Review

Does the Brain-Derived Neurotrophic Factor Val66Met Polymorphism Modulate the Effects of Physical Activity and Exercise on Cognition?

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Abstract

The Val66Met is a polymorphism of the brain-derived neurotrophic factor (BDNF) gene that encodes a substitution of a valine (Val) to methionine (Met) amino acid. Carrying this polymorphism reduces the activity-dependent secretion of the BDNF protein, which can potentially affect brain plasticity and cognition. We reviewed the biology of Val66Met and surveyed 26 studies (11,417 participants) that examined the role of this polymorphism in moderating the cognitive response to physical activity (PA) and exercise. Nine observational studies confirmed a moderating effect of Val66Met on the cognitive response to PA but differences between Val and Met carriers were inconsistent and only significant in some cognitive domains. Only five interventional studies found a moderating effect of Val66Met on the cognitive response to exercise, which was also inconsistent in its direction. Two studies showed a superior cognitive response in Val carriers and three studies showed a better response in Met carriers. These results do not support a general and consistent effect of Val66Met in moderating the cognitive response to PA or exercise. Both Val and Met carriers can improve specific aspects of cognition by increasing PA and engaging in exercise. Causes for discrepancies among studies, effect moderators, and future directions are discussed.

Keywords

exercise, physical activity, physical exercise, cognition, memory, executive function, learning, genotype, polymorphism, brain-derived neurotrophic factor

Introduction

Physical activity (PA) is defined as any bodily movement produced by the contraction of skeletal muscles that results in a substantial increase in caloric requirements over resting energy expenditure (Box 1). Higher levels of PA and subsequent improvements in cardiorespiratory fitness (CRF) have been associated with positive effects on different aspects of brain function and cognition (Hillman and others 2008). Observational studies have reported positive associations between levels of CRF and cognitive function (Barnes and others 2003), although this association is complex and potentially moderated by many other factors (Etnier and others 2006). Higher levels of PA appear to protect against the development of neurodegenerative diseases such as Alzheimer's disease and other types of dementia (Blondell and others 2014; Larson 2006).

Exercise is defined as a type of PA consisting of planned, structured, and repetitive bodily movements performed to improve and/or maintain one or more components of physical fitness (Box 1). Interventional studies investigating the effects of both acute and chronic exercise interventions on cognition have also demonstrated that exercise leads to improvements in the performance of cognitive tasks involving different aspects of learning (Winter and others 2007), memory (Roig and others 2013), and executive function (Colcombe and Kramer

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Box 1. Glossary of Key Terms Used in the Review.

Allele: One of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous.
Cardiorespiratory fitness: The capacity to perform large-muscle, whole-body exercise at moderate to vigorous intensities for extended periods of time. It depends on the capacity of the circulatory and respiratory system to supply oxygen during sustained physical activity.
Chromosome: Thread-like structures located inside the nucleus of a cell and that are made of protein and a single molecule of deoxyribonucleic acid (DNA) containing genetic instructions.
Codon: A trinucleotide sequence of DNA or ribonucleic acid (RNA) that corresponds to a specific amino acid or stop signal that regulate protein synthesis.
Exercise: A form of physical activity that is planned, structured, repetitive, and performed with the goal of improving health or fitness. Although all exercise is physical activity, not all physical activity is exercise.
Genotype: Genetic makeup of an organism that describes its complete set of genes. The genotype determines the phenotype of an organism.
Long-term potentiation: Biological process by which synaptic stimulation results in a long-lasting increase in the strength of synaptic transmission.
Long-term depression: Biological process by which synaptic stimulation results in a long-lasting decrease in the strength of synaptic transmission.
Methionine: Essential amino acid that plays a critical role in the biosynthesis of proteins and metabolism.
Neurotrophins: Proteins regulating survival, growth, morphological plasticity and synthesis of proteins for differentiated functions of neurons.
Phenotype: Observable physical properties of an organism, including the organism's appearance, development, and behavior.
Physical activity: Any bodily movement produced by skeletal muscles that results in energy expenditure above resting levels. Physical activity encompasses exercise, sports, and physical activities done as part of daily living, occupation, leisure, and active transportation.
Polymorphism: One of two or more variants of a particular DNA sequence. The most common type of polymorphism involves variation at a single base pair.
Valine: Essential amino acid used in the biosynthesis of proteins helping to determine their threedimensional structure.

2003). In line with the findings reported in observational studies, interventional studies have also demonstrated that regular exercise can confer protection against the cognitive decline commonly experienced during aging and neurodegenerative processes (Farina and others 2014; Lautenschlager and others 2008).

Despite the positive effects that higher levels of PA and exercise have on cognition, the results of the studies available show a large degree of variability in the magnitude of such effects. Recent meta-analyses have revealed that, certainly, the effects of exercise on cognition can range from null to large (effect sizes = −0.13 to 0.75) (Roig and others 2013). This variability could be explained in part by differences among studies in the characteristics of the exercise used (eg, type, intensity, frequency, volume), and the cognitive domain studied (eg, memory, executive function). However, variability in the effect has also been observed within each study, where exercise and cognitive domains are the same, therefore suggesting that individual differences also moderate the cognitive response to PA and exercise (Roig and others 2016). Besides differences in age and biological sex, genotype is another important factor that could contribute to increasing the individual variability in the cognitive response to PA and exercise (Barha and others 2017; Leckie and others 2012).

One of the genes most frequently associated with the effects of exercise on brain plasticity and cognition-related processes is the brain-derived neurotrophic factor (BDNF) gene (Vaynman and Gomez-Pinilla 2005). Although many other candidates exist, Val66Met, a functional single nucleotide polymorphism (SNP) of the BDNF gene that modulates the secretion of BDNF protein, has attracted most of the attention (Chen 2004; Egan and others 2003). Given the key role of the BDNF protein in mediating the benefits of exercise on the brain (Vaynman and others 2004), it is conceivable that Val66Met could moderate the cognitive response to PA and exercise by regulating the secretion of this protein. The primary goal of this article was to examine the current evidence supporting the role of Val66Met in moderating the cognitive response to PA and exercise. To this end, we reviewed observational and interventional studies that investigated the influence of this polymorphism on the cognitive response to PA and exercise, respectively. Observational studies allowed us to assess whether Val66Met modulated the association between PA or CRF and cognition while interventional studies allowed us to evaluate directly if the cognitive response to both acute and chronic exercise interventions was modulated by this SNP of the BDNF gene. Definitions of the most important terminology used in the article are provided in Box 1.

