



Interactions Among Brain-Derived Neurotrophic Factor and Neuroimmune Pathways Are Key Components of the Major Psychiatric Disorders

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Abstract

The purpose of this review is to summarize the current knowledge regarding the reciprocal associations between brain-derived neurotrophic factor (BDNF) and immune-inflammatory pathways and how these links may explain the involvement of this neurotrophin in the immune pathophysiology of mood disorders and schizophrenia. Toward this end, we delineated the protein–protein interaction (PPI) network centered around BDNF and searched PubMed, Scopus, Google Scholar, and Science Direct for papers dealing with the involvement of BDNF in the major psychosis, neurodevelopment, neuronal functions, and immune-inflammatory and related pathways. The PPI network was built based on the significant interactions of BDNF with neurotrophic (NTRK2, NTF4, and NGFR), immune (cytokines, STAT3, TRAF6), and cell–cell junction (CTNNB, CDH1) DEPs (differentially expressed proteins). Enrichment analysis shows that the most significant terms associated with this PPI network are the tyrosine kinase receptor (TRKR) and Src homology region two domain-containing phosphatase-2 (SHP2) pathways, tyrosine kinase receptor signaling pathways, positive regulation of kinase and transferase activity, cytokine signaling, and negative regulation of the immune response. The participation of BDNF in the immune response and its interactions with neuroprotective and cell–cell adhesion DEPs is probably a conserved regulatory process which protects against the many detrimental effects of immune activation and hyperinflammation including neurotoxicity. Lowered BDNF levels in mood disorders and schizophrenia (a) are associated with disruptions in neurotrophic signaling and activated immune-inflammatory pathways leading to neurotoxicity and (b) may interact with the reduced expression of other DEPs (CTNNB1, CDH1, or DISC1) leading to multiple aberrations in synapse and axonal functions.

Keywords Major depression · Schizophrenia · Inflammation · Neuroimmune · Biomarkers · Psychiatry · Pathways

Abbreviations

BDNF	Brain-derived neurotrophic factor	ChIP analysis	Chromatin immunoprecipitation analysis
BD	Bipolar disorder	CIRS	Compensatory immune regulatory system
CDH	Cadherin gene/protein	CPE	Carboxypeptidase E
CDC	Cell division cycle gene/protein	CSF	Cerebrospinal fluid
		CRK	CRK proto-oncogene
		CREB	CAMP response element-binding protein
		CTNNB	Catenin beta protein

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CTBBB1	Catenin beta 1 gene
DBS	Deep brain stimulation
DISC1	Disrupted in schizophrenia 1 protein
DEPs	Differentially expressed proteins
FEP	First-episode psychosis
FES	First-episode schizophrenia
GABA	Gamma aminobutyric acid
GO	Gene ontology
GSK	Glycogen synthase kinase
GRB2	Growth factor receptor-bound protein 2
HDAC	Histone deacetylase
HMGB1	High mobility group box 1 DNA-binding nuclear protein
HRAS	GTPase HRas
Hp	Haptoglobin
hESC-NSCs	Human embryonic spinal cord NSCs
IFN	Interferon
IL	Interleukin
IRS	Inflammatory response system
JAK-STAT	Janus kinases/signal transducer and activator of transcription
JNK	C-Jun N-terminal kinase
KEGG	Kyoto encyclopedia of genes and genomes
LIMK1	LIM domain kinase 1
LPS	Lipopolysaccharide
LTD	Long-term depression
LTP	Long-term potentiation
MAPK	Ras-mitogen-activated protein kinase
MDD	Major depressive disorder
MECP2	Methyl-CpG-binding protein 2
MFB	Medial forebrain bundle
MMP	Matrix metalloproteinase
NMDAR	<i>N</i> -Methyl-D-aspartate receptor
NGF	Beta-nerve growth factor
NGFR	Tumor necrosis factor receptor superfamily member 16
NPC	Intracellular cholesterol transporter
NSC	Neural stem cells
NTF	Neurotrophin
NTRK1	High affinity nerve growth factor receptor
NTRK2	BDNF/NT-3 growth factors receptor
PBMC	Peripheral blood mononuclear cells
PFC	Prefrontal cortex
PI3K	Phosphatidylinositol-3-kinase
PIK3R	Phosphatidylinositol-3-kinase receptor
PLC	Phospholipase C
PPI	Protein-protein interaction
qRT-PCR	Real-time quantitative reverse transcription
RAGE	Receptor for advanced glycation end products
RIP2	Serine/threonine protein kinase 2
SHP2	Two domain-containing phosphatase-2

STAT3	Signal transducer and activator of transcription 3
STRING	Significant database-annotated interactions
SORT	Sortilin
Th	T helper cells
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
TP53	Tumor protein p53
TRAF6	Tumor necrosis factor 6 receptor factor
T reg	T regulatory cells
TRK	Tropomyosin receptor kinase
TRKR	Tyrosine kinase receptor
TRYCAT	Tryptophan catabolite

Introduction

Maes and Smith [1, 2] developed novel theories in 1995 based on pioneering findings that the major psychoses, including major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia, are characterized by activated immune-inflammatory pathways. Thus, the monocyte-T-lymphocyte theory of major depression postulated that increased M1 macrophage activity associated with increased complement factors and acute phase proteins induced by pro-inflammatory cytokines such as interleukin (IL)-1 and IL-6, as well as increased T-helper 1 (Th-1) activity associated with IL-2 and interferon (IFN), underpins the pathogenesis of this condition [1]. Smith and Maes [2] also pioneered the macrophage – Th-1 lymphocyte theory of schizophrenia, hypothesizing that prenatal bacterial and viral infections may cause neurodevelopmental disorders, increasing postnatal susceptibility to immune-inflammatory stimuli via the neurotoxic effects of the aforementioned cytokines, the associated nitro-oxidative pathways, and induction of the tryptophan catabolite (TRYCAT) pathway with increased levels of neurotoxic TRYCATs.

There is now evidence that immune-inflammatory pathways play a critical role in the pathophysiology of major psychosis. Recent conceptualizations of both affective disorders and schizophrenia indicate that the major psychoses are associated with activation of the immune-inflammatory response system (IRS) and concurrent activation of the compensatory immune regulatory system (CIRS), which tends to downregulate the immune response and protects against an excessive immune response and hyperinflammation [3, 4]. Both MDD and BD are associated with IRS activation markers such as M1, Th-1, and Th-17 activation, as well as CIRS activation markers such as negative immune-regulatory cytokines including Th-2 (e.g., IL-4) and T regulatory (Treg) cytokines (e.g., IL-10), increased levels of soluble cytokine

receptors which may inhibit cytokine signaling, e.g., the soluble tumor necrosis factor (TNF) receptor (sTNFR) and sIL-2R and sIL-1R antagonist (sIL-1RA), and some positive acute phase proteins including haptoglobin (Hp) [3]. Similarly, schizophrenia is associated with the same markers of IRS activation, such as M1, Th-1, and Th-17 activation, as well as CIRS activation, such as increased Treg and Th-2 shifts [4]. In both affective disorders (MDD and BD) and schizophrenia, acute episodes are associated with a shift in the homeostatic IRS/CIRS setpoint, as shown by an increased IRS/CIRS ratio, indicating a net immune-inflammatory response [3, 4].

According to the aforementioned theories, numerous different pathways including some cytokines (e.g., IL-1 β , IL-6, TNF- α) and chemokines such as IL-8 (CXCL-8) and exotoxin (CCL-11), TRYCATS, and nitro-oxidative stress increase neurotoxicity in vulnerable brain regions, resulting in neuro-affective toxicity in affective disorders and more widespread neurotoxicity in schizophrenia [3, 4]. Additionally, enrichment and annotation analysis of differentially expressed proteins (DEPs) in first-episode psychosis (FEP) and new findings in schizophrenia indicate that activation of nuclear factor- κ B, Toll-like receptor (TLR)-4, and Janus kinases/signal transducer and activator of transcription (JAK-STAT) pathways are involved in FEP and play a role in the subsequent transition from FEP to first episode schizophrenia (FES) [5]. Notably, both affective disorders and FES are associated with increased Gram-negative bacteria translocation via increased gut permeability, and it is believed that these biotic stimuli contribute to affective disorders and schizophrenia by activating the TLR2/4 complex, eliciting neuro-immune and nitro-oxidative pathways in the major psychosis, autoimmune responses in affective disorders, and intracellular pathways in FEP/FES [5, 6].

However, decreased neuroprotection because of reduced levels of neurotrophic factors also contributes to affective disorders and schizophrenia [5, 7]. Among these neurotrophic factors is brain-derived neurotrophic factor (BDNF), a multifunctional neurotrophin with numerous functions in the brain [8–10]. The evidence for the participation of BDNF and BDNF/TRK tropomyosin receptor kinase (encoded by the NTRK1 gene and binds BDNF) signaling in a wide range of neurophysiological processes continues to mount, including synaptic plasticity, connections, structure and formation, synaptogenesis, axonal growth, sprouting and guidance, dendritic arborization, neuronal differentiation and survival, neurogenesis, and modulation of neurotransmitter release [5, 11]. BDNF is found in nearly every brain region and participates in all stages of brain development and aging [12, 13]. It is regarded as an instructive mediator of structural and functional plasticity in the central nervous system [12]. Not only the major psychoses, but also other neuropsychiatric illnesses such as Alzheimer's, Huntington's, and Parkinson's

disease, as well as anxiety disorders, have been associated with decreased or altered BDNF signaling [14, 15]. While BDNF is not a biomarker for neurodegenerative or neuropsychiatric diseases due to its nonspecific deregulation in a variety of pathological conditions, it is believed to be specifically associated with the occurrence and/or progression of mnemonic symptoms associated with a variety of conditions characterized by cognitive deficits [12].

The purpose of this review is to summarize the current knowledge regarding the associations between BDNF and immune-inflammatory pathways in general and in the major psychoses more specifically.

Methods

In this narrative review, we examine (a) the role of BDNF in the major psychoses with respect to its role in neurodevelopment and neuronal plasticity and (b) the reciprocal associations between BDNF and immune-inflammatory pathways. Toward this end, we delineated the protein–protein interaction (PPI) network in which BDNF participates and searched PubMed, Scopus, Google Scholar, and Science Direct for papers dealing with involvement of BDNF in the major psychosis, neurodevelopment, neuronal functions, and immune-inflammatory and related pathways.

