Brain-Derived Neurotrophic Factor in Brain Disorders: Focus on Neuroinflammation

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Abstract
Brain-derived neurotrophic factor (BDNF) is one of the most studied neurotrophins in the healthy and diseased brain. As a result, there is a large body of evidence that associates BDNF with neuronal maintenance, neuronal survival, plasticity, and neurotransmitter regulation. Patients with psychiatric and neurodegenerative disorders often have reduced BDNF concentrations in their blood and brain. A current hypothesis suggests that these abnormal BDNF levels might be due to the chronic inflammatory state of the brain in certain disorders, as neuroinflammation is known to affect several BDNF-related signaling pathways. Activation of glia cells can induce an increase in the levels of pro- and antiinflammatory cytokines and reactive oxygen species, which can lead to the modulation of neuronal function and neurotoxicity observed in several brain pathologies. Understanding how neuroinflammation is involved in disorders of the brain, especially in the disease onset and progression, can be crucial for the development of new strategies of treatment. Despite the increasing evidence for the involvement of BDNF and neuroinflammation in brain disorders, there is scarce evidence that addresses the interaction between the neurotrophin and neuroinflammation in psychiatric and neurodegenerative diseases. This review focuses on the effect of acute and chronic inflammation on BDNF levels in the most common psychiatric and neurodegenerative disorders and aims to shed some light on the possible biological mechanisms that may influence this effect. In addition, this review will address the effect of behavior and pharmacological interventions on BDNF levels in these disorders.

Keywords Brain-derived neurotrophic factor · Neuroinflammation · Neurological disorders · Neurotoxicity

Introduction
Brain disorders are among the major causes of disability and morbidity worldwide. According to recent projections, the incidence of such diseases will increase in the next decades [1]. The lack of adequate treatment turns these diseases into a significant problem worldwide, and the absence of effective treatment can partly be ascribed to our incomplete knowledge of the etiology of most brain disorders. Many mental diseases, however, are tightly associated with environmental stimuli, such as stress [2]. Challenging events can pose a significant burden on individuals, especially those more sensitive to its effects. Although acute stress can have benefits (e.g., enhanced attention, memory), it can also become life threatening when stressful events become a routine part of the life of individuals. A number of studies have already shown that stress is associated with metabolic changes, cardiovascular risk, endocrine abnormalities, mood changes, and impairment of cognitive functions (i.e., mild cognitive impairment), leading to an increased risk of developing psychiatric and neurologic disorders [2, 3]. Chronic stress can lead to the activation of pro-inflammatory microglia, releasing cytokines and pro-inflammatory substances, and recruitment of peripheral immune cells to the brain, thus creating the inflammatory environment that is characteristic for many brain pathologies.

In order to cope with stressful events, brain cells release several substances that can promote neuronal survival, such as antiinflammatory cytokines, growth factors and neurotrophic factors. One of the best-studied neurotrophins is the brain-derived neurotrophic factor (BDNF). Brain pathologies are usually associated with a downregulation of BDNF release, resulting in reduced BDNF levels in the brain and in blood.
BDNF has been suggested as a candidate biomarker of pathological conditions, and therapy efficacy, as most of current treatments are accompanied by a significant change in blood BDNF levels. However, there is still a gap in our understanding of the physiological mechanisms that lead to changes in BDNF levels under pathological conditions.

This review will summarize our current knowledge of BDNF in the pathophysiology of the most common brain disorders. Since neuroinflammation has been considered an important mediator for the onset and progression of many brain pathologies, this review will also attempt to explore the interaction between neuroinflammation and BDNF expression in the brain.

## BDNF Expression and Function

BDNF is a member of the neurotrophin family, which also includes neural growth factor (NGF) and neurotrophins 3 and 4. The Bdnf gene is comprised of a common 3'-exon that encodes the pro-BDNF region of the protein, and several species-dependent 5'-noncoding, promoter-regulated regions, terminating in a coding 5'-exon that encompasses the gene expression [4, 5]. Bdnf gene expression is strongly regulated by a wide array of endogenous and exogenous stimuli (e.g., stress, physical activity, brain injury, diet). BDNF is translated as a pro-neurotrophin (pro-BDNF) that can be cleaved into mature BDNF in the cytoplasm by endoproteases or in the extracellular matrix by plasmin or matrix metalloproteinases (MMP). Both mature BDNF and pro-BDNF can be secreted and bind to the low affinity p75 neurotrophin receptor (p75NTR), which causes activation of the apoptosis cascade [6, 7]. On the other hand, cleaved, mature BDNF binds to its high-affinity receptor tyrosine kinase B (TrkB), activating several signaling cascades, including the Ras-mitogen-activated protein kinase (MAPK), the phosphatidylinositol-3-kinase (PI3K), and the phospholipase Cγ (PLC-γ) pathway. These signaling cascades induce an increase in Ca2+ entry, phosphorylation of transcription factors, and de novo expression of the Bdnf gene (Fig. 1) [8]. Although pro-BDNF can act as a signaling factor for the apoptotic cascade, it is not yet clear if pro-BDNF is secreted by neurons under normal conditions as its concentration in presynaptic terminals is relatively low when compared to mature BDNF. Indeed, in animal models, the concentration of mature BDNF can be ten times higher than the concentration of pro-BDNF [9, 10], which poses a question regarding the efficacy of pro-BDNF as a proper signaling factor.

BDNF has a wide array of functions within the brain and is highly abundant in several brain structures. In the brain, BDNF is involved in plasticity, neuronal survival, formation of new synapses, dendritic branching, and modulation of excitatory and inhibitory neurotransmitter profiles [11, 12]. BDNF is active at all stages of development and aging [13]. Knockout mice lacking BDNF rarely reach adulthood and, when they do, there is a development of several sensory impairments [14, 15]. BDNF is also found in peripheral organs, such as the heart, gut, thymus, and spleen [16, 17]. Around 90% of the BDNF in blood is stored within platelets [18]. Many brain pathologies cause reduction of BDNF protein levels both in the brain and serum of patients [19–22]. Unfortunately, it is still unclear whether BDNF protein levels measured in serum samples reflect BDNF levels in the brain, as studies in animal models gave contradictory results so far [23–25].

## BDNF in Neuroinflammation

After inflammatory signaling (e.g., stress, pro-inflammatory signals), several signaling cascades are changed within the cell. This signaling generates a sequence of events that may eventually lead to neuronal malfunction and apoptosis. Microglia also participate actively in the development of pathological neuroinflammatory process by releasing pro-inflammatory cytokines, which contribute to the neurotoxicity. This cycle is repeated as long as the stressor is present, which can develop into serious consequences (e.g., cognitive impairment, behavioral dysfunction, neurological and psychiatric disorders). One of the main factors of inflammatory activation is the nuclear factor-kappa B (NF-κB), a transcription factor that induces the expression of several pro- and antiapoptotic genes, including Bdnf [26]. Interestingly, binding of BDNF to the TrkB receptor can also induce the expression of NF-κB, although the pathways for this modulation are yet unclear (Fig. 2). NF-κB is closely involved in the innate and adaptive immune response in several psychiatric and neurodegenerative diseases [27]. NF-κB is a regulator of, e.g., apoptosis, neuronal survival and proliferation, and migration and maturation of immune cells [28]. BDNF-induced NF-κB expression stimulates PLC-γ/PKC signaling through the activation of the kinases IKKa and IKKβ. These kinases phosphorylate the NF-κB inhibitory unit IkBa, resulting in the binding of ubiquitin and subsequently degradation of IkBa by proteasomes [29]. IkBa degradation induces the release of the NF-κB and formation of the p50/p65 dimer, which binds to the DNA and induces the expression of genes related to neuronal proliferation, survival, and inflammatory response [29, 30]. Furthermore, it is known that BDNF can also bind to the p75NTR. Even though the affinity of BDNF for the p75NTR receptor is several times lower than for TrkB [31], a p75NTR-mediated effect on NF-κB expression can be observed. Studies have shown that activation of p75NTR increases apoptotic and inflammatory signaling in neurons and glial cells by activation of c-Jun N-terminal kinases (JNK) and NF-κB expression, respectively [32, 33]. However, the effect the p75NTR has on neurotrophic signaling is still under debate, as there is no clear evidence on how large the role of the p75NTR is in mediating such processes.
Thus, the role of BDNF in neuroinflammation is strongly related to its ability to induce—and being induced by—NF-κB. However, the exact regulatory mechanisms are not yet clear.

**BDNF and Aging**

The aging process can lead to the impairment of several brain functions. Studies have reported a decrease in whole brain volume in elderly when compared with young adults, especially in brain regions related to cognition [34–37]. Upon aging, microglia increasingly adopt a pro-inflammatory state due to a decrease in the resting signaling by neurons and astrocytes [38, 39]. As a result, external stimuli (e.g., stress, trauma, infection) can submit the aged brain more easily into a state of mild chronic neuroinflammation, making the brain more prone to apoptotic signaling [40]. This can lead to volume loss and the associated cognitive impairment [41]. Animal studies in stress models, such as chronic stress,
maternal separation, and social defeat, have confirmed that stress is associated with glial activation and that aging decreases cognitive function [42, 43]. The loss of volume is indicative of a reduction in the global neuronal network, and consequently a diminished brain plasticity that could support the brain in such events, thus reducing the cognitive function [44, 45].

It is known that BDNF plays a role in maintaining brain function by inducing survival signaling and neuroplasticity. Although the effect is more visible in younger population, elderly subjects also benefit from it, especially those cognitively, physically, and socially active, reducing the risk of age-related comorbidities [46]. Studies in animal models report an increase in brain BDNF levels when aged animals are submitted to protocols such as long-term environmental enrichment [47–49] or physical activity [50, 51]. Studies on aged mice demonstrated that animals heterozygous for BDNF showed decreased fear extinction learning [52] and conditioned fear learning [53] when compared with young heterozygous mice, but the mechanism responsible for the behavioral effects is not completely clear yet. Better understanding of the processes that are modulated by BDNF may facilitate the development of novel therapeutic methods that could help to prevent or counteract the aging effects on the human brain.

