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Review Article

The Brain Derived Neurotrophic Factor and Personality

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The study of the biological basis of personality is a timely research endeavor, with the aim of deepening our understanding of human nature. In recent years, a growing body of research has investigated the role of the brain derived neurotrophic factor (BDNF) in the context of individual differences across human beings, with a focus on personality traits. A large number of different approaches have been chosen to illuminate the role of BDNF for personality, ranging from the measurement of BDNF in the serum/plasma to molecular genetics to (genetic) brain imaging. The present review provides the reader with an overview of the current state of affairs in the context of BDNF and personality.

1. What Is Personality?

1.1. Why Study Human Personality? The study of the individual differences of humans is as old as mankind. The first Greek philosophers, such as Hippocrates, were interested in finding an answer to the question of why humans differ. According to Hippocrates, the essence of individuality was found in four bodily fluids; for example, black bile was associated with a melancholic personality structure [1, 2]. Since then, generations of scientists have strived to shed light on human personality.

Beyond the scientist's pure curiosity in this topic, the study of personality yields important insights into the nature of humans. Here, it has been put forward that an understanding of the healthy aspects of personality must inform the understanding of psychopathological conditions, because the latter are much harder to study given imbalances, for example, in the neurotransmitter systems of humans (e.g., [3, 4]). Many personality traits, such as neuroticism, are known to be of large importance for public health outcomes [5]. Therefore, an understanding of personality is also a key to disentangling the complex nature of psychopathology.

1.2. A Short Definition of Personality. Definitions of personality are numerous in the literature (e.g., [6–8]). In my opinion, the most common denominator among these definitions represents the concept of "traits," referring to the stability of personality dimensions, such as being cooperative or curious over long time periods across the lifespan. These personality characteristics influence the way a person thinks, behaves, and reacts emotionally towards a large number of environmental stimuli [6]. Of note, and for a better understanding of the above introduced term "traits," it needs to be mentioned that in some situations a person will always show a particular emotional reaction such as being sad, for example, when a beloved person has died or a relationship has broken up. This relates to the present mood of a person and of course is strongly influenced by the demands of a situation. Clearly, the loss of a loved person would overwhelm nearly all humans from an emotional point of view. Using the concept "traits," personality psychologists describe the overall pattern of states over a long time period, being conceptually independent of one incident. In simple terms, a trait is a disposition, for example, to be more sad or more happy across a large number of different circumstances (and in terms of the above-mentioned example to deal with personal losses; e.g., [9]). Nevertheless, the concepts "traits" and "states" are logically intertwined. This is supported by the correlations between mean-state and trait measures ranging between 0.39 and 0.64 [10].

1.3. Individual Differences in Emotional Reactions as the Evolutionarily Oldest Part of Personality. More specifically, individual differences in personality as related to the emotional reactions mentioned above [6] are of interest in the present review because "brain derived neurotrophic factor" (BDNF) is known to strongly influence negative emotionality [11]. Individual differences in emotional reactions towards environmental demands can also be studied in other mammalian species, not only humans, because the primary emotional systems (on which BDNF can act as a transmitter) are evolutionarily conserved across phylogenetic parts of the mammalian brain [12]. Therefore, animal research can be an excellent guide for human research in the context of individual differences in emotional reactions. Emotional reactions arising from primary emotional systems reflect "ancestral tools for living" [13, page 533], because they helped our ancestors (and help us today) respond adequately to dangers in the environment to seek food or explore the environment carefully and to find a mating partner to pass on one's own DNA to the next generation. Complex emotions or feelings (these terms are still a matter of great debate; see [14]), such as guilt or shame, result from a complex interaction of the primary emotional systems, such as SEEK, FEAR, RAGE, PLAY, CARE/LUST, SADNESS (primary emotional systems are written in capitals to not confuse them with similar sounding terms in the literature (according to [15])), with cortical areas of the brain [16]. The conservation of the primary emotional systems across the mammalian species makes it very likely that the neuroanatomy and activity of these systems is strongly influenced by genetics (otherwise these emotional systems would not be that similar over the species). This is a crucial point, and I deal with the molecular genetics of BDNF and personality later on.

The idea of (primary) emotional systems as an evolutionary heritage has already been outlined by Darwin in 1872 in his work on emotional expressions in man and animals [17]. It has also been indirectly outlined in the context of brain organization by MacLean in his triune brain concept [18]. In MacLean's theory the brain has been described as the only organ in the human body which clearly mirrors the evolutionary development bottom up, from the reptilian brain to the mammalian brain (where (social) emotions are anchored) to the neocortex. To illustrate this idea, I invite you to undertake a short mind game: imagine yourself standing in front of the Grand Canyon. The deeper you see into the Canyon (the deeper you see into your brain structures) the older the structures are from an evolutionary point of view. As primary emotional systems can be found in ancient brain structures, individual differences in these systems should reflect the oldest part of personality. From a psychobiological point of view, personality could be described as arising from individual differences in the neuroanatomy of the brain.

1.4. Some Notes on Personality Theories. A large number of personality theories exist. As an introduction to the most important personality theories is beyond the scope of the present review article, I refer to short introductions on the biological personality theories of Eysenck, Gray, Cloninger, and Panksepp in two of my own recently published review articles [19, 20]. Nevertheless, two personality theories are briefly introduced in the following text, because they are of substantial interest in the context of the following BDNF-personality literature.

Most of the studies in BDNF-personality-research deal with the Five Factor Model of Personality [8, 21] or with the Biosocial Theory of Personality [7, 22].

