Psychoneuroendocrinology 144 (2022) 105861

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

HTR1B genotype and psychopathy: Main effect and interaction with paternal maltreatment

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ARTICLE INFO

Keywords:
Psychopathy
HTR1B
Genotype
Serotonin
rs13212041
environment
paternal maltreatment
incarcerated adolescents
institutionalized individuals

ABSTRACT

Psychopathy is a condition characterized by atypical emotions and socially maladaptive behavioral patterns. Among incarcerated people, psychopathy has been associated with higher rates of crimes, recidivism, and resistance to treatment. Many studies have indicated significant heritability of psychopathic traits, but little is known about the specific contribution of genes and their interaction with adverse experiences in life. Considering the primary role that serotonin plays in cognition and emotion, we investigated TPH2-rs4570625, 5-HTTLPR, MAOA-uVNTR, HTR1B-rs13212041 and HTR2A-rs6314 as risk factors for psychopathy in the largest sample of institutionalized individuals studied so far, consisting of 793 US White male incarcerated adults, and in a replication sample of 168 US White male incarcerated adolescents. In a subgroup of the adult sample, the interaction between genetics and parenting style, assessed by the Measure of Parental Style (MOPS) questionnaire, was also evaluated. The HTR1B-rs13212041-T/T genotype, as compared to HTR1B-rs13212041-C allele, predicted higher psychopathy scores in both the adult and the adolescent samples. The interaction between HTR1B-rs13212041-T/T genotype and paternal MOPS scores, investigated in a subgroup of the adult sample, was an even stronger predictor of higher levels of psychopathy than either the genetics or the environment taken individually. Overall, these data, obtained in two independent samples, shed new light on neurobiological correlates of psychopathy with promising implications both at a clinical and forensic level.

1. Introduction

As reported by Hare and Neumann in 2009 (Hare and Neumann, 2009), psychopathy represents "a formidable therapeutic challenge for the mental health and criminal justice systems".

In the US, for example, from 15 up to 25% of institutionalized males meet criteria for severe psychopathy, contrarily to only 1% of the general population (Kiehl and Hoffman, 2011; Neumann and Hare, 2008; Coid et al., 2009; Hare, 1991, 1996, 2003). Among incarcerated subjects, psychopathy has been associated with higher rates of crimes (Cornell et al., 1996; Harris et al., 1991; Porter et al., 2011), recidivism (Harris et al., 1991; Walters et al., 2008) and resistance to treatment (see Reidy et al., 2013 for a comprehensive review of the treatment literature (Reidy et al., 2013)).

Over the past 25 years, neuroscientific research has begun to unveil the neural processes and neuroanatomical features underlying psychopathy (Kiehl and Hoffman, 2011; Johanson et al., 2019; Deming and Koenigs, 2020). In addition, behavioral genetics has revealed several genetic alleles and epigenetic mechanisms that modulate human behavior, including the expression of impulsive, aggressive, and antisocial acts (Iofrida et al., 2014; Palumbo et al., 2018; Veroude et al., 2016; Alia-Klein et al., 2020). Overall, research suggests the likelihood for genetic and environmental factors contributing to developmental vulnerability by promoting psychopathic traits (Kiehl and Hoffman, 2011; Anderson and Kiehl, 2014; Tuvblad et al., 2017). As indicated by twin studies, heritability appears to explain from 32% up to 69% of the psychopathic trait variance, while the rest has been attributed to non-shared environmental factors (Tuvblad et al., 2014; Blonigen et al.,

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https://doi.org/10.1016/j.psyneuen.2022.105861
Received 12 August 2021; Received in revised form 20 May 2022; Accepted 5 July 2022
Available online 7 July 2022

2005; Forsman et al., 2008; Viding et al., 2005; Bezdjian et al., 2011a; Beaver et al., 2011; Brook et al., 2010). However, only a few genetic studies exist reporting discordant evidence of associations between polymorphisms of the serotonin (Hollerbach et al., 2018, 2021; Fowler et al., 2009; Sadeh et al., 2013; Golimbet et al., 2003; Fox et al., 2020; Jackson and Beaver, 2016, 2015; Romero-Rebollar et al., 2015; Tikkanen et al., 2011; Beaver et al., 2013), dopamine (Fowler et al., 2009), and oxytocin (Verona et al., 2018) pathways and psychopathy, which require further investigations in large and well characterized samples.

In the present work we investigated the role of genes in predisposing to psychopathic traits in a large sample of incarcerated adults and in an independent replication sample of institutionalized adolescents.

To this aim, we investigated five polymorphisms of the serotonergic pathway: TPH2-rs4570625, 5-HTTLPR, MAOA-uVNTR, HTR1B-rs13212041, and HTR2A-rs6314. We chose these five genes and allelic variants as, overall, they examine all the aspects of serotonin neurotransmission (i.e. synthesis, re-uptake, metabolism, transmission). Serotonin, indeed, represents a fundamental intermediary between early life experiences and adult behavior, because of its central role both as a neuronal growth factor since the earliest stages of life and as a neurotransmitter implicated in cognitive and emotional processes in the mature brain (Booij et al., 2015).

The adoption of a candidate gene rather than a genome wide association study (GWAS) approach was motivated by the fact that the available samples were numerically inadequate for a GWAS (Mehta and Czamara, 2019). Nevertheless, the present study was based on a strong a priori hypothesis and was conducted in a well-characterized sample of US incarcerated individuals that represents the largest cohort of criminals studied to date.

Furthermore, as maladaptive parenting (e.g., failure to bond with babies, neglect and abuse) has been often associated with callous-unemotional (CU) traits in youth (Bezdjian et al., 2011b; Frick et al., 2003; Salekin, 2017; Trentacosta et al., 2019), and CU traits resemble some of the emotional deficits observed in adult psychopathy (Frick, 2009) (e.g. shallow affect and lack of empathy and guilt), we decided to study the gene by childhood environment interplay in modulating the risk for psychopathy, in a subgroup of the incarcerated adults, for whom parenting data were available.

Our study is the first report of a genetic association between the T/T genotype of HTR1B-rs13212041 and psychopathy replicated in an independent sample.

2. Materials and methods

Research was carried out in compliance with ethical standards and in accordance with the International Ethical Guidelines of the Declaration of Helsinki. The governing IRB is the Ethical and Independent Review Services (E&I); earlier versions included approval from the University of New Mexico Health Science Center IRB. Each participant provided a written informed consent to participate to the study. Participants could withdraw from the study at any time.