**BDNF in Psychiatric Disorders**

Whenever the brain is challenged by harmful events, its coping mechanisms are activated in order to revert the system to
homeostasis. When these coping mechanisms fail, e.g., due to excessive damage, enhanced sensitivity, and chronic or recurrent exposure to stimuli, a disturbance of normal brain function may occur that can lead to the onset of neuropsychiatric disorders (Table 1). Although psychiatric diseases can display wide spectra of symptoms, common phenomena in these disorders are a disarray of excitatory/inhibitory neurotransmitter signaling and loss of neuronal function, leading to mood and behavioral disturbances, and cognitive impairment.

In humans, BDNF is known to be a useful biomarker for several psychiatric disorders [54]. Most chronic psychiatric diseases are accompanied by changes in BDNF levels, but it is still unclear if changes in BDNF levels are the cause or the result of the disturbances of normal brain function. Therefore, the effects of BDNF levels have been investigated in animal models. Heterozygous BDNF mice show increased weight gain, aggressiveness, anxiety, and contextual memory impairment and therefore have been suggested as an animal model for mood disorders [55]. These results suggest that BDNF could be a key player in the development of several symptoms associated with psychiatric disorders. This hypothesis is supported by the fact that effective treatment of these symptoms resulted in normalization of BDNF levels [56]. In this section, we will further discuss the role of BDNF in the main psychiatric disorders: major depressive disorder, bipolar disorder, and schizophrenia.

Table 1. Effects of BDNF on several neuropsychiatric and neurodegenerative conditions

| Condition            | Peripheral BDNF                                                                 | Brain BDNF                                                                 | References                                                                 |
|----------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Major depressive disorder (MDD) | Decreased serum and plasma levels of BDNF protein; some literature findings showing no change or increased levels in MDD patients; euthymic patients have normalized BDNF levels in serum or plasma; increased methylation of the Bdnf gene is associated with a decrease in mRNA expression; treatment-resistant patients show lower BDNF levels in serum compared to treatment-responsive patients | Decreased BDNF and TrkB mRNA expression in hippocampal slices of MDD patients; use of antidepressant medication was associated with increased Bdnf mRNA expression | Elfving et al. (2012), Karege et al. (2005), Martisiciano et al. (2009), Pandey et al. (2008), Thompson Ray et al. (2011), Hong et al. (2014) |
| Bipolar disorder (BD) | Decreased serum and plasma levels of BDNF in both manic and depressive stages of BD; euthymic patients show no difference from controls | Decreased BDNF mRNA expression in hippocampus of suicidal BD patients; no difference in Bdnf expression between different disease stages (euthymic, depressive or manic) | Banerjee et al. (2013), Knable et al. (2004), Monteleone et al. (2008), Sklar et al. (2002), Ray et al. (2014) |
| Schizophrenia (SCZ) | Decreased BDNF protein levels in serum of SCZ patients; no changes in BDNF levels after treatment | Decreased expression of Bdnf and Trkb genes in hippocampus and dorsolateral prefrontal cortex of SCZ patients; increased methylation of Bdnf gene in prefrontal cortex of SCZ patients | Dong et al. (2015), Pillai (2008), Rao et al. (2015), Reinhart et al. (2015), Rizos et al. (2008), Weickert et al. (2003), Weickert et al. (2005), Xiu et al. (2009), Zhang et al. (2012) |
| Alzheimer disease (AD) | Low serum BDNF levels correlate with development of dementia—especially AD; decreased levels of BDNF in serum of AD patients; BDNF levels are not related to severity of disease; successful treatment transiently increases BDNF in AD | BDNF genotype is related with reduced Hippocampal activity and cognitive function in subjects with high levels of A-β and AD patients; decreased BDNF mRNA levels in the hippocampus of AD patients; increase in methylation pattern of the Bdnf gene in the frontal cortex of AD patients | Buchman et al. (2016), Honea et al. (2013), Lee et al. (2005), Lim et al. (2014), Phillips et al. (1991), Rao et al. (2012), Weinstein et al. (2014) |
| Parkinson disease (PD) | Serum BDNF levels are directly correlated with degeneration of striatum in PD; low serum levels of BDNF is correlated with decreased cognitive function in early PD patients; BDNF decrease in serum is associated with the progression of motor symptoms | Low BDNF mRNA expression in the striatum of PD patients; association between BDNF polymorphism and disease progression | Cagni et al. (2016), Howells et al. (2000), Scalzo et al. (2010), Y. Wang et al. (2016), Ziebell et al. (2012) |
| Epilepsy | BDNF val66met single nucleotide polymorphism is associated with higher BDNF protein expression and an increased risk of developing epilepsy; increased serum BDNF protein levels after epileptic seizures are associated with increased glutamate signaling | Increased mRNA expression of Bdnf exons in the hippocampus and cortex of temporal lobe epilepsy patients; increased BDNF protein expression in the hippocampus of temporal lobe epilepsy patients | Brooks-Kayal et al. (2009), Kandratavicius et al. (2013), Martinez-Levy et al. (2016), Martinez-Levy et al. (2017), N. et al. (2016), Warburton et al. (2016) |
Major Depressive Disorder

Major depressive disorder (MDD) is a common psychiatric disease characterized by abnormal behavior, anhedonia, sleep and dietary problems, cognitive impairment, and, in more severe cases, suicidal tendencies. Biologically, depression is related to a decrease of neurotransmitter signaling in the brain, dysfunction of hypothalamus pituitary adrenal axis (HPA-axis), increase in inflammatory signaling, and reduction in hippocampal volume.

Both MDD patients [57–59] and animal models of depression [60, 61] show a remarkable reduction in serum BDNF levels. Karege and colleagues have shown that this decrease is not related to platelet-associated BDNF release in the bloodstream [62], suggesting that reduced BDNF levels in the brain rather than a reduction in the peripheral release of BDNF by platelets are the cause of altered protein levels in blood. The magnitude of the decrease in plasma BDNF levels is associated with disease duration [63], but it is not clear yet whether the severity of symptoms is related to BDNF levels. BDNF single nucleotide polymorphism (val66met), however, is associated with the severity of depression in patients [64]. Successful antidepressant treatment is usually associated with an increase in BDNF levels in serum and plasma [65, 66], whereas treatment failure is associated with a lack of response of plasma BDNF levels. Thus, BDNF seems an important player in the pathophysiology and might be a biomarker for monitoring treatment response in depression [65, 67]. Epidemiological studies show that a third of all MDD patients experience no changes in the symptoms when treated with the most commonly used antidepressants. Postmortem studies revealed that these treatment-resistant patients have significantly lower BDNF levels, especially in BDNF-rich brain structures, such as the hippocampus [68–70]. Treatment with the rapidly acting antidepressant ketamine was able to increase plasma BDNF levels to the level of healthy controls [71, 72]. Ketamine is an inhibitor of NMDA receptors, inducing rapid, glutamate-dependent Ca\(^{2+}\) signaling and activation of cAMP response element-binding protein (CREB). Clearly, there is a need to increase our knowledge on the role of BDNF in MDD.

Induction of a pro-inflammatory response by systemic application of lipopolysaccharide (LPS) causes depressive-like symptoms (i.e., sickness behavior) in rodents [73, 74], which may also affect BDNF levels. Increased pro-inflammatory signaling leads to a reduction in the mRNA expression of Bdnf and other neurotrophins in plasticity-related brain structures, especially cortical regions [75]. The effects of reduced BDNF expression levels in mice, treated with a systemic LPS injection, can be counteracted by induction of TrkB-mediated signaling with the agonist 7,8-dihydroxyflavone, which leads to a reduction of depressive-like behavior [76]. Gibney and colleagues have found increased expression of interleukins IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) and reduced expression of Bdnf genes in depressive-like rats 6 h after an inflammatory challenge. In this study, expression of cytokines returned to baseline levels after 48 h, but Bdnf mRNA remained low in frontal cortex and hippocampus [77]. In humans, chronic stress is one of the main precursors of depressive symptoms [78, 79]. In laboratory stress-conditioning, depressed patients show a higher inflammatory response, characterized by increased IL-6 release and NF-κB DNA binding, than healthy controls [80]. Depressive symptoms can also be caused by treatment that stimulate the immune system, such as interferon-α (IFN-α). Patients treated with IFN-α were shown to have decreased serum BDNF levels in combination with increased protein levels of the cytokines IL-1 and IL-2 [81, 82]. Interestingly, individuals that had higher BDNF levels at baseline showed better resilience to IFN-α-induced MDD.

These preclinical and clinical findings show that long-term exposure to stress or inflammation leads to a decrease in BDNF levels, reducing the capacity of the neurons to cope with further challenges (i.e., neuronal plasticity), and ultimately leading to a decreased function and neuronal death. Interestingly, treatment with antidepressants can result in an antiinflammatory response throughout the brain, mitigating the inflammatory unbalance to homeostatic levels and normalizing BDNF concentrations [83, 84]. However, further research is needed to understand the mechanisms involved in the regulation of BDNF by neuroinflammation.