The Five-Factor Model of Personality has been derived from a lexical approach. By factor-analyzing words describing human characteristics (e.g., taken from dictionaries) five personality dimensions emerged named openness to experience, conscientiousness, agreeableness, extraversion, and neuroticism (easily remembered by the acronym OCEAN). Extraversion and neuroticism particularly turned out to be of special relevance in a large number of studies, because of their relevance for a better understanding of positive and negative emotionality in humans [23, 24] and also related psychopathological disorders (e.g., [25]). Among other terms, extraverted humans can be best described as outgoing, seeking social interactions, and impulsive. Neurotics tend to be anxious, moody, and emotionally unstable. These examples illustrate the closeness between personality and emotional tendencies.

In contrast to the Five Factor Model of Personality, the Biosocial Theory of Personality by Cloninger et al. [7] has a strong theoretical biological background. Cloninger divides human personality into temperament and character traits. According to his theory temperament traits are strongly influenced by genetics from early on in life, and character traits are more influenced by the environment in adolescence/adulthood. Most importantly, Cloninger's theory makes assumptions about the underlying neurotransmitter system involved in his temperament dimensions novelty seeking, harm avoidance, and reward dependence. According to Cloninger, high novelty seeking (being curious and impulsive) is associated with low dopamine levels, high harm avoidance (being anxious) is linked to high serotonin levels, and high reward dependence (being dependent on social approval) is linked to low norepinephrine. Although Cloninger's model has only been partly empirically supported, it is still of large value as a theoretical framework.

Some BDNF studies have also used classical personality self-report questionnaires to measure extraversion and neuroticism, such as that by Eysenck [26], which is not presented here in detail. For a better understanding of the studies presented below, I would note that correlations between Eysenck's constructs neuroticism and extraversion and the same dimensions measured with the Five Factor Model are very high.

2. Classical Biological Targets to Understand Personality

The most important targets across the last few decades in studying the biological basis of individual differences in personality have clearly been the neurotransmitters dopamine and serotonin. A potential reason for a focus on these

biogenic amines lies in the importance of the most prescribed psychopharmaceuticals to treat schizophrenia and affective disorders. Schizophrenic patients are usually treated with dopamine antagonists to diminish the positive symptoms of psychosis such as hallucinations [27]. As a consequence, dopamine has become an important target to understand schizotypy personality traits (e.g., [28]). Due to the role of dopamine in reward [29] and motivation [30], dopamine also represents a classical target to understand individual differences in extraversion [31] or as mentioned novelty seeking [7], because both extraversion and novelty seeking are linked to individual differences in reward processing (e.g., [32–34]).

Another candidate often investigated to better understand human personality is the hormone cortisol. Cortisol plays a pivotal role in the stress axis of the human body. When the human body is confronted with a stressful situation the hypothalamic-pituitary-adrenal (HPA) axis is activated and as a consequence cortisol is secreted from the adrenal cortex [35]. Given the important influence of cortisol on the regulation of corticotropin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) secretion in the human brain and the observation of an altered HPA axis in depression [36], cortisol became an important target to study individual differences in personality with mixed results (e.g., [37, 38]). Besides these key players, in the last few years a growing interest can also be observed in neuropeptides such as oxytocin to understand human personality (e.g., [39, 40]).

3. The Brain Derived Neurotrophic Factor

A reasonably new target in studying individual differences in personality is the brain derived neurotrophic factor (BDNF). BDNF belongs to the neurotrophin family and its secretion has been strongly linked to neurogenesis, including dendritic spine formation and synaptic plasticity [41–44]. Two forms of BDNF can be distinguished, proBDNF and matureBDNF. Simply put, the proBDNF molecule represents the precursor of the matureBDNF form. Both BDNF forms signal via different receptor types. ProBDNF is known to target the $p75^{ntr}$ receptor; matureBDNF targets the tyrosine kinase B (TrkB) receptor. A Yin and Yang theory has been proposed to explain the dissociative effects of proBDNF and matureBDNF on the human brain [45]. While higher levels of proBDNF have been linked to depression [46], and even atrophic effects in the brain [47], matureBDNF is linked to positive effects on nerve growth in the brain [48].

In my opinion, the interest in BDNF for personality research can be traced to the antidepressant effects of BDNF. It has been demonstrated that (mature) BDNF levels (the debate on what kind of BDNF is usually dealt with in studies measuring BDNF will be discussed at the end of Section 4 in this review) are diminished in depressed patients (e.g., [49]), as well as in suicidal individuals [50], and show a rise after successful treatment [51, 52]. Moreover, it has been put forward in the so called neurotrophin hypothesis of depression [53] that stress could be associated with a downregulation of BDNF [54]. As a consequence the "brain fertilizer" BDNF is not secreted in sufficient amounts, which could in part explain why mood disorders occur together with atrophic effects of the hippocampus in depression [55, 56]. Of relevance for an understanding of the healthy aspects of the personality traits neuroticism or harm avoidance, negative correlations have been observed between these personality traits and hippocampal gray matter volumes ([57] see also review by Montag et al. [4]). This makes a role for BDNF in personality likely.

4. Linking BDNF Levels to Personality Traits

Although a large number of studies have dealt with the question of whether BDNF levels are associated with depressive conditions (mostly they are), only a small number of studies have investigated the role of BDNF levels in related personality traits in subclinical healthy participants. Of note, these studies differ somewhat with respect to the administered self-report personality questionnaires and also in terms of the BDNF variables under investigation, ranging from serum to plasma to whole blood BDNF. As most studies analyse BDNF levels from blood drawn from the periphery of the human body, the question arises as to how peripheral BDNF levels relate to central BDNF levels. Although this important question cannot be conclusively answered, it has been demonstrated in a recent animal model that peripheral BDNF is itself able to exert antidepressant effects [58]. Moreover, BDNF levels can cross the blood brain barrier and can therefore migrate from the body to the brain (e.g. [59]). In addition, Karege et al. [60] were able to show a strong positive correlation between cortical BDNF and serum BDNF in the peripheral parts of the body in young rats ($r = 0.81$, $P < 0.01$). Following these findings, the investigation of peripheral BDNF levels is possibly related to BDNF functioning in the central nervous system. Of note, a study by Martin et al. [61] questioned the correlation between hippocampal BDNF and plasma BDNF in the periphery as a result of their animal data.