A Brief Introduction to the Brain-Derived Neurotrophic Factor

The BDNF gene is responsible for the transcription of the BDNF protein, the most abundant neurotrophin in the brain (Hofer and others 1990). This neurotrophin is

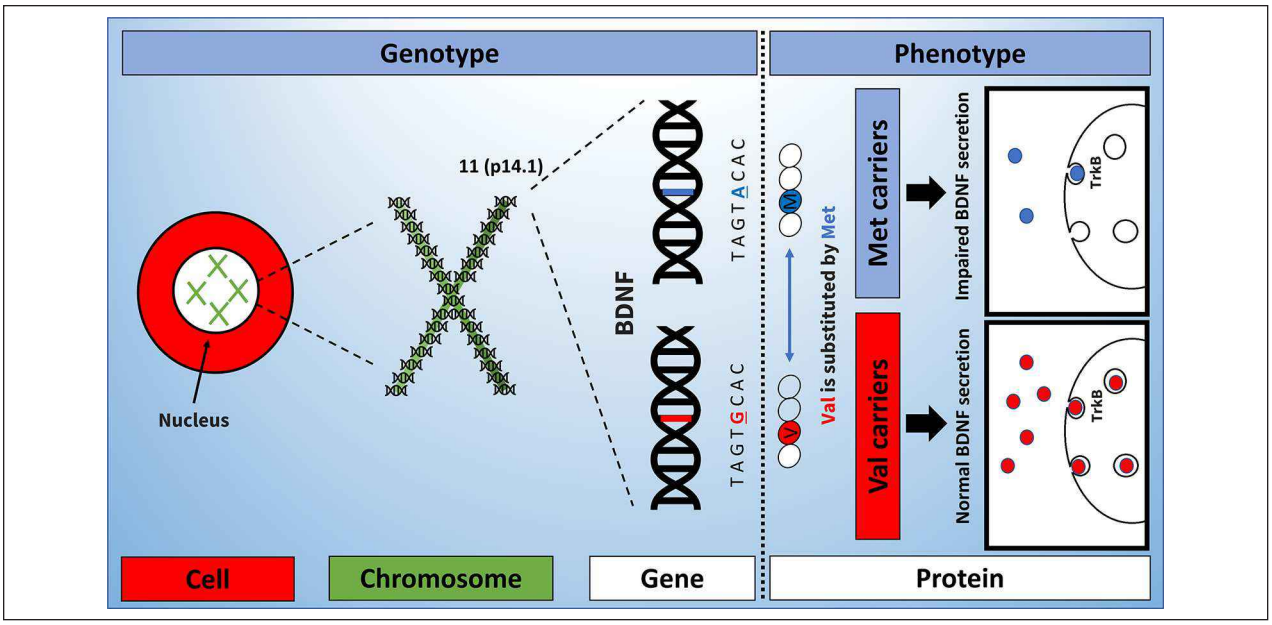

Figure 1. Val66Met brain-derived neurotrophic factor (BDNF) single nucleotide polymorphism (SNP). Schematic representation showing the location on the chromosome 11 (p14.1) of the BDNF gene. The val66met (rs6265) single nucleotide polymorphism consists on a single nucleotide change A>G on the chromosome 11:27658369 (GRCh38.p12) position. The consequence is a missense variant producing an amino acid substitution of a Valine (Val) for a Methionine (Met) within the BDNF protein. The proposed molecular consequences on the Met Carriers is an impaired BDNF secretion and a reduced binding to the high affinity tyrosine kinase receptor B (TrkB).

involved in neuronal growth, differentiation, and survival in brain areas such as the prefrontal cortex and the hippocampus, where BDNF is particularly abundant (Poo 2001). BDNF binds to a high affinity tyrosine kinase receptor B (TrkB) to activate downstream signaling mediators (Fig. 1). BDNF can be expressed in two different isoforms, proBDNF and mature (m)BDNF, both functioning in an opposing manner but essential to neural health and performance. While proBDNF has been linked with eliciting apoptosis and dendritic and synaptic retraction, mBDNF facilitates neurogenesis and dendritic and synaptic spine formation (Lu and others 2005). Similarly, the two isoforms have shown to affect neural activity differently, with proBDNF eliciting long-term depression (LTD), and mBDNF eliciting long-term potentiation (LTP), both crucial molecular mechanisms for cognitive processes such as the formation of long-term memory (Bekinschtein and others 2014). Several animal studies have shown that suppressing BDNF protein expression can hamper synaptic plasticity and impair behavioral and cognitive abilities (Ernfors and others 1994). In contrast, increasing BDNF levels via endogenous manipulation has been shown to enhance LTP induction in the hippocampus (Rex and others 2006).

Since in vivo measurements of BDNF in the brain are not possible, studies in humans have had to rely on inferences about the levels of BDNF on the central nervous system by assessing BDNF concentration in the blood (Skriver and others 2014). Converging evidence indicates that reductions in the peripheral concentration of BDNF are typical in aging and neurodegenerative processes (Bekinschtein and others 2014). These reductions are clinically relevant, as they have been associated with structural and functional changes in the brain such as reductions in hippocampal volume and deficits in episodic memory, respectively (Erickson and others 2012).

Exercise has been shown to increase BDNF expression in the rat hippocampus and this increase has been directly associated with learning and memory improvements post-exercise (Vaynman and others 2004). Inhibiting the action of BDNF abolishes completely the learning and memory gains obtained through exercise, thereby reinforcing the central role of this neurotrophin in orchestrating the effects of exercise on cognition (Cotman 2002). A single bout of intense cardiovascular exercise transiently increases the peripheral concentration of BDNF in humans (Knaepen and others 2010). Some human studies have shown that increases in both serum (Winter and others 2007) and plasma (Skriver and others 2014) BDNF concentration after acute exercise correlate with improvements in cognition. A small number of studies have shown that long-term (chronic) exercise interventions ranging from 1 to 6 months can upregulate peripheral BDNF levels (Anderson-Hanley and others 2018; Griffin and others 2011; Nascimento and others 2015). Most longitudinal studies, however, have not

found any significant increase in BDNF concentration, and only a few found that exercise-induced increases in BDNF were associated with improvements in cognition (Heisz and others 2017; Loprinzi 2019; Maass and others 2016). While animal studies demonstrate a robust association between exercise-induced increases in BDNF expression and performance in cognitive tasks, the strength of this association and the effects of chronic exercise on the peripheral levels of BDNF in humans are clearly more variable (Loprinzi 2019).

The Effect of Val66Met on Brain Plasticity and Cognition

Val66Met is a functional SNP (rs6265) that encodes a valine (Val) to methionine (Met) substitution at position (codon) 66 in the BDNF gene (Fig. 1). The combination of Val and Met alleles results in three different Val66Met genotypes: Val/Val, Val/Met and Met/Met. The frequency of Val66Met varies from 0% to 72% across populations, with the Met allele being more prevalent in Asian populations and less prevalent in Caucasian, Central and South American, and African populations (Petryshen and others 2010). Several studies have shown that Val66Met can have pleiotropic effects on different biological levels, affecting brain structure and function, cognition, and the risk of developing some neuropsychiatric disorders (Fig. 2). For example, Met carriers tend to show reduced age-related cerebral white matter integrity (Kennedy and others 2009), hippocampal volume (Pezawas 2004), and an abnormal distribution of BDNF within hippocampal neurons as well as a significant reduction of mature BDNF secretion (Chen 2004; Egan and others 2003). Met carriers have also shown to have alterations in the capacity to activate brain regions such as the hippocampus, prefrontal cortex, and amygdala during the performance of cognitive tasks (Hashimoto and others 2008; Kambeitz and others 2012). Reduced BDNF secretion has been directly associated with poorer performance in memory (Hariri and others 2003) and executive function (Ward and others 2015) cognitive tasks. Whether carrying the Met allele is detrimental to all aspects of cognition is, however, still unclear (Mandelman and Grigorenko 2012; Toh and others 2018).