Bipolar Disorder

Bipolar disorder (BD) is characterized by fluctuations of mood throughout lifetime, oscillating between depressive, euthymic, and manic episodes. BD is associated with cognitive impairment and other comorbidities that affect the quality of life of the individual [85–87]. BD is characterized by alterations in dopaminergic and glutamatergic neurotransmitter systems, mitochondrial dysfunction, and increased oxidative stress, which in turn are related to neuroinflammation, neurotoxicity and eventually neuronal death [87]. Two recent meta-analyses have shown that serum and plasma levels of BDNF in BD patients during depressive and manic episodes are decreased, but no difference in BDNF levels between BD patients in an euthymic episode and healthy controls was found [88, 89]. It is known that treatment with mood stabilizers increases BDNF levels in prefrontal cortex and hippocampus of animals by inducing promoter IV-driven expression [90, 91]. Also in humans, treatment for the manic or depressive phases of BD is associated with an increase in serum BDNF levels [92, 93].

Recent studies have shown an association between manic and depressive stages of BD and a pro-inflammatory profile of immune cells [94, 95]. Steiner and colleagues have found that suicidal mood disorder patients had a significant increase
of microglial cell density in the dorsolateral prefrontal cortex, anterior cingulate gyrus, and mediodorsal thalamus compared to healthy controls and non-suicidal, mood disorder patients [96]. The presence of immune cells clusters in these brain regions suggests a strong inflammatory response, which could trigger the suicidal predisposition of these patients [96]. Although plenty of literature is available on BDNF or neuro-inflammation in BD, there is a severe lack of studies regarding the association between both mechanisms on BD. Only two studies have analyzed both BDNF and cytokine levels in BD patients, with somewhat different conclusions. Patas and colleagues have shown an association between both serum BDNF and plasma IL-6 levels with a depressive episode associated with melancholic trait [97], while Wang and colleagues have found an association for serum BDNF levels, but not for IL-1β or IL-6 [98]. Clearly, more studies are needed to elucidate the interaction between neuroinflammation, BDNF, and disease symptoms in BD.

Interestingly, the most commonly used therapeutic drugs—lithium and valproate—were able to reverse the inflammatory state in mood disorders [99–101]. The most common assumption is that lithium and valproate can inhibit glycogen synthase kinase 3 (GSK-3) and sodium channel function, respectively [102]. Inhibition of GSK-3 activity by lithium increases cellular levels of BDNF. GSK-3 can inhibit mammalian target-of-rapamycin (mTOR)—an important modulator of BDNF-dependent neuronal plasticity and survival—and thus affect proper BDNF signaling and impair optimal cellular function. In the manic phase of BD, there is a remarkable increase in PKC-mediated signaling, which is associated with BDNF-dependent Ca²⁺ induction. PKC isozenymes are involved in the pro-inflammatory response mediated by macrophages [103] and, more recently, microglia [104] through activation of the NF-κB inflammation pathway. Treatment of BD patients with lithium or valproate inhibits PKC upregulation, normalizing its level to that of euthymic subjects, and increases BDNF levels [105]. PKC inhibitor tamoxifen enhances the capacity of lithium to reduce symptoms of mania in BD [105–107]. PKC inhibition probably suppresses the expression of NF-κB and consequently resolves the NF-κB-mediated inhibition of Bdnf expression, resulting in an increase in peripheral BDNF levels in BD. However, the mechanisms underlying the increase in BDNF levels in response to treatment should still be further investigated. Yet, current evidence suggest that a decrease in BDNF levels can be considered as a biomarker for both depressive and manic stages of BD.

**Schizophrenia**

Schizophrenia is a disease characterized by disturbances in the proper perception of a person’s surroundings. Schizophrenia is associated with a high suicide rate and accounts for a large number of hospitalizations, causing a significant burden to healthcare systems worldwide. The symptoms of schizophrenia comprise positive (e.g., hallucinations, delusions, confused thoughts, concentration impaired) negative (e.g., depression,anhedonia, self-neglect) and cognitive effects (e.g., memory, attention, reason impairments). Schizophrenic patients exhibit a decreased activation of γ-aminobutyric acid (GABA) signaling [108], inducing impaired neuronal activation, especially in dopaminergic neurons [109]. The etiology of schizophrenia is not fully understood yet and symptoms can vary between individual patients, making the diagnosis of schizophrenia challenging.

A recent meta-analysis revealed that serum BDNF levels in both drug-naïve and medicated schizophrenic patients are reduced. Serum BDNF levels in schizophrenic patients decrease with age but were independent of the dosage of medication [110]. However, it remains unclear if and how BDNF levels in the brain are altered in schizophrenic patients. Some studies report increased BDNF levels in frontal and temporal structures [111, 112], while others report decreased levels in the same brain structures [108, 113, 114]. Besides clinical observations, in vitro studies using the phencyclidine (PCP) psychosis model also give ambiguous results. Adachi and colleagues reported that exposure of cortical cultures to the non-competitive NMDA agonist PCP initially resulted in an increase in BDNF levels, whereas TrkB, ERK1/2, and Akt signaling were decreased [115]. In contrast, two other studies reported decreased BDNF mRNA expression in cortical slices after exposure to a low dose of PCP [116]. Taken together, in vitro, in vivo and clinical results seem to indicate that plasma BDNF levels are decreased in schizophrenic patients, but data on brain BDNF levels are contradictory.

Schizophrenia is a multifactorial disease, in which both genetic and environmental factors play a role. It is well established that physical and mental distresses can trigger psychotic behavior in (genetically) vulnerable patients [117]. These triggers can induce inflammatory changes that are associated with reduced neurotransmitter signaling, increased oxidative stress, and reduced synaptic branching [118]. Mondelli and colleagues have shown in leukocytes of first-episode schizophrenic patients that childhood trauma and the number recent stressful life events were negatively correlated with BDNF mRNA levels. BDNF levels were also negatively correlated with IL-6 expression, suggesting an inflammation mediated decrease in BDNF expression, or vice versa. Moreover, BDNF, IL-6, and cortisol levels correlated inversely with hippocampal volume [119]. A postmortem study demonstrated that schizophrenic patients have an increased inflammatory profile in dorsolateral prefrontal cortex. The group of patients with high levels of neuroinflammation had lower expression of BDNF [120]. As psychotic episodes are related with increased neuroinflammation and activated microglia [120, 121], it can be hypothesized that pro-
inflammatory cytokines may be modulating BDNF mRNA expression via interaction of NF-κB or CREB transcription factors. It is known that schizophrenia patients have upregulated genes for inflammatory cytokines [122, 123], and downregulated Bdnf gene transcription [124, 125]. Neuroinflammation could be the key factor for the decrease of Bdnf gene expression in schizophrenic patients, as pro-inflammatory cytokines increase methylation of Bdnf gene, leading to a decrease of CREB binding to the specific Bdnf site.

Remarkably, drug treatment that is effective in controlling disease progression in schizophrenic patients can have diverse effects on peripheral BDNF protein levels [126–128]. In addition, some studies suggest that baseline BDNF levels in schizophrenia patients might reflect the susceptibility towards available drug therapies [129, 130]. Clearly, the interaction between neuroinflammation, BDNF levels, and treatment response should be better understood, as this could lead to identification of new targets for improved therapies.

**BDNF in Neurodegenerative Disorders**

Despite research on neurodegenerative disorders has been increasing exponentially, there are still gaps in our knowledge on the etiology, onset and progression of most neurodegenerative diseases. Treatment is usually restricted to mitigation of the symptoms, rather than cure or delay of progression. Diagnosis of neurodegenerative diseases is usually based on subjective cognitive tests in combination with neuroimaging [131–133], but the current techniques are not able to successfully diagnose these diseases in their earlier stages, when the pathology is already present but does not cause symptoms yet. Attempts to discover new biomarkers for the diagnosis of early stages of the disease are ongoing [134–136]. Possibly, BDNF could qualify as such a biomarker.

In the following sections, we will discuss the role of BDNF in neurodegenerative disorders, focusing of Alzheimer’s disease, Parkinson’s disease, and epilepsy. We will also address the possible use of BDNF as a biomarker for diagnosis. In addition, we describe the role of neuroinflammation in the development of these diseases and explain how BDNF can help the brain to cope with inflammation.

**Alzheimer’s Disease**

AD is characterized by a progressive loss of neurons in the brain, leading to impairment in memory and general cognition. Hallmarks of AD pathology are deposition of amyloid-β plaques in the extracellular matrix, formation of tau-phosphorylated neurofibrillary tangles within the cell and neuritic plaques. Tangles and plaques disrupt the signaling activity of neurons, eventually leading to neuronal apoptosis. As the disease progress, the axonal transport is constantly reduced, and the general function of neurons is impaired. These changes decrease BDNF axonal transport, resulting in reduced availability of BDNF within the synaptic cleft and consequently diminished signaling through TrkB receptors [137, 138]. BDNF mRNA and protein levels are also reduced in cognition-related structures such as hippocampus and frontal cortex, which corroborates BDNF depletion to be involved in the cognitive deficit leading to AD dementia [139]. BDNF levels are also reduced in plasma of patients with mild cognitive impairment (MCI) [140] and AD [141]. AD patients with higher serum concentrations of BDNF showed less cognitive decline after 1 year; this effect was more pronounced in the more severe stages of the disease [142, 143]. These studies suggest that BDNF might be a predictor for the rate of disease progression in AD.

Neuroinflammation is a key factor in the development and progression of AD [144, 145]. Amyloid-β deposits induce pro-inflammatory activation of microglia which might be an effort of microglia to mitigate the antigen-related damage [146]. Some studies have reported inflammatory challenges as an associated risk factor for the development of dementia-related symptoms, as they show increased pro-inflammatory cytokines levels [147, 148]. On the other hand, treatment with antiinflammatory medication tends to mitigate cognitive impairment in animal models of amyloid-β injection [149, 150]. Interestingly, PET imaging studies have shown that subjects with high amounts of amyloid-β, but no dementia, had decreased microglia activation [151–153], indicating a fundamental participation of microglia in the development and progression of AD.