BDNF and immune pathways play a role in complex mood and psychotic disorders, involving interactions between genetic factors, immune and BDNF pathways, and their intracellular signaling networks, metabolic pathways, and protein/enzyme alterations. Until recently, the majority of genetic, pathway, and metabolic studies on BDNF in psychiatry have focused on identifying and characterizing individual gene variants, as well as BDNF mRNA and protein levels in a variety of neuropsychiatric diseases. Nonetheless, BDNF and immune genes/proteins have a small to moderate effect on susceptibility and outcome in complex diseases, such as schizophrenia [5]. Enrichment and annotation analyses may shed light on how BDNF and immune genes and proteins interact to affect disease susceptibility. Additionally, network analysis of PPIs may reveal novel drug targets for modulating BDNF, immune pathways, and transcription factors. The objectives of this section are to define (a) the BDNF interactome and its interactions with the neuroimmune network; (b) the biological functions, pathways, molecular patterns, and cellular components that define the BDNF networks; and (c) the possible trigger factors for changes in the BDNF-neuroimmune interactome.

The enrichment and annotation analyses were conducted as described previously [5]. We constructed three types of expanded networks: (1) a first-order PPI network based on BDNF as only seed protein and 10 interactions in the first shell and none in the second (with a minimum required

interaction score of 0.900 and set organism: homo sapiens), (2) a first order–enlarged PPI network with BDNF as only seed protein and 50 interactions in the first shell and none in the second shell (again with a minimum required interaction score of 0.900 and set organism: homo sapiens), and (3) giant networks based on the network established in or the combination of the latter with the major M1, Th-1, Th-2, Th-17, and Treg genes common to affective disorders and schizophrenia [3, 4]. The networks were constructed using STRING version 11.0 (<https://string-db.org>), a predictive database, and the IntAct Molecular Interaction Database (<https://www.ebi.ac.uk/intact/>), a primary database based on peer-reviewed publications. STRING and the Cytoscape plugin Network Analyzer were used to compute the network characteristics. The network backbone was defined as a collection of top hubs (nodes with the highest degree) and top non-hub bottlenecks (nodes with the highest betweenness centrality). STRING, Gene Ontology (GO) net (<https://tools.dice-database.org/Gonet/>), OmicsNet (OmicsNet), and Metascape (<https://metascape.org>) were used to visualize the physical interactions between the proteins/genes. The different PPI networks were analyzed for their enrichment scores and annotated terms using the following tools: (a) STRING to establish GO biological processes and molecular functions, as well as KEGG (<https://genome.jp/kegg/>) and REACTOME (the European Bioinformatics Institute Pathway Database; <https://reactome.org>) pathways, (b) OmicsNet (using InAct, mirNET, TTRUST, and KEGG metabolic reactions) to establish REACTOME and PANTHER (PANTHER—Gene List Analysis (pantherdb.org) biological processes) and the OmicsNet regulation explorer to establish TTRUST transcriptional regulatory relationships (www.grnpedia.org/trrust); and (c) Metascape to establish and visualize the over-represented REACTOME, KEGG, PANTHER, and Wiki (WikiPathways—WikiPathways) pathways. The latter are based on accumulative hypergeometric *p*-values that are used for filtering, after which the remaining terms are hierarchically clustered into a tree and cast into term clusters using a 0.3 kappa score threshold. As such, Metascape was also combined with Molecular Complex Detection (MCODE) to delineate and visualize enriched ontology clusters.

Human BDNF

The human BDNF gene is composed of 11 exons and nine alternative promoters, with the coding sequence located in exon IX and present in all BDNF messenger RNA isoforms. The presence of many gene controlling regions suggests for complex BDNF expression in response to a wide variety of stimuli [16]. Alternative splicing enables the formation of transcripts that are tissue- and stimulus-specific [17].

BDNF is released as a mixture of pro- and mature forms with opposing effects and involvement of distinct cellular pathways. BDNF is translated as a proneurotrophin (pro-BDNF) and is cleaved in the cytoplasm by endoproteases or in the extracellular matrix by plasmin or matrix metalloproteinases to produce the mature BDNF [11].

Both mature BDNF and pro-BDNF can be secreted and bind to the neurotrophin receptor p75 NTR and induce apoptosis [18]. Only the mature BDNF binds to tyrosine kinase receptors (TrkB) and activates a variety of signaling cascades [19]. By creating cleavage-resistant pro-BDNF knock-in mouse, Yang et al. [20] demonstrated that pro-BDNF negatively regulates hippocampal dendritic complexity and spine density through p75(NTR). Low synaptic transmission and enhanced long-term depression were detected suggesting that pro-BDNF has distinct functions from those of mature BDNF, which acts as a biologically active factor that regulates hippocampal structure, synaptic transmission, and plasticity [20]. When activated, the phosphatidylinositol-3-kinase (PI3K), the Ras-mitogen-activated protein kinase (MAPK), and the phospholipase C (PLC-) pathways result in the phosphorylation of transcription factors and the de novo transcription of the BDNF gene [19], ultimately promoting cell survival [21]. On the other hand, truncated TrkB receptors act as dominant negative inhibitors of BDNF signaling, whereas proBDNF helps regulate BDNF in physiological conditions [22].

Apart from the two isoforms, a single nucleotide polymorphism at position 66 within the BDNF gene's prodomain encoding region influences neurotrophin's functionality [23]. The Val66Met substitution is shown to result into a condensed protein explaining neuronal growth cone retraction [24]. The Met66 prodomain variant is also proposed to function as a ligand with independent significance for BDNF communication [25]. BDNF isoforms appear to play a role in the regulation of processes throughout the brain's development, as well as in diverse cellular populations and body systems.

BDNF PPI Networks

Figure 1 shows a first-order PPI network constructed using STRING with BDNF as seed protein and 10 interactions in the first shell (none in the second shell; minimum required interaction score > 0.900). This network consists of 11 nodes, and the number of edges ($n=26$) exceeds the expected number of edges ($n=11$), with *p*-enrichment value of $9.54e-05$, and average node degree = 4.73 and average local clustering coefficient = 0.811. Table 1 shows the descriptions and functions of the ten added genes of this PPI network.

Figure 2 shows a PPI network constructed using STRING with BDNF as seed protein and 50 interactions in the first

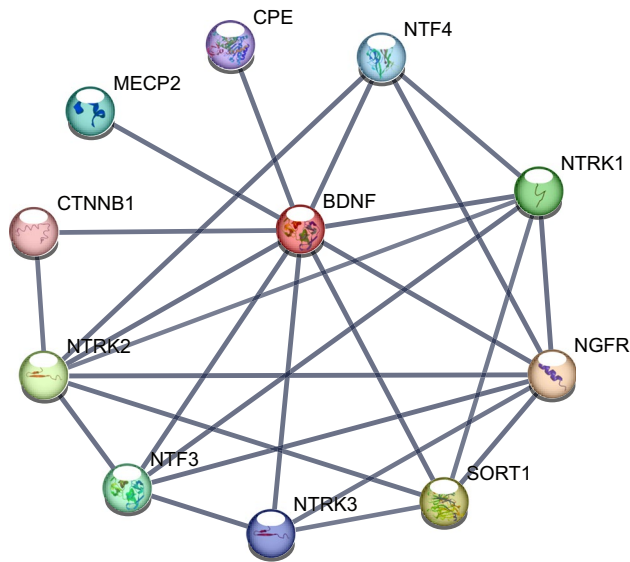


Fig. 1 A first-order protein–protein interaction network constructed using STRING with brain-derived neurotrophic factor (BDNF) as seed protein and 10 interactions in the first shell (none in the second shell; minimum required interaction score > 0.900)

shell (none in the second shell; minimum required interaction score > 0.900). This network consists of 51 nodes, and the number of edges ($n = 380$) exceeds the expected number of edges ($n = 115$), with p-enrichment value of $< 1e-16$ and average node degree = 14.9 and average local clustering coefficient = 0.709. Degree and betweenness centrality analysis showed that BDNF (degree = 50), NGF (35), NTRK2 (27), NTRK1 (27), HRAS (25), and GRB2 (25) were the top five hubs. BDNF (betweenness centrality = 0.3987), NGF (0.0767), NTRK2 (0.0245), NTRK1 (0.0239), and NGFR (0.0214) were the top bottlenecks in this network. As such the backbone of this enlarged network consists of BDNF (seed gene), NGF, NTRK2, NTRK1, HRAS, GRB2, and NGFR. Table 1 shows the names and descriptions of NGF, HRAS, and GRB2.

Table 2 shows the top twenty biological GO-enriched terms in this PPI network, indicating that the five most important over-represented terms are the neurotrophin signaling pathway, transmembrane receptor protein tyrosine kinase signaling pathway, cell surface receptor signaling pathway, and positive regulation of cell communication and signaling. Figure 3 displays the top 10 KEGG terms that were over-expressed in the BDNF-enlarged network with the neurotrophin, RAS and MAPK, and ErbB signaling pathways as top pathways. Figure 4 displays the top 10 performing cellular GO terms that are accumulated in the BDNF PPI network indicating that neuron projection, axon, and dendrites are the top terms followed at a distance by focal adhesion, cell junctions, phosphatidylinositol 3-kinase complex, Sin3 complex, and catenin complex. Figure 5 shows a

giant PPI network constructed using OmicsNet and IntAct using BDNF and the 50 BDNF-interacting proteins shown in Fig. 2. This giant network consists of 294 nodes and 308 edges, and the hubs in this enlarged network are GRB2 (degree = 729), TRAF6 (373), TP53 (367), HDAC1 (234), CRK (227), PIK3R1 (181), CTBBB1 (153), CDC42 (129), and STAT3 (129). Table 3 shows the top REACTOME and PANTHER pathways enriched in this PPI network.

BDNF and Key Molecular Pathways

Transcriptional activation of BDNF occurs when PI3K (phosphatidylinositol 3-Phosphate) is activated, which results in mTOR-dependent translation of BDNF [26]. Apart from binding to low affinity p75NTR, cleaved, mature BDNF binds to its high-affinity receptor tyrosine kinase B (TrkB), activating several signaling cascades which induce an increase in Ca^{2+} intake, phosphorylation of transcription factors, and de novo expression of the BDNF gene [8]. BDNF-dependent phospholipase C-gamma (PLC- γ) can provoke short-term signaling by increasing Ca^{2+} neuronal response and inhibit inflammatory-dependent apoptosis cascade by suppression of glycogen synthase kinase 3-beta (GSK-3 β) [10].

BDNF can also influence gene regulation via activating transcription factors such as NF- κ B and CREB, which activate Akt and Erk, respectively, through downstream pathways [27]. By modifying these genes, BDNF may modulate neuronal survival, development, and long-term potency [28]. Furthermore, BDNF-independent transactivation of TrkB can also play a vital role in the neurotrophic pathway regulated by adenosine, zinc, epidermal growth factor (EGF), glucocorticoids, and pituitary adenylate-cyclase-activating polypeptide (PACAP), further enhancing TrkB signaling in the synapse [11].