A literature search using the key words "BDNF" and "personality" in Google Scholar and pubmed.com on 5 November, 2013, revealed seven studies investigating the link between peripheral (plasma, serum, or whole blood) BDNF levels and individual differences in personality traits. Summing up the findings, these studies show an inverse relationship between peripheral BDNF levels and traits related to negative emotionality ([62–64]). Fitting with this, another study showed a positive correlation between BDNF levels and extraversion, but the inverse association with negative emotionality could not be demonstrated here [65]. The positive association between the personality trait extraversion and BDNF could only be observed with the variable plasma BDNF.

The basic finding presented above (high levels of BDNF being associated with low scores on negative emotion-related personality traits) clearly needs to be taken as an oversimplification, because two studies revealed this association while investigating serum BDNF levels [62, 63], one study revealed this link with plasma BDNF [64], and one study showed a more complicated interaction effect with the variables

"stressful life events," "sex," and "whole blood BDNF levels" [66]. One earlier study by Terracciano et al. [67] even reported a positive association between plasma BDNF levels and two facets of neuroticism. The detailed results of these studies are presented in Table 1.

The importance of distinguishing plasma and serum BDNF levels for the summary and interpretation of the results becomes apparent when considering the research findings on these two different aspects of BDNF levels (serum represents plasma without blood clotting factors). BDNF measured in the serum indicates BDNF being attached to platelets, which could represent a storage site or depot for BDNF. Support for this idea came from Fujimura et al. [90], who observed that after stimulation of BDNF in the platelets with agonists, such as thrombin/collagen or stress, only about half of BDNF was released. Adding to this Terracciano et al. [63] reported a positive correlation between platelet count and BDNF in the serum ($r = 0.41$, $P < 0.001$). In sum, serum BDNF levels are known to be rather stable. In contrast, BDNF levels in the plasma have been observed to be very unstable with respect to retest-reliability measures, and these levels vary across the day, especially in males [91]. Choi et al. [92] also reported that plasma variation (with a decline of plasma BDNF over the day) could be observed in males but not in females. Of importance, for serum BDNF levels no diurnal variation could be observed for both sexes. These findings might explain the contradictory results (BDNF correlates positively with neuroticism) reported by Terracciano et al. [67] in relation to plasma BDNF, although Yasui-Furukori et al. [64] recently reported the often observed inverse association between the more unreliable plasma BDNF and harm avoidance in their Japanese sample. Besides this, numbers from Terracciano et al. [63] show that plasma and serum BDNF levels only have moderate correlations ($r = 0.21$, $P < 0.001$).

Considering the issues mentioned here and taking into account the findings from the depression research, I cautiously propose a continuum model from healthiness to psychopathological behavior, with lower BDNF levels being associated with higher degrees of traits linked to negative emotionality. But the correlations observed in the reviewed studies are all very small. Therefore, BDNF taken alone explains only small parts of a complex phenotype such as personality. As Lu et al. [45] noted, the different effects of pro- and matureBDNF on the brain might cause one to ask what form of BDNF is investigated in the studies dealing with (peripheral) BDNF levels. An answer to this question is given by Katoh-Semba et al. [93, page 371]: "Posttranscriptionally, BDNF protein is well known to be in the processed mature form upon release from cells. Therefore, if circulating BDNF is derived from external sources, it is reasonable that the protein bound to platelets is already processed into the observed mature form." Moreover, Katoh-Semba et al. [93] reported for their sample that 99% of BDNF in the serum represents mature BDNF.

A question not answered until now is as follows: do changing BDNF levels (such as seen in remission from depression, Molendijk et al. [94]) also go along with changes in personality? My answer to this question is purely speculative, because no studies directly addressed this topic to my best knowledge. Of interest, Jylhä et al. [95] reported no effects of antidepressant treatment on personality, thereby indirectly pointing towards no association between changing BDNF levels and a change of personality. Underlining this notion, personality usually is stable from middle age on [8]. Therefore, it is unlikely that changing BDNF levels can drastically change personality. How can the above presented BDNF-personality link then be understood? Personality traits such as neuroticism could be connected to tonic (basic or steady) BDNF levels, which in turn could be strongly determined by the genetic makeup of a person and form the biochemical sediment. In contrast, states (also depressive states) could be more linked to phasic BDNF bursts shaking BDNF levels for a shorter time period. These phasic BDNF bursts might be triggered by pharmaceuticals but also sport exercise or psychotherapy. Logically, tonic and phasic BDNF levels are hard to disentangle, because they total up in the actual amount of measured BDNF levels.

Besides this line of thought (and as outlined later on), BDNF is influenced strongly by other transmitter systems, too. Thereby, it is possible that BDNF is only indirectly linked to personality. Again, these thoughts are very speculative and my present ideas just reflect a superficial answer to this complex question.

