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Review

Risk and Resilience: The Role of Brain-derived Neurotrophic Factor in Alcohol Use Disorder

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Abstract: Brain-derived neurotrophic factor (BDNF) is well known for its role in synaptic plasticity. More recently, BDNF has come to be regarded as a potential resilience factor in a variety of conditions that are characterized by maladaptive neuroplasticity, including alcohol use disorder. Research in animal models suggests that BDNF may serve as a protective gatekeeper in the transition from social drinking to compulsive alcohol consumption. Further, stress-induced modification of BDNF signaling may have an important role in anxiety-modulated alcohol consumption. In this article, we will review recent studies of BDNF and alcohol use in human participants. Studies included in this review have used genetic or epigenetic approaches or have measured peripheral BDNF protein levels in serum or plasma. Importantly, a number of these studies have incorporated neuroimaging methods to provide information about structural and/or functional central nervous system correlates of BDNF measures in relation to alcohol use. While there remains a great deal of variability in research findings from human participants on this issue, a number of studies suggest that behavioral or pharmacological interventions designed to enhance neuroplasticity may be a promising avenue for future research on alcohol use disorder.

Keywords: brain-derived neurotrophic factor; BDNF; alcohol use disorder; alcohol; stress; resilience;

neuroplasticity

1. Introduction

Like many human conditions, the development of alcohol use disorder (AUD) is influenced by complex interactions of genetic and environmental factors that shape both risk and resilience to the spiral of addiction. Historically, AUD research has tended to focused on risk. Researchers have sought to determine which factors or combinations of factors might increase an individual's chances of transitioning from social drinking to AUD and/or relapsing after periods of abstinence from alcohol. However, as noted in a recent review by Logrip and colleagues [1], alcohol is widely consumed, but only a small percentage of drinkers (i.e., 5% [2]) go on to develop AUD. These statistics have prompted researchers to shift their attention to uncovering factors that might promote resilience in the face of risk for AUD [3]. Research findings from animal models and human participants are converging to suggest that brain-derived neurotrophic factor (BDNF) may have a role in this process. BDNF may function as a resilience peptide [4] in an endogenous protective pathway [1] that could potentially be exploited in the prevention and treatment of AUD. In the current review, we will describe contemporary models of BDNF and alcohol interactions, which have derived largely from animal research, and summarize recent studies of such interactions in human populations. Potential avenues for future research will also be discussed.

1.1. Brain-derived neurotrophic factor

Brain derived neurotrophic factor is the most abundant neurotrophin in the mammalian central nervous system (CNS) [5]. Synthesized in the endoplasmic reticulum as a pre-pro-molecule, BDNF undergoes two cleavage steps from pre-pro via pro-BDNF to its mature form, which is then packaged in secretory vesicles [5–7]. Following neural activity-dependent release, BDNF binds to tropomyosin-related kinase (TrkB) receptors, activating downstream signaling cascades that are essential for neuronal integrity and survival [5,8,9]. Historically, BDNF is perhaps best known as a protein essential for long-term potentiation (LTP) in the hippocampus, a neuronal process that is necessary for learning and episodic memory [10–12]. In this role and others, BDNF promotes the formation and survival of dendritic spines, which are crucial for proper synaptic plasticity and connectivity in the adult brain [13,14].

The human *BDNF* gene is located on the short arm of chromosome 11. The most commonly studied *BDNF* polymorphism is $Val^{66}Met$ (rs6265), a single-nucleotide substitution of A for G at nucleotide position 196, producing a non-conservative substitution of a valine with a methionine at codon 66 of this gene [10,15–17]. The location of this single-nucleotide polymorphism (SNP) in the

pro-domain of the *BDNF* gene results in impaired intracellular processing, trafficking, and extracellular secretion of BDNF protein [10]. As a result, this SNP may impair neuronal plasticity [18–20] and ultimately has the potential to affect higher functions such as memory and cognition [20,21]. In a number of studies, the *BDNF* $Val^{66}Met$ polymorphism has also been associated with genetic susceptibility to neuropsychiatric disorders including Alzheimer's disease, autism, depression, eating disorders and schizophrenia [22,23].

Alcohol use disorder (AUD) has also been described as a disease of maladaptive plasticity [24–26], though there is some debate as to whether structural plasticity and synaptic changes drive addictive behaviors, or whether they reflect homeostatic compensations to drug use [27]. Recently, researchers have begun to appreciate the potential role of BDNF as a protective gatekeeper in the transition from casual drinking to compulsive alcohol consumption [1]. One model of direct BDNF and alcohol interactions [1] suggests that BDNF signaling in corticostriatal pathways may act to keep alcohol consumption in moderation through mechanisms related to habit learning and compulsive behaviors, while risk for transition to uncontrolled drinking may occur when BDNF levels in the medial prefrontal cortex are reduced. Another model [28] suggests that BDNF may serve as a mediator in the relationship between stress and alcohol consumption. These models will be reviewed in the next section of this article.

1.2. BDNF and alcohol—a corticostriatal connection

Earlier work in rodent models (i.e., 1990s to 2010) has been reviewed by Ghitza and colleagues [29]. More recently, Logrip and colleagues [1] have provided an extensive review of direct interactions between BDNF and alcohol based on the recent animal research literature. The effects that Logrip and colleagues [1] describe are alcohol-specific, that is, these interactions with BDNF do not occur in response to other appetitive reinforcers such as sucrose [30]. They are regionally specific, in that the interactions appear in the dorsal striatum, corticostriatal pathways and the medial prefrontal cortex, rather than in other addiction-relevant areas such as the nucleus accumbens in the ventral striatum [30–33]. Further, the effects are moderated by alcohol dose. The relationship between BDNF levels and alcohol use appears to change as alcohol administration levels transition from moderate to heavy exposure. For instance, Logrip and colleagues [1] report that, in response to acute low-dose and/or longer-term moderate alcohol administration below the level of intoxication, *BDNF* mRNA increased in the dorsal striatum [32,33]. Further, acute application of alcohol onto striatal neurons increased *BDNF* expression, translation and secretion of BDNF protein, and TrkB receptor activation [1,34]. In contrast, when animals consumed alcohol at levels sufficient to induce intoxication, particularly over longer periods of time, researchers reported long-lasting reductions of cortical *BDNF* mRNA levels and a decrease in *BDNF* expression, specifically in the medial prefrontal cortex [1,30,31]. Logrip and colleagues [1] describe this breakdown in alcohol's ability to upregulate *BDNF* expression as a possible loss of a protective mechanism. In other words, the presence of sufficient levels of BDNF in

these corticostriatal pathways may promote resilience and serve as a gatekeeper in the transition to more compulsive alcohol consumption.

1.3. BDNF as a mediator of stress and alcohol interactions

In addition to the model described by Logrip and colleagues [1], other researchers point to the involvement of BDNF in the relationship between stress and alcohol consumption. Many people view alcohol use as an effective means of coping with stress. This perception is due in part to alcohol's anxiolytic effects on the $GABA_A$ receptor [35,36]. In particular, acute alcohol consumption increases pre-synaptic GABA release and enhances post-synaptic $GABA_A$ receptor function in the central amygdala, ultimately resulting in an acute reduction of anxiety and responsiveness to stress [37–39]. In fact, the central amygdala has recently been described as a hub for anxiety and AUD [40]. These connections may explain, in part, why stressful life events tend to prompt alcohol consumption for some people, and may increase risk of relapse for those with AUD [41–44]. However, it is also important to note that alcohol is perceived as a stressor by the body, and thus activates the neuroendocrine stress response system [44]. Chronic alcohol exposure and withdrawal may trigger dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the brain's stress-reward circuitry, leading to an escalating spiral of stress, negative affect and alcohol consumption [24,44–47].