The data for this study were collected in conjunction with several NIH-supported research projects, between 2007 and 2015, investigating mental health characteristics of juveniles and adults incarcerated in New Mexico and Wisconsin facilities. Data collection procedures have remained identical across the whole collection period and the demographic representation of incarcerated volunteers has remained stable over the years. Participants were recruited through fliers passed out and by word-of-mouth. Participation was completely voluntary, and participants were informed that involvement in research has no bearing on their incarceration or parole status. Participants were compensated at an hourly rate commensurate with pay otherwise available for work assignments through the corrections department. Inclusion criteria for the present analysis required availability of genetic samples and, in order to address ancestral and gender heterogeneity in genetic factors, White race and male gender as self-reported on initial screening instruments. As race and ethnicity are accounted for separately, participants included 793 US White male incarcerated adults (age range: 19–65; mean age: 35 ± 10 years), belonging to two ethnicities: Latin/Hispanic (n = 355) and not-Latin/Hispanic (n = 438) and 168 US White male incarcerated adolescents (age range: 14–18 years; mean age: 17.02 ± 1.12; ethnicity: 125 Latin/Hispanic and 43 not-Latin/Hispanic). Intelligent quotient (IQ) in these subjects, estimated by using the Wechsler adult Intelligence Scale (WAIS 3rd Edition) (Wechsler and Welchesler, 1997) was 98.08 ± 13.30 in adults and 92.05 ± 12.96 in adolescents. Adult participants underwent a semi-structured diagnostic interview to help complete the Hare Psychopathy Checklist-Revised (PCL-R) (Hare, 2003). A total score, ranging from 0 to 40 (PCL-R Total score; Cronbach's alfa= 0.77), was calculated. Scores were also computed for PCL-R Factor 1, to evaluate the interpersonal/affective dimension of psychopathy, described by glibness, shallow affect and lack of empathy, guilt or remorse, and for PCL-R Factor 2, to assess the social deviance dimension of psychopathy that includes irresponsibility, impulsivity, aggression and antisocial behavior from childhood through adolescence and into adulthood (Hare, 2003). Psychopathic traits in adolescents were assessed by the Hare Psychopathy Checklist: Youth Version (PCL:YV) (Forth et al., 2003). A total score, ranging from 0 to 40 (PCL:YV Total score; internal consistency: Cronbach's alpha= 0.7), was calculated. Scores were also separately computed for PCL:YV Factor 1, to evaluate interpersonal/affective problems and for PCL-R Factor 2, to assess developmental/antisocial lifestyle tendencies.

Data about family environment, as collected by the Measure of Parental Style (MOPS), were available in a subsample of 231 incarcerated adults. MOPS is a validated self-report questionnaire useful to retrospectively measure the perceived parental indifference, overcontrol and abuse experienced during the first 16 years of life (Parker et al., 1997). A total score, ranging from 0 to 45, was calculated for each parent (Maternal MOPS Total score N = 226, and Paternal MOPS Total score N = 201).

Each participant provided a sample of saliva by an Oragene collection tube (DNA Genotek Inc., Kanata, ON, Canada). DNA was extracted from saliva by the prepITL2P kit following the standardized manufacturer's protocol (DNA Genotek Inc.) and stored at − 20 °C.

Genotyping was performed by using an iCycler iQ™ Real-time PCR detection system (Bio-rad, Hercules, CA, USA) as follows:

TPH2-rs4570625 was genotyped by Polymerase Chain Reaction (PCR) (95 °C/5 min, 95 °C/10 s-60 °C/30 s-72 °C/10 s for 45 cycles, 95 °C/60 s)-High Resolution Melting (HRM), by using the following primers:

5′-GCATCACAGGATTAAGAAGAAGC-3′ / 5′-TCTTATCCCTCCCATCAGCA-3′. The HRM analysis was performed with a temperature resolution of 0.2 °C ranging from 65 °C to 85 °C. Genotype calling was performed by the CFX Manager™ software (error rate: 2%; call rate: 98%).

5-HTTLPR included both the VNTR and the rs25531 SNP. The VNTR was genotyped by PCR (95 °C/15 min, 94 °C/30 s-60 °C/90 s-72 °C/60 s for 35 cycles, 72 °C/10 min) by using the following primers:

5′-CGTTGCCGCTCTGAATGC−3′ / 5′-GGGAGATCCTGGGAGAGGT3′.

The amplicons were visualized on 2% agarose gel; rs25531 (G/A) was genotyped by Restriction Fragment Length Polymorphism (RFLP) by using the restriction endonuclease *Msp*I (Thermo Fisher Scientific, Waltham, MA, USA) and visualizing the undigested A allele (263 bp long) and digested G allele (97 bp and 166 bp long fragments) on 2% agarose gel (error rate: 0.1%; call rate: 99.9%).

MAOA-uVNTR was genotyped by PCR (95 °C/15 min, 94 °C/30 s-62 °C/30 s-72 °C/60 s for 35 cycles, 72 °C/10 min), by using the following primers:

5′-ACAGCCTGACCGTGGAGAAG3′ / 5′-GAACGGACGCTCCATTCG GA3−3′, and visualized on 2% agarose gel (error rate: 0.3%; call rate: 99.7%).

HTR1B-rs13212041 was genotyped by PCR (95 °C/5 min, 95 °C/10 s-60 °C/30 s-95 °C/60 s for 40 cycles, 72 °C/90 s)-HRM, by using the

following primers: 5′-AGTGACAGGTACATGAAATTAAGAGA3/5−3′ / 5′-AACAAACAAACCATTATGTGTGCTA−3′. The HRM analysis was performed with a temperature resolution of 0.2 °C ranging from 70 °C to 85 °C. Genotype calling was performed by the CFX Manager™ software (error rate: 0.1%; call rate: 99.9%).

HTR2A-rs6314 was genotyped by PCR (95 °C/5 min, 95 °C/10 s-60 °C/30 s-72 °C/10 s for 45 cycles, 95 °C/1 min)-HRM, by using the following primers:

5′-CAGGCTCTACAGTAATGACT−3′ / 5′-TCACAGGAAAGGTTG GTT−3′. The HRM analysis was performed with a temperature resolution of 0.2 °C ranging from 70 °C to 80 °C. Genotype calling was performed by the CFX Manager™ software (error rate: 0.3%; call rate: 99.7%).