5. Linking a Genetic Variation of the BDNF Gene to Personality Traits

5.1. Main Effects of BDNF Val66Met on Human Personality. Besides measuring the levels of peripheral BDNF, a large body of research has also investigated the BDNF gene in the context of personality traits. The BDNF gene is located on chromosome 11p14.1. The most prominent polymorphism on this gene is called BDNF Val66Met (rs6265) located on codon 66 of the BDNF gene. The functionality of this single nucleotide polymorphism has been supported, with the BDNF Val66Met polymorphism being responsible for an exchange of amino acids from valine (Val) to methionine (Met) in the to-be-built neurotrophin. The BDNF 66Met allele has been associated with diminished activity-dependent secretion of BDNF in a study by Egan et al. [96]. Fitting with this, genetic imaging studies have reported an association with the Met-allele and diminished volume of the hippocampus [97, 98], an effect also extending to the parahippocampus and the amygdala [99, 100] in healthy participants. Contradictory findings also exist (e.g., in a sample of depressed patients by [101]). A recent meta-analysis by Kambeitz et al. [102] showed that the 66Met allele is indeed associated with smaller hippocampus volume, although the effects are rather small. Genetic imaging studies using fMRI, such as that by Montag et al. [103], revealed that (right) amygdala activity while processing (un)pleasant pictures is modulated by the BDNF Val66Met polymorphism. 66Met+ carriers responded with higher amygdala activity to all emotional stimuli (pleasant and unpleasant). Mukherjee et al. [104] investigated the role of BDNF Val66Met for the processing of fearful faces. Here the 66Met allele was associated with overactivity of a neural network comprising the anterior cingulate cortex, the bilateral insula, and the

Table 1: Overview on studies investigating BDNF levels in the context of personality traits (presented in alphabetical order of first authors).

Authors	Participants	Inventory	Results
Lang et al. [62]	$N = 118$ healthy participants (Caucasians)	NEO-FFI	A negative correlation between serum BDNF levels and neuroticism ($r = -0.21, P = 0.02$) could be observed.
Minelli et al. [68]	$N = 107$ healthy participants	TCI	A negative correlation could be observed between serum BDNF levels and harm avoidance scores ($r = -0.25, P = 0.01$).
Okuno et al. [65]	$N = 269$ healthy participants (Japanese employees)	NEO-FFI	Positive correlation between plasma BDNF levels and extraversion ($r = 0.17, P = 0.01$) could be observed. In contrast, no significant correlation with neuroticism and plasma BDNF was reported.
Terracciano et al. [67]	$N = 391$ healthy participants (mixed ethnicity)	NEO-PI(-R)	Males showed a positive association between plasma BDNF levels and the facets "depression" ($r = 0.23, P < 0.01$) and "vulnerability" ($r = 0.25, P < 0.01$) of neuroticism and a negative correlation with plasma BDNF and conscientiousness ($r = -0.20, P < 0.01$). Additional significant results (but weaker) turned up. Please see the original paper.
Terracciano et al. [63]	$N = 2099$ healthy participants, only a smaller subsample was investigated with respect to plasma BDNF ($n = 482$ Italian participants)	NEO-PI(-R)	Serum BDNF levels were inversely correlated with neuroticism scores (especially the "depression" facet of neuroticism; $r = -0.07, P = 0.001$, after controlling for CES-D depressive symptoms score). No association with plasma BDNF and personality could be observed.
Trajkovska et al. [66]	$N = 206$ participants divided in four groups mono-/dizygotic low and high risk twins for affective disorders (Danish sample)	EPQ	Females with high genetic risk for affective disorders and a high number of stressful life events were associated with lower whole blood BDNF levels compared to females with high risk and a lower number of stressful life events. In males with risk for depression and a high number of stressful life events the BDNF levels were higher, which was interpreted by an appropriate counteraction of BDNF against a potential emerging affective disorder.
Yasui-Furukori et al. (2013) [64]	$N = 178$ healthy participants (Japanese)	TCI	Harm avoidance was negatively associated with plasma BDNF levels ($r = -0.18, P = 0.02$). A positive association was reported with self-directedness ($r = 0.17, P = 0.03$)

NEO-FFI represents the short version of the NEO-PI(-R)[1]. EPQ is Eysenck's Personality Questionnaire measuring the personality dimensions neuroticism, extraversion, and psychoticism. Moreover, the here presented results represent only parts of the results reported in the mentioned studies, because some of the studies focused on aspects beyond BDNF and personality.

[1]Either the NEO-personality inventory or its revised version was used in the studies of Table 1.

brainstem. A study by Lau et al. [105] compared the processing of emotional faces in nonmedicated patients suffering from anxiety disorders with healthy controls. Here, the Met66 allele could only be associated with higher neural activity in response to the emotional stimuli in the patient group.

Following from the functionality of the BDNF single nucleotide polymorphism (SNP) and the results from genetic imaging, one would expect theoretically that the 66Met allele is associated with higher negative emotionality. I explain my thoughts on this theoretical assumption in detail: as the 66Met allele is associated with lower activity-dependent BDNF secretion, lower hippocampus volume should be observed due to lower secretion of BDNF. The idea of lower hippocampus volume in 66Met allele carriers has found some empirical support in the meta-analyses of Kambeitz et al. [102]. Moreover, lower hippocampus volume has been associated with higher harm avoidance and neuroticism scores in a series of studies (e.g., [4, 57]), and so the 66Met allele should be indirectly associated with higher negative emotionality. Of note is a recent meta-analysis by Terracciano et al. [106] showing no link between BDNF Val66Met and serum BDNF levels, therefore weakening the line of argument that the BDNF Val66Met polymorphism might be a partial cause of lower hippocampus volume due to the lower activity-dependent BDNF secretion. Clearly, BDNF levels are not only influenced by this single SNP but also from a complex mix of diverse factors, including both genetic (not only the BDNF gene) and environment factors. The line of argument/hypothesis is also depicted in Figure 1. We shall see if this overall hypothetical framework is supported by the empirical findings.

Until now, a large number of studies have been conducted to investigate the role of the BDNF Val66Met polymorphism on human personality. To start off, the results of these studies are very heterogeneous and only in part support the 66Met allele negative emotionality link.

