Life Span and Disability XXVI, 1 (2023), 7-27

Effects of BDNF and COMT epigenetic regulatory polymorphisms on Executive Functions in adolescents

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Abstract

Executive Functions (EFs) are higher-order cognitive processes required for goal-directed behaviors. Literature on the genetic basis of executive functions suggests that these functions are mediated by the modulation of dopaminergic neurotransmission. The aim of the present study was to investigate how the Brain-derived neurotrophic factor (BDNF) Val66Met and the catechol-O-methyltransferase (COMT) Val158Met polymorphisms affect Cool and Hot executive functions. A total of 48 healthy Italian preadolescents, between 8 and 14 years of age, were included in the study. Participants completed the Digit Span Test, the Tower of London, The Balloon Analogue Risk Task, and The Iowa Gambling Task (IGT). The participants who were homozygous for the Val allele for BDNF performed better on the memory task and the decision-making task than Val/Met and Met/Met subjects, while those who were homozygous for the Met allele for COMT performed better on the decision-making task. Results suggest that the Val allele for BDNF and the Met allele for COMT are associated with higher performances on

Received: January 13, 2022; *Revised:* April 6, 2023; *Accepted:* May 18, 2023

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Conflict of Interest: The authors declare that there is no financial, general, and institutional conflict of interest regarding the publication of this article.

doi: 10.57643/lsadj.2023.26.1_01

some tasks of EFs.
The results reinforce the hypothesis that Val and Met alleles show functional changes related to high order cognitive processes both for BDNF and COMT polymorphisms.

Keywords: BDNF; COMT; Polymorphisms; Executive Functions; Adolescence.

1. Introduction

Executive Functions (EFs) represent a set of higher-order, self-regulatory cognitive processes required for goal-directed thought and behavior (Best, Miller, & Naglieri, 2011; Carlson, Zelazo, & Faja, 2013). EFs include three main cognitive components, such as working memory, inhibition, and cognitive flexibility (Miyake, Friedman, Emerson, Witzki, Howerter, & Wager, 2000), as well as emotional control. Working memory concerns the ability to manipulate items and mental representations that are held in mind; inhibition refers to the ability to control and suppress a prevailing response in favor of another response or no response, while cognitive flexibility refers to the ability to switch from one perspective or mindset to another (van der Ven, Kroesbergen, Boom, & Leseman, 2012). Moreover, these cognitive processes are closely related to other higher processes, such as reasoning, problem-solving, planning, and emotional control. Working memory, inhibition and cognitive flexibility are classified as "Cool" EFs (Poon, 2017) and designate cognitive components of self-regulation, while "Hot" EFs are characterized by emotional and motivational components. The latter require a person to process positive or negative emotional cues to achieve a goal and assess risk in everyday tasks that are ecologically conditioned by motivational and emotional influences (Prencipe, Kesek, Cohen, Lamm, Lewis, & Zelazo, 2011). Procrastination or decision-making tasks are typical examples of Hot EFs. The development of EFs suggests that they emerge during infancy, they change during the preschool years, and they continue to develop throughout adolescence in line with the maturation of the prefrontal cortex (Zelazo, Carlson, & Kesek, 2008). During adolescence, brain maturation follows an ongoing structural development of neural regions associated with both Hot and Cool EFs (Prencipe *et al.*, 2011). Further knowledge on the characteristics of EFs has come from genetic studies showing that interindividual differences in phenotype result from gene-gene interactions and gene-environment interactions (McClearn, 2006). Considering the involvement of the pre-frontal cortex and dopaminergic circuits in cognition, this study focused on genes that are involved in the regulation of the dopaminergic function and on the neuronal growth factor, like the Brain-derived neurotrophic factor (BDNF), as well as in the metabolism of the neurotransmitter involved in cognitive function, like catechol-O-methyltransferase (COMT) (Khanthiyong, Thanoi, Reynold, & Nudmamud-Thanoi, 2019). In the metabolism of catecholamines, including dopamine, the COMT gene plays an important role in the proper functioning