There is no clear evidence on how effective BDNF can be in controlling neuroinflammation-dependent progression of the disease. Prakash shows that rats injected with Aβ in the hippocampus have a remarkable decrease in BDNF and increased TNF-α, IL-6, and caspase-3 protein levels 3 weeks after intracerebroventricular injection. These changes were associated with inability lack of memory retention in Morris Water Maze test [154]. Another study confirmed the increase in pro-inflammatory cytokines and reduced antiinflammatory cytokines and BDNF protein levels and gene expression after Aβ₁₋₄₂ injection [155]. In humans, two studies have shown an increase in pro-inflammatory cytokines and a decrease in BDNF levels in the serum of early- and late-onset AD, although there was no correlation with pro-inflammatory and neurotrophin results in both studies [141, 156].

It is known, however, that pro-inflammatory cytokines—especially IL-1β—can cause downregulation of BDNF expression in cognition-related brain structures, such as the hippocampus [157, 158]. As these cytokines are upregulated in AD, a decrease of BDNF levels is expected to occur in such brain structures, leading to a decrease in survival signaling and, consequently, neuronal death. Moreover, increase in
hyper-phosphorylated tau impairs anterograde transport of BDNF to the axon, further decreasing BDNF signaling in the synaptic cleft. As AD is a disease that inflicts several different physiological effects in both the internal and external milieu of the brain, efficient analysis of the role of BDNF in these processes is challenging and the overall effect of BDNF on brain function may be variable.

**Parkinson’s Disease**

PD is characterized by movement impairment (bradykinesia, tremors, and rigidity), often combined with mild cognitive symptoms (decreased attention, executive function, memory) and mood disturbances (apathy, aggressiveness, anhedonia, depression) [159, 160]. The onset of PD is caused by the formation of aggregated α-synuclein plaques (i.e., Lewy bodies) in the substantia nigra pars compacta, leading to a progressive loss of dopaminergic neurons [161]. It is estimated that clinical symptoms start to appear when more than 50% of the neurons in the substantia nigra are already lost [162]. Movement symptoms are usually the first signs leading to the diagnosis of PD. As the disease progresses, more brain structures become affected by the neuronal loss and non-motor symptoms become evident [161, 163]. The severity of symptoms increases as the disease progresses and as a result, the patient loses gradually independence until patients become highly dependent on caregiver support in the late stages of the disease.

PD patients have lower concentrations of BDNF mRNA and protein in the substantia nigra pars compacta than healthy controls [164, 165]. Neurons with the lowest BDNF levels were suggested to be most prone to injury. Porritt and colleagues demonstrated that local inhibition of the production of BDNF with an antisense oligonucleotide leads to a significant loss of dopaminergic neurons in the substantia nigra pars compacta of rats, which suggests that BDNF has an important role in neuronal survival [166]. In contrast to the aforementioned studies, some reports describe that the BDNF levels in serum are increased in PD patients, especially in moderate to severe stages of the disease [167, 168]. This could mean that the CNS tries to cope with the loss of neurons by increasing BDNF production, resulting in enhanced serum levels of the protein. However, there is no direct evidence that supports this hypothesis.

The onset and progression of PD are also associated with neuroinflammation. Several studies in animal models of PD have reported increased microglial activation and pro-inflammatory cytokines [169, 170]. In humans, PD is associated with neuroinflammation in both postmortem [171] and in vivo analysis [172, 173]. Sawada and colleagues have found a remarkable increase of microglial cells in the hippocampus, amygdala, and entorhinal cortex of PD patients, which was associated with a decrease of BDNF mRNA expression and increased IL-6 in those regions [174]. Nagatsu has shown increased levels of IL-1β, IL-2, IL-6, and TNF-α in the striatum of PD patients, associated with a decreased BDNF protein levels in the same structure. Aggregated α-synuclein can induce an acute, local neuroinflammatory process in PD-associated brain structures, which suppresses BDNF expression and reduces BDNF protein levels. However, there is no evidence on how changes in BDNF levels in the brain affect the progression of PD and further analysis of the interaction between pro-inflammatory cytokines and BDNF is therefore necessary.

**Epilepsy**

Epilepsy patients are affected by seemingly unprovoked seizures but usually also suffer from significant mood and cognitive changes [175]. The symptoms of epilepsy are induced by a disarray of excitatory neuronal connections, generating deregulated firing, or lack of inhibition of excitatory neurons. Although there are several treatment strategies to reduce seizures, 30% of the patients show little to no response to common antiepileptic drugs.

Seizures have been associated with an increased expression of several neurotrophic-related genes, including transcription factors [176], neuropeptides [177], and growth factors [178]. Two recent reports have shown that BDNF gene expression is increased in the hippocampus and temporal cortex of temporal lobe epilepsy patients [179, 180]. Seizures also increased hippocampal and cortical BDNF protein levels in animal model of epilepsy [181–183]. BDNF seems to be involved in epileptogenesis by regulating several signaling pathways within excitatory neurons, increasing Ca\(^{2+}\) signaling and glutamate expression [13, 184]. Overexpression of BDNF may also contribute to the epilepsy-induced cortical network deregulation by increasing even further the plasticity and dendritic branching signaling and causing an overexcitation state of glutamatergic neurons, thus reducing seizure threshold [185]. This creates a positive feedback loop: as upregulated glutamate neurotransmitter increases BDNF signaling and expression, it further increases glutamate signaling. Other studies have shown that transient inhibition of the BDNF receptor TrkB after seizure induction prevents the development of temporal lobe epilepsy [186, 187]. These findings indicate that BDNF is intimately related to the pathogenesis of epilepsy, and new therapeutic methods should take BDNF into consideration. However, it is worth noting that BDNF may also play a part in protecting neurons against harmful stimuli; therefore, treatment aiming to reduce BDNF levels as a whole should be carefully considered.

In epilepsy, chronic seizures lead to excitotoxicity and neuronal apoptosis with associated gliosis [188]. Studies in animal models have reported that seizures are associated with increased activation of microglia, especially of the M1
subtype [189], and an increased release of pro-inflammatory mediators [190, 191]. Although studies that link BDNF with neuroinflammation in epilepsy are lacking, a hypothesis for such a link can be formulated based on existing knowledge. In healthy conditions, BDNF signaling induces the activation of transcription factor NF-κB, which in turn induces de novo expression of the Bdnf gene [26, 192]. It is possible that overexpression of the BDNF leads to an inflammatory response mediated by NF-κB, leading to astrocyte activation, increased production of cytokines and neurotoxic reactive oxygen species, and local recruitment of activated microglia [193]. Activated pro-inflammatory microglia are known to elicit apoptotic response after chronic stimulation, which causes neurotoxicity and further neuronal death. As BDNF is overexpressed at the onset of seizures [194], there is also an increase in BDNF-mediated glutamate signaling, contributing to the systemic neuronal imbalance. Although there are several players involved in the development of seizures, BDNF might be an important factor in modulating the disease. BDNF inducing, or being induced, by NF-κB also highlights the importance of neuroinflammation in modulating BDNF-dependent regulation. However, there is a need for further research to better understand the role of BDNF in epilepsy, especially regarding its role in modulation of inflammatory processes.

**BDNF a Potential Therapy for Brain Pathologies**

BDNF has been regarded as a possible biomarker for monitoring the onset, progression, and treatment of brain pathologies. However, recent studies suggest that BDNF may also be a potential target for new treatment strategies. Some promising results have been published from studies showing that therapeutic use of BDNF can, directly or indirectly, modulate changes within the brain [195]. An important finding is that peripheral BDNF is able to cross the blood-brain barrier [196], which is a prerequisite for BDNF-related therapy. However, the rate at which BDNF is taken up by the brain has not been quantified yet. Nonetheless, experimental therapy has been investigated in vivo and in vitro with promising results in animal models of AD [197], PD [198], and MDD [199] (a comprehensive review on BDNF drug delivery in brain pathologies and current stage of clinical trial can be found in [200]). For example, BDNF infusion into the hippocampus of adult rats was able to increase neurogenesis and regional neuronal activity [201]. Delivery of the BDNF mimetic 7,8-dihydroxiflavone is able to revert cognitive deficits in an AD animal model [202]. Also, gene transfection of BDNF into a 6-hydroxydopamine-induced unilateral lesion in the striatum was able to revert motor deficits in this animal model of PD [203].

The current need for improved treatments for brain disorders is pressing, and although large amounts of resources are spent on new therapies, few have been able to bring the desired results. The initial findings suggest that BDNF may be more than a biomarker for brain disorders; it may also become a possible target for the treatment of brain disorders. However, there is still a need for more information about the pharmacological features of BDNF-based substances in order to develop new treatments.

BDNF levels are activity-dependent, which means that the expression of BDNF changes under positive (e.g., physical activity, cognitive enhancement) and negative (e.g., obesity, sedentarism) behavioral and environmental stimuli. Several studies on both humans and animals show that physical activity, cognitive stimulation, and a balanced diet can stimulate BDNF expression [204–207]. Physical activity is the best studied positive factor for stimulation of BDNF expression. Thus, exercise can act as an inducer of neuronal plasticity, neurogenesis and neuronal survival [208, 209]. Several studies in both animals and humans have assessed the effects of physical activity on BDNF levels in psychiatric [210–213] and neurodegenerative diseases [214–217]. These studies indeed indicated that physical activity augments neuronal protection in brain disorders by stimulating BDNF expression. However, there are still some questions regarding the required time of the physical intervention, the optimal type of exercise (i.e., strength, endurance, aerobic exercises). Although less studied, diet can also provoke changes BDNF levels in physiological conditions. BDNF is known to affect the regulation of feeding and energy metabolism [218–221]. Decreased levels of BDNF were found in subjects consuming diets with high sugar and fat [222, 223]. On the other hand, dietary restriction (i.e., the maintenance of a balanced diet) or addition of supplementary substances (e.g., omega-3 fatty acids; resveratrol) can induce an increase in BDNF levels and reduce cognitive impairment in animal models [224–226]. It is not clear yet how large the effect of dietary management on BDNF protein levels in psychiatric or neurodegenerative disorders, but it is known that BDNF affects—and is affected by—dietary behavior. More research is needed in order to better understand the dietary influence on brain disorders.