In addition, a growing body of literature suggests that risk for the development of addictive behaviors is influenced by both genetic and environmental factors [48]. For example, environmental influences such as negative early life experiences may cause long-lasting epigenetic changes in expression of stress-related genes that influence brain function and behavior, thus increasing risk for affective disorders and AUD later in life [49,50]. Such epigenetic changes do not modify the DNA sequence itself, but rather result in covalent modifications of either DNA (i.e., methylation) or of the histone skeleton (i.e., acetylation) around which it is packaged into chromatin [50,51]. Thus, one's adaptive or maladaptive responses to stressors in adulthood may reflect the resilience or vulnerability of one's neuroendocrine profile that was shaped by early gene x environment interactions [5]. Further, the use of addictive substances including alcohol may further interact with one's genome and modify responses throughout the lifespan [3,52]. Cadet [3] provides an excellent review of how interactions of drugs of abuse with an individual's genome, and the impact of the environment, may shape an individual's response to addictive substances.

BDNF may be a key component in these processes. Moonat and Pandey [28] describe a model, in which stress-induced changes in BDNF signaling lead to altered synaptic plasticity, which ultimately increases risk for both anxiety and alcohol consumption. It is well known that stressful experiences, and the resulting release of glucocorticoids such as cortisol, impact neuroplasticity in the brain through BDNF-related mechanisms [5,53,54], though it is important to recognize that other molecules are also involved in stress-induced neuroplasticity [55]. The influence of stress on the

brain has been described as an inverted U-shaped curve, in which moderate stress for short periods may have a positive effect on neuronal activities. Conversely, intense stress tends to have a negative effect that intensifies over time. As described by McEwen and colleagues [55], *moderate short-term stress* results in enhanced synaptic transmission and LTP, while *moderate chronic stress* facilitates remodeling of neural architecture and successful adaptation. In contrast, *intense acute stress* may lead to a short-term suppression of these functions, and *intense chronic stress* may lead to neurochemical distortions, loss of resilience, impaired remodeling and lack of recovery [55]. Stress-related changes in neuroplasticity may be particularly pronounced in areas of the brain that underlie behavioral coping responses; however, the direction of the effects may differ by brain region [5,55,56]. For example, some studies of human participants suggest that early life stress may induce volumetric *decreases* in the prefrontal cortex, along with *increases* in amygdala volume [57], and greater vulnerability to affective disorders [58].

Through epigenetic mechanisms, early life stress may upset the equilibrium of glucocorticoid- and BDNF-signaling pathways, thus tilting the aforementioned inverted U-shaped curved in the direction of increased risk [5]. For instance, studies suggest that rats reared in stressful environments may have increased methylation of *BDNF* DNA, leading to decreased *BDNF* expression in the prefrontal cortex in adulthood [50,59], a profile that has been associated with excessive alcohol consumption in other animal models [1]. It is particularly interesting to note that the opposite may also be true. Branchi and colleagues [60] devised a study in which young mice were provided with environmental enrichment through a communal nesting arrangement (i.e., three mothers with their offspring) that offered enhanced maternal behavior and peer interactions compared to the standard laboratory conditions (i.e., one mother with her offspring). As adults, mice reared in a communal nest had higher levels of histone acetylation in the *BDNF* gene, a condition that is permissive of *BDNF* expression, and exhibited a faster increase in BDNF protein levels following environmental challenge [60].

1.4. BDNF as a resilience protein

Taken together, these models and their supporting studies reinforce the notion that BDNF may function as a resilience factor at key risk points in the trajectory toward development of AUD. Theoretically, environmental enrichment interventions might be expected to combat the negative effects of early life stressors, leading to positive changes in BDNF levels in key brain areas such as the prefrontal cortex. These neuroplastic modifications might facilitate the development of better behavioral coping responses [60], thus, decreasing an individual's vulnerability to self-medication [37] and transition to compulsive alcohol consumption in later life [1]. However, it is important to note that the aforementioned models, describing how BDNF might contribute to resilience in AUD, were built largely on animal research. The results of studies with human participants have been more varied. The remainder of this review will focus on that work.

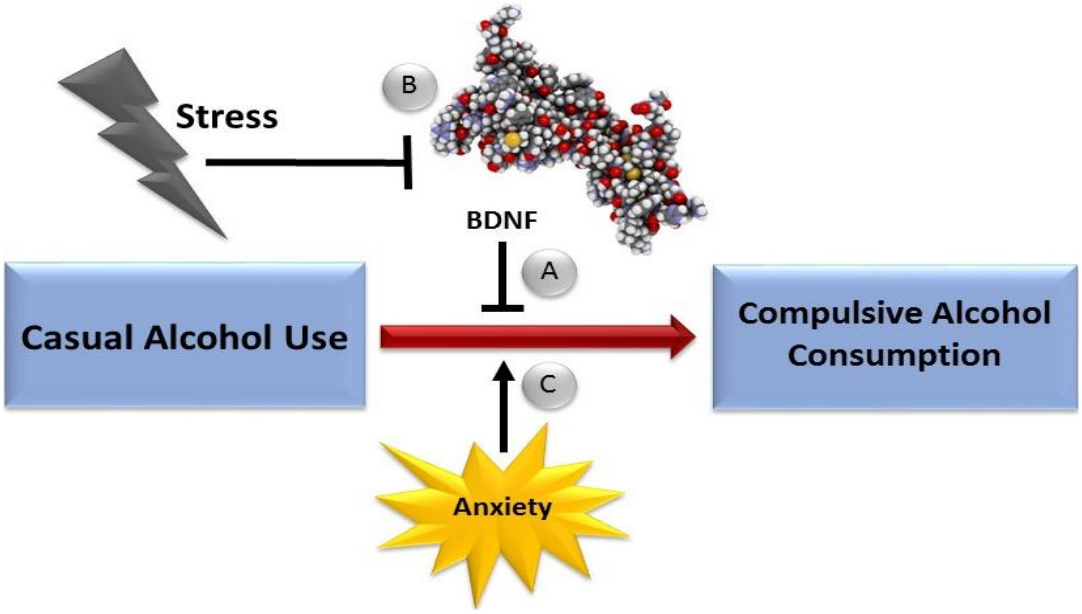

Figure 1. BDNF as a Resilience Protein. A) BDNF may serve as a resilience factor to impede the transition from casual alcohol use to compulsive alcohol consumption. B) Further, various types of stress may have a negative impact on BDNF levels in key brain areas such as the prefrontal cortex, leading to a breakdown of BDNF's protective influence, and C) a potential escalation of anxiety-modulated alcohol misuse. Theoretically, successful treatment to reduce these negative effects of stress might prompt positive changes in BDNF levels, thus decreasing vulnerability to self-medication and potentially interrupting the transition to compulsive alcohol consumption.

2. Materials and Method

2.1. Procedure

The literature review procedure focused on recent studies relevant to BDNF in AUD or the development thereof. Articles were retrieved using search engines such as PubMed, GoogleScholar and PsychInfo, and search terms included combinations of *brain-derived neurotrophic factor (BDNF)*, *alcohol*, and *stress.* Original research studies focusing on human participants and published in English between January 2010 and February 2016 were reviewed. For review of articles prior to 2010, Forero and colleagues [61] and Haerian and colleagues [62] summarize genetic association studies of *BDNF* and AUD, and Meng and colleagues [63] cover previous work on peripheral BDNF protein levels in AUD.