Based on the analysis of PPI networks, BDNF seems to interact most widely with the neurotrophin receptors, catenin β 1 (a downstream component of the canonical Wnt signaling pathway), the TNFR superfamily member 16 (a low affinity receptor binding to NGF, BDNF, NT-3, and NT-4), and sortilin (SORT1, a sorting receptor in the Golgi compartment). The interactions of BDNF with neurotrophin receptors NTRK1, NTRK2, and NTRK3 are important for the early stages of neurodevelopment. While NTRK3 is required for initial neurite outgrowth and regulation of surviving cells numbers, BDNF promotes survival and differentiation of motoneurons. Depletion of NT-3 or BDNF may affect the development of the peripheral or central nervous systems [29]. Moreover, synergistic interactions between BDNF and NTRK3 may be crucial for spiral ganglion neuron survival during the final stages of development [30]. By single-cell transcriptome analysis BDNF is identified as a STAT3 target gene in a unique

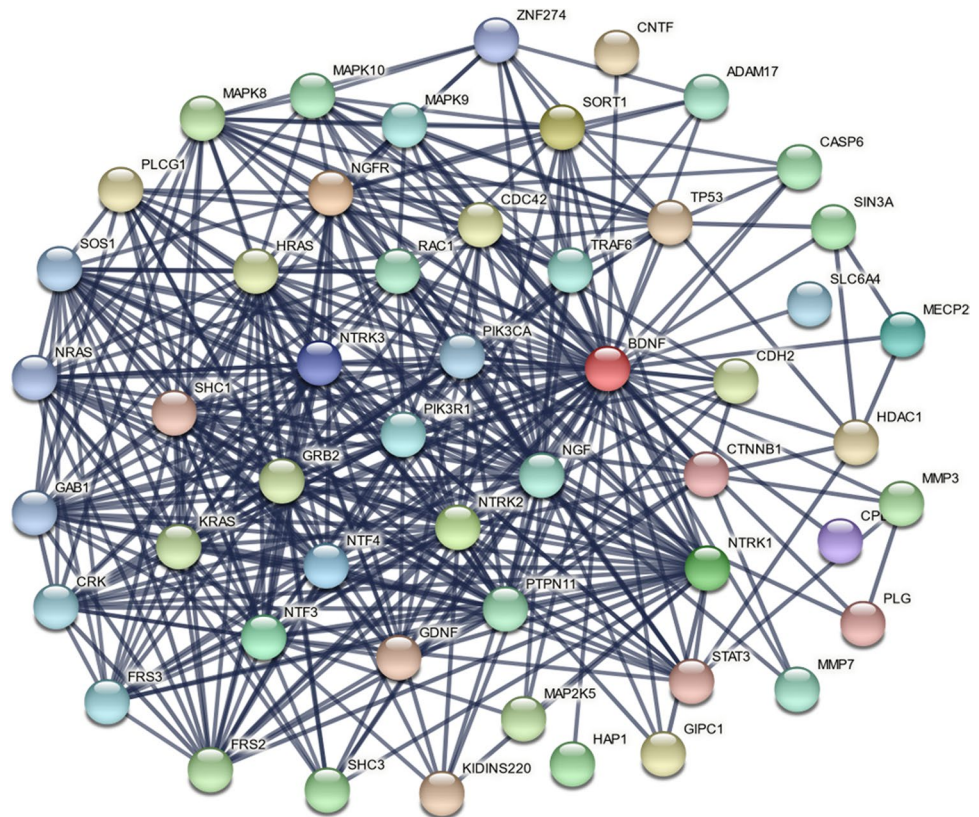
Table 1 Descriptions and functions of genes belonging to the protein–protein interaction network constructed around brain-derived neurotrophic factor (BDNF)

Gene	Name	Summary, descriptions of the proteins	Interaction scores with BDNF
BDNF	Brain-derived neurotrophic factor	Survival and differentiation of neuronal populations Axonal growth, pathfinding and in the modulation of dendritic growth and morphology Synaptic transmission and plasticity at adult synapses Long-term potentiation (LTP) Long-term depression (LTD)	-
CPE	Carboxypeptidase E	Endoprotease cleavage during prohormone processing Processes proinsulin Peptidase M14 family	0.984
CTNNB1	Catenin beta-1	Key component of the Wnt signaling pathway In the presence of Wnt ligand, CTNNB1 accumulates in the nucleus and promotes expression of genes that regulate cell adhesion	0.966
MECP2	Methyl-CpG-binding protein 2	Chromosomal protein that binds to methylated DNA Transcriptional repression through interaction with histone deacetylase	0.988
NGRF	Tumor necrosis factor receptor superfamily member 16	Regulation of the translocation of GLUT4 to the cell surface in adipocytes and skeletal muscle cells in response to insulin Low affinity receptor which bind to NGF, BDNF, NT-3, and NT-4 Cell survival and cell death of neural cells Circadian oscillation of the clock genes	0.999
NTF3	Neurotrophin-3	Promote the survival of visceral and proprioceptive sensory neurons	0.993
NTF4	Neurotrophin-4	Target-derived survival factor for peripheral sensory sympathetic neurons	0.986
NTRK1	High affinity nerve growth factor receptor	Receptor tyrosine kinase development and the maturation of the nervous system Proliferation, differentiation and survival of sympathetic and nervous neurons High affinity receptor for NGF	0.999
NTRK2	BDNF/NT-3 growth factors receptor	Receptor tyrosine kinase development and maturation of the nervous system Neuron survival, proliferation, migration, differentiation, and synapse formation and plasticity. Receptor for BDNF and NTF4	0.999
NTRK3	NT-3 growth factor receptor	Receptor tyrosine kinase Nervous system development Activates different signaling pathways, e.g., phosphatidylinositol 3-kinase/AKT and the MAPK pathways Control cell survival and differentiation	0.985
SORT1	Sortilin	Sorting receptor in the Golgi compartment Clearance receptor on the cell surface Protein transport from the Golgi apparatus to the lysosomes and endosome neuronal apoptosis by mediating endocytosis of the proapoptotic precursor forms of BDNF (proBDNF) and NGFB (proNGFB) Receptor for neurotensin	0.999
NGF	Beta-nerve growth factor	Development and maintenance of the sympathetic and sensory nervous systems Ligand for the NTRK1 and NGFR receptors Activates cellular signaling cascades Neuronal proliferation, differentiation and survival	0.920
HRAS	GTPase HRas	Activation of Ras protein signal transduction Ras proteins bind GDP/GTP and possess intrinsic GTPase activity	0.994

Table 1 (continued)

Gene	Name	Summary, descriptions of the proteins	Interaction scores with BDNF
GRB2	Growth factor receptor-bound protein 2	Adapter protein Provides a critical link between cell surface growth factor receptors and the Ras signaling pathway Cellular proliferation, differentiation, survival, gene expression	0.960

Fig. 2 A protein–protein interaction network constructed using STRING with brain-derived neurotrophic factor (BDNF) as seed protein and 50 interactions in the first shell (none in the second shell; minimum required interaction score > 0.900)



population of regenerating type II alveolar pneumocytes, and hence the therapeutic importance of the STAT3-BDNF-TrkB axis in regulating alveolar epithelial regeneration after lung injury is recognized [31].

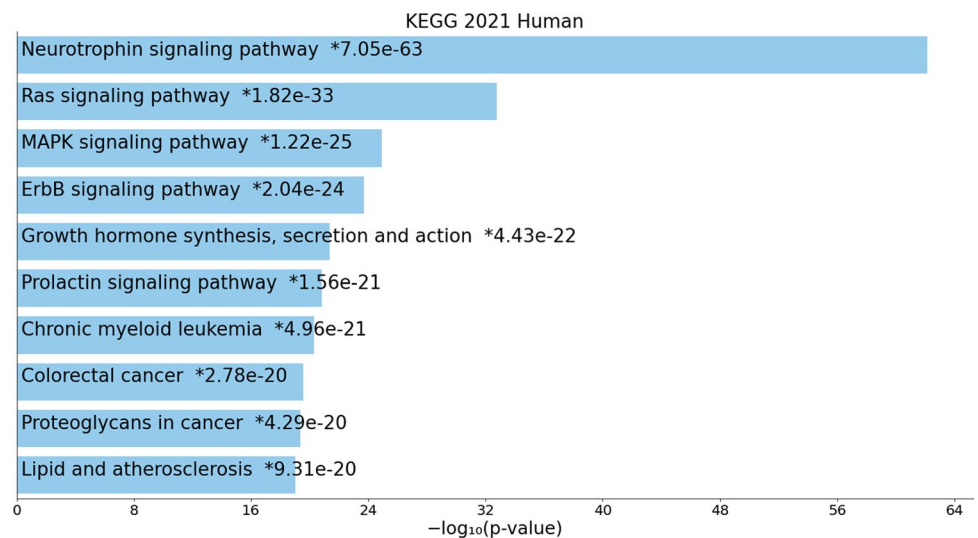
Soritin promotes neuronal apoptosis by mediating endocytosis of the proapoptotic precursor forms of BDNF (proBDNF) and NGFB (proNGFB). The soritin pathway has distinct roles in pro-neurotrophin-induced apoptotic signaling in pathological conditions, as well as in specific stages of neuronal development and aging [32].

BDNF, Embryonic Brain Development, and Neurodevelopment

Being the most abundant neurotrophin in the mammalian CNS, BDNF plays a key role in the development and physiology of the fetal brain [10, 33]. Its biological role is not only limited to neurogenesis but also affects the processes of placental angiogenesis and fetal development [34–36]. Functionally, BDNF acts through the TrkB and

Table 2 The top twenty biological GO-enriched terms in the protein–protein interaction (PPI) network constructed around brain-derived neurotrophic factor (BDNF)

GO ID	Term description	Observed gene count	Background gene code	Strength	False discovery rate <i>p</i> value
GO:0,038,179	Neurotrophin signaling pathway	15	28	2.31	4.32E-25
GO:0,007,169	Transmembrane receptor protein tyrosine kinase signaling pathway	27	518	1.3	5.48E-25
GO:0,007,166	Cell surface receptor signaling pathway	40	2325	0.82	9.48E-24
GO:0,010,647	Positive regulation of cell communication	37	1823	0.89	1.51E-23
GO:0,023,056	Positive regulation of signaling	37	1831	0.89	1.51E-23
GO:0,007,167	Enzyme linked receptor protein signaling pathway	28	720	1.17	2.88E-23
GO:0,048,584	Positive regulation of response to stimulus	39	2257	0.82	3.30E-23
GO:0,070,887	Cellular response to chemical stimulus	41	2919	0.73	9.68E-22
GO:0,009,967	Positive regulation of signal transduction	34	1654	0.9	2.98E-21
GO:0,022,008	Neurogenesis	34	1657	0.9	2.98E-21
GO:0,030,182	Neuron differentiation	29	1019	1.04	6.66E-21
GO:0,048,699	Generation of neurons	33	1551	0.91	6.66E-21
GO:0,048,011	Neurotrophin trk receptor signaling pathway	12	20	2.36	6.89E-21
GO:0,071,363	Cellular response to growth factor stimulus	23	494	1.25	3.66E-20
GO:0,071,310	Cellular response to organic substance	37	2369	0.78	3.90E-20
GO:0,010,941	Regulation of cell death	33	1696	0.87	7.37E-20
GO:0,010,646	Regulation of cell communication	41	3514	0.65	5.78E-19
GO:0,023,051	Regulation of signaling	41	3553	0.65	8.39E-19
GO:0,042,981	Regulation of apoptotic process	31	1550	0.88	1.31E-18
GO:0,048,666	Neuron development	25	827	1.06	4.22E-18
GO:0,042,221	Response to chemical	43	4333	0.58	5.65E-18
GO:0,007,399	Nervous system development	35	2371	0.75	7.20E-18
GO:0,031,399	Regulation of protein modification process	32	1870	0.82	1.55E-17
GO:0,031,401	Positive regulation of protein modification process	28	1252	0.93	1.55E-17

