HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2019 January 28.

Published in final edited form as:

J Alzheimers Dis. 2018 ; 65(4): 1055–1064. doi:10.3233/JAD-180585.

The Influence of the Val66Met Polymorphism of Brain-Derived Neurotrophic Factor on Neurological Function after Traumatic Brain Injury

John D. Finan*, **Shreya V. Udani**, **Vimal Patel**, and **Julian E. Bailes**

Department of Neurosurgery, NorthShore University Health System, Evanston, IL, USA

Abstract

Functional outcomes after traumatic brain injury (TBI) vary widely across patients with apparently similar injuries. This variability hinders prognosis, therapy, and clinical innovation. Recently, single nucleotide polymorphism (SNPs) that influence outcome after TBI have been identified. These discoveries create opportunities to personalize therapy and stratify clinical trials. Both of these changes would propel clinical innovation in the field. This review focuses on one of most well-characterized of these SNPs, the Val66Met SNP in the brain-derived neurotrophic factor (BDNF) gene. This SNP influences neurological function in healthy subjects as well as TBI patients and patients with similar acute insults to the central nervous system. A host of other patient-specific factors including ethnicity, age, gender, injury severity, and post-injury time point modulate this influence. These interactions confound efforts to define a simple relationship between this SNP and TBI outcomes. The opportunities and challenges associated with personalizing TBI therapy around this SNP and other similar SNPs are discussed in light of these results.

Keywords

Brain-derived neurotrophic factor; precision medicine; single nucleotide polymorphism; traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) causes approximately 56,000 deaths, 282,000 hospitalizations, and 2.5 million emergency room visits in the United States every year [1]. Survivors of TBI may have prolonged or permanent deficits in social, emotional, cognitive, and motor function, depending on the severity of the injury and the location of the lesion. Functional outcomes vary widely across patients with TBI. This is true for both mild and severe TBI at both acute and chronic time scales. Several demographic and environmental factors are known to influence functional TBI outcomes, including age, gender, and history of TBI [2–4]. In addition, evidence is accumulating that genetic factors influence TBI outcomes [5–8].

*Correspondence to: John D. Finan, NorthShore University Health System Research Institute, 1001 University Place, Evanston, IL 60201, USA. Tel.: +1 224 364 7578, jfinan@northshore.org.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-0585r2).

Understanding these genetic factors is perhaps the most important challenge in modern TBI research, with ramifications for prognosis, therapy, and clinical trial design. Prognosis is exceptionally difficult in TBI [9]. Some patients continue to make functional gains steadily for years after a severe TBI while others do not. Also, some patients decline several years after exposure to mild head impacts while others do not [10]. A genetic factor that partially explained these differences would be valuable to patients and clinicians attempting to plan around likely future neurological function. On the therapeutic front, genetic factors that influence pathology may also influence how that pathology responds to therapy. An understanding of these influences may enable more effective personalized therapy. On a related note, it is increasingly clear that future trials of TBI therapies must be stratified to have any chance of success. More than 30 phase III clinical trials of candidate therapeutics for TBI have been conducted and all have failed [11]. The consensus in the research community is that TBI trials fail in part because of the heterogeneity of the patient population [12]. This heterogeneity creates a signal-to-noise problem: the more outcomes vary within treatment groups, the more treatment effect is required to achieve statistical significance. The solution is to stratify patients according to likely outcome and a genetic outcome predictor would be invaluable in this regard. In order to be useful, the genetic predictor must be common and must exert a powerful influence on TBI outcomes. The Val66Met single nucleotide polymorphism (SNP) of brain-derived neurotrophic factor (BDNF) occurs in about 30% of the U.S. population [13]. It has been shown to influence neurological function in healthy subjects [14], TBI patients [15, 16], and stroke patients [17, 18]. In this review, we summarize what is known about how this SNP influences TBI outcomes and explore its potential to inform prognosis, therapy, and clinical trial design.

BDNF AND THE VAL66MET SNP

The complex architecture of the human nervous system is established and maintained by local interactions between specialized neurons and their targets. Neurons require chemical signals called neurotrophins supplied by their targets for survival [19]. This simple mechanism organizes the nervous system during development and maintains this organization in adulthood. Neurons are generated in great excess during embryogenesis. However, only those neurons that enervate an appropriate target receive the neurotrophins they need to survive [20] so supernumerary neurons apoptote. In an analogous way, neurotrophins regulate the branching of surviving neurons and the formation of synapses so that neural circuits adapt to the requirements of their targets [21]. There are four neurotrophins: neural growth factor (NGF), BDNF, neurotrophin 3 (NT-3), and neurotrophin-4/5 (NT-4/5). Certain classes of neuron depend on certain neurotrophins for survival while remaining indifferent to others. This selectivity dynamically organizes neurons around their targets. BDNF plays a prominent role in hippocampal functions including learning and memory [22] because it regulates long term potentiation (LTP) [23]. Suppressing BDNF in mice by genetic knock out [24] or RNA interference [25] impairs performance in learning and spatial memory tasks. BDNF is well suited to its role in LTP because it is released in an activity-dependent fashion while all other neurotrophins are released at a constant rate [26]. Electrical stimulation triggers secretion of BDNF which then

promotes synapse formation and enhances synaptic transmission. These changes are the cellular basis of LTP.

When translated, the BDNF molecule contains three important domains: the signal peptide, the pro domain, and the functional BDNF molecule. The signal peptide sequesters the molecule in the endoplasmic reticulum and is then removed [27]. Subsequently removing the pro-domain produces mature BDNF. The pro-domain must interact with the sortilin receptor in the Golgi wall to allow proper folding of the mature domain. Proper folding allows a motif in the mature domain to connect to carboxypeptidase E, and then BDNF is sorted into large dense core vesicles to be released via the regulated secretory pathway [28]. The pro-domain may be removed intracellularly in the trans-Golgi network by enzymes such as furin [29] or extracellularly by enzymes such as plasmin [30] or matrix metalloproteinase 7 [30]. Mature BDNF and pro-BDNF function antagonistically to regulate neuroplasticity [30]. Mature BDNF binds to the tyrosine related kinase receptor (TrkB) to activate pathways involved in LTP [31], cell survival [32], and dendrite formation [33]. ProBDNF acts via the p75 neurotrophin receptor (p75NTR) and sortilin to activate pathways involved in long term depression [34], apoptosis [35], and reducing dendritic complexity [34].