of the prefrontal cortex, encoding the enzyme which is involved in the metabolism of dopamine (Bowers, Buzzell, Salo, Troller-Renfree, Hodgkinson, Goldman *et al.*, 2020). More specifically, COMT is responsible for the inactivation of dopamine at the pre-frontal cortex. Consequently, alterations in the activity of this enzyme have a high impact on neurological activity. Several functional polymorphisms, associated with this gene, regulate the modification of enzymatic activity; among these, the most studied is a single-nucleotide polymorphism (SNPs) rs4680, also called Val158Met. This polymorphism involves the replacement of guanine with adenine, which determines a replacement in amino acids from methionine to valine (Egan, Goldberg, Kolachana, Callicott, Mazzanti, Straub *et al.*, 2001). In terms of enzymatic activity, methionine determines an alteration of the metabolism of dopamine that induces a longer presence stay in the synaptic space of the neurotransmitter, determining an improvement in cognitive functions (Bowers *et al.*, 2020). Several studies have been carried out to explain the relationship between COMT polymorphisms and cognitive functions, but the results are conflicting. Most of them emphasized the presence of the Val allele being more advantageous compared with the Met allele while other studies showed a strong correlation between an improvement in cognitive function and the Met allele (Moriguchi & Shinohara, 2018; Bowers *et al.*, 2020). Of note is a difference between children and adults in the performance on attention tasks in which the Met/Met genotype was associated with better adult performance, whereas a Val/Met genotype was associated with better adolescent performance (Wahlstrom, Hooper, Vrshek-Schallhorn, Oetting, Brott, & Luciana, 2007). BDNF is the main neurotrophin responsible of the correct functioning of the brain because of its role in the growth and differentiation of neurons and in synaptic plasticity involving dopaminergic neurons (Huang & Reichardt, 2001; De Assis, Gasanov, De Sousa, Kozacz, & Murawska-Cialowicz, 2018). A growing number of studies from the last two decades has shown that BDNF influences synaptic plasticity by causing changes in cognitive functions, learning, and memory (Nieto, Kukuljan, & Silva, 2013). The BDNF gene is located on chromosome 11 and several polymorphisms associated with this gene are known but, since 2008, most studies have focused on rs6265, also known as Val66Met. This single nucleotide polymorphism is the result of the replacement of the amino acid valine with the amino acid methionine at position 66 of the sequence that codes for the protein. This determines the existence of two alleles: the A allele (containing methionine) and the G allele (containing valine). The Val66Met

polymorphism has a deep impact on the cell biology of BDNF resulting in trafficking and subcellular behavior of BDNF alteration in both humans and mice. Historically, empirical evidence has indicated that the Met allele confers disadvantaged phenotypes at the cellular, structural, physiological, and behavioral level (Di Carlo, Punzi, & Ursini, 2019) and possibly prevents the interaction with molecules responsible for intracellular transport, such as sortilin and translin (Chen, 2006), which determines the inability of BDNF molecules to be vehiculated in the Golgi apparatus and subsequently secreted into the external environment (Egan, Kojima, Callicott, Goldberg, Kolachana, Bertolino *et al.*, 2003). Consistently, the BDNF genotype that characterizes Val homozygotes was demonstrated to moderate the relationship between cognitive reserves and EFs (Ward, Summers, Saunders, Ritchie, Summers, & Vickers, 2015), whilst BDNF Met alleles were found to be associated with decreased memory abilities (Egan *et al.*, 2003). Moreover, BDNF affects the dopaminergic system and this has focused the attention on the possible link between the polymorphism Val66Met and the Val158Met of the COMT gene. The possible relationship between BDNF and COMT starts from the interaction influencing both working memory and executive functions: the coexistence of the H (Val) variant of COMT and the A (Met) variant of BDNF seems to determine a decrease in EFs (Chen, Chen, Xia, Wu, Chen, He *et al.*, 2016).

