs given alterations in cerebral metabolic rates [323], ROS-induced lipid peroxidation, and antioxidant enzyme activity in BP [81, 324, 325] and MDD [99, 326, 327]. Moreover, oxidative changes in the milieu interfere with the stability of genomic DNA in the brain in MDs [328], changes that are correlated with severity of depressive and manic symptoms [329] and frequency of manic episodes [330].

Notably, aerobic exercise appears to increase adaptability to ROS-induced lipid peroxidation and decrease overall levels of ROS [25, 331]. These mechanisms stem in part from

the ability of PA to increase antioxidant gene expression (e.g., superoxide dismutases and glutathione peroxidase) and, thereby, antioxidant enzymatic housekeeping activities in the brain [332, 333]. Together, these studies suggest that long-term exercise may optimize the enzymatic antioxidant system and mitigate oxidative damage. Such is imperative for persons with MDs given that the kinase proteins that induce structural and functional changes in synapses require specific redox environments and that synaptic activity can be modulated via ROS levels [26].

13. Circadian Rhythmicity and Physical Activity

Physiological processes such as feeding behavior, motor activity, hormonal secretion, and autonomic nervous function exhibit naturally occurring rhythms that are referred to as circadian rhythmicity [334]. Central to the control of circadian rhythmicity is the suprachiasmatic nucleus (SCN), a structure located in the anterior hypothalamus and composed of neurons that regulate different body functions according to rhythms that vary with the 24-hour night/day light cycle [335]. The SCN's rhythm is endogenously generated but can be synchronized to the environment (in a process referred to as entrainment) by capturing exogenous and endogenous cues that are referred to as zeitgebers. Common zeitgebers include PA, light, temperature, and food. For instance, light exposure decreases the production of melatonin (a hormone that controls sleep and wakefulness). Conversely, darkness effectuates increases in melatonin secretion, particularly two hours prior to bedtime, a change that increases the propensity for sleep [336]. Then, melatonin levels continue to increase, peak in the middle of the night, and finally decline towards the beginning of day [337]. Thereby, melatonin levels signal to the SCN the time of day. In turn, the SCN can interpret the information and use it to regulate other clocks in the brain and periphery.

Another SCN pathway involves cortisol. Cortisol levels typically peak after waking and then wane during the night, a fluctuation that can adjust the peripheral clocks in almost all organs of the body [337]. Importantly, cortisol is unable to reach the SCN. Therefore, abatement of stress provides a critical window for the SCN to resynchronize peripheral clocks [338]. Poststress resynchronization is important because desynchronization is linked to psychiatric illness [339, 340]. Indeed, reductions in nocturnal melatonin with concomitant increases in nocturnal ACTH and cortisol make it difficult to maintain sleep [341]. In turn, insufficient quantity and quality of sleep engenders disruptions in multiple regulatory systems, particularly the metabolic, immune, and cardiovascular systems [342, 343].

Multiple lines of evidence have implicated circadian disturbances and MDs. Genome-wide association studies have linked polymorphisms in core circadian genes with MDD [344, 345] and BP [345, 346]. Sleep disturbances have been documented in persons with MDD [85] and BP during the manic, depressive, and euthymic states [86, 347]. An estimated 70% of persons with MDD have reported problems with transitioning to sleep, frequent awakenings, and nonrestorative sleep [348]. For persons with BP, poor sleep quality, nighttime awakenings, and inadequate sleep are predictive factors for conversion [346]. During manic episodes, 69–99% of patients exhibited a decreased need for sleep, whereas 23–78% of persons experiencing depression exhibited hypersomnia [349]. Insomnia has been reported during the euthymic phase [349]. Some evidence suggests that persons with BP exhibit lower levels of melatonin during the euthymic, depressed, and manic phases [350]. Additionally, persons with BP exposed to a light source at night exhibit a greater suppression of melatonin synthesis than healthy controls [351], an effect that is mitigated by administration of lithium carbonate and sodium valproate [352, 353]. Similarly, a decrease in serum melatonin has been reported in persons with MDD [354]. Finally, persons with BP exhibit elevated night cortisol during the manic and depressive episodes [355, 356], an effect that can be mitigated therapeutically by administration of cortisol antagonists [357].

Given that SCN disturbances are associated with chronic stress [358] and disease [359], that persons with MDD and BP exhibit sleep disturbances and altered SCN function [360], and that gene expression patterns that regulate neuroplasticity vary with the sleep/wake cycle [361, 362], it is logical to surmise that persons with MDs exhibit circadian-related deficits in neuroplasticity [363]. Fortunately, evidence suggests that zeitgebers like PA [364], light exposure [365], social contacts, and the scheduling of rest and activity [366] can modulate rhythmic abnormalities by altering body temperature, gene expression, or the activity of several brain regions that project to the SCN (e.g., raphe nuclei and pineal gland) [367].

Supporting this notion is evidence that regular PA induces neurochemical changes that qualitatively and quantitatively improve sleep across patient populations [27–29, 368–372]. One RCT in sedentary adults with insomnia demonstrated that increasing PA to the level recommended in public health guidelines (≥150 min of moderate- to vigorous-intensity PA per week) improved sleep quality [28], whereas other studies demonstrated that adults who fail to achieve sufficient levels of PA incur sleep problems [372–375]. Other work showed that 3 months of fitness training in the middle of the day improved the consolidation of the sleep/wake cycle in older men [376]. Another study demonstrated that late-afternoon exercise improved measures of cognitive abilities in older adults [29]. Parallel investigations demonstrated that exercise induced phase delays in humans [377, 378] and accelerated re-entrainment of an acutely shifted sleep-wake cycle [379, 380]. Also, it has been demonstrated that PA between noon and evening can phase-advance melatonin rhythms [381]. In patients with nonremitted MDD, a 12-week RCT showed that PA augmentation effectuated improvements in self-reported sleep quality [382]. Later work revealed that PA-induced reductions in hypersomnia were positively correlated with reductions in BDNF and IL-1β, a trend that was not present in those with insomnia, suggesting differential biomarker associations for hypersomnia and insomnia [383]. Finally, preclinical work in a rodent model of BP demonstrated that both melatonin and voluntary wheel running were effective at reducing mania-related behavior [250].

While the practical implications of the aforementioned studies have yet to be clarified fully, they suggest that sleep abnormalities in MDs can be reduced with long-term PA [384–386]. Efforts to reduce sleep deficits are warranted given the morbidity associated with insomnia and the deleterious effects of sedatives. Moreover, adequate sleep is essential for plasticity processes: reactivation of regions used during the day must occur at night to consolidate memories and promote cognitive, emotional, and motor recovery [387–389].

14. Adaptive Epigenetic Signaling and Physical Activity

Epigenetic mechanisms have been implicated in the neurobiology of MDs [390–396]. Epigenetics refers to functional alterations in chromatin structure (e.g., DNA methylation, histone methylation, and histone acetylation) that induce modifications in gene expression, not changes in DNA sequence per se [397, 398]. That is, the chromatin structure that is determined by acetylation and methylation patterns can relax the spacing between nucleosomes to permit an increase or decrease in gene transcription, respectively [399]. Neurons utilize dynamic epigenetic modifications to regulate gene expression in an experience-dependent manner [400]. Thus, it has been suggested that neuronal plasticity is controlled in part by chromatin-remodeling processes [401], and emergent evidence has implicated chromatin modification in stress-induced illness, memory impairments, depression, and different phases of BP [402–406]. Basic support for epigenetic mechanisms in the pathobiology of MDD stems from evidence of discordance among monozygotic twins [407] along with evidence that environmental factors (e.g., early adversity) can increase the risk for depression [408, 409]. Similarly, a study of monozygotic twins discordant for BP revealed that four regions of the genome have significant alterations in methylation patterns, differences that may contribute to altered dopamine transmission and neuroendocrine function [410]. While the means by which these mechanisms impinge on MD pathobiology are not understood fully, it has become increasingly clear that these adaptations mediate long-lasting changes in vulnerability and resilience, factors relevant for MDs.

Fortunately, endogenous biochemical signals derived from peripheral cues such as PA appear to alter gene expression epigenetically [30, 411, 412] and induce physiological responses throughout the body. Thereby, PA may mitigate stress-induced changes in gene expression in persons with MDD and BP. Recent work in young and aged rats showed that two weeks of treadmill exercise induced age-dependent changes on epigenetic parameters in the hippocampus [413]. Tsankova and colleagues demonstrated that repeated stress increased histone H3K27 methylation in the hippocampus and suppressed the BDNF gene promoter region, an effect that was reversible with imipramine administration [414] or PA [415]. Recently, Januar and colleagues [416] reported similar results. They found that persons with depression at baseline, as well those with chronic late-life depression, demonstrated higher *BDNF* methylation levels, an effect that was influenced by the presence of three single-nucleotide polymorphisms (*rs6265*, *rs7103411*, and *rs908867*) [416]. Lindholm and colleagues [30] demonstrated that long-term, unilateral exercise (45 minutes, 4 times per week × 3 months) induced more than 5000 methylation changes in regulatory enhancement regions that alter gene expression, providing direct evidence that the regulation and maintenance of exercise-training adaptation is associated with epigenetic changes. In addition to preclinical data demonstrating that a multiplicity of genes that regulate synaptic structure and plasticity are altered by PA [31], the aforementioned studies make it seem plausible that epigenetic changes are responsible for a significant portion of MD-related pathobiological changes and suggest that PA is a strong candidate for reversing symptoms, particularly by promoting stable changes in BDNF gene expression. Moreover, given that chromatin modifications are associated with stress-induced illness, memory impairments, depression, and different phases of BP [393, 394, 402–406, 415, 417, 418], it seems likely that epigenetic profiles in the peripheral blood, particularly in BDNF, could be used as a biomarker for those who are susceptible to MDs, as well as for tracking therapeutic response following PA interventions in persons with MDs [30]. The latter notion is based on evidence that BDNF is robustly upregulated centrally and peripherally [419–422] following acute and long-term exercise [423, 424] and that plasma BDNF levels are linked to alterations in brain BDNF levels [270, 425], synaptic plasticity, and learning ability [271].

15. Telomere Length and Physical Activity

Recent evidence suggests a correlation between telomere length and MD pathobiology. Telomeres—the tiny, protective caps found on the terminals of DNA strands—protect DNA from damage during the processes of cell division and replication. Telomeres naturally shorten and fray with cellular aging, a hallmark process that is accelerated by adverse health and lifestyle circumstances [426]. Although the specific mechanisms underlying telomere shortening remain unknown, recent evidence has intimated that telomere shortening in MDs may be attributed to oxidative stress and inflammation, processes that can induce telomeric DNA damage and accelerate aging by 10 years [99, 427–429]. Moreover, it has been shown that telomere maintenance is critical for stem cell function in the context of persistent neuronal turnover and that adult stem cells exhibit high levels of telomerase (an enzyme that extends the telomere sequences after cell division) [430–432], making it seem likely that hippocampal neurogenesis depends on telomere dynamics [433].

Shorter telomere length has been reported in persons with remitted MDD and current MDD, findings that correlate with the severity and duration of symptoms [434] and may relate to a person's overall state of resiliency [435]. In postmortem samples, shortened telomere length was observed across brain regions, including the hippocampus in persons with MDD [436]. Also, telomere shortening has been reported in persons with BP [437], and the length was inversely correlated with the number of depressive episodes and response to lithium [438]. Strikingly, recent findings show that lithium increases the expression of the gene that encodes telomerase in human neural progenitor cells [439], intimating that the

accelerated aging processes that occur in BP may be mitigated through the neuroprotective effects of lithium.

Similarly, recent clinical studies suggest that PA has protective effects on telomeres [32]. In general, persons who report more PA have significantly longer telomere length [440, 441]. Loprinzi and colleagues [33] reported a clear dose-dependent relationship between the degree of PA engagement and shorter leukocyte telomere lengths: persons who participated in a single type of PA were 3% less likely to have very short telomeres compared to a sedentary individual, whereas persons who reported that they engaged in 4 types of PA were 59% less likely to have very short telomeres. Werner and colleagues [442] reported that peripheral blood leukocytes from professional endurance athletes exhibited increased telomerase activity and reduced expression of cell-cycle inhibitors compared with those from untrained individuals. Preclinical evidence suggests that PA has a protective effect on telomere length in neurons in brain regions associated with depression [34, 35].

Together, this emerging evidence suggests that PA may attenuate MD-related disease and provide a means to protect telomeres from accelerated aging. The fact that telomere maintenance is critical for stem cell function in the context of persistent turnover [430–432] makes it seem likely that hippocampal neurogenesis depends on telomere dynamics and that PA may positively affect these processes, a notion that awaits further investigation.

16. Implications for Translation, Unresolved Issues, and Future Directions

Finding an effective treatment for MD-related impairments and symptoms remains an unmet goal. Notwithstanding, the use of animal models and human research have resulted in considerable progress toward understanding common neuroplasticity substrates that are implicated in MDD and BP, along with the identification of new targets and biomarkers for therapeutic intervention. Presented here is a broad assessment of biomedical evidence intimating that PA can optimize neuroplasticity substrates and processes across brain regions so that neuronal networks responsible for emotional and cognitive regulation can reestablish their connectivity to better meet environmental and biological demands in a use-dependent manner [84, 399, 443–445]. Consistent with the delayed effects of PA, this process would take weeks to induce network changes of sufficient magnitude to effectuate downstream changes in mood and behavior. Another key thrust of this notion is that the interplay between these neuroplasticity substrates is important for appropriate network function, not isolated factors per se. Studies of these interrelated processes are imperative given evidence that interventions applied earlier in the course of disease are more likely to achieve disease modification, whereas those applied later may have a significant but more limited effect [446, 447].

While the beneficial nature of PA for persons with MDD has been clearly established [10, 448], there is a relative dearth of evidence for persons with BP. Cooney and colleagues conducted a meta-analysis of high-quality RCTs published up to March 2013 to determine whether there is enough evidence to support the deployment of PA in clinical populations with depression [10]. Thirty-nine studies with a total of 2326 participants were included in the review. The authors reported that exercise produced effects comparable to treatment with antidepressants or psychotherapy. Another meta-analytic study reported that aerobic exercise moderately reduced the signs of depression, with populations over 60 years of age deriving the greatest effect [448]. A more recent meta-analytic review attempted to determine optimal parameters for using exercise to treat depression (e.g., frequency, intensity, duration, and type of exercise). They noted that all five RCTs meeting inclusion criteria were aerobic in nature (walking on treadmill or outdoors, cycling on a stationary bike, or training on an elliptical machine) [449]. Moreover, positive evidence was found that aerobic exercise of moderate intensity, undertaken 3 times weekly for a minimum of 9 weeks, was successful in treating depression [449]. Separate clinical studies in persons with BP suggest that exercise, in combination with mood stabilizers, improves outcomes [450, 451], and routine exercise is a common wellness strategy practiced by persons with high-functioning BP [452]. For instance, one preliminary trial noted a trend towards significance for persons with BP in an inpatient psychiatric treatment unit that participated voluntarily in a walking group during their admission [451]. Another preliminary trial in persons with BP found the addition of 100 minutes of weekly exercise to baseline activities, in conjunction with nutrition and wellness activities, effectuated improvements in quality of life, depressive symptoms, and weight loss [453]. A meta-analysis of six studies reported the feasibility and benefit of PA in persons with BP, particularly noting decrements in symptoms of depression, anxiety, and stress [454].

Given that it is generally held that positive, supportive relationships have a beneficial effect on the maintenance of psychological health [455], further consideration of the influence of social interactions during group exercise is warranted, particularly in aging individuals. Group activities such as exercise may help retirees deal more effectively with the loss of social relationships and influence in the workplace by providing an opportunity to meet and socialize with others [456]; disproving stereotypes; and promoting feelings of autonomy, relatedness to others, and competence [457]. In turn, positive social relationships may facilitate the adherence to leisure-time PA. A large prospective cohort study of middle-aged adults found that adults who experienced high levels of emotional support were more likely to adhere to recommended levels of leisure-time PA at follow-up in comparison to those with lower levels of social support [458]. Alternatively, social participation and engagement may reflect an index of behavioral plasticity [459, 460] wherein social engagement helps aging persons to compensate for changes in neural systems involved in emotional and cognitive functioning, a notion that awaits future investigation.

Clearly, large-scale, multiple-site clinical investigations that study the relationship between exercise and MDs are needed. The degree to which polymorphisms (common

variations in gene sequence) determine an individual's response to PA is largely unknown. Future work that combines the study of genetic background (e.g., polymorphisms in BDNF), postexercise serum BDNF, and affective and cognitive measures with neuroimaging studies of MD-related circuits could be used to determine the "dose" of PA requisite to mitigate structural and functional changes in the brain across patient populations. Moreover, strategies for overcoming the core symptoms of depression (e.g., loss of interest, motivation, and energy; low self-worth feelings and self-confidence; psychosomatic complaints; and comorbid health problems) and mania need to be clearly delineated and articulated so that exercise can be personalized.

In summary, the data presented here suggest that moderate PA—a target that is practical, well tolerated, and likely to optimize exercise adherence—can be used to improve the neurobiological impairments and behavioral symptoms associated with MDD and BP. Because of this, PA should be advocated to reduce symptoms, prevent relapse, and mitigate residual symptoms vis-a-vis the promotion of good health habits [461]. The success of prevention campaigns will require significant changes in philosophy and approach. Evidence suggests that 50% or less of mental health professionals recommended exercise for depression, and less than a third of those felt confident in making individualized recommendations [364, 462]. Ultimately, it is hoped that a more consolidated treatment view and research approach will translate into novel therapeutic avenues of preventive and curative value for persons with MDD and BP.