Articles focusing on BDNF in healthy control participants while measuring functions relevant to dopaminergic reward were included in the review, as long as alcohol consumption was measured in the study. Articles focusing exclusively on substance use disorder (SUD) without considering AUD

separately were excluded. Using this procedure, we identified a total of 32 studies. When these were categorized by methodology, 18 studies used genetic or epigenetic approaches to study the relationship between BDNF and AUD or factors affecting risk for AUD. These are summarized in Table 1. The remaining 14 studies measured serum or plasma levels of BDNF protein in relation to alcohol use or risk for AUD. These are summarized in Table 2. In Tables 1 and 2, studies are presented chronologically, and alphabetically within a given year. Information includes authors, population and study design, as well as outcomes relevant to BDNF. Prior to reviewing these studies, methodological considerations for working with human participants will be discussed in the next subsection.

2.2. Methodological considerations in human studies

Human participants bring with them a plethora of genetic and environmental factors that add variability to scientific research. Some of these factors can be controlled through careful study design and/or may be addressed using sophisticated multivariate statistical techniques. In other cases, the experimental approaches used in animal research are simply impossible to replicate with human participants. Before embarking on a description of study results in Tables 1 and 2, it is important to briefly consider several issues relevant to investigations of BDNF and alcohol use in human populations.

2.2.1. Peripheral versus central measurement of *BDNF*

Whereas studies in animal models have focused on CNS levels of *BDNF* mRNA or concentrations of BDNF protein in specific brain regions, the majority of studies in human populations have been constrained to measurement of peripheral BDNF protein levels, as found in serum or plasma. This is a limitation of human studies, as the mechanisms behind BDNF concentration changes in the peripheral circulation are not as well understood [64] and may have uncertain relevance to changes in the CNS [65]. BDNF protein can cross the blood brain-barrier in both directions [64,66,67], and studies in rodent models have reported significant positive correlations between levels of BDNF found in serum or whole blood with levels of BDNF in brain tissue [68–70]. Further, a study in human participants by Lang and colleagues [71] addressed this issue by using proton magnetic resonance spectroscopy to examine the relationship between serum BDNF levels and in vivo concentrations of cerebral N-acetylaspartate, a marker of neuronal integrity. Results indicated a positive association between peripheral serum BDNF levels and cerebral N-acetylaspartate concentrations in the anterior cingulate, but not in the hippocampus [71]. These results at least partially suggest that BDNF serum concentrations could reflect some aspect of neuronal plasticity in the human brain [71].

Timing of sample collection and participant characteristics may also influence results [72]. Researchers have noted that peripheral BDNF levels in humans oscillate in a circadian fashion with the highest concentrations of peripheral BDNF occurring in the morning and levels decreasing

throughout the day [66]. This pattern has been noted for plasma BDNF levels in both males and females [66,73,74], but perhaps not for serum BDNF levels [75]. Further, in women, BDNF levels may be influenced by ovarian function, resulting in a blunted diurnal rhythm during the luteal phase of the menstrual cycle [66,74]. Other studies suggest that BDNF levels decrease with age in both sexes, a phenomenon that may contribute to age-related synaptic loss and cognitive decline [76]. Use of over-the-counter or prescribed medications, or illicit substances, may also influence BDNF levels and should be assessed via questionnaire in any study where BDNF samples are obtained. Bus and colleagues [72] note that time of sample storage, food intake before sampling, and participants' urbanicity may be additional factors that affect peripheral BDNF levels. Finally, as mentioned earlier in this review, the *BDNF* Val^{66}Met polymorphism affects activity-dependent release of BDNF [10], which could increase individual variability in studies of peripheral BDNF levels.

2.2.2. Sensitive information obtained via self-report

In all of the studies of human participants that are summarized in Tables 1 and 2, researchers obtained alcohol consumption data from self-report questionnaires or interviews with study participants. This approach is influenced by the interaction of social and contextual factors, respondent characteristics and task attributes [77]. In general, people tend to under-report their alcohol use [78,79]. Despite these limitations, in the field of alcohol research, self-report remains the standard method of assessing alcohol use among human participants [79].

In addition, some studies in Tables 1 and 2 included information about participants' early life experiences. These data were also gathered by retrospective self-report with or without collateral information from family members or other individuals. As a result, these studies also suffer from a number of limitations, which have been reviewed by Thabrew and colleagues [80]. For example, previous research has shown poor agreement between actual childhood events and adolescent retrospective reports of childhood treatment [81], as well as considerable temporal instability in repeated reports on childhood physical punishment and sexual abuse from 18- to 21-year-olds [80,82]. Here again, participants have a tendency to under-report negative events. Studies of this issue suggest a situation in which victims may be more likely to provide false negative reports, rather than non-victims providing false positive reports [80,82]. However, researchers in this field suggest that instability over time is likely to have only a minimal impact on statistical models linking childhood maltreatment and adult psychiatric disorders [80,81].

3. Results

3.1. Studies using genetic or epigenetic approaches

All publications included in Table 1 featured either *BDNF* genotyping, or assessment of *BDNF*

gene methylation. Beyond these aspects, the study designs encompassed a wide range of methods from genetic association studies and drug trials to laboratory stress manipulations, neuropsychological assessments and neuroimaging.

3.1.1. Positive associations between *BDNF* and *AUD*

Genetic association studies have focused predominantly on the relationship between AUD and the *BDNF* Val^{66}Met polymorphism (rs6265). In our review of the literature, 13 of the 18 studies summarized in Table 1 included a comparison of *BDNF* Val^{66}Met allelic frequency in participants with alcohol use disorder (AUDs) versus healthy controls (HCs) or in HCs with and without a family history of AUD. Of these 13 studies, five reported differential allelic frequencies across AUD or family history groups. For example, in a study of older Korean men with and without AUD, Shin and colleagues [83] found a higher frequency of Met/Met and Val/Met alleles among AUDs compared to HCs. Colzato and colleagues [84] studied male social drinkers from The Netherlands and found that Met carriers (i.e., Met/Met and Val/Met genotypes combined for statistical analyses) reported higher levels of alcohol consumption, and had higher anxiety levels and anticipatory stress responses, compared to those with the Val/Val genotype. Su and colleagues [85] studied Chinese men with and without AUD and found that the Met allele appeared more frequently among AUDs with co-morbid depression compared to AUDs without depression and HCs. Cheah and colleagues [86] studied European participants with schizophrenia, AUD or the co-morbid condition, along with healthy controls. Results of that study suggested that the Val^{66}Met polymorphism was associated with AUD and risk-taking behavior after drinking, with the strongest associations noted for the Met/Met allele. It is interesting to note that these associations in Cheah and colleagues' study [86] were significant only among AUDs with co-morbid schizophrenia and not among AUDs without schizophrenia; further, the relationship appeared to be strongest for males. Finally, a longitudinal study of Caucasian, European adolescents by Nees and colleagues [87] found that Met carriers with high levels of alcohol use had a lower level of reward reactivity in the putamen (notably, part of the dorsal striatum; see [1]) and were more likely to orient toward alcohol and to drink alcohol two years later. Taken together, these five studies support the notion that individuals with the *BDNF* Val^{66}Met polymorphism, particularly those homozygous for the Met allele, may have greater risk for developing AUD. It is important to note that participants' sex and psychiatric co-morbidity were recognized in these studies as influential factors.

3.1.2. Studies suggesting underlying mechanisms

Other studies in Table 1 suggest potential mechanisms that may underlie an enhanced risk for AUD among Met allele carriers. For instance, Hill and colleagues [88] studied adolescent/young adult high-risk offspring of multiplex AUD families and found that offspring of AUDs had greater

cerebellar gray matter volumes compared to HCs. This difference in cerebellar gray matter was associated with an interaction of *BDNF* and allelic variants of *GABRA2* (i.e., the gene encoding the alpha-2 subunit of the $GABA_A$ receptor), suggesting that these gene/gene interactions may impact AUD risk and brain morphology via signaling in early development and/or gene expression throughout adolescence and young adulthood [88]. Hill and colleagues [88] noted that the potential involvement of cerebellar morphology in risk for AUD is a topic of ongoing research, however, the cerebellum may be involved in addictive processes via its critical roles in attention, memory, facial recognition, theory of mind, emotional monitoring and time perception [89–95].

