Acta Psychologica 216 (2021) 103299

Contents lists available at ScienceDirect

Acta Psychologica

journal homepage: www.elsevier.com/locate/actpsy

Allele-dosage genetic polymorphisms of cannabinoid receptor 1 predict attention, but not working memory performance in humans

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ARTICLE INFO

Keywords:
Attention
Attention Network Test
Working memory
Endocannabinoid system
CB1 receptor
Single-nucleotide polymorphism

ABSTRACT

Attention and working memory (WM) are under high genetic regulation. Single nucleotide polymorphisms (SNPs) of the CNR1 gene, that encode for CB1R, have previously been shown to be related with individual differences in attentional control and WM. However, it remains unclear whether there is an allele-dosage or a dominant contribution of polymorphisms of CNR1 affecting attention and WM performance. This study evaluated the associations between attention and WM performance and three SNPs of CNR1: rs1406977, rs2180619, and rs1049353, previously associated with both processes. Healthy volunteers ($n = 127$) were asked to perform the Attention Network Task (ANT) to evaluate their overall attention and alerting, orienting, and executive systems, and the n-back task for evaluating their WM. All subjects were genotyped using qPCR with TaqMan assays; and dominant and additive models were assessed using the risk alleles of each SNP as the predictor variable. Results showed an individual association of the three SNPs with attention performance, but the composite genotype by the three alleles had the greatest contribution. Moreover, the additive-dosage model showed that for each G-allele added to the genotypic configuration, there was an increase in the percentage of correct responses respect to carriers who have no risk alleles in their genotypic configuration. The number of risk alleles in the genotypic configurations did not predict efficiency in any of the attention systems, nor in WM performance. Our model showed a contribution of three single nucleotide polymorphisms of the CNR1 gene to explain 9% of the variance of attention in an additive manner.

1. Introduction

Attention is a crucial cognitive function for successfully carrying out a variety of everyday conscious activities (Han, 2017b; Lundwall et al., 2017). It allows selection of information (Han, 2017a; Stevens & Bavelier, 2012) and it filters out irrelevant (distracting) stimuli (Noudoost et al., 2010), prioritizing a deeper processing of relevant stimuli for goal-directed behavior. On the other hand, working memory (WM) is a cognitive system that allows one to maintain and manipulate task-relevant information for guiding subsequent behavior (Gazzaley & Nobre, 2012).

There is extensive evidence of individual differences in attention and WM (Dong et al., 2015; Gaspar et al., 2016; Vogel & Machizawa, 2004; Zanto & Gazzaley, 2009). Genetic variability seems to modulate these individual differences (Bouchard & Loehlin, 2001; Friedman et al., 2008; Luciano et al., 2001; Plomin, 2003). The estimation of heritability for attention is between 0.41 and 0.89 (Arden et al., 2016; Fan et al., 2001; Posthuma et al., 2002; Stins et al., 2005), whereas it is between 0.36 and 0.78 for WM (Blokland et al., 2008; Etzel et al., 2020; Gustavson et al., 2018; Posthuma et al., 2002). Although some candidate genes, such as those involved in the dopaminergic or glutamatergic systems, have been associated with attention and WM performance regulation (Fossella et al., 2002; Parasuraman et al., 2006; Rampino et al., 2017; Voelker et al., 2017). Recently, the CNR1 gene (6q14-15),

Abbreviations: WM, working memory; ANT, Attention Network Task; CB1R, cannabinoid receptor 1.

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https://doi.org/10.1016/j.actpsy.2021.103299
Received 3 June 2020; Received in revised form 5 March 2021; Accepted 17 March 2021
Available online 31 March 2021

which encodes for cannabinoid receptor 1 (CB1R), has been considered a candidate gene for WM regulation (Papassotiropoulos & de Quervain, 2015; Ruiz-Contreras et al., 2017); and potentially for attention regulation, as well (Ruiz-Contreras et al., 2014; Stadelmann et al., 2011).

CB1R belongs to a complex system with multiple roles (Dinu et al., 2009), named the endocannabinoid system (ECS). It is composed of cannabinoid receptors CB1 and CB2, their respective genes (CNR1 and CNR2), and their endogenous ligands, (e.g., anandamide, 2-arachidonoylglycerol, oleamide); and the enzymes which mediate endogenous ligands,' biosynthesis and degradation (fatty acid amide hydrolase and monoacylglycerol lipase, among others). CB1R is one of the most abundant and widely expressed G protein-coupled receptors in the brain, including those areas involved in attention and in WM, such as the prefrontal cortex (PFC), hippocampus, striatum, and caudate (Tao et al., 2020). CB1R modulates the release of other neurotransmitters, such as glutamate, GABA, and dopamine (Lenkey et al., 2015; Pistis et al., 2002). CB1R agonists change the metabolic activity and expression of immediate early genes (e.g., c-fos and c-jun) in the prefrontal cortex and in the nucleus accumbens (Molaei et al., 2016), thereby impinging upon mechanisms that are regulating cognitive function. Besides, the administration of CB1R agonists produces deleterious effects on attention (Arguello & Jentsch, 2004; Weinstein et al., 2016) and WM performance (Bossong et al., 2012).

