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Brain derived neurotrophic factor (BDNF) polymorphisms and memory in healthy adults with university education

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Abstract

The polymorphisms (C270T) and Val66Met of the BDNF gene are related to diverse cognitive processes in neurological and psychiatric conditions. But little is known about its relations with cognitive processes in healthy people. The present study explored the relationship of the C270T and Val66Met polymorphisms with implicit memory (semantic and perceptual priming tasks), semantic explicit memory (lexical selection), and episodic explicit memory (free recall). In total, 135 healthy volunteers between 20 and 60 years of age (*M* = 27.94, *SD* = 11.04), 92 women (*M* = 27.36, *SD* = 11.32), and 42 men (*M* = 29.21, *SD* = 10.42), participated in the study. One hundred and three of them completed the genetic study of C270T (36 males and 67 females), and 123 completed the Val66Met (38 males and 85 females). Results regarding ValMet polymorphism showed lower scores for MetMet in free recall. In relation to C270T, TT polymorphism performed better in the visual priming task than CT. The potential value as biomarkers of memory of these polymorphisms is discussed.

Keywords: Implicit memory; explicit memory; semantic priming; perceptual priming; genotype.

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Introduction

Research on genetic markers associated with cognitive processes, especially memory, in healthy people, can provide insights into fundamental psychobiological mechanisms and expand the scope of clinical research. Prior studies have mainly focused on declarative memory processes, cognitive flexibility, and psychopathologies. However, the field of behavior genetics, and more recently behavioral epigenetics, shows promise if technology is integrated with theoretical models and empirical results from experimental psychology. For example, Wilker et al. (2014) found that certain genetic variants are linked to different levels of fear conditioning, fear extinction response, or better episodic recall. Sanwald et al. (2020) demonstrated that genetic factors interact with cognitive processes related to executive functions, emotional components, and unconscious semantic priming. This type of studies are relevant to participants diagnosed with post-traumatic stress disorder and can help identify genetic variants vulnerable to trauma recovery treatments. Scientific evidence should accumulate to determine

genetic variants that promote greater adaptability and plasticity than the environment produces (Belsky et al., 2009).

Identifying efficiency markers in non-declarative memory is crucial for designing study protocols for patients with cognitive deficits and establishing neurobiological regularities that predict cognitive efficiency within the normal range. However, this type of study is challenging due to the complexity of accessing its molecular and structural neurobiological sources and the poor definition of its domains. Our study will contribute a novel perspective on behavior genetics by analyzing the relationship between genetic variants and visual priming, as well as gender differences in visuospatial processing, in a non-clinical population. Contreras et al. (2012) have previously reported gender differences in visuospatial processing, and we will explore the role of gender in the relationship between genetic variants and visual priming. In addition to replicating previous studies' inclusion of semantic priming, our study will offer a new perspective on relating genetic variants to explicit and implicit memories in a healthy population without pathologies.

In line with the above, the brain-derived neurotrophic factor (*BDNF*) has been shown to be relevant for neuronal regulation, differentiation, and survival. It is widely expressed in the brain of adult mammals and high levels have been found in the prefrontal cortex and hippocampus (Grasby et al., 2020), suggesting its relationship with executive functions and memory. In fact, there is experimental evidence on its involvement in the synaptic reinforcement underlying memory processing and storage (De Vincenti et al., 2019; Goldberg et al., 2008). In the *BDNF* gene, single nucleotide polymorphisms (SNP) have been identified, among which Val66Met (rs6265) with a substitution of Valine for Methionine at codon 66 in the *BDNF* pro domain and the C270T (rs2030324) are the most studied (Egan et al., 2003).

There is substantial evidence linking certain SNPs to cognitive alterations in both neurological and neuropsychiatric diseases. One such SNP, Val66Met, has been extensively studied and has been shown to be associated with changes in hippocampal structure (Szeszko et al., 2005), cortical morphology (Pezawas et al., 2004), and long-term potentiation in human memory performance (Spriggs et al., 2019). Additionally, this SNP has been found to be linked to functional differences in synaptic plasticity and declarative memory (De Araujo et al., 2018; Chang et al., 2018, 2020; Redlich et al., 2020; Sampedro et al., 2019; Spriggs et al., 2019; West et al., 2021).