For all the samples, genotyping was performed by the same research group (PI, Silvia Pellegrini) at the Clinical Biochemistry and Molecular Biology Lab at the Department of Clinical and Experimental Medicine of the University of Pisa, Pisa (Italy). Genotypes were assigned in smaller batches: VNTRs and RFLPs by comparing the obtained amplicons with a DNA molecular weight ladder (GeneRuler DNA ladder, Thermofisher Scientific, Waltham, MA, USA), SNPs by the comparison with previously sequenced reference samples.

Regarding SNPs, homozygotes for the minor allele were grouped with heterozygotes (i.e., HTR1B-rs13212041 C/C + C/T, HTR2A-rs6314 C/T + T/T, TPH2-rs4570625 T/T + G/T) and compared to the homozygotes for the ancestral allele. Concerning VNTRs, genotypes were grouped based on their functional effect, as reported in the scientific literature. Specifically, the MAOA-uVNTR low activity alleles (2r, 3r and 5r; r = repeats) were compared to the high activity alleles (3.5r and 4r) (Sabol et al., 1998), while the 5-HTTLPR low activity genotypes (S/S, $S/L_{G(rs25531)}$, $S/L_{A(rs25531)}$ and L_G/L_A; S= "short" allele, L= "long" allele) were compared to the high activity genotype (L_A/L_A) (Greenberg et al., 1999).

Statistical analysis was performed by the SPSS 21 software package (IBM Corporation, Armonk, NY, USA). For each variable, the deviation from a normal distribution was assessed by the Shapiro-Wilk test. The Hardy-Weinberg equilibrium (χ^2 test) was assessed for each allelic variant except for MAOA gene because males are hemizygous, being the MAOA gene located on the X chromosome (see Tables 1 and 2).

PCL-R Total score was analyzed both as a continuous variable and as a discrete variable by using 21 and 30 as cut-off values. PCL-R Total scores < 21 indicated absence of psychopathic traits, while scores ≥ 30 denoted severe psychopathy (Hare, 1991, 2003). The probability of scoring ≥ 21 or ≥ 30 as a function of genotype and of MOPS Total scores was calculated as odds ratio with a confidence interval (CI) of 95% and tested by a one-sided Fisher exact test. MOPS Total scores were divided into ≤ 8 or > 8, according to the median split method, in order to turn MOPS variable from a continuous into a categorical variable (Allen, 2017).

PCL:YV Total score was also analyzed both as a continuous variable and as a discrete variable by using 25 and 30 as cut-off values. PCL:YV Total scores < 25 indicated absence of psychopathic traits, while scores ≥ 30 denoted severe psychopathy (Brazil and Forth, 2016). The probability of scoring ≥ 25 or ≥ 30, as a function of genotype, was calculated as odds ratio with a confidence interval (CI) of 95% and tested by a one-sided Fisher exact test.

Generalized Estimating Equations (GEE) with an exchangeable working matrix and Tweedie model with identity link function were used for the association analysis between genotype and PCL-R or PCL:YV score, and among genotype, PCL-R and MOPS scores. Concerning PCL-R, the association analysis was adjusted for ethnicity, age and IQ as they were significantly associated with PCL-R scores (Table S1). Ethnicity, age and IQ, at the opposite, were not associated with PCL:YV scores

Table 2
Incarcerated adolescents: Genotype frequencies and Hardy-Weinberg equilibrium. r = repeats, L= long, S= short, XL= extra-large.

Replication sample of 168 incarcerated adolescents				
Polymorphism	**Genotype**	**N**	**Frequency**	**Hardy-Weinberg equilibrium**
HTR1B-rs13212041	**C/C**	8	0.047	$\chi^2 = 1.635$
	C/T	45	0.266	p = 0.201
	T/T	115	0.680	
MAOA-uVNTR	**2r**	1	0.006	Not applicable
	3r	52	0.308	
	3.5r	2	0.012	
	4r	113	0.669	
	5r	0	0.000	
5-HTTLPR	**L_A/L_A**	43	0.254	$\chi^2 = 3.375 \times 10^{-6}$
	L_A/XL	1		p = 0.999
	S/L_A +	78	0.497	
	L_G/L_A	5		
	S/S + S/L_G	41	0.243	
HTR2A-rs6314	**C/C**	149	0.882	$\chi^2 = 3.710$
	C/T	16	0.095	p = 0.054
	T/T	2	0.012	
TPH2-rs4570625	**G/G**	87	0.515	$\chi^2 = 0.837$
	G/T	63	0.373	p = 0.360
	T/T	16	0.095	

Table 1
Genotype frequencies and Hardy-Weinberg equilibrium in incarcerated adults. r = repeats, L= long, S= short, XL= extra-large.

		Whole sample of 793 incarcerated adults			Subsample of 231 incarcerated adults with MOPS data		
Polymorphism	**Genotype**	**N**	**Frequency**	**Hardy-Weinberg equilibrium**	**N**	**Frequency**	**Hardy-Weinberg equilibrium**
HTR1B-rs13212041	**C/C**	34	0.043	$\chi^2 = 0.541$	10	0.043	$\chi^2 = 1.995$
	C/T	244	0.308	p = 0.462	60	0.259	p = 0.158
	T/T	514	0.649		159	0.694	
MAOA-uVNTR	**2r**	1	0.001	Not applicable	0	0.000	Not applicable
	3r	260	0.329		80	0.345	
	3.5r	13	0.016		3	0.013	
	4r	510	0.645		145	0.629	
	5r	7	0.009		3	0.013	
5-HTTLPR	**L_A/L_A**	167	0.211	$\chi^2 = 0.026$	41	0.181	$\chi^2 = 0.412$
	L_A/XL	1	0.001	p = 0.871	0	0.000	p = 0.521
	S/L_A + L_G/L_A	396	0.499		119	0.523	
	S/S + S/L_G	228	0.288		71	0.306	
HTR2A-rs6314	**C/C**	663	0.836	$\chi^2 = 2.481$	192	0.832	$\chi^2 = 0.302$
	C/T	126	0.159	p = 0.115	37	0.159	p = 0.582
	T/T	2	0.003		1	0.004	
TPH2-rs4570625	**G/G**	434	0.559	$\chi^2 = 3.574$	118	0.513	$\chi^2 = 0.724$
	G/T	279	0.359	p = 0.059	85	0.366	p = 0.395
	T/T	63	0.082		20	0.086	

(Table S2).

Significance level was set according to the Bonferroni method by considering the number of simultaneously tested hypotheses: genotype interaction (α_{level}= 0.05/5), Maternal and Paternal MOPS (α_{level}= 0.05/2), post hoc for genotype groupings (α_{level}= 0.05/2).