There are several hundred known polymorphisms of the BDNF gene [36]. Of these, Val66Met (also known as rs6265) is the most widely studied. It is a SNP at nucleotide 196 that causes the substitution of the typical valine with methionine at codon 66 (Val66Met). About 30% of the population is at least heterozygous for this SNP in the United States [13], but this proportion varies widely across global populations [13, 37]. Val66Met occurs in the portion of the BDNF gene that encodes the pro-domain. Therefore, it does not alter the function of the mature protein. For example, the Val66Met allele does not modulate the neurotrophic effect of mature BDNF on PC12 cells in culture [14]. However, it does alter intracellular sorting and secretion of the protein. Specifically, the SNP occurs in a portion of the prodomain that interacts with sortilin [38]. BDNF proteins with methionine at codon 66 (mBDNF) do not sort from the Golgi into secretory vesicles as well as BDNF proteins with valine at codon 66 (vBDNF) [14]. As a result, mBDNF tends to accumulate in the soma while vBDNF accumulates in punctate vesicles in the dendrites. Neurons secrete vBDNF but not mBDNF in response to activity. Activity-dependent release of BDNF drives LTP [21] so Met carriers have impaired neuroplasticity [14]. Hippocampal volume has been reported to be reduced in Met carriers by several investigators [39–41], although this conclusion remains controversial [42]. The Met allele is also associated with reduced grey matter volume in other brain structures including the amygdala [43] and dorsolateral prefrontal cortex [40]. The Val66Met SNP has functional consequences in healthy subjects. Human Met carriers generally have worse episodic memory than matched Val carriers [14] and show less activation of the hippocampus during memory tasks as measured using magnetic resonance imaging techniques [44]. Met carriers have inferior motor function and motor learning compared to Val/Val subjects [45]. While the SNP is generally deleterious in healthy subjects, benefits emerge in some disease states, including TBI.

VAL66MET IN TBI

The Met allele partially protects patients with severe TBI. In a study of male Vietnam veterans with penetrating TBI, TBI impaired executive function among Val/Val individuals but not among Met carriers [16]. In the same cohort, Val/Met individuals had better general intelligence, working memory, and processing speed than Val/Val individuals after TBI, although there was no difference between these groups before TBI [15]. It is worth noting that brain function was assessed in these individuals at very long-term time points, up to 40 years post injury. Met carriers secrete less of both mature BDNF and proBDNF in response to activity. The Met allele is protective after severe TBI, suggesting that the apoptotic action of proBDNF overcomes the survival signaling of mature BDNF in this context. Under these circumstances, impaired secretion would become neuroprotective [15, 16]. The Val allele may also aggravate the deleterious effects of proBDNF. *In vitro*, the Val form of proBDNF inhibits LTP and promotes tau hyperphosphorylation while the Met form does not [46]. Another possibility is that the Met allele improves long term outcomes because it shifts the excitatory / inhibitory balance of the brain toward excitation. The mouse model of the Val66Met SNP [47] has not been subjected to experimental TBI, to our knowledge, but it has been subjected to experimental stroke. The Met allele led to worse short term motor outcomes after stroke in this mouse model [48], due to inferior neuroplasticity and angiogenesis, but better long term outcomes [49], due to higher excitability in the striatum opposite the lesion.

The protective effect of the Met allele in severe TBI depends on age at chronic time points. A study of BDNF SNPs in severe TBI tested the hypothesis that the Met allele of Val66Met in conjunction with another putative high-risk polymorphism of BDNF, rs7124442, would increase the risk of death. In fact, the putative high-risk alleles reduced the risk of death at short time points (<7 days). At long time points (8–365 days), an interaction with age emerged. The Met allele along with the other hypothetical risk allele did indeed increase risk of death for patients under 45 years of age. However, for those over 45, these alleles were again protective [50]. Note that long term death rates were higher overall in the over 45 age group. This age dependence may arise because the balance of receptors that mediate pro-survival and pro-apoptotic effects of BDNF changes with age [51, 52]. Severe TBI uncouples the autonomic and cardiovascular systems [53] so the role of the Val66Met SNP in autonomic function is also important. Healthy Met/Met individuals have altered sympathovagal balance and less parasympathetic activity compared to Val/Val individuals [54]. Also, healthy Met/Met individuals had less cardiovascular reactivity to acute psychosocial stress than Val/Val individuals [55]. However, the effect of the Val66Met SNP on autonomic function after TBI is currently unknown.

The influence of the Val66Met SNP in mild TBI depends on gender and the post-injury time point. Female concussed athletes carrying a Met allele performed significantly better on assessments of olfactory function than their Val/Val counterparts [56]. Participants in this study were assessed an average of 27 months after their concussion. On the other hand, tests of mood conducted at 1 and 6 weeks post-injury in another cohort of patients with mild TBI found more depression and anxiety in Met carriers. The effect on depression was modulated by gender, being significant at both time points in males but only at the first time point in

females [57]. Mild TBI increased depressive rumination and reduced cognitive flexibility among Met carriers but not among Val/Val homozygotes. Unfortunately, no data about the time of injury was collected in this study [58]. In this context, it is worth noting that Met allele carriers are more prone to rumination than Val/Val homozygotes in the absence of TBI [59] and that this trend becomes more pronounced under stress in Met homozygotes [60]. The Val66Met SNP lowered performance among both injured subjects and uninjured controls in a study of reaction times after mild to moderate TBI (Glasgow Coma Score 9–15) but this effect did not interact with TBI. However, several other polymorphisms of BDNF did influence the effect of TBI in a gender dependent fashion with more influence in males [61]. Table 1 summarizes what is known about the influence of the SNP on acute and chronic TBI pathology in males and females for mild TBI.

In addition to modulating the pathology of TBI, the Val66Met SNP modulates the risk of sustaining a TBI according to two consistent but small studies in human subjects [62, 63]. The reasons for this trend may be behavioral or physiological or both. Behaviors modulated by this SNP include addiction [64, 65], aggression [66, 67], participation in high risk sports [68], and hyper-active impulsivity (in people with attention deficit hyperactivity disorder) [69]. Met carriers have greater hostility and aggression, supporting a behavioral explanation for this trend [63]. However, larger human studies are needed to fully explain this phenomenon [70].