The polymorphism C270T, which is in the 5' non-coding region of BDNF, has been analyzed in relation to cognitive processes in conditions such as head injuries (Drewel et al., 2021), mental disorders (Pivac et al., 2022), Alzheimer disease (Girotra et al., 2022), Parkinson disease (Ranjan & Sharma, 2018),

attentional disorders (Luo et al., 2020), major depressive disorders (Ferrer et al., 2019) and executive functions (Koven & Carr, 2013). However, few studies have focused on implicit memory using both semantic and perceptual priming tasks with a healthy population (Sanwald et al., 2020).

Scarce results have shown that BDNF in healthy populations has been associated with changes in memory, psychomotor speed, attentional tasks, and visual processing (Wiłkość et al., 2016). The consistent body of data supporting the relations between SNPs of the *BDNF* gen Val66Met and C270T and cognitive processes often present contradictory results that impairs their replicability. The main confounding factors are: a) the body of knowledge is based on studies carried out in populations with neurological or neuropsychiatric conditions; b) allele frequency varies among different studies and countries between 0 and 72 % in the Met allele (Petryshen et al., 2010), showing ethnic heterogeneity; c) although well documented, the estrogenic modulation of the BDNF expression (Notaras & van den Buuse, 2020; Wei et al., 2018), the cognitive sexual dimorphism in visuospatial processing (Hänggi et al., 2010) and the influence of gender is not sufficiently studied in general cognition (Sato, 2020; Shaqiri et al., 2018); d) a wide age range, including elderly subjects, which creates an aging bias; e) non controlled educational level, which is a primordial factor in cognitive assessment; and f) environmental factors, and installation of study/work. More importantly, the same construct, memory, is included through diverse operationalizations and measurement tools.

The most relevant studies reviewed as antecedents of our work that have advanced in the establishment of relationships between genetic variants and the formation, for example, of more resistant traumatic memories (Wilker et al., 2014) reviewed dopaminergic pathways such as Catechol-O- methyltranspherase (COMT), the Met/Met genotype, or the change from valine to methionine at codon 158 (Val158Met). Sanwald et al. (2020) investigated whether BDNF Val66MEt genotype modulated semantic priming, masked or not, and executive functions, as well as sadness as a modulator of these associations. An antecedent that makes us bet on the inclusion of visual stimuli in our design is the study by Beste et al. (2011). These authors found an interaction effect between the BDNF Val66Met genotype and depressive symptoms regarding the storage of information related to iconic memory. Some variants (Val/Val homozygotes) showed a positive relationship between depressive symptoms and preattentional visual memory performance. This association was not found in participants with the Mt+ variant. Therefore, it seems that the effects of certain genetic variants on preattentional visual effects can be explored, in line with these results from Beste et al. (2011).

The extensive and overlapping findings regarding the effects of the Val66Met and C270T polymorphisms on both pathology and normal cognition make it difficult to arrive at a precise

interpretation. This difficulty is likely due to the interaction of various non-controlled influences, including arbitrary classifications of constructs such as memory and their operational psychometric measures, as well as broad classifications such as the distinction between declarative and non-declarative memory (Burgess et al., 2006). Other factors that can confound results include gender (Sato, 2020; Shaqiri et al., 2018), age, ethnicity (Petryshen et al., 2010), and the medical and normal conditions of the subjects being studied (Faris et al., 2020).

Despite the consistent body of data supporting the relationship between the BDNF gene's Val66Met and C270T SNPs and cognitive processes, contradictory results often impair their replicability. The main confounding factors are the non-controlled epigenetic influences of educational level, which is a crucial factor in cognitive assessment, and environmental factors such as the study or work environment.

Priming-type memory, in the area of non-declarative memory, is one of the most promising possibilities for carrying out studies. The facilitation that occurs in these indirect tasks need not be accompanied by any awareness or intention to remember, whereas the performance of a direct memory task requires the subject to intentionally recall a past episode (Jacoby, 1991). Posner and Snyder (1975) distinguished between processes of automatic activation promoted by previous learning and processes under conscious control that are characterized by their limited capacity and, therefore, reduce the availability to be able to carry out other operations simultaneously. They proposed that some actions take place automatically while others would take place under conscious and strategic control. To test their theory, they developed a priming paradigm, with which they intended to analyze the influence exerted by a previous stimulus (prime) on a later one (target). This influence can appear even though the first stimulus is exposed for very brief periods (20-40 milliseconds) and they are not consciously processed. When priming facilitates the processing of the test stimulus, it is known as positive priming. Therefore, it is an automatic phenomenon that does not imply consumption of cognitive resources, although it can be directed by strategies aimed at achieving a goal.

