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Review

Environmental Enrichment Effects on the Brain-Derived Neurotrophic Factor Expression in Healthy Condition, Alzheimer's Disease, and Other Neurodegenerative Disorders

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Abstract. Brain-derived neurotrophic factor (BDNF), a protein belonging to the neurotrophin family, is known to be heavily involved in synaptic plasticity processes that support brain development, post-lesion regeneration, and cognitive performances, such as learning and memory. Evidence indicates that BDNF expression can be epigenetically regulated by environmental stimuli and thus can mediate the experience-dependent brain plasticity. Environmental enrichment (EE), an experimental paradigm based on the exposure to complex stimulations, constitutes an efficient means to investigate the effects of high-level experience on behavior, cognitive processes, and neurobiological correlates, as the BDNF expression. In fact, BDNF exerts a key role in mediating and promoting EE-induced plastic changes and functional improvements in healthy and pathological conditions. This review is specifically aimed at providing an updated framework of the available evidence on the EE effects on brain and serum BDNF levels, by taking into account both changes in protein expression and regulation of gene expression. A further purpose of the present review is analyzing the potential of BDNF regulation in coping with neurodegenerative processes characterizing Alzheimer's disease (AD), given BDNF expression alterations are described in AD patients. Moreover, attention is also paid to EE effects on BDNF expression in other neurodegenerative disease. To investigate such a topic, evidence provided by experimental studies is considered. A deeper understanding of environmental ability in modulating BDNF expression in the brain may be fundamental in designing more tuned and effective applications of complex environmental stimulations as managing approaches to AD.

Keywords: Alzheimer's disease, animal models, brain-derived neurotrophic factor, environmental enrichment, neurodegeneration, neuroplasticity, rodents

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NEUROPLASTICITY AND ENVIRONMENTAL ENRICHMENT

Neuroplasticity is the ability of nervous system to change its structure and function as a result of the experience [1]. Such a brain prerogative is the basis of its ability to successfully adapt to the environment, a fundamental property in both ordinary learning processes and extraordinary phases, such as those linked to brain development and repair [2].

Accordingly, evidence has been provided that individuals with dissimilar life experiences differently cope with brain damage and degeneration. This concept has been structured in the *reserve hypothesis* [3, 4] that posits that the experience-induced plastic changes are able to constitute a cerebral reserve that supports the individual in demanding conditions. Such a cerebral reserve is developed at three levels, such as: *brain reserve* – referred to the structural equipment of an individual, consisting of brain volume, number and morphological features of neurons, glial cells, and synapses, circulatory and neurotransmitter systems, etc.; *cognitive reserve* – referred to cognitive strategies engaged in performances and tasks; *neural reserve* – referred to the efficient recruitment of neural circuitries [4–7]. More recently, another level has been added, namely the *brain maintenance*, referred to the ability of maintaining the nervous system integrity [8, 9].

Three experiential factors have been identified as the ones that potentiate the nervous system structure and function: the *social factor* – regarding all the ties that insert an individual in a thick social network (such as familiar status, friendship, etc.) [10, 11]; the *cognitive factor* – regarding all the mentally demanding activities that involve an individual (such as education and work, but also a number of cognitive leisure activities, multilingualism, etc.) [12–15]; the *physical factor* – regarding all the components of a healthy lifestyle (such as motor activity, salubrious diet, etc.) [16–19].

To investigate the effects of the experience on the nervous system, the three enlisted experiential factors are mimicked in animal studies by using the classical experimental paradigm of environmental enrichment (EE), which is based on advanced social, cognitive, and physical stimulations [20, 21]. Such a protocol is commonly used with rodents, by enhancing laboratory housing condition on several dimensions in order to mimic the three human lifestyle factors that are indicated as reserve-builders. The rearing in groups of animals more numerous than the regular ones mimics the *social factor*; the complex and always-changing environment—created by placing, repositioning, and often renewing a large amount of objects in the cage—mimics the *cognitive factor*; and, finally, the large cages provided with ladders, running wheels, and shelves that allow and stimulate exploration and motor activity, sometimes in combination with the offer of supplementary nutrients, mimic the *physical factor* [22]. EE paradigm allows evaluating the effects of a single factor among the cited ones or of more than one factor in combination; modifying the age of the animals at the starting of the exposure and the duration of the exposure; primarily stimulating a single sensory channel or more than one in combination; enriching animals in healthy or pathological state. On the whole, EE allows a high-level control and manipulation of the single involved variables, a possibility hardly achievable in human studies [6, 23].

Animal studies based on the exposure to EE consistently demonstrate that enriched rodents show improved performances in multifarious behavioral and cognitive tasks, both in healthy conditions and in the presence of neural damage and cognitive decline [24–28]. In correlation, large evidence has been provided that EE induces a reinforcement of neural structure, circuitries, and processes ([29–34]; for a review, see [35]), among which the expression of neurotrophic factors [36, 37].

BRAIN-DERIVED NEUROTROPHIC FACTOR

Brain-derived neurotrophic factor (BDNF), firstly isolated in the eighties from pig brain [38], belongs to the neurotrophin family of growth factors, together with the homologs nerve growth factor (NGF) and neurotrophins 3, 4, 5, and 6 [39]. Neurotrophins are synthetized mainly in the central nervous system, but also in non-neural cells (such as lymphocytes, monocytes, vascular endothelial and muscle cells) [40], and fundamentally support and regulate neural growth, differentiation, survival, and plasticity both in central and peripheral nervous system [41].

In the adult brain, BDNF is the predominant member of the neurotrophin family, and it is expressed in several areas, with the highest levels in hippocampus, and then in cerebral cortex, amygdala, and cerebellum. However, BDNF expression has also been described in hypothalamus, striatum, midbrain, pons, and medulla oblongata [40, 42]. It has been reported that BDNF is expressed by glutamatergic

neurons and glial cells, such as astrocytes and microglia [43]. Recently, it has been reported that it may also be expressed by inhibitory cells [44]. BDNF is synthetized as pro-BDNF precursor, and it is then converted in mature BDNF at both intra- and extracellular levels [45]. Both pro-BDNF and mature BDNF are expressed in activity-dependent way, but they provoke opposite effects on cellular functioning, following two different pathways [46, 47]. Pro-BDNF induces long-term depression and apoptosis, by preferably binding p75NTR receptor; conversely, mature BDNF supports long-term potentiation, synaptogenesis, and neuronal survival, by selectively binding to tyrosine kinase receptor [42, 48, 49]. In particular, several studies assigned to BDNF a prominent role in modulating synaptic plasticity and strength, affecting *N*-methyl-D-aspartate (NMDA) receptor expression [50], dendritic spine density and morphology [51, 52], and neurogenesis [53]. At a functional level, BDNF expression supports and modulates cognitive functioning, namely, the learning and memory processes [54, 55].