A post hoc power analysis for two-group independent sample t-test was conducted by using G*power 3.1.9.2 software (University of Düsseldorf) to determine the power (1-β) and the effect size (Cohen's coefficient, "d") (Cohen, 1998) of the observed differences between means.

3. Results

3.1. Genotype by PCL interaction

Allele frequencies were in Hardy Weinberg equilibrium (see Tables 1 and 2).

PCL-R and PCL:YV mean scores, obtained from adults and adolescents respectively, are reported in Table 3, divided by genotype groupings.

3.2. Main study: incarcerated adults

Carriers of the HTR1B-rs13212041-T/T genotype showed a mean PCL-R Total score significantly higher than C allele carriers (Waldχ^2 = 11.989, df= 1, $p_{Bonf.}$= 5 × 10^{-3}; 1-β = 0.95, d= 0.25; Fig. 1a). Linear regression showed that HTR1B-rs13212041 produced a significant model (R= 0.116, R^2 = 0.014, $F_{1, 790}$ = 10.862, $p_{Bonf.}$= 5 × 10^{-3}) that explained 1.2% of the variance of PCL-R Total score. Moreover, 428 (54%) of the incarcerated adults showed PCL-R Total scores ≥ 21, and 87 (11%) ≥ 30. T/T genotype increased 1.3 times (95% CI 1.00–1.79, p = 3.2 × 10^{-2}) and 1.8 times (95% CI 1.06–3.00, p = 2 × 10^{-2}) the risk of PCL-R Total scores ≥ 21 or ≥ 30, respectively.

The HTR1B-rs13212041-T/T carriers also scored higher than C allele carriers at both PCL-R Factor 1 (Waldχ^2 = 8.9341, df= 1, $p_{Bonf.}$= 6 ×10^{-3}; 1-β = 0.95, d= 0.19; Fig. 1b) and PCL-R Factor 2 (Waldχ^2 = 11.551, df= 1, $p_{Bonf.}$= 2 × 10^{-3}; 1-β = 0.99, d= 0.24; Fig. 1c). Linear regression showed that the HTR1B-rs13212041 produced a significant model that explained 0.5% of the variance of PCL-R Factor 1 scores (R= 0.081, R^2 = 0.007, $F_{1, 790}$ = 5.185, $p_{Bonf.}$= 4.6 ×10^{-2}) and 1.4% of the variance of PCL-R Factor 2 scores (R= 0.122, R^2 = 0.015, $F_{1, 790}$ = 12.034, $p_{Bonf.}$= 2 × 10^{-3}).

None of the other polymorphisms showed any statistically significant association with PCL-R scores (Table S3).

Number of individuals in whom genotyping was attempted: 793 for all the five variants; numbers of individuals in whom genotyping was successful: 777 for TPH2-rs4570625, 792 for 5-HTTLPR, 791 for MAOA-uVNTR, 792 for HTR1B-rs13212041 and 791 for HTR2A-rs6314.

3.3. Replication study: incarcerated adolescents

Carriers of the HTR1B-rs13212041-T/T genotype showed a mean PCL:YV Total score significantly higher than the HTR1B-rs13212041-C allele carriers (Waldχ^2 = 10.372, df= 1, p = 1 × 10^{-3}; 1-β = 0.93, d= 0.52; Fig. 2a). Linear regression showed that HTR1B-rs13212041 produced a significant model (R= 0.231, R^2 = 0.053, $F_{1, 167}$ = 9.368, p = 4 ×10^{-3}) that explained 4.8% of the variance of PCL:YV Total scores.

Moreover, 47 (28%) of the incarcerated adolescents showed PCL:YV Total scores ≥ 25 and 30 (18%) ≥ 30. The HTR1B-rs13212041-T/T genotype increased 2.05 times (95% CI 1.04–4.03, p = 2.6 × 10^{-2}) and 5.63 times (95% CI 1.59–19.94, p = 2 × 10^{-3}) the risk of PCL:YV Total scores ≥ 25 or ≥ 30, respectively. The HTR1B-rs13212041-T/T carriers also scored higher than the HTR1B-rs13212041-C allele carriers at PCL:YV Factor 1 (Waldχ^2 = 9.462, df= 1, $p_{Bonf.}$= 4 ×10^{-3}; 1-β = 0.91, d= 0.5; Fig. 2b), but not at PCL:YV Factor 2 (Waldχ^2 = 3.057, df= 1, $p_{Bonf.}$= 0.16; 1-β = 0.53, d= 0.29). Linear regression showed that HTR1B-rs13212041 produced a significant model (R= 0.222, R^2 = 0.049, $F_{1, 167}$ = 8.598, $p_{Bonf.}$= 8 ×10^{-3}) that explained 4.4% of the variance of PCL:YV Factor 1 scores, while the model was not significant for PCL:YV Factor 2 (R= 0.137, R^2 = 0.019, $F_{1, 167}$ = 8.598, $p_{Bonf.}$= 0.154).

None of the other polymorphisms showed any statistically significant association with PCL:YV scores (Table S6).

Number of individuals in whom genotyping was attempted: 168 for all the five variants; numbers of individuals in whom genotyping was successful: 166 for TPH2-rs4570625, 168 for 5-HTTLPR, 168 for MAOA-uVNTR, 168 for HTR1B-rs13212041 and 167 for HTR2A-rs6314.

3.4. Correlations between PCL-R and MOPS scores

MOPS data were only available for a subsample of 231 incarcerated adults. Paternal MOPS Total scores positively correlated with PCL-R Total scores (Waldχ^2 = 8.984, df= 1, $p_{Bonf.}$= 6 ×10^{-3}; Fig. 3a) and with both PCL-R Factor 1 (Waldχ^2 = 6.507, df= 1, $p_{Bonf.}$= 2.2 × 10^{-2}; Fig. 3b) and Factor 2 (Waldχ^2 = 6.276, df= 1, $p_{Bonf.}$= 2.4 ×10^{-2}; Fig. 3c) scores. Participants with Paternal MOPS Total scores > 8 obtained a mean PCL-R Total score significantly higher than individuals with Paternal MOPS Total scores ≤ 8 (Waldχ^2 = 8.161, df= 1, p = 4 ×10^{-3}; β = 0.61 and d= 0.4; Fig. 3d). Specifically, Paternal MOPS Total scores > 8 increased 1.9 times (95% CI 1.07–3.30, p = 1.9 ×10^{-2}) and 2.64 times (95% CI 1.13–6.16, p = 1.9 ×10^{-2}) the risk of PCL-R Total scores ≥ 21 or ≥ 30, respectively.