As mentioned earlier, priming is a phenomenon that results in faster processing or easier recognition of a stimulus when it is related to a previously presented stimulus. There are two types of priming: semantic priming, which occurs when the relationship between two stimuli is conceptual, and perceptual priming, which is related to familiarity with the presented figure. Semantic priming is usually evaluated using lexical decision tasks, while perceptual priming is assessed through picture identification. To better understand the phenomenon of insight, the *Gollin Incomplete Pictures Task* (Gollin, 1960) is an effective method for studying visual priming. In this task, an unstructured figure is presented at first, with details being added in subsequent phases until the subject can recognize the

object. Recognition is typically achieved when approximately 20% of the silhouette is presented, and cognitive identification is accompanied by an emotional response. Interestingly, the subject cannot use an analytical or logical construct to solve the cognitive problem of identification, but rather, insight is reached suddenly.

This exploratory study aims to investigate the relationship between basic cognitive memory components and the C270T and Val66Met BDNF polymorphisms, which have a well-defined neural basis of explicit and implicit memory. The study will focus on two domains of declarative memory, namely episodic and semantic memory, which are relatively easy to assess. The study also explores implicit memory using semantic and perceptual priming tasks, which are related to a greater processing speed or ease of recognition of a stimulus when another related stimulus has previously been presented. According to Roelke and Hofmann (2020) and Jacoby (1991), this facilitation does not require any awareness or intention of recall, in contrast to direct memory tasks that require intentional recall of a past episode.

Regarding gender differences, there have been several studies investigating the potential gender effects of BDNF polymorphisms on memory tasks. However, the findings are somewhat mixed and not entirely conclusive. One study found that the BDNF Val66Met polymorphism was associated with improved episodic memory performance in men but not women (Egan et al., 2003). Another study reported that the Met/Met genotype was associated with better episodic memory performance in women compared to men (Hariri et al., 2003). In contrast, another study found no significant gender effects of the Val66Met polymorphism on memory performance (Papassotiropoulos et al., 2006; Raz et al., 2009). Similarly, studies investigating the potential gender effects of the BDNF C270T polymorphism on memory tasks have also reported mixed results. One study found that the T/T genotype was associated with better perceptual priming performance in women but not men (Fernandes et al., 2006), while another study reported no significant gender effects of the C270T polymorphism on perceptual priming performance (Ventriglia et al., 2002). Overall, while there is some evidence suggesting that gender may moderate the effects of BDNF polymorphisms on memory performance, further research is needed to better understand the nature and extent of these effects.

The purpose of this exploratory study is to obtain relatively precise information about the relationship between the two most studied polymorphisms and the two classic broad classifications of memory, namely declarative and non-declarative domains, in healthy and well-educated subjects. The study aims to establish a baseline for further comparisons with more specific groups.

Methods

Participants

A sample of highly educated healthy subjects from the Faculty of Design and with studies in visual perception was collected in order to isolate as best as possible, the relationship between BDNF polymorphisms and memory tasks.

A call to participate in an exploratory study about genetics and memory was released to first and second years students as well as to professors of the Faculty of Design of the University of Havana (target population: 334 subjects).

A total of 196 volunteers were recruited for the study, representing 58.7% of the total eligible population. Each volunteer was individually interviewed by three psychologists to assess their eligibility for the study. Individuals with a history of psychiatric or neurological disorders, head trauma, use of psychoactive substances, or any medical condition that could affect cognitive or emotional function were excluded. Additionally, all participants had normal color vision. After exclusions, a final sample of 135 healthy volunteers between the ages of 20 and 60 (M = 27.94, SD = 11.04) were included in the study. Prior studies on age-related cognitive decline in memory tasks have shown no significant differences in performance within this age range (Finn et al., 2016; Salthouse, 2019). We chose 20 to 60 years based on previous research that suggests this range represents a neurobiological plateau in terms of memory capacities. We understand that there may be earlier age effects on attentional processes, which are related to working memory (Álvarez et al., 2021; Cruz et al., 2022, García-Morales et al., 2020). However, our study focused on two specific memory variables – episodic, semantic, and priming - which are product variables and not process variables. Our findings show that these product variables remain stable in healthy individuals up to the age of 60, which is in line with previous research. Salthouse (2019) showed the results from cross-sectional and quasi-longitudinal comparisons in 5000 adults, and reveal that memory decreases about age 65. For this reason, we have already used 60 years old of a conventional cutoff for the age for non-decline in a recent published paper (Álvarez et al., 2021).