Fig. 3 Top 10 KEGG terms that are over-expressed in the brain-derived neurotrophic factor (BDNF) enlarged network

p75 NGFR receptors, located in the central and peripheral nervous system of the fetus in the midpregnancy [37, 38]. The binding of proBDNF to 75NTR receptors determines

synaptic pruning in the prenatal brain and initiates the proBDNF / p75NTR / sortiline signaling cascade [39]. This results in activation of c-Jun amino-terminal kinase

Fig. 4 The top 10 performing cellular GO terms that are accumulated in the brain-derived neurotrophic factor protein–protein interaction network

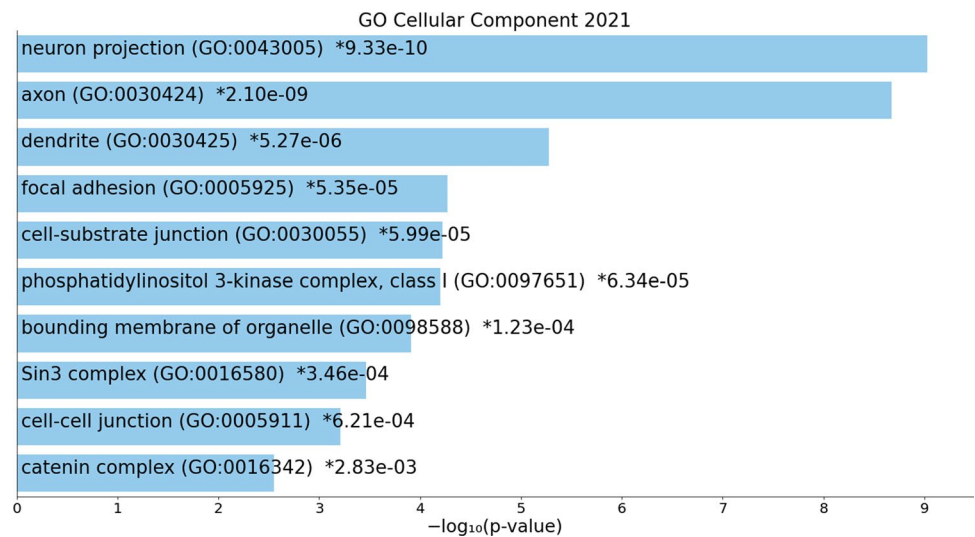
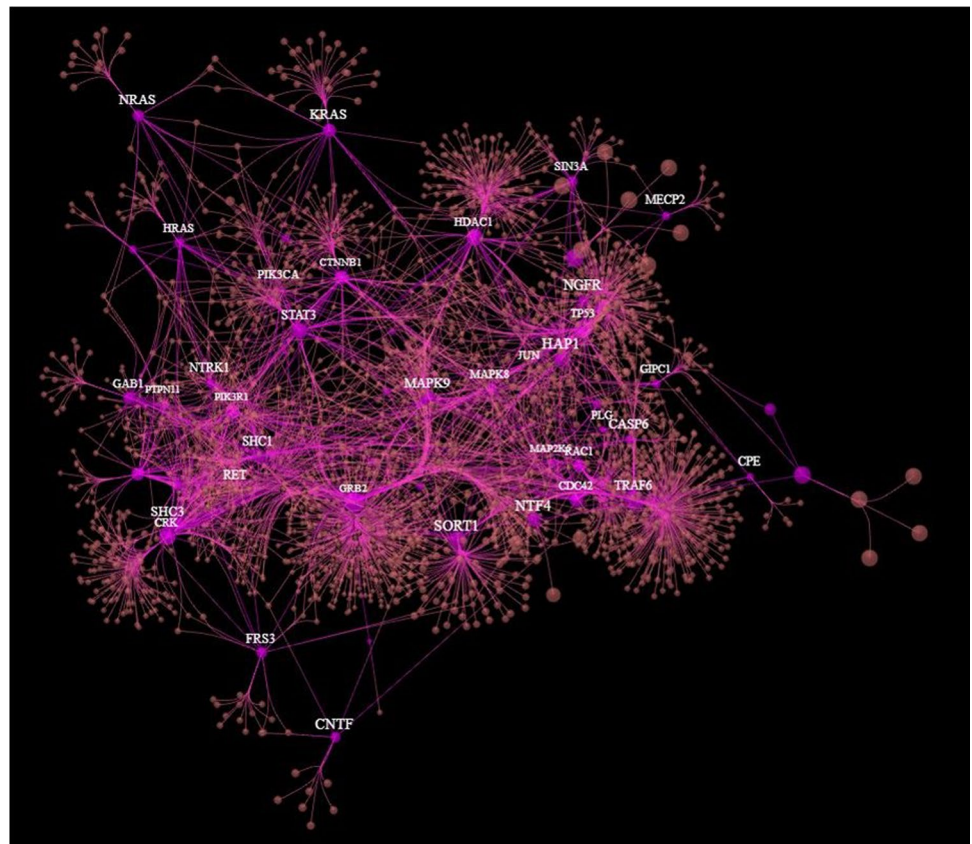


Fig. 5 A giant protein–protein interaction network constructed using OmicsNet and IntAct using brain-derived neurotrophic factor (BDNF) and 50 BDNF-interacting proteins as determined using STRING



(JNK) that is involved in neuronal apoptosis [40, 41]. On the other hand, the binding of the mature domain of BDNF to the p75NTR receptors, RIP2 (serine / threonine protein kinase 2) / TRAF6 (tumor necrosis factor 6 receptor factor), initiates a pathway to ensure the survival and maintenance of neurons during embryogenesis [40, 42].

During the early brain development, BDNF coordinates the processes of glio-, neuro-, and synaptogenesis on one

hand and the elimination of improperly formed connections on the other, in order to form the functional and morphological integrity of the nervous system [10, 43–45]. During the fourth month of pregnancy, the number of BDNF-positive neurons increases which is associated with its involvement in the development of the frontal lobe of the fetal brain [46].

TrkB receptors for the neuroprotein are expressed at the beginning of neurulation in the neural tube [29]. An in situ

Table 3 The top REACTOME and PANTHER pathways enriched in the giant protein–protein interaction (PPI) network centered around brain-derived neurotrophic factor (BDNF)

	Total	Expected	Hits	<i>p</i> -value	False discovery rate <i>p</i> value
REACTOME pathway terms					
Immune system	1140	212	386	1.22E-42	1.71E-39
Signaling by the B cell receptor (BCR)	199	37.1	110	7.42E-32	5.20E-29
Signaling by NGF	290	54.1	139	2.67E-31	1.25E-28
Signaling by interleukins	116	21.6	76	5.42E-29	1.90E-26
Adaptive immune system	654	122	234	3.83E-28	1.08E-25
Innate immune system	521	97.1	196	1.51E-26	3.54E-24
NGF signaling via TRKA from the plasma membrane	207	38.6	104	1.33E-25	2.66E-23
Downstream signaling events of B cell receptor (BCR)	173	32.3	92	4.49E-25	7.87E-23
Fcγ receptor (FCγR)-dependent phagocytosis	86	16	58	2.42E-23	3.77E-21
Signaling by SCF-KIT	142	26.5	78	1.42E-22	1.80E-20
Cytokine signaling in immune system	286	53.3	122	6.82E-22	7.96E-20
Signaling by EGFR	179	33.4	88	5.77E-21	5.78E-19
Signaling by ERBB4	152	28.3	78	3.82E-20	3.57E-18
Apoptosis	158	29.5	78	7.80E-19	6.83E-17
Activated TLR4 signaling	100	18.6	58	1.33E-18	1.03E-16
Interleukin-3, 5 and GM-CSF signaling	51	9.51	38	4.54E-18	3.35E-16
Downstream signal transduction	163	30.4	78	8.13E-18	5.70E-16
Toll-like receptor 4 (TLR4) cascade	103	19.2	58	9.24E-18	6.17E-16
Signaling to ERKs	37	6.9	31	1.30E-17	8.29E-16
Regulation of actin dynamics for phagocytic cup formation	62	11.6	42	2.44E-17	1.49E-15
Degradation of beta-catenin by the destruction complex	65	12.1	43	3.96E-17	2.22E-15
Signaling by Wnt	65	12.1	43	3.96E-17	2.22E-15
Panther biological process					
Viral process	448	69.6	181	1.97E-38	3.82E-36
Protein phosphorylation	627	97.5	218	1.82E-34	1.77E-32
Negative regulation of apoptotic process	577	89.7	187	2.85E-25	1.84E-23
Chromatin organization	358	55.7	117	2.03E-16	9.85E-15
Cell proliferation	386	60	121	2.10E-15	8.14E-14
Apoptotic process	699	109	185	1.41E-14	4.55E-13
Translation	315	49	97	4.45E-12	1.23E-10
Rhythmic process	124	19.3	50	2.15E-11	5.20E-10
Cytoskeleton organization	170	26.4	60	1.53E-10	3.29E-09

hybridization study of mouse and chicken embryos showed that TrkB is detected in the hindbrain in the area of the neuraxis, which generates motor neurons [47–49]. Likewise, BDNF acts as a mitogen for motoneurons and guides neuronal differentiation, and blocking BDNF/TrkB receptors with trkB-Ig reduces the number of neurons [29, 48]. Therefore, BDNF deficiency leads to fewer motor neurons, which affects the development of the central or peripheral nervous system. Evidence of this are animals with knocked out BDNF and TrkB, which have severe neuronal deficits, difficulty in coordination, and short life [50–52]. The lowest BDNF mRNA expression was detected in the brain of early rat embryos, and it gradually increased [53] between

embryonic days 11–13, and the time corresponded to the beginning of neurogenesis [54, 55]. These findings can be explained by dynamically developing neuronal populations during the early stages of ontogenesis.

In addition, BDNF supplied by the mother during pregnancy supports the development of the fetal nervous system. BDNF concentrations in the amniotic fluid influence its levels in the fetus [56–61]. Thus, fetal brain development is a strictly regulated process, as evidenced by pathological changes occurring with the rapid increase of BDNF in the fetal brain [62, 63]. For example, injection of the protein into the brain ventricles of the mouse embryo *in vitro* leads to premature neurogenesis and abnormal cell proliferation [62].