Some single nucleotide polymorphisms (SNP) of the CNR1 gene are associated with cognition. The G allele of rs1406977 (Table 1) is associated with less accuracy during the performance of a WM task and diminished prefrontal connectivity compared with AA subjects. Also, G-carriers exhibited less mRNA expression in the prefrontal cortex than the AA subjects in postmortem analysis (Colizzi et al., 2015).

Also, an association between rs2180619 (Table 1) and performance in attentional control and WM tasks has been previously reported (Ruiz-Contreras et al., 2014; Ruiz-Contreras et al., 2017). Nevertheless, what remains unclear is if the genotype effect is on WM, attention, or both. In independent studies, each of these SNPs (rs1406977 and rs2180619) showed that G-allele carriers exhibited worse WM performance than the A carriers (Colizzi et al., 2015; Ruiz-Contreras et al., 2014; Ruiz-Contreras et al., 2017); however, it is unknown if both SNPs can be associated with attention.

Regarding rs1049353 (Table 1), it has been broadly associated with cognitive function: healthy GG subjects showed less electroencephalographic theta power, indicative of lower performance on numerous cognitive tasks, during a resting state condition, compared with A-carriers (Finnigan & Robertson, 2011; Heitland et al., 2012), albeit, there is no direct evidence of its association with attention performance or WM. Given the previous results pointing to broad cognitive function, in this study, we will consider the G allele as the risk allele for cognitive performance.

Our study aimed to test the association of these three SNPs of CNR1, rs1406977, rs2180619, and rs1049353, with attention and WM performance, considering the risk alleles for these SNPs (G/G/G, respectively) forming a genotypic configuration. In this regard, we expected an association of the risk alleles in the genotypic configuration with a negative impact on attention and WM performance in healthy Mexican mestizo young adults. For the purposes of the study we defined "Mexican-Mestizo" as the genetic admixture given by the European, Native American, African, and Asian ancestry in the vast majority of the Mexican population (Martínez-Cortés et al., 2015; Romero-Hidalgo et al., 2017; Silva-Zolezzi et al., 2009). On the other hand, the G risk allele for these SNPs was evaluated as to whether it is acting in a dominant or in an additive-dosage genetic manner in the genotype, associated with attention and WM performance.

2. Methods

2.1. Participants

Volunteers between 20 and 30 years old were recruited through printed advertisements in different areas throughout Mexico City and by social media (Facebook and email). The sample size required for achieving a power of 0.8 for the one-sided at level $\alpha = 0.05$ was 150. This sample size was calculated according to our previous work (Ruiz-Contreras et al., 2017) and it is relatively similar to previous works where the SNPs investigated here were associated with a cognitive measure (Supplementary Table 1). We recruited 150 individuals; however, our final sample was 127 young participants (66 women). Twenty-three subjects were excluded from the final sample, mainly for two reasons. One, because some samples could not be genotyped for technical reasons, for at least one of the three SNPs in 16 subjects; and second, seven subjects presented more than 10% of no response in either one of our two cognitive tasks, attention, or WM. Nonetheless, our sample size was relatively similar to those previously reported (Supplementary Table 1). All participants were right-handed (Oldfield, 1971), and had normal or corrected to normal vision; all of them had at least 12 years of schooling, mainly university students, and all were native Spanish speakers. They responded to a structured interview based on the MINI International Neuropsychiatric Interview (Sheehan & Lecrubier, 2011). This helped to rule out any neurological or psychiatric disorder (including any illicit drug disorder, or any head trauma resulting in loss of consciousness that required clinical evaluation). Raven's Advanced Progressive Matrices were used to evaluate general cognitive ability (Raven et al., 1998); and data were transformed to intelligence quotient according to (O'Leary et al., 1991). Exclusion criteria were to have severe symptoms associated with depression and/or anxiety (measured using the Beck Depression Inventory and the Beck Anxiety Inventory, respectively, validated in

Table 1
Information about the Single Nucleotide Polymorphisms for the CNR1 gene. The risk allele was defined as the allele associated with lower cognitive performance (see Introduction section).

SNP	Alleles	Ancestral allele	Gene: consequence	MAF	Frequency[a]	Risk-allele	Position in genome	HapMap 3-MEX[b]				
rs1406977	A/C/G[c]	A	None	G	0.239	G	88,175,102	AA[d]	AG[d]	GG[d]	A[e]	G[e]
								0.420	0.440	0.140	0.640	0.360
rs2180619	G/A	G	2KB upstream variant	G	0.468	G	88168233[f]	AA[d]	AG[d]	GG[d]	A[e]	G[e]
								0.286	0.469	0.245	0.520	0.480
rs1049353	G/A[c]	G	Synonymous variant	A	0.129	G	88,143,916	AA[d]	AG[d]	GG[d]	A[e]	G[e]
								0.000	0.180	0.820	0.090	0.910

Data are obtained from the dbSNP https://www.ncbi.nlm.nih.gov/snp.
MAF: Minor Allele Frequency.
[a] Based on 1000G.
[b] Data from the HapMap 3 of Mexican ancestry in Los Angeles, California.
[c] Alleles are reported in reverse orientation to genome.
[d] Genotypic proportion.
[e] Allelic proportion.
[f] 6869 nucleotides downstream from rs1406977.