Table 3
Mean PCL-R and PCL:YV scores, in the incarcerated adults and adolescents, respectively, divided by genotype groupings.

		Sample of 793 incarcerated adults PCL-R mean scores			Replication sample of 168 incarcerated adolescents PCL:YV mean scores		
		Total	Factor 1	Factor 2	Total	Factor 1	Factor 2
HTR1B-rs13212041	C-allele	20.16 ± 6.22	5.74 ± 3.11	12.21 ± 3.85	21.46 ± 5.48	5.80 ± 2.94	13.73 ± 3.39
	T/T	21.74 ± 6.29	6.37 ± 3.41	13.09 ± 3.42	24.48 ± 6.17	7.34 ± 3.28	14.69 ± 3.18
MAOA-uVNTR	Low	21.16 ± 6.54	6.36 ± 3.55	12.43 ± 3.81	22.91 ± 5.35	6.44 ± 2.75	13.21 ± 3.07
	High	21.16 ± 6.12	5.93 ± 3.17	12.81 ± 3.45	23.74 ± 6.49	7.04 ± 3.45	14.48 ± 3.38
5-HTTLPR	S-allele	21.15 ± 6.21	6.09 ± 3.26	12.67 ± 3.62	23.32 ± 5.94	6.69 ± 3.10	14.30 ± 3.23
	L/L	21.21 ± 6.56	6.26 ± 3.57	12.58 ± 3.58	23.92 ± 6.75	7.30 ± 3.65	14.48 ± 3.46
HTR2A-rs6314	C/C	21.32 ± 6.24	6.15 ± 3.30	12.77 ± 3.60	23.42 ± 6.11	6.85 ± 3.26	14.29 ± 3.26
	T-allele	20.58 ± 6.67	6.11 ± 3.55	12.11 ± 3.69	24.26 ± 6.57	7.00 ± 3.29	15.11 ± 3.34
TPH2-rs4570625	G/G	21.44 ± 6.19	6.27 ± 3.33	12.83 ± 3.53	23.09 ± 6.28	6.67 ± 3.23	14.27 ± 3.30
	T-allele	20.99 ± 6.43	5.97 ± 3.34	12.53 ± 3.71	24.05 ± 5.60	7.11 ± 3.29	14.49 ± 3.30

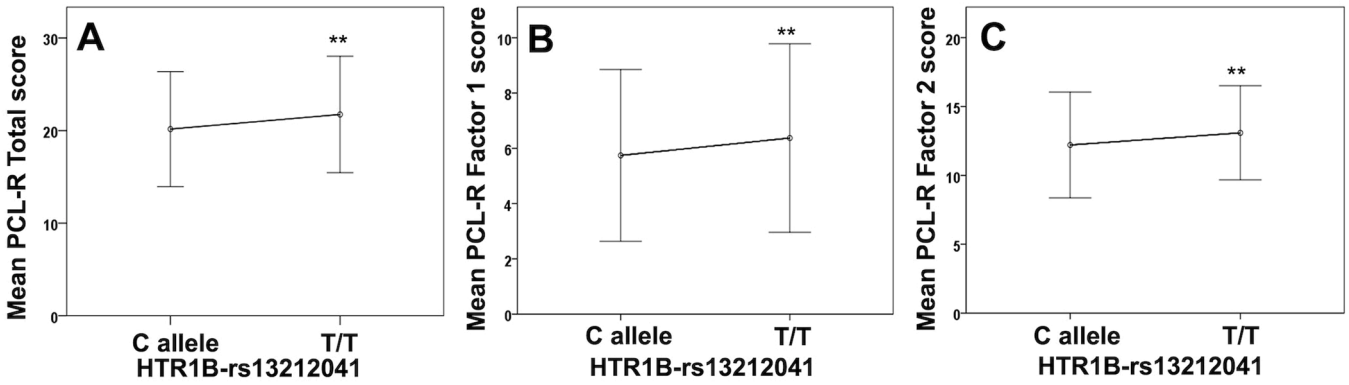

Fig. 1. Mean PCL-R scores divided by HTR1B-rs13212041 genotype groupings in incarcerated adults. T/T genotype carriers scored higher than C allele carriers at (a) PCL-R Total, (b) PCL-R Factor 1 and (c) PCL-R Factor 2. Data are expressed as mean ± SD (standard deviation).

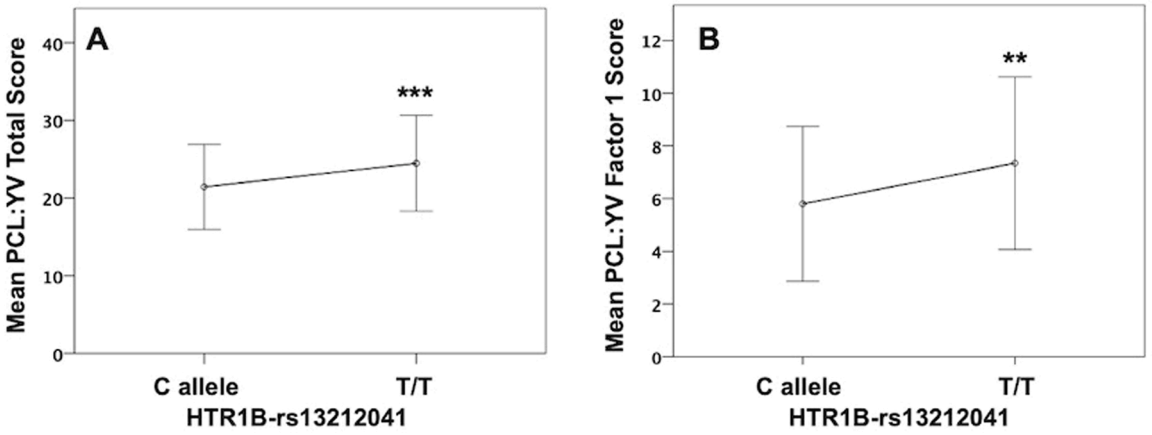

Fig. 2. Replication study in incarcerated adolescents: Mean PCL-R scores divided by HTR1B-rs13212041 genotype groupings. T/T genotype carriers scored higher than C allele carriers at (a) PCL-R Total, (b) PCL-R Factor 1 and (c) PCL-R Factor 2. Data are expressed as mean ± SD (standard deviation).