Besides its moderating effects on brain plasticity and cognition, some recent studies have associated Val66Met with the pathogenesis of neuropsychiatric diseases, for example, bipolar disorder (Neves-Pereira and others 2002; Sklar and others 2002), suicidal behavior (Gonzalez-Castro and others 2017), and anxiety disorder (Gonzalez-Castro and others 2019). However, it should be noted that in most of these studies, associations between the presence of the Met allele and increased susceptibility to developing these conditions were significant only in subgroups of participants (Tsai 2018). More important, several follow-up studies have failed to replicate consistently the findings of some of these initial studies (Hong and others 2011). Converging evidence indicates that the potential effect of Val66Met on brain plasticity, cognition, and risk of neuropsychiatric disorders, is highly complex and heavily influenced by ethnicity, age, biological sex and the interaction with other genes (Tsai 2018). Variations in all of these moderating factors could explain the inconsistencies commonly found among studies investigating associations between Val66Met, brain function and structure, cognition and the risk of developing neuropsychiatric diseases.

Val66Met and the Cognitive Response to Exercise and Physical Activity

Since carrying the Val66Met can, in principle, reduce the BDNF response to exercise (Nascimento and others 2015), the possibility that variability in the cognitive response to PA or exercise could be explained in part by this SNP is not inconceivable. Different hypotheses have been proposed to explain the potential role of Val66Met in moderating the response to PA or exercise (Fig. 3). In short, it has been suggested that carrying the Val allele of Val66Met could enhance the cognitive response to PA and exercise through the increased secretion of BDNF (Mang and others 2013). However, the possibility that the carriers of the hypothetically less favourable variants of Val66Met (Met carriers) could precisely benefit more so from the exposure to high levels of PA and exercise to compensate for a potential genetic disadvantage in BDNF secretion cannot be discarded (Moreau and others 2017). Furthermore, whether carrying the Met allele could amplify the deleterious effects of lack of PA and exercise on cognition or, by contrast, Val carriers could be more vulnerable to the effects of physical inactivity, are still to be determined (Fig. 3).

We conducted a systematic review including 11 observational (Table 1) and 16 interventional (Table 2) studies (Supplemental Figure 1) with healthy participants as well as persons diagnosed with chronic conditions to analyze the evidence regarding the effect of Val66Met in modulating the association between PA and exercise on cognition. Our primary objective was to answer the question: Does Val66Met modify the cognitive response to PA and exercise in humans? Gaining insight into how Val66Met mediates the effects of PA and exercise on cognition could have important practical implications. Improving our capacity to predict the individual cognitive response to different types of exercise based on individual genetic traits would allow the design of more personalized training programs that are individually tailored, thus maximizing the benefits of exercise on cognition (Medalia

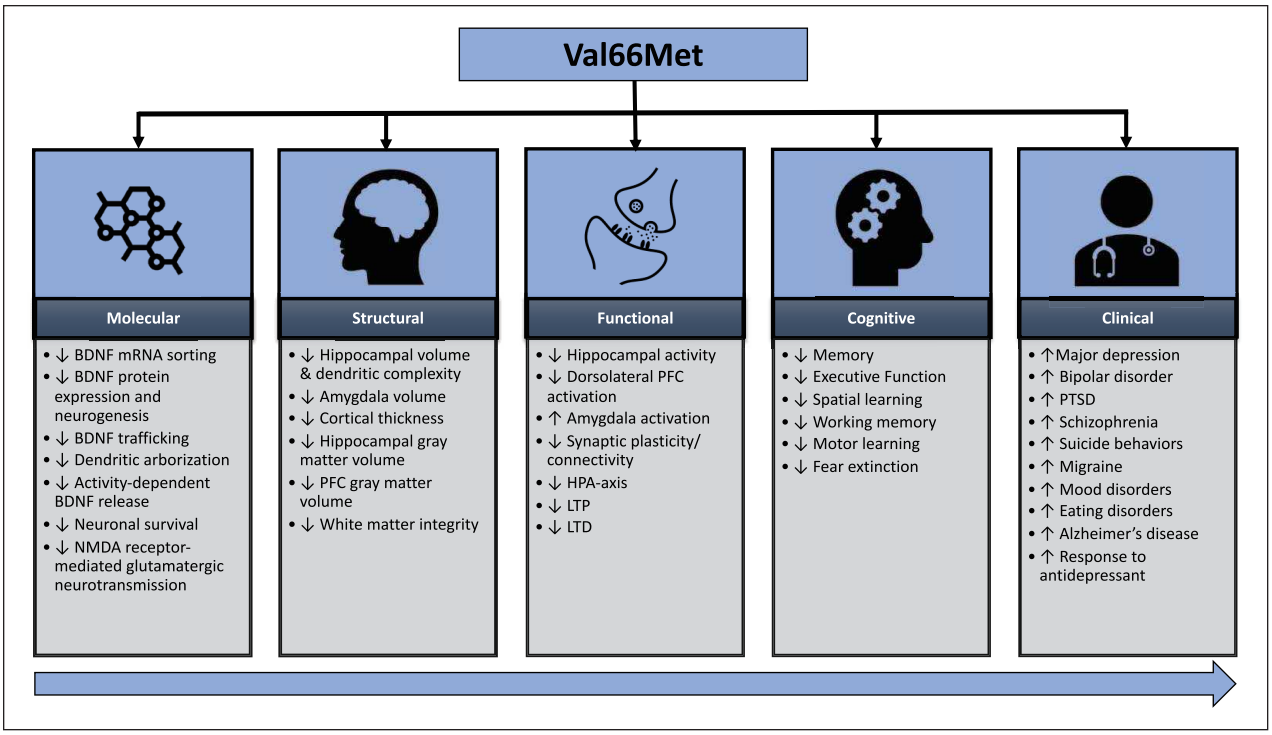

Figure 2. The BDNF Val66Met polymorphism has been associated with different phenotypes at molecular, structural, functional, cognitive and clinical level. At a molecular level, Val66Met leads to altered activity-dependent BDNF secretion, expression, and trafficking as well as acute growth cone retraction, impaired neurogenesis, dendritic arborization, neuronal survival, and reduced N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission. At structural level, Val66Met has been associated with morphological changes in certain brain regions linked to key cognitive processes. Reduced volumes in cortical thickness and brain areas such as the hippocampus, prefrontal cortex (PFC), caudate nucleus, and amygdala have been reported among Met carriers. Decreases in hippocampal and PFC gray matter volume and white matter integrity have also been identified. In vivo and human studies have also provided evidence supporting functional brain dysregulations associated with Val66Met. Altered activation in brain areas such as the hippocampus, PFC and amygdala have been reported in Met carriers. Decreases in synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD), as well as hypothalamic–pituitary–adrenal (HPA) axis dysregulation have been associated with Val66Met. Multiple studies have also explored how this genetic variant modulates different aspects of cognition. Discrepancies between studies are frequent but Val66Met has been linked to reduced performance in episodic and spatial memory tasks, executive function, working memory, processing speed, motor learning and fear extinction. At clinical level, most association studies have identified Val66Met as a potential risk allele for the development of neurological diseases such as major depression, anxiety, bipolar disorder, post-traumatic stress disorder (PTSD), schizophrenia, and Alzheimer's disease among others. However, although many studies revealed numerous neuropsychological phenotypes associated with Val66Met, much controversy still exists regarding the exact role of Val66Met as a risk factor and findings cannot be replicated. This inconsistency may result from the interaction between different factors such as age, sex, environmental factors, ethnicity and gene-gene interactions. Figure generated from the following reviews: Bath and Lee 2006; Chen, Bath, McEwen, Hempstead and Lee 2008; Dincheva, Glatt and Lee 2012; Miranda, Morici, Zanoni and Bekinschtein 2019; Notaras, Hill and Van Den Buuse.