Mexican populations (Jurado et al., 1998)), having an illness, being currently under medication, having consumed alcohol 24 h before the experimental session or taken any illicit drug in the last six months. Experiments were performed between 10:00 and 18:00 h, to control the diurnal effect in cognitive performance (Valdez, 2019). All participants signed a written informed consent before the evaluations. The experimental protocol is part of a larger research project that was endorsed by the Research and Ethics Committee at UNAM's School of Medicine. Participants received a detailed description of the research basis at the end of the experimental session.

2.2. Cognitive tasks

2.2.1. The Attention Network Task (ANT)

The ANT is depicted in Supplementary Fig. 1, as detailed previously (Fan et al., 2002). We considered two manipulations: cue and type of trial. There were three possibilities for cue condition: no-cue (no warning about the target arrival), double cue (two asterisks displayed, one above and the other below the fixation point, warning of the upcoming arrival of the target), and spatial cue (an asterisk which was displayed right on the target location, above or below the fixation point, warning of target's arrival; visual angle of each asterisk was 1.8° displayed 0.55° above or below the fixation point); and two possibilities for the type of trial (congruent vs. incongruent, see below).

For each trial, a fixation point was presented at the center of the screen (with a variable interval to avoid habituation, between 400 and 1600 ms, mean: 999.40 ms; standard deviation = 349 ms), followed by a cue displayed above or below the fixation point (100 ms or it was absent); next, the sole presence of the fixation point (400 ms) was followed by the target stimulus (1700 ms). It consisted of an arrangement of five horizontal arrows displayed 0.55° above or below the fixation point. The target stimulus could be one of two types of trials, based on two flanking conditions: a central arrow pointing in the same direction as the flanking arrows (congruent target trial; i.e., →→→→→); or a central arrow pointing in the opposite direction of the arrows which are flanking it (incongruent target trial; i.e., →→←→→). Participants had to determine the direction of the central arrow, left or right, by pushing the corresponding button; subjects had up to 1700 ms to answer. At a viewing distance of 100 cm, the central arrow was at a visual angle of 0.3°. The total visual angle of the central arrow with the five flankers was 1.1° × 1.7° (vertical and horizontal, respectively). The trial ended with a blank displayed for 1000 ms. The fixation point, cues, and target stimuli were dark gray (with RGB values of $R = 100$, G = 100, B = 100) displayed on bright gray wallpaper (RGB: 200, 200, 200), to avoid post images.

Participants performed a total of 120 trials; there were 40 trials for each type of cue (no-cue, double cue, and spatial cue); half of them were congruent, and the other half incongruent. Reaction times for correct responses were measured and used to obtain the alerting score (the mean reaction time of the no-cue condition minus that of the double cue condition; i.e., participants are expecting to see the target stimuli), the orienting score (the mean reaction time of the double cue condition minus that of the spatial cue condition; i.e., participants know the exact position of the target), and the executive score (the mean reaction time of the incongruent condition minus that of the congruent trials; i.e., subjects have to solve the conflict in incongruent trials). In addition, the overall mean reaction times, as well as the percentage of correct responses, were measured. Accurate and fast responses were stressed.

2.2.2. N-back task

Supplementary Fig. 1 shows the n-back task, as reported earlier (Ruiz-Contreras et al., 2017). Briefly, the task consisted of the sequential presentation of 120 individual consonant letters that have a similar phoneme in Spanish (i.e., B, C, D, G, K, P, T) displayed for 500 ms, followed by a blank screen for 1000 ms. Participants had to indicate if the current letter on display was the same (target) or different (non-target) from that presented n-trials (2 or 3) before in the sequence. Participants indicated by pressing a button using one of their index fingers, counterbalanced among subjects, if the current letter was a target (a match), and using the other index finger if it was a non-target (a non-match). They had 1500 ms to respond to the task. To challenge our participants' performance, they solved levels of complexity of the n-back task (i.e., 2- and 3-back) in independent blocks. In each one, 24 trials were targets, and 96, non-targets. Dark gray letters (visual angles: 0.69° vertical, and 0.45° horizontal) on a light gray background were displayed (to avoid post-images) at the center of the screen. The d' index was calculated to identify the accuracy of each participant to discriminate targets from non-targets, for 2- and 3-back tasks, as previously reported (Haatveit et al., 2010).

Participants were seated 1 m away from the monitor screen; experiments were run in a light chamber. An Acer Aspire 5920 Core Duo (1.2 GHz) laptop was used for running the experiments and E-prime v1.2 (Psychology Software Tools Inc., Pittsburgh, PA, USA) was used for time-controlled presentations and responses for the ANT and n-back tasks. Experiments are available for the scientific community, upon request.