Such BDNF actions support its potentially beneficial role in neurodegeneration, and specifically in Alzheimer's disease (AD). In AD patients' post-mortem brains, *BDNF* mRNA and BDNF protein levels are reduced; a similar decrease is present also in mild cognitive impairment (MCI) [39]. It has been reported a negative interaction between amyloid-β (Aβ) senile plaques and BDNF expression linked to the downregulation of axonal transport and the inhibition of the conversion from pro-BDNF to mature BDNF [56–58]. However, findings related to BDNF serum levels in AD patients are still conflicting, since decreased [59], equal [60], and even increased [61] levels have been found in comparison to healthy controls. A recent meta-analysis confirmed that BDNF serum level is reduced in AD, but not in MCI patients [62]. Methodological biases have been advanced as the cause of this conundrum [63]. Moreover, it is worth noting that animal studies suggest that changes in central mature BDNF protein are not always reflected by changes in peripheral mature BDNF levels [64].

EPIGENETIC REGULATION OF BDNF EXPRESSION

In humans, the *BDNF* gene is located at chromosome 11, region p13-14 [65]. The *BDNF* gene has a very complex structure that encompasses eleven different exons in humans and nine different exons in rodents. However, in both humans and rodents only the last exon—that is the exon IX— is the coding one at the 3′-end [43, 66]. Anyway, nine of the eleven exons contain nine alternative promoters, in both humans and rodents. This quite exceptional characteristic of *BDNF* gene has probably the role to finely regulate its complex expression in both spatial and temporal sense [43, 65, 67]. In fact, the existence of multiple promoters determines tissue-specific expression of *BDNF* transcripts [66]. In the brain, all exons are expressed, but different degrees of expression are found in different regions and in different developmental stages [43]. Moreover, the multiple promoters support the high and specific responsiveness of BDNF to a large variety of environmental stimuli, on the basis of a number of regulatory elements recruiting proper transcription factors that modulate their activity. As a consequence, since *BDNF* promoters mediate differential BDNF isoform expression in diverse brain areas, the environment-induced changes in their activity are able to modulate cellular and behavioral phenotypes [43].

A fundamental epigenetic mechanism involved in *BDNF* gene expression regulation is DNA methylation, which is able to modulate gene silencing throughout lifespans by triggering dynamic and reversible processes. A relevant role in this process has been attributed to the methyl-CpG-binding protein 2 (MeCP2), which is able to act on chromatin structure by recruiting transcriptional repressor complexes in an activity-dependent manner [65, 68, 69]. Moreover, in consequence of environmental stimulations BDNF expression levels are also modulated by histone post-translational modifications, mediated by a number of processes, such as methylation and acetylation [67, 69]. Post-transcriptional regulation of *BDNF* mRNA levels may be mediated by non-coding RNAs, such as microRNAs. In fact, the *BDNF* 3'-untraslated region contains up to twenty binding sites for thirteen different families of microRNAs that can modulate *BDNF* mRNA expression and protein synthesis [65, 69].

At the translational level, the BDNF protein is firstly synthesized in the endoplasmic reticulum as a precursor protein, the pre-pro-BDNF, that is successively converted in pro-BDNF by the cleavage of its signal [43, 66]. However, it has been advanced that four different pre-pro-BDNF protein isoforms could be synthesized, showing different length of the pre-domain according to the transcribed exon. The length of the pre-domain may be able to affect the

intracellular BDNF trafficking, and a greater length may promote the secretion of the immature isoform [65]. In the brain, pro-BDNF can indeed undergo editing in Golgi and be secreted as mature BDNF protein; in alternative, it can be secreted as immature molecule and then be cleaved as mature BDNF in the synaptic space; finally, it can also be secreted as pro-BDNF without further digestion. Environmental stimuli can affect differential expression of *BDNF* transcript also modulating the pro-BDNF/mature BDNF ratio [65]. Given that, as said above, pro- and mature BDNF provoke opposite effects on cellular functioning, following two different pathways [46, 47], this is a key issue to be investigated.

ENVIRONMENTAL ENRICHMENT AND BDNF

Given the BDNF role in promoting neuroplasticity and supporting neuroprotection [42, 48–55] and the changes in brain and serum BDNF levels reported in consequence of stimulations of various nature (e.g., [37, 70, 71]), BDNF is considered a good candidate in mediating EE neuroprotective action, in both healthy and pathological conditions [72, 73]. Accordingly, as it will be shown below, a great number of studies have been carried out to investigate the EE effects on BDNF expression in the central and peripheral nervous system, and a number of epigenetic mechanisms have been suggested to be involved in the EE-dependent modulation of BDNF expression. Kuzumaki and colleagues [74] showed that a 4-week exposure to EE induces in the adult mouse hippocampus a significant increase in tri-methylation of histone H3 at lysine 4, an activated histone modification marker, at the *BDNF* P3 and P6 promoters. In addition, a significant decrease in repressive histone modification markers, such as tri-methylation of histone H3 at lysine 9 at the *BDNF* P4 promoter and of histone H3 at lysine 27 at the *BDNF* P3 and P4 promoters was found. Neidl et al. [75] reported that *BDNF Exon-1* transcripts appear significantly upregulated in aged rats exposed to EE for 6 months. Also, Morse et al. [76] demonstrated that learning increases tri-methylation of histone H3 at lysine 4 levels around the *BDNF Exon-IV* promoter in the hippocampus of aged rats previously exposed to EE for five weeks (1 h/day).