2005). A detailed description of the methodology employed, and the results of the systematic review are provided in the Supplemental Material files.

The Moderating Effect of Val66Met in Observational Studies

Consistent with recent studies (Mandelman and Grigorenko 2012; Toh and others 2018), most observational studies did not find differences in cognitive capacity independent of the effects of PA between Val and Met carriers. When PA was considered, nine out of 11 observational studies reported significant interactions between Val66Met, PA or CRF, and cognitive function (Table 1). Nevertheless, the direction of the effect of Val66Met in those nine studies was inconsistent and only reached statistical significance in a small number of cognitive tests, which reinforces the possibility that some aspects of cognition are more susceptible than others to the modulatory effects of this polymorphism (Toh and others 2018). When

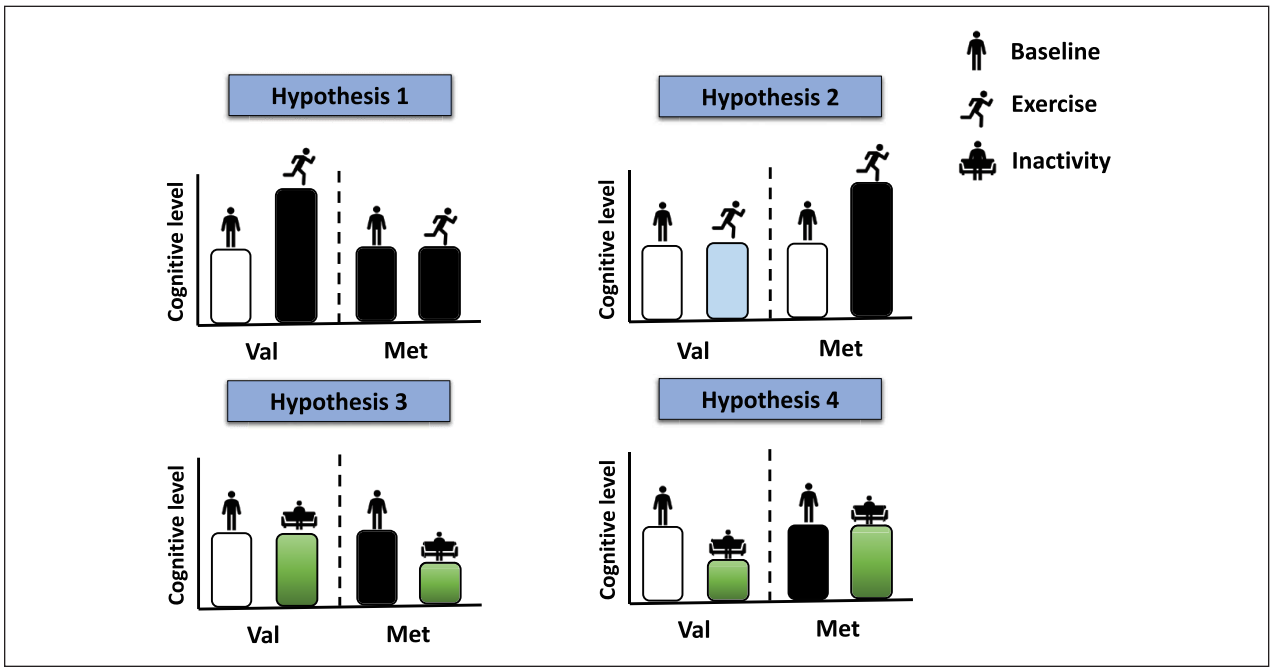

Figure 3. Potential hypotheses proposed to explain the effect of Val66Met in moderating the cognitive response to physical activity (PA) and exercise. Hypothesis 1. Due to a more effective activity dependent secretion of brain-derived neurotrophic factor (BDNF), Val carriers might have a greater cognitive response to PA and exercise compared to Met carriers. Hypothesis 2. Due to a less effective activity dependent secretion of BDNF, exposure to activities that promote increases in BDNF secretion such as PA and exercise will result in Met carriers showing a greater cognitive response compared to Val carriers. Hypothesis 3. Due to a more effective activity dependent secretion of BDNF, Val carriers might be protected from the deleterious effects of lack of PA and exercise on cognition. Hypothesis 4. Due to the higher reliance on BDNF secretion to maintain cognition, Val carriers might be more susceptible to the effects of lack of PA and exercise on cognition.

only Val carriers were compared, four studies showed that high levels of PA were associated with better performance in memory (Canivet and others 2015; Watts and others 2018) and executive function (Canivet and others 2017; Thibeau and others 2016; Watts and others 2018), while one study found no association with memory (Brown and others 2019). When only Met carriers were compared, two studies showed that higher PA levels were associated with better performance in memory (Brown and others 2019) and global cognition (Pitts and others 2020), while two studies showed no influence of PA level in memory (Canivet and others 2015) or executive function (Thibeau and others 2016). Strikingly, one study found that male Met carriers engaging in moderate PA performed poorer than sedentary male Met carriers in memory and executive function (Watts and others 2018). Three studies showed that lower PA Val carriers outperformed lower PA Met carriers in executive function (Canivet and others 2017), working memory (Erickson and others 2013) as well as in both global cognition and incident dementia (Kim and others 2011). However, these differences were abolished when only higher PA Val and Met participants were compared, suggesting that increasing PA might offset the potential cognitive disadvantage of carrying the Met allele. It should be noted, however, that the results of all observational studies analyzed together provided no evidence of a consistent direction of the effect of Val66Met in moderating the impact of PA on different aspects of cognition.

The Moderating Effect of Val66Met in Interventional Studies

Most (Baird and others 2018; Hopkins and others 2012; Keyan and Bryant 2017, 2019; Leckie and others 2014; Moreau and others 2017; Nascimento and others 2015; Piepmeier and others 2020) but not all (Charalambous and others 2018; Helm and others 2017; Maass and others 2016) of the interventional studies that compared the effects of an exercise and control intervention found that exercise had a positive effect on cognitive performance independently of Val66Met genotype. Only five out of the 16 interventional studies found a significant effect of Val66Met in mediating the cognitive response to exercise (Table 2). Similar to the results of observational studies, the direction of the moderating effect of Val66Met among

Table 1. Main Characteristics of the Observational Studies Included in the Review.