2.3. Genetic analysis

Participants provided a saliva sample for genetic analysis using the Oragene collection kit (OG-500; DNA Genotek Inc., Ottawa, ON, Canada). Genomic deoxyribonucleic acid was isolated using the Prep-ITL2P DNA Purification Protocol (DNA Genotek Inc.). DNA concentrations and purity were quantified by using NanoDrop-1000 digital spectrophotometer (Thermo Fisher Scientific Inc., Wilmington, DE, USA). Its integrity was verified by using 1% agarose gel electrophoresis. Genotypes for rs1406977, rs2180619, and rs1049353 were determined by using a TaqMan allelic discrimination assay (ID: C_30749303_10, C_15841551_10, and C_1652590_10, for rs1406977, rs2180619, and rs1049353, respectively; Applied Biosystems, Foster City, CA, USA) in the 7900HT Fast Real-Time PCR System (Thermo-Applied Biosystems, FosterCity, CA, USA). Samples, including no-template controls, were genotyped by duplicate, and only consistent results were included in the study. Genotypes were confirmed by comparing the allelic discrimination plot with its amplification plot. A genotypic configuration refers to the genotypic set of the alleles of the rs1406977, rs2180619, and rs1049353 of the CNR1 gene. Thus, the number of risk alleles in the genotypic configuration can be determined (see further dominant and additive models). Supplementary Table 2 shows the genotypic configurations detected in our sample.

2.4. Statistical analysis

Database is available on the Open Science Framework at https://osf.io/5c64b/ Analyses were carried out using jamovi. (Version 1.2) (https://www.jamovi.org).

The Hardy–Weinberg equilibrium for the rs2180619, rs1406977, and the rs1049353 CNR1 SNPs was calculated. Chi-square (χ^2) was worked out for the allelic distributions.

Given the allelic distribution for rs1406977 and rs1049353 two genotype groups were compared in behavioral results. For rs1406977, GG and GA were combined to form a G-carrier; for rs104353, AA and AG were combined to form an A-carrier group. Each SNP was tested for its individual association with the dependent variables of the ANT (for alerting, orienting, executive control, percentage of correct responses, and reaction times for correct responses) and WM n-back task (d'). For that purpose, independent samples Student's t-test was used for rs1406977 and rs1049353; and one-way Analysis of Variance (ANOVA), for rs2180619. Whereas a mixed two-way ANOVA was used for WM, considering each SNP as an independent factor, and task difficulty (2- vs. 3-back) as repeated measures factor. Tukey Honestly Significant Difference Test was used as a post hoc test for equal variances; and Games-Howell for unequal variances. Cohen's d and η_p^2 were reported as effect

sizes for the Student's t-test and ANOVAs, respectively.

To test the type of association of the three SNPs with ANT and WM performance, two genetic models were tested, a dominant one and an additive one, using the G allele for each SNP. For both models, a simple regression analysis was performed for the ANT (percentage of correct responses, reaction times, alert, orientation, and executive control systems) and WM (d' for 2- and 3-back) variables. For the dominant model, the presence of the G allele in a dominant manner was used (i.e., G allele in homozygous or heterozygous form would be equal to 1, and the absence of G allele would be equal to zero) for each SNP as a predictor. In contrast, for the additive model, the number of the risk alleles in the genotypic configuration was used as the predictor (i.e., counting the number of G alleles in the genotypic configuration regardless of whether it is in the homozygous or heterozygous form). This way, for example, for rs1406977-rs2180619-rs1049353 someone who has a genotypic configuration AA-AG-AA is considered as having one risk allele for dominant (i.e., one G allele) and additive models; in contrast, someone who has a GG-GG-GG genotypic configuration is considered as having three risk alleles in the dominant model (i.e., at least one G-allele for each SNP) and six risk alleles in the additive model (i.e., the total number of G-alleles for each SNP; see Supplementary Table 2).

Demographic data were compared as a function of the number of risk alleles in the genotypic configuration, depending on which model better predicted the ANT or WM variables. These were used to discard whether any of the demographic variables explained the potential association with attention and/or WM performance. Thus, a one-way analysis of variance (ANOVA), Pearson's $|^2$ or Kruskal–Wallis tests were used, as appropriate. Results were considered statistically significant when $p < 0.05$.

3. Results

3.1. Demographic data

The allelic distribution in our healthy young adult Mexican mestizo sample for the rs1406977 within the Hardy–Weinberg equilibrium (HWE; A: 0.43 G: 0.57; $\chi^2(1) = 7.16$, $p = 0.007$). The allelic distribution of the other two SNPs was within the HWE (rs2180619, A: 0.56 G: 0.44;

Table 2
Means and standard error of the means for all the behavioral measures of the Attention Network Test and Working memory n-back task, as a function of the individual CNR1 single nucleotide polymorphisms. Statistical differences are in bold.