Abbreviations

ACTH: Adrenocorticotropic hormone
BDNF: Brain-derived neurotrophic factor
BP: Bipolar disorder
CRH: Corticotropin-releasing hormone
FNDC5: Fibronectin type III domain-containing protein 5
GABA: Gamma aminobutyric acid
HPA: Hypothalamic-pituitary-adrenal axis
IGF-1: Insulin-like growth factor 1
IL-1: Interleukin-1
IL-6: Interleukin-6
MDD: Major depressive disorder
MDs: Mood disorders
NMDAR: N-Methyl-D-aspartate receptor
PA: Physical activity
PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
RCT: Randomized controlled trial
ROS: Reactive oxygen species
SCN: Suprachiasmatic nucleus
TNF-α: Tumor necrosis factor-α
VEGF: Vascular endothelial growth factor.

Conflicts of Interest

The author declares no competing interests.

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Hindawi
Neural Plasticity
Volume 2017, Article ID 4605971, 11 pages
https://doi.org/10.1155/2017/4605971

Review Article

New Treatment Strategies of Depression: Based on Mechanisms Related to Neuroplasticity

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Received 3 November 2016; Revised 10 March 2017; Accepted 23 March 2017; Published 11 April 2017

Academic Editor: Bingjin Li

Major depressive disorder is a severe and complex mental disorder. Impaired neurotransmission and disrupted signalling pathways may influence neuroplasticity, which is involved in the brain dysfunction in depression. Traditional neurobiological theories of depression, such as monoamine hypothesis, cannot fully explain the whole picture of depressive disorders. In this review, we discussed new treatment directions of depression, including modulation of glutamatergic system and noninvasive brain stimulation. Dysfunction of glutamatergic neurotransmission plays an important role in the pathophysiology of depression. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has rapid and lasting antidepressive effects in previous studies. In addition to ketamine, other glutamatergic modulators, such as sarcosine, also show potential antidepressant effect in animal models or clinical trials. Noninvasive brain stimulation is another new treatment strategy beyond pharmacotherapy. Growing evidence has demonstrated that superficial brain stimulations, such as transcranial magnetic stimulation, transcranial direct current stimulation, cranial electrotherapy stimulation, and magnetic seizure therapy, can improve depressive symptoms. The antidepressive effect of these brain stimulations may be through modulating neuroplasticity. In conclusion, drugs that modulate neurotransmission via NMDA receptor and noninvasive brain stimulation may provide new directions of treatment for depression. Furthermore, exploring the underlying mechanisms will help in developing novel therapies for depression in the future.

1. Introduction

Major depressive disorder (MDD) is a severe major mental disorder. The lifetime prevalence of major depressive disorder is high, around 16.9% in the United States [1]. In addition to potential suicidal risk, depression leads to functional impairment which causes burden of patients, their families, and the society. In WHO report, depressive disorder is the ninth leading cause of functional disability-adjusted life years (DALYs) and the first leading cause in years lost due to disability (YLD) in 2012 [2]. However, treatment outcome of depression is suboptimal. The use of currently available antidepressants is limited by their side effects, slow response, and inadequate treatment efficacy [3]. Full remission is difficult to be achieved. Patients may still suffer from residual depressive symptoms and cannot return to their premorbid functional level. In SART*D study, the remission rate was approximately 30% in first-line antidepressant treatment and the overall cumulative remission rate after receiving 4 step treatment was only 67% [4]. In a meta-analysis study, the overall pooled response rate of antidepressant treatment augmented with atypical antipsychotics was only 44.2% [5].

In addition to neurotransmission theory of depression, disrupted signalling pathway and neuroplasticity also play key roles in the pathophysiology of depression. Reduced

neurotropic factor expressions and altered functional connectivity of neurocircuitry are found in depression [6], and these may be the new therapeutic target in the treatment of depression. In fact, current antidepressants may exert their antidepressive effect by increasing neural plasticity [7, 8]. Chronic administration of fluoxetine can enhance synaptic plasticity and increase postsynaptic spine density [9]. Therefore, novel treatment strategies are being developed to fulfill the need in the treatment of depressive disorder.

2. Modulating Glutamatergic System in the Treatment of Depression

Investigation of the relationship between glutamatergic system and depression begins from N-methyl-D-aspartate (NMDA) receptor. The function of NMDA receptor plays an important role in long-term potentiation (LTP), which is the neural basis of memory [10] and pathophysiology of anxiety and depressive disorder [11]. Furthermore, chronic treatments with conventional antidepressants that target the monoamine system can alter the NMDA receptor function [12]. Dysfunction of glutamatergic neurotransmission is found in patients with MDD [13]. Therefore, glutamatergic system is thought to be another keystone in the pathophysiology of depression. Compounds acting on the glutamatergic system, especially via NMDA receptor, may be potential novel antidepressants.

2.1. Ketamine and Other Nonselective NMDA Receptor Antagonists. Since increased activity of glutamatergic neurotransmission was found in depression and some conventional antidepressants antagonized NMDA receptor activity [14], NMDA receptor antagonist was first investigated as potential antidepressant [15]. Ketamine, one of the NMDA receptor antagonists, has rapid antidepressive effects in clinical studies [16–18]. A single subanesthetic (0.5 mg/kg) dose of ketamine over 40-minute IV infusion can improve depressive symptoms in patients with MDD [17, 19]. The response rate of a single-dose ketamine for the treatment of depression is about 50~70% [16, 17]. The antidepressant effect occurs in 4 hours after 40-minute IV infusion of ketamine and can last for 3–7 days after administration [20]. Clinically, ketamine also improves depressive symptoms in depressive patients resistant to electroconvulsive therapy (ECT) and attenuates suicidal ideation [19]. In addition to IV injection of ketamine, intranasal ketamine is another safe route for treating depression. Intranasal ketamine has been used in the treatment of chronic pain [21] and migraine with prolonged aura [22]. In a randomized, double-blind, crossover study, intranasal ketamine could improve depressive symptoms in patients with major depressive disorder at 24 hours after receiving ketamine [23].

The long-term antidepressant effect of ketamine is still under investigation. One study found that only 27% responders to a single dose of ketamine could maintain their antidepressant effect for 28 days [24]. Therefore, repeated infusion may be needed for maintaining the antidepressant effect of ketamine. In one repeated infusion trial, the overall response rate was 70.8% after receiving IV infusions of ketamine for 6 times over 12 days. Among responders, median time to relapse was 18 days after the last infusion [25]. Although several clinical studies also showed antidepressant effects of repeat-dose ketamine infusion, the sample size of these studies were small (the largest trial only enrolled 24 patients) [25–27]. No protracted adverse effects were found in these repeated dose studies [19].

Ketamine is a mixture of two isoforms, R (−) ketamine and S (+) ketamine. As analgesics, S (+) ketamine is about three to four times more potent than R (−) ketamine [28, 29]. However, S (+) ketamine has more psychotomimetic effect [30] and is associated with more cerebral and systemic hemodynamic side effect compared with R (−) ketamine [31]. Both isomers of ketamine had rapid antidepressant effect in mice model of depression [32]. Attenuated depression-like behavior in tail suspension test, forced swimming test, and 1% sucrose preference test was noted 27 to 48 hours after a single dose of ketamine injection (both isomers? Yes). However, only R (−) ketamine had a long-acting antidepressant effect. Decreased depression-like behavior was still noted in tail suspension test and forced swimming test at day 7 after injection of R (−) ketamine [32]. In another animal study, both ketamine isomers decreased depression-like behavior at 30 minutes and 24 hours after injection, but only R (−) ketamine showed antidepressant effect at 48 hours after injection [33]. In a mice study conducted by Yang et al., both isomers could improve depressive symptoms at 6-7 days after a single injection, but R (−) ketamine was significantly more potent than S (+) ketamine in antianhedonia and antidepressant effect [34].

The underlying mechanism of ketamine's antidepressant effect is complex (See Figure 1). One hypothesized model is that ketamine increases presynaptic glutamate release, resulting in activation of Akt and extracellular signal-regulated kinase (ERK) signalling, which in turn stimulates mammalian target of rapamycin (mTOR) signalling [35, 36]. Then, activated mTOR pathway increases downstream synaptic protein synthesis by phosphorylating p70 S6 kinase (p70S6K) and inhibiting 4E binding proteins (4E-BP) [35, 36]. A low dose of ketamine (10 mg/kg) can rapidly activate mTOR signalling pathway in the prefrontal cortex of rats [37]. Besides, this mTOR activation only occurs at subanesthetic doses of ketamine (5 to 10 mg/kg), but not at a higher anesthetic dose of ketamine [37]. In addition to activating mTOR signalling, ketamine also stimulates Akt and ERK pathways rapidly. Furthermore, inhibition of the Akt and ERK signalling blocks ketamine's effect on mTOR activation [37].

Ketamine also modulates mTOR signalling by increasing brain-derived neurotrophic factor (BDNF) activity [36]. In an animal study, ketamine's antidepressant effect was blocked in BDNF conditional deletion mutant [38]. Ketamine increases BDNF activity by stimulating α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which leads to activity-dependent release of BDNF [39]. Ketamine also suppresses NMDA receptor activities and then inhibits downstream eukaryotic elongation factor-2 kinase (eEF2K), which relieves its inhibition upon BDNF translation [40]. Then, BDNF interacts with

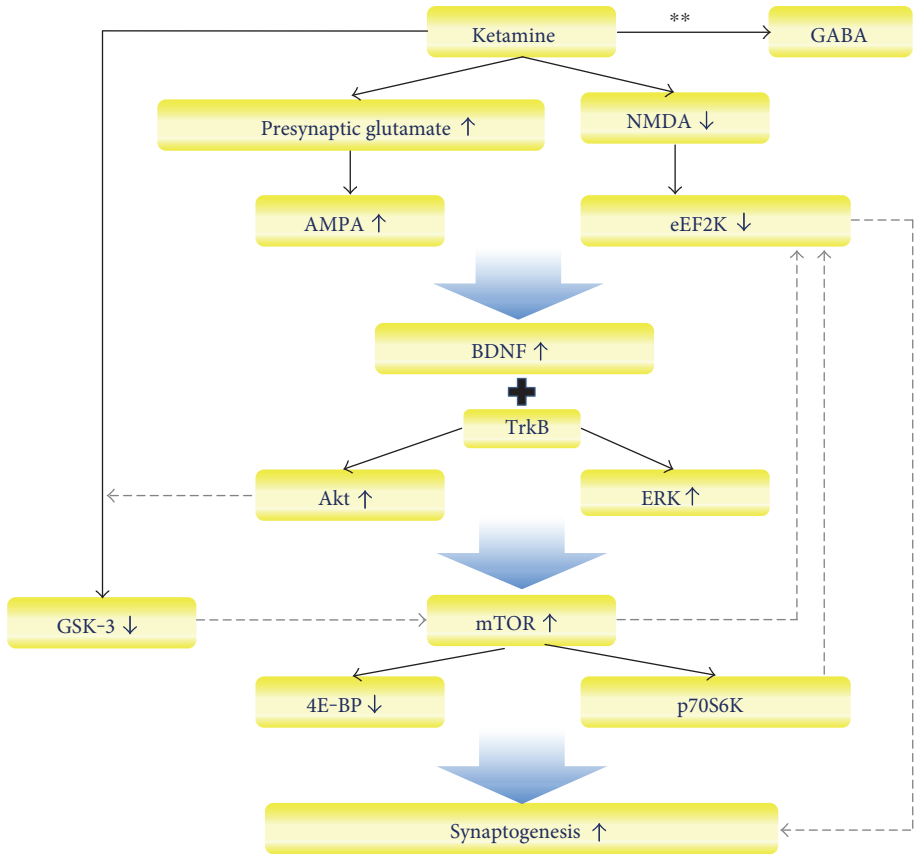

Figure 1: The hypothesized mechanism of ketamine's antidepressant effect. Ketamine increases AMPA receptor activities and suppresses NMDA receptor activities, which lead to activation of BDNF activity. The BDNF-TrkB signalling activates Akt and ERK pathways, which stimulate mTOR signalling. mTOR signalling increases synaptic protein synthesis by inhibiting 4E-BP and phosphorylating p70S6K. Ketamine also inhibits GSK-3 activity and may interact with GABA. *Dash line: the interaction was known in other studies, but it is still unclear in the mechanism of ketamine's antidepressant effect. **The interaction is still unclear because the study results are inconsistent. AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA: N-methyl-D-aspartate; eEF2K: elongation factor-2 kinase; BDNF: brain-derived neurotrophic factor; TrkB: tropomyosin receptor kinase B; ERK: extracellular signal-regulated kinases; mTOR: mammalian target of rapamycin; 4E-BP: 4E binding proteins; p70S6K: p70 S6 kinase; GSK-3: glycogen synthase kinase-3; GABA: γ-aminobutyric acid.

tropomyosin receptor kinase B (TrkB) receptors and Akt and ERK signalling, which increase downstream mTOR activation [36, 37].

All the changes described above increase synaptogenesis and contribute to the rapid antidepressant effect of ketamine [35, 36, 38]. P70S6K and 4E-BP1 phosphorylation were increased after ketamine administration [35]. A single dosage of ketamine can increase levels of postsynaptic density proteins, including activity-regulated cytoskeletal protein (Arc), glutamate-AMPA receptor-1 (GluR1), postsynaptic density protein-95 (PSD95), and synapsin I [37]. These changes occur within 1-2 hours after ketamine infusion and can persist to 72 hours after ketamine administration [36, 37]. The effect of ketamine to synaptogenesis can be proved by increasing the number of mature mushroom-shaped spines and increasing excitatory postsynaptic currents in prefrontal cortex [35].

Glycogen synthase kinase-3 (GSK-3) may be also involved in the underlying mechanism of ketamine's antidepressant effect. GSK-3 is another important protein in brain function. Inhibition of GSK-3 may have a mood stabilizing effect [41]. Ketamine can inhibit GSK-3 by increasing its phosphorylation in mouse model of depression [42]. Besides, in this animal study, ketamine's antidepressant effect was absent in GSK-3 knock-in mice, whose GSK-3 activity was persistently active [42].

The antidepressant effect of ketamine may be also through modulating cortical GABA (γ-aminobutyric acid) levels. Decreased GABA levels are found in the anterior cingulate of patients with MDD [43]. In an animal study, administration of ketamine can blunt the depression-like behavior and increase GABA levels in the anterior cingulate following unpredictable stress [44]. In one clinical study, ketamine injection was associated with increased GABA/water ratio [45]. However, inconsistent results were found in different studies about the association between these neurotransmitter alternations and the antidepressant response of ketamine [45].

There are still some concerns about applying ketamine to clinical practice in the treatment of depression. First, strong evidence of treatment efficacy of ketamine is still lacking, especially for the long-term outcome [46]. Besides, the administration routes of ketamine in current studies are usually through intravenous injection which will limit its clinical use [46]. Most important of all, the safety issues of long-term ketamine administration, such as the risk of psychotomimetic effect, cognitive impairment, abuse, and dependence, need to be clarified in further investigations [47].

Since ketamine has a risk of psychotomimetic effects, such as dissociative state, other NMDA receptor antagonists are developed as potential antidepressant. AZD6765 (lanicemine) is a nonselective NMDA receptor antagonist which may have an antidepressant effect with a better safety profile. In a double-blind, randomized, crossover, placebo-controlled trial, a single infusion of AZD6765 produced rapid but short-lived antidepressant effect without producing psychotomimetic effects. The duration of antidepressant effect of AZD6765 in this study was only 110 minutes [48]. In another study, the antidepressant effect of single-dose AZD6765 peaked at 72 hours postinfusion and disappeared by 10–13 days after infusion [49]. This study also found that multiple infusions of AZD6765 (3 weeks treatment with an interval of three infusions per week) can sustain antidepressant effect to 5 weeks after the last infusion [49]. However, AZD6765 failed to show its efficacy in treatment-resistant MDD in phase II clinical trials [3].

2.2. Selective NMDA Receptor Subtype 2B (NR2B) Antagonists. Another way to develop NMDA receptor antagonists with more specificity and possibly better safety profile is targeting at specific subtypes of NMDA receptors. Among all NMDA receptor subtypes, NMDA receptor subtype 2B (NR2B) might be the most suitable candidate because NR2B subunit only expresses in the forebrain and it is associated with NMDA neurotoxicity [50]. In an animal study, mice with NR2B subunit knockdown in the bed nucleus of the stria terminalis had similar behavior as the affective effect after ketamine treatment [51]. Furthermore, genetic deletion of NR2B from principal cortical neurons in mice blocked ketamine's antidepressant effect, including suppression of depression-like behavior, increasing mTOR activation, and synaptic protein synthesis [52]. Therefore, several selective NR2B antagonists are being investigated as potential antidepressants.

CP-101, 606 (traxoprodil) is one of the selective NR2B antagonists. A single dose of CP-101, 606, like ketamine, can enhance synaptic activity in rat hippocampus. This indicates its potential antidepressant effect [53]. In a double blind, randomized, controlled clinical trial, a single infusion of CP-101, 606 had better antidepressant effect than placebo and this response can maintain for at least one week [54]. Unfortunately, further development of this compound was stopped because of QTc prolongation [3].

MK-0657 is the first oral form selective NR2B antagonist developed as an antidepressant [55]. In a pilot study, MK-0657 monotherapy (4–8 mg/d for 12 days) can significantly decrease the depressive symptoms compared to placebo in patients with treatment-resistant depression [55]. More studies are needed to validate the antidepressant effect of MK-0657.

Ro25-6891 is another NR2B antagonist showing potential antidepressant effect in some preclinical studies. Ro25-6891 can activate mTOR signalling [36]. Pretreatment with Ro25-6981 can prevent the acute stress-facilitated long-term depression in rat hippocampus [56]. Ro25-6981 also showed antidepressant effect in the behavior model of depression in rats [57]. Applying Ro25-6891 to clinical use is still under investigation.

2.3. NMDA Partial Agonists. NMDA partial agonists are usually seen as NMDA receptor modulators because they have agonist effect at low doses, but become antagonists at high doses. Therefore, NMDA partial agonists are investigated as potential antidepressants.