2. Aim and hypotheses

The aim of this study was to compare the performance on Cool and Hot EF tasks among adolescents with different polymorphisms of BDNF and COMT with the attempt to fill the knowledge gap in this age group.

Since the literature published to date found that Val/Val for COMT and Met/Met for BDNF determine a reduction of EFs, we hypothesized that the other alleles for COMT (Met) and BDNF (Val) could determine an increase in EFs performance. More specifically, we tested the following hypotheses:

Hypothesis 1. Participants that are Val/Val homozygous for BDNF and Met/Met homozygous for COMT might show a better performance on tasks measuring Cool EFs (working memory, fluency, and inhibitory control) compared to peers with Met/Met for BDNF and Val/Val for COMT.

Hypothesis 2. Participants with the Val/Val allele for BDNF and the Met/Met allele for COMT might show a better performance on tasks measuring Hot EFs (decision-making) compared to peers with Met/Met for BDNF and Val/Val for COMT.

3. Methods

3.1. Sample

Participants were 128 Italian preadolescents and adolescents (69 boys, 59 girls) with an average age of 12.9 years old (*SD* = 2.92). Of these, 48 attended all research phases, included the salivary sampling. Thus, the final sample of this study was composed of 48 participants with an average age of 12.5 years old (± 2.07) and a higher percentage of boys (70.8%) over girls (29.2%). The 48 participants were divided, in turn, in three subsamples for BDNF (8 = Val/Val, 35 = Val/Met, 5 = Met/Met) and in three groups for COMT (16 = Val/Val, 23 = Val/Met, 9 = Met/Met). Inclusion criteria were the following: 1. the absence of intellectual disability, visual or neurological impairment; 2. the absence of neurodevelopmental disorder; 3. to be Caucasian. A medium socio-economic level was predominant, based on the parameters of parents' education and employment. Participants were recruited in their schools or gyms. Parents were contacted through flyers announcing the research project with the aims and procedures clearly described, and anonymity and confidentiality were guaranteed for all the participants. Parents were invited to allow their children to participate in the study and asked to provide written consent. This study was carried out following the recommendations of the Declaration of Helsinki (World Medical Association, 2013) and the Ethical Code of the Italian Association of Psychology (AIP, 1997). Participants were provided with all the information for the correct compilation of the consent form and confidentiality and anonymity were guaranteed making it clear that participants to the study could decide to withhold from participation at all phases of the research. Firstly, a Socio-Demographic Schedule was administered to collect participants' information concerning their age, education, school grades, and SES. The criteria for SES evaluation were parents' number of children, parents' education, and employment. A medium-high status was attributed in the presence of parental qualification at high school or graduation and a job requiring a diploma or a higher qualification. Medium SES status was given if parental qualification was middle school and a high-qualified job, such as a shop assistant or similar. Medium-low status was attributed if the parental qualification was primary school, and the job was qualified as a housekeeper or student.

3.2. Instruments: Executive Functions assessment

Executive Functions were measured by multiple standardized tasks. Four neuropsychological tests derived by the Inquisit Millisecond Software[2] were administered with keyboard inputs: The Digit Span Test (Gugliotta, Bisiacchi, Cendron, Tressoldi, & Vio, 2019), The Tower of London (Shallice, 1982), The Balloon Analogue Risk Task - BART (Lejuez, Read, Kahler, Richards, Ramsey, Stuart *et al.*, 2002), and the Iowa Gambling Task – IGT (Bechara, Damasio, Damasio, & Anderson, 1994).