However, a comprehensive framework on the effects of the exposure to EE in central and peripheral nervous system BDNF levels is still lacking. Despite the repeated observations that environmental experiences (physical exercise, cognitive training, etc.) are able to modulate BDNF expression, in human studies, evidence is controversial [77–80]. Taking into account the significance of this topic and the confounding data present in literature, we systematically analyze the effects of environmental stimulations on BDNF expression. It is important to consider that only in animal studies it is possible to manipulate genetic and environmental factors independently from each other and therefore disentangle the single environmental factors that may influence the direction of the changes in brain BDNF levels. Thus, it appears just an occasion in which it is worth following the approach "from bedside to bench and back to bedside": the brain and cognitive reserve hypothesis (developed in humans) is modeled in animals to achieve a high-level control of the involved variables; then, evidence obtained in animal models can provide useful indications to be applied in human pathology. On such a basis, the present review has collected and synthesized the evidence on EE effects on brain and serum BDNF expression in animal models, with a particular focus on the effects reported in healthy subjects and AD models, to investigate if the exposure to EE is systematically accompanied by increased BDNF expression in a brain region-specific manner and/or in serum, and which factors influence the association between exposure to EE and BDNF expression in brain and serum.

To provide a broad overview on this topic, a methodical literature search was conducted in PubMed, by screening all titles and abstracts obtained by searching for the combination of the "environmental enrichment" OR "enriched environment" AND "brain-derived neurotrophic factor" OR "BDNF" keywords. Moreover, full texts and reference lists were screened to identify further potentially relevant articles. Articles fulfilling the following criteria were included in the present overview: 1) as *population of interest*, we selected rodents, and in particular healthy subjects and AD models; 2) as *intervention of interest*, we selected the exposure to multidimensional EE or unidimensional EE when the articles presented relevant cases that provide indications on multidimensional EE components' effects; 3) as *control group of interest*, we selected animal reared in standard laboratory conditions; 4) as *outcomes of interest*, we selected brain and serum *BDNF* gene and BDNF protein levels, regardless of the determination method. No language limitation was selected. No publication period limitation was selected. Records indexed up to June 2021 have been screened.

Consequently, 35 relevant papers (31 on healthy subjects and 4 on AD models) that met the criteria were included in the present review.

We collected the following data: authors; year of publication; animal species; AD model, when present; animals' age or weight at the start of the exposure to EE; EE type (by specifically noting if the paradigm encompasses running wheels and novelty manipulation); EE duration; animal age at BDNF expression determination; EE effects on *BDNF* gene or BDNF protein levels. As for BDNF expression data, we registered the method used for BDNF expression determination, the cerebral areas in which the findings have been obtained, and the direction (increased/unchanged/decreased) of the changes in BDNF expression. Moreover, when specific analyses were performed on single or both BDNF isoforms (pro-BDNF and mature BDNF), we registered the data for them. Where not specified, we assumed that the analysis was conducted on BDNF mature isoform, and so it is to be understood in the manuscript.

All data collected are illustrated in Tables 1 and 2.

ENVIRONMENTAL ENRICHMENT EFFECTS ON BDNF EXPRESSION IN HEALTHY ANIMALS

Details on data regarding EE effects on brain and serum BDNF levels in healthy animals are provided in Table 1.

The majority of the studies conducted on healthy rodents (24 out of 31) evaluated EE effects on BDNF expression in the hippocampus, the cerebral region in which EE effects are mostly investigated, given it is heavily involved in learning and memory, emotion, motivation, and stress responses [73]. On the whole, most studies (19 out of 24) report an EE-dependent increase of BDNF protein and *BDNF* gene levels in the hippocampus [36, 64, 74–76, 81–94], while none of these studies reports a decrease in BDNF expression after the exposure to EE. Noteworthy, an appreciable number of studies (11 out of 24) reports the absence of EE effects in BDNF expression (i.e., [74–76, 83, 89, 94–99]) in both protein and gene levels. In some cases, the same study reports both increased and unchanged hippocampal BDNF levels after exposure to EE, in association with disparate factors, such as the age at the start of the exposure to EE [94], duration of the exposure to EE [74], presence of physical enrichment [89], hippocampal areas analyzed [83], and kind of analysis performed [75, 76].

Similarly, increased BDNF protein [36, 82] and *BDNF* mRNA [86, 100] levels have been found in neocortex after the exposure to EE, but also unchanged gene and protein levels have been reported [83, 86, 95, 99].

After the exposure to EE, enhanced *BDNF* mRNA expression has been reported in the hypothalamus [101, 102], even if a significant number of studies found unchanged gene and protein levels [86, 99, 102]. A study investigating the effects of singularly manipulating social or physical variables revealed no changes due to the mono-dimensional stimulation, and increased BDNF protein expression after the combined exposure to social and physical enhanced stimulations [103].

As for the cerebellum, both unchanged [83, 104] and increased [36, 104] BDNF protein levels have been reported. Vasquez-Sanroman and colleagues [104] reported different results in the cerebellum (likely linked to the different durations of the exposure to EE and techniques of BDNF level determination). An investigation carried out on the entire hind brain area revealed increased BDNF protein levels [82].

When the basal forebrain area has been analyzed, increased BDNF protein expression has been revealed [82].

As for the amygdala, unchanged *BDNF* gene [99, 102] and BDNF protein [83] expression has been reported in enriched animals, even if decreased BDNF protein expression has been also reported [105]. As for the striatum, some studies described no effects of EE on *BDNF* gene and BDNF protein levels [99, 106], although decreased protein levels have been also reported [36]. In raphe nuclei, unchanged *BDNF* gene levels have been found after exposure to EE [99]. Thus, these brain areas might be less involved in BDNF-mediated EE neuroprotective effects.

As for the effect of the exposure to EE on BDNF protein levels in serum, unchanged [64, 95] or decreased [105] levels have been reported.

ENVIRONMENTAL ENRICHMENT EFFECTS ON BDNF EXPRESSION IN THE PRESENCE OF ALZHEIMER'S DISEASE (AD)

A small proportion (4 out of 35) of the analyzed studies investigated the effects of EE on BDNF levels in rodent models of AD. Details on data reported are provided in Table 2.