BDNF has also a key role in some pregnancy-associated disorders, whereby high BDNF levels in the amniotic fluid are associated with reduced fetal growth. Thus, macrosomic and small for gestational age fetuses show higher BDNF amniotic fluid levels [34]. According to the authors, these changes are a compensatory mechanism associated with the accelerated development and maturation of the fetal brain, which limits its growth [34]. Roth and Sweatt (2011) emphasize that adverse environmental stressors during pregnancy may modulate cortical BDNF gene expression. This epigenetic mechanism leads to methylation [64–67] and changes in the genes regulated by BDNF, significantly reducing the expression of BDNF in the hippocampus [68, 69], blood, and brain [66, 70]. This reflects the role of epigenetic factors and the influence of stress in the early life of the individual.

Various animal models reveal that elevated levels of hippocampal BDNF are associated with higher levels of maternal care, and the result is a high propensity to the social interaction of the individual in adulthood [71]. On the other hand, the isolation from the mother is associated with reduced levels of both mRNA and protein in the prefrontal cortex, amygdala, and hippocampus [72]. This again shows the key role of BDNF in brain development and the regulation of complex behavioral responses.

BDNF as Master Regulator of Neurogenesis and Synaptic Plasticity

The term neuroplasticity describes the ability of the brain to reorganize its neural circuits in response to experience, which is of fundamental importance for learning and memory [73]. In turn, neurogenesis allows the incorporation of newly generated neurons into the existing neural networks [74]. As a member of the neurotrophin family, BDNF controls neuronal development and promotes neuronal function and plasticity through various mechanisms.

The initial hypothesis that BDNF may contribute to synaptic plasticity arose from the discovery that high frequency stimulation (HFS) can promote overexpression of BDNF in the hippocampus [75, 76]. Direct evidence of such contribution was provided by Figurov et al. [77], who described that BDNF treatment promotes the induction of long-term potentiation (LTP) in the hippocampus. Furthermore, the observed effects were reversed following the application of TrkB-IgG, which scavenges endogenous BDNF, thus decreasing the strength of LTP. In addition, in BDNF knockout mice, hippocampal LTP was significantly affected [78, 79]. In line with these findings, application of exogenous BDNF can trigger LTP in a protein synthesis-dependent manner and can modulate translation in dendrites [80].

In general, BDNF-mediated regulation of synaptic plasticity depends on the two main types of BDNF receptors.

These include the Trk family and the p75 neurotrophin receptor (p75NTR), part of the TNF receptor superfamily [81]. By interacting with these receptors, BDNF triggers various pathways of intracellular signaling, especially the MAPK-, PI3K-, and PLC γ -dependent signaling cascades [19], to regulate neuronal differentiation and survival, axonal growth, and dendritic pruning [82].

The TrkB is highly selective and interacts with great affinity with BDNF and NT-4, but not with the other two neurotrophins, NGF and NT-3. Conversely, all four neurotrophins recognize p75NTR with equal affinity [83]. Among the signal transducers involved in MAPK and PI3K pathways, MAPK/ERK and PIK3CA are closely activated following BDNF-TrkB binding. Behavioral studies revealed the role of BDNF-MAPK pathway in mood control and anxiety [84]. BDNF activates MAPK signaling to upregulate Bcl-2 gene expression in neural stem cells (NSCs), which inhibits apoptosis and promotes cell survival. Furthermore, siRNA-mediated suppression of BDNF synthesis or U0126 inhibition of the MAPK signal transduction significantly decreases Bcl-2 levels, which confirms that the neuroprotective effect of BDNF is MAPK-dependent [85].

It has been suggested that the interaction between BDNF and TrkB initiates MAPK/ERK signal transduction to increase the dendritic spine density in hippocampal neurons. The activated MAPK pathway also promotes enhanced spine maturation. Inhibition of TrkB with k-252a disrupts the effects of BDNF on spine density and morphology [83].

In the past two decades, emerging evidence has suggested the involvement of MMP-9 (matrix metalloproteinase 9) in neuronal plasticity [86]. MMP-9 is an endopeptidase that takes part in the remodeling of the extracellular matrix. The enzyme has been associated with LTP and memory, as well as with dendritic spine reorganization. In line with this association is the fact that elevated MMP-9 expression can result from KCl-induced neuronal depolarization and chemically evoked seizures. Researchers have demonstrated that MMP-9 transcription is modulated by synaptic activity and depends on TrkB signaling [86]. The latter experimental data suggest that bicuculline administration in rat primary cortical neurons enhances synaptic activity and upregulates the expression of BDNF. The upregulated BDNF then regulates the MMP-9 levels in a mechanism that requires MAPK/ERK-signaling and c-Fos expression. Apparently, the observed changes in both BDNF and MMP-9 expression levels resulted from the elevated synaptic activity, which is a crucial trigger of neuronal plasticity [86].

The complex interplay between local protein synthesis and remodeling of the actin cytoskeleton plays a key role in the growth cones of axons and may also participate in LTP [87, 88]. The BDNF receptor, TrkB, appears pivotal for the signal network that regulates the local production of many factors involved in cytoskeletal dynamics

including RhoA and LIMK1 [89, 90]. Stable LTP in *gyrus dentatus* requires persistent Arc synthesis for the phosphorylation of cofilin and the steady accumulation of synaptic F-actin content [91]. In this context, application of exogenous BDNF significantly elevates the Arc-mediated LTP [91], while LTP in *gyrus dentatus* strongly associates with increased TrkB activation and enhanced release of BDNF [92, 93].

Numerous studies on cultured hippocampal neurons have demonstrated that BDNF regulates synaptic transmission and enhances N-methyl-D-aspartic acid receptor (NMDAR) function [94]. BDNF also stimulates the maturation of neuromuscular synapses and increases their activity in vitro [95]. In addition to the excitatory transmission, BDNF also regulates inhibitory neuronal signaling [96]. It promotes neuronal potentiation while affecting both pre- and post-synaptic processes. In the presynaptic compartment, BDNF improves glutamate secretion in cortical neurons in vitro by activating the PLC- γ (phospholipase C- γ)/Ca²⁺ pathway, thus increasing the frequency of the miniature excitatory postsynaptic currents [97]. Conversely, the elevated neuronal activity resulting in LTP was shown to cause significant hippocampal BDNF overexpression, suggesting the presence of regulatory feedback mechanisms [76]. On the postsynaptic side, BDNF increases the sensitivity of the NMDAR and modulates its opening probability [98]. NMDAR-mediated Ca²⁺ influx is essential for neuronal differentiation, neuronal migration, synaptogenesis, synaptic remodeling, long-lasting changes in synaptic efficacy, such as LTP and LTD (long-term depression), and cognitive functions such as learning and memory [99].

NMDAR activation results in increased Ca²⁺ influx that couples synaptic activation and the intracellular signaling pathways, which regulate neuronal differentiation, synaptic remodeling, and plasticity [99]. It has also been reported that BDNF increases the expression of voltage-dependent Ca²⁺ and voltage-dependent Na⁺ channels on the surface of the neurons. As for the role of BDNF in the inhibitory neural circuits, BDNF regulates the formation of GABAergic synapses in the hippocampus [100]. Moreover, artificially applied BDNF decreases the inhibitory synaptic GABAergic currents in the hippocampus via TrkB receptor activation [101].

Apart from its well-established role in remodeling the existing neuronal circuits, BDNF has an important function in neural maturation and neurogenesis. It is involved in the proliferation of NPCs and the prolonged maintenance of newly emerging neurons [102–104]. Direct application of BDNF in the hippocampus and its administration in peripheral blood have been correlated with strong stimulation of hippocampal neurogenesis [103]. According to Kuipers et al. [105], BDNF-induced neurogenesis in *gyrus dentatus* is associated with LTP, while inhibition of Arc translation

restricts the induction of LTP and its positive effects on neurogenesis [104, 106].

BDNF and the Wnt/Catenin Pathway

Using confocal microscopy, Bamji et al. [107] demonstrated that BDNF supports neuronal plasticity by disrupting the association between cadherin and β -catenin (CTNNB1) in neuronal synapses. This results in enhanced mobility of synaptic vesicles, as well as in long-term increase in synapse number. BDNF hampers cadherin- β -catenin interactions by increasing β -catenin phosphorylation [107]. This phosphorylation occurs on tyrosine 654 and is catalyzed by Src kinases. At the same time, BDNF stimulates the formation of new synapses, which is blocked by the artificial preservation of cadherin- β -catenin interactions.

β -catenin is a protein with versatile functions, which participates in the cell-cell adhesion and in the canonical Wnt signaling pathway [108]. It forms a complex with the cytoplasmic domain of cadherin and binds to the actin fibers of the cytoskeleton via α -catenin [109]. The cadherin-catenin complex engages in intercellular adhesion and plays a pivotal role in synaptogenesis and synaptic remodeling, affecting both synaptic size and strength [110]. Destabilization and reassociation of the cadherin-catenin complex contribute to morphological changes in neurons that result in new synapse formation. From another perspective, β -catenin functions as a transducer in the Wnt signaling pathway. In the absence of Wnt activation, β -catenin is phosphorylated by glycogen synthase kinase-3 β (GSK-3 β) and readily degraded by the proteasome [111]. Conversely, Wnt signaling stabilizes β -catenin by inhibiting GSK-3 β , which allows the translocation of β -catenin into the nucleus. There β -catenin interacts with transcription factors of the TCF/LEF family to regulate the expression of Wnt-targeted genes [112, 113]. Accordingly, experimental evidence suggests that Wnt signaling is implicated in the regulation of synaptic plasticity in hippocampal slices.

Maguschak et al. [114] have confirmed the role of β -catenin in the amygdala-dependent fear memory. The application of LiCl, which unspecifically inhibits β -catenin degradation, results in increased fear retention. Consolidation of fear memory involves changes in both the expression and phosphorylation levels of β -catenin. The observed changes are accompanied by dynamic regulation of the β -catenin/cadherin complex. Genetic analyses involving region-specific deletion of loxP-flanked CTNNB1 further confirmed the importance of β -catenin for long-term memory consolidation [114].

Alterations in β -catenin phosphorylation and distribution are involved not only in long-term memory but also in trauma response [115]. Heat acclimation provides robust

antecedent neuroprotection against traumatic brain injury via a mechanism involving tyrosine phosphorylation of β -catenin and weakening of the β -catenin/cadherin complex. According to Umschweif et al. [115], high basal levels of BDNF and N-cadherin stimulate a rapid increase in the Akt phosphorylation upon a cerebral injury, leading to the inhibition of both JNK (c-Jun N-terminal kinase) and GSK-3 β . The inhibition of GSK-3 β alters ser33/37thr41 phosphorylation of β -catenin, while elevated levels of BDNF result in induced tyrosine 654 phosphorylation of β -catenin. The new phosphorylation state allows β -catenin to escape degradation or nuclear translocation, which is crucial for the reorganization of β -catenin/cadherin complexes. This complex dynamic of β -catenin/cadherin interactions promotes the reestablishment of intercellular adhesion and plays a key role in trauma recovery.