Study	Design	Population	PA and CRF Measures (Categorization)	Cognitive Domain	Cognitive Tests	Main Findings
(Brown and others 2019)	Cross-sectional	N = 99 E = NA M/F = 45/54 A = 69.10 ± 5.20 Val = 61; Met = 38	GXT on a cycle ergometer (VO_2peak)	Learning and memory	CVLT, BVMT, CPAL	Lower-fit Met carriers underperformed higher-fit Met carrier in the CPAL task. Differences between lower-fit and higher-fit Val carriers were not significant.
(Canivet and others 2015)	Cross-sectional	N = 205 E = Caucasian M/F = 88/117 A = 72.72 ± 9.16 Val = 118; Met = 87	NASA/JSC PA Scale, HLAQ *(inactive, active)*	Learning and memory	WMS-III (Logical memory II)	Higher-PA Val carriers outperformed lower-PA Val carriers in episodic memory. Differences between higher-PA Met carriers and lower-PA Met carriers were not significant.
(Canivet and others 2017)	Cross-sectional	N = 114 E = Caucasian M/F = 56/58 A = 71.53 ± 9.13 Val = 58; Met = 56	NASA/JSC PA Scale, HLAQ *(inactive, active)*	Executive function	Computerized Simon-like reaction time task	Lower-PA Val carriers underperformed higher-PA Val carriers and lower-PA Met carriers in the incongruent trials of the Simon-like task. Differences between higher-PA Val carriers and higher-PA Met carriers were not significant.
(Erickson and others 2013)	Cross-sectional	N = 1032 E = Non-Hispanic Caucasian M/F = 494/538 A = 44.59 ± 6.78 Val = 671; Met = 361	Paffenbarger Physical Activity Questionnaire *(weekly kilocalories spent)*	Learning and memory Executive function	TMT-A&B, WMS-III (Logical memory I and II, visual reproduction, backward spatial span) Letter n-back, Spatial n-back.	Lower-PA Val carriers outperformed lower-PA Met carriers in working memory tasks. Differences between higher-PA Val and higher-PA Met carriers were not significant.
(Kim and others 2011)	Longitudinal (2.4 years)	N = 732 E = Asian M/F = 300/432 A = 74.85 ± 6 Val = 158; Met = 467	Self-reported 4-point scale of participation in PA *(sedentary, not very active, fairly active, very active)*	Global cognition	MMSE	Lower-PA Met carriers showed worse cognitive decline (MMSE) and incidence dementia than Lower-PA Val carriers during the follow up period. Differences between higher-PA Val carriers and higher-PA Met carriers were not significant.
(Pitts and others 2020)	Cross-sectional	N = 1386 E = Caucasian M/F = 1260/126 A = 62.60 ± 14.30 Val = 945; Met = 441	Self-reported questionnaire of participation in PA *(no exercise, any exercise)*	Global cognition	MOS-CFS Cogstate brief battery	Depressed higher-PA Met carriers outperformed depressed lower-PA Met carriers in the MOS-CFS and the Cogstate measures of working memory and visual learning.

(continued)

Table 1. (continued)

Study	Design	Population	PA and CRF Measures (Categorization)	Cognitive Domain	Cognitive Tests	Main Findings
(Swardfager and others 2011)	Cross-sectional	N = 88 E = Caucasian, Other M/F = 75/13 A = 62.79 ± 10.47 Val = 55; Met = 29	GXT on a cycle ergometer (VO_2peak)	Learning and memory Executive function Global cognition	CVLT TMT-B, Stroop test, WAIS-III (Digit symbol-coding task), MMSE	Val66Met did not moderate the interaction between CRF and cognitive performance.
(Sanders and others 2020)	Longitudinal (12 years)	N = 3337 E = NA M/F = 1469/1868 A = 74.40 ± 6.56 Val = 2108; Met = 1112	Self-reported questionnaire of participation in PA *(sedentary, light, moderate, vigorous)*	Global cognition	3MS	Val66Met did not moderate the interaction between PA and cognitive performance.
(Stojanovic and others 2020)	Longitudinal (3 years)	N= 3 27 E = NA M/F = 127/200 A = 72.80 ± 8 Val = 203; Met = 100	Self-reported questionnaire of participation in PA previous 10 years *(low, high activity)*	Learning and memory Executive function	FCSRT, WMS-III (Logical memory, associate learning/verbal paired associates, Digit span forward and backward, Letter-number sequencing), WAIS-III (Digit symbol-coding task), TMT-A&B, Category Fluency and Letter Word Fluency test	Val66Met did not moderate the interaction between PA and cognitive performance.
(Thibeau and others 2016)	Longitudinal (9 years)	N = 577 E = NA M/F = 197/380 A = 70.47 ± 8.59 Val = 380; Met = 197	Four-item PA subscale from the VLS-Activity Lifestyle Questionnaire *(continuous scale)*	Executive function	Hayling sentence completion test, Stroop test, Brixton spatial anticipation test, CTT	Higher-PA Val carriers outperformed lower-PA Val carriers in executive function at baseline and over time. PA level did not affect executive function in Met carriers.
(Watts and others 2018)	Longitudinal (12 years)	N = 2449 E = Caucasian, Asian, Other M/F = 1260/1189 A = 62.53 ± 1.51 Val = 1474; Met = 744	Self-reported Questionnaire. of participation in PA *(none to mild, moderate, vigorous)*	Learning and memory Executive function	SDMT, CVLT, WMS-III (Digit span backward task)	Male Val carriers engaged in moderate and vigorous PA showed slower decline in memory and executive function task over time than male Val carriers with low or non-PA. Male Met carriers engaged in moderate PA showed worse memory and executive function performance over time than male Met carriers with non-PA. Cross-sectional differences were not significant.

A = age; BVMT = Brief Visuospatial Memory Test; CRF = cardiorespiratory fitness; CTT = Color Trails Test; CPAL = Continuous Paired Associate Learning; CVLT = California Verbal Learning Test; E = ethnicity; F = female; FCSRT = Free and Cued Selective Reminding Test; GXT = Graded Exercise Test; HLAQ = Historical Leisure Activity Questionnaire; M = male; Met = methionine; MMSE = Mini-Mental State Examination; MOS-CFS = Medical Outcomes Study Cognitive Functioning Scale; N = number of subjects; NA = not available; NASA/JSC = National Aeronautics and Space Administration/Johnson Space Center; PA = physical activity; SDMT = Symbol-Digit Modalities Test; TMT-A&B = Trail Making Test Parts A & B; Val = valine; VLS = Victoria Longitudinal Study; VO_2peak = peak oxygen consumption; WMS-III = Wechsler Memory Scale–Thirrd Edition; WAIS-III = Wechsler Adult Intelligence Scale Third Edition; 3MS = Modified Mini-Mental State.