The Digit Span Test is composed of two types of assessment: Forward Digit Span, which requires participants to repeat a sequence of digits in the same order, and Backward Digit Span, which requires participants to repeat the digits in reverse order. Forward Digit Span consists of 27 sequences ranging from two to nine digits, while Backward Digit Span consists of 24 sequences ranging from two to eight digits. The experimenter verbally presented each sequence at the rate of one digit per second, after which participants were asked to repeat the digits immediately. Two trials were administered for each sequence length; if participants were correct on either trial, then they advanced to the next sequence with the number of digits increasing by one. The test ended when participants failed on two consecutive trials of the same length. Scores were computed by counting the total number of digits successfully remembered in each condition. Forward Digit Span and Backward Digit Span were analyzed as separate variables (Lezak, 1995).

The Tower of London (ToL) is generally considered a measure of visuospatial problem solving because it requires planning strategy. Participants were shown a wooden set with three pegs and three balls (red, blue, and green) on the laptop screen. In the task, participants were asked to move the balls to reach the right configuration (with two or one ball, respectively) in each peg, by using a predetermined set of moves and following specific rules (i.e. only one ball could be moved at a time, no ball could be placed outside the set). ToL is composed of 12 trials with an increasing level of difficulty. The following indexes were calculated: the total score, which corresponds to the sum of the scoring on each trial (maximum score = 48); the planning time in seconds, which results from the sum of the time spent on each item between the instruction and the first move; and execution time in seconds, which results from the difference between the sum of the total time spent on each item and the planning time.

[2] Inquisit Millisecond is a platform to deliver tests to measure cognitive and neuropsychological variables.

The Balloon Analogue Risk Task (BART) is a computerized measure of risk decision-making. In the task, the participants were shown a virtual small balloon with a balloon pump and were offered the opportunity to earn money by pumping up the balloon by pressing a button. As the size of the balloon increased, the associated risk of explosion, as well as the monetary reward, also increased. Each pump allowed the balloon to inflate and 5 cents were collected in a counter until its explosion point was reached, then a "pop" sound effect was emitted from the computer. As soon as the balloon exploded, the money was lost and the new uninflated balloon appeared on the screen. The participant could stop pumping the balloon and collect the money at any time of the test. The exposure to a specific balloon ended following each balloon explosion or money collection and a new balloon appeared up to a total of 90 balloons. Two scores were derived: total balloons exploded and total balloons not exploded.

Finally, the Iowa Gambling Task (IGT) is a computerized card game used to assess decision-making, by simulating real-life situations with rewards and punishments. It is composed of four card decks: A, B, C, and D. The A and B decks are "disadvantageous", short-term and risky card desks. Each participant was asked to choose a card and s/he immediately gained money, but the choice was followed by a high penalty. The C and D are "advantageous", long-term, and safe card decks. Participant's choice, in this case, was followed by a smaller gain and a lower penalty. The task consisted of 100 trials (1 trial = 1 card drawn, 20 trials = 1 block), which were blind to each participant. Long-term decision-making is reflected in the IGT score that is calculated as the number of cards selected from the advantageous, safe decks minus those selected from the disadvantageous, risky decks. The net score of the first 40 trials reflects decision-making in the uncertainty phase because the choice outcomes are relatively unknown in the initial trials; the net score of the last 40 trials reflects decision-making in the risk phase because the choice outcomes are known in the later trials (Brand, Recknor, Grabenhorst, & Bechara, 2007). A high net score is given by selecting fewer cards from the disadvantageous but immediate reward decks (A and B) and drawing more cards from the advantageous reward decks (C and D). Two singles scores were obtained: 1. "good play", given by the choice from advantageous, good, decks outweighing those from disadvantageous, bad decks; 2. "bad play" given by the choice from risky, bad decks exceeding those from safe, good decks.

3.3. Procedure

The above tasks were administered individually to participants in a quiet room of his/her school/gym and required 1 session of 30 to 40 minutes. Tasks were presented in a balanced order to avoid the effect of sequence.