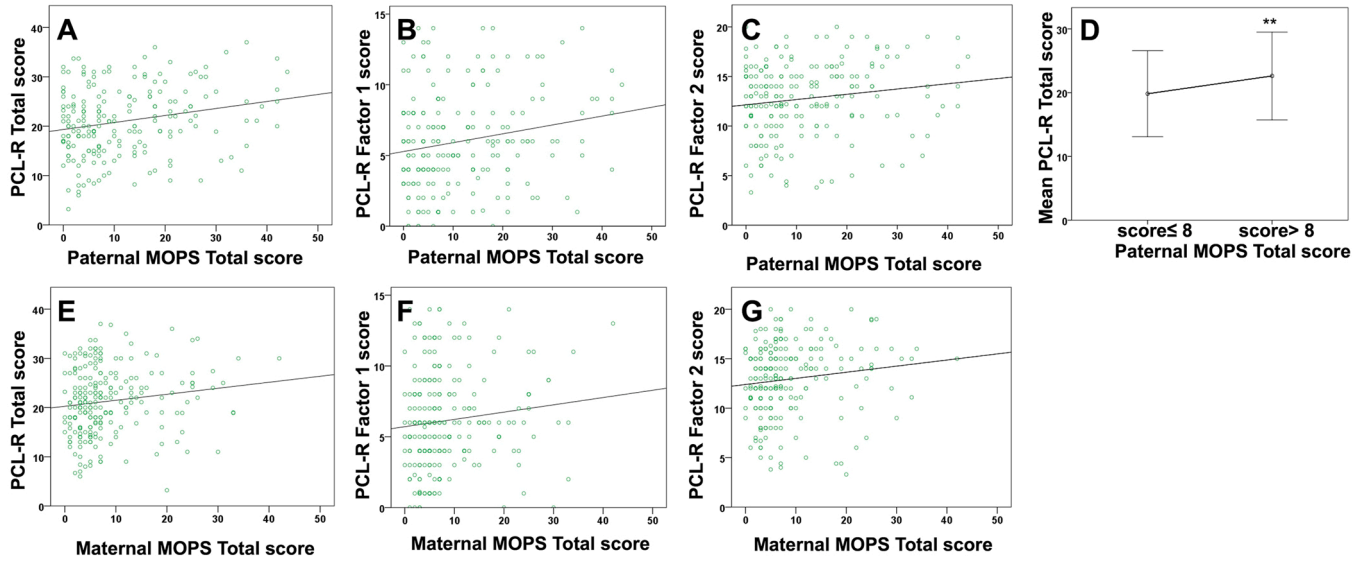

Fig. 3. Correlations between PCL-R and both Maternal and Paternal MOPS scores in incarcerated adults. a) PCL-R Total, b) PCL-R Factor 1, and c) PCL-R Factor 2 scores positively correlated with Paternal MOPS Total score. d) Mean PCL-R Total scores was higher in participants with Paternal MOPS total scores > 8. Data are expressed as mean ± SD.

Maternal MOPS Total scores did not show any statistically significant correlation with PCL-R Total scores (Fig. 3e-g and Table S4).

3.5. Genotype by MOPS by PCL-R interaction

A significant interaction among the HTR1B-rs13212041 genotype, Paternal MOPS Total scores, and PCL-R Total scores was observed (Waldχ^2 = 14.174, df= 2, $p_{Bonf.}= 1 \times 10^{-2}$). Specifically, Paternal MOPS Total scores positively correlated with PCL-R Total scores in the HTR1B-rs13212041-T/T carriers ($p_{Bonf.}= 3.68 \times 10^{-4}$; n = 140), but not in the C allele carriers (n = 60) (Fig. 4a). This correlation was statistically significant with both PCL-R Factor 1 ($p_{Bonf.}= 1.2 \times 10^{-2}$; Fig. 4b) and Factor 2 ($p_{Bonf.}= 8 \times 10^{-3}$; Fig. 4c) scores.

Among the HTR1B-rs13212041-T/T subjects, those with Paternal MOPS Total scores > 8 obtained a mean PCL-R Total score significantly higher than individuals with Paternal MOPS Total scores ≤ 8 ($p = 3 \times 10^{-3}$; $\beta = 0.8$ and d= 0.6; Fig. 4d). Specifically, for Paternal MOPS Total scores > 8, the HTR1B-rs13212041-T/T genotype increased 2.28 times (95% CI 1.14–4.54, $p = 1.4 \times 10^{-2}$) and 2.93 times (95% CI 1.12–7.63, $p = 2.3 \times 10^{-2}$) the risk of PCL-R Total scores ≥ 21 or ≥ 30, respectively.

None of the other analyzed polymorphisms showed any statistically significant effect that survived the Bonferroni correction (Table S5).

4. Discussion

In the largest sample of US institutionalized adult individuals studied so far, and in a replication sample of incarcerated adolescents, we investigated five polymorphisms of the serotonin pathway as potential risk factors for psychopathy. Furthermore, in a subgroup of the adult sample, we studied the same genetic variants in interaction with parenting style experienced during the first 16 years of life, as measured by MOPS.

In the adult sample, carriers of the HTR1B-rs13212041-T/T genotype showed significantly higher mean PCL-R Total, Factor 1 and Factor 2 scores, as compared to the HTR1B-rs13212041-C allele carriers, suggesting that the HTR1B-rs13212041-T/T genotype may represent a susceptibility factor for both the interpersonal/affective and the social deviance dimensions of psychopathy.

Of note, the direct association between psychopathy and the HTR1B-rs13212041-T/T genotype was replicated in adolescents. Carriers of the HTR1B-rs13212041-T/T genotype, indeed, showed significantly higher mean PCL:YV Total and Factor 1 scores, as compared to the HTR1B-rs13212041-C allele carriers. Noteworthy: (A) the sample size of adolescents useful to observe the genetic associations (168) was much smaller than that of adults (793); (B) the effect sizes of the difference in Total and Factor 1 psychopathy scores, between HTR1B-rs13212041-T/T genotype and C-allele carriers, in adolescents (d= 0.52 and 0.5, respectively) were more than double than in adults (d= 0.25 and 0.19, respectively); (C) the risk for the HTR1B-rs13212041-T/T genotype carriers of having high psychopathy scores was two/three times higher in adolescents (odds ratio of PCL:YV Total scores ≥ 25 or ≥ 30: 2.05 and 5.63, respectively) than in adults (odds ratio of PCL-R Total scores ≥ 21 or ≥ 30: 1.3 and 1.8, respectively). Overall, these findings indicated that the influence of the HTR1B-rs13212041-T/T genotype on psychopathy was stronger in youths than in adults, in line with the hypothesis that genetic factors should not be considered as "factors of stability", but rather as "developmentally dynamic factors", that is dynamic entities whose influence on behavior changes over time (Takahashi et al., 2021). This hypothesis assumes that novel gene by gene or gene by environment interactions occurring with age (Takahashi et al., 2021) may mitigate previous effects of other genes (Hyde et al., 2016; Waller et al., 2016). This phenomenon, named "genetic innovation", may result from developmental processes underpinning brain maturation and/or from extensive hormonal, neuroanatomical, and neurochemical changes occurring during puberty (Takahashi et al., 2021; Spear, 2000).