Table 2. Main Characteristics of the Interventional Studies Included in the Review.[a]

Study	Design	Population	Intervention	Cognitive Domain	Cognitive Tests	Main Findings
(Baird and others 2018)	Acute	N = 48 E = NA M/F = 17/31 A = 23.34 ± 3.20 Val = 32; Met = 16	Type: Cycle ergometer Duration: until 200 kcal Intensity: Moderate and vigorous	Learning and memory	3D Serial target task	Met carriers exhibited faster response times in response to exercise.
(Christiansen and others 2019)	Acute	N = 65 E = NA M/F = 65/0 A = 24.22 ± 2.44 Val = 46; Met = 19	Type: Cycle ergometer Duration: 17 min Intensity: Light and vigorous	Learning and memory	VAT	Val66Met did not moderate the effect of exercise on motor learning.
(Charalambous and others 2018)	Acute	N = 45 E = NA M/F = NA A = 58 ± 11.70[b] Val = 34; Met = 11	Type: Treadmill and total body exerciser Duration: 15 min Intensity: Moderate to vigorous	Learning and memory	Split-belt treadmill locomotor learning task	Met carriers in the vigorous intensity group showed a similar rate of relearning than Val carriers.
(Gomes-Osman and others 2017)	Long-term	N = 14 E = NA M/F = 5/9 A = 27 ± 12.30 Val = 8; Met = 6	Type: Treadmill Length: 4 weeks Frequency: 4/week Duration: 30 min Intensity: Light	Learning and memory Executive Function	BVMT, RAVLT, CPT-3, TMT-A&B, Stroop test	Met carriers showed greater improvements in memory yet smaller improvements in executive function than Val carriers in response to exercise but differences did not reach statistical significance.
(Harper and others 2019)	Long-term	N = 35 E = NA M/F = 23/12 A = 64.96 ± 8.01[b] Val = 25; Met = 10	Type: Cycle ergometer Length: 1 week Frequency: 3/week Duration: 40 min Intensity: Light to moderate	Executive function Global cognition	Webneuro MoCA	Val66Met did not moderate the effect of exercise on executive function and global cognition.
(Helm and others 2017)	Acute	N = 54 E = NA M/F = NA A = 24.19 ± 2.61 Val = 28; Met = 26	Type: Upper body ergometer Duration: 5 min Intensity: Vigorous	Learning and memory	Split-belt treadmill locomotor learning task	Val66Met did not moderate the effect of exercise on motor learning.

(continued)

Table 2. (continued)

Study	Design	Population	Intervention	Cognitive Domain	Cognitive Tests	Main Findings
(Hopkins and others 2012)	Acute/long-term	N = 54 E = NA M/F = 14/40 A = 20.60 ± 0.4 Val = 31; Met = 23	Type: Treadmill Length: 4 weeks Frequency: 4/week Duration: 30 min Intensity: Moderate	Learning and memory	NOR	Val carriers showed better NOR performance than Met carriers in the group that performed 4 weeks of exercise and one last bout of exercise 2-4 hours prior testing.
(Keyan and Bryant 2017)	Acute	N = 62 E = NA M/F = 20/42 A = 20.87 ± 3.02[b] Val = 30; Met = 32	Type: Stepping exercise Duration: 10 min Intensity: Vigorous	Learning and memory	Free recall picture test	Val66Met did not moderate the exercise response to emotional memory.
(Keyan and Bryant 2019)	Acute	N = 70 E = Caucasian, Asian, and other M/F = 40/30 A=20.64 ± 2.97[b] Val = 33; Met = 36	Type: Cycle ergometer Duration: 20-25 min Intensity: Vigorous	Learning and memory	Differential fear conditioning and extinction paradigm	Met carriers did not benefit from the effects of exercise on fear extinction.
(Leckie and others 2014)	Long-term	N = 92 E = NA M/F = 33/59 A = 66.82 ± 5.60 Val = 85; Met = 7	Type: Walking Length: 1 year Frequency: 3/week Duration: 40 min Intensity: Moderate to vigorous	Executive function	Task-switch paradigm	Val66Met did not moderate the exercise response task-switch paradigm performance.
(Maass and others 2016)	Long-term	N = 40 E = NA M/F = 18/22 A = 68.40 ± 4.30 Val = 23; Met = 17	Type: Treadmill Length: 12 weeks Frequency: 3/week Duration: 40 min Intensity: Moderate to vigorous	Learning and memory	CF test, VLMT	Val66Met did not moderate the exercise response to verbal or visuospatial memory performance.
(Mang and others 2017)	Acute	N = 32 E = Caucasian, Asian, Hispanic M/F = 14/18 A = 24.80 ± 4.20 Val = 14; Met = 18	Type: Cycle ergometer Duration: 20 min Intensity: Vigorous	Learning and memory	CT, ST	Val66Met did not moderate the exercise response to motor learning.

(continued)

Table 2. (continued)

Study	Design	Population	Intervention	Cognitive Domain	Cognitive Tests	Main Findings
(Moreau and others 2017)	Long-term	N = 305 E = Caucasian, Asian, Pacific, Other M/F = 118/187 A = 9.90 ± 1.74 Val = NP; Met = NP	Type: Video-based training Length: 6 weeks Frequency: 5/week Duration: 10 min Intensity: Vigorous	Executive function	Flanker task, Go-No-Go task, Stroop test, Backward digit span, Visual 2-back, Backward corsi blocks	Met carriers exhibited larger gains in cognitive control and working memory response after 6 weeks of training.
(Nascimento and others 2015)	Long-term	N = 45 E = NA M/F = 13/32 A = 67.50 ± 4[b] Val = 26; Met = 19	Type: Multimodal Length: 16 weeks Frequency: 3/week Duration: 60 min Intensity: Moderate to vigorous	Global cognition	MoCA	Val66Met did not moderate the exercise response to global cognition.
(Piepmeier and others 2020)	Acute	N = 29 E = NA M/F= 29/0 A = 21.69 (18-29) Val = 18; Met = 11	Type: Cycle ergometer Duration: 35 min Intensity: Light and vigorous	Learning and memory	RAVLT, spatial memory task	Val66Met did not moderate the exercise response to memory.

A = age; BVMT = Brief Visuospatial Memory Test; CF = complex figure; CPT-3 = Connors' Continuous Performance Test–Third Edition; CT = continuous tracking; E = ethnicity; F = female; HRmax = heart rate maximum; HRR = heart rate reserve; M = male; Met = methionine; MoCA = Montreal Cognitive Assessment; N = number of subjects; NA = not available; NOR = Novel Object Recognition; RAVLT = Rey Auditory Verbal Learning Test; ST = Serial Targeting; TMT-A&B = Trail Making Test Parts A & B; Val = valine; VAT = visuomotor accuracy tracking; VLMT = Verbal Learning and Memory Test.

[a]In controlled studies, the total number of participants (N) include both the exercise and control group.

[b]Groups average.

these five interventional studies was also equivocal. Two studies showed that Val carriers had a better response to exercise than Met carriers in memory (Hopkins and others 2012) and fear extinction (Keyan and Bryant 2019), while three other studies showed that Met carriers had a greater response to exercise in motor learning (Baird and others 2018; Charalambous and others 2018) and executive function (Moreau and others 2017).