Possession of the Met allele may also influence cognitive recovery in abstinent AUDs. In a study of adult AUDs following approximately one month of abstinence from alcohol, Mon and colleagues [96] reported increases in frontal and parietal gray matter volume over time in Val/Val homozygotes but not in Met carriers. Increases in gray matter volume were associated with improvements on neuropsychological tests over time, suggesting that *BDNF* genotype may influence functionally significant brain tissue volume recovery in abstinent AUDs [96]. In another article by the same research team [97], AUDs were tested at approximately 7, 33 and 213 days of abstinence. At all time-points, AUDs had smaller hippocampi than HCs, and at one month of abstinence, lower hippocampal volume was associated with neuropsychological decrements in AUDs. In terms of recovery with continued abstinence, hippocampal volume was increased at a 7-month follow-up for the Val/Val homozygotes, but not for Met carriers. Hoefer and colleagues [97] interpreted these results to suggest that *BDNF* genotype may regulate functional hippocampal recovery in AUDs. If this is the case, then Val/Val homozygotes may possess a potential advantage over Met carriers in terms of cognitive recovery and resilience in AUD.

Other studies examined reward processing in healthy controls, an issue that is relevant to the development of addictive disorders. Pecina and colleagues [98] studied the potential influence of the *BDNF* $Val^{66}Met$ polymorphism on dopaminergic stress and reward processes in HCs using an fMRI task of monetary incentive delay and a PET task measuring striatal dopamine neurotransmission during two challenges of opposite valence: a pain-stress challenge and a placebo analgesic. Results indicated that during the anticipation of monetary loss (large loss minus null condition), *BDNF* Met carriers had greater blood-oxygen-level-dependent activation in the ventral tegmental area-nucleus accumbens-medial prefrontal cortex circuit as compared to Val/Val homozygotes [98]. No genotype differences were seen during the anticipation of reward (large gain minus null condition). Further, in the PET experiment, Met carriers had greater baseline dopamine receptor (D2/3) availability in the left and right ventral striata as compared to Val/Val homozygotes. Relative to Val/Val homozygotes, Met carriers also exhibited greater bilateral dopamine release in the nucleus accumbens during pain challenge and an overall reduction in dopamine neurotransmission during the placebo condition [98]. Pecina and colleagues [98] suggest that these results support the notion that the *BDNF* $Val^{66}Met$ polymorphism influences a) dopamine-mediated responses to stress, b) the cognitive regulation of such responses by positive expectations, and c) anticipatory responses to risk/reward conditions via

the ventral tegmental area-nucleus accumbens pathway.

In a more comprehensive genetics study, Chen and colleagues [99] used parallel independent component analysis with multiple references (pICA-MR) to examine potential relationships between genome-wide SNPs and alcohol cue-induced brain activations in heavy drinkers. The alcohol cue condition consisted of exposure to and brief tasting of the participants' preferred alcoholic beverage type (versus juice, in a control condition) during fMRI scans. Results of pICA-MR analyses on fMRI (54,937 voxels) and SNP (717,129 loci) data indicated 15 fMRI components and 11 SNP components. For drinkers with more severe symptoms of AUD, a genetic component derived from the *CREB-BDNF* pathway was associated with an imaging component reflecting hyperactivation in the precuneus, superior parietal lobule, and posterior cingulate areas, regions that have been previously associated with craving and alcohol use severity [99–104]. This association remained significant after correction for multiple testing and when age, sex and race were statistically controlled.

3.1.3. No Association between *BDNF* and *AUD*

In contrast to the studies described above, seven of the 13 studies that examined *BDNF* Val^{66}Met allelic frequencies in AUDs versus HCs, or in HCs with and without a family history of AUD, found no significant associations between Val^{66}Met and AUD [105–111]. Thus, despite the compelling evidence of studies suggesting potential mechanisms of enhanced AUD risk among Met carriers (or conversely, endogenous resilience to AUD risk among Val/Val homozygotes), the majority of association studies on this topic have actually yielded negative findings, a result that is reinforced by recent meta-analyses [61,62].

3.1.4. Epigenetic Approaches

We reviewed only one study that used an epigenetic approach. Heberlein and colleagues [112] examined potential alterations in *BDNF* gene methylation and BDNF protein levels in serum during days 1, 7 and 14 of alcohol withdrawal in AUDs. In particular, this study examined DNA methylation at the *BDNF* promotor, which would be expected to repress gene transcription [113]. Relative to baseline *BDNF* methylation of HCs, methylation of the *BDNF* promotor was increased in AUDs on days 1 and 7 of alcohol withdrawal. In terms of within-group differences for AUDs, methylation of the *BDNF* promotor was successively decreased at each time point during alcohol withdrawal, and decreasing methylation was associated with decreasing symptoms of depression during this time-period [112]. Somewhat counterintuitively, AUDs with lower *BDNF* methylation levels at day 14 of alcohol withdrawal were less likely to remain abstinent from alcohol in the long-term, compared to AUDs with higher methylation levels at that time point. However, the researchers reported that peripheral serum levels of BDNF protein were not statistically associated with methylation of the *BDNF* promotor in this study and did not differ between AUDs and HCs [112].

Additional studies are needed to clarify the significance of *BDNF* methylation during alcohol withdrawal in relation to long-term sobriety. Recent studies that examined peripheral BDNF protein levels without a genetic or epigenetic component will be summarized in the next section (see Table 2).

3.2. Studies examining peripheral BDNF protein levels and alcohol-related variables

Fourteen studies were identified which examined alcohol-related variables along with peripheral BDNF protein levels in serum and/or plasma. These investigations included a wide variety of study designs. They are summarized chronologically in Table 2 and described by study type, below.

3.2.1. BDNF and Alcohol Use in the General Population

In two studies [114,115], researchers recruited participants from non-treatment-seeking, community populations and categorized them into AUDs or other alcohol-using groups versus HCs based on self-reported alcohol consumption and standardized diagnostic criteria. Lhullier and colleagues [114] grouped participants based on responses to the CAGE questionnaire [116], where participants with CAGE scores ≥ 2 were considered to have moderate to severe AUD, and those with scores < 2 were categorized as HCs. In Zhang and colleagues' study [115], participants were grouped as "alcohol users" if they reported more than occasional alcohol use and had a total score of at least 3 on the Michigan Alcohol Screening Test (MAST [117]). The comparison group of "non-alcohol users" was comprised of those who had never used alcohol or who occasionally consumed fewer than 5 drinks per episode [115]. Neither Lhullier and colleagues [114], nor Zhang and colleagues [115] reported statistically significant differences in serum BDNF levels between alcohol and control groups. Further, Zhang and colleagues detected no significant correlation between BDNF and MAST scores or neuropsychological test scores in their sample.

3.2.2. BDNF in Alcohol Use Disorder

Other studies directly compared BDNF levels in clinical samples of participants with alcohol use disorder (AUDs) versus healthy controls (HCs) under various conditions of alcohol withdrawal and abstinence.

One strategy involved monitoring BDNF protein levels in AUDs undergoing withdrawal from alcohol and then comparing these values to typical BDNF levels in HCs. In two studies, there were no significant differences in BDNF protein levels of HCs versus AUDs entering treatment for alcohol withdrawal. Heberlein and colleagues [118] monitored serum BDNF in AUDs on days 1, 7 and 14 of alcohol withdrawal and found no significant differences in AUDs versus HCs at baseline or over time. However, BDNF levels were negatively associated with alcohol withdrawal severity in AUDs on day 1; AUDs with higher BDNF levels had less severe alcohol withdrawal symptoms [118]. Costa and

colleagues [119] studied serum BDNF in AUDs at the time of initial alcohol withdrawal and at a 6-month follow-up session. Similar to Heberlein and colleagues [118], Costa and colleagues [119] found no significant differences in serum BDNF between HCs and AUDs at treatment intake. Further, when AUDs were categorized based on abstinence status at the 6-month follow-up, it was noted that abstinent and non-abstinent AUDs did not differ on BDNF at intake. However, at the 6-month follow-up session, BDNF levels were higher in abstinent AUDs relative to both HCs and non-abstinent AUDs [119].