Moreover, for each participant, a saliva sample was taken by passive drool. The samples were collected in a sterile 15-mL centrifuge tube and stored at −80 °C until assay. Genomic DNA was isolated from 1 ml of the whole saliva using a PureLink kit (PureLink Genomic DNA ThermoFisher Scientific) according to the manufacturer's protocol. The genotyping was carried out by polymerase chain reaction (PCR) in a total reaction volume of 50 µl containing 50 ng of template, 1 µl of 10 mM deoxynucleoside triphosphate (dNTPs), 1 µl of 30 pmol each primer, and 5 µl of 10X reaction buffer with $MgCl_2$. The target sequence was amplified using a 5U/µl Dream Taq (Thermo Fisher Scientific) and the primers were the following: P1 (forward) 5' CCTACAGTTCCACCAGGTGAGAAGAGTG-3'; P2 (reverse) 5' TCATGGACATGTTTGCAGCATCTAGGTA 3'; P3 (G allele specific-reverse) 5' CTGGTCCTCATCCAACAGCTCTTCTATaAC 3'; P4 (A allele specific-forward) 5' ATCATTGGCTGACACTTTCGAAC cCA 3' used to determine the BDNF genotype and 5' GGAGCTGGGGGC CTACTGTG 3' (forward) and 5' 59- GGCCCTTTTTCCAGGTCTGACA 3' (reverse) used to determine the COMT genotype. PCR amplification was performed with the following protocol: denaturation at 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 62,5°C for 60 seconds for BDNF and at 60°C for 60 seconds for COMT, extension at 72°C for 60 seconds and final extension at 72°C for 7 minutes. The fragments were separated on 8% vertical polyacrylamide gel at 100 V for one hour and visualized with .5 mg/ml of ethidium bromide.

4. Data analysis

The SPSS software (Released 16, SPSS Inc. NY, USA) was used to run statistical analysis. A preliminary analysis showed that data was not normally distributed. Since assumption was not satisfied, the Spearman rho was used to measure the correlations between the variables studied. A Kruskal-Wallis ANOVA was further performed to examine the possible differences in mean rankings between the rankings obtained in the three groups (Val/Val, Val/Met, Met/Met) for BDNF and the three groups (Val/Val, Val/Met, Met/Met) for COMT.

Non-parametric ANOVA was used to compare the outcome of EFs in the two groups, setting the significance level at $p \leq .05$. The independent variables were the polymorphisms (BDNF and COMT), while the dependent variables were the scores on Hot and Cool EF tasks.

5. Results

A significant correlation was found between Cool and Hot EFs. More specifically, between the planning measured by the ToL execution and the IGT good play ($r = -.286$). Correlations are shown in Table 1.

Table 1 – *Correlation between Cool and Hot EFs tests for BDNF and COMT*

Variables	M (SD)	1	2	3	4	5	6	7	8	9	10
Forward WM	4.71 (1.74)	-									
Backward WM	4.25 (1.74)	.606**	-								
WM tot	9.27 (3.23)	.761**	.897**	-							
ToL	8.73 (2.87)	.049	.112	.090	-						
ToL plan	33.7 (38.4)	.093	.013	.036	.053	-					
ToL exec	120 (75.5)	.247	.249*	.353*	.180	.746**	-				
BART exploded	6.90 (3.57)	.042	.216	.119	.101	-.169	-.105	-			
BART not exploded	23.1 (5.73)	-.042	-.216	-.119	-.101	.169	.105	NA	-		
IOWA good play	73.8 (17.0)	-.101	-.166	-.103	-.070	-.286*	-.213	.135	-.135	-	
IOWA bad play	74.9 (14.2)	-.184	-.227	-.190	.010	-.005	-.092	.171	-.171	.838**	-

Legend: WM = working memory; WM tot = sum of Forward and Backward working memory; ToL = Tower of London test; ToL plan = time spent planning on the Tower of London (seconds); ToL exec = time spent in execution on the Tower of London (seconds); BART exploded = number of exploded balloons on the Balloon Analogue Risk Task; BART not exploded = number of not exploded balloons on the Balloon Analogue Risk Task; IOWA good play = score given by the sum of the choices from advantageous decks; IOWA bad play = score given by the sum of the choices from disadvantageous decks.
*$p < .05$. **$p < .01$.