VAL66MET AND NEURODEGENERATION

One of the most important and mysterious questions in modern TBI research is how does TBI influence the likelihood of subsequent dementia. Striking evidence of early-life tauopathy has been discovered in athletes [10] and military veterans [71] with a history of repeated mild TBI. The unique spatial distribution of this tauopathy defines it as a distinct neuropathological entity: chronic traumatic encephalopathy [72]. Unfortunately, the prevalence of this condition is currently unknown. TBI also increases the risk of Alzheimer's disease (AD) [73, 74]. A recent study of a large population of U.S. military veterans found that all forms of TBI increased the risk of dementia with hazard ratios ranging from 2.36 for mild TBI without loss of consciousness to 3.77 for moderate to severe TBI [75]. The apolipoprotein E (APOE) gene exists in 3 isoforms, one of which, APOE s4, increases the risk of AD [76]. TBI amplifies the impact of APOE s4 on AD risk. One study reported that APOE s4 doubled the risk of AD absent a history of TBI but that the combination of APOE s4 with TBI history increased the risk of AD 10-fold [77]. Therefore, it is possible that other genetic risk factors for AD also synergize with TBI. The Val66Met SNP has been investigated as a genetic risk factor for AD. Early studies found that Met carriers had lower incidence of the disease [78] and, in the case of Met homozygotes, better reasoning skills in late life [79]. However, subsequent studies failed to replicate these findings [80, 81]. This inconsistency may arise in part from interactions of the Val66Met SNP with other factors. For example, the effect of the Val66Met SNP on phenotypes associated with AD was age dependent, with Met carriers being protected in late life but more susceptible in early life [82]. Gender also moderates the effect. The Met allele increased risk of AD in women but not in men in a Japanese cohort [83]. While both TBI and the Val66Met SNP influence the

risk of dementia, there is as yet no published evidence demonstrating synergy between them. Nevertheless, the possibility of such a synergy merits investigation.

VAL66MET AND THERAPY

Determined efforts to discover a therapy that improves outcomes for all TBI patients have not yet succeeded. Therefore, the more modest goal of discovering a therapy that benefits a subset of TBI patients deserves attention. The Val66Met SNP may define such a subset because it has been shown to modulate the effectiveness of neurological drugs in a number of settings. For example, olanzapine for the treatment of schizophrenia is less effective in Met carriers [84]. Memantine was more effective as an add-on therapy for depressive symptoms in heterozygous bipolar disorder patients than in Val/Val homozygotes [85]. However, most of the pharmacogenetic investigation of the Val66Met SNP has addressed its influence on selective serotonin reuptake inhibitors (SSRIs), a popular class of anti-depressants. Two meta-analyses concluded that heterozygotes were more responsive to SSRIs than either Val or Met homozygotes. This effect was modulated by race, being stronger among Asians [86, 87]. However, TBI patients with depression were most likely to respond to citalopram (an SSRI) if they were Val homozygotes [88]. This discrepancy may indicate that post-TBI depression requires a different strategy for therapy personalization than other types of depression or it may reflect the fact that Val66Met was combined with another genetic predictor in this study (a polymorphism in the methylene tetrahydrofolate reductase gene). These results have immediate clinical relevance. Up to 53% of TBI patients experience depression in the first year after their injury [89] and SSRIs are a proven, first line therapy for this post-TBI depression [90].

The Val66Met SNP may also modulate the effectiveness of non-pharmaceutical therapies for TBI. Exercise improves emotional and cognitive outcomes after TBI [91, 92]. This effect depended on expression of BDNF [93]. Positive neurobiological effects of exercise in mice were diminished by the Met allele of the Val66Met SNP [94]. Since the Met allele impairs activity-dependent release of BDNF [14], it is reasonable to hypothesize that physical exercise does not promote recovery after TBI as readily in these individuals. This hypothesis has not as yet been tested directly in the literature. In a small study of spinal cord injury patients, Met carriers increased circulating BDNF less in response to physical exercise than Val/Val patients [95]. This trend approached but did not meet the threshold for statistical significance. Low levels of physical activity increased the risk of cognitive decline and dementia in an elderly Korean cohort and this effect was modulated by the Val66Met SNP, with Met alleles increasing risk [96]. In a study of healthy young adults, physical exercise improved performance on a memory task in Val/Val individuals but not in Met carriers [97]. A short period of motor training increased corticospinal output and motor map area in Val/Val human subjects but not in Met carriers, implying impaired experience-dependent plasticity in the motor cortex among Met carriers [98]. Val/Val subjects performed better on a motor learning task and retained more of what they learned. The Val66Met allele also caused differences in brain activation during motor activity as measured by functional magnetic resonance imaging [45]. However, persistent training overcame these deficits [99], suggesting that patience in motor rehabilitation of Met carriers will be rewarded.

CONCLUSION

TBI has been described as “the most heterogeneous of all neurological disorders” [11]. Several different pathologies, including edema, ischemia, hemorrhage, and diffuse axonal injury may or may not occur [100]. The distribution of TBI patients by age has three widely separated peaks at 0–4, 15–19, and >65 years of age [101]. In addition to Val66Met, there are several other common polymorphisms in genes such as DRD2, COMT, and ANKK1 that modulate outcomes [5–8, 102]. This heterogeneity implies that precision medicine could have many benefits in TBI. Clinical trial stratification would make expensive trials more likely to detect treatment effects in spite of confounding factors. Personalized therapy would allow new medicines to benefit some patients even if they cannot benefit all patients. However, daunting challenges must be overcome to realize the potential of personalized medicine in TBI. Not only do multiple patient-specific factors influence outcome, but these factors interact with each other in ways that cannot be ignored. This review took a reductionist approach, focusing on one SNP known to influence outcomes in TBI. However, it proved impossible to fully describe the role of this SNP without also considering how it interacts with ethnicity, age, injury severity, post injury time point, and gender. New interactions are likely to emerge over time as investigations continue, including interactions with other genetic polymorphisms. These interactions create confusion in the field because they lead to conflicting results in human studies conducted in different populations [103]. It is very difficult to eliminate all potentially confounding interactions from a human study but human *in vitro* models can be used to reduce confounds in a human system. In these models, induced pluripotent stem cell (iPSC) technology is used to create neurons or other neural cell types from a patient. These cells retain the genetic identity of the donor patient. Furthermore, gene editing technology can be used to introduce genetic variants one at a time against a uniform genetic background [104]. In these experiments, genetic risk factors can be eliminated or introduced individually to test hypotheses definitively. While this approach eliminates some confounds associated with conventional human studies, it has its own limitations. As in any *in vitro* system, the normal architecture of the tissue is lost. Also, human iPSC-derived neurons are typically immature, resembling fetal or neonatal neurons more than adult neurons [105]. However, rapid progress is being made to address these limitations. Brain organoids have been developed that juxtapose several neural cell types derived from human iPSCs in biofidelic configurations [106]. Aging of iPSC-derived neurons can be accelerated by expressing progerin, a truncated form of lamin A associated with premature aging disorders [107], or by telomerase manipulation [108]. Human *in vitro* models have already made significant contributions in other neurological disorders, including amyotrophic lateral sclerosis [109, 110]. They have recently been introduced in neurotrauma [111, 112] where they may eventually provide a powerful complement to traditional pre-clinical tools. The challenges associated with personalizing TBI medicine around patient-specific traits such as the Val66Met SNP are great. However, the potential rewards are greater still and this type of personalization will be a vital frontier for innovation in the field in the near future.