Attention Network Task

		Alerting		Orienting		Executive control		Percentage of correct responses		Reaction times of correct responses (ms)	
SNP		Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
rs1406977	GG/GA ($n = 93$)	18.27	3.54	0.71	2.58	64.18	3.74	97.25	0.28	605.7	9.19
	AA (n = 34)	16.85	4.54	4.92	4.08	73.24	4.64	95.93	0.51	590.51	13.24
	p[1]	0.83		0.97		0.19		**0.02**		0.38	
	Effect size[1]							**0.47**			
	Power							**0.65**			
rs2180619	AA ($n = 36$)	17.38	5.65	5.04	4.02	68.19	5.93	**96.11**	0.58	605.85	12.78
	AG ($n = 70$)	18.92	3.95	1.44	3.16	66.16	4.06	**96.89**	0.31	599.83	10.55
	GG ($n = 21$)	15.31	5.98	−2.35	3.99	65.38	7.22	**98.25**	0.36	600.43	20.77
	p[2]	0.90		0.57		0.91		**0.003**[3]		0.94	
	Effect size[2]							**0.06**			
	Power							**0.70**			
rs1049353	GG ($n = 100$)	17.65	3.23	2.48	2.36	66.44	3.16	97.26	0.26	600.57	8.46
	AA/AG ($n = 27$)	18.79	6.26	−0.54	5.44	67.24	8.18	95.56	0.66	605.56	17.53
	p[1]	0.87		0.57		0.91		**0.02**		0.80	
	Effect size[1]							**0.56**			
	Power							**0.81**			

Working memory: N-back task

		Total (d′)		2-back (d′)		3-back (d′)	
SNP		Mean	SEM	Mean	SEM	Mean	SEM
rs1406977	GG/GA (n = 93)	0.84	0.07	1.02	0.08	0.66	0.08
	AA (n = 34)	0.85	0.07	1.23	0.09	0.47	0.09
	p[4]	SNP		Task difficulty		SNP × Task difficulty	
		0.92		**<0.00001**		**0.009**[5]	
	Effect size[4]			**0.31**		**0.05**	
	Power			**1.00**		**0.75**	
rs2180619	AA (n = 36)	0.76	0.08	1.05	0.10	0.46	0.10
	AG (n = 70)	0.82	0.07	1.03	0.09	0.60	0.09
	GG (n = 21)	0.97	0.09	1.17	0.12	0.76	0.12
	p[4]	SNP		Task difficulty		SNP × Task difficulty	
		0.29		**<0.00001**		0.55	
	Effect size[4]			**0.24**			
	Power			**1.00**			
rs1049353	GG (n = 100)	0.85	0.07	1.07	0.08	0.62	0.08
	AA/AG (n = 27)	0.85	0.07	1.14	0.1	0.56	0.10
	p[4]	SNP		Task difficulty		SNP × Task difficulty	
		0.97		**<0.00001**		0.43	
	Effect size[4]			**0.23**			
	Power			**1.00**			

[1] Student's *t*-test for independent samples was used, and Cohen's d was reported as effect size.
[2] One-way analysis of variance was used, and η_p^2 was reported as effect size.
[3] Games-Howell post hoc Test revealed intragroup differences: GG group statistically differed from AA ($p = 0.007$) and AG ($p = 0.02$) groups.
[4] Mixed analysis of variance was used, and η_p^2 was reported as effect size.
[5] Tukey post hoc Test indicated differences between 2- and 3-back ($p < 0.0001$) but not between genotypes ($p > 0.34$).

$\chi^2(1) = 1.77$, $p = 0.18$; rs1049353, G: 0.89 A: 0.11; $\chi^2(1) = 0.24$, $p = 0.62$).

Given that the Mexican-Mestizo population is admixed, spurious results can occur because of population stratification at markers with unusual allele frequency differences among parental populations. Specifically, for rs1406977, rs2180619, and rs1049353, the allele frequency for the European population (99 CEU individuals from 1000 Genome Project; CEU means Utah residents with Northern and Western European ancestry) is 25%, 46%, and 79%, for the G allele, respectively. Whereas the corresponding allele frequency for the Mexican-Mestizo (64 MXL individuals from 1000 Genome Project; MXL means Mexican Ancestry from Los Angeles, USA) population is 39%, 49%, and 88% for the same allele.

3.2. Individual association of SNPs of CNR1 with ANT and WM

Table 2 shows the means and standard error of the means or standard deviation, probabilities, effect sizes, and power results for the dependent variables for ANT and n-back task, for the individual association of SNPs of CNR1.

For rs1406977, between G-carriers and AA groups in ANT, there were differences only for the percentage of correct responses in the ANT ($t_{125} = 2.36$, $p = 0.02$, Cohen's d = 0.47). G-carriers had a higher percentage of correct responses than AA subjects. No other difference was detected for the rest of the dependent variables in the ANT for this SNP ($p > 0.05$; see Table 2 for specific probabilities). For the n-back task, there was only a significant interaction between rs1406977 and task difficulty ($F_{1,125} = 6.99$, $p = 0.009$, $\eta_p^2 = 0.05$). Post hoc showed differences in the intra-genotype groups between 2- and 3-back, but not between genotypes.