In contrast, other studies have noted significant differences in HCs relative to AUDs at treatment intake. A cross-sectional study by Zanardini and colleagues [120] measured both serum and plasma BDNF. While there were no significant differences in plasma BDNF between groups, serum BDNF levels were lower in AUDs at treatment intake, as compared to HCs. The researchers noted that this finding was not related to blood alcohol concentration at intake or treatment with prescription medications [120]. Huang and colleagues [121] reported a similar result (i.e., BDNF of AUDs at intake < HCs) and further noted that the lowest levels of serum BDNF for AUDs at intake occurred among those who had experienced delirium tremens (DTs) during alcohol withdrawal. Patients were then followed over the initial withdrawal period. By day 7 after alcohol withdrawal, serum BDNF had increased significantly in AUDs, such that BDNF of non-DT AUDs was comparable to HCs [121]. A more recent study by Kohler and colleagues [122] also found reduced serum BDNF levels in AUDs admitted for alcohol withdrawal, as compared to HCs. After an initial decrease, BDNF levels in AUDs showed a tendency to increase between days 3 and 14 of alcohol withdrawal, but these changes remained below the level of statistical significance [122]. Finally, Reynolds, Mueller and MacLaren [123] examined the effects of dexmedetomidine administration on BDNF levels during alcohol withdrawal in AUDs (without comparison to HCs) and found no significant differences in plasma BDNF at baseline or over time (up to 120 hours after starting drug therapy) in low and high dose dexmedetomidine groups versus placebo.

Another research strategy involved monitoring peripheral BDNF protein levels in detoxified, abstinent AUDs relative to HCs. Two studies examined BDNF levels in AUDs who had attained a significant level of abstinence prior to testing. In a cross-sectional study, Meng and colleagues [63] found no significant differences in serum BDNF between AUDs who were 4 to 6 weeks abstinent at the time of the study compared to HCs. This study [63] also found that BDNF levels increased to a similar extent in both groups following a 15-minute session of the Trier Social Stressor Task, which is composed of public speaking and mathematics challenges [124]. D'Sa and colleagues [68] also examined serum and plasma BDNF levels in AUDs with one month of abstinence compared to HCs. Using average values from morning blood samples taken over three consecutive days, D'Sa and colleagues [68] found higher serum BDNF levels in AUDs compared to HCs, but no significant differences in plasma BDNF levels.

Finally, four of the studies in Table 2 focused on comorbid diagnoses in AUDs or other drinking groups. For example, Kim and colleagues [125] studied plasma BDNF levels in male AUDs with

normal glucose tolerance, pre-diabetes mellitus, or diabetes mellitus diagnoses at intake and after 30 days of AUD treatment. Only the pre-diabetes mellitus group showed a significant increase in BDNF after 30 days of AUD treatment. Further, increased BDNF in the pre-diabetes mellitus group was significantly greater than that of the normal glucose tolerance group [125].

Miguez-Burbano and colleagues published two studies [126,127] focusing on plasma BDNF levels in participants positive for the human immunodeficiency virus (HIV), as well as HIV seronegative controls. To examine alcohol consumption, they used participants' self-reported alcohol use and hazardous drinking definitions from the National Institute on Alcohol Abuse and Alcoholism (NIAAA [128]). In the first report [126], the researchers found that plasma BDNF levels were negatively correlated with the number of alcoholic beverages consumed per day, but this relationship appeared only after a threshold level of 3 or more drinks per day had been reached. Further, among hazardous drinkers, these findings were largely due to consumption of beer and liquor rather than wine, a finding that the researchers linked to the antioxidant content of wine versus other alcoholic beverages [126]. In multivariate analyses, both hazardous alcohol use and plasma BDNF alterations were independent predictors of HIV-associated neurocognitive disorders. As predicted by long-standing literature (e.g., [129]), hazardous alcohol use was associated with decrements in neurocognitive function. However, Miguez-Burbano and colleagues [126] are among the first to note an inverted U- or J-shaped relationship between plasma BDNF levels and neurocognitive performance in human participants, in which only intermediate levels of BDNF seemed to produce a protective effect.

In a second analysis of this study population by Miguez-Burbano and colleagues [127], the researchers focused on participants' drinking trajectories, plasma BDNF levels, and mood states over a 6-month period. At baseline, there was a negative correlation between BDNF levels and participants' endorsement of feeling nervous and stressed. Next, three drinking trajectories were identified based on participants who (1) increased drinking; (2) drank at constant levels; or (3) decreased drinking over the 6-month study period. Results indicated that women in trajectories 1 and 2 reported greater stress and had lower plasma BDNF than those in trajectory 3. Men in trajectory 1 had lower plasma BDNF and marginally greater stress compared to men in trajectories 2 and 3. The researchers noted that dual diagnoses of anxiety plus stress, or depression plus stress, were present in 26% of the study population and in this case all affected participants reported increased drinking during the study period. This reinforces the notion that stress is a significant factor in BDNF and alcohol relationships [127].

Finally, Neupane and colleagues [130] examined potential associations between serum BDNF and lifetime diagnosis of major depression, recent depression symptoms, or AUD severity. Their participants were abstinent male AUDs with an average of 34 days of sobriety at the time of testing. While the researchers found no association between serum BDNF and lifetime diagnosis of major depression, BDNF was negatively correlated with participants' number of recent depressive symptoms. Further, participants with more severe AUD symptoms or a previous binge-drinking pattern tended to have higher levels of BDNF at the time of testing, although duration of abstinence

from alcohol was not correlated with BDNF level [130].

Together, the results from studies of peripheral BDNF protein levels in AUD and other drinking populations suggest that BDNF levels may differ between drinking groups, and may fluctuate during alcohol withdrawal and continued abstinence. Changes in peripheral BDNF levels may parallel neuroplastic modifications [71] that occur with chronic alcohol consumption and recovery [96]. Additional studies are needed to determine the nature of the relationship between peripheral BDNF levels and neuronal changes during the critical period of early abstinence and AUD treatment.

4. Discussion and Conclusions

There is no doubt that BDNF is one of the key factors in neuroplasticity [55]. In recent years, the alcohol research field has gained an increasing appreciation for the involvement of neuroplasticity in risk or resilience to addiction, and AUD has been characterized as a disease of maladaptive plasticity [24–26]. Animal research suggests that BDNF may directly influence the transition from light to compulsive drinking through actions in the dorsal striatum and prefrontal cortex [1]. It is also likely that BDNF plays a key role in stress and alcohol interactions [28]. There has been a recent increase in the number of studies examining these issues in human participants. However, the results of these human studies have been more contentious than those derived from animal models. For example, although meta-analyses of genetic association studies suggest that the *BDNF* Val^{66}Met polymorphism may not be linked to the development of AUD [61,62], other researchers have found greater AUD vulnerability and poorer long-term prognoses among abstinent AUDs who are Met carriers (See Table 1). Among studies examining peripheral levels of BDNF protein in serum or plasma of human participants, the majority of these have noted some relationship between BDNF levels and drinking histories or trajectories, often in relation to other factors such as stress, anxiety or depression. In the majority of these studies, higher peripheral BDNF levels appear to confer resilience, although Miguez-Burbano and colleagues [126] describe an inverted U- or J-shaped relationship between BDNF levels and neuropsychological performance (See Table 2). As in the studies of genetic association, some counterintuitive findings have been noted, and additional research is needed to clarify the relationship between peripheral BDNF and CNS neuroplasticity in human participants with AUD.