Numerous studies have shown that BDNF significantly contributes to the longevity, proliferation, and differentiation of neural stem cells (NSCs) through the Wnt/ β -catenin signaling pathway [116, 117]. Transfection of human embryonic spinal cord NSCs (hESC-NSCs) with a plasmid vector expressing BDNF stimulates cell growth in vitro. The plasmid-mediated overexpression of BDNF upregulates the expression of Wnt, Frizzled, and Dsh, while decreasing the levels of GSK-3 β . The opposite effects are evoked following siRNA silencing of BDNF.

BDNF increases neuronal growth in terms of perikaryon size and neurite length through the Wnt/ β -catenin signaling pathway. Experimental data from Western blot and qRT-PCR analyses have demonstrated that BDNF overexpression upregulates key Wnt signaling factors, Wnt, Frizzled, and Dsh, and their downstream target β -catenin, while downregulates GSK-3 β . These expression changes can be reverted with the application of BDNF siRNA, which also decreases neuronal growth. Furthermore, BDNF signaling factors, Wnt pathway components, and β -catenin were all downregulated, whereas GSK-3 β was upregulated. Further treatment of the neurons with the GSK-3 β inhibitor 6-bromoindirubin-3'-oxime (BIO) suppresses the effects of BDNF on neuronal growth and reduces the BDNF-dependent activation of the Wnt signaling pathway. These findings confirm that BDNF stimulates neuronal growth by modulating the Wnt/ β -catenin signaling pathway [118].

In addition, BDNF can markedly stimulate the differentiation of induced pluripotent stem cells (iPSCs) into NSCs through the Wnt/ β -catenin and MAPK/ERK signaling cascades. Zhang et al. demonstrated that BDNF increases the expression of β -catenin and ERK 5 in BDNF-treated iPSCs in comparison with untreated ones [119]. The authors have also suggested that the inhibition of ERK5 affects the activity of the Wnt/ β -catenin signaling pathway. This finding implies a functional overlapping

between Wnt/ β -catenin and MAPK signaling in the context of BDNF-induced iPSCs differentiation.

Altogether these vast experimental data confirm the role of BDNF as an important regulator of the Wnt/ β -catenin signaling pathway. However, Wnt/ β -catenin signaling is not only regulated by BDNF but also participates in the activity-dependent control of BDNF expression [120]. It has been widely acknowledged that BDNF expression is regulated by neuronal activity which elevates BDNF transcription via an increased Ca²⁺ influx through ligand- and voltage-gated calcium channels. The Ca²⁺ entry triggers the activation of the cAMP response element-binding protein (CREB). CREB serves as a transcription factor that binds to the cAMP/Ca²⁺-response elements within the BDNF promoter, thus increasing the transcription of the BDNF gene. The activation of CREB can occur through multiple Ca²⁺-dependent signal transduction pathways such as the cAMP/PKA, Ras/MAPK, and calmodulin/calmodulin kinase pathways. Despite that CREB activation constitutes the primary mechanism for activity-regulated BDNF transcription, the activity-dependent expression of BDNF also relies on the Wnt/ β -catenin signaling. Synaptic activity and NMDAR stimulation modulate the Wnt/ β -catenin pathway and the transcription of Wnt/ β -catenin target genes. The activation of the Wnt/ β -catenin pathway is mediated by Frizzled receptors together with LRP5 and LRP6 co-receptors. This leads to the translocation of β -catenin into the nucleus where it supports the transcription of its target genes including BDNF and Axin2 [120].

BDNF and the JAK/STAT Pathway

Apart from the ERK1/2, PI3K, and PLC pathways, BDNF can induce JAK/STAT signaling to stimulate neurite growth [121–124]. In the rat major pelvic ganglion (MPG), BDNF increases the phosphorylation of JAK2, STAT1, and STAT3, thus promoting neurite elongation [124]. The neurite-stimulating effect of exogenous BDNF on cultured MPGs is dosage-dependent with an optimal range between 25 and 50 ng/ml. In the presence of BDNF, this effect can be significantly reduced by the JAK/STAT inhibitor AG490, which confirms the predominant role of the JAK/STAT pathway in the BDNF-related neurite stimulation.

After nerve injury, BDNF activates the JAK/STAT pathway in Schwann cells to facilitate nerve regeneration [125], and BDNF stimulates the phosphorylation of STAT1 and STAT3, which in Schwann cells occurs in a delayed manner. Following an initial peak 1 h after BDNF treatment, the levels of STAT1/2 decrease to baseline levels and peak again 24 h after treatment. As a result of BDNF administration, Schwann cells produce cytokines, especially OSM-M and IL-6 that promote nerve regeneration.

Using a full transcriptome sequencing approach on BDNF-treated neurons with and without JAK/STAT inhibitors, Hixson et al. [126] have determined the complete pool of genes that undergo BDNF-dependent JAK/STAT-mediated regulation in cultured cortical neurons. Their analyses revealed 2869 differentially regulated genes whose expression changes after BDNF application. One thousand five hundred fifty-nine of these 2659 genes appeared to be most strongly associated with JAK/STAT signaling in neurons. Among the targets of BDNF-induced JAK/STAT signaling, the authors identified genes for ion channels, neurotransmitter receptors, and several factors of synaptic plasticity and neurogenesis. This work has also revealed that the BDNF-induced JAK/STAT pathway regulates many epilepsy-associated genes. The presumed mechanism by which BDNF triggers the JAK/STAT activation in neurons is non-canonical and potentially involves an interaction between STAT3 and Heterochromatin Protein 1 alpha (HP1 α).

A major BDNF downstream mediator, STAT3 (Signal transducer and activator of transcription 3), has been associated with the prenatal development of the neocortex [127, 128] and the neuronal fitness in response to insulin-like growth factor [129]. STAT3 regulates axonal outgrowth [130, 131] and participates in the formation of hypothalamic neural circuits [132]. Tang et al. [133] have described significant upregulation of STAT3 at both mRNA and protein levels in rat brain samples following movement training. STAT3 binds to the promoters of brain-related genes, including BDNF, thus mediating their transcriptional control [133].

Oncogenic Properties of BDNF

Alternatively, BDNF is well-known to exhibit oncogenic properties, which are closely related to its neurogenetic activity [134, 135]. Researchers have suggested that glial malignancies may arise from neural stem cells that undergo an aberrant differentiation. It has been also shown that the interaction between BDNF and TrkB stimulates Ras activation, which intensifies the cell cycle progression [134]. Accordingly, overexpression of BDNF and TrkB significantly contributes to oncogenesis of neuroblastoma. In neuroblastoma cells, BDNF reduces the upregulated expression of p53 and promotes the survival of tumor cells following etoposide treatment [136]. BDNF may stimulate cell proliferation in glioblastoma multiforme and in retinoblastoma. Intriguingly, the oncogenic activity of BDNF can be markedly suppressed by p53 which upregulates the long non-coding antisense RNA of the BDNF gene, encoded by BDNF-AS. Using a ChIP analysis, Lv et al. [137] demonstrated that the p53 transcription factor readily binds to the promoter region of the BDNF-AS gene. This discovery was further

validated by a luciferase reporter assay. The authors have also shown that p53 transfection dramatically increases the expression of BDNF-AS.

Upregulation of BDNF and TrkB has been demonstrated in a vast set of cancer types, including bladder cancer [138], breast cancer [139, 140], ovarian cancer [141], hepatocellular carcinoma [142, 143], gastric cancer [144], and colorectal cancer [145, 146]. When triggered by BDNF, TrkB promotes the activation of numerous downstream factors, such as Akt, Src, ERK, and MAPK, resulting in abnormal cell proliferation, ineffective apoptosis, invasion, metastasis, and chemotherapy resistance [147–149]. Cervical cancer cells manifest higher levels of TrkB and BDNF than normal cells. Notably, the siRNA-mediated knockdown of TrkB reduces the invasiveness of cancer cells in a way involving the suppression of N-cadherin, vimentin, MMP-2, and MMP-9. Conversely, the silencing of TrkB results in overexpression of the epithelial cadherin (E-cadherin) and the tissue inhibitor of metalloproteinases 2 (TIMP2). This newly established pattern of gene expression suppresses cell division, migration, and invasion [150].

Except from cervical cancer, upregulation of TrkB and BDNF along with downregulation of E-cadherin has been demonstrated in salivary adenoid cystic carcinoma (SACC). Moreover, the levels of TrkB correlate negatively with the expression of E-cadherin in SACC. These alterations in gene expression have been associated with higher invasive potential of SACC cells and with poor prognosis of affected patients. In agreement with this, the exogenous addition of BDNF markedly activates TrkB and induces the progression of SACC cells, while TrkB inhibition by k252a significantly reduces SACC proliferation [151].

BDNF and Immunity

PPI Network of BDNF and Immune Molecules

Recently, Maes et al. [5] reported the PPI network of first-episode psychosis (FEP) and first-episode schizophrenia (FES) which include BDNF and immune differentially expressed proteins (DEPs), and they constructed a dense PPI network with 92 nodes and 1063 edges ($n = 1063$). Immune genes (including IL-6, IL-2, IL10, and TNF- α) were top hubs, while BDNF, CTNNA1, and CDH1 were the most important non-hub bottlenecks. As such the backbone of this network consisted of CTNNA1, IL6, TNF, CDH1, IL4, IL10, and BDNF [5]. MCL cluster analysis performed at an inflation parameter of 2.5 showed two PPI clusters, namely an immune cluster, which comprised cytokines, chemokines and immune DEPs, and a cell–cell junction cluster, which comprised CTNNA1 and CDH1. Importantly, BDNF was allocated to the immune cluster and functioned as a switch

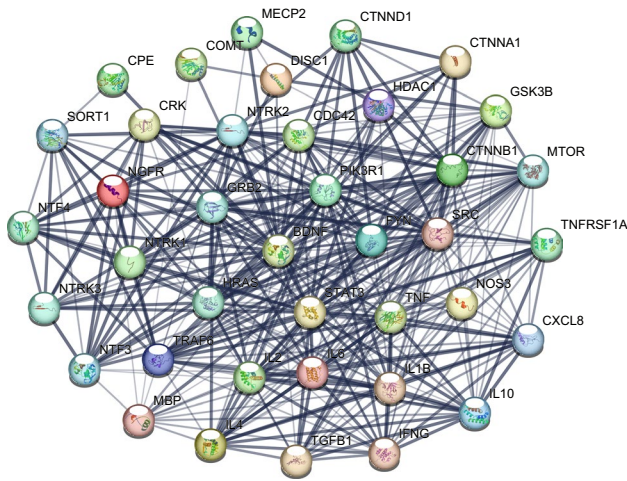


Fig. 6 A protein–protein interaction network centered around brain-derived factor (BDNF) and comprising major neurotrophic, immune-inflammatory, and cell–cell junction genes

between both clusters with many relevant interactions with DEPs in the cell–cell junction (e.g., with CTNNA1, NTRK2, CTNND1, and CTNNA1) and immune (e.g., STAT3, TRAF6, NTF4, NGFR, IL6, TNF, IL4, IL10, IFNG) clusters.