For rs2180619, differences among genotypes were observed for the percentage of correct responses in the ANT ($F_{2,59.59} = 6.34$, $p = 0.003$, $\eta_p^2 = 0.06$). Post hoc revealed GG subjects had a higher percentage of correct responses than AG subjects ($p = 0.007$) and AA subjects (p = 0.02). No other significant association was found for the ANT or the n-back task.

Finally, for rs1049353, there were differences between genotypes only in the percentage of correct responses ($t_{34.22} = 2.41$, p = 0.02, Cohen's d = 0.56). GG individuals performed higher than A-carriers. There was no other difference in the rest of the dependent variables depending on this SNP.

3.3. Prediction of genotypic configuration on ANT

This section has a description of the effect of the dominant and the additive models for each dependent variable.

3.3.1. Percentage of correct responses

The dominant model significantly predicted the percentage of correct responses [β = 0.22, SE = 0.09, t(126) = 2.47, $p = 0.01$]. Thus, having the G allele as dominant on the genotypic configuration explained a significant proportion of the variance in the percentage of correct responses [$R^2 = 0.05$, F(1,125) = 6.11, p = 0.01; power = 0.69; Akaike Information Criterion, AIC = 623.94].

The additive model also showed a significant effect of the number of risk alleles on the genotypic configuration in the percentage of correct responses [β = 0.68, SE = 0.19, t(126) = 3.60, $p = 0.0005$]. The number of risk alleles in the genotypic configuration explained a significant proportion of the variance in the percentage of correct responses [$R^2 = 0.09$, F(1,125) = 12.96, p = 0.0005; power = 0.95; AIC = 617.48; Fig. 1A]. For each risk allele in the genotypic configuration of rs1406977, rs2180619, and rs1049353, 0.68 is added to the percentage of correct responses with respect to carriers who have no risk alleles in their genotypic configuration.

3.3.2. Reaction times of correct responses

The dominant ($p = 0.79$) or additive (p = 0.79) models did not significantly predict the reaction times for correct responses.

3.3.3. Attention networks

Alerting System: No significant prediction was detected as a function of the dominant ($p = 0.94$) or additive ($p = 0.99$) model for this system.

Orienting System: No prediction for the orienting score was observed for the dominant ($p = 0.33$) or additive ($p = 0.40$) model.

Executive System: Neither the dominant ($p = 0.42$) nor the additive ($p = 0.69$) model significantly predict the executive system.

3.4. Prediction of genotypic configuration on WM

Neither the dominant or additive model significantly predicted the *d'* for 2-back (dominant model: $p = 0.39$; additive model: $p = 0.62$) or 3-back (dominant model: $p = 0.05$, power: 0.50; additive model: $p = 0.065$, power: 0.46; Fig. 1B).

In order to test if the prediction of the additive-dosage allele model

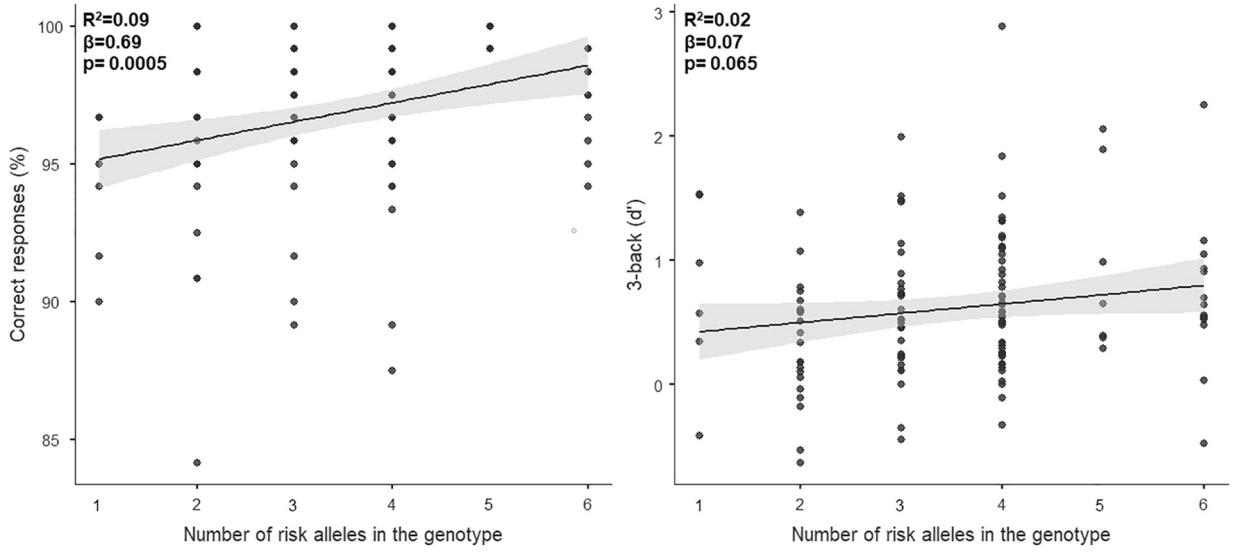

Fig. 1. The additive model, which considers the number of G-alleles in the genotypic configuration (rs1406977, rs2180619, and rs1045393), positively predicted the percentage of correct responses in the ANT (left) but not WM (right). Shadow shows the standard error.

was exclusively for attention and not for WM (i.e., 3-back), a Student's *t*-test was used. The slope for percentage of correct responses for ANT vs. slope of 3-back d′ significantly differed ($t(250) = 3.13, p = 0.002$), it was steeper for the percentage of correct responses for ANT.