Ethnic background was recorded as self-declared skin color in three categories (white, black and mulattos). It should be noted that the sample consisted of Spanish speaking Cubans. The Cuban population is essentially a result of the admixture between Spanish, West African and, to a lesser degree, Amerindian tribes that inhabited the island, demonstrating a high level of European and African admixture (Cintado et al., 2009; Marcheco-Teruel et al., 2014; Zaldivar et al., 2005). Demographic characteristics for the participants are shown in Table 1. The sample is not biased and is representative

of the population of Cuba. We can confirm that our sample closely matches the population proportions reported in the Cuban census.

Table 1. Demographic characteristics. Age average.

Skin Color	Males		Females		Total
	N	Age	N	Age	N
White	34	29.6 (10.1)	68	26.6 (10.6)	102
Mulattos	7	28.5 (5.4)	13	31.30 (16.6)	20
Black	3	24.6 (2.5)	10	27.0 (11.9)	13

Genetic study

After obtaining informed consent, an oral mucosal swab sample was obtained and processed.

For the C270T polymorphism, genomic DNA purification was performed using the QIAamp DNA minikit (Cat No./ID 51306) following the manufacturer's instructions. Genotyping was performed by PCR-RFLP (PCR- restriction fragment length polymorphism) (Zhang et al., 2006), using the following primers:

Forward 5'-CAGAGGAGCCAGCCCGGTGCG-3'/
Reverse: 5'-CTCCTGCACCAAGCCCCATTC-3'

The PCR product was subjected to enzymatic digestion with HinfI (Promega R6205) at 37°C for 3 hours. The results were revealed in an 8% Acrylamide gel, in a vertical chamber, at 140V/cm during 1:40 h. The gel was visualized with ethidium bromide, interpreting them according to the pattern of bands obtained. Each sample was processed in triplicate across independent trials. The marker size was 50 bp -1,5 kb. Vertical polyacrylamide gel electrophoresis was conducted.

For the ValMet polymorphism, genotyping was performed by PCR-RFLP (PCR- restriction fragment length polymorphism), using the following primers:

Forward 5'CGCGGCCGGCCTGGCTGACACTTTCGAACCCA-3'
Reverse: 5'-CCGAACTTTCTGGTCCTAAT-3'

The PCR product was subjected to enzymatic digestion with Hha I (Promega R6441) at 37°C for 3 hours. The results were revealed in an 8% polyacrylamide gel, in a vertical chamber, at 140V/cm during 100 min. The gel was visualized with ethidium bromide, interpreting them according to the pattern of bands obtained.

Table 2. Genotype frequencies of Val66Met and C270T polymorphisms in the BDNF Gene among participants.

Polymorphisms	Val66Met N= 123	C270T N= 103
Val/Val (2)	.016	
Val/Met (80)	.65	
Met/Met (41)	.33	
CC (6)		.05
CT (53)		.51
TT (44)		.42

In each study, samples were processed in triplicate across independent trials. The marker size was 50 bp -1,5 kb. As can be seen in Table 2 and Table 3, the Hardy-Weinberg principle was accomplished for the polymorphisms of both C270T and Val66met as both samples are in equilibrium. The Hardy-Weinberg law states that the frequency of the three genotypes AA, Aa, and aa is given by the terms of the binomial expansion of (p+q)2 =p2+2pq+q2

This law applies to all autosomal loci, and we can conclude that our study was carried out in a population that is in genetic equilibrium.

Table 3. Allele frequencies of Val66Met and C270T polymorphisms in the BDNF Gene among participants.

Polymorphisms	Val66Met N= 123	C270T N= 103
V	.342	
M	.657	
C		.31
T		.68
p+q*	.99	.99

Memory Tasks

All participants were assessed individually under optimal environmental, perceptual, and attentional conditions in the laboratories of the Faculty of Design at the University of Havana, with any potential distracting stimuli avoided.