Significant mean rank differences among the three groups with different BDNF polymorphisms (Val/Val, Val/Met, Met/Met) were found for both Cool (memory tasks) and Hot (decision-making tasks) EFs. As regards Cool EF tasks, significant differences were found for the Forward Memory Task ($p = .010$; see Tab. 2 for more details).

Table 2 – *Mean ranks of the three subsamples of BDNF and COMT for the Digit Span Test, the Tower of London, the Balloon Analogue Risk Task and the Iowa Gambling Task*

	BDNF					COMT				
	Met/Val (*n* = 35)	Val/Val (*n* = 8)	Met/Met (*n* = 5)	*p*	Post hoc	Met/Val (*n* = 23)	Val/Val (*n* = 16)	Met/Met (*n* = 9)	*p*	Post hoc
Forward WM	21.16	37.00	27.90	.01**	1,2	23.61	24.34	27.06	.81	
Backward WM	25.97	16.13	27.60	.15		21.61	27.34	26.83	.36	
WM tot	23.93	25.50	26.90	.88		21.46	27.84	26.33	.33	
ToL	24.90	23.63	23.10	.94		27.17	20.72	24.39	.36	
ToL plan	23.14	28.38	27.80	.54		23.57	27.25	22.00	.60	
ToL exec	24.14	24.56	26.90	.92		22.11	27.66	25.00	.47	
BART exploded	29.00	10.81	14.90	.001***	1,2	19.63	28.13	30.50	.06	
BART not exploded	20.00	38.19	34.10	.001**	1,2	29.37	20.88	18.50	.06	
IOWA good play	25.07	24.81	20.00	.75		19.24	30.22	27.78	.04*	1,3
IOWA bad play	25.51	25.06	16.50	.40		20.46	29.19	26.50	.14	

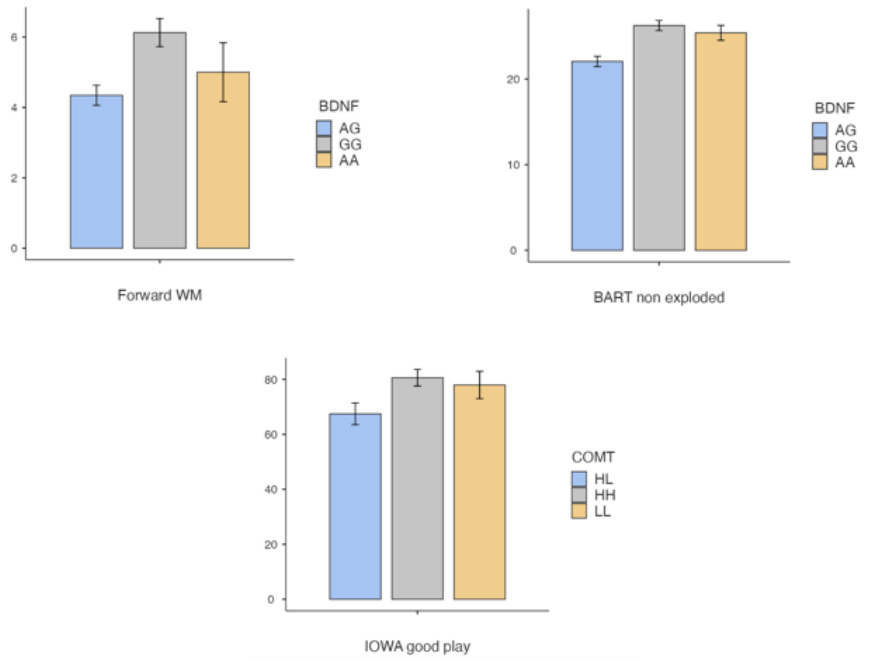
Legend: WM = working memory; WM tot = sum of Forward and Backward working memory; ToL = Tower of London test; ToL plan = time spent planning on the Tower of London (seconds); ToL exec = time spent in execution on the Tower of London (seconds); BART exploded = number of exploded balloons on the Balloon Analogue Risk Task; BART not exploded = number of not exploded balloons on the Balloon Analogue Risk Task; IOWA good play = score given by the sum of the choices from advantageous decks; IOWA bad play = score given by the sum of the choices from disadvantageous decks.
1 Met/Val
2 Val/Val
2 Met/Met
*p < .05. **p < .01. ***p < .001.