Table 3 shows the descriptive and neuropsychological data from healthy Mexican mestizo subjects, stratified by the number of risk alleles in their genotype, according to the additive model. There were no statistical differences in sex, age, years of schooling, Raven's Standard Progressive Matrices, and Beck Depression and Anxiety inventories among groups (Table 3).

4. Discussion

This study assessed the dominant and the additive effect of the risk alleles of three SNPs of CNR1, in the genotypic configuration, on attention and WM. In this regard, the risk allele for this research was the G allele for each of these SNPs. We observed an individual association of the three SNPs with attention performance. Thus, we tested two alternative genetic models, one dominant and the other additive, for G alleles in the genotypic configuration. Our results confirmed, based on the AIC, that the additive model better explains the impact of the G alleles on the genotypic configuration in the percentage of correct responses in the ANT than the dominant model. This suggests a larger influence of G alleles in the genotypic configuration of attention, albeit they do not influence any of the attention systems, i.e., the alert, orientation, or executive control. Thus, the effect we found suggests a broad modulatory effect of CB1R on attention rather than specifically on any one system of attention. On the other hand, dominant nor additive models explained the impact of the G allele on the genotypic configuration in WM. Indeed, it can be considered that the additive model showed a trend to be associated with WM (i.e., $p = 0.065$). Besides the comparison of slopes of the percentage of correct responses in ANT and *d′* in 3-back task in the additive model (Fig. 1), we could suggest a selective association of the G allele-dosage effect with attention and not with WM. We emphasize that our findings did not depend on variables that are known to affect attention performance (see Table 3), because they did not differ as a function of the number of risk alleles in the genotypic configuration.

It is noteworthy that the ANT does not evaluate selective or divided attention or top-down or bottom-up mechanisms (i.e., suppression of salient information or singletons). Therefore, further research is required to detect the potential role of CB1R in those domains of attention. On the other hand, the percentage of correct responses in our study explained 9% of the variance, a larger size effect compared to other SNPs, i.e., MAOA, which have explained around 2% of ANT total variance (Fossella et al., 2002). Our results highlight the relevance of the genetic regulation of the CNR1 gene on attentional performance.

The fact that general performance in the ANT was predicted by the number of risk alleles of CNR1, suggests that CNR1 may impact other cognitive functions, given that attention shares between 30 and 70% of the variance with general fluid intelligence (Ren et al., 2013; Schweizer et al., 2005). In this context, it was unexpected that the number of risk alleles of CNR1 did not predict WM efficiency; we anticipated that the more G alleles in the genotypic configuration, the worse the performance. One plausible explanation can be as follows: for the rs2180619 and rs1049353, the G allele is the ancestral allele, whereas, for the rs1406977, the G allele is the derived allele. Attention is a basic cognitive function that works like a spotlight affecting other cognitive abilities. Moreover, attention helps to allocate cognitive resources (i.e., top-down process) in order to increase the likelihood of achieving a goal. In this regard, it is possible that the more ancestral alleles in the genotypic configuration (i.e., AA-GG-GG, for rs1406977, rs2180619, and rs1049353, respectively), the more efficiency in attention, providing a higher likelihood to an adaptive response to its demands. However, it was not possible to test this hypothesis here because of the frequency of the genotypic configurations we already had in our sample.

Previous studies agreed that attention and WM are closely related (Machizawa & Driver, 2011; Oelhafen et al., 2013), but they are different in several ways (Oberauer, 2019). They share some neurophysiological mechanisms, but they present differential connectivity to be performed (Mayer et al., 2010). For example, it has been reported that the left hemisphere is associated with attention, particularly, ventrolateral, medial prefrontal cortex and lateral temporal cortex, whereas the right hemisphere with WM, specifically, medial prefrontal cortex, medial parietal and lateral temporo-parietal cortices (Mayer et al., 2010), regions that may have differential expression of CB1R (Laurikainen et al., 2019). It would be important in further research to test if differential expression of CB1R is associated with ANT and n-back tasks. Hence, not only the brain mechanisms (Awh et al., 2006; Dixon et al., 2018; Fan et al., 2005), but gene expression too, involved in WM (Eriksson et al., 2015; Yaple et al., 2019) are quite different from those involved in attention. Thus, the differential expression of CB1R in those regions may explain the predictive relationship on attention and not in WM processes with the G alleles for the CNR1 gene in the genotypic configuration.