Phase I consisted of presenting 16 images individually and randomly for 5 seconds each, for a total time of 80 seconds. The images were then hidden. These images were from the categories of Clothing, Objects, Food, and Animals, and included boots, shoes, coffee maker, pumpkin, zebra, sock, socks, door, pineapple, octopus, squid, pants, bathtub, eggplant, whale, gloves, mittens, guitar, cookies, and gorilla. Each category contained four images, with one beginning with the letters B, C, P, and G in the Spanish language. None of the words corresponding to the images shown were among the 5000 most frequently used words in Spanish, according to the Royal Academy of the Spanish Language. All words had between 2 and 4 syllables.

Phase II of the study consisted of a free recall task where participants were asked to remember the previously presented images in any order for a total time of 1 minute.

Moving on to Phase III, participants were required to generate all possible words beginning with the letters B, C, G, and P for 30 seconds each. This phase aimed to evaluate Semantic Priming by measuring the total number of words mentioned that coincided with those previously presented, with a maximum score of 16. To measure Lexical Selection, the number of total words generated was taken into consideration.

For Phase IV, a variant of the *Gollin Incomplete Pictures Task* (Gollin, 1960) was used to measure Perceptual Priming. In this task, a completely fragmented figure was presented at the beginning, which would become defined in 5 levels. The images represented synthesized forms of animals, vegetables, and objects present in everyday contexts, and were drawn in black lines on a white background with free vector illustration software. The images were presented on a PC monitor, with a size of 1,653.54 by 1,653.54 pixels (140 x 140 mm) and 300 dpi resolution, during 1000 milliseconds of exposure. Participants were required to recognize the presented figure as soon as possible.

In this Phase, eight of the figures previously presented in Phase I and another 8 new figures were shown, with each level lasting for 2 seconds each. The level at which the participant correctly identified the

figures was recorded. To measure perceptual priming, the mean levels necessary for the identification of the drawings previously seen in Phase I were calculated.

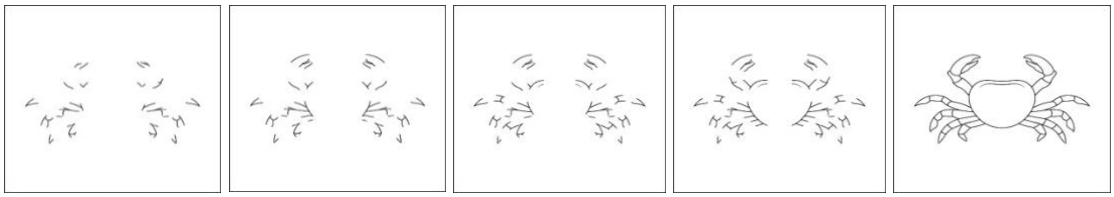

Figure 1. Example of an image being defined in 5 levels for perceptual priming.

The tasks were administered in a continuous manner, with participants performing the free recall task first, followed immediately by the lexical selection and semantic priming, and finally the perceptual priming tasks. Participants provided their responses verbally, and it was the researcher who entered them into the application.

Ethical Aspects

Participation in the study was voluntary and took place after signing the informed consent. The principles of the Declaration of Helsinki for the study with humans were met and it was approved by the Research Ethics Committee and Scientific Council of the Institute of Neurology and Neurosurgery.

Statistical analyses

The statistical analyses were performed in SPSS, Version 27. Factorial analysis ANOVAs were performed using free recall, lexical selection, semantic priming and perceptual priming as dependent variables and C270T and Val66Met polymorphisms as well as gender as independents factors. Eta-square was used to estimate the effect size. The cognitive variables were calculated for kurtosis (-0.49, -0.40, -0.55, and -0.57, respectively, for free recall, lexical selection, perceptual priming, and perceptual non-priming) and skewness values (-0.14, -0.15, -0.17, and -0.23, respectively), indicating that parametric statistics are appropriate.

Analyses were conducted to study potential differences in task performance between students and teachers. The results indicated that there were no statistically significant differences for any of the tasks; therefore, they were analyzed as a single sample.