D-Cycloserine is one of the NMDA partial agonists. D-Cycloserine can restore impaired long-term potentiation in neural cell adhesion molecule-deficient mice model [58] and facilitate NMDA receptor-mediated synaptic potentials in rat hippocampal slices [59]. D-Cycloserine also increases expression of the activity-regulated cytoskeletal (Arc) protein, which was associated with memory consolidation [60]. It failed to produce antidepressant effect at dose 250 mg/d as adjuvant therapy for treatment-resistant MDD [61]. However, at high dose (1000 mg/day), D-cycloserine was effective as an add-on treatment for treatment-resistant depression [62].

GLYX-13 is another NMDA glycine-site functional partial agonist which has a potential antidepressant effect. A single infusion of GLYX-13 can sustain its antidepressant effect for 7 days in rat study [63]. In the same study, the authors also found that GLYX-13 could facilitate long-term potentiation, increase the proportion of whole-cell NMDA receptor current, and increase mature spine density in the brain [63]. The antidepressant effect of GLYX-13 may not only be related to NMDA receptor but also rely on AMPA/kainate receptor activation. In an animal study, pretreatment with AMPA receptor antagonist blocked GLYX-13's antidepressant effect [64]. Currently, the use of GLYX-13 in the treatment for depression is under phase II trial [64].

Sarcosine is a natural compound with activity of NMDA partial agonist. Sarcosine can improve depressive symptoms in both rodent models and patients with MDD. In a 6-week randomized, double-blinded, citalopram-controlled trial, sarcosine had better treatment response and less adverse effect than citalopram [65]. In an animal study, sarcosine decreased depressive-like behavior in forced swim test in rat and activated mTOR signalling pathway [66]. In the following study, sarcosine also increased mTOR signalling pathway activation and enhanced AMPA receptor membrane insertion in rodent model [67].

2.4. Glutamate Release Inhibitors. Other compounds involved in glutamatergic system are also being investigated as potential antidepressants. Riluzole, a glutamate release inhibitor, has multiple effects in glutamatergic system. In addition to inhibiting glutamate release, riluzole increases glutamate

reuptake, blocks NMDA receptor activity, and increases AMPA receptor trafficking [3]. In animal model of depression, treatment of riluzole decreased hyperemotional response and improved depressive-like behavior [68, 69]. Besides, under higher dosage (60 μg/ml), riluzole can restore hippocampal BDNF expression and increase glutamate glial transporter 1 expression [69]. In some pilot studies with small sample size, riluzole was effective in improving depressive symptoms in patients with depression [70, 71], but more rigorous study with larger sample size is needed to prove its antidepressant effect.

2.5. Metabotropic Glutamate Receptor Antagonist. In addition to NMDA receptor, metabotropic glutamate receptor (mGlu) may be another target for treating depression. LY341495 and MGS0039, which are competitive nonselective orthosteric mGlu2/3 receptor antagonists, have antidepressant-like effects in the animal model of depression [72, 73]. Coadministration of subeffective dose of LY341495 can enhance the antidepressant effect of scopolamine [74] and ketamine [75] in forced swimming test. In addition to rapid antidepressant effect, the antidepressant action of MGS0039 can sustain 3–7 days after a single-dose injection [72]. RO4491533, an mGluR2/3 negative allosteric modulator, reduces depression-like behavior in rodents [75]. Recently, a novel mGlu2/3 receptor antagonist which belongs to bicyclo[3.1.0]hexane glutamic acid analogs shows antidepressant-like effect in forced swimming test of mice [76]. The clinical studies of these mGlu 2/3 receptor antagonists including MGS0039 and RO4995819 are still under investigation [73].

mGlu5 receptor is another target for developing potential antidepressant. Basimglurant (RG7090, RO4917523) is a selective mGlu5 negative allosteric modulator with potential antidepressant activity and excellent drug-like properties [77]. In a phase 2b, double blind, randomized, placebo-controlled clinical trial, basimglurant (0.5 mg or 1.5 mg once daily) was adjunctive to antidepressant for six weeks. Although adjunctive basimglurant did not have significant difference to placebo in the major outcome (the change of clinician-rated of Montgomery-Asberg Depression Rating Scale (MADRS) score) [78], there were significant improvements in the 1.5 mg/d group in secondary outcomes, including patient-rated MADRS score, quick inventory of depressive symptomatology—self-report, clinical global impression—improvement mean score, and patient global impression—improvement mean score [78]. DSR-98776, another mGlu5 negative allosteric modulator, also shows antidepressant effect in rodent model of depression [79].

3. Brain Stimulation in the Treatment of Depression

In addition to medication, brain stimulation is another method to treat depressive disorders. Impaired neurocircuitry activity and reduced neuroplasticity are found in depressive disorders and play important roles in the pathophysiology of depression [6, 80–82]. Depressive patients had decreased motor-evoked potentials compared to normal subjects in paired associated stimulation [80]. Impaired connectivity in prefrontal cortex and anterior cingulate gyrus was related to the pathogenesis of depressive symptoms [6].

Brain stimulation therapy may exert its antidepressant effect by modulating neuroplasticity [83, 84]. Electroconvulsive therapy (ECT) which is used in treating depression refractory to medication is among the oldest brain stimulations. Several synaptic plasticity-associated transcripts and their encoding proteins in the hippocampus were affected by ECT [85]. In animal studies, microtubule-associated protein 2 in the dentate gyrus [86] and two endocytosis-related scaffolding proteins were increased after electroconvulsive seizure, and the authors implied that neurotransmitter transport trafficking may be involved in the therapeutic effect of ECT [87]. Hippocampal connectivity or volume of patients with MDD had been reported to be increased after receiving ECT in several clinical studies [88–92]. In addition to hippocampus, ECT can stimulate neurogenesis in frontal brain area in animal model [93] and modulate white matter microstructure in pathways connecting frontal and limbic areas in patients with MDD [94]. However, the association between these changes of neuroplasticity and depressive symptoms was still unclear [95, 96].

ECT also influences glutamatergic system. In depression model of rat, glutamate content was decreased and NR2B expression was upregulated following ECT [97]. Combining ketamine and ECT may have synergic effect in antidepressant effect. In a retrospective study, patients receiving ECT with ketamine needed fewer ECT sessions and had better antidepressant treatment response and cognitive function than those receiving ECT with thiopental (an anaesthetic agent) as a comparator [98].

3.1. Transcranial Magnetic Stimulation (TMS). Since ECT has some side effects such as cognitive deficits, safer brain stimulation modalities are developed for the treatment of depressive disorders. Repetitive transcranial magnetic stimulation (rTMS) is a Food and Drug Administration- (FDA-) approved treatment for patients with MDD who are resistant to antidepressant treatment [99]. Transcranial magnetic stimulation (TMS) uses an electromagnetic coil on the scalp to create an alternating magnetic field. This magnetic field induces a secondary electric current in the brain without interference from the skin, muscle, and bone. According to the frequency of magnetic pulse administration, TMS can be divided into many types. rTMS is a kind of TMS given magnetic pulses repetitively for duration from seconds to minutes [100].

The mechanism about how TMS works on depression is still unclear. Like ECT, TMS may stimulate neurogenesis [101]. In a small clinical study, left amygdala volume was increased following TMS and this change was associated with the antidepressant treatment response [102]. TMS may also modulate brain activity and neurotransmitters, such as serotonin and dopamine [103]. One hypothesis is that depressive patients have impaired modulation of cortical excitability and TMS may alter this imbalance [104]. Evidences from functional imaging indicate that reduction in prefrontal

cortex activation may be related to the treatment effect of TMS [105]. Recently, another study showed that TMS may exert its antidepressant effect by modulating functional connectivity between the central executive work and default mode network [106].

Current paradigm of TMS is based on previous studies, but the most effective protocol of TMS which should include precise position, optimal amplitude, frequency, and course is still under investigation [100]. In order to increase the treatment response, minimize individual variability, and avoid potential adverse effects of standard rTMS, some new protocols have been developed. Theta burst stimulation (TBS) is designed for reducing administration duration. It only requires 1 to 3 minutes of stimulation [107]. Some studies showed that TBS has similar or better efficacy in treating depression compared to rTMS [107]. Low-field synchronized transcranial magnetic stimulation (sTMS) tries to achieve clinical response under much lower energy than conventional rTMS. sTMS delivers stimulation at individual's alpha frequency (IAF) and uses brain's natural resonance at the IAF [108]. Although sTMS can improve depressive symptoms as an add-on treatment for MDD [109], no treatment efficacy is found in sTMS as a monotherapy for the treatment of MDD [110].

3.2. Transcranial Direct Current Stimulation (tDCS). Transcranial direct current stimulation (tDCS) is another method of noninvasive brain stimulation for the treatment of depressive disorders. The device of tDCS has two electrodes, anode and cathode. tDCS applies a constant low current (0.5–2 mA) directly to the brain via these electrodes on the scalp and changes the cortical excitability. The brain area underlying anode becomes hyperexcitable, whereas the area underlying cathode becomes less excitable [111]. A noninferiority, triple-arm, placebo-controlled trial showed that tDCS was similarly effective to escitalopram in treating depression [112]. Meta-analysis also revealed that tDCS was significantly superior to sham group for all outcome measures in depression treatment [113]. Furthermore, not only improving depressive symptoms, tDCS also increases paired associative stimulation-induced neuroplasticity [114]. However, the results of following studies investigating treatment efficacy of tDCS were disappointing. In a randomized, sham controlled study, a 5-day session of tDCS did not improve depressive symptoms in treatment-resistant depression [115]. A systematic review article indicates that tDCS had better response and remission rate than the control group, but the difference was not significant statistically [111]. More studies are needed to elucidate the antidepressant effect of tDCS.

3.3. Cranial Electrotherapy Stimulation (CES). Cranial electrotherapy (CES) applies pulsed, low amplitude electrical currents (usually less than 1 mA) to the brain via scalp electrodes. CES has been approved for the treatment of anxiety, depression, and insomnia from Food and Drug Administration in the United States [116]. Clinically, CES can decrease comorbid depression in anxiety disorders [117]. However, the Cochrane library review indicates that methodologically rigorous studies to examine the antidepressant effect of CES in the treatment of acute depression are lacking [118]. How CES exert its antidepressant effect is still unknown. CES may affect limbic system, reticular activating system, and the hypothalamus [119]. A recent study showed that CES could deactivate cortical brain activity and alter connectivity in default mode network [120]. How CES modulate underlying neuroplasticity or signalling pathway needs further investigation.

3.4. Magnetic Seizure Therapy (MST). Magnetic seizure therapy (MST) is a new variant of TMS. The rationale of this therapy is based on ECT. It uses high-intensity rTMS to evoke seizures like ECT but with better control. The treatment effect of MST in depression is still under study [104]. In previous studies, the response rate of MST for depression was about 50–60% [121]. The mechanism of MST is still unclear. In a positron emission tomography study, the relative glucose metabolism was increased in the basal ganglia, orbitofrontal cortex, medial frontal cortex, and dorsolateral prefrontal cortex after receiving a treatment course of MST [122]. This implies that these regional brain activities may be related to the mechanism of treatment effect of MST. More studies are needed to investigate the MST effect on neuroplasticity or signalling.

4. Conclusion

MDD is a complex mental disorder. Effective clinical treatment strategy with favourable adverse effect profile is still lacking until now. Neurotransmission via NMDA receptors may be a new target for the treatment of depression. Ketamine has a rapid antidepressive effect, but its long-term efficacy and safety raises concerns and still needs further investigation. Other NMDA receptor and glutamate modulators also show antidepressive effects in small-scale studies. Future studies with more rigorous design and in larger scale are needed to validate their efficacy and safety. In addition to medication, noninvasive brain stimulation is another treatment strategy for MDD. Developing and standardizing the most effective and safest protocol are the key points in the future.

The discussion of the underlying neurobiological mechanisms of the aforementioned treatments for depression is based on the theory of neuroplasticity impairment. Current evidences seem to imply that dysfunction of neurotransmission might be only a tip of iceberg in the pathophysiology of depressive disorders. Signalling pathways, such as mTOR signalling and their effect on downstream synaptogenesis, synaptic plasticity, neurotransmission, and functional connectivity are keystones in the genesis of depressive disorders. This indicates a novel direction in the future development of antidepressive treatment.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study is partially supported by China Medical University Hospital Grant DMR-105-073.

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Hindawi
Neural Plasticity
Volume 2017, Article ID 3682752, 18 pages
https://doi.org/10.1155/2017/3682752

Review Article

Zinc in the Monoaminergic Theory of Depression: Its Relationship to Neural Plasticity

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Received 4 November 2016; Accepted 24 January 2017; Published 19 February 2017

Academic Editor: Aijun Li

Preclinical and clinical studies have demonstrated that zinc possesses antidepressant properties and that it may augment the therapy with conventional, that is, monoamine-based, antidepressants. In this review we aim to discuss the role of zinc in the pathophysiology and treatment of depression with regard to the monoamine hypothesis of the disease. Particular attention will be paid to the recently described zinc-sensing GPR39 receptor as well as aspects of zinc deficiency. Furthermore, an attempt will be made to give a possible explanation of the mechanisms by which zinc interacts with the monoamine system in the context of depression and neural plasticity.

1. Introduction

The original monoamine hypothesis of depression was based on serendipitous discoveries. Clinical observations on iproniazid, a tuberculostatic, and imipramine, which was designed as a neuroleptic, showed that these medications reduce depressive symptoms [1]. Extensive research on their mechanism of action further revealed that iproniazid inhibits monoamine oxidase (MAO), an enzyme responsible for the oxidative deamination of monoamines, such as norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT), while imipramine, which became the first tricyclic antidepressant (TCA), inhibits the serotonin transporter (SERT) and the norepinephrine transporter (NET), which account for clearance of the neurotransmitters from the synaptic cleft [1]. These and other observations have contributed to the monoamine hypothesis, which postulated that depression is associated with decreased levels of NE and/or 5-HT in the brain [2, 3]. Although the monoamine hypothesis is now regarded as too simplistic to explain the complexity of the pathophysiology of depression, it has led to the development of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), which are now widely used. It should be noted that almost all currently used antidepressant drugs target the monoamine system. However, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest and longest study conducted with the aim of determining antidepressants effectiveness, demonstrated that only one-third of the participants given an SSRI as a first-line treatment reached remission, and that about 10–15% more responded [4]. These data emphasize the need for novel pharmacological treatments and/or augmentation strategies for depression. It has been shown in preclinical and

clinical studies that zinc possesses antidepressant properties [5] and is able to enhance the effects of antidepressant drugs belonging to the group of SSRIs or TCAs [6, 7]. This review aims to discuss the role of zinc in the pathophysiology and treatment of the disease with regard to the monoamine hypothesis. Particular attention will be paid to the recently described zinc-sensing GPR39 receptor [8] and aspects of zinc deficiency. Furthermore, an attempt will be made to give a possible explanation of the mechanisms by which zinc interacts with the monoamine system in the context of depression and neural plasticity.

2. Zinc

Recent years have brought a new evidence supporting the involvement of zinc in depression in terms of both pharmacological and clinical/epidemiological data. Preclinical tests and models of depression showed antidepressant-like activity of zinc [9–15]. Clinical data pointed towards potential benefits of zinc administration in depressed patients [16, 17]. Zinc supplementation was shown to be effective as an adjunct therapy [6, 7, 18] or as a stand-alone intervention [19, 20] for depression. Moreover, the intake of zinc was suggested to be among the dietary factors that may be associated with a risk for depression. Studies performed in rodents indicated a causative role of dietary zinc restriction in the induction of depressive-like symptoms [21–24] or anhedonia [25–27]. Some large, cross-sectional, population-based epidemiological studies have suggested that a low dietary zinc intake is associated with depression in women [28, 29], but not in men [28]. Although the first prospective study aimed to examine the association of zinc intake and depression risk demonstrated a modest, but significant, inverse correlation between the intake of this element and depression in a cross-sectional setting, the 20-year prospective follow-up observations have indicated that a low dietary zinc intake may not precede depression in initially depression-free men [30]. However, because the study sample comprised exclusively men who have received a hospital discharge diagnosis of unipolar depression, the results cannot be generalized to women or patients not warranting hospitalization [30]. In contrast, in a prospective study of both men and women, a low dietary zinc intake emerged as a risk factor for depression [31]. Also mice lacking the GPR39 receptor, a G protein-coupled receptor, which is activated by zinc [8, 32], display depressive-like behavior [33]. Recently, TC G-1008, an agonist of GPR39, was found to exhibit antidepressant-like activity [34]. These observations further support the involvement of zinc in the treatment of depression.

In the human body zinc is the second most prevalent trace element. It is necessary for proper brain development and functioning. Even subclinical zinc deficiency impairs human brain function [35]. In the brain the ion is present in presynaptic vesicles of a subset of glutamatergic neurons [36]. Somas of the zinc containing neurons are located in the cerebral cortex and in the amygdala, whereas their axonal projections reach cerebral cortex and amygdala, striatum as well as structures of the limbic system [37]. Zinc is packed into the synaptic vesicles by means of a zinc transporter 3 (ZnT-3) [38], which is localized on the membranes of the vesicles [39]. After action potential it is released from the presynaptic vesicles into the synaptic cleft. To date, there is no consensus on the concentration to which the ion rises in the synaptic cleft or its time-course. It is estimated to range from sub-μM to over 100 μM [40]. Zinc released from the presynaptic vesicles modulates a variety of receptors or transporters on the postsynaptic side, including those for monoamines [41, 42].