ACKNOWLEDGMENTS

The authors would like to acknowledge financial support from the National Institutes of Health (R21NS098129).

REFERENCES

[1]. Taylor CA, Bell JM, Breiding MJ, Xu L (2017) Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. MMWR Surveill Summ 66, 1–16.

[2]. Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, Murray GD, Maas AI (2003) Patient age and outcome following severe traumatic brain injury: An analysis of 5600 patients. J Neurosurg 99, 666–673. [PubMed: 14567601]

[3]. Berry C, Ley EJ, Tillou A, Cryer G, Margulies DR, Salim A (2009) The effect of gender on patients with moderate to severe head injuries. J Trauma 67, 950–953. [PubMed: 19901653]

[4]. Corrigan JD, Bogner J, Mellick D, Bushnik T, Dams-O'Connor K, Hammond FM, Hart T, Kolakowsky-Hayner S (2013) Prior history of traumatic brain injury among persons in the Traumatic Brain Injury Model Systems National Database. Arch Phys Med Rehabil 94, 1940–1950. [PubMed: 23770276]

[5]. Yue JK, Winkler EA, Rick JW, Burke JF, McAllister TW, Oh SS, Burchard EG, Hu D, Rosand J, Temkin NR, Korley FK, Sorani MD, Ferguson AR, Lingsma HF, Sharma S, Robinson CK, Yuh EL, Tarapore PE, Wang KK, Puccio AM, Mukherjee P, Diaz-Arrastia R, Gordon WA, Valadka AB, Okonkwo DO, Manley GT (2017) DRD2 C957T polymorphism is associated with improved 6-month verbal learning following traumatic brain injury. Neurogenetics 18, 29–38. [PubMed: 27826691]

[6]. Winkler EA, Yue JK, McAllister TW, Temkin NR, Oh SS, Burchard EG, Hu D, Ferguson AR, Lingsma HF, Burke JF, Sorani MD, Rosand J, Yuh EL, Barber J, Tarapore PE, Gardner RC, Sharma S, Satris GG, Eng C, Puccio AM, Wang KK, Mukherjee P, Valadka AB, Okonkwo DO, Diaz-Arrastia R, Manley GT (2016) COMT Val 158 Met polymorphism is associated with nonverbal cognition following mild traumatic brain injury. Neurogenetics 17, 31–41. [PubMed: 26576546]

[7]. Yue JK, Pronger AM, Ferguson AR, Temkin NR, Sharma S, Rosand J, Sorani MD, McAllister TW, Barber J, Winkler EA, Burchard EG, Hu D, Lingsma HF, Cooper SR, Puccio AM, Okonkwo DO, Diaz-Arrastia R, Manley GT (2015) Association of a common genetic variant within ANKK1 with six-month cognitive performance after traumatic brain injury. Neurogenetics 16, 169–180. [PubMed: 25633559]

[8]. McAllister TW (2015) Genetic factors in traumatic brain injury. Handb Clin Neurol 128, 723–739. [PubMed: 25701917]

[9]. Stocchetti N, Zanier ER (2016) Chronic impact of traumatic brain injury on outcome and quality of life: A narrative review. Crit Care 20, 148. [PubMed: 27323708]

[10]. McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE, Santini VE, Lee HS, Kubilus CA, Stern RA (2009) Chronic traumatic encephalopathy in athletes: Progressive tauopathy after repetitive head injury. J Neuropathol Exp Neurol 68, 709–735. [PubMed: 19535999]

[11]. Kabadi SV, Faden AI (2014) Neuroprotective strategies for traumatic brain injury: Improving clinical translation. Int J Mol Sci 15, 1216–1236. [PubMed: 24445258]

[12]. Bodien YG, McCrea M, Dikmen S, Temkin N, Boase K, Machamer J, Taylor SR, Sherer M, Levin H, Kramer JH, Corrigan JD, McAllister TW, Whyte J, Manley GT, Giacino JT (2018) Optimizing outcome assessment in multicenter TBI trials: Perspectives from TRACK-TBI and the TBI Endpoints Development Initiative. J Head Trauma Rehabil 33, 147–157. [PubMed: 29385010]

[13]. Shimizu E, Hashimoto K, Iyo M (2004) Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: The possibility to explain ethnic mental traits. Am J Med Genet B Neuropsychiatr Genet 126B, 122–123. [PubMed: 15048661]

[14]. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257–269. [PubMed: 12553913]

[15]. Barbey AK, Colom R, Paul E, Forbes C, Krueger F, Goldman D, Grafman J (2014) Preservation of general intelligence following traumatic brain injury: Contributions of the Met66 brain-derived neurotrophic factor. PLoS One 9, e88733. [PubMed: 24586380]

[16]. Krueger F, Pardini M, Huey ED, Raymont V, Solomon J, Lipsky RH, Hodgkinson CA, Goldman D, Grafman J (2011) The role of the Met66 brain-derived neurotrophic factor allele in the recovery of executive functioning after combat-related traumatic brain injury. J Neurosci 31, 598–606. [PubMed: 21228168]

[17]. Kim JM, Stewart R, Park MS, Kang HJ, Kim SW, Shin IS, Kim HR, Shin MG, Cho KH, Yoon JS (2012) Associations of BDNF genotype and promoter methylation with acute and long-term stroke outcomes in an East Asian cohort. PLoS One 7, e51280. [PubMed: 23240009]

[18]. Helm EE, Tyrell CM, Pohlig RT, Brady LD, Reisman DS (2016) The presence of a single-nucleotide polymorphism in the BDNF gene affects the rate of locomotor adaptation after stroke. Exp Brain Res 234, 341–351. [PubMed: 26487176]

[19]. Barde YA (1989) Trophic factors and neuronal survival. Neuron 2, 1525–1534. [PubMed: 2697237]

[20]. Hamburger V, Levi-Montalcini R (1949) Proliferation, differentiation and degeneration in the spinal ganglia of the chick embryo under normal and experimental conditions. J Exp Zool 111, 457–501. [PubMed: 18142378]

[21]. Poo MM (2001) Neurotrophins as synaptic modulators. Nat Rev Neurosci 2, 24–32. [PubMed: 11253356]

[22]. Tyler WJ, Alonso M, Bramham CR, Pozzo-Miller LD (2002) From acquisition to consolidation: On the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. Learn Mem 9, 224–237. [PubMed: 12359832]