Table 1
Studies on the environmental enrichment effects on BDNF levels in healthy animals

Reference	Species (*age or weight at the start of the environmental enrichment*)	Environmental enrichment type (*duration*)	Age at BDNF level determination	Environmental enrichment effects on BDNF level (*determination method*)
Angelucci et al., 2009 [36]	Male Wistar rats (*postnatal day 21*)	Environmental enrichment – with running wheels and novelty manipulation (*20 weeks*)	About 5,5 months	***Hippocampus; frontal cortex; cerebellum:*** increased BDNF protein (+) ***Striatum:*** decreased BDNF protein (−) (*ELISA*)
Babri et al., 2018 [105]	Male Wistar rats (*at weaning*)	Environmental enrichment – with running wheels and novelty manipulation (*98 days*)	About 4 months	***Amygdala***: decreased BDNF protein (−) ***Serum***: decreased BDNF protein (−) (*ELISA*)
Bardi et al., 2016 [97]	Male Long-Evans rats (*about 30 days*)	Environmental enrichment (natural; artificial; mixed) – without running wheels; with novelty manipulation (*6 weeks*)	About 10 weeks	***Hippocampus***: unchanged BDNF immunoreactivity (=) (*immunohistochemistry*)
Bechara and Kelly, 2013 [89]	Male Wistar rats (*3 months*)	Environmental enrichment – without running wheels; with novelty manipulation (*3 weeks*)/ Physical enrichment – treadmill (*1 week*)/ Environmental enrichment – without running wheels; with novelty manipulation+ Physical enrichment – treadmill (*3 weeks with physical enrichment in the last week*)	About 15 weeks	***Hippocampus***: unchanged *BDNF* mRNA (=)/ increased *BDNF* mRNA (+)/ increased *BDNF* mRNA (+) (*quantitative real-time PCR*)
Candemir et al., 2019 [99]	Male and female CD1 mice (*at birth*)	Environmental enrichment – without running wheels; with novelty manipulation (*6–8 weeks*)	6–8 weeks	***Hippocampus; frontal cortex; hypothalamus; amygdala; striatum; raphe nuclei***: unchanged *BDNF* gene (=) (*quantitative real-time PCR*)
Cao et al., 2014 [81]	Male Wistar rats (*3 weeks*)	Environmental enrichment – without running wheels; with novelty manipulation (*7 weeks*)	10 weeks	***Hippocampus:*** increased mature BDNF (+) and unchanged pro-BDNF (=) proteins (*western blot*)
Chourbaji et al., 2012 [86]	Male and female C57BI6/N mice [wild-type of $BDNF^{+/-}$] (*4 weeks*)	Environmental enrichment – without running wheels and novelty manipulation (*7–8 weeks*)	11–12 weeks	***Hippocampus***: increased BDNF protein and *BDNF* mRNA (+) ***Frontal cortex***: unchanged BDNF protein (=); increased *BDNF* mRNA (+) ***Hypothalamus***: unchanged BDNF protein and *BDNF* mRNA (=) (*ELISA; quantitative real-time PCR*)
Foglesong et al., 2016 [101]	Male C57BL/6 mice (*3 weeks*)	Environmental enrichment – with running wheels; without novelty manipulation (*6 days/4 weeks*)	4 weeks/7 weeks	***Hypothalamus***: increased *BDNF* mRNA (+)/ increased *BDNF* mRNA (+) (*quantitative real-time PCR*)

(Continued)

Table 1
(Continued)

Reference	Species (*age or weight at the start of the environmental enrichment*)	Environmental enrichment type (*duration*)	Age at BDNF level determination	Environmental enrichment effects on BDNF level (*determination method*)
Giacobbo et al., 2019 [64]	Male Wistar rats (*6/17 months*)	Environmental enrichment – without running wheels; with novelty manipulation (*90 min/day; 12 weeks*)	9/20 months	***Hippocampus***: increased mature BDNF and pro-BDNF proteins (+)/ increased mature BDNF and pro-BDNF proteins (+) ***Serum***: unchanged mature BDNF protein (=)/ unchanged mature BDNF protein (=) (*ELISA; western blot*)
Gualtieri et al., 2017 [98]	Female ICR mice (*13 weeks*)	Environmental enrichment – with running wheels; without novelty manipulation (*8 days*)	14 weeks	***Hippocampus***: unchanged BDNF immunoreactivity (=); unchanged *BDNF* gene (=) (*immunohistochemistry; quantitative real-time PCR*)
Heinla et al., 2015 [91]	Male C57BL/6 and 129Sv mice (*at weaning*)	Environmental enrichment – with running wheels and novelty manipulation (*7–8 weeks*)	10–11 weeks	***Hippocampus***: increased *BDNF* mRNA (+) (*quantitative real-time PCR*)
Ickes et al., 2000 [82]	Male Sprague–Dawley rats (*2 months*)	Environmental enrichment – with running wheels and novelty manipulation (*12 months*)	14 months	***Hippocampus***: Increased BDNF protein (+) ***Cerebral cortex***: Increased BDNF protein (+) ***Basal forebrain:*** increased BDNF protein (+) ***Hind brain area:*** Increased BDNF protein (+) (*ELISA*)
Kazlauckas et al., 2011 [84]	Male albino CF1 mice (*2 months*)	Environmental enrichment – with running wheels and novelty manipulation (*2 months*)	4 months	***Hippocampus***: increased BDNF protein (+) (*western blot*)
Kobilo et al., 2011 [85]	Female C57B1/6 mice (*5 weeks*)	Environmental enrichment – without running wheels; with novelty manipulation / Environmental enrichment – with running wheels and novelty manipulation/ Physical enrichment – continuous access to running wheels (*43 days*)	About 11 weeks	***Hippocampus***: unchanged mature BDNF protein (=)/ increased mature BDNF protein (+)/ increased mature BDNF protein (+) (*western blot*)
Kondo et al., 2012 [87]	Male C57BL/6J mice (*3–4 weeks*)	Environmental enrichment – with running wheels; without novelty manipulation (*1/2/3/4 weeks*)	4–5/5–6/6–7/7–8 weeks	***Hippocampus***: increased *BDNF* mRNA (+)/ increased *BDNF* mRNA (+)/ increased *BDNF* mRNA (+)/ increased *BDNF* mRNA (+) (*semiquantitative real-time PCR*)
Kuzumaki et al., 2011 [74]	Male C57BL/6J mice (*18–23 g*)	Environmental enrichment – with running wheels; without novelty manipulation (*1/2/3/4 weeks*)	-	***Hippocampus***: *1–2 weeks*: unchanged *BDNF* mRNA (=)/*3–4 weeks*: increased *BDNF* mRNA (+) (*quantitative real-time PCR*)