Table 3
Descriptive data of the sample depending on the number of risk alleles in the genotype. There were no differences among groups in any of the variables.

	Number of risk alleles in the genotype						
	1	2	3	4	5	6	*p*
n[a]	6	23	30	48	7	13	
Men/women (n)[a]	2/4	6/17	14/16	26/22	6/1	7/6	0.23
Age (Mean/SEM)[b]	22.33	22.26	22.53	23.56	22.57	23.62	0.28
	1.06	0.54	0.47	0.38	0.98	0.72	
Years of schooling	14.92	15.33	15.52	15.69	15.14	15.16	0.74
(Mean/SEM)[b]	0.64	0.33	0.29	0.23	0.59	0.43	
Raven's Standard Progressive Matrices[b,d]							
Estimation of intelligence Quotient (Mean/SEM)	93.43	99.14	100.12	100.70	99.80	99.80	0.21
	3.80	1.21	1.30	0.99	2.23	2.23	
Score (Mean/SEM)	38.67	45.17	46.07	46.73	46.29	38.62	0.30
	4.38	1.31	1.51	1.15	2.54	3.83	
Beck Depression Inventory[c] (Median, Min-Max)	5	9	6	6	7	6	0.38
	2–11	1–23	1–22	0–14	1–27	0–24	
Beck Anxiety Inventory[c] (Median, Min-Max)	4	5	4	4.5	6	5	0.80
	0–6	0–14	0–19	0–20	3–10	0–16	

SEM: Standard Error of the Mean.
[a] Statistical test used: Pearson's χ^2 test.
[b] Statistical test used: One-way Analysis of Variance.
[c] Statistical test used: Kruskal-Wallis.
[d] Based on O'Leary et al. (1991).

For rs1406977, prefrontal mRNA expression of CB1R was lower for G-carriers (Colizzi et al., 2015); for rs1049353, mRNA and protein expression of CB1R is lower for GG, compared to A-carriers (Horne et al., 2008; Moudi et al., 2021). No evidence of mRNA or protein expression has been reported for rs2180619. Regarding these results, it is likely that subjects who have in their genotypic configuration more G alleles of these SNPs of CNR1 present a reduced expression of CB1R, an optimal -homeostatic- level, i.e., not as low as experienced frequent cannabis users who have reduced CB1R expression (Ceccarini et al., 2015; Hirvonen et al., 2012) and is associated with a deleterious effect on attention (Ortega-Mora et al., in press; Abdullaev et al., 2010; Bocker et al., 2010; Cengel et al., 2018; Solowij et al., 1991; Solowij et al., 2002) and WM (Bossong et al., 2012; D'Souza et al., 2012; Robinson et al., 2007). Therefore, further research is required to test the hypothesis of the expression of CB1R depending on this G additive-dosage.

The present study has some strengths and limitations. It was conducted on a well-characterized sample of Mexican mestizo individuals, without symptoms related to any psychiatric or psychological illness and without use and/or dependence on any illicit substance. It took a great effort to get this sample, at least in the evaluated population of young adults, mostly university students. Our study may not be the first suggesting the interaction of CNR1 gene variants with attention performance (Buchmann et al., 2015; Cosker et al., 2018; Johnson et al., 1997; Ruiz-Contreras et al., 2014); however, this is the first study to prove this association directly. Even when the sample size can be considered small, we obtained a high statistical power for the prediction of the G allele-dosage effect for these three SNPs on attention. However, our results need to be replicated in larger samples, or in genome-wide association studies (GWAS). On the other hand, a limitation we had in this study was that we were unable to register any neurophysiological measure to associate it with the behavioral performance and with genetic polymorphisms to associate behavior with neurophysiological changes. Moreover, another important limitation was that we do not know the functional effect of the rs2180619 on CB1R expression, that would help us understand the potential relationship with the other polymorphisms more precisely.

In conclusion, our model showed that there is an allele-dosage effect of the G allele of rs1406977, rs2180619, and rs1049353 of the CNR1 gene on general performance in attention, but not on WM. Thus, our data point to the cannabinoid system as a contributor to attention performance, and the CNR1 gene is a candidate gene to understand individual differences in attention.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.actpsy.2021.103299.

Declaration of competing interest

None.

Acknowledgments

We are very grateful to Edith Monroy for her careful editing of the English manuscript. We also thank Dr. Raúl Aguilar-Roblero and Dr. Zeidy Muñoz-Torres for the discussion of the data of this research.

This work is Elsa Ivett Ortega-Mora's Doctoral Dissertation in the Programa de Doctorado en Ciencias Biomédicas of UNAM [fellowship number 586812 from CONACYT].

This work was supported by Dirección General de Asuntos del Personal Académico-Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica, Universidad Nacional Autónoma de México (DGAPA-PAPIIT-UNAM) [Grant numbers: IN217918 to AERC, IN218620 to OPG, and IA205218 MMD; and ISSSTE-010.2015 to JAGB].

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