Based on this PPI, we here constructed a new PPI centered around BDNF only and added all Fig. 1 DEPs as well key Fig. 2 DEPs (HRAS, PIK3R1) to make a new immune, neurotrophic, and cell–cell junction PPI network, whereby all DEPs show relevant interactions with BDNF. Figure 6 shows this new neurotrophic, immune–cell–cell junction PPI network centered around BDNF. This network consists of 39 nodes, and the number of edges ($n = 362$) exceeds the

expected number of edges ($n = 123$), with p-enrichment value of $1.0e-016$ and average node degree = 18.6 and average local clustering coefficient = 0.739. Metascape enrichment analysis shows that the most significant terms associated with this network were the SHP2 ($\log_{10} p = -26.2$) and TRKR ($\log_{10} p = -25.7$) pathway and signaling by receptor tyrosine kinases ($\log_{10} p = -24.7$).

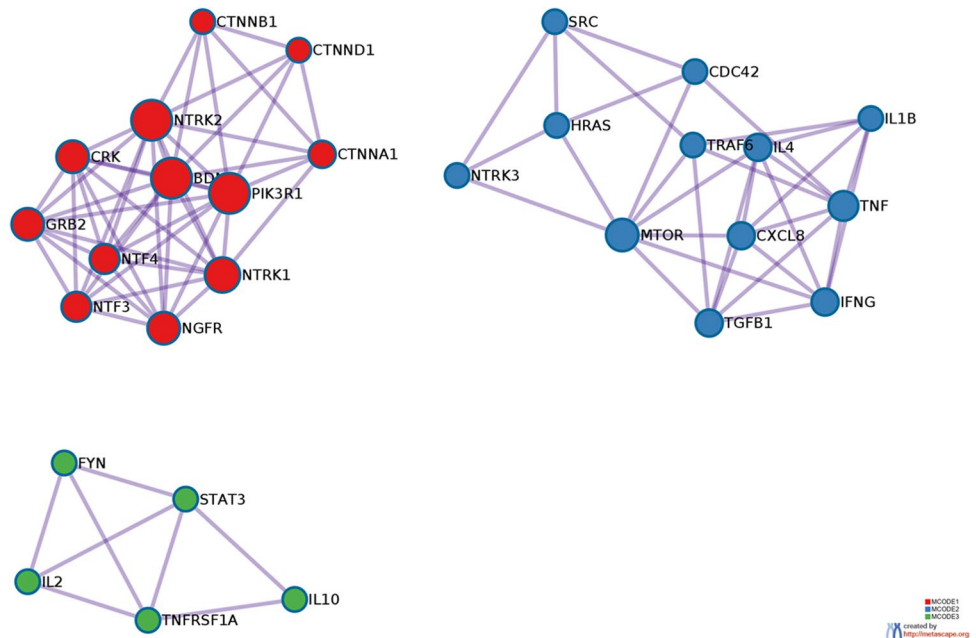
Table 4 and Fig. 7 show the results of MCODE analysis with GO enrichment analysis applied to the three molecular components to extract “biological meanings”. The top terms retained in the first MCODE component revolve around signaling by receptor tyrosine kinases and NTRKs, positive regulation of kinase and transferase activity in the second MCODE component, and cytokine signaling in the immune system and negative regulation of the immune response in the third component. This indicates that changes in BDNF may affect a wide variety of neurotrophic, immune, and cell–cell junction functions and their associated signaling pathways. As such, a wide spectrum of processes is controlled by BDNF, and therefore, BDNF is a crucially involved in different intercellular communications and intracellular functions and is implicated in the bidirectional interactions between the immune system and neuronal functions.

Brunelli et al. [152] showed that human PBMCs produce and secrete BDNF isoforms as part of the physiological stress response showing that immune cells and BDNF are interconnected. In a rat model of optic nerve injury, mRNA expression of BDNF in T cells is demonstrated together with mRNAs of other neurotrophins [153]. BDNF and NGF levels are regulated by TNF- α and its receptors even under immunologically unchallenged conditions [154]. Additionally, BDNF may have anti-inflammatory and anti-apoptotic

Table 4 Results of molecular complex detection (MCODE) analysis performed on a protein–protein interaction network centered around brain-derived neurotrophic factor (BDNF) and a neurotrophic immune–cell–cell junction network centered around BDNF

MCODE components	Annotation ID	Annotations	Log10 (p)
1 ALL (Fig. 2)	M187	TRKR PATHWAY	–23.4
	GO:0,002,521	Leukocyte differentiation	–21.8
	WP2380	Brain-derived neurotrophic factor (BDNF) signaling pathway	–21.4
1 MCODE1 (Fig. 2)	WP2380	Brain-derived neurotrophic factor (BDNF) signaling pathway	–22.0
	M100	SHP2 PATHWAY	–21.6
	M187	TRKR PATHWAY	–21.2
2 MCODE1 (Fig. 6)	M187	TRKR PATHWAY	–22.2
	R-HSA-9006934	Signaling by receptor tyrosine kinases	–18.4
	GO:0,005,165	Neurotrophin receptor binding	–18.1
2 MCODE2 (Fig. 6)	GO:0,033,674	Positive regulation of kinase activity	–18.8
	GO:0,051,347	Positive regulation of transferase activity	–18.0
	GO:0,045,860	Positive regulation of protein kinase activity	–17.1
2 MCODE3 (Fig. 6)	R-HSA-449147	Signaling by interleukins	–9.1
	GO:0,050,728	Negative regulation of inflammatory response	–8.2
	R-HSA-1280215	Cytokine signaling in immune system	–8.1

Fig. 7 Results of molecular complex detection (MCODE) analysis with enrichment analysis applied to the three molecular components



properties via its regulation of the MyD88/NFB and PI3K/AKT signaling pathways [155]. Pretreatment with BDNF may increase the expression of IL-10 and Trk and inhibit the production of IL-6, TNF- α , and IL-1 and NF- κ B following bacterial infection.

BDNF is implicated in neuroinflammation and shows neuroprotective effects. For example, in a mouse model of aging, the critical role of BDNF-TrkB signaling in regulating microglia inflammation was shown. Decreases of BDNF-TrkB signaling in microglia during aging are associated with their activation in the *substantia nigra*, while systemic delivery of BDNF reversed aging-related microglial activation [13]. The authors also used a cultured microglial cell line, and BDNF blocked LPS-induced microglial activation. Activation of the TrkB/Erk/CREB pathway is necessary for the BDNF-induced antimicroglial activation response. BDNF overexpression in the hippocampus diminishes synaptic impairments and improves neuroinflammation induced by hyperglycemia, which may be mediated by inhibiting the HMGB1/RAGE/NF- κ B signaling pathway [156]. A study on Alzheimer's dementia revealed associations between BDNF and proBDNF with immune markers, such as VEGF, EGF, and CD95 + CD3 + ratio [157].

In multiple sclerosis, BDNF secreted by immune cells is associated with sites of higher inflammatory activity and may represent a crucial factor associated with the white matter volume [158]. An animal model of MS mice deficient for BDNF in immune cells displays an attenuated immune response in the acute phase of the disease but progressive disability with enhanced axonal loss in the chronic phase. In mice deficient for CNS-derived BDNF, a more severe course and an overall increased axonal loss was observed

[159]. This indicated again the protective role of BDNF in autoimmune demyelination by mediating axon protection. Another study comparing BDNF to Tau proteins revealed that BDNF is a good biomarker for the diagnosis of MS but not for severity or progression of the disease [160]. High proBDNF expression is found in circulating lymphocytes and infiltrated inflammatory cells at the lesion sites of the brain and spinal cord of patients [161]. The latter authors showed that the systemic administration of anti-proBDNF blocking antibodies attenuated clinical severity scores. Yoshimura et al. [162] reported that IFN- β caused a significant increase in serum BDNF levels produced by T cells as well as in *TrkB* expression levels in peripheral blood mononuclear cells of MS patients.

After brain damage or inflammation, BDNF shows a neuroprotective effect resulting from its binding to the TrkB receptor and activation of a signaling cascade [163]. This leads to anti-inflammatory and anti-apoptotic effects by modulating MyD88 / NF- κ B and PI3K / AKT signaling pathways [155, 164]. Activation of the MyD88 pathway triggers NF- κ B and MAPK, which increase the expression of cytokines and proinflammatory mediators [165, 166]. Therefore, BDNF is a part of an endogenous defense pathway during bacterial and viral inflammatory processes and helps to eliminate the negative effect of the inflammatory response [165]. BDNF is involved in the modulation of the inflammatory response and in the regulation of its detrimental effects [163, 165, 167]. By blocking the activation of caspase-3 [168–170], BDNF reduces the translocation of apoptosis-inducing factor (AIF) [171] and the excitotoxicity of glutamate. Moreover, BDNF augments the activity of antioxidant

enzymes [172] and improves the binding capacity of intracellular calcium increasing cell survival [168, 173].

BDNF is implicated not only in neuroinflammation but also in inflammatory processes in visceral organs. Qiao et al. [174] showed that both BDNF and pro-BDNF levels were increased in inflamed urinary bladder. The BDNF high affinity receptor TrkB and general receptor p75 expression levels were elevated, with an increased level of TrkB tyrosine phosphorylation/activity. These results suggest that in vivo BDNF release is an important event in neurogenic inflammatory states and implies a possible pro-proliferative effect of BDNF in the inflamed bladder. The significant interplay between BDNF and immune mediators is also indicated by increased BDNF serum levels and increased NGFR expression on T-cells in patients with rheumatoid arthritis [175]. Furthermore, mRNA for TrkA, TrkB, and p75 receptors were expressed in the injured nerve, suggesting that these specific receptors can mediate the effects of the T-cell-derived neurotrophins [153].

Therefore, it is safe to posit that the participation of BDNF in the immune cluster and its interactions with neuroprotective and cell–cell adhesion DEPs is a conserved regulatory process which protects against the many detrimental effects of immune activation and hyperinflammation [5]. Overall, the results of the PPI network in Fig. 6 and the above review on the interactions between BDNF and the immune system indicate that (a) BDNF belongs to the immune response PPI network, (b) BDNF regulates many immune functions and signaling and may downregulate the immune-inflammatory response, and (c) lowered BDNF levels during chronic stress are associated with increased inflammatory responses.