Lifestyle changes that modulate BDNF levels in the brain may prove capable to control symptoms and delay progression in brain pathologies and thus might become cheap and easily accessible (adjuvant) treatment for these pathologies in the near future. However, a possible concern about such therapies is the compliance of the patients with the treatment. Most of behavioral therapies are based on long periods of treatment with a relatively slow improvement when compared with medications. This may reduce the motivation of patients to continue treatment, especially because most psychiatric and neurodegenerative disorders can be accompanied by mood symptoms (e.g., anhedonia, hopelessness, aggressiveness).
Therefore, slow-acting lifestyle therapies could yield better results if they are combined with fast-acting pharmacological interventions.

Concluding Remarks

BDNF is involved in several processes that are essential for the optimal functioning of the brain. Several studies report altered brain and plasma BDNF levels in patients with various brain pathologies. However, the pathophysiological mechanisms that underlie these changes are still not fully understood yet. There is also no conclusive evidence that can discriminate whether changes in BDNF levels are a causative or the consequence of the disease onset. It is challenging to prove a causative role of BDNF in psychiatric and neurodegenerative disorders. Some circumstantial evidence suggest such a causative role for BDNF. Human populations with a genetic variant that decreases the BDNF concentration appear to be more susceptible to psychiatric disorders. However, it should be noted that BDNF is highly affected by environmental changes, which in turn may affect genetic findings. In animals, injection of BDNF in the hippocampus was shown to cause a decrease of depressive-like behavior. However, it remains unclear how these findings translate to the clinical situation, as current disease models are not able to properly reproduce complex human disorders, because they usually only mimic part of the symptoms (i.e., low predictive validity). Direct translation of the animal findings to humans would imply an intervention by intrathecal BDNF injection in the brain or spinal cord of patients. However, such an intervention would be highly invasive and the success would depend on the ability of BDNF to migrate to the target region. Alternatively, interventions that aim to stimulate the production of BDNF could be prospectively investigated in patients with low BDNF levels, either due to a genetic predisposition or environmental factors. BDNF levels should be monitored repetitively to determine if changes in BDNF levels precede alleviation of symptoms or vice versa. In a population with a genetic predisposition for low BDNF levels, preventive intervention with a BDNF stimulating treatment could also be considered, but this would require a large study population and a long follow-up time.

Evidence from preclinical studies and clinical trials suggests that treatment strategies aiming to increase brain BDNF levels could have a beneficial effect on many brain disorders. In this respect, epilepsy is an exception as it is associated with increased levels of BDNF. At present, pharmacological intervention by administration of exogenous BDNF is still challenging, but lifestyle changes could provoke the desired effect. Environmental and physiological stimuli, such as physical activity, social interactions, and sensory and cognitive stimuli, are powerful modifiers of neurotrophin levels, including BDNF levels, and have been shown to alleviate symptoms of brain pathologies in both humans and animal models. Plasma BDNF can be reliably assayed, and samples are easily collected and therefore BDNF has been proposed as a potential peripheral biomarker for the assessment of the status of the brain and the efficacy of treatment. However, discrepancies between brain and plasma BDNF alterations have been observed and need to be further elucidated before plasma BDNF can qualify as a suitable biomarker.

Neuroinflammation is regulated by factors that are also involved in modulation of BDNF expression. Both neuroinflammation and altered BDNF expression are common phenomena in many brain disorders. Remarkably, there are only few studies that have investigated the link between BDNF and neuroinflammation. Better understanding of the interaction between BDNF and neuroinflammation could open new ways for therapy management and could facilitate the development of new therapeutic strategies for brain diseases.