(Continued)

Table 1
(Continued)

Reference	Species (*age or weight at the start of the environmental enrichment*)	Environmental enrichment type (*duration*)	Age at BDNF level determination	Environmental enrichment effects on BDNF level (*determination method*)
McMurphy et al., 2018 [102]	Female C57Bl/6 mice (*10 months*)	Environmental enrichment – with running wheels; without novelty manipulation (*6 weeks/12 months*)	11,5 months/ 22 months	***Hypothalamus***: increased *BDNF* mRNA (+)/ unchanged *BDNF* mRNA (=) ***Amygdala***: unchanged *BDNF* mRNA (=)/ unchanged *BDNF* mRNA (=) (*quantitative real-time PCR*)
McQuaid et al., 2018 [100]	Male CD-1 mice (*at weaning*)	Environmental enrichment – with running wheels; without novelty manipulation (*6 weeks*)	9 weeks	***Prefrontal cortex***: increased *BDNF* mRNA (+) (*reverse transcription-quantitative real-time PCR*)
Meng et al., 2015 [92]	Male C57BL/6J mice (*5 weeks*)	Environmental enrichment – with running wheels and novelty manipulation (*about 5 months*)	About 6 months	***Hippocampus***: increased *BDNF* mRNA (+) (*reverse transcription-quantitative real-time PCR*)
Morse et al., 2015 [76]	Male Fischer-344 rats (*3/19–22 months*)	Environmental enrichment – without running wheels; with novelty manipulation (*1 h/day; 5 weeks*)	About 4 months/20–23 months	***Hippocampus***: unchanged *BDNF* Exon IX mRNA (=); increased *BDNF* mRNA in CA1 pyramidal neurons (+)/ unchanged *BDNF* Exon IX mRNA (=); increased *BDNF* mRNA in CA1 pyramidal neurons (+) (*quantitative real-time PCR*)
Neidl et al., 2016 [75]	Female Long-Evans rats (*18 months*)	Environmental enrichment – without running wheels; with novelty manipulation (*6 months*)	24 months	***Hippocampus***: unchanged total *BDNF* mRNA (=); increased *BDNF* Exon-I (+); unchanged *BDNF* Exon IV and Exon VI (=) (*quantitative real-time PCR*)
O'Connor et al., 2019 [106]	Mice (*at birth*)	Environmental enrichment – with running wheels and novelty manipulation (*8/10/15 days*)	Postnatal days 8/10/15	***Striatum***: unchanged BDNF protein (=)/ unchanged BDNF protein (=)/ unchanged BDNF protein (=) (*ELISA*)
O'Leary et al., 2019 [94]	Male Sprague Dawley rats (*4/8 weeks*)	Physical enrichment – continuous access to a running wheel (*4 weeks*)	11/15 weeks	***Hippocampus***: increased *BDNF* mRNA (+) / unchanged *BDNF* mRNA (=) (*quantitative real-time PCR*)
Pietropaolo et al., 2004 [103]	Male CD-1 mice (*postnatal day 35*)	Social enrichment – rearing in pairs compared to isolation/ Physical enrichment - plastic compartments joined by tunnels and a running wheel/ Social and physical enrichment (*5 days*)	About 4 months	***Hypothalamus***: unchanged BDNF protein (=) / unchanged BDNF protein (=) / increased BDNF protein (+) (*ELISA*)
Ramírez-Rodríguez et al., 2014 [90]	Female BalbC mice (*6 months*)	Environmental enrichment – with running wheels and novelty manipulation (*45 days*)	7,5 months	***Hippocampus***: increased BDNF protein (+) (*ELISA*)
Sheikhzadeh et al., 2015 [96]	Male Wistar rats (*250 ± 50 g*)	Physical enrichment – treadmill (*2/8 weeks*)	Adult	***Hippocampus***: unchanged BDNF protein (=)/ unchanged BDNF protein (=) (*ELISA*)

(Continued)

Table 1
(Continued)

Reference	Species (*age or weight at the start of the environmental enrichment*)	Environmental enrichment type (*duration*)	Age at BDNF level determination	Environmental enrichment effects on BDNF level (*determination method*)
Vazquez-Sanroman et al., 2013 [104]	Male Balb/c AnNHsd mice (*postnatal day 21*)	Environmental enrichment – without running wheels; with novelty manipulation (*1/4/8 weeks*)	4/7/11 weeks	***Cerebellum***: unchanged pro-BDNF and mature BDNF proteins (=); increased BDNF immunoreactivity at granular layer (+) / increased BDNF immunoreactivity at granular and Purkinje layers (+)/ increased pro-BDNF and mature BDNF proteins (+); increased BDNF immunoreactivity at granular and Purkinje layers (+) (*western blot; immunohistochemistry*)
Vedovelli et al., 2011 [95]	Male Wistar rats (*40 days*)	Environmental enrichment – without running wheels; with novelty manipulation (*2 months*)	About 3,5 months	***Hippocampus***; ***frontal cortex; serum***: unchanged BDNF protein (=) (*ELISA*)
Williamson et al., 2012 [88]	Male Sprague-Dawley rats (*67 days*)	Environmental enrichment – with running wheels; without novelty manipulation (*12 h/day; 7 weeks*)	About 4 months	***Hippocampus***: increased *BDNF* mRNA (+) (*quantitative real-time PCR*)
Zhang et al., 2016 [93]	Male Wistar rats (*adult; 220–250 g*)	Environmental enrichment – with running wheels and novelty manipulation (*30 days*)	Adult	***Hippocampus***: increased BDNF protein (+) (*western blot*)
Zhu et al., 2006 [83]	Male and female C57BL6/J mice (*postnatal day 21*)	Environmental enrichment – with running wheels and novelty manipulation (*about 4 months*)	About 5 months	***Hippocampus***: ***ventral area*** – increased BDNF protein (+) ***dorsal area; entorhinal cortex*** – unchanged BDNF protein (=) ***Frontal cortex; Amygdala; Cerebellum:*** unchanged BDNF protein (=) (*ELISA*)

The characterization reported for the environmental enrichment paradigm specifies the variables manipulated, when variations on the classical paradigm (described in the paper) are involved, and in particular when only one enriching variable is manipulated. Presence or absence of running wheels in the paradigm is recorded; presence or absence of the explicit reporting of novelty manipulation is also recorded.