3. Serotonin (5-HT)

In 1967 Coppen emphasized the role of 5-HT in the pathophysiology of depression [2]. Approximately 90% of 5-HT is synthesized by enterochromaffin cells in the gastrointestinal tract, while most of the remaining 5-HT is produced by the neurons of the raphe nuclei in the brain. The axonal projections of the raphe nuclei innervate almost the entire central nervous system (CNS), and thus play an important role in the regulation of mood, memory, cognition, sleep, appetite, and so forth. 5-HT is synthesized from the precursor amino acid L-tryptophan [43, 44]. After tryptophan is transported into the 5-HT neuron, it is converted by tryptophan hydroxylase, the rate-limiting enzyme in 5-HT production. Aromatic amino acid decarboxylase then converts 5-hydroxytryptophan into 5-HT, which is taken up into the synaptic vesicles by the vesicular monoamine transporter (VMAT2) [45]. Tryptophan can be also catabolized by indoleamine 2,3-dioxygenase (IDO) into kynurenine, which is further broken down into kynurenic acid and quinolinic acid [46]. Activation of the IDO pathway causes lowered plasma tryptophan availability to the brain and, subsequently, lower production of 5-HT [47]. MAO, which is localized in the mitochondrial outer membrane, degrades 5-HT [46]. SERT, which belongs to the neurotransmitter/sodium symporter family besides NET and dopamine transporter (DAT), is a high-affinity transporter for 5-HT and plays a crucial role in maintaining its extracellular levels [48]. Drugs that selectively inhibit SERT, namely, SSRIs, have revolutionized clinical psychopharmacology and nowadays are among the first-line medications used for depression [4]. Although the newest drugs, such as the multimodal agent vortioxetine, combine action occurring at different 5-HT receptor subtypes, SERT inhibition remains an important element of their action [49]. The current view on the mechanism of action of SSRIs states that, following acute treatment, the 5-HT level rises in the somatodendritic area located in the raphe nuclei and stimulates the 5-HT_{1A} autoreceptors. Following chronic use, the 5-HT_{1A} receptors become downregulated and desensitized and thus no longer inhibit 5-HT release. This leads to increased 5-HT release from the axon terminals [50]. As well as targeting SERT, vortioxetine targets 5-HT G-protein-coupled (5-HT_{1A} and 5-HT_{1B} partial agonism and 5-HT_7 antagonism) and 5-HT ionotropic (5-HT_3 antagonism) receptors [49]. Other medications, such as trazodone, as well as inhibiting SERT, possess 5-HT_{2A} and 5-HT_{2C} antagonistic properties [51].

3.1. The Interaction of Zinc with the Serotonergic System. Several preclinical studies have shown the interaction of zinc with the components of the serotonergic system with regard to its antidepressant-like action. Pretreatment with p-chlorophenylalanine (pCPA), an inhibitor of 5-HT synthesis, abolished the antidepressant-like effect of zinc in the forced swim test (FST), which is a common preclinical paradigm used to assess antidepressant properties [52]. The antidepressant-like effect of zinc in the FST was also blocked by the 5-HT_{1A} receptor antagonist WAY-100635 [52]. A study by Cichy et al. [53] showed adaptive changes in serotonergic receptors following chronic zinc hydroaspartate administration. Treatment with zinc for 2 weeks increased the density of the hippocampal and cortical 5-HT_{1A} and 5-HT_{2A} receptors in rats. Similarly, adaptive changes of 5-HT_{1A} and 5-HT_{2A} receptors were found following chronic administration of imipramine [54].

Effect on serotonergic receptors is one of the explanations of the antidepressant-like properties of zinc, which are observed in both preclinical and clinical studies. Satała et al. [42] extensively explored the pharmacological profile of zinc at the 5-HT_{1A} receptors using the agonist of 5-HT_{1A}, [3H]-8-OH-DPAT. In this study, the effects of zinc on [3H]-8-OH-DPAT binding to 5-HT_{1A} stably expressed in HEK293 cells were investigated by means of the in vitro radioligand binding method. A biphasic effect, which involved allosteric potentiation of agonist binding at sub-μM zinc concentrations and inhibition at sub-mM zinc concentrations, was observed [42]. Given that it is estimated that after depolarization the concentration of zinc in the synaptic cleft ranges from sub-μM to 100 μM [40], the effects observed with lower doses should be physiologically more relevant. Additionally, in vivo studies, aimed at differentiating between action at pre- and postsynaptic 5-HT_{1A}, demonstrated that zinc did not induce lower lip retraction or elements of behavioral syndrome (flat body posture, forepaw treading), but pretreatment with zinc blocked these effects induced by the agonist [3H]-8-OH-DPAT, which suggest that zinc may act as an antagonist of this receptor at the postsynaptic site. However, zinc decreased body temperature similarly to [3H]-8-OH-DPAT. On the other hand, the experiments using 5-HT_{1A} autoreceptor knockout mice showed that lack of this receptor completely blocked the hypothermia induced by zinc, while in wild-type littermate mice a consistent decrease in body temperature was observed, which may indicate agonist-like profile at the presynaptic 5-HT_{1A}. In the FST ineffective doses of zinc potentiated the effects of ineffective doses of [3H]-8-OH-DPAT. In the FST conducted with 5-HT_{1A} autoreceptor knockout mice zinc induced a slight decrease in the immobility time while in wild-type littermates a significant decrease in the immobility time was observed, which suggest that presynaptic 5-HT_{1A} receptors are necessary for the antidepressant-like effect of zinc [42]. To sum up, this comprehensive study shows that zinc (depending on its concentration) may act as positive allosteric modulator of agonist binding to 5-HT_{1A} receptors or inhibitor. Moreover, both agonist and antagonist-like effects were found and it may target both pre- and postsynaptic 5-HT_{1A}.

A 10-day administration of pCPA, an inhibitor of 5-HT synthesis, caused downregulation of GPR39 protein in the hippocampus of mice [55], which suggests a link between GPR39 and 5-HT signaling. There was also a decrease in the level of 5-HT precursor, tryptophan, in the hippocampus of GPR39 knockout mice [55]. Moreover, there is some evidence indicating a link between GPR39 and 5-HT_{1A} receptors function. GPR39 was found to form heterodimers with 5-HT_{1A} as well as heterotrimers with 5-HT_{1A} and galanin receptor 1 ($GalR_1$) upon coexpression of the two or three of them in mammalian cells [56]. Galanin is a neuropeptide which is widely distributed in the brain and whose effects are mediated via three G protein-coupled receptors: $GalR_1$, $GalR_2$, and $GalR_3$ [57]. 5-HT_{1A} and $GalR_1$, which share the same signal transduction pathway (i.e., activate $G_{\alpha i}$ protein which leads to inhibition of adenylyl cyclase), have been described to heterodimerize and functional characteristic of the heterodimers revealed absence of addictive effects what can be explained by the existence of allosteric antagonistic communication to avoid excessive inhibition of adenylyl cyclase [58]. Furthermore, zinc was found to disrupt the heterodimerization process of 5-HT_{1A} and $GalR_1$ [59]. Activities of the monohomomeric receptors: 5-HT_{1A}, $GalR_1$, and GPR39, and the heteroreceptor complexes: 5-HT_{1A}-GPR39 and 5-HT_{1A}-GPR39-$GalR_1$, were measured by their ability to activate response elements: the serum response element (SRE) and nuclear factor kappa beta response element (NF$\kappa\beta$-RE) [56]. Because GPR39 signals via G_q, $G_{\alpha 12/13}$, and $G_{\alpha s}$ proteins [32], which leads to activation of both response elements, whereas 5-HT_{1A} signals via $G_{\alpha i}$ protein [60] and activates SRE only in the presence of agonist, 8-OH-DPAT, SRE, and NF$\kappa\beta$-RE were chosen to analyze potential differences in signaling between monohomomers and heteromers [56]. 5-HT_{1A}-GPR39 heteromer exposure to 8-OH-DPAT and zinc chloride resulted in higher response compared to those yielded by each one of the compounds indicating additive signaling upon coactivation of these receptors. The complex including also $GalR_1$ (5-HT_{1A}-GPR39-$GalR_1$ heteromer) displayed no response in the presence of 8-OH-DPAT or zinc chloride, but enhancement of response was observed in the presence of galanin, while stimulation with all agonists together evoked the same response as galanin, suggesting that the presence of $GalR_1$ blocks 5-HT_{1A} and GPR39 signaling.

In addition to targeting 5-HT_{1A} receptors, zinc was found to target other subtypes of 5-HT receptors. Electrophysiological studies of HEK293 cells expressing 5-HT_3 receptors showed that low concentrations of zinc (0.3–10 μM) enhanced and high concentrations of zinc (30–200 μM) depressed the 5-HT-induced response [61]. 5-HT reuptake by SERT is not affected by zinc [62].

3.2. Interactions between Zinc and Antidepressants Targeting the Serotonergic System. Preclinical and clinical studies showed that zinc interacts with the serotonergic system and therefore enhances antidepressant-like effects. Joint administration of zinc with SSRIs such as fluoxetine or citalopram (all in subeffective doses) produced an antidepressant-like effect in the FST [52]. Moreover, an increase in the swimming parameter, but not in the climbing parameter, in the FST was

observed following zinc administration [52]. It is suggested that in the FST the swimming parameter is connected with serotonergic neurotransmission, and the climbing is linked to noradrenergic neurotransmission (based on the observation that SSRIs increase the swimming time whereas selective norepinephrine reuptake inhibitors (NRIs) increase the climbing time [63]). Thus, these results suggest that the serotonergic system is involved in the antidepressant-like activity of zinc. Combined administration of zinc chloride with SSRIs such as fluoxetine or paroxetine significantly reduced immobility scores in the tail suspension test (TST), another preclinical paradigm used to assess antidepressant activity, without affecting locomotion in the open field test [13]. Moreover, joint administration of zinc and imipramine (both in ineffective doses) caused an antidepressant-like effect in the chronic unpredictable stress (CUS) protocol, which is a commonly used preclinical model of depression [14]. Imipramine was also found to be active in the FST following the administration of ineffective doses together with ineffective doses of zinc sulfate [11, 12]. Wróbel et al. [64] demonstrated antidepressant-like properties of zinc in a dexamethasone-induced model of depression in mice. In this study, the joint administration of zinc and imipramine (both in ineffective doses) reversed dexamethasone-induced depressive-like behavior, as measured by the FST.

The interaction between zinc and antidepressants targeting the serotonergic system has been observed not only following zinc supplementation, but also under zinc-deficient conditions. Chronic administration of the zinc-deficient diet was found to alter the responsiveness to antidepressant drugs [65]. Animals subjected to a zinc-deficient diet and treated with an acute injection of escitalopram or imipramine displayed increased immobility time in the FST, compared to animals treated with a zinc-adequate diet and the respective antidepressant agent [65]. Additionally, increased immobility time was observed in mice that received a zinc-deficient diet and chronic treatment with escitalopram, compared to mice that received a zinc-adequate diet and the drug, whereas chronic imipramine treatment did not result in such differences between the zinc-deficient and zinc-adequate rats [65]. Chronic dietary deprivation of zinc produces a depressive- and anxiety-like phenotype [22–24, 66, 67]. Chronic administration of fluoxetine to the zinc-deficient rats resulted in the normalization of depressive-like behavior induced by the diet, as measured by decreased immobility time in the FST [66]. On the contrary, Tassabehji et al. [25] did not observe a significant reduction in the immobility time in the zinc-deficient rats treated with fluoxetine, compared to zinc-deficient rats that did not receive the antidepressant. However, Tassabehji et al. [25] also did not observe depressive-like behavior (increased immobility time) in the zinc-deficient rats compared to control rats. This finding may have resulted from different study design. In the study of Doboszewska et al. [66] the rats received the zinc-deficient diet for 4 weeks (i.e., for a period of time after which behavioral (increased immobility time in the FST, anhedonia) and neurobiological changes associated with depression are established [27]) and for subsequent 2 weeks they received fluoxetine (10 mg/kg/day intraperitoneally (i.p.)) in addition to the diet, whereas in the study of Tassabehji et al. [25] the rats received the zinc-deficient diet and fluoxetine (10 mg/kg/day via drinking water) for 3 weeks. Therefore, a shorter duration of the zinc-deficient diet in the study of Tassabehji et al. [25] (3 weeks) may have been an insufficient amount of time in which to observe a depressive-like behavior. Yet other authors demonstrated depressive-like behavior in the FST following a shorter duration of the zinc-deficient diet, namely, 2 weeks [21, 68]. It should be noted that Tassabehji et al. [25] observed anhedonia, which is one of the core symptoms of depression, in the zinc-deficient rats. Whereas the two studies in which increased immobility time in the FST following 2 weeks of the diet utilized the zinc-deficient diet containing 0.37 mg zinc/kg and the zinc-adequate diet containing 52.8 mg zinc/kg [21, 68], similarly, we utilized the following diets: zinc-deficient 3 mg zinc/kg; zinc-adequate 50 mg zinc/kg [66], the study which did not demonstrate a depressive-like behavior after 3 weeks of the diet utilized: zinc-deficient diet 1 mg/kg; zinc-adequate diet 30 mg/kg [25]. Hence, when interpreting data on the effectiveness of antidepressants in the zinc-deficient animals it is important to take into account the duration of the diet, the amount of the ion, and the schedule of treatment. Positive behavioral effects (reversal of depressive-like behavior) in zinc-deficient mice were observed following chronic treatment with desipramine (a TCA with a less potent inhibitory effect on 5-HT than on NA reuptake) in the FST and the TST [22].

Administration of antidepressants that influence the serotonergic system under zinc-deficient conditions also normalized changes that were observed in the brain. Fluoxetine prevented the higher levels of the hippocampal N-methyl-D-aspartate receptor (NMDAR) subunits (GluN1, GluN2A, GluN2B) and the reduced levels of phosphorylated on Serine-845 GluA1 subunit of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) (pS485-GluA1), phosphorylated cyclic AMP response element binding protein (p-CREB) and brain-derived neurotrophic factor (BDNF) that were evoked by zinc deficiency [66]. Chronic desipramine treatment normalized the exaggerated immediate-early gene expression in the amygdala that was induced by zinc deficiency [22].

There is also a link between GPR39 receptor and antidepressants acting on the 5-HT system. Chronic (a 2-week) treatment with escitalopram but not with imipramine induced upregulation of GPR39 receptor at the protein level in the frontal cortex of mice [69]. Moreover, acute administration of imipramine or escitalopram to mice fed with the zinc-deficient diet caused downregulation of GPR39 protein, while chronic administration of these agents (which is required in order to relieve depressive symptoms) induced upregulation of this protein in the frontal cortex of mice [70]. Furthermore, imipramine and escitalopram reduced immobility time in the FST in wild-type mice, but they were inactive in this paradigm in GPR39 knockout mice, which suggest that GPR39 receptor is necessary for the antidepressant effect of drugs targeting the 5-HT system [71].

Besides preclinical studies, clinical studies have also demonstrated the interaction between zinc and antidepressants targeting the serotonergic system. The first clinical

report indicating the beneficial effects of zinc in human depression showed that it is effective as an augmentation strategy in conjunction with TCAs (clomipramine, amitriptyline) or SSRIs (citalopram, fluoxetine) [6]. This preliminary observation was further confirmed in trials using a bigger sample size. The study of Ranjbar et al. showed that zinc supplementation of therapy involving administration of SSRIs, citalopram or fluoxetine, reduced major depressive disorder symptoms more effectively than administration of the respective drug plus placebo [7]. This effect was not associated with changes in plasma levels of IL-6, TNF-α or BDNF [72]. Importantly, zinc supplementation of therapy involving administration of imipramine was found to be more effective than administration of imipramine plus placebo in treatment-resistant patients [18]. Although a recent systematic review and meta-analysis of adjunctive nutraceuticals for depression found mixed results for zinc [17], zinc supplementation shows promise as a strategy for improving an inadequate response to antidepressants.

3.3. Effects on Zinc Levels of Antidepressants Targeting the Serotonergic System. In preclinical studies, chronic treatment with citalopram (but not with imipramine) significantly increased the serum zinc level. Chronic treatment with both drugs slightly increased the zinc level in the hippocampus and slightly decreased it in the cortex, the cerebellum and the basal forebrain [73]. Moreover, escitalopram and imipramine normalized serum zinc levels previously reduced by a 6-week zinc-deficient diet [65]. Also, chronic treatment with fluoxetine normalized a decrease in the serum zinc level induced by dietary zinc deficiency [66].

A clinical study by Maes et al. [74] examining the serum zinc level in treatment-resistant depression showed a decreased serum zinc level in treatment-resistant patients compared with healthy controls and patients who were not resistant to treatment. The study also showed that subsequent treatment with antidepressants for 5 weeks (with trazodone alone or in combination with fluoxetine and pindolol) did not induce significant changes in the level of serum zinc. Therefore, the serum zinc level was proposed as a marker for treatment resistance. Moreover, a study of the use of zinc supplementation in imipramine therapy showed significantly lower serum zinc level in depressed patients than in healthy volunteers. All groups demonstrated a gradual increase in zinc concentrations over the period of treatment with imipramine with or without zinc supplementation. It is of note that treatment-resistant patients demonstrated lower concentrations of zinc than patients who were not resistant to treatment. Importantly, following 12 weeks of treatment with imipramine, a significant negative correlation was demonstrated between the Montgomery-Åsberg Depression Rating Scale and the serum zinc level, together with a concomitant increase in serum zinc in patients in remission, which suggests that the serum zinc level is a state marker for depression (with the exception of treatment-resistant patients for whom it may be a trait marker) [75]. More studies are needed in a clinical setting to elucidate the effects of antidepressants with different mechanisms of action on serum zinc.

4. Norepinephrine (NE)

NE, also called noradrenaline (NA), is one of the principal catecholaminergic neurotransmitters that have been implicated in the monoamine hypothesis of depression and antidepressant action [3].