References

1. Whiteford HA, Degenhardt L, Rehm J et al (2013) Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382:1575–1586. https://doi.org/10.1016/S0140-6736(13)61611-6
2. Lupien SJ, McEwen BS, Gunnar MR, Heim C (2009) Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 10:434–445. https://doi.org/10.1038/nrn2639
3. McEwen BS (2012) Brain on stress: how the social environment gets under the skin. Proc Natl Acad Sci U S A 109(Suppl):17180–17185. https://doi.org/10.1073/pnas.1121254109
4. Aid T, Kazantseva A, Pirroo M et al (2007) Mouse and rat BDNF gene structure and expression revisited. J Neurosci Res 85:525–535. https://doi.org/10.1002/jnr.21139
5. Pruunsild P, Kazantseva A, Aid T et al (2007) Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. Genomics 90:397–406. https://doi.org/10.1016/j.ygeno.2007.05.004
6. Barker PA (2009) Whither proBDNF? Nat Neurosci 12:105–106. https://doi.org/10.1038/nn0209-105
7. Lu B, Pang PT, Woo NH (2005) The yin and yang of neurotrophin action. Nat Rev Neurosci 6:603–614. https://doi.org/10.1038/nrn1726
8. Minichiello L (2009) TrkB signalling pathways in LTP and learning. Nat Rev Neurosci 10:850–860. https://doi.org/10.1038/nrn2738
9. Matsumoto T, Rauskolb S, Polack M et al (2008) Biosynthesis and processing of endogenous BDNF: CNS neurons store and secrete
BDNF, not pro-BDNF. Nat Neurosci 11:131–133. https://doi.org/10.1038/nn2038
10. Dieni S, Matsumoto T, Dekkers M et al (2012) BDNF and its pro-peptide are stored in presynaptic dense core vesicles in brain neurons. J Cell Biol 196:775–788. https://doi.org/10.1083/jcb.201201038
11. Edelmann E, Lessmann V, Brigadski T (2014) Pre- and postsynaptic twists in BDNF secretion and action in synaptic plasticity. Neuropsychopharmacology 49(Pt C):610–627. https://doi.org/10.1016/j.neuropharm.2013.05.043
12. Panja D, Bramham CR (2014) BDNF mechanisms in late LTP formation: a synthesis and breakdown. Neuropsychopharmacology 76(Pt C):664–676. https://doi.org/10.1016/j.neuropharmac.2013.06.024
13. Park H, Poo MM (2013) Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci 14:7–23. https://doi.org/10.1038/nrn3379
14. Emsfors P, Lee K-F, Jaensch R (1994) Mice lacking brain-derived neurotrophic factor develop with sensory deficits. Nature 368:147–150. https://doi.org/10.1038/368147a0
15. Jones KR, Faría’s I, Backus C, Reichardt LF (1994) Targeted disruption of the BDNF gene perturbs brain and sensory neuron development but not motor neuron development. Cell 76:989–999. https://doi.org/10.1016/0092-8674(94)90377-8
16. Lommatzsch M, Quarcoo D, Schulte-Herbrüggen O et al (1999) Abundant neurotrophins in murine visceras: a dynamic pattern from birth to adulthood. Int J Dev Neurosci 20:23–50. https://doi.org/10.1016/s0304-4577(98)00045-0
17. Lommatzsch M, Braun A, Mannsfeldt A et al (1999) Abundant production of brain-derived neurotrophic factor by adult visceral epithelia. Implications for paracrine and target-derived neurotrophic functions. Am J Pathol 155:1183–1193. https://doi.org/10.1016/s0002-9440(10)65221-2
18. Fujiwara H, Altar CA, Chen R et al (2002) Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. Thromb Haemost 87:728–734. https://doi.org/10.1016/s0304-4577(02)78826-3
19. Jiang H, Chen S, Li C et al (2017) The serum protein levels of the tPA-BDNF pathway are implicated in depression and antidepressant treatment. Transl Psychiatry 7:e1079. https://doi.org/10.1038/tp.2017.43
20. Borba EM, Duarte JA, Bristot G et al (2016) Brain-derived neurotrophic factor serum levels and hippocampal volume in mild cell survival, plasticity, and disease. Cell Death Differ 13:852–860. https://doi.org/10.1038/sj.cdd.4418377
21. Mattson MP, Meffert MK (2006) Roles for NF-kappaB in cell death by transcriptional regulation of the apoptotic machinery. Curr Opin Cell Biol 15:732–737. https://doi.org/10.1016/j.cceb.2003.10.005
22. Bernard-Gauthier V, Boudjemeline M, Rosa-Neto P et al (2013) Towards tropomyosin-related kinase B (TrkB) receptor ligands for brain imaging with PET: radiosynthesis and evaluation of 2-(N-methyl-11C-(dimethylamino)phenyl)-7,8-dihydroxy-4H-chromen-4-one and 2-(4-[18F] fluoro)phenyl)-7,8-dihydroxy-4H-chromen-4-one. Bioorganic Med Chem 21:7816–7829. https://doi.org/10.1016/j.bmc.2013.10.012
23. Hempstead BL (2002) The many faces of p75NTR. Curr Opin Pharmacol 12:260–267. https://doi.org/10.1016/s0959-4388(02)00021-5
24. Tisserand DJ (2004) A voxel-based morphometric study to determine individual differences in gray matter density associated with age and cognitive change over time. Cereb Cortex 14:966–973. https://doi.org/10.1093/cercor/bhi037
25. Giorgio A, Santelli L, Tomassini V et al (2010) Age-related changes in grey and white matter structure throughout adulthood. Neuroimage 51:943–951. https://doi.org/10.1016/j.neuroimage.2010.03.004
26. Marini AM, Jiang X, Wu X et al (2004) Role of brain-derived neurotrophic factor and NF-kappaB in neuronal plasticity and survival: from genes to phenotype. Restor Neurol Neurosci 22:121–130
27. Tilstra JS, Clauson CL, Niedermhofer LJ, Robbins PD (2011) NF-κB in aging and disease. Aging Dis 2:449–465
28. Ockinghaus A, Ghosh S (2009) The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol 1:1–14. https://doi.org/10.1101/cshperspect.a000034
29. Sousa VC, Vital J, Costenla AR et al (2014) Maternal separation impairs long term-potentiation in CA1-CA3 synapses and hippocampal-dependent memory in old rats. Neurobiol Aging 35:1680–1685. https://doi.org/10.1016/j.neurobiolaging.2014.01.024
44. Goh JO, Park DC (2009) Neuroplasticity and cognitive aging: the scaffolding theory of aging and cognition. Restor Neurol Neurosci 27:391–403
45. Calabrese F, Guidotti G, Racagni G, Riva MA (2013) Reduced neuroplasticity in aged rats: a role for the neurotrophin brain-derived neurotrophic factor. Neurobiol Aging 34:2768–2776. https://doi.org/10.1016/j.neurobiaging.2013.06.014
46. Stem Y (2012) Cognitive reserve in ageing and Alzheimer’s disease. Lancet Neurol. 11:1006–1012
47. Nithianantharajah J, Hannan AJ (2006) Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nat Rev Neurosci 7:697–709. https://doi.org/10.1038/nrn1970
48. Cao W, Duan J, Wang X et al (2014) Early enriched environment induces an increased conversion of proBDNF to BDNF in the adult rat’s hippocampus. Behav Brain Res 265:76–83. https://doi.org/10.1016/j.bbr.2014.02.022
49. Jha S, Dong BE, Xue Y et al (2016) Antidepressive and BDNF effects of enriched environment treatment across ages in mice lacking BDNF expression through promoter IV. Transl Psychiatry 6:e896. https://doi.org/10.1038/tpp.2016.160
50. Marlatt MW, Potter MC, Lucassen PJ, van Praag H (2012) Running throughout middle-age improves memory function, hippocampal neurogenesis, and BDNF levels in female C57BL/6J mice. Dev Neurobiol 72:943–952. https://doi.org/10.1002/dneu.22009
51. O’Callaghan RM, Griffin EW, Kelly AM (2009) Long-term treadmill exposure protects against age-related neurodegenerative change in the rat hippocampus. Hippocampus 19:1019–1029. https://doi.org/10.1002/hipo.20591
52. Psotta L, Lessmann V, Endres T (2013) Impaired fear extinction learning in adult heterozygous BDNF knock-out mice. Neurobiol Learn Mem 103:34–38. https://doi.org/10.1016/j.nlm.2013.03.003
53. Endres T, Lessmann V (2012) Age-dependent deficits in fear learning in heterozygous BDNF knock-out mice. Learn Mem 19:561–570. https://doi.org/10.1101/lm.028068.112
54. Chen S, Jiang H, Liu Y et al (2017) Combined serum levels of multiple proteins in tPA-BDNF pathway may aid the diagnosis of five mental disorders. Sci Rep 7:8671. https://doi.org/10.1038/s41598-017-06832-6
55. Lindholm JSO, Castrén E (2014) Mice with altered BDNF signaling as models for mood disorders and antidepressant effects. Front Behav Neurosci 8:143. https://doi.org/10.3389/fnbeh.2014.00143
56. Nithianantharajah J, Hannan AJ (2006) Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nat Rev Neurosci 7:697–709. https://doi.org/10.1038/nrn1970
57. Shimizu E, Hashimoto K, Okamura N et al (2003) Alterations of neurotrophins in the rat hippocampus. Hippocampus 19:1019–1029. https://doi.org/10.1002/hipo.20591
58. Karege F, Bondolfi G, Gervasoni N et al (2005) Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 57:1068–1072. https://doi.org/10.1016/j.biopsych.2005.01.008
59. Bus BAA, Molenдж M, Tendolkar I et al (2015) Chronic depression is associated with a pronounced decrease in serum brain-derived neurotrophic factor over time. Mol Psychiatry 20:602–608. https://doi.org/10.1038/mp.2014.83
60. Hosang GM, Shiles C, Tansey KE et al (2014) Interaction between stress and the BDNFVal66Met polymorphism in depression: a systematic review and meta-analysis. BMC Med 12:7. https://doi.org/10.1186/1741-7015-12-7
61. Björkholm C, Monteggia LM (2016) BDNF—a key transducer of antidepressant effects. Neuropsychopharmacology 102:72–79. https://doi.org/10.1016/j.neuropharm.2015.10.034
62. Molenдж M, Bus BAA, Spinhoven P et al (2011) Serum levels of brain-derived neurotrophic factor in major depressive disorder: state–trait issues, clinical features and pharmacological treatment. Mol Psychiatry 16:1088–1095. https://doi.org/10.1038/mp.2010.98
63. Piccinni A, Del Debbio A, Medda P et al (2009) Plasma brain-derived neurotrophic factor levels in depressed patients receiving electroconvulsive therapy. Eur Neuropsychopharmacol 19:349–355. https://doi.org/10.1016/j.euroneuro.2009.01.002
64. Castrén E, Rantamäki T (2010) The role of BDNF and its receptors in depression and antidepressant drug action: reactivation of developmental plasticity. Dev Neurobiol. 70:289–297
65. Bruñon AR, Machado-Vieira R, Zarate CA et al (2014) BDNF plasma levels after antidepressant treatment with sertraline and transcranial direct current stimulation: results from a factorial, randomized, sham-controlled trial. Eur Neuropsychopharmacol 24:1144–1151. https://doi.org/10.1016/j.euroencephal.2014.03.006
66. Colla M, Kronenberg G, Deuschle M et al (2007) Hippocampal volume reduction and HPA-system activity in major depression. J Psychiatr Res 41:553–560. https://doi.org/10.1016/j.jpsychires.2006.06.011
67. Allen AP, Naughton M, Dowling J et al (2015) Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid antidepressant response: a comparison of ketamine and ECT. J Affect Disord 186:306–311. https://doi.org/10.1016/j.jad.2015.06.033
68. Kim Y-K, Na K-S (2016) Role of glutamate receptors and glial cells in the pathophysiology of treatment-resistant depression. Prog Neuro-Psychopharmacol Biol Psychiatry 70:117–126. https://doi.org/10.1016/j.pnpbp.2016.03.009
69. Mehta M, Blithe RM, Kelley KW, Dantzer R (1992) Sickness behavior as a new target for drug development. Trends Pharmacol Sci 13:24–28. https://doi.org/10.1016/0165-6147(92)90012-U
70. Qin L, Wu X, Block ML et al (2007) Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia 55:453–462. https://doi.org/10.1002/glia.20467
71. Guan Z, Fang J (2006) Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. Brain Behav Immun 20:64–71. https://doi.org/10.1016/j.bbi.2005.04.005
72. Zhang JC, Wu J, Fujita Y et al (2014) Antidepressant effects of TrkB ligands on depression-like behavior and dendritic changes in mice after inflammation. Int J Neuropsychopharmacol 18:1–12. https://doi.org/10.1093/ijnp/pyu077
73. Gibney SM, McGuinness B, Prendegast C et al (2013) Poly I: C-induced activation of the immune response is accompanied by chronic unpredictable stress rat model and the effects of chronic antidepressant treatment. J Psychiatr Res 44:808–816. https://doi.org/10.1016/j.jpsychires.2010.01.005
74. Karege F, Bondolfi G, Gervasoni N et al (2005) Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 57:1068–1072. https://doi.org/10.1016/j.biopsych.2005.01.008
75. Guan Z, Fang J (2006) Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. Brain Behav Immun 20:64–71. https://doi.org/10.1016/j.bbi.2005.04.005
76. Zhang JC, Wu J, Fujita Y et al (2014) Antidepressant effects of TrkB ligands on depression-like behavior and dendritic changes in mice after inflammation. Int J Neuropsychopharmacol 18:1–12. https://doi.org/10.1093/ijnp/pyu077
77. Gibney SM, McGuinness B, Prendegast C et al (2013) Poly I: C-induced activation of the immune response is accompanied by chronic unpredictable stress rat model and the effects of chronic antidepressant treatment. J Psychiatr Res 44:808–816. https://doi.org/10.1016/j.jpsychires.2010.01.005
depression and anxiety-like behaviours, kynurenine pathway activation and reduced BDNF expression. Brain Behav Immun 28: 170–181. https://doi.org/10.1016/j.bbi.2012.11.010

78. Capuron L, Miller AH (2004) Cytokines and psychopathology: lessons from interferon-α. Biol Psychiatry 56:819–824. https://doi.org/10.1016/j.biopsych.2004.02.009

79. Raison CL, Miller AH (2011) Is depression an inflammatory disorder? Curr Psychiatry Rep 13:467–475. https://doi.org/10.1007/s11920-011-0232-0

80. Pace TWW, Mietzko TC, Alagbe O et al (2006) Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry 163: 1630–1633. https://doi.org/10.1176/appi.ajp.163.9.1630

81. Lotrich FE, Albusaysi S, Ferrell RE (2013) Brain-derived Neurotrophic factor serum levels and genotype: association with depression during interferon-alpha treatment. Neuropsychopharmacology 38:985–995. https://doi.org/10.1038/npn.2012.263

82. Kenis G, Prickaerts J, van Os J et al (2011) Depressive symptoms following interferon-α therapy: mediated by immune-induced reductions in brain-derived neurotrophic factor? Int J Neuropsychopharmacol 14:247–253. https://doi.org/10.1017/S1461145710000830

83. Dahl J, Ormstad H, Aass HCD et al (2014) The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. Psychoneuroendocrinology 45:77–86. https://doi.org/10.1016/j.psyneuen.2014.03.019

84. Hamnset J, Dellaﬁoia N, Bloch M (2011) The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology 36: 2452–2459. https://doi.org/10.1038/npn.2011.132