The studies by Jiang et al. [77] and Montag et al. [80] both give support for this link, although they differ in one

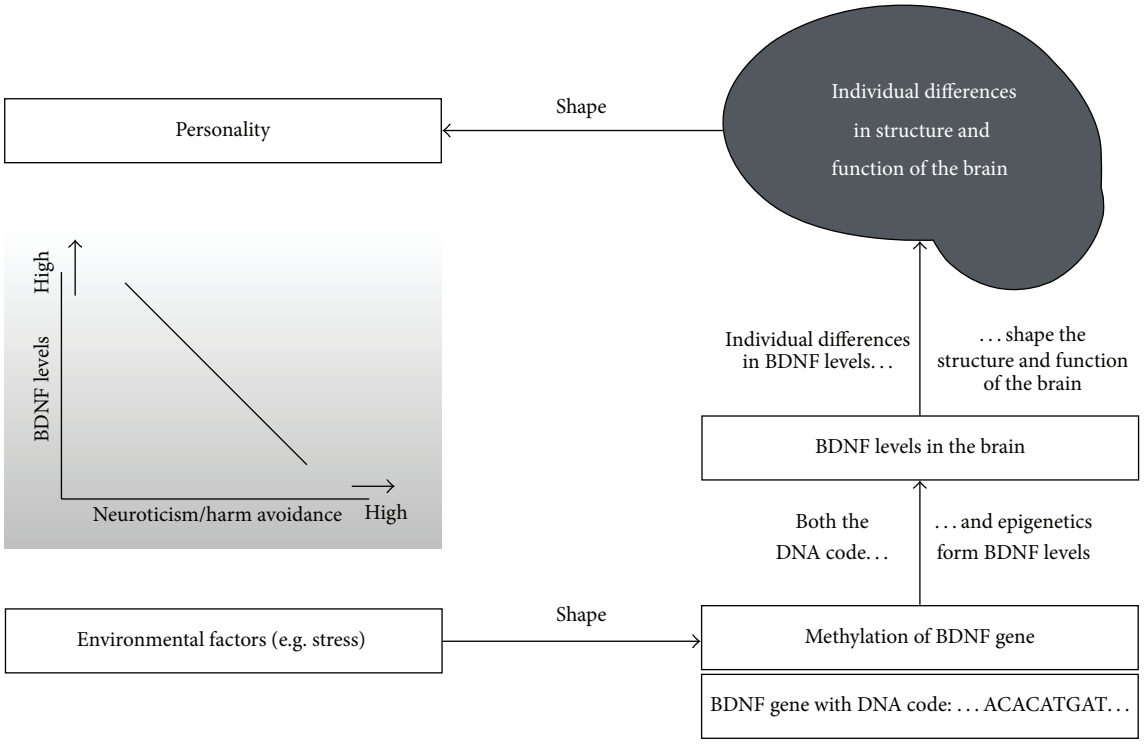

Figure 1: The role of BDNF for personality—a simplified framework.

important aspect. Jiang et al. [77] combined all carriers of at least one 66Met allele into a 66Met+ group and tested these against the 66Met− (Val66Val carriers). These groups are often tested in research articles, because in Caucasians the group of homozygous Met66Met carriers only occurs with a prevalence of 3%. Nevertheless, Montag et al. [80] tested these low-frequency homozygous carriers against carriers of the 66Val allele. This low-frequency group ($n = 19$ out of $N = 610$) showed significantly elevated scores on the subscales "anticipatory worry" and "fear of uncertainty" from Cloninger's temperament dimension harm avoidance. No effect could be observed for the contrast 66Met+ versus 66Met−. Interestingly, a prominent knock in mice model by Chen et al. [107] also demonstrated that especially mice carrying the homozygous Met66Met variant showed the highest anxiety related behavior in paradigms such as the open field test and the lowest dendritic arborization and hippocampus volume. This model hints at the Met66Met genotype constellation being of most relevance to anxiety. This stands somewhat in contrast to the genetic imaging findings presented above. Until now, no study has investigated if this special group of Met66Met carriers differs from the Val66Val and Val66Met in terms of Met dosage in the human neuroanatomy. This will be an interesting research endeavor for the future.

Other studies investigating the influence of BDNF Val66Met on personality clearly find empirical support for the Val allele—negative emotionality—link (e.g., [79, 83]). Some studies could not even find any effects on personality (e.g., [86, 87, 89]) and mood [108]. Two meta-analyses have been conducted to investigate the effect of BDNF Val66Met on negative emotionality related personality traits over all studies [85, 109]. The newest study, including 13 samples from 2003 to 2009, by Terracciano et al. [85] revealed no effects of BDNF Val66Met on negative emotionality. Independently of this, the effects of this SNP have to be classified as very small on human personality, because human personality represents a complex endophenotype, being influenced by a very large number of genetic variants. The fact that human personality is usually normally distributed hints towards the fact that clearly one or two genetic variations alone cannot be responsible for a person being anxious or extraverted [19]. Despite studies dealing with the main effects of BDNF Val66Met on human personality, studies also need to deal with the potential interactive effects of BDNF Val66Met and other polymorphisms or genetic by environment effects need to reviewed to get a fuller picture of the molecular genetics of BDNF and personality.

Two more interesting points should be highlighted at this point. The effect of BDNF Val66Met could not only be observed on personality traits but also on perceptions of social support. Here, a study by Taylor et al. [110] reported that elderly participants carrying the 66Met+ variant reported less social support. Another interesting approach in the investigation of the BDNF gene and personality has been introduced by Joffe et al. [78]. They combined personality assessment and the investigation of the BDNF gene with structural brain imaging. They reported that 66Met allele carriers could be characterized by an inverse relationship between lower hippocampus gray matter volume and neuroticism, whereas

this correlation was absent in Val66Val carriers. This again outlines the complexity of an understanding of the link between molecular genetics, brain structure, and human personality. Finally, a study investigating BDNF Val66Met in the context of schizotypal personality revealed no significant association after correction for multiple testing [111]. Please see Table 2 for a more complete overview on molecular genetic BDNF personality studies (including studies from the next section).