As regards Hot EF tasks, significant differences were found for tasks connected to decision-making. In fact, both exploded and not exploded balloon measures of the BART task were highly significant (p = .001). The post hoc Bonferroni test showed significant differences between the Met/Val

and Val/Val groups on the Forward Memory Task (p = .003) and on both the exploded balloon (p = .03) and not exploded balloon (p = .004) of the BART test. The Val/Val groups showed the best memory performance. Moreover, Val/Val showed the best performance with the lowest number of exploded balloons and highest number of not exploded balloons.

Regarding the COMT polymorphism, significant differences were found only for Hot EFs but not for Cool EFs. More specifically, significant between-subject differences were found for the Iowa "good play" measure (p = .04; refer to Tab. 2 for more details). The post hoc Bonferroni test showed significant differences between the Val/Met and Val/Val groups on the IGT "good play" (p = .02) with the Val/Val group scoring the highest performance. Figure 1 depicts the significant differences among the subsamples for BDNF and COMT.

Figure 1 – *Significant differences among the subsamples for BDNF and COMT*



6. Discussion

This study was aimed to examine COMT and BDNF polymorphisms on Hot and Cool EFs in adolescents.

We hypothesized that participants with Val/Val for BDNF and Met/Met for COMT would show a better performance both on tasks measuring Cool EFs (working memory and planning tasks) and Hot EFs (decision-making).

Indeed, as assumed, COMT and BDNF had some effect on EFs. For BDNF, in the case of Cool EFs, our findings showed that Val/Val homozygosity resulted in significant differences for tasks that involved Forward Memory abilities. Although the Backward Digit Span task is considered a better index of EF since it requires both the maintenance and manipulation of information in working memory, the Forward Digit Span task is still a reliable measure of short-term memory and was used in this study as a warm-up task of memory abilities. Participants with Val/Val for BDNF were better on memory performance than peers with Met/Val and Met/Met. This result is coherent with previous research that highlighted the association between the Met-BDNF allele and the decreased hippocampal function in humans, such as, the decreased performance on episodic memory tasks (Egan *et al.*, 2003; Hariri, Goldberg, Mattay, Kolachana, Callicott, Egan *et al.*, 2003; Galloway, Woo, & Lu, 2008) as well as the reduction in PFC gray matter volume (Pezawas, Verchinski, Mattay, Callicott, Kolachana, & Straub, 2004). However, other studies did not support these significant impairments in working memory (Egan *et al.*, 2003; Hansell, James, Duffy, Birley, Luciano, Geffen *et al.*, 2007).

Hot EFs displayed significant differences in the risk decision-making task for the BART test. Participants who were Val/Val homozygous for BDNF showed better risk decision-making abilities, scoring the highest number of not exploded balloons and the lowest number of exploded balloons. Thus, they appeared more cautious by using more inhibitory control. This positive correlation of the BDNF Val allele with cognitive abilities is consistent with previous research (Sheldrick, Krug, Markov, Leube, Michel, Zerres *et al.*, 2008; Kang, Namkoong, Ha, Jhung, Kim, & Kim, 2010; Jasinska, Molfese, Kornilov, Mencl, Frost, Lee *et al.*, 2016). In a previous study, Kang and colleagues (Kang *et al.*, 2010) demonstrated that the Met allele of BDNF was associated with a poorer performance in decision-making tasks in adults, measured by the IGT.