As far as the subsample of 231 participants with MOPS data is concerned, PCL-R Total, Factor 1 and Factor 2 scores positively correlated with Paternal MOPS scores only in carriers of the HTR1B-rs13212041-T/T genotype, but not in the HTR1B-rs13212041-C allele carriers. These results are in line with and expand previous findings showing a link between childhood maltreatment and psychopathy (Dargis et al., 2016; Waller et al., 2018; Durand and de Calheiros Velozo, 2018).

HTR1B encodes for the serotonin receptor 1B that is mostly expressed at pre-synaptic terminals of serotonin neurons, where it regulates neuronal firing by inhibiting the serotonin release in the synaptic cleft (Hoyer et al., 2002). At post-synaptic level, HTR1B acts either as an auto-receptor on serotoninergic neurons or as an hetero-receptor on dopaminergic, glutamatergic, GABAergic and acetyl-cholinergic neurons (Pauwels, 1997). A number of studies, both in humans and animals, indicate the potential implication of low HTR1B levels in aggressive and impulsive behavior (Nautiyal et al., 2015; Zhuang et al., 1999; Saudou et al., 1994; De Almeida et al., 2006; Faccidomo et al., 2012; Gowin et al., 2010; Jensen et al., 2009; Hakulinen et al., 2013; Conner et al., 2010; Zouk et al., 2007).

The T/T genotype of the SNP investigated here, rs13212041, has been associated with higher levels of anger and hostility as well (Jensen et al., 2009; Conner et al., 2010). The T allele of HTR1B-rs13212041

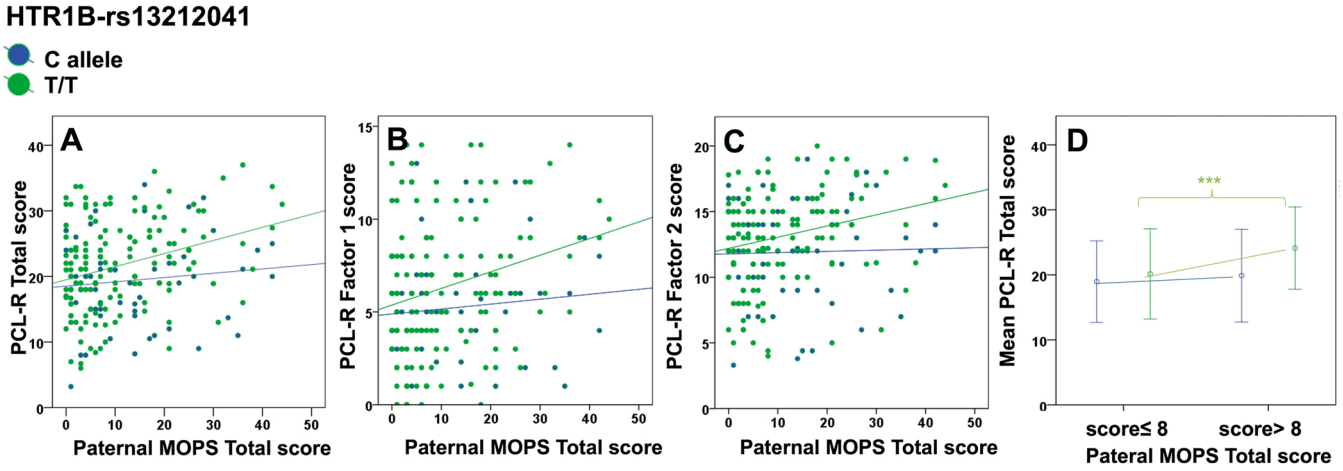

Fig. 4. Correlations between PCL-R Total and Paternal MOPS scores divided by HTR1B-rs13212041 genotype groupings in incarcerated adults. In T/T genotype carriers, Paternal MOPS Total scores positively correlated with a) PCL-R Total, b) PCL-R Factor 1 and c) PCL-R Factor 2 scores. d) In T/T genotype carriers, mean PCL-R Total scores was higher in participants with Paternal MOPS Total scores > 8. Data are mean ± SD.

allows for the interaction with a regulatory microRNA (i.e., miR-96), thus enabling a miRNA-mediated reduction of HTR1B gene expression; conversely, the C allele hampers the interaction with miR-96 (Jensen et al., 2009).

Our findings indicate that a lower expression of HTR1B, mediated by the rs13212041-T/T genotype, not only predicted antisocial psychopathic traits in adults, but also higher interpersonal-affective problems both in adults and in adolescents. This latter association has never been described before in psychopaths, but HTR1B methylation, a molecular mechanism that decreases gene expression, has been previously reported as positively correlated with callous unemotional traits in youth (Moul et al., 2015), in line with a potential role of HTR1B on affective dysfunction.

In the subsample of participants with MOPS data, the HTR1B-rs13212041-T/T genotype appeared to synergistically interact with paternal maltreatment, by increasing again the risk for both dimensions of psychopathy.

Considering these results, we hypothesize that the HTR1B-rs13212041-T/T genotype may represent a risk factor for both the dimensions of psychopathy, albeit to a different extent. Due to the dual activity of HTR1B, both as an auto-receptor at pre-synaptic terminals and as an auto- or hetero-receptor on post-synaptic neurons, we propose that HTR1Bs with different localizations and functions may differentially affect the two dimensions of psychopathy. In line with this hypothesis, it has been previously proposed that pre-synaptic HT1B autoreceptors play a role in the introductory/appetitive phases of aggressive behavior, while post-synaptic HT1B hetero-receptors modulate the executive, consummatory phases of aggressive behavior (Olivier and van Oorschot, 2005). Finally, some pieces of evidence have pointed out that HTR1Bs have opposite behavioral effects on different brain areas and show different patterns of sensitivity to variations of the serotonergic tone (Sari, 2004; Liu et al., 2015). As far as psychopathy is concerned, we may picture a complex scenario for HTR1B action, involving not only serotonin, but also other excitatory or inhibitory pathways of neurotransmission, able to influence different psychopathic traits.