5.2. Interaction Effects of BDNF Val66Met with Other Polymorphisms on Human Personality. A number of studies have also investigated interaction effects between BDNF Val66Met and other polymorphisms on human personality. Here, a clear focus has been on an interaction between the above-mentioned BDNF genetic variant and dopaminergic or serotonergic genetic variants. This is not a surprise, because interactions of BDNF with dopamine or serotonin have been shown in animal models before.

Serotonin and BDNF are known to interact. Martinowich et al. [11] summarized in their review that BDNF and serotonin influence each other in both directions. While the secretion of BDNF is of importance for the survival and plasticity of serotonergic neurons, the administration of selective serotonin reuptake inhibitors are known to elevate BDNF levels. Following the close relationship between the two different systems BDNF and serotonin on a biochemical level in the brain, it is a logical consequence to search for interaction effects between BDNF Val66Met and serotonergic polymorphisms on a molecular genetic level. Arias et al. [69] observed in their sample that despite the lack of a BDNF Val66Met main effect on anxiety-related personality traits, an interaction effect could be observed between BDNF Val66Met and 5-HTTLPR on harm avoidance. The serotonin transporter polymorphism (5-HTTLPR) represents another classic genetic target in biological psychiatry, because the short variant (s-variant) of this insertion deletion polymorphism has been associated with lower mRNA expression and higher neuroticism scores [112, 113]. Given the important role of the serotonin transporter in psychopharmacology (as selective serotonin reuptake inhibitors (SSRIs) are often prescribed to treat depression), it is understandable why the gene coding for the serotonin transporter called SLC6A4 is heavily investigated. In the study by Arias et al. [69] participants carrying the homozygous Met66Met variant together with the s/s variant of the 5-HTTLPR showed the highest harm avoidance scores. Of note, these results are hard to replicate, because this genotypic configuration rarely occurs. In the study by Arias et al. only $n = 6$ out of $N = 937$ participants could be observed in this particular group. The findings by Arias et al. mirror my first intuitive expectation that the risk variants of each gene loci should somehow add up and be associated with highest negative emotionality. This idea is far too simplistic though, when one considers the whole literature on BDNF Val66Met and 5-HTTLPR. Prominent studies by Pezawas et al. [114] showed that the 66Met allele might even represent a protective factor for depression when also being a carrier of the risk variant of 5-HTTLPR (the s-allele). This was derived, among others, from a volume reduction in the rostral anterior cingulate cortex in carriers of the Val66Val/s+ configuration. Adding to the heterogeneity of the data, the study by Terracciano et al. [85] reported that carriers of the homozygous Val66Val variant, together with the LL variant of 5-HTTLPR, showed the lowest neuroticism scores and differed in that point with all other genotypic constellations.

Besides the interaction of BDNF and serotonin, an interaction between BDNF and dopamine can also be observed. Animal research has revealed that BDNF modulates the mesolimbic dopaminergic pathways in the context of learning from social defeat [115]. Earlier studies also indicated the importance of BDNF for the plasticity of dopaminergic neurons in the substantia nigra [116]. Following the same logic as with BDNF and serotonin, the investigation of interaction effects of BDNF and dopaminergic gene targets represents an interesting research endeavor. Here, a larger number of genetic targets on the side of the dopaminergic system have been investigated until now. BDNF Val66Met has been demonstrated to interact in a series of studies with the so called DRD2/ANKK1 Taq Ia polymorphism, known for its influence on D2 receptor density in structures of the striatum (e.g., [117]). Carriers of at least one 66Met allele carrying also the A1+ variant (being constructed by the A1/A1 and A1/A2 carriers) were associated with lowest novelty seeking scores and highest harm avoidance scores at the same time [81]. Fittingly, this interaction effect could be transferred to the anterior cingulate cortex in a genetic imaging study: again, carriers of the 66Met+/A1+ variant represented the "special" group, because they were associated with the lowest ACC gray matter volume. Finally, Walter et al. were able to extend these findings to alexithymia. Again, the genetic constellation 66Met+/A1+ represented the vulnerability constellation.

Besides the interaction of BDNF Val66Met with a genetic variation of the DRD2/ANKK1 Taq Ia polymorphism on personality, interaction effects have been observed in the dopamine context with a genetic variation of the dopamine transporter (DAT) gene [74] and the catechol-o-methyltransferase (COMT) gene [118]. In further detail, besides the BDNF Val66Met polymorphism, Hünnerkopf et al. [74] investigated the variable number of tandem repeat (VNTR) polymorphism of the gene SLC6A3 coding for DAT. Again, an association between the gene loci and negative emotion-related personality traits could be observed. More specifically, carriers of at least one 66Met allele together with the DAT 9+ variant reported the lowest neuroticism scores. The DAT 9+ allele has been associated with both higher and lower mRNA expressions of this gene up to now (e.g., [119, 120]). Therefore, the functional consequences of this VNTR polymorphism are still unclear.

Another important genetic target for a better understanding of dopaminergic neurotransmission represents the COMT Val158Met polymorphism. This genetic variation of the COMT gene is known to influence the catabolism of dopamine. The Met allele of this SNP has been associated with lower catabolism of dopamine [121] and putatively higher dopamine levels in the prefrontal cortex due to the paucity of dopamine transporters in this brain area (COMT exerts its effects mainly in the synaptic cleft; see [122]). In the In

Table 2: Overview on genetic association studies investigating the BDNF Val66Met polymorphism and personality.