The sample size required for this study was calculated using the G*power software. The results indicated that, for the proposed analyses (F tests, main effects and interactions) and considering an effect size f = .30, and α = .05, β = .80, the recommended number of participants would be 90. Therefore, the 135 selected participants (103 for the C270T study and 123 for Val66Met) constituted a sufficient sample size.

Results

C270T

One hundred and three participants (*M* = 27.29, *SD* = 10.46), 67 women (*M* = 27.19, *SD* = 11.30) and 36 men (*M* = 27.47, *SD* = 8.84), completed the C270T genetic study. The genotypic distribution of the studied sample was 6 CC (2 women and 4 men), 53 CT (40 women and 13 men), and 44 TT (25 women and 19 men). CC participants were excluded from the statistical analysis because the sample was too small. Although they were not included in the comparison of means with the other two genotypes, for informative purposes, the results obtained in this CC subgroup, less frequent in the general population, are shown in Tables 4 and 5.

Episodic memory

No effect was found for C270T polymorphism on free recall, $F(1,92) = 0.201$, $p = .655$, $\eta 2 = .002$; no effects of gender on free recall, $F(1,92) = 0.428$, $p = .515$, $\eta 2 = .005$; nor of the C270T x gender interaction were found, $F(1,92) = 0.882$, $p = .350$, $\eta 2 = .009$.

Semantic memory

No effect was found for C270T polymorphism on lexical selection, $F(1,92) = 0.021$, $p = .885$, $\eta 2 = .000$; no effects of gender on lexical selection, $F(1,92) = 0.003$, $p = .956$, $\eta 2 = .000$; nor of the C270T x gender interaction were found, $F(1,92) = 0.295$, $p = .588$, $\eta 2 = .003$.

Implicit memory

Table 4 shows the mean values in Perceptual Priming tasks for the variables gender and C270T polymorphism.

In all conditions, the previously seen figures needed fewer levels of definition than the new ones, thus, a perceptual priming effect was produced $F(1,96) = 273.145$, $p < .001$, $\eta 2 = .746$.

Effects of C270T polymorphism on perceptual priming for previously presented figures was found, $F(1,95) = 4.722$, $p < .05$, $\eta 2 = .047$; and for new figures, $F(1,95) = 4.176$, $p < .05$, $\eta 2 = .042$. TT genotypes performed better than others identifying the figures.

Table 4. Mean scores (and standard deviations) in the perceptual priming task according to genotype and gender.

	Female				**Male**				**Total**			
	Priming		**No priming**		**Priming**		**No priming**		**Priming**		**No priming**	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
CC	1.87	0.70	2.62	0.88	2.81	0.85	3.46	0.99	2.50	0.87	3.18	0.97
CT	2.20	0.60	2.95	0.69	1.80	0.40	2.58	0.55	2.10	0.58	2.86	0.67
TT	1.92	0.53	2.57	0.71	1.78	0.46	2.51	0.68	1.86	0.50	2.57	0.71
Total	2.07	0.59	2.79	0.73	1.76	0.40	2.50	0.58	1.97	0.55	2.69	0.69

No effect of the C270T x gender interaction was found, $F(1,93) = 0.801$, $p = .373$, $\eta 2 = .009$. CT women and TT men needed similar levels to identify the previously presented figures.

No main effects of gender were found, $F(1,93) = 2.209$, $p = .141$, $\eta 2 = .023$. Women and men performed similarly.

Table 5 shows the mean values in the semantic priming task according to gender and the C270T polymorphisms. No C270T effect was found on semantic priming, $F(1,93) = 0.468$; $p = .496$; $\eta 2 = .005$. The number of prior stimuli retrieved in the semantic task was low and approximately the same in all conditions.

Table 5. Mean scores and standard deviations in the semantic priming task according to genotype and gender.

	Female		Male		Total	
	M	*SD*	*M*	*SD*	*M*	*SD*
CC	4.50	2.12	1.75	1.50	2.66	2.06
CT	1.77	1.68	1.30	1.18	1.66	1.58
TT	2.11	1.16	1.42	1.60	1.81	1.40
Total	1.98	1.57	1.41	1.42	1.78	1.53

Also, no gender effect, $F(1,93) = 3.096$; $p = .082$; $\eta 2 = .032$; nor effects of interaction C270T x gender were found, $F(1,93) = 0.115$; $p = .735$; $\eta 2 = .001$.