The differential findings across studies of human participants are undoubtedly related to the greater variability that is inherent in this type of research and influential factors that may be overlooked in study designs or statistical models. Human beings are extremely complex. The studies summarized in Tables 1 and 2 suggest that race, ethnicity, sex and gender, co-morbid medical history, and use of other prescribed or abused substances are all factors that should be addressed in the design or analyses of projects examining BDNF and addiction. Further, studies that examine SNPs in isolation or use peripheral protein levels from blood samples collected at a single time point may fail to account for the incredible complexity of gene × gene, gene × environment and environment ×

environment interactions that exist in human populations [50]. These are issues of ongoing concern that have been addressed in numerous recent publications, in which researchers have called for additional thoughtful discussion about which strategies to pursue in order to have the greatest impact on the field of alcohol research [48,51,131,132].

In particular, the characterization of the environmental component in studies of human gene × environment interactions has often been surprisingly limited [131]. Heath and colleagues [131] suggest that future studies could employ "big-data" approaches by including appropriate questions in aggregate databases to capture information on neighborhood environments that could be used to increase consistency across studies. Big-data approaches may also address the important issue of sufficient sample size in studies of gene × environment interactions [133]. The possibility of false discoveries due to type I error is a recognized consequence of low power, and may account for some of the inconsistency of outcomes in these types of studies [133]. Finally, epigenetic approaches have been described as a key missing link in the etiology of addiction [51]. Cecil and colleagues [51] note that longitudinal modeling of environmental and epigenetic data could be used to identify windows of vulnerability when at-risk individuals might benefit most from preventive interventions.

4.1. Interventions to Promote Resilience

In a recent review of the emerging neuroscience of resilience, Srinivasan and colleagues [134] observed that individuals have the capacity to enhance their resilience to stress and addiction through behavioral and pharmacological interventions. Given the proposed role for BDNF in resilience to addiction, it is logical to suggest that strategies that enhance BDNF and neuroplasticity in relevant brain areas might have a positive effect on individuals at risk for development of AUD or those in recovery from AUD. As noted recently by Davidson and McEwen [57], exercise [135], cognitive therapy [136,137] and meditation [138] have all been shown to induce plasticity-related alterations in the brain and to support positive behavioral outcomes for a variety of human conditions. For instance, long-duration, moderate exercise and heavy exercise appear to have a positive effect on signaling and trafficking of the BDNF receptor TrkB, which facilitates neuroplasticity and long-term potentiation in the hippocampus [139], an area of the brain that has been implicated in cognitive recovery during the first seven months of abstinence in AUDs ([97], see Table 1). Other activities which decrease stress, and promote pro-social behavior and well-being may lead to measurable improvements in brain structure and function, such as increases in prefrontal activation and decreases in amygdala activation with corresponding changes in brain volume in these areas [57]. This is a particularly exciting result, as animal studies have directly implicated both of these brain areas in BDNF and alcohol interactions that influence the development of addiction [1]. A more holistic approach to the study of factors influencing resilience to AUD, encompassing families, communities, and other sources of enrichment (e.g., [3]) may be promising avenue for future research.

Table 1. Studies using genetic or epigenetic approaches to study *BDNF* and alcohol in human participants (2010–2016). *

Authors	Population and Study Design	Outcome
Grzywacz et al., 2010 [105]	Participants from AUD families were 141 (125 male) Caucasians from northwest Poland with M_{age} = 34 years. Comparison group was 138 HCs matched on ethnicity and gender. Participants were *BDNF* genotyped (rs6265).	Authors found no association between the *BDNF* $Val^{66}Met$ gene polymorphism and AUD.
Shin et al., 2010 [83]	Participants were Korean men aged ≥ 65 years: 68 AUDs and 232 HCs. Participants were *BDNF* genotyped (rs6265).	AUDs had higher *BDNF* Met/Met and Val/Met allele frequencies compared to HCs.
Colzato et al., 2011 [84]	Participants were 98 HCs (44 male). All were Caucasians from The Netherlands. They were *BDNF* genotyped (rs6265). Also measured were alcohol use, cold pressor response, anxiety, cortisol, blood pressure, and heart rate. Met/Met were merged with Val/Met for comparison to Val/Val.	Met carriers had higher anticipatory stress responses, anxiety, and alcohol consumption compared to Val/Val.
Hill et al., 2011 [88]	Participants were 71 adolescent/young adult high-risk offspring (37 male) of multiplex AUD families from the United States (race/ethnicity not specified). Comparisons group was 60 low risk HCs (28 male) with no family history of AUD. Groups were matched on demographics and IQ. Study included MRI for cerebellar volume and genotyping for *BDNF* (rs6265) and *GABRA2*.	Offspring of AUDs had greater total cerebellar volume and total gray matter compared to HCs. Significant effects for *GABRA2* or *BDNF* alone were not seen, however, gray matter volumes were associated with an interaction between *GABRA2* and *BDNF* allelic variants.
Muschler et al., 2011 [106]	Participants were 239 male and female AUDs (gender distribution not specified) and 99 HCs from ongoing studies in Germany. Participants were *BDNF* genotyped (rs6265).	Authors found no differences in *BDNF* allele frequencies in AUDs compared to HCs. There were no associations between genotype distribution and scores on an obsessive-compulsive drinking scale.

Su et al., 2011 [85]	Participants were 382 AUDs without depression (AD-nD), 166 AUDs with depression (AD-D) and 312 HCs. Participants were Chinese males. *BDNF* was genotyped (rs6265) and treatment response to sertraline was monitored over an 8-week period.	Met allele frequency was higher in AD-Ds compared to HCs and AD-nDs. Among AD-Ds, Met allele carriers had better response to sertraline treatment.
Benzerouk et al., 2013 [107]	Participants were healthy adult children of AUDs (HACA, n = 46; 11 males) and 82 HCs (19 males). Participants were Caucasians recruited in France. *BDNF* was genotyped (rs6265) and neuropsychological tests were administered.	HACAs and HCs did not differ on allele distributions of *BDNF*. A group by allele interaction was observed. In the HACA group, Met carriers had poorer executive function scores, suggesting that the Val/Met polymorphism may contribute to AUD risk through lower executive function.
Mon et al., 2013 [96]	Participants were 62 AUDs (53 male) and 17 age-matched HCs (gender distribution not specified) with M_{age} = 48 years; 84% were White. MRIs were obtained at 6 days abstinent and 34 days abstinent for AUDs and at baseline and 7 months for HCs. Neuropsychological tests were completed at both time points and participants were *BDNF* genotyped (rs6265).	Among AUDs, Val/Met and Val/Val participants had similar regional brain volumes at both time points. Gray matter volume increases were seen in Val/Val participants, and white matter increases were seen in Val/Met participants. Gray matter increases were associated with improvements in neurocognitive measures over time.
Nedic et al., 2013 [109]	Participants were 675 AUDs (549 male) and 914 HCs (655 male). All were ethnically homogenous Caucasians of Croatian origin. Participants were *BDNF* genotyped (rs6265).	Authors found no association between *BDNF* allelic variants and AUD or alcohol-related phenotypes
Serretti et al., 2013 [110]	Participants were drawn from 1336 mood disordered patients enrolled in a European multicenter study and treated with antidepressants for at least 4 weeks. Participants were genotyped for *BDNF* (rs6265) and *CREB1* and completed diagnostic instruments and assessment for alcohol dependence. One analysis compared these variables in patients with (n = 105, 80 female) and without (n = 517, 361 female) early parental loss (EPL). Another	Authors found no gene main effects or gene by environment interactions for *BDNF* or *CREB1*. Compared to those without PA, patients with a history of PA had higher levels of alcohol dependence and disorders related to stress and anxiety. EPL effects on alcohol abuse were rendered non-significant by statistical correction.