In the four analyzed studies, three AD transgenic models are used, namely APP23, 5xFAD, and APPswe/PS1ΔE9 transgenic mice. The amyloid precursor protein (APP23) transgenic mouse model is based on the expression of the human APP751 with the Swedish double mutation. APP23 mice are characterized by augmented Aβ plaque formation, neuronal loss, and progressive age-related cognitive decline [107]. 5xFAD model exhibits AD hallmarks of amyloid violent burden and cognitive decline already in the early phases [108]. APPswe/PS1ΔE9 model resembles the initial stages of AD, with Aβ deposit appearing from 4 to 6 months of age, and plaques from 9 months [109]. However, it is worth noting that in three of the studies included in this review [110–112], the pathological conditions were characterized by the lack of the alterations in the BDNF expression levels conversely reported in AD patients. Wolf and colleagues (2006) did not investigate the possible presence of alterations in BDNF expression in APP23 mice compared to controls [107].

Prolonged (starting from the age of 10 weeks and maintained for about 15 months) exposure to EE increased hippocampal *BDNF* mRNA levels in female APP23 mice [107]. Conversely, the mere physical stimulation by free access to a running wheel for the same period did not change *BDNF*

Table 2
Studies on the environmental enrichment effects on BDNF levels in Alzheimer's disease animal models

Reference	Species and Alzheimer's disease model (*age or weight at the start of the environmental enrichment*)	Environmental enrichment type (*duration*)	Age at BDNF level determination	Environmental enrichment effects on BDNF level (*determination method*)
Griñán-Ferré et al., 2018 [112]	Female 5xFAD mice (*4 months*)	Environmental enrichment (novel objects paradigm) – without running wheels; with novelty manipulation (*2 months*)	6 months	***Hippocampus***: unchanged *BDNF* mRNA (=) [*pathological condition*: unchanged *BDNF* mRNA (=)] (*quantitative real-time PCR*)
Hu et al., 2013 [110]	Male APPswe/PS1ΔE9 mice (*21 days*)	Environmental enrichment – with running wheels and novelty manipulation (*3 h/day; 1 month*)	2 months (before the onset of pathology)	***Hippocampus***: increased *BDNF* mRNA and BDNF protein (+) [*pathological condition*: unchanged *BDNF* mRNA and BDNF protein (=)] ***Cortex***: unchanged BDNF protein (=) [*pathological condition*: unchanged BDNF protein (=)] (*ELISA; reverse transcription-Quantitative real-time PCR*)
Stuart et al., 2017 [111]	Male APPswe/PS1ΔE9 mice (*6 months*)	Environmental enrichment – with running wheels; without novelty manipulation (*6 months*)	12 months	***Hippocampus***: increased BDNF protein (+) [*pathological condition*: unchanged BDNF protein (=)] ***Neocortex***: unchanged BDNF protein (=) [*pathological condition*: unchanged BDNF protein (=)] (*ELISA*)
Wolf et al., 2006 [107]	Female APP23 mice (*10 weeks*)	Environmental enrichment – without running wheels and novelty manipulation/ Physical enrichment - running wheel (*about 15 months*)	17 months	***Hippocampus***: increased *BDNF* mRNA (+)/ unchanged *BDNF* mRNA (=) ***Cortex***: unchanged *BDNF* mRNA (=)/decreased *BDNF* mRNA (−) [*pathological condition*: not specifically investigated] (*reverse transcription-quantitative real-time PCR*)

The characterization reported for the environmental enrichment paradigm specifies the variables manipulated, when variations on the classical paradigm (described in the paper) are involved, and in particular when only one enriching variable is manipulated. Presence or absence of running wheels in the paradigm is recorded; presence or absence of the explicit reporting of novelty manipulation is also recorded.

mRNA levels. As for the cortical levels of *BDNF* mRNA, EE did not exert any effect, whereas the physical stimulation with running wheel induced decreased *BDNF* mRNA level. Differently, 2 months of exposure to EE did not modulate the hippocampal *BDNF* mRNA levels in 4/6-month-old 5xFAD mice [112].

The other two studies were based on APPswe/PS1ΔE9 mice. Hu and colleagues [110] exposed the animals to EE for 1 month starting at weaning. Note that EE treatment and BDNF evaluation occurred before symptomatology onset. EE treatment increased *BDNF* mRNA and protein expression in the hippocampus but did not change BDNF protein expression in the cortex. Differently, Stuart and colleagues [111] exposed mice to EE from 6 to 12 months of age. The exposure to the enriched environment resulted in increased BDNF protein level in the hippocampus, and unchanged BDNF protein level in the neocortex.

Notably, since the basal alterations in BDNF expression were not present or not investigated in the used models, the translational value of the not univocal increase in the brain BDNF expression appears rather weak.

It is worth noting to add here that conflicting indications are retrievable also by looking at some studies specifically investigating the effects of the only physical activity on BDNF expression in rodent AD models. Liu et al. [113] exposed APP/PS1 transgenic mice to treadmill running for 5 months (from the third to the eighth months of age). Hippocampal *BDNF* mRNA levels (examined by real-time PCR analysis) increased in AD mice as compared to controls but decreased in exercised AD mice as compared to the non-exercised ones. In another study based on a different AD model [114], Tg-NSE/hPS2m mice were exposed to treadmill running for 3 months, starting from 24 months of age. In this case, hippocampal BDNF protein levels (examined by western blot analysis) decreased in AD mice as compared to controls and increased in exercised AD mice as compared to the non-exercised ones. In a recent study, Naghibi et al. [115] exposed male and female Wistar rats (11–12 months of age) to treadmill running for 12 weeks, 8 weeks before and 4 weeks after the stereotaxic induction of AD by microinjections of streptozocin. AD did not affect BDNF protein levels (examined by ELISA analysis) in both the hippocampus and prefrontal cortex of male and female non-exercised rats. Exercise increased BDNF protein levels in the hippocampus of the only female rats, regardless of the presence of AD. A similar absence of AD effects in hippocampal BDNF protein expression (examined by ELISA analysis) was found by Bashiri et al. [116] in a study based on the same model but realized in adult male NMRI mice (13–14 weeks of age). After a week from the AD induction, mice were exposed to a 4-week swimming exercise program. Exercise did increase hippocampal BDNF protein levels in AD mice.