85. Angst F, Stassen HH, Clayton PJ, Angst J (2002) Mortality of patients with mood disorders: follow-up over 34-38 years. J Affect Disord 68:167–181. https://doi.org/10.1016/S1054-3270(01)00377-9

86. Goldstein TR, Birmaher B, Axelson D et al (2009) Psychosocial functioning among bipolar youth. J Affect Disord 114:174–183. https://doi.org/10.1016/j.jad.2008.07.001

87. Berk M, Kapczinski F, Andreazza AC et al (2011) Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 35:804–817. https://doi.org/10.1016/j.neubiorev.2010.11.002

88. Fernandes BS, Gama CS, Maria Cereser K et al (2011) Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res 45:995–1004. https://doi.org/10.1016/j.jpsychires.2011.03.002

89. Tunca Z, Ozerdem A, Ceylan D et al (2014) Alterations in BDNF (brain derived neurotrophic factor) and GDNF (glial cell line-derived neurotrophic factor) serum levels in bipolar disorder: the role of lithium. J Affect Disord 166:193–200. https://doi.org/10.1016/j.jad.2014.05.012

90. Munion A (2016) Bipolar disorder: role of inflammation and the development of disease biomarkers. Psychiatry Investig 13:18–33. https://doi.org/10.4306/pi.2016.13.1.18

91. Munkholm K, Braüner JV, Kessing LV, Vinberg M (2013) Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. J Psychiatr Res 47:1119–1133. https://doi.org/10.1016/j.jpsychires.2013.05.018

92. Steiner J, Bielau H, Brisch R et al (2008) Immuno logical aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. J Psychiatr Res 42:151–157. https://doi.org/10.1016/j.jpsychires.2006.10.013

93. Patas K, Penninx BWH, Bus BAA et al (2014) Association between serum brain-derived neurotrophic factor and plasma interleukin-6 in major depressive disorder with melancholic features. Brain Behav Immun 36:71–79. https://doi.org/10.1016/j.bbi.2013.10.007

94. Wang T-Y, Lee S-Y, Chen S-L et al (2016) Comparing clinical responses and the biomarkers of BDNF and cytokines between subthreshold bipolar disorder and bipolar II disorder. Sci Rep 6:27431. https://doi.org/10.1038/srep27431

95. Basselin M, Kim HW, Chen M et al (2010) Lithium modifies brain arachidonic and docosahexaenoic metabolism in rat lipopolysaccharide model of neuroinflammation. J Lipid Res 51:1049–1056. https://doi.org/10.1194/jlr.M002469

96. Boufidou F, Nikolau C, Alexizos B et al (2004) Cytokine production in bipolar affective disorder patients under lithium treatment. J Affect Disord 82:309–313. https://doi.org/10.1016/j.jad.2004.01.007

97. Kim YK, Jung HG, Myint AM et al (2007) Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord 104:91–95. https://doi.org/10.1016/j.jad.2007.02.018

98. Gould TD, Quiroz JA, Singh J et al (2004) Emerging experimental therapeutics for bipolar disorder: insights from the molecular and cellular actions of current mood stabilizers. Mol Psychiatry 9:734–755. https://doi.org/10.1038/sj.mp.4001518

99. Yadav M, Clark L, Schorey JS (2006) Macrophage’s proinflammatory response to a mycobacterial infection is dependent on sphingosine kinase-mediated activation of phosphatidylinositol phospholipase C, protein kinase C, ERK1/2, and phosphatidylinositol 3-kinase. J Immunol 176:5494

100. Song XM, Yu Q, Dong X et al (2017) Aldose reductase inhibitors attenuate β-amyloid-induced TNF-α production in microglia via ROS–PKC-mediated NF-κB and MAPK pathways. Int Immunopharmacol 50:30–37. https://doi.org/10.1016/j.intimp.2017.06.005

101. Zarete CA, Manji HK (2009) Protein kinase C inhibitors: rationale for use and potential in the treatment of bipolar disorder. CNS Drugs 23:569–582

102. Yildiz A, Guleryuz S, Ankerst DP et al (2008) Protein kinase C inhibition in the treatment of mania. Arch Gen Psychiatry 65:255–263. https://doi.org/10.1001/archgenpsychiatry.2007.43

103. Zarete CA, Singh JB, Carlson PJ et al (2007) Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. Bipolar Disord 9:561–570. https://doi.org/10.1111/j.1399-5618.2007.00530.x

104. Radha N, Dominguez LG, Farzan F et al (2015) Evidence for inhibitory deficits in the prefrontal cortex in schizophrenia. Brain 138:483–497. https://doi.org/10.1093/brain/awu360
Okello A, Edison P, Archer HA et al (2009) Microglial activation
Koivunen J, Scheinin N, Virta JR et al (2011) Amyloid PET im-
Holmes C, Cunningham C, Zotova E et al (2009) Systemic in-
Iwashyna TJ, Ely EW, Smith DM, Langa KM (2010) Long-term
Laske C, Stellos K, Hoffmann N et al (2011) Higher BDNF serum
gene expression is associated with slower cognitive decline in
older adults. Neurology 86:735–741. https://doi.org/10.1212/ WNL.000000000002387
Town T, Tan J, Flavell RA, Mullan M (2005) T-cells in Alzheimer’s
disease. NeuroMolecular Med 7:255–264. https://doi.org/10.1385/MMM:7:3:255
Heneka MT, Kümmer MP, Latz E (2014) Innate immune activa-
tion with atypical proinflammatory cytokine expression in a rat
model of Parkinson’s disease. Eur J Neurosci 18:273–283. https://doi.org/10.1111/j.1471-4159.2009.06189.x
Kawabata T, Ohishi S, Yamanaka T et al (2007) Intraperitoneal
administration of the anti-inflammatory agents reduces
inflammation in the substantia nigra of a 6-OHDA treated
mouse model of Parkinson’s disease. J Neurosci Res 85:2752–2764. https://doi.org/10.1002/jnr.21179
Lynch MA (2015) Neuroinflammatory changes negatively impact
on LTP; a focus on IL-1β. Brain Res 1621:197–204. https://doi. org/10.1016/j.brainres.2014.08.040
Tong L, Prieto GA, Kramár E et al (2012) Brain-derived neuro-
Lynch MA, Ohishi S, Yamanaka T et al (2007) Inhibiting
reactive oxygen species protects the substantia nigra against
neurodegeneration in a 6-OHDA mouse model of Parkinson’s
disease. J Neurosci Res 85:2765–2774. https://doi.org/10.1002/jnr.21180
Surmeier DJ, Obeso JA, Halliday GM (2017) Selective neuronal
vulnerability in Parkinson disease. Nat Rev Neurosci 18:101–113. https://doi.org/10.1038/nrn.2016.178
Cheng HC, Ulat-CM, Burke RE (2010) Clinical progression in
Parkinson disease and the neurobiology of axons. Ann Neurol 67:
715–725
Jucker M, Walker LC (2013) Self-propagation of pathogenic pro-
tein aggregates in neurodegenerative diseases. Nature 501:45–51. https://doi.org/10.1038/nature12481
Janakiraman U, Manivasagam T, Justin Thenmozhi A et al (2017)
Chronic mild stress augments MPTP induced neurotoxicity in
a murine model of Parkinson’s disease. Physiol Behav 173:132–
143. https://doi.org/10.1016/j.physbeh.2017.01.046
Howells DW, Porritt MJ, Wong JFY et al (2000) Reduced
BDNF mRNA expression in the Parkinson’s disease substantia
nigra. Exp Neurol 166:127–135. https://doi.org/10.1006/exnr.2000.7483
Porritt MJ, Batchelor PE, Howells DW (2005) Inhibiting BDNF
expression by antisense oligonucleotide infusion causes loss of
nigral dopaminergic neurons. Exp Neurol 192:226–234. https://doi.org/10.1016/j.expneurol.2004.11.030
Ventriglia M, Zanardini R, Bonomi C et al (2013) Serum brain-
derived neurotrophic factor levels in different neurological dis-
bases. Biomed Res Int 2013:901082. https://doi.org/10.1155/ 2013/901082
Scalzo P, Kümmér A, Bretas TL et al (2010) Serum levels of brain-
derived neurotrophic factor correlate with motor impairment in
Parkinson’s disease. J Neuro 257:540–545. https://doi.org/10. 1007/s00415-009-5357-2
Marinova-Mutafchieva L, Sadeghian M, Broom L et al (2009)
Relationship between microglial activation and dopaminergic
neural loss in the substantia nigra: a time course study in a 6-
hydroxydopamine model of Parkinson’s disease. J Neurochem
110:966–975. https://doi.org/10.1111/j.1471-4159.2009.06189.x
Depino AM, Earl C, Kaczmarczyk E et al (2003) Microglial activa-
tion with atypical proinflammatory cytokine expression in a rat
model of Parkinson’s disease. Eur J Neurosci 18:2731–2742. https://doi.org/10.1046/j.1460-9586.2003.03014.x
Main BS, Zhang M, Brody KM et al (2016) Type-1 interferons
contribute to the neuroinflammatory response and disease progress-
ion of the MPTP mouse model of Parkinson’s disease. Glia 64:
1590–1604. https://doi.org/10.1002/glia.23028
Femininella GD, Ninan S, Atkinson R et al (2016) Does microglial
activation influence hippocampal volume and neuronal
function in Alzheimer’s disease and Parkinson’s disease demen-
tia? J Alzheimer’s Dis 51:1275–1289. https://doi.org/10.3233/ JAD-150827
Gerhard A, Pavese N, Hotton G et al (2006) In vivo imaging of
microglial activation with [11C](R)-PK11195 PET in idiopathic
Parkinson’s disease. Neurobiol Dis 21:404–412. https://doi.org/ 10.1016/j.nbd.2005.08.002
174. Savada M, Imamura K, Nagatsu T (2006) Role of cytokines in inflammatory process in Parkinson’s disease. J Neural Transm Suppl 70:373–381