Authors	Participants	Inventory	Results
Arias et al. [69]	$N = 937$ healthy participants (Castelló/Asturias)	TCI, a part of the sample ($n = 533$) filled in the Big Five questionnaire (BFQ), too.	No main effect of BDNF Val66Met on neuroticism or harm avoidance could be observed. Instead, an interaction effect between BDNF Val66Met and 5-HTTLPR was reported: the seldom Met66Met/ss genotype constellation was associated with highest harm avoidance scores.
De Beaumont et al. [70]	$N = 132$ participants (the study was conducted in Canada; no information on ethnicity available)	NEO-FFI	66Met+ variant was associated with lower extraversion.
Gong et al. [71]	594 healthy participants (Chinese Han)	EPQ	No main effect of BDNF Val66Met on personality, but extraverted 66Met allele carriers had more problems in shifting their attention away from positive words.
Ham et al. [72]	$N = 170$ healthy Asian participants (Korean)	TCI	BDNF Val66Met was associated with individual differences in persistence in females. Val66Val and Met66Met significantly differed from each other (direction of effect cannot be reported here, because the article is in Korean language).
Hiio et al. [73]	Two samples $N = 420$ healthy participants (Sample 1) and $N = 389$ healthy participants (Sample 2) (Estonia) investigated together	Estonian personality item pool NEO (Sample 1) and NEO-PI(-R)[1] (Sample 2)	A main effect of BDNF Val66Met on conscientiousness could be observed (the Met66+ variant was associated with lower conscientiousness). Moreover, an interaction effect between BDNF Val66Met and 5-HTTLPR on conscientiousness was observed (Met66+/homozygous ss-carriers were associated with lowest conscientiousness scores).
Hünnerkopf et al. [74]	$N = 272$ healthy participants (Caucasian)	NEO-PI(-R), TPQ	No main effects of BDNF Val66Met on personality were reported. Instead, an interaction effect with genetic variation of the dopamine transporter gene could be observed: carriers of the 66Met+/DAT 9+ genotype constellation were associated with lowest neuroticism scores.
Itoh et al. [75]	$N = 151$ healthy Asian participant (Japanese)	TCI/NEO-PI-(R)	Female carriers of the Met66Met variant showed higher reward dependence and extraversion scores compared to female 66Val+ carriers. No effects for males could be observed.
Kim et al. [76]	$N = 391$ healthy participants (Korean)	TCI; center for epidemiological studies for depression scale	No main effect of BDNF Val66Met on TCI (or depression) could be observed. An interaction effect could be observed with the variable life stressors: Val66Val carriers under the influence of high recent life stressors showed highest harm avoidance scores.
Jiang et al. [77]	$N = 153$ healthy participants (mainly Caucasian participants from the general US population)	TPQ	66Met allele was associated with higher harm avoidance scores.
Joffe et al. [78]	$N = 467$ healthy participants (Caucasian); $n = 113$ also underwent structural magnetic resonance imaging	NEO-FFI, DASS-21	No significant main effects of BDNF Val66Met on personality or DASS-21 (anxiety, depression, and stress) could be observed. In a subsample the 66Met allele carriers could be characterized by an inverse relationship between neuroticism and hippocampus gray matter volume.
Lang et al. [79]	$N = 343$ healthy participants (Caucasian)	NEO-FFI, state-trait anxiety inventory	Lower trait anxiety in carriers of the 66Met allele could be observed.
Minelli et al. [68]	$N = 217$ healthy participants	TCI	No significant association between BDNF Val66Met and personality could be observed.
Montag et al. [80]	$N = 610$ healthy participants (Caucasians)	TCI	Homozygous Met66Met carriers show significantly higher anticipatory worry and fear of uncertainty scores (subscales of harm avoidance).

Table 2: Continued.

Authors	Participants	Inventory	Results
Montag et al. [81]	$N = 768$ healthy participants (Caucasians)	TCI	In addition to Montag et al. [80] and in a slightly enlarged sample, carriers of the Met66+/A1+ variant show both lowest novelty seeking and highest harm avoidance scores.
Savitz et al. [82]	$N = 241$ participants (consisting both of healthy participants and patients suffering from affective disorders; South Africa)	Among others TCI and TEMPS-A	An increasing Met allele dosage effect on hyperthymic temperament (TEMPS-A, HT dimension) but not on TCI scale was reported.
Sen et al. [83]	$N = 441$ healthy participants (99% non-Hispanic Caucasians)	NEO-PI(-R)	The 66Met allele (especially the homozygous Met66Met genotype) was associated with lower neuroticism scores.
Suzuki et al. [84]	$N = 710$ healthy participants (Japanese)	TCI, parental bonding instrument	No main effect of BDNF Val66Met on personality could be observed. An interaction effect between genetic variation of BDNF and parental style on personality appeared, which is discussed in Section 5.3.
Terracciano et al. [85]	Two samples (sample called SardiNIA consisted of $N = 1560$ Italians; the sample called BLSA consisted of $N = 1131$ participants from mixed ethnicity)	NEO-PI(-R)	The 66Met allele was associated with higher introversion in two samples; moreover, an interaction effect could be observed between BDNF Val66Met and 5-HTTLPR on neuroticism: carriers of the BDNF Val66Val genotype carrying also the LL variant of 5-HTTLPR showed lowest neuroticism scores.
Tochigi et al. [86]	569 healthy participants (Japanese)	NEO-PI(-R), state-trait anxiety inventory	No association between BDNF Val66Met and personality could be observed.
Tsai et al. [87]	$N = 114$ healthy participants (Chinese)	TPQ	No association between BDNF Val66Met and personality could be observed.
Walter et al. [88]	$N = 664$ healthy participants (Caucasians)	Toronto alexithymia scale (TAS-20)	Carriers of the 66Met+/A1+ variant (the latter being an allelic variant of the DRD2/ANKK1 Taq Ia polymorphism) are associated with highest alexithymia scores.
Willis-Owen et al. [89]	Three samples consisting of $N = 4843$, $N = 571$, and $N = 516$ participants (participants from Southwest-England)	EPQ	No association of BDNF Val66Met with personality could be observed.

The here presented results represent only parts of the results reported in the mentioned studies, because some of the studies focused on aspects beyond BDNF Val66Met and personality.
[1]Either the NEO-personality inventory or its revised version was used in the studies of Table 2.