NE is synthesized by both the CNS and the sympathetic nervous system. In the brain, NE is produced in nuclei, of which the most important is the locus coeruleus (LC), the most extensively projecting nucleus in the brain [76, 77]. The NE projections from the LC reach brain regions such as the cortex, the hippocampus and the amygdala, which govern memory, cognition and mood [78]. Exposure to stress, which is considered to be a precipitant of depression [79], activates the LC through efferents from the corticotropin-releasing factor (CRF) system [80]. Therefore, LC projections and inputs have received great attention with regard to depressive disorders.

NE is synthesized from the precursor amino acid tyrosine by a series of enzymatic steps. Tyrosine is transported to the CNS from the blood by means of an active transport pump. First, tyrosine is converted into DOPA by tyrosine hydroxylase, the rate-limiting enzyme in NE synthesis. Then, DOPA is converted into dopamine (DA) by DOPA decarboxylase. The third enzymatic step is the conversion of DA into NE by dopamine β-hydroxylase. While the first two steps occur predominantly in the cytoplasm, the last one takes place mainly in the synaptic vesicles. NE is degraded to inactive metabolites by either MAO [81], which is localized in the mitochondrial outer membrane [82], or catechol-O-methyltransferase (COMT) [81], which is located intracellularly [83]. The other mechanism terminating synaptic NE action is NET, which belongs to the neurotransmitter/sodium symporter family and which is localized on the presynaptic noradrenergic nerve terminals [84, 85]. Following reuptake into the presynaptic neuron by NET, NE can be either stored again in the synaptic vesicles by the VMAT2 [86] or degraded by enzymes. NE exerts its action via the family of G protein-coupled receptors (α and β subtypes). Of particular interest in terms of antidepressant pharmacology are α_2 adrenergic receptors, which can act as presynaptic autoreceptors, and thereby regulate NE release [87, 88]. Many antidepressants target NET (e.g., SNRIs such as venlafaxine, duloxetine, and milnacipran; norepinephrine-dopamine reuptake inhibitors (NDRIs) such as bupropion; selective norepinephrine reuptake inhibitors (NRIs) such as reboxetine; and TCAs such as imipramine and amitriptyline) and/or adrenergic receptors (e.g., drugs with prominent α_2-blocking properties, such as mirtazapine and mianserin). Moreover, chronic administration of antidepressants induces adaptive changes in the adrenergic receptors (i.e., β-downregulation [89, 90], α_1-upregulation [91, 92], or α_2-downregulation [90]).

4.1. Interactions between Zinc and the Noradrenergic System. Despite a high sequence identity between DAT, which possesses an endogenous, high-affinity zinc-binding site, and NET, the latter does not possess a zinc-binding site [41]. NET contains two of the three zinc coordinating residues found in DAT, but monoamine reuptake by NET is not affected by

zinc. However, if the third DAT zinc coordinating residue (H193) is introduced into NET (position 189), NET becomes susceptible to inhibition by zinc [93]. It has been reported that the expression of NET was decreased in the locus coeruleus by the cooccurrence of social isolation and zinc deficiency compared with zinc deficiency alone, and that this change was accompanied by an increase in the blood concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), an NE metabolite [94]. It was long assumed that the peripheral measurement of MHPG reflects similar activity of the CNS NE system; however, further studies have shown that the brain contains about 20% of the peripheral levels of this metabolite [81].

Apart from NET, zinc targets other NE system components, including the α_1 and β_2 receptors, which are expressed in the CNS and which are implicated in the pathophysiology of depression and antidepressant action [95]. The ion interacts with the α_{1A}-adrenoceptor with affinities in the low μM range and acts as a negative allosteric modulator for this receptor [96]. Moreover, it acts as a positive allosteric modulator for NE, which suggests that it may bind to two distinct binding sites of the α_{1A} [96]. Zinc is also a positive allosteric modulator of agonist binding for the β_2-adrenoreceptor [97, 98].

Zinc administration may affect levels of central NE and/or levels of its metabolites. A 3-day i.p. administration of 5 mg zinc acetate/kg body weight resulted in a significant increase in NE levels in the whole brains of rats, whereas DA levels slightly decreased [99]. Wallwork et al. [100] observed that the NE level increased in the brains of rats fed a zinc-deficient diet for 9-10 days compared with pair-fed or ad libitum-fed control rats, which received the same diet as the zinc-deficient group but were given zinc acetate via their drinking water. When measured by in vivo microdialysis, NE concentration was found to have decreased in the paraventricular nucleus (PVN) of the hypothalamus of rats fed the zinc-deficient diet for 2 weeks compared with rats fed the zinc-adequate diet [101]. Moreover, decreased concentrations of NE and its metabolite 3,4-dihydroxyphenylglycol (DHPG) were found in the PVN of rats subjected to a 2-week zinc-deficient diet, and this was associated with increased NE activity measured as a higher ratio of DHPG to NE [102]. These data indicate that dietary zinc deficiency may also affect central NE levels. Furthermore, prenatal exposure to zinc oxide nanoparticles was found to increase the level of normetanephrine, another NE metabolite, in the hippocampus of mouse offspring, as well as to decrease the MHPG level in the hypothalamus and cerebellum; however, it did not affect the NE level in any of the brain regions examined [103].

4.2. Interactions between Zinc and Antidepressants Targeting the Noradrenergic System. Zinc was found to be active in a number of preclinical tests (e.g., FST, TST) and models of depression [9–13, 15]. Low, ineffective doses of zinc administered together with low, ineffective doses of imipramine were active in the FST [104] and the TST [13]. However, the combined treatment of subeffective doses of zinc and reboxetine did not result in a significantly reduced immobility time in the FST [52]. Moreover, an increase in the swimming parameter but not in the climbing parameter in the FST was observed following zinc administration [52]. It is suggested that in the FST the swimming parameter is connected with serotonergic neurotransmission, and the climbing parameter is linked to noradrenergic neurotransmission [63]. Therefore, the above-mentioned results suggest that the noradrenergic system is not involved in the antidepressant-like activity of zinc. However, this may be a phenomenon observed only in the FST, as combined treatment, involving the administration of subeffective doses of zinc chloride together with subeffective doses of desipramine, a TCA with better selectivity for NE reuptake, induced a significant reduction in immobility time in the TST [13].

Zinc deficiency induces depression-like behavior [21, 22, 24, 25, 27]. Animals subjected to a zinc-deficient diet and treated with an acute injection of imipramine or reboxetine displayed increased immobility time in the FST compared with animals treated with a zinc-adequate diet and the respective antidepressant [65]. Also, increased immobility time was observed in mice fed a zinc-deficient diet after chronic reboxetine administration, compared with mice fed a zinc-adequate diet and treated with the antidepressant drug, whereas chronic imipramine treatment in mice subjected to either a zinc-deficient or a zinc-adequate diet resulted in no significant differences in immobility time between the groups [65]. These results indicate that zinc deficiency alters responsiveness to antidepressants targeting the NE system.

The zinc-sensing GPR39 receptor is involved in the pathophysiology of depression and antidepressant action [32]. Chronic treatment with reboxetine but not with imipramine induced upregulation of the GPR39 protein in the frontal cortex of mice [69]. GPR-39 knockout mice display depressive-like behavior [33]. While imipramine and reboxetine reduced immobility time in the FST in wild-type (WT) mice, they were inactive in this test in GPR39 knockout mice, suggesting that the GPR39 receptor is required for the antidepressant effect of antidepressants targeting the noradrenergic system [71]. Moreover, administration of α-methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in NE synthesis, which causes inhibition of NE and DA synthesis, induced upregulation of the GPR39 protein level in the frontal cortex after a 3-day administration and downregulation of this receptor in the hippocampus after a 10-day administration [55], indicating a possible role of the GPR39 receptor in NE transmission.

The first communication suggesting a beneficial effect of zinc supplementation in clinical depression showed that patients receiving TCAs (clomipramine, amitriptyline) together with zinc displayed significantly reduced depression scores compared with patients receiving TCAs and placebo [6]. Furthermore, a randomized, double-blind, placebo-controlled study showed that zinc supplementation augments the efficacy of imipramine in treatment-resistant patients [18]. Whereas zinc supplementation of therapy with SSRIs was found to be beneficial in depressed patients [7], so far no study has examined the effects of the joint administration of zinc and an antidepressant selectively blocking NE reuptake.

4.3. Effects on Zinc Levels of Antidepressants Targeting the Noradrenergic System. Repeated treatment with imipramine

slightly increases the zinc level in the hippocampus and slightly decreases it in the cortex, the cerebellum, and the basal forebrain, but it does not affect the serum zinc level [73]. No significant differences were observed in the serum zinc level between mice that received a zinc-deficient diet and chronic imipramine or reboxetine treatment and mice that received a zinc-adequate diet and the respective drug treatment, while the level of the stress hormone, corticosterone, was increased in the serum of the zinc-deficient mice [65]. A clinical study in which zinc supplemented imipramine therapy found a significantly lower serum zinc level in depressed patients than in healthy volunteers. All groups demonstrated a gradual increase in zinc concentrations over the period of imipramine treatment with or without zinc supplementation. It is of note that treatment-resistant patients demonstrated lower concentrations of zinc than patients who were not resistant to treatment. Importantly, over the course of 12 weeks of imipramine treatment, a significant negative correlation was demonstrated between the Montgomery-Åsberg Depression Rating Scale and the serum zinc level, together with a concomitant increase in serum zinc in patients in remission [75]. So far no study has examined the effects of antidepressants that selectively block NE reuptake on serum zinc level in a clinical setting.

5. Dopamine (DA)

Dopamine (DA), another catecholaminergic neurotransmitter, has initially received less attention in relation to the original monoamine hypothesis of depression; however, in the 1970s its role was postulated [105].

In the brain, most DA-synthesizing neurons are located in the brainstem nuclei: the substantia nigra and the ventral tegmental area (VTA). VTA neurons project to the cortex via the mesocortical pathway, and to the nucleus accumbens, the hippocampus and the amygdala via the mesolimbic pathway. Projections from the substantia nigra to the dorsal striatum constitute the nigrostriatal pathway. The other pathway is the tuberoinfundibular pathway, which regulates prolactin secretion [106]. DA pathways are involved in various CNS functions, such as memory, learning, attention, movement, reward, and affect [106].

DA is synthesized from the amino acid tyrosine and is a precursor for NE. Tyrosine hydroxylase converts tyrosine into DOPA, whereas DOPA decarboxylase converts DOPA into DA. After synthesis, which occurs in the cytoplasm, DA is transported into the synaptic vesicles by VMAT2. DA is cleared from the extracellular space by DAT, which, like NET and SERT, belongs to the neurotransmitter/sodium symporter family and is inactivated by COMT and MAO. The prefrontal cortex possesses a few DATs, and DA is terminated in this region by NET [106, 107]. DA exerts its action via G protein-coupled D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) receptors, which are widely expressed in the brain [107]. Pharmacological agents targeting DA system components are largely used in the treatment of psychiatric and neurological diseases (e.g., schizophrenia, bipolar disorder, depression, Parkinson's disease, attention deficit hyperactivity disorder). Bupropion, which belongs to the NDRIs, is among the antidepressants targeting DAT [108]. Unlike SSRIs, it has a very low rate of sexual dysfunction being experienced as a side effect [108]. Sertraline is among the SSRIs which inhibit DAT [109]; however, it remains controversial whether this action is clinically relevant. Nevertheless, adding bupropion to SSRI therapy is effective as an augmentation strategy [108], and adding bupropion to sertraline treatment is also effective, probably because of the combination of the weak DAT properties of both. It should be noted that drugs inhibiting NET cause an increase in the DA level in the prefrontal cortex. Additionally, chronic administration of antidepressants induces adaptive changes to DA receptors (D_1-downregulation [110] and D_2-upregulation [111]), and DA receptors are involved in the antidepressant-like effect of different compounds [95].

5.1. Zinc Interactions with the Dopaminergic System. The binding of zinc to DAT is long established. Extracellular zinc binds to DAT and restricts the transporter's movement through the conformational cycle, resulting in a decrease in substrate uptake. Two major coordinating histidine residues (H193 in the large second extracellular loop (ECL2) and H375 in the fourth extracellular loop (ECL4)) in the zinc-binding site of DAT were identified [93]. Next, it was shown that the zinc-binding site of DAT consists not only of H193 and H375 but also of E396 and D206 [112]. Extracellular zinc is a potent inhibitor of DAT in cells expressing human DAT [93] and in synaptosomes [113] with an IC50 in the low μM range. Considering that after depolarization the concentration of zinc in the synaptic cleft is estimated to be between sub-μM and 100 μM [40], zinc action on DAT seems to be physiologically relevant. Also, zinc modulates the dopaminergic receptors. The ion was reported to allosterically inhibit the binding of subtype-specific antagonists of the D_{1A} and D_{2L} receptors [114]. The binding of the selective antagonists to the respective receptors was reduced in the presence of μM zinc concentrations [114]. Moreover, it was shown that zinc inhibits the binding of the selective antagonist (spiperone analogue: [^{3}H]methylspiperone) to D_2-like receptors. Zinc inhibition of antagonist binding to the D_4 receptor was found to be noncompetitive, whereas in the case of D_{2L} and D_3 it was found to be a competitive allosterism [115]. Zinc was shown to modulate antagonistic binding to the entire D_2-like subfamily with concentrations in the low μM range [115]. Furthermore, it was found that zinc binding to H394 and H399 on the dopamine D_2 receptor contributes to the allosteric regulation of antagonist binding [116].

An increased DA level in the hippocampus of mouse offspring following prenatal exposure to zinc oxide nanoparticles was observed [103]. This change was associated with increased levels of DA metabolites: homovanillic acid in the prefrontal cortex and in the hippocampus, as well as 3,4-dihydroxyphenylacetic acid (DOPAC) in the prefrontal cortex [103]. Prenatal exposure to zinc oxide nanoparticles also increased DA turnover in the prefrontal cortex, the neostriatum, the nucleus accumbens and the amygdala [103]. There were no changes in DA, DOPAC, or DOPAC-to-DA ratios in the PVN of rats subjected to administration of a zinc-deficient diet [102].

5.2. Interactions between Zinc and Antidepressants Targeting the Dopaminergic System. The joint administration of low, ineffective doses of bupropion and low, ineffective doses of zinc produced a significant decrease in immobility time in the TST, which suggests the involvement of dopaminergic neurotransmission in the antidepressant-like activity of zinc [13, 52]. Animals subjected to a zinc-deficient diet and treated with an acute injection of bupropion showed increased immobility time in the FST compared with animals treated with a zinc-adequate diet and the drug [65]. In addition, increased immobility time was observed in mice fed a zinc-deficient diet after chronic bupropion administration, compared with mice fed a zinc-adequate diet and given the antidepressant [65]. These behavioral changes were associated with increased serum corticosterone concentrations [65]. In animals chronically administered with bupropion, the serum zinc concentrations did not differ between those that received zinc-deficient diets and those that received zinc-adequate diets [65].

To date, no clinical study has examined the effects of the joint administration of zinc and antidepressants targeting DA reuptake or the effects of administration of antidepressants with this mechanism of action on serum zinc levels.

6. Link to Neural Plasticity

In 1998, after the pioneering work of Altman [117], followed by the studies of Kaplan and Hinds [118], contrary to the earlier dogma which stated that the adult nervous system does not produce new neurons, Eriksson et al. [119] demonstrated the occurrence of neurogenesis in the dentate gyrus of the hippocampus of adult humans. The discovery had a great impact on the way of thinking about the human brain and diseases. Preclinical and clinical studies have suggested that the pathophysiology of depression is associated with the inability of neuronal systems to exhibit appropriate plasticity [120]. It was shown that psychosocial stress causes atrophy of CA3 pyramidal cells in the hippocampus [121] and decreases neurogenesis in the dentate gyrus of adult animals [122]. It was postulated that these damaging effects of stress could contribute to the reduced volume of the hippocampus observed in depressed patients [123]. The initial report on the effect of antidepressants on hippocampal neurogenesis in the adult rats has contributed to the neural plasticity theory of depression and antidepressant action [124]. The antidepressants tested in the first series of studies aimed to examine their effects on the production of neurons in the adult rat brain included a MAO inhibitor: tranylcypromine, an SSRI: fluoxetine, and an NRI: reboxetine, as well as electroconvulsive seizures. It was shown that chronic antidepressant treatment (14–21 days in case of the above-mentioned drugs, 10 days in case of electroconvulsive seizures) significantly increased the number of cells positive for bromodeoxyuridine (BrdU), the thymidine analogue that labels DNA during the S-phase, in the dentate gyrus of the hippocampus [124], one of a few brain regions where production of neurons occurs throughout the lifetime [119]. In contrast, administration of fluoxetine for 1 or 5 days did not significantly affect the number of BrdU-positive cells [124], consistent with the finding that antidepressants require weeks to produce therapeutic effect. Angiogenesis is a process coupled to neurogenesis. It was shown that SSRIs increased human hippocampal progenitor cells and angiogenesis selectively in the anterior and central dentate gyrus suggesting angiogenesis as a therapeutic strategy [125]. Also newer compounds, like a multimodal agent vortioxetine, after chronic treatment were shown to increase dendritic length and the number of dendrite intersections as well as to increase cell proliferation, cell survival and stimulate maturation of immature granule cells in the subgranular zone of the dentate gyrus [126]. Moreover, vortioxetine [127] but also other generations of antidepressants like SSRIs (escitalopram) [128] or SNRIs (milnacipran) [129] were found to prevent the effects of stress on hippocampal long term potentiation (LTP), one of the phenomena underlying synaptic plasticity [130]. In the next paragraph we will discuss the role of zinc in the processes related to neural plasticity and then possible interactions between zinc and monoamine-based antidepressants in the context of neural plasticity.