	analysis compared patients with (n = 143, 117 female) and without (n = 1185, 821 female) history of physical abuse (PA).	
Dalvie et al., 2014 [111]	Participants were 80 adolescent AUDs and 80 age- and gender-matched HCs. All were English- and Afrikaans-speaking and recruited from schools in the Cape Flats region of Cape Town, South Africa. Participants were *BDNF* genotyped (rs6265) and completed a childhood trauma questionnaire. MRIs were obtained from a subset (58 AUDs and 58 HCs). One set of analyses compared all genotype groups, and another merged Met/Met with Val/Met for comparison to Val/Val.	After correction for multiple comparisons, no significant associations were found between *BDNF* allelic variants, brain volumes, and AUD.
Pecina et al., 2014 [98]	Participants were 72 HCs (34 female) with M_{age} = 26 years and alcohol consumption < 5 drinks/week; 75% were Caucasian, and race/ethnicity was addressed in statistical analyses. Participants were *BDNF* genotyped (rs6265; Met/Met combined with Val/Met and compared to Val/Val), completed an fMRI task of monetary incentive delay and a PET task measuring striatal dopamine neurotransmission during a stress-pain challenge and placebo analgesic.	Met carriers had greater brain response to anticipation of monetary losses, greater baseline D2/3 receptor availability and greater pain-stress-induced dopamine release in the nucleus accumbens. Met carriers showed no changes in brain activation in response to monetary gains, and showed a blunted dopamine response to analgesic placebo.
Cheah et al., 2014 [86]	Participants of European descent were categorized into a schizophrenic group (n = 157; 23 female, M_{age} = 36), a second schizophrenic replication group (n = 235; 70 female, M_{age} = 44 years), an AUD group without co-morbid schizophrenia (n = 231; 74 female, M_{age} = 41 years), and HCs (n = 225; 121 female, M_{age} = 45 years). Two *BDNF* SNPs (rs6265 and rs7103411) were genotyped.	In the replication sample, both *BDNF* SNPs were associated with comorbid alcohol dependence and risk taking behavior after drinking (highest in rs6265 Met/Met). In males, both *BDNF* SNPs were associated with AUD. In females, *BDNF* SNPs were associated with behavioral measures reflecting repetitive alcohol consumption (highest in rs6265 Met/Met). These associations were only noted among schizophrenic participants and not in AUDs without schizophrenia (following

		correction for multiple testing).
Nees et al., 2015 [87]	Participants were 530 Caucasian European adolescent HCs (248 female). Participants were *BDNF* genotyped (rs6265) and completed an fMRI monetary incentive delay task at two time points. M_{ages} of participants were 14 years at baseline and 16 at follow-up. Alcohol consumption and orientation toward alcohol were measured at each time point. Met/Met and Val/Met were combined for comparison to Val/Val.	Met carriers with high levels of alcohol use had a lower reward reactivity in the putamen and were more likely to orient toward alcohol and to drink alcohol two years later.
Heberlein et al., 2015 [112]	Participants were 99 male AUDs (M_{age} = 42 years) and 33 age-matched HCs recruited in Germany. Alterations in the methylation of the *BDNF* gene and serum BDNF levels were measured during alcohol withdrawal (days 1, 7 and 14), and participants were followed for self-reported duration of alcohol abstinence before relapse.	On days 1 and 7, methylation of the *BDNF* promoter was increased in AUDs relative to the baseline of HCs. Methylation was successively decreased at each time point during alcohol withdrawal in the AUDs and mirrored decreases in depression over time. Participants with lower methylation levels at day 14 were less likely to remain abstinent from alcohol versus those who had higher methylation levels. BDNF serum levels were not statistically associated with methylation of the *BDNF* promoter and did not differ between AUDs and HCs.
Hoefer et al., 2014 [97]	Participants were 121 AUDs (9 female; M_{age} = 52; 76% Caucasian) in treatment and 35 HCs (3 female; M_{age} = 46; 71% Caucasian). Participants were *BDNF* genotyped (rs6265) and underwent quantitative MRI and neurocognitive assessments. AUDs were tested at approximately 7, 33 and 213 days of abstinence. HCs were tested at baseline and approximately 290 days later. Val/Met and Met/Met participants were combined for comparison to Val/Val.	At all time-points, AUDs had smaller hippocampi than HCs. At one month of abstinence, hippocampal volume correlated with neuropsychological decrements in AUDs. Hippocampal volume increases were observed over the 7 months of abstinence in Val/Val AUDs only, and this group also had larger hippocampi at 7 months compared to Met carriers.

Benzerouk et al., 2015 [108]	Participants were 35 female HACAs (M_{age} = 36 years) and 63 HCs (M_{age} = 35 years). All were White and recruited in France. Participants were *BDNF* genotyped (rs6265) and completed personality questionnaires. Val/Met and Met/Met were combined for comparison to Val/Val.	HACAs and HCs did not differ on genotype distributions. Overall, Val/Val participants had lower levels of the reward dependence personality trait compared to Met carriers. There was also an allele by group interaction. In the Val/Val group, HACAs had lower reward dependence compared to HCs. This difference was not significant for Met carriers, whose reward dependence scores were more similar to Val/Val HCs.
Chen et al., 2015 [99]	Participants were 315 (220 male) heavy drinkers (M_{age} = 32 years; 45% Caucasian) recruited from the Southwest United States. This study investigated relationships between genome-wide SNPs and alcohol cue-elicited brain activations.	For drinkers with more severe AUD symptoms, the genetic component derived from the *CREB-BDNF* pathway was associated with an imaging component reflecting hyperactivation in the precuneus, superior parietal lobule, and posterior cingulate.

*AUDs = participants with alcohol use disorder; HCs = healthy control participants without alcohol use disorder; HACAs = healthy adult children of participants with alcohol use disorder; M_{age} = mean age; SNPs = single nucleotide polymorphisms.

Table 2. Studies measuring peripheral BDNF protein and alcohol-related variables in human participants (2010–2016).*

Authors	Population and Study Design	Outcome
Heberlein et al., 2010 [118]	Participants were 81 male AUDs (M_{age} = 44 years) admitted for detoxification and 41 male HCs (M_{age} = 37 years). All were German. BDNF serum levels were monitored on days 1, 7 and 14 of alcohol withdrawal in AUDs. Fasting blood samples were drawn between 8 and 10 a.m.	Serum BDNF levels did not differ in AUDs versus HCs and did not change significantly during alcohol withdrawal. BDNF levels were negatively associated with alcohol withdrawal severity on day 1.
Costa et al., 2011 [119]	Patients were 101 AUDs (84 male; M_{age} = 45 years) and 41 HCs (28 male; M_{age} = 43 years). Participants were recruited in France. AUDs were studied at the time of hospitalization for alcohol withdrawal (time 1) and at a 6-month follow-up (time 2). Serum BDNF levels were measured, along with mood questionnaires. Fasting blood samples from AUDs were collected at the time of admission at time 1 and time 2. HCs data were derived from routine donor blood samples.	AUDs and HCs were equivalent on serum BDNF at time 1. Abstinent and non-abstinent AUDs were equivalent on BDNF at time 1, and BDNF levels increased over time in both AUD groups. However, at the 6 month-follow-up, BDNF was higher in abstinent AUDs relative to non-abstinent AUDs, and higher in abstinent AUDs versus HCs.
Meng et al., 2011 [63]	Participants were 14 male AUDs (8 White; M_{age} = 40 years; 4-6 weeks abstinent) and 10 male HCs (6 White; M_{age} = 37 years). Participants were recruited from the South Central United States. BDNF and NPY (from serum) and ACTH and cortisol (from plasma) were measured before and after a psychological stressor. Basal samples were collected between 6:45 and 6:55 p.m., and post-stress samples were obtained between 7:20 and 7:30 p.m.	AUDs and HCs did not differ on basal or post-stress measures. BDNF, NPY, ACTH and cortisol were all significantly increased by the stressor in both groups. Basal and delta peak concentrations of BDNF, NPY, ACTH and cortisol were not significantly correlated in either AUDs, or HCs.
Huang et al., 2011 [121]	Participants were 65 inpatient AUDs with (n = 25; 25 male; M_{age} =	Serum BDNF was highest in the control group, followed by the