[23]. Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B (1996) Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature 381, 706–709. [PubMed: 8649517]

[24]. Linnarsson S, Bjorklund A, Ernfors P (1997) Learning deficit in BDNF mutant mice. Eur J Neurosci 9, 2581–2587. [PubMed: 9517463]

[25]. Mizuno M, Yamada K, Olariu A, Nawa H, Nabeshima T (2000) Involvement of brain-derived neurotrophic factor in spatial memory formation and maintenance in a radial arm maze test in rats. J Neurosci 20, 7116–7121. [PubMed: 10995859]

[26]. Goodman LJ, Valverde J, Lim F, Geschwind MD, Federoff HJ, Geller AI, Hefti F (1996) Regulated release and polarized localization of brain-derived neurotrophic factor in hippocampal neurons. Mol Cell Neurosci 7, 222–238. [PubMed: 8726105]

[27]. Lessmann V, Gottmann K, Malcangio M (2003) Neurotrophin secretion: Current facts and future prospects. Prog Neurobiol 69, 341–374. [PubMed: 12787574]

[28]. Lu B, Pang PT, Woo NH (2005) The yin and yang of neurotrophin action. Nat Rev Neurosci 6, 603–614. [PubMed: 16062169]

[29]. Mowla SJ, Farhadi HF, Pareek S, Atwal JK, Morris SJ, Seidah NG, Murphy RA (2001) Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor. J Biol Chem 276, 12660–12666. [PubMed: 11152678]

[30]. Lee R, Kermani P, Teng KK, Hempstead BL (2001) Regulation of cell survival by secreted proneurotrophins. Science 294, 1945–1948. [PubMed: 11729324]

[31]. Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER (1996) Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron 16, 1137–1145. [PubMed: 8663990]

[32]. Atwal JK, Massie B, Miller FD, Kaplan DR (2000) The TrkB-Shc site signals neuronal survival and local axon growth via MEK and P13-kinase. Neuron 27, 265–277. [PubMed: 10985347]

[33]. Dijkhuizen PA, Ghosh A (2005) BDNF regulates primary dendrite formation in cortical neurons via the PI3-kinase and MAP kinase signaling pathways. J Neurobiol 62, 278–288. [PubMed: 15514998]

[34]. Yang J, Harte-Hargrove LC, Siao CJ, Marinic T, Clarke R, Ma Q, Jing D, Lafrancois JJ, Bath KG, Mark W, Ballon D, Lee FS, Scharfman HE, Hempstead BL (2014) proBDNF negatively

regulates neuronal remodeling, synaptic transmission, and synaptic plasticity in hippocampus. Cell Rep 7, 796–806. [PubMed: 24746813]

[35]. Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, Kermani P, Torkin R, Chen ZY, Lee FS, Kraemer RT, Nykjaer A, Hempstead BL (2005) ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J Neurosci 25, 5455–5463. [PubMed: 15930396]

[36]. Rostami E, Krueger F, Zoubak S, Dal Monte O, Raymont V, Pardini M, Hodgkinson CA, Goldman D, Risling M, Grafman J (2011) BDNF polymorphism predicts general intelligence after penetrating traumatic brain injury. PLoS One 6, e27389. [PubMed: 22087305]

[37]. Petryshen TL, Sabeti PC, Aldinger KA, Fry B, Fan JB, Schaffner SF, Waggoner SG, Tahl AR, Sklar P (2010) Population genetic study of the brain-derived neurotrophic factor (BDNF) gene. Mol Psychiatry 15, 810–815. [PubMed: 19255578]

[38]. Chen ZY, Ieraci A, Teng H, Dall H, Meng CX, Herrera DG, Nykjaer A, Hempstead BL, Lee FS (2005) Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway. J Neurosci 25, 6156–6166. [PubMed: 15987945]

[39]. Szeszko PR, Lipsky R, Mentschel C, Robinson D, Gunduz-Bruce H, Sevy S, Ashtari M, Napolitano B, Bilder RM, Kane JM, Goldman D, Malhotra AK (2005) Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. Mol Psychiatry 10, 631–636. [PubMed: 15768049]

[40]. Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR (2004) The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci 24, 10099–10102. [PubMed: 15537879]

[41]. Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubieta JK (2006) BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. Biol Psychiatry 59, 812–815. [PubMed: 16442082]

[42]. Harrisberger F, Spalek K, Smieskova R, Schmidt A, Coynel D, Milnik A, Fastenrath M, Freytag V, Gschwind L, Walter A, Vogel T, Bendfeldt K, de Quervain DJ, Papassotiropoulos A, Borgwardt S (2014) The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: A joint meta-analysis of published and new data. Neurosci Biobehav Rev 42, 267–278. [PubMed: 24674929]

[43]. Montag C, Weber B, Fliessbach K, Elger C, Reuter M (2009) The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: Incremental support for a genetic risk factor for depression. Psychol Med 39, 1831–1839. [PubMed: 19335934]

[44]. Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF, Weinberger DR (2003) Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. J Neurosci 23, 6690–6694. [PubMed: 12890761]

[45]. McHughen SA, Rodriguez PF, Kleim JA, Kleim ED, Marchal Crespo L, Procaccio V, Cramer SC (2010) BDNF val66met polymorphism influences motor system function in the human brain. Cereb Cortex 20, 1254–1262. [PubMed: 19745020]

[46]. Kailainathan S, Piers TM, Yi JH, Choi S, Fahey MS, Borger E, Gunn-Moore FJ, O'Neill L, Lever M, Whitcomb DJ, Cho K, Allen SJ (2016) Activation of a synapse weakening pathway by human Val66 but not Met66 probrain-derived neurotrophic factor (proBDNF). Pharmacol Res 104, 97–107. [PubMed: 26687096]

[47]. Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, Herrera DG, Toth M, Yang C, McEwen BS, Hempstead BL, Lee FS (2006) Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science 314, 140–143. [PubMed: 17023662]

[48]. Qin L, Kim E, Ratan R, Lee FS, Cho S (2011) Genetic variant of BDNF (Val66Met) polymorphism attenuates stroke-induced angiogenic responses by enhancing antiangiogenic mediator CD36 expression. J Neurosci 31, 775–783. [PubMed: 21228186]

[49]. Qin L, Jing D, Parauda S, Carmel J, Ratan RR, Lee FS, Cho S (2014) An adaptive role for BDNF Val66Met polymorphism in motor recovery in chronic stroke. J Neurosci 34, 2493–2502. [PubMed: 24523540]