6.1. Zinc and Neural Plasticity. Adult male rats fed with a zinc-deficient (1 mg zinc/kg) diet for 3 weeks had ca. 50% fewer stem cells positive for Ki67, a marker for proliferation (which is expressed in cells that are in all active phases of the cell cycle but not expressed in G0 phase), in the subgranular zone and granular cell layer of the dentate gyrus [131], suggesting that zinc is required for neuronal precursor cell proliferation. When cultured human Ntera-2 (NT2) neuronal precursor cells were deprived of zinc using the chelator N,N,N,N-tetrakis(2-pyridylmethyl)ethylenediamine (TPEN), a significant decrease in cellular proliferation, as measured by BrdU uptake was observed [131]. When rats were fed a zinc-deficient (2.7 mg zinc/kg) diet for 6 weeks, a decrease in the number of progenitor cells and immature neurons was observed in the dentate gyrus. The number of progenitor cells and immature neurons was restored after a 2-week reversal to a zinc-adequate (44 mg zinc/kg) diet. Moreover, a 1-week treatment with the zinc chelator, clioquinol, decreased zinc staining in the hippocampus and reduced the number of progenitor cells. Furthermore, zinc chelation reduced hypoglycemia-induced progenitor cell proliferation and neurogenesis [132]. Additionally, ZnT-3 knockout mice, which lack vesicular zinc [133], had significantly fewer proliferating progenitor cells and immature neurons after hypoglycemia [132]. Also, mice fed a zinc-deficient (0.85 mg zinc/kg) diet for 5 weeks displayed reduced vesicular zinc in CA1 and CA3 regions of the hippocampus, which was associated with a reduction in proliferating cells labeled with BrdU and immature neurons labeled with doublecortin (DCX) immunoreactivity in the dentate gyrus. The processes of DCX-positive neurons were shortened and flexuously went through into the granular cell layer in the zinc-deficient hippocampus, suggesting that zinc deficiency, in addition to stem cell proliferation, impairs neuronal differentiation [134]. These converging data provide evidence for the important role of zinc in hippocampal neurogenesis. Zinc was also found to participate in the regulation of angiogenesis, a process which accompanies neurogenesis, through effects on pro- and antiangiogenic factors [135]. In NT2 cells deprived

of zinc an increase in caspase 3/7-dependent apoptosis was observed, which was associated with a nuclear translocation of the tumor suppressor protein p53, a transcription factor involved in the regulation of cell cycle and apoptosis. The examination of p53 downstream target genes in zinc-deficient NT2 cells revealed the induction of a variety of proapoptotic genes in the initial phase of zinc restriction (6 h after TPEN treatment), like reprimo gene, which induces G2 cell cycle arrest, and, in the latter phase (18 h after TPEN treatment), the induction of proapoptotic genes such as transforming growth factor-β (TGF-β) and retinoblastoma-1 (Rb-1), as well as cellular protection genes such as glutathione peroxidase (GPx), suggesting that prolonged restriction of zinc induces mechanisms for cellular protection [131]. The apoptosis proteins, including Fas, Fas ligand (FasL), apoptosis inducing factor (AIF), and caspase-3, were significantly activated in zinc-deficient mouse hippocampus [134]. These data show that zinc deficiency induces neuronal apoptosis. Studies with human induced pluripotent stem (iPS) cells differentiated into motor neurons demonstrated that expression of zinc homeostasis regulating genes, from the zinc transporters (ZnTs) family and metallothioneins (MTs), is regulated at various stages of differentiation, that is, at stages of iPS cells, embryoid bodies, neural rosettes, neuronal stem cells and motor neurons. When iPS cells were differentiated using zinc-deficient medium the number of neuronal stem cells clusters was reduced. In this study, at this stage no differences in markers for apoptosis were observed, but increase in the number of cells undergoing apoptosis was observed at the stage of embryoid bodies. Importantly, under zinc deficiency conditions electrophysiological recording revealed a reduction of glutamate, both AMPAR and NMDAR currents, and a reduction in the total number of cells responding to glutamate stimulation [136]. Taken together, the data show that zinc may have an impact not only on neurogenesis, but also on synaptogenesis. Zinc is necessary for the structural integrity of the postsynaptic density (PSD), a specialized electron dense region of the postsynaptic membrane of excitatory synapses. The ion was found to influence the recruitment of ProSAP/Shank proteins, which are observed at PSD early during synaptogenesis, to PSD during the course of synaptogenesis and synapse maturation [137]. It was shown that the overexpression of zinc-sensitive ProSAP1/Shank2 or ProSAP2/Shank3 increases synapse density, whereas depletion of synaptic zinc along with the knockdown of zinc-insensitive Shank1 causes the rapid disintegration of PSD and the loss of several postsynaptic molecules including NMDARs [137].

NMDARs and AMPARs, which are well known to mediate synaptic plasticity, are among targets for zinc released from glutamatergic vesicles. NMDAR functions as a heteromeric complex composed of four subunits surrounding a central cation-selective pore. Three major subtypes of NMDAR subunits have been identified: GluN1, GluN2A-D, and GluN3A-B [138]. The most widely expressed NMDAR is composed of two glycine binding GluN1 subunits and two glutamate-binding GluN2 subunits (GluN2B or GluN2A or a mixture of the two). Zinc inhibits NMDAR and two different mechanisms of action were described: a voltage-independent, noncompetitive (allosteric) inhibition, responsible for reducing channel-opening frequency, and voltage-dependent inhibition, representing an open channel blocking effect of zinc [36, 139]. The comparison of GluN1/GluN2A and GluN1/GluN2B receptors showed that the voltage-dependent inhibition is similar in both types of receptors but the voltage-independent zinc inhibition is subunit-specific, with an affinity ranging from low nM for GluN1/GluN2A receptors to about 1 μM for GluN1/GluN2B receptors and $\geq$10 μM for GluN1/GluN2C and GluN1/GluN2D receptors [36]. Recent study using GluN2A-H128S knockin mice, in which the high-affinity (nM) zinc inhibition of NMDAR is specifically eliminated, indicated that under resting conditions zinc levels are too low for tonic inhibition of GluN2A at hippocampal mossy fiber synapses, the most zinc enriched synapses in the brain, which is in contrast to the earlier belief that zinc levels are high enough to tonically occupy the nM zinc sites. The study showed that following neuronal activity zinc increases transiently in the synaptic cleft, where it has a short lifetime (<2 ms at Schaffer collateral-CA1 synapse; <30–40 ms at mossy fiber-CA3 synapses) and reaches concentrations sufficient to occupy the high-affinity (nM), but not the low affinity (μM), zinc sites on postsynaptic receptors [140]. It should be noted, however, that the concentration of zinc reached in the synaptic cleft has long been a matter of debate and has been estimated to range from sub-μM to over 100 μM according to different groups [40, 140]. Moreover, it is plausible that pathological conditions associated with intense neuronal activity will affect its concentration. Zinc was also found to modulate another subtype of ionotropic glutamatergic receptors—AMPARs. These receptors are composed of four types of subunits: GluA1, GluA2, GluA3 and GluA4 [141]. GluA2-lacking-AMPAR are permeable for Ca^{2+}, which has an important consequences for neural plasticity [142, 143]. At lower concentrations ($\approx$30 μM) zinc potentiates AMPAR-induced currents, but at higher (mM) concentrations it inhibits them [144].

Stimulation of NMDAR as well as stimulation of GluA2-lacking-AMPAR results in the Ca^{2+} influx and induction of intracellular signaling pathways including: Ca^{2+}-calmodulin-dependent protein kinase (CaMK), cAMP response element binding protein (CREB), BDNF and its receptor, tropomyosin-related kinase B (TrkB) [145]. BDNF binding to TrkB induces receptor dimerization and triggers its intrinsic tyrosine kinase activity, which results in activation of signaling cascades that lead to enhanced neuronal survival and differentiation. BDNF signaling via the TrkB receptor divides into three pathways, all of which converge on CREB, which in turn upregulates gene expression. These pathways include Ras-microtubule-associated protein kinase (MAPK)/extracellular signal regulated kinase (ERK) pathway; phosphatidyl inositol-3 kinase (PI3K)/Akt kinase pathway; and phospholipase C- (PLC-) γ/CaMK or protein kinase C (PKC) pathway [145]. Exposure to μM zinc concentrations was found to transactivate TrkB in cultured cortical neurons [146]. The same group, using brain sections isolated from ZnT-3 knockout mice, surprisingly found increased immunoreactivity for activated TrkB in axons but not synaptic boutons of hippocampal mossy fibers, which suggested that vesicular zinc does not activate TrkB in hippocampal

mossy fiber axons under physiological conditions [147]. However, the latter study does not contradict the previous one, because under different conditions zinc concentrations may vary and therefore trigger different effects. Mice fed with a zinc-deficient diet (0.85 mg zinc/kg) for 5 weeks have decreased protein levels of calmodulin and phosphorylated CaMKII and CREB in the hippocampus, which was associated with learning and memory impairments in the Morris water maze [148]. In turn, exposure to μM zinc concentrations was found to activate MAPK and ERK1/2 in rat cultured neurons [149] and an increase in ERK1/2 phosphorylation was observed after chronic treatment with zinc [150]. Also activation of GPR39 receptor was found to induce signaling pathways involved in neural plasticity [32]. GPR39 signals through $G\alpha_s$, $G\alpha_q$ and $G\alpha_{12/13}$ proteins and displays high constitutive activity via $G\alpha_q$ and $G\alpha_{12/13}$ but not via $G\alpha_s$ pathway [151]. Downstream kinases of $G\alpha_s$ (protein kinase A (PKA)) and $G\alpha_q$ (CaMK, MAPK) activates CREB, whereas $G\alpha_{12/13}$ stimulates SRE-mediated transcription [8]. Application of μM zinc concentrations to hippocampal slices induced phosphorylation of ERK1/2 and CaMKII. Application of the Gαq inhibitor reduced the zinc-dependent phosphorylation of ERK1/2 and CaMKII, suggesting that activation of Gαq pathway is necessary for the zinc-dependent phosphorylation of these kinases in CA3 region of the hippocampus [152].

The above-mentioned data, although not exhaustive, point to the role of zinc in neuro- and synaptogenesis as well as to the relationship between zinc and signaling pathways critical for neural plasticity. Importantly, elements of these signaling pathways were found to participate in the antidepressant-like activity of zinc and/or were affected by the condition of zinc deficiency which concomitantly induced depressive-like behavior [153].

6.2. Zinc, Monoamine-Based Antidepressants, and Neural Plasticity: Possible Interactions. As it was shown in the STAR*D study the average time required to achieve remission is 6-7 weeks [4]. A delayed onset of action of conventional antidepressants and time needed to achieve response/remission are among the main reasons underlying the need for novel antidepressant treatments. Evidence indicates that neural adaptations are involved in the mechanism of action of conventional antidepressants after chronic administration [154]. In contrast, a single infusion of subanaesthetic doses of the NMDAR antagonist ketamine exerts rapid and sustained antidepressant effects in patients with treatment-resistant depression [155]. Ketamine is NMDAR channel blocker, which enters the open channel in an activity-dependent manner and binds with low μM affinity. After channel closure, ketamine can become blocked within the pore, therefore, belongs to "trapping blockers", whose block is slow to reverse [156]. As we have already mentioned, zinc, depending on its concentration, can bind to the subunits of the NMDAR or block the channel. Allosteric inhibition of NMDAR by zinc was found to be highly subunit-specific with an affinity ranging from low nM for GluN1/GluN2A receptors to about 1 μM for GluN1/GluN2B receptors and $\geq$10 μM for GluN1/GluN2C and GluN1/GluN2D receptors [36]. NMDAR open channel block by zinc was described when the concentrations of the ion were between 20 and 100 μM [156]. It was found that a low dose of ketamine, which produces antidepressant-like effect in behavioral paradigms [157], rapidly and transiently activated the mammalian target of rapamycin (mTOR) signaling pathway, leading to enhanced and sustained elevation of synaptic proteins expression (e.g., postsynaptic density protein 95 (PSD95), synapsin I or GluA1) and an increased number and function of new synapses in the prefrontal cortex of rats [158]. In contrast, antidepressants such as imipramine or fluoxetine or electroconvulsive seizures did not significantly influence mTOR signaling [158]. Recent study demonstrated that a single dose of zinc (5 mg/kg) administered 30 minutes prior to the FST produced antidepressant-like effect, which lasted up to 3 h [159]. Unlike ketamine, zinc did not produce a sustained antidepressant-like effect [159]; however, in contrast to conventional antidepressants (imipramine, fluoxetine) or electroconvulsive seizures [158], it induced a transient (observed 30 min and 3 h after the treatment) increase in the protein levels of phosphorylated mTOR and ribosomal protein S6 kinase (p70S6K). An elevated level of GluA1 and synapsin I was still observed 24 h after the zinc treatment. In addition, antidepressant-like effect of zinc in the FST was blocked by pretreatment with rapamycin, mTOR inhibitor [159], which suggest that mTOR is involved in the antidepressant-like action of zinc. Also, blockade of mTOR signaling blocked ketamine behavioral effects and induction of synaptogenesis [158]. Although further studies are needed, it is plausible that the beneficial effects of zinc as an augmentation strategy in conjunction with imipramine [18] or fluoxetine [7], that have been observed in clinical trials, result from adding zinc effects on mTOR to the effects of the above-mentioned drugs, which lack these action (Figure 1). Moreover, the activation of glycogen synthase kinase-3 (GSK-3) leads to inhibition of mTOR pathway [160]. Zinc was found to inhibit GSK-3 [161]. Zinc administered in combination with AR-A014418, GSK-3β inhibitor, produced synergistic effects in the FST [162], suggesting that the antidepressant-like effect of zinc depends on GSK-3, which further supports the link between zinc and mTOR with regard to depressive disorders.

Fast-acting behavioral antidepressant-like effect of ketamine depends also on the rapid synthesis of BDNF. Enhanced synthesis of BDNF was observed 30 min [163] or 1 h [164] after ketamine administration. In contrast, conventional antidepressants require weeks to induce an increase in BDNF protein expression, for example, 2 weeks of treatment with fluoxetine produced region-specific increase in BDNF mRNA, whereas BDNF protein level remained unaltered until 3 weeks of the treatment and reached significance after 3 weeks in CA1 and CA3 but not in other subregions of the hippocampus [165]. There were no changes in the level of BDNF protein in the prefrontal cortex 30 min after zinc treatment [159]. Also, 1 h after zinc administration Manosso et al. did not observe changes in BDNF protein levels in either the prefrontal cortex or hippocampus [162]. However, an increase in the level of BDNF protein in the prefrontal cortex was found 3 h after zinc treatment [159]. Ranjbar et al. [72] observed in patients with major depression that zinc supplementation of the therapy with

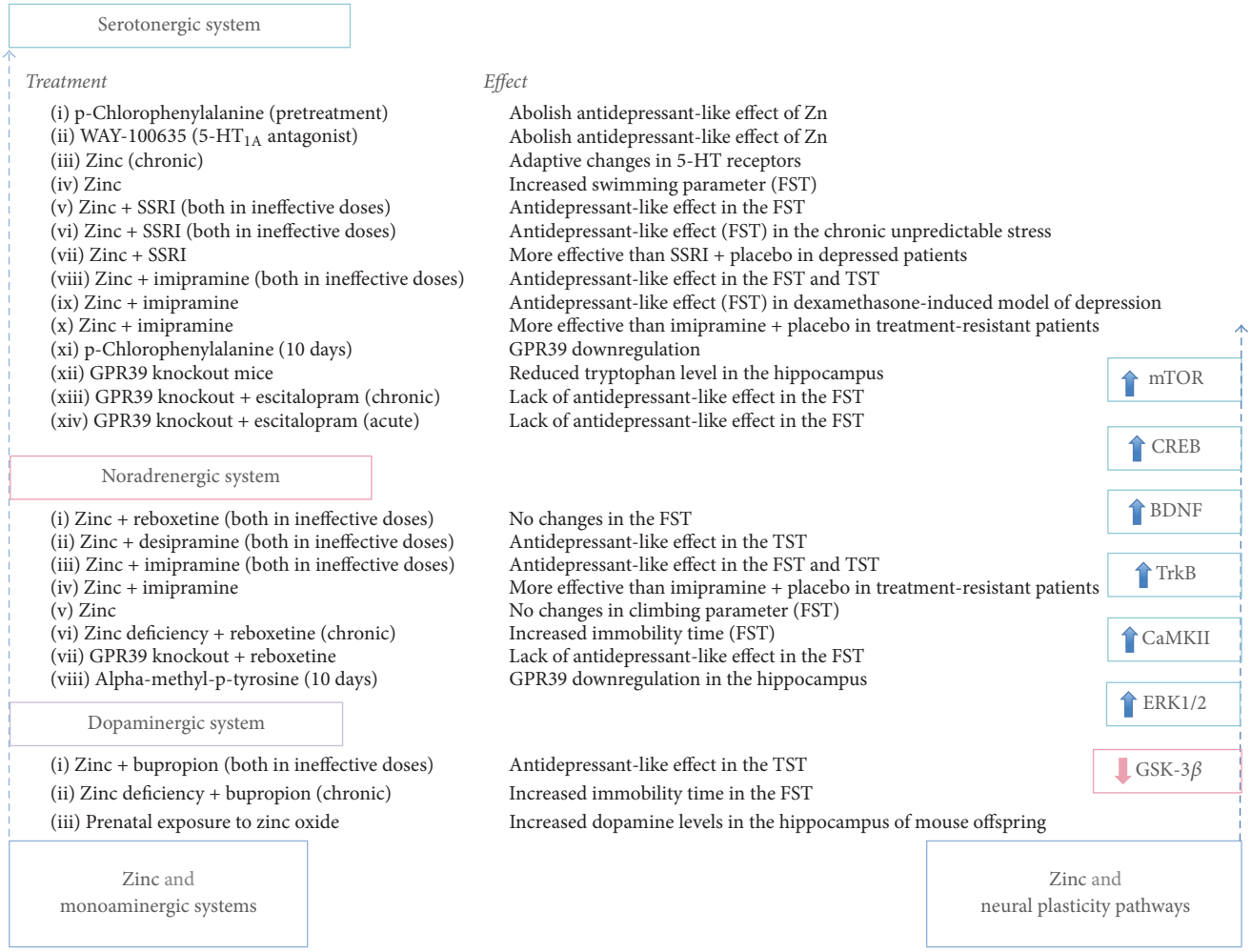

Figure 1: The summary of the findings related to interactions between zinc and monoaminergic systems and neural plasticity pathways.