	46 years) and without (n = 40; 36 male; M_{age} = 41 years) delirium tremens (DTs) during detoxification. The comparison group was 39 HCs (36 male; M_{age} = 43 years). Participants were recruited in Taiwan. Serum BDNF was sampled on day 1 and day 7 of alcohol withdrawal in AUDs. For AUDs, day 1 blood samples were collected on the next morning following admission (between 8–9 a.m.).	non-DT group and was lowest in the DT group. By day 7 after alcohol withdrawal, BDNF had increased significantly in both AUD groups. On day 7, BDNF of non-DT AUDs was comparable to controls, while the improved DT group BDNF levels remained lower than the other groups.
Zanardini et al. 2011 [120]	Participants were 37 AUDs (25 male; M_{age} = 50) and 37 HCs (25 male; M_{age} = 50). Participants were recruited in Italy. Blood samples were collected between 8 and 9 a.m. Both serum and plasma BDNF were assayed.	Plasma and serum BDNF levels were correlated in the entire sample (AUDs plus HCs). AUDs and HCs did not differ on BDNF plasma levels, however, BDNF serum levels were lower in AUDs compared to HCs. This group difference was not statistically related to blood alcohol concentration at intake or treatment with prescription medications.
D'Sa et al. 2012 [68]	Participants were 16 AUDs (7 male; M_{age} = 39 years; 9 Caucasian), 16 HCs (8 male; M_{age} = 29 years; 10 Caucasian) recruited from the Northeastern United States. Blood samples were collected on 3 consecutive days in a controlled, inpatient environment between 8 and 8:30am.	There were no significant day-to-day differences in serum or plasma BDNF. Average serum BDNF was higher for AUDs compared to HCs. No significant differences were noted for plasma BDNF levels between AUDs and HCs.
Kim et al., 2013 [125]	Participants were 64 abstinent male AUDs (M_{age} = 48 years) with normal glucose tolerance (NGT; n = 30), pre-diabetes mellitus (pre-DM; n = 26), or diabetes mellitus (DM; n = 8). Participants were recruited from South Korea. Blood samples were taken upon admission to a treatment program and after 30 days of treatment. Pre- versus post-treatment changes in plasma BDNF and other biomarkers were measured.	Only the pre-DM group showed a significant increase in BDNF after 30 days of treatment. Further, the increased BDNF in the pre-DM group was significantly greater than that in the NGT group.

Kohler et al., 2013 [122]	Participants were 15 AUDs (11 males; M_{age} = 49 years) and 15 HCs (11 males; M_{age} = 49 years). Participants were German. Serum BDNF was measured in AUDs during alcohol withdrawal and over time (days 1, 2, 3, 4, 8 and 14). Fasting blood samples were drawn between 8 and 10 a.m.	At admission for acute alcohol withdrawal, serum BDNF and NGF were decreased in AUDs relative to HCs. In AUDs, NGF decreased significantly from day 3 to day 14. After an initial decrease, BDNF levels in AUDs showed a tendency to increase between day 3 and day 14.
Miguez-Burbano et al., 2014a [126]	Participants were 400 people living with HIV. By NIAAA definition, 198 were hazardous alcohol users (132 male; M_{age} = 43 years; 70% African American) and 199 were non-hazardous alcohol users (120 male; M_{age} = 41 years; 66% African American). Fifty HIV seronegative HCs were also tested (demographics not available). Participants were recruited from the Southeastern United States. Neuropsychological assessments were administered, and plasma BDNF was assayed from fasting blood samples.	BDNF was negatively correlated with drinks per day of beer and liquor, but not wine. BDNF level had an inverted U- or J-shaped relationship to neuropsychological performance, where participants with intermediate BDNF levels exhibited the highest test scores. Multivariate analyses showed hazardous alcohol use and BDNF were significant predictors of HIV-associated neurocognitive disorders.
Miguez-Burbano et al., 2014b [127]	Participants were 400 people living with HIV, divided into 200 hazardous alcohol users by NIAAA definition (134 male; M_{age} = 43 years; 70% African American) and 200 non-HAU (120 male; M_{age} = 41 years; 66% African American). Participants were recruited from the Southeastern United States. Fasting plasma BDNF, alcohol use and mood were studied longitudinally.	Participants who reported feeling nervous and stressed were more likely to have lower BDNF levels. There were three longitudinal drinking trajectories: 1) increased drinking, 2) constant drinking, and 3) decreased drinking. Women in trajectories 1 and 2 had higher stress and lower BDNF than those in trajectory 3. Men in trajectory 1 had lower BDNF levels and marginally higher stress compared to other groups.
Lhullier et al., 2015 [114]	Participants were 795 (346 male; M_{age} = 26 years) individuals categorized as moderate to severe AUD based on CAGE ≥ 2 (n = 77; 50 male) or HCs based on CAGE < 2 (n = 718). Participants were recruited in Brazil. Serum BDNF was measured	There was no statistically significant difference between AUDs and HCs. AUDs had marginally higher BDNF levels versus HCs (p < .07). There were no gender differences in BDNF.

	between 8 and 11 a.m.	
Neupane et al., 2015 [130]	Participants were 152 abstinent male AUDs (M_{age} = 36 years) recruited in Nepal. The study examined possible associations between serum BDNF and major depression, recent depression symptoms, and AUD severity.	BDNF was not associated with major depression diagnosis but was negatively correlated with number of recent depressive symptoms. Patients with more severe AUD or previous binge-pattern drinking had higher BDNF, but duration of abstinence was not correlated with BDNF.
Reynolds, Mueller, and MacLaren, 2015 [123]	Participants were 24 AUDs in severe alcohol withdrawal who were randomized to dexmedetomidine high dose (HD, n = 8, 7 male, M_{age} = 50; 88% Caucasian), low dose (LD, n = 8, all male, M_{age} = 47; 63% Caucasian), or placebo (n = 8, 7 male, M_{age} = 51; 50% Caucasian). Blood was collected at 0 (T0), 48 (T48), and 96-120 (T96) hours after starting the drug. Plasma drug levels, BDNF, and other biomarkers were measured.	BDNF levels were not statistically different among groups and did not change significantly over time. T0 values of BDNF were inversely associated with the need for mechanical ventilation before study enrollment. Concentrations of BDNF and epinephrine were positively correlated throughout the study.
Zhang et al. 2016 [115]	Participants were 191 healthy Chinese males (M_{age} = 43 years): 47 cigarette smokers, 31 chronic alcohol users, 58 combined cigarette smokers and chronic alcohol users, and 55 non-smokers and non-alcohol users. Serum BDNF was measured, along with alcohol and nicotine use and neuropsychological tests.	BDNF levels did not differ among the four groups. BDNF was not correlated with MAST or neuropsychological test scores.

*AUD = alcohol use disorder; AUDs = participants with alcohol use disorder; HCs = healthy control participants; NGF = nerve growth factor; NPY = neuropeptide Y; CAGE questionnaire [116]; MAST = Michigan Alcohol Screening Test [117].

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Conflict of Interest

The authors have no conflicts of interest.

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