Val66Met

One hundred and twenty-three participants ($M = 27.63$, $SD = 10.75$), 86 were women ($M = 26.81$, $SD = 10.66$) and 37 were men ($M = 29.55$, $SD = 10.87$), completed the genetic study of Val66Met. The genotype distribution was 41 MetMet (25 women and 16 men), 80 ValMet (59 women and 21 men), and 2 ValVal (2 men). As the number of ValVal cases was scarce, the two participants were excluded from the data analysis.

Episodic memory

A significant effect was found for Val66Met on free recall, $F(1,115) = 6.715$, $p = .011$, $\eta 2 = .055$. MetMet participants remembered more figures ($M = 11.37$, $SD = 1.82$) than ValMet participants ($M = 10.59$, $SD = 2.01$).

No effects of gender on free recall, $F(1,115) = 0.087$, $p = .769$, $\eta 2 = .001$; nor of the Val66Met x gender interaction were found, $F(1,115) = 2.963$, $p = .088$, $\eta 2 = .025$.

Semantic memory

No effect was found for Val66Met on lexical selection, $F(1,115) = 3.160$, $p = .078$, $\eta 2 = .027$. No effects of gender on lexical selection, $F(1,115) = 1.664$, $p = .200$, $\eta 2 = .014$; nor of the C270T x gender interaction were found, $F(1,115) = 0.393$, $p = .532$, $\eta 2 = .003$.

Implicit memory

Table 6 shows the mean values in Perceptual Priming tasks for the variables gender and Val66Met polymorphism.

Table 6. Mean scores (and standard deviations) in the perceptual priming task according to genotype and gender.

	Female				Male				Total			
	Priming		No priming		Priming		No priming		Priming		No priming	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
MetMet	0.66	0.38	2.58	0.76	0.74	0.29	2.68	0.76	0.69	0.35	2.62	0.75
ValMet	0.72	0.38	2.84	0.73	0.69	0.46	2.83	0.87	0.71	0.40	2.84	0.77
Total	0.70	0.38	2.76	0.75	0.71	0.39	2.78	0.81	0.70	0.38	2.77	0.76

A perceptual priming effect was found, $F(1,101) = 1032.025$, $p < .001$, $\eta 2 = .898$. In all conditions, the previously seen figures needed fewer levels of definition than the new ones.

No effects of Val66Met polymorphism on perceptual priming for previously presented figures were found, $F(1,117) = 0.009$, $p = .925$, $\eta 2 = .000$; nor for new figures, $F(1,117) = 1.699$, $p = .195$, $\eta 2 = .014$.

No effects of the Val66Met x gender interaction, $F(1,117) = 0.550$, $p = .460$, $\eta 2 = .005$; nor effects of gender were found, $F(1,117) = 0.083$, $p = .774$, $\eta 2 = .001$.

Table 7 shows the mean values in the semantic priming task according to gender and the Val66Met polymorphisms. No Val66Met effect was found on semantic priming, $F(1,117) = 0.003$; $p = .960$; $\eta 2 = .000$. The number of prior stimuli retrieved in the semantic task was low and approximately the same in all conditions.

However, a gender effect was found, $F(1,117) = 4.841$; $p = .030$; $\eta 2 = .040$. Females retrieved more previously presented items than males. No effects of interaction Val66Met x gender were found, $F(1.117) = 1.362$; $p = .510$; $\eta 2 = .004$.

Table 7. Mean scores and standard deviations of words retrieved in the semantic priming task according to genotype and gender.

	Female		Male		Total	
	M	*SD*	*M*	*SD*	*M*	*SD*
MetMet	2.16	1.86	1.25	1.80	1.80	1.87
ValMet	1.96	1.49	1.47	1.03	1.83	1.40
Total	2.02	1.60	1.37	1.40	1.82	1.56

Discussion

The complexity of neurobiology of memory domains is far from being completely understood and these results add more doubts (Clewett et al., 2019). The relation of the observed memory processes and the molecular basis of memory are in two very distant distal poles of a neurobiological hierarchical chain characterized by emergent properties of the more complex systems. Human cognition, therefore, is not a process that can be explained by molecular interactions, but the final product of the brain plasticity is culturally modulated.