SSRIs (fluoxetine, citalopram) reduced depressive symptoms more effectively that a respective SSRI and placebo, however, these effects were not associated with alterations in serum BDNF level. In contrast, in the study of Solati et al. [20], who examined zinc treatment as a monotherapy in overweight or obese subjects with depressive symptoms, a significant inverse correlation was observed between serum BDNF levels and depression severity. Is should be stressed that Solati et al. [20] found zinc monotherapy to be effective in reducing depressive symptoms in those subjects. In addition, dietary zinc deficiency [27] and GPR39-knockout induced decreased BDNF protein expression in brain regions (hippocampus, prefrontal cortex) [33], while administration of a GPR39 agonist (TC G-1008), in parallel to antidepressant-like effect, induced upregulation of BDNF protein in the hippocampus [34]. Thus, mTOR and BDNF pathway may be a link between zinc, depression and neural plasticity.

The proposed sequence of events triggered by ketamine in depression involves blocking of NMDAR on gamma-aminobutyric acid- (GABA-) ergic interneurons in the prefrontal cortex, which causes disinhibition and increases glutamate release, which primarily excites AMPAR, leading to activation of BDNF [145]. Ketamine was reported to increase extracellular glutamate in the prefrontal cortex as measured by the in vivo microdialysis [166]. Perfusion of the CA1 regions of the hippocampus by zinc was found to decrease glutamate concentration in the perfusate [167]. Extracellular glutamate concentration was increased in the hippocampus of the zinc-deficient rats [168]. Also our study showed an increase in evoked glutamate release in the prefrontal cortex of the zinc-deficient rats [169]. These studies suggest that zinc, unlike ketamine, inhibits glutamate release.

Three rapid acting antidepressant agents (ketamine, metabotropic glutamate $mGlu_{2/3}$ receptor antagonist LY341495, and NMDAR glycine site agent GLYX-13) were found to rapidly increase the levels of the phosphorylated (activated) forms of ERK and BDNF release in rat primary cortical culture neurons [170], showing that ERK signaling is an important step in antidepressant action. An increase in ERK1/2 phosphorylation was observed after chronic (30 days) treatment with zinc (administered via drinking water that contained 300 mg of zinc chloride/L) and was associated with antidepressant-like effect in the FST. Moreover, it was accompanied by an increase in total glutathione levels in the hippocampus and cerebral cortex [150].

Of note, relationships between altered zinc homeostasis, increased oxidative/inflammatory status, and NMDAR function were implicated in depressive disorders [47, 171]. It was shown that proinflammatory cytokines, such as IL-1β, and reactive oxygen species can enhance the activity of IDO, which catabolizes tryptophan into kynurenine, which is further catabolized into kynurenic acid and quinolinic acid [46]. Because kynurenic acid is an endogenous antagonist, whereas quinolinic acid is a strong agonist of the NMDAR, IDO activation can lead to abnormal function of the NMDAR. Dietary zinc deficiency-induced depression-like behavior with concomitant upregulation of the NMDAR [27] and oxidative as well as inflammatory parameters (IL-1α, IL-1β) were generally enhanced in the tissue (serum, prefrontal cortex, and hippocampus) of the zinc deprived rats [169]. Also the study of GPR39 knockout mice, which display depressive-like behavior, showed immune malfunction: reduced thymus weight, reduced cell viability of splenocytes and reduced proliferative response of splenocytes [172]. Further studies are needed to elucidate changes within the immune system of GPR39 knockout mice as well as effects of antidepressants on zinc deficiency-induced and GPR39-knockout-induced immune alterations, that may be linked to neural plasticity events.

It was shown that 5-HT_{1A} knockout mice were insensitive to the effects of chronic fluoxetine administration in the novelty suppressed feeding test (NSF), which demonstrates changes in behavior in a response to chronic, but not acute antidepressant treatment, but were responsive to imipramine and desipramine. Moreover, when wild-type and 5-HT knockout mice were injected with BrdU, after a 27-day treatment with fluoxetine, imipramine or vehicle, fluoxetine caused a doubling of BrdU-labeled cells in the dentate gyrus of the hippocampus in wild-type mice but had no effect in 5-HT knockout mice. These results indicate that 5-HT_{1A} receptors are required for fluoxetine-induced neurogenesis [173]. As it was discussed earlier, 5-HT_{1A} receptors are involved in the antidepressant-like activity of zinc. This observation may provide another route linking zinc and depression with regard to neural plasticity.

6.3. Future Perspectives. As it has been discussed, zinc is able to enhance the effects of conventional, that is, monoamine-based, antidepressants, not only in preclinical paradigms, but also in clinical setting. Studies conducted so far point to the positive effects of zinc supplementation to the therapy with SSRIs or TCAs. More clinical studies are needed that will elucidate the possibility of augmentation with zinc a therapy involving antidepressants with different mechanisms of action (e.g., SNRIs, NRIs, or NDRIs). Given the involvement of zinc in processes related to neural plasticity, it is plausible that the beneficial effects of zinc in depressed patients result from activation of signaling pathways associated with neural plasticity events.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

Acknowledgments

This study was supported by a grant from the Polish Ministry of Science and Higher Education "Iuventus Plus" program for the period 17.03.2015–16.03.2017 (Project no. 0314/IP1/2015/73), by a grant from the National Science Centre (2015/19/B/NZ7/00255), and by the statutory funds of the Faculty of Pharmacy, Jagiellonian University Medical College.

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Hindawi
Neural Plasticity
Volume 2017, Article ID 6871089, 11 pages
https://doi.org/10.1155/2017/6871089

Review Article

The Role of Neural Plasticity in Depression: From Hippocampus to Prefrontal Cortex

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Received 3 November 2016; Accepted 4 January 2017; Published 26 January 2017

Academic Editor: Aijun Li

Neural plasticity, a fundamental mechanism of neuronal adaptation, is disrupted in depression. The changes in neural plasticity induced by stress and other negative stimuli play a significant role in the onset and development of depression. Antidepressant treatments have also been found to exert their antidepressant effects through regulatory effects on neural plasticity. However, the detailed mechanisms of neural plasticity in depression still remain unclear. Therefore, in this review, we summarize the recent literature to elaborate the possible mechanistic role of neural plasticity in depression. Taken together, these findings may pave the way for future progress in neural plasticity studies.

1. Introduction

The establishment and realization of neural functions are based on generation, transformation, and storage of information in neural networks. The brain is developing and progressing at high speed in the six- to nineteen-year-old age group, and the unique plasticity of neural development is crucial to mature neural function. In a neural network, neurons are the fundamental functional units that integrate and transmit signals in response to intrinsic and extrinsic information [1]. Neuronal functions are dynamic processes that occur in response to environmental stimuli, emotions, injury, and so forth. This is the theoretical basis of neural plasticity, which is an umbrella term to describe structural and functional changes in the brain in response to various stimuli, including stress and depression. Depression is a prevalent, chronic, and recurrent disease. Depression, one of most devastating diseases, has a worldwide lifetime prevalence of 20%. Moreover, to patients with depression, depression not only brings profound mental agony but also causes pathophysiological disorders and enhances susceptibility to some diseases, for instance, cardiac diseases and cerebrovascular illness [2]. Therefore, patients with depression suffer from higher mortality than the healthy population. Unfortunately, to date, no completely effective treatments for depressed patients have been developed. Currently available antidepressant treatments, whether medications, psychotherapies, or other methods, have limited efficacy in depression and can cause significant side effects [2]. Hence, it is profoundly significant to explore the pathophysiology of depression. Though a large number of studies on the correlation between depression and neural plasticity have revealed some of their mechanisms, the neurobiological mechanisms of depression are still not well known. Negative stimuli, such as stress, pain, and cognitive impairment, can result in both depression and changes in neural plasticity. The neuroplasticity hypothesis of major depressive disorder proposes the theory that dysfunction of neural plasticity is a basic pathomechanism of the disorder [3]. However, depression is not an inexorable outcome of dysfunction of neural plasticity. To our knowledge, there are no authoritative research results or expert consensus to confirm whether depression or changes

in neural plasticity are the initial factor. Most of the studies suggest that depression and dysfunction of neural plasticity act on and influence each other. In this perspective, we review the recent literature to elaborate what is known about neural plasticity in depression to pave the way for ongoing and future studies.

2. Hippocampal Plasticity in Depression

The hippocampus is the most commonly studied brain region in depression research. From a structural point of view, the hippocampus is part of the limbic system and develops nerve fiber connectivity with emotion-related brain regions, for instance, the prefrontal cortex and amygdala. In addition, the hippocampus contains high levels of glucocorticoid receptors and glutamate and regulates the hypothalamus-pituitary-adrenal (HPA) axis, which makes it more susceptible to stress and depression. Changes in hippocampal plasticity can result from stress and other negative stimuli. Stress impacts hippocampal plasticity in many ways. Chronic and severe stress has been shown to impair hippocampus-dependent explicit memory in animal models of depression [4]. This effect can be explained by changes in hippocampal synaptic plasticity modeled by long-term potentiation (LTP) and long-term depression (LTD). Hippocampal synaptic plasticity is widely considered to play an important role in hippocampus-dependent explicit memory formation [5]. Severe stress can impair LTP and enhance LTD in the hippocampi of rodent models [6, 7]. Stress can also decrease neuronal dendrite branching and plasticity in the hippocampus [8]. In addition, stress can trigger activation of the hypothalamic-pituitary-adrenal axis, increase level of corticosteroids, and downregulate hippocampal neurogenesis [9]. Cognitive impairment can enhance long-term potentiation in the CA1 region and markedly elevate protein levels of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluA1 in the mouse hippocampus and then induce depression in mouse models [10]. In addition, neuropathic pain-induced depressive-like behavior may be associated with hippocampal neurogenesis and plasticity through tumor necrosis factor receptor 1 signaling [11]. Hippocampal plasticity in depression involves hippocampal volumetric changes, hippocampal neurogenesis, and apoptosis of hippocampal neurons.

2.1. Synaptic Plasticity in the Hippocampus. Synaptic plasticity is one of the most fundamental and important functions of the brain. The efficacy of transmission at a synapse depends on modulation of the connectivity between neurons and neuronal circuits during adaptation to the environment [12]. Stress has profound effects on synaptic plasticity in the hippocampus and presents different influences in different subfields of the hippocampus. Stress can impair LTP in CA3 while facilitating LTD and spike-timing-dependent LTD (tLTD) in CA1 [12]. In addition, depression can downregulate synaptic proteins and growth factors required for hippocampal LTP in animal models.

Electroacupuncture can alleviate depression-like behaviors and reverse the impairment induced by long-term potentiation in the CA1 synapses of the hippocampus in depressive rats [13]. Physical exercise may prevent changes in synaptic plasticity and increases in synaptic transmission in hippocampal CA1 pyramidal neurons caused by stress but cannot reverse the present glutamatergic synaptic alterations induced by depression [14]. Glucocorticoid receptor antagonists and monoaminergic antidepressants can protect against negative synaptic plasticity in CA1 induced by stress. TJZL184, a monoacylglycerol lipase inhibitor, exhibited antidepressant effects by enhancing adult neurogenesis and long-term synaptic plasticity in the dentate gyrus of the hippocampus [15]. *Lycium barbarum* was found to reduce depression-like behavior mediated by enhanced synaptic plasticity in the hippocampus of rats [16].

2.2. Hippocampal Volumetric Changes in Depression. It has been widely reported that there is a significant reduction in hippocampal volume in depression patients [17]. This situation was found in both adult and adolescent depressed patients, whether they were in their first or recurrent depressive episodes. A recent study reported that, in female patients with recurrent familial pure depressive disorder (rFPDD), volumetric reductions of the right hippocampal body and tail were significantly larger than those of the left, while the whole brain volume was approximately equal to that of healthy subjects [18]. Consistent with this, a significant increase in right hemispheric hippocampal gray matter volume has been found in elderly patients with severe depression treated with electroconvulsive therapy [19, 20]. However, hippocampal volumetric reduction was also found in patients who had recovered from depression [17]. The volumetric changes may result from a neurodegenerative reaction to increased glucocorticoid levels in depression [20]. The changes in synaptic plasticity induced by depression are associated with structural and functional changes in the hippocampus. The volume reduction of the prefrontal cortex and hippocampus may also result from the disruption and atrophy of neurons and glia in depression [21, 22]. Nonetheless, the hippocampal volumetric changes are not associated with the severity of depression [18]. Evidence supports that larger hippocampal volumes indicate quicker recovery in depressed individuals [23]. This can be explained by hippocampal regulation in stress reactivity. Reduced hippocampal volumes may be a neural scar marker of depression and a vulnerability marker for future episodes [17]. The clinical application of hippocampal volumetric changes still needs large-sample research to confirm.

2.3. Hippocampal Neurogenesis. Brain neurogenesis lasts from birth to adulthood in many animals, including humans. Hippocampal neurogenesis occurs markedly in the dentate gyrus, with approximately 700 granule cells born daily, corresponding to an annual turnover of 1.75% of the neurons within the renewing fraction [24].

The rate of hippocampal neurogenesis decreases modestly with age. Compared with the millions of granule cells in the granular layer of the hippocampus, newborn neurons are few in number, but they can be sufficient to achieve functional

significance [25]. Though the rates of neuronal regeneration are comparable in middle-aged humans and mice, the patterns of adult hippocampal neurogenesis are significantly different between them. In humans, approximately one-third of hippocampal neurons are subject to exchange. By contrast, the proportion is 10% in mice [26]. The relative decline rate of hippocampal neurogenesis during adulthood in humans is lower than that in mice. In addition, hippocampal neurogenesis in mice is additive, and newborn neurons can compensate for lost cells, while new neurons in humans cannot keep up with the losses [25]. Therefore, hippocampal neurogenesis in humans may have an additive function in the circuitry and enhance synaptic plasticity to achieve maximum impact.

The neurogenic hypothesis of depression emphasizes the theory that impaired adult hippocampal neurogenesis results in depression, and newborn neurons in the adult brain are critical to mood regulation and antidepressant efficacy [27, 28]. Impaired adult hippocampal neurogenesis and depression may be reciprocally causative [29]. High levels of glucocorticoids in depression also hinder adult hippocampal neurogenesis, but adrenalectomy can promote adult hippocampal neurogenesis.

The effects of antidepressant treatments on adult hippocampal neurogenesis have shown discrepancies in different species. In rodents, most antidepressant treatments that are used in humans, including electroconvulsive shock and medication, were subsequently shown to facilitate hippocampal neurogenesis [30–34]. However, the facilitation of fluoxetine treatment was sensitive to stress, corticosterone levels, and route of medication [29]. The effects of fluoxetine treatment on non-human primates are similar to those in rodents. In addition, electroconvulsive shock can also boost hippocampal neurogenesis in non-human primates [35]. There is a lack of research data to illustrate the effects of medication on non-human primates. In humans, total dentate granule cell number and dentate gyrus size in medicated patients with depression are larger than those in nonmedicated patients based on postmortem studies [36]. Selective serotonin reuptake inhibitors, lithium treatment, and electroconvulsive shock produce larger increases in hippocampus volume in treated depressed patients than in nontreated patients [37, 38]. In line with this observation, research evidence from the hippocampal subfields has revealed larger dentate gyri in medicated depressed patients [39]. These data are relevant to multiple forms of neural plasticity and suggest an increase in hippocampal neurogenesis. Nevertheless, there is no adequate evidence to establish that hippocampal neurogenesis is necessary for antidepressant efficacy, and its increase is sufficient for antidepressive therapy.

2.4. Hippocampal Apoptosis in Depression. Proliferation, differentiation, and apoptosis are continuous progressions in adult hippocampal neurons. Many studies have demonstrated that depression and stress can induce hippocampal apoptosis in rodents, non-human mammals, and humans, though hippocampal apoptosis can also be found in nondepressed rodents [40]. Similarly, hippocampal apoptosis may result in depression. Evidence showed an increase of apoptosis in dentate gyrus of maternal rats with repeated separation of their pups and impairment of memory capability with depression-like behavioral changes [41]. In maternal-separation rat models, tadalafil, a phosphodiesterase type 5 inhibitor, exerts antidepressant effects by suppressing maternal-separation-induced apoptosis and increasing cell proliferation in the dentate gyrus [42]. Though some studies support the idea that hippocampal apoptosis is a causative factor in hippocampal volumetric changes, histopathological studies on depressed patients have yielded inconsistent results [43]. There are differences in the stimulative effects of chronic depression and acute depression on hippocampal apoptosis. In animal models and human studies, chronic depression showed longer lasting apoptosis-promoting effects in the hippocampus than acute depression [40]. The apoptosis-promoting effects induced by acute depression can fully subside in one day of recovery, while the adverse effects in chronic depression may need up to three weeks for recovery. However, it is uncertain in what stage depression and stress start to mediate apoptosis progression. In addition, their effects showed differences among subfields of the hippocampus. Compared with the apoptosis increase in the whole dentate gyrus caused by acute depression, the number of cells in the granular cell layer can increase even as the cell count in the whole dentate gyrus is declining [44]. This discrepancy may be due to the different sensitivities of granular cells to acute and chronic stress.

In addition to tadalafil (mentioned above), several types of drugs may have antidepressant effects owing to hippocampal apoptosis. For instance, venlafaxine, a serotonin/norepinephrine dual reuptake inhibitor, suppresses hippocampal apoptosis by upregulating brain-derived neurotrophic factor [45]. In addition, fluoxetine, a 5-hydroxytryptamine reuptake inhibitor, regulates hippocampal plasticity by alleviating the upregulation of synaptosomal polysialic neural cell adhesion molecule caused by depression and elicits an antiapoptotic response in the hippocampus [46].