[50]. Failla MD, Kumar RG, Peitzman AB, Conley YP, Ferrell RE, Wagner AK (2015) Variation in the BDNF gene interacts with age to predict mortality in a prospective, longitudinal cohort with severe TBI. Neurorehabil Neural Repair 29, 234–246. [PubMed: 25063686]

[51]. Silhol M, Bonnichon V, Rage F, Tapia-Arancibia L (2005) Age-related changes in brain-derived neurotrophic factor and tyrosine kinase receptor isoforms in the hippocampus and hypothalamus in male rats. Neuroscience 132, 613–624. [PubMed: 15837123]

[52]. Croll SD, Ip NY, Lindsay RM, Wiegand SJ (1998) Expression of BDNF and trkB as a function of age and cognitive performance. Brain Res 812, 200–208. [PubMed: 9813325]

[53]. Goldstein B, Toweill D, Lai S, Sonnenthal K, Kimberly B (1998) Uncoupling of the autonomic and cardiovascular systems in acute brain injury. Am J Physiol 275, R1287–1292. [PubMed: 9756562]

[54]. Yang AC, Chen TJ, Tsai SJ, Hong CJ, Kuo CH, Yang CH, Kao KP (2010) BDNF Val66Met polymorphism alters sympathovagal balance in healthy subjects. Am J Med Genet B Neuropsychiatr Genet 153b, 1024–1030. [PubMed: 20213725]

[55]. Alexander N, Osinsky R, Schmitz A, Mueller E, Kuepper Y, Hennig J (2010) The BDNF Val66Met polymorphism affects HPA-axis reactivity to acute stress. Psychoneuroen-docrinology 35, 949–953.

[56]. Larson-Dupuis C, Chamard E, Falardeau V, Frasnelli J, Beaulieu C, Poirier J, Carrier J, Lassonde M, Theoret H, Bacon BA, De Beaumont L (2015) Impact of BDNF Val66Met polymorphism on olfactory functions of female concussed athletes. Brain Inj 29, 963–970. [PubMed: 25950261]

[57]. Wang YJ, Chen KY, Kuo LN, Wang WC, Hsu YW, Wong HS, Lin CM, Liao KH, Zhang YF, Chiang YH, Chang WC (2018) The association between BDNF Val66Met polymorphism and emotional symptoms after mild traumatic brain injury. BMC Med Genet 19, 13. [PubMed: 29357818]

[58]. Gabrys RL, Dixon K, Holahan MR, Anisman H (2017) Self-reported mild traumatic brain injuries in relation to rumination and depressive symptoms: Moderating role of sex differences and a brain-derived neurotrophic factor gene polymorphism. Clin J Sport Med doi: 10.1097/JSM.0000000000000550

[59]. Beevers CG, Wells TT, McGeary JE (2009) The BDNF Val66Met polymorphism is associated with rumination in healthy adults. Emotion 9, 579–584. [PubMed: 19653783]

[60]. Clasen PC, Wells TT, Knopik VS, McGeary JE, Beevers CG (2011) 5-HTTLPR and BDNF Val66Met polymorphisms moderate effects of stress on rumination. Genes Brain Behav 10, 740–746. [PubMed: 21745335]

[61]. McAllister TW, Tyler AL, Flashman LA, Rhodes CH, McDonald BC, Saykin AJ, Tosteson TD, Tsongalis GJ, Moore JH (2012) Polymorphisms in the brain-derived neurotrophic factor gene influence memory and processing speed one month after brain injury. J Neurotrauma 29, 1111–1118. [PubMed: 22188054]

[62]. Dretsch MN, Williams K, Emmerich T, Crynen G, AitGhezala G, Chaytow H, Mathura V, Crawford FC, Iverson GL (2016) Brain-derived neurotropic factor polymorphisms, traumatic stress, mild traumatic brain injury, and combat exposure contribute to postdeployment traumatic stress. Brain Behav 6, e00392. [PubMed: 27110438]

[63]. Dretsch MN, Silverberg N, Gardner AJ, Panenka WJ, Emmerich T, Crynen G, Ait-Ghezala G, Chaytow H, Mathura V, Crawford FC, Iverson GL (2017) Genetics and other risk factors for past concussions in active-duty soldiers. J Neurotrauma 34, 869–875. [PubMed: 27396498]

[64]. Heinzerling KG, Shoptaw S (2012) Gender, brain-derived neurotrophic factor Val66Met, and frequency of metham-phetamine use. Gend Med 9, 112–120. [PubMed: 22445683]

[65]. Heinzerling KG, McCracken JT, Swanson AN, Ray LA, Shoptaw SJ (2012) COMT Val158Met, BDNF Val66Met, and OPRM1 Asn40Asp and methamphetamine dependence treatment response: Preliminary investigation. J Clin Psychopharmacol 32, 135–137. [PubMed: 22217949]

[66]. Spalletta G, Morris DW, Angelucci F, Rubino IA, Spoletini I, Bria P, Martinotti G, Siracusano A, Bonaviri G, Bernardini S, Caltagirone C, Bossu P, Donohoe G, Gill M, Corvin AP (2010) BDNF Val66Met polymorphism is associated with aggressive behavior in schizophrenia. Eur Psychiatry 25, 311–313. [PubMed: 20430595]

[67]. Wagner S, Baskaya O, Dahmen N, Lieb K, Tadic A (2010) Modulatory role of the brain-derived neurotrophic factor Val66Met polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. Genes Brain Behav 9, 97–102. [PubMed: 19817874]

[68]. Thomson CJ, Power RJ, Carlson SR, Rupert JL, Michel G (2015) A comparison of genetic variants between proficient low- and high-risk sport participants. J Sports Sci 33, 1861–1870. [PubMed: 25751253]

[69]. Bergman O, Westberg L, Lichtenstein P, Eriksson E, Larsson H (2011) Study on the possible association of brain-derived neurotrophic factor polymorphism with the developmental course of symptoms of attention deficit and hyperactivity. Int J Neuropsychopharmacol 14, 1367–1376. [PubMed: 21466746]

[70]. Panenka WJ, Gardner AJ, Dretsch MN, Crynen GC, Crawford FC, Iverson GL (2017) Systematic review of genetic risk factors for sustaining a mild traumatic brain injury. J Neurotrauma 34, 2093–2099. [PubMed: 28100103]

[71]. Goldstein LE, Fisher AM, Tagge CA, Zhang XL, Velisek L, Sullivan JA, Upreti C, Kracht JM, Ericsson M, Wojnarowicz MW, Goletiani CJ, Maglakelidze GM, Casey N, Moncaster JA, Minaeva O, Moir RD, Nowinski CJ, Stern RA, Cantu RC, Geiling J, Blusztajn JK, Wolozin BL, Ikezu T, Stein TD, Budson AE, Kowall NW, Chargin D, Sharon A, Saman S, Hall GF, Moss WC, Cleveland RO, Tanzi RE, Stanton PK, McKee AC (2012) Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Sci Transl Med 4, 134ra160.