In conclusion, we propose that the HTR1B-rs13212041-T/T genotype has a stronger effect in increasing the risk for interpersonal/affective psychopathy in youths as compared to adults. However, in adults, we observed that HTR1B-rs13212041-T/T genotype may increase the individual sensitivity to childhood negative environment, thus potentiating the effects that paternal maltreatment exerts to predispose to psychopathy. As previous findings in humans showed that childhood adversities induced hyper-methylation and reduced the expression of HTR1B (Murrough et al., 2011), we might hypothesize that paternal maltreatment lead to epigenetic changes on HTR1B gene, able to amplify the HTR1B-rs13212041-T/T mediated effect of miR96. This latter hypothesis is corroborated by findings from animal studies showing that early developmental trauma, like social isolation, decrease the transcription of HTR1B (Bibancos et al., 2007).

5. Limitations of the study

5.1. The current study presents some potential limitations

First, the adoption of a candidate gene rather than a GWAS approach may be an issue for discussion. We would like to underline, however, that the present study was conducted in a well-characterized sample of US institutionalized participants that represents the largest cohort of incarcerated individuals studied to date. This sample, however, was far from being numerically adequate for a GWAS (Mehta and Czamara, 2019). GWAS, indeed, are typically conducted on several dozen thousands of subjects, as they explore the whole genome being not based on a-priori hypotheses. At the opposite, this study was based on a strong a priori hypothesis: the central role that serotonin exerts both as a neuronal growth factor since the earliest stages of life and as a neurotransmitter implicated in cognitive and emotional processes in the mature brain (Brummelte et al., 2017). Worth of notice, the association between the HTR1B-rs13212041-T/T genotype and the interpersonal/affective dimension of psychopathy was observed in two independent groups: the adults and the adolescents.

A second limitation is that only White male participants were included in the present work, as they were the largest collected sample of institutionalized subjects. Extending the study to females and other ethnicities, as well as to non-institutionalized subjects, will be worthy. Finally, even though we did not find any association with maternal parenting style, we cannot exclude a role for maternal behavior in predisposing to psychopathy, as in our sample we did not observe high maternal MOPS scores.

The use of cut-off scores for the analysis of PCL data also deserves some discussion. Whether psychopathy should be considered a dimensional or a categorical variable, indeed, is still under debate (Edens et al., 2006; Spear, 2000). A PCL-R score equal or higher than 21 is considered as the cut-off score for psychopathy diagnosis, while a score equal or higher than 30 indicates severe psychopathy (Hare and Neumann, 2009). Some authors, however, have pointed out that applying cut-offs at PCL-R is an imprecise way to diagnose psychopathy (Balsis et al., 2017). Concerning PCL:YV (Forth and Mailloux, 2020) some researchers have suggested to adopt a cut-off of 25 to identify subjects with psychopathic traits, [e.g., (Murrie and Cornell, 2002)], while others have used the threshold score of 30 to differentiate subjects with the most severe traits [e.g., (Gretton et al., 2001)]. Taking into account all these different positions, we ran two different analyses: one by measuring psychopathy as a dimensional construct and the other one by considering psychopathy as a discrete variable with both 21 (PCL-R) or 25 (PCL:YV) and 30 as cut-off scores. Considering psychopathy as a categorical variable also allowed us to calculate odds ratio to estimate the risk for the HTR1B-rs13212041-T/T carriers to show high PCL-R scores, as compared to the HTR1B-rs13212041-C allele carriers.

No threshold or cut-off are usually set for MOPS scores but, according to the median split method (Greenberg et al., 1999), we turned MOPS variable from a continuous into a categorical variable, scoring ≤ 8 or > 8. We would like to emphasize, however, that 8 did not represent a threshold to separate maltreated from non-maltreated subjects, but only a strategy to observe the effect size of the environmental influence on psychopathy.

Finally, we would like to acknowledge that cultural and neighborhood contexts, as well as family structures, which are known to influence parenting beliefs and behaviors (for instance, see Bornstein, 2012; McBride Murry and Lippold, 2018; Byrnes and Miller, 2012) were not accounted for in our analysis. Wider cultural factors, indeed, are not easily assessable with the current methods but would warrant further discussion in future research.

6. Conclusions

The results of the present study provide evidence in support of a role for the HTR1B-rs13212041-T/T genotype in increasing the risk for both the interpersonal/affective and the antisocial dimension of psychopathy, consistent with the primary role that CNS serotoninergic system plays in regulating mood, cognition, and behavior. The effect of the HTR1B-rs13212041-T/T genotype on the increased risk for the interpersonal/affective dimension of psychopathy was even more evident in the youngest group of participants. Interestingly, in the group of incarcerated adults, we observed that the HTR1B-rs13212041-T/T genotype in interaction with paternal MOPS scores was an even stronger predictor of higher levels of psychopathy than either the genetic or the environmental factor taken individually, thus reinforcing the role that a negative childhood environment exerts in predisposing to deviant behavior. We suggest that HTR1B-rs13212041-T/T genotype might represent a biological correlate of vulnerability to psychopathy, useful to identify youths with deviant behavior particularly sensitive to parent maltreatment, who might benefit from early interventions aimed at improving

their family environment, in order to decrease the risk of developing psychopathy.

Overall, these findings highlight once again the importance of gene by environment interactions in modulating human behavior and shed new light on the neurobiological underpinnings of psychopathy, with important implications both at a clinical and forensic level.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Silvia Pellegrini, Pietro Pietrini and Kent A. Kiehl conceived and supervised the study. Silvia Pellegrini acquired the project funding. Carla Harenski, Nathaniel Anderson and Kent A. Kiehl recruited the sample, collected psychometric data and salivas. Carla Harenski and Nathaniel Anderson organized the sample database. Sara Palumbo and Silvia Pellegrini planned the experimental design. Sara Palumbo, Veronica Mariotti, Klizia Antonelli and Stefano Vellucci carried out the experiments. Sara Palumbo performed the statistical analysis and produced figures and tables. Sara Palumbo and Silvia Pellegrini interpreted the results and wrote the manuscript. Veronica Mariotti contributed to interpret the results and write the manuscript. Pietro Pietrini and Kent A. Kiehl critically reviewed the manuscript. All the authors edited and approved the final version of the manuscript.

Declaration of interests

None.

Acknowledgments

This work was financed by Gio.I.A. ("Giovani In Armonia" (Youths in Harmony)) Foundation, Pisa (Italy).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105861.

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