3. The Prefrontal Cortex in Depression

The prefrontal cortex (PFC), as a significant nerve center of thinking and behavior regulation in the brain, is also associated with depression [47]. In view of anatomical connectivity and functional specialization, the prefrontal cortex is divided into two subregions: ventromedial prefrontal cortex (vmPFC) and dorsolateral sectors (dlPFC) [48]. VmPFC involves the regulation of affection, including the generation of negative emotion, and dlPFC mediates cognitive functions, such as intention formation, goal-directed action, and attentional control [49]. The two sectors have both been shown to have significant roles in depression. However, their effects present discrepancies, according to reports in the literature. Functional imaging studies have shown opposite changes of activity in the two sectors: during the progression of depression, hyperactivity appeared in the vmPFC, while hypoactivity appeared in dlPFC; in the recovery phase in response to psychotherapy or medication for depression, hypoactivity was found in the vmPFC, while hyperactivity was found in dlPFC [48, 50–53]. Furthermore, in lesion models, dlPFC loss can aggravate depression, whereas vmPFC loss can exhibit an alleviative effect on depression [54, 55]. Dysfunction caused

by dlPFC damage in stroke is considered a predisposing factor to poststroke depression [56]. In addition, a decrease of cortical thickness in the right vmPFC, which occurs in the early stages of neurodevelopment, results in depression in preschoolers [57]. Volume reduction of the prefrontal cortex may result from the disruption and atrophy of neurons and glia in depression, as observed in the hippocampus [21, 22]. Energy and glutathione metabolic pathways in the prefrontal cortex were shown to be significant biological pathways in depressive rats [58]. Many studies have indicated that changes in glutamate metabolism were associated with depression [59–67]. In a stress-induced depressive mouse model, the prefrontal cortex in depression showed a significant reduction of glutamate in the GABAergic pathway, which may contribute to depression [62]. Activation of metabotropic glutamate receptor 3, which plays a significant role in regulating the function and cognition of the prefrontal cortex, can result in long-term depression in the medial prefrontal cortex of rats in vitro [68]. The GRIN2A gene, which encodes the glutamatergic N-methyl-D-aspartate (NMDA) receptor subunit epsilon-1 in the prefrontal cortex, is probably disturbed in the regulation of synaptic plasticity in depression [69].

In addition, a novel miRNA (miR-101b) was found to be downregulated in depression and could decrease mRNA and protein levels of glutamate transporter SLC1A1 in the prefrontal cortex [59]. In addition, in the medial prefrontal cortices of chronic unpredictable mild stress-induced depressive mice, there was a downregulation of mRNAs encoding proteins for the GABAergic synapses, dopaminergic synapses, synaptic vesicle cycle, and neuronal growth and an upregulation of miRNAs of regulating these mRNAs [70]. In a chronic corticosterone-mediated depressive rat model, the majority of the related miRNAs and associated gene networks showed glucocorticoid receptor element binding sites; this is a potential mechanism whereby corticosterone may mediate depression [71].

There is also a decrease in prefrontal hemodynamic responses in depression and a significant and positive correlation between prefrontal hemodynamic responses and the role of the emotional domain [72, 73]. In addition, the lack of activation of oxygenated hemoglobin in the prefrontal cortex indicates that it may be a mechanism of depression [74]. Observing changes in hemoglobin concentration in the prefrontal cortex detected by near-infrared spectroscopy may be a convenient approach to evaluate and predict antidepressant improvement in late-onset depression [58]. Furthermore, increases in mean oxygenated hemoglobin may be positively correlated with the severity of depression [75].

Repetitive transcranial magnetic stimulation of the dorsomedial prefrontal cortex (dmPFC) and dlPFC exhibits effectiveness and safety in treatment-resistant depression [76–80]. In electroconvulsive therapy for depression, an early decrease of intralimbic functional connectivity and a later increase of limbic-prefrontal functional connectivity were found [81]. Epidural prefrontal cortical stimulation over the PFC has also been shown to be a promising novel therapeutic method for treatment-resistant depression [82]. Positive emotional learning can facilitate N-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity in the medial prefrontal cortex and then exert positive effects on promoting rehabilitation in depressive rats [83]. Some studies have reported that NMDA receptor antagonists, such as ketamine and lanicemine, can increase mammalian target of rapamycin complex 1 (mTORC1) signaling by activating threonine kinase (AKT) and extracellular signal-regulated kinase (ERK) signaling pathways and increase synaptic number and function in the prefrontal cortex [2, 84, 85]. A recent study on protein level changes in the prefrontal cortex suggested that treatment with the tricyclic antidepressant clomipramine in neonates was a reliable model to study the effects of antidepressants on the early phase of brain development [86]. Hence, the effects of antidepressant treatment on early brain development may induce constant pathological changes in the prefrontal cortex. YY-23, a new extractive compound, and fluoxetine can reverse the inhibitory effects of chronic mild stress on spontaneous burst firing of medial prefrontal cortex pyramidal neurons in depression [87]. Mecamylamine, a nicotinic antagonist, is a novel antidepressant that exerts antidepressant actions by increasing PFC levels of BDNF and monoamines [88]. Interestingly, in a depressive rat model, nutritional supplements, such as n-3 polyunsaturated fatty acids (PUFA), may prevent the development of depression by impeding HPA axis hyperactivity [89]. This study suggests that dystrophy may be another mechanism of depression.

4. Amygdalar Changes in Depression

The amygdala plays a significant role in affective modulation and memory encoding [90]. The amygdala is also a critical site of neuronal plasticity for fear conditioning [91]. Morphological and functional changes of the amygdala associated with depression have been verified in many studies [92, 93]. In contrast, with the hippocampus and prefrontal cortex, stress and depression enhance synaptic plasticity in the amygdala and the ventral emotional network [3]. Stress was found to induce dendrite retraction in the PFC and hippocampus, while it induced dendritic arborization of pyramidal and spiny neurons in the basolateral amygdala [12]. Expression of brain-derived neurotrophic factor (BDNF), which is known to play a central role in synaptic plasticity induced by stress, increased in the basolateral amygdala but decreased in the hippocampal CA3 in rats [9, 94]. Depression disrupted glutamate signaling at the NMDA receptor in the amygdala in humans [95]. Neonatal glucocorticoid treatment enhanced LTP response and the phosphorylation level of MAPK in the lateral nucleus of the amygdala and promoted depression-like behavior in adult rats [91].

Amygdala kindling, as a classic model of temporal lobe epilepsy with convulsion, can cause depression-like behaviors in both immature rats and adult rats [96]. Amygdalar functional connectivity differs in late-life depression phenotypes, and this discrepancy may be a criterion to distinguish phenotypes of late-life depression and evaluate the severity [97].

In addition, the volume of the amygdala varied with the severity of the depression [98]. Interestingly, a recent study showed that larger gray matter volume in the bilateral amygdala was found in first-degree relatives of depressed

patients [99]. Furthermore, amygdala perturbations caused by negative stimuli, which elicit greater amygdala activation, might be an early and subtle risk marker for depression [100]. Recent evidence suggests that postpartum depression can increase amygdalar response to infant stimuli and decrease bilateral amygdala-right insular cortex connectivity [101]. The latter may have a stimulative effect on depression and anxiety. However, abnormal functional connectivity in depression is discrepant in the left amygdala [102]. In the left amygdala, the functional connectivity decreased in the amygdala positive network, while it increased in the amygdala negative network. In a clinical study of early-childhood-onset depression, functional connectivity was reduced in the bilateral amygdala [103]. Abnormal amygdala functional connectivity is also found in late-onset depressed patients [104]. Hence, a distributed neuronal network including cortical and limbic regions rather than a discrete brain region contributes to depression. The amygdala-associated frontolimbic circuits, amygdala-dorsal lateral prefrontal cortex, and amygdala-ventromedial prefrontal cortex, which integrate affective processes, may have characteristic dysfunctions in adolescent depression [104]. These circuits may change exponentially in association with depression severity and potentially be considered as a biomarker to analyze the effect of treatment on depression. Interestingly, some of the amygdalar changes in depression differ by gender. A recent study indicated that women but not men possess an IL18 haplotype that increases threat-related left centromedial amygdala reactivity and boosts susceptibility to stress-related depression by promoting proinflammatory responses [105]. Depression-associated single-nucleotide polymorphisms can regulate the expression of the bicaudal C homolog 1 (BICC1) gene and decrease its promoter activity on the PKA signaling pathway in amygdalar neurons [106]. These changes may cause mood disorders. In addition, prenatal maternal depression can influence the functional connectivity of the amygdala in early postnatal life, particularly in 6-month-old infants [107]. Prenatal maternal depression can also incur the risk of aggression in offspring [108]. In contrast, many studies have suggested that amygdala hyperactivity may improve symptoms of depression [109].

Some antidepressant treatments have been shown to play a role in amygdala regulation. Transcutaneous vagus nerve stimulation is a noninvasive peripheral neuromodulation therapy administered at the ear for depressed patients and has been shown to be effective for depression treatment [110]. It can promote amygdala-lateral prefrontal network resting state functional connectivity in the right amygdala of depressed patients [111]. Real-time fMRI neurofeedback training is another novel noninvasive treatment for depression [112]. It can enhance blood-oxygenation-level-dependent activity in the amygdala and benefit depressed patients. In addition, the effects of electroconvulsive therapy in patients with depression may also be associated with neuroplasticity changes in the amygdala, and this phenomenon may be due to neurotrophic processes, including neurogenesis [112]. Medication associated with the amygdala in depressed patients includes quetiapine, citalopram, and ketamine [113–115]. In depressive rat models, the amygdala has shown a significant role in fluoxetine-stimulated cell survival and a potential to modulate antidepressant action in hippocampal neurogenesis [116].

5. Neural Plasticity in Other Brain Regions in Depression

The ventral striatum participates in the mechanisms of natural reward, and its dysregulation contributes to symptoms of anhedonia in depression [4]. Chronic stress can cause long-term adaptations in the ventral tegmental area-accumbens pathway that may contribute to its dysregulation in major depression [4]. α_1-Adrenoceptor dependent downregulation of the membrane GluR1 subunit in the mouse ventral tegmental area mediated the depressive-like behavior induced by lipopolysaccharide [117]. In rats with postpartum depression, gestational stress could decrease dendritic length, branching, and spine density on medium spiny neurons in the nucleus accumbens shell and promote depressive-like behavior in the early/mid-postpartum phase [118].

Hypothalamic synaptic plasticity in depression can be caused by increased mRNA expression of synaptotagmin I and synapsin I, and the latter may contribute to depression-like behaviors and HPA axis hyperactivity [119]. In addition, the extracellular matrix may be involved in synaptic stabilization and transmission and may modulate synaptic plasticity in the central nervous system [120]. In recent studies, modeling of bidirectional modulations in synaptic plasticity, designed to reveal the mechanism of long-term potentiation and long-term depression, suggested that Ca^{2+}/calmodulin (CaM) pool size played a critical role in coordinating LTP/LTD expression [121].

6. Summary and Conclusion

Overall, neural plasticity is a vital feature of the brain in response to intrinsic and extrinsic stimuli, including stress and depression. Mounting clinical and basic research studies have illuminated the correlations between neural plasticity and depression. As the summaries in Tables 1 and 2, the effects of depression on neural plasticity are complex pathophysiological processes, involving multiple encephalic regions, such as the hippocampus, prefrontal cortex, and amygdala as well as complicated interactions of many signal pathways, such as NMDA, glutamate, and glucocorticoid. On the other hand, the changes in neural plasticity induced by stress and other negative stimuli can contribute to the onset and development of depression. The majority of antidepressant treatments, including psychotherapies, physiotherapies, and medications, exert antidepressant effects associated with neural plasticity. Unfortunately, to date, no ideal and completely effective treatment has been found for depressed patients. Though we have done extensive work in this review, the detailed mechanisms of neural plasticity in depression still remain unclear. Targeting neural plasticity in depression may lead to novel breakthroughs.

Competing Interests

The authors confirm that this article content has no conflict of interests.

Table 1: Changes of neural plasticity induced by depression in various brain regions.

Brain region	Changes of neural plasticity	Mechanisms
Hippocampus	Synaptic plasticity	(1) Impairment of LTP in CA3
		(2) Facilitation of LTD and tLTD in CA1
		(3) Downregulation of synaptic proteins and growth factors
	Volumetric changes	(1) Disruption and atrophy of neurons and glia
		(2) Neurodegenerative reaction to high levels of glucocorticoid
	Neurogenesis	(1) Hindered by high levels of glucocorticoids and enhanced by adrenalectomy
		(2) Additive effects in mice, while reduced in humans
		(3) Additive function in the circuitry
	Apoptosis	(1) Depression promotes apoptosis in the hippocampus
		(2) The effects caused by chronic depression last longer than those of acute depression
Prefrontal cortex	Synaptic plasticity	(1) Disturb expression of NMDA receptor gene
		(2) Downregulation of proteins for the GABAergic synapses, dopaminergic synapses, synaptic vesicle cycle
		(3) Downregulation of mRNA and protein levels of glutamate transporter SLC1A1
	Activity in vmPFC and dlPFC	(1) Hyperactivity in vmPFC and hypoactivity in dlPFC during progression of depression; hyperactivity in dlPFC and hypoactivity in vmPFC during recovery phase
		(2) Decrease of cortical thickness of right vmPFC through disruption and atrophy of neurons and glia
	Energetic metabolism	(1) Reduction of glutamate in the GABAergic pathway
		(2) Activation of metabotropic glutamate receptor 3
		(3) Disturbed expression of NMDA receptor gene
		(4) Downregulation mRNA and protein levels of glutamate transporter SLC1A1
	Hemodynamic responses	(1) Lack of activation of oxygenated hemoglobin
		(2) Changes in hemoglobin concentration may be positively correlated with severity of depression
Amygdala	Synaptic plasticity	(1) Increased expression of BDNF
		(2) Disrupted glutamate signaling at the NMDA receptor
		(3) Neonatal glucocorticoid treatment enhances LTP response
	Volumetric changes	(1) Larger gray matter volume in the bilateral amygdala
	Functional connectivity	(1) Decreased bilateral amygdala-right insular cortex connectivity
		(2) In the left amygdala, the functional connectivity decreased in positive network and increased in negative network
		(3) Amygdala-associated brain circuits may change with depression severity
		(4) Prenatal maternal depression increases functional connectivity in infants
Ventral striatum		(1) Caused long-term adaptations in the ventral tegmental area-accumbens pathway
		(2) α_1-Adrenoceptor dependent downregulation of the membrane GluR1 subunit
		(3) Decreased dendritic length, branching, spine density on medium spiny neurons in the nucleus accumbens shell
Hypothalamus	Synaptic plasticity	(1) Increased mRNA expression of synaptotagmin I and synapsin I

Table 2: Neural plasticity in the treatment of depression.

Therapy	Model	Mechanism and influence of neural plasticity
Electroacupuncture	Rats	Reverses the impairment induced by long-term potentiation in CA1 synapses of hippocampus
Electroconvulsive shock	Rats and humans	Facilitates hippocampal neurogenesis, an early decrease of intralimbic functional connectivity and a later increase of limbic-prefrontal functional connectivity, and makes neuroplasticity changes in the amygdala due to neurotrophic processes including neurogenesis
Transcutaneous vagus nerve stimulation	Humans	Promotes amygdala-lateral prefrontal network resting state functional connectivity in right amygdala
Real-time fMRI neurofeedback training	Humans	Enhances blood-oxygenation-level-dependent activity in amygdala
Positive emotional learning	Rats	Facilitates N-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity learning
Physical exercise	Rats	Prevents changes in synaptic plasticity and increases in synaptic transmission in hippocampal CA1 pyramidal neurons caused by stress
Nutritional substance supplementation	Rats	Prevents the development of depression through impeding HPA axis hyperactivity
Glucocorticoid receptor antagonists	Rats	Protects against negative synaptic plasticity in CA1 induced by stress
Monoaminergic antidepressants	Rats	Protects against negative synaptic plasticity in CA1 induced by stress
TJZL184 (a monoacylglycerol lipase inhibitor)	Rats	Enhances adult neurogenesis and long-term synaptic plasticity in the DG of the hippocampus
Lycium barbarum	Rats	Enhances synaptic plasticity in the hippocampus
Lithium (selective serotonin reuptake inhibitor)	Rats and humans	Facilitates hippocampal neurogenesis
Fluoxetine (selective serotonin reuptake inhibitor)	Rats	Amygdala neuroplasticity, alleviates upregulation of synaptosomal polysialic neural cell adhesion molecule and reverses the inhibitory effects of chronic mild stress on spontaneous burst firing of medial prefrontal cortex pyramidal neurons
Tadalafil (phosphodiesterase inhibitor)	Rats	Suppresses maternal separation-induced apoptosis and increases cell proliferation in the dentate gyrus
Venlafaxine (serotonin/norepinephrine dual reuptake inhibitor)	Rats	Suppresses hippocampal apoptosis by upregulating brain-derived neurotrophic factor
Ketamine and lanicemine (NMDA receptor antagonists)	Rats	Increases mammalian target of rapamycin complex 1 (mTORC1) signaling by activating threonine kinase (AKT) and extracellular signal-regulated kinase (ERK) signaling pathways and increases synaptic number and function in the prefrontal cortex
Mecamylamine (nicotinic antagonist)	Rats	Increases PFC levels of BDNF and monoamines

Acknowledgments

This work was supported by grants from the Natural Science Foundation of China (NSFC) (nos. 31471120, 31540076, and 31171123) and the Program for New Century Excellent Talents in University (NCET-13-0715).

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