Regarding COMT, only one significant difference was found on the IGT test. Participants who were homozygous for Val/Val performed better on the

measure of "good play". This result was not in line with our hypotheses. A plausible explanation for this result lies in the nature of the IGT. This test was used to measure the ability to learn to sacrifice immediate rewards in favor of long-term gains. Participants' performance tends to change from the initial, potentially adverse, phase of exploration, in which a participant has no explicit knowledge of rewards/punishments, to the next phase, in which subjects can learn about the choices made with long-term rewards (Brand *et al.*, 2007). Subjects become increasingly more able to understand the logic of the game and to differentiate between advantageous and disadvantageous decks. However, some findings demonstrated that the Met polymorphism of COMT was significantly associated with a lack of improvement on the IOWA score. Improvement requires the gradual learning by the experience accumulated concerned with the choice-outcomes of rewards and punishments (Wahlstrom *et al.*, 2007). Other studies demonstrated a disadvantageous choice on the decision-making task by adults with the Met allele for COMT (van der Bos, Homberg, Gijsbers, den Heijer, & Cuppen, 2009; Malloy-Diniz, Lage, Campos, de Paula, de Souza Costa, Romano-Silva *et al.*, 2013). Malloy-Diniz and colleagues found that the Met allele in adult individuals was linked with a poor performance in a decision-making task, using IGT (Malloy-Diniz *et al.*, 2013). Moreover, we assume that the participants' age may account for discrepancies between our findings and those of other studies. To date, most studies were carried out on adult samples and performances on IGT have been shown to be very sensitive to developmental differences. Previous research demonstrated that the propensity to avoid play by drawing cards from the riskiest decks enhances with age in a linear way and adults tend to avoid disadvantageous decks and delay immediate gratification more than preadolescents and adolescents (Cauffman, Shulman, Steinberg, Claus, Banich, Graham *et al.*, 2010).

A potential reason for the lack of consistency between the results obtained on the BART and IGT tests lies in their nature because they measure different aspects of the decision-making ability (Balagueró, Jodar Vicente, Garcia Molina, Tormos, & Roig Rovira, 2016). IGT is more difficult to perform because it requires abilities of complex verbal comprehension and intact functioning of most executive functions, i.e. mnesic and attentional abilities, to realize the reward and punishment. Instead, the BART test is a simpler computerized task that requires a simpler decision to obtain as much money as possible without any predetermined logic.

Despite the limitations, a strength of this study was the extensive testing of Cool and Hot EFs performed, while previous studies addressed one or the other component of the EFs. Moreover, another strength was the age of the participants. To the best of our knowledge, the study of BDNF and COMT polymorphisms on Hot EFs was carried out only in adult samples or clinical samples (Colliva, Ferrari, Benatti, Guerra, Tascedda, & Blom, 2019). Our study addresses adolescence, which as a developmental phase is crucial in the long process of maturation of the EF system. Thus, we argue that the impact of the findings of the present study has targeted the area of social science genetic research aimed at better understanding environmental effects (family parenting, educational and school environment, policy interventions, economic conditions etc.) and at explaining whether and how genetic differences would influence differences in behavioral outcomes and contribute to educational attainment (Harden & Koellinger, 2020).

However, a shortcoming of this study lies in the limited sample size due to recruitment difficulties. Only a minority of parents in the initial sample gave consent to allow their children to participate in the saliva sampling and genotyping. This caused the higher prevalence of males in our final sample, which prevented us from comparing performances on EF tasks between boys and girls. But at the same time this indicates skepticism of the genetic procedures on the part of the parents, even if the saliva sampling was not invasive, as they were told.

Future research on the involvement of BDNF and COMT in EFs during preadolescence and adolescence is needed to better understand the delicate processes underlying their role in EFs.

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