BDNF and Immune Cell Interactions and Inflammatory Pathways in the Major Psychoses

Major Depression

Depression is regarded as a life-threatening disease as well as a severe cause of disability [176]. The growing body of evidence in the literature supports the central role of a moderate chronic immune-inflammatory process as a driver for the onset and progression of depression, as evidenced by over 10,000 publications published on the subject [3]. Glial and endothelial cells in the brain produce cytokines and chemokines [177] that function as neuromodulators in brain development and to maintain a healthy brain homeostasis in general [178, 179]. Nonetheless, major depressive individuals have heightened immune-inflammatory responses, including increased levels of acute phase reactants as well as elevated proinflammatory cytokines and receptors,

chemokines, and soluble adhesion molecules in the CSF, post-mortem tissue, and peripheral blood [3].

The literature shows that neurotrophic pathways, as well as activated immune-inflammatory pathways, have a role in the etiology of MDD. Thus, neurotrophic and inflammatory processes may interact in depression, with BDNF playing a key role due to its impact on brain plasticity and neuronal functioning [180–182]. There is evidence that BDNF levels are reduced in MDD/MDE patients, but that levels in remitted patients are comparable to those in healthy people [183]. In a cohort study, Hsieh et al. [184] compared the methylation patterns of BDNF exon IX promoter as well as the serum BDNF protein and mRNA levels in 51 patients with MDD and 62 healthy controls. The authors' results suggest that in peripheral blood, the expression of BDNF protein and mRNA is significantly lower in MDD as compared with healthy controls [184]. These observations are concordant with the findings of Schroter et al. [185], who also described lower serum BDNF levels in patients with MDD. According to Chiou and Huang [186], drug-naïve patients with first-episode MDD exhibit lower BDNF protein levels than healthy individuals. Moreover, a ROC (receiver operating characteristic) analysis conducted by the same authors [187] showed that BDNF expression can discriminate male patients with MDD from controls with moderate accuracy. Additionally, alterations in the methylation patterns of histone H3 at lysine 9 within the BDNF exon IV have been observed in patients with schizophrenia [188]. BDNF levels that are decreased can also be utilized to externally validate the diagnosis of MDD. Chen and coauthors were able to design an algorithm based on serum BDNF, cortisol, and IFN- γ levels with an accurate confusion matrix (AUC of 0.884, 86.7 percent sensitivity, and 83.3 percent specificity). The Val66Met polymorphism (rs6265) of BDNF is linked to reduced BDNF levels as well as higher inflammation in depressed patients [189–192].

Inflammation generated by lipopolysaccharides (LPS) may alter BDNF/TrkB signaling in the prefrontal cortex, hippocampus, and *nucleus accumbens*, which is associated with the onset of depressive behaviors [120]. This is critical because mood symptoms are related with increased bacterial translocation, which results in elevated levels of IgA/IgM directed against Gram-negative bacteria's LPS, while the latter are associated with enhanced immunological and autoimmune responses [6]. Inflammatory chemokines and cytokines, such as CXCL1/2, activate the GSK3b pathway in mice, generating depression-like behaviors [193]. LPS administration can induce depressive-like behaviors in mice models of inflammation by modulating the N-methyl-D-aspartate (NMDA) receptor functions [194], whereas LPS-treated mice lacking the NMDA receptor GluN2A subunit do not develop depressive-like behaviors and have increased

levels of proBDNF and BDNF in the prefrontal cortex (PFC) and/or hippocampus [195]. This shows that BDNF-mediated alterations in the GluN2A subunit may contribute to depression associated with neuroinflammation.

Additionally, chronic stress-induced depression-like behaviors are related with increased chemokine production (e.g., CXCL1/CXCL2) and GSK3b pathway regulation, which disrupts the CREB-BDNF pathway. Similarly, chronic stress-induced depression-like behaviors may be reversed by inhibiting CXCR2, which regulates GSK3b, apoptosis, and the CREB-BDNF signaling pathway [193]. All of this evidence suggests that activation of immune-inflammatory pathways plays a critical role in the development of major depression or depressive-like behaviors and that targeting these pathways may be a viable therapeutic strategy [196, 197].

Because BDNF levels are decreased in critical cortical and limbic brain regions in depressed patients, novel therapeutic approaches may focus on increasing BDNF levels [9, 192, 198–200]. Another strategy involves the use of PPAR γ agonists, which have been shown to raise BDNF levels [9, 201–203]. In the rodent, deep brain stimulation (DBS) of the medial forebrain bundle (MFB), a novel treatment for treatment-resistant depression [204, 205], ameliorates anhedonia-like behaviors induced by chronic unpredictable mild stress in association with normalization of the plasma, CSF, and hippocampus BDNF levels.

Heterozygous (BDNF +/) individuals exhibit anhedonia- and anxiety-like behaviors in association with changes in neurogulin-1, glucocorticoid receptor, and disrupted-in-schizophrenia (DISC) 1 gene expression in the prefrontal cortex, all of which may play a role in depression [206]. These findings imply that a decrease in BDNF levels alters the expression of genes related with affective disorders, potentially precipitating the onset of depressive-like symptoms. The BDNF exon IV promoter is involved in BDNF transcription and depressive-like behavior in humans and rodents. Patients with MDD who had hypomethylation of the CpG-87 site in the promoter IV region have a worse response to antidepressant therapy [207, 208]. Additional research established a relationship between stress exposure and a particular methylation pattern in the BDNF promoter IV, which results in depression [207, 209]. Promoter IV mutant mice (BDNF-KIV) have severe abnormalities in prefrontal GABAergic interneurons and decreased GABAergic activity in conjunction with depressive-like behaviors [210]. Additionally, antidepressant therapy boosts BDNF mRNA and protein levels in the cerebral cortex and hippocampus in rodent models due to histone acetylation in the promoter regions [211, 212].

Schizophrenia

As described in the “Introduction” [1], the early monocyte-T-lymphocyte theory of schizophrenia postulated that prenatal bacterial or viral infections could result in neurodevelopmental disorders, which, when combined with subsequent immune hits, could result in the onset of schizophrenia via increased neurotoxicity [2]. A recent meta-analysis showed that schizophrenia has been linked to decreased BDNF levels (Hedges $g = 0.458$, $p = 0.004$) [213]. BDNF levels are adversely related with a greater immune-inflammatory response in antipsychotic naïve first-episode psychosis (FEP), which may progress to deficit schizophrenia [214]. Additionally, an interaction between polymorphisms in the BDNF and NTRK2 genes increase susceptibility to paranoid schizophrenia [215]. The BDNF Met and DISC1 Cys mutations are associated with schizophrenia, and this BDNF variant is connected with a biomarker associated with schizophrenia, namely dysfunctions in exploratory eye movement [216]. Another study established a mutational profile for the BDNF (rs6265) and DISC1 (rs821597) variants in schizophrenia patients compared to healthy controls, demonstrating that the BDNF variant was associated with global cognitive impairment, working memory impairment, and attention deficits [217].

As discussed before in the section titled “PPI network of BDNF and immune molecules,” decreased BDNF levels in FEP are associated with the immunological cluster (which contains M1, Th1, Th2, and Treg cytokines and pro-inflammatory chemokines and reflects the immune-inflammatory response in FEP). Not only is BDNF connected with immunological (cytokines, STAT3, TRAF6) and neurotrophic (NTRK2, NTF4, and NGFR) DEPs in this FEP PPI network, but also with cell–cell junction (CTNNB1, CTNNA1, CTNND1, CDH1) DEPs [5]. BDNF not only acts as a neurotrophic and immunological regulating factor within this intricate yet tightly interconnected network, but also connects the immune cluster to a cell–cell junction cluster that regulates the beta-catenin complex, adherence junction architecture, and Wnt/catenin signaling pathways [5]. Thus, it seems that the immune-inflammatory response in FEP/FES involves not only IRS and CIRS components, but also neurotrophic (BDNF, NTF4, and NGFR) and cell adhesion (CTNNB1 and CDH1) components [5]. As BDNF levels are decreased in FEP/FES, the neurotoxic effects of the IRS may not be adequately mitigated by the neuroprotective and CIRS capabilities of BDNF and its related cell–cell adhesion network. As a result, decreased BDNF levels contribute to FEP and its progression to deficit schizophrenia by impairing neuroprotective and immunological regulatory functions [5].

Additionally, unique combinations of the downregulated BDNF, DISC1, CHD1, and CTNNB1 DEPs are related with

abnormalities in synaptic formation (CDH1 and BDNF), positive control of axonogenesis (BDNF and DISC1), and neuron projection development (BDNF, CTNNB1, and CDH1) [5]. The BDNF and CTNNB1 genes exhibit very significant database-annotated interactions (STRING), and the BDNF and CTNNB1 pathways are also functionally linked [5]. BDNF-mediated breakdown of cadherin–catenin complexes is associated with increased synaptic density in hippocampal neurons [107]. Polymorphisms in BDNF are associated with changes in the Wnt/-catenin pathway, which may in part govern BDNF synthesis [218, 219]. This may explain why individuals with impaired CIRS functions, such as deficiencies in natural IgM, protective cytokine receptors, neurotrophin/Trk, and Wnt/catenin signaling, decreased DISC1 expression, and interactions between diminished BDNF, CDH1, CTNNB, and DISC1 expression may be at an increased risk of developing FEP and FES following immune hits [5].

Conclusions

A growing body of research indicates the involvement of immune-inflammatory pathways in the development of neuropsychiatric disorders. In the present review, we have summarized the link between BDNF and immune-inflammatory pathways and underlined how those interactions delineate the neuro-immune pathophysiology of mood disorders and schizophrenia. The built PPI network showed significant interactions between BDNF and neurotrophic (NTRK2, NTF4, and NGFR), immune (cytokines, STAT3, TRAF6), and cell–cell junction (CTNNB, CDH1) DEPs in the major psychosis, neurodevelopment, neuronal functions, and immune-inflammatory and related pathways. TRKR and Src homology region SHP2 pathways, Trk signaling pathways, positive regulation of kinase and transferase activity, cytokine signaling, and negative regulation of the immune response were the most significant participants identified to belong to this PPI network. We conclude that decreased BDNF levels in mood disorders and schizophrenia most probably contribute to alterations in neurotrophic signaling and increase the vulnerability to activation of immune-inflammatory pathways, followed by neurotoxicity. Also, BDNF may cause alterations in the expression of other DEPs (CTNNB1, CDH1, or DISC1) leading to multiple aberrations in synaptic and axonal functions. The available data suggest that BDNF is an instructive mediator of structural and functional plasticity in the CNS and its interactions with the immune pathways are the key components in major psychiatric disorders. Consequently, future research which examines the expression of BDNF in psychiatric disorders should examine not only BDNF but also the expression (protein-mRNA) of its major interacting proteins as

determined in this review. Moreover, such measurements should be added to the existing precision nomothetic models of affective disorders and schizophrenia which were constructed based on the neurotoxic effects of immune and nitro-oxidative pathways [6, 220–222]. As such, these neurotoxicity precision models may be enriched and improved by adding the neuroprotective BDNF-associated pathways.

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