The study by Moreau and others (2017) is particularly relevant because, among all the interventional studies, this was the only high-quality randomized placebo-controlled trial with a large sample size (n = 305). Although the results of this study support the hypothesis that Met carriers are more responsive to the effects of exercise (Fig. 3), when analyzed together, the results of all the interventional studies also provided little evidence of a consistent moderating effect of Val66Met. It is important to note, however, that except for the study by Moreau and others (2017), the number of participants allocated into exercise groups in the interventional studies was small. Furthermore, the small prevalence of Met alleles in the populations investigated in the studies (Hashimoto 2016; Pivac and others 2009) reduced even more the number of Met carriers. Hence, most interventional studies were possibly underpowered to detect reliably potential differences between Val and Met carriers in the cognitive response to exercise.

Inconsistencies Among Studies

Eighty-two percent of the observational studies and only 31% of the interventional studies found a moderating effect of Val66Met polymorphism. At face value, this difference could be interpreted as if Val66Met modifies the association between PA and cognition more strongly than the response to exercise. However, this difference could be explained by the fact that the observational studies were better designed to capture the moderating effects of Val66Met. The larger sample sizes of observational studies allowed for better control of potential moderators that could influence the effect of Val66Met (Barha and others 2017; Leckie and others 2012) and provided sufficient statistical power for detecting even small interactions. Furthermore, participants in the observational studies tended to be older than participants in the interventional studies. It has been suggested that, due to a reduction of brain resources, the genetic effects of Val66Met are more likely to result in cognitive differences later in life (Lindenberger 2008). Hence, one could speculate that the different sensitivities of observational and interventional studies for detecting a potential Val66Met effect could be due to differences in the age of participants. However, age alone cannot explain these differences; four of the five interventional studies that involved older participants did not show any effect of Val66Met in moderating the cognitive response to exercise (Harper and others 2019; Leckie and others 2014; Maass and others 2016; Nascimento and others 2015).

Inconsistencies in the findings of both observational and interventional studies could also be explained by methodological differences. It is possible that the use of different cognitive tests (Supplemental Table 1) with different sensitivities to capture the effects of Val66Met could have contributed to the disparity of results in both observational and interventional studies. However, we were not able to identify clear trends suggesting that specific areas of cognition were more susceptible to the moderating effect of Val66Met (Toh and others 2018). A potential source of heterogeneity specific to observational studies was the use of different methods to assess PA. Except for two observational studies, which used exercise tests to determine CRF (Brown and others 2019; Swardfager and others 2011), the rest of the studies used self-reported questionnaires to estimate PA. Self-reported measures of PA are prone to bias and measurement errors (Ainsworth and others 2012), which could have led to inaccuracies in the allocation of participants into different PA level groups. Furthermore, PA measures assessed with self-reported questionnaires are not always well correlated with the gold standard exercise test–based measures of CRF (Lee and others 2011), which are potentially more strongly associated with cognition than measures of PA (Barnes and others 2003). Thus, it is possible that the use of self-reported PA questionnaires and the inherent inaccuracies of this method might have masked potential associations between Val66Met, PA, and cognition. Besides the inaccuracies of the self-reported PA questionnaires, an additional aspect that could have contributed to augment discrepancies in the results among observational studies is the lack of consistency in the categorization of the level of PA. Indeed, the studies used very different approaches and categorizations of the level of PA (Table 1). For example, while Canivet and others (2015) divided the participants into two categories (active, inactive), Kim and others (2011) categorized participants into four groups (very active, fairly active, not very active, not at all active). Erickson and others (2013), alternatively, estimated weekly kilocalories expended using a PA questionnaire as a continuous measure to assess PA.

Differences in the design, number and characteristics of participants as well as in the exercise interventions used could have also contributed to increase the inconsistency observed in the results of the interventional studies. However, due to the high level of heterogeneity and the small number of studies showing a moderating effect of Val66Met, we could not identify which of these variables explained why some interventional studies found a significant effect while others did not. It was also not

possible to determine what drove the direction of the moderating effect of Val66Met and why, in some studies, Val carriers demonstrated a better cognitive response to exercise (Hopkins and others 2012; Keyan and Bryant 2019) while in other studies Met carriers seemed to respond more effectively (Baird and others 2018; Charalambous and others 2018; Moreau and others 2017). The characteristics of the participants, exercise interventions, and cognitive domains assessed did not seem to consistently explain either the presence or the direction of the effect of Val66Met in moderating the cognitive response to exercise.

The Potential Influence of Other Moderators

Besides the potential influence of age-related decline in brain resources (Lindenberger 2008), which we have already discussed previously, it is possible that the effect of Val66Met could have also been influenced by other moderators such as biological sex (Barha and others 2017), interactions with other genes (Leckie and others 2012), as well as ethnicity and pathophysiological factors (Tsai 2018). Biological sex has been shown to moderate the effect of Val66Met on brain plasticity and cognition. When compared with males Met carriers, female Met carriers have lower hippocampal resting blood flow (Wei and others 2012) and are more susceptible to age-related cognitive decline (Laing and others 2012), reductions in brain volume (Nemoto and others 2006) and increased risk of Alzheimer's disease (Fukumoto and others 2010). Female Met carriers also tend to show reduced increases in peripheral BDNF in response to exercise training (Nascimento and others 2015). Only two studies included in the review specifically investigated differences between males and females (Sanders and others 2020; Watts and others 2018), and only one found a significant effect in the moderating effect of Val66Met (Watts and others 2018). Watts and coworkers demonstrated that only males were influenced by Val66Met genotype, with male Val carriers who engaged in moderate and vigorous PA showing a slower decline in memory and executive function task over time when compared to male Val carriers with low or non-PA. Since the rest of the studies did not directly analyze the impact of biological sex, we cannot discard that the inclusion of both males and females could have diluted the moderating effects of Val66Met. Clearly, more studies exploring the effects of biological sex in the interaction between genotype, PA, exercise and cognition are needed (Barha and others 2017).

Interactions with other genes could have also influenced the effects of Val66Met in moderating the response to PA and exercise and cognition (Leckie and others 2012). A recent study demonstrated synergistic associations between Val66Met, catechol-O-methyltransferase (COMT), and the apolipoprotein E (APOE) genes in mediating the association between lifestyle activities (including PA) and executive function (Sapkota and others 2017). Specifically, the study revealed that APOE ε4+ SNP moderated the effects of Val66Met, increasing the risk of cognitive deficits, even in the group with high PA levels. They also observed that APOE ε4+ carriers with Val66Met and COMT genotypes presented poorer executive function performance. Similar results were presented by Ward and others (2014), who found that APOE and Val66Met interacted with each other in predicting performance in episodic memory. Some observational studies of the review excluded APOE ε2/ε4 carriers (Watts and others 2018), some others included the specific APOE variant (SNP) in the analysis as a covariate (Kim and others 2011; Pitts and others 2020; Sanders and others 2020), while some others did not consider the potential influence of APOE status (Brown and others 2019; Canivet and others 2015; Canivet and others 2017; Erickson and others 2013; Swardfager and others 2011; Thibeau and others 2016). No consistent differences among these groups of studies were found in relation to the moderating effect of Val66Met.