[72]. McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Keene CD, Litvan I, Perl DP, Stein TD, Vonsattel JP, Stewart W, Tripodis Y, Crary JF, Bieniek KF, Dams-O'Connor K, Alvarez VE, Gordon WA, group TC (2016) The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathol 131, 75–86. [PubMed: 26667418]

[73]. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A (2003) Head injury as a risk factor for Alzheimer's disease: The evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry 74, 857–862. [PubMed: 12810767]

[74]. Guo Z, Cupples LA, Kurz A, Auerbach SH, Volicer L, Chui H, Green RC, Sadovnick AD, Duara R, DeCarli C, Johnson K, Go RC, Growdon JH, Haines JL, Kukull WA, Farrer LA (2000) Head injury and the risk of AD in the MIRAGE study. Neurology 54, 1316–1323. [PubMed: 10746604]

[75]. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K (2018) Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. JAMA Neurology, doi: 10.1001/jamaneurol.2018.0815

[76]. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericakvance MA (1993) Gene dose of apolipoprotein-E type-4 allele and the risk of Alzheimer's disease in late-onset families. Science 261, 921–923. [PubMed: 8346443]

[77]. Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, Ginsberg H, Chun M, Tycko B, Shelanski M (1995) Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology 45, 555–557. [PubMed: 7898715]

[78]. Ventriglia M, Bocchio Chiavetto L, Benussi L, Binetti G, Zanetti O, Riva MA, Gennarelli M (2002) Association between the BDNF 196 A/G polymorphism and sporadic Alzheimer's disease. Mol Psychiatry 7, 136–137. [PubMed: 11840305]

[79]. Harris SE, Fox H, Wright AF, Hayward C, Starr JM, Whalley LJ, Deary IJ (2006) The brain-derived neurotrophic factor Val66Met polymorphism is associated with age-related change in reasoning skills. Mol Psychiatry 11, 505–513. [PubMed: 16446742]

[80]. Li Y, Rowland C, Tacey K, Catanese J, Sninsky J, Hardy J, Powell J, Lovestone S, Morris JC, Thal L, Goate A, Owen M, Williams J, Grupe A (2005) The BDNF Val66Met polymorphism is not associated with late onset Alzheimer's disease in three case-control samples. Mol Psychiatry 10, 809–810. [PubMed: 15970929]

[81]. Houlihan LM, Harris SE, Luciano M, Gow AJ, Starr JM, Visscher PM, Deary IJ (2009) Replication study of candidate genes for cognitive abilities: The Lothian Birth Cohort 1936. Genes Brain Behav 8, 238–247. [PubMed: 19077115]

[82]. Voineskos AN, Lerch JP, Felsky D, Shaikh S, Rajji TK, Miranda D, Lobaugh NJ, Mulsant BH, Pollock BG, Kennedy JL (2011) The brain-derived neurotrophic factor Val66Met polymorphism and prediction of neural risk for Alzheimer disease. Arch Gen Psychiatry 68, 198–206. [PubMed: 21300947]

[83]. Fukumoto N, Fujii T, Combarros O, Kamboh MI, Tsai SJ, Matsushita S, Nacmias B, Comings DE, Arboleda H, Ingelsson M, Hyman BT, Akatsu H, Grupe A, Nishimura AL, Zatz M, Mattila KM, Rinne J, Goto Y, Asada T, Nakamura S, Kunugi H (2010) Sexually dimorphic effect of the Val66Met polymorphism of BDNF on susceptibility to Alzheimer's disease: New data and meta-analysis. Am J Med Genet B Neuropsychiatr Genet 153b, 235–242. [PubMed: 19504537]

[84]. Nikolac Perkovic M, Nedic Erjavec G, Zivkovic M, Sagud M, Uzun S, Mihaljevic-Peles A, Kozumplik O, Muck-Seler D, Pivac N (2014) Association between the brain-derived neurotrophic factor Val66Met polymorphism and therapeutic response to olanzapine in schizophrenia patients. Psychopharmacology (Berl) 231, 3757–3764. [PubMed: 24595507]

[85]. Lee SY, Chen SL, Chang YH, Chen SH, Chu CH, Huang SY, Tzeng NS, Wang CL, Wang LJ, Lee IH, Yeh TL, Yang YK, Hong JS, Lu RB (2014) Genotype variant associated with add-on memantine in bipolar II disorder. Int J Neuropsychopharmacol 17, 189–197. [PubMed: 24103632]

[86]. Niitsu T, Fabbri C, Bentini F, Serretti A (2013) Pharmacogenetics in major depression: A comprehensive meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 45, 183–194. [PubMed: 23733030]

[87]. Yan T, Wang L, Kuang W, Xu J, Li S, Chen J, Yang Y (2014) Brain-derived neurotrophic factor Val66Met polymorphism association with antidepressant efficacy: A systematic review and meta-analysis. Asia Pac Psychiatry 6, 241–251. [PubMed: 25231750]

[88]. Lanctot KL, Rapoport MJ, Chan F, Rajaram RD, Strauss J, Sicard T, McCullagh S, Feinstein A, Kiss A, Kennedy JL, Bassett AS, Herrmann N (2010) Genetic predictors of response to treatment with citalopram in depression secondary to traumatic brain injury. Brain Inj 24, 959–969. [PubMed: 20515362]

[89]. Bombardier CH, Fann JR, Temkin NR, Esselman PC, Barber J, Dikmen SS (2010) Rates of major depressive disorder and clinical outcomes following traumatic brain injury. JAMA 303, 1938–1945. [PubMed: 20483970]

[90]. Plantier D, Luaute J (2016) Drugs for behavior disorders after traumatic brain injury: Systematic review and expert consensus leading to French recommendations for good practice. Ann Phys Rehabil Med 59, 42–57. [PubMed: 26797170]

[91]. Perry SA, Coetzer R, Saville CWN (2018) The effectiveness of physical exercise as an intervention to reduce depressive symptoms following traumatic brain injury: A meta-analysis and systematic review. Neuropsychol Rehabil doi: 10.1080/09602011.2018.1469417

[92]. Wise EK, Hoffman JM, Powell JM, Bombardier CH, Bell KR (2012) Benefits of exercise maintenance after traumatic brain injury. Arch Phys Med Rehabil 93, 1319–1323. [PubMed: 22840829]