Kang et al. study the sensation seeking scale was administered [123]. One of its subscales measuring boredom susceptibility was influenced by an interaction effect between BDNF Val66Met and COMT Val158Met in the female subsample. Here, carriers of the configuration COMT Val158Val/BDNF Val66Val and COMT 158Met+/BDNF 66Met+ both showed lowest boredom susceptibility scores.

The interaction studies between two genetic loci in the present section outline the complexity of the molecular genetic underpinnings of personality and clearly show that risk alleles do not necessarily add up to elevate negative emotionality.

5.3. Interaction Effects of BDNF Val66Met and Environmental Influences on Human Personality. The last aspect to be discussed in the present review belongs to studies dealing with gene by environmental effects on personality traits, which have become a strong focus of research in recent years.

One of the most important studies in the field for gene by environmental effects represents the Caspi et al. [124] study investigating an interaction effect between 5-HTTLPR and stressful life events to predict depression in adulthood. Caspi and colleagues demonstrated that the s-allele is only associated with depression in adulthood when the participants of the study experienced adversity in particular in early life. Following from this seminal finding, several studies ensued investigating gene by environmental effects also with a focus on personality (e.g., [20, 125–127]). Focusing on the BDNF gene, Kim et al. [76] reported that carriers of the homozygous Val66Val variant under the influence of negative stressors

reported higher harm avoidance scores. Notably, no main effects of BDNF Val66Met on personality could be observed in this study. A BDNF Val66Met by early life stress interaction effect was reported by Gatt et al. [128]: In contrast to Kim et al. [76], they found evidence for the 66Met allele to be the vulnerability factor for neuroticism under high early life stress. Again, it is of importance to keep in mind that the studies differed in terms of measured stress (recent life stress versus early life stress) and also with respect to ethnicity. The 66Met allele occurs more often in the Asian population compared to Caucasian samples, and this can have effects on the power of the statistical analyses. Interestingly, Suzuki et al. [84] reported in another Asian sample (Japan) an interaction effect between BDNF Val66Met genotype and maternal care more in line with the data of Gatt et al. [128], who investigated Caucasians. Here, careless maternal behavior was associated with both higher harm avoidance and lower self-directedness scores particularly for carriers of the Met66Met variant ($n = 126$ out of $N = 710$ participants carried here the less frequent Met66Met variant). As one can see from these numbers, the occurrence of the homozygous Met66Met clearly is higher in Asian populations compared to Caucasian populations (3%). Besides the investigation of BDNF by life stress interaction effects on personality, much research deals with the prediction of affective disorders in this field (e.g., [129, 130]).

6. Conclusions and Outlook

The present review highlighted the role of the brain derived neurotrophic factor for personality. One particularly robust finding from the BDNF personality research extends the observation from depression research, namely, that low BDNF levels are associated with higher negative emotionality in the form of higher degrees of neuroticism and harm avoidance. In sum, bearing in mind the limitations discussed in Section 4, this link seems to be valid for personality traits related to negative emotionality, as well as for psychopathology. In contrast, the meta-analysis on the link between the prominent BDNF Val66Met and BDNF serum levels [106] and between BDNF Val66Met and personality traits, such as harm avoidance/neuroticism [85], revealed no robust association. This does not mean that this association does not exist, because BDNF exerts its influence on human personality in a complicated pattern of interactions with other transmitter systems and is also modulated by the environment. Clearly, the effects of BDNF taken alone are rather small, as has been pointed out both by studies investigating BDNF levels and the BDNF gene. Moreover, most findings of BDNF research link BDNF to negative, but not positive, personality traits (only a few exceptions exist in the literature, as reported by Jiang et al. [77] or Montag et al. [81]). Future studies will probably detect new genetic variants for human personality of larger interest than BDNF Val66Met. Such potential genetic variations have already been observed in the near of or on the BDNF (e.g., in the near of the BDNF gene in a GWAS study by Terracciano et al. [131] or on the BDNF gene by Jiang et al. [77]). Besides this, genes coding for the receptor structures TrkB and $p75^{ntr}$, on which BDNF acts as a transmitter, are largely under-studied in the context of personality research.

Along this line of research, the study of BDNF gene activity in the context of personality will be of large importance in the near future. The latest development in the study of the BDNF gene goes one step beyond the studies reviewed here to understand exactly how environmental factors influence gene activity. The new emerging field of epigenetics will be of tremendous importance to better understand gene by environmental effects on psychological phenotypes [132]. A recent review article by Roth and Sweatt [133] outlined that early life environmental stressors shape the gene activity of BDNF. Here, rats that experienced abusive parents were associated with a hypermethylation of the BDNF gene, which means that the gene cannot be read sufficiently. This hypermethylation was accompanied by low BDNF mRNA levels, indicating lower BDNF levels. Most of the epigenetic studies are still conducted in animal models. In the near future, personality psychologists will surely also conduct their research in this fascinating new area, combining nature and nurture in one model.

7. Limitations of This Review

The present study dealt with a rather narrow view on BDNF, namely, its link to human personality traits. Clearly, an influence of BDNF has been shown in the literature beyond personality on a wide range of endophenotypes including cognition (e.g., [134] see reviews on pleiotropy by [135, 136]), which has not been highlighted in the present paper. I hope that all relevant "personality BDNF studies" are presented in the study. As 600 papers deal with the BDNF Val66Met polymorphism and 13.060 with BDNF right now, this is very unlikely (numbers retrieved via pubmed.com by entering in "BDNF" or "BDNF Val66Met" on 5 November 2013). Therefore, I regret any omissions. Finally, personality is influenced by a complex concert of different neurotransmitters and neuropeptides. In this context, some findings above illustrated how BDNF interacts with molecules such as dopamine. Reviews with a focus on other molecular systems of the brain are warranted to get deeper insights into the biological basis of personality.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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