ENVIRONMENTAL ENRICHMENT EFFECTS ON BDNF EXPRESSION IN THE PRESENCE OF NOT-AD NEURODEGENERATION

Given the lack of clearness of the EE effects on BDNF expression in AD models, it may be interesting to look at the evidence available on this topic in models of some other neurodegenerative diseases, such as Parkinson's disease (PD) and Huntington's disease (HD). Once more, the picture that emerges from such an analysis provides not univocal although interesting suggestions.

Some interest has been directed to the EE effects on brain BDNF expression in rodent models of PD. In a study on mice treated with the pro-parkinsonian neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), Bezard et al. [117] reported increased striatal *BDNF* mRNA levels (as revealed by *in situ* hybridization) after about 2 months of exposure to EE started on weaning. Such an upregulation was retained to mediate the EE neuroprotective effects against MPTP neurodegenerative actions. Faherty et al. [118] more directly addressed this issue by investigating BDNF expression in the substantia nigra pars compacta and striatum of MPTP-treated female mice previously exposed to EE or only to physical activity (wheel-running) for about 3 months starting at 2–3 months of age. However, *BDNF* mRNA levels of MPTP-treated mice were unchanged in both the analyzed regions. The only significant result found was an EE-induced decrement in substantia nigra pars compacta *BDNF* mRNA levels (examined by real-time PCR analysis). More recently, Campêlo et al. [119] investigated the effects of a prolonged EE (from 2 to 5 months of age) on prefrontal cortex and striatum BDNF levels (examined by immunohistochemistry) in male mice submitted to a progressive model of PD (induced by repeated treatment with a low doses of reserpine). The only significant result found in analyses on combined lesion and EE influences was a lesion-induced decrement in the striatum, while no significant effects of EE were revealed. Further studies specifically investigated the effects of exercise (treadmill-running) in different models of PD. Tajiri et al. [120] investigated striatal BDNF protein levels (by western blot analysis) in adult female rats unilaterally treated with 6-hydroxydopamine (6-OHDA) in the striatum and then exposed to compulsive running 5 days a week for 4 weeks. BDNF levels decreased in the striatum of the lesioned side, but this effect was reversed by exercise. A concordant result was found by Tuon et al. [121] in unilaterally treated with 6-OHDA adult male rats after the exposure to compulsive running 4 days a week for 8 weeks. BDNF levels (examined by western blot analysis) decreased in the striatum of lesioned animals, but this effect was not present in previously exercised animals. Finally, in a study focused on neuroinflammation, which is implied in the development of PD, Wu et al. [122] exposed 2-month-old male mice to compulsive running 5 days a week for 4

weeks and then treated them with an intraperitoneal lipopolysaccharide injection to induce neuroinflammation. BDNF levels (examined by ELISA analysis) decreased in the substantia nigra of the injected animals, but this effect was not present in the previously exercised animals. Notably, only an enhancing exercise effect was found on striatal BDNF levels, without any significant effect of neuroinflammation.

Interesting indications could be provided also by studies on rodent HD models, since alterations in BDNF expression are reported also in this neurodegenerative disorder [123]. Spires et al. [124] investigated by western blot analysis the striatal, antero-medial cortex, and hippocampal BDNF levels in male and female R6/1 transgenic mice exposed to EE from one to five months of age. They found that striatal and hippocampal BDNF levels were decreased by HD, but this decrement was rescued by EE. No significant effects were found in the antero-medial cortex. This datum has been further investigated by Zajac et al. [125], who in a relevant study in the same HD model analyzed hippocampal exon-specific *BDNF* mRNA expression (by real-time PCR analysis) separately in 12-week-old males and females after the exposure to wheel-running (8 weeks) or EE (4 weeks). On the whole, they found that HD reduced total hippocampal *BDNF* mRNA levels in both male and female mice, wheel-running reversed this datum in female but not in male mice, and EE did not reverse this datum. The analysis on *BDNF* I, II, III, IV, and VI transcripts showed sex-specific changes due to both HD and housing condition. Interestingly, the authors demonstrated that the reported wheel-running and EE effects were not linked to DNA methylation. Finally, further interesting suggestions come from a study [126] that investigated BDNF both protein (by ELISA analysis) and mRNA (by real-time PCR analysis) levels in the anterior cortex, striatum, and hippocampus of 10-week-old R6/1 transgenic mice exposed to wheel-running for 10 weeks. BDNF protein levels were increased by HD in frontal cortex, and this finding was unaffected by the exercise. As for the *BDNF* mRNA levels, they were reduced in all the analyzed brain areas of HD mice, and the reduction was rescued by exercise only in the striatum.

DISCUSSION

On the whole, the framework offered by the literature on healthy animals does not allow to achieve a clear indication about the EE effects on BDNF expression, and the hypothesis that EE may induce an increase in brain and serum BDNF expression is not univocally confirmed in any brain areas.

Anyway, when all the available results are considered as a whole, it turns out that the studies that report a decrease in BDNF levels following the exposure to EE are really scarce in comparison to the ones that report an increase. Thus, a qualitative suggestion that supports the increasing effect of EE on BDNF expression may be advanced, especially for the hippocampus and, even if in a more cautious manner, for the neocortex, cerebellum, and hypothalamus. Nevertheless, even this idea needs to be definitively validated. Moreover, appears to be very interesting to identify factors able to influence the association between EE and BDNF expression.

By splitting up results on BDNF protein and *BDNF* gene levels, findings appear rather inconsistent in all investigated areas. A slightly more informative observation may derive by splitting up the results on the basis of the technique used to determine BDNF expression levels. In fact, when BDNF expression was determined by means of immunohistochemistry, univocal results in two brain areas are obtained. Namely, Bardi et al. [97] and Gualtieri et al. [98] indicated the absence of changes in BDNF immunoreactivity in hippocampus after 6 weeks and 8 days of exposure to EE respectively, in both healthy rats and mice. By using the same technique, Vasquez-Sanroman et al. [104] found increased BDNF expression in the cerebellum in mice exposed to EE for 4, 7, and 11 weeks. Studies using PCR [99, 102] found unchanged *BDNF* gene expression in amygdala after the exposure of mice to EE. Studies using ELISA and western blot in the different brain areas once more provided not univocal findings.