175. Jensen FE (2011) Epilepsy as a spectrum disorder: implications from novel clinical and basic neuroscience. Epilepsia 52:1–6. https://doi.org/10.1111/j.1528-1167.2010.02904.x

176. Lee B, Dziema H, Lee KH et al (2007) CRE-mediated transcription and COX-2 expression in the pilocarpine model of status epilepticus. Neurobiol Dis 25:80–91. https://doi.org/10.1016/j. nbd.2006.08.015

177. Li L, Deng J, Liu C et al (2016) Altered expression of neurotide Y receptors caused by focal cortical dysplasia in human intractable epilepsy. Oncotarget 7:15329–15338. https://doi.org/10.18632/oncotarget.7855

178. Wang Y, Qi J-S, Kong S et al (2009) BDNF-TrkB signaling pathway mediates the induction of epileptiform activity induced by a convulsant drug cyclothiazide. Neuropharmacology 57:49–59. https://doi.org/10.1016/j.nphar.2009.04.007

179. Martínez-Levy GA, Rocha L, Rodríguez-Pineda F, et al (2017) Increased expression of brain-derived neurotrophic factor transcripts I and VI, cAMP response element binding, and glucocorticoid receptor in the cortex of patients with temporal lobe epilepsy. Mol Neurobiol. https://doi.org/10.1007/s12035-017-0597-0

180. Martínez-Levy GA, Rocha L, Lubin FD et al (2016) Increased expression of BDNF transcript with exon VI in hippocampi of patients with pharmaco-resistant temporal lobe epilepsy. Neuroscience 314:12–21. https://doi.org/10.1016/j.neuroscience.2015.11.046

181. Unsain N, Montroull LE, Mascó DH (2009) Brain-derived neurotrophic factor facilitates TrkB down-regulation and neuronal injury after status epilepticus in the rat hippocampus. J Neurochem 111:428–440. https://doi.org/10.1111/j.1471-4159.2009.06342.x

182. Otsuka S, Ohkido T, Iakura M et al (2016) Dual mechanisms of rapid expression of anxiety-related behavior in pilocarpine-treated epileptic mice. Epilepsy Res 123:55–67. https://doi.org/10.1016/j. eplepsiyres.2016.04.007

183. de Souza Bernardino TC, Teixeira AL, Miranda AS et al (2015) Wistar Audiogenic Rats (WAR) exhibit altered levels of cytokines and brain-derived neurotrophic factor following audiogenic seizures. Neurosci Lett 597:154–158. https://doi.org/10.1016/j. neulet.2015.04.004

184. Carvalho AL, Caldeira MV, Santos SD, Duarte CB (2008) Role of the brain-derived neurotrophic factor at glutamatergic synapses. Br J Pharmacol 153(Suppl):S310–S324. https://doi.org/10.1038/ sj.bjp.0705709

185. Binder DK, Croll SD, Gall CM, Scharfman HE (2001) BDNF and epilepsy: too much of a good thing? Trends Neurosci 24:47–53. https://doi.org/10.1016/S0166-2236(00)01682-9

186. Liu G, Gu B, He X-P et al (2013) Transient inhibition of TrkB kinase after status epilepticus prevents development of temporal lobe epilepsy. Neuron 79:31–38. https://doi.org/10.1016/j.neuron.2013.04.027

187. Liu G, Kotloski RJ, McNamara JO (2014) Antiseizure effects of TrkB kinase inhibition. Epilepsia 55:1264–1273. https://doi.org/10.1111/epi.12671

188. Vezzani A, French J, Bartfai T, Baram TZ (2011) The role of inflammation in epilepsy. Nat Rev Neurol 7:31–40. https://doi.org/10.1038/nrneurol.2010.178

189. Benson MJ, Manzaneiro S, Borges K (2015) Complex alterations in microglial M1/M2 markers during the development of epilepsy in two mouse models. Epilepsia 56:895–905. https://doi.org/10.1111/epi.12960

190. Lehtimäki KA, Peltola J, Koskilakko E et al (2003) Expression of cytokines and cytokine receptors in the rat brain after kaicnic acid-induced seizures. Brain Res Mol Brain Res 110:253–260

191. Zheng H, Zhu W, Zhao H et al (2009) Kainic acid-activated microglia mediate increased excitability of rat hippocampal neurons in vitro and in vivo: crucial role of interleukin-1beta. Neuroimmunomodulation 17:31–38. https://doi.org/10.1159/000243083

192. Kairisalo M, Korhonen L, Sepp M et al (2009) NF-κB-dependent regulation of brain-derived neurotrophic factor in hippocampal neurons by X-linked inhibitor of apoptosis protein. Eur J Neurosci 30:958–966. https://doi.org/10.1111/j.1460-9586.2009.06898.x

193. Mattson MP, Camandola S (2001) NF-κB in neuronal plasticity and neurodegenerative disorders. J Clin Invest 107:247–254

194. Lubin FD, Ren Y, Xu X, Anderson AE (2007) Nuclear factor-κB regulates seizure threshold and gene transcription following convulsive stimulation. J Neurochem 103:1381–1395. https://doi.org/10.1111/j.1471-4159.2007.04865.x

195. Nagahara AH, Tuszyński MH (2011) Potential therapeutic uses of BDNF in neurological and psychiatric disorders. Nat Rev Drug Discov 10:209–219. https://doi.org/10.1038/nrd3366

196. Liu G, Kotloski RJ, McNamara JO (2011) CRE-mediated transcription and COX-2 expression in the pilocarpine model of status epilepticus. Neurobiol Dis 25:80–91. https://doi.org/10.1016/j. nbd.2006.08.015
207. Farmer J, Zhao X, van Praag H et al (2004) Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. Neuroscience 124:71–79. https://doi.org/10.1016/j.neuroscience.2003.09.029

208. Huang T, Larsen KT, Ried-Larsen M et al (2014) The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: a review. Scand J Med Sci Sports 24:1–10. https://doi.org/10.1111/sms.12069

209. Zoladz JA, Pilk A (2010) The effect of physical activity on the brain derived neurotrophic factor: from animal to human studies. J Physiol Pharmacol 61:533–541. https://doi.org/10.1016/j.jphysparmac.2010.09.005

210. Hoffman JR, Ostfeld I, Kaplan Z et al (2015) Exercise enhances synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. Neuroscience 308:180–193. https://doi.org/10.1016/j.neuroscience.2015.12.011

211. Kirshenbaum GS, Burgess CR, Déry N et al (2014) Attenuation of mania-like behavior in Na+,K+-ATPase α3 mutant mice by pro-spective therapies for bipolar disorder: melatonin and exercise. Neuroscience 308:180–193. https://doi.org/10.1016/j.neuroscience.2015.09.005

212. García-Mesa Y, Pareja-Galeano H, Bonet-Costa V et al (2014) Physical exercise neuroprotects ovariectomized 3xTg-AD mice through BDNF mechanisms. Psychoneuroendocrinology 45:154–166. https://doi.org/10.1016/j.psyneuen.2014.03.021

213. Tuon T, Valvassori SS, Dal Pont GC et al (2014) Physical training prevents depressive symptoms and a decrease in brain-derived neurotrophic factor in Parkinson’s disease. Brain Res Bull 108:106–112. https://doi.org/10.1016/j.brainresbull.2014.09.006

214. Coelho FG d M, Vital TM, Stein AM et al (2014) Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer’s disease. J Alzheimer’s Dis 39:401–408. https://doi.org/10.3233/JAD-131073

215. Dao AT, Zagaar MA, Levine AT et al (2013) Treadmill exercise prevents learning and memory impairment in Alzheimer’s disease-like pathology. Curr Alzheimer Res 10:507–515

216. Noble EE, Billington CJ, Kotz CM, Wang C (2011) The lighter side of BDNF. Am J Physiol Regul Integr Comp Physiol 300:R1053–R1069. https://doi.org/10.1152/ajpregu.00776.2010

217. Schwartz E, Mobbs CV (2012) Hypothalamic BDNF and obesity: found in translation. Nat Med 18:496–497. https://doi.org/10.1038/nm.2716

218. Kernie SG, Liebl DJ, Parada LF (2000) BDNF regulates eating and locomotor activity in mice. EMBO J 19:1290–1300. https://doi.org/10.1093/emboj/19.6.1290

219. Sharma S, Fulton S (2013) Diet-induced obesity promotes depressive-like behaviour that is associated with neural adaptations in brain reward circuitry. Int J Obes 37:382–389. https://doi.org/10.1038/ijo.2012.48

220. Beilharz JE, Maniam J, Morris MJ (2014) Short exposure to a diet rich in both fat and sugar or sugar alone impairs place, but not object recognition memory in rats. Brain Behav Immun 37:134–141. https://doi.org/10.1016/j.bbi.2013.11.016

221. Noble EE, Hsu TM, Kanosi SE (2017) Gut to brain dysbiosis: mechanisms linking western diet consumption, the microbiome, and cognitive impairment. Front Behav Neurosci 11:9. https://doi.org/10.3389/fnbeh.2017.00009

222. Duan W, Lee J, Guo Z, Mattson MP (2001) Dietary restriction stimulates BDNF production in the brain and thereby protects neurons against excitotoxic injury. J Mol Neurosci 16:1–12. https://doi.org/10.1385/JMN:16:1:1

223. Duan W, Guo Z, Jiang H et al (2003) Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. Proc Natl Acad Sci U S A 100:2911–2916. https://doi.org/10.1073/pnas.0536856100

224. Wu A, Ying Z, Gomez-Pinilla F (2004) Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. J Neurotrauma 21:1457–1467. https://doi.org/10.1089/neu.2004.21.1457