Thibeau and colleagues observed a significant interaction between Val66Met and insulin-degrading enzyme gene (IDE) with levels of PA and executive function (Thibeau and others 2016) and Sanders and colleagues reported that, while Val66Met did not show any moderating effects, the nerve growth factor receptor SNP (rs2072446) of the BDNF gene moderated the association between PA and cognitive performance in males (Sanders and others 2020). Together, these findings highlight the importance of studying interactions with other genetic or epigenetic factors that could interact with the moderating effects of Val66Met (Watts and others 2018).

Several studies have shown that ethnicity is another potential moderator of the effect of Val66Met on cognition and the risk of developing neuropsychiatric disorders (Tsai 2018). For example, meta-analyses have shown that carrying the Met allele can increase the risk of bipolar disorder (Li and others 2016) and Parkinson's disease (Lee and Song 2014) in Europeans but not in Asians, suggesting that the direction of the Val66Met effect can vary completely depending on the ethnicity of participants. It is therefore possible that differences in ethnicity could have contributed to increase the inconsistencies among the results of the studies in the review. The ethnicity of the participants of each study is reported in Tables 1 and 2. However, only 10 studies provided specific information about the ethnicity of their participants, and most of these studies included different ethnic groups. Hence, it was not possible to determine

whether ethnicity influenced the moderating effects of Val66Met or not.

As discussed previously, BDNF and the Val66Met polymorphism have been implicated in the pathogenesis of certain neuropsychiatric disorders (Neves-Pereira and others 2002; Sklar and others 2002; Zhao and others 2018). Reduced expression and activity of BDNF protein have been observed in neuropsychiatric conditions, including major depression, schizophrenia, and mood disorders in both animal and human studies (Angelucci and others 2005; Lee and Kim 2010; Thompson Ray 2011) (Fig. 2). Physical activity and exercise have demonstrated to attenuate the detrimental effects that some of these clinical conditions have on cognition and BDNF has been suggested to play a key mediating role (Lin and others 2015; Wang and Holsinger 2018). However, whether the moderating effect of Val66Met on the cognitive response to exercise is increased or, on the contrary, hindered in persons with these clinical conditions is currently unknown.

The review included six studies with patients with clinical conditions, including stroke (Charalambous and others 2018), Parkinson's disease (Harper and others 2019), depression (Pitts and others 2020), mild cognitive impairment (Nascimento and others 2015), dementia (Kim and others 2011) and coronary artery disease (Swardfager and others 2011). Only three of these studies showed significant effects of Val66Met in moderating the cognitive response to PA or exercise and the results suggested that Met carriers could be especially sensitive to improve cognition when exposed to high levels of PA (Kim and others 2011; Pitts and others 2020) and exercise (Charalambous and others 2018) (Hypothesis 2; Fig. 3). However, due to the reduced number of studies, it is not possible to determine conclusively if Met carriers with clinical conditions are more susceptible to the effects of PA or exercise. More studies investigating the role of Val66Met in moderating the effects of exercise on cognitive function in clinical populations are clearly needed.

Conclusions

This review provided a detailed analysis of the evidence derived from observational and interventional studies investigating the role of Val66Met in modulating the effects of PA and exercise on cognition. Our results do not consistently support any of the hypotheses proposed to explain the potential moderating effect of Val66Met (Fig. 3). The influence of Val66Met was more common among observational than interventional studies, possibly due to the lack of power of the interventional studies. The effect of Val66Met, if any, is possibly small, does not affect all aspects of cognition and might be influenced by many other moderators such as age, biological sex, ethnicity, and interaction with other genes. Importantly, the effect does not lead to a consistent superior cognitive response to PA and exercise in Val carriers nor a lower response in Met carriers. Conversely, the disparity of results suggests that both genotypes can benefit from the effects of PA and exercise to improve some aspects of cognition and that any potential difference in cognitive capacity between Val and Met carriers, if present, tends to diminish when high levels of PA are achieved.

Limitations

The most important limitation of this review was the considerable heterogeneity of the studies, which varied substantially in terms of design, participants characteristics, PA levels assessment and categorization, exercise interventions, as well as cognitive domains and cognitive tests used. This large heterogeneity deterred us from conducting a full meta-analysis to obtain an overall effect of the influence of Val66Met in modulating interactions between PA or exercise on cognition. Given the disparity in the direction of the Val66Met effect, however, it is unlikely that such meta-analysis would have provided results different from the ones reported here. Heterogeneity was also the main reason why, as we have done in previous meta-analyses (Roig and others 2013), we did not perform a formal assessment of the methodological quality of the studies. The methodological rigor of the studies could have been used to factorize in the level of evidence provided by each study; however, the heterogeneity in study designs and the disparity of the results reduced the usefulness of any methodological quality assessment.

An additional challenge of this review was the classification of the distinct cognitive tests, which we broadly classified into the domains of learning and memory, executive function, and global cognition. Currently, there is no consensus regarding the most accurate categorization of cognitive tests and some of the tests used in the studies encompassed multiple cognitive functions that were difficult to categorize. To circumvent this limitation and maximize consistency, we used one of the most well-established compendiums for neuropsychological assessment (Strauss and others 2006), which provides precise definitions and categorizations of tests into different cognitive domains. It should be noted, however, that since some of the tests used (e.g., motor learning) were not described in the compendium, we categorized them based on their description. Regardless, even if a more precise categorization of the cognitive tests used in the studies could have been performed, it is unlikely that the interpretation of the results of the review would have differed.

Future Directions

Future genetic studies controlling for variables that can potentially influence the effects of exercise in cognition

(e.g., biological sex and age) are needed to understand the mediating role of Val66Met. Single-gene candidate studies need to evolve toward both multiple-gene candidate studies and genome-wide association studies (GWAS). GWAS and polygenic risk scores in multiple-gene candidate studies would allow for better control of the variance embedded in small sets of SNPs, increasing in turn, the power of set-based analysis (Baker and others 2018; Ritchie and others 2001). While candidate gene studies select only certain genes based on prior tested associations, GWAS test hundreds of thousands of SNPs operating as a "data-mining tool," for which no prior knowledge of specific target genes is required. GWAS could be a suitable and effective method to detect new associations between genes and complex phenotypes such as cognitive function in more robust studies (Hagenaars and others 2016; Hillman and Biggan 2017; Trampush and others 2017).

Multicenter studies and large research consortia provide an opportunity to circumvent methodological challenges required by these novel approaches such as large sample sizes (Davies and others 2018). We should also reconsider the methods by which we study whether genetics modulates the effects of exercise on cognition. Implementing statistical models that account for multiple covariates and reflect the proportion of accounted variance of genotype in complex phenotypes, would provide a more precise picture of the extent to which our genes impact the response to exercise in cognition (Christiansen and others 2019). Finally, observational studies should also use more accurate, consistent, reliable, and easy to implement measures of PA to study interactions between different genes and measures of cognition. Finally, interventional studies should be sufficiently powered to detect the potential effect of Val66Met and other SNPs in mediating the effects of exercise on cognition.

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Supplemental Material

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