Unfortunately, similarly not univocal frames are obtained even when other factors, as animals' species, age and so on are considered.

As for the rodent species, 14 studies have been carried out in rats and 17 studies have been carried out in mice, but inconsistent results are obtained within each species. The only specific indication that is possible to obtain is that the decreased levels of BDNF expression in amygdala [105] and striatum [36] are obtained only in rats, while in mice no changes are found after the exposure to EE [83, 99, 102].

As for the age of the animals at the start of the exposure to EE, it is worth noting that the studies in which the exposure started at the birth did not find any change in BDNF expression after 8, 10, 15 [106], or

49 [99] days of exposure to EE. Conversely, a relevant number of studies based on the exposure of the animals to EE from weaning (about 21 days of age) onward found increased BDNF expression in the hippocampus [36, 81, 83, 87, 91, 100], regardless of the exposure duration (from 7 to 140 days). Once again, when the EE is started after weaning, the studies provide conflicting results.

As for duration of EE exposure, it is possible to note that the hypothalamic BDNF expression increased after 5 to 42 days of exposure to EE [101–103], whereas after longer exposures (49 to 360 days) no changes have been reported [86, 99, 102].

To evaluate if habituation to the enriched environmental conditions played a role in eliciting BDNF level changes, the explicit notifications of novelty manipulation in the EE paradigm were evaluated. Namely, we recorded when the authors explicitly reported that enriching objects were regularly changed throughout the EE period or when the object arrangement was regularly changed in the cages. Anyway, this factor did not significantly influence BDNF expression, since increased or unchanged BDNF levels have been found after the exposure to EE with or without novelty manipulation, regardless the brain area considered.

Finally, even by considering a key-component of the EE paradigm, namely the presence or absence of physical activity, and in particular of running wheels [84], it is not possible to identify its role on BDNF expression changes, since increased or unchanged BDNF levels have been found after the exposure to EE with or without running wheels.

It may be interesting to add that in healthy animals, when both the above cited conditions (novelty manipulation and running wheels presence) are met, the hippocampal BDNF levels were always increased [36, 82–85, 90–93]. This consideration might suggest that the combination of such key components of cognitive and physical stimulation could exert a powerful role in steadily promoting hippocampal neuroplasticity. However, further studies are needed to support this insight, since sometimes increased BDNF levels are reported also when only one of such EE components is present.

A specific consideration has to be made for the conflicting findings obtained in AD models. A key issue regards the basal BDNF expression, which is not evaluated or does not result altered in the used models. It is possible that such confusing framework is linked to the lack of systematization in the studies based on divergent methods in type and duration of EE, animals' age at the moment of EE starting and BDNF expression determination, BDNF expression indices investigated, and so on, even if none of these factors seems to consistently influence the association between the exposure to EE and BDNF expression changes. As shown above, literature evidence on some other neurodegenerative disorder did not succeed in shedding light on this conundrum, since the multifarious characteristics of the experimental designs once more led to inconsistent results. However, the specific analyses concurrently conducted on both BDNF protein and *BDNF* mRNA expression, exon-specific transcripts, epigenetic mechanisms, and different populations and EE-types provide precious indications on the convenience of studying this topic in a more deep and articulate manner.

Finally, it is worth mentioning a not yet sufficiently investigated question, namely the specific effects of EE on the two different BDNF isoforms, and in particular on the ratio between the two. In fact, as reported above, both the precursor pro-BDNF molecule and the mature BDNF protein are expressed in activity-dependent way, but they provoke opposite effects on cellular functioning, following two different pathways [44, 45]. Unfortunately, to date scarce studies have specifically analyzed the EE effects on the conversion of pro-BDNF to BDNF. Cao and colleagues [81] suggested that the EE upregulated matrix metalloproteinase-9 levels within the hippocampus might facilitate the conversion of pro-BDNF to BDNF. In fact, they found that in rats after the EE exposure from weaning to ten weeks of age a remarkably enhanced ratio of BDNF to pro-BDNF was observed. However, similar studies on pro- and mature BDNF proteins [64, 104] found enhanced both the isoforms after the exposure to EE. Given the negative interaction between Aβ senile plaques and BDNF expression linked to the inhibition of the conversion from pro-BDNF to mature BDNF [56–58], EE potential effects on this process constitute a key issue to be clarified.

CONCLUSIONS

As it is clear from such detailed evidence, the findings regarding EE effects on BDNF expression are not univocal, and it cannot be certainly affirmed that EE induces an increase in central and peripheral BDNF expression. Although some specific observations are proposed in the above synthesis (such as in

particular that the majority of the studies analyzed the hippocampus and in the most cases found increased expression of hippocampal BDNF, both in healthy and AD subjects, and that this is true especially if the EE starts from weaning, and if both running wheels and novelty manipulation are included in the EE paradigm), it is difficult to attribute a real meaning to indications that appear sporadic and not integrated in a univocal frame. Thus, the main achievement of this work is the collation of the disparate evidence on such a topic indicating the strong need of further primary studies and quantitative systematic investigations able to reply to the questions remained open and to overcome the multiple limitations of the analyzed studies.

In particular, the analysis of the specific effects of EE on the two different isoforms of BDNF and on the ratio between the two, is a key issue, given the different action pathways of pro- and mature BDNF and the yet inconsistent data available on this point. In addition, systematic studies deeply analyzing at which level of *BDNF* gene transcription and translation EE-mediated epigenetic mechanisms should be conducted, in order to provide powerful insights on the processes on which neuroprotective actions may be directed. A specific attention has also to be devoted to the effects of the exposure to complex environmental stimulations in AD models, to support a more tuned and effective application of such stimulations as neuroprotective and rehabilitative approaches to AD. The data analyzed in the present review provide open perspectives for the future studies. Although addressing such a topic in animals poses a number of challenging issues, effective studies carried out with this aim could make a significant translational contribution to the managing of AD.

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