[93]. Griesbach GS, Hovda DA, Gomez-Pinilla F (2009) Exercise-induced improvement in cognitive performance after traumatic brain injury in rats is dependent on BDNF activation. Brain Res 1288, 105–115. [PubMed: 19555673]

[94]. Ieraci A, Madaio AI, Mallei A, Lee FS, Popoli M (2016) Brain-derived neurotrophic factor Val66Met human polymorphism impairs the beneficial exercise-induced neurobiological changes in mice. Neuropsychopharmacology 41, 3070–3079. [PubMed: 27388329]

[95]. Leech KA, Hornby TG (2017) High-intensity locomotor exercise increases brain-derived neurotrophic factor in individuals with incomplete spinal cord injury. J Neurotrauma 34, 1240–1248. [PubMed: 27526567]

[96]. Kim JM, Stewart R, Bae KY, Kim SW, Yang SJ, Park KH, Shin IS, Yoon JS (2011) Role of BDNF val66met polymorphism on the association between physical activity and incident dementia. Neurobiol Aging 32, 551.e555–512.

[97]. Hopkins ME, Davis FC, Vantieghem MR, Whalen PJ, Bucci DJ (2012) Differential effects of acute and regular physical exercise on cognition and affect. Neuroscience 215, 59–68. [PubMed: 22554780]

[98]. Kleim JA, Chan S, Pringle E, Schallert K, Procaccio V, Jimenez R, Cramer SC (2006) BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. Nat Neurosci 9, 735–737. [PubMed: 16680163]

[99]. McHughen SA, Pearson-Fuhrhop K, Ngo VK, Cramer SC (2011) Intense training overcomes effects of the Val66Met BDNF polymorphism on short-term plasticity. Exp Brain Res 213, 415–422. [PubMed: 21769545]

[100]. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT, Workshop Scientific T, Advisory Panel M (2008) Classification of traumatic brain injury for targeted therapies. J Neurotrauma 25, 719–738. [PubMed: 18627252]

[101]. Faul MXL, Wald MM, Coronado V (2010) Traumatic brain injury in the United States: Emergency department visits, hospitalizations, and deaths, 2002–2006 CDC, National Center for Injury Prevention and Control, Atlanta, GA.

[102]. Weaver SM, Portelli JN, Chau A, Cristofori I, Moretti L, Grafman J (2014) Genetic polymorphisms and traumatic brain injury: The contribution of individual differences to recovery. Brain Imaging Behav 8, 420–434. [PubMed: 22878895]

[103]. Notaras M, Hill R, van den Buuse M (2015) The BDNF gene Val66Met polymorphism as a modifier of psychiatric disorder susceptibility: Progress and controversy. Mol Psychiatry 20, 916–930. [PubMed: 25824305]

[104]. Kim HS, Bernitz JM, Lee DF, Lemischka IR (2014) Genomic editing tools to model human diseases with isogenic pluripotent stem cells. Stem Cells Dev 23, 2673–2686. [PubMed: 25075441]

[105]. Dage JL, Colvin EM, Fouillet A, Langron E, Roell WC, Li J, Mathur SX, Mogg AJ, Schmitt MG, Felder CC, Merchant KM, Isaac J, Broad LM, Sher E, Ursu D (2014) Pharmacological characterisation of ligand- and voltage-gated ion channels expressed in human iPSC-derived forebrain neurons. Psychopharmacology (Berl) 231, 1105–1124. [PubMed: 24429870]

[106]. Qian X, Nguyen HN, Song MM, Hadiono C, Ogden SC, Hammack C, Yao B, Hamersky GR, Jacob F, Zhong C, Yoon KJ, Jeang W, Lin L, Li Y, Thakor J, Berg DA, Zhang C, Kang E, Chickering M, Nauen D, Ho CY, Wen Z, Christian KM, Shi PY, Maher BJ, Wu H, Jin P, Tang H, Song H, Ming GL (2016) Brain-region-specific organoids using mini-bioreactors for modeling ZIKV exposure. Cell 165, 1238–1254. [PubMed: 27118425]

[107]. Miller JD, Ganat YM, Kishinevsky S, Bowman RL, Liu B, Tu EY, Mandal PK, Vera E, Shim JW, Kriks S, Taldone T, Fusaki N, Tomishima MJ, Krainc D, Milner TA, Rossi DJ, Studer L (2013) Human iPSC-based modeling of late-onset disease via progerin-induced aging. Cell Stem Cell 13, 691–705. [PubMed: 24315443]

[108]. Vera E, Bosco N, Studer L (2016) Generating late-onset human iPSC-based disease models by inducing neuronal age-related phenotypes through telomerase manipulation. Cell Rep 17, 1184–1192. [PubMed: 27760320]

[109]. Kiskinis E, Sandoe J, Williams LA, Boulting GL, Moccia R, Wainger BJ, Han S, Peng T, Thams S, Mikkilineni S, Mellin C, Merkle FT, Davis-Dusenbery BN, Ziller M, Oakley D, Ichida J, Di Costanzo S, Atwater N, Maeder ML, Goodwin MJ, Nemesh J, Handsaker RE, Paull D, Noggle S, McCarroll SA, Joung JK, Woolf CJ, Brown RH, Eggan K (2014) Pathways disrupted in human ALS motor neurons identified through genetic correction of mutant SOD1. Cell Stem Cell 14, 781–795. [PubMed: 24704492]

[110]. Wainger BJ, Kiskinis E, Mellin C, Wiskow O, Han SS, Sandoe J, Perez NP, Williams LA, Lee S, Boulting G, Berry JD, Brown RH, Jr., Cudkowicz ME, Bean BP, Eggan K, Woolf CJ (2014) Intrinsic membrane hyperexcitability of amyotrophic lateral sclerosis patient-derived motor neurons. Cell Rep 7, 1–11. [PubMed: 24703839]

[111]. Sherman SA, Phillips JK, Costa JT, Cho FS, Oungoulian SR, Finan JD (2016) Stretch injury of human induced pluripotent stem cell derived neurons in a 96 well format. Sci Rep 6, 34097. [PubMed: 27671211]

[112]. Phillips JK, Sherman SA, Oungoulian SR, Finan JD (2018) Method for high speed stretch injury of human induced pluripotent stem cell-derived neurons in a 96-well format. J Vis Exp doi: 10.3791/57305

Table 1

Influence of the Val66Met SNP on mild TBI pathology

	Acute	Chronic
Female	Deleterious [57]	Protective [56] Neutral [57]
Male	Deleterious [57]	Deleterious [57]

Note that different studies use different outcomes and different definitions of acute and chronic time periods.