The state of the art of the gene-cognition knowledge is only a crude expression of exploratory studies. The main finding of this study is the relation of the two polymorphisms of the BDNF gen Val66Met with explicit episodic memory and C270T with some tasks of implicit perceptual memory. These results suggest a differential pattern relating the studied polymorphisms with relative independent brain areas and networks.

Regarding the effects of Val66Met, which show differences in performance on explicit memory tasks, previous studies (Davis, 2016; Roberts et al., 2016) have shown that free recall and lexical selection tasks rely on networks such as the Left Executive Control, the Default Mode and the Precuneus that include brain areas like anterior regions of the superior and middle temporal gyrus, the left temporoparietal junction, posterior regions of the middle and inferior temporal gyrus, and right anterior prefrontal cortex.

Regarding the lack of effect of Val66Met on performance in visual priming tasks, no previous study has identified specific molecular mechanisms that could explain the relationship between MetMet and priming memory. However, the following findings have been reported in previous research which justified our study: a) in surface EEG, subjects with MetMet genotype compared to ValMet and ValVal showed focal increases in right frontoparietal delta, and decreases in right hemispheric alpha-1 and alpha-2 amplitudes (Roy et al., 2020); b) the neural substrates of semantic and perceptual priming

involve individual and shared networks, with a core involving the left fusiform gyrus, hippocampus, anterior cingulate cortex, and orbitofrontal cortex (Roelke & Hofmann, 2020); and c) the neural basis of visual perceptual priming includes areas responsible for visual object processing and extends to the ventral and frontotemporal network located in the fusiform gyrus, which has connections to the left inferior temporal region, left prefrontal cortex, left and right precuneus, and occipital region (Khachatryan et al., 2019). Therefore, potential effects of Val66Met on priming tasks were anticipated, although no significant findings of Val66Met have been observed in the present study.

However, significant findings have been observed for C270T in relation to perceptual priming, but not in relation to semantic priming. Neural substrates of semantic and perceptual priming have particular and shared networks and have as their nucleus the left fusiform gyrus (FG), specifically BA37. This area is probably the intersection of the neural pathways for visual recognition and the semantic properties of language (Kraft et al., 2014). In this study, the task used in the identification of the fragmented figures contemplates both visual insight and semantic nomination. The correct responses to perceptual priming are made through verbal identification of the incomplete figure, so this response could involve an overlapping of both perceptual and lexical networks (Palejwala et al., 2020; Patterson et al., 2007; Weiner & Zilles, 2016).

Regarding gender, volumetric studies of the brain have shown that men have a greater volume of gray matter than women in the FG, although this has not always translated into better cognitive performance and these differences have been influenced by the levels of sex hormones (Pletzer, 2019). The gender effect on perceptual priming memory is a very interesting result since it introduces a new variable in the classical cognitive sex dimorphic pattern (Asperholm et al., 2019).

Our hypothesis that an effect of gender would appear was not confirmed, however, some results let us formulate a conclusion with promising new approaches to develop in future studies. The present study found principal effects in memory and perceptual tasks, and some of them could be associated with the polymorphisms analysed.

Limitations and conclusions

The main results obtained were a) effects of C270T polymorphism on perceptual priming for previously presented figures were found and TT genotypes performed better than others in identifying the figures; b) a significant effect was found for Val66Met on free recall, MetMet participants remembered more

figures than ValMet participants; and c) Val66Met: Females retrieved more previously presented items than males.

These preliminary results suggest two broad research pathways. The first is the differentiation between two patterns of explicit and implicit memory with different polymorphisms. Briefly, we can state that the results confirm that explicit and implicit memory are different. They are associated with different neurobiological substrates. The second is the modulation of memory performance within the variability of the normal range of cognition.

Although the present study does not present problems regarding age or ethnic heterogeneity of the samples, it would be recommended to replicate the present study with larger samples, even though the sample size evaluated is sufficient and larger than that of most studies of these characteristics. In the present case, the very unique characteristics of the studied population hinder the possibility of exploring these relationships in larger samples.

Also, our study lacks both hemodinamics (MNRf) or electromagnetic (event related potentials) imaging data that could provide new data about the networks involved.

Although we obtained significant results only in some conditions, those ones let us to conclude that different memory networks are associated to different BDNF polymorphisms. These results open new research pathways that should be explored in future studies.